Evidence Report: Appropriate Patient Preparation for Renal Replacement Therapy

Final Report

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Abbreviations

1α-HCC	1-alpha-hydroxycholecalciferol
ABD	Adynamic bone disease
ACE	Angiotensin converting enzyme
ACE-I	Angiotensin converting enzyme inhibitor
AHRQ	Agency for Healthcare Research and Quality
ApoA	Apolipoprotein A
ApoB	Apolipoprotein B
ARB	Angiotensin II receptor blockers
ASN	American Society of Nephrology
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CAPD	Chronic ambulatory peritoneal dialysis
CCPD	Continuous cyclic peritoneal dialysis
CHF	Congestive heart failure
CKD	Chronic kidney disease
CPG	Clinical practice guidelines
CrCl	Creatinine clearance
CRF	Chronic renal failure
CRI	Chronic renal insufficiency
DEXA	Dual energy X-ray absorptiometry
EAA	Essential amino acid
EAST	Erythrocyte aspartate aminotransferase
EPC	Evidence-based Practice Center
EPO	Erythropoetin
ESRD	End-stage renal disease
GFR	Glomerular filtration rate
Hct	Hematocrit
HD	Hemodialysis
HDL-C	High-density lipoprotein cholesterol

Hgb	Hemoglobin
HMO	Health maintenance organization
HPTH	Hyperparthyroidism
HTN	Hypertension
IBW	Ideal body weight
IL	Interleukine
IM	Intra-muscular
iPTH	Immunoreactive parathyroid hormone
IV	Intravenous
JNC VI	Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure
KA	Ketoacids
KDOQI	Kidney disease outcomes quality initiative
KDQ	Kidney disease questionnaire
LDL-C	Low-density lipoprotein cholesterol
LE	Level of evidence
LOS	Length of stay
LPD	Low-protein diet
LVH	Left ventricular hypertrophy
LVMI	Left ventricular mass index
MAP	Mean arterial pressure
MDRD Study	Modification of Diet in Renal Disease Study
MeSH	Medical subject heading
MMPG	Magnesium pyridoxal 5-phosphate glutamate
NHANES	National Health and Nutrition Examination Survey
NKF	National Kidney Foundation
NS	Not statistically significant
OR	Odds ratio
PAERI	Prevalence of Anemia in Patients with Early Renal Insufficiency
PD	Peritoneal dialysis
PLP	Pyridoxal-5'phosphate
PTH	Parathyroid hormone

QOL	Quality of life
QS	Quality score
RBF	Renal blood flow
RBP	Retinol-binding protein
RCT	Randomized controlled trial
r-HuEPO	Recombinant human erythropoietin
ROD	Renal osteodystrophy
RPA	Renal Physicians Association
RRF	Residual renal function
RRT	Renal replacement therapy
RVR	Renal vascular resistance
SC	Subcutaneous
SCr	Serum creatinine
SD	Standard deviation
SEM	Standard error of the mean
SIP	Sickness Impact Profile
SOC score	Sense-of-coherence score
STAI	State-trait Anxiety Inventory
TG	Triglycerides
TNF	Tumor necrosis factor
UPD	Usual-protein diet
UUN	Urinary urea nitrogen
VLDL-C	Very low-density lipoprotein cholesterol
VLPD	Very low-protein diet

Summary of Evidence Report

The purpose of this report is to identify and summarize the available published evidence on the management of patients who have severe chronic kidney disease (CKD) and are not yet on renal replacement therapy (RRT) but are expected to progress and require RRT within 6 to 18 months. Key management issues to be addressed for this population include: timing of initiation of RRT; counseling and rehabilitation prior to initiation of RRT; and the management of anemia, hypertension, bone disease, lipid abnormalities, and nutrition. The report has been compiled with the goal of informing a panel charged with developing a clinical practice guideline (CPG) for patient preparation for renal replacement therapy. This evidence report constitutes Phase I of a three-step process whose final product is the CPG.

The most important goal in caring for a patient with CKD and declining kidney function is to preserve kidney function as long as possible. However, some of the interventions used to preserve kidney function (e.g., low protein diet, aggressive blood pressure control) may no longer be beneficial to patients beginning RRT, particularly to those patients beginning hemodialysis. For example, although aggressive blood pressure control delays the onset of kidney failure, some epidemiological evidence suggests that mortality is increased among hemodialysis patients with lower blood pressure. Care of patients with impending kidney failure also presents some unique dilemmas. For example, low-protein diets are usually prescribed to preserve kidney function in patients with severe CKD; however, this may interfere with the healing of arteriovenous fistulae or grafts placed for hemodialysis. This report is designed specifically to examine the effect of a variety of management strategies in the population of CKD patients for whom RRT is imminent.

The annual mortality rate for ESRD patients is approximately 20% per year, and half these deaths are from cardiovascular complications such as myocardial infarction and congestive heart failure. This mortality translates into a life expectancy that is only 16-37% of the age-, gender-, and race-matched general population. The highest death risk occurs during the incident year of RRT. The hospitalization rate for ESRD patients is also several times higher than that for age- and risk-adjusted comparative cohorts of patients without kidney failure. In 1997, the total cost of care for the Medicare ESRD Program was approximately $11.76 billion, rendering it the largest single Medicare program fiscally, despite the fact that it funds care for a relatively small population.

Target practice settings

We expect that the Evidence Report and later guidelines will focus on practice settings in the United States and will consider a range of organizational structures. Care for patients with severe chronic kidney disease may involve

primary care practices, nephrology clinics, transplant programs, or dialysis centers.

Target audience
We expect the primary audience for the Guideline will include primarily physicians involved in decision making in the preparation for RRT, which is usually shared between primary care physicians and nephrologists. However, the planned Guideline will also be extremely useful to other health care providers involved in the care of patients with ESRD, as well as to patients and their families. Because the care of patients with CKD is so costly, federal and third-party payers will also be part of audience for the evidence report, guidelines, and management tools.

Methodology
We performed an in-depth literature review, weighing and summarizing the current body of knowledge regarding preparation of the patient for RRT, focusing on the following seven principal areas:

1. Optimal management of anemia secondary to erythropoietin deficiency;
2. Prevention of hyperparathyroidism, hyperphosphatemia, hypocalcemia, and metabolic bone disease;
3. Blood pressure control;
4. Maintenance of adequate nutrition;
5. Managing qualitative and quantitative lipid disorders;
6. Timing of the initiation of dialysis;
7. Counseling for choices of renal replacement therapy, patient rehabilitation, and psychosocial and economic preparation.

A description of our technical approach follows.

Literature review and synthesis – overview
A comprehensive analytical review of available published information was conducted to provide the scientific basis for decisions to prepare patients for RRT. Information from the literature was abstracted into evidence tables. The final products of the literature review are summaries of the published studies that meet the established methodological standards. The results are provided in a format that permits a direct linkage between the recommendations of future guidelines planned by the Renal Physicians Association.

The following sections describe the selection of topics for review, method of identifying the pertinent literature, process for selection of the literature, means of abstracting data, construction of evidence tables, meta-analysis of pertinent parameters, and summary of areas for future research. This process was carried out in a collaborative effort between Duke University physicians and methodologists, a jointly-appointed panel of content experts, and the Renal Physicians Association.

Systematic literature review

Our strategy primarily involved MEDLINE, a computerized bibliographic database of the National Library of Medicine, as the main source to screen for articles. The MEDLINE search strategies retrieved articles pertaining to each of the key questions. The searches were implemented in an information retrieval software package that offers full-text searching in addition to Medical Subject Heading (MeSH) term searching.

We excluded articles not pertaining to humans and articles not in the English language. We also limited initial searches to studies published since 1988 (although pre-1988 articles were identified through references in included studies).

We also made use of existing evidence-based clinical practice guidelines, review articles, and articles already known to the Working Group in order to identify potential articles as efficiently as possible. In addition, citations from included articles were examined. Working Group members and content experts were queried about their knowledge of other information sources such as unpublished trials.

Screening

Titles and abstracts identified by the MEDLINE search and through other sources were screened for inclusion by two physicians, one nephrologist and one methodologist. The decision whether to include or exclude an article was made according to criteria that took into account the type of interventions, the type of patients, the study design, and the reported data. Articles were excluded if no empirical data were presented; if the population was not composed of pre-ESRD, ESRD, post-transplant, or other CKD patients; and if no clinically relevant outcomes were presented. The reliability of this selection process was examined by assessing the agreement between paired reviewers. An article was included for further review if either reviewer included it; this process leads to greater sensitivity, minimizing the chance that a valuable article might be overlooked.

Articles not excluded were submitted to a second screening process using a full-text version of the article and performed by two physicians. At this step, articles were excluded if on review the study population did not meet the definition of pre-ESRD (see above). If the study included both patients with pre-ESRD and without pre-ESRD, the study was excluded if outcomes were not reported separately for patients with pre-ESRD. Small case series (< 10 cases) and unique case reports were excluded, with the exception of articles reporting adverse events of drugs used for the management of hypertension and/or dyslipidemias. Finally, articles were excluded if they did not address one or more of the issues formulated in the key questions for the specific topic. Included articles were then abstracted by a physician investigator using a standardized abstraction form, and then summarized into an evidence table.

The seven topics used common inclusion criteria for acceptable study populations. For a study to be included in this systematic review, the study population was required to have a mean or median glomerular filtration rate (GFR) below 30 ml/min/1.73 m^2, either measured directly or estimated using the Cockcroft-Gault formula. When an estimation of the creatinine clearance (CrCl) was not available, a mean or median serum creatinine (SCr) greater than 2.5 mg/ml was considered as fulfilling the criteria for inclusion. If no quantitative data were reported on GFR, CrCl or SCr, articles were eligible for inclusion if the population studied was clearly described as a pre-ESRD population. In addition, two types of studies where patients did not meet these criteria were nevertheless considered for inclusion: (1) prospective studies in which a population of patients was followed as GFR declined to pre-ESRD range, and (2) retrospective studies in which an RRT population (most often patients then undergoing dialysis treatment) had data collected for the pre-ESRD period.

In addition, all topics generally required the number of subjects to be greater than 10. Further explicit criteria regarding interventions, outcomes and study design were developed for each specific research question for use by the reviewers. These are described in each chapter.

Data abstraction and evidence tables
We developed data abstraction forms to collect data regarding details of patient population, interventions, study design, results, and study quality. These forms were completed by the Duke clinicians and reviewed in detail during reformatting the data into evidence tables.

Assessment of the quality of available evidence
Each included and abstracted article was evaluated and rated for level of evidence (LE) using a generic scale that rates studies according to their purpose (assessment of efficacy, natural history, etc.) into categories relating to their susceptibility to bias based primarily on study design.

In addition, each study was evaluated according to six criteria testing for internal and external validity. These criteria explored the study population's selection and representativeness, how attrition was considered, and how well the study population fit our definition of pre-ESRD. Finally, a global, subjective quality score (QS) was assigned using a 4-point scale (excellent, good, fair, poor).

Results

Anemia summary
To address the issue of the management of anemia in patients with pre-ESRD, the following five key questions were formulated:

1. What is the prevalence of anemia in pre-ESRD?

2. What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion?
3. What proportion of patients without nutritional deficiencies are resistant to EPO?
4. What proportion of pre-ESRD patients have low EPO levels?
5. What is the efficacy of EPO in improving intermediate and ultimate outcomes in patients with pre-ESRD?

The available evidence on anemia in CKD led to us being able to provide data that addressed only three of our five key questions. Two of the questions posed were therefore not answered by the current review. The majority of the literature abstracted focused on the treatment of the anemia of CKD with EPO therapy and the effect of such therapy on intermediate and surrogate outcomes.

Key Question 1: What is the prevalence of anemia in pre-ESRD?
The modest evidence emerging from two studies using different criteria for pre-ESRD, and with overlapping populations, suggests that the prevalence of anemia in this population is in the range of 16% to 18%. It has been shown consistently that the prevalence of anemia increases markedly as kidney disease becomes more advanced.

Key Question 2: What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion?
No specific estimate of this proportion can be derived from the available literature. Iron deficiency in particular appears to be not uncommon. Patients on EPO who are iron deficient have been shown to require higher EPO levels to attain a target hemoglobin concentration.

Key Question 3: What proportion of patients without nutritional deficiencies are resistant to EPO?
No direct evidence was identified to answer this question.

Key Question 4: What proportion of pre-ESRD patients have low EPO levels?
The few studies of this question suggest that EPO levels in CKD are similar to levels in non-CKD patients without anemia. However, CKD patients are more likely to have EPO levels inappropriately for relative to their degree of anemia.

Key Question 5: What is the efficacy of EPO in improving intermediate and ultimate outcomes in patients with pre-ESRD?
We identified no studies relating use of EPO in all or a subset of the pre-ESRD population to mortality. One study examined the impact of EPO on quality of life, indicating that relief of anemia with EPO was associated with significant improvement in quality of life measures. The remainder examined the impact of EPO on hypertension, LVMI, renal hemodynamics, or endothelial function. Although not the target of this question, impact of EPO on deterioration of renal

function was evaluated in 17 identified studies; on balance, the evidence does not suggest a detrimental effect of EPO on kidney function.

Of 16 studies that assessed blood pressure effects of EPO therapy in CKD, eight suggested at least some increase in the risk of developing or suffering an exacerbation of hypertension associated with EPO therapy. No study reported improvement in blood pressure with EPO

Two studies involving small, highly selected populations suggest EPO may be associated with improvement in LVMI

Two limited studies did not reveal any significant effect of EPO on renal hemodynamics.

One study suggested that EPO therapy may improve endothelial function as evidenced by a reduction in the elevation of thrombomodulin levels. The importance of this finding is unclear as the significance thrombomodulin in endothelial pathobiology has not been elucidated.

Conclusions

On the order of 1 in 5 pre-ESRD patients are anemic. It is unclear how many of these patients are nutritionally deficient, but iron deficiency is not uncommon and (in addition to causing anemia) can interfere with the efficacy of EPO. Individuals who use EPO for anemia appear to have improved quality of life, as well as improvement in several intermediate outcomes; although exacerbation is associated with EPO use. No studies were identified that provide guidance on the threshold for treatment, or the optimal dose in the population of individuals with pre-ESRD.

Bone disease summary

Key Question 1: Does the correction of acidosis reduce the risk of bone disease (osteomalacia, osteitis, osteoporosis) and/or other negative outcomes in pre-ESRD patients?

- No prospective randomized controlled trials were identified that addressed this question
- Based upon the only identified retrospective case series, metabolic acidosis may actually prevent the development of adynamic bone disease and its correction may be of limited benefit in improving bone disease in pre-ESRD patients if improvement in osteomalacia, osteitis fibrosa, and osteoporosis is offset by worsening of adynamic bone disease.

Key Question 2: Does the use of estrogen replacement therapy reduce the risk of bone disease (osteomalacia, osteitis, osteoporosis) and/or other negative outcomes in pre-ESRD patients?

- No published studies of the effects of estrogen replacement therapy among pre-ESRD patients was identified.

Key Question 3: Does the use of phosphate binders and/or active vitamin D sterols reduce the risk of complications from hyperparathyroidism in pre-ESRD patients?

- No articles were identified that addressed the complications of interest which included parathyroidectomy, hypertension, LVH, coronary artery calcification, and CHF

Key Question 4: Does the use of phosphate binders and/or active vitamin D sterols increase the risk of adynamic bone disease, cardiovascular disease, and/or other negative outcomes in pre-ESRD patients?

- No articles were identified that addressed the question of cardiovascular disease
- Based on 9 prospective, randomized controlled trials evaluating the effects of active vitamin D sterols, we conclude that alfacalcidol (0.5mcg daily) or calcitriol (0.125-0.25 mcg daily) is safe and effective in preventing progression of bone disease among pre-ESRD patients with elevated plasma intact PTH, as well as upon metabolic markers of bone disease and/or bone histomorphometry.
- These doses do not appear to have a detrimental effect upon residual renal function.

Hypertension summary

The general question to be addressed is: "How should physicians manage blood pressure in subjects with severe chronic kidney disease as they prepare for ESRD?" The issue of blood pressure management to slow progression of chronic kidney disease is beyond the scope of this guideline development project; hypertension and chronic kidney disease progression is a focus of the new K/DOQI Chronic Kidney Disease Clinical Practice Guidelines.

There are several questions or themes to keep in mind as the evidence is summarized:

1. What kind of statements should this guideline make regarding blood pressure management for pre-ESRD patients?
2. What blood pressure goals should the guideline recommend?
3. Are there particular pharmaceutical agents that should be used, should not be used, or should be monitored carefully in pre-ESRD patients?

Key Question 1: What is the distribution of blood pressure or the prevalence of hypertension in pre-ESRD patients?

No evidence is available on the distribution of untreated blood pressure in pre-ESRD patients.

Based on two retrospective studies and one prospective trial, the majority of pre-ESRD subjects have systolic blood pressure greater than 140 OR diastolic blood pressure greater than 90.

Based on two retrospective studies and two prospective trials, greater than 80% of pre-ESRD subjects have hypertension based on either elevated blood pressure or use of anti-hypertensive agents.

Key Question 2: What is the prevalence of antihypertensive treatment in the pre-ESRD population?
Based on two retrospective studies and one prospective trial, approximately 81% of pre-ESRD patients are receiving antihypertensive treatement (studies reported 69%, 82%, 86%, and 87%).

Key Question 3: Is there evidence that treatment of elevated blood pressure with antihypertensive agents in pre-ESRD patients improves clinical outcomes before and/or after kidney replacement therapy?
Data from eleven prospective intervention trials show that blood pressure may be lowered in pre-ESRD patients. Usually, these studies do not show blood pressure lowered to the degree recommended by JNC VI.

A number of studies have shown that particular agents (ACE inhibitors and possibly calcium channel antagonists) may reduce the decline in kidney function or may lower protein excretion in pre-ESRD patients.

There are no interventional data showing what level of blood pressure control during pre-ESRD is optimal for clinical outcomes such as mortality, cardiac morbidity, or hospitalization.

Several large, randomized intervention trials show that antihypertensives affecting the renin-angiotensin axis improve some surrogate and clinical outcomes in patients with earlier stages of chronic kidney disease (HOPE, RENAAL, IDNT, AASK). These findings do not specifically address the issue of improving clinical outcomes for pre-ESRD subjects who are preparing to initiate kidney replacement therapy within 6 to 18 months.

Key Question 4: What is the risk of antihypertensive agent toxicities or side effects that occur as a consequence of reduced kidney function?
There are no systematic, population-based reports of antihypertensive drug toxicities or side effects that are specifically associated with reduced kidney function. Studies regarding this topic are generally reported as either single case reports or small case series.

Bradycardia with either beta-blockers or calcium channel antagonists is often a concern in advanced kidney failure. There is little data in the literature to systematically evaluate this phenomenon.

ACE-inhibitors and angiotensin receptor blockers have been related to both hyperkalemia and acute kidney failure in subjects with advanced kidney impairment. Two prospective trials involving a total of 124 pre-ESRD subjects did not show clinically significant hyperkalemia or acute kidney failure associated with either ACE-inhibitors or ARBS.

Nutrition summary

To address the issues of nutritional interventions and management of nutritional status in pre-ESRD patients, the following six key questions were formulated:

1. Are pre-ESRD patients at risk for malnutrition?
2. What risks does malnutrition confer to pre-ESRD patients?
3. What is the tolerability/feasibility of nutritional interventions in patients with pre-ESRD?
4. After appropriate nutritional evaluation, does nutritional intervention result in improved intermediate outcomes and/or clinical outcomes in pre-ESRD patients?
5. What is the rate of change in nutritional parameters in pre-ESRD patients?
6. What is the effect of follow-up nutritional evaluation in improving intermediate outcomes and/or clinical outcomes in pre-ESRD patients?

Key Question 1: Are pre-ESRD patients at risk for malnutrition?

- Based on three cross-sectional studies of > 200 patients each and three smaller cross-sectional studies, we conclude that there is reasonable evidence demonstrating that nutritional status declines as GFR declines and that this may be a function of decreased protein and energy intake.
- Based on four small (n = 9, n = 15, n = 9, n = 9) cohort/cross-sectional studies, we conclude that there is limited and conflicting evidence regarding the rate of protein metabolism in pre-ESRD patients. There also exists limited evidence demonstrating that protein catabolism increases as serum creatinine increases, serum bicarbonate decreases, or as plasma cortisol increases. In addition, protein catabolism may be reduced by correction of acidosis using sodium bicarbonate supplementation .
- Based on one small (n = 25) cohort study, we conclude that there is limited evidence demonstrating that nutritional status is less compromised in pre-ESRD patients than in those status post renal replacement therapy.
- Based on one small (n=20) before/after study , we conclude that there is limited evidence demonstrating that erythropoietin does not affect

nutritional status in pre-ESRD patients. This study also demonstrated that pre-ESRD patients had lower nutritional status than healthy controls.

Key Question 2: What risks does malnutrition confer to pre-ESRD patients?

- Based on one cross-sectional study, we conclude that there is no evidence to suggest that atherosclerosis is associated with malnutrition.

Key Question 3: Do nutritional interventions improve the nutritional status of patients with pre-ESRD?

- Based on one small (n = 67) retrospective cohort study, we conclude that there is limited evidence that suggests that a LPD may delay mortality in patients with pre-ESRD who subsequently go onto hemodialysis.
- Based on two randomized controlled trials, two large (n = 139 and n = 51) uncontrolled trials, and one medium (n = 28), four small (n < 10) uncontrolled trials, and two case series we conclude that there is inconsistent and insufficient evidence to support or reject that a LPD has a favorable impact on nutritional parameters of patients with pre-ESRD.
- Based on one crossover study, we conclude that there is limited evidence to suggest that a soy-based LPD can be substituted for an animal-based LPD without compromising nutritional status.
- Based on one randomized controlled trial of 57 patients we conclude that there is limited evidence that a LPD may result in deficiencies of thiamine (B_1), riboflavin (B_2), and pyridoxine (B_6) in pre-ESRD patients.
- Based on two randomized controlled trials of 56 and 90 patients, respectively, we conclude that there is reasonable evidence that a LPD does not result in vitamin E deficiencies.
- Based one small dual-arm, parallel-design trial (n = 59) and one crossover study (n = 8), we conclude that there is limited evidence to suggest that choice of supplement (essential amino acids versus ketoacids) does not affect nutritional status in pre-ESRD patients following a VLPD.
- Based on one uncontrolled study of eight patients, we conclude that there is limited evidence demonstrating that vitamin B_6 supplementation improves vitamin B_6 status in pre-ESRD patients.

Key Question 4: What is the rate of change in nutritional parameters in pre-ESRD patients?

Only one study that attempted to address this question met inclusion criteria. Gentile et al. reported the rate of change in nutritional parameters in 50 patients with estimated creatinine clearance of 36 $\pm$ 16 mL/min (LE: 4, QS: poor). Patients were randomized to two diets (protein intake 0.6 or 1.0 g/kg/day); however, results were reported only for the two groups combined. Over 18 months, body weight decreased significantly from 67 $\pm$ 11 to 65 $\pm$ 11 kg ($p < 0.01$).

Key Question 5: What is the effect of follow-up nutritional evaluation in improving intermediate outcomes and/or clinical outcomes in pre-ESRD patients?
We did not identify any studies addressing this question that met our inclusion criteria.

Key Question 6. What is the tolerability/palatability and feasibility of nutritional interventions in patients with pre-ESRD?

- Based on two large uncontrolled trials and one large randomized controlled trial, we conclude that there is reasonable evidence suggesting that pre-ESRD patients have difficulty adhering to and have low satisfaction with LPD.
- Based on one large randomized controlled trial, we conclude that there is reasonable evidence suggesting that administering a LPD to pre-ESRD patients consumes slightly more time resources from a dietician than does a standard diet.

Lipids summary

To address the issue of the management of lipids in patients with pre-ESRD, the following three key questions were formulated:

1. Do dyslipidemias (hyperlipidemia or low lipids) cause increased risk of adverse clinical outcomes (defined below) in patients with pre-ESRD?
2. Does the treatment of dyslipidemias (by diet and lifestyle modification and/or pharmacologic therapy) reduce the risk of adverse intermediate and clinical outcomes in patients with pre-ESRD?
3. Is there an association between pharmacologic lipid therapy and drug toxicity in patients with pre-ESRD?

Key Question 1: Do dyslipidemias (hyperlipidemia or low lipids) cause increased risk of clinical outcomes in patients with pre-ESRD?
From the one available study, we conclude that there is limited evidence that dyslipidemias increase the risk of carotid plaques in patients with pre-ESRD.

Key Question 2: Does the treatment of dyslipidemias (by diet and lifestyle modification and/or pharmacologic therapy) reduce the risk of intermediate and clinical outcomes in patients with pre-ESRD?

- Based on these trials, we conclude that there is no available direct evidence that pharmacological or dietary interventions reduce the risk of clinical outcomes (as defined above) in patients with pre-ESRD.

- Based on one randomized controlled trial and one uncontrolled trial, we conclude that there is limited evidence that gemfibrozil is effective in lowering total cholesterol, LDL-C, and triglycerides levels, and might be effective in increasing HDL-C levels in patients with pre-ESRD. This is supported by effects observed in non-renally impaired people.
- Based on one uncontrolled trial, we conclude that there is limited evidence that lovastatin combined with a low-cholesterol and low-protein diet is effective in lowering total cholesterol, LDL-C, VLDL-C, and apoB levels. Although scant, this is consistent with data on non-renally impaired people.
- Based on dietary intervention studies, we conclude: (1) that there is inconsistent and insufficient evidence to support or reject that a low-protein diet has a favorable impact on lipid profiles of patients with pre-ESRD; (2) that there is limited evidence that a high-carbohydrate/high-fiber diet is effective in lowering cholesterol levels; (3) that there is insufficient evidence on the effectiveness of fish oil supplementation in modifying lipid profile to draw any conclusions; and (4) that there is limited evidence that MPPG is effective in lowering total cholesterol, LDL-C, and triglycerides, and in increasing HDL-C levels.

Key Question 3: Is there an association between pharmacologic lipid therapy and drug toxicity in patients with pre-ESRD?
In summary, based on these trials, we conclude that there is insufficient evidence to support or reject that gemfibrozil, lovastatin, or MMPG are more or less safe in patients with pre-ESRD compared to the general population of patients with dyslipidemias.

Timing summary

To address the issue of timing of initiation of RRT in patients with pre-ESRD, three key questions were formulated:

1. When – in terms of GFR, symptoms of uremia, or other complications – is RRT initiated among patients with pre-ESRD?
2. What factors affect the timing of initiation of RRT among patients with pre-ESRD?
3. What is the effect of early initiation of RRT (at GFR > 20 ml/min, before development of uremia symptoms) on health and resource utilization outcomes?

Key Question 1: When – in terms of GFR, symptoms of uremia, or other complications – is RRT initiated among patients with pre-ESRD?
In summary, the majority of patients at the time of RRT had an early referral to a nephrologist. Of those referred early to a nephrologist, residual kidney function was modestly better at the initiation of RRT. Nevertheless, a substantial proportion of patients referred early to a nephrologist undergo emergent RRT.

Key Question 2: What factors affect the timing of initiation of RRT among pre-ESRD patients?

In summary, available studies do not reveal a consistent pattern to explain the variation in timing of RRT, particularly in laboratory parameters. Two non-US studies highlight the importance of distance to a facility as a limiting factor; however this may not be applicable to the somewhat unique US environment. The finding that Blacks tend to receive RRT later than Whites is concerning, but has not been studied sufficiently to separate the effect of race per se from other clinical or health system factors.

Key Question 3: What is the effect of early initiation of RRT (at GFR > 20 ml/min, before development of uremia symptoms) on health and resource utilization outcomes?

Impact of timing on hospitalizations

Morbidity differences have been examined as a function of the timing of referral to a nephrologist rather than the GFR at initiation of RRT, and fail to perform adequate multivariate analyses. Some studies report no difference in hospitalizations (reported as hospital days after 3 months of RRT), whereas others observe differences with patients referred late having more hospital days and duration of hospitalization.

Economic impact of timing

Two studies attempt economic analyses comparing the cost of care for patients referred to a nephrologist early or late. These are limited analyses, focusing on hospital charges. However, both studies suggest that late referral may be associated with increased hospital costs.

Impact of timing on the use of temporary vascular access

Use of temporary vascular access is a of concern as limited evidence indicates that patients dialyzing with a catheter have higher mortality (LE: 4, QS: poor). Using a retrospective ESRD cohort of 178 patients in UK from August 1993 to April 1995, 71.3% of patients required temporary vascular access incident to RRT. Twenty-five of 127 patients with temporary access died in the first 90 days of RRT versus 1 of 51 with permanent vascular access ($p < 0.01$). Notably, the patients' demographics and co-morbid conditions are not reported, so it is difficult to assign the mortality effect to the temporary vascular access.

The impact of timing of referral on the use of a temporary catheter at the initiation of RRT has been explored in four studies. European and American cohorts showed that patients referred late are more likely to require hemodialysis with a temporary catheter rather than an internal vascular access. Conversely, the percentage of patients with an autologous fistula is lower among patients referred late to a nephrologist.

Impact of timing on modality selection for RRT
We identified three studies that examine the relationship between timing of referral and modality selection for RRT.

One large retrospective cohort analysis of Medicare beneficiaries in New Jersey found no relationship between the timing of referral and the selection of peritoneal versus hemodialysis.

Similarly, an analysis of patients in West Virginia and Pennsylvania found no relationships between late and early referral and the percentage of patients switching from hemodialysis to peritoneal dialysis after 4 months of RRT (LE: 2b, QS: fair).

For kidney transplantation, one study reported no difference (LE: 4, QS: fair), and another reported a significant difference, with late-referred patients being less likely to be transplanted in follow-up (LE: 2b, QS: good). Both cohorts are from Europe where transplantation practices may differ from the US. Moreover, neither study performed appropriate adjustments of confounders such as patients' ages, co-morbid conditions, HLA types, insurability, preferences, etc. that will substantially influence transplantation rates.

Impact of timing on kidney transplantation outcomes
In a retrospective cohort analysis of 1,849 kidney transplant recipients from a single center in Minneapolis, Minnesota from January 1984 to June 1998, patients were classified by the type of organ donor (cadaveric (n = 775) versus living (n = 1,074)). Patient and transplant survival were compared by type of organ donor and by whether or not patients underwent hemodialysis prior to kidney transplantation (LE: 2b, QS: fair). The 5-year post-transplant patient survival was better for patients not dialyzed than those dialyzed regardless of the type of organ donor (92.6% versus 76.6%, respectively, for cadaver donor kidneys; p = 0.001 and 93.3% versus 89.5%, respectively, for living donor kidneys; p = 0.02). The graft survival rate was at 5 years was no different for cadaveric kidneys, but for living donor kidneys was greater without dialysis (92.3% versus 84.8%; p = 0.006).

These findings were extended by a retrospective cohort analysis of 8,481 cadaveric kidney transplant recipients from the entire US using a national Medicare kidney transplant registry (LE: 2b, QS: good). Living related kidney transplant donors were excluded from this analysis. In comparison to the 6,662 kidney transplant recipients who underwent dialysis of varying duration before kidney transplants (329 $\pm$ 638 days of dialysis), the 1,819 patients had a 1-year allograft failure (defined as death, repeated kidney transplant, or resumption of dialysis) rate ratio of 0.48 (p = 0.002) and a 2-year failure rate ratio of 0.18 (p = 0.001). The duration of dialysis was positively associated with the occurrence of acute rejection by kidney biopsy (p = 0.001 for the trend).

Counseling & rehabilitation summary

Education/counseling

We considered evidence related to three questions:

1. Does early systematic education about RRT choices improve patients' satisfaction or compliance with RRT or RRT-related health outcomes, compared with usual care (at time of need; no systematic early education)?
2. Do comprehensive prepared educational programs, multidisciplinary teams or specialty educators educate patients better than usual care (informal, non-specialty educators)?
3. Is there an association between better knowledge about RRT and greater satisfaction, compliance or health outcomes with RRT?

Exercise

1. Is there an association between physical function and outcomes in pre-ESRD patients?
2. Does exercise counseling in pre-ESRD patients result in improved self-reported activity, performance-based measures, or exercise capacity?
3. Does exercise counseling in pre-ESRD patients result in improved health outcomes compared to no exercise counseling?
4. Does supervised exercise therapy improve outcomes compared to no exercise therapy?

Key Question 1: Is there an association between physical function and outcomes in pre-ESRD patients?

We did not identify any studies of pre-ESRD patients that describe the relationship between level of physical functioning and health outcomes such as quality of life, mortality, complications, and deterioration in kidney function. To a certain extent, the intervention studies described under key questions 2 and 3, below, indirectly address this issue, but they fail to report health outcomes, focusing instead on measures of physical functioning.

Employment counseling

Key Question 1: Does employment counseling in pre-ESRD patients result in improved maintenance of employment during RRT?

A single study suggests that predialysis counseling of employed patients, particularly blue-collar workers, improves maintenance of employment; however, this study likely overestimates the strength of this effect because of the retrospective design and long duration of time between surveying employment status and the intervention. The sample of patients in this study is highly selected based upon that fact that at the time of enrollment in the study, they belonged to an HMO, were employed, and had already survived an average of

over 4 years after initiating hemodialysis. Were this study performed prospectively, mortality would likely have reduced the observed odds ratio of 2.8 favoring the intervention group.

Evaluation (individualized assessment)

Key Question 1: Does systematic individualized clinical assessment improve outcomes in pre-ESRD patients compared to usual care with no systematic individualized psychosocial or rehabilitation assessment (until dialysis or other RRT)?

We found only one study that described the use of individualized clinical assessment. This study is described in the section on "Education."

Encouragement (emotional support)

Key Question 1: Is there an association between clinician-delivered encouragement and outcomes in pre-ESRD patients?

We found no studies describing clinician-delivered encouragement, broadly defined, offered to pre-ESRD patients. Although encouragement was certainly a component of some of the multidisciplinary interventions involving nurses, social workers, and other health professionals described in education, its effect or association cannot be determined from the studies described previously.

Future Research

The available literature regarding management of pre-ESRD patients is quite limited. Current practice and guidelines for this population are likely based on extrapolation of data from patients with a broader range of kidney failure severity, or in some cases, data from patients with normal renal function. The lack of research on the pre-ESRD population as opposed to the hemodialysis population seems to be one of access. Although the number of patients with pre-ESRD is substantial and comparable to the number of patients on hemodialysis, pre-ESRD patients are not as easily accessible for inclusion in research studies. The prevalence in the general population is low – too low for population-based studies to be a feasible way to identify this subpopulation. Within health care systems, access to pre-ESRD patients has been problematic because of great variability in consulting behavior. Pre-ESRD patients often do not present to nephrologists until they require RRT. Increasingly, computerized patient record systems are available which should allow identification of patients with severe CKD based on estimates of creatinine clearance from integrated laboratory (serum creatinine course over time), clinical (body weight) and demographic data (age). Systematic identification of such patients could allow entry into trials comparing individual interventions or comprehensive disease management approaches, which may be tested for whether they modify clinical outcomes before or after RRT.

Each of the topics covered in this report suffers from a lack of data linking interventions in the pre-ESRD phase to improved health outcomes. The relatively short time patients spend in the pre-ESRD phase makes for limited time for interventions to exert an effect that would be measurable. This is a particular problem for conditions that develop over a protracted period of time, such as atherosclerotic disease and its clinical manifestations or metabolic bone disease. Thus, intermediate outcomes are routinely substituted. Whether the link between intermediate outcomes (blood pressure, serum lipid levels, etc.) and important health outcomes is the same as in other more well-studied populations is somewhat uncertain in pre-ESRD patients. Demonstrating these relationships will require large studies, with sufficient numbers of patients followed for sufficiently long to accrue enough clinical events for statistical power, while controlling for potential confounders such as comorbid conditions. Identification of large numbers of incident ESRD patients may be feasible in large heath care systems with integrated medical record systems.

1. Introduction

1.1 Purpose and scope

The purpose of this report is to identify and summarize the available published evidence on the management of patients who have severe chronic kidney disease (CKD) and are not yet on renal replacement therapy (RRT) but are expected to progress and require RRT within 6 to 18 months. Key management issues to be addressed for this population include: timing of initiation of RRT; counseling and rehabilitation prior to initiation of RRT; and the management of anemia, hypertension, bone disease, lipid abnormalities, and nutrition. The report has been compiled with the goal of informing a panel charged with developing a clinical practice guideline (CPG) for patient preparation for renal replacement therapy. This evidence report constitutes Phase I of a three-step process whose final product is the CPG.

The most important goal in caring for a patient with CKD and declining kidney function is to preserve kidney function as long as possible. However, some of the interventions used to preserve kidney function (e.g., low protein diet, aggressive blood pressure control) may no longer be beneficial to patients beginning RRT, particularly to those patients beginning hemodialysis. For example, although aggressive blood pressure control delays the onset of kidney failure, some epidemiological evidence suggests that mortality is increased among hemodialysis patients with lower blood pressure. Care of patients with impending kidney failure also presents some unique dilemmas. For example, low-protein diets are usually prescribed to preserve kidney function in patients with severe CKD; however, this may interfere with the healing of arteriovenous fistulae or grafts placed for hemodialysis. This report is designed specifically to examine the effect of a variety of management strategies in the population of CKD patients for whom RRT is imminent.

1.2 Definition, incidence and prevalence

CKD is established based upon a combination of evidence of kidney damage (such as proteinuria), elevated blood pressure, and level of kidney function (as indicated by glomerular filtration rate, or GFR). Nomenclature for describing the clinical spectrum of CKD has recently been developed by the CKD Work Group of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI; Table 1). The prevalence of CKD can be estimated from cross-sectional epidemiologic data, such as the Third National Health and Nutrition Examination Survey (NHANES III), which suggests that at least 6.2 million Americans have reduced kidney function, defined as a serum creatinine concentration > 1.5 mg/dL.[1]

End-stage renal disease (ESRD) is defined by level of GFR and the occurrence of uremic signs and symptoms that require initiation of treatment by kidney replacement therapy. In the United States, ESRD is an administrative term, based on conditions for health care payment by the Medicare ESRD Program. The prevalence of ESRD can be reliably estimated by enrollment in the Medicare-ESRD program; in 1997, 304,083 patients were enrolled.[2] The annualized increase in incidence of ESRD in the United States is approximately 7% to 9%.[3] In 1999, 80,128 patients entered the ESRD

program; 90% started hemodialysis, 8% started peritoneal dialysis, and 2% received kidney transplants.[3] The principal etiologies of ESRD remain diabetes and hypertension. In addition, for reasons that are likely multifactorial, certain racial and ethnic groups have a higher incidence of ESRD. For example, the rate of ESRD due to diabetes is three- to four-fold higher in Black, Hispanic, and Native American populations than in the Caucasian population.[3]

There is no reliable estimate of the incidence or prevalence of the specific population of patients with severe CKD and who are not yet on RRT but are expected to progress and require RRT within 6 to 18 months. Estimates of this population, herein referred to as "pre-ESRD," have only been inferred from the incidence of ESRD patients.

1.3 Burden of disease

The annual mortality rate for ESRD patients is approximately 20% per year, and half these deaths are from cardiovascular complications such as myocardial infarction and congestive heart failure.[2] This mortality translates into a life expectancy that is only 16-37% of the age-, gender-, and race-matched general population.[4] The highest death risk occurs during the incident year of RRT.[2,5] ESRD patients also experience high morbidity. In 1997, Medicare-eligible ESRD patients incurred an average of 1.4 hospital admissions and 10.8 hospitalized days per year.[2] This hospitalization rate is several times higher than that for age- and risk-adjusted comparative cohorts of patients without kidney failure.[6] Morbidity and hospitalizations are principal cost drivers for ESRD patients, resulting in an enormous financial burden. In 1997, the total cost of care for the Medicare ESRD Program was approximately $11.76 billion, rendering it the largest single Medicare program fiscally,[2] despite the fact that it funds care for a relatively small population.

1.4 Disease biology

The K/DOQI Clinical Practice Guidelines Work Group has divided the clinical and physiologic spectrum of CKD into five stages (Table 1). These stages generally overlap an earlier description by Knochel.[7] A reduction in kidney function by 25% or less represents CKD stage 1. At this stage, metabolic imbalances are not paramount because the remaining nephrons display adaptive increases in function. GFR may be normal or even increased. However, intraglomerular hypertension and lipid deposition are present, and a multitude of growth factors interact to initiate and further glomerular sclerosis and interstitial fibrosis. Early markers of this kidney damage may include proteinuria and elevations in blood pressure. As CKD progresses to stages 2 and 3, kidney function may be reduced up to 75%. During these stages, erythropoietin production decreases and anemia may become clinically evident. Further progression, generally through stages 4 and 5, is characterized by a host of metabolic disturbances, including worsening anemia and the onset of acidemia, hypocalcemia, hyperphosphatemia, osteodystrophy, and possibly hyperkalemia. Clinical symptoms such as itching, fatigue, and nausea may present themselves during this period. At that point, the disease usually progresses rapidly to overt uremic symptoms and the patient suffers extreme fatigue, malaise, and anorexia. Plasma volume overload due to reduced excretion by the kidney may cause pulmonary edema or hypertensive crisis.

This level of reduction in kidney function combined with the presence of clinical signs and symptoms generally mandate initiation of kidney replacement therapy to treat these systemic disturbances and prolong survival of the patient.

Although relatively few data exist on the natural progression of chronic kidney disease, it has long been believed that once kidney insufficiency is established and a "critical" amount of kidney function is lost, kidney disease progresses inexorably to kidney failure and ESRD. This critical level of kidney function has not been defined; however, data from prospective trials such as the Modification of Diet in Renal Disease (MDRD) Study suggest that the majority of patients with GFR reduced to 55 mL/min or lower will continue to progress. In the MDRD Study, of 840 patients with glomerular filtration rates between 13 and 55 mL/min, 87% lost kidney function over the 3-year follow-up.[8] These data support the clinical bias that despite excellent therapeutic intervention and risk factor modification, many patients with kidney disease will continue to progress and will reach a point where ESRD is anticipated within 6 to 18 months. In this group of patients, defined as pre-ESRD and corresponding to CKD stages 4 and 5 (but not receiving kidney replacement therapy – see Table below), proactive preparation for kidney replacement therapy is recommended to ease the transition into ESRD and reduce the burden of clinical risk factors known to be associated with worse outcome in ESRD patients.

Table 1 – Stages of Chronic Kidney Disease

Stage	Description	GFR ($mL/min/1.73\ m^2$)	Action
1	Kidney damage with normal or increased GFR	$\geq$ 90	Diagnosis and treatment, treatment of comorbid conditions, slowing progression, CVD risk reduction
2	Kidney damage with mild decrease in GFR	60-89	Estimating progression
3	Moderate decrease in GFR	30-59	Evaluating and treating complications
4	Severe decrease in GFR	15-29	Preparation for kidney replacement therapy
5	Kidney failure	<15	Replacement (if uremia present)

National Kidney Foundation, K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. Am J Kidney Dis 39:S19, 2002 (suppl 1). Adapted with permission.

The classification of patients as pre-ESRD is therefore based on overlapping boundary points that are imposed upon a disease spectrum. Nevertheless, this classification is useful from both physiologic and practical standpoints. Patients who progress to the point where further deterioration and ESRD are expected will also be subject to a myriad of clinical symptoms not seen during earlier kidney disease. Pre-ESRD patients are also separated from later ESRD by the therapeutic intervention of RRT. Either through dialysis or kidney transplantation, this intervention itself introduces new

elements into the disease process, including blood pressure homeostasis, complement activation, and immune modulation. Recognition of a patient as pre-ESRD should focus attention on treatment of clinical symptoms associated with overt kidney failure as well as preparation for eventual RRT. Such preparation should involve medical, psychosocial, and economic components. It is hoped that appropriate patient preparation for RRT will both ease the transition into ESRD and improve clinical outcomes.

1.5 Target population and practice settings

The target population of this Evidence Report is adult patients with severe CKD who are expected to progress and require RRT within 6 to 18 months. While this definition incorporates the clinical judgment of the physician, the GFR of the population is expected to be less than 30 mL/min. The definition implies expected continued progression to ESRD; the term “pre-ESRD” is therefore the chosen descriptor for the population within this Evidence Report. This pre-ESRD population definition overlaps that of the K/DOQI definitions for CKD stages 4 and 5 (but not including subjects on RRT). In this Evidence Report and the upcoming Clinical Practice Guidelines based on it, we will use the shorthand term “pre-ESRD” to refer to CKD levels 4 and 5, not on dialysis.

We expect that the Evidence Report and later Guidelines will focus on practice settings in the United States and will consider a range of organizational structures. Care for patients with severe chronic kidney disease may involve primary care practices, nephrology clinics, transplant programs, or dialysis centers.

1.6 Target audience

We expect the primary audience for the Guideline will include primarily physicians involved in decision making in the preparation for RRT, which is usually shared between primary care physicians and nephrologists. However, the planned Guideline will also be extremely useful to other health care providers involved in the care of patients with ESRD, as well as to patients and their families. Because the care of patients with CKD is so costly, federal and third-party payers will also be part of audience for the evidence report, guidelines, and management tools.

1.7 Methodology

We performed an in-depth literature review, weighing and summarizing the current body of knowledge regarding preparation of the patient for RRT, focusing on the following seven principal areas:

1. Optimal management of anemia secondary to erythropoietin deficiency;
2. Prevention of hyperparathyroidism, hyperphosphatemia, hypocalcemia, and metabolic bone disease;
3. Blood pressure control;
4. Maintenance of adequate nutrition;
5. Managing qualitative and quantitative lipid disorders;

6. Timing of the initiation of dialysis;
7. Counseling for choices of renal replacement therapy, patient rehabilitation, and psychosocial and economic preparation.

A description of our technical approach follows.

Literature review and synthesis – overview

A comprehensive analytical review of available published information was conducted to provide the scientific basis for decisions to prepare patients for RRT. Information from the literature was abstracted into evidence tables. The final products of the literature review are summaries of the published studies that meet the established methodological standards. The results are provided in a format that permits a direct linkage between the recommendations of future guidelines planned by the Renal Physicians Association.

The following sections describe the selection of topics for review, method of identifying the pertinent literature, process for selection of the literature, means of abstracting data, construction of evidence tables, meta-analysis of pertinent parameters, and summary of areas for future research. This process was carried out in a collaborative effort between Duke University physicians and methodologists, a jointly-appointed panel of content experts, and the Renal Physicians Association.

Advisory groups

We were guided in the planning and conduct of this project by two organizations: the Agency for Healthcare Research and Quality (AHRQ) and an appointed panel of experts.

The Duke Evidence-based Practice Center (EPC) is one of twelve centers selected and funded by AHRQ to produce state-of-the art evidence syntheses. Evidence reports funded by private organizations but conducted according to the EPC methodology may be designated as EPC products with approval by AHRQ. Such approval requires that AHRQ reviews and has an opportunity to comment on the project throughout its course.

Duke University and the Renal Physicians Association together appointed a working committee for this project. This committee, hereafter referred to as the Working Group, assumed an ongoing advisory role throughout the production of the Evidence Report. RPA and Duke solicited nominations from various stakeholder organizations, such as the Renal Physicians Association, American Society of Nephrology, American Association of Kidney Patients, American Nephrology Nurses Association, National Renal Administrators Association, Council of Nephrology Social Workers, American College of Physicians, American Academy of Family Physicians, and American Association of Dietitians. We selected the Working Group to reflect the diversity of caregivers involved in management of chronic kidney disease.

Expectations of panel members were carefully specified at the time an offer of appointment was made. These expectations include policies regarding confidentiality,

ownership of information generated by the panel, and reimbursement for service and travel. Each candidate offered an appointment was required to disclose any conflict of interest, commit to attendance at planned panel meetings, and complete assigned work in a timely fashion. One of the panelists was identified as Chair: W. Kline Bolton, MD, of the University of Virginia. The group continues to serve as primary advisors to Duke's efforts in the literature review.

Assessing and refining the topic

In our first full meeting, the Working Group assisted in refining the key questions. In facilitated small group discussions the panelists identified key clinical issues related to each topic area. For each question we defined patients or clinical presentations that would and would not be considered. One criterion for the target population was suggested in the original proposal: GFR < 30 ml/min. However, age criteria for the target population were specified as well.

The Duke team and the panelists also discussed specific interventions to be considered, outcomes of interest, and the type and quality of available research for each topic area. We developed the parameters of the literature search with the Working Group, including key search words, key databases to be searched, and search limitations.

We eliminated a proposed vascular access topic because an evidence-based guideline by the National Kidney Foundation's K/DOQI group had just been completed.[9]

Following the initial panel meeting, the Duke team drafted specific key questions for each of the seven remaining topic areas. These questions were distributed to the panelists for approval and comment.

Preliminary literature review

We estimated the scope and volume of literature on each topic in preliminary literature searches designed and conducted in MEDLINE. These searches provided estimates of the quantity and quality of published studies relating to the proposed key questions. These data helped the Working Group in the topic refinement process described above.

Systematic literature review

Searches

Explicit and reproducible methods in conducting the literature should lead to an unbiased assessment of available published data. We used the following process to provide a complete list of the relevant literature.

Our strategy primarily involved MEDLINE, a computerized bibliographic database of the National Library of Medicine, as the main source to screen for articles. The MEDLINE search strategies retrieved articles pertaining to each of the key questions. The searches were implemented in an information retrieval software package that offers full-text searching in addition to Medical Subject Heading (MeSH) term searching.

We excluded articles not pertaining to humans and articles not in the English language. We also limited initial searches to studies published since 1988 (although pre-1988 articles were identified through references in included studies).

Our initial searches revealed a difficulty in distinguishing between studies of patients undergoing dialysis and studies of patients with predialysis chronic kidney disease. In part, this is because the MeSH term *Chronic Kidney Failure* does not distinguish between ESRD and CKD. Although other MeSH terms exist that describe treatments for ESRD (*renal replacement therapy* and subheadings *hemodialysis, hemofiltration, peritoneal dialysis* and *chronic ambulatory peritoneal dialysis*), they do not permit reliable discrimination between studies of predialysis versus dialysis patients. However, text word searching for the phrase *hemodialysis patients* was a more reliable discriminator. Thus, we used the following terms to target studies of patients with chronic kidney disease in the predialysis stage:

1 kidney failure, chronic/ (MeSH)
2 chronic renal insufficiency (text word)
3 chronic renal failure (text word)
4 hemodialysis patients (text word)
5 (1 or 2 or 3) not 4
6 predialysis (text word)
7 pre-dialysis (text word)
8 5 or 6 or 7

These terms were supplemented with key words related to each topic to perform separate searches for each of the key questions. The key words used are described in each of the following seven chapters.

We also made use of existing evidence-based clinical practice guidelines, review articles, and articles already known to the Working Group in order to identify potential articles as efficiently as possible. In addition, citations from included articles were examined. Working Group members and content experts were queried about their knowledge of other information sources such as unpublished trials.

Screening

Titles and abstracts identified by the MEDLINE search were screened for inclusion by two physicians, one nephrologist and one methodologist. The decision whether to include or exclude an article was made according to criteria that took into account the type of interventions, the type of patients, the study design, and the reported data. Articles were excluded if no empirical data were presented; if the population was not composed of pre-ESRD, ESRD, post-transplant, or other CKD patients; and if no clinically relevant outcomes were presented. The reliability of this selection process was examined by assessing the agreement between paired reviewers. An article was included for further review if either reviewer included it; this process leads to greater sensitivity, minimizing the chance that a valuable article might be overlooked.

Articles not excluded were submitted to a second screening process using a full-text version of the article and performed by two physicians. At this step, articles were excluded if on review the study population did not meet the definition of pre-ESRD (see above). If the study included both patients with pre-ESRD and without pre-ESRD, the study was excluded if outcomes were not reported separately for patients with pre-ESRD. Small case series (< 10 cases) and unique case reports were excluded, with the exception of articles reporting adverse events of drugs used for the management of hypertension and/or dyslipidemias. Finally, articles were excluded if they did not address one or more of the issues formulated in the key questions for the specific topic. Included articles were then abstracted by a physician investigator using a standardized abstraction form, and then summarized into an evidence table.

The seven topics used common inclusion criteria for acceptable study populations. For a study to be included in this systematic review, the study population was required to have a mean or median glomerular filtration rate (GFR) below 30 ml/min/1.73 m^2, either measured directly or estimated using the Cockcroft-Gault formula.[10] When an estimation of the creatinine clearance (CrCl) was not available, a mean or median serum creatinine (SCr) greater than 2.5 mg/ml was considered as fulfilling the criteria for inclusion. If no quantitative data were reported on GFR, CrCl or SCr, articles were eligible for inclusion if the population studied was clearly described as a pre-ESRD population. In addition, two types of studies where patients did not meet these criteria were nevertheless considered for inclusion: (1) prospective studies in which a population of patients was followed as GFR declined to pre-ESRD range, and (2) retrospective studies in which an RRT population (most often patients then undergoing dialysis treatment) had data collected for the pre-ESRD period.

In addition, all topics generally required the number of subjects to be greater than 10. Further explicit criteria regarding interventions, outcomes and study design were developed for each specific research question for use by the reviewers. These are described in each chapter. A sample of the screening forms used for full-text review is provided in Appendix 1.

Data abstraction and evidence tables

We developed data abstraction forms to collect data regarding details of patient population, interventions, study design, results, and study quality. These forms were completed by the Duke clinicians and reviewed in detail during reformatting the data into evidence tables. A sample data abstraction form is provided in Appendix 2.

Assessment of the quality of available evidence

Each included and abstracted article was evaluated and rated for level of evidence (LE) using a generic scale that rates studies according to their purpose (assessment of efficacy, natural history, etc.) into categories relating to their susceptibility to bias based primarily on study design (see the last scale on the sample data abstraction form, Appendix 2).[11]

In addition, each study was evaluated according to six criteria testing for internal and external validity. These criteria explored the study population's selection and representativeness, how attrition was considered, and how well the study population fit our definition of pre-ESRD. Finally, a global, subjective quality score (QS) was assigned using a 4-point scale (excellent, good, fair, poor).

Peer review

This document has undergone a process of peer review. In consultation with the Working Group, RPA, and AHRQ, we identified health professionals representative of the target audience to review a draft report. Members of the Working Group and AHRQ also reviewed this Evidence Report concurrent with the external peer review. The authors have addressed comments from all reviewers, in some cases describing changes to the document, in others offering a rationale for our disagreement if we believed no change was indicated. The final Evidence Report and our responses to comments will be reviewed by the Working Group and AHRQ.

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2. Anemia

2.1 Chapter summary

To address the issue of the management of anemia in patients with pre-ESRD, the following five key questions were formulated:

1. What is the prevalence of anemia in pre-ESRD?
2. What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion?
3. What proportion of patients without nutritional deficiencies are resistant to EPO?
4. What proportion of pre-ESRD patients have low EPO levels?
5. What is the efficacy of EPO in improving intermediate and ultimate outcomes in patients with pre-ESRD?

The available evidence on anemia in CKD led to us being able to provide data that addressed only three of our five key questions. Two of the questions posed were therefore not answered by the current review. The majority of the literature abstracted focused on the treatment of the anemia of CKD with EPO therapy and the effect of such therapy on intermediate and surrogate outcomes.

Key Question #1: What is the prevalence of anemia in pre-ESRD?
The modest evidence emerging from two studies using different criteria for pre-ESRD, and with overlapping populations, suggests that the prevalence of anemia in this population is in the range of 16% to 18%. It has been shown consistently that the prevalence of anemia increases markedly as kidney disease becomes more advanced.

Key Question #2: What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion?
No specific estimate of this proportion can be derived from the available literature. Iron deficiency in particular appears to be not uncommon. Patients on EPO who are iron deficient have been shown to require higher EPO levels to attain a target hemoglobin concentration.

Key Question #3: What proportion of patients without nutritional deficiencies are resistant to EPO?
No direct evidence was identified to answer this question.

Key Question #4: What proportion of pre-ESRD patients have low EPO levels?
The few studies of this question suggest that EPO levels in CKD are similar to levels in non-CKD patients without anemia. However, CKD patients are more likely to have EPO levels inappropriately for relative to their degree of anemia.

Key Question #5: What is the efficacy of EPO in improving intermediate and ultimate outcomes in patients with pre-ESRD?

We identified no studies relating use of EPO in all or a subset of the pre-ESRD population to mortality. One study examined the impact of EPO on quality of life, indicating that relief of anemia with EPO was associated with significant improvement in quality of life measures. The remainder examined the impact of EPO on hypertension, LVMI, renal hemodynamics, or endothelial function. Although not the target of this question, impact of EPO on deterioration of renal function was evaluated in 17 identified studies; on balance, the evidence does not suggest a detrimental effect of EPO on kidney function.

Of 16 studies that assessed blood pressure effects of EPO therapy in CKD, eight suggested at least some increase in the risk of developing or suffering an exacerbation of hypertension associated with EPO therapy. No study reported improvement in blood pressure with EPO.

Two studies involving small, highly selected populations suggest EPO may be associated with improvement in LVMI.

Two limited studies did not reveal any significant effect of EPO on renal hemodynamics.

One study suggested that EPO therapy may improve endothelial function as evidenced by a reduction in the elevation of thrombomodulin levels. The importance of this finding is unclear as the significance thrombomodulin in endothelial pathobiology has not been elucidated.

Conclusions

On the order of 1 in 5 pre-ESRD patients are anemic. It is unclear how many of these patients are nutritionally deficient, but iron deficiency is not uncommon and (in addition to causing anemia) can interfere with the efficacy of EPO. Individuals who use EPO for anemia appear to have improved quality of life, as well as improvement in several intermediate outcomes; although exacerbation is associated with EPO use. No studies were identified that provide guidance on the threshold for treatment, or the optimal dose in the population of individuals with pre-ESRD.

2.2 Background

Anemia is common in patients with chronic kidney disease and has a detrimental effect on cardiac function, exercise capacity, quality of life, and cognitive function.[1-5] In addition, it has been suggested that mortality and major complications that develop in ESRD are associated with anemia that develops early in the course of chronic kidney disease (CKD). This leads to the hypothesis that correcting anemia before the initiation of renal replacement therapy (RRT) may improve health outcomes.

Use of erythropoietin (EPO) for treating anemia has become standard practice for patients receiving RRT). Greater than 90% of adults receiving RRT receive EPO, and the mean hemoglobin for ESRD patients in the US is 11.1 g/dL.[6] There is little epidemiological data as to the prevalence of anemia among pre-ESRD patients in the US. However, Obrador et al.[7] report that among a cohort of individuals identified at the

point of initiating RRT, 51% had a hematocrit below 28%. Fink[8] also recently reported in a large cohort of patients initiating RRT derived from Medicare claims data that mean hematocrit among the 23% of patients who received EPO prior to the initiation of dialysis was 28.2%, compared to 27% for the 73% of patients who did not receive EPO. It is notable that dialysis patients with levels of anemia in this range are known to be at increased risk of death.[9] In addition, during the years from 1995 to 1997, despite this high prevalence of anemia, less than a quarter of incident ESRD patients received EPO before initiating RRT, and this low level of use was relatively constant over the period of observation.[10] Thus, if anemia correction with EPO in the pre-ESRD period is beneficial, then there may be substantial room to improve care and patients' outcomes.

Evidence of the benefits of aggressive correction of anemia is found in other clinical situations. For example, outcomes are improved with blood transfusions following myocardial infarction in elderly patients,[11] as well as following gastrointestinal hemorrhage.[12] There is also recent data suggesting that successful treatment of anemia to hemoglobin $\geq$ 12 g/dL in patients with advanced congestive heart failure is associated with a significant improvement an cardiac function and reduction in the need for hospitalizations.[13] However, the argument for aggressive anemia correction is not consistently supported. One study demonstrated that a restrictive strategy of red-cell transfusion (transfusion for hemoglobin < 10 g/dL) in a critical care population was at least as effective as a more liberal transfusion policy (transfusion for hemoglobin < 7.0 g/dL with the possible exception of patients with acute myocardial infarction and unstable angina).[14] A recent meta-analysis of trials involving treatment of anemia associated with cancer therapy suggested that the available evidence was inadequate to determine whether outcomes were superior if EPO therapy was initiated when the hemoglobin concentration was substantially higher than 10 g/dL compared with starting treatment when the hemoglobin declines to nearly 10 g/dL.[15]

A number of factors may influence the likelihood of anemia developing and the susceptibility of such anemia to EPO therapy in patients with earlier forms of kidney disease. Such factors include etiology of kidney disease, co-morbid conditions, concomitant medications, endogenous EPO levels, EPO resistance, and nutritional deficiencies.

The purpose of this chapter is to systematically review the available literature on the prevalence of anemia and of low EPO levels, the role of nutritional deficiencies in the development of anemia and EPO resistance, and the efficacy of EPO in improving intermediate and ulitimate outcomes for patients with pre-ESRD.

2.3 Methods

To address the issue of the management of anemia in patients with pre-ESRD, the following five key questions were formulated:

1. What is the prevalence of anemia in pre-ESRD?
2. What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion?
3. What proportion of patients without nutritional deficiencies are resistant to EPO?

4. What proportion of pre-ESRD patients have low EPO levels?
5. What is the efficacy of EPO in improving intermediate and ultimate outcomes in patients with pre-ESRD?

To identify the literature addressing the five questions related to the management of anemia, the following search terms were used: "erythropoietin" "anemia," "hypochromic anemia," and "iron, dietary." Articles of interest were also identified from the reference lists of other articles reviewed.

Intermediate outcomes considered included blood pressure, hemoglobin, and hematocrit; ultimate outcomes considered included angina, congestive heart failure, activity/function, quality of life, cognition, and mortality.

2.4 Results

Five hundred and five titles and abstracts were initially screened. Of these, 70 were identified for full-text screening. We were unable to obtain a copy of two of these articles.[16,17] Of the remaining 68, twenty-five were excluded during full-text review for the following reasons: outcomes not reported separately for the pre-ESRD population (n = 1), did not meet the criteria for the pre-ESRD population (n = 3), did not address at least one of the key questions (n = 21). The remaining non-review articles (thirty-two) were abstracted using a standardized form and are summarized in Evidence Table 1.

Key Question 1: What is the prevalence of anemia in pre-ESRD?

Seven studies were identified that focus on the prevalence of anemia in pre-ESRD.[18,19,20-24] Two of these were cohort studies from individual nephrology clinics,[18-20] two were US population-based studies,[21,22] one was an analysis based on a multi-center community-based outpatient clinic patient sample,[24] one was based on an analysis of outpatients from a single medical center[23] and one was based on a population receiving nephrology outpatient care at two tertiary care centers in the same geographic region.[19]

The first single-center-based cohort study was performed at Walter Reed Army Medical Center in Washington DC and involved 106 adult patients with chronic kidney disease and adult patients with creatinine > 1.5 mg/dL.[18] The patients were identified retrospectively by reviewing medical records of all patients seen between July 1, 1986, and June 30, 1987. Patients with other explanations for their anemia, those with rapid deterioration in kidney function (1-month change in creatinine in excess of 1.0 mg/dL), and patients who had received prior kidney transplants were excluded from analysis. Patients with incomplete records were also excluded, as were 27 patients who met pre-ESRD criteria but did not have simultaneous blood count and chemistries available. The final sample for analysis comprised of 106 patients. Thirty-three percent were Black and 60% were male. The mean hematocrit in this group of patients was 35.5 $\pm$ 0.7 g/dL. Criteria for "anemia" were not defined, and the actual prevalence of anemia was not therefore reported. The authors demonstrated significant correlations between hematocrit and three conventional measures of kidney function: serum creatinine, BUN, and creatinine clearance. Using multivariate linear regression they found a significant interaction between gender and kidney function as predictors of hematocrit, in that

reduced kidney function was more profoundly associated with lower hematocrits in males than in females.

Holland et al.[20] explored predictors of hospitalization and death in a cohort of 362 adult patients with chronic irreversible kidney failure attending a pre-dialysis clinic in Ontario, Canada. The patients were seen between January 1990 and July 1997, and the majority of patients studied were older than 65 years (51.7%) and male (61%). One hundred and sixty-four (34%) patients had serum creatinine > 300 µmol/L. Overall, 16.3% of patients were found to have hemoglobin < 9.5 g/L. Of those with creatinine > 300 µmol/L (3.4 mg/dL) the proportion of patients with anemia was significantly higher. In addition, lower hemoglobin was found to be an independent predictor of hospitalization using multivariate analyses.

Using the National Health and Nutrition Examination Survey (NHANES II), Strauss et al. attempted to estimate the size of the US pre-ESRD population and to estimate the fraction of those patients with anemia.[21] Out of a total study population of 10,453 patients, 44 patients were identified with serum creatinine > 2.0 mg/dL and hemoglobin < 8.0 mg/dL. As this number was considered too few to accurately estimate the proportion of pre-ESRD patients with anemia, data from two other studies of patients with pre-ESRD were added to the NHANES II data. One of these studies was the aforementioned by Howard et al.,[18] and the other was a study of EPO levels in patients with pre-ESRD.[25] The combination of these three populations added up to 181 patients with pre-ESRD, and, of these, 34 or 18.8% were identified to have anemia (defined as a hematocrit < 30%). The prevalence of anemia increased considerably with more advanced levels of kidney disease, in that 2.8% of those with creatinine > 2.0 and $\leq$ 3.0 mg/dL were anemic, whereas 17.2% of those with creatinine > 3.0 and $\leq$ 4.0 mg/dL and 36% of those with creatinine > 4.0 and $\leq$ 8.0 mg/dL were anemic. When the analysis was confined to the 44 patients identified from the population-based survey, the prevalence of anemia was 15.9%. The reported combination of these three data sets may not have been appropriate because two of the studies refer to incident ESRD cohorts and one is a population-based sample.

In a large retrospective, cross-sectional population-based analysis of ambulatory patients from Brigham and Women's Hospital in Boston, Hsu et al.[23] reviewed the records of 12,055 adult patients and found that a decrease in hemoglobin is apparent even among patients with mild to moderate kidney disease. The hemoglobin decreased progressively below CrCl of 60 mL/min in men and below 40 mL/min in women. Between 10% and 15% of patients with a GFR less than 50 mL/min had hemoglobin levels below 11.0 g/dL. Because the prevalence of impaired kidney function below a GFR of 50 mL/min was less than 10% of the population, there were, however, relatively small numbers of subjects in this study.

A population-based analysis using NHANES III data similarly demonstrates an association of level of hemoglobin and level of GFR below an estimated GFR of 60 ml/min. This study analyzed data from 15,419 patients aged 20 years and older; the survey was conducted from 1988 to 1994. The prevalence of anemia (hemoglobin

< 12 g/dL in men and < 11g/dL in women) increased from 1% for patients with estimated GFR of 60 ml/min to 9% for patients at an estimated GFR of 30 mL/min. This study was limited by the paucity of data points for patients with CrCl < 30 mL/min.

Preliminary results of the Prevalence of Anemia in Patients with Early Renal Insufficiency (PAERI) Study were presented in abstract form at the ASN meeting in San Francisco in 2001.[24] A prospective, multicenter observational study enrolled patients with a serum creatinine level of 2.0 to 6.0 g/dL for men and 1.5 to 6.0 g/dL for women. Patients who received rHuEPO or iron supplementation within 3 months prior to enrollment were considered ineligible. Preliminary results of 4,006 patients revealed hemoglobin levels of less than 12, 11, and 10 g/dL in 47%, 23%, and 9% of the population, respectively. Multivariate logistic regression analysis revealed that in addition to level of renal function, female sex, non-White race, and diabetes were significant predictors of anemia in this population.

Kazmi et al.[19] retrospectively reviewed the records of 604 patients receiving nephrology outpatient care at two tertiary care centers in the Boston area. Patients included were those aged > 18 years with persistently elevated serum creatinine for at least 6 months (1.5 mg/dL in men and 2.0 mg/dL in women). The mean estimated GFR of the study group was 23.1 (± 9.3) mL/min and the mean hematocrit was 34.9 (± 5.6) %. In the 19% of patients who underwent iron studies 54% had values consistent with iron deficiency (transferrin saturation < 20%). Linear regression revealed that for every 10 mL/min decrease in predicted creatinine clearance there was a 3.1% drop in hematocrit and a hematocrit of 36% or greater was maintained only among patients with a mean predicted GFR of 27.4 mL/min or greater.

Based on these studies we conclude that the evidence as to the prevalence of anemia in pre-ESRD remains somewhat inconclusive as the available reports are not based on a representative sample of pre-ESRD patients and in general focus on patients with earlier degrees of kidney disease. Reliance on nephrology clinic data may lead to bias in that those referred for care may be more unwell than those who remain unreferred and population-based data is limited by the number of patients with advanced CKD. The absence of clear outcome data for anemia correction in this population also makes defining anemia prevalence difficult, as the hemoglobin/hematocrit level at which patients benefit from therapeutic intervention is not clear. The four most recent studies demonstrate that anemia begins to develop early in the course of CKD and is evident below CrCl of 60 mL/min. It is also apparent that anemia increases in severity as CKD progresses to ESRD.

Key Question 2: What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion?

No papers were identified that addressed this question.

Key Question 3: What proportion of patients without nutritional deficiencies are resistant to EPO?

No papers were identified that addressed this question.

Key Question 4: What proportion of pre-ESRD patients have low EPO levels?

Three papers were identified that addressed this question. McGonigle et al.[25] assessed EPO levels in a group of 60 CKD patients identified at two hospitals in New Orleans with serum creatinine levels ranging from 1.6-10.9 mg/dL and hematocrit values ranging from 16.5% to 52%. The mean EPO level was 34.67 (± 6.7) mU/ml. This was slightly higher than that found in 40 normal subjects. EPO concentrations were, however, inexplicably extremely high in three of the CKD patients. Serum EPO concentrations in kidney failure patients were not found to correlate with plasma creatinine levels or with hematocrit, whereas EPO levels were found to correlate with hematocrit in non-kidney failure anemia patients, suggesting a relative erythropoietin deficiency in CKD. The authors also found evidence of inhibition of erythroid progenitor cell formation in CKD.

Yamazaki et al.[26] reported mean EPO levels of approximately 23.1 mU/mL in 20 pre-dialysis patients. The patients included in this study visited the hospital as outpatients. No other selection processes are described in the study. This study was designed to compare the pharmacokinetics of IV and SC EPO, and as normal ranges for the EPO assay offered were not provided and the population studied appears to have been a selected anemic population, the study did not provide meaningful estimates of the prevalence of EPO deficiency.

Kamper et al.[27] reported baseline mean EPO levels of 32 (range 10 – 86) mU/mL in a 59-patient randomized controlled trial of enalapril versus conventional anti-hypertensive therapy in pre-ESRD patients. The corresponding mean baseline hematocrit value reported in the study was 7.6 g/dL (range 4.9 – 10.2). After 90 days of therapy the mean EPO level in the enalapril treated group decreased from 32 (range 10-59) mU/mL to 24 (range 7-70) mU/mL and was unchanged in the control group 34 (range11-86) mU/mL to 35 (range 10-92) mU/mL.

Key Question 5: What is the efficacy of EPO in improving intermediate and ultimate outcomes in patients with pre-ESRD?

Twenty studies were identified that assessed the effect of EPO therapy on intermediate outcomes, including blood pressure effects, deterioration of kidney function, left ventricular geometry, kidney hemodynamics, levels of vasoactive substances, and nutritional status and quality of life. Of these, eight were randomized controlled trials,[26,28-34] three were cohort studies,[35-37] and nine were before/after studies.[1,38-45]

Effects on hematopoietic outcomes or direct assessment of drug efficacy were not considered, but a number of studies that focused on such efficacy outcomes did provide evidence of EPO effects on other outcomes and were therefore considered. These are summarized in Evidence Table 1.

No studies were identified that assessed mortality.

Blood pressure

Seventeen studies addressed the issue of blood pressure effects of EPO therapy.[1,4,26,30-32,34-36,38-43,46] None of these was primarily designed to assess blood pressure. Ten of the 17 studies compared blood pressure of EPO-treated and non-treated patients based on actual blood pressure measurements.[1,4,31,34-36,38,46,47] Of these ten, six were randomized trials,[4,30,31,34,46] two cohort studies,[35,36] and two before-after studies.[1,38] The other seven studies[26,32,39-43] did not report blood pressure measurements but did comment on changes in antihypertensive medication or adverse effects of medications.

Of the ten studies reporting blood pressure measurements, nine[1,4,31,34-36,46,47] did not show a difference in blood pressure between EPO-treated and non-treated groups. One study of 11 pre-ESRD patients before and after EPO demonstrated a significant increase in systolic and mean blood pressures, but no difference in diastolic pressures.[38] Of the nine studies that reported no differences between measured blood pressure values, two studies which together included a total of 201 patients specifically reported no increased in blood pressure "adverse events" recorded. The adverse events recorded were not predefined or categorized and included "hypertension," "headache," "arthralgia," "edema," and others.[31,35] Of the seven studies that commented on EPO blood pressure effects but did not involve measured BP outcomes, five[26,39-41,43] reported an increase in antihypertensive medications in patients treated with EPO, one[32] reported an increase in "hypertension-related" adverse events, and one[42] reported no difference in anti-hypertensive medication prescription between groups treated with EPO and those without.

In conclusion, of the 17 studies that assessed blood pressure effects of EPO therapy in CKD, eight suggested at least some increase in the risk of developing hypertension or suffering an exacerbation of hypertension associated with EPO therapy. As there were no studies that suggested improvement in blood pressure with EPO, the balance of evidence appears to suggest that EPO use is associated with at least a modest exacerbation of hypertension.

Deterioration in renal function

The effect of EPO on residual renal function was evaluated in 18 studies.[4,26,30-36,39-44,46,47] Renal function was assessed by a variety of different methods, including reciprocal of creatinine (12 studies),[26,31,34-36,39-42,44] slopes of the reciprocal of creatinine over time (11 studies),[26,31,34-36,39-42,44] differences in slope between EPO treated and non-treated groups (one study),[43] creatinine clearance (two studies),[32,46] and time to dialysis (one study, which also measured creatinine clearance).[32] No single study had sufficient power to detect a minimally clinically important difference.

Although one study did suggest a trend toward possible reduction in slope of deterioration of renal function with EPO therapy ($p = 0.06$),[40] none of the 11 trials that used reciprocal of creatinine curves as a measure of renal deterioration found any difference between EPO-treated and non-treated patients.

Two studies that compared EPO-treated and non-treated groups assessed differences in renal deterioration using creatinine clearance.[32,46] One of these studies also compared patients based on time to dialysis using survival analyses.[32] Neither study described any difference in the rate of renal deterioration between EPO-treated and non-treated groups. Two other studies compared pretreatment serum creatinine with serum creatinine during treatment with EPO and observed no difference in serum creatinine associated with EPO therapy.[4,47] Watson et al., in a study that primarily evaluated the safety and efficacy of subcutaneous EPO therapy in patients with CKD, reported that two of the 11 patients studied were discontinued from the trial because of rapid deterioration in renal function.[33] Finally, Kuriyama et al., in a study specifically designed to assess the impact of EPO therapy on renal deterioration, observed a reduction in renal deterioration (defined as time to doubling of serum creatinine) when 42 anemic CKD patients treated with EPO were compared with 31 untreated anemic CKD patients ($P = 0.0003$).[30] This comparison was unadjusted, however, and the results could possibly be attributable to some extent to the fact that there was a higher prevalence of diabetes in the untreated group.

In conclusion, of the 17 studies that addressed the effect of EPO therapy on deterioration in renal function, 14 demonstrated no change in the rate of deterioration of renal function associated with EPO therapy, one demonstrated improvement in renal function with EPO therapy,[30] one showed a non-significant trend toward improvement,[40] and one suggested that there may be an increase in deterioration in renal function with EPO therapy.[33]

Left ventricular geometry

Two studies were identified that assessed the effect of EPO therapy on left ventricular geometry.[1,45] Portoles et al.[1] described a selected group of 11 patients before and at the end of 6 months of EPO therapy. Mean left ventricular mass index (LVMI) was 178.2 ± 20.6 g/m^2 pre-therapy and 147.3 ± 20.6 g/m^2 ($p < 0.01$) after 6 months of EPO therapy. Hayashi et al.[45] studied nine patients with hematocrit < 25% who underwent normalization of hematocrit with EPO over 10 months and demonstrated a reduction in LVMI from 140.6 ± 12.1 g/m^2 to 111.2 ± 8.3 g/m^2 ($p < 0.05$).

These studies were both significantly underpowered and the populations studied were also highly selected. The effect of EPO therapy on left ventricular geometry in this population remains, therefore, uncertain.

Renal hemodynamics

There were two studies identified that briefly addressed the issue of alteration of renal hemodynamics with EPO therapy. Frenken et al.[48] determined that increases in effective renal plasma flow and renal blood flow noted in anemic patients treated with captopril were not as evident in patients whose anemia had been corrected with EPO prior to receiving captopril. Abraham et al.[46] compared four patients who received EPO with four controls receiving placebo and derived renal vascular resistance (RVR) values for each patient using mean arterial pressure (MAP) and p-aminohippurate clearance derived estimates of renal blood flow (RBF) (RVR = MAP/RBF x 80,000 [dyn\s\cm^{-5}]).

EPO-treated and untreated patients were not noted to have different values for this parameter.

Quality of life

Three papers were identified that assessed quality of life measures in EPO-treated CKD patients. In a randomized, parallel-group, open-label clinical trial of EPO versus placebo involving 83 CKD patients, Revicki et al.[2] demonstrated that quality of life was relatively better in EPO-treated patients than in those who received placebo. This study involved follow-up evaluations over 48 weeks. Hematocrit levels were measured at baseline and monthly, and quality of life was assessed at baseline and at 16-week intervals for a total of 48 weeks. Significant improvements in assessments of energy ($P < 0.05$), physical function ($P < 0.05$), home management ($P < 0.05$), social activity ($P < 0.05$), and cognitive function ($P < 0.05$) were found for the r-HuEPO-treated group. Between-group differences favoring the r-HuEPO-treated group were found for energy ($P < 0.05$) and physical functioning ($P < 0.05$). The quality-of-life analysis reported in this paper was for the same group of patients for whom pharmacokinetic data and progression of kidney disease and blood pressure outcomes were reported in an earlier paper.[34]

Three of the studies that primarily addressed blood pressure and deterioration in renal function issues also discussed quality-of-life issues. One study, an RCT comparing three different EPO dosing strategies with placebo over 8 weeks, described significant improvement in energy levels and work capacity in patients whose anemia had been corrected (i.e., achievement of a hematocrit of 40% for men and 35% for women).[31] Using a scale ranging from 1-5, 60% of patients whose anemia had been corrected reported increased energy at the final evaluation versus 42% of those whose anemia had not been corrected. The other study was a double-blind RCT of 14 patients comparing different EPO dosing strategies over 8 weeks. Seven patients who received EPO and one who received placebo underwent exercise tolerance assessment as measured by oxygen consumption using breath testing and a cycle ergometer.[4] The one placebo-treated patient showed a slight decrease in exercise tolerance, and the seven EPO-treated patients were found to have developed increased oxygen consumption at anaerobic threshold (9.23 ± 1.05 mL/min at baseline vs. 9.94 ± 1.03 mL/min at 8 weeks, $P < 0.02$) and at maximal work rate (16.0 ± 1.8 mL/min at baseline vs. 17.5 ± 1.9 mL/min at 8 weeks ($P < 0.02$)) following 8 weeks of EPO therapy. Kleineman et al.[3] used a quality of life assesment consisting of three questions related to energy level in a study primarily designed to assess the effects of anemia correction on blood pressure and renal function. The EPO treated patients showed a greater mean increase in quality of life than the placebo group.

We conclude that the evidence supporting quality-of-life improvement with EPO therapy is reasonably convincing and is consistent with data in oncology and hematology patients.

Levels of vasoactive substances

Two of the studies outlined earlier also assessed the influence of EPO therapy on various vasoactive substances. Kuriyama et al.[47] demonstrated that thrombomodulin levels correlated with increasing creatinine in CKD patients and that EPO therapy resulted in a reduction in the expected increase in thrombomodulin levels, suggesting that EPO may have a beneficial effect on endothelial dysfunction in CKD. Portoles et al. assessed levels of Endothelin 1, plasma renin activity, epinephrine, norepinephrine, and dopamine pre- and post-EPO therapy in 11 CKD patients and found no differences.[1]

The effect of EPO therapy on various vasoactive mediators is thus an interesting but understudied area that may offer insights into EPO's effect on important clinical outcomes in the future.

Nutrition

Lastly, Nishikage et al., in a prospective clinical trial of 27 CKD patients identified from an outpatient clinic setting, assessed the effect of EPO therapy on amino acid metabolism.[37] There were no significant changes noted in the concentrations of non-essential amino acids, essential amino acids, or branched chain amino acids after treatment with EPO to a target hematocrit of 30% in patients with CKD and anemia. There is a notable paucity of data in the literature as to the effect of EPO therapy on more global measures of nutrition such as weight, BMI, muscle mass or nutritional intake.

In conclusion, the association of EPO therapy with nutritional indices is not well studied.

2.5 Discussion

The available evidence on anemia in CKD led to us being able to provide data that addressed only three of our five key questions. Two of the questions posed were therefore not answered by the current review. The majority of the literature abstracted focused on the treatment of the anemia of CKD with EPO therapy and the effect of such therapy on intermediate and surrogate outcomes. Based on the studies that evaluated the prevalence of anemia in CKD we concluded that the evidence remains somewhat inconclusive. Using different criteria for pre-ESRD, and with overlapping populations, two studies estimated the prevalence of anemia to be 16.3 and 18.3% respectively. All studies identified demonstrated that the prevalence of anemia increases markedly as kidney disease becomes more advanced.

Information about EPO levels in CKD is scarce but suggests that EPO levels in CKD were not necessarily lower than in patients who were not anemic, but that CKD patients may suffer from a relative EPO deficiency; that is, EPO levels were inappropriately low considering level of anemia.

Research on intermediate outcomes following EPO therapy in CKD patients focused primarily on two areas, blood pressure and progression of CKD. Of 16 studies that assessed blood pressure effects of EPO therapy in CKD, eight suggested at least some increase in the risk of developing or suffering an exacerbation of hypertension associated with EPO therapy. As there were no studies that suggested improvement in blood pressure with EPO, the balance of evidence appears to suggest that EPO use is associated with an exacerbation in blood pressure.

Of the 17 studies that addressed the effect of EPO therapy on deterioration in renal function, 14 demonstrated no change in the rate of deterioration of renal function associated with EPO therapy, one demonstrated improvement in renal function with EPO therapy,[30] one showed a non-significant trend toward improvement,[40] and one suggested that there may be an increase in deterioration in renal function with EPO therapy.[33] In this case, therefore, the majority of the evidence suggests that EPO therapy is associated with no change and if anything a slight improvement in the rate of renal function deterioration.

Although the number of studies that address the issues of blood pressure control and progression of kidney disease is considerable it is important to note that none of the studies described were adequately powered to detect small or even moderate differences in these parameters.

Two studies suggested improvement in LVMI but involved small highly selected populations, and further evidence is required in larger population-based samples before it can be conclusively stated that EPO therapy leads to a reduction in LVMI in CKD patients.

The papers that assessed renal hemodynamics did not conclusively demonstrate any significant differences between EPO-treated and non-treated patients, but neither study was designed to comprehensively evaluate such questions

The evidence supporting quality-of-life improvement with EPO therapy is reasonably convincing for EPO having an associated quality-of-life benefit and is not surprising in the light of extensive other data describing improvement in oncology and hematology patients.

Lastly, one study suggested that EPO therapy may improve endothelial function as evidenced by a reduction in the elevation of thrombomodulin levels. The use of surrogate outcomes such as this makes conclusions difficult in that the pathobiology of endothelial function and the role of EPO and thrombomodulin in that pathobiology may not yet be completely elucidated.

In conclusion, therefore, the available literature on anemia and its management in patients with pre-ESRD predominantly addresses the management of anemia with EPO. Data as to the prevalence of anemia in CKD is limited and inconclusive but

suggests that 15-20% of pre-ESRD patients are anemic. Anemia treatment with EPO is probably associated with an increased risk of developing hypertension or of exacerbating current hypertension and does not appear to be associated with an increased risk of deterioration in renal function. Substantial opportunities remain for further research into the prevalence of anemia and its treatment in this population and into the role of nutrition and nutritional interventions in both the pathobiology of the disease and its management.

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Evidence Table 1 – Anemia

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Abraham, Opsahl, Rachael, et al., 1990	Design: RCT (n = 8) Intervention(s) studied: 1) Placebo administered intravenously or subcutaneously 3 times per week for up to 8-12 weeks to achieve a goal Hct of 40% for males and 37% for females (n = 4). Mean duration of treatment (± SD), 9.4 ± 2.2 weeks. 2) Intravenous or subcutaneous EPO 3 times per week for up to 8-12 weeks to achieve a goal Hct of 40% for males and 37% for females. Doses used were 50 U/kg (n = 1), 100 U/kg (n = 2), and 150 U/kg (n = 1). Mean duration of treatment (± SD), 7.6 ± 2.7 weeks. At the completion of the RCT phase, all patients were given EPO and entered into a long-term open-label study. Dates: NR Location: Minneapolis, MN Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 8 Inclusion criteria: Anemia (Hct ≤ 36%) secondary to chronic renal failure (SCr ≥ 3.0 mg/dl); predialysis; clinically stable for at least 1 month prior to start of study Exclusion criteria: Other causes of anemia; androgen, immuno-suppressant, or corticosteroid therapy in previous 2 months; any condition that might interfere with or complicate EPO therapy Age (mean, with range): Placebo, 54 (43-69); EPO, 39 (26-50) Sex: Placebo, 75% M, 25% F; EPO, 50% M, 50% F Race: NR Renal function at entry: CrCl (mean, ml/min): Placebo: 33.5 EPO: 19.8 SCr (mean ± SD, mg/dl): Placebo: 3.7 ± 0.4 EPO: 5.2 ± 1.6 Inulin clearance (mean ± SD, ml/min): Placebo: 27 ± 8 EPO: 16 ± 13 Hgb at entry: NR Hct at entry (mean ± SD): Placebo: 28 ± 2% EPO: 32 ± 3% p < 0.05	*Key Question 1) What is the prevalence of anemia in pre-ESRD?:* Not addressed *Key Question 2) What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion?:* Not addressed *Key Question 3) What proportion of patients without nutritional deficiencies are resistant to EPO?:* Not addressed *Key Question 4) What proportion of pre-ESRD patients have low EPO levels?:* Not addressed *Key Question 5) What is the efficacy of EPO in improving intermediate and ultimate outcomes?* a) Hct (mean ± SD): Baseline / End of treatment Placebo: 28 ± 2% / 29 ± 3% EPO: 32 ± 3% / 37 ± 2% Both groups, end of treatment vs. baseline, p < 0.05. EPO vs. placebo, at baseline and at end of treatment, p < 0.05. b) Blood pressure: Mean blood pressure (mean ± SD, mmHg): Baseline / End of treatment Placebo: 106 ± 15 / 98 ± 7 EPO: 102 ± 12 / 100 ± 7 No significant pre-/post- or between-group differences. Antihypertensive medication was increased in 2 patients in each group.	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: Completely Incl/excl described: Partially Dropouts discussed: Partially Sample size justified: No/not assessable 3) GFR/CrCl: Measured by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 2b Note: Very small sample size (n = 8).

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Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
		EPO levels at entry: NR Nutritional parameters at entry: NR Co-morbidities at entry: Diabetes as cause of CRF: 50% each group Antihypertensive medication: 100% of patients in placebo group; 75% of patients in EPO group	c) Total protein excretion (mean ± SD, mg/day): Baseline / End of treatment Placebo: 1,527 ± 1,015 / 1,294 ± 973 EPO: 1,100 ± 1,023 / 1,477 ± 1,592 Placebo, end of treatment vs. baseline, $p < 0.05$; otherwise no significant pre-/post- or between-group differences. d) Renal vascular resistance (mean ± SD, dyn x s x cm^{-5}): Baseline / End of treatment Placebo: 58,753 ± 13,135 / 66,801 ± 8,492 EPO: 183,625 ± 170,622 / 129,167 ± 103,548 No significant pre-/post- or between-group differences. e) Inulin clearance (mean ± SD, ml/min): Baseline / End of treatment Placebo: 27 ± 8 / 20 ± 7 EPO: 16 ± 13 / 18 ± 11 No significant pre-/post- or between-group differences.	

Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Albertazzi, Di Liberato, Daniele, et al., 1998	Design: Cohort study Intervention(s) studied: Subcutaneous EPO 2,000 units twice per week for 6 weeks. If at the end of the 6th week Hgb had not increased by 1 g%, then dosage of 3,000 units given twice per week for a further 6 weeks. Further increases of 1,000 units per administration were then permitted, if necessary, "through reducing time treatment to 4 weeks." Doses reduced by 50% and given once per week when Hgb levels stabilized between 10-11 g%. Therapy suspended if SCr increased by > 30%. Mean EPO doses (± SD) were 4,000 units/week at start of study, 4,784 ± 1,535 units/week at 3 months, 3,592 ± 1,685 units/week at 6 months, and 2,840 ± 1,178 units/week at 12 months. 65 patients were followed through 6 months, 25 through 12 months. Dates: NR Location: 12 sites in Italy Recruitment setting: Nephrology clinics/departments	No. of pre-ESRD subjects: 84 started therapy; 65 were followed up through 6 months; 25 were followed up through 12 months Inclusion criteria: Age 18-75; SCr 3-9 mg%; Hgb 6-9 g%; SCr measured at least 6 times in previous 8 months Exclusion criteria: Previous treatment with EPO, cytostatics, and/or immunosuppressors; accelerated hypertension; severe hyperparathyroidism (alkaline phosphatase > 300 U/l); blood transfusion in previous 2 months Age (mean ± SD): 61.7 ± 13.9 Sex: 45% M, 55% F Race: NR Renal function at entry: SCr (mean ± SD): 5.17 ± 1.42 mg% Hgb at entry (mean ± SD): 8.00 ± 0.77 Hct at entry (mean ± SD): 24.9 ± 3.0% EPO levels at entry: NR Nutritional parameters at entry (mean ± SD): Serum iron: 66.6 ± 24.9 ug/dl Serum ferritin: 148.6 ± 37.6 ng/ml Co-morbidities at entry: Hypertension: 45/84 (54%), of whom 29 were good responders to antihypertensive therapy, and 16 maintained diastolic BP > 95 mmHg	*Key Question 1) What is the prevalence of anemia in pre-ESRD?:* Not addressed *Key Question 2) What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion?:* Not addressed *Key Question 3) What proportion of patients without nutritional deficiencies are resistant to EPO?:* Not addressed *Key Question 4) What proportion of pre-ESRD patients have low EPO levels?:* Not addressed *Key Question 5) What is the efficacy of EPO in improving intermediate and ultimate outcomes?* a) Hematocrit (means ± SD, in %): Baseline (n = 84): 24.9 ± 3.0 3 months (n = ?): 29.7 ± 3.5 (p < 0.001 vs. baseline) 6 months (n = 65): 31.5 ± 3.2 (p < 0.001 vs. baseline) 12 months (n = 25): 32.51 ± 2.52 (p < 0.001 vs. baseline) b) Hemoglobin (means ± SD, in g%): Baseline (n = 84): 8.00 ± 0.77 3 months (n = ?): 9.35 ± 1.00 (p < 0.001 vs. baseline) 6 months (n = 65): 10.06 ± 1.04 (p < 0.001 vs. baseline) 12 months (n = 25): 10.25 ± 0.62 (p < 0.001 vs. baseline) c) Blood pressure: Systolic BP (mean ± SD, mmHg): Baseline (n = 84): 146 ± 19.2 3 months (n = ?): 152 ± 19.8	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: Partially Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: ?? 4) % pre-ESRD: ?? 5) Level of evidence: 2b Notes: A total of 9 patients suspended EPO therapy to start dialysis treatment. 1 patient each withdrew due to an increase in SCr of > 30%, heart failure/angina, and phlebitis.

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Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			6 months (n = 65): 151 ± 21.7 12 months (n = 25): 151 ± 19.3 p = not significant Diastolic BP (mean ± SD, mmHg): Baseline (n = 84): 81 ± 8.6 3 months (n = ?): 85 ± 9.5 6 months (n = 65): 86 ± 9.2 12 months (n = 25): 87 ± 13.5 p = not significant 13 patients had an increase in BP during treatment. Of these, 2 completed EPO therapy, 7 were withdrawn, and 4 were suspended for start of dialysis. d) Renal function: Treatment with EPO did not impair residual renal function (assessed by plotting the reciprocal of SCr vs. time – results reported only in graphic form).	

Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Anastas-siades, Howarth, Howarth, et al., 1993	Design: Prospective clinical trial (before/after study) Intervention(s) studied: Subcutaneous EPO, initial dose 60 units/kg twice a week, with subsequent dose adjustments to achieve a Hgb > 10 g/dl (n = 11). Antihypertensive therapy and fluid status optimized in the 2-week run-in period before start of EPO therapy. Treatment continued for 12 weeks. Dates: NR Location: Manchester, UK Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 11 Inclusion criteria: Severe renal failure, but not yet requiring dialysis Exclusion criteria: None specified Age: NR Sex: NR Race: NR Renal function at entry: NR Hgb at entry (mean ± SEM): 6.90 ± 0.35 g/dl Hct at entry: NR EPO levels at entry: NR Nutritional parameters at entry: NR Co-morbidities at entry: Hypertension: Antihypertensive drug score (mean ± SEM) at baseline was 1.16 ± 0.27 (score of 1 = maximal daily dose of a single drug, with lower doses of a drug having proportionately lower scores)	*Key Question 1) What is the prevalence of anemia in pre-ESRD?:* Not addressed *Key Question 2) What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion?:* Not addressed *Key Question 3) What proportion of patients without nutritional deficiencies are resistant to EPO?:* Not addressed *Key Question 4) What proportion of pre-ESRD patients have low EPO levels?:* Not addressed *Key Question 5) What is the efficacy of EPO in improving intermediate and ultimate outcomes?:* a) Hgb (mean ± SEM, in g/dl): Baseline: 6.90 ± 0.35 12 weeks: 10.05 ± 0.47 p < 0.0001 b) Blood pressure: Mean BP (± SEM, mmHg): Baseline: 95 ± 5 12 weeks: 103 ± 6 p = 0.028 Systolic BP (mean ± SEM, mmHg): Baseline: 132 ± 7 12 weeks: 146 ± 9 p = 0.029 Diastolic BP (mean ± SEM, mmHg): Baseline: 77 ± 5 12 weeks: 81 ± 5	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: No/not assessable Incl/excl described: No/not assessable Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Not assessable 4) % pre-ESRD: 50-75% 5) Level of evidence: 4 Note: Study also included 16 patients on continuous ambulatory peritoneal dialysis, whose results are not described here.

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Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			p = not significant This study demonstrated a marked increase in expansion of red cell volume and blood volume in pre-dialysis patients after treatment with EPO. This was offered as a possible explanation for the increase in BP.	

Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Astor, Muntner, Levin, et al., in Press	Design: Population-based cohort study Intervention(s) studied: None. Investigators used data from the third National Health Nutrition Examination Survey (NHANES III) to assess the association of kidney function and Hgb levels across the range of kidney function among non-institutionalized adults in the US. Dates: NHANES III conducted from 1988 to 1994; results projected to 1990 Location: Nationally representative population-based survey Recruitment setting: Community setting	No. of pre-ESRD subjects: 15,625 individuals age 20 or older were surveyed for NHANES III; 15,419 of these had SCr and Hgb measurements and GFR ≥ 15 and were included in the analysis; 52 of these had GFR 15-29 ml/min/1.73 m^2 Inclusion criteria: Surveyed in NHANES III; age ≥ 20; non-institutionalized Exclusion criteria: None specified Age (n = 15,419 included subjects): 40% 20-39; 27% 40-59; 14% 60-69; 19% 70+ Sex (n = 15,419 included subjects): 46% M, 54% F Race (n = 15,419 included subjects): 42% non-Hispanic White; 27% non-Hispanic Black; 27% Mexican-American; 4% other Renal function at entry: NR Hgb at entry (n = 52 subjects with predialysis renal insufficiency; mean ± SEM): 11.8 ± 0.33 g/dl Hct at entry: NR EPO levels at entry: NR Nutritional parameters at entry: NR Co-morbidities at entry: NR	*Key Question 1) What is the prevalence of anemia in pre-ESRD?:* The NHANES III survey found the following anemia prevalences (anemia defined as Hgb < 12 g/dl for men and < 11 g/dl for women) among patients of varying GFR (GFR expressed in ml/min/1.73 m^2): GFR 90+: 1.8% anemic GFR 60-89: 1.3% anemic GFR 30-59: 5.2% anemic GFR 15-29: 44.1% anemic *Key Question 2) What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion?:* Not addressed *Key Question 3) What proportion of patients without nutritional deficiencies are resistant to EPO?:* Not addressed *Key Question 4) What proportion of pre-ESRD patients have low EPO levels?:* Not addressed *Key Question 5) What is the efficacy of EPO in improving intermediate and ultimate outcomes?:* Not addressed	Quality Scoring: 1) Global assessment: Excellent 2) Validity criteria: Population described: Completely Incl/excl described: Completely Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: < 50%/not assessable 5) Level of evidence: 2b Note: Best available evidence on the prevalence of anemia among patients with chronic kidney disease. Limited by small number of patients with GFR < 30 (n = 52).

Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Austrian Multicenter Study Group of r-HuEPO in Predialysis Patients, 1992	Design: Cohort study Intervention(s) studied: Subcutaneous EPO 10,000 U once per week for 3 months. Dose adjustments made every 4 weeks based on an increase or decrease in Hgb of 1 g/dl or more. Dose adjustments generally made in 4,000-U/week increments. Mean dose at end of treatment (± SEM) was 9,000 ± 4,000 U. Dates: NR Location: 20 sites "all over Austria" Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 130 (of whom 123 were included in the analysis) Inclusion criteria: Progressive renal failure; predialysis; renal anemia (with no other causes of anemia); Hgb < 10 g/dl Exclusion criteria: None specified Age (mean, with range): 56.6 (18-84) Sex: 48% M, 52% F Race: NR Renal function at entry: SCr (mean ± SEM): 6.2 ± 0.2 mg/dl Hgb at entry (mean): Either 9.0 g/dl (abstract) or 8.4 g/dl (figure) Hct at entry (mean): 25% (estimated from figure) EPO levels at entry: NR Nutritional parameters at entry: Serrum ferritn (mean): 180 ng/ml (estimated from figure) Co-morbidities at entry: Diabetes as cause of CRF: 13% Antihypertensive medication: 75%	*Key Question 1) What is the prevalence of anemia in pre-ESRD?:* Not addressed *Key Question 2) What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion?:* Not addressed *Key Question 3) What proportion of patients without nutritional deficiencies are resistant to EPO?:* Not addressed *Key Question 4) What proportion of pre-ESRD patients have low EPO levels?:* Not addressed *Key Question 5) What is the efficacy of EPO in improving intermediate and ultimate outcomes?:* a) Hgb (mean): Baseline: 9.0 g/dl (abstract) or 8.4 g/dl (figure) 3 months: 10.8 g/dl p < 0.05 b) Blood pressure: Mean systolic BP (estimated from figure): Baseline: 152 mmHg 3 months: 158 mmHg p = not significant Mean diastolic BP (estimated from figure): Baseline: 100 mmHg 3 months: 86 mmHg p = not significant Percentage of patients on antihypertensive medication: Baseline: 75% 3 months: 75%	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: No/not assessable Incl/excl described: Partially Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: SCr 4) % pre-ESRD: < 50%/not assessable 5) Level of evidence: 4 Note: No clear statistics or power statements.

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Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			c) Renal function: Slope of 1/SCr curve was not significantly affected by EPO treatment (results presented only graphically).	

Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Eschbach, Kelly, Haley, et al., 1989	Design: RCT (8-12 weeks), followed by long-term, uncontrolled follow-up Intervention(s) studied: 1) Intravenous placebo (n = ?; 6 placebo-treated patients altogether) 2) Intravenous EPO 50 U/kg (n = ?; 11 EPO-treated patients altogether) 3) Intravenous EPO 150 U/kg (n = ?; 11 EPO-treated patients altogether) 4) Subcutaneous placebo (n = ?; 6 placebo-treated patients altogether) 5) Subcutaneous EPO 100 U/kg (n = ?; 11 EPO-treated patients altogether) Intravenous doses given 3 times per week for 8 weeks or until target Hct reached (37% for women, 40% for men). Subcutaneous doses given 3 times per week for 12 weeks or until target Hct reached (38% for women, 40% for men). No dose adjustments described for this period. Once RCT complete (8-12 weeks), all patients invited to continue in an open-label, long-term maintenance study, in which subcutaneous EPO given, with dose adjusted according to Hct response. Patients followed until RRT	No. of pre-ESRD subjects: 17 Inclusion criteria: Chronic renal failure (SCr 4-11 mg/dl); anemia (Hct ≤ 30%); predialysis Exclusion criteria: Inflammatory disease that might impair the response to EPO; use of immunosuppressive therapy Age: Range, 24-72 Sex: 59% M, 41% F Race: NR Renal function at entry: NR Hgb at entry: NR Hct at entry (mean): Placebo (n = 6): 29% EPO (n = 11): 25% EPO levels at entry: NR Nutritional parameters at entry: NR Co-morbidities at entry: Diabetes as cause of CRF: 12% Antihypertensive medication: 82%	*Key Question 1) What is the prevalence of anemia in pre-ESRD?:* Not addressed *Key Question 2) What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion?:* Not addressed *Key Question 3) What proportion of patients without nutritional deficiencies are resistant to EPO?:* Not addressed *Key Question 4) What proportion of pre-ESRD patients have low EPO levels?:* Not addressed *Key Question 5) What is the efficacy of EPO in improving intermediate and ultimate outcomes?:* a) Hct (mean ± SD; RCT phase; 3 EPO groups combined, 2 placebo groups combined): Baseline / End of RCT Placebo: 29% / 28 ± 2% EPO: 25% / 37 ± 4% EPO vs. placebo, p = 0.0001 b) Blood pressure (RCT and open phases): 9/14 patients taking antihypertensive medication at the start of the study required increased or additional medications. Two patients who were normotensive at the start of the study required antihypertensive therapy. c) Renal function: SCr (mean ± SD; RCT phase; 3 EPO groups combined, 2 placebo groups combined): Baseline / End of RCT Placebo: NR / 6.5 ± 1.3 mg/dl EPO: NR / 8.6 ± 2.3 mg/dl EPO vs. placebo at baseline, p = not significant	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: Partially Dropouts discussed: Partially Sample size justified: No/not assessable 3) GFR/CrCl: SCr 4) % pre-ESRD: < 50%/not assessable 5) Level of evidence: 4 Notes:

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Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
	instituted. Dates: NR Location: Seattle, WA Recruitment setting: Nephrology clinic/department		EPO vs. placebo at end of RCT, p = 0.2 Slope of 1/Scr x 100 (RCT and open phases): There was no significant difference in the pre-treatment and post-treatment slopes after a median of 12 months of EPO therapy (p = 0.78). 7 patients (41%) required hemodialysis as a result of CrCl declining to ≤ 5 ml/min at a mean of 6.5 months.	

Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Frenken, Verberck-moes, Michielsen, et al., 1989	Design: RCT Intervention(s) studied: Intravenous EPO initially given 3 times per week for 8 weeks or until Hct exceeded target value by 2 percentage points (correction phase), then once per week thereafter (maintenance phase). Patients were randomized to three initial doses: 1) 50 U/kg (n = 8) 2) 100 U/kg (n = 8) 3) 150 U/kg (n = 8) After initial (correction) treatment period, same total weekly dose given (adjusted for response), but once per week. Total treatment period 8 months (2-month correction phase + 6-month maintenance phase). Target Hct values initially 37% for women and 39% for men, but changed to 35% for both in Oct 1987 for safety reasons. Dates: NR Location: Nijmegen, The Netherlands Recruitment setting: Not specified/unable to determine	No. of pre-ESRD subjects: 24 Inclusion criteria: Progressive chronic renal failure; anemia (not attributable to other causes); no other clinically significant diseases; hypertension either absent or medically controlled; dietary and medication regimens stable for at least 1 month before study entry Exclusion criteria: Blood transfusion within 30 days of start of study; acute illness with 7 days of start of trial Age: Range, 23-68 Sex: 46% M, 54% F Race: NR Renal function at entry: SCr: Range, 375 to 1204 µmol/l Hgb at entry: Range, 5.3 to 10.2 g/dl Hct at entry: Range, 0.16 to 0.30 l/l EPO levels at entry: NR Nutritional parameters at entry: Serum ferritin (estimated from graph): 90 µg/l Co-morbidities at entry: Anemia: 100% Hypertensive treatment: 75%	*Key Question 1) What is the prevalence of anemia in pre-ESRD?:* Not addressed *Key Question 2) What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion?:* Not addressed *Key Question 3) What proportion of patients without nutritional deficiencies are resistant to EPO?:* Not addressed *Key Question 4) What proportion of pre-ESRD patients have low EPO levels?:* Not addressed *Key Question 5) What is the efficacy of EPO in improving intermediate and ultimate outcomes?:* a) Hgb: At the end of the 8-week correction phase, Hgb had risen significantly in all three dosage groups ($p < 0.01$ for each comparison vs. baseline); the increase was significantly lower in the 50-U/kg group than in the other two dosage groups ($p < 0.05$). Mean values (in g/dl, ± SD) were as follows: Baseline / 8 weeks 50 U/kg: 9.3 ± 0.6 / 11.1 ± 1.3 100 U/kg: 7.9 ± 1.4 / 11.8 ± 1.7 150 U/kg: 8.4 ± 1.0 / 12.1 ± 1.1 b) Blood pressure: There were no significant changes in MAP in any of the three dosage groups during the correction phase. Mean values (in mmHg, ± SD): Baseline / 8 weeks 50 U/kg: 99 ± 10 / 98 ± 9 100 U/kg: 105 ± 11 / 113 ± 9	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: No/not assessable Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: SCr 4) % pre-ESRD: < 50%/not assessable 5) Level of evidence: 2b Notes:

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Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			150 U/kg 107 ± 23 109 ± 24 Mean systolic BP, diastolic BP, and MAP did not change during the maintenance period (detailed data not reported). 9/18 patients on antihypertensive medication at the start of the study had to increase their dose during the course of the study; none of the initially normotensive patients developed hypertension. c) Renal function: There were no significant differences in the slopes of 1,000/SCr versus months before therapy and after therapy (n = 14 patients with adequate data).	

Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Frenken, Wetzels, Sluiter, et al., 1992	Design: Prospective clinical trial (before/after) Intervention(s) studied: Intravenous EPO initially given 3 times per week for 8 weeks, then once per week thereafter. Patients randomized to three initial doses (no between-group comparisons made): 1) 50 units/kg 2) 100 units/kg 3) 150 units/kg After initial 8-week treatment period, same total weekly dose (adjusted for response), but given once per week. Post-treatment measures taken when Hct had been stable within target range (0.35-0.45 liter/liter) for at least 3 weeks, which was at 89 ± 19 days (mean ± SD) after start of EPO therapy. Dates: NR Location: Nijmegen, The Netherlands Recruitment setting: Nephrology department/clinic	No. of pre-ESRD subjects: 8 Inclusion criteria: Progressive chronic renal failure; dietary and medication regimens stable for at least 1 month before study entry Exclusion criteria: Blood transfusion within 3 months of start of study; use of ACE inhibitors Age: Median, 33; range, 25-66 Sex: 50% M, 50% F Race: NR Renal function at entry: CrCl (mean ± SD): 13 ± 5 ml/min/1.73 m^2 Hgb at entry: NR Hct at entry (mean ± SD): 0.24 ± 0.05 liter/liter EPO levels at entry: NR Nutritional parameters at entry: NR Co-morbidities at entry: Anemia: 100% Antihypertensive treatment: 50%	*Key Question 1) What is the prevalence of anemia in pre-ESRD?:* Not addressed *Key Question 2) What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion?:* Not addressed *Key Question 3) What proportion of patients without nutritional deficiencies are resistant to EPO?:* Not addressed *Key Question 4) What proportion of pre-ESRD patients have low EPO levels?:* Not addressed *Key Question 5) What is the efficacy of EPO in improving intermediate and ultimate outcomes?:* a) Hct (mean ± SD): Baseline: 0.24 ± 0.05 liter/liter Post-treatment: 0.39 ± 0.03 liter/liter (no p-value reported) b) Renal function: Captopril-induced increases in renal blood flow and effective renal plasma flow were diminished following correction of Hct with EPO.	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: No/not assessable Incl/excl described: No/not assessable Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Measured by investigators 4) % pre-ESRD: < 50%/not assessable 5) Level of evidence: 4 Notes:

Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Hayashi, Suzuki, Shoji, et al., 2000	Design: Prospective clinical trial (before/after study) Intervention(s) studied: Intravenous EPO given at 6,000 U/week to a target level of Hct 30%. Hct maintained at this target level for 2 months using subcutaneous EPO. Dose then increased to reach a target Hct level of 40%, again using subcutaneous EPO. Target level of 40% maintained for 2 months. Dates: NR Location: Osaka, Japan Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 9 Inclusion criteria: Pre-dialysis patients; Hct < 25% Exclusion criteria: Valvular disease; arrhythmia; active ischemic heart disease; history of seizures; cerebrovascular disease; severe or uncontrolled hypertension; malignancy Age (mean ± SEM): 62.4 ± 3.3 Sex: 56% M, 44% F Race: NR Renal function at entry: GFR (mean): 8.4 ml/min/1.73 m^2 SCr (mean ± SEM): 6.2 ± 0.7 mg/dl Hgb at entry: NR Hct at entry (mean ± SEM): 23.6 ± 0.5% EPO levels at entry: NR Nutritional parameters at entry: Serum ferritin (mean ± SEM): 105.8 ± 40.6 ng/ml Co-morbidities at entry: Diabetes: 11% Antihypertensive medication: 100% Other: Left ventricular mass index (LVMI) (mean ± SEM): 140.6 ± 12.1 g/m^2	*Key Question 1) What is the prevalence of anemia in pre-ESRD?:* Not addressed *Key Question 2) What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion?:* Not addressed *Key Question 3) What proportion of patients without nutritional deficiencies are resistant to EPO?:* Not addressed *Key Question 4) What proportion of pre-ESRD patients have low EPO levels?:* Not addressed *Key Question 5) What is the efficacy of EPO in improving intermediate and ultimate outcomes?:* a) Hct (mean ± SEM): Baseline: 23.6 ± 0.5% Partial correction (Hct 30%): 32.1 ± 0.6% Normalization (Hct 40%): 39.1 ± 0.8% p < 0.0001 b) Blood pressure (mean ± SEM, mmHg): Systolic BP: Baseline: 147.8 ± 7.7 Partial correction (Hct 30%): 151.3 ± 7.6 Normalization (Hct 40%): 148.2 ± 7.4 p = not significant Diastolic BP: Baseline: 74.2 ± 4.9 Partial correction (Hct 30%): 76.5 ± 2.6 Normalization (Hct 40%): 72.7 ± 3.2 p = not significant	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: Completely Incl/excl described: Completely Dropouts discussed: Completely Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by reviewers 4) % pre-ESRD: > 75% 5) Level of evidence: 4 Note: Issue of statistical power not addressed.

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Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			c) LVMI (mean ± SEM, g/m^2): Baseline: 140.6 ± 12.1 Partial correction (Hct 30%): 126.9 ± 10.0 Normalization (Hct 40%): 111.2 ± 8.3 $p < 0.01$	

Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Holland and Lam, 2000	Design: Cohort study (retrospective) Intervention(s) studied: None (univariate and multivariate Cox proportional hazard models used to identify predictors of hospitalization prior to initialization of dialysis) Dates: Included patients were referred to nephrology service between Jan 1990 and July 1997 Location: Kingston, Ontario, Canada Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 362 Inclusion criteria: Age > 16; chronic irreversible renal failure; pre-dialysis; attendance at pre-dialysis clinic at least once Exclusion criteria: None specified Age: 48% ≤ 65; 52% > 65 Sex: 61% M, 39% F Race: NR Renal function at entry: SCr: 55% ≤ 300 µmol/l; 45% > 300 µmol/l Hgb at entry: 16% ≤ 9.5 g/dl; 84% > 9.5 g/dl Hct at entry: NR EPO levels at entry: NR Nutritional parameters at entry: Serum albumin: 46% ≤ 3.5 g/dl; 54% > 3.5 g/dl Co-morbidities at entry: Diabetes as cause of renal failure: 38% Hypertension: 77% of patients had systolic BP > 140 mmHg CHF: 15% Myocardial infarction: 10.5%	*Key Question 1) What is the prevalence of anemia in pre-ESRD?:* 16.3% of patients had Hgb < 9.5 mg/dl *Key Question 2) What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion?:* Not addressed *Key Question 3) What proportion of patients without nutritional deficiencies are resistant to EPO?:* Not addressed *Key Question 4) What proportion of pre-ESRD patients have low EPO levels?:* Not addressed *Key Question 5) What is the efficacy of EPO in improving intermediate and ultimate outcomes?:* Not addressed	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: Completely Dropouts discussed: Partially Sample size justified: No/not assessable 3) GFR/CrCl: Not assessable 4) % pre-ESRD: > 75% 5) Level of evidence: 2b Notes:

Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Howard, Moore, Welch, et al., 1989	Design: Cohort study (retrospective) Intervention(s) studied: None (simple and multiple regression analyses examining the relationship between anemia and CRF) Dates: Patients seen between July 1986 and June 1987 Location: Washington, DC Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 106 Inclusion criteria: Age > 18; chronic renal failure (SCr > 1.5 mg/dl); complete medical records Exclusion criteria: Rapid deterioration in renal function (change in SCr > 1.0 mg/dl/month); dialysis; previous transplantation; other causes of anemia Age (mean ± SEM): 56 ± 1.6 Sex: 66% M, 34% F Race: 63% Caucasian; 31% Black; 6% Oriental Renal function at entry (mean ± SEM): CrCl: 31.0 ± 1.6 ml/min/1.73 m^2 Scr: 3.7 ± 0.2 mg/dl Hgb at entry (mean ± SEM): 118 ± 2.6 g/l Hct at entry (mean ± SEM): 35.5 ± 0.7% EPO levels at entry: NR Nutritional parameters at entry: NR Co-morbidities at entry: Diabetes as cause of renal failure: 24.5% Hypertension as cause of renal failure: 35%	*Key Question 1) What is the prevalence of anemia in pre-ESRD?:* 12/83 (14.5%) patients with SCr > 2.0 mg/dl and ≤ 8.0 mg/dl had anemia (Hct < 30%). The prevalence of anemia varied by SCr level: 1/33 patients (3.0%) with SCr between 2.0 and 3.0 mg/dl were anemic, compared with 2/14 (14.3%) of those with SCr between 3.0 and 4.0, and 9/36 (25.0%) of those with SCr between 4 and 8. Mean Hgb (± SEM) in the cohort was 118 ± 2.6. *Key Question 2) What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion?:* Not addressed *Key Question 3) What proportion of patients without nutritional deficiencies are resistant to EPO?:* Not addressed *Key Question 4) What proportion of pre-ESRD patients have low EPO levels?:* Not addressed *Key Question 5) What is the efficacy of EPO in improving intermediate and ultimate outcomes?:* Not addressed	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: Completely Dropouts discussed: Completely Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 2b Notes: This study demonstrated that SCr and CrCl correlated with Hct imprecisely. Statistics on the prevalence of anemia are not clear. Data on prevalence of anemia (under Key Question 1) taken from Strauss, Port, Somen, et al., 1993.

Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Hsu, Bates, Kuperman, et al., 2001	Design: Cohort study (cross-sectional, retrospective, population-based) Intervention(s) studied: None (observational study) Dates: Jan 1990 - Dec 1998 Location: Boston, MA Recruitment setting: Primary care (hospital-based clinics, community health clinics, and a variety of community-based practices)	No. of pre-ESRD subjects: 12,055 (8,495 women and 3,560 men) Inclusion criteria: Adult (age ≥ 18) ambulatory patients; ≥ 2 SCr measurements, 2 or more years apart, during study period; weight recorded; Hct measured Exclusion criteria: None specified Age (mean ± SD): Women, 49 ± 16; men, 51 ± 15 Sex: 30% M, 70% F Race: Women / Men White 45% / 44% Black 27% / 22% Other/unknown 28% / 34% Renal function at entry (mean ± SD): CrCl (ml/min): Women: 85 ± 39 Men: 89 ± 32 SCr (mg/dl): Women: 1.0 ± 0.4 Men: 1.3 ± 0.7 Hgb at entry (mean ± SD; g/dl): Women: 12.9 ± 1.3 Men: 14.3 ± 1.4 Hct at entry (mean ± SD): Women: 38.7 ± 3.6% Men: 42.8 ± 4.0% EPO levels at entry: NR Nutritional parameters at entry: Serum albumin (mean ± SD; g/dl): Women (n = 8,255): 4.3 ± 0.4	*Key Question 1) What is the prevalence of anemia in pre-ESRD?:* Not addressed *Key Question 2) What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion?:* Not addressed *Key Question 3) What proportion of patients without nutritional deficiencies are resistant to EPO?:* Not addressed *Key Question 4) What proportion of pre-ESRD patients have low EPO levels?:* Not addressed *Key Question 5) What is the efficacy of EPO in improving intermediate and ultimate outcomes?:* Not addressed	Quality Scoring: 1) Global assessment: Good 2) Validity criteria: Population described: Partially Incl/excl described: Partially Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: < 50% 5) Level of evidence: 2b Note: 741/12,055 subjects (6%) had a GFR ≤ 50 ml/min/1.73 m^2.

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Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
		Men (n = 3,462): 4.5 ± 0.4 Co-morbidities at entry: NR		

Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Kaizu, Uriu, and Eto, 1993	Design: Prospective clinical trial (before/after study) Intervention(s) studied: Intravenous EPO 6,000 IU once per week for 8 weeks (freeze-dried epoetin beta preparation dissolved in saline). IV iron (ferric oxide 40 mg) also given once per week. Dates: May 1990 – Mar 1991 Location: Kitakyushu, Japan Recruitment setting: Nephrology department/clinic	No. of pre-ESRD subjects: 11 Inclusion criteria: Pre-dialysis ESRD; renal anemia; no blood transfusion in 2 weeks prior to start of study Exclusion criteria: None specified Age (mean ± SEM): 62.3 ± 4.6 Sex: 36% M, 64% F Race: NR Renal function at entry (mean ± SEM): CrCl: 16.1 ± 6.2 ml/min SCr: 5.15 ± 0.6 mg/dl Hgb at entry (mean ± SEM): 7.76 ± 0.34 g/dl Hct at entry (mean ± SEM): 23.5 ± 1.0% EPO levels at entry: NR Nutritional parameters at entry (mean ± SEM): Serum iron: 91.6 ± 18.54 µg/dl Total IBC: 157.5 ± 21.29 µg/dl Serum ferritin: 239.8 ± 61.22 ng/dl Co-morbidities at entry: Diabetes: 18%	*Key Question 1) What is the prevalence of anemia in pre-ESRD?:* Not addressed *Key Question 2) What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion?:* Not addressed *Key Question 3) What proportion of patients without nutritional deficiencies are resistant to EPO?:* Not addressed *Key Question 4) What proportion of pre-ESRD patients have low EPO levels?:* Not addressed *Key Question 5) What is the efficacy of EPO in improving intermediate and ultimate outcomes?:* a) Hgb and Hct: Treatment with EPO significantly increased Hgb and Hct (results reported only graphically; quantitative data could not be transcribed). b) Renal function: There was no significant difference between the reciprocal changes in SCr concentrations before (-0.660 ± 0.2477 x 10^{-3} dl/mg/day) and after (-0.117 ± 0.1999 x 10^{-3} dl/mg/day EPO therapy (slope of the regression line of 1/Cr over time; mean ± SEM). c) Coagulation, fibrinolytic and platelet systems: There were no significant changes in PT, APTT, fibrinogen, thrombin, FDP, plasmin inhibitor complex, or platelet throbogloburin after treatment with EPO. d) Iron: Serum iron levels were significantly decreased after EPO therapy. e) Adverse effects: 1/11 patients (9%) reported an adverse effect of EPO (upper abnormal pain)	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: No/not assessable Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Measured by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 2b Notes:

Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Kamper and Nielsen, 1990	Design: RCT Intervention(s) studied: 1) Enalapril (n = 27). Dose started at 2.5 mg, then increased depending on BP response and level of renal function. Mean dose 9.4 mg (range, 2.5-40). Other anti-hypertensive drugs given as needed. 2) Control = "conventional antihypertensive treatment" (n = 32). In both groups, therapeutic goal was systolic BP of 120-140 mmHg and diastolic BP of 80-90 mmHg. Patients followed for 90 days. Dates: NR Location: Copenhagen, Denmark Recruitment setting: Nephrology clinic or department	No. of pre-ESRD subjects: 59 Inclusion criteria: Progressive chronic nephropathy; SCr 150-900 µmol/l Exclusion criteria: Steroid or NSAID therapy Age: Median, 46 (enalapril) and 49 (control); range, 25-75 Sex: 54% M, 46% F Race: NR Renal function at entry: GFR (median, with range; ml/min/ 1.73 m^2): Enalapril: 15 (6-54) Control: 19 (7-47) SCr (median, with range; µmol/l): Enalapril: 375 (150-806) Control: 397 (184-862) Hgb at entry (median, with range; mmol/l): Enalapril: 7.6 (5.7-10.8) Control: 7.6 (4.9-10.2) Hct at entry: NR EPO levels at entry (median, with range; U/l): Enalapril: 32 (10-59) Control: 34 (11-86) Nutritional parameters at entry: NR Co-morbidities at entry: NR	*Key Question 1) What is the prevalence of anemia in pre-ESRD?:* Median Hgb at entry only relevant data reported (see under "Patient Population," at left) *Key Question 2) What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion?:* Not addressed *Key Question 3) What proportion of patients without nutritional deficiencies are resistant to EPO?:* Not addressed *Key Question 4) What proportion of pre-ESRD patients have low EPO levels?:* Median EPO levels at entry only relevant data reported (see under "Patient Population," at left) *Key Question 5) What is the efficacy of EPO in improving intermediate and ultimate outcomes?:* Not addressed	Quality Scoring: 1) Global assessment: Excellent 2) Validity criteria: Population described: No/not assessable Incl/excl described: Partially Dropouts discussed: Completely Sample size justified: No/not assessable 3) GFR/CrCl: Measured by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 2b Notes:

Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Kazmi, Kausz, Khan, et al., 2001	Design: Cohort study (retrospective) Intervention(s) studied: None (observational study). Patients followed from time of first visit after Oct 1, 1994 until initiation of dialysis, transplantation, death, transfer to another facility, loss to follow-up, or end of study. Median follow-up, 5.7 months (range, 0.2 to 47.9 months). Dates: Oct 1, 1994 - Sep 30, 1998 Location: 5 sites in Greater Boston area Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 545 Inclusion criteria: Age > 18; SCr persistently > 1.5 mg/dl (women) or 2.0 mg/dl (men) for at least 6 months; outpatient visit during study period; at least one Hct level recorded during study period Exclusion criteria: None specified Age (mean ± SD): 63 ± 16 Sex: 53% M, 47% F Race: 81% White, 7% Black, 9% Asian, 3% other Renal function at entry (mean ± SD): GFR: 23.1 ± 9.3 ml/min/1.73 m^2 SCr: 3.0 ± 1.5 mg/dl Hgb at entry: NR Hct at entry (mean ± SD): 34.9 ± 5.6 EPO levels at entry: NR Nutritional parameters at entry: NR Co-morbidities at entry: NR	*Key Question 1) What is the prevalence of anemia in pre-ESRD?:* In the 19% of patients who underwent iron studies, 54% met criteria for iron deficiency (transferrin saturation < 20%). 45% of patients with SCr ≤ 2 mg/dl had Hct < 36%; 8% had Hct < 30%. Linear regression analysis showed that for every 10-ml/min decrease in CrCl, there was a 3.1% drop in Hct. Hct ≥ 36% was maintained only among patients with a mean predicted GFR of 27.4 ml/min or greater. *Key Question 2) What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion?:* Not addressed *Key Question 3) What proportion of patients without nutritional deficiencies are resistant to EPO?:* Not addressed *Key Question 4) What proportion of pre-ESRD patients have low EPO levels?:* Not addressed *Key Question 5) What is the efficacy of EPO in improving intermediate and ultimate outcomes?:* Not addressed	Quality Scoring: 1) Global assessment: Good 2) Validity criteria: Population described: Completely Incl/excl described: Partially Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: 50-75% 5) Level of evidence: 2b Notes:

Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Kleinman, Schweitzer, Perdue, et al., 1989	Design: RCT Intervention(s) studied: 1) Placebo (n = 7) 2) EPO 100 U/kg (n = 7) Both treatments administered subcutaneously 3 times per week, at no less than 48-hour intervals, for 12 weeks or until a target Hct of 38-40% attained. Dates: NR Location: Van Nuys, CA Recruitment setting: NR	No. of pre-ESRD subjects: 14 Inclusion criteria: Chronic renal insufficiency of at least 3 months' duration; SCr 265 -972 µmol/l; clinically stable; constant diet and medication for ≥ 2 weeks prior to start of study; stable lab values; adequate serum folate levels, B12 levels, and iron stores; no evidence of chronic GI blood loss Exclusion criteria: Marked obesity; active hepatitis or hepatic disease; asthma; severe atopic illness; significant cardiovascular, pulmonary, malignant, or hematologic diseases; severe or uncontrolled hypertension (supine diastolic BP > 110 mmHg); neurological disease; history of seizures; gross hematuria; sickle cell anemia; untreated ischemic heart disease; clinically significant GI disease; conditions that might interfere with the effects of EPO; thrombocytopenia or leukopenia; alcohol or drug abuse; acute illness within 7 days of screening period; use of androgen within prior 2 months; use of immunosuppressive medications within prior month Age: Mean, 57.9; range, 38-73 Sex: 64% M, 36% F Race: NR Renal function at entry: NR Hgb at entry: NR Hct at entry (mean):	*Key Question 1) What is the prevalence of anemia in pre-ESRD?:* Not addressed *Key Question 2) What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion?:* Not addressed *Key Question 3) What proportion of patients without nutritional deficiencies are resistant to EPO?:* Not addressed *Key Question 4) What proportion of pre-ESRD patients have low EPO levels?:* Not addressed *Key Question 5) What is the efficacy of EPO in improving intermediate and ultimate outcomes?:* a) Blood pressure: There were no significant differences between the two treatment groups in systolic or diastolic BP at baseline or in change in systolic or diastolic BP from 0-12 weeks as measured by slopes. b) Slope of 1/SCr: There were no significant differences between the two treatment groups in 1/SCr at baseline, and no significant differences in average change in 1/SCr per week as measured by individual slope parameters. c) Quality of life (mean scores ± SD; level of energy, ability to do work, and overall quality of life): Baseline / 12 weeks Placebo: 38 ± 16 / 33 ± 21 EPO: 40 ± 22 / 68 ± 22 p = 0.03	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: Partially Incl/excl described: Completely Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Not assessable 4) % pre-ESRD: > 75% 5) Level of evidence: 2b Note: Study underpowered for BP and 1/SCr endpoints.

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Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
		Placebo: 28.2% EPO: 28.1% EPO levels at entry: NR Nutritional parameters at entry (mean): Serum transferrin saturation: Placebo: 24.2% EPO: 28.3% Serum ferritin (ng/ml): Placebo: 239.4 EPO: 406.3 Co-morbidities at entry: NR		

Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Koch, Koene, Messinger, et al., 1995	Design: Prospective clinical trial (before/after study) Intervention(s) studied: Subcutaneous EPO, given according to one of the following regimens: 1) 3 times per week (n = 48): 3 x 1,000 IU per week if body weight ≤ 75 kg; 3 x 2,000 IU per week if body weight > 75 kg to target Hct of 33-37%; dose reduced thereafter. 2) Daily (n = 177): 7 x 500 IU per week if body weight ≤ 75 kg; 7 x 1,000 IU per week if body weight > 75 kg to target Hct of 33-37%; dose reduced thereafter. Median duration of therapy was 211 days (range, 105-350). Dates: NR Location: Multiple sites in Germany and The Netherlands Recruitment setting: Not specified/unable to determine	No. of pre-ESRD subjects: 275 enrolled; 266 included in safety analysis; 225 included in efficacy analysis Inclusion criteria: Adult pre-dialysis patients with renal anemia (Hct < 30%) and stable chronic renal failure; 8-10 SCr values available from the last 1-4 years Exclusion criteria: Epilepsy; thrombocytosis; poorly controlled hypertension; iron, vitamin B12, or folic acid deficiency; malignant tumor; acute or chronic infection Age (median, with interquartile range): 56 (46-66) Sex: 37% M, 63% F Race: NR Renal function at entry: SCr: Median, 6.0 mg/dl ≤ 4 mg/dl: 20% > 4 to ≤ 6 mg/dl: 35% > 6 mg/dl: 45% Hgb at entry (median, with inter-quartile range): 8.6 g/dl (7.8 to 9.1) Hct at entry (median, with inter-quartile range): 25.6% (23.7% to 27.4%) EPO levels at entry: NR Nutritional parameters at entry (median): Serum transferring saturation: 21% Serum ferritin: 143.0 µg/ml	*Key Question 1) What is the prevalence of anemia in pre-ESRD?:* Not addressed *Key Question 2) What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion?:* Not addressed *Key Question 3) What proportion of patients without nutritional deficiencies are resistant to EPO?:* Not addressed *Key Question 4) What proportion of pre-ESRD patients have low EPO levels?:* Not addressed *Key Question 5) What is the efficacy of EPO in improving intermediate and ultimate outcomes?:* a) Blood pressure: 24% of patients showed a hypertensive reaction to EPO during the correction stage, an additional 26% in the maintenance phase. b) Renal function: Difference in slope of 1/SCr (x 10^{-4} dl/mg) from baseline to post-treatment (median, with interquartile range; n = 253): Baseline: -1.828 (-3.652 to -1.001) Post-treatment: -1.660 (-4.626 to -0.353) Median difference: 0.303 (-1.858 to 1.838; p = 0.854) c) Iron: Iron supplementation was required during the course of treatment by 40/135 patients not taking iron at start of study. d) Adverse events: 44/250 reported AEs were classified as possibly related to EPO administration.	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: Partially Dropouts discussed: Partially Sample size justified: No/not assessable 3) GFR/CrCl: Not assessable 4) % pre-ESRD: > 75% 5) Level of evidence: 2b Notes:

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Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
		Co-morbidities at entry: Diabetes as cause of CKD: 17%		

Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Kulzer, Schaefer, Krahn, et al., 1994	Design: Cohort study (prospective) Intervention(s) studied: Subcutaneous EPO 50 U/kg 3 times per week for 24 weeks, with dose adjustments as needed to achieve and maintain target Hgb of 10-12 g/dl. Maximum weekly dose 300 U/kg. EPO administration discontinued if Hgb > 12 g/dl. Dates: NR Location: 15 sites in Denmark, Finland, France, Germany, Norway, and Sweden Recruitment setting: Not specified/unable to determine	No. of pre-ESRD subjects: 75 Inclusion criteria: Chronic renal failure (SCr 350-800 µmol/l); anemia (Hgb < 9.0 g/dl); slow decline in renal function (rise in SCr ≤ 20% in last 3 months); clinically stable Exclusion criteria: Other causes of anemia; uncorrected folate, vitamin B12, or iron deficiencies; use of corticosteroids, androgens, or other drugs known to affect erythropoiesis; uncontrolled hypertension; severe secondary hyperparathyroidism; aluminum intoxication; uncontrolled diabetes; lipodystrophy caused by insulin injection Age (mean ± SD): 56 ± 15 Sex: 53% M, 47% F Race: 97% White, 1% Black, 1% Oriental Renal function at entry: SCr (mean ± SD): 599.68 ± 167.50 µmol/l Hgb at entry: Mean NR; 28/75 patients (37%) had a baseline Hgb < 8 g/dl, 47/75 (63%) had a baseline Hgb ≥ 8 g/dl Hct at entry (mean ± SD): 24.73 ± 2.68% EPO levels at entry: NR Nutritional parameters at entry: Serum albumin (mean ± SD): 38.77 ± 5.40 g/dl	*Key Question 1) What is the prevalence of anemia in pre-ESRD?:* Not addressed *Key Question 2) What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion?:* Not addressed *Key Question 3) What proportion of patients without nutritional deficiencies are resistant to EPO?:* Not addressed *Key Question 4) What proportion of pre-ESRD patients have low EPO levels?:* Not addressed *Key Question 5) What is the efficacy of EPO in improving intermediate and ultimate outcomes?:* a) Hct: Mean change (± SD) from baseline to 12 weeks (n = 66): 9.30 ± 4.50% (p < 0.001) Mean change (± SD) from baseline to 24 weeks (n = 54): 7.47 ± 5.04% (p < 0.001) b) Hgb: 64/75 patients (85%) achieved the target Hgb of 10-12 g/dl and did so in a mean time (± SD) of 6.8 ± 5.2 weeks on a mean EPO dose (± SD) of 158.1 ± 50.5 U/kg. 75% of patients with baseline Hgb < 8 g/dl achieved the target, as did 92% of patients whose baseline Hgb was ≥ 8 g/dl. c) Blood pressure: Diastolic BP (mmHg): Baseline (mean ± SD): 82.3 ± 8.4 Mean change from baseline to 12 weeks (± SD): + 2.5 ± 11.2 (p = 0.061)	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: Partially Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Not assessable 4) % pre-ESRD: > 75% 5) Level of evidence: 2b Note: 23/75 patients (31%) dropped out before 24 weeks, 17 (23%) because of a need for dialysis.

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Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
		Co-morbidities at entry: Diabetes as cause of CRF: 8% Hypertension as cause of CRF: 27%	Mean change from baseline to 24 weeks (± SD): + 2.0 ± 10.3 (p = 0.076) Systolic BP (mmHg): Baseline (mean ± SD): 147.7 ± 20.9 Mean change from baseline to 12 weeks (± SD): - 0.8 ± 18.8 (p = 0.996) Mean change from baseline to 24 weeks (± SD): + 2.0 ± 10.3 (p = 0.076) 6/75 patients (8%) reported worsening of hypertension as an AE. d) Renal function: SCr (µmol/l): Baseline (mean ± SD): 599.68 ± 167.50 Change from baseline to 12 weeks (mean ± SD): + 64.94 ± 86.38 (p = 0.020) Change from baseline to 24 weeks (mean ± SD): + 130.37 ± 174.86 (p = 0.006) Slope of 1/SCr during treatment with EPO similar to the pre-study phase. e) Adverse events: 31/75 patients (41%) reported ≥ 1 AE.	

Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Kuriyama, Hopp, Yoshida, et al., 1996	Design: Cohort study (prospective) Intervention(s) studied: Intravenous EPO 6,000 units once per week for 16 weeks (n = 16). IV iron given as appropriate. All patients put on low-protein diet. Dates: NR Location: Tokyo, Japan Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 16 of 20 patients completed treatment and were included in the analysis Inclusion criteria: Chronic renal failure at the pre-dialysis stage; SCr 2-5 mg/dl; anemia secondary to renal failure Exclusion criteria: None specified Age: Mean, 57; range, 32-70 Sex: 50% M, 50% F Race: NR Renal function at entry (mean ± SD): CrCl: 15 ± 4 ml/min/1.73 m^2 SCr: 3.8 ± 1.0 Hgb at entry (mean, estimated from graph): 9.2 g/dl Hct at entry (mean ± SD): 27.1 ± 2.6% EPO levels at entry: NR Nutritional parameters at entry: nr Co-morbidities at entry: Diabetes as cause of CRF: 40%	*Key Question 1) What is the prevalence of anemia in pre-ESRD?:* Not addressed *Key Question 2) What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion?:* Not addressed *Key Question 3) What proportion of patients without nutritional deficiencies are resistant to EPO?:* Not addressed *Key Question 4) What proportion of pre-ESRD patients have low EPO levels?:* Not addressed *Key Question 5) What is the efficacy of EPO in improving intermediate and ultimate outcomes?:* a) Hct and Hgb: Both increased significantly during treatment ($p < 0.05$, 12 weeks vs. baseline; $p < 0.01$, 16 weeks vs. baseline). Mean Hct (± SD) rose from 27.1 ± 2.6% to 34.6 ± 3.2% ($p < 0.001$) (Hgb data reported in graphical form only and could not be reliably transcribed.) b) Blood pressure (mean ± SD, in mmHg): Systolic BP: Baseline: 137 ± 19 16 weeks: 136 ± 12 p = not significant Diastolic BP: Baseline: 79 ± 8 16 weeks: 76 ± 9 p = not significant c) Thrombomodulin concentration (mean ± SD; n = 16): Baseline: 7.9 ± 2.8 ng/ml	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: Partially Dropouts discussed: Completely Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: < 50%/not assessable 5) Level of evidence: 2b Note: 4/20 patients dropped out after the study started because they were unable to receive periodical EPO injections.

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Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			16 weeks: 6.6 ± 2.4 ng/ml p < 0.01 d) SCr (mean ± SD): Baseline: 3.8 ± 1.0 mg/dl 16 weeks: 4.4 ± 1.6 mg/dl p = not significant e) A positive correlation was found between thrombomodulin concentration and SCr (r = 0.61; p < 0.05), but no correlation was found between endothelin-1 concentration and SCr.	

Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Kuriyama, Tomonari, Yoshida, et al., 1997	Design: RCT Intervention(s) studied: 1) No treatment (n = 31). 2) Intravenous EPO (n = 42). Initial dose 6,000 IU once per week; dose could be decreased on a monthly basis over 36 weeks. When Hct reached 38%, dose adjusted to maintain it at a level of 33-35%. All patients completed an 8-week stabilization period before the start of the trial to achieve control of BP and nutritional parameters. Daily protein intake 0.6 g/kg/day and daily salt intake of 7 g/day prescribed for all patients. Iron therapy could be started at the discretion of the physician. Dates: Trial began Jan 1993 Location: Tokyo, Japan Recruitment setting: Hospital	No. of pre-ESRD subjects: 73 Inclusion criteria: Outpatient; age 30-75; SCr 2-4 mg/dl; predialysis; Hct < 30%; systolic and diastolic BP < 160 and 95 mmHg, respectively, at end of pre-study stabilization period Exclusion criteria: Iron deficiency anemia; transfusion dependency; any other systemic disease; any other inflammatory condition or infection that might interfere with the effect of EPO Age (mean ± SD): Control, 59.2 ± 13.4; EPO, 63.8 ± 10.6 Sex: Control, 52% M, 48% F; EPO, 55% M, 45% F Race: NR Renal function at entry (mean ± SD): CrCl (ml/min): Control: 17.1 ± 7.2 EPO: 19.1 ± 7.2 SCr (mg/dl): Control: 3.0 ± 0.7 EPO: 2.9 ± 0.7 Hgb at entry: NR Hct at entry (mean ± SD): Control: 27.9 ± 1.8% EPO: 27.0 ± 2.3% (see Note) EPO levels at entry: NR Nutritional parameters at entry: Serum albumin (mean ± SD, g/dl): Control: 3.3 ± 0.3	*Key Question 1) What is the prevalence of anemia in pre-ESRD?:* Not addressed *Key Question 2) What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion?:* Not addressed *Key Question 3) What proportion of patients without nutritional deficiencies are resistant to EPO?:* Not addressed *Key Question 4) What proportion of pre-ESRD patients have low EPO levels?:* Not addressed *Key Question 5) What is the efficacy of EPO in improving intermediate and ultimate outcomes?:* a) Hct (mean ± SD): 0 weeks / 36 weeks Control: 27.9 + 1.8% / 25.3 ± 1.9% EPO: 27.0 ± 2.3%* / 35.5 ± 4.4%* Control, 36 weeks vs. baseline, p < 0.001 (decrease) EPO, 36 weeks vs. baseline, p < 0.001 (increase) * See Note, at right b) Renal function: Cumulative renal survival rate (derived from time it took to double baseline SCr) was significantly better in the EPO group than in the control group (p = 0.0003; results depicted only in figure). Within the EPO group, renal survival rates were significantly better among non-diabetics (n = 19) than among diabetics (n = 23) (p = 0.0038).	Quality Scoring: 1) Global assessment: Good 2) Validity criteria: Population described: No/not assessable Incl/excl described: Partially Dropouts discussed: Completely Sample size justified: No/not assessable 3) GFR/CrCl: Measured by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 1b Notes: Study included an additional no-treatment (and nonrandomized) control group of patients who had chronic renal failure but did *not* have anemia (n = 35). Results for this group are not reported here. Article gives 2 different values for baseline Hct in EPO group: 27.0 ± 2.3% (abstract and Table 1) and 25.5 ± 7.8% (p. 179). Also gives 2 different values for end-of-treatment Hct in EPO group: 32.1 ± 3.2% (abstract) and 35.5 ± 4.4% (p. 179).

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Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
		EPO: 3.2 ± 0.4 Co-morbidities at entry: Diabetes: 55% Antihypertensive medication: 69%		

Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Lim, DeGowin, Zavala, et al., 1989	Design: RCT Intervention(s) studied: 1) Placebo administered intravenously 3 times per week for 8 weeks (n = 3). 2) Intravenous EPO 50 U/kg 3 times per week for 8 weeks (n = 3). 3) Intravenous EPO 100 U/kg 3 times per week for 8 weeks (n = 4). 4) Intravenous EPO 150 U/kg 3 times per week for 8 weeks (n = 4). EPO doses unchanged throughout trial. If Hct reached 0.41, then EPO suspended temporarily until Hct fell below 0.35 again. Dates: NR Location: Iowa City, IA Recruitment setting: Hospital	No. of pre-ESRD subjects: 14 Inclusion criteria: Progressive renal insufficiency; anemia; normal nutritional status Exclusion criteria: Active lupus; malignancy; hemolysis; bleeding; clinically unstable; use of steroid or immunosuppressive medication Age: Range, 30-70 Sex: 71% M, 29% F Race: NR Renal function at entry: SCr: Range, 265 to 1,061 µmol/l Hgb at entry: Range, 59-102 g/l Hct at entry: Range, 0.17-0.29 EPO levels at entry: NR Nutritional parameters at entry: NR Co-morbidities at entry: Diabetes as cause of renal insufficiency: 21%	*Key Question 1) What is the prevalence of anemia in pre-ESRD?:* Not addressed *Key Question 2) What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion?:* Not addressed *Key Question 3) What proportion of patients without nutritional deficiencies are resistant to EPO?:* Not addressed *Key Question 4) What proportion of pre-ESRD patients have low EPO levels?:* Not addressed *Key Question 5) What is the efficacy of EPO in improving intermediate and ultimate outcomes?:* a) Hct (mean): Placebo: Baseline 0.27, 8 Weeks 0.24 EPO 50 U/kg: Baseline 0.27, 8 Weeks 0.35 EPO 100 U/kg: Baseline 0.27, 8 Weeks 0.36 EPO 150 U/kg: Baseline 0.28, 8 Weeks 0.41 Placebo, 8 weeks vs. baseline, p = not significant. EPO groups combined, 8 weeks vs. baseline, $p < 0.0001$. At 8 weeks, significant differences among all the groups except the 50- and 100-U/kg EPO groups. b) Exercise tolerance (n = 1 placebo patient and 7 EPO patients [all doses combined]): Placebo: Patient analyzed "showed a slight decrease in exercise tolerance at the end of week 8" EPO: O_2 consumption at anerobic threshold (Vo_2 AT; mean ± SD): Baseline: 9.23 ± 1.05 ml/min x kg	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: Partially Incl/excl described: Partially Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Not assessable 4) % pre-ESRD: > 75% 5) Level of evidence: 2b Note: Placebo results reported only for some outcomes.

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Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			8 weeks: 9.94 ± 1.03 ml/min x kg p < 0.02 O_2 consumption at maximal work rate (Vo_2 max; mean ± SD): Baseline: 16.0 ± 1.8 ml/min x kg 8 weeks: 17.5 ± 1.9 ml/min x kg p < 0.002 c) Blood pressure (EPO-treated patients only [and combined]): Systolic BP (mean ± SEM): Baseline: 144 ± 5 mmHg 8 weeks: 144 ± 4 mmHg Diastolic BP (mean ± SEM): Baseline: 77 ± 2 mmHg 8 weeks: 75 ± 2 mmHg Antihypertensive medications were increased in 3 patients. d) SCr (mean ± SEM; EPO-treated patients only [and combined]): Baseline: 473 ± 61 µmol/l 8 weeks: 518 ± 46 µmol/l	

Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
McGonigle, Wallin, Shadduck, et al., 1984	Design: Cohort study (prospective) Intervention(s) studied: None Dates: NR Location: New Orleans, LA Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 60 Inclusion criteria: Renal insufficiency Exclusion criteria: Dialysis; oral androgen therapy Age (mean ± SEM): 54 ± 2.0 Sex: 70% M, 30% F Race: NR Renal function at entry: SCr: Range, 1.6 to 10.9 mg/dl Hgb at entry: NR Hct at entry: Range, 16.5% to 52% EPO levels at entry (mean ± SEM): 34.67 ± 6.7 mU/ml Nutritional parameters at entry: NR Co-morbidities at entry: Diabetes as cause of CKD: 15% Hypertension as cause of CKD: 32%	*Key Question 1) What is the prevalence of anemia in pre-ESRD?:* 16/55 (29.1%) patients with SCr > 2.0 mg/dl and ≤ 8.0 mg/dl had anemia (Hct < 30%). The prevalence of anemia varied by SCr level: 0/11 patients with SCr between 2.0 and 3.0 mg/dl were anemic, compared with 2/10 (20.0%) of those with SCr between 3.0 and 4.0, and 14/33 (42.4%) of those with SCr between 4 and 8. *Key Question 2) What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion?:* Not addressed *Key Question 3) What proportion of patients without nutritional deficiencies are resistant to EPO?:* There was a relative EPO deficiency among chronic renal insufficiency (CRI) patients (mean ± SEM): CRI patients (n = 60): 34.7 ± 6.7 mU/ml Normal controls (n = 40): 23.1 ± 0.98 mU/ml *Key Question 4) What proportion of pre-ESRD patients have low EPO levels?:* Not addressed *Key Question 5) What is the efficacy of EPO in improving intermediate and ultimate outcomes?:* Not addressed	Quality Scoring: 1) Global assessment: Good 2) Validity criteria: Population described: Partially Incl/excl described: No/not assessable Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Not assessable 4) % pre-ESRD: < 50%/not assessable 5) Level of evidence: 2b Notes: Data on prevalence of anemia (under Key Question 1) taken from Strauss, Port, Somen, et al., 1993.

Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Mitwalli, Abuaisha, Al Wakeel, et al., 1993	Design: Prospective clinical trial (before/after study) Intervention(s) studied: Subcutaneous EPO 50 U/kg twice per week for 4 weeks, then 25 U/kg twice per week to the end of the study at 12 weeks. Target Hgb 100-120 g/l; target Hct 32-38%. EPO therapy suspended temporarily if Hct exceeded the target range. Dates: NR Location: Riyadh, Saudi Arabia Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 21 Inclusion criteria: Age > 18; chronic renal failure; SCr 200-900 µmol/l; CrCl 12-40 ml/min; Hgb < 90 g/l Exclusion criteria: Need for dialysis; anemia due to severe iron deficiency; chronic liver disease; chronic infections; blood dyscrasias Age: Mean, 34; range, 22-89 Sex: 62% M, 38% F Race: NR Renal function at entry (median): CrCl: 18 ml/min SCr: 453 µmol/l Hgb at entry (median): 71 g/l Hct at entry (median): 25% EPO levels at entry: NR Nutritional parameters at entry (median): Serum iron: 13.7 µmol/l Serum ferritin: 262 µg/l Co-morbidities at entry: Diabetes: 14%	*Key Question 1) What is the prevalence of anemia in pre-ESRD?:* Not addressed *Key Question 2) What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion?:* Not addressed *Key Question 3) What proportion of patients without nutritional deficiencies are resistant to EPO?:* Not addressed *Key Question 4) What proportion of pre-ESRD patients have low EPO levels?:* Not addressed *Key Question 5) What is the efficacy of EPO in improving intermediate and ultimate outcomes?:* a) Hct (median): Baseline: 25% 12 weeks: 37% p = 0.001 b) Hgb (median): Baseline: 71 g/l 12 weeks: 110 g/l p = 0.001 c) Blood pressure: Diastolic BP (median): Baseline: 87 mmHg 12 weeks: 83 mmHg p = not significant 7 patients (33%) had a mild increase in BP necessitating an increase in antihypertensive medication.	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: Partially Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Measured by investigators 4) % pre-ESRD: 50-75% 5) Level of evidence: 2b Note: Study underpowered.

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Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			d) Renal function: CrCl (median): Baseline: 18 ml/min 12 weeks: 20 ml/min p = not significant 1/SCr slope: Baseline: 0.018 12 weeks: 0.021 p = not significant	

Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Nishikage, Kosugi, Danbara, et al., 2000	Design: Prospective clinical trial (before/after study) Intervention(s) studied: Intravenous EPO 6,000 U per week until target Hct of 30% achieved, then 3,000 units per week thereafter. Dates: NR Location: Nagoya, Japan Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 27 at baseline and 3 months; 20 or 21 (precise number uncertain) at 6 months Inclusion criteria: Chronic renal failure; renal anemia; pre-dialysis Exclusion criteria: Diabetes mellitus Age (mean ± SD): 63 ± 15 Sex: NR Race: NR Renal function at entry: Estimated CrCl: Mean, 9.48 SCr (mean ± SD): 5.3 ± 2.0 mg/dl Hgb at entry: NR Hct at entry (mean ± SD): 24.2 ± 2.6% EPO levels at entry: NR Nutritional parameters at entry (mean ± SD): Serum transferrin: 197 ± 42 mg/dl Serum albumin: 3.7 ± 0.5 g/dl Co-morbidities at entry: NR	*Key Question 1) What is the prevalence of anemia in pre-ESRD?:* Not addressed *Key Question 2) What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion?:* Not addressed *Key Question 3) What proportion of patients without nutritional deficiencies are resistant to EPO?:* Not addressed *Key Question 4) What proportion of pre-ESRD patients have low EPO levels?:* Not addressed *Key Question 5) What is the efficacy of EPO in improving intermediate and ultimate outcomes?:* a) Hct (mean ± SD): Baseline (n = 27): 24.2 ± 2.6% 3 months (n = 27): 29.6 ± 4.5% (p < 0.01 vs. baseline) 6 months (n = 20 or 21): 28.4 ± 4.2% (p < 0.01 vs. baseline) b) Amino acid measures: Non-essential amino acids (mean ± SD, in nmol/ml): Baseline (n = 27): 2,313 ± 414 3 months (n = 27): 2,231 ± 301 6 months (n = 20 or 21): 2,268 ± 196 p = not significant (3 months vs. baseline, 6 months vs. baseline) Essential amino acids (mean ± SD, in nmol/ml): Baseline (n = 27): 745 ± 118 3 months (n = 27): 735 ± 103 6 months (n = 20 or 21): 732 ± 76 p = not significant (3 months vs. baseline, 6 months vs.	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: Partially Dropouts discussed: Completely Sample size justified: No/not assessable 3) GFR/CrCl: SCr 4) % pre-ESRD: < 50%/not assessable 5) Level of evidence: 4 Notes: 6 or 7 patients (precise number uncertain) started hemodialysis between 3 and 6 months after start of treatment and were not included in the 6-month evaluation. Study also included 19 “control” patients, who were, however, not described.

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Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			baseline) Branched chain amino acids (mean ± SD, in nmol/ml): Baseline (n = 27): 303 ± 56 3 months (n = 27): 303 ± 54 6 months (n = 20 or 21): 301 ± 40 p = not significant (3 months vs. baseline, 6 months vs. baseline)	

Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Portolés, Torralbo, Martin, et al., 1997	Design: Prospective clinical trial (before/after study) Intervention(s) studied: Self-administered subcutaneous EPO. Initial dose 1,000 U three times per week for patients with body weight < 75 kg and 2,000 U three times per week for patients with body weight > 75 kg. Dose adjusted according to fortnightly Hct determinations (target Hct 35%). Dates: NR Location: Madrid, Spain Recruitment setting: Not specified/unable to determine	No. of pre-ESRD subjects: 11 Inclusion criteria: ESRD; Hct < 30%; symptomatic anemia Exclusion criteria: Dialysis expected within 8 months based on assessment of the regression line of 1/SCr versus time; poorly controlled high BP; arrhythmia; valvular disease; any other condition that might affect echocardiographic follow-up Age (mean ± SEM): 53.8 ± 12.9 Sex: 55% M, 45% F Race: NR Renal function at entry (mean ± SEM): CrCl: 13.3 ± 1.5 ml/min SCr: 6.3 ± 1.3 mg/dl Hgb at entry (mean ± SEM): 9.0 ± 0.3 g/dl Hct at entry (mean ± SEM): 26.3 ± 0.8% EPO levels at entry: NR Nutritional parameters at entry: NR Co-morbidities at entry: Antihypertensive medication: 73%	*Key Question 1) What is the prevalence of anemia in pre-ESRD?:* Not addressed *Key Question 2) What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion?:* Not addressed *Key Question 3) What proportion of patients without nutritional deficiencies are resistant to EPO?:* Not addressed *Key Question 4) What proportion of pre-ESRD patients have low EPO levels?:* Not addressed *Key Question 5) What is the efficacy of EPO in improving intermediate and ultimate outcomes?:* a) Hct (mean ± SEM, %): Baseline: 26.3 ± 0.8 3 months: 34.4 ± 1.1 6 months: 34.7 ± 1.3 p < 0.001 b) Hgb (mean ± SEM, g/dl): Baseline: 9.0 ± 0.3 3 months: 11.6 ± 0.4 6 months: 11.7 ± 0.4 p < 0.001 c) Blood pressure (mean ± SEM, in mmHg): Systolic BP – daytime: Baseline: 142.1 ± 8.1 3 months: 140.0 ± 7.0 6 months: 144.2 ± 9.5 p = not significant	Quality Scoring: 1) Global assessment: Good 2) Validity criteria: Population described: No/not assessable Incl/excl described: Partially Dropouts discussed: Partially Sample size justified: No/not assessable 3) GFR/CrCl: Measured by investigators 4) % pre-ESRD: < 50%/not assessable 5) Level of evidence: 2b Notes:

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Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			Systolic BP – nighttime: Baseline: 132.7 ± 7.8 3 months: 127.5 ± 7.1 6 months: 137.0 ± 9.5 p = not significant Diastolic BP – daytime: Baseline: 80.7 ± 5.5 3 months: 82.1 ± 4.0 6 months: 81.7 ± 4.8 p = not significant Diastolic BP – nighttime: Baseline: 71.4 ± 4.9 3 months: 72.3 ± 3.5 6 months: 73.5 ± 4.0 p = not significant When BP readings for each patient were aggregated over 24 hrs, six hypertensive patients had significant increases in the systolic BP after 6 months of treatment with EPO. Only one of 8 patients on antihypertensive medication at the start of the study required a change to this medication. d) Left ventricular mass index (LVMI; mean ± SEM, in g/m^2): Baseline: 178.2 ± 20.6 3 months: 161.7 ± 20.8 6 months: 147.3 ± 20.6 $p < 0.05$ (6 months vs. baseline) e) Vasoactive substances: There were no significant changes in the levels of vasoactive substances (endothelin-1, renin, epinephrine, norepinephrine, dopamine) after treatment with EPO.	

Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Roth, Smith, Schulman, et al., 1994 **and** **Revicki, Brown, Feeny, et al., 1995**	Design: RCT (not blinded) Intervention(s) studied: 1) Subcutaneous EPO (n = 43). Initial dose 50 U/kg 3 times per week for 4 weeks. If Hct had not increased by 2-3%, then dosage increased to 75 U/kg 3 times per week. Thereafter, dosage could be increased by 75 U/kg per week to a maximum dose of 450 U/kg per week. When patients reached a Hct of 36%, then dosage titrated to maintain Hct of 35%. Maintenance doses given as a single weekly injection. Treatment and follow-up continued for total of 48 weeks. 2) No treatment (n = 40) Dates: NR Location: 11 sites in the US Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 83 Inclusion criteria: Age 18-75; chronic renal failure; SCr 3-8 mg/dl; Hct ≤ 30%; mean arterial pressure controllable below 114 mmHg; not currently receiving hemodialysis Exclusion criteria: Proteinuria > 5 g per day; iron-deficiency anemia; transfusion dependency; systemic disease, inflammatory condition, or infection that might interfere with the effects of EPO treatment; failure to complete a BP and diet stabilization phase prior to start of trial Age (mean ± SEM): EPO, 56.5 ± 11.4; control, 58.4 ± 13.2 Sex: EPO, 35% M, 65% F; control, 30% M, 70% F Race: EPO, 70% White, 30% Black; control, 80% White, 20% Black Renal function at entry (mean ± SEM): GFR: EPO: 10.2 ± 4.1 ml/min Control: 10.0 ± 4.1 ml/min SCr: EPO: 5.5 ± 1.6 mg/dl Control: 5.5 ± 1.8 mg/dl Hgb at entry: NR Hct at entry (mean ± SEM): EPO: 26.8 ± 4.5% Control: 26.8 ± 3.6% EPO levels at entry: NR	*Key Question 1) What is the prevalence of anemia in pre-ESRD?:* Not addressed *Key Question 2) What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion?:* Not addressed *Key Question 3) What proportion of patients without nutritional deficiencies are resistant to EPO?:* Not addressed *Key Question 4) What proportion of pre-ESRD patients have low EPO levels?:* Not addressed *Key Question 5) What is the efficacy of EPO in improving intermediate and ultimate outcomes?:* a) Hct: Intention-to-treat analysis showed a significant increase in Hct from baseline to last available value in the EPO group ($p < 0.001$), but not in the control group (no p-value reported). Mean change in Hct was significantly higher in the EPO group (+4.7%) than in the control group (-1.0%; $p < 0.0001$). The target Hct of 36% was reached b 79% of patients in the EPO group, compared with 0 patients in the control group ($p < 0.05$). b) Health-related quality of life (HRQL): Measured using a combination of selected scales from the Sickness Impact Profile, selected Medical Outcome Study measures, the life satisfaction scale from the Quality of American Life survey, and the Center for Epidemiologic Studies Depression scale. *Within-group comparisons (intention-to-treat analysis):* EPO: Significant improvements from baseline to 48 weeks in energy ($p = 0.045$), physical function ($p =$	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: No/not assessable Incl/excl described: Completely Dropouts discussed: Partially Sample size justified: No/not assessable 3) GFR/CrCl: Measured by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 2b Note: 23/43 EPO patients (53%) and 25/40 control patients (63%) dropped out of the study before the 48-week treatment period was completed. Reasons for withdrawal were as follows: EPO: 16/43 patients (37%) began hemodialysis treatment; 1/43 dropped out due to adverse events; 1/43 dropped out due to pulmonary edema; reasons for withdrawal of 5/43 patients not described Control: 13/40 patients (33%) began hemodialysis; 4/40 dropped out due to adverse events; 1/40 dropped out due to CHF, and 1/40 due to MI; 1/40 died; reasons for withdrawal of 5/40 patients not described

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Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			0.046), and cognitive function (p = 0.015).	
		Nutritional parameters at entry: NR	Control: No significant changes in HRQL scores from baseline to 48 weeks except for a significant decrease	
		Co-morbidities at entry: NR	in physical function (p = 0.03).	
			Between-group comparisons (intention-to-treat analysis): EPO was significantly better than control for energy (p = 0.038) and physical function (p = 0.005).	
			Correlation between changes in Hct and HRQL scores: After 48 weeks of treatment, significant correlations were found between Hct and energy scores (r = 0.37; p < 0.02), physical function (r = 0.35; p < 0.03), sexual dysfunction (r = -0.45; p < 0.02), and social activities (r = 0.39; p < 0.02).	
			c) Blood pressure: No significant differences within or between groups in the mean change from baseline to last available value for systolic BP (p = 0.673), diastolic BP (p = 0.721), or mean arterial pressure (p = 0.773). 26% of EPO patients and 10% of control patients reported hypertension as an adverse event (p = not significant).	
			d) Renal function: Change in GFR: There was a significant decrease in GFR from baseline to last available value in both the EPO (p < 0.001) and control (p < 0.001) groups, but no significant difference between the two groups (p = 0.376). Mean changes (± SEM) were -2.1 ± 3.2 ml/min in the EPO group and -2.8 ± 3.5 ml/min the control group.	
			Time to dialysis: No significant difference between the two groups in the Kaplan-Meier survival curves for time to dialysis.	

Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Strauss, Port, Somen, et al., 1993	Design: Population-based cohort study Intervention(s) studied: None. Investigators used data from the second National Health Nutrition Examination Survey (NHANES II) to estimate the size of the US population with predialysis renal insufficiency and the fraction of those patients who also have anemia. Methods involved (1) selecting predialysis renal insufficiency patients aged 12-74 years from the NHANES II survey, (2) adjusting for population changes between 1978 and 1988, (3) adding estimates for pediatric and geriatric populations, (4) projecting results to 1990, and (5) excluding nonanemic patients. Dates: NHANES II conducted between 1976 and 1980; results projected to 1990 Location: Nationally representative population-based survey Recruitment setting: Community setting	No. of pre-ESRD subjects: 25,286 individuals surveyed for NHANES II; 10,453 of these had valid measurements of SCr and Hct; 44 of these were determined to have predialysis renal insufficiency (SCr > 2.0 mg/dl and < 8.0 mg/dl) Inclusion criteria: Surveyed in NHANES II Exclusion criteria: None specified Age (n = 10,453 NHANES II subjects with valid measurements of SCr and Hct): 67% 12-54; 33% 55-74 Sex (n = 10,453 NHANES II subjects with valid measurements of SCr and Hct): 46% M, 54% F Race (n = 10,453 NHANES II subjects with valid measurements of SCr and Hct): 87% White, 11% Black, 2% other Renal function at entry: NR Hgb at entry: NR Hct at entry: NR EPO levels at entry: NR Nutritional parameters at entry: NR Co-morbidities at entry: NR	*Key Question 1) What is the prevalence of anemia in pre-ESRD?:* The NHANES II survey found that 6/44 (13.6%) patients with predialysis renal insufficiency (SCr > 2.0 mg/dl and ≤ 8.0 mg/dl) had anemia (Hct < 30%). The prevalence of anemia varied by SCr level: 1/28 patients (3.6%) with SCr between 2.0 and 3.0 mg/dl were anemic, compared with 2/11 (18.2%) of those with SCr between 3.0 and 4.0, and 3/6 (50.0%) of those with SCr between 4 and 8. Study investigators estimated that in 1990 there were between 68,000 and 75,000 individuals in the US who had both predialysis renal insufficiency and anemia. *Key Question 2) What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion?:* Not addressed *Key Question 3) What proportion of patients without nutritional deficiencies are resistant to EPO?:* Not addressed *Key Question 4) What proportion of pre-ESRD patients have low EPO levels?:* Not addressed *Key Question 5) What is the efficacy of EPO in improving intermediate and ultimate outcomes?:* Not addressed	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: Completely Dropouts discussed: Completely Sample size justified: No/not assessable 3) GFR/CrCl: SCr 4) % pre-ESRD: < 50%/not assessable 5) Level of evidence: 2b Notes:

Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
US Recombinant Human Erythropoietin Predialysis Study Group, 1991	Design: RCT Intervention(s) studied: 1) Placebo (n = 31) 2) Intravenous EPO 50 U/kg (n = 28) 3) Intravenous EPO 100 U/kg (n = 28) 4) Intravenous EPO 150 U/kg (n = 30) All treatments given 3 times per week for 8 weeks or until Hct reached 40% in men or 35% in women. No dose adjustments described. Patients invited to participate in long-term, open-label, maintenance study at conclusion of RCT. Dates: NR Location: 15 sites in US Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 117 Inclusion criteria: Chronic renal failure (SCr between 260 and 880 µmol/l); pre-dialysis; anemia (Hgb ≤ 130 g/l for men and ≤ 110 g/l for women; Hct ≤ 38% for men and ≤ 32% for women; reticulocyte counts < 0.03 for both sexes); clinically stable; adequate nutritional status Exclusion criteria: Significant clinical conditions affecting the hepatic, cardiovascular, hematologic, neurologic, or pulmonary systems; uncontrollable hypertension; use of androgens within 2 months prior to start of study; use of corticosteroids, immunosuppressants, or any drug know to affect Hct within 1 month prior to start of study; donating blood within 30 days prior to start of study; acute illness within 7 days of start of study Age (mean, with range): 57.1 (24-79) Sex: 61% M, 39% F Race: 78% White, 21% Black, < 1% Oriental, < 1% American Indian Renal function at entry: CrCl (mean ± SD, ml/s x 1.73/body surface area): Placebo: 0.28 ± 0.15 EPO 50 U/kg: 0.28 ± 0.25 EPO 100 U/kg: 0.36 ± 0.35 EPO 150 U/kg: 0.19 ± 0.11 (no p-values reported)	*Key Question 1) What is the prevalence of anemia in pre-ESRD?:* Not addressed *Key Question 2) What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion?:* Not addressed *Key Question 3) What proportion of patients without nutritional deficiencies are resistant to EPO?:* Not addressed *Key Question 4) What proportion of pre-ESRD patients have low EPO levels?:* Not addressed *Key Question 5) What is the efficacy of EPO in improving intermediate and ultimate outcomes?:* a) Hct: Percentage of patients with an increase in Hct of ≥ 6% over baseline values: Placebo: 3/31 (10%) EPO 50 U/kg: 16/28 (57%) EPO 100 U/kg: 22/28 (79%) EPO 150 U/kg: 27/30 (90%) p < 0.05 for each EPO group vs. placebo p < 0.05 for EPO 150 U/kg vs. EPO 50 U/kg Percentage of patients with correction of anemia (i.e., reached targets of 40% for men or 35% for women): Placebo: 1/31 (3%) EPO 50 U/kg: 13/28 (46%) EPO 100 U/kg: 18/28 (64%) EPO 150 U/kg: 26/30 (87%) p < 0.05 for each EPO group vs. placebo p < 0.05 for EPO 150 U/kg vs. EPO 50 U/kg and vs. EPO 100 U/kg	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: No/not assessable Incl/excl described: Partially Dropouts discussed: Partially Sample size justified: No/not assessable 3) GFR/CrCl: Measured by investigators 4) % pre-ESRD: < 50%/not assessable 5) Level of evidence: 2b Notes:

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Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
		SCr (mean ± SD, µmol/l): Placebo: 500 ± 250 EPO 50 U/kg: 510 ± 200 EPO 100 U/kg: 520 ± 190 EPO 150 U/kg: 610 ± 220 Hgb at entry (mean ± SD, g/l): Placebo – men: 99 ± 16 Placebo – women: 94 ± 8 EPO 50 U/kg – men: 97 ± 13 EPO 50 U/kg – women: 93 ± 9 EPO 100 U/kg – men: 97 ± 15 EPO 100 U/kg – women: 88 ± 7 EPO 150 U/kg – men: 93 ± 18 EPO 150 U/kg – women: 92 ± 12 No "meaningful differences" between groups Hct at entry (mean ± SD, %): Placebo – men: 29.9 ± 4.1 Placebo – women: 28.4 ± 3.1 EPO 50 U/kg – men: 29.7 ± 3.8 EPO 50 U/kg – women: 28.4 ± 2.6 EPO 100 U/kg – men: 29.4 ± 4.7 EPO 100 U/kg – women: 27.0 ± 2.1 EPO 150 U/kg – men: 28.2 ± 5.6 EPO 150 U/kg – women: 27.9 ± 3.3 No "meaningful differences" between groups EPO levels at entry (mean, mU/ml): Placebo – men: 26.8 Placebo – women: 15.7 EPO 50 U/kg – men: 19.0 EPO 50 U/kg – women: 14.5 EPO 100 U/kg – men: 14.2 EPO 100 U/kg – women: 13.0 EPO 150 U/kg – men: 12.8 EPO 150 U/kg – women: 13.8 (excludes 1 patient with a baseline value of 851.3 mU/ml) No significant differences between groups	b) Quality of life (patients whose anemia was corrected [all treatment groups] vs. those whose anemia was not corrected [all treatment groups]): Energy level (assessed using scale ranging from 1 = poor to 5 = excellent): 60% of patients whose anemia had been corrected had increased energy at the final evaluation vs. 42% of those whose anemia had not been corrected ($p < 0.05$) Work capacity (assessed on same scale): 62% of patients whose anemia had been corrected reported an increase in work capacity of ≥ 1 units at the final evaluation vs. 38% of those whose anemia had not been corrected ($p < 0.05$). Improvement in work capacity was significantly better in the EPO 150 U/kg group than in the placebo group ($p < 0.05$). c) Blood pressure: The incidence of systolic hypertension (systolic BP > 140 mmHg on one or more occasions during the study) was as follows: Placebo: 29/31 (94%) EPO 50 U/kg: 26/28 (93%) EPO 100 U/kg: 25/28 (89%) EPO 150 U/kg: 28/30 (93%) No significant differences between groups A "similarly uniform distribution" was observed for diastolic hypertension (diastolic BP > 95 mmHg). Detailed figures not reported. Analysis of the mean changes in BP from baseline to maximum value showed no statistically significant differences among the treatment groups. No medically significant change in mean systolic or diastolic BP was observed in any group. (Quantitative data not reported.) Incidence of hypertension as an adverse event (increase in BP judged to be clinically significant by investigator): Placebo: 6/31 (19%) EPO 50 U/kg: 4/28 (14%) EPO 100 U/kg: 5/28 (18%) EPO 150 U/kg: 11/30 (37%)	*(continued on next page)*

Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
		Nutritional parameters at entry: NR Co-morbidities at entry: Hypertension: 86%	No significant differences between groups d) Renal function: Mean change in SCr (µmol/l): Placebo: + 9 EPO 50 U/kg: - 3 EPO 100 U/kg: +20 EPO 150 U/kg: + 40 No significant difference between any one EPO group and placebo Mean change in CrCl (ml/s x 1.73/body surface area): Placebo: - 0.04 EPO 50 U/kg: - 0.04 EPO 100 U/kg: - 0.12 EPO 150 U/kg: - 0.14 No significant difference between any one EPO group and placebo Slope of 1/SCr (n = 83): Slope did not increase after start of EPO therapy e) Adverse events: 102/117 patients reported 630 AEs. 11/117 (9%) dropped out due to AEs (placebo, n = 4; EPO 50 U/kg, 1; EPO 100 U/kg, 3; EPO 150 U/kg, 3)	

Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Watson, Gimenez, Cotton, et al., 1990	Design: RCT Intervention(s) studied: 1) Placebo administered subcutaneously 3 times per week for 12 weeks or until a target Hct of 36% was reached (n = ?). 2) Subcutaneous EPO 100 U/kg, 3 times per week for 12 weeks or until a target Hct of 36% was reached (n = ?). At the end of the 12-week RCT phase, all patients were treated with EPO during a long-term maintenance phase. Dates: NR Location: Baltimore, MD Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 11 Inclusion criteria: Chronic renal failure; predialysis; anemia Exclusion criteria: None specified Age: Range, 43-79 Sex: 55% M, 45% F Race: NR Renal function at entry (mean ± SEM): CrCl (ml/min): Placebo: 13.02 ± 4.4 EPO: 12.4 ± 3.5 SCr (mg/dl): Placebo: 7.4 ± 1.2 EPO: 5.9 ± 1.4 Hgb at entry: NR Hct at entry (mean ± SEM): Placebo: 28 ± 2% EPO: 29 ± 2% EPO levels at entry: NR Nutritional parameters at entry: NR Co-morbidities at entry: Diabetes as cause of CRF: 9%	*Key Question 1) What is the prevalence of anemia in pre-ESRD?:* Not addressed *Key Question 2) What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion?:* Not addressed *Key Question 3) What proportion of patients without nutritional deficiencies are resistant to EPO?:* Not addressed *Key Question 4) What proportion of pre-ESRD patients have low EPO levels?:* Not addressed *Key Question 5) What is the efficacy of EPO in improving intermediate and ultimate outcomes?:* a) Hct (mean ± SEM): Placebo: Baseline 28 ± 2%, 12 weeks 26 ± 2% EPO: Baseline 29 ± 2%, 12 weeks 35 ± 2% EPO, 12 weeks vs. baseline, p < 0.001 12 weeks, EPO vs. placebo, p < 0.001 b) Mean systolic/diastolic BP (in mmHg; SEM not reported): Placebo: Baseline 135/75, 12 weeks 149/83 EPO: Baseline 169/83, 12 weeks 136/76 No p-values reported (though investigators stated that "[m]ean blood pressure values were comparable before and after treatment"). c) Two patients receiving EPO dropped out because of a suspicion of acceleration of renal failure (decreasing GFR).	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: No/not assessable Incl/excl described: Partially Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Measured by investigators (in subset of patients) 4) % pre-ESRD: > 75% 5) Level of evidence: 2b Notes:

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Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			d) Serum iron, percent transferrin saturation, and serum ferritin showed a tendency to diminish with time, and all patients eventually required iron supplementation (no quantitative data reported).	

Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Yagil, 1997	Design: Cohort study (prospective) Intervention(s) studied: Subcutaneous EPO 4,000 U once per week for 24 weeks. Dose adjusted every 4 weeks in response to increase or decrease in Hgb of > 1 g/dl. Target Hgb was 10-12 g/dl. Dose adjustments usually made in increments of 1,000 U or 2,000 U per week. Treatment with EPO initiated only after adequacy of iron stores (defined as transferring saturation ≥ 20% and ferritin concentration ≥ 100 ng/ml) ensured. Dates: NR Location: 10 sites in Israel Recruitment setting: 10 "medical centers"	No. of pre-ESRD subjects: 31 entered study; 12 patients dropped out before the study ended, 7 of them due to worsening of renal function that required initiation of dialysis Inclusion criteria: Age 15-75; chronic renal failure; predialysis; SCr < 9 mg/dl; Hct < 30% or Hgb < 10 g/dl Exclusion criteria: Causes of anemia other than CRF; folate or vitamin B12 deficiency; uncontrol-lable hypertension; pregnancy; acute illness within 7 days prior to start of study; alcohol or drug abuse; abnormal liver functions; severe secondary hyperparathyroidism; aluminum intoxication; treatment with corticosteroids or other drugs known to affect erythropoiesis; lipodystrophy caused by use of insulin; uncontrollable diabetes mellitus Age (mean ± SEM): 63 ± 2 Sex: 45% M, 55% F Race: NR Renal function at entry (mean ± SEM): CrCl: 16 ± 1 ml/min SCr: 4.7 ± 0.2 mg/dl Hgb at entry (mean ± SD): 8.8 ± 0.1 g/dl Hct at entry: NR EPO levels at entry: NR	*Key Question 1) What is the prevalence of anemia in pre-ESRD?:* Not addressed *Key Question 2) What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion?:* Not addressed *Key Question 3) What proportion of patients without nutritional deficiencies are resistant to EPO?:* Not addressed *Key Question 4) What proportion of pre-ESRD patients have low EPO levels?:* Not addressed *Key Question 5) What is the efficacy of EPO in improving intermediate and ultimate outcomes?:* a) Hgb: Hgb rose significantly from the mean baseline value of 8.8 to > 10 g/dl within 8 weeks and remained stable throughout the rest of the study. (On-treatment data reported only graphically.) b) Blood pressure: Weekly administration of EPO did not affect systolic or diastolic BP as measured 15 minutes before and after each injection (data reported only graphically). 1 patient developed hypertension during the study, and 8 needed an increase in their antihypertensive medication. c) Renal function: There was no deterioration in renal function, as measured by SCr and the slope of 1/SCr, in the 19 patients who completed the study. Seven patients dropped out 4-16 weeks after starting EPO therapy because they required dialysis; data from 5 of these 7 showed that the slope of 1/SCr had not been significantly altered with the onset of EPO therapy.	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: Completely Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Measured by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 2b Notes:

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Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
		Nutritional parameters at entry (mean ± SEM): Serum iron: 77 ± 4 µg/dl Total iron-binding capacity: 282 ± 26 µg/dl Serum transferrin saturation: 27 ± 2% Serum ferritin: 207 ± 28 ng/ml Folate: 18 ± 4 ng/ml B12: 400 ± 38 pg/ml Co-morbidities at entry: Diabetes as cause of CRF: 13% Hypertension: 74%	d) Iron status: 27/31 patients (87%) received iron supplementation during the study. As Hgb rose, transferrin saturation and serum ferritin tended to decline, despite iron supplementation, but the declines were not statistically significant (data reported only graphically).	

Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Yamazaki, Watanabe, and Sakamoto, 1993	Design: RCT (n = 20) Intervention(s) studied: 1) Subcutaneous EPO (n = 10) administered in a dose of 3,000 IU (n = 5) or 6,000 IU (n = 5) once per week for 8 weeks. Dose adjusted for anemia correction at discretion of physician. 2) Intravenous EPO (n = 10) administered in doses of 3,000 IU (n = 3), 6,000 IU (n = 4), or 9,000 IU (n = 3) once per week for 8 weeks. Dose adjusted for anemia correction at discretion of physician. Dates: NR Location: Nagoya, Japan Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 20 Inclusion criteria: ESRD (with SCr > 3.0 mg/dl); Hgb ≤ 9.0 g/dl; Hct ≤ 27%; clinical course observed for at least 1 month before start of study Exclusion criteria: Blood transfusion within 1 month prior to start of study Age (mean ± SEM): SC: 55.9 ± 3.6 IV: 52.4 ± 4.9 Sex: Both groups 50% M, 50% F Race: NR Renal function at entry (mean ± SEM): CrCl (ml/min): SC: 10.52 ± 1.69 IV: 7.19 ± 1.17 SCr (mg/dl): SC: 6.26 ± 0.65 IV: 7.13 ± 0.60 Hgb at entry (mean ± SEM, in g/dl): SC: 7.46 ± 0.22 IV: 6.76 ± 0.25 Hct at entry (mean ± SEM): SC: 21.87 ± 0.67% IV: 21.37 ± 0.63% EPO levels at entry (mean ± SEM, in mIU/ml): SC: 20.0 ± 0.9 IV: 26.1 ± 7.5 Nutritional parameters at entry (mean ± SEM):	*Key Question 1) What is the prevalence of anemia in pre-ESRD?:* Not addressed *Key Question 2) What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion?:* Not addressed *Key Question 3) What proportion of patients without nutritional deficiencies are resistant to EPO?:* Not addressed *Key Question 4) What proportion of pre-ESRD patients have low EPO levels?:* Not addressed *Key Question 5) What is the efficacy of EPO in improving intermediate and ultimate outcomes?:* a) Hct (mean ± SEM, %): SC: 21.87 ± 0.67 — 26.64 ± 1.00 — < 0.001 IV: 21.37 ± 0.63 — 28.00 ± 1.27 — < 0.01 (Baseline — 8 weeks — p-value (8 weeks vs. baseline)) No significant differences between the two groups at any time point (ANOVA, p = 0.9457) b) Hgb (mean ± SEM, in g/dl): SC: 7.46 ± 0.22 — 9.05 ± 0.35 — < 0.001 IV: 6.76 ± 0.25 — 8.82 ± 0.35 — < 0.01 (Baseline — 8 weeks — p-value (8 weeks vs. baseline)) No significant differences between the two groups at any time point (ANOVA, p = 0.9383)	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: No/not assessable Incl/excl described: No/not assessable Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 2b Note: Small sample size (n = 20). *(continued on next page)*

Evidence Table 1 – Anemia (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
		Serum iron (µg/dl): SC: 63.0 ± 8.30 IV: 65.2 ± 15.3 Serum ferritin (ng/ml): SC: 230.8 ± 47.4 IV: 206.0 ± 50.2 Co-morbidities at entry: NR	c) Blood pressure: Systolic BP (mean ± SEM, in mmHg): Baseline / 8 weeks / p-value (8 weeks vs. baseline) SC: 149.4 ± 4.7 / 148.2 ± 6.8 / NS IV: 138.0 ± 5.0 / 135.6 ± 5.5 / NS No between-group comparisons reported Diastolic BP (mean ± SEM, in mmHg): Baseline / 8 weeks / p-value (8 weeks vs. baseline) SC: 80.4 ± 3.0 / 84.0 ± 4.4 / NS IV: 77.7 ± 3.3 / 81.1 ± 3.2 / NS No between-group comparisons reported "Some patients" developed hypertension during course of study, but in every case it was controlled easily by antihypertensive drugs. d) Renal function: No significant difference between the SC and IV groups in the slope of 1/SCr per day.	

3. Bone disease

3.1 Chapter summary

Question 1: Does the correction of acidosis reduce the risk of bone disease (osteomalacia, osteitis, osteoporosis) and/or other negative outcomes in pre-ESRD patients?

- No prospective randomized controlled trials were identified that addressed this question
- Based upon the only identified retrospective case series, metabolic acidosis may actually prevent the development of adynamic bone disease and its correction may be of limited benefit in improving bone disease in pre-ESRD patients if improvement in osteomalacia, osteitis fibrosa, and osteoporosis is offset by worsening of adynamic bone disease.

Question 2: Does the use of estrogen replacement therapy reduce the risk of bone disease (osteomalacia, osteitis, osteoporosis) and/or other negative outcomes in pre-ESRD patients?

- No published studies of the effects of estrogen replacement therapy among pre-ESRD patients was identified.

Question 3: Does the use of phosphate binders and/or active vitamin D sterols reduce the risk of complications from hyperparathyroidism in pre-ESRD patients?

- No articles were identified that addressed the complications of interest which included parathyroidectomy, hypertension, LVH, coronary artery calcification, and CHF

Question 4: Does the use of phosphate binders and/or active vitamin D sterols increase the risk of adynamic bone disease, cardiovascular disease, and/or other negative outcomes in pre-ESRD patients?

- No articles were identified that addressed the question of cardiovascular disease
- Based on 9 prospective, randomized controlled trials evaluating the effects of active vitamin D sterols, we conclude that alfacalcidol (0.5mcg daily) or calcitriol (0.125-0.25 mcg daily) is safe and effective in preventing progression of bone disease among pre-ESRD patients with elevated plasma intact PTH, as well as upon metabolic markers of bone disease and/or bone histomorphometry.
- These doses do not appear to have a detrimental effect upon residual renal function.

3.2 Background

Renal osteodystrophy (ROD) is a multifactorial and complex disorder of bone remodeling that occurs with chronic kidney disease (CKD) and continues to be a major long-term complication which is associated with high rates of morbidity.[1] The metabolic derangements that lead to ROD occur early in CKD. Parathyroid hormone (PTH) levels

have been shown to increase and $1,25(OH)_2D_3$ levels have been shown to decrease when the GFR falls into the range of 40-80 mL/min.[2-4] Phosphate retention or altered phosphate metabolism, with little or no change in serum phosphorus levels, is common when creatinine clearance falls below 50 mL/min contributing to secondary hyperparathyroidism by inhibiting 1α-hydroxylase and further decreasing renal production of $1,25(OH)_2D_3$.[5] Other factors include impaired calcemic response to PTH (skeletal resistance to PTH), altered vitamin D metabolism and resistance to calcitriol, autonomous parathyroid cell proliferation, decreased degradation of PTH, and abnormal regulation of calcium-controlled PTH release (calcium sensing receptor). Metabolic acidosis can also contribute to ROD by stimulating osteoclastic activity or by causing direct physiochemical dissolution of calcium.[6] The resultant skeletal changes as well as parathyroid hyperplasia are not easily reversed, and, therefore, early interventions to prevent the development and/or progression of secondary hyperparathyroidism (HPTH) and its sequelae, and control of metabolic acidosis, are crucial.

Histological evidence of bone disease is highly prevalent among patients with end-stage renal disease (ESRD) and may be present in up to 75% of patients with a creatinine clearance (CrCl) < 60 mL/min.[7,8] Renal osteodystrophy is comprised of a variety of bone disorders including osteitis fibrosa (the hallmark lesion of secondary hyperparathyroidism), osteomalacia (due to vitamin D deficiency or excess aluminum), aplastic bone disease (excess aluminum or oversuppression of parathyroid hormone production with calcitriol), or mild and mixed lesions.[9]

The classic histologic form of renal osteodystrophy is osteitis fibrosa, which is caused by secondary HPTH with contributions from locally derived cytokines and a deficiency of $1,25(OH)_2D_3$. The hallmarks of osteitis fibrosa are peritrabecular marrow fibrosis and increased frequency of bone remodeling, leading to increased resorption of bone. The increased resorption is caused by an increase in both the number and the activity of osteoclasts. Bone formation is also increased, as reflected by increased amounts of osteoid and nonlamellar bone, which are hallmarks of a high rate of bone turnover.[10]

Osteomalacia was a common component of bone disease among ESRD patients; its prevalence is, however, decreasing.[11] The disorder is characterized by low rates of bone turnover, a mineralization defect, and an accumulation of unmineralized osteoid (bone matrix). The most common cause of osteomalacia was intoxication with aluminum and other heavy metals associated with dialysis; however, the prevalence is high among CKD patients with creatinine clearance < 10 ml/min who are being evaluated to start dialysis; in these patients there seems to be no relation to prior intake of aluminum.[12]

Mixed uremic osteodystrophy is caused primarily by HPTH and defective mineralization with or without increased bone formation. These features may coexist in varying degrees in different patients and comprises of features of both osteitis fibrosa and osteomalacia.

Adynamic bone disease (ABD) and its pathogenesis are poorly understood. This disease is most common among patients with ESRD who do not have secondary HPTH, who have been treated with large doses of calcium carbonate and/or vitamin D, or who have diabetes mellitus or aluminum intoxication. Adynamic bone disease is characterized by decreased bone formation and cellular activity without an increase in osteoid thickness.[13] Although this disorder was first described among ESRD patients on chronic hemodialysis, several authors have reported ABD in dialysis patients without aluminum accumulation,[11] especially among patients with diabetes mellitus or on maintenance peritoneal dialysis, particularly with dialysate calcium of 3.0 to 3.5 mEq/l.[14] There have also been studies that have found significant prevalence of ABD among patients with advanced CKD (CCr < 10ml/min) that is not related to aluminum.[12]

The treatment of ROD is directed toward its pathogenetic mechanisms. The goal is to maintain normal serum calcium and phosphorus levels and minimize exposure to aluminum. Phosphate restriction should be instituted relatively early in renal failure and has been effective in attenuating the progression of secondary HPTH. The role of calcitriol in the management of predialysis patients, however, is still undefined. There were early concerns that calcitriol might hasten the loss in kidney function by causing hypercalcemia, hyperphosphatemia, and hypercalciuria. Reports to date have generally shown no change in renal function in association with calcitriol administrations as long as serum calcium is increased only slightly and the doses are kept relatively low.[8,15] A prospective, randomized, multicenter study including 176 patients with creatinine clearance between 15 and 50 mL/min, 75% of whom had histologic evidence of bone disease at baseline, evaluated the efficacy of alfacalcidol versus placebo.[8] After at least 2 years of follow-up, alfacalcidol significantly reduced PTH levels during the first 6 months, bone biopsies improved in 29% of alfacalcidol-treated patients, while bone disease worsened in 90% of placebo-treated patients. There was no difference in the rate of progression of kidney failure between groups. These findings suggest that alfacalcidol is both safe and effective in preventing progression of bone disease among predialysis patients with elevated plasma intact PTH levels. Another study has shown that daily calcium carbonate administration is also highly effective in treating secondary HPTH among predialysis patients with mild to moderate kidney failure.[16]

The purpose of this chapter is to systematically review the available literature on the impact of bone disease on clinical outcomes, and on the impact and risks of secondary hyperparathyroidism management interventions in patients with pre-ESRD, defined as patients with GFR below 30 ml/min per 1.73 m^2, and not receiving any kind of renal replacement therapy.

3.3 Methods

To address the issue of the management of bone disease in patients with pre-ESRD, the following four key questions were formulated:

1. Does the correction of acidosis reduce the risk of bone disease (osteomalacia, osteitis, osteoporosis) and/or other negative outcomes in pre-ESRD patients?

2. Does the use of estrogen replacement therapy reduce the risk of bone disease (osteomalacia, osteitis, osteoporosis) and/or other negative outcomes in pre-ESRD patients?
3. Does the use of phosphate binders and/or active vitamin D sterols reduce the risk of complications from hyperparathyroidism in pre-ESRD patients?
4. Does the use of phosphate binders and/or active vitamin D sterols increase the risk of adynamic bone disease, cardiovascular disease, and/or other negative outcomes in pre-ESRD patients?

To identify the literature addressing the four questions related to the management of bone disease, we obtained a bibliographic database of prescreened citations from ECRI, a non-profit research organization and contractor to the National Kidney Foundation (NKF), for their evidence report on bone and mineral disease in CKD.[17] These citations were derived from a comprehensive search of MEDLINE and selected using criteria broader than this project in scope of patient populations and interventions. Thus, the ECRI database of 467 pre-selected citations was screened for articles pertinent to our topic.

Clinical outcomes of interest were bone disease and effects on other organs (e.g., congestive heart failure [CHF], anemia, cognitive function). Intermediate outcomes considered included serum measures of bone metabolism (calcium, phosphorus, PTH). Complications of interest included parathyroidectomy, hypertension, LVH, coronary artery calcification, and CHF.

3.4 Results

Four hundred and seventy-two titles and abstracts were screened (467 from the ECRI database plus five others). One hundred and twenty of these were identified for full-text screening. We were unable to obtain copies of five of these articles[18-22]. Of the remaining 115, 95 were excluded during full-text review for the following reasons: outcomes not reported separately for the pre-ESRD population (n = 4), did not meet the criteria for the pre-ESRD population (n = 31), did not address at least one of the key questions (n = 61). Fourteen articles were included at the full-text screening stage: one of these was a review article; the remaining 13 were abstracted using a standardized form and are summarized in Evidence Table 2.

Key Question 1 : Does the correction of acidosis reduce the risk of bone disease (osteomalacia, osteitis, osteoporosis) and/or other negative outcomes in pre-ESRD patients?

No prospective randomized controlled trials were identified that addressed this question. However, one retrospective case series by Coen et al. noted that a group of 12 uremic patients (mean CrCl 18.05 ± 3.92 mL/min) with metabolic acidosis had significantly higher osteoid volume and mineralization lag time, and less mineralizing surface on bone biopsies compared to 12 matched uremic patients (mean CrCl 19.84 ± 6.2 mL/min) with normal acid-base equilibrium.[23] Calcitriol administration, 0.25 µg daily for a period of 1 year in five cases in the group without and six cases in the group with metabolic acidosis induced significant improvement of bone lesions. None of the

patients with metabolic acidosis were found to have adynamic bone disease even following a year of calcitriol therapy, whereas 2 of 5 CKD patients without acidosis had ABD, and a total of 4 of 5 were diagnosed with ABD following one year of calcitriol therapy. Thus, metabolic acidosis may prevent development of ABD, and its correction may be of limited benefit in improving bone disease if improvement in osteomalacia, osteitis fibrosa, and osteoporosis is offset by worsening of ABD.

Lin et al. designed an in-vivo study to determine the role of alkali therapy in osteoblast function in CKD by assessing serum bone isoenzyme of alkaline phosphatase and osteocalcin before and after bicarbonate infusion.[24] The investigators studied 18 patients with moderate to severe CKD (CrCl ranging from 5.4-28.8 mL/min), as well as mild to moderate metabolic acidosis, none of whom had received dialysis therapy. Metabolic acidosis was corrected by continuous bicarbonate infusion while plasma ionized calcium was held at the preinfusion levels. After bicarbonate levels and pH were normalized, serum markers for bone metabolism were obtained. There was a significant increase in serum total calcium and osteocalcin, which is a marker for osteoblast activity and bone formation. Conversely, there was no significant change in concentrations of alkaline phosphatase. The protocol only followed short-term effects and therefore does not demonstrate long-term benefit, however this study supports the hypothesis that correction of metabolic acidosis may improve osteoblast function in CKD.

Key Question 2: Does the use of estrogen replacement therapy reduce the risk of bone disease (osteomalacia, osteitis, osteoporosis) and/or other negative outcomes in pre-ESRD patients?

No published studies of the effects of hormone treatment on renal osteodystrophy were identified.

Key Question 3: Does the use of phosphate binders and/or active vitamin D sterols reduce the risk of complications from hyperparathyroidism in pre-ESRD patients?

No articles were identified that addressed the complications of interest, which included parathyroidectomy, hypertension, LVH, coronary artery calcification, and CHF.

Key Question 4: Does the use of phosphate binders and/or active vitamin D sterols increase the risk of adynamic bone disease, cardiovascular disease, and/or other negative outcomes in pre-ESRD patients?

No articles were identified that addressed the question of cardiovascular disease and the use of phosphate binders and/or vitamin D supplementation. Regarding the risk of adynamic bone disease, nine articles were identified that allowed some assessment of the risk of vitamin D supplementation therapy.

The first randomized, double-blind, placebo-controlled trial to explore the efficacy of $1,25(OH)_2D_3$ on bone histology and serum biochemistry in patients with mild to

moderate renal failure was performed by Baker et al.[15] Sixteen patients with CKD (CrCl 20-59 ml/min) received either $1,25(OH)_2D_3$ at a dose of 0.25 to 0.5 mcg daily (n = 8), or placebo. Bone histology was abnormal in all patients. Treatment with $1,25(OH)_2D_3$ was associated with a significant fall in serum phosphorus and alkaline phosphatase concentrations as well as with histological evidence of an amelioration of hyperparathyroid changes compared with controls. No mention of adynamic bone disease on biopsy was documented. Of note, four patients developed hypercalcemia when the dose of $1,25(OH)_2D_3$ dose was increased to 0.5 mcg daily. These episodes resolved within one week of stopping treatment, and these patients subsequently tolerated $1,25(OH)_2D_3$ at 0.25 mcg daily with no further hypercalcemia. These episodes of hypercalcemia corresponded to increases in urinary calcium excretion, serum creatinine concentration, and a fall in CrCl in the treatment group, which corrected with dose adjustments.

Hamdy et al.[8] conducted the largest randomized, double-blind, placebo-controlled trial of alfacalcidol in the management of overt renal bone disease. Utilizing 17 nephrology centers from Belgium, France, the Netherlands, and the United Kingdom, 176 patients aged 18-81years with mild to moderate CKD (CrCl 15-50 ml/min) and with no clinical, biochemical, or radiographic evidence of bone disease were randomized to receive either alfacalcidol 0.25 micrograms (titrated according to serum calcium concentration) or placebo for 2 years. Seventy-five percent of the patients had histological evidence of bone disease at start of the study. After treatment, mean serum alkaline phosphatase activity and intact PTH concentration increased by 13% and 126%, respectively, in controls, but had not significantly changed in the patients given alfacalcidol. Hypercalcemia developed in three patients given placebo and 10 patients given alfacalcidol; the hypercalcemia responded to decreases in alfacalcidol dose. Histological indices of bone turnover significantly improved in patients given alfacalcidol and significantly deteriorated in controls: among patients with abnormal bone histology before treatment, bone disease resolved in 42% of those given alfacalcidol compared with 4% of controls. Adynamic bone lesions resolved in 4 of 6 patients taking alfacalcidol from the beginning of the study and in 2 of 3 patients taking placebo. Adynamic bone lesions developed in 8 of 55 (14%) paired biopsies obtained from patients treated with alfacalcidol and 4 of 45 (9%) from patients treated with placebo. None was attributable to aluminum toxicity. As mentioned above, there was no difference in rate of progression of kidney failure between the two groups.

In another prospective, randomized, placebo-controlled trial, Nordal and Dahl[25] studied 30 consecutive non-dialyzed patients with moderate to severe CKD (mean CrCl 24 ml/min among treated group and 30 ml/min in placebo). Patients were randomly allocated to receive either calcitriol 0.25 mcg or matching placebo daily for 14 days and then two tablets per day for a total of 8 months. Serum calcium, ionized calcium and urinary calcium increased, while serum immunoreactive PTH levels decreased in the treatment group. Conversely, serum calcium and ionized calcium decreased while PTH levels increased in the placebo group. In the placebo group, no significant change in any of the histomorphometric bone indices occurred during the study, while calcitriol treatment led to significantly lower values in osteoid volume and cancellous bone

volume remained constant. This indicated more mineralized bone after 8 months of therapy. The calcitriol dose had to be reduced at least once in eight patients due to elevated serum calcium levels, and all returned to normal levels. The mean daily dose was 0.36 mcg. There was no significant difference in rate of decline in renal function between the two groups.

In another prospective clinical trial, Coen et al. identified 38 patients with slowly evolving CKD from outpatient clinics in Rome, Italy.[26] Patients were divided in two groups with a comparable rate of decline of renal function and cause of kidney failure and not by age or sex. Fifteen patients with moderate to severe CKD (calculated mean CrCl 18.4 ± 9.1 ml/min) were treated with $1,25(OH)_2D_3$, 0.25 mcg daily for an average period of 16.2 ± 11.3 months. Twenty-three patients with comparable rates of decline in renal function as calculated by retrospective analysis of the reciprocal serum creatinine (no CrCl reported for this group) served as controls. At the end of treatment, serum creatinine, calcium, phosphorus, and $1,25(OH)_2D_3$ significantly increased, while serum alkaline phosphatase decreased. There was no significant change in urinary calcium or serum immunoreactive PTH levels (iPTH). In the control group, there was a significant increase in iPTH levels from baseline levels to those at the end of the study (at time of bone biopsy). The bone histomorphometric tests showed improvement in active resorption surface and active osteoblastic surface compared to controls. There was no diagnosis of adynamic bone disease in either group, however only histomorphometric parameters were reported. There were no cases of hypercalcemia reported nor were there significant differences between groups in terms of rate of decline in renal function (as assessed by the slopes of serum creatinine reciprocals versus time).

Przedlacki et al. studied bone mineral density after 1 year of treatment with calcitriol versus placebo among 26 Finnish patients with moderate to severe CKD (mean GFR < 31 ml/min).[27] Patients were randomized to receive either calcitriol 0.25 mcg or placebo daily (13 in each group). All of the patients were following a low phosphorus diet and being administered calcium acetate (except for patients with hypercalcemia and/or hypophosphatemia). Following 1 year of study, bone mineral density evaluated by dual-energy X-ray absorptiometry (DEXA) was performed. The calcitriol group had a significant increase in bone mineral density in lumbar spine (3.93%) and femoral neck (3.37%) when compared to placebo patients, who were noted to have decreased values. The calcitriol group also had a significant reduction in serum alkaline phosphatase and iPTH, whereas no significant difference was seen among the placebo patients. There was no significant difference between the rate of decline in renal function between the two groups.

In one prospective, double-blind, placebo-controlled, multicenter trial, Ritz et al. studied 45 patients with moderate CKD (estimated CrCl for the entire group was 30 ml/min) and the effects of low-dose calcitriol on markers of secondary hyperparathyroidism and bone metabolism.[28] Patients were randomly assigned to receive oral calcitriol 0.125 mcg daily or placebo for 1 year. The patients received calcium carbonate if serum phosphorus levels exceeded 1.7 mmol/l. Following therapy with calcitriol, there was no significant change in iPTH or alkaline phosphatase levels; however, the placebo group

had a significant increase in iPTH levels at the end of 1 year. Bone alkaline phosphatase levels, which were used as a non-invasive index of bone metabolism, did not decrease to subnormal levels. There were no episodes of hypercalcemia nor was a difference in renal function decrement noted.

In another controlled trial, Christiansen[29] studied the effects of vitamin D metabolites on parameters of bone, parameters of bone metabolism, and renal function among 17 undialyzed patients with moderate (CrCl 5-35 ml/min) and severe CKD (CrCl < 5 ml/min) and compared them with normal controls. Patients were randomly allocated into two groups: one treated with $1,25(OH)_2D_3$ 1 mcg daily (mean dose 0.5 mcg over 6 months), the other with vitamin D3 (25OHD) 100 mcg orally. After 6 months of treatment all the patients were studied for another 3 months. At the initiation of the study, the CKD patients had significantly lower bone mineral content and calcification rate with higher osteoid surface, osteoid volume, and bone resorption (%) when compared to normal, consistent with features of ROD. The CKD patients also had higher serum phosphorus, alkaline phosphatase, and iPTH (both C- and N-terminal) levels, and significantly lower serum calcium and $1,25(OH)_2D_3$ levels at the time of enrollment. After 6 months of therapy, the osteoid volume and bone resorption decreased significantly to within the normal range in the $1,25(OH)_2D_3$ group but not in the vitamin D3 group. Both groups had significant improvement of iPTH (both C- and N-terminal); however, only the $1,25(OH)_2D_3$ group showed significant declines in serum alkaline phosphatase levels. The authors also noted that the rate of decline in renal function during the study period was significantly greater than the 6 months prior to entry into the study and concluded that vitamin D supplementation could hasten renal failure.

Tougaard et al.[30] performed a randomized, double-blind, placebo-controlled trial evaluating the effect of 1alpha-hydroxycholecalciferol (1α-HCC) therapy on serum calcium, phosphorus, iPTH, alkaline phosphatase, bone mineral content (by photon absorptiometry of forearm), intestinal calcium absorption and GFR among patients with moderate to severe CKD (GFR 5-25 ml/min). Patients were randomly assigned to receive 1α-HCC 1 mcg or placebo daily for 11 weeks. Treatment resulted in significant increases in the intestinal absorption of calcium and in plasma calcium, which reached normal levels within 2 weeks. Therapy with 1α-HCC also induced a significant reduction of iPTH levels; however, there were no significant changes in plasma phosphorus, alkaline phosphatase, or in the degree of bone mineralization. The mineral content in the forearm measured by photon absorptiometry decreased to the same extent in both groups. However, the fall in GFR during treatment was 2.5 times greater in the 1α-HCC group compared to placebo, although this difference was not significant.

3.5 Discussion

There is a significant paucity of interventional trials involving patients with moderate to severe CKD in the literature currently available. Consequently, we were unable to identify sufficient data to answer the majority of our clinical questions. There were, however, data from multiple prospective, randomized interventional trials that tested the efficacy and safety of several vitamin D metabolites upon secondary HPTH, renal

function, and bone histomorphometry among subjects with varying degrees of CKD that did not fall within our pre-specified range. One study by Bianchi et al.[31] evaluated the effects of combined low-dose therapy of calcitriol and calcium carbonate on bone metabolism in the early stages of CKD. Seventeen subjects with creatinine clearance ranging from 36-64 ml/min were given 0.25 mcg of calcitriol orally each day along with calcium carbonate 1 g/day for 24 months. The investigators noted a significant decrease in serum iPTH, alkaline phosphatase, and osteocalcin levels by the end of the study period. Bone biopsies revealed decreased osteoblastic and osteoclastic activity as well as the proportion of non-mineralized bone among these subjects and bone densitometry studies revealed slowing in rate of loss. Renal function remained stable throughout the follow up period. From these and other data, it appears that alfacalcidol (0.5 mcg daily) or calcitriol (0.25 mcg daily) is effective in preventing progression of bone disease among predialysis patients with elevated plasma intact PTH, as well as histologic evidence of ROD at initiation of therapy. Hypercalcemia and progression of renal failure have been associated with these treatments, but these complications appear to be reversible based on response to dose adjustments. It is important to state, however, that there are currently no data regarding the long-term cardiovascular complications from these regimens.

The role for correction of metabolic acidosis, hormone replacement therapy, or the impact of phosphate binders on the risk of complications from secondary HPTH (e.g., parathyroidectomy, HTN, LVH, coronary artery calcification, and CHF) is ill-defined within the available literature. Substantial opportunities remain for further research into the long-term effects of different alternative intervention regimens of secondary hyperparathyroidism among this population.

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Evidence Table 2 – Bone disease

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Baker, Abrams, Roe, et al., 1989	Design: RCT Intervention(s) studied: 1) Placebo (n = 6); 2) $1,25(OH)_2D_3$ (n = 7). Initial dose 0.25 µg daily. If serum calcium remained < 2.6 mmol/l and urinary calcium < 7 mmol/24 hours, then dose doubled 4-8 weeks after start of therapy. If hypercalcemia and/or hypercalciuria occurred, then treatment stopped. When serum and/or urinary calcium had returned to normal, then dose reduced by one half. Patients in both groups received 400 IU of vitamin D_3 per day. Treatment continued for 12 months. Dates: NR Location: London, UK Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 16 enrolled; 13 completed the trial and were included in the analysis Inclusion criteria: Chronic renal failure (CrCl 20-60 ml/min) Exclusion criteria: Pregnancy; hypercalcemia; renal stones; poorly controlled hypertension; GI or liver disease; urinary protein > 3 g/day; psychosis; known tetracycline allergy; treatment with medications known to affect bone or vitamin D metabolites in pharmacological doses within previous 6 months Age (mean, with range): Placebo: 47.7 (31-63) Active: 56.6 (51-64) Sex: Placebo, 67% M, 33% F; active, 43% M, 57% F Race: NR Renal function at entry (mean ± SD): CrCl (ml/min): Placebo: 44.7 ± 13.1 Active: 34.7 ± 14.0 SCr (mmol/l): Placebo: 0.220 ± 0.103 Active: 0.240 ± 0.071 Serum measures of bone metabolism at entry (mean ± SD): Calcium (mmol/l): Placebo: 2.48 ± 0.07 Active: 2.47 ± 0.06 Phosphorous (mmol/l): Placebo: 1.12 ± 0.14	*Key Question 1) Does the correction of acidosis reduce the risk of bone disease (osteomalacia, osteitis, osteoporosis) and/or other negative outcomes in pre-ESRD patients?:* Not addressed *Key Question 2) Does the use of hormone replacement therapy reduce the risk of bone disease (osteomalacia, osteitis, osteoporosis) and/or other negative outcomes in pre-ESRD patients?:* Not addressed *Key Question 3) Does the use of phosphate binders and/or vitamin D supplementation reduce the risk of complications from hyperparathyroidism in pre-ESRD patients?:* Not addressed *Key Question 4) Does the use of phosphate binders and/or vitamin D supplementation increase the risk of adynamic bone disease, cardiovascular disease, and/or other negative outcomes in pre-ESRD patients?:* a) Bone formation and resorption: 12 months of treatment with $1,25(OH)_2D_3$ resulted in significant ($p < 0.05$ vs. baseline) reductions in: lamellar osteoid volume and thickness, woven osteoid volume and surface, and osteoblastic index. After 12 months of treatment with placebo, woven osteoid volume and surface were significantly ($p < 0.05$ vs. baseline) increased. b) Serum alkaline phosphatase (mean ± SD, IU/ml): Placebo: Baseline 72.3 ± 22.0; 12 months 75.5 ± 18.8 Active: Baseline 73.7 ± 27.1; 12 months 56.6 ± 18.3 $p < 0.01$, active vs. placebo for change from baseline to 12 months	Quality Scoring: 1) Global assessment: Good 2) Validity criteria: Population described: Completely Incl/excl described: Completely Dropouts discussed: Completely Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: 50-75% 5) Level of evidence: 1b Note: 3/16 patients dropped out or were withdrawn, 1 from the active group and 2 from the placebo group.

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Evidence Table 2 – Bone disease (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
		Active: 1.40 ± 0.27 PTH (µg/ml): Placebo: 0.67 ± 0.23 Active: 0.87 ± 0.43 Alkaline phosphatase (IU/ml): Placebo: 72.3 ± 22.0 Active: 73.7 ± 27.1 $1,25(OH)_2D$ (pg/ml): Placebo: 16.0 ± 9.5 Active: 16.0 ± 2.5 Anatomic measures of bone disease at entry (mean ± SD): Lamellar osteoid volume (mm^3/cm^3): Placebo: 6.27 ± 2.51 Active: 4.66 ± 1.07 Mean osteoid seam thickness (µm): Placebo: 9.76 ± 0.90 Active: 9.47 ± 0.85 Woven osteoid volume (mm^3/cm^3): Placebo: 0.58 ± 0.16 Active: 1.95 ± 0.70 $p < 0.05$ Osteoblastic index: Placebo: 444 ± 144 Active: 429 ± 58 Osteoclastic index: Placebo: 54 ± 13 Active: 42 ± 7.3 Effects on other organs at entry: NR Co-morbidities at entry: NR	c) Serum PTH (µg/ml): |	Baseline	12 months
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Placebo	0.67 ± 0.23	0.60 ± 0.23
Active	0.87 ± 0.43	0.63 ± 0.24	 p = not significant, 12 months vs. baseline for both groups	

Evidence Table 2 – Bone disease (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Christian-sen, 1983	Design: RCT Intervention(s) studied: 1) 1,25$(OH)_2D_3$ (n = ?). Initial dose 1 µg per day; mean daily dose over the 6-month treatment period, 0.5 µg. 2) Vitamin D_3 100 µg per day (n = ?). Treatment continued for 6 months. During this time, patients in both groups received 0.5 g calcium daily. 6-month treatment period preceded by a 6-month observation period (t_{-6} to t_0) and followed by a 3-month observation period (t_6 to t_9). Dates: NR Location: Glostrup, Denmark Recruitment setting: Not specified/unable to determine	No. of pre-ESRD subjects: 17 Inclusion criteria: CrCl 5-35 ml/min; renal function relatively stable for > 1 year Exclusion criteria: None specified Age (mean, with range): 53 (26-70) Sex: 29% M, 71% F Race: NR Renal function at entry (t_0): CrCl (mean ± SD; at t_0): 22.4 ± 11.9 ml/min Serum measures of bone metabolism at entry (mean, with range): Calcium (mean, with range; unclear whether t_{-6} or t_0): 2.34 mmol/l (2.01-2.69) Phosphorus (mean, with range; unclear whether t_{-6} or t_0): 1.4 mmol/l (1.0-2.4) iPTH (N-terminal; mean ± SD; t_0): 0.29 ± 0.36 µg/l iPTH (C-terminal; mean ± SD; t_0): 2.60 ± 2.16 µg/l Alkaline phosphatase (mean, with range; unclear whether t_{-6} or t_0): 221 U/l (114-452) 1,25-dihydroxy vitamin D (mean ± SD; t_0): 17.7 ± 11.6 pg/ml Anatomic measures of bone disease at entry: Bone mineral content (mean ± SD; % of normal; t_0): 1,25$(OH)_2D_3$: 81.3 ± 5.1 Vitamin D_3: 70.2 ± 12.3	*Key Question 1) Does the correction of acidosis reduce the risk of bone disease (osteomalacia, osteitis, osteoporosis) and/or other negative outcomes in pre-ESRD patients?:* Not addressed *Key Question 2) Does the use of hormone replacement therapy reduce the risk of bone disease (osteomalacia, osteitis, osteoporosis) and/or other negative outcomes in pre-ESRD patients?:* Not addressed *Key Question 3) Does the use of phosphate binders and/or vitamin D supplementation reduce the risk of complications from hyperparathyroidism in pre-ESRD patients?:* Not addressed *Key Question 4) Does the use of phosphate binders and/or vitamin D supplementation increase the risk of adynamic bone disease, cardiovascular disease, and/or other negative outcomes in pre-ESRD patients?:* a) iPTH (N-terminal) (mean percentage change from t_0 value): 3 months / 6 months 1,25$(OH)_2D_3$: -42* / -43* Vitamin D_3: -19* / -39* * p < 0.05 vs. baseline (t_0) b) iPTH (C-terminal) (mean percentage change from t_0 value): 3 months / 6 months 1,25$(OH)_2D_3$: -40** / -54** Vitamin D_3: -21* / -28** * p < 0.05 vs. baseline (t_0) ** p < 0.01 vs. baseline (t_0)	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: No/not assessable Incl/excl described: No/not assessable Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 2b Notes:

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Evidence Table 2 – Bone disease (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
		Effects on other organs at entry: NR Co-morbidities at entry: NR	c) 1,25$(OH)_2$ (mean percentage change from t_0 value): 3 months / 6 months 1,25$(OH)_2D_3$ +54* +63* Vitamin D_3 +20 +6 * $p < 0.05$ vs. baseline (t_0) d) Bone mineral content (mean ± SD; % of normal): Baseline (t_0) / 6 months 1,25$(OH)_2D_3$ 81.3 ± 5.1 / 80.5 ± 5.7 Vitamin D_3 70.2 ± 12.3 / 68.0 ± 10.6 p = not significant e) Calcification rate (mean ± SD; µm/day): Baseline (t_0) / 6 months 1,25$(OH)_2D_3$ 0.30 ± 0.17 / 0.33 ± 0.20 Vitamin D_3 0.41 ± 0.15 / 0.43 ± 0.20 p = not significant f) Active trabecular calcification surfaces (mean ± SD; %): Baseline (t_0) / 6 months 1,25$(OH)_2D_3$ 14.0 ± 10.6 / 19.4 ± 26.2 Vitamin D_3 17.4 ± 13.3 / 26.6 ± 23.9 p = not significant g) Renal function: During the 6-month treatment period (t_0 to t_6), CrCl was reduced in both groups. Compared with the reduction observed during the 6-month pretreatment period (t_{-6} to t_0), the on-treatment decline in the 1,25$(OH)_2D_3$ treatment group was statistically significant ($p < 0.01$); the on-treatment decline in the Vitamin D_3 group was not. (Results reported only graphically.)	

Evidence Table 2 – Bone disease (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Coen, Manni, Addari, et al., 1995	Design: Case series, concomitant controls (retrospective) Intervention(s) studied: In first phase of the analysis, investigators compared the baseline characteristics of 2 groups of patients: Group A, with normal acid-base equilibrium (serum HCO_3 > 20 mEq; n = 12), and Group B, with metabolic acidosis (HCO_3 < 18 mEq and pH < 7.34; n = 12). The second phase of the analysis examined the effects of treatment with calcitriol 0.25 µg daily for a period of 1 year on a subset of patients from each group, Group A-treated (n = 5) and Group B-treated (n = 6). Dates: NR Location: Rome, Italy Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 24 patients total, of whom 11 were treated with calcitriol Inclusion criteria: Chronic renal failure; not on dialysis Exclusion criteria: None specified Age (mean ± SD): Group A, 49.75 ± 12.9; Group B, 51.16 ± 11.9 Sex: Both groups 67% M, 33% F Race: NR Renal function at entry (mean ± SD): CrCl (ml/min): Group A: 19.84 ± 6.2 Group B: 18.05 ± 3.92 SCr (mg/dl): Group A: 4.52 ± 1.8 Group B: 4.89 ± 1.0 Serum measures of bone metabolism at entry (mean ± SD): Serum calcium (mg/dl): Group A: 8.83 ± 0.4 Group B: 8.82 ± 0.61 Serum phosphorus (mg/dl): Group A: 4.20 ± 1.1 Group B: 4.23 ± 0.6 iPTH (C-terminal; ng/ml): Group A: 1.64 ± 1.55 Group B: 2.66 ± 1.66 Anatomic measures of bone disease at entry: (see under "Results," at right)	*Key Question 1) Does the correction of acidosis reduce the risk of bone disease (osteomalacia, osteitis, osteoporosis) and/or other negative outcomes in pre-ESRD patients?:* a) Renal osteodystrophy (no. of patients): Osteomalacia: Group A 0/12, Group B 2/12 Mixed severe osteodystrophy: Group A 3/12, Group B 5/12 Mixed mild osteodystrophy: Group A 6/12, Group B 5/12 Normal bone: Group A 1/12, Group B 0/12 Adynamic bone disease: Group A 2/12, Group B 0/12 b) Osteoid volume (mean ± SD; %): Group A: 4.52 ± 3.4 Group B: 10.2 ± 6.6 p = 0.007 c) Osteoid surface (mean ± SD; %): Group A: 27.7 ± 18.7 Group B: 48.4 ± 1.95 p = 0.007 d) Mineralization lag time (mean ± SD; days): Group A: 56.5 ± 54 Group B: 170.5 ± 189.0 p = 0.05 e) Osteocalcin (mean ± SD; ng/ml): Group A: 23.7 ± 18.0 Group B: 42.31 ± 24.3 p = 0.02 *Key Question 2) Does the use of hormone replacement therapy reduce the risk of bone disease (osteomalacia, osteitis, osteoporosis) and/or other negative outcomes in pre-ESRD patients?:* Not addressed *Key Question 3) Does the use of phosphate binders and/or vitamin D supplementation reduce the risk of complications from hyperparathyroidism in pre-ESRD*	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: Partially Incl/excl described: No/not assessable Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 4 Notes:

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Evidence Table 2 – Bone disease (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
		Effects on other organs at entry: NR	*patients?:*	
		Co-morbidities at entry: NR	Not addressed	
		Other: HCO_3 (mean ± SD; mmol/l): Group A: 22.89 ± 2.6 Group B: 16.7 ± 1.8 p = 0.0000005 pCO_2 (mean ± SD; mmHg): Group A: 38.08 ± 2.2 Group B: 34.4 ± 2.7 p = 0.0001 pH (mean ± SD): Group A: 7.38 ± 0.03 Group B: 7.30 ± 0.03 p = 0.000003	*Key Question 4) Does the use of phosphate binders and/or vitamin D supplementation increase the risk of adynamic bone disease, cardiovascular disease, and/or other negative outcomes in pre-ESRD patients?:* Renal osteodystrophy (no. of patients): Before *treatment with calcitriol:* Osteomalacia: Group A-treated 0/5; Group B-treated 1/6 Mixed severe osteodystrophy: 1/5; 2/6 Mixed mild osteodystrophy: 2/5; 3/6 Normal bone: 0/5; 0/6 Adynamic bone disease: 2/5; 0/6 After *treatment with calcitriol:* Osteomalacia: Group A-treated 0/5; Group B-treated 0/6 Mixed severe osteodystrophy: 0/5; 2/6 Mixed mild osteodystrophy: 0/5; 3/6 Normal bone: 1/5; 1/6 Adynamic bone disease: 4/5; 0/6	

Evidence Table 2 – Bone disease (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Coen, Mazaferro, Bonucci, et al., 1986	Design: RCT Intervention(s) studied: 1) No treatment (n = 23); 2) $1,25(OH)_2D_3$ (n = 15). Dose was 0.25 μ g daily for an average period of 16.2 ± 11.3 months. Patients in both groups followed a diet moderately restricted in protein (0.8 g/kg) and phosphorous (12 mg/kg), containing approximately 35 cal/kg. All received oral calcium supplements (500 mg elemental calcium). Dates: NR Location: Rome, Italy Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 38 Inclusion criteria: Slowly evolving chronic renal failure; predialysis Exclusion criteria: None specified Age (mean ± SD): Placebo: 42.3 ± 17.7 Active: 51.2 ± 16.9 Sex: 61% M, 39% F Race: NR Renal function at entry: CrCl (mean ± SD; reported for active group only): 4.93 ± 1.70 mg/dl SCr (mean ± SD; reported for active group only): 4.93 ± 1.7 mg/dl Serum measures of bone metabolism at entry (mean ± SD): Calcium (mg/dl): Control: NR Active: 9.10 ± 0.37 Phosphorus (mg/dl): Control: NR Active: 3.95 ± 0.96 iPTH (ng/ml): Control: 2.21 ± 1.89 Active: 2.04 ± 1.49 Alkaline phosphatase (mU/ml): Control: NR Active: 207.23 ± 162.86 1,25-dihydroxy vitamin D (ng/ml): Control: NR Active: 16.65 ± 8.28	*Key Question 1) Does the correction of acidosis reduce the risk of bone disease (osteomalacia, osteitis, osteoporosis) and/or other negative outcomes in pre-ESRD patients?:* Not addressed *Key Question 2) Does the use of hormone replacement therapy reduce the risk of bone disease (osteomalacia, osteitis, osteoporosis) and/or other negative outcomes in pre-ESRD patients?:* Not addressed *Key Question 3) Does the use of phosphate binders and/or vitamin D supplementation reduce the risk of complications from hyperparathyroidism in pre-ESRD patients?:* Not addressed *Key Question 4) Does the use of phosphate binders and/or vitamin D supplementation increase the risk of adynamic bone disease, cardiovascular disease, and/or other negative outcomes in pre-ESRD patients?:* a) iPTH (mean ± SD; ng/ml): Control: Baseline 2.21 ± 1.89; End of study 3.01 ± 2.52 Active: Baseline 2.04 ± 1.49; End of study 1.90 ± 0.92 Control, end of study vs. baseline, p < 0.01 Active, end of study vs. baseline, p = not significant b) Alkaline phosphatase (mean ± SD; mU/ml): Control: Baseline NR; End of study 182.1 ± 121.8 Active: Baseline 207.23 ± 162.86; End of study 126.40 ± 109.46 Active, end of study vs. baseline, p < 0.0005 End of study, active vs. control, p = not significant c) Active osteoid surface (mean ± SD; at end-of-treatment biopsy): Control: 3.36 ± 3.39%	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: No/not assessable Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 2b Notes: Active treatment and control groups matched for rate of decline of renal function and cause of renal failure. Relationship between this study population and that described in Coen, Mazzaferro, Costantini, et al. (1989) unclear.

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Evidence Table 2 – Bone disease (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
		Anatomic measures of bone disease at entry: No evidence of tissue calcification Effects on other organs at entry: NR Co-morbidities at entry: NR	Active: 1.36 ± 2.00% p < 0.05 d) Resorption surface (mean ± SD; at end-of-treatment biopsy): Control: 5.63 ± 4.76% Active: 2.30 ± 2.37% p < 0.02 e) Active resorption surface (mean ± SD; end-of-treatment biopsy): Control: 1.11 ± 1.22% Active: 0.24 ± 0.27% p < 0.01 f) Osteoclastic index(mean ± SD; end-of-treatment biopsy): Control: 1.18 ± 1.39 n/mm^2 Active: 0.23 ± 0.26 n/mm^2 p < 0.01 g) Effect of 1,25$(OH)_2D_3$ on renal function (n = 15 active-treatment patients only): CrCl (mean ± SD; ml/min): Baseline: 18.45 ± 9.10 End of study: 12.74 ± 6.16 p < 0.0025	

Evidence Table 2 – Bone disease (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Coen, Mazzaferro, Costantini, et al., 1989	Design: RCT Intervention(s) studied: 1) No treatment (n = 16); 2) $1,25(OH)_2D_3$ (n = 16). Dose was 0.25 μ g daily for an average period of 13.5 ± 6.7 months. Patients in both groups followed a diet moderately restricted in protein (0.8 g/kg) and phosphorous (12 mg/kg), containing approximately 35 cal/kg. All received oral calcium supplements (500 mg elemental calcium). Dates: NR Location: Rome, Italy Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 32 Inclusion criteria: Slowly evolving chronic renal failure; predialysis; no exposure to aluminum-containing antacids (serum phosphate < 5.5 mg/dl) Exclusion criteria: None specified Age (mean ± SD): Control: 55.5 ± 12.8 Active: 56.5 ± 12.7 Sex: Both groups, 50% M, 50% F Race: NR Renal function at entry: SCr (overall; mean ± SD): 6.51 ± 2.92 mg/dl Serum measures of bone metabolism at entry: NR Anatomic measures of bone disease at entry: NR Effects on other organs at entry: NR Co-morbidities at entry: NR	*Key Question 1) Does the correction of acidosis reduce the risk of bone disease (osteomalacia, osteitis, osteoporosis) and/or other negative outcomes in pre-ESRD patients?:* Not addressed *Key Question 2) Does the use of hormone replacement therapy reduce the risk of bone disease (osteomalacia, osteitis, osteoporosis) and/or other negative outcomes in pre-ESRD patients?:* Not addressed *Key Question 3) Does the use of phosphate binders and/or vitamin D supplementation reduce the risk of complications from hyperparathyroidism in pre-ESRD patients?:* Not addressed *Key Question 4) Does the use of phosphate binders and/or vitamin D supplementation increase the risk of adynamic bone disease, cardiovascular disease, and/or other negative outcomes in pre-ESRD patients?:* a) Post-treatment iPTH (mean ± SD; ng/ml): Control: 3.08 ± 2.43 Active: 1.47 ± 0.85 p < 0.01 b) Post-treatment bone formation rate (mean ± SD; μ^3/μ^2/day): Control (n = 11): 0.269 ± 0.208 Active (n = 11): 0.549 ± 0.514 p = not significant c) Post-treatment mineral apposition rate (mean ± SD; μm/day): Control (n = 11): 0.485 ± 0.165 Active (n = 11): 0.641 ± 0.215 p < 0.05	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: No/not assessable Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: SCr 4) % pre-ESRD: > 75% 5) Level of evidence: 2b Note: Relationship between this study population and that described in Coen, Mazzaferro, Bonucci, et al. (1986) unclear.

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Evidence Table 2 – Bone disease (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			d) Post-treatment alkaline phosphatase (mean ± SD; mU/ml): Control: 111.12 ± 55.11 Active: 85.18 ± 38.33 p = not significant	

Evidence Table 2 – Bone disease (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Hamdy, Kanis, Beneton, et al., 1995	Design: RCT Intervention(s) studied: 1) Placebo (n = 87); 2) Alfacalcidol (1α-hydroxycholecalciferol) (n = 89). Starting dose 0.25 µg per day as a single morning dose. Doses adjusted between 0.25 µg every other day and 1 µg per day to maintain serum calcium concentration at the upper limit of the normal range. Both treatments given for 24 months. Dates: NR Location: 17 sites in Belgium, France, The Netherlands, and the UK Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 176 Inclusion criteria: CrCl 15-50 ml/min; no clinical, biochemical, or radiographic evidence of renal bone disease; no previous vitamin D therapy Exclusion criteria: Symptomatic bone disease; raised serum calcium concentration or total alkaline phosphatase activity; disturbance in liver function (≥ 1.5-fold increase in liver aminotransferase activity) Age (mean ± SD): Placebo: 51 ± 16 Alfacalcidol: 53 ± 15 Sex: Both groups, 61% M, 39% F Race: NR Renal function at entry (mean ± SD): CrCl (ml/min): Placebo: 32.9 ± 11.6 Alfacalcidol: 31.6 ± 10.8 SCr (mmol/l): Placebo: 263 ± 127 Alfacalcidol: 263 ± 119 Serum measures of bone metabolism at entry (mean ± SD): Corrected calcium (mmol/l): Placebo: 2.37 ± 0.14 Alfacalcidol: 2.36 ± 0.15 Phosphorus (mmol/l): Placebo: 1.33 ± 0.33 Alfacalcidol: 1.29 ± 0.28 Intact PTH (pmol/l):	*Key Question 1) Does the correction of acidosis reduce the risk of bone disease (osteomalacia, osteitis, osteoporosis) and/or other negative outcomes in pre-ESRD patients?:* Not addressed *Key Question 2) Does the use of hormone replacement therapy reduce the risk of bone disease (osteomalacia, osteitis, osteoporosis) and/or other negative outcomes in pre-ESRD patients?:* Not addressed *Key Question 3) Does the use of phosphate binders and/or vitamin D supplementation reduce the risk of complications from hyperparathyroidism in pre-ESRD patients?:* Not addressed *Key Question 4) Does the use of phosphate binders and/or vitamin D supplementation increase the risk of adynamic bone disease, cardiovascular disease, and/or other negative outcomes in pre-ESRD patients?:* a) Intact PTH – mean change (± SD) from baseline to 24 months (pmol/l): Placebo: 8.1 ± 2.1 Alfacalcidol: 0.6 ± 1.0 p < 0.001 b) Bone abnormalities: |	Baseline	24 months
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Placebo (n = 62):	73%	82%
Alfacalcidol (n = 72):	76%	54%	 No p-values reported Among patients with histological abnormalities at the start of the study, 42% of patients given alfacalcidol showed normal histological appearances at the end of the study compared with only 4% of those given placebo (p < 0.001).	Quality Scoring: 1) Global assessment: Excellent 2) Validity criteria: Population described: Completely Incl/excl described: Completely Dropouts discussed: Completely Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 1b Note: 16/89 patients (18%) receiving alfacalcidol and 22/87 patients (25%) receiving placebo withdrew prematurely, most commonly because of the need to start dialysis. No patient withdrew due to side effects, persistent hypercalcemia, or unexpected progression of renal disease.

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Evidence Table 2 – Bone disease (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
		Placebo: 6.4 ± 4.6 Alfacalcidol: 10.3 ± 15.9 Alkaline phosphatase (IU/l): Placebo: 152 ± 71 Alfacalcidol: 154 ± 69 Anatomic measures of bone disease at entry: Osteitis fibrosa: Placebo: 71% Alfacalcidol: 75% Osteitis fibrosa and osteomalacia: Placebo: 20% Alfacalcidol: 18% Osteomalacia alone: Placebo: 1% Alfacalcidol: 0 Aluminum staining of bone: Placebo: 0 Alfacalcidol: 2% Adynamic bone lesions: Placebo: 3% Alfacalcidol: 7% Effects on other organs at entry: NR Co-morbidities at entry: NR		

Evidence Table 2 – Bone disease (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Lin, Shieh, Diang, et al., 1994	Design: Prospective clinical trial (before/after) Intervention(s) studied: Bicarbonate infusion to raise serum HCO_3 to 24 mmol/l or pH to approximately 7.4 (n = 18). Calcium gluconate also infused to maintain ionized calcium at preinfusion levels. Potassium chloride infused to prevent hypokalemia. Mean quantities of bicarbonate and calcium infusion solutions (± SD) were 132.18 ± 24.26 ml and 54.45 ± 12.76 ml, respectively. Mean infusion time was 3.42 ± 0.86 hours. Dates: NR Location: Taipei, Taiwan Recruitment setting: Not specified/unable to determine	No. of pre-ESRD subjects: 18 Inclusion criteria: Recent diagnosis of CRF; CrCl < 30 ml/min; mild to moderate metabolic acidosis; predialysis; product of plasma calcium and inorganic phosphorus < 60 mg/dl Exclusion criteria: Use of aluminum, vitamin D analogs, Dilantin, H_2 blockers, or β-blockers; parathyroidectomy; intercurrent illness Age (mean, with range): 55.89 (36-73) Sex: 67% M, 33% F Race: NR Renal function at entry: CrCl (ml/min): Mean, 12.0; range, 5.4-28.8 Serum measures of bone metabolism at entry (mean ± SD): Total calcium (mmol/l): 2.013 ± 0.235 Ionized calcium (mmol/l): 1.08 ± 0.18 Phosphorus (mmol/l): 1.63 ± 0.36 iPTH (ng/l): 153.71 ± 88.55 Bone-specific alkaline phosphatase (µkat/l): 1.85 ± 1.29 Anatomic measures of bone disease at entry: NR Effects on other organs at entry: NR Co-morbidities at entry: NR	*Key Question 1) Does the correction of acidosis reduce the risk of bone disease (osteomalacia, osteitis, osteoporosis) and/or other negative outcomes in pre-ESRD patients?:* a) HCO_3 (mean ± SD; mmol/l): Baseline: 18.46 ± 2.49 Post-treatment: 23.66 ± 2.72 p < 0.001 b) pH (mean ± SD): Baseline: 7.31 ± 0.04 Post-treatment: 7.40 ± 0.03 p < 0.001 c) Osteocalcin (mean ± SD; µg/l): Baseline: 15.6 ± 6.45 Post-treatment: 18.79 ± 6.71 p < 0.05 d) iPTH (mean ± SD; ng/l): Baseline: 153.71 ± 88.55 Post-treatment: 111.51 ± 78.71 p < 0.001 e) Bone-specific alkaline phosphatase (mean ± SD; µkat/l): Baseline: 1.85 ± 1.29 Post-treatment: 1.79 ± 1.18 p = 0.252 *Key Question 2) Does the use of hormone replacement therapy reduce the risk of bone disease (osteomalacia, osteitis, osteoporosis) and/or other negative outcomes in pre-ESRD patients?:* Not addressed *Key Question 3) Does the use of phosphate binders and/or vitamin D supplementation reduce the risk of complications from hyperparathyroidism in pre-ESRD patients?:*	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: Partially Incl/excl described: Partially Dropouts discussed: Completely Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 4 Notes:

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Evidence Table 2 – Bone disease (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			Not addressed *Key Question 4) Does the use of phosphate binders and/or vitamin D supplementation increase the risk of adynamic bone disease, cardiovascular disease, and/or other negative outcomes in pre-ESRD patients?:* Not addressed	

Evidence Table 2 – Bone disease (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Nordal and Dahl, 1988	Design: RCT Intervention(s) studied: 1) Placebo (n = 15); 2) Calcitriol (n = 15) 0.25 µg per day for first 14 days, then 0.50 µg for duration of study. Treatment suspended for 3 days if serum calcium ≥ 2.7 mmol/l and then adjusted to maintain level between 2.4 and 2.7 mmol/l. In both groups, treatment lasted 8 months. Dates: NR Location: Oslo, Norway Recruitment setting: Not specified/unable to determine	No. of pre-ESRD subjects: 30 Inclusion criteria: SCr > 180 µmol/l; stable renal function for previous 4 months; predialysis; not taking medication known to influence bone metabolism (except phosphate-binding agents) Exclusion criteria: None specified Age (mean, with range): Placebo: 47 (23-69) Calcitriol: 48 (26-71) Sex: Placebo, 73% M, 27% F; calcitriol, 60% M, 40% F Race: NR Renal function at entry: CrCl (mean; estimated from graph): Placebo: 30 ml/min Calcitriol: 24 ml/min Scr (mean; estimated from graph): Placebo: 400 µmol/l Calcitriol: 400 µmol/l Serum measures of bone metabolism at entry (median, with 25th and 75th percentile values): Calcium (mmol/l): Placebo: 2.40 (2.30-2.40) Calcitriol: 2.30 (2.20-2.40) Ionized calcium (mmol/l): Placebo: 1.27 (1.21-1.32) Calcitriol: 1.25 (1.22-1.34) Phosphorus (mmol/l): Placebo: 1.40 (1.25-1.73) Calcitriol: 1.60 (1.38-1.73)	*Key Question 1) Does the correction of acidosis reduce the risk of bone disease (osteomalacia, osteitis, osteoporosis) and/or other negative outcomes in pre-ESRD patients?:* Not addressed *Key Question 2) Does the use of hormone replacement therapy reduce the risk of bone disease (osteomalacia, osteitis, osteoporosis) and/or other negative outcomes in pre-ESRD patients?:* Not addressed *Key Question 3) Does the use of phosphate binders and/or vitamin D supplementation reduce the risk of complications from hyperparathyroidism in pre-ESRD patients?:* Not addressed *Key Question 4) Does the use of phosphate binders and/or vitamin D supplementation increase the risk of adynamic bone disease, cardiovascular disease, and/or other negative outcomes in pre-ESRD patients?:* a) PTH (median, with 25th and 75th percentile values; µg/l): Baseline / 8 months Placebo 0.94 (0.63-1.58) 1.37 (1.06-2.61) Calcitriol 1.33 (0.54-2.39) 0.98 (0.43-1.79) 8 months vs. baseline, p < 0.01 in each group b) CrCl (mean; ml/min; estimated from graph): Baseline / 8 months Placebo 30 24 Calcitriol 24 20 8 months vs. baseline, p < 0.01 in each group Between-group comparison, p = not significant c) SCr (mean; µmol/l; estimated from graph): Baseline / 8 months Placebo 400 495 Calcitriol 400 465	Quality Scoring: 1) Global assessment: Good 2) Validity criteria: Population described: Completely Incl/excl described: Partially Dropouts discussed: Completely Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 2b Note: 1 patient in each group did not complete the 8-month treatment period.

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Evidence Table 2 – Bone disease (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
		PTH (µg/l): Placebo: 0.94 (0.63-1.58) Calcitriol: 1.33 (0.54-2.39) Alkaline phosphatase (U/l): Placebo: 209 (142-351) Calcitriol: 201 (151-297) Serum aluminum (estimated from graph; µg/l): Placebo: 18 Calcitriol: 30 Anatomic measures of bone disease at entry (median, with 25th and 75th percentile values): Mineral apposition rate (µm/day): Placebo: 0.55 (0.46-0.61) Calcitriol: 0.53 (0.49-0.61) Mineralizing surface (%): Placebo: 10 (8-15) Calcitriol: 12 (8-29) Effects on other organs at entry: NR Co-morbidities at entry: NR	8 months vs. baseline, $p < 0.01$ in each group Between-group comparison, p = not significant	

Evidence Table 2 – Bone disease (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Przedlacki, Manelius, and Huttunen, 1995	Design: RCT Intervention(s) studied: 1) Placebo (n = 12); 2) Calcitriol 0.25 µg per day (n = 13). Treatment was continued for 1 year. Patients in both groups were given calcium acetate (0.75-1.5 g/day) when serum calcium levels were ≤ 2.6 mmol/l, blood ionized calcium level was ≤ 1.29 mmol/l, or serum phosphorus level was ≥ 0.8 mmol/l. Dates: NR Location: Oulu, Finland Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 26 were randomized to treatment; 25 completed the trial Inclusion criteria: Age < 70; GFR ≤ 51.2 ml/min Exclusion criteria: Pregnancy; hypercalcemia (serum > 2.6 mmol/l); renal stones; intestinal diseases; diabetes; treatment with steroids, vitamin D metabolites, anti-coagulants, or anticonvulsants. Age (mean ± SEM): Placebo, 50.3 ± 2.9; calcitriol, 49.3 ± 3.0 Sex: Placebo, 67% M, 33% F; calcitriol, 15% M, 85% F Race: NR Renal function at entry (mean ± SEM): GFR (ml/min): Placebo: 31.3 ± 4.0 Calcitriol: 21.5 ± 3.2 SCr (µmol/l): Placebo: 272.6 ± 32.8 Calcitriol: 340.6 ± 35.5 Serum measures of bone metabolism at entry (mean ± SEM): Calcium (mmol/l): Placebo: 2.29 ± 0.04 Calcitriol: 2.34 ± 0.01 Ionized calcium (mmol/l): Placebo: 1.23 ± 0.01 Calcitriol: 1.21 ± 0.02 Phosphorus (mmol/l):	*Key Question 1) Does the correction of acidosis reduce the risk of bone disease (osteomalacia, osteitis, osteoporosis) and/or other negative outcomes in pre-ESRD patients?:* Not addressed *Key Question 2) Does the use of hormone replacement therapy reduce the risk of bone disease (osteomalacia, osteitis, osteoporosis) and/or other negative outcomes in pre-ESRD patients?:* Not addressed *Key Question 3) Does the use of phosphate binders and/or vitamin D supplementation reduce the risk of complications from hyperparathyroidism in pre-ESRD patients?:* Not addressed *Key Question 4) Does the use of phosphate binders and/or vitamin D supplementation increase the risk of adynamic bone disease, cardiovascular disease, and/or other negative outcomes in pre-ESRD patients?:* a) Bone mineral density – lumbar spine (mean ± SEM; g/cm^2): Baseline / 1 year Placebo 1.214 ± 0.071 / 1.201 ± 0.075 Calcitriol 1.111 ± 0.049 / 1.133 ± 0.053 1 year vs. baseline: p < 0.05, placebo; p< 0.01, calcitriol Mean changes from baseline to 1 year were -0.022 g/cm^2 in the placebo group and +0.028 in the calcitriol group (p < 0.01). b) Alkaline phosphatase (mean ± SEM; U/l): Baseline / 1 year Placebo 184.2 ± 21.5 / 180.3 ± 18.5 Calcitriol 165.0 ± 19.5 / 143.0 ± 15.1 Calcitriol, 1 year vs. baseline, p < 0.05 Calcitriol vs. placebo, p = not significant	Quality Scoring: 1) Global assessment: Excellent 2) Validity criteria: Population described: Partially Incl/excl described: Completely Dropouts discussed: Completely Sample size justified: No/not assessable 3) GFR/CrCl: Measured by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 1b Note: 1 patient randomized to the placebo group died of myocardial infarction in the 9th month of the study.

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Evidence Table 2 – Bone disease (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
		Placebo: 1.27 ± 0.11 Calcitriol: 1.44 ± 0.12 iPTH (ng/l): Placebo: 122.6 ± 26.1 Calcitriol: 150.3 ± 26.2 Alkaline phosphatase (U/l): Placebo: 184.2 ± 21.5 Calcitriol: 165.0 ± 19.5 $1,25(OH)_2D_3$ (pmol/l): Placebo: 63.3 ± 7.2 Calcitriol: 43.8 ± 4.0 Aluminum (µmol/l): Placebo: 0.24 ± 0.04 Calcitriol: 0.23 ± 0.04 Gla protein (µmol/l): Placebo: 24.6 ± 3.0 Calcitriol: 26.3 ± 2.3 Anatomic measures of bone disease at entry (mean ± SEM): Densitometry results (g/cm^2): Lumbar spine: Placebo: 1.214 ± 0.071 Calcitriol: 1.111 ± 0.049 Femoral neck: Placebo: 0.860 ± 0.052 Calcitriol: 0.806 ± 0.028 Trochanter: Placebo: 0.800 ± 0.045 Calcitriol: 0.708 ± 0.028 Effects on other organs at entry: NR Co-morbidities at entry: NR	c) iPTH (mean ± SEM; ng/l): Baseline 1 year Placebo 122.6 ± 26.1 151.4 ± 26.2 Calcitriol 150.3 ± 26.2 105.8 ± 29.0 Calcitriol, 1 year vs. baseline, p < 0.05 Calcitriol vs. placebo, p < 0.05 d) Calcium (mean ± SEM; mmol/l): Baseline 1 year Placebo 2.29 ± 0.04 2.34 ± 0.03 Calcitriol 2.34 ± 0.01 2.39 ± 0.08 1 year vs. baseline comparisons, p = not significant Calcitriol vs. placebo comparisons, p = not significant e) Gla protein (mean ± SEM; µmol/l): Baseline 1 year Placebo 24.6 ± 3.0 28.3 ± 3.4 Calcitriol 26.3 ± 20.0 20.0 ± 2.6 1 year vs. baseline, p < 0.05, both groups f) GRF (mean ± SEM; ml/min): Baseline 1 year Placebo 31.3 ± 4.0 26.3 ± 3.7 Calcitriol 21.5 ± 3.2 18.7 ± 5.2 1 year vs. baseline, p < 0.05, both groups Calcitriol vs. placebo, p = not significant	

Evidence Table 2 – Bone disease (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Ritz, Küster, Schmidt-Gayk, et al., 1995	Design: RCT Intervention(s) studied: 1) Placebo (n = 21); 2) Calcitriol 0.125 µg per day (n = 24). Treatment continued for 12 months. Patients to be withdrawn if they had hypercalcemia (≥ 2.7 mmol/l) or hyperphosphatemia (≥ 2.2 mmol/l) on 3 consecutive occasions (did not occur). Calcium carbonate to be administered if serum phosphate > 1.7 mmol/l. Aluminum hydroxide permitted in case of hypercalcemia > 2.7 mmol/l (did not occur). Dates: NR Location: 5 sites in Germany (Heidelberg, Jena, Hannover, Greifswald, and Würzburg) Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 52 patients in intention-to-treat analysis; 45 completed trial Inclusion criteria: SCr between 1.4 and 6.5 mg/dl; 1,84 iPTH levels above normal range (6 pmol/l) on 3 separate occasions during recruitment phase Exclusion criteria: Nephrotic proteinuria (> 3.5 g/24 hours); diabetes mellitus; immunosuppressive therapy; frank vitamin D deficiency (< 10 nmol $25(OH)D_{3/1}$); anticonvuslant therapy; nephrocalcinosis Age (median, with range): Placebo: 55 (26-68) Calcitriol: 54 (27-70) Sex: Placebo, 48% M, 52% F; calcitriol, 67% M, 23% F Race: NR Renal function at entry: SCr (median, with range; mg/dl): Placebo: 3.06 (1.57-6.26) Calcitriol: 3.31 (1.47-5.46) Serum measures of bone metabolism at entry (median, with range): Calcium (mmol/l): Placebo: 2.44 (2.00-2.6) Calcitriol: 2.40 (2.13-2.40) Phosphorus (mmol/l): Placebo: 1.20 (0.82-1.7) Calcitriol: 1.19 (0.56-1.8) 1,84 iPTH (pmol/l):	*Key Question 1) Does the correction of acidosis reduce the risk of bone disease (osteomalacia, osteitis, osteoporosis) and/or other negative outcomes in pre-ESRD patients?:* Not addressed *Key Question 2) Does the use of hormone replacement therapy reduce the risk of bone disease (osteomalacia, osteitis, osteoporosis) and/or other negative outcomes in pre-ESRD patients?:* Not addressed *Key Question 3) Does the use of phosphate binders and/or vitamin D supplementation reduce the risk of complications from hyperparathyroidism in pre-ESRD patients?:* Not addressed *Key Question 4) Does the use of phosphate binders and/or vitamin D supplementation increase the risk of adynamic bone disease, cardiovascular disease, and/or other negative outcomes in pre-ESRD patients* a) 1,84 iPTH (median, with range; pmol/l; intention-to-treat analysis): Baseline / 1 year Placebo 14.0 (6.7-63.3) 27.8 (4.2-68.5) Calcitriol 16.2 (6.85-82.0) 18.2 (4.45-75.5) Calcitriol vs. placebo, p = 0.05 b) Alkaline phosphatase (median, with range; U/l): Baseline / 1 year Placebo 118 (65-205) 119 (61-302) Calcitriol 113 (57-220) 99 (55-241) Calcitriol vs. placebo, p = not significant c) Bone-specific alkaline phosphatase (median, with range; U/l): Baseline / 1 year Placebo 22 (6.1-40) 22 (8.0-34) Calcitriol 15 (7.5-37) 13.5 (6.5-32)	Quality Scoring: 1) Global assessment: Good 2) Validity criteria: Population described: Completely Incl/excl described: Completely Dropouts discussed: Completely Sample size justified: No/not assessable 3) GFR/CrCl: SCr 4) % pre-ESRD: > 75% 5) Level of evidence: 1b Note: 7/52 patients dropped out before the end of the study, 4 from the placebo group and 3 from the calcitriol group.

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Evidence Table 2 – Bone disease (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
		Placebo (n = 24): 14.0 (6.7-63.3) Calcitriol (n = 18): 16.2 (6.85-82.0) Alkaline phosphatase (U/l): Placebo: 118 (65-205) Calcitriol: 113 (57-220) Bone-specific alkaline phosphatase (U/l): Placebo: 22 (6.1-40) Calcitriol: 15 (7.5-37) 25(OH)D (nmol/l): Placebo: 49 (17-193) Calcitriol: 75.5 (19-221) Aluminum (µg/l): Placebo: 18 (5-34) Calcitriol: 19 (5-34) Osteocalcin (µg/l): Placebo: 6.6 (1.3-19) Calcitriol: 6.5 (1.1-28) Anatomic measures of bone disease at entry: NR Effects on other organs at entry: NR Co-morbidities at entry: NR	Calcitriol vs. placebo, p = not significant d) SCr (median, with range; mg/dl): Baseline 1 year Placebo 3.06 (1.57-6.26) 3.48 (1.01-9.58) Calcitriol 3.31 (1.47-5.46) 4.07 (1.53-10.2) Calcitriol vs. placebo, p = not significant	

Evidence Table 2 – Bone disease (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Saha, Pietilä, Mustonen, et al., 1991	Design: Nonrandomized controlled trial, crossover design (half the patients were given calcium carbonate and half calcium citrate on the 1st day; the other calcium salt was given on the 2nd day) Intervention(s) studied: 1) Calcium carbonate providing 2 g elemental calcium; 2) Calcium citrate providing 2 g elemental calcium. Interventions given after an overnight fast. Medications containing calcium, vitamin D, or bicarbonate discontinued 3 days prior to start of study. Outcomes measured for 3 hours after calcium salt administration. Dates: NR Location: Tampere, Finland Recruitment setting: Not specified/unable to determine	No. of pre-ESRD subjects: 14 Inclusion criteria: Moderate to severe impairment of renal function Exclusion criteria: Dialysis Age: Mean, 48.5; range, 29-67 Sex: 57% M, 43% F Race: NR Renal function at entry: SCr (mean ± SD): 759 ± 365 µmol/l) Serum measures of bone metabolism at entry: NR Anatomic measures of bone disease at entry: NR Effects on other organs at entry: NR Co-morbidities at entry: NR	*Key Question 1) Does the correction of acidosis reduce the risk of bone disease (osteomalacia, osteitis, osteoporosis) and/or other negative outcomes in pre-ESRD patients?:* Not addressed *Key Question 2) Does the use of hormone replacement therapy reduce the risk of bone disease (osteomalacia, osteitis, osteoporosis) and/or other negative outcomes in pre-ESRD patients?:* Not addressed *Key Question 3) Does the use of phosphate binders and/or vitamin D supplementation reduce the risk of complications from hyperparathyroidism in pre-ESRD patients?:* Not addressed *Key Question 4) Does the use of phosphate binders and/or vitamin D supplementation increase the risk of adynamic bone disease, cardiovascular disease, and/or other negative outcomes in pre-ESRD patients?:* Not addressed *Other outcomes:* Decrease in plasma intact PTH at 2 hours* (mean decrease ± SD): Calcium carbonate: 9.2 ± 18.9% (p = not significant) Calcium citrate: 35.9 ± 24.8% (p < 0.001) *Maximal suppression of PTH secretion observed at this time point.	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: No/not assessable Incl/excl described: No/not assessable Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: SCr 4) % pre-ESRD: 50-75% 5) Level of evidence: 2b Notes:

Evidence Table 2 – Bone disease (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Tessitore, Venturi, Adami, et al., 1987 **Study 1**	Design: Cohort study [?] Intervention(s) studied: Low-protein, low-phosphorous diet containing approximately 0.6 g/kg body weight protein, 700 mg phosphate, and 1,300-1,800 mg calcium (700-1,200 mg of which were orally supplemented as a mixture of calcium carbonate and gluconolactate). Diet continued for 29 ± 2 months (mean ± SEM). Dates: NR Location: Rome, Italy Recruitment setting: Not specified/unable to determine	No. of pre-ESRD subjects: 17 Inclusion criteria: Early renal failure; normal serum proteins; proteinuria < 1.0 g/24 hours; low baseline levels of $1,25(OH)_2D_3$ Exclusion criteria: Use of steroids, anticonvulsant drugs, intestinal phosphate binders, vitamin D, or vitamin D analogs Age: NR Sex: NR Race: NR Renal function at entry: GFR (mean): 45.3 ml/min Serum measures of bone metabolism at entry (mean): Serum calcium: 9.2 mg/dl Serum phosphorus: 3.2 mg/dl Serum PTH: 2.9 mU/ml Serum $1,25(OH)_2D_3$: 11.0 pg/ml Anatomic measures of bone disease at entry: NR Effects on other organs at entry: NR Co-morbidities at entry: NR	*Key Question 1) Does the correction of acidosis reduce the risk of bone disease (osteomalacia, osteitis, osteoporosis) and/or other negative outcomes in pre-ESRD patients?:* Not addressed *Key Question 2) Does the use of hormone replacement therapy reduce the risk of bone disease (osteomalacia, osteitis, osteoporosis) and/or other negative outcomes in pre-ESRD patients?:* Not addressed *Key Question 3) Does the use of phosphate binders and/or vitamin D supplementation reduce the risk of complications from hyperparathyroidism in pre-ESRD patients?:* Not addressed *Key Question 4) Does the use of phosphate binders and/or vitamin D supplementation increase the risk of adynamic bone disease, cardiovascular disease, and/or other negative outcomes in pre-ESRD patients?:* Not addressed *Other outcomes:* Those patients who had a significant decline in GFR during the course of the study (n = 6) had a significant increase in PTH, a significant decrease in urinary phosphate, and a non-significant decrease in serum $1,25(OH)_2D_3$ on the prescribed diet; serum calcium was unchanged: a) PTH (mean ± SEM; mU/ml): Baseline: 2.7 ± 1.1 Post-treatment: 5.2 ± 0.7 $p < 0.005$ b) Urinary phosphate (mean ± SEM; mg/24 hours): Baseline: 493 ± 39	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: No/not assessable Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Measured by investigators 4) % pre-ESRD: 50-75% 5) Level of evidence: 2b Notes:

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Evidence Table 2 – Bone disease (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			Post-treatment: 312 ± 49 p < 0.005 c) Serum $1,25(OH)_2D_3$ (mean ± SEM; pg/ml): Baseline: 15.0 ± 9.7 Post-treatment: 11.9 ± 7.6 p = not significant d) Serum calcium (mean ± SEM; mg/dl): Baseline: 9.0 ± 0.6 Post-treatment: 9.1 ± 0.4 p = not significant Those patients with preserved renal function (n = 11) had significant increases in serum $1,25(OH)_2D_3$ and serum calcium, and a significant decrease in urinary phosphate on the prescribed diet; serum PTH was unchanged: e) PTH (mean ± SEM; mU/ml): Baseline: 3.0 ± 1.4 Post-treatment: 2.6 ± 0.7 p = not significant f) Urinary phosphate (mean ± SEM; mg/24 hours): Baseline: 520 ± 112 Post-treatment: 409 ± 50 p < 0.05 g) Serum $1,25(OH)_2D_3$ (mean ± SEM; pg/ml): Baseline: 8.8 ± 6.4 Post-treatment: 27.3 ± 14.9 p < 0.005 h) Serum calcium (mean ± SEM; mg/dl): Baseline: 9.3 ± 0.5 Post-treatment: 9.7 ± 0.2 p < 0.05	

Evidence Table 2 – Bone disease (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Tessitore, Venturi, Adami, et al., 1987 **Study 2**	Design: Retrospective cohort study Intervention(s) studied: 1) Low-phosphate (500-600 mg), high-calcium (1,300-1,800 mg) diet (n = 83); 2) Unrestricted diet (n = 68). Both diets followed "for 2-4 years." Dates: NR Location: Rome, Italy Recruitment setting: Not specified/unable to determine	No. of pre-ESRD subjects: 151 Inclusion criteria: Advanced renal failure (GFR 10-30 ml/min) Exclusion criteria: More than short-term use of vitamin D or its analogs; use of aluminum-containing phosphate binders Age: NR Sex: NR Race: NR Renal function at entry: NR Serum measures of bone metabolism at entry: NR Anatomic measures of bone disease at entry: NR Effects on other organs at entry: NR Co-morbidities at entry: NR	*Key Question 1) Does the correction of acidosis reduce the risk of bone disease (osteomalacia, osteitis, osteoporosis) and/or other negative outcomes in pre-ESRD patients?:* Not addressed *Key Question 2) Does the use of hormone replacement therapy reduce the risk of bone disease (osteomalacia, osteitis, osteoporosis) and/or other negative outcomes in pre-ESRD patients?:* Not addressed *Key Question 3) Does the use of phosphate binders and/or vitamin D supplementation reduce the risk of complications from hyperparathyroidism in pre-ESRD patients?:* Not addressed *Key Question 4) Does the use of phosphate binders and/or vitamin D supplementation increase the risk of adynamic bone disease, cardiovascular disease, and/or other negative outcomes in pre-ESRD patients?:* Not addressed *Other outcomes:* a) Osteomalacia: Low-phosphate, high-calcium diet: 34% Unrestricted diet: 32% p = not significant b) Bone resorption: Low-phosphate, high-calcium diet: 61% Unrestricted diet: 17% p < 0.001	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: No/not assessable Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Measured by investigators 4) % pre-ESRD: 50-75% 5) Level of evidence: 2b Notes:

Evidence Table 2 – Bone disease (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Tougaard, Sørensen, Brøchner-Mortensen, et al., 1976	Design: RCT Intervention(s) studied: 1) Placebo (n = 12); 2) 1α-hydroxycholecalciferol (1α-HCC) 1 µg per day (n = 12). Treatment continued for 11 weeks. Patients in both groups received calcium lactogluconate (500 mg elemental Ca++) daily. All were on a normal diet and continued with their usual medication during the trial. Dates: NR Location: Aarhus, Denmark Recruitment setting: Not specified/unable to determine	No. of pre-ESRD subjects: 24 Inclusion criteria: Relatively stable GFR between 5 and 25 ml/min; predialysis; not taking phosphate binders, anticonvulsants, or hormones Exclusion criteria: None specified Age: Range, 20-70 Sex: 37.5% M, 62.5% F Race: NR Renal function at entry: GFR (mean; ml/min): Placebo: 13.5 1α-HCC: 11.2 Serum measures of bone metabolism at entry (mean): Calcium (mmol/l): Placebo: 2.27 1α-HCC: 2.30 Phosphorus (mmol/l): Placebo: 1.47 1α-HCC: 1.56 iPTH (log pg/ml): Placebo: 2.53 1α-HCC: 2.64 Alkaline phosphatase (u/l): Placebo: 34.8 1α-HCC: 49.0 Anatomic measures of bone disease at entry (mean): Mineral content (% of normal): Placebo: 86.8 1α-HCC: 86.4	*Key Question 1) Does the correction of acidosis reduce the risk of bone disease (osteomalacia, osteitis, osteoporosis) and/or other negative outcomes in pre-ESRD patients?:* Not addressed *Key Question 2) Does the use of hormone replacement therapy reduce the risk of bone disease (osteomalacia, osteitis, osteoporosis) and/or other negative outcomes in pre-ESRD patients?:* Not addressed *Key Question 3) Does the use of phosphate binders and/or vitamin D supplementation reduce the risk of complications from hyperparathyroidism in pre-ESRD patients?:* Not addressed *Key Question 4) Does the use of phosphate binders and/or vitamin D supplementation increase the risk of adynamic bone disease, cardiovascular disease, and/or other negative outcomes in pre-ESRD patients* a) iPTH (mean change from baseline to 11 weeks [± SD]; log pg/ml): Placebo: 0.00 ± 0.16 1α-HCC: -0.40 ± 0.22 p < 0.001 b) Alkaline phosphatase (mean change from baseline to 11 weeks [± SD]; u/l): Placebo: -1.7 ± 7.4 1α-HCC: -12.3 ± 20.9 p = not significant c) Bone mineral content (mean change from baseline to 11 weeks [± SD]; % of normal): Placebo: -0.9 ± 2.2 1α-HCC: -0.8 ± 1.1 p = not significant	Quality Scoring: 1) Global assessment: Good 2) Validity criteria: Population described: Partially Incl/excl described: Partially Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Measured by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 1b Notes:

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Evidence Table 2 – Bone disease (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
		Phosphorus/hydroxyproline (% of normal): Placebo: 96.3 1α-HCC: 94.3 Effects on other organs at entry: NR Co-morbidities at entry: NR	d) Phosphorus/hydroxyproline (mean change from baseline to 11 weeks [± SD]; % of normal): Placebo: 0.6 ± 5.9 1α-HCC: 2.1 ± 6.3 p = not significant e) Calcium (mean change from baseline to 11 weeks [± SD]; mmol/l): Placebo: 0.00 ± 0.12 1α-HCC: 0.20 ± 0.17 p < 0.01 f) Phosphorus(mean change from baseline to 11 weeks [± SD]; mmol/l): Placebo: 0.07 ± 0.18 1α-HCC: -0.03 ± 0.39 p = not significant g) GFR (mean change from baseline to 11 weeks [± SD]; ml/min): Placebo: -1.1 ± 3.1 1α-HCC: -2.8 ± 2.5 p = not significant	

4. Hypertension

4.1 Chapter summary

The purpose of the Hypertension section is to compile evidence related to the management of hypertension in pre-ESRD patients who are expected to progress to ESRD and initiate renal replacement therapy within 6 to 18 months. The general question to be addressed is: "How should physicians manage blood pressure in subjects with severe chronic kidney disease as they prepare for ESRD?" The issue of blood pressure management to slow progression of chronic kidney disease is beyond the scope of this guideline development project; hypertension and chronic kidney disease progression is a focus of the new K/DOQI Chronic Kidney Disease Clinical Practice Guidelines.

There are several questions or themes to keep in mind as the evidence is summarized:

1. What kind of statements should this guideline make regarding blood pressure management for pre-ESRD patients?
2. What blood pressure goals should the guideline recommend?
3. Are there particular pharmaceutical agents that should be used, should not be used, or should be monitored carefully in pre-ESRD patients?

Key Question #1: What is the distribution of blood pressure or the prevalence of hypertension in pre-ESRD patients?

No evidence is available on the distribution of untreated blood pressure in pre-ESRD patients.

Based on two retrospective studies and one prospective trial, the majority of pre-ESRD subjects have systolic blood pressure greater than 140 OR diastolic blood pressure greater than 90.

Based on two retrospective studies and two prospective trials, greater than 80% of pre-ESRD subjects have hypertension based on either elevated blood pressure or use of anti-hypertensive agents.

Key Question #2: What is the prevalence of antihypertensive treatment in the pre-ESRD population?

Based on two retrospective studies and one prospective trial, approximately 81% of pre-ESRD patients are receiving antihypertensive treatement (studies reported 69%, 82%, 86%, and 87%).

Key Question #3: Is there evidence that treatment of elevated blood pressure with antihypertensive agents in pre-ESRD patients improves clinical outcomes before and/or after kidney replacement therapy?

Data from eleven prospective intervention trials show that blood pressure may be lowered in pre-ESRD patients. Usually, these studies do not show blood pressure lowered to the degree recommended by JNC VI.

A number of studies have shown that particular agents (ACE inhibitors and possibly calcium channel antagonists) may reduce the decline in kidney function or may lower protein excretion in pre-ESRD patients.

There are no interventional data showing what level of blood pressure control during pre-ESRD is optimal for clinical outcomes such as mortality, cardiac morbidity, or hospitalization.

Several large, randomized intervention trials show that antihypertensives affecting the renin-angiotensin axis improve some surrogate and clinical outcomes in patients with earlier stages of chronic kidney disease (HOPE, RENAAL, IDNT, AASK). These findings do not specifically address the issue of improving clinical outcomes for pre-ESRD subjects who are preparing to initiate kidney replacement therapy within 6 to 18 months.

Question #4: What is the risk of antihypertensive agent toxicities or side effects that occur as a consequence of reduced kidney function?

There are no systematic, population-based reports of antihypertensive drug toxicities or side effects that are specifically associated with reduced kidney function. Studies regarding this topic are generally reported as either single case reports or small case series.

Bradycardia with either beta-blockers or calcium channel antagonists is often a concern in advanced kidney failure. There is little data in the literature to systematically evaluate this phenomenon.

ACE-inhibitors and angiotensin receptor blockers have been related to both hyperkalemia and acute kidney failure in subjects with advanced kidney impairment. Two prospective trials involving a total of 124 pre-ESRD subjects did not show clinically significant hyperkalemia or acute kidney failure associated with either ACE-inhibitors or ARBS.

4.2 Background

Hypertension is a leading cause of morbidity and mortality in the general population. Epidemiological associations between elevated blood pressure and adverse clinical outcomes such as myocardial infarction, stroke, and death have been reported in large population-based cohort studies, while interventional trials have shown that modification of elevated blood pressure reduces these risks[1]. More intensive lowering of blood pressure (reduction of diastolic blood pressure to 85 mmHg or less) has been studied by the Hypertension Optimal Treatment (HOT) Study[2]. While such an approach is not

clearly beneficial in the general population, it appears to be safe and to result in a reduction of cardiovascular events in persons with diabetes mellitus.

Hypertension has particular relevance to patients with chronic kidney disease. In this population, elevated blood pressure plays a dual role: it is both the result of parenchymal damage within the kidney as well as a provocateur of further deterioration in kidney function. Moreover, hypertension is both more common and more severe in patients with chronic kidney disease than in the general population. The K/DOQI Chronic Kidney Disease Clinical Practice Guidelines have recently reviewed data from epidemiological investigations and prospective interventional trials establishing that elevated blood pressure hastens the progression of kidney failure.[3] Few randomized trials have examined target levels of blood pressure control in patients with kidney dysfunction. Better blood pressure control was examined in both the HOT Study (diastolic blood pressure 80 mm Hg or less) and the UKPDS (blood pressure below 150/85)[2]. Both investigations showed that better blood pressure control is associated with decreased clinical cardiovascular events in patients with diabetes mellitus, but neither study specifically enrolled subjects with chronic kidney disease. The UKPDS examined patients with type II diabetes, showing that tight blood pressure control reduced the development of microalbuminuria as well as microvascular and macrovascular complications[4]. The current report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) recommends blood pressure goals of below 135/85 for patients with chronic kidney disease or those with a high risk of developing kidney failure, such as patients with diabetes mellitus[1].The NKF Task Force on Cardiovascular Disease recommends blood pressure goals of below 125/75 in patients with kidney dysfunction and either proteinuria greater than 1 gram per day or diabetes mellitus as the etiology of kidney disease. A blood pressure goal of less than 135/85 is recommended for non-diabetic kidney disease with proteinuria less than 1 gram per day[5].

As patients with chronic kidney disease transition into end-stage renal disease (ESRD) and require kidney replacement therapy, specific blood pressure goals becomes less clear. There are no large, prospective interventional trials in ESRD patients targeting different levels of blood pressure control and reporting clinical outcomes. Epidemiological investigations routinely report that hypertension is not a risk factor for mortality, and ESRD patients with blood pressures above 140/90 have greater survival than those with pressures below 140/90, at least up to systolic pressures of 175 mmHg[6-9]. Thus, in the ESRD population, hypertension appears not to be predictive of future risk. These data suggest that the pathobiology and predictive associations of blood pressure in the ESRD population are unlike those of the general population. One explanation for this may be the extremely high prevalence (> 70%) of cardiac dysfunction in the ESRD population[10]. ESRD patients with cardiac dysfunction, such as congestive heart failure, have greater risk of death and may also be unable to generate elevated blood pressures[11,12]. Thus the relationship between blood pressure and death in ESRD patients may be confounded by cardiac status. There is some evidence to suggest that measures of cardiac dysfunction, such as left ventricular hypertrophy, may be improved by lowering blood pressure in ESRD patients[13-16]. Currently, in the

absence of strong scientific data to define therapeutic targets, ESRD blood pressure goals remain extrapolations from the general population. The NKF Task Force on Cardiovascular Disease recommends that ESRD patients receiving kidney replacement therapy have a blood pressure goal of less than 140/90[5].

Pre-ESRD patients are individuals expected to require kidney replacement therapy within 6 to 18 months. They are situated at a crossroads between patients with less severe kidney disease – where blood pressure control is a mainstay of therapy – and patients with ESRD – where blood pressure goals are not well understood. Data from incident ESRD patients suggest that more than 80% have hypertension at the time kidney replacement therapy is first required. This high prevalence of hypertension may be due in part to the hypervolemic status that is typical of individuals initiating kidney replacement therapy. Since pre-ESRD patients usually have greater control over plasma volume, data from patients initiating kidney replacement therapy may overestimate the true prevalence of hypertension in the pre-ESRD population. Complicating decision-making for hypertension therapy is the fact that pre-ESRD patients may face competing risks, where the potential benefit of a specific medication must be weighed against the potential risks in a patient with severe kidney disease. Changes in drug metabolism in kidney failure and the physiologic effects of certain drug classes on blood supply to the kidneys present additional opportunities for adverse drug-related consequences in pre-ESRD subjects. For example, angiotensin-converting enzyme (ACE) inhibitors are powerful antihypertensives that have been shown to slow the progression of diabetic and non-diabetic nephropathies and reduce cardiac morbidity and mortality in at-risk populations. The use of these beneficial agents must be weighed against the potential for serious hyperkalemia or worsening of kidney function in patients with severe reduction in GFR. Additionally, while antihypertensive therapy slows progression of chronic kidney dysfunction and remains the mainstay of therapy for many types of chronic progressive kidney disease, it is important to examine the benefits of therapy – as well as potential hazards – in terms of other measures of morbidity and mortality in patients who will progress to ESRD within 6 to 18 months. This will enable the development of evidence-based goals for blood pressure management in the pre-ESRD population.

The purpose of this chapter is to systematically review the available literature on the impact of blood pressure therapy with antihypertensive medication on clinical outcomes in patients with pre-ESRD, defined as a GFR between 30 and 10 mL/min and expected to require kidney replacement therapy within 6-18 months. A systematic review of the literature on blood pressure interventions affecting surrogate measures, such as decline in GFR, is beyond the scope of this Evidence Report. Similarly, blood pressure interventions in populations with less advanced kidney disease are not considered, except where specifically noted. In addition to clinical outcomes in patients with pre-ESRD, emphasis is placed on aspects of antihypertensive agent usage specific to the pre-ESRD population, such as important drug toxicities related to reduced kidney function.

4.3 Methods

The literature review gathered published evidence regarding four key questions:

1. What is the distribution of blood pressure or the prevalence of hypertension in pre-ESRD patients?
2. What is the prevalence of antihypertensive treatment in pre-ESRD patients?
3. Is there evidence that treatment of elevated blood pressure with antihypertensive agents in pre-ESRD patients improves clinical outcomes before and/or after kidney replacement therapy?
4. What is the risk of antihypertensive agent toxicities or side effects that occur as a consequence of reduced kidney function?

To identify the literature addressing these questions, the search terms “blood pressure” and “hypertension” were used.

Outcomes considered included intermediate outcomes such as blood pressure control, and clinical outcomes such as myocardial infarction, CHF, angina, stroke, cardiac hypertrophy, cardiac perfusion, quality of life, and death. Information was also sought on the risk of toxicities or side effects of antihypertensive medication occurring as a consequence of reduced kidney function.

In order to be eligible for consideration, studies needed to have representative samples from the pre-ESRD population. For this reason, studies that used blood pressure or a definition of hypertension as an inclusion/exclusion criterion were ineligible.

4.4 Results

Two hundred and sixty-two titles and abstracts were initially screened. Of these, 89 were identified for full-text screening. We were unable to obtain copies of six of these articles.[17-22] Of the remaining 83, 62 were excluded during full-text review for the following reasons: outcomes not reported separately for the pre-ESRD population (n = 1); did not meet the criteria for the pre-ESRD population (n = 11); small case series/single case report (n = 3); did not address at least one of the key questions (n = 47). Twenty-three articles were included at the full-text screening stage: they were abstracted using a standardized form and are summarized in Evidence Table 3.

Key Question 1: What is the distribution of blood pressure or the prevalence of hypertension in pre-ESRD patients?

The included studies reported hypertension in different manners. Some gave the distribution of blood pressure as a mean with standard deviation for either systolic and diastolic or mean arterial pressure. Other studies reported the percentage of the population with “hypertension,” usually defined as a blood pressure exceeding a certain value (such as 140/90) or the use of antihypertensive medications for controlling blood pressure. Six studies were identified that reported blood pressure distribution or categorized blood pressure parameters as hypertensive or not.

Brazy et al.[23] retrospectively evaluated 200 patients attending a nephrology clinic at a Veterans' Administration hospital from 1979 to 1988. Level of kidney function and evidence of reduction in function over time were the primary inclusion criteria. Mean serum creatinine at study entry was over 3.0 mg/dL. Blood pressure was estimated for the population stratified by race. Blacks had a mean systolic blood pressure of 156 (SD 19.2) and a diastolic pressure of 91.5 (SD 8.7). Whites had a mean systolic blood pressure of 147 (SD 16.1) and a diastolic pressure of 88 (SD 9.1). The difference in diastolic pressures between the two groups was statistically significant. This study did not report the proportion of patients with hypertension for any definition.

Ellis et al.[24] reported a retrospective analysis of 198 patients initiating dialysis during 1996 and 1997. The medical records of the cohort were examined to abstract information from time of first detection of kidney disease and the time of first referral to a nephrologist. At the time of nephrology referral, 159 (80%) had evidence of hypertension; however, the specific definition of hypertension used by the author is not reported.

Holland et al.[25] retrospectively evaluated 362 pre-dialysis patients taken from the population of all out-patients referred to a nephrology service in Ontario, Canada, from 1990 to 1997. Patients were labeled as "pre-dialysis" if chronic kidney failure was present and if the patient was attending a pre-dialysis clinic. According to the authors, attendance at the clinic implied that the nephrologist providing care believed that future dialysis was inevitable and would be of benefit to the patient; however, no specific measure of kidney function was used for study inclusion. Of the 362 subjects, 77% had a systolic pressure above 140, while 27% had a diastolic pressure greater than 90. The percentage of patients with elevated blood pressure was similar for those with serum creatinine below 3.4 mg/dL compared to those with serum creatinine above 3.4 mg/dL (systolic, 76% versus 78%; diastolic, 28% versus 26%).

Another retrospective study used the computerized record system of a primary care clinic to identify subjects with chronic kidney disease based on calculated creatinine clearances of less than 50 mL/min.[26] Of 603 eligible patients, 360 (60%) agreed to participate in the study, which included elements of prospective data collection. Apart from being slightly younger, the participating cohort had no significant differences in demographics compared to non-participants. The study cohort was predominantly female (69%), Black (83%), and diabetic (57%), with a mean calculated creatinine clearance of 27 mL/min. Hypertension was defined by the diagnosis of hypertension in the medical record, taking antihypertensive medications, or a mean recorded blood pressure greater than 140/90 mmHg for the 6 months prior to study enrollment. Using this definition, 92% of the patient population was hypertensive. This percentage is likely an overestimation of hypertension prevalence in the pre-ESRD population because the population was over represented by Black and diabetic subjects, two populations with high rates of hypertension.

The studies listed above have all been retrospective. Although a number of prospective interventional trials have investigated antihypertensive agents in subjects with kidney

disease, most have blood pressure requirements as inclusion criteria, thus limiting the ability to ascertain true prevalence information regarding blood pressure. Moreover, few have populations (or identifiable sub-populations) with kidney function low enough to be considered pre-ESRD. Kamper et al.[27] conducted a randomized, placebo-controlled trial of enalapril in 70 subjects with kidney disease. Inclusion and exclusion criteria involved kidney function but did not include blood pressure. The study population had a low GFR (13.0 mL/min in the enalapril group, 18.8 mL/min in the control group). The mean systolic blood pressure for the entire group was 145.5 mmHg; mean diastolic blood pressure was 91 mmHg. Patients with blood pressure greater than 140/90 or who were taking antihypertensive medications were called hypertensive. Using this definition, hypertension was seen in 84%.

The Modification of Diet in Renal Disease (MDRD) Study was comprised of two study population (Study A or Study B) based on baseline GFR. The Study B population had a GFR between 13 and 24 mL/min, making it one of the few studies to specifically examine blood pressure control in subjects meeting the Work Group's definition of pre-ESRD. Participants were excluded for a mean arterial pressure of greater than 125 mmHg, making assessment of true hypertension prevalence problematic. Despite this caveat, 88% of the 255 subjects in Study B were classified as hypertensive, based on physician review of the medical history and ascertainment of antihypertensive medications. Mean baseline blood pressure in subjects less than or equal to 60 years of age was 132/82 (n=185); mean blood pressure in subjects over 60 years of age was 143/79.

Key Question 2: What is the prevalence of antihypertensive treatment in the pre-ESRD population?

Four studies provided information regarding the prevalence of antihypertensive usage in pre-ESRD populations.[23-25,27] Brazy et al.[23] reported that 87% of hypertensive patients in a nephrology clinic had at least one antihypertensive medication prescribed. Diuretics were the most commonly prescribed medication (76%), followed by beta-blockers (56%) and prazosin (32%). This study examined a time period from 1979 to 1988 in a Veterans' Administration hospital setting. These factors explain the low frequency of calcium channel blocker and angiotensin-converting enzyme inhibitor prescriptions (8% and 3%, respectively).

While Brazy et al. reported high usage of antihypertensive agents, Ellis et al.[24] reported that 31% of the 159 hypertensive pre-ESRD patients in a primary care practice were initiated on antihypertensive therapy at the time of referral to a nephrologist. This means that approximately one-third of hypertensive subjects were <u>not</u> receiving therapy until referred to a nephrologist. The difference between the two studies may be due to the setting: nephrology clinic versus primary care (transitioning to a nephrology clinic). Ellis et al. also reported that a substantial percentage of diabetics did not receive angiotensin-converting enzyme inhibitor therapy prior to nephrology referral. Only one-third of the diabetic pre-ESRD subjects were referred already on an ACE inhibitor or an angiotensin receptor blocker (ARB).

The cohort analyzed by Holland et al.[25] had an 82% baseline rate of antihypertensives usage. Most patients (33%) were taking one blood pressure medication; 29% were prescribed two; and 20% had three or more. Among diabetic patients with a serum creatinine below 3.4 mg/dL, 56% had not been prescribed an ACE inhibitor at the time of referral to a nephrologist. Kamper et al.[27] reported a similar rate of antihypertensive usage (84%) at baseline prior to randomization. No information was given regarding usage of specific drug classes.

The MDRD Study also reports potentially useful information regarding the prevalence of antihypertensive treatment in pre-ESRD patients, with two important limitations. First, the exclusion of subjects with very high blood pressure (mean arterial pressure greater than 125 mmHg), may result in the underestimation of true prevalence. Second, subjects enrolled in this prospective, randomized trial were identified through prior physician contact and were selected, in part, for the ability to adhere to a strict regimen of blood pressure and dietary protein control, potentially overestimating baseline prevalence of blood pressure treatment. Eight-six percent of Study B participants, a population of 255 subjects with a mean GFR of 21 mL/min, were receiving antihypertensive medications at baseline. Of those classified as hypertensive, 96% were receiving antihypertensive pharmacotherapy.

Key Question 3: Is there evidence that treatment of elevated blood pressure with antihypertensive agents in pre-ESRD patients improves clinical outcomes before and/or after kidney replacement therapy?

Consideration of this question first requires discussion of what is meant by a "clinical outcome", a term which is often intermingled with "surrogate outcome". A National Institutes of Health working group recently generated definitions contrasting clinical and surrogate endpoints. The former, "[a] characteristic or variable that reflects how a patient feels, functions, or survives," is related to the surrogate, "[a] biomarker that is intended to substitute for a clinical endpoint." Within this framework, clinical outcomes encompass discernible events such as myocardial infarction, stroke, or death. Measures of kidney function and blood pressure, while serving as important parameters that predict clinical outcomes, constitute surrogate outcomes. Therefore, studies measuring decline in GFR, for example, are not included within this document as studies of clinical outcomes. Because blood pressure response is the typical measure by which antihypertensive therapy is titrated, several studies of blood pressure response in pre-ESRD patients are included. The time of ESRD incidence as an event is problematic as a strict clinical outcome because the timing of that event (generally defined as the initiation of kidney replacement therapy) has subjective components. However, because of clear impact on "how a patient feels, functions, and survives", incident ESRD status is included as a clinical outcome. As previously mentioned, investigations of subjects with milder kidney disease (CKD stages 1-3) are beyond the scope of this Evidence Report. While several recent and important clinical trials in early kidney disease are discussed at the end of this section, they do not specifically address the Key Question of improving outcomes for pre-ESRD patients.

While many prospective trials have investigated lowering blood pressure in subjects with kidney impairment, there have been relatively few in populations that are clearly identified as pre-ESRD, and the range of clinical outcomes is limited. Of the 12 identified reports, eight primarily investigated the ability of antihypertensive agents to lower blood pressure in pre-ESRD subjects. Two papers reported short- and long-term follow-up of the same investigational trial, which included death and initiation of kidney replacement therapy as clinical outcomes;[27,28] one study reported echocardiographic measures of left ventricular geometry,[29] and another study retrospectively investigated the association between blood pressure and hospitalizations.[25]

A number of antihypertensive agents have been tested to determine their ability to lower blood pressure in pre-ESRD subjects. Some studies identified in the literature review were prospective clinical trials with a before/after design and no parallel control group.[30-33] These studies enrolled relatively small numbers of subjects (range 4-33) with advanced kidney impairment (CrCl < 30 mL/min) and hypertension. Two such studies, by Acchiardo et al.[30] (indapamide [a diuretic]) and Weidmann et al.[31] (nitrendpine [a dihydropyridine calcium antagonist]), utilized a washout or placebo period with no other antihypertensive agents administered during the active phase. Two other studies, by Hammond et al.[32] (minoxidil [a vasodilator]) and Toto et al.[33] (losartan [an angiotensin receptor antagonist]), allowed other antihypertensive agents if needed to control hypertension. Each of these investigations showed that blood pressure was significantly lowered after administration of the particular agent after a variable period of follow up (range, 1-20 months). In each, the blood pressure after treatment was not lowered below 145/80 mmHg.

Other studies utilized randomized controlled trial designs.[25,28,29,34-37] Shiigai et al.[34] (ACE inhibitor vs. beta blocker) and Bianchi et al.[35] (ACE inhibitor vs. calcium antagonist) randomized subjects to specific agents in head-to-head comparisons. In each study, additional blood pressure agents were to be added if necessary. Shiigai et al.[34] compared enalapril and metoprolol in 36 pre-ESRD subjects; no differences in blood pressure were noted between the two groups. The group randomized to the ACE inhibitor exhibited a reduction in urinary protein excretion and a stabilization of decline in kidney function over 2 years compared to the group receiving beta blocker. The report by Bianchi et al.[35] involved 16 pre-ESRD subjects randomized to enalapril or nicardipine. A significant reduction in blood pressure in each group was noted at 52 weeks. There was no difference in the degree of blood pressure reduction between the randomized groups. Level of kidney function remained stable in both groups; subjects receiving the ACE inhibitor exhibited a reduction in urinary albumin excretion.

Three studies randomized subjects to a specific antihypertensive versus a variety of blood pressure agents. Kamper et al.[27] studied the effects of an ACE inhibitor compared to “conventional antihypertensive therapy” in 70 pre-ESRD patients. Subjects taking the ACE inhibitor were also given conventional agents (diuretics, beta blockers, vasodilators) if needed to control blood pressure. The intervention was carried out for 2 years, at which time the investigators reported a lowering of blood pressure from study entry to study end within each group; no differences were noted

between groups. Additionally, a significant decrease in 24-hour urinary albumin excretion was seen in the ACE inhibitor group. A second publication was issued in 1995,[28] reporting on the results of further follow-up of the patients in the original study. After the end of the 2-year intervention phase of the trial, subjects received antihypertensive therapy as administered by their primary physicians. Over an additional mean follow-up of 81 months, four patients in the ACE inhibitor groups discontinued the drug; two patients in the control group initiated ACE inhibitor therapy. Using an intent-to-treat analysis, the authors reported that 12 of 35 (34%) in the ACE inhibitor group were alive without reaching ESRD compared to only 5 of 35 (14%) in the control group ($p = 0.05$). Subjects reaching ESRD numbered 21 of 35 (60%) in the ACE inhibitor group compared to 23 of 35 (66%) in the control group (p = not significant). Non-renal deaths were seen in 2 of 35 in the ACE inhibitor group compared to 7 of 35 in the control group (no p-value reported). This study is one of the few to report clinical outcomes such as vital status and time to ESRD in the pre-ESRD population.

Plum et al.[36] performed a much smaller randomized study including 10 pre-ESRD subjects given either an angiotensin receptor blocker (ARB) or therapy with other antihypertensive medications (ACE inhibitors were not allowed in the control group). Over a 6-month intervention, blood pressure fell significantly from baseline in the ARB group. Blood pressure was reduced to a non-significant degree in the control therapy group. Other significant findings included a drop in hemoglobin concentration (12.1 to 10.5 g/dL) in the ARB group, with no change seen in the control group ($p < 0.05$). Serum creatinine increased slightly in the ARB group but not in the control group; proteinuria decreased significantly in the ARB group but not in the control group. Potassium increased in ARB users (4.4 to 4.9 mEq/L) ($p < 0.05$).

Blau et al.[37] performed a study in 38 subjects, comparing a dihydropyridine calcium antagonist to other blood pressure medications over 23 months. More subjects receiving calcium antagonist had a significant lowering of blood pressure and reduction in decline of kidney function compared to those not receiving calcium antagonists. Although the other antihypertensive medications used in the study were not specifically mentioned, the work was published in 1990 and it is likely that ACE inhibitors were not used by subjects in the control group.

In 1997, Dyadyk et al.[29] reported a study comparing the effects of two ACE inhibitors (captopril and enalapril) on blood pressure reduction and echocardiographic parameters over 12 months. Seventy-two pre-ESRD subjects (mean CrCl 18 mL/min) entered the intervention phase of the study and had blood pressure agents titrated to achieve a goal diastolic blood pressure $\leq$ 90 mmHg or a reduction of at least 10 mmHg from baseline. Subjects who did not meet this goal by 8 weeks of therapy were dropped from the study. Over a subsequent 12-month intervention, blood pressure fell significantly in these pre-ESRD subjects, with no significant difference between the two randomized groups. There was also evidence of a significant 20% reduction in left ventricular mass index (LVMI), as well as an improvement in diastolic filling over 12 months.

Holland et al.[25] performed a retrospective analysis to determine baseline predictors of hospitalization in a cohort of 362 pre-ESRD patients enrolled in a pre-dialysis clinic over 7 years. While systolic pressure trended towards significance in univariate analysis, multivariate regression did not show that blood pressure level was related to subsequent first non-elective hospitalization.

Recently, several large, randomized trials of antihypertensive agents have enrolled patients with kidney dysfunction and incorporated clinical outcomes as either primary or secondary endpoints. These trials do not specifically target pre-ESRD subjects and thus do not directly address the Key Question. However, because they may provide some insight to the issue of clinical outcomes in patients with kidney disease, several will be mentioned. The Heart Outcomes Prevention Evaluation (HOPE) study[38] randomized 9,297 with evidence of clinical vascular disease or diabetes plus one other cardiovascular risk factor to ramipril (10 mg per day) or placebo. Although subjects with baseline serum creatinine greater than 2.3 mg/dL or dipstick-positive proteinuria were excluded, 980 subjects had a serum creatinine greater than 1.4 and 3,394 subjects had a calculated creatinine clearance of 65 mL/min or less. The primary outcome was a composite endpoint of incident cardiovascular death, myocardial infarction, or stroke. Analysis revealed that as baseline serum creatinine concentration increased the risk for the primary outcome also increased significantly. Treatment with ramipril reduced the risk of clinical events in patients with kidney disease (serum creatinine greater than 1.4 mg/dL) at least as much as in those without kidney disease. For cardiovascular death, all-cause death, and heart failure-associated hospitalizations, the risk reduction associated with ramipril was significantly greater in patients with kidney disease compared to those without kidney disease.

The RENAAL (Reduction of Endpoints in NIDDM with the Antiogensin II Antagonist Lovasartan) Study[39] randomized 1,512 patients with type II diabetes mellitus and nephropathy (urinary albumin to creatinine ratio at least 300 or total urinary protein excretion at least 0.5 g/day, and serum creatinine between 1.3 and 3.0 mg/dL) to losartan (50 to 100 mg/day) or placebo. The primary outcome was the composite of doubling of baseline serum creatinine, development of ESRD, or death. Over a mean follow-up of 3.4 years, losartan reduced the risk of primary outcome by 16 percent (p=0.02). This difference was driven by the surrogate outcome, doubling of serum creatinine (p=.006), and the clinical outcome of ESRD (p=0.002). There was no effect on the rate of death or a composite of cardiovascular events. A secondary analysis did show that rate of first hospitalization for heart failure was significantly lowered with losartan (p=.005).

The IDNT (Irbesartan Diabetic Nephropathy Trial)[40] randomized 1,715 subjects with type II diabetes mellitus and both hypertension (blood pressure greater than 135/85 mmHg or on antihypertensvie therapy) and nephropathy (urinary protein excretion at least 900 mg/day and serum creatinine between 1.0 and 3.0 mg/dL) to treatment with irbesartan (300 mg/day), amlodipine (10 mg/day), or placebo. Target blood pressure was below 135/85 in all groups. The primary outcome was time to doubling of serum creatinine, development of ESRD, or death. Over a mean follow-up of 2.6 years,

irbesartan was associated with a 20 percent lower risk of primary outcome compared to placebo (p=.02) and a 23 percent lower risk compared to amlodipine (p=0.006). These differences were again driven by the surrogate measure, doubling serum creatinine. Time to ESRD was only marginally reduced with irbesartan compared to amlodipine or placebo (both p=.07). There were no significant differences in the rates of death from any cause or in a cardiovascular event composite endpoint.

The AASK (African American Study of Kidney Disease and Hypertension) Study[41] randomized 1,094 African American subjects with essential hypertension and presumed hypertensive nephrosclerosis (GFR between 20 and 65 mL/min, no other identified etiology of kidney disease) to a 3 x 2 factorial design of two blood pressure goals and three antihypertensive study drugs. Blood pressure goals were a mean arterial pressure of 102 to 107 mmHg or 92 mmHg or lower. Antihypertensive study medications were metoprolol, ramipril, and amlodipine. The primary outcome was the rate of change in GFR (GFR slope). A secondary composite endpoint consisted of a reduction in GFR by 50%, development of ESRD, and death. Recently, the amlodipine arm of the trial was stopped by the Data Safety Monitoring Board because of evidence of a significantly greater rate of decline in kidney function and increased rate of reaching the secondary composite endpoint in patients with greater baseline levels of proteinuria (urinary protein to creatinine ratio > 0.22) randomized to amlodipine compared to those randomized to ramipril. The risk reduction in the secondary composite endpoint appears to have been driven primarily by the two kidney disease progression outcomes, reduction in GFR by 50% and development of ESRD. Death alone was not reported to be significantly increased in the amlodipine arm compared to ramipril. The AASK Study is continuing with the ramipril and metoprolol treatment arms.

In summary, data from interventional trials show that blood pressure may be lowered in pre-ESRD subjects. Usually, these studies do not show blood pressure lowered to the degree recommended by current guidelines[1] A number of studies have shown that particular agents (ACE inhibitors and possibly calcium antagonists) may reduce the decline in kidney function or may lower protein excretion. However, there are no interventional data showing what level of blood pressure control during pre-ESRD is optimal for clinical outcomes such as mortality, cardiac morbidity, or hospitalization outcomes, either during the pre-ESRD period or after the onset of ESRD. The HOPE, RENAAL, IDNT, and AASK trials principally show that antihypertensives affecting the renin-angiotensin axis improve some surrogate and clinical outcomes in patients with earlier stages of kidney disease (CKD stages 1-3). These are important findings, but do not specifically address the issue of improving clinical outcomes in pre-ESRD subjects who are preparing to initiate kidney replacement therapy within 6 to 18 months.

Key Question 4: What is the risk of antihypertensive agent toxicities or side effects that occur as a consequence of reduced kidney function?

There are no systematic, population-based reports of drug toxicities or side effects that are specifically associated with reduced kidney function. Studies are generally reported

as either single case reports or small case series. Therefore, it may be difficult to apply this knowledge to the entire pre-ESRD population.

Because of the effect of beta blockers and calcium antagonists on the electrical conduction system of the heart, bradycardia is often a concern in advanced kidney failure. Metoprolol is routinely suggested as a replacement for atenolol therapy due to preferential metabolism of metoprolol in the liver as compared to kidney. In fact, if the drug dosing is altered in accordance with known level of kidney function, atenolol can continue to be used with great effect in even dialysis populations. At least one report noted the risk of bradycardia and sinus arrest with the use of diltiazem in 10 pre-ESRD patients.[42]

ACE inhibitors and ARBs have been related to both hyperkalemia and acute kidney failure in subjects with advanced kidney impairment. In an investigation of the safety of ACE inhibitors and ARBs, 108 subjects with a creatinine clearance between 20-45 mL/min (mean 29 mL/min) were randomized into three groups: ARB alone, low dose ARB plus ACE inhibitor, and high dose ARB plus ACE inhibitor.[43] Over 5 weeks, the serum creatinine increased significantly by approximately 0.2 mg/dL in each group, a difference that did not appear to be clinically relevant. No subject developed acute kidney failure by clinical criteria. Serum potassium increased between 0.28 and 0.48 mmol/L and was significant only in the two combination groups. Only one patient in each of the combined therapy groups withdrew from the study because of hyperkalemia. Zanella et al.[44] investigated hyperkalemia due to ACE inhibition in 16 patients with kidney disease. Over 4 weeks of therapy, plasma potassium increased from 3.9 mEq/L to 5.5 mEq/L ($p < 0.001$), and the final potassium levels correlated directly with plasma creatinine levels ($r = 0.67$). Six patients had plasma potassium levels greater than 6 mEq/L; however, no ECG changes were noted and no therapy for hyperkalemia was required.

These data reflect the experience of a number of interventional trials investigating both ACE inhibitors and ARBs. By the very nature of a reduction in post-glomerular arteriole resistance, an initial decline in glomerular pressure and filtration rate is to be expected. While this reduction may be clinically significant and represent actual “acute kidney failure” in a small number of subjects dependent on post-glomerular vasoconstriction to maintain filtration rate, in the vast majority of subjects the reduction in glomerular pressure is beneficial to long-term preservation of kidney function.

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Evidence Table 3 – Hypertension

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Acchiardo and Skoutakis, 1983	Design: Prospective clinical trial (before/after) Intervention(s) studied: Indapamide 2.5 mg/day for 42 days. Treatment period was preceded by a 1-month placebo run-in and followed by a 2-week placebo follow-up period. Dates: NR Location: Memphis, TN Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 4 (of a total of 29 study participants) Inclusion criteria: Hypertension (not defined); "severely decreased renal function" Exclusion criteria: Infection; need for any other medications; other disease states Age: NR Sex: NR Race: NR Renal function at entry (means ± SD): CrCl: 16 ± 8 ml/min SCr: 7.3 ± 4.0 mg/dl Blood pressure data at entry (means ± SD, in mmHg): Systolic standing: 176 ± 19 Systolic supine: 178 ± 22 Diastolic standing: 104 ± 15 Diastolic supine: 105 ± 8 Mean arterial pressure: 129 Co-morbidities at entry: NR	*Key Question 1) Does treatment with anti-hypertensives improve outcomes before and/or after renal replacement?:* a) Systolic BP (means ± SD, in mmHg): Standing: At entry: 176 ± 19 Post-treatment: 150 ± 34 p < 0.05 Supine: At entry: 178 ± 22 Post-treatment: 167 ± 27 p< 0.05 b) Diastolic BP (means ± SD, in mmHg): Standing: At entry: 104 ± 15 Post-treatment: 88 ± 16 p < 0.05 Supine: At entry: 105 ± 8 Post-treatment: 88 ± 16 p < 0.05 c) Mean arterial pressure: At entry: 129 Post-treatment: 112 p < 0.05 *Key Question 2) What is the distribution of blood pressure in pre-ESRD patients?:* Not addressed *Key Question 3) What is the prevalence of antihypertensive treatment in pre-ESRD patients?:* Not addressed *Key Question 4) What is the risk of toxicities or side effects of antihypertensive drug treatment occurring as*	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: No/not assessable Incl/excl described: Partially Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 4 Note: Four of 29 patients met pre-ESRD criteria. The remaining 25 patients had normal renal function or varying degrees of renal impairment. Results described here were reported separately for the pre-ESRD group.

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Evidence Table 3 – Hypertension (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			a consequence of reduced renal function?: Treatment did not significantly affect CrCl. Data were as follows: CrCl (means ± SD, in ml/min): At entry: 16 ± 8 Post-treatment: 16 ± 9 p = not significant	
Andrivet, Beaslay, Kiger, et al., 1994	Design: Multiple case report (toxicity data only) Intervention(s) studied: Patients all treated for diltiazem-induced complete sinus arrest Dates: 1985-1993 Location: Briis/Forges, France Recruitment setting: Hospital (intensive care unit)	No. of pre-ESRD subjects: 10 Inclusion criteria: NA (see under "Other," below) Exclusion criteria: NA (see under "Other," below) Age (mean ± SEM): 78.5 ± 3.4 Sex: 30% M, 70% F Race: NR Renal function at entry (means ± SEM): CrCl : 25 ± 3 ml/min SCr: 198 ± 31 µmol/l Blood pressure data at entry: Systolic BP (at time of admission to ICU; mean ± SEM): 94.5 ± 5 mmHg Co-morbidities at entry: NR Other: Patients were admitted to an ICU for treatment of diltiazem-induced bradycardia	*Key Question 1) Does treatment with anti-hypertensives improve outcomes before and/or after renal replacement?:* Not addressed *Key Question 2) What is the distribution of blood pressure in pre-ESRD patients?:* Not addressed *Key Question 3) What is the prevalence of antihypertensive treatment in pre-ESRD patients?:* Not addressed *Key Question 4) What is the risk of toxicities or side effects of antihypertensive drug treatment occurring as a consequence of reduced renal function?:* A risk of bradycardia exists when diltiazem is used in patients with renal impairment.	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: NA Incl/excl described: NA Dropouts discussed: NA Sample size justified: NA 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: NA Notes:

Evidence Table 3 – Hypertension (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Bianchi, Bigazzi, Baldari, et al., 1991	Design: RCT Intervention(s) studied: 1) Enalapril 20 mg daily for 52 weeks; 2) Nicardipine SR 40 mg 2x/day for 52 weeks. Dates: NR Location: Livorno, Italy Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 16 Inclusion criteria: Hypertension; chronic renal insufficiency Exclusion criteria: None specified Age (mean, with range): Enalapril, 53.3 36-66); nicardipine, 50.1 (39-62) Sex: Enalapril, 50% M, 50% F; nicardipine, 37.5% M, 62.5% F Race: NR Renal function at entry: Creatinine clearance (mean ± SEM): Enalapril: 35 ± 3.6 ml/min Nicardipine: 40 ± 4.1 ml/min Blood pressure data at entry: Mean arterial pressure (± SEM): Enalapril: 125 ± 1.3 mmHg Nicardipine: 122 ± 1.9 mmHg % of patients with hypertension (not defined): 100% % of patients taking antihypertensive medication: 100% Co-morbidities at entry: NR Other: Fractional clearance of albumin at entry (mean ± SEM): Enalapril: $3.5 \pm 0.5 \times 10^{-4}$ Nicardipine: $3.1 \pm 0.5 \times 10^{-4}$	*Key Question 1) Does treatment with anti-hypertensives improve outcomes before and/or after renal replacement?:* a) Mean arterial pressure (± SEM; mmHg): Enalapril / Nicardipine At entry: 125 ± 1.3 / 122 ± 1.9 52 weeks: 109 ± 1.4* / 112 ± 1.8* *p < 0.01, vs. baseline; no significant differences between enalapril and nicardipine b) Fractional clearance of albumin (mean ± SEM; $\times 10^{-4}$): Enalapril / Nicardipine At entry: 3.5 ± 0.5 / 3.1 ± 0.5 52 weeks: 1.3 ± 0.2* / 3.0 ± 0.6 *p < 0.01, vs. baseline; no between-group results reported *Key Question 2) What is the distribution of blood pressure in pre-ESRD patients?:* Not addressed *Key Question 3) What is the prevalence of antihypertensive treatment in pre-ESRD patients?:* Not addressed *Key Question 4) What is the risk of toxicities or side effects of antihypertensive drug treatment occurring as a consequence of reduced renal function?:* Not addressed	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: No/not assessable Incl/excl described: No/not assessable Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: < 50%/not assessable 5) Level of evidence: 2b Notes:

Evidence Table 3 – Hypertension (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Brazy and Fitzwilliam, 1990	Design: Cohort study (retrospective) Intervention(s) studied: Observational study – physicians prescribed antihypertensive drugs according to their preference. Agents used included (in order of frequency) diuretics, beta-blockers, prazosin, clonidine, minoxidil, calcium channel blockers, hydralazine, and ACE inhibitors. 13% of patients received no antihypertensive medication. Dates: 1979-1988 Location: Durham, NC Recruitment setting: Nephrology clinic/department (of VA medical center)	No. of pre-ESRD subjects: 200 (112 Black, 88 White) Inclusion criteria: Renal insufficiency (SCr > 1.5 mg/dl); ≥ 4 SCr and blood pressure measurements over at least 6 months prior to ESRD treatment; progression of disease as indicated by a ≥ 20% decline in 1/SCr Exclusion criteria: None specified Age (mean ± SD): Black patients, 58.9 ± 11.2; White patients, 56.4 ± 12.3 Sex: 98% M, 2% F Race: 56% Black, 44% White Renal function at entry: SCr (mean ± SD): Black patients: 3.2 ± 1.8 mg/dl; White patients, 3.0 ± 1.7 mg/dl Blood pressure data at entry: Systolic BP (mean ± SD): Black patients, 155.5 ± 19.2 mmHg; White patients, 147.2 ± 16.1 mmHg Diastolic BP (mean ± SD): Black patients, 91.5 ± 8.7 mmHg; White patients, 87.7 ± 9.1 mmHg (p < 0.05) Co-morbidities at entry: NR	*Key Question 1) Does treatment with anti-hypertensives improve outcomes before and/or after renal replacement?:* a) Results showed that a change in BP medication was associated with lower diastolic BP (the changes were statistically significant for all drugs except prazosin), and that the slope of 1/SCr versus time improved significantly when minoxidil or calcium channel blockers were prescribed. b) Change in slope of 1/SCr versus time (mean paired differences [after minus before] ± SEM): Minoxidil: +0.53 ± 0.18 (p = 0.006) Calcium-channel blockers: +0.53 ± 0.16 (p = 0.02) *Key Question 2) What is the distribution of blood pressure in pre-ESRD patients?:* See baseline values at left. *Key Question 3) What is the prevalence of antihypertensive treatment in pre-ESRD patients?:* 87% of eligible patients received some type of antihypertensive medication. *Key Question 4) What is the risk of toxicities or side effects of antihypertensive drug treatment occurring as a consequence of reduced renal function?:* Not addressed	Quality Scoring: 1) Global assessment: Good 2) Validity criteria: Population described: Completely Incl/excl described: Completely Dropouts discussed: Completely Sample size justified: No/not assessable 3) GFR/CrCl: SCr 4) % pre-ESRD: < 50%/not assessable 5) Level of evidence: 2b Notes:

Evidence Table 3 – Hypertension (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Dyadyk, Bagriy, Lebed, et al., 1997	Design: RCT Intervention(s) studied: 1) Captopril (n = 28). Initial dose 6.25 mg/day. This dosage increased every 2 weeks by 6.25-mg increments during a 6- to 8-week dose titration phase until goal BP reached (diastolic BP < 90 mmHg or reduction in diastolic BP of ≥ 10 mmHg). Patients reaching this goal continued on maintenance therapy for 12 months. Mean dose (± SD) 23 ± 8 mg/day. 2) Enalapril (n = 22). Initial dose 2.5 mg/day. This dosage increased every 2 weeks by 2.5-mg increments during a 6- to 8-week dose titration phase until goal BP reached (diastolic BP < 90 mmHg or reduction in diastolic BP of ≥ 10 mmHg). Patients reaching this goal continued on maintenance therapy for 12 months. Mean dose (± SD) 10 ± 2 mg/day. Dates: NR Location: Donetsk, Ukraine Recruitment setting: Not specified/unable to determine	No. of pre-ESRD subjects: 72, of whom 50 completed the trial; baseline data given below are for the 50 who completed the trial Inclusion criteria: Moderate to severe chronic renal failure not requiring dialysis; chronic mild to moderate hypertension (diastolic BP 95-116 mmHg); no antihypertensive medication for at least 3 months prior to start of study; left ventricular hypertrophy (left ventricular mass index [LVMI] ≥ 134 g/m^2 in men or ≥ 110 g/m^2 in women) Exclusion criteria: Significant valvular or coronary heart disease; cardiac arrhythmia or conduction defects; uninterpretable two-dimensional echocardiogram; echocardiographic regional wall motion abnormalities; left ventricular shortening fraction < 25%; other secondary causes of hypertension Age (mean ± SD): Captopril, 43 ± 10; enalapril, 44 ± 12 Sex: Captopril, 46% M, 54% F; enalapril, 45% M, 55% F Race: NR Renal function at entry: SCr (mean ± SD): Captopril: 0.48 ± 0.07 mmol/l Enalapril: 0.49 ± 0.06 mmol/l Estimated CrCl (for 72 patients entering study): 17.5 ml/min Blood pressure data at entry: Systolic BP (mean ± SD): Captopril: 174 ± 18 mmHg	*Key Question 1) Does treatment with anti-hypertensives improve outcomes before and/or after renal replacement?:* a) Systolic BP (means ± SD, in mmHg): Captopril / Enalapril At entry: 174 ± 18 / 182 ± 24 At 12 months: 146 ± 13 / 143 ± 13 p < 0.05, each treatment 12 months vs. baseline p = not significant, captopril vs. enalapril b) Diastolic BP (means ± SD, in mmHg): Captopril / Enalapril At entry: 107 ± 6 / 106 ± 8 At 12 months: 91 ± 6 / 92 ± 6 p < 0.05, each treatment 12 months vs. baseline p = not significant, captopril vs. enalapril c) LVMI (means ± SD, in g/m^2): Captopril / Enalapril At entry: 147 ± 24 / 154 ± 34 At 12 months: 120 ± 24 / 121 ± 26 p < 0.05, each treatment 12 months vs. baseline p = not significant, captopril vs. enalapril *Key Question 2) What is the distribution of blood pressure in pre-ESRD patients?:* Not addressed *Key Question 3) What is the prevalence of antihypertensive treatment in pre-ESRD patients?:* Not addressed *Key Question 4) What is the risk of toxicities or side effects of antihypertensive drug treatment occurring as a consequence of reduced renal function?:* Not addressed	Quality Scoring: 1) Global assessment: Good 2) Validity criteria: Population described: Partially Incl/excl described: Completely Dropouts discussed: Completely Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by reviewers 4) % pre-ESRD: < 50%/not assessable 5) Level of evidence: 1b Notes:

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Evidence Table 3 – Hypertension (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
		Enalapril: 182 ± 24 mmHg Diastolic BP (mean ± SD): Captopril: 107 ± 6 mmHg Enalapril: 106 ± 8 mm Hg 100% of patients hypertensive Co-morbidities at entry: NR Other: LVMI (mean ± SD): Captopril: 147 ± 24 g/m^2 Enalapril: 154 ± 34 g/m^2		

Evidence Table 3 – Hypertension (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Ellis, Reddy, Bari, et al., 1998	Design: Cohort study (retrospective) Intervention(s) studied: None. Observational study based on chart review of new dialysis patients grouped according to time of nephrology referral (early = started dialysis > 12 weeks after referral [n = 134]; late = started dialysis < 12 weeks after referral [n = 64]). Dates: Patients accepted for RRT between Jan 1, 1996 and Dec 31, 1997 Location: London, UK Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: No pre-ESRD patients; 198 patients on RRT Inclusion criteria: ESRD; accepted for RRT during study period Exclusion criteria: None specified Age (mean, with range): Early: 59.6 (16-88) Late: 59.6 (26-88) Sex: Early: 55% M, 45% F Late: 66% M, 36% F Race: Early: 67% White, 22% Black, 10% other Late: 72% White, 18% Black, 11% other Renal function *at time of initiation of RRT:* SCr (mean, with range; µmol/l): Early: 743.4 (320-2014) Late: 931.7 (386-2200) Blood pressure data at entry: NR Co-morbidities at entry: NR	*Key Question 1) Does treatment with anti-hypertensives improve outcomes before and/or after renal replacement?:* Not addressed *Key Question 2) What is the distribution of blood pressure in pre-ESRD patients?:* Not addressed *Key Question 3) What is the prevalence of antihypertensive treatment in pre-ESRD patients?:* 80% of cohort had hypertension (not defined) prior to ESRD. 29% of these were initiated on antihypertensive medication only after nephrology referral. Only 33% of diabetics were on an ACE-inhibitor at the time of referral. *Key Question 4) What is the risk of toxicities or side effects of antihypertensive drug treatment occurring as a consequence of reduced renal function?:* Not addressed	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: Partially Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Not assessable 4) % pre-ESRD: > 75% (in past) 5) Level of evidence: 2b Notes:

Evidence Table 3 – Hypertension (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Greene, Bour-goignie, Habwe, et al., 1993 **(Study B only)**	Design: RCT Intervention(s) studied: Study participants were randomized to one of two diets and to one of two levels of blood pressure control. Diets were as follows: 1) Diet L = Low-protein and low-phosphorous diet (0.575 g/kg/day protein and 5-10 mg/kg/day phosphorous); 2) Diet K = Very low-protein and very low-phosphorous diet (0.28 g/kg/day protein and 4-9 mg/kg/day phosphorous, supplemented with mixture of ketoacid analogs of essential amino acids). Blood pressure control groups were as follows: 1) Moderate blood pressure goal (MAP ≤ 107 mmHg for participants ≤ 60 years old; and ≤ 113 for those ≥ 61 years old); 2) Low blood pressure goal (MAP ≤ 92 mmHg for participants ≤ 60 years old; and ≤ 98 for those ≥ 61 years old) Dates: Patients recruited Jan 1989 - Aug 1991 Location: 15 sites throughout the US Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 255 Inclusion criteria: Age 18-70; SCr within past year of 1.4-7.0 mg/dl for men and 1.2-7.0 mg/dl for women; MAP ≤ 125 mmHg; not a kidney transplant recipient; urinary protein excretion ≤ 10 g/day; not taking insulin Exclusion criteria: None specified (see reference 6) Age (mean): 52.1 (men), 48.3 (women) Sex: 59% M, 41% F Race: 86% White, 5% Black, 5.5 % Hispanic, 3.5% other Renal function at entry (mean ± SD): GFR: 20.2 ± 4.4 ml/min/1.73 m^2 SCr: 3.3 ± 0.9 mg/dl Blood pressure data at entry: Mean systolic pressure: Age ≤ 60: 132.0 Age ≥ 61: 143.0 Mean diastolic pressure: Age ≤ 60: 82.4 Age ≥ 61: 79.2 Mean arterial pressure (± SD): Age ≤ 60: 99.0 ± 12.0 Age ≥ 61: 100.7 ± 13.8 % of patients with hypertension (not defined): 88% % of patients taking antihypertensive medication: 86% Co-morbidities at entry: NR Other: Employment status was as follows:	*Key Question 1) Does treatment with anti-hypertensives improve outcomes before and/or after renal replacement?:* Not addressed (see Note) *Key Question 2) What is the distribution of blood pressure in pre-ESRD patients?:* 88% of participants hypertensive *Key Question 3) What is the prevalence of antihypertensive treatment in pre-ESRD patients?:* 86% of patients on antihypertensive treatment *Key Question 4) What is the risk of toxicities or side effects of antihypertensive drug treatment occurring as a consequence of reduced renal function?:* Not addressed (see Note)	Quality Scoring: 1) Global assessment: Excellent 2) Validity criteria: Population described: Completely Incl/excl described: Partially Dropouts discussed: (see reference 4) Sample size justified: Completely 3) GFR/CrCl: Measured by investigators 4) % pre-ESRD: < 50%/not assessable 5) Level of evidence: 1b Note: Article describes demographic, biochemical, and clinical characteristics at baseline of participants in the Modification of Diet in Renal Disease study. No on- or after-treatment results reported.

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Evidence Table 3 – Hypertension (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
		Full-time employment: 62% Part-time employment: 10% Unemployed: 27%		
Hammond and Kirkendall, 1979	Design: Case series, no controls Intervention(s) studied: Minoxidil – Mean daily dose of 30 mg for a mean duration of 20.2 months (range, 8-34 months). In addition to minoxidil, all patients received furosemide plus one or more of three sympathetic inhibitors. Dates: NR Location: Houston, TX Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 13 patients (of total of 14) had elevated SCr levels Inclusion criteria: Severe hypertension uncontrolled by conventional agents Exclusion criteria: None specified Age: Mean, 36.8 Sex: 77% M, 23% F Race: 77% Black, 23% White Renal function at entry: SCr (mean): 4.6 mg/dl Blood pressure data at entry: Mean systolic pressure: 208.8 Mean diastolic pressure: 133.0 % of patients with hypertension (not defined): 100% % of patients taking antihypertensive medication: 100% Co-morbidities at entry: NR	*Key Question 1) Does treatment with anti-hypertensives improve outcomes before and/or after renal replacement?:* a) Mean systolic blood pressure: At study entry: 208.8 After treatment: 149.0 (no p-value reported) b) Mean diastolic blood pressure: At study entry: 133.0 After treatment: 88.8 (no p-value reported) *Key Question 2) What is the distribution of blood pressure in pre-ESRD patients?:* Not addressed *Key Question 3) What is the prevalence of antihypertensive treatment in pre-ESRD patients?:* Not addressed *Key Question 4) What is the risk of toxicities or side effects of antihypertensive drug treatment occurring as a consequence of reduced renal function?:* All 13 patients reported hypertrichosis. 11/13 (85%) reported fluid retention ± CHF symptoms; only 2 required hospitalization to correct.	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: No/not assessable Incl/excl described: Partially Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: SCr 4) % pre-ESRD: 50-75% 5) Level of evidence: 4 Notes:

Evidence Table 3 – Hypertension (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Holland and Lam, 2000	Design: Cohort study (retrospective) Intervention(s) studied: None (univariate and multivariate Cox proportional hazard models used to identify predictors of hospitalization prior to initialization of dialysis) Dates: Included patients were referred to nephrology service between Jan 1990 and July 1997 Location: Kingston, Ontario, Canada Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 362 Inclusion criteria: Age > 16; chronic irreversible renal failure; pre-dialysis; attendance at pre-dialysis clinic at least once Exclusion criteria: None specified Age: 48% ≤ 65; 52% > 65 Sex: 61% M, 39% F Race: NR Renal function at entry: SCr: 55% ≤ 300 µmol/l; 45% > 300 µmol/l Blood pressure data at entry: Systolic BP: > 140 mmHg in 77% of patients Diastolic BP: > 90 mmHg in 27% of patients Mean arterial pressure: > 100 mmHg in 77% of patients 82% of patients taking one or more antihypertensive medication Co-morbidities at entry: CHF: 15% Myocardial infarction: 10.5% Peripheral vascular disease: 14%	*Key Question 1) Does treatment with anti-hypertensives improve outcomes before and/or after renal replacement?:* Patients with systolic BP > 140 mmHg had lower hospital-free survival estimates than did patients with systolic BP < 140 mmHg. *Key Question 2) What is the distribution of blood pressure in pre-ESRD patients?:* Not addressed *Key Question 3) What is the prevalence of antihypertensive treatment in pre-ESRD patients?:* Not addressed *Key Question 4) What is the risk of toxicities or side effects of antihypertensive drug treatment occurring as a consequence of reduced renal function?:* Not addressed	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: Partially Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: SCr 4) % pre-ESRD: 50-75% 5) Level of evidence: 2b Notes:

Evidence Table 3 – Hypertension (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Kamper, Strand-gaard, and Leyssac, 1992 (original trial report) **and** **Kamper, Strand-gaard, and Leyssac, 1995 (long-term follow-up)**	Design: RCT Intervention(s) studied: 1) Enalapril (n = 35). Dose started at 2.5 mg, then increased depending on BP response and level of renal function. Mean dose was 7.9 mg at 3-month follow-up, 6.9 mg at end of study. Other antihypertensive drugs also given as needed. Treatment continued for at least 2 years or until dialysis required. Long-term follow-up results also reported. 2) Control (n = 35). Patients on "conventional antihypertensive treatment" (diuretics, beta-blockers, vasodilators, and/or calcium antagonists) at start of treatment who BP was at the goal level remained on their antihypertensive treatment. Those not on antihypertensive treatment at start of treatment whose BP was at goal level remained without antihypertensive treatment. Treatment continued for at least 2 years or until dialysis required. Long-term follow-up results also reported. Dates: Patients recruited Mar 1986-Oct 1987; median initial follow-up (with range) was 26 months (1-42) in the enalapril group and 26 months (8-42) in the control group; median long-term follow-up (from time of randomization, with range) was	No. of pre-ESRD subjects: 70 Inclusion criteria: Age 15-75; progressive chronic nephropathy, regularly controlled for at least 1 year; plasma creatinine values between 150 and 900 µmol/l Exclusion criteria: Known renal artery stenosis; urinary tract obstruction; treatment with immunosuppressive drugs or NSAIDs; cancer or other serious nonrenal disease; past or present treatment with an ACE inhibitor Age (mean, with range): Enalapril, 48 (29-71); control, 49 (25-75) Sex: Enalapril, 49% M, 51% F; control, 57% M, 43% F Race: NR Renal function at entry: GFR (median, with range, in ml/mi/1.73 m^2): Enalapril: 13.0 (6-54) Control: 18.8 (7-47) Blood pressure data at entry: Systolic BP (median, with range): Enalapril: 151 (120-220) mmHg Control: 140 (110-200) mmHg Diastolic BP (median, with range): Enalapril: 92 (70-110) mmHg Control: 90 (70-120) mmHg % of patients with hypertension (on antihypertensive medication or BP > 140/90): 84% % of patients on antihypertensive medication: 84% Co-morbidities at entry: NR	*Key Question 1) Does treatment with anti-hypertensives improve outcomes before and/or after renal replacement?:* a) Systolic BP (median, with range, in mmHg): Enalapril / Control At entry: 151 (120-220) / 140 (110-200) "During study": 133 (107-177) / 136 (100-168) Long-term f/u: 143 (109-180) / 141 (127-164) No significant differences between groups at any time point b) Diastolic BP (median, with range, in mmHg): Enalapril / Control At entry: 92 (70-110) / 90 (70-120) "During study": 82 (72-96) / 86 (71-92) Long-term f/u: 81 (69-94) / 82 (67-95) No significant differences between groups at any time point c) Median decrease in 24-hour urinary albumin excretion (with range; measured at 6-month follow-up): Enalapril: 4.7 (-16.5 to 83.9) µmol Control: 0.9 (-46.4 to 30.3) µmol $p < 0.05$ *Key Question 2) What is the distribution of blood pressure in pre-ESRD patients?:* 84% of patients hypertensive (on antihypertensive medication or BP > 140/90) at baseline. *Key Question 3) What is the prevalence of antihypertensive treatment in pre-ESRD patients?:* 84% of patients on antihypertensive medication at baseline. *Key Question 4) What is the risk of toxicities or side effects of antihypertensive drug treatment occurring as a consequence of reduced renal function?:*	Quality Scoring: 1) Global assessment: Good 2) Validity criteria: Population described: Partially Incl/excl described: Completely Dropouts discussed: Completely Sample size justified: No/not assessable 3) GFR/CrCl: Measured by investigators 4) % pre-ESRD: < 50%/no assessable 5) Level of evidence: 1b Notes: Preliminary results (at 90 days for 59 patients) from this trial described in Kamper and Nielsen, 1990. Following long-term follow-up results also reported: 1) No. of patients alive without RRT: Enalapril: 12/35 (34%) Control: 5/35 (14%) p = 0.05 2) No. of patients reaching ESRD: Enalapril: 21/35 (60%) Control: 23/35 (66%) p = not significant 3) No. of patients with non-renal death: Enalapril: 2/35 (6%) Control: 7/35 (20%) No p-value reported 4) No differences in baseline blood pressure between the above outcome groups.

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Evidence Table 3 – Hypertension (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
	81 months (68-87) in the enalapril group and 81 months (72-87) in the control group Location: Herlev, Denmark Recruitment setting: Nephrology clinic/department	Other: 24-hour urinary albumin excretion at entry (median, with range): Enalapril: 12.2 (1.2-168.6) µmol Control: 20.7 (0.1-75.0) µmol	a) Significant increase in serum potassium with enalapril (no reported clinical events): Enalapril: From 4.6 (3.5-5.6) mmol/l to 5.1 (3.8-6.4) mmol/l ($p < 0.01$) Control: Remained stable at 4.5 mmol/l. b) Anemia was exacerbated in patients taking enalapril. Median hemoglobin values (in mmol/l, with ranges) were as follows: Enalapril / Control At entry: 7.6 (5.7-10.8) / 7.6 (4.9-10.2) At 3 months: 6.9 (4.4-9.4) / 7.4 (5.2-10.0) $p < 0.01$ (between-group comparison of median reductions)	

Evidence Table 3 – Hypertension (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Krehlik, Hindson, Crowley, et al., 1985	Design: Case report (included for toxicity data only) Intervention(s) studied: Minoxidil 10 mg twice per day Dates: NR Location: Boise, ID Recruitment setting: Hospital	No. of pre-ESRD subjects: 1 Inclusion criteria: NA (case report) Exclusion criteria: NA (case report) Age: 70 Sex: Male Race: NR Renal function at entry: SCr 2.5-3.5 mg/dl Blood pressure data at entry: Patient had history of severe hypertension for at least 17 years Co-morbidities at entry: Congestive heart failure, type II diabetes, hypercholesterolemia, severe diffuse atherosclerotic coronary vascular disease	*Key Question 1) Does treatment with anti-hypertensives improve outcomes before and/or after renal replacement?:* Not addressed *Key Question 2) What is the distribution of blood pressure in pre-ESRD patients?:* Not addressed *Key Question 3) What is the prevalence of antihypertensive treatment in pre-ESRD patients?:* Not addressed *Key Question 4) What is the risk of toxicities or side effects of antihypertensive drug treatment occurring as a consequence of reduced renal function?:* Case report describing hemorrhagic pericarditis in a patient receiving minoxidil and heparin.	Quality Scoring: 1) Global assessment: Good 2) Validity criteria: Population described: NA Incl/excl described: NA Dropouts discussed: NA Sample size justified: NA 3) GFR/CrCl: SCr 4) % pre-ESRD: > 75% 5) Level of evidence: NA Notes:

Evidence Table 3 – Hypertension (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Neil and Waters, 1981	Design: Case report (included for toxicity data only) Intervention(s) studied: Methyldopa 250 mg 3 times per day Dates: 1980 Location: Otley, UK Recruitment setting: Hospital	No. of pre-ESRD subjects: 1 Inclusion criteria: NA (case report) Exclusion criteria: NA (case report) Age: 59 Sex: M Race: White Renal function at entry (in 1980, at time of admission to hospital): CrCl: 4.8 ml/min SCr: 963 µmol/l Blood pressure data at entry : 200/110 mmHg in 1973, when methyldopa therapy initiated 160/90 mmHg in 1980, at time of admission to hospital Co-morbidities at entry: NR Other: Patient had no history or clinical evidence of cerebrovascular disease and had been on the same dose of methyldopa for 7 years	*Key Question 1) Does treatment with anti-hypertensives improve outcomes before and/or after renal replacement?:* Not addressed *Key Question 2) What is the distribution of blood pressure in pre-ESRD patients?:* Not addressed *Key Question 3) What is the prevalence of antihypertensive treatment in pre-ESRD patients?:* Not addressed *Key Question 4) What is the risk of toxicities or side effects of antihypertensive drug treatment occurring as a consequence of reduced renal function?:* Patient was on methyldopa for 7 years for control of hypertension. As renal function deteriorated, he developed bilateral choreiform movements; these movements resolved 36 hours after discontinuation of the drug.	Quality Scoring: 1) Global assessment: Good 2) Validity criteria: Population described: NA Incl/excl described: NA Dropouts discussed: NA Sample size justified: NA 3) GFR/CrCl: Calculated by reviewers 4) % pre-ESRD: > 75% 5) Level of evidence: NA Notes:

Evidence Table 3 – Hypertension (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Plum, Bünten, Németh, et al., 1998 **and** **Plum, Bünten, Németh, et al., 1999**	Design: RCT Intervention(s) studied: 1) Valsartan 80 mg 1x/day (n = 5) for 6 months 2) Placebo (n = 4) 1x/day for 6 months *In both groups,* BP controlled during 3-month run-in period with antihypertensive drugs, including beta-blockers, alpha-blocker, calcium antagonists, clonidine, and minoxidil. ACE inhibitors withdrawn 4 weeks prior to start of trial period. Furosemide allowed if necessary. Medications used during run-in period continued unchanged throughout trial period unless marked changes in BP were registered. Dates: NR Location: Düsseldorf, Germany Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 9 Inclusion criteria: Arterial hypertension (diastolic BP < 105 mmHg, systolic BP < 180 mmHg at end of run-in period); stable renal insufficiency (SCr 200-600 µmol/l); stable proteinuria (≥ 500 mg/24 hours); no increase of SCr over 30% in previous 6 months Exclusion criteria: History of heart failure, malignancy, or any disorders requiring immunosuppressive therapy Age (means ± SD): Valsartan, 57 ± 7; placebo, 62 ± 11 Sex: Valsartan, 60% M, 40% F; placebo, 75% M, 25% F Race: NR Renal function at entry (mean ± SD): GFR (ml/min): Valsartan: 20 ± 7 Placebo: 19 ± 5 CrCl: Valsartan: 21.8 Placebo: 24.1 SCr (µmol/l): Valsartan: 365 ± 122 Placebo: 346 ± 61 Blood pressure data at entry: Mean arterial pressure (± SD): Valsartan: 112 ± 8 mmHg Placebo: 117 ± 6 mmHg 100% of patients had hypertension 100% on antihypertensive medication	*Key Question 1) Does treatment with anti-hypertensives improve outcomes before and/or after renal replacement?:* Mean arterial pressure (± SD, in mmHg): Valsartan / Placebo At entry: 112 ± 8 / 117 ± 6 At 6 months: 99 ± 2 / 113 ± 7 p< 0.01, Valsartan 6 months vs. entry p = not significant, placebo 6 months vs. entry p < 0.05, Valsartan vs. placebo *Key Question 2) What is the distribution of blood pressure in pre-ESRD patients?:* Not addressed *Key Question 3) What is the prevalence of antihypertensive treatment in pre-ESRD patients?:* Not addressed *Key Question 4) What is the risk of toxicities or side effects of antihypertensive drug treatment occurring as a consequence of reduced renal function?:* a) Hemoglobin (means ± SD, in g/dl): Valsartan / Placebo At entry: 12.1 ± 1.0 / 11.6 ± 1.0 At 6 months: 10.5 ± 1.2 / 11.5 ± 1.0 p< 0.05, Valsartan 6 months vs. entry p = not significant, placebo 6 months vs. entry p < 0.05, Valsartan vs. placebo b) SCr (means ± SD, in µmol/l): Valsartan / Placebo At entry: 366 ± 122 / 346 ± 61 At 6 months: 392 ± 135 / 352 ± 59 p< 0.05, Valsartan 6 months vs. entry p = not significant, placebo 6 months vs. entry	Quality Scoring: 1) Global assessment: Excellent 2) Validity criteria: Population described: Partially Incl/excl described: Completely Dropouts discussed: Completely Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by reviewer 4) % pre-ESRD: > 75% 5) Level of evidence: 1b Notes:

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Evidence Table 3 – Hypertension (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
		Co-morbidities at entry: NR Other (all means ± SD): Hemoglobin: Valsartan: 12.1 ± 1.0 g/dl Placebo 11.6 ± 1.0 g/dl Proteinuria: Valsartan: 1672 ± 1113 mg/24 hrs Placebo: 1568 ± 1152 mg/24 hrs Serum potassium: Valsartan: 4.4 ± 0.4 mmol/l Placebo 4.2 ± 0.4 mmol/l	p = not significant, Valsartan vs. placebo c) Proteinuria (means ± SD, in mg/24 hours): Valsartan Placebo At entry: 1672 ± 1113 1568 ± 1152 At 6 months: 1276 ± 1217 2055 ± 1971 p< 0.05, Valsartan 6 months vs. entry p = not significant, placebo 6 months vs. entry p < 0.05, Valsartan vs. placebo d) Serum potassium (means ± SD, in mmol/l): Valsartan Placebo At entry: 4.4 ± 0.4 4.2 ± 0.4 At 6 months: 4.9 ± 0.5 4.1 ± 0.3 p< 0.05, Valsartan 6 months vs. entry p = not significant, placebo 6 months vs. entry p < 0.05, Valsartan vs. placebo	

Evidence Table 3 – Hypertension (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Pontremoli, Robaudo, Gaiter, et al., 1991	Design: Cohort study Intervention(s) studied: Minoxidil started at 2.5 mg/day and increased over time as needed. Beta-blockers and diuretics given to counteract fluid retention and tachycardia. Patients with moderate renal insufficiency (RI) (CrCl 20-50 ml/min/1.73 m^2; n = 9) followed up for 18 months. Patients with severe RI (n = 5) followed up for 12 months. Dates: 1978-1990 Location: Genoa, Italy Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 14 Inclusion criteria: "Severe or accelerated hypertension" Exclusion criteria: None specified Age: Mean, 45.3 Sex: 93% M, 7% F Race: NR Renal function at entry: GFR (mean ± SEM; ml/min/1.73 m^2): Moderate RI: 30 ± 3 Severe RI: 6.0 ± 1.7 Blood pressure data at entry (mean ± SEM; mmHg): Systolic BP: Moderate RI: 192 ± 9 Severe RI: 243 ± 13 Diastolic BP: Moderate RI: 119 ± 4 Severe RI: 137 ± 6 Co-morbidities at entry: NR	*Key Question 1) Does treatment with anti-hypertensives improve outcomes before and/or after renal replacement?:* a) Systolic BP (mean ± SEM; mmHg): Moderate RI / Severe RI Baseline: 192 ± 9 / 243 ± 13 3 months: 157 ± 6* / 173 ± 12* End of follow-up: 150 ± 8* / NR * p < 0.001 vs. baseline b) Diastolic BP (mean ± SEM; mmHg): Moderate RI / Severe RI Baseline: 119 ± 4 / 137 ± 6 3 months: 98 ± 4* / 98 ± 5* End of follow-up: 90 ± 5** / NR * p < 0.01 vs. baseline ** p < 0.001 vs. baseline *Key Question 2) What is the distribution of blood pressure in pre-ESRD patients?:* Not addressed *Key Question 3) What is the prevalence of antihypertensive treatment in pre-ESRD patients?:* Not addressed *Key Question 4) What is the risk of toxicities or side effects of antihypertensive drug treatment occurring as a consequence of reduced renal function?:* Not addressed	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: No/not assessable Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by reviewers 4) % pre-ESRD: 50-75% 5) Level of evidence: 2b Note: Study also included 8 patients with normal renal function, not described here.

Evidence Table 3 – Hypertension (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Portaluppi, Vergnani, Manfredini, et al., 1995	Design: RCT (crossover) Intervention(s) studied: 1) Placebo (AM) + placebo (PM) (n = 16); 2) Sustained-release isradipine 5 mg (AM) + placebo (PM) (n = 16); 3) Placebo (AM) + sustained-release isradipine 5 mg (PM) (n = 16). Trial preceded by 2-week run-in period, during which all antihypertensive drugs were discontinued. Each active treatment lasted 4 weeks; double-placebo treatment lasted 2 weeks. Dates: NR Location: Ferrara, Italy Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 16 Inclusion criteria: Chronic renal failure due to parenchymal kidney disease; hypertension (3 or more casual sitting diastolic BP measurements ≥ 100 mmHg during run-in period) Exclusion criteria: Parkinson's disease; diabetes mellitus; alcoholism; any reversible disorder that may temporarily worsen renal function (including heart failure) Age (mean ± SD): 56.6 ± 14.1 Sex: 63% M, 37% F Race: NR Renal function at entry: CrCl (mean ± SD): 26.4 ± 8.1 ml/min Blood pressure data at entry: NR Co-morbidities at entry: NR	*Key Question 1) Does treatment with anti-hypertensives improve outcomes before and/or after renal replacement?:* Isradipine restored the nocturnal fall in BP that is not normally observed in CRI patients who do not receive antihypertensive treatment. Reductions in nighttime BP were significantly greater with PM administration of isradipine than with AM administration. a) Daytime systolic BP (mean ± SD; mmHg): AM placebo: 162.1 ± 15.7 AM isradipine: 149.2 ± 15.8 p < 0.04, isradipine vs. placebo PM placebo: 160.9 ± 14.6 PM isradipine: 149.3 ± 16.6 p< 0.04, isradipine vs. placebo p = not significant, isradipine PM vs. AM b) Daytime diastolic BP (mean ± SD; mmHg): AM placebo: 99.0 ± 8.6 AM isradipine: 90.0 ± 8.6 p < 0.04, isradipine vs. placebo PM placebo: 97.9 ± 9.8 PM isradipine: 90.7 ± 10.2 p< 0.04, isradipine vs. placebo p = not significant, isradipine PM vs. AM c) Nighttime systolic BP (mean ± SD; mmHg): AM placebo: 162.3 ± 16.8 AM isradipine: 142.1 ± 18.4 p < 0.04, isradipine vs. placebo PM placebo: 161.8 ± 16.4 PM isradipine: 138.1 ± 16.2 p< 0.04, isradipine vs. placebo p < 0.05, isradipine PM vs. AM b) Nighttime diastolic BP (mean ± SD; mmHg): AM placebo: 96.0 ± 7.6 AM isradipine: 82.2 ± 8.7	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: No/not assessable Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by reviewers 4) % pre-ESRD: > 75% 5) Level of evidence: 2b Notes: *(continued on next page)*

Evidence Table 3 – Hypertension (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			p < 0.04, isradipine vs. placebo PM placebo: 95.4 ± 8.9 PM isradipine: 80.8 ± 7.3 p< 0.04, isradipine vs. placebo p < 0.05, isradipine PM vs. AM *Key Question 2) What is the distribution of blood pressure in pre-ESRD patients?:* Not addressed *Key Question 3) What is the prevalence of antihypertensive treatment in pre-ESRD patients?:* Not addressed *Key Question 4) What is the risk of toxicities or side effects of antihypertensive drug treatment occurring as a consequence of reduced renal function?:* Not addressed	

Evidence Table 3 – Hypertension (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Ruilope, Aldigier, Ponticelli, et al., 2000	Design: RCT Intervention(s) studied: 1) Valsartan 160 mg once per day (n = 22); 2) Valsartan 80 mg + benazepril 5 or 10 mg once per day (n = 42); 3) Valsartan 160 mg + benazepril 5 or 10 mg once per day (n = 44). One-week lead-in period, during which patients were randomized to receive either 80 mg or 160 mg of valsartan. Allotted to above treatment groups after 1 week, at second randomization. Dose of benazepril determined by CrCl values (5 mg for CrCl < 30 ml/min; 10 mg for CrCl 30-45 ml/min). Treatment continued for 5 weeks after second randomization. Dates: NR Location: Multiple sites in France, Germany, Italy, and Spain Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 108 Inclusion criteria: Age > 18; CrCl 20-45 ml/min; normotensive or treated hypertensive with mean seated diastolic BP 80-110 mmHg Exclusion criteria: Secondary hypertension of any other etiology; malignant hypertension; serious heart or liver disease; immune disorders; malignancy; diseases treated with steroids, NSAIDs, immunomodulators, or cytostatics during the previous year Age: Mean, 57.3 Sex: 69% M, 31% F Race: 99% Caucasian, 1% Black Renal function at entry: SCr (mean; µmol/l): Valsartan 160 mg: 259 Valsartan 80 mg +benazepril: 240 Valsartan 160 mg + benazepril: 226 Blood pressure data at entry: NR Co-morbidities at entry: NR	*Key Question 1) Does treatment with anti-hypertensives improve outcomes before and/or after renal replacement?:* Not addressed *Key Question 2) What is the distribution of blood pressure in pre-ESRD patients?:* Not addressed *Key Question 3) What is the prevalence of antihypertensive treatment in pre-ESRD patients?:* Not addressed *Key Question 4) What is the risk of toxicities or side effects of antihypertensive drug treatment occurring as a consequence of reduced renal function?:* Only 2 patients (1 in valsartan 80 mg + benazepril group, 2 in valsartan 160 mg + benazepril group) discontinued due to hyperkalemia. Mean increase in serum potassium values from baseline to end of treatment were as follows (mmol/l): Valsartan 160 mg: 0.28 Valsartan 80 mg +benazepril: 0.48 Valsartan 160 mg + benazepril: 0.36 *Other outcomes:* Mean increase in SCr from baseline to end of treatment was as follows (µmol/l): Valsartan 160 mg: 11 Valsartan 80 mg +benazepril: 9 Valsartan 160 mg + benazepril: 15	Quality Scoring: 1) Global assessment: Good 2) Validity criteria: Population described: Completely Incl/excl described: Completely Dropouts discussed: ? Sample size justified: No/not assessable 3) GFR/CrCl: SCr 4) % pre-ESRD: 50-75% 5) Level of evidence: 2b Notes:

Evidence Table 3 – Hypertension (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Schatz, Meso-logites, Hyun, et al. 1989	Design: Case report (toxicity data only) Intervention(s) studied: Captopril 25 µg 3x/day. Patient had taken this dosage for 2 years until angiography precipitated acute tubular necrosis; drug then discontinued. Captopril restarted at same dose 4 days prior to admission described in this case report. Dates: NR Location: Hartford, CT Recruitment setting: Hospital	No. of pre-ESRD subjects: 1 Inclusion criteria: NA (see under "Other," below) Exclusion criteria: NA (see under "Other," below) Age: 77 Sex: M Race: NR Renal function at entry: SCr: On presentation, 4.0 mg/dl; baseline, 2.7 mg/dl Blood pressure data at entry: BP on presentation, 178/100 mmHg Co-morbidities at entry: Congestive heart failure Other: Case report of 77-year-old man with captopril-induced hypersensitivity lung disease	*Key Question 1) Does treatment with anti-hypertensives improve outcomes before and/or after renal replacement?:* Not addressed *Key Question 2) What is the distribution of blood pressure in pre-ESRD patients?:* Not addressed *Key Question 3) What is the prevalence of antihypertensive treatment in pre-ESRD patients?:* Not addressed *Key Question 4) What is the risk of toxicities or side effects of antihypertensive drug treatment occurring as a consequence of reduced renal function?:* Patient developed hypersensitivity pneumonitis likely related to captopril. Unclear if chronic renal insufficiency was a linking/causal factor.	Quality Scoring: 1) Global assessment: Good 2) Validity criteria: Population described: NA Incl/excl described: NA Dropouts discussed: NA Sample size justified: NA 3) GFR/CrCl: SCr 4) % pre-ESRD: > 75% 5) Level of evidence: NA Notes:

Evidence Table 3 – Hypertension (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Shiigai, Hattori, Iwamoto, et al., 1998	Design: RCT Intervention(s) studied: 1) Enalapril 5-10 mg 1x/day for 24 months (n = 14). If BP not adequately controlled (≤ 150/90 mmHg) on monotherapy, then α_1-blocker added. If BP still not controlled, then α-methyl-dopa (250 mg 2x-3x/day) added. 2) Metoprolol 20-60 mg 2x-3x/day for 24 months (n = 14). If BP not adequately controlled (≤ 150/90 mmHg) on monotherapy, then α_1-blocker added. If BP still not controlled, then α-methyl-dopa (250 mg 2x-3x/day) added. Dates: NR Location: Toride-City, Japan Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 36 randomized to treatment; 28 completed 24 months of treatment and were included in the analysis Inclusion criteria: SCr ≤ 3.5 mg/dl; good compliance with low-protein diet (0.6 g/kg/day) and restricted sodium intake (100-120 mEq/day) for 6 months prior to start of trial; hypertension (systolic BP ≥ 150 mmHg and/or diastolic BP ≥ 90 mmHg) Exclusion criteria: SCr ≥ 3.6 mg/dl; potassium ≥ 6 mEq/l Age (mean ± SD): Enalapril, 57.9 ± 12.3; metoprolol, 58.9 ± 11.3 Sex: Enalapril, 50% M, 50% F; metoprolol, 71% M, 29% F Race: NR Renal function at entry: CrCl (estimated from graph): Enalapril: 31 ml/min Metoprolol: 33 ml/min Blood pressure data at entry: Reported only in graphic form; values could not be reliably read off of graph Co-morbidities at entry: NR	*Key Question 1) Does treatment with anti-hypertensives improve outcomes before and/or after renal replacement?:* Mean arterial pressure (MAP) and mean diastolic BP were significantly lower at 6 months with enalapril; otherwise, there were no significant differences between the two treatments for systolic BP, diastolic BP, or MAP at any time point. Values were reported graphically and could not be reliably transcribed. *Key Question 2) What is the distribution of blood pressure in pre-ESRD patients?:* Not addressed *Key Question 3) What is the prevalence of antihypertensive treatment in pre-ESRD patients?:* Not addressed *Key Question 4) What is the risk of toxicities or side effects of antihypertensive drug treatment occurring as a consequence of reduced renal function?:* a) Mean CrCl (± SD) was significantly ($p < 0.05$) higher at 24 months in the enalapril group (33.3 ± 10.9 ml/min) than in the metoprolol group (22.4 ± 10.1 ml/min). b) Progression of renal failure was significantly faster in the metoprolol group than in the enalapril group, both in terms of the slope of CrCl (-0.45 ± 0.40 vs. 0.006 ± 0.48 ml/min/month, $p < 0.05$) and the slope of GFR (-0.89 ± 0.61 vs. -0.16 ± 0.15 ml/min/month, $p < 0.0005$).	Quality Scoring: 1) Global assessment: Good 2) Validity criteria: Population described: Partially Incl/excl described: Partially Dropouts discussed: Completely Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: < 50%/not assessable 5) Level of evidence: 1b Notes:

Evidence Table 3 – Hypertension (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Toto, Shultz, Raij, et al., 1998	Design: Prospective clinical trial (before/after study) Intervention(s) studied: Losartan 50 mg 1x/day for 12 weeks. Dose could be increased to 100 mg after 4 weeks if necessary. Additional, non-ACE-inhibiting drug added at 8 weeks if necessary. Trial preceded by a 3-week placebo run-in period, during which all current antihypertensive medications withdrawn. Dates: NR Location: 18 sites in the US Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 33 of a total of 112 patients had "moderate renal insufficiency" (CrCl 10-29 ml/min/1.73 m^2); baseline data given below refers only to the 33 pre-ESRD patients Inclusion criteria: Age > 21; hypertension associated with impaired renal function; diastolic BP 90-115 mmHg at end of 3-week run-in period; CrCl ≤ 60 ml/min/1.73 m^2 at end of 3-week run-in period Exclusion criteria: Known or suspected renal artery stenosis Age (mean ± SD): 57.4 ± 14.0 Sex: 73% M, 27% F Race: 48% White, 36% Black, 16% other Renal function at entry: CrCl (mean ± SD): 20.48 ± 5.43 ml/min/1.73 m^2 Blood pressure data at entry: Systolic BP (mean ± SD): 160.7 ± 23.2 mmHg Diastolic BP (mean ± SD): 100.4 ± 7.3 mmHg 100% of patients hypertensive Co-morbidities at entry: 36% of patients diabetic	*Key Question 1) Does treatment with anti-hypertensives improve outcomes before and/or after renal replacement?:* Systolic and diastolic BP were significantly decreased at 12 weeks ($p \leq 0.05$). Post-treatment values were reported only in graphic form and could not be reliably transcribed. *Key Question 2) What is the distribution of blood pressure in pre-ESRD patients?:* Not addressed *Key Question 3) What is the prevalence of antihypertensive treatment in pre-ESRD patients?:* Not addressed *Key Question 4) What is the risk of toxicities or side effects of antihypertensive drug treatment occurring as a consequence of reduced renal function?:* a) CrCl (mean ± SD; n = 23): At entry: 20.5 ± 5.4 ml/min/1.73 m^2 At 12 weeks: 19.1 ± 10.3 ml/min/1.73 m^2 p = not significant 2/33 patients (6%) reported a decrease in CrCl as an "adverse experience" b) 1/33 patients (3%) discontinued treatment due to high potassium c) Proteinuria decreased from a mean of 3692 mg/24 hrs at entry to 2795 mg/24 hrs at 12 weeks ($p \leq 0.05$).	Quality Scoring: 1) Global assessment: Excellent 2) Validity criteria: Population described: Partially Incl/excl described: Completely Dropouts discussed: Completely Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 4 Notes:

Evidence Table 3 – Hypertension (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Weidmann, Gnädinger, Schohn, et al., 1989	Design: Prospective clinical trial Intervention(s) studied: Study protocol was as follows: 2-week washout period (no drugs), followed by 4-week placebo period, followed by 6-week nitrendipine period. Nitrendipine started at dose of 20 mg/day and increased as needed up to a maximum of 60 mg/day (therapeutic goal was BP ≤ 140/90 mmHg). Dates: NR Location: NR (Berne, Switzerland and/or Strasbourg, France) Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 15 Inclusion criteria: Hypertension; mild to marked chronic renal insufficiency Exclusion criteria: Drug treatment for renal disease (corticosteroids, immunosuppressants, NSAIDs, etc.); use of oral contraceptives; nephrotic syndrome; congestive heart failure; edema of other etiology; retinal hemorrhages, exudates, or papilledema; previous stroke or MI, diabetes mellitus; endocrine or metabolic dysfunction not related to renal failure; alcohol or drug abuse Age: Mean, 52 ± 3 (SEM); range, 40-69 Sex: 60% M, 40% F Race: NR Renal function at entry (means ± SEM): Creatinine clearance: 33 ± 5 ml/min/1.73 m^2 SCr: 371 ± 44 µmol/l = 4.19 ± 0.50 mg/dl Blood pressure data at entry (means ± SEM): Supine systolic: 173 ± 5 mmHg Supine diastolic: 102 ± 2 mmHg Upright systolic: 170 ± 5 mmHg Upright diastolic: 105 ± 2 mmHg 100% of patient hypertensive Co-morbidities at entry: NR	*Key Question 1) Does treatment with anti-hypertensives improve outcomes before and/or after renal replacement?:* a) Supine BP (mean systolic ± SEM/mean diastolic ± SEM): At entry: 173 ± 5/102 ± 2 mmHg After nitrendipine: 146 ± 3/81 ± 3 mmHg p < 0.001 b) Upright BP (mean systolic ± SEM/mean diastolic ± SEM): At entry: 170 ± 5/105 ± 2 mmHg After nitrendipine: 145 ± 4/86 ± 3 mmHg p < 0.001 *Key Question 2) What is the distribution of blood pressure in pre-ESRD patients?:* Not addressed *Key Question 3) What is the prevalence of antihypertensive treatment in pre-ESRD patients?:* Not addressed *Key Question 4) What is the risk of toxicities or side effects of antihypertensive drug treatment occurring as a consequence of reduced renal function?:* a) CrCl (mean ± SEM) was unaffected by nitrendipine treatment: At entry : 33 ± 5 ml/min/1.73 m^2 After nitrendipine: 32 ± 6 ml/min/1.73 m^2 p = not significant b) Adverse effects reported with nitrendipine included headache (n = 4), palpitations (n = 3), tingling of the extremities (n = 2), postural light-headedness (n = 1), and general weakness (n = 1). These symptoms were mild to moderate and did not require drug withdrawal.	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: No/not assessable Incl/excl described: Partially Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: < 50%/not assessable 5) Level of evidence: 4 Note: Baseline/entry values are from the end of the placebo period.

Evidence Table 3 – Hypertension (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Zanella, Mattei, Draibe, et al., 1985	Design: Prospective clinical trial Intervention(s) studied: Captopril 150 mg/day for 4 weeks. All other antihypertensive medication stopped at least 1 week before start of trial. Dates: NR Location: São Paulo, Brazil Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 16 Inclusion criteria: Hypertension; chronic renal failure Exclusion criteria: Diabetes Age: Range, 12-63 Sex: 62.5% M, 37.5% F Race: NR Renal function at entry: SCr: Range, 1.6-12.4 mg/dl Blood pressure data at entry: Mean arterial pressure (± SEM): 144 ± 6.3 mmHg 100% of patients hypertensive 100% on antihypertensive medication Co-morbidities at entry: NR Other: Potassium at entry (mean ± SEM): 3.9 ± 0.1 mEq/l	*Key Question 1) Does treatment with anti-hypertensives improve outcomes before and/or after renal replacement?:* Mean arterial pressure (± SEM): At entry: 144 ± 6.3 mmHg After 7 days: 123 ± 6.5 mmHg $p < 0.01$ Authors stated that the reductions in MAP observed after 7 days were sustained through the 4-week treatment period. *Key Question 2) What is the distribution of blood pressure in pre-ESRD patients?:* Not addressed *Key Question 3) What is the prevalence of antihypertensive treatment in pre-ESRD patients?:* Not addressed *Key Question 4) What is the risk of toxicities or side effects of antihypertensive drug treatment occurring as a consequence of reduced renal function?:* Plasma potassium levels increased significantly during treatment (means ± SEM): At entry: 3.9 ± 0.1 mEq/l At 4 weeks: 5.5 ± 0.2 mEq/l $p < 0.001$ There was also a correlation between final potassium concentrations and baseline SCr levels ($p < 0.01$; $r = 0.67$).	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: Partially Dropouts discussed: Partially Sample size justified: No/not assessable 3) GFR/CrCl: SCr 4) % pre-ESRD: < 50%/not assessable 5) Level of evidence: 4 Notes:

5. Nutrition

5.1 Chapter Summary

To address the issues of nutritional interventions and management of nutritional status in pre-ESRD patients, the following six key questions were formulated:

1. Are pre-ESRD patients at risk for malnutrition?
2. What risks does malnutrition confer to pre-ESRD patients?
3. What is the tolerability/feasibility of nutritional interventions in patients with pre-ESRD?
4. After appropriate nutritional evaluation, does nutritional intervention result in improved intermediate outcomes and/or clinical outcomes in pre-ESRD patients?
5. What is the rate of change in nutritional parameters in pre-ESRD patients?
6. What is the effect of follow-up nutritional evaluation in improving intermediate outcomes and/or clinical outcomes in pre-ESRD patients?

Key Question 1: Are pre-ESRD patients at risk for malnutrition?

- Based on three cross-sectional studies of > 200 patients each and three smaller cross-sectional studies, we conclude that there is reasonable evidence demonstrating that nutritional status declines as GFR declines and that this may be a function of decreased protein and energy intake.
- Based on four small (n = 9, n = 15, n = 9, n = 9) cohort/cross-sectional studies, we conclude that there is limited and conflicting evidence regarding the rate of protein metabolism in pre-ESRD patients. There also exists limited evidence demonstrating that protein catabolism increases as serum creatinine increases, serum bicarbonate decreases, or as plasma cortisol increases. In addition, protein catabolism may be reduced by correction of acidosis using sodium bicarbonate supplementation .
- Based on one small (n = 25) cohort study, we conclude that there is limited evidence demonstrating that nutritional status is less compromised in pre-ESRD patients than in those status post renal replacement therapy.
- Based on one small (n=20) before/after study , we conclude that there is limited evidence demonstrating that erythropoietin does not affect nutritional status in pre-ESRD patients. This study also demonstrated that pre-ESRD patients had lower nutritional status than healthy controls.

Key Question 2: What risks does malnutrition confer to pre-ESRD patients?

- Based on one cross-sectional study, we conclude that there is no evidence to suggest that atherosclerosis is associated with malnutrition.

Key Question 3: Do nutritional interventions improve the nutritional status of patients with pre-ESRD?

- Based on one small (n = 67) retrospective cohort study, we conclude that there is limited evidence that suggests that a LPD may delay mortality in patients with pre-ESRD who subsequently go onto hemodialysis.
- Based on two randomized controlled trials, two large (n = 139 and n = 51) uncontrolled trials, and one medium (n = 28), four small (n < 10) uncontrolled trials, and two case series we conclude that there is inconsistent and insufficient evidence to support or reject that a LPD has a favorable impact on nutritional parameters of patients with pre-ESRD.
- Based on one crossover study, we conclude that there is limited evidence to suggest that a soy-based LPD can be substituted for an animal-based LPD without compromising nutritional status.
- Based on one randomized controlled trial of 57 patients we conclude that there is limited evidence that a LPD may result in deficiencies of thiamine (B_1), riboflavin (B_2), and pyridoxine (B_6) in pre-ESRD patients.
- Based on two randomized controlled trials of 56 and 90 patients, respectively, we conclude that there is reasonable evidence that a LPD does not result in vitamin E deficiencies.
- Based one small dual-arm, parallel-design trial (n = 59) and one crossover study (n = 8), we conclude that there is limited evidence to suggest that choice of supplement (essential amino acids versus ketoacids) does not affect nutritional status in pre-ESRD patients following a VLPD.
- Based on one uncontrolled study of eight patients, we conclude that there is limited evidence demonstrating that vitamin B_6 supplementation improves vitamin B_6 status in pre-ESRD patients.

Key Question 4: What is the rate of change in nutritional parameters in pre-ESRD patients?

Only one study that attempted to address this question met inclusion criteria. Gentile et al. reported the rate of change in nutritional parameters in 50 patients with estimated creatinine clearance of 36 $\pm$ 16 mL/min (LE: 4, QS: poor). Patients were randomized to two diets (protein intake 0.6 or 1.0 g/kg/day); however, results were reported only for the two groups combined. Over 18 months, body weight decreased significantly from 67 $\pm$ 11 to 65 $\pm$ 11 kg ($p < 0.01$).

Key Question 5: What is the effect of follow-up nutritional evaluation in improving intermediate outcomes and/or clinical outcomes in pre-ESRD patients?

We did not identify any studies addressing this question that met our inclusion criteria.

Key Question 6. What is the tolerability/palatability and feasibility of nutritional interventions in patients with pre-ESRD?

- Based on two large uncontrolled trials and one large randomized controlled trial, we conclude that there is reasonable evidence suggesting that pre-ESRD patients have difficulty adhering to and have low satisfaction with LPD.

- Based on one large randomized controlled trial, we conclude that there is reasonable evidence suggesting that administering a LPD to pre-ESRD patients consumes slightly more time resources from a dietician than does a standard diet.

5.2 Background

Nutritional interventions are commonly advised for patients with chronic kidney disease (CKD). The main goal of these dietary recommendations is to retard the progression of kidney disease and therefore delay the need for renal replacement therapy. The standard recommendation to achieve this goal has been to restrict the intake of dietary protein, especially animal protein. The reasoning behind this recommendation is based on animal studies that have shown that higher dietary intakes of protein can accelerate the progression of CKD, and in turn, restriction of dietary protein intake has been shown to slow progression of CKD in rat models.[1,2] Another major goal of low-protein diets (LPD) is to reduce the symptoms of uremia that occur as CKD inevitably progresses.

Since the initial animal studies of the 1930's that spurred interest in LPDs, there have been a multitude of studies reporting the beneficial effects of a LPD in humans with CKD. However, few of these were randomized controlled trials. Moreover, results from the higher quality studies have been inconclusive regarding the beneficial effects of these diets on progression of kidney disease and, further, have suggested that patients on lower protein diets may be at risk for malnutrition.[3] For these reasons, the use of low-protein diets in CKD patients remains controversial.

In addition to slowing the progression of CKD, nutritional interventions have several other important goals. Even when not following a low-protein diet, CKD patients are at risk for malnutrition, generally because of inadequate energy intake. Because of this, many dietary interventions include a recommendation to increase energy intake. Another goal is prevention of hyperphosphatemia; therefore it is often recommended that CKD patients restrict intake of inorganic phosphorus. Other goals of dietary interventions include prevention of bone disease; prevention of serum vitamin and mineral abnormalities; avoidance of growth retardation in children; and regulation of endocrinologic/metabolic abnormalities, such as glucose intolerance or hyperlipidemia.

The purpose of this paper is to systematically review the available literature regarding nutrition in pre-ESRD patients (defined as individuals with a GFR below 30 mL/min/1.73 m^2 and expected to require RRT within 6 to 18 months).

5.3 Methods

To address the issues of nutritional interventions and management of nutritional status in pre-ESRD patients, the following six key questions were formulated:

1. Are pre-ESRD patients at risk for malnutrition?
2. What risks does malnutrition confer to pre-ESRD patients?
3. What is the tolerability/feasibility of nutritional interventions in patients with pre-ESRD?
4. After appropriate nutritional evaluation, does nutritional intervention result in

improved intermediate outcomes and/or clinical outcomes in pre-ESRD patients?
5. What is the rate of change in nutritional parameters in pre-ESRD patients?
6. What is the effect of follow-up nutritional evaluation in improving intermediate outcomes and/or clinical outcomes in pre-ESRD patients?

To identify the literature addressing these questions, the following search terms were used: "nutrition," "dietetics," "diet," "diet therapy," "dietary supplements," "avitaminosis," "protein deficiency," "nutrition assessment," "nutritional status," and "nutritional requirements."

Because renal replacement therapy is considered to be inevitable in pre-ESRD, the effect of dietary interventions on the progression of kidney disease will not be addressed in this review. In addition, studies of the effects of dietary interventions on non-traditional nutritional outcomes (e.g., bone disease, serum lipids, or endocrinologic abnormalities) have been excluded. Finally, studies of pediatric patients were also excluded. The most common outcomes reported in the included studies were dietary adherence, vitamin and mineral status, anthropometry, other measurements of body composition, protein turnover, and serum markers of malnourishment. The majority of reviewed studies evaluated similar diets (i.e., low-protein, low-phosphorus, high-energy diets). Therefore, this chapter organizes the results according to the goal or primary outcome of the study, as opposed to the type of diet intervention. Information on the six key questions described above is summarized below.

5.4 Results

Seven hundred and ninety-six titles and abstracts were initially screened. Of these, 138 were identified for full-text screening. We were unable to obtain copies of 14 of these articles[4-17]. Of the remaining 124, 83 were excluded during full-text review for the following reasons: outcomes not reported separately for the pre-ESRD population (n = 1), did not meet the criteria for the pre-ESRD population (n = 9), small case series/single case report (n = 2), did not address at least one of the key questions (n = 71). Sixty-five articles were included at the full-text screening stage: 29 of these were review articles; the remaining 36 were abstracted using a standardized form and are summarized in Evidence Table 4.

Key Question 1: Are pre-ESRD patients at risk for malnutrition?

Eight studies specifically examined nutritional parameters or nutrient intakes of pre-ESRD patients prior to any nutritional intervention, while three studies examined nutritional parameters of pre-ESRD patients, some of whom had followed a LPD. Another study reported nutritional parameters in pre-ESRD patients prior to and after a nutritional intervention without specifically evaluating the effect of the nutritional intervention. Finally, one study examined the nutritional effects of erythropoietin administration in patients following a LPD.

In a cross-sectional analysis, Kopple et al.[18] reported the baseline nutritional status and anthropometric measurements from the patients entered into the multicenter Modification of Diet in Renal Disease (MDRD) Study (LE: 2b, QS: fair). Patients with

chronic kidney disease were assigned to three groups according to kidney disease severity. In general, as kidney function declined, nutritional status also worsened. Sample size ranged from 226 to 350 depending on the outcome measured. As compared with patients with GFR > 37 mL/min/1.73 m^2, male patients with GFR < 21 mL/min/1.73 m^2 had significantly lower dietary protein intake; dietary energy intake; body weight; percent body fat; skin-fold thickness measurements; and serum albumin, transferrin, and total cholesterol measurements. Female patients with GFR < 21 mL/min/1.73 m^2 had slightly fewer discrepancies than did their male counterparts. For both sexes, patients with GFR 21-37 mL/min/1.73 m^2 had fewer discrepancies than did their counterparts with GFR < 21 mL/min/1.73 m^2. Many of the nutritional parameters correlated directly with GFR; however, in multivariate regression analyses, the association was attenuated or eliminated by controlling for protein and energy intakes. Finally, the authors demonstrated that patients of Black race may have lower nutritional status as compared with non-Blacks.

Greene et al.[19] also reported a cross-sectional analysis of the baseline characteristics of the MDRD Study participants (LE: 2b, QS: fair). These authors reported similar findings to those of Kopple et al.,[18] but used different GFR cutpoints. As compared with participants from "Study A" (GFR 25-55 mL/min/1.73 m^2, n = 585), participants from "Study B" (GFR 13-24 mL/min/1.73 m^2, n = 255) had significantly lower BMI, body weight, elbow width, and body surface area; lower caloric intake, phosphorus intake, and protein intake; lower serum albumin, protein, and transferrin; and lower plasma essential amino acids and ratio of plasma essential to non-essential amino acids.

In a cohort study examining nutritional status and body composition by bioelectric impedance, Dumler et al.[20] compared 25 pre-ESRD patients (estimated creatinine clearance 19 $\pm$ 5 mL/min) with hemodialysis and living-donor kidney transplant patients over a period of 9 months (LE: 4, QS: fair). Pre-ESRD patients had significantly higher body weight, body mass index, fat free mass, and body cell mass compared with each of the other groups. Serum albumin, total body water, and intracellular and extracellular water content were similar among the groups.

In a cross-sectional study, Lusvarghi et al.[21] evaluated nutrient intake prior to dietetic manipulation in 441 patients with estimated creatinine clearance of 28.2 $\pm$ 16.1 mL/min (LE: 4, QS: poor). Comparisons were made with (I) a sample of kidney disease patients without kidney failure, (2) families from northwest Italy and (3) Italian dietary reference values; however tests of significance were not reported. Total energy intake was 29 $\pm$ 7.4 kcal/kg for males and 28.4 $\pm$ 7.4 kcal/kg for females. These intakes were lower than those of the three comparison groups. In regard to proportion of energy from each of the macronutrients, male pre-ESRD patients consumed 14.25% (1.02 $\pm$ 0.2 g/kg/day), 34.6% (1.10 $\pm$ 0.2 g/kg/day) and 51.2% (3.7 $\pm$ 1.1 g/kg/day) of total energy from proteins, fats and carbohydrates, respectively. For females, the distribution was 13.6% (0.96 $\pm$ 0.2 g/kg/day), 37.4% (1.17 $\pm$ 0.3 g/kg/day) and 49% (3.49 $\pm$ 1.0 g/kg/day), respectively. Protein intakes were lower than those of families from northwest Italy, but comparable to the other comparison groups. Females consumed less total fat than the first two comparison groups but not the dietary reference values. In this Italian sample

of pre-ESRD patients, both males and females consumed more monounsaturated fats than dietary reference values. In both male and female patients, carbohydrate intake was lower than families from northwest Italy and dietary reference values. In addition, calcium intake in female patients was lower than dietary reference values, while phosphorus intake in male and female patients was higher than dietary reference values.

Abdullah et al.[22] compared nutritional parameters of 20 patients with serum creatinine of 551 $\pm$ 105 µmol/L to 25 age-matched healthy volunteers (LE: 4, QS: poor). These patients had received a recommendation to consume at least 35 kcal/kg/day, but no recommendation was given regarding protein restriction. Despite this, patients consumed only 0.62 g protein/kg/day and 32.05 $\pm$ 4.45 kcal/kg/day. Compared with the control group, the patients had lower serum total protein, serum albumin, serum prealbumin, triceps skinfold thickness, and midarm muscle circumference. BMI was also lower, but the difference was not statistically significant. This study also examined the role certain inflammatory mediators play in the malnutrition that occurs in CKD patients. Plasma tumor necrosis factor-alpha (TNF-alpha) levels correlated negatively with protein intake ($r = -0.53$, $p < 0.01$), BMI ($r = -0.49$, $p < 0.05$), midarm muscle circumference ($r = -0.69$, $p < 0.01$), whereas insulin-like growth factor-I (IGF-I) levels correlated positively with subjective global nutritional assessment, BMI, triceps skinfold thickness, and midarm muscle circumference. Neither interleukin-1beta (IL-1beta) nor IL-6 correlated with any of the nutritional parameters.

Protein turnover was measured by leucine flux in nine patients with mean serum creatinine of 1087 $\pm$ 300 µmol/L and compared with measurements from five healthy controls by Lim et al.[23] (LE: 1b, QS: fair). Two measurements were made prior to initiation of dialysis (one after acidosis was corrected with one week of oral sodium bicarbonate supplementation), and one measurement occurred after hemodialysis had been initiated. Regardless of acid-base status, prior to hemodialysis, total leucine flux (rate of leucine appearance in the postabsorptive state) and leucine synthesis were lower than measurements made after initiation of dialysis or in controls. Leucine oxidation prior to dialysis was also lower as compared with controls. These data indicate that prior to dialysis, the patients were not in a catabolic state.

Conflicting evidence comes from an article by Biolo et al.[24] These authors measured protein turnover by leucine flux in 15 patients (mean serum creatinine 5.7$\pm$ 0.4 mg/dL) who were following a weight-maintaining diet consisting of 0.6-0.8 g protein/kg/day and $\geq$ 300 g carbohydrates/day (LE: 4, QS: fair). Rate of whole-body protein turnover (rate of leucine appearance) was 2.02 $\pm$ 0.13 µmol/kg/min. This measurement correlated with serum creatinine ($r = 0.59$, $r^2 = 0.35$), indicating that protein catabolism increased as degree of kidney failure increased.

Similar results were obtained by Garibotto et al{#310461}, who examined phenylalanine kinetics across the forearm in 9 patients (estimated creatinine clearance 24 $\pm$ 3) and used healthy controls for comparison (LE: 4, QS: fair). Rate of appearance and disposal of phenylalanine were higher in pre-ESRD patients than in controls. However,

the rates were higher by similar amounts, meaning that net proteolysis was not significantly different compared with controls. In correlation analyses, the authors found that net proteolysis increased as arterial bicarbonate increased. In addition, plasma cortisol was inversely correlated with arterial bicarbonate and directly correlated with net proteolysis.

Another study specifically examined the effect that correction of acidosis with oral sodium bicarbonate supplements had on protein turnover (LE: 4, QS: fair){#310451}. Nine patients with mean serum creatinine 7.7 mg/dL underwent leucine turnover analysis in the following sequence: at baseline, after 4 weeks of sodium bicarbonate 1.2 g three times per day (adjusted to optimize correction of acidosis), and after 4 weeks of salt (NaCl) as a control. Mean levels of oxidation, protein degradation and protein synthesis were lower after intervention with sodium bicarbonate as compared with measurements at baseline and after NaCl. These results suggest that protein catabolism can be reduced by correction of acidosis using sodium bicarbonate supplementation. Serum amino acids were also measured at the three intervals and no significant differences were seen.

In a cross-sectional study, Woodrow et al.[25] evaluated the body composition of 23 patients with estimated creatinine clearance of 7.3 $\pm$ 3.6 mL/min by using dual energy X-ray absorptiometry (DEXA), bioelectric impedance, and skinfold anthropometry (LE: 1b, QS: fair). Pre-ESRD patients were instructed to follow a restricted protein diet (0.6 to 0.8 g/kg IBW/day, 70% of protein intake to be of high biological value) in the latter stages of the predialysis period. Compared with normal controls, pre-ESRD patients had similar total lean tissue, trunk lean tissue, and limb lean tissue measurements, but significantly lower ratio of limb:trunk lean tissue measurements. In addition, females had significantly lower arm lean tissue, and males had significantly lower percentage total body fat compared with controls. Pre-ESRD patients were more likely than controls to be below the 10th percentile of triceps skinfold thickness (26% vs. 3%) and mid-arm circumference (43% vs. 6%).

Gentile et al.[26] reported the rate of change in nutritional parameters in 50 patients with estimated creatinine clearance of 36 $\pm$ 16 mL/min (LE: 4, QS: poor). Patients were randomized to two diets (protein intake 0.6 or 1.0 g/kg/day); however, results were reported only for the two groups combined. Over 18 months, body weight decreased significantly from 67 $\pm$ 11 to 65 $\pm$ 11 kg ($p < 0.01$). On several other nutritional parameters (serum total protein, serum albumin, serum transferrin, triceps skinfold thickness, arm circumference, arm muscle circumference), no signs of caloric or protein malnutrition were seen at 18 months. However, baseline measurements for these parameters were not provided for comparison.

From the feasibility study for the MDRD study, Kopple et al. [27] (LE:4) reported nutritional parameters of 95 pre-ESRD patients (measured GFR 21.6 $\pm$ 1.2 at the end of the borderline period) prior to and after dietary intervention (4 diets of differing protein, phosphorus and supplemental amino acid contents). The authors did not evaluate the effects of the individual diets. Prior to the nutritional intervention, there was a mildly

positive correlation between GFR and protein intake in all patients. There was also a mildly positive correlation between GFR and % standard weight and arm muscle area in men and a moderately positive correlation between GFR and energy intake in women. At the end of 12.4 months, GFR correlated positively with energy intake, arm muscle area, and serum transferrin in all patients. In addition, patients were grouped by GFR at the end of the study ($\geq$ 25, 10-24, < 10 ml/min/1.73 m^2) and compared on several nutritional parameters. In men and women combined, energy intake and serum transferrin were significantly lower with lower GFR while serum albumin did not change. In men and women analyzed separately, the following measurements did not differ among the different GFR groups: % desirable weight, BMI, skin-fold thickness (triceps, biceps, subscapular), % body fat, and arm muscle area.

Nishikage et al. [28] examined nutritional parameters in 27 patients with mean creatinine 5.3 $\pm$ 2.0 mg/dl before and after treatment with recombinant human erythropoietin (rHuEPO) (LE: 4, QS: poor). Patients followed a LPD (0.6g protein/kg/day, 0.35 kcal/kg/day) and received rHuEPO 6,000 units intravenously each week until hematocrit reached 30%, at which point rHuEPO was decreased to 3,000 units each week. At baseline, patients had lower body weight, total protein, albumin, transferrin and amino acid levels (non-essential, essential, branched chain) compared with healthy controls. Over 6 months, body weight, BMI, total protein, albumin, prealbumin, transferrin, IGF-1 and amino acid levels (total, non-essential, essential, branched chain) did not change significantly in the 20 patients who remained in the study.

In summary:

- Based on three cross-sectional studies of > 200 patients each[18,19,21] and three smaller cross-sectional studies,[22,25,26] we conclude that there is reasonable evidence demonstrating that nutritional status declines as GFR declines and that this may be a function of decreased protein and energy intake.
- Based on four small (n = 9, n = 15, n = 9, n = 9) cohort/cross-sectional studies,[23,24 29] {#310461} we conclude that there is limited and conflicting evidence regarding the rate of protein metabolism in pre-ESRD patients. There also exists limited evidence demonstrating that protein catabolism increases as serum creatinine increases [24], serum bicarbonate decreases, or as plasma cortisol increases [30]. In addition, protein catabolism may be reduced by correction of acidosis using sodium bicarbonate supplementation [29].
- Based on one small (n = 25) cohort study,[20] we conclude that there is limited evidence demonstrating that nutritional status is less compromised in pre-ESRD patients than in those status post renal replacement therapy.
- Based on one small (n=20) before/after study [28], we conclude that there is limited evidence demonstrating that erythropoietin does not affect nutritional status in pre-ESRD patients. This study also demonstrated that pre-ESRD patients had lower nutritional status than healthy controls.

Key Question 2: What risks does malnutrition confer to pre-ESRD patients?

One article examined the vascular risks association with malnutrition in pre-ESRD patients.

Stenvinkel et al.[31] measured nutritional, vascular, lipid and inflammatory parameters in 109 patients (mean creatinine clearance 7 ± 1) immediately prior to initiation of RRT and looked for associations (LE: 4, QS: fair). Patients were divided into 2 groups (well-nourished vs. malnourished) based on subjective global assessment (SGA) of nutritional status. In regard to vascular parameters as measured by carotid ultrasound, malnourished individuals had higher mean intima-media thickness, mean intima-media area, prevalence of carotid plaques and prevalence of symptomatic vascular disease on history. However, these patients were also older (57 ± 2 vs. 47 ± 2 years) and more likely to smoke or have smoked cigarettes (65% vs. 39%). In fact, in multivariate analyses adjusting for these and other factors, nutritional status was not significantly associated with vascular disease.

In summary:

- Based on one cross-sectional study, we conclude that there is no evidence to suggest that atherosclerosis is associated with malnutrition.

Key Question 3: Do nutritional interventions improve the nutritional status of patients with pre-ESRD?

One study reporting survival after initiation of a LPD was identified. Thirteen studies reporting the overall nutritional effects of a low-protein diet (LPD) were identified. In addition, three studies examined the effect of LPD on vitamin stores, one examined the additional nutritional effect of amino acid/ketoacid supplements to LPD, and one examined the effectiveness of vitamin B_6 supplementation.

Effects of low-protein diets on mortality

Coresh et al.[32] retrospectively evaluated the effect of a very low-protein diet (0.3 g/kg IBW/day) initiated prior to dialysis on survival once treated with dialysis (LE: 2b, QS: fair). Between the years 1985 and 1994, 67 patients with mean serum creatinine of 4.3 mg/dL were prescribed 0.3 g/kg IBW/day protein intake and supplemented with essential amino acids or ketoacid-amino acid mixture. Mean duration of follow-up was 27 months; vital status of patients was determined in 1994. During follow-up, body weight decreased by 0.08 ± 0.27 kg per month, which was statistically significant. Observed death rates were compared with US Renal Data System (USRDS) death rates (matched for age, sex, and underlying cause for kidney disease of the study cohort) from 1987, a relatively early comparison year given that follow-up in the study took place from 1986-1994. Observed death rates in the cohort were significantly less than expected in year 1 of follow-up, but significantly more than expected in years 4 and 5 combined. Overall, at 5 years of follow-up (96.4 person-years), there were 10 observed and 14.9 expected deaths, a non-significant difference.

Effects of low-protein diets on overall nutritional status

Four reports from randomized controlled trials, two crossover controlled trials, seven uncontrolled trials, and two retrospective chart reviews evaluated the overall nutritional effects of a low-protein diet in adults with pre-ESRD.

Kopple et al.[33] reported the nutritional effects resulting from the MDRD Study, a large, multicenter, randomized controlled trial (LE: 1b, QS: good). In Study B of this trial, 255 patients with GFR 13-24 mL/min/1.73 m^2 were randomized to either a LPD consisting of 0.58 g protein/kg/day or a very low-protein diet (VLPD) consisting of 0.28 g protein/kg/day supplemented with a mixture of ketoacids and amino acids (0.28 g/kg/day). A usual protein diet control group was not included in study B. Patients were also randomized concurrently to either intensive or less intensive blood pressure management. The most common causes of kidney disease in this study were polycystic kidney disease (25% of patients) and glomerular diseases (24%). The two groups differed slightly, but significantly, on the amount of daily protein intake. In examining the changes that occurred in the groups over the duration of the trial, the LPD group had significant decreases in body weight, body fat percentage, and transferrin, while the VLPD had significant decreases in body weight, arm muscle area, and transferrin. Both groups had significant increases in albumin. After an average duration of 2.2 years, there were no significant differences between the groups in regards to the following: energy intake, body weight, relative body weight, skinfold thickness, percent body fat, arm muscle circumference, albumin or transferrin. In between-group comparisons of the changes from baseline, the LPD group had a significantly greater decrease in body fat percentage than the VLPD group. One patient in the LPD group died compared with four patients in the VLPD group, a non-significant difference. One patient in the LPD group and one in the VLPD group reached a stop point due to malnutrition. In correlation analyses, none of the examined nutritional status variables correlated significantly with protein intake.

Herselman et al.[34] randomized 22 patients with estimated creatinine clearance 30 $\pm$ 17 mL/min and 27 $\pm$ 11 mL/min, respectively, to a LPD (0.6 g protein/kg/day; 70% high biological value) or VLPD (0.54 g protein/kg/day; 0.4 g/kg/day mixed quality and 0.14 g/kg/day essential amino acids supplements), respectively (LE: 2b, QS: fair). Recommended intakes of energy (150 kJ/kg/day), calcium, phosphorus, a multivitamin and glucose polymers were similar between groups. Nutritional analysis revealed that patients in both groups were unable to adhere to diet recommendations. The LPD group consumed 125 $\pm$ 34 kcal/kg/day and 0.73 $\pm$ 0.25 g protein/kg/day, while the VLPD consumed 116 $\pm$ 34 kcal/kg/day and 0.63 $\pm$ 0.17 g protein/kg/day. Protein and fat intakes were significantly less than at baseline for both groups; however, there were no significant nutrient intake differences in comparisons between groups. In addition, after 9 months of the intervention, there were no significant differences between groups when comparing serum albumin, serum transferrin, BMI, arm muscle area, or body fat percentage.

Using a crossover design, Soroka et al.[35] examined the 6-month effects of a soy-based vegetarian low-protein diet compared with an animal-based low-protein diet in 15 patients with measured GFR 28.81 $\pm$ 3.3 mL/min/1.73 m^2 (LE: 2b, QS: fair). Both diets

were designed to provide 32 kcal/kg/day, 0.75 g protein/kg/day, similar proportions of calories from each of the macronutrients (carbohydrates 60%, fat 30%, protein 10%), and similar amounts of phosphorus (11 mg/kg/day), calcium (1,000 mg/day), and cholesterol (280 mg/day). The vegetarian diet consisted of prepackaged soy foods, three eggs per week, vegetable oils, and sweetened beverages, while the animal-based diet stipulated half of daily protein intake from meats and eggs and half from grains, fruits and vegetables. The nine participants who completed the study consumed significantly more energy, total fat, polyunsaturated fat, and iron, and significantly less protein (including smaller amounts of seven of the essential amino acids), phosphate, saturated fat, and monounsaturated fat while on the vegetarian diet. Translating this into rates of adherence, participants were more likely to meet energy goals and protein restrictions while on the vegetarian diet. Albumin levels were similarly increased from baseline on both diets. Transferrin increased similarly on both diets, but was not statistically significantly different from baseline values.

In the largest of the uncontrolled trials, Rayner et al.[36] reported the nutritional effects of a low-protein diet (0.6 g/kg IBW/day, 35 kcal/kg IBW/day) in 139 patients with mean serum creatinine of 555 ± 152 µmol/L (LE: 4, QS: poor). Median duration of follow-up was 16 months. Albumin increased significantly by 0.72% per year; however weight decreased by 0.64% per year. Triceps skin-fold thickness and arm-muscle circumference decreased non-significant amounts each year.

Cupisti et al.[37] reported on 51 patients with estimated creatinine clearance of 7.8 ± 3.5 mL/min who were prescribed a LPD (LE: 4, QS: fair). The diet recommendations consisted of plant protein (0.3 g/kg BW/day), energy (35 Kcal/kg BW/day), inorganic phosphorus (< 500 mg/day), potassium (60-80 mEq/day), and sodium (7-11 mEq/day). In addition, the following supplements were given: essential amino acids, calcium carbonate (2-6 g/day), vitamin B12 (500 µg IM each week), and iron. After an average duration of 13.5 ± 6.8 months, weight increased 0.8 kg, total protein increased 0.2 g/dL, and albumin increased 0.3 g/dL. In addition, triceps skinfold thickness increased by 0.1 cm in males. All of these changes were statistically significant. Transferrin, C3, C4, and muscle arm circumference did not change significantly.

Five studies reported the nutritional effects of low-protein diets in very small cohorts (≤ 10) of pre-ESRD patients. Four of these studies used very similar diet approaches,[38-41] while the fifth did not describe the diet in the article.[42] The diets used in the first three studies described below were vegetarian and consisted of the following recommendations: protein (0.25-0.35 g/kg/day), phosphorus (3.5-7 mg/kg/day), and energy (35 kcal/kg/day), with 60-67% of kcal from carbohydrate and 30% from fat. The diet used in the fourth study had similar macronutrient, energy and phosphorus intakes but meat was allowed. The following supplements were provided in each study: amino acid/keto analogs, calcium carbonate (2-6 g/day), iron supplements, and multivitamins.

Barsotti et al.[38] reported the effects of the regimen in eight patients with diabetic nephropathy (LE: 4, QS: poor). Baseline estimated creatinine clearance was 15.6 ± 11.2 mL/min. After an average of 15.6 months, statistically significant decreases

occurred in serum glucose, BUN, and total cholesterol. Non-statistically significant decreases occurred in body weight, exogenous insulin dose, serum triglycerides, and serum HDL-cholesterol.

In another study of eight patients with diabetic nephropathy by the same research group,[39] baseline estimated creatinine clearance was 19.2 ± 13.4 mL/min (LE: 4, QS: poor). After an average of 17.4 months on the diet, statistically significant changes occurred in the following parameters: albumin (+0.5 mg/dL), total protein (+ 0.93 mg/dL), and exogenous insulin dose (-12 units/day). Changes in the following measurements were not statistically significant: body weight, triceps skin-fold thickness, middle arm muscle circumference, transferrin, C3, C4, BUN, glucose, PTH, and T3.

In a study of 10 pre-ESRD patients by Chauveau et al.,[40] baseline measured GFR was 13.2 ± 4.8 mL/min/1.73 m^2 (LE: 4, QS: poor). After 1 year of the diet intervention, DEXA scan revealed significant increases in body fat mass and body fat percentage and a decrease in limb/trunk lean tissue ratio. Changes in the following parameters were not significant: lean body mass by DEXA, body mass index, triceps skinfold thickness, arm muscle circumference, albumin, prealbumin, retinol binding protein (RBP), and transferrin.

Aparicio et al.[41] reported findings on 239 patients with various levels of kidney failure severity; average measured GFR was 13.1 ± 4.8 mL/min/1.73 m^2 (LE: 4, QS: poor). Results were separated according to renal replacement therapy (RRT) outcome, but a group of 28 patients remained on the diet without progressing to RRT. In this group, serum albumin increased significantly from ~39 to ~41 g/L over ~36 months.

In another study,[42] eight patients with baseline estimated creatinine clearance of 39.7 mL/min were followed on a diet described as a low-protein diet for 5.5 years (LE: 4, QS: poor). After this time period, the following measurements of nutritional status decreased significantly: albumin, prealbumin, transferrin, C3, and C4. The following measurements did not change significantly: BMI, triceps and subscapular skinfold thickness, arm muscle circumference, arm muscle area, total protein, pseudocholinesterase, and muscle biopsy analysis.

A retrospective chart review by Walser et al.{#29580} evaluated the effects of a LPD (0.3 g protein /kg IBW, 35 kcal/kg IBW, plus amino acid or ketoacid supplements) on nutritional status in 43 patients with mean serum creatinine 4.8 ± 1.6 mg/dl (LE: 4, QS: poor). After a median duration of 26 months (range 6-72 months), only 2 patients had a serum albumin less than 3.4 g/dl and 8 had a transferrin level less than 200 mg/dl. However, baseline measurements of these nutritional parameters were not provided, except in the 5 patients who had baseline hypoalbuminemia. In 4 of these 5 patients, both serum albumin and transferrin increased to normal while on the LPD plus supplements. In correlation analyses, duration of LPD was not associated with serum albumin or transferrin levels.

Walser and Hill reported another case series{#310421} that included patients from previous reports and utilized the same diet approach as above (LE: 4, QS: poor). There were 23 patients (mean measured GFR 7.4 ± 1.9) with baseline data. Protein intake during the intervention was estimated at 0.52 ± 0.15 g/kg. Following a median survival to RRT of 353 days, body weight decreased from 72.1 ± 13.9 to 69.1 ± 13.0 kg, transferrin decreased from 233 ± 38 to 223 ± 46 mg/dL, and albumin did not change.

Effects of low-protein diets on vitamin status

Gentile et al.[43] randomly assigned 57 patients with average creatinine > 2.5 mg/dL to a LPD (protein 0.6 g/kg BW/day, phosphorus 7.8 mg/kg BW/day, fat 1.2 g/kg BW/day, carbohydrate 5.7 g/kg BW/day) or to a "free" diet (protein 1.0 g/kg BW/day, phosphorus 13.1 mg/kg BW/day, fat 1.1 g/kg BW/day, carbohydrate 4.0 g/kg BW/day) (LE: 2b, QS: fair). Vitamin status was assessed every 6 months for 2 years by measuring activity of enzymes for which water-soluble vitamins are cofactors. While statistical tests of significance were not reported, patients on the LPD appeared more likely to develop deficiencies of thiamine (B_1), riboflavin (B_2), and pyridoxine (B_6) than the "free" diet group. Furthermore, the percentage of patients with deficiency increased as duration of the diet increased. Food diaries confirmed inadequate intakes of these vitamins for both groups, but more inadequate for the LPD group. This study also reported that serum levels of vitamin A, retinal-binding protein, and vitamin E were higher in pre-ESRD patients than in normal controls. Porrini et al.[44] reported the same water-soluble vitamin results from this patient sample in another journal.

In a randomized controlled trial,[45] the effects of a LPD on vitamin E status were measured in 90 patients with mean serum creatinine of 3.6 ± 1.9 mL/min (LE: 2b, QS: fair). Patients were randomized to follow either a 0.6 g protein/kg/day diet or a 1.0 g protein/kg/day diet. Both diets consisted of 15 mg/day of vitamin E, and neither diet group received vitamin E supplements or blood transfusions during the study. These patients were also compared with 30 healthy persons with normal serum creatinine. Plasma vitamin E levels were measured every 6 months for 18 months. At all time points, there were no significant differences comparing the two diet groups or comparing either diet group with the control group. Moreover, there were no insufficient plasma levels (< 5.0 µg/ml) in any of the patients.

Effects of amino acid/ketoacid supplements on overall nutritional status

To evaluate the nutritional effects of amino acid versus ketoacid supplements, 59 patients with estimated creatinine clearance of 11 mL/min were placed on a LPD; 22 patients received essential amino acids (EAA) and 37 received ketoacids (KA), but no mention of randomization was made (LE: 2b, QS: fair).[46] After 12 months, there were no marked differences between groups regarding percent of ideal body weight, skin-fold thickness, upper arm muscle circumference, albumin, transferrin, cholinesterase, absolute lymphocyte count, Cutan test, or immunoglobulins, but tests of significance were not reported.

In a crossover comparison of the effects of EAA or KA on protein turnover (measured by leucine kinetics), eight patients with measured GFR of 18.8 ± 2.7 mL/min/1.73 m^2

followed a VLPD (0.28 g protein/kg/day) supplemented with EAA (3.29 g/10 kg/day) or KA (2.8 g/10 kg/day) (LE: 2b, QS: fair).[47] After 14 days on each of the regimens, the following measurements were similar regardless of the type of supplement taken by the patient: energy intake; protein intake; body weight; serum albumin; serum transferrin; calculated nitrogen balance; and rates of whole-body protein degradation, protein synthesis, and leucine oxidation. Leucine kinetics were similar in both the fasted and fed states. Five of the patients and one new patient then followed the KA regimen for 1 year. Nitrogen balance and rates of whole-body protein degradation, protein synthesis, and leucine oxidation did not change significantly over that period of time.

Effect of vitamin B_6 supplementation on vitamin B_6 status

Laso Guzman et al.[48] gave pyridoxine HCl 150 mg (729 μmol pyridoxine) daily to 26 kidney failure patients, eight of whom were pre-ESRD (estimated creatinine clearance 12.93 ± 6.03 mL/min) (LE: 4, QS: fair). After 4 weeks, vitamin B_6 status improved in the eight patients as measured by erythrocyte aspartate aminotransferase (EAST) activity with and without pyridoxal-5'phosphate (PLP) added in vitro.

Summary

In summary:

- Based on one small (n = 67) retrospective cohort study,[32] we conclude that there is limited evidence that suggests that a LPD may delay mortality in patients with pre-ESRD who subsequently go onto hemodialysis.
- Based on two randomized controlled trials,[33,34] two large (n = 139 and n = 51) uncontrolled trials,[36,37] one medium (n = 28), four small (n < 10) uncontrolled trials,[38-42] and two case series [49 50], we conclude that there is inconsistent and insufficient evidence to support or reject that a LPD has either a favorable or an unfavorable impact on nutritional parameters of patients with pre-ESRD.
- Based on one crossover study,[35] we conclude that there is limited evidence to suggest that a soy-based LPD can be substituted for an animal-based LPD without compromising nutritional status.
- Based on one randomized controlled trial of 57 patients,[43] we conclude that there is limited evidence that a LPD may result in deficiencies of thiamine (B_1), riboflavin (B_2), and pyridoxine (B_6) in pre-ESRD patients.
- Based on two randomized controlled trials of 56 and 90 patients, respectively,[43,45] we conclude that there is reasonable evidence that a LPD does not result in vitamin E deficiencies.
- Based on one small dual-arm, non-randomized trial (n = 59)[46] and one crossover study (n = 8),[47] we conclude that there is limited evidence to suggest that choice of supplement (essential amino acids versus ketoacids) does not affect nutritional status in pre-ESRD patients following a VLPD.
- Based on one uncontrolled study of eight patients,[48] we conclude that there is limited evidence demonstrating that vitamin B_6 supplementation improves vitamin B_6 status in pre-ESRD patients.

Key Question 4: What is the rate of change in nutritional parameters in pre-ESRD patients?

Only one study that attempted to address this question met inclusion criteria. Gentile et al.[26] reported the rate of change in nutritional parameters in 50 patients with estimated creatinine clearance of 36 ± 16 mL/min (LE: 4, QS: poor). Patients were randomized to two diets (protein intake 0.6 or 1.0 g/kg/day); however, results were reported only for the two groups combined. Over 18 months, body weight decreased significantly from 67 ± 11 to 65 ± 11 kg ($p < 0.01$).

Key Question 5: What is the effect of follow-up nutritional evaluation in improving intermediate outcomes and/or clinical outcomes in pre-ESRD patients?

We did not identify any studies addressing this question that met our inclusion criteria.

Key Question 6: What is the tolerability/palatability and feasibility of nutritional interventions in patients with pre-ESRD?

Three studies examined adherence to and satisfaction with a LPD, while a fourth evaluated the amount of resources used by dieticians to administer a LPD.
In a large uncontrolled trial, Cianciaruso et al.[51] measured adherence to a LPD (protein 0.5-0.6 g/kg IBW/day, phosphate 6-9 mg/kg IBW/day, energy 35-40 kcal/kg IBW/day) in 171 outpatients with estimated creatinine clearance of 21.6 mL/min (LE: 4, QS: fair). Adherence was assessed on average every 10 weeks by dietetic interviews, measurement of urinary urea nitrogen (UUN), and measurement of 24-hour urinary phosphate excretion. Over a duration of 17 ± 10 months, only 38% of patients satisfied compliance criteria for protein restriction, and only 51% were able to consume as much energy as was recommended. Only 22% of patients were able to adhere to both the protein and energy intake guidelines.

In another study by Cianciaruso et al.,[52] adherence to a low-protein diet was examined in 150 patients with mean serum creatinine of 3.9 ± 1.6 mg/dL (LE: 4, QS: poor). Patients were prescribed protein intake of 0.5-0.6 g/kg IBW/day, energy intake of 35-40 kcal/kg/IBW/day, and phosphate intake of 6-9 mg/kg IBW/day, and were followed an average of 16.7 ± 10.3 months. Adherence to the diet was uniquely evaluated by using a survival analysis such that once a patient satisfied compliance criteria (within 10% of prescribed goals), the patient was designated a non-survivor and dropped from further analyses. Therefore, compliance could only increase as time passed. At 1 year, adherence to phosphate, protein, calories, and combined protein/calories was 41%, 33%, 37%, and 20%, respectively. At 3 years, compliance increased to 77%, 78%, 59%, and 50%, respectively. However, the results of this study should be interpreted with scrutiny due to its analytical methods.

In a large randomized controlled trial, Coyne et al.[53] measured patient satisfaction with the prescribed diet in the MDRD Study (LE: 1b, QS: good). Over a duration of greater than 1 year, overall satisfaction with the diet was significantly lower in the LPD group compared with the usual protein diet (UPD) group, and satisfaction was lower in the

VLPD group as compared with the LPD group. In addition, the proportion of patients adherent to the prescribed diet decreased as the recommended level of protein intake decreased, but this was not tested statistically (UPD 59%, LPD 41%, VLPD 29%).

Dolecek et al.[54] used data from the MDRD Study to evaluate the amount of resources utilized by dieticians while administering each of the three diets (LE: 1b, QS: good). Dieticians spent significantly more time (8-18 minutes/patient/month) counseling patients who followed the LPD and VLPD as compared with those who followed the UPD.

In summary:

- Based on two large uncontrolled trials[51,52] and one large randomized controlled trial,[53] we conclude that there is reasonable evidence suggesting that pre-ESRD patients have difficulty adhering to and have low satisfaction with LPD.
- Based on one large randomized controlled trial,[54] we conclude that there is reasonable evidence suggesting that administering a LPD to pre-ESRD patients consumes slightly more time resources from a dietician than does a standard diet.

5.5 Discussion

While CKD patients frequently receive dietary recommendations to restrict protein intake, we found virtually no high-quality evidence to support these recommendations in pre-ESRD patients. As stated earlier, it remains to be proven in randomized controlled trials whether LPDs retard the progression of CKD. The goal of this review was to determine the degree to which any dietary recommendations can be supported by scientific evidence. Specifically, we sought to identify, appraise, and summarize studies regarding the magnitude of nutritional problems in the pre-ESRD population and the degree to which dietary interventions affect intermediate outcomes (e.g., satisfaction, general nutritional status, vitamin and mineral status) or ultimate clinical outcomes (e.g., survival). The issue of effect on progression of kidney disease in this population is not addressed in this report as, unlike patients with early kidney disease, progression is virtually assumed.

In pre-ESRD patients, it may be more important to optimize nutritional status prior to RRT. Therefore, it is crucial to know if the commonly recommended “renal” diet causes malnutrition, vitamin deficiencies, or other problems in patients with pre-ESRD. In addition, it is valuable to know whether it is worthwhile to expend time and resources teaching the diet to patients.

The studies reviewed in this article help to answer some of these questions, but several remain unanswered. There exists reasonable evidence that worsening kidney function confers a risk for malnutrition.[18,19] In addition, there is good evidence demonstrating that LPDs are somewhat difficult for patients to follow and slightly more labor-intensive to administer.[51,53,54] Unfortunately, there have been few quality studies that examine diet and other interventions designed to improve nutritional status in these patients. Only one small retrospective cohort study that used historical controls has specifically

examined the effect of a LPD on mortality[32] (LE: 2b, QS: fair). The only large randomized controlled trial in the adult pre-ESRD population to evaluate the nutritional effects of a LPD demonstrated a possible mild decline in nutritional status[33] (LE: 1b, QS: good). Other studies were small or uncontrolled making it difficult to interpret their results. Several studies reported modest improvements in or maintenance of nutritional status, but it is unclear which agent is responsible, the LPD itself or the heightened care that occurs during a research study.[37-41,49] Similarly, three studies reported declines in several nutritional parameters; however, these changes might have been a result of the diet or natural progression of the disease, or both.[36,42,50]

In conclusion, the available literature regarding optimization of nutritional status in pre-ESRD patients is limited. Current practice and guidelines for this population are likely based on extrapolation of data from patients with a broader range of kidney failure severity. However, there is reason to believe that the nutritional needs and goals of pre-ESRD patients may be different from other CKD patients. Consequently, there exists substantial opportunity for future research into the enhancement of nutritional status in this population.

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Evidence Table 4 – Nutrition

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Abdullah, Wild, Jacob, et al., 1997	Design: Cross-sectional cohort study Intervention(s) studied: None (observational study). All patients encouraged to consume an adequate amount of calories (35 kcal/kg/day). No dietary protein restriction. Dates: NR Location: Sheffield, UK Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 20; compared with 25 age-matched controls Inclusion criteria: Moderate to severe chronic renal failure Exclusion criteria: None specified Age (mean ± SD): CRF patients, 51.8 ± 18.7; controls, 49.6 ± 14.3 Sex: CRF patients, 75% M, 25% F; controls, 64% M, 36% F Race: NR Renal function at entry: SCr (mean ± SD; µmol/l): CRF patients: 551 ± 105 Controls: 91.5 ± 14.9 Nutritional markers at entry: See at right, under "Results" Co-morbidities at entry: Diabetes: 15%	*Key Question 1) After appropriate nutritional evaluation, does nutritional intervention result in improved intermediate outcomes and/or clinical outcomes in pre-ESRD patients?* Not addressed *Key Question 2) What is the rate of change in nutritional parameters in pre-ESRD patients?:* Not addressed *Key Question 3) What is the effect of follow-up nutritional evaluation in improving intermediate outcomes and/or clinical outcomes in pre-ESRD patients?:* Not addressed *Other outcomes:* a) Protein intake (mean ± SD; CRF patients only): 0.62 ± 0.12 g/kg/day b) Caloric intake (mean ± SD; CRF patients only): 32.05 ± 4.45 kcal/kg/day c) Serum total protein (mean ± SD; g/l): CRF patients: 69.9 ± 4.4 Controls: 75.5 ± 4.3 p < 0.01 d) Serum albumin (mean ± SD; g/l): CRF patients: 37.1 ± 3.3 Controls: 41.9 ± 2.8 p < 0.001 e) Serum prealbumin (mean ± SD; g/l): CRF patients: 0.38 ± 5.9 Controls: 0.29 ± 0.05 p < 0.001	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: Partially Incl/excl described: No/not assessable Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: SCr 4) % pre-ESRD: 50-75% 5) Level of evidence: 4 Notes:

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Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			f) Triceps skinfold thickness (TST) (mean ± SD; mm): CRF patients: 16.1 ± 8.7 Controls: 20.5 ± 7.2 p < 0.01 35% of CRF patients < 25th percentile for TST. g) Midarm muscle circumference (MAMC)(mean ± SD; cm): CRF patients: 23.6 ± 3.2 Controls: 26.1 ± 3.1 p < 0.01 65% of CRF patients < 25th percentile for MAMC. h) BMI (mean ± SD): CRF patients: 25.8 ± 5.1 Controls: 28.6 ± 4.4 p = not significant i) Role of inflammatory mediators: Plasma tumor necrosis factor-alpha (TNF-alpha): Correlated negatively with protein intake (r = -0.53, p < 0.01), BMI (r = -0.49, p < 0.05), and midarm muscle circumference (r = -0.69, p < 0.01) Insulin-like growth factor-I (IGF-I): Correlated positively with subjective global nutritional assessment, BMI, triceps skinfold thickness, and midarm muscle circumference Interleukin-1beta (IL-beta): Did not correlate with any nutritional parameters Interleukin-6 (IL-6): Did not correlate with any nutritional parameters	

Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Aparicio, Chauveau, De Précigout, et al., 2000	Design: Prospective (?) clinical trial (before/after study; may be retrospective) Intervention(s) studied: Supplemented very low-protein diet (SVLPD), as follows: Protein: 0.3 g/kg/day, of vegetable origin; Phosphorus: 5-7 mg/kg/day; Energy: 35 kcal/kg/day, in mix of 67% carbohydrates, 30% lipids, and 3% protein; Supplemental essential amino acids and ketoanalogs, 1 tablet/5kg/day; Supplemental calcium carbonate (400 mg elemental); Supplemental iron + multivitamin. Patients with proteinuria of > 2 g/day were given animal proteins 1.25 g/1g of protein in urine. Mean duration of treatment (± SD) was 29.6 ± 25.1 months. Dates: Dec 1985 - Jan 1998 Location: Bordeaux, France Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 239 patients followed diet for at least 3 months and were included in the analysis Inclusion criteria: Advanced chronic renal failure (GFR < 25 ml/min/1.73 m^2) Exclusion criteria: Immediate need for hemodialysis; severe co-morbid conditions; "obviously incapable" of following diet and monitoring schedule Age (mean ± SD): 50.2 ± 15.6 Sex: 59% M, 41% F Race: NR Renal function at entry (mean ± SD): GFR (n = 142): 13.1 ± 4.8 ml/min/1.73 m^2 SCr: 437 ± 120 µmol/l Nutritional markers at entry (mean ± SD): Albumin: 38.4 ± 5.3 g/l Weight: Men, 69.4 ± 10.3 kg; women, 56.2 ± 9.9 BMI: Men, 23.2 ± 2.8 kg/m^2; women, 21.2 ± 3.6 kg/m^2 Co-morbidities at entry: NR Other (mean ± SD): Serum PTH : 213 ± 168 pg/ml Proteinuria: 2 ± 2.3 g/day Serum bicarbonate: 22.6 ± 3.7 mmol/l Plasma urea: 21.8 ± 6.4 mmol/l	For purposes of reporting results, patients were divided into 5 groups based on their clinical outcome at the end of the follow-up period: "Discontinued" = had spontaneously stopped treatment: 20 (8%); "Dead": 14 (6%) "Dialyzed": 165 (69%) "Transplanted": 12 (5%) "SVLPD" = still following prescribed diet: 28 (12%) *Key Question 1) After appropriate nutritional evaluation, does nutritional intervention result in improved intermediate outcomes and/or clinical outcomes in pre-ESRD patients?* a) BMI "remained unchanged" in all groups (no quantitative data reported) b) Serum albumin (mean ± SD): *All patients:* At entry: 38.4 ± 5.3 g/l At end of study: 39.2 ± 5.1 g/l p = 0.052 *SVLPD group only (n = 28):* At entry: 39.3 ± 5.9 g/l At end of study: 42.2 ± 5.3 g/l *Key Question 2) What is the rate of change in nutritional parameters in pre-ESRD patients?:* Not addressed *Key Question 3) What is the effect of follow-up nutritional evaluation in improving intermediate outcomes and/or clinical outcomes in pre-ESRD patients?:* Not addressed	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: Partially Incl/excl described: Partially Dropouts discussed: Partially Sample size justified: No/not assessable 3) GFR/CrCl: Measured by investigators (in some patients) 4) % pre-ESRD: > 75% 5) Level of evidence: 4 Note: 12% of patients had CRF secondary to "chronic rejection," presumably from a previous renal transplant.

Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Barsotti, Ciardella, Morelli, et al., 1988	Design: Prospective clinical trial (before/after) Intervention(s) studied: Low-protein (0.25-0.35 g/kg/day), low-phosphorus (4.5-5.5 mg/kg/day), high-carbohydrate (65% of total caloric intake), vegetarian diet, supplemented with essential amino acids and keto analogs (Alfa-Kappa, 144 mg/kg/day), calcium carbonate (up to 6 g/day), iron, and multivitamins. Small amounts of wine (400 ml/day) permitted. 4/8 patients were permitted to consume wheat flour products. Protein and phosphorous targets for these patients were 0.5-0.6 g/kg/day and 8.0-12 mg/kg/day, respectively. Diet was followed for a mean of 17.4 months. Dates: N/S Location: Pisa, Italy Recruitment setting: N/S	No. of pre-ESRD subjects: 8 Inclusion criteria: Type 1 diabetes; renal failure Exclusion criteria: None specified Age: Mean, 44.7; range, 22-58 Sex: 62.5% M, 37.5% F Race: N/S Renal function at entry (means ± SD): CrCl: 19.2 ± 13.4 ml/min SCr: 4.3 ± 2.3 mg/dl Nutritional markers at entry (means ± SD): Weight: 69.1 ± 9.9 kg Albumin: ~3.2 ± ~5 g/dl (estimated from figure) Total protein: 6.04 ± 0.9 g/dl Proteinuria: 5.7 ± 1.9 g/day Triceps skinfold thickness: ~1.6 ± ~2.5 mm (estimated from figure) Middle arm muscle circumference: ~23 ± ~2 cm (estimated from figure) Transferrin: ~230 ± ~50 mg/dl (estimated from figure) Co-morbidities at entry: Diabetes: 100%	*Key Question 1) After appropriate nutritional evaluation, does nutritional intervention result in improved intermediate outcomes and/or clinical outcomes in pre-ESRD patients?* a) Weight (mean ± SD): At entry: 69.1 ± 9.9 kg Post-treatment: 64.8 ± 8.5 kg p = not significant b) Albumin (mean ± SD): At entry: ~3.2 ± ~5 g/dl (estimated from figure) Post-treatment: ~3.7 ± ~2 g/dl (estimated from figure) p < 0.001 c) Total protein: At entry: 6.04 ± 0.9 g/dl Post-treatment: 6.97 ± 0.3 g/dl p < 0.05 d) Proteinuria: At entry: 5.7 ± 1.9 g/day Post-treatment: 3.07 ± 0.6 g/day p < 0.001 e) Triceps skinfold thickness: At entry: ~1.6 ± ~2.5 mm (estimated from figure) Post-treatment: ~1.7 ± ~1 mm (estimated from figure) p = not significant f) Middle arm muscle circumference: At entry: ~23 ± ~2 cm (estimated from figure) Post-treatment: ~24 ± ~3 cm (estimated from figure) p = not significant g) Transferrin: At entry: ~230 ± ~50 mg/dl (estimated from figure) Post-treatment: ~250 ± ~40 mg/dl (estimated from figure) p = not significant *Key Question 2) What is the rate of change in nutritional parameters in pre-ESRD patients?:*	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: Partially Incl/excl described: No/not assessable Dropouts discussed: Partially Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 4 Note: Extent of overlap in patient population between this study and Barsotti, Navalesi, Giampietro, et al., 1988 unclear.

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Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			Not addressed *Key Question 3) What is the effect of follow-up nutritional evaluation in improving intermediate outcomes and/or clinical outcomes in pre-ESRD patients?:* Not addressed	

Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Barsotti, Navalesi, Giampietro, et al., 1988	Design: Prospective clinical trial (before/after) Intervention(s) studied: Low-protein (0.3 g/kg/day), low-phosphorus (3.5 mg/kg/day), high-carbohydrate (60% of total caloric intake), vegetarian diet, supplemented with essential amino acids and keto analogs (Alfa-Kappa, 126 mg/kg/day), calcium carbonate (3-6 g/day), iron, and multivitamins. Diet was followed for a mean of 11.4 months. Dates: N/S Location: Pisa, Italy Recruitment setting: N/S	No. of pre-ESRD subjects: 8 Inclusion criteria: Overt diabetic nephropathy; mild or severe renal insufficiency Exclusion criteria: None specified Age: Mean, 48.1; range, 32-57 Sex: 75% M, 25% F Race: N/S Renal function at entry: CrCl (mean ± SD): 15.6 ± 11.2 ml/min Nutritional markers at entry: Weight (mean ± SD): 68.4 ± 9.2 Co-morbidities at entry: Diabetes: 100%	*Key Question 1) After appropriate nutritional evaluation, does nutritional intervention result in improved intermediate outcomes and/or clinical outcomes in pre-ESRD patients?* Weight (mean ± SD): At entry: 68.4 ± 9.2 kg Post-treatment: 64.8 ± 6.3 kg p = not significant *Key Question 2) What is the rate of change in nutritional parameters in pre-ESRD patients?:* Not addressed *Key Question 3) What is the effect of follow-up nutritional evaluation in improving intermediate outcomes and/or clinical outcomes in pre-ESRD patients?:* Not addressed	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: Partially Incl/excl described: No/not assessable Dropouts discussed: Partially Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 4 Note: Extent of overlap in patient population between this study and Barsotti, Ciardella, Morelli, et al., 1988 unclear.

Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Biolo, Toigo, Ciocchi, et al., 1998	Design: Cohort study Intervention(s) studied: None (observational study) Dates: NR Location: Trieste, Italy Recruitment setting: Not specified/unable to determine	No. of pre-ESRD subjects: 15 Inclusion criteria: Chronic renal failure; on a weight-maintaining diet containing 0.6-0.8 g protein/kg/day and ≥ 300 g carbohydrate/day; weight stable for ≥ 3 months prior to start of study Exclusion criteria: No other major organ system disease Age (mean ± SEM): 53 ± 4 Sex: 60% M, 40% F Race: NR Renal function at entry: SCr (mean ± SEM): 5.7 ± 0.4 mg/dl Nutritional markers at entry (mean ± SEM): Weight: 72 ± 3 kg BMI: 24.7 ± 6 Co-morbidities at entry: NR	*Key Question 1) After appropriate nutritional evaluation, does nutritional intervention result in improved intermediate outcomes and/or clinical outcomes in pre-ESRD patients?* Not addressed *Key Question 2) What is the rate of change in nutritional parameters in pre-ESRD patients?:* Not addressed *Key Question 3) What is the effect of follow-up nutritional evaluation in improving intermediate outcomes and/or clinical outcomes in pre-ESRD patients?:* Not addressed *Other outcomes:* a) Leucine rate of appearance (μmol/kg/min): Mean ± SEM, 2.02 ± 0.13; range, 1.29 to 3.19 b) Correlation between leucine rate of appearance and SCr: Regression coefficient (R) = 0.59; R^2 = 0.35. c) Leucine rate of appearance did not significantly correlate with plasma Hgb, plasma albumin, serum urea, serum calcium, blood bicarbonate, or blood pH (no quantitative data reported).	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: No/not assessable Dropouts discussed: Partially Sample size justified: No/not assessable 3) GFR/CrCl: SCr 4) % pre-ESRD: < 50%/not assessable 5) Level of evidence: 4 Notes:

Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Chauveau, Barthe, Rigalleau, et al., 1999	Design: Prospective clinical trial (before/after study) Intervention(s) studied: Very low-protein diet, as follows: 0.3 g/day vegetable protein; 5-7 mg/kg/day phosphorus; 35 kcal/kg/day energy (67% carbohydrates, 30% fat, 3% protein); mixture of calcium salts of essential amino acids and ketoanalogs in tablet form (Ketosteril), in dose of 1 tablet/5 kg/day; calcium carbonate 2 g/day; iron; water-soluble vitamins. Diet maintained for 1 year. Dates: NR Location: Bordeaux Cedex, France Recruitment setting: NR	No. of pre-ESRD subjects: 10 Inclusion criteria: Advanced chronic renal failure; clinically stable Exclusion criteria: None specified Age (mean ± SD): 57.1 ± 9.3 Sex: 60% M, 40% F Race: NR Renal function at entry: GFR (mean ± SD): 13.2 ± 4.8 ml/min/1.73 m^2 SCr: 44.1 ± 11.1 mg/l Nutritional markers at entry (means ± SD): Albumin: 40.7 ± 7.4 g/l Prealbumin: 0.39 ± 0.8 g/l Transferrin: 2.16 ± 0.5 g/l Weight: 69 ± 13.6 kg BMI: 24.6 ± 2.9 kg/m^2 Triceps skinfold thickness: 14.5 ± 7.3 mm Arm muscle circumference: 30.9 ± 2.1 cm Co-morbidities at entry: NR	*Key Question 1) After appropriate nutritional evaluation, does nutritional intervention result in improved intermediate outcomes and/or clinical outcomes in pre-ESRD patients?* a) Albumin (mean ± SD): At entry: 40.7 ± 7.4 g/l At 1 year: 40.5 ± 4.7 g/l p = not significant b) Prealbumin (mean + SD): At entry: 0.39 ± 0.8 g/l At 1 year: 0.44 ± 0.06 g/l p = not significant c) Transferrin (mean + SD): At entry: 2.16 ± 0.5 g/l At 1 year: 2.02 ± 0.40 g/l p = not significant d) Weight (mean + SD): At entry: 69.0 ± 13.6 kg At 1 year: 69.1 ± 12.6 kg p = not significant e) BMI (mean + SD): At entry: 24.6 ± 2.9 kg/m^2 At 1 year: 24.7 ± 3.3 kg/m^2 p = not significant f) Triceps skinfold thickness (mean + SD): At entry: 14.5 ± 7.3 mm At 1 year: 15.7 ± 8.1 mm p = not significant g) Arm muscle circumference (mean + SD): At entry: 30.9 ± 2.1 cm At 1 year: 31.1 ± 2.4 cm p = not significant *Key Question 2) What is the rate of change in nutritional parameters in pre-ESRD patients?:*	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: Partially Incl/excl described: No/not assessable Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Measured by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 4 Notes:

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Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			Not addressed *Key Question 3) What is the effect of follow-up nutritional evaluation in improving intermediate outcomes and/or clinical outcomes in pre-ESRD patients?:* Not addressed	

Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Cianciaruso, Capuano, D'Amaro, et al., 1990 (full report) **and** **Cianciaruso, Capuano, D'Amaro, et al., 1989 (preliminary results through Dec 1987)**	Design: Prospective clinical study (before/after study) Intervention(s) studied: Low-protein, low-phosphate diet, as follows: Protein: 0.5-0.6 g/kg IBW/day Energy: 35-40 kcal/kg IBW/day Phosphate: 6-9 mg/kg IBW/day Carbohydrates: 272-379 g/day Lipids: 80-130 g/day Sodium: 112-782 mg/day Potassium: 696-2,207 mg/day Calcium: 185-957 mg/day Magnesium: 76-300 mg/day. Protein lost in urine was replaced gram for gram. All patients received multivitamin supplements. Mean duration of follow-up (± SD) was 17 ± 10 months. Dates: Dec 1984 - Dec 1988 Location: Naples, Italy Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 171 Inclusion criteria: "Various degrees of chronic renal failure"; CrCl ≤ 60 ml/min Exclusion criteria: None specified Age (mean ± SD): 50 ± 14 Sex: 58% M, 42% F Race: NR Renal function at entry: CrCl (mean): 21.6 ml/min/1.73 m^2 SCr (mean ± SD): 3.9 ± 1.6 mg/dl Nutritional markers at entry: NR Co-morbidities at entry: NR	*Key Question 1) After appropriate nutritional evaluation, does nutritional intervention result in improved intermediate outcomes and/or clinical outcomes in pre-ESRD patients?* Not addressed *Key Question 2) What is the rate of change in nutritional parameters in pre-ESRD patients?:* Not addressed *Key Question 3) What is the effect of follow-up nutritional evaluation in improving intermediate outcomes and/or clinical outcomes in pre-ESRD patients?:* Not addressed *Other outcomes:* a) Compliance with protein prescription: Compliance with prescribed protein intake (defined as protein intake ≤ 110% prescribed amount) was achieved by 38% of patients. b) Compliance with caloric prescription: Compliance with prescribed calorie goals (defined as caloric intake ≥ 90% of prescribed amount; assessed through clinical interviews) was achieved by 51% of patients. c) Compliance with diet (both protein and caloric intake prescriptions): 22% d) Cumulative compliance with diet (both protein and caloric intake prescriptions; analyzed using a life-table method of survival analysis): Year 1: 22% Year 2: 33% Year 3: 50% Year 4: 50%	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: No/not assessable Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by reviewers 4) % pre-ESRD: > 75% 5) Level of evidence: 4 Note: "Survival" analysis used to estimate cumulative compliance with diet biased to show increasing compliance over time.

Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Coresh, Walser, and Hill, 1995	Design: Cohort study (retrospective) Intervention(s) studied: Very low protein diet (0.3 g/kg ideal body weight/day) plus a supplement of either essential amino acids or a ketoacid-amino acid mixture. All patients received supplements of $CaCO_3$ and multivitamins. Complications of CRF managed with standard-of-care medications. Mean duration of dietary treatment was 27 months (range, 2-72 months). Dates: 1985 - 1994 Location: Baltimore, MD Recruitment setting: Clinical research facility	No. of pre-ESRD subjects: 67 Inclusion criteria: Chronic renal failure; prescribed diet described at left (under "Interventions") for at least 2 months; at least 4 SCr measurements $\geq$ 1.3 mg/dl in different weeks before starting treatment Exclusion criteria: None specifed Age (median, with 25th-75th quartile range): 51 (37 to 65) Sex: 60% M, 40% F Race: 97% White Renal function at entry: SCr (median, with 25th-75th quartile range): 4.2 mg/dl (3.1 to 5.3) Nutritional markers at entry (median, with 25th-75th quartile range): Serum albumin: 4.3 mg/dl (3.9 to 4.6) BMI: 23 kg/m^2 (22 to 27) Co-morbidities at entry: Diabetes: 22% Hypertension: 18%	*Key Question 1) After appropriate nutritional evaluation, does nutritional intervention result in improved intermediate outcomes and/or clinical outcomes in pre-ESRD patients?* a) Average weight loss on diet: -0.08 $\pm$ 0.27 kg/month (p = 0.024) b) Effect on mortality after starting dialysis (n = 44 patients who started dialysis): Observed deaths / Expected deaths* / p-value Year 1: 1 / 7.59 / 0.009 Year 2: 1 / 3.59 / < 0.01 Years 4+5: 6 / 1.7 / 0.01 Overall: 10 / 14.9 / 0.25 *Expected death rates based on US Renal Data System (USRDS) death rates from 1987, matched to study cohort for age, sex, and underlying cause of renal disease *Key Question 2) What is the rate of change in nutritional parameters in pre-ESRD patients?:* Not addressed *Key Question 3) What is the effect of follow-up nutritional evaluation in improving intermediate outcomes and/or clinical outcomes in pre-ESRD patients?:* Not addressed	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Completely Incl/excl described: Partially Dropouts discussed: Completely Sample size justified: No/not assessable 3) GFR/CrCl: SCr 4) % pre-ESRD: 50-75% 5) Level of evidence: 2b Notes:

Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Cupisti, Guidi, and Giovannetti, 1990	Design: Prospective clinical trial (before/after) Intervention(s) studied: Low-protein diet as follows: Plant protein, 0.3 g/kg/day; energy intake, 35 kcal/kg/day; inorganic phosphorus, < 500 mg/day; potassium, 60-80 mEq/day; and sodium, 7-11 mEq/day. Diet supplemented with essential amino acids and keto analogs (Alfa-Kappa, 0.2 tablets/kg/day), calcium carbonate (2-6 g/day), iron, and B-vitamins. Diet was followed for a mean of 13.5 months. Dates: NR Location: Pisa, Italy Recruitment setting: NR	No. of pre-ESRD subjects: 51 Inclusion criteria: Chronic renal failure Exclusion criteria: Nephrotic grade proteinuria (> 3.5 g/day); diabetic nephropathy; systemic disease Age: Range, 18-76 Sex: 63% M, 37% F Race: NR Renal function at entry: CrCl (mean ± SD): 7.8 ± 3.5 ml/min Nutritional markers at entry (means ± SD): Albumin: 3.8 ± 0.5 g/dl Total protein: 6.7 ± 0.6 g/dl Transferrin: 243.5 ± 54.2 mg/dl Weight: 65.0 ± 10 kg Triceps skinfold thickness: Men, 1.1 ± 0.3 cm; women, 1.6 ± 0.5 cm Middle arm muscle circumference: Men, 23.7 ± 2.4 cm; women, 21.8 ± 2.2 cm Co-morbidities at entry: NR Other: Patients who did not comply with the prescribed diet were excluded from analysis	*Key Question 1) After appropriate nutritional evaluation, does nutritional intervention result in improved intermediate outcomes and/or clinical outcomes in pre-ESRD patients?* a) Albumin (mean ± SD): At entry: 3.8 ± 0.5 g/dl Post-treatment: 4.1 ± 0.5 g/dl p ≤ 0.005 b) Total protein (mean ± SD): At entry: 6.7 ± 0.6 g/dl Post-treatment: 6.9 ± 0.5 g/dl p < 0.001 c) Transferrin (mean ± SD): At entry: 243.5 ± 54.2 mg/dl Post-treatment: 252.4 ± 58.5 mg/dl p = not significant d) Weight (mean ± SD): At entry: 65.0 ± 10 kg Post-treatment: 65.8 ± 10 kg p < 0.05 e) Triceps skinfold thickness (mean ± SD): Men at entry: 1.1 ± 0.3 cm Men post-treatment: 1.2 ± 0.3 cm p < 0.05 Women at entry: 1.6 ± 0.5 cm Women post-treatment: 1.6 ± 0.4 cm p = not significant f) Middle arm muscle circumference (mean ± SD): Men at entry: 23.7 ± 2.4 cm Men post-treatment: 24.1 ± 2.4 p = not significant Women at entry: 21.8 ± 2.2 cm Women post-treatment: 22.1 ± 2.3 cm p = not significant	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: Partially Dropouts discussed: Partially Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 4 Notes:

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Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			Key Question 2) What is the rate of change in nutritional parameters in pre-ESRD patients?: Not addressed *Key Question 3) What is the effect of follow-up nutritional evaluation in improving intermediate outcomes and/or clinical outcomes in pre-ESRD patients?:* Not addressed	

Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Dumler and Kilates, 1999	Design: Cohort study (prospective) Intervention(s) studied: None (observational study) Dates: NR (9-month observation period) Location: Royal Oak and Detroit, Michigan Recruitment setting: Not specified/unable to determine	No. of pre-ESRD subjects: 25 (abstract) or 35 (table) predialysis patients; controls were 58 established hemodialysis (HD) patients and 14 renal transplant (RT) patients Inclusion criteria: None specified Exclusion criteria: None specified Age (mean ± SD): Predialysis: 61 ± 12 HD: 64 ± 17 RT: 42 ± 12 Sex: Predialysis: 54% M, 46% F HD: 57% M, 43% F RT: 57% M, 43% F Race: NR Renal function (over 9 months): CrCl (mean ± SD; ml/min): Predialysis: 19 ± 5 HD: 8 ± 3 RT: 69 ± 20 Nutritional markers at entry: NR Co-morbidities at entry: NR	*Key Question 1) After appropriate nutritional evaluation, does nutritional intervention result in improved intermediate outcomes and/or clinical outcomes in pre-ESRD patients?* Not addressed *Key Question 2) What is the rate of change in nutritional parameters in pre-ESRD patients?:* Not addressed *Key Question 3) What is the effect of follow-up nutritional evaluation in improving intermediate outcomes and/or clinical outcomes in pre-ESRD patients?:* Not addressed *Other outcomes:* Predialysis patients had significantly higher body weight, body mass index (BMI), fat-free mass, and body cell mass than patients in the other two groups, as follows: a) Body weight (mean ± SD; kg): Predialysis: 91 ± 24 HD: 71 ± 16 RT: 70 ± 18 p < 0.01, predialysis vs. other groups b) BMI (mean ± SD; kg/m^2): Predialysis: 30.9 ± 6.6 HD: 24.5 ± 4.9 RT: 25.6 ± 4.9 p < 0.01, predialysis vs. other groups c) Fat-free mass (mean ± SD; kg): Predialysis: 62 ± 17 HD: 54 ± 14 RT: 51 ± 15 p < 0.01, predialysis vs. other groups	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Paritally Incl/excl described: No/not assessable Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: 50-75% 5) Level of evidence: 4 Note: No differences in time were observed by ANOVA for repeated measures during the 9-month observation period, so mean values for the entire observation period were used for comparisons.

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Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			d) Body cell mass (mean ± SD; kg): Predialysis: 28 ± 8 HD: 24 ± 7 RT: 22 ± 7 $p < 0.01$, predialysis vs. other groups Serum albumin, total body water, and intracellular and extracellular water content were similar among the 3 groups.	

Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Garibotto, Russo, Sofia, et al., 1994	Design: Cohort study (cross-sectional) Intervention(s) studied: None Dates: NR Location: Genoa, Italy Recruitment setting: Not specified/unable to determine	No. of pre-ESRD subjects: 9 patients with chronic renal failure; 8 healthy controls Inclusion criteria: Chronic renal failure Exclusion criteria: None specified Age (mean ± SEM): Patients: 49 ± 5 Controls: 40 ± 4 Sex: Patients: 78% M, 22% F Controls: 75% M, 25% F Race: NR Renal function at entry (patients): CrCl (mean ± SEM): 24 ± 3 ml/min/1.73 m^2 Nutritional markers at entry (mean ± SEM): Body weight (mean ± SEM): Patients: 68 ± 3 kg Controls: 73 ± 4 kg Co-morbidities at entry: Diabetes: 0 Congestive heart failure: 0	*Key Question 1) After appropriate nutritional evaluation, does nutritional intervention result in improved intermediate outcomes and/or clinical outcomes in pre-ESRD patients?* Not addressed *Key Question 2) What is the rate of change in nutritional parameters in pre-ESRD patients?:* Not addressed *Key Question 3) What is the effect of follow-up nutritional evaluation in improving intermediate outcomes and/or clinical outcomes in pre-ESRD patients?:* Not addressed *Other outcomes:* a) Phenylalanine kinetics across the forearm in post-absorptive state (all values mean ± SEM; nmol/min/100 ml forearm): Rate of appearance: Patients: 61 ± 3 Controls: 48 ± 3 p < 0.01 Rate of disposal: Patients: 40 ± 3 Controls: 29 ± 3 p < 0.01 Net release: Patients: 21 ± 2 Controls: 19 ± 2 p = not significant b) Correlation analysis of factors influencing net proteolysis: *(continued on next page)*	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: No/not assessable Dropouts discussed: Completely Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 4 Note: Control group consisted of “eight healthy volunteers.”

Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes

	Controls		Patients	
Variable	r	P	r	P
Arterial HCO3	-0.387	NS	-0.775	< 0.015
Plasma insulin	-0.67	< 0.075	0.233	NS
Plasma cortisol	-0.301	NS	0.843	< 0.005

Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Gentile, Fellin, Manna, et al., 1988	Design: RCT (though results not reported separately by intervention) Intervention(s) studied: 1) Dietary intervention, as follows: Protein 0.6 g/kg/day Energy 30-35 kcal/kg/day NaCl < 2 g/day if hypertensive (DBP ≥ 100 mmHg or on diuretic or antihypertensive therapy) 2) Dietary intervention, as follows: Protein 1.0 g/kg/day Energy 30-35 kcal/kg/day NaCl < 2 g/day if hypertensive (DBP ≥ 100 mmHg or on diuretic or antihypertensive therapy) In both groups, diets followed for 18 months. Dates: NR Location: Milan, Italy Recruitment setting: Not specified/unable to determine	No. of pre-ESRD subjects: 50 Inclusion criteria: Mild chronic renal insufficiency Exclusion criteria: None specified Age (mean ± SD): 48 ± 12 Sex: 58% M, 42% F Race: NR Renal function at entry: CrCl (mean ± SD): 36 ± 16 ml/min Nutritional markers at entry (mean ± SD): Body weight: 67 ± 11 kg % ideal body weight (IBW): 110 ± 24% Co-morbidities at entry: NR	*Key Question 1) After appropriate nutritional evaluation, does nutritional intervention result in improved intermediate outcomes and/or clinical outcomes in pre-ESRD patients?* Not addressed *Key Question 2) What is the rate of change in nutritional parameters in pre-ESRD patients?:* a) Actual body weight (mean ± SD; both groups combined): Baseline: 67 ± 11 kg 18 months: 65 ± 11 kg p < 0.01 b) % IBW (mean ± SD; both groups combined): Baseline: 110 ± 24 18 months: 105 ± 19 p = not significant *Key Question 3) What is the effect of follow-up nutritional evaluation in improving intermediate outcomes and/or clinical outcomes in pre-ESRD patients?:* Not addressed *Other outcomes:* At 18 months, no signs of caloric or protein malnutrition were seen as judged by (mean ± SD): Serum total protein: 6.9 ± 0.49 /dl Serum albumin: 4.5 ± 0.33 g/dl Serum transferrin: 295 ± 49.8 ng/dl Triceps skinfold thickness: 13.4 ± 8 mm Arm circumference: 27.4 ± 2.23 mm Arm muscle circumference: 23.2 cm (no SD reported) Baseline values were not reported for these outcomes.	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: Partially Incl/excl described: No/not assessable Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: < 50%/not assessable 5) Level of evidence: 2b (see Note, below) Note: RCT, but results reported only for both intervention groups together.

Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Greene, Bour-goignie, Habwe, et al., 1993	Design: Cross-sectional cohort study Intervention(s) studied: None (observational study) Dates: Patients enrolled Jan 1989 - Mar 1991 Location: 15 sites "throughout the United States" Recruitment setting: Not specified/unable to determine	No. of pre-ESRD subjects: 840 (255 with GFR 13-24 ml/min/1.73 m^2 and 585 with GFR 25-55) Inclusion criteria: Age 18-70; chronic renal insufficiency (SCr 1.2-7.0 mg/dl for men, 1.4-7.0 mg/dl for women, measured within previous year); MAP $\leq$ 125 mmHg; urinary protein excretion $\leq$ 10 g/day Exclusion criteria: Kidney transplant recipient; taking insulin Age: Under 20, < 1%; 20-39, 19%; 40-59, 49%; $\geq$ 60, 32% Sex: 60% M, 40% F Race: 85% White, 8% Black, 5% Hispanic, 3% other Renal function at entry (mean $\pm$ SD): GFR (ml/min/1.73 m^2): GFR 13-24 group: 20.2 $\pm$ 4.4 GFR 25-55 group: 39.3 $\pm$ 9.3 SCr (mg/dl): GFR 13-24 group: 3.3 $\pm$ 0.9 GFR 25-55 group: 1.9 $\pm$ 0.5 Nutritional markers at entry: See at right, under "Results" Co-morbidities at entry: 88.2% had hypertension	*Key Question 1) After appropriate nutritional evaluation, does nutritional intervention result in improved intermediate outcomes and/or clinical outcomes in pre-ESRD patients?* Not addressed *Key Question 2) What is the rate of change in nutritional parameters in pre-ESRD patients?:* Not addressed *Key Question 3) What is the effect of follow-up nutritional evaluation in improving intermediate outcomes and/or clinical outcomes in pre-ESRD patients?:* Not addressed *Other outcomes:* All outcomes expressed as mean $\pm$ SD. a) BMI (kg/m^2): GFR 13-24 (n = 255): 26.0 $\pm$ 4.2 GFR 25-55 (n = 583): 27.6 $\pm$ 4.6 α = 0.05 b) Body weight (kg): GFR 13-24 (n = 255): 75.8 $\pm$ 14.7 GFR 25-55 (n = 584): 80.9 $\pm$ 16.7 α = 0.05 c) Elbow width (cm): GFR 13-24 (n = 255): 6.9 $\pm$ 0.6 GFR 25-55 (n = 583): 7.0 $\pm$ 0.6 α = 0.05 d) Body surface area (m^2): GFR 13-24 (n = 255): 1.87 $\pm$ 0.21 GFR 25-55 (n = 585): 1.92 $\pm$ 0.23 α = 0.05 e) Caloric intake (kcal/kg/day):	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: Completely Dropouts discussed: Partially Sample size justified: No/not assessable 3) GFR/CrCl: Measured by investigators 4) % pre-ESRD: 100% of group with GFR 13-24; not assessable for group with GFR 25-55 5) Level of evidence: 2b Note: Cross-sectional cohort study of baseline characteristics of all 840 patients randomized to treatment in the MDRD study. *(continued on next page)*

Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			GFR 13-24 (n = 255): 25.2 ± 6.6 GFR 25-55 (n = 585): 26.9 ± 7.9 α = 0.05 f) Phosphorus intake (mg/kg/day): GFR 13-24 (n = 255): 14.8 ± 4.6 GFR 25-55 (n = 585): 16.7 ± 5.2 α = 0.05 g) Protein intake (g/kg/day): GFR 13-24 (n = 255): 0.9 ± 0.3 GFR 25-55 (n = 585): 1.1 ± 0.3 α = 0.05 h) Serum albumin (g/dl): GFR 13-24 (n = 252): 3.98 ± 0.39 GFR 25-55 (n = 575): 4.04 ± 0.33 α = 0.05 i) Serum transferrin (mg/dl): GFR 13-24 (n =252): 263.0 ± 45.1 GFR 25-55 (n = 575): 275.6 ± 45.7 α = 0.05 k) Plasma essential amino acids (μM): GFR 13-24 (n = 252): 838.9 ± 147.5 GFR 25-55 (n = 567): 899.9 ± 147.5 α = 0.05 l) Ratio of plasma essential to nonessential amino acids: GFR 13-24 (n = 252): 0.4 ± 0.1 GFR 25-55 (n = 567): 0.5 ± 0.1 α = 0.05	

Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Herselman, Albertse, Lombard, et al., 1995	Design: RCT Intervention(s) studied: 1) Low-protein diet (LPD), as follows (n = 11): Energy: 150 kJ/kg/day Protein: 0.60 g/kg/day (70% of high biological value) Calcium: 500-750 mg/day Phosphorus: < 800 mg/day 2) Very low-protein diet + essential amino acids (VLPD), as follows (n = 11): Energy: 150 kJ/kg/day Protein: 0.54 g/kg/day (0.40 g/kg/day mixed quality + 0.14 g/kg/day essential amino acids) Calcium: 500-750 mg/day Phosphorus: < 800 mg/day Patients in both groups received multivitamin supplements and glucose polymers. Diets were followed for 9 months. Dates: NR Location: Cape Town, South Africa Recruitment setting: Hospital (outpatients)	No. of pre-ESRD subjects: 22 Inclusion criteria: Age 18-65; history of confirmed chronic renal failure for ≥ 6 months; SCr 150-700 µmol/l; predialysis Exclusion criteria: Diabetes mellitus; liver disease; alcoholism; malignancy; psychiatric disorders; use of corticosteroids, cyclophosphamide, ACE inhibitors, calcium entry blockers, or other bone toxic drugs Age (mean ± SD): LPD, 43 ± 15; VLPD, 42 ± 13 Sex: LPD, 45% M, 55% F; VLPD, 64% M, 36% F Race: NR Renal function at entry (mean ± SD): CrCl (ml/min/1.73 m2): LPD: 30 ± 17 VLPD: 27 ± 11 SCr (µmol/l): LPD: 317 ± 171 VLPD: 287 ± 91 Nutritional markers at entry (mean ± SD): Serum albumin (g/l): LPD: 39 ± 9 VLPD: 39 ± 9 Serum transferrin (g/l): LPD: 3.3 ± 0.9 VLPD: 3.0 ± 1.1 Arm muscle area (cm^2):	*Key Question 1) After appropriate nutritional evaluation, does nutritional intervention result in improved intermediate outcomes and/or clinical outcomes in pre-ESRD patients?* All outcomes reported as mean ± SD. a) Serum albumin (g/l): Baseline / 9 months LPD 39 ± 9 / 43 ± 5 VLPD 39 ± 9 / 41 ± 5 p = not significant, (VLPD vs. LPD) (no p-values reported for 9 months vs. baseline) b) Serum transferrin (g/l): Baseline / 9 months LPD 3.3 ± 0.9 / 3.3 ± 0.6 VLPD 3.0 ± 1.1 / 3.2 ± 0.8 p = not significant, (VLPD vs. LPD) (no p-values reported for 9 months vs. baseline) c) Arm muscle area (cm^2): Baseline / 9 months LPD 49 ± 14 / 50 ± 14 VLPD 51 ± 12 / 53 ± 13 p = not significant, (VLPD vs. LPD) (no p-values reported for 9 months vs. baseline) d) Body fat %: Baseline / 9 months LPD 26 ± 11 / 27 ± 12 VLPD 31 ± 7 / 32 ± 7 p = not significant, (VLPD vs. LPD) (no p-values reported for 9 months vs. baseline) e) BMI (kg/m^2): Baseline / 9 months LPD 24 ± 5 / 24 ± 5 VLPD 25 ± 4 / 25 ± 4 p = not significant, (VLPD vs. LPD) (no p-values reported for 9 months vs. baseline)	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: Completely Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: 50-75% 5) Level of evidence: 2b Note: Small sample size (n = 22).

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Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
		LPD: 49 ± 14 VLPD: 51 ± 12 Body fat %: LPD: 26 ± 11 VLPD: 31 ± 7 BMI (kg/m^2): LPD: 24 ± 5 VLPD: 25 ± 4 Co-morbidities at entry: NR	*Key Question 2) What is the rate of change in nutritional parameters in pre-ESRD patients?:* Not addressed *Key Question 3) What is the effect of follow-up nutritional evaluation in improving intermediate outcomes and/or clinical outcomes in pre-ESRD patients?:* Not addressed *Other outcomes:* Nutritional analysis showed that patients in both groups were unable to adhere to dietary recommendations concerning total energy and protein intake. The LPD group took in 125 ± 34 kJ/kg/day and 0.73 ± 0.25 g protein/kg/day, and the VLPD group took in 116 ± 34 kJ/kg/day and 0.63 ± 0.17 g protein/kg/day.	

Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Kopple, Berg, Houser, et al., 1989	Design: RCT (results from 2 trials combined) Intervention(s) studied: Patients randomized to one of 4 diets: 1) 1.0-1.4 g protein/kg/day and 16-20 mg phosphorus/kg/day (Diet M, prescribed in Study A only; n = 11); 2) 0.58 g protein/kg/day and 5-10 mg phosphorus/kg/day (Diet L, prescribed in Study A [n = 10] and Study B [n = 23]); 3) 0.28 g protein/kg/day and 4-9 mg phosphorus/kg/day, supplemented with 2.8 g/10 kg body weight/day of ketoacid mixture EE (Diet K, prescribed in Study A [n = 8] and Study B [n = 22]); 4) 0.28 g protein/kg/day and 4-9 mg phosphorus/kg/day, supplemented with 2.16 g/10 kg body weight/day of essential amino acids (Diet J, prescribed only in Study B [n = 21]). In all groups, the prescribed energy intake was designed to equal the patient's average daily energy intake during the baseline period, unless the patient weighed more than 120% of his desirable body weight and voluntarily expressed a wish to lose weight, in which case energy intake reduced. Adjustments made when weight lost or gained.	No. of pre-ESRD subjects: 95 Inclusion criteria: Chronic progressive renal insufficiency (decrease in 1/SCr of at least 0.003 dl/mg/month); GFR 8-80 ml/min/1.73 m^2 Exclusion criteria: Chronic serious medical illness (e.g., malignancy, chronic heart or liver failure, collagen vascular disease, insulin dependent diabetes mellitus, uncontrolled hypertension); severe psychiatric illness; evidence that patient would not comply with study protocol; use of immunosuppressive drugs or corticosteroids; proteinuria ≥ 10g per day; malnutrition (body weight < 80% or > 160% of standard body weight or serum albumin < 3.0 g/dl) Age: NR Sex: 60% M, 40% F Race: NR Renal function at entry: GFR (mean ± SEM): 21.6 ± 1.2 ml/min/1.73 m^2 (range, 8.0-56.0) Nutritional markers at entry: NR Co-morbidities at entry: NR	*Key Question 1) After appropriate nutritional evaluation, does nutritional intervention result in improved intermediate outcomes and/or clinical outcomes in pre-ESRD patients?* Not addressed *Key Question 2) What is the rate of change in nutritional parameters in pre-ESRD patients?:* Not addressed *Key Question 3) What is the effect of follow-up nutritional evaluation in improving intermediate outcomes and/or clinical outcomes in pre-ESRD patients?:* Not addressed *Other outcomes:* a) Prescribed vs. actual energy intake (mean ± SEM; kcal/kg/day): |	Prescribed	Actual
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Men & women:		
Study A & B (n = 95)	29.8 ± 0.53	24.8 ± 0.69*
Study A (n = 29)	31.1 ± 0.95	26.5 ± 1.07*
Study B (n = 66)	29.2 ± 0.62	24.0 ± 0.86*
Men only:		
Study A (n = 20)	31.2 ± 1.11	25.8 ± 1.09*
Study B (n = 37)	30.5 ± 0.90	25.3 ± 1.21*
Women only:		
Study A (n = 9)	30.9 ± 1.94	28.1 ± 2.48**
Study B (n = 29)	27.4 ± 0.73	22.4 ± 1.15*	 *p < 0.005 **p < 0.05 b) Correlation coefficients for nutritional parameters with GFR: *At the end of the baseline period:*	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: No/not assessable Incl/excl described: Completely Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Measured by investigators 4) % pre-ESRD: 50-75% 5) Level of evidence: 2b Note: Patients were participants in pilot phase of Modification of Diet in Renal Disease (MDRD) Study.

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Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
	Average follow-up was 12.4 months (range, 0 to 21.6 months). Dates: NR Location: 9 sites in the US Recruitment setting: Not specified/unable to determine		<u>All</u> <u>Men</u> <u>Women**</u> Protein intake: 0.28* 0.25 0.27 Energy intake: 0.18 -0.06 0.53** % Standard weight: 0.06 0.33* -0.21 Arm muscle area: 0.18 0.34* -0.16 *p < 0.05; **p < 0.005 *At the final visit (figures in parentheses are for patients with body weight ≤115% of desirable body weight):* <u>All</u> <u>Men</u> <u>Women</u> Energy intake: 0.27* 0.16 0.48** (0.25) (0.13) (0.50*) Serum transferrin: 0.32** 0.31* 0.38* (0.25) (0.13) (0.45*) Arm muscle area: 0.19 0.32* -0.10 *p < 0.05; **p < 0.005	

Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Kopple, Greene, Chumlea, et al., 2000	Design: Cross-sectional cohort study Intervention(s) studied: None (observational study) Dates: NR Location: 15 sites "throughout the United States" Recruitment setting: Not specified/unable to determine	No. of pre-ESRD subjects: 1,785 (350 with GFR < 21 ml/min/1.73 m^2, 566 with GFR 21-37, and 869 with GFR > 37) Inclusion criteria: Moderate to advanced chronic renal failure; clinically stable; baseline GFR available Exclusion criteria: None specified Age (mean ± SD): 50.4 ± 12.8 Sex: 60% M, 40% F Race: 80% White, 13% Black, 5% Hispanic, 1% Asian, 1% other Renal function at entry: GFR (mean ± SD): 39.8 ± 21.1 ml/min/1.73 m^2 Nutritional markers at entry: See at right, under "Results" Co-morbidities at entry: NR	*Key Question 1) After appropriate nutritional evaluation, does nutritional intervention result in improved intermediate outcomes and/or clinical outcomes in pre-ESRD patients?* Not addressed *Key Question 2) What is the rate of change in nutritional parameters in pre-ESRD patients?:* Not addressed *Key Question 3) What is the effect of follow-up nutritional evaluation in improving intermediate outcomes and/or clinical outcomes in pre-ESRD patients?:* Not addressed *Other outcomes:* P-values represent comparisons with GFR > 37 group. a) Protein intake (mean ± SD; g/kg/day): Men: GFR < 21 (n = 157): 0.90 ± 0.27 (p < 0.01) GFR 21-37 (n = 310): 1.05 ± 0.34(p < 0.01) GFR > 37 (n = 337): 1.13 + 0.35 Women: GFR < 21 (n = 108): 0.84 ± 0.28 (p < 0.01) GFR 21-37 (n = 210): 0.97 ± 0.31 (p = not significant) GFR > 37 (n = 203): 0.99 ± 0.30 b) Energy intake (mean ± SD; kcal/kg/day): Men: GFR < 21 (n = 157): 26.4 ± 6.90 (p < 0.01) GFR 21-37 (n = 309): 29.2 ± 10.0 (p < 0.05) GFR > 37 (n = 337): 31.0 ± 9.30 Women: GFR < 21 (n = 108): 24.6 ± 8.58 (p < 0.01) GFR 21-37 (n = 210): 27.9 ± 8.58 (p = not significant) GFR > 37 (n = 201): 27.7 ± 8.84	Quality Scoring: 1) Global assessment: Good 2) Validity criteria: Population described: Partially Incl/excl described: Partially Dropouts discussed: Partially Sample size justified: No/not assessable 3) GFR/CrCl: Measured by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 2b Note: Cross-sectional cohort study of baseline characteristics of all 1,785 patients evaluated during the baseline phase of the MDRD study.

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Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			c) Body weight (mean ± SD; kg): Men: GFR < 21 (n = 204): 82.4 ± 13.2 (p < 0.01) GFR 21-37 (n = 334): 84.9 ± 15.6 (p < 0.05) GFR > 37 (n = 539): 87.4 ± 14.4 Women: GFR < 21 (n = 146): 68.2 ± 14.7 (p = not significant) GFR 21-37 (n = 231): 70.8 ± 15.6 (p = not significant) GFR > 37 (n = 325): 70.9 ± 15.1 d) Percent body fat (mean ± SD; %): Men: GFR < 21 (n = 134): 24.9 ± 5.39 (p < 0.01) GFR 21-37 (n = 251): 27.1 ± 5.97 (p = not significant) GFR > 37 (n = 264): 27.7 ± 5.89 Women: GFR < 21 (n = 91): 32.5 ± 6.23 (p < 0.01) GFR 21-37 (n = 171): 34.5 ± 6.35 (p = not significant) GFR > 37 (n = 152): 35.5 ± 5.69 e) Skinfold thickness (sum of biceps, triceps, and subscapular; mean ± SD): Men: GFR < 21 (n = 134): 34.1 ± 11.5 (p < 0.01) GFR 21-37 (n = 250): 39.2 ± 13.8 (p = not significant) GFR > 37 (n = 264): 40.8 ± 13.8 Women: GFR < 21 (n = 92): 45.1 ± 17.4 (p < 0.01) GFR 21-37 (n = 169): 50.9 ± 18.2 (p = not significant) GFR > 37 (n = 149): 53.7 ± 17.5 f) Serum albumin (mean ± SD; g/dl): Men: GFR < 21 (n = 201): 3.99 ± 0.40 (p < 0.01) GFR 21-37 (n = 331): 4.03 ± 0.38 (p < 0.01) GFR > 37 (n = 533): 4.10 ± 0.39 Women: GFR < 21 (n = 145): 3.88 ± 0.36 (p < 0.01)	

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Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			GFR 21-37 (n = 227): 3.96 ± 0.34 (p < 0.01) GFR > 37 (n = 326): 4.06 ± 0.32 g) Serum transferrin (mean ± SD; mg/dl): Men: GFR < 21 (n = 201): 255 ± 42.5 (p < 0.01) GFR 21-37 (n = 331): 270 ± 48.3 (p < 0.01) GFR > 37 (n = 533): 280 ± 45.9 Women: GFR < 21 (n = 145): 261 ± 46.0 (p < 0.01) GFR 21-37 (n = 227): 276 ± 45.3 (p < 0.01) GFR > 37 (n = 326): 287 ± 46.2 h) Serum total cholesterol (mean ± SD; mg/dl): Men: GFR < 21 (n = 201): 204 ± 47.4 (p < 0.01) GFR 21-37 (n = 330): 217 ± 49.9 (p = not significant) GFR > 37 (n = 532): 216 ± 48.4 Women: GFR < 21 (n = 145): 225 ± 48.9 (p = not significant) GFR 21-37 (n = 227): 228 ± 54.2 (p = not significant) GFR > 37 (n = 322): 222 ± 46.9	

Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Kopple, Levey, Greene, et al., 1997 (MDRD study – main results) **and** **Coyne, Olson, Bradham, et al., 1995 (patient satisfaction)** **and** **Dolocek, Olson, Caggiula, et al., 1995 (dietician time require-ments)**	Design: RCT Intervention(s) studied: 1) Low-protein diet (0.58 g protein/kg/day) (LPD; n = 129). 2) Very low-protein diet (0.28 g protein/kg/day) + mixture of ketoacids and amino acids (0.28 g/kg/day) (VLPD; n = 126). Mean duration of follow-up was 2.2 years (range, 0-44 months). Dates: NR Location: NR ("multicenter") Recruitment setting: Not specified/unable to determine	No. of pre-ESRD subjects: 255 Inclusion criteria: Age 18-70; SCr 1.4 to 7.0 mg/dl (men) or 1.2 to 7.0 (women); GFR 13-24 ml/min/1.73 m^2; relative body weight 80% to 160% (body weight/standard body weight [as defined by NHANES I and II data] x 100%); serum albumin ≥ 3.0 g/dl; urine protein < 10 g/day Exclusion criteria: Diabetes mellitus requiring insulin; previous renal transplant Age (mean ± SD): LPD: 51.1 ± 12.8 VLPD: 50.5 ± 12.9 Sex: LPD, 60% M, 40% F; VLPD, 58% M, 42% F Race: NR Renal function at entry (mean ± SD): GFR (ml/min/1.73 m2): LPD: 18.7 ± 3.21 VLPD: 18.3 ± 3.55 SCr (mg/dl): LPD: 3.46 ± 0.85 VLPD: 3.39 ± 0.91 Nutritional markers at entry: See at right, under "Results" Co-morbidities at entry: NR	*Key Question 1) After appropriate nutritional evaluation, does nutritional intervention result in improved intermediate outcomes and/or clinical outcomes in pre-ESRD patients?* All results reported as mean ± SD. a) Energy intake (kcal/kg/day): *Men:* LPD VLPD Baseline: 25.3 ± 7.04 25.9 ± 7.48 Follow-up: 22.5 ± 4.83 22.7 ± 4.92 *Women:* LPD VLPD Baseline: 24.1 ± 5.83 23.3 ± 5.81 Follow-up: 20.6 ± 3.78 21.1 ± 4.74 b) Protein intake (g/kg/day): *Men:* LPD VLPD Baseline: 0.84 ± 0.20 0.87 ± 0.18 Follow-up: 0.72 ± 0.11 0.66 ± 0.11 p ≤ 0.001, between groups at follow-up *Women:* LPD VLPD Baseline: 0.89 ± 0.15 0.87 ± 0.21 Follow-up: 0.73 ± 0.09 0.65 ± 0.11 p ≤ 0.001, between groups at follow-up c) Body weight (kg): *Men:* LPD VLPD Baseline: 80.8 ± 11.5 81.9 ± 11.2 Follow-up: 79.6 ± 11.5 79.3 ± 10.9 *Women:* LPD VLPD Baseline: 67.6 ± 12.4 66.1 ± 15.7 Follow-up: 65.9 ± 11.9 65.0 ± 14.3 There was a significant decrease in body weight from baseline to follow-up in both dietary groups (men and women combined). The difference between the two groups (for change from baseline to follow-up) was not significant.	Quality Scoring: 1) Global assessment: Good 2) Validity criteria: Population described: Fair Incl/excl described: Completely Dropouts discussed: Partially Sample size justified: No/not assessable 3) GFR/CrCl: Measured by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 1b Notes: N's varied from outcome to outcome at baseline and follow-up. Unclear precisely when follow-up measurements taken. Also unclear whether follow-up values for a given patient represent a single measure-ment or the average of several values. During the study, there were 2 deaths in the LPD group (both due to cardiovascular disease) and 4 in the VLPD group (2 due to cardiovascular disease and 2 due to trauma). MDRD study also included 585 patients with GFR 25-55 ml/min/1.73 m^2 (all other inclusion criteria the same).

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Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes

d) Relative body weight (%):

Men:	LPD	VLPD
Baseline:	104 ± 11.7	106 ± 12.5
Follow-up:	102 ± 11.9	103 ± 11.2

Women:	LPD	VLPD
Baseline:	109 ± 15.8	108 ± 22.1
Follow-up:	106 ± 14.4	106 ± 20.2

e) Biceps skinfold thickness (mm):

Men:	LPD	VLPD
Baseline:	5.88 ± 2.85	6.01 ± 2.69
Follow-up:	5.96 ± 3.60	6.33 ± 3.03

Women:	LPD	VLPD
Baseline:	9.47 ± 4.81	10.5 ± 7.42
Follow-up:	9.43 ± 5.58	9.88 ± 5.65

f) Triceps skinfold thickness (mm):

Men:	LPD	VLPD
Baseline:	13.1 ± 5.97	12.8 ± 5.09
Follow-up:	12.6 ± 5.87	12.7 ± 4.77

Women:	LPD	VLPD
Baseline:	20.4 ± 6.67	19.4 ± 7.56
Follow-up:	19.3 ± 5.87	19.9 ± 7.74

g) Subscapular skinfold thickness (mm):

Men:	LPD	VLPD
Baseline:	17.1 ± 5.63	16.5 ± 5.04
Follow-up:	16.8 ± 6.01	16.6 ± 4.93

Women:	LPD	VLPD
Baseline:	18.2 ± 7.89	16.1 ± 8.00
Follow-up:	16.8 ± 6.53	16.5 ± 7.07

h) Percent body fat (%):

Men:	LPD	VLPD
Baseline:	25.9 ± 5.46	25.3 ± 5.20
Follow-up:	25.7 ± 5.73	25.9 ± 5.16

Women:	LPD	VLPD
Baseline:	33.2 ± 6.53	32.0 ± 6.84

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Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes

Follow-up: 32.6 ± 6.22 33.0 ± 6.24

There was a significant decrease in percent body fat from baseline to follow-up in the LPD group, but not the VLPD group (men and women combined). The difference between the two groups (for change from baseline to follow-up) was significant.

i) Arm muscle area (cm^2):

Men:	LPD	VLPD
Baseline:	41.5 ± 9.64	43.2 ± 11.2
Follow-up:	40.2 ± 9.64	39.7 ± 8.59

Women:	LPD	VLPD
Baseline:	29.3 ± 10.6	23.6 ± 10.4
Follow-up:	29.8 ± 10.9	27.0 ± 14.3

$p \leq 0.01$, between groups at baseline

There was a significant decrease in arm muscle area from baseline to follow-up in both dietary groups (men and women combined). The difference between the two groups (for change from baseline to follow-up) was not significant.

j) Albumin (g/dl):

Men:	LPD	VLPD
Baseline:	4.05 ± 0.36	4.08 ± 0.33
Follow-up:	4.14 ± 0.32	4.11 ± 0.35

Women:	LPD	VLPD
Baseline:	3.86 ± 0.36	3.91 ± 0.37
Follow-up:	4.03 ± 0.35	4.01 ± 0.34

There was a significant rise in albumin from baseline to follow-up in both dietary groups (men and women combined). The difference between the two groups (for change from baseline to follow-up) was not significant.

k) Transferrin (mg/dl):

Men:	LPD	VLPD
Baseline:	257 ± 40.4	266 ± 48.3
Follow-up:	250 ± 36.6	258 ± 44.1

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Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes

Women:

	LPD	VLPD
Baseline:	270 ± 41.2	266 ± 46.3
Follow-up:	253 ± 34.9	252 ± 42.9

There was a significant decrease in transferrin from baseline to follow-up in both dietary groups (men and women combined). The difference between the two groups (for change from baseline to follow-up) was not significant.

l) Correlation between protein intake (at follow-up) and rates of change in nutritional status variables: Not significant for body weight, percent body fat, albumin, and transferrin

Key Question 2) What is the rate of change in nutritional parameters in pre-ESRD patients?:

Not addressed

Key Question 3) What is the effect of follow-up nutritional evaluation in improving intermediate outcomes and/or clinical outcomes in pre-ESRD patients?:

Not addressed

Other outcomes:

a) Overall satisfaction with the prescribed diet (measured using a visual analog scale ranging from 1 ["dislike extremely"] to 5 ["like very much"]):

	LPD (n = 59)	VLPD (n = 65)
Baseline:	3.8 ± 1.0	3.6 ± 1.0
1 Year:	3.6 ± 0.9	3.1 ± 0.9
Final:	3.6 ± 0.9	3.1 ± 0.9

$p < 0.01$, LPD vs. VLPD, 1 year
$p < 0.01$, LPD vs. VLPD, final
$p < 0.01$, VLPD, final vs. baseline

b) Dietician time requirements: An analysis of data from the group of patients described here and another group with GFR 25-55 ml/min/1.73 m^2 (see "Notes")

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Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			showed that dieticians spent significantly more time with patients on the LPD and VLPD than with patients instructed to follow a “usual protein diet” (1.30 g protein/kg/day) during the first 24 months of the study. Time spent on the 3 groups was similar during months 25-36.	

Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Lim, Yarasheski, and Flanigan, 1998	Design: Cohort study Intervention(s) studied: None (observational study) Dates: NR Location: Iowa City, IA Recruitment setting: Not specified/unable to determine	No. of pre-ESRD subjects: 9; compared with 5 normal controls Inclusion criteria: Chronic renal failure; clinically stable Exclusion criteria: Use of steroid or immunosuppressive drugs Age (mean ± SD): CRF patients: 55.8 ± 10.6 Controls: 50.2 ± 12.0 Sex: CRF, 89% M, 11% F; controls, 80% M, 20% F Race: NR Renal function at entry: SCr (mean ± SD): 1,087 ± 300 µmol/l Nutritional markers at entry (mean ± SD): Weight (kg): CRF: 86.5 ± 25.0 Controls: 79.8 ± 7.2 BMI: CRF: 27.4 ± 5.6 Controls: 27.0 ± 1.8 Co-morbidities at entry: NR	*Key Question 1) After appropriate nutritional evaluation, does nutritional intervention result in improved intermediate outcomes and/or clinical outcomes in pre-ESRD patients?* Not addressed *Key Question 2) What is the rate of change in nutritional parameters in pre-ESRD patients?:* Not addressed *Key Question 3) What is the effect of follow-up nutritional evaluation in improving intermediate outcomes and/or clinical outcomes in pre-ESRD patients?:* Not addressed *Other outcomes:* Leucine flux measured once in normal controls and 3 times in CRF patients (A = predialysis, acidotic; AC = predialysis, acidosis corrected; D = on dialysis). All results expressed as mean ± SD. a) Total leucine flux (µmol/kg/hour): CRF-A: 101.3 ± 11.7 CRF-AC: 94.6 ± 9.2 CRF-D: 113.4 ± 22.3 Controls: 117.0 ± 6.3 p = not significant, CRF-A vs. CRF-AC p < 0.05, CRF-A vs. CRF-D p < 0.05, CRF-AC vs. CRF-D p = 0.05, controls vs. CRF-A p = 0.001, controls vs. CRF-AC p = not significant, controls vs. CRF-D b) Leucine synthesis (µmol/kg/hour): CRF-A: 84.8 ± 10.2 CRF-AC: 84.9 ± 8.2 CRF-D: 101.1 ± 19.8 Controls: 93.8 ± 5.8 p = not significant, CRF-A vs. CRF-AC	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: No/not assessable Dropouts discussed: Completely Sample size justified: No/not assessable 3) GFR/CrCl: SCr 4) % pre-ESRD: > 75% 5) Level of evidence: 1b Note: 8/9 CRF patients proceeded to dialysis, (7 to hemodialysis, and 1 to chronic ambulatory peritoneal dialysis). 1 patient did not complete the dialysis portion of the study because of renal transplantation.

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Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			p < 0.05, CRF-A vs. CRF-D p < 0.05, CRF-AC vs. CRF-D p = not significant, controls vs. CRF-A p = not significant, controls vs. CRF-AC p = not significant, controls vs. CRF-D c) Leucine oxidation (µmol/kg/hour): CRF-A: 16.52 ± 5.40 CRF-AC: 9.68 ± 3.73 CRF-D: 12.28 ± 3.02 Controls: 23.20 ± 3.11 p < 0.05, CRF-A vs. CRF-AC p = not significant, CRF-A vs. CRF-D p = not significant, CRF-AC vs. CRF-D p = not significant, controls vs. CRF-A p = 0.003, controls vs. CRF-AC p = 0.003, controls vs. CRF-D	

Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Lusvarghi, Fantuzzi, Medici, et al., 1996	Design: Cross-sectional cohort study (prospective) Intervention(s) studied: None (observational study) Dates: 1988 - 1995 Location: Modena, Italy Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 441 patients with chronic renal failure (SCr 133-963 µmol/l); this cohort was compared with a) 43 patients with kidney disease without renal failure (SCr < 133 µmol/l), b) families from the same geographical region (northwest Italy), and c) Italian dietary reference values Inclusion criteria: Kidney disease; no prior exposure to dietary intervention Exclusion criteria: None specified Age (CRF patients; mean ± SD): Men: 62 ± 14 Women: 65 ± 15 Sex: 64% M, 36% F Race: NR Renal function at entry (CRF patients; mean ± SD): GFR (ml/min): Men: 31.3 ± 16.7 Women: 22.7 ± 13.5 CrCl (µmol/l): Men: 301 ± 178 Women: 288 ± 156 Nutritional markers at entry (CRF patients; mean ± SD): Body weight (kg): Men: 74.9 ± 12.4 Women: 64.1 ± 14.0 BMI: Men: 25.8 ± 3.7 Women: 25.6 ± 5.1	*Key Question 1) After appropriate nutritional evaluation, does nutritional intervention result in improved intermediate outcomes and/or clinical outcomes in pre-ESRD patients?* Not addressed *Key Question 2) What is the rate of change in nutritional parameters in pre-ESRD patients?:* Not addressed *Key Question 3) What is the effect of follow-up nutritional evaluation in improving intermediate outcomes and/or clinical outcomes in pre-ESRD patients?:* Not addressed *Other outcomes:* The following dietary intake outcomes were reported for CRF patients (n = 441): a) Total energy intake (mean ± SD): Men: 29 ± 7.4 kcal/kg/day Women: 28.4 ± 7.4 kcal/kg/day b) Total protein intake (mean ± SD): Men: 1.02 ± 0.2 g/kg/day (14.25% of total energy intake) Women: 0.96 ± 0.2 g/kg/day (13.6% of total energy intake) c) Total lipid intake (mean ± SD): Men: 1.10 ± 0.2 g/kg/day (34.6% of total energy intake) Women: 1.17 ± 0.3 g/kg/day (37.4% of total energy intake) d) Total carbohydrate intake (mean ± SD): Men: 3.7 ± 1.1 g/kg/day (51.2% of total energy intake) Women: 3.49 ± 1.0 g/kg/day (49% of total energy intake)	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: Partially Incl/excl described: No/not assessable Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: 50-75% 5) Level of evidence: 4 Note: P-values not reported for comparisons with control groups.

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Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
		Co-morbidities at entry: Diabetes as cause of CRF: 5.4%	Total energy intake in the CRF group was lower than in the three comparison groups. Protein intakes were lower than those of families from northwest Italy, but comparable to the other two comparison groups. Women consumed less total fat than kidney disease patients without renal failure and families from northwest Italy, but not less than the dietary reference values. Both men and women with CRF consumed more monounsaturated fats than dietary reference values and fewer carbohydrates than families from northwest Italy and dietary reference values.	

Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Maroni, Tom, Masud, et al., 1996	Design: RCT (crossover) Intervention(s) studied: 1) Very low-protein diet (VLPD) (protein, 0.28 g/kg/day; total energy, 35 kcal/kg/day; PO_4, ≤ 9 mg/kg/day; sodium, 2-4 g/day) + ketoacids (KA) (2.8 g/10 kg SBW). 2) VLPD (as above) + essential amino acids (EAA) (3.29 g/10 kg SBW). Patients followed first study diet for 14 days, then consumed a conventional low-protein diet (protein, 0.6 g/kg/day; total energy, 35 kcal/kg/day; PO_4, ≤ 10 mg/kg/day; sodium, 2-4 g/day) during a ≥ 4-week "washout" period, then followed second study diet for 14 days. Dates: NR Location: Atlanta, GA Recruitment setting: Not specified/unable to determine	No. of pre-ESRD subjects: 8 Inclusion criteria: Chronic renal failure Exclusion criteria: None specified Age (mean ± SEM): 50 ± 3 Sex: 37.5% M, 62.5% F Race: NR Renal function at entry: GFR (mean ± SEM): 18.8 ± 2.7 ml/min Nutritional markers at entry: NR Co-morbidities at entry: NR	*Key Question 1) After appropriate nutritional evaluation, does nutritional intervention result in improved intermediate outcomes and/or clinical outcomes in pre-ESRD patients?* All outcomes reported as mean ± SEM. a) Energy intake (kcal/kg/day): VLPD + KA: 34.8 ± 0.1 VLPD + EAA: 34.5 ± 0.3 p = not significant b) Protein intake (g/day): VLPD + KA: 20.5 ± 1.2 VLPD + EAA: 20.5 ± 1.2 p = not significant c) Body weight (kg): VLPD + KA: 67.0 ± 3.2 VLPD + EAA: 66.7 ± 3.1 p = not significant d) Serum albumin (g/dl): VLPD + KA: 3.7 ± 0.1 VLPD + EAA: 3.7 ± 0.1 p = not significant e) Serum transferrin (mg/dl): VLPD + KA: 238 ± 15 VLPD + EAA: 231 ± 16 p = not significant *Key Question 2) What is the rate of change in nutritional parameters in pre-ESRD patients?:* Not addressed *Key Question 3) What is the effect of follow-up nutritional evaluation in improving intermediate outcomes and/or clinical outcomes in pre-ESRD patients?:* Not addressed	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: No/not assessable Dropouts discussed: Completely Sample size justified: No/not assessable 3) GFR/CrCl: Measured by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 2b Notes: Small sample size (n = 8). 6 patients (5 from the RCT described here + 1 new patient) were followed up for an additional year on the VLPD + KA regimen.

Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Nishikage, Kosugi, Danbara, et al., 2000	Design: Prospective clinical trial (before/after study) Intervention(s) studied: Intravenous EPO 6,000 U per week until target Hct of 30% achieved, then 3,000 units per week thereafter. All patients on diet providing energy 35 kcal/kg/day, protein 0.6 g/kg/day, and salt 7 g/day. Dates: NR Location: Nagoya, Japan Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 27 at baseline and 3 months; 20 or 21 (precise number uncertain) at 6 months Inclusion criteria: Chronic renal failure; renal anemia; pre-dialysis Exclusion criteria: Diabetes mellitus Age (mean ± SD): 63 ± 15 Sex: NR Race: NR Renal function at entry: Estimated CrCl: Mean, 9.48 SCr (mean ± SD): 5.3 ± 2.0 mg/dl Nutritional markers at entry: See under Key Question 1, at right Co-morbidities at entry: NR	*Key Question 1) After appropriate nutritional evaluation, does nutritional intervention result in improved intermediate outcomes and/or clinical outcomes in pre-ESRD patients?* a) Albumin (mean ± SD; g/dl): Baseline (n = 27): 3.7 ± 0.5 3 months (n = 27): 4.0 ± 0.6 6 months (n = 20 or 21): 4.1 ± 0.5 Controls (n = 19): 4.5 ± 0.2 p = not significant, 3 months vs. baseline, 6 months vs. baseline p < 0.01, baseline vs. controls b) Total protein (mean ± SD; g/dl): Baseline (n = 27): 6.3 ± 0.7 3 months (n = 27): 6.5 ± 0.7 6 months (n = 20 or 21): 6.8 ± 0.9 Controls (n = 19): 7.18 ± 0.29 p = not significant, 3 months vs. baseline, 6 months vs. baseline p < 0.01, baseline vs. controls c) Transferrin (mean ± SD; mg/dl): Baseline (n = 27): 197 ± 42 3 months (n = 27): 212 ± 38 6 months (n = 20 or 21): 205 ± 39 Controls (n = 19): 289 ± 45 p = not significant, 3 months vs. baseline, 6 months vs. baseline p < 0.01, baseline vs. controls d) Prealbumin (mean ± SD; mg/dl): Baseline (n = 27): 32 ± 6.2 3 months (n = 27): 34 ± 6.6 6 months (n = 20 or 21): 33 ± 7.7 Controls (n = 19): 30.4 ± 5.3 p = not significant, 3 months vs. baseline, 6 months vs. baseline, baseline vs. controls e) IGF-1 (mean ± SD; ng/ml): Baseline (n = 27): 129 ± 44 3 months (n = 27): 138 ± 49	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: Partially Dropouts discussed: Completely Sample size justified: No/not assessable 3) GFR/CrCl: SCr 4) % pre-ESRD: < 50%/not assessable 5) Level of evidence: 4 Notes: 6 or 7 patients (precise number uncertain) started hemodialysis between 3 and 6 months after start of treatment and were not included in the 6-month evaluation. 19 "control" patients not described.

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Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			6 months (n = 20 or 21): 115 ± 47 Controls (n = 19): 137 ± 46 p = not significant, 3 months vs. baseline, 6 months vs. baseline, baseline vs. controls f) Body weight (mean ± SD; kg): Baseline (n = 27): 47.6 ± 7.9 3 months (n = 27): 47.0 ± 7.4 6 months (n = 20 or 21): 47.0 ± 8.6 Controls (n = 19): 56.5 ± 11 p = not significant, 3 months vs. baseline, 6 months vs. baseline p < 0.01, baseline vs. controls g) Body mass index (mean ± SD; kg/m^2): Baseline (n = 27): 20.2 ± 2.5 3 months (n = 27): 20.1 ± 2.4 6 months (n = 20 or 21): 19.5 ± 2.4 Controls (n = 19): 21.0 ± 2.4 p = not significant, 3 months vs. baseline, 6 months vs. baseline, baseline vs. controls h) Amino acid measures: Total amino acids (mean ± SD; nmol/ml): Baseline (n = 27): 3,057 ± 496 3 months (n = 27): 2,965 ± 343 6 months (n = 20 or 21): 3,000 ± 205 Controls (n = 19): 2,788 ± 306 p = not significant, 3 months vs. baseline, 6 months vs. baseline, baseline vs. controls Non-essential amino acids (mean ± SD; nmol/ml): Baseline (n = 27): 2,313 ± 414 3 months (n = 27): 2,231 ± 301 6 months (n = 20 or 21): 2,268 ± 196 Controls (n = 19): 1,849 ± 213 p = not significant, 3 months vs. baseline, 6 months vs. baseline p < 0.01, baseline vs. controls Essential amino acids (mean ± SD; nmol/ml): Baseline (n = 27): 745 ± 118 3 months (n = 27): 735 ± 103	*(continued on next page)*

Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			6 months (n = 20 or 21): 732 ± 76 Controls (n = 19): 939 ± 117 p = not significant, 3 months vs. baseline, 6 months vs. baseline p < 0.01, baseline vs. controls Branched chain amino acids (mean ± SD; nmol/ml): Baseline (n = 27): 303 ± 56 3 months (n = 27): 303 ± 54 6 months (n = 20 or 21): 301 ± 40 Controls (n = 19): 389 ± 72 p = not significant, 3 months vs. baseline, 6 months vs. baseline p < 0.01, baseline vs. controls *Key Question 2) What is the rate of change in nutritional parameters in pre-ESRD patients?:* Not addressed *Key Question 3) What is the effect of follow-up nutritional evaluation in improving intermediate outcomes and/or clinical outcomes in pre-ESRD patients?:* Not addressed	

Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Porrini, Simonetti, Ciappellano, et al., 1989 **and** **Gentile, Porrini, Manna, et al., 1992**	Design: RCT Intervention(s) studied: 1) Diet A: Protein 1.0 g/kg/day; phosphorus 13.1 mg/kg/day; fat 1.1 g/kg/day; carbohydrates 4.0 g/kg/day. 2) Diet B: Protein 0.6 g/kg/day; phosphorus 7.8 mg/kg/day; fat 1.2 g/kg/day; carbohydrates 5.7 g/kg/day. Dates: NR Location: Milan, Italy Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: For outcomes described here, pre-ESRD populations were as follows: Thiamine (B1)/riboflavin (B2): n = 57 Pyridoxine (B6): n = 40 (subset of B1/B2 patient population) Inclusion criteria: Early chronic renal insufficiency (not defined) Exclusion criteria: None specified Age: B1/B2 group: Range, 22-76 B6 group: Mean, 50 Sex: NR Race: NR Renal function at entry: SCr (mg/dl): B1/B2 group: Mean, 2.9; range, 1.3-9.5 B6 group: Mean, 2.8; range, 1.4-6.1 Nutritional markers at entry: NR Co-morbidities at entry: NR	*Key Question 1) After appropriate nutritional evaluation, does nutritional intervention result in improved intermediate outcomes and/or clinical outcomes in pre-ESRD patients?* a) Thiamine (B1) deficiency (number of patients [%]): b) Riboflavin (B2) deficiency (number of patients [%]): c) Pyridoxine (B6) deficiency (number of patients [%]): *Key Question 2) What is the rate of change in nutritional parameters in pre-ESRD patients?:* Not addressed *Key Question 3) What is the effect of follow-up nutritional evaluation in improving intermediate outcomes and/or clinical outcomes in pre-ESRD patients?:* Not addressed	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: No/not assessable Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: SCr 4) % pre-ESRD: 50-75% 5) Level of evidence: 2b Note: No tests of statistical significance reported for the outcomes considered here.

a) Thiamine (B1) deficiency (number of patients [%]):

	Diet A	Diet B
At entry:	0/25	0/32
At 6 months:	0/25	2/32 (6%)
At 1 year:	0/25	3/32 (10%)
At 2 years:	1/18 (6%)	3/27 (11%)

b) Riboflavin (B2) deficiency (number of patients [%]):

	Diet A	Diet B
At entry:	2/25 (8%)	8/32 (25%)
At 6 months:	3/25 (12%)	7/32 (22%)
At 1 year:	5/25 (20%)	10/32 (32%)
At 2 years:	4/18 (22%)	11/27 (41%)

c) Pyridoxine (B6) deficiency (number of patients [%]):

	Diet A	Diet B
At entry:	0/20	1/20 (5%)
At 6 months:	0/20	1/20 (5%)
At 1 year:	0/20	1/20 (5%)
At 2 years:	1/7 (14%)	3/13 (23%)

Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Porrini, Simonetti, Testolin, et al., 1989 **and** **Gentile, Porrini, Manna, et al., 1992**	Design: RCT Intervention(s) studied: 1) Diet A (n = 39): Protein 1.0 g/kg/day; phosphorus 13.1 mg/kg/day; fat 1.1 g/kg/day; carbohydrates 4.0 g/kg/day . 2) Diet B (n = 51): Protein 0.6 g/kg/day; phosphorus 7.8 mg/kg/day; fat 1.2 g/kg/day; carbohydrates 5.7 g/kg/day. Dates: Patients enrolled Jan 1985 - June 1986 Location: Milan, Italy Recruitment setting: Not specified/unable to determine	No. of pre-ESRD subjects: 90; compared with 30 normal controls Inclusion criteria: Early chronic renal insufficiency (not defined) Exclusion criteria: Vitamin E supplementation; transfusion Age (mean ± SD): 50.8 ± 13.3 Sex: 59% M, 41% F Race: NR Renal function at entry: SCr (mean ± SD): 3.6 ± 1.9 mg/dl Nutritional markers at entry: NR Co-morbidities at entry: NR	*Key Question 1) After appropriate nutritional evaluation, does nutritional intervention result in improved intermediate outcomes and/or clinical outcomes in pre-ESRD patients?* Vitamin E levels (mean ± SD; µg/ml): Diet A / Diet B At entry: 12.5 ± 5.3 (n = 39) / 12.6 ± 4.6 (n = 51) At 6 months 12.9 ± 4.4 (n = 30) / 12.6 ± 4.3 (n = 40) At 1 year: 10.9 ± 4.7 (n = 20) / 12.5 ± 5.1 (n = 26) At 2 years: 12.8 ± 4.7 (n = 15) / 13.4 ± 5.4 (n = 15) Vitamin E levels in control patients were 10.9 ± 2.3 µg/ml. There were no significant differences in vitamin E levels over time for either diet, between diets, or between either diet and the control group. *Key Question 2) What is the rate of change in nutritional parameters in pre-ESRD patients?:* Not addressed *Key Question 3) What is the effect of follow-up nutritional evaluation in improving intermediate outcomes and/or clinical outcomes in pre-ESRD patients?:* Not addressed	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: No/not assessable Dropouts discussed: Partially Sample size justified: No/not assessable 3) GFR/CrCl: SCr 4) % pre-ESRD: < 50%/not assessable 5) Level of evidence: 2b Notes:

Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Rayner, Burton, Bennett, et al., 1993	Design: Prospective clinical trial (before/after study) Intervention(s) studied: Low-protein diet: 0.6 g protein/kg ideal body weight/day; total energy intake 35 kcal/kg ideal body weight/day. Glucose polymers to supplement if needed. Median follow-up of 16 months (range, 5 months to 8.6 years) Dates: Patients started diet Jan 1985 - Mar 1990 (3 patients started before Jan 1985); followed up until dialysis started or until Sep 1990 Location: Leicester, UK Recruitment setting: Renal unit	No. of pre-ESRD subjects: 142 Inclusion criteria: Moderate to severe chronic renal failure Exclusion criteria: Malignant disease Age (mean ± SD): 50.3 ± 18.3 Sex: 60% M, 40% F Race: NR Renal function at entry: SCr (mean ± SD): 555 ± 152 µmol/l Nutritional markers at entry: BMI (median, with range): 24.5 kg/m^2 (16.1-41.4) Co-morbidities at entry: NR	*Key Question 1) After appropriate nutritional evaluation, does nutritional intervention result in improved intermediate outcomes and/or clinical outcomes in pre-ESRD patients?* a) Mean % change in body weight (per year, with 95% CI): -0.64% (-0.34 to -0.95%; p < 0.0001) b) Mean % change in arm muscle circumference (per year, with 95% CI): -0.22 (+0.02 to -0.46%; p = not significant) c) Mean % change in triceps skinfold thickness (per year, with 95% CI): -1.2% (+0.56 to -2.96%; p = not significant) d) Mean % change in serum albumin (per year, with 95% CI): +0.72% (+0.20 to ± 1.24%; p = 0.0007) *Key Question 2) What is the rate of change in nutritional parameters in pre-ESRD patients?:* Not addressed *Key Question 3) What is the effect of follow-up nutritional evaluation in improving intermediate outcomes and/or clinical outcomes in pre-ESRD patients?:* Not addressed	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: Partially Incl/excl described: Partially Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: SCr 4) % pre-ESRD: < 50%/not assessable 5) Level of evidence: 4 Note: 79/142 patients (56%) started dialysis before Sep 1990 after a median of 13 months on the diet (range, 5 monhs to 8.6 years).

Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Reaich, Channon, Scrimgeour, et al., 1993	Design: Prospective clinical trial (before/after study) Intervention(s) studied: Following interventions given during two consecutive 4-week treatment periods: 1) $NaHCO_3$ in an initial dose of 1.2 g three times per day (n = 9). Dose adjusted weekly based on plasma HCO_3 to optimize correction of acidosis. 2) NaCl, given in daily equimolar amounts of sodium to that of first period (n = 6). Dates: NR Location: Dundee, UK Recruitment setting: Not specified/unable to determine	No. of pre-ESRD subjects: 9 Inclusion criteria: Chronic renal failure; pre-dialysis; subjectively well Exclusion criteria: Diabetes; uncontrolled hypertension; fluid overload; use of insulin or corticosteroids Age: Mean, 42.4; range, 18-66 Sex: 67% M, 33% F Race: NR Renal function at entry: SCr (mg/dl): Mean, 7.7; range, 6.4-9.2 Nutritional markers at entry: Weight (kg): Mean, 77; range, 50-120 Co-morbidities at entry: NR	*Key Question 1) After appropriate nutritional evaluation, does nutritional intervention result in improved intermediate outcomes and/or clinical outcomes in pre-ESRD patients?* Not addressed *Key Question 2) What is the rate of change in nutritional parameters in pre-ESRD patients?:* Not addressed *Key Question 3) What is the effect of follow-up nutritional evaluation in improving intermediate outcomes and/or clinical outcomes in pre-ESRD patients?:* Not addressed *Other outcomes:* a) Leucine kinetics (all values are mean ± SEM; µmol/kg/hour): Leucine oxidation: Baseline: 13.0 ± 1.2 $NaHCO_3$: 9.2 ± 0.9 NaCl: 15.0 ± 1.9 $p < 0.05$, $NaHCO_3$ vs. baseline $p < 0.01$, $NaHCO_3$ vs. NaCl p = not significant, NaCl vs. baseline Leucine derived from protein degradation: Baseline: 122.4 ± 6.1 $NaHCO_3$: 88.3 ± 6.9 NaCl: 116.2 ± 9.1 $p < 0.01$, $NaHCO_3$ vs. baseline $p < 0.01$, $NaHCO_3$ vs. NaCl p = not significant, NaCl vs. baseline Leucine incorporated into body protein via protein synthesis: Baseline: 109.4 ± 5.6 $NaHCO_3$: 79.0 ± 6.3	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: No/not assessable Dropouts discussed: Completely Sample size justified: No/not assessable 3) GFR/CrCl: SCr 4) % pre-ESRD: > 75% 5) Level of evidence: 4 Note: Only 6 patients (67% of original sample) contributed data for the NaCl endpoints.

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Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes

NaCl: 101.3 ± 7.7
$p < 0.01$, $NaHCO_3$ vs. baseline
$p < 0.01$, $NaHCO_3$ vs. NaCl
p = not significant, NaCl vs. baseline

b) Post-absorptive plasma amino acid concentrations: There were no significant differences in post-absorptive amino acid concentrations at the various time points measured (all values are mean ± SEM; μM):

	Baseline	$NaHCO_3$	NaCl
Taurine:	70 ± 9	77 ± 9	87 ± 5
Aspartate:	14 ± 1	15 ± 1	15 ± 1
Threonine:	129 ± 12	102 ± 15	134 ± 15
Serine:	111 ± 6	98 ± 5	109 ± 7
Asparagine:	40 ± 8	40 ± 8	44 ± 12
Glutamate:	97 ± 18	177 ± 39	205 ± 71
Glutamine:	684 ± 57	586 ± 76	538 ± 88
Glycine:	376 ± 37	361 ± 45	370 ± 54
Alanine:	415 ± 24	388 ± 29	419 ± 32
Citrulline:	97 ± 12	101 ± 9	114 ± 13
Valine:	170 ± 7	172 ± 16	219 ± 16
Methionine:	32 ± 3	32 ± 5	37 ± 7
Isoleucine:	60 ± 4	63 ± 6	69 ± 8
Leucine:	97 ± 6	101 ± 7	118 ± 12
Tyrosine:	46 ± 4	48 ± 3	59 ± 12
Phenylalanine:	58 ± 3	62 ± 4	75 ± 10
Ornithine:	75 ± 4	68 ± 2	69 ± 13
Lysine:	163 ± 13	156 ± 9	180 ± 21
Histidine:	122 ± 10	116 ± 10	137 ± 12
3-Methylhistidine:	27 ± 3	25 ± 2	27 ± 2
Arginine:	85 ± 8	90 ± 8	97 ± 9
Hydroxyproline:	69 ± 6	62 ± 13	75 ± 18
Proline:	236 ± 6	218 ± 21	236 ± 9

Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Soroka, Silverberg, Greemland, et al., 1998	Design: RCT (crossover) Intervention(s) studied: 1) Soya-based vegetarian low-protein diet (VLPD). Included pre-packaged soya-based schnitzels, hamburgers, and sausages; soya drink; one egg, 3 times per week; vegetable oils; and sweet beverages. 2) Animal-based low-protein diet (ALPD). Included eggs, chicken, meat, turkey, fish, milk, bread, other cereal products, fruits, and vegetables. Two diets matched for macronutrients, phosphate, calcium, and cholesterol. Each diet maintained for 6 months. Dates: NR Location: Tel Aviv, Israel Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 15, of whom 9 completed the trial and were included in the analysis Inclusion criteria: CrCl 15-50 ml/min/1.73 m^2; 24-hour urinary protein excretion < 3 g/day/1.73 m^2; previously followed in clinic for ≥ 1 year; previously instructed about use of 0.75 g/kg/day low-protein diet Exclusion criteria: Diabetes or other systemic diseases; use of ACE inhibitors Age: Range, 30-85 Sex: 56% M, 44% F Race: NR Renal function at entry (mean ± SD): CrCl: 30.5 ± 3.6 ml/min/1.73 m2 SCr: 3.11 ± 0.2 mg/dl Nutritional markers at entry (mean ± SD): Serum albumin: 4.08 ± 0.18 g/dl Serum transferrin: 252 ± 15 mg/dl Co-morbidities at entry: Hypertension: 100%	*Key Question 1) After appropriate nutritional evaluation, does nutritional intervention result in improved intermediate outcomes and/or clinical outcomes in pre-ESRD patients?* a) Serum albumin (mean ± SD; g/dl): Baseline: 4.08 ± 0.18 VLPD: 4.53 ± 0.13 ALPD: 4.54 ± 0.11 p < 0.05, each diet vs. baseline p = not significant, VLPD vs. ALPD b) Serum transferrin (mean ± SD; mg/dl): Baseline: 252 ± 15 VLPD: 304 ± 29 ALPD: 304 ± 35 p = not signficant, each diet vs. baseline p = not significant, VLPD vs. ALPD *Key Question 2) What is the rate of change in nutritional parameters in pre-ESRD patients?:* Not addressed *Key Question 3) What is the effect of follow-up nutritional evaluation in improving intermediate outcomes and/or clinical outcomes in pre-ESRD patients?:* Not addressed *Other outcomes:* a) Percentage of actual/suggested calorie intake: VLPD: 97% ALPD: 88% p < 0.05 b) Percentage of actual/suggested protein intake: VLPD: 94% ALPD: 112% p < 0.05	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: Partially Dropouts discussed: Completely Sample size justified: No/not assessable 3) GFR/CrCl: Measured by investigators 4) % pre-ESRD: 50-75% 5) Level of evidence: 2b Note: Small sample size, with high dropout rate (6/15 patients = 40%).

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Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			c) Percentage of actual/suggested phosphate intake: VLPD: 102% ALPD: 116% (no p-value reported)	

Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Stenvinkel, Heimbürger, Paultre, et al., 1999	Design: Cohort study (cross-sectional) Intervention(s) studied: None Dates: NR Location: Stockholm, Sweden Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 109, of whom 61 were judged to be well-nourished and 48 were judged to be malnourished Inclusion criteria: Chronic renal failure; pre-dialysis Exclusion criteria: Age > 70; hospitalized with clinical signs of infection and/or vasculitis Age (mean ± SEM): Well-nourished: 47 ± 2 Malnourished: 57 ± 2 Sex: Well-nourished: 66% M, 34% F Malnourished: 54% M, 46% F Race: NR Renal function at entry (all values mean ± SEM): CrCl (all patients): 7 ± 1 ml/min SCr (µmol/l): Well-nourished: 742 ± 22 Malnourished: 593 ± 25 Nutritional markers at entry: BMI (mean ± SEM): 24.4 ± 0.4 kg/m^2 Co-morbidities at entry: Diabetes: 28% Smokers/former smokers: Well-nourished: 39% Malnourished: 65% Atherosclerotic vascular disease: 31% (11% stroke; 8% MI; 7% angina; 7% peripheral vascular disease; 1% aortic aneurysm)	*Key Question 1) After appropriate nutritional evaluation, does nutritional intervention result in improved intermediate outcomes and/or clinical outcomes in pre-ESRD patients?* Not addressed *Key Question 2) What is the rate of change in nutritional parameters in pre-ESRD patients?:* Not addressed *Key Question 3) What is the effect of follow-up nutritional evaluation in improving intermediate outcomes and/or clinical outcomes in pre-ESRD patients?:* Not addressed *Other outcomes:* a) Nutritional markers, well-nourished vs. malnourished patients: Albumin (mean ± SEM; g/l): Well-nourished: 34.8 ± 0.8 Malnourished: 32.2 ± 0.9 $p < 0.05$ Lean body mass (mean ± SEM; kg): Well-nourished: 51.5 ± 1.5 Malnourished: 44.5 ± 1.4 $p < 0.01$ Body mass index (mean ± SEM; kg/m^2): Well-nourished: 25.5 ± 0.5 Malnourished: 22.9 ± 0.7 $p < 0.01$ b) Vascular parameters, well-nourished vs. malnourished patients: Intima-media thickness (mean ± SEM; mm):	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: Partially Dropouts discussed: Completely Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 4 Note: Patients divided into two groups (well-nourished vs. malnourished) based on subjective global assessment of nutritional status.

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Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			Well-nourished: 0.70 ± 0.02 Malnourished: 0.79 ± 0.03 p < 0.01 Intima-media area (mean ± SEM; mm): Well-nourished: 16.9 ± 0.7 Malnourished: 20.2 ± 0.8 p < 0.01 Prevalence of carotid plaques: Well-nourished: 60% Malnourished: 90% p < 0.0001 Prevalence of symptomatic vascular disease: Well-nourished: 16% Malnourished: 52% p < 0.0001	

Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Toigo, Oldrizzi, Situlin, et al., 1989	Design: Prospective clinical trial (before/after study) Intervention(s) studied: Protein-restricted diet (not described). Mean protein intakes (± SD) at 5- and 10-year assessments were 0.76 ± 0.13 g/kg desirable body weight/day and 0.73 ± 0.09 g/kg desirable body weight/day, respectively. Dates: NR Location: Verona, Italy Recruitment setting: NR	No. of pre-ESRD subjects: 8 Inclusion criteria: Early renal insufficiency; normal acid-base status; normal glucose tolerance Exclusion criteria: Systemic disease; intercurrent illness Age (mean ± SD): At 5-year assessment, 55 ± 7 Sex: 62.5% M, 37.5% F Race: NR Renal function at entry: Baseline data NR. At 5-year assessment, mean SCr (± SD) was 1.9 ± 0.8 mg/dl Nutritional markers at entry: Baseline data NR Co-morbidities at entry: NR	*Key Question 1) After appropriate nutritional evaluation, does nutritional intervention result in improved intermediate outcomes and/or clinical outcomes in pre-ESRD patients?* No pre-treatment data reported. For comparison of 5- and 10-year outcomes, see next question. *Key Question 2) What is the rate of change in nutritional parameters in pre-ESRD patients?:* a) Total protein (mean ± SD): At 5 years: 7.3 ± 0.5 g/dl At 10 years: 7.1 ± 1.1 g;dl p = not significant b) Albumin (mean ± SD): At 5 years: 4593 ± 521 mg/dl At 10 years: 3340 ± 413 mg/dl p = 0.002 c) Prealbumin (mean ± SD): At 5 years: 75 ± 12 mg/dl At 10 years: 46 ± 8 mg/dl p = 0.001 d) Transferrin (mean ± SD): At 5 years: 243 ± 72 mg/dl At 10 years: 145 ± 36 mg/dl p = 0.016 e) Triceps skinfold thickness (mean ± SD): At 5 years: 11.6 ± 6.5 mm At 10 years: 9.0 ± 4.5 mm p = not significant f) Body mass index (mean ± SD): At 5 years: 24.0 ± 1.4 At 10 years: 23.0 ± 1.9 p = not significant g) Arm muscle circumference (mean ± SD): At 5 years: 244 ± 13 mm	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: Paritally Incl/excl described: Partially Dropouts discussed: Partially Sample size justified: No/not assessable 3) GFR/CrCl: SCr 4) % pre-ESRD: < 50%/not assessable 5) Level of evidence: 4 Notes: *(continued on next page)*

Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			At 10 years: 249 ± 8 mm p = not significant *Key Question 3) What is the effect of follow-up nutritional evaluation in improving intermediate outcomes and/or clinical outcomes in pre-ESRD patients?:* Not addressed	

Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Vetter, Kaschube, Metzner, et al., 1990	Design: Prospective clinical trial (non-randomized controlled trial) Intervention(s) studied: 1) Essential amino acid-supplemented low-protein diet (EAA) (n = 22): Protein 0.4 g/kg/day; total energy intake at least 35 kcal/kg/day, amino acids supplemented corresponding to 1 g of nitrogen (14 tablets of EAS-Oral® per day). 2) Keto acid-supplemented low-protein diet (KA) (n = 37): Diet same as above. Keto acids supplemented corresponding to 0.5 g of nitrogen (15 tablets of Ketosteril® per day). Dates: NR Location: Potsdam, East Germany Recruitment setting: NR	No. of pre-ESRD subjects: 59 of 112 pre-ESRD patients completed both the pre-treatment and 1-year assessments and were included in the analysis Inclusion criteria: Chronic renal failure Exclusion criteria: None specified Age (median?): EAA, 51; KA, 45 Sex: EAA, 45% M, 55% F; KA, 43% M, 57% F Race: NR Renal function at entry (median? mean?): CrCl: EAA, 11.4 ml/min; KA, 10.8 ml/min SCr: EAA, 562 µmol/l; KA, 661 µmol/l Nutritional markers at entry: Albumin (median? mean?): EAA, 40.2 g/l; KA, 44.2 g/l Transferrin (median? mean?): EAA, 2.10 g/l; KA, 2.10 g/l Weight (% of normal; median? mean?): EAA, ~108%; KA, ~101% (estimated from graph) Triceps skinfold thickness (median % of normal): EAA, ~105%; KA, ~120% (estimated from graph) Upper arm muscle circumference (median % of normal): EAA, ~95%; KA, ~89% (estimated from graph) Co-morbidities at entry: NR	*Key Question 1) After appropriate nutritional evaluation, does nutritional intervention result in improved intermediate outcomes and/or clinical outcomes in pre-ESRD patients?* a) Albumin (unclear whether median or mean; in g/l): EAA KA At entry: 40.2 44.2 At 1 year: 40.3 43.2 b) Transferrin (unclear whether median or mean; in g/l): EAA KA At entry: 2.10 2.10 At 1 year: 2.20 2.10 c) Weight (% of normal; unclear whether median or mean; estimated from graph): EAA KA At entry: ~108% ~101% At 1 year: ~107% ~101% d) Triceps skinfold thickness (median % of normal; estimated from graph): EAA KA At entry: ~105% ~120% At 1 year: ~ 95% ~105% e) Upper arm muscle circumference (median % of normal; estimated from graph): EAA KA At entry: ~ 95% ~ 89% At 1 year: ~ 97% ~ 95% *Key Question 2) What is the rate of change in nutritional parameters in pre-ESRD patients?:* Not addressed *Key Question 3) What is the effect of follow-up nutritional evaluation in improving intermediate outcomes and/or clinical outcomes in pre-ESRD patients?:* Not addressed	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: No/not assessable Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 2b? Notes: No tests of statistical significance reported. 2-year results also reported, but dropouts substantial (26/59 = 44%).

Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Walser, 1993	Design: Case series (retrospective chart review) Intervention(s) studied: Very low protein diet (0.3 g/kg ideal body weight), plus supplemental amino acids or ketoacids. Caloric prescription generally 35 kcal/kg ideal body weight (less if patient wished to lose weight). Patients followed diet for median of 26 months. Dates: NR Location: Baltimore, MD Recruitment setting: Not specified/unable to determine	No. of pre-ESRD subjects: 43 Inclusion criteria: On diet described at left for at least 6 months before initiating RRT Exclusion criteria: None specified Age: NR Sex: NR Race: NR Renal function at entry: SCr (mean ± SD): 4.8 ± 1.6 mg/dl Nutritional markers at entry: NR Co-morbidities at entry: NR	*Key Question 1) After appropriate nutritional evaluation, does nutritional intervention result in improved intermediate outcomes and/or clinical outcomes in pre-ESRD patients?* a) Serum albumin: Overall study population: No baseline values reported. Mean final serum albumin (± SD) was 4.1 ± 0.4 g/dl. Only 2 patients had a serum albumin < 3.4 g/dl. Final serum albumin was not correlated with the duration of protein restriction. In 5 patients who were hypoalbuminemic when first seen (mean ± SD): Baseline: 3.1 ± 0.3 g/dl Final: 3.5 ± 0.4 g/dl $p < 0.01$ b) Serum transferrin: Overall study population: No baseline values reported. Mean final serum transferrin (± SD) was 241 ± 56 mg/dl. 8 patients had serum transferrin < 200 mg/dl. Final serum transferrin was not correlated with the duration of protein restriction. In 5 patients who were hypoalbuminemic when first seen (mean ± SD): Baseline: 208 ± 36 mg/dl Final: 242 ± 28 mg/dl $p < 0.01$ c) Body mass index (BMI): Overall study population: No baseline values reported. Mean final BMI (± SD) was 24 ± 4 kg/m^2. d) Estimated protein intake: Overall study population: No baseline values reported. Estimated protein intake at end of study was 34 g/day (based on average urine urea N [± SD] of 5.0 ± 1.2 g/day). *Key Question 2) What is the rate of change in nutritional parameters in pre-ESRD patients?:*	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: No/not assessable Incl/excl described: Partially Dropouts discussed: Completely Sample size justified: No/not assessable 3) GFR/CrCl: SCr 4) % pre-ESRD: > 75% 5) Level of evidence: 4 Notes:

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Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			Not addressed *Key Question 3) What is the effect of follow-up nutritional evaluation in improving intermediate outcomes and/or clinical outcomes in pre-ESRD patients?:* Not addressed	

Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Walser and Hill, 1999	Design: Case series (retrospective), no controls Intervention(s) studied: Low-protein diet, as follows: 0.3 g/kg of ideal body weight (IBW) protein; 7-9 mg/kg IBW phosphorus; 35 kcal/kg IBW; either 10 g/day essential amino acids (Aminess) or 2.8 g/10 kg IBW ketoacid mixture (Cetolog); $CaCO_3$; multivitamin. Dates: Records reviewed of all patients prescribed the above dietary regimen from 1984-1999 Location: Baltimore, MD Recruitment setting: Not specified/unable to determine	No. of pre-ESRD subjects: 23 Inclusion criteria: Age > 18; started RRT after meeting the Medicare criteria for severity; willing to undertake dietary therapy; presented with GFR < 10 ml/min Exclusion criteria: Use of steroids, immunosuppressive drugs, or NSAIDs more than once per week; pregnant or planning to become pregnant; inability to empty bladder Age (mean ± SD): 57 ± 14 Sex: 65% M, 35% F Race: NR Renal function at entry (mean ± SD): GFR: 7.4 ± 1.9 ml/min SCr: 5.8 ± 1.4 mg/dl Nutritional markers at entry (mean ± SD): Albumin: 4.1 ± 0.5 g/dl Transferrin: 233 ± 38 mg/dl Weight: 72.1 ± 13.9 kg Co-morbidities at entry: NR	*Key Question 1) After appropriate nutritional evaluation, does nutritional intervention result in improved intermediate outcomes and/or clinical outcomes in pre-ESRD patients?* a) Albumin (mean ± SD; g/dl): Baseline: 4.1 ± 0.5 During treatment: 4.1 ± 0.4 Start of RRT: 4.1 ± 0.6 b) Transferrin (mean ± SD; mg/dl): Baseline: 233 ± 38 During treatment: 221 ± 28 Start of RRT: 223 ± 46 c) Weight (mean ± SD; kg): Baseline: 72.1 ± 13.9 During treatment: NR Start of RRT: 69.1 ± 13.0 *Key Question 2) What is the rate of change in nutritional parameters in pre-ESRD patients?:* Not addressed *Key Question 3) What is the effect of follow-up nutritional evaluation in improving intermediate outcomes and/or clinical outcomes in pre-ESRD patients?:* Not addressed	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: Partially Incl/excl described: Completely Dropouts discussed: Completely Sample size justified: No/not assessable 3) GFR/CrCl: Measured by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 4 Note: Patients “mostly self-referred and therefore are not representative of the renal failure population as a whole.”

Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Woodrow, Oldroyd, Turney, et al., 1996	Design: Cross-sectional cohort study Intervention(s) studied: None (observational study). Predialysis patients "at the latter stage of the predialysis period" had been encouraged to restrict protein intake to 0.6-0.8 g/kg ideal body weight/day. Dates: NR Location: Manchester, UK Recruitment setting: Not specified/unable to determine	No. of pre-ESRD subjects: 23; compared to 33 normal controls Inclusion criteria: Advanced chronic renal failure (serum urea > 30 mmol/l or SCr > 500 µmol); predialysis; under regular outpatient follow-up Exclusion criteria: Diabetes Age (mean ± SD): Men: 57.4 ± 12.4 Women: 52.2 ± 17.0 Sex: 52% M, 48% F Race: 100% Caucasian Renal function at entry: CrCl (mean ± SD): 7.3 ± 3.6 ml/min Nutritional markers at entry: See at right, under "Results" Co-morbidities at entry: NR	*Key Question 1) After appropriate nutritional evaluation, does nutritional intervention result in improved intermediate outcomes and/or clinical outcomes in pre-ESRD patients?* Not addressed *Key Question 2) What is the rate of change in nutritional parameters in pre-ESRD patients?:* Not addressed *Key Question 3) What is the effect of follow-up nutritional evaluation in improving intermediate outcomes and/or clinical outcomes in pre-ESRD patients?:* Not addressed *Other outcomes:* a) Total DEXA lean tissue (mean ± SD; kg): CRF men: 53.9 ± 7.2 Control men: 54.0 ± 4.4 p = not significant CRF women: 38.2 ± 3.3 Control women: 39.7 ± 5.4 p = not significant b) Total DEXA trunk lean tissue (mean ± SD; kg): CRF men: 27.0 ± 3.9 Control men: 26.0 ± 2.2 p = not significant CRF women: 19.4 ± 2.3 Control women: 19.0 ± 2.7 p = not significant c) Total DEXA limb lean tissue (mean ± SD; kg): CRF men: 23.0 ± 3.9 Control men: 24.3 ± 2.3 p = not significant	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: Partially Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: 50-75% 5) Level of evidence: 1b Note: CRF patients also compared to 24 patients on peritoneal dialysis and 22 patients on hemodialysis.

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Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			CRF women: 16.0 ± 1.4 Control women: 17.6 ± 2.7 p = not significant d) Ratio of DEXA limb:trunk lean tissue (mean ± SD): CRF men: 0.86 ± 0.13 Control men: 0.94 ± 0.05 p < 0.05 CRF women: 0.83 ± 0.08 Control women: 0.92 ± 0.08 p < 0.005 e) DEXA arm lean tissue (mean ± SD; kg): CRF men: 5.8 ± 0.8 Control men: 6.3 ± 0.8 p = not significant CRF women: 3.8 ± 0.6 Control women: 4.4 ± 0.8 p < 0.05 f) Percentage total body fat (mean ± SD): CRF men: 18.8 ± 8.7% Control men: 25.2 ± 7.0% p < 0.05 CRF women: 31.4 ± 14.2% Control women: 34.3 ± 7.6% p = not significant g) Triceps skinfold thickness (% of patients below the 10th centile): CRF patients: 26% Controls: 3% No p-value reported h) Mid-arm circumference (% of patients below the 10th centile): CRF patients: 43% Controls: 6% No p-value reported	

(continued on next page)

Evidence Table 4 – Nutrition (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			i) BMI (mean ± SD; kg/m2): CRF men: 24.2 ± 3.6 Control men: 26.2 ± 3.3 p = not significant CRF women: 24.6 ± 5.5 Control women: 25.1 ± 3.0 p = not significant	

6. Dyslipidemias

6.1 Chapter summary

To address the issue of the management of lipids in patients with pre-ESRD, the following three key questions were formulated:

1. Do dyslipidemias (hyperlipidemia or low lipids) cause increased risk of adverse clinical outcomes (defined below) in patients with pre-ESRD?
2. Does the treatment of dyslipidemias (by diet and lifestyle modification and/or pharmacologic therapy) reduce the risk of adverse intermediate and clinical outcomes in patients with pre-ESRD?
3. Is there an association between pharmacologic lipid therapy and drug toxicity in patients with pre-ESRD?

Key Question 1: Do dyslipidemias (hyperlipidemia or low lipids) cause increased risk of clinical outcomes in patients with pre-ESRD?

From the one available study, we conclude that there is limited evidence that dyslipidemias increase the risk of carotid plaques in patients with pre-ESRD.

Key Question 2: Does the treatment of dyslipidemias (by diet and lifestyle modification and/or pharmacologic therapy) reduce the risk of intermediate and clinical outcomes in patients with pre-ESRD?

- Based on these trials, we conclude that there is no available direct evidence that pharmacological or dietary interventions reduce the risk of clinical outcomes (as defined above) in patients with pre-ESRD.
- Based on one randomized controlled trial[21] and one uncontrolled trial,[22] we conclude that there is limited evidence that gemfibrozil is effective in lowering total cholesterol, LDL-C, and triglycerides levels, and might be effective in increasing HDL-C levels in patients with pre-ESRD. This is supported by effects observed in non-renally impaired people.
- Based on one uncontrolled trial,[23] we conclude that there is limited evidence that lovastatin combined with a low-cholesterol and low-protein diet is effective in lowering total cholesterol, LDL-C, VLDL-C, and apoB levels. Although scant, this is consistent with data on non-renally impaired people.
- Based on dietary intervention studies, we conclude: (1) that there is inconsistent and insufficient evidence to support or reject that a low-protein diet has a favorable impact on lipid profiles of patients with pre-ESRD;[24-26] (2) that there is limited evidence that a high-carbohydrate/high-fiber diet is effective in lowering cholesterol levels;[27] (3) that there is insufficient evidence on the effectiveness of fish oil supplementation in modifying lipid profile to draw any conclusions;[28] and (4) that

there is limited evidence that MPPG is effective in lowering total cholesterol, LDL-C, and triglycerides, and in increasing HDL-C levels.[29]

Key Question 3: Is there an association between pharmacologic lipid therapy and drug toxicity in patients with pre-ESRD?

In summary, based on these trials, we conclude that there is insufficient evidence to support or reject that gemfibrozil, lovastatin, or MMPG are more or less safe in patients with pre-ESRD compared to the general population of patients with dyslipidemias.

6.2 Background

Major progress has been made during the last 10 years in the identification and understanding of dyslipidemias as major risk factors for cardiovascular diseases in the general population. Large randomized controlled trials testing different lipid-lowering agents have shown their clinical benefit in a population of patients with normal kidney function, and these trials have been used as the basis for national guidelines on the management of dyslipidemias.[1-3] Despite the considerable amount of evidence regarding the harm of dyslipidemias and the benefit of their treatment in the general population, there are gaps in our knowledge of the amplitude of the problem and its management in patients with chronic kidney diseases.

First, the prevalence of dyslipidemias in patients with chronic kidney disease is certainly higher than in a population of patients without altered kidney function, but varies widely depending on the patient population characteristics, the cause of kidney failure, the presence or absence of nephrotic syndrome, the type of lipids considered, and the severity of kidney failure.[4-7] As many as 90 percent of patients with nephrotic syndrome have abnormal cholesterol levels, and about one-third to 45 percent of non-nephrotic patients with CKD have abnormal levels of cholesterol, HDL cholesterol, triglycerides, or lipoprotein(a).[5]

Second, although large observational studies have demonstrated the relationship between dyslipidemias and coronary heart diseases in patients with unaltered kidney function,[8-10] data on the impact of the increased prevalence of lipid abnormalities on clinical outcomes, and especially on cardiovascular outcomes, are scarce in the population of patients with kidney diseases. There is some evidence that the risk of coronary events is higher in patients with nephrotic syndrome than in healthy non-nephrotic controls.[11] In addition, cardiovascular complications are the leading cause of mortality in the ESRD population, and dyslipidemias are suspected of playing a major role in the development of atherosclerosis in this population.[12-15] Despite these observations, there is no consistent evidence on the clinical impact of lipid abnormalities in a population of patients with altered kidney function but without nephrotic syndrome and not undergoing renal replacement.

Finally, despite the importance of the problem among patients with pre-ESRD, there is no clear consensus on the management of such patients.[13,16] Should these patients be considered as high-risk patients for cardiovascular diseases? Should they be treated accordingly to guidelines designed for a general population, or should there be special concerns about the risks and benefits of lipid-lowering agents in this specific population?

The purpose of this chapter is to systematically review the available literature on the impact of dyslipidemias on clinical outcomes, and on the impact and risks of lipid management interventions in patients with pre-ESRD, defined as patients with glomerular filtration rate (GFR) below 30 ml/min/1.73 m^2 who are not receiving any kind of renal replacement therapy but are expected to require RRT within 6 to 18 months.

6.3 Methods

To address the issue of the management of lipids in patients with pre-ESRD, the following three key questions were formulated:

4. Do dyslipidemias (hyperlipidemia or low lipids) cause increased risk of adverse clinical outcomes (defined below) in patients with pre-ESRD?
5. Does the treatment of dyslipidemias (by diet and lifestyle modification and/or pharmacologic therapy) reduce the risk of adverse intermediate and clinical outcomes in patients with pre-ESRD?
6. Is there an association between pharmacologic lipid therapy and drug toxicity in patients with pre-ESRD?

To identify the literature addressing these questions, the following search terms were used: "hyperlipidemia," "HMG-Coa reductase inhibitor," "niacin," "antilipemic agents," "diet, fat-restricted," "anticholesteremic agents," "lipids," "cholesterol," and "triglycerides." In addition, the population of interest was expanded to nephrotic patients using the index term "nephrotic syndrome."

Clinical outcomes of interest were coronary heart diseases, including myocardial infarction; cerebrovascular diseases, including stroke; death; and drug toxicity. Intermediate outcomes considered were lipid values.

6.4 Results

Five hundred and twenty-two titles and abstracts were screened. Seventy of these were identified for full-text screening. Of these 70 articles, 58 were excluded at the full-text screening stage for the following reasons: outcomes not reported separately for the pre-ESRD population (n = 4), did not meet the criteria for the pre-ESRD population (n = 13), small case series/single case report (n = 2), did not address at least one of the key questions (n = 39). We were unable to obtain copies of two articles.[17,18] Of the 12 articles included at the full-text screening stage, one was a review article;[19] the remaining 11 were abstracted using a standardized form and are summarized in Evidence Table 5.

Key Question 1: Do dyslipidemias (hyperlipidemia or low lipids) cause increased risk of clinical outcomes in patients with pre-ESRD?

Only one study was identified (LE: 4, QS: good).[20] In this cross-sectional study, carotid ultrasonography was performed on 109 predialysis (mean ± SEM creatinine clearance of 7 ± 1 ml/min) patients, and predictors of carotid plaques were explored in logistic regression analyses. Predictors used in the different analyses included common cardiovascular risk factors (age, smoking, gender, diabetes, lipids levels), nutritional parameters (malnutrition, body mass index, albumin), and inflammatory parameters (C-reactive protein, tumor necrosis factor alpha, fibrinogen). In a univariate logistic regression analysis, age, malnutrition, serum albumin, smoking, and small ApoA isoform size were identified as predictors of carotid plaque. Using a multivariate analysis, the presence of carotid plaques was significantly associated with age, small ApoA isoform size, and log-oxidized low-density lipoprotein.

There are two major limitations to these findings. First, this study examined a large number of variables as potential predictors, relative to the number of patients. Second, there was no separate set of patients among which the model could be validated. In conclusion, this study provides weak evidence of association between LDL and carotid atherosclerosis in patients with pre-ESRD, but it is consistent with the large body of evidence among other populations.

We conclude that there is limited evidence that dyslipidemias increase the risk of carotid plaques in patients with pre-ESRD.

Key Question 2: Does the treatment of dyslipidemias (by diet and lifestyle modification and/or pharmacologic therapy) reduce the risk of intermediate and clinical outcomes in patients with pre-ESRD?

Three studies using pharmacological interventions and six studies reporting dietary interventions were identified. The principal results of these studies are summarized in Table 1.

Pharmacological interventions

Two studies explored the use of gemfibrozil,[21,22] and one evaluated the use of lovastatin.[23] Fifty-seven patients were randomly assigned to either gemfibrozil 300-900 mg/day or individual counseling on a triglyceride lowering diet (LE: 2b, QS: fair).[21] At baseline, mean ± SD GFR was 36.2 ± 12.9 and 34.8 ± 18.6 for the gemfibrozil and diet groups, respectively. Only 19/28 patients receiving gemfibrozil and 28/29 receiving diet counseling were included in the final analysis. The other patients were excluded due either to progression of kidney failure, or to adverse events (see Key Question 3,

below). After 12 months, significant decreases from baseline in total cholesterol, triglycerides, VLDL-C, LDL-C, and apoB were observed with gemfibrozil, as well as an increase in HDL-C. In contrast, only a significant increase in HDL-C was observed in patients who received the dietary counseling. Compared to diet counseling, gemfibrozil was associated with significantly larger decreases in total cholesterol, VLDL-C, and triglycerides. In contrast, no significant differences were observed between the two interventions in their effect on HDL-C and LDL-C.

In an uncontrolled study, the effects of gemfibrozil 300 mg bid were explored in 22 patients with pre-ESRD (mean ± SD CrCl of 18 ± 4 ml/min) and high TG or low HDL-C (LE: 4, QS: fair).[22] After 6 months of treatment, there were significant decreases in total cholesterol, TG levels, and LDL-C levels, but no changes in HDL-C levels were observed.

In a study designed to explore the impact of lovastatin on serum testosterone and cortisol levels, 25 hyperlipidemic nephrotic patients with chronic kidney disease (CKD) (mean ± SD CrCl of 9 ± 13 ml/min) received lovastatin 40 mg/day for a mean duration of 11 ± 0.5 months (LE: 4, QS: fair).[23] At the end of the study period, a significant decrease from baseline values (ranging from 11 to 30%) was observed for total cholesterol, LDL-C, VLDL-C, and apoB levels. No significant changes in HDL-C, TG, or apoA1 levels were observed.

Dietary interventions

Coggins et al. explored the impact of three different diet regimens on the lipid profiles of a subset of patients with pre-ESRD (median GFR of 19.0 ml/min/1.73m^2) previously included in a randomized controlled trial (LE: 2b, QS: fair).[24] In the initial trial, 96 patients were randomly assigned to a daily dietary protein intake of 1.3, 0.575, or 0.28 g/kg. Thirty-five were subsequently excluded from the lipid analysis because of changes in blood pressure medications with a potential to alter lipid levels. After 6 months on the assigned diets, a non-significant decrease in total, HDL-C, LDL-C, and TG was observed with the first diet. A significant decrease in total and HDL cholesterol was obtained with the second regimen ($p < 0.05$). The third diet resulted in a marginal decrease in total, HDL and LDL cholesterol ($p < 0.1$).

An uncontrolled trial evaluated the impact of a 1-1.2 g/kg protein diet on lipids in 10 patients with pre-ESRD (mean GFR of 27 ml/min/1.73m^2, range 13-48) (LE: 4, QS: fair).[25] After 12 and 36 months, no significant changes in total and LDL cholesterol were observed. Despite a significant increase in HDL-cholesterol, no significant changes in cholesterol/HDL ratio were noted.

In a retrospective study, Loschiavo et al. analyzed the impact on lipids levels of a low-protein diet (0.6 g/kg/day) in five groups of 20 patients with pre-ESRD (mean ± SEM serum creatinine ranging from 2.51 ± 0.44 to 3.54 ± 0.34 mg/dl), with a follow-up varying from 1 to 5 years. Lipid values from the patients on the low-protein diet were compared with lipid values of a diet-free control group of 20 patients (mean ± SEM serum creatinine of 2.97 ± 0.35 mg/dl) (LE: 4, QS: poor).[26] Compared to the control group, patients on the low-protein diet had significantly lower levels of TG and HDL-C. In contrast, no differences in cholesterol, ApoA1, or ApoB levels were observed, although the apoA1/apoB ratio was significantly higher in patients on the low-protein diet.

In a sequential non-randomized study, Parillo et al. compared a high-carbohydrate (50%), high-fiber, moderate protein (12%) diet with a low-carbohydrate (40%), low-fiber, low-protein (9%) diet in six diabetic patients with pre-ESRD (mean ± SD serum creatinine of 336 ± 168 mmol/l) (LE: 4, QS: poor).[27] Both diets were administered during a 10-day period. Significantly lower cholesterol values were observed at the end of the high-carbohydrate diet period compared to the low-carbohydrate one ($p < 0.05$), but no differences in TG levels were noted.

In a small uncontrolled clinical trial, five patients with progressive kidney disease (mean ± SD serum creatinine of 315 ± 29 μmol/l) received a diet supplemented in omega-3 fatty acid (fish oil) for 6 months (LE: 4, QS: poor).[28] At the end of this period, no significant changes in cholesterol or TG levels were observed, but the study was not powered to detect a difference.

In a placebo-controlled trial, 30 patients with pre-ESRD (serum creatinine above 2 mg/dl) and hyperlipidemia were randomly assigned to magnesium pyridoxal 5-phosphate glutamate (MPPG) 50 mg tid or placebo for 12 weeks (LE: 1b, QS: good).[29] After 12 weeks of treatment, significant decreases in total cholesterol, TG, LDL-C, and LDL/HDL ratio, and a significant increase in HDL-C were observed in the MPPG group compared to placebo.

Summary

In summary:

- Based on these trials, we conclude that there is no available direct evidence that pharmacological or dietary interventions reduce the risk of clinical outcomes (as defined above) in patients with pre-ESRD.
- Based on one randomized controlled trial[21] and one uncontrolled trial,[22] we conclude that there is limited evidence that gemfibrozil is effective in lowering total cholesterol, LDL-C, and triglycerides levels, and might be effective in increasing HDL-C levels in patients with pre-ESRD. This is supported by effects observed in non-renally impaired people.

- Based on one uncontrolled trial,[23] we conclude that there is limited evidence that lovastatin combined with a low-cholesterol and low-protein diet is effective in lowering total cholesterol, LDL-C, VLDL-C, and apoB levels. Although scant, this is consistent with data on non-renally impaired people.
- Based on dietary intervention studies, we conclude: (1) that there is inconsistent and insufficient evidence to support or reject that a low-protein diet has a favorable impact on lipid profiles of patients with pre-ESRD;[24-26] (2) that there is limited evidence that a high-carbohydrate/high-fiber diet is effective in lowering cholesterol levels;[27] (3) that there is insufficient evidence on the effectiveness of fish oil supplementation in modifying lipid profile to draw any conclusions;[28] and (4) that there is limited evidence that MPPG is effective in lowering total cholesterol, LDL-C, and triglycerides, and in increasing HDL-C levels.[29]

Key Question 3: Is there an association between pharmacologic lipid therapy and drug toxicity in patients with pre-ESRD?

Five studies reporting adverse events of pharmacological or dietary interventions were identified, two on gemfibrozil,[21,22] two on lovastatin,[23,30] and one on MMPG.[29]

Gemfibrozil

In a randomized controlled trial of gemfibrozil versus dietary counseling, the treatment was interrupted in eight patients treated with gemfibrozil: in two patients because of initiation of dialysis due to progression of kidney failure, and in six others because of mild gastrointestinal symptoms (LE: 2b, QS: fair).[21] Only one patient receiving dietary counseling did not complete the study because of progression of kidney failure requiring initiation of dialysis.

In another uncontrolled trial of 55 ESRD and pre-ESRD patients (22 patients with pre-ESRD) treated with gemfibrozil 300 mg bid, no significant increase in CPK, aldolase, AST, or ALT values was observed (LE: 4, QS: fair).[22]

Lovastatin

In a prospective clinical trial, 25 patients received lovastatin 40 mg/day during 11 months, and no side effects were observed (LE: 4, QS: fair).[23] Biesenbach et al. report the case of a 67-year old patient treated with lovastatin for hypercholesterolemia as result of nephrotic syndrome (LE: 5, QS: poor).[30] The patient was admitted with elevated CK, AST, ALT, and LDH values and with acute impairment of kidney function requiring initiation of dialysis. The diagnosis of lovastatin-induced rhabdomyolysis was made; lovastatin was withdrawn, and enzyme levels returned into the normal range.

MMPG

In a RCT of MMPG in 30 patients, one patient complained of headache and dizziness in the MMPG group, and 4 patients complained of fatigue, weakness, dizziness, stomach pressure, headache, dry mouth or increased quarrelsomeness (LE: 1b, QS: good).[29]

Summary

In summary, based on these trials, we conclude that there is insufficient evidence to support or reject that gemfibrozil, lovastatin, or MMPG are more or less safe in patients with pre-ESRD compared to the general population of patients with dyslipidemias.

6.5 Discussion

Despite the scarcity of the available evidence to answer our three key questions, a few useful statements can be formulated. We found limited evidence on the deleterious impact of dyslipidemias in the pre-ESRD population, no evidence on the potential clinical benefit of treating dyslipidemias in this population, and fragmentary evidence on the impact of dietary or drug interventions on lipids levels and on drug-related adverse events.

One might argue that an overly restrictive definition of pre-ESRD, our search strategy, or our selection process could explain the limited yield of this review, while the target population used for the review was selected to ensure generalizability. Some useful information might be identified by the review of articles used for the production of guidelines for other groups of patients, or by the review of the available evidence on the population of patients with ESRD. Unfortunately, examination of these other sources indicates that expanding the review in this way would have limited impact on the guideline development process.

First, we reviewed the inclusion and exclusion criteria, and the study population description of 36 randomized controlled trials testing dietary interventions or lipid-lowering agents identified through the review of references of national guidelines for the management of dyslipidemias in adults.[1-3] Twenty-six studies did not include any patients with impaired kidney function,[31-56] and six other studies did not report sufficient information on the patient characteristics to determine whether patients with kidney disease were included or not.[57-63] Four studies included specifically patients with kidney diseases, either nephrotic syndrome[64-66] or diabetic nephropathy,[67] but only two patients in these studies met our inclusion criterion (CrCl < 30 ml/min). Therefore, applying the results obtained in these studies to the pre-ESRD population should be considered with great caution.

Second, we considered studies performed in the ESRD population (dialysis or other form of renal replacement population) as an alternative source of information. During our screening process, we excluded 96 articles describing a non-pre-ESRD population.

Forty-six of these articles were reviewed despite their initial exclusion as they were identified as providing potentially relevant information regarding the three key questions formulated by the panel.

Twenty-three articles addressed the first key question, the relationship between lipid levels and clinical outcomes. In these studies, high TG levels,[68,69] high Lp(a) levels,[70-75] high VLDL-C levels,[76] and high LDL-C levels[77] were significantly associated with higher risk of cardiovascular events, progression of atherosclerosis, or fistula dysfunction.[78] In another study, high Lp(a) levels were significantly linked to coronary artery death.[79] Similarly, high Lp(a) levels,[68,80] low cholesterol and low ApoB levels,[81] high LDL-C levels,[77,82] high cholesterol,[82] and ApoA and ApoB levels [82] were independent predictors of mortality. In contrast, others studies have failed to show any association between lipids anomalies and clinical outcomes.[12,83-89]

Twenty-three other articles addressed the second and third key questions, reporting on 14 different dietary or drug interventions in patients under hemodialysis or CAPD.[90-96,96-111] Most were uncontrolled trials with small sample size, and none reported clinical outcomes. Therefore, although these trials might provide modestly useful information on the impact of these interventions on lipid levels of patients with ESRD, their impact on the care of patients with pre-ESRD is even more limited.

In conclusion, the available literature on the impact and management of dyslipidemias in patients with pre-ESRD is very limited, and it does not appear that including more general studies of lipid treatment or studies of patients with ESRD adds substantially to our base of evidence for guidelines on management of dyslipidemias in patients with pre-ESRD. Substantial opportunities are open for further research into the implications of dyslipidemia and its treatment in this significant population.

Ref	Intervention	Results	LE QS
[24]	A. 1.3 g/kg/d protein diet vs. B. 0.575 g/kg/d protein diet vs. C. 0.28 g/kg/d protein diet	Total cholesterol: A. ↓, -19 / B. ↓, -11 / C. ↓, -30 HDL: A. ↓, -3 / B. ↔, -0.5 / C. ↓, -4 LDL: A. ↓, -13.5 / B. ↓, -8.5 / C. ↓, -30 Triglycerides: A. ↓, -14 / B. ↔, +8 / C. ↔, +4 Numerical values are absolute changes at 6 months from baseline in mg/dl	2b Fair
[25]	1-1.2 g/kg diet	Total cholesterol: ↑, + 17% HDL: ↑, + 54% LDL: ↑, + 13% Total cholesterol/HDL: ↓, - 31% Numerical values are relative changes at 36 months from baseline	4 Fair
[26]	A. 0.6 g/kg/d diet during 12-60 months vs. B. no diet	Total cholesterol: A. vs. B.: ↓, -10% to -22% HDL: A. vs. B.: ↑, +54% to +88% Triglycerides: A. vs. B.: ↓, -48 to -61% ApoA1: ↔, -6% to +19% ApoB: ↔, -4% to -23% Ratio A1/B: ↑, +43% to +78% Numerical values are relative differences in lipid levels comparing the diet groups to the control group	4 Poor
[27]	A. High-carbohydrate/high-fiber diet during 10 days vs. B. Low-carbohydrate/low-fiber diet during 10 days	Cholesterol: A. vs. B.: - 18% Triglycerides: A. vs. B.: - 6% Numerical values are relative changes comparing A and B	4 Poor
[28]	Omega-3 fatty acid supplemented diet	Cholesterol: ↔, - 4% Triglycerides: ↓, - 13% Numerical values are relative changes at 6 months from baseline	4 Poor
[29]	A. Mg-pyridoxal 5-P glutamate B. Placebo	Total cholesterol: A. ↓, - 20% / B. ↔, + 3% HDL: A. ↑, + 26% / B. ↓, - 11% LDL: A. ↓, - 35% / B. ↑, + 7% Triglycerides: A. ↓, - 23% / B. ↑, + 6% LDL/HDL: A. ↓, - 51% / B. ↑, + 20% Numerical values are relative changes at 12 weeks from baseline	1b Good

Ref	Intervention	Results	LE QS
[22]	Gemfibrozil 300 mg bid po	Total cholesterol: ↓, - 15% HDL: ↑, + 19% LDL: ↓, - 14% Triglycerides: ↓, - 26% Total cholesterol/HDL: ↓, - 25% Numerical values are relative changes at 6 months from baseline	4 Fair
[21]	A. Gemfibrozil 300-600 mg/d po vs. B. Dietary counseling	Total cholesterol: A. ↓, - 13% / B. ↔, - 4% HDL: A. ↑, + 18% / B. ↑, + 20% LDL: A. ↓, - 14% / B. ↓, - 7% VLDL: ↓, - 43% / ↓, - 12% Triglycerides: A. ↓, - 47% / B. ↓, - 10% Numerical values are relative changes at 12 months from baseline	2b Fair
[23]	Lovastatin 40 mg/d + 300 mg cholesterol, 0.3 g/kg/d protein diet	Total cholesterol: ↓, - 29% HDL: ↓, - 18% LDL: ↓, - 30% VLDL: ↓, - 18% Triglycerides: ↓, - 7% ApoA1: ↔, + 2% ApoB: ↓, - 11% Numerical values are relative changes at 11 months from baseline	4 Fair

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Evidence Table 5 – Dyslipidemias

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Biesenbach, Janko, Stuby, et al., 1996	Design: Case report (included for toxicity data only) Intervention(s) studied: Lovastatin 20 mg daily Dates: NR Location: Linz, Austria Recruitment setting: Hospital	No. of pre-ESRD subjects: 1 Inclusion criteria: NA Exclusion criteria: NA Age: 67 Sex: Male Race: NR Renal function at entry: SCr: 9.0 mg/dl before episode; 9.8 mg/dl at time of episode Lipid values at entry: Cholesterol: > 470 mg/dl Liver function tests at entry: NR Muscle enzymes at entry: NR Co-morbidities at entry: NR	*Key Question 1) Do dyslipidemias (hyperlipidemia or low lipids) cause increased risk of clinical outcomes in pre-ESRD patients?:* Case report – not applicable *Key Question 2) Does the treatment of dyslipidemias (by diet and lifestyle modification and/or pharmacologic therapy) reduce the risk of intermediate and clinical outcomes in pre-ESRD patients?:* Case report – not applicable *Key Question 3) Is there an association between pharmacologic lipid therapy and drug toxicity in pre-ESRD patients?:* Patient admitted with pain in the legs and darkly discolored urine. Labs at admission: CK 9470 U/L, SGOT 309 U/L, SGPT 142 U/L, LDH 1280 U/L. The diagnosis of lovastatin-induced rhabdomyolysis was made. Patient became anuric, and dialysis was initiated. Within the next 10 days, elevated enzyme levels returned to the normal range.	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: No/not assessable Incl/excl described: No/not assessable Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: SCr 4) % pre-ESRD: > 75% 5) Level of evidence: 5 Notes:

Evidence Table 5 – Dyslipidemias (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Coggins, Dwyer, Greene, et al., 1994	Design: RCT Intervention(s) studied: 1) Diet M = 1.3 g/kg/day protein, with 16-20 mg/kg/day of phosphorus; 2) Diet L = 0.575 g/kg/day protein, with 5-10 mg/kg/day phosphorus; 3) Diet J = 0.28 g/kg/day protein, with 4-9 mg/kg/day phosphorus, plus an amino acid mixture; 4) Diet K = 0.28 g/kg/day protein, with 4-9 mg/dg/day phosphorus, plus a keto acid mixture. Dates: NR Location: 9 centers in Boston, MA; Torrance, CA; Baltimore, MD; Iowa City, IA; Los Angeles, CA; and Nashville, TN Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 61 Inclusion criteria: Age 18-75; GFR 7.5-80 ml/min/1.73 m^2; progressive increase in SCr during 3 years prior to entry into study Exclusion criteria: Pregnancy; doubtful compliance; abnormal nutritional status; current therapy with insulin or immunosuppressive, steroidal, or non-steroidal drugs; hemodynamically significant renal artery stenosis; urinary tract obstruction or reflux; chronic medical conditions Age: Mean, 49; range, 25-73 Sex: 56% M, 44% F Race: NR Renal function at entry: Median GFR, 19.00 ml/min/1.73 m^2 Lipid values at entry (medians, in mg/dl): Cholesterol: 215 Triglycerides: 191 LDL: 134.5 HDL: 34 Liver function tests at entry: NR Muscle enzymes at entry: NR Co-morbidities at entry: NR	*Key Question 1) Do dyslipidemias (hyperlipidemia or low lipids) cause increased risk of clinical outcomes in pre-ESRD patients?:* Not addressed *Key Question 2) Does the treatment of dyslipidemias (by diet and lifestyle modification and/or pharmacologic therapy) reduce the risk of intermediate and clinical outcomes in pre-ESRD patients?:* Investigators reported median changes from baseline to 6-month follow-up for the following lipid values (all in mg/dl): a) Total cholesterol: Diet M: -19 Diet L: -11 ($p < 0.10$) Diets J/K: -30 ($p < 0.05$) b) HDL: Diet M: -3 Diet L: -0.50 Diets J/K: -3 ($p < 0.05$) c) LDL: Diet M: -13.5 Diet L: -8.50 ($p < 0.10$) Diets J/K: -30 ($p < 0.05$) d) Triglycerides: Diet M: -14 Diet L: +8 Diets J/K: +4 *Key Question 3) Is there an association between pharmacologic lipid therapy and drug toxicity in pre-ESRD patients?:* Not addressed	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: No/not assessable Incl/excl described: Completely Dropouts discussed: Partially Sample size justified: No/not assessable 3) GFR/CrCl: Measured by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 2b Note: The baseline to follow-up change in protein intake (calculated from urinary urea measurements) was significantly correlated with the change in serum total cholesterol ($r = 0.31$, $p < 0.05$) and with the change in LDL cholesterol ($r = 0.34$, $p < 0.01$).

Evidence Table 5 – Dyslipidemias (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Elisaf, Dardamanis, Papagalanis, et al., 1993	Design: Prospective clinical trial Intervention(s) studied: Gemfibrozil PO 300 mg 2x/day Dates: NR Location: Athens, Greece Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 56, of whom 22 received treatment Inclusion criteria: Chronic renal failure; triglycerides > 300 mg/dl or HDL cholesterol < 28 mg/dl Exclusion criteria: None specified Age (n = 56 pre-ESRD patients): Mean, 45; range, 22-70 Sex (n = 56 pre-ESRD patients): 64% M, 36% F Race: NR Renal function at entry (n = 56 pre-ESRD patients): Estimated Cr Cl (mean ± SD): 18.0 ± 4.0 ml/min Lipid values at entry (means ± SD; n = 22 treated patients): Cholesterol: 199.3 ± 56.6 mg/dl Triglycerides: 162 ± 86 mg/dl LDL: 127 ± 51.5 mg/dl HDL: 32.4 ± 11.2 mg/dl Total/HDL cholesterol: 6.29 ± 1.2 Liver function tests at entry: NR Muscle enzymes at entry: NR Co-morbidities at entry: Diabetes: 0%	*Key Question 1) Do dyslipidemias (hyperlipidemia or low lipids) cause increased risk of clinical outcomes in pre-ESRD patients?:* Not addressed *Key Question 2) Does the treatment of dyslipidemias (by diet and lifestyle modification and/or pharmacologic therapy) reduce the risk of intermediate and clinical outcomes in pre-ESRD patients?:* a) Cholesterol (means ± SD, in mg/dl): At entry: 199.3 ± 56.6 2 months: 172 ± 3.2 (p < 0.001 vs. entry) 6 months: 168.5 ± 31.2 (p < 0.001 vs. entry) b) Triglycerides (means ± SD, in mg/dl): At entry: 162 ± 86 2 months: 132 ± 4.4 (p < 0.01 vs. entry) 6 months: 119.5 ± 38 (p < 0.001 vs. entry) c) HDL (means ± SD, in mg/dl): At entry: 32.4 ± 11.2 2 months: 35 ± 6.8 6 months: 38.7 ± 12.8 d) LDL (means ± SD, in mg/dl): At entry: 127 ± 51.5 2 months: 114 ± 2.8 6 months: 109.2 ± 27.3 (p < 0.05 vs. entry) e) Total/HDL cholesterol (means ± SD): At entry: 6.29 ± 1.2 2 months: 5 ± 1 (p < 0.001 vs. entry) 6 months: 4.7 ± 0.8 (p < 0.001 vs. entry) *Key Question 3) Is there an association between pharmacologic lipid therapy and drug toxicity in pre-ESRD patients?:* No significant increases in CPK, aldolase, AST, or ALT were noted during treatment with gemfibrozil in a combined group of 55 ESRD and pre-ESRD patients.	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: No/not assessable Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: < 50%/not assessable 5) Level of evidence: 4 Notes:

(continued on next page)

Evidence Table 5 – Dyslipidemias (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			Results were not reported separately for pre-ESRD patients.	
Jureidini, Hogg, van Renen, et al., 1990	Design: Prospective clinical trial Intervention(s) studied: Low-protein, low-phosphorous diet (1-1.2 g/kg protein, 500-1000 mg phosphorous per day); maintained for 3 years Dates: Late 1984-1987 Location: Adelaide, Australia Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 10 Inclusion criteria: NR Exclusion criteria: NR Age: Range, 3-14 Sex: NR Race: NR Renal function at entry: GFR (in ml/min per 1.73 m^2): Mean, 27; range, 13-48 Lipid values at entry (mean ± SD, all in mmol/l): Cholesterol: 5.10 ± 1.25 Triglycerides: 1.60 + 0.85 LDL: 3.23 ± 1.14 HDL: 1.04 + 0.30 TC/HDL ratio: 5.33 ± 2.40 Liver function tests at entry: NR Muscle enzymes at entry: NR Co-morbidities at entry: NR	*Key Question 1) Do dyslipidemias (hyperlipidemia or low lipids) cause increased risk of clinical outcomes in pre-ESRD patients?:* Not addressed *Key Question 2) Does the treatment of dyslipidemias (by diet and lifestyle modification and/or pharmacologic therapy) reduce the risk of intermediate and clinical outcomes in pre-ESRD patients?:* a) Cholesterol (mean ± SD, in mmol/l): Baseline: 5.10 ± 1.25 12 months: 5.36 ± 1.17 (p = NS) 36 months: 5.71 ± 1.05 (p = NS) b) HDL (mean ± SD, in mmol/l): Baseline: 1.04 + 0.30 12 months: 1.38 ± 0.33 (p < 0.05) 36 months: 1.61 ± 0.37 (p < 0.001) c) LDL (mean ± SD, in mmol/l): Baseline: 3.23 ± 1.14 12 months: 3.00 ± 0.89 (p = NS) 36 months: 3.64 ± 1.04 (p = NS) d) Cholesterol/HDL ratio (mean ± SD, in mmol/l): Baseline: 5.33 ± 2.40 12 months: 4.05 ± 1.30 (p = NS) 36 months: 3.68 ± 0.92 (p = NS) *Key Question 3) Is there an association between pharmacologic lipid therapy and drug toxicity in pre-ESRD patients?:* Not addressed	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: No/not assessable Incl/excl described: No/not assessable Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 4 Notes: Height and weight velocity significantly increased after 3 years on diet. Psychological well-being score significantly improved (vs. baseline) at 2 and 3 years.

Evidence Table 5 – Dyslipidemias (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Kirsten Heintz, Nelson, et al., 1988	Design: RCT Intervention(s) studied: 1) Magnesium pyridoxal 5-phosphate glutamate (MPPG) 50 mg 3x/day for 12 weeks; 2) Placebo 3x/day for 12 weeks. Dates: NR Location: Frankfurt, Germany Recruitment setting: NR	No. of pre-ESRD subjects: 30 Inclusion criteria: Creatinine > 2 mg/100 ml; cholesterol > 250 mg/100 ml; hyperlipidemia types IIa, IIb, or IV Exclusion criteria: None specified Age (mean ± SD): MPPG, 51.7 ± 6.3; placebo, 51.1 ± 11.4 Sex: 40% M, 60% F Race: NR Renal function at entry: NR (SCr > 2 mg/100 ml required for entry into study) Lipid values at entry (means ± SD, in mg/dl): Cholesterol: MPPG, 382 ± 79.1; placebo, 343 ± 71.7 Triglycerides: MPPG, 346 ± 224; placebo 343 ± 156 LDL: MPPG, 271 ± 73.9; placebo, 229 ± 67.2 HDL: MPPG, 39.7 ± 8.8; placebo, 45.1 ± 15.2 LDL/HDL ratio: MPPG, 7.30 ± 3.11; placebo, 5.43 ± 1.93 Liver function tests at entry: NR Muscle enzymes at entry: NR Co-morbidities at entry: NR	*Key Question 1) Do dyslipidemias (hyperlipidemia or low lipids) cause increased risk of clinical outcomes in pre-ESRD patients?:* Not addressed *Key Question 2) Does the treatment of dyslipidemias (by diet and lifestyle modification and/or pharmacologic therapy) reduce the risk of intermediate and clinical outcomes in pre-ESRD patients?:* a) Total cholesterol (mean ± SD; mg/dl): MPPG / Placebo At entry: 382 ± 79.1 / 343 ± 71.7 12 weeks: 282 ± 76.0 / 354 ± 89.9 p < 0.02, MPPG vs. placebo at 12 weeks b) Triglycerides (mean ± SD; mg/dl): MPPG / Placebo At entry: 346 ± 224 / 343 ± 156 12 weeks: 265 ± 195 / 362 ± 155 p < 0.02, MPPG vs. placebo at 12 weeks c) LDL (mean ± SD; mg/dl): MPPG / Placebo At entry: 271 ± 73.9 / 229 ± 67.2 12 weeks: 176 ± 66.4 / 244 ± 81.8 p < 0.03, MPPG vs. placebo at 12 weeks d) HDL (mean ± SD; mg/dl): MPPG / Placebo At entry: 39.7 ± 8.8 / 45.1 ± 15.2 12 weeks: 50.1 ± 12.1 / 40.3 ± 14.5 p < 0.05, MPPG vs. placebo at 12 weeks e) LDL/HDL ratio (mean ± SD): MPPG / Placebo At entry: 7.30 ± 3.11 / 5.43 ± 1.93	Quality Scoring: 1) Global assessment: Good 2) Validity criteria: Population described: No/not assessable Incl/excl described: Partially Dropouts discussed: Partially Sample size justified: Completely 3) GFR/CrCl: SCr 4) % pre-ESRD: > 75% 5) Level of evidence: 1b Notes:

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Evidence Table 5 – Dyslipidemias (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			12 weeks: 3.56 ± 1.08 6.83 ± 3.93 p < 0.0006, MPPG vs. placebo at 12 weeks *Key Question 3) Is there an association between pharmacologic lipid therapy and drug toxicity in pre-ESRD patients?:* Adverse events were as follows: MPPG: 1 patient complained of headache and dizziness Placebo: 4 patients complained of fatigue, weakness, stomach pressure, dizziness, headache, dry mouth, and "increased quarrelsomeness in the morning"	

Evidence Table 5 – Dyslipidemias (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Loschiavo, Ferrari, Panebianco, et al., 1988	Design: Case series (retrospective), concomitant controls Intervention(s) studied: Patients divided into 6 groups retrospectively: 1) Free diet (duration not specified); 2) Protein-restricted diet (40 kcal/kg/day; 47% carbo-hydrates, 47% lipids, 6% protein; total protein intake 0.6 g/kg/day; phosphorus intake 700 mg/day; calcium intake 1500 mg/day), maintained for 12 months; 3) Protein-restricted diet (as above), maintained for 24 months; 4) Protein-restricted diet (as above), maintained for 36 months; 5) Protein-restricted diet (as above), maintained for 48 months; 6) Protein-restricted diet (as above), maintained for 60 months. Dates: NR Location: Verona, Italy Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 122 Inclusion criteria: Chronic renal failure Exclusion criteria: None specified Age: Mean, 49.0 Sex: 57% M, 43% F Race: NR Renal function at entry: SCr (mean): 3.01 mg/dl Lipid values at entry: NR Liver function tests at entry: NR Muscle enzymes at entry: NR Co-morbidities at entry: Diabetes: 0% Hypertension (DBP ≥ 100 mmHg): 58.2%	*Key Question 1) Do dyslipidemias (hyperlipidemia or low lipids) cause increased risk of clinical outcomes in pre-ESRD patients?:* Not addressed *Key Question 2) Does the treatment of dyslipidemias (by diet and lifestyle modification and/or pharmacologic therapy) reduce the risk of intermediate and clinical outcomes in pre-ESRD patients?:* The following end-of-treatment results were reported (LP = low-protein diet; p-values are for LP vs. free diet): a) Triglycerides (mean ± SEM; in mg/dl): Free diet: 335 ± 42 LP, 12 mo: 132 ± 8 ($p < 0.001$) LP, 24 mo: 144 ± 10 ($p < 0.05$) LP, 36 mo: 149 ± 13 ($p < 0.02$) LP, 48 mo: 175 ± 11 ($p < 0.01$) LP, 60 mo: 170 + 20 ($p < 0.02$) b) Cholesterol (mean ± SEM; in mg/dl): Free diet: 247 ± 17 LP, 12 mo: 219 ± 8 LP, 24 mo: 209 ± 11 LP, 36 mo: 193 ± 12 LP, 48 mo: 222 ± 10 LP, 60 mo: 205 ± 11 c) HDL (% of total cholesterol; mean ± SEM): Free diet: 14 ± 0.7 LP, 12 mo: 24 ± 1.2 ($p < 0.001$) LP, 24 mo: 23 ± 1.1 ($p < 0.001$) LP, 36 mo: 26 ± 1 ($p < 0.001$) LP, 48 mo: 21 ± 0.7 ($p < 0.001$) LP, 60 mo: 25 ± 1.4 ($p < 0.001$) d) ApoA1 (mean ± SEM; in mg/dl): Free diet: 127 ± 7 LP, 12 mo: 136 ± 5 LP, 24 mo: 152 ± 7	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: No/not assessable Incl/excl described: No/not assessable Dropouts discussed: No/not assessable Sample size justified: No/not assesable 3) GFR/CrCl: SCr 4) % pre-ESRD: > 75% 5) Level of evidence: 4 Notes:

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Evidence Table 5 – Dyslipidemias (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			LP, 36 mo: 132 ± 7 LP, 48 mo: 120 ± 6 LP, 60 mo: 148 ± 6 e) ApoB (mean ± SEM; in mg/dl): Free diet: 118 ± 9 LP, 12 mo: 96 ± 6 LP, 24 mo: 96 ± 6 LP, 36 mo: 91 ± 7 LP, 48 mo: 113 ± 6 LP, 60 mo: 93 ± 4 f) Ratio of ApoA1/ApoB (mean ± SEM): Free diet: 1.10 ± 0.08 LP, 12 mo: 1.57 ± 0.10 LP, 24 mo: 1.80 ± 0.09 ($p < 0.001$) LP, 36 mo: 1.90 ± 0.11 ($p < 0.05$) LP, 48 mo: 1.96 ± 0.04 ($p < 0.05$) LP, 60 mo: 1.65 ± 0.10 ($p < 0.02$) *Key Question 3) Is there an association between pharmacologic lipid therapy and drug toxicity in pre-ESRD patients?:* Not addressed	

Evidence Table 5 – Dyslipidemias (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Parillo, Riccardi, Pacioni, et al., 1988	Design: RCT (crossover) Intervention(s) studied: 1) High-carbohydrate, high-fiber diet (12% protein, 38% fat, 50% carbohydrate, with 65 g of fiber per day); 2) Low-carbohydrate, low-fiber diet (9% protein, 51% fat, 40% carbohydrate, with 22 g of fiber per day). Dates: NR Location: Naples, Italy Recruitment setting: Hospital	No. of pre-ESRD subjects: 6 Inclusion criteria: Insulin-dependent diabetes; chronic renal failure Exclusion criteria: None specified Age (mean ± SD): 48.5 ± 14.8 Sex: NR Race: NR Renal function at entry: SCr (mean ± SD): 336 ± 168 mmol/l Lipid values at entry: NR Liver function tests at entry: NR Muscle enzymes at entry: NR Co-morbidities at entry: 100% diabetes	*Key Question 1) Do dyslipidemias (hyperlipidemia or low lipids) cause increased risk of clinical outcomes in pre-ESRD patients?:* Not addressed *Key Question 2) Does the treatment of dyslipidemias (by diet and lifestyle modification and/or pharmacologic therapy) reduce the risk of intermediate and clinical outcomes in pre-ESRD patients?:* a) Cholesterol (mean ± SD, in mmol/l): High-carb, high-fiber: 6.37 ± 0.88 Low-carb, low-fiber: 7.77 ± 1.55 p < 0.05 b) Triglycerides (mean ± SD, in mmol/l): High-carb, high-fiber: 2.91 ± 1.30 Low-carb, low-fiber: 3.10 ± 1.98 p = not significant *Key Question 3) Is there an association between pharmacologic lipid therapy and drug toxicity in pre-ESRD patients?:* Not addressed	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: No/not assessable Incl/excl described: No/not assessable Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: SCr 4) % pre-ESRD: > 75% 5) Level of evidence: 2b Notes:

Evidence Table 5 – Dyslipidemias (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Richard, Sirajeddine, Cordonnier, et al., 1993	Design: Prospective clinical trial Intervention(s) studied: Omega-3 fatty acid supplementation: Fish oil in the form of 6 Maxepa® capsules (6 g) daily to obtain a dose of 1.08 g of eicosapentaenoic acid and 0.72 g of docosahexaenoic acid, plus 10.5 mg/day of vitamin E. Dates: NR Location: Grenoble, France Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 5 Inclusion criteria: Progressive renal insufficiency Exclusion criteria: None specified Age: Mean, NR; range, 21-74 Sex: 40% M, 60% F Race: NR Renal function at entry (mean ± SD): SCr: 315 ± 29 µmol/l Lipid values at entry (mean ± SD): Cholesterol: 2.29 ± 1.1 g/l Triglycerides: 1.93 ± 0.60 g/l Liver function tests at entry: NR Muscle enzymes at entry: NR Co-morbidities at entry: 100% hypertension (all on antihypertensive therapy)	*Key Question 1) Do dyslipidemias (hyperlipidemia or low lipids) cause increased risk of clinical outcomes in pre-ESRD patients?:* Not addressed *Key Question 2) Does the treatment of dyslipidemias (by diet and lifestyle modification and/or pharmacologic therapy) reduce the risk of intermediate and clinical outcomes in pre-ESRD patients?:* a) Cholesterol (mean ± SD; in g/l): Baseline: 2.29 ± 1.1 6 months: 2.18 ± 0.7 p = not significant b) Triglycerides (mean ± SD; in g/l): Baseline: 1.93 ± 0.60 6 months: 1.67 ± 0.56 p = not significant *Key Question 3) Is there an association between pharmacologic lipid therapy and drug toxicity in pre-ESRD patients?:* Not addressed	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: No/not assessable Incl/excl described: No/not assessable Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: SCr 4) % pre-ESRD: < 50%/not assessable 5) Level of evidence: 4 Notes:

Evidence Table 5 – Dyslipidemias (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Samuelsson, Attman, Knight-Gibson, et al., 1997	Design: RCT Intervention(s) studied: 1) Gemfibrozil (n = 19): Starting dose 300 mg 1x/day; increased to 300 mg 2x/day after 1 month. In patients with GFR > 25 ml/min x 1.73 m^2, the dose could be further titrated at the 3-month visit up to 450 mg 2x/day, if the serum triglyceride level was > 1.7 mmol/l. 2) Dietary intervention (n = 28): Individual counseling (patient and spouse) by a professional dietician trained in counseling patients with renal disease about a triglyceride-lowering diet. Patients provided with written information, including recipes. After 1 month, dietician contacted each patient by phone for follow-up and to strengthen the dietary advice given. Dates: NR Location: 5 cities in Sweden Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 57 randomized; 47 completed 12 months of treatment; data reported here for 47 completers only Inclusion criteria: Moderately advanced renal insufficiency; non-diabetic primary renal disease Exclusion criteria: None specified Age (mean ± SD): Gemfibrozil, 53.1 ± 12.0; diet, 50.2 ± 13.2 Sex: Gemfibrozil, 63% M, 37% F; diet, 79% M, 21% F Race: NR Renal function at entry (mean ± SD): GFR (ml/min x 1.73 m^2 BSA): Gemfibrozil, 38.9 ± 12.3; diet, 35.7 ± 18.3 SCr (mmol/l): Gemfibrozil, 169 ± 74; diet, 222 ± 102 Lipid values at entry (mean ± SD, in mmol/l unless otherwise specified): Cholesterol: Gemfibrozil, 6.1 ± 1.4; diet, 6.4 ± 1.2 Triglycerides: Gemfibrozil, 1.5 ± 0.8; diet, 2.0 ± 1.2 LDL: Gemfibrozil, 4.3 ± 1.3; diet, 4.4 ± 1.0 HDL: Gemfibrozil, 1.1 ± 0.4; diet, 1.0 ± 0.3 VLDL: Gemfibrozil, 0.7 ± 0.4; diet, 0.8 ± 0.4 LP-A1 (mg/100 ml): Gemfibrozil, 31.3 ± 7.0; diet, 34.1 ± 5.4 Liver function tests at entry: NR	*Key Question 1) Do dyslipidemias (hyperlipidemia or low lipids) cause increased risk of clinical outcomes in pre-ESRD patients?:* Not addressed *Key Question 2) Does the treatment of dyslipidemias (by diet and lifestyle modification and/or pharmacologic therapy) reduce the risk of intermediate and clinical outcomes in pre-ESRD patients?:* a) Total cholesterol (mean ± SD; mmol/l): Gemfibrozil / Diet At entry: 6.1 ± 1.4 / 6.4 ± 1.2 12 months: 5.3 ± 1.1* / 6.1 ± 1.4** *p < 0.01, Gemfibrozil 12 months vs. entry ** p < 0.05, Gemfibrozil 12 months vs. diet 12 months b) Triglycerides (mean ± SD; mmol/l): Gemfibrozil / Diet At entry: 1.5 ± 0.8 / 2.0 ± 1.2 12 months: 0.8 ± 0.3* / 1.8 ± 1.3** *p < 0.01, Gemfibrozil 12 months vs. entry ** p < 0.01, Gemfibrozil 12 months vs. diet 12 months c) HDL (mean ± SD; mmol/l): Gemfibrozil / Diet At entry: 1.1 ± 0.4 / 1.0 ± 0.3 12 months: 1.3 ± 0.4* / 1.2 ± 0.3** *p < 0.01, Gemfibrozil 12 months vs. entry ** p < 0.05, Diet 12 months vs. entry d) LDL (mean ± SD; mmol/l): Gemfibrozil / Diet At entry: 4.3 ± 1.3 / 4.4 ± 1.0 12 months: 3.7 ± 1.1* / 4.1 ± 1.2 *p < 0.01, Gemfibrozil 12 months vs. entry e) VLDL (mean ± SD; mmol/l): Gemfibrozil / Diet At entry: 0.7 ± 0.4 / 0.8 ± 0.4 12 months: 0.4 ± 0.1* / 0.7 ± 0.3** *p < 0.001, Gemfibrozil 12 months vs. entry	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: No/not assessable Incl/excl described: Partially Dropouts discussed: Completely Sample size justified: 3) GFR/CrCl: Measured by investigators 4) % pre-ESRD: < 50%/not assessable 5) Level of evidence: 2b Note: Some confusion about number of dropouts. Overall numbers reported suggest that 10 patients randomized to treatment did not complete the study, but report describes only 9 dropouts, 1 from diet group (started hemodialysis due to rapid decline in renal function), and 8 from the gemfibrozil group (2 started renal replacement therapy, 6 dropped out due to GI symptoms).

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Evidence Table 5 – Dyslipidemias (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
		Muscle enzymes at entry: NR Co-morbidities at entry: NR	** p < 0.01, Gemfibrozil 12 months vs. diet 12 months *Key Question 3) Is there an association between pharmacologic lipid therapy and drug toxicity in pre-ESRD patients?:* 6 patients receiving gemfibrozil withdrew due to mild gastrointestinal symptoms. No rhabdomyolysis was reported.	

Evidence Table 5 – Dyslipidemias (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Segarra, Chacón, Vilardell, et al., 1996	Design: Prospective clinical trial Intervention(s) studied: Lovastatin 40 mg/day + diet with 40 kcal/kg/day, 300 mg cholesterol/day, and 0.3 g protein/kg/day (administered to pre-ESRD patients only) Dates: NR Location: Barcelona, Spain Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 25, all of whom received lovastatin; compared with 25 matched healthy controls Inclusion criteria: Chronic renal failure; proteinuria; hyperlipidemia; 6 months free of immunosuppressive drugs; 6 months free of lipid-lowering medication Exclusion criteria: None specified Age (mean ± SD): Pre-ESRD patients, 25 ± 15; controls, NR Sex: 100% M (pre-ESRD and controls) Race: NR Renal function at entry (mean ± SD): CrCl: Pre-ESRD patients, 9 ± 13 ml/min/1.73 m^2; controls, 96 ± 9 ml/min/1.73 m^2 ($p < 0.001$) SCr: Pre-ESRD patients, 300 ± 22 µmol/l; controls, 1.27 ± 6 µmol/l ($p < 0.001$) Lipid values at entry (mean ± SD, in mmol/l, unless otherwise specified): Cholesterol: Pre-ESRD, 8 ± 2.6; controls, 4.9 ± 0.2 ($p < 0.001$) Triglycerides: Pre-ESRD, 2.7 ± 1.1; controls 1.75 ± 1.1 ($p \leq 0.001$) LDL: Pre-ESRD, 5.4 ± 1.8; controls, 3.5 ± 1.2 ($p < 0.001$) HDL: Pre-ESRD, 1.1 ± 0.6; controls, 1.2 ± 0.5 VLDL: Pre-ESRD, 1 ± 0.3; controls, 0.32 ± 0.5 ($p < 0.001$) Apo A1 (in mg/dl): Pre-ESRD, 114 ± 9.8; controls, 125 ± 10 Apo B (in mg/dl): Pres-ESRD, 202 ±	*Key Question 1) Do dyslipidemias (hyperlipidemia or low lipids) cause increased risk of clinical outcomes in pre-ESRD patients?:* Not addressed *Key Question 2) Does the treatment of dyslipidemias (by diet and lifestyle modification and/or pharmacologic therapy) reduce the risk of intermediate and clinical outcomes in pre-ESRD patients?:* a) Cholesterol (mean ± SD, in mmol/l): Before: 8 ± 2.6 After (11 ± 0.5 months): 5.67 ± 3 ($p = 0.001$) b) HDL (mean ± SD, in mmol/l): Before: 1.1 ± 0.6 After: 0.9 ± 0.4 (p = not significant) c) LDL (mean ± SD, in mmol/l): Before: 5.4 ± 1.8 After: 3.8 ± 1.1 ($p = 0.001$) d) VLDL (mean ± SD, in mmol/l): Before: 1 ± 0.3 After: 0.82 ± 0.5 ($p = 0.005$) e) Triglycerides (mean ± SD, in mmol/l): Before: 2.7 ± 1.1 After: 2.5 ± 1.3 (p = not significant) f) Apo A1 (mean ± SD, in mg/dl): Before: 114 ± 9.8 After: 116 ± 7.5 (p = not significant) g) Apo B (mean ± SD, in mg/dl): Before: 202 ± 15 After: 180 ± 10 ($p = 0.05$) *Key Question 3) Is there an association between pharmacologic lipid therapy and drug toxicity in pre-ESRD patients?:*	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: No/not assessable Incl/excl described: Partially Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 4 Notes:

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Evidence Table 5 – Dyslipidemias (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
		15; controls, 114 ± 14 ($p < 0.001$) Liver function tests at entry: NR Muscle enzymes at entry: NR Co-morbidities at entry: NR	No side effects were observed during the 12 months of observation.	

Evidence Table 5 – Dyslipidemias (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Stenvinkel, Heimbürger, Paultre, et al., 1999	Design: Case series, concomitant controls Intervention(s) studied: None Dates: NR Location: Stockholm, Sweden Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 109 = 79 with carotid plaques and 30 without carotid plaques; controls were 22 healthy subjects (32% of whom had carotid plaques) Inclusion criteria: Pre-dialysis Exclusion criteria: Age > 70; hospitalized with clinical signs of infection and/or vasculitis Age (mean ± SEM): Pre-ESRD w/ plaques: 56 ± 4 Pre-ESRD w/o plaques: 40 ± 2 Controls: 50 ± 2 Sex: Pre-ESRD w/ plaques: 59% M, 41% F Pre-ESRD w/o plaques: 63% M, 37% F Controls: 59% M, 41% F Race: NR Renal function at entry (all values mean ± SEM): CrCl (pre-ESRD patients overall): 7 ± 1 ml/min SCr: Pre-ESRD patients w/ plaques, 659 ± 21 µmol/l; w/o plaques, 721 ± 32 µmol/l Lipid values at entry (pre-ESRD patients only; mean ± SEM, in mmol/l, except where otherwise specified): Cholesterol: Plaque, 5.9 ± 0.2; no plaque, 6.1 ± 0.3 Triglycerides: Plaque, 2.3 ± 0.1; no plaque, 2.5 ± 0.3 LDL: Plaque, 3.6 ± 0.2; no plaque,	*Key Question 1) Do dyslipidemias (hyperlipidemia or low lipids) cause increased risk of clinical outcomes in pre-ESRD patients?:* The following predictors were identified as statistically significant risk factors for carotid plaques in univariate logistic regression analysis: Age, malnutrition, serum albumin, smoking, and Apo(a) isoform size. In logistic multiple regression analysis, the following predictors were significant: Age, log oxLDL, and Apo(a) isoform size. *Key Question 2) Does the treatment of dyslipidemias (by diet and lifestyle modification and/or pharmacologic therapy) reduce the risk of intermediate and clinical outcomes in pre-ESRD patients?:* Not addressed *Key Question 3) Is there an association between pharmacologic lipid therapy and drug toxicity in pre-ESRD patients?:* Not addressed	Quality Scoring: 1) Global assessment: Good 2) Validity criteria: Population described: No/not assessable Incl/excl described: Partially Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 4 Notes: *(continued on next page)*

Evidence Table 5 – Dyslipidemias (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
		3.7 ± 0.2 HDL: Plaque, 1.3 ± 0.1; no plaque, 1.4 ± 0.1 Apo A1 (in g/l): Plaque, 1.42 ± 0.04; no plaque, 1.44 ± 0.09 Apo B (in g/l): Plaque, 1.22 ± 0.04; no plaque, 1.21 ± 0.08 Lp(a) (median, with range, in mg/dl): Plaque, 15 (1-147); no plaque, 13 (1-72) CRP (in mg/l): Plaque, 20 ± 3; no plaque, 10 ± 1 (p < 0.01) Liver function tests at entry: NR Muscle enzymes at entry: NR Co-morbidities at entry: Diabetes: Plaque group: 32% No-plaque group: 18% (p = not significant) Smoking: Plaque group: 54% No-plaque group: 37% (p = not significant) Malnutrition: Plaque group: 54% No-plaque group: 17% (p < 0.01)		

7. Timing the Initiation of Renal Replacement Therapy

7.1 Chapter summary

To address the issue of timing of initiation of RRT in patients with pre-ESRD, three key questions were formulated:

1. When – in terms of GFR, symptoms of uremia, or other complications – is RRT initiated among patients with pre-ESRD?
2. What factors affect the timing of initiation of RRT among patients with pre-ESRD?
3. What is the effect of early initiation of RRT (at GFR > 20 ml/min, before development of uremia symptoms) on health and resource utilization outcomes?

Key Question 1: When – in terms of GFR, symptoms of uremia, or other complications – is RRT initiated among patients with pre-ESRD?

In summary, the majority of patients at the time of RRT had an early referral to a nephrologist. Of those referred early to a nephrologist, residual kidney function was modestly better at the initiation of RRT. Nevertheless, a substantial proportion of patients referred early to a nephrologist undergo emergent RRT.

Key Question 2: What factors affect the timing of initiation of RRT among pre-ESRD patients?

In summary, available studies do not reveal a consistent pattern to explain the variation in timing of RRT, particularly in laboratory parameters. Two non-US studies highlight the importance of distance to a facility as a limiting factor; however this may not be applicable to the somewhat unique US environment. The finding that Blacks tend to receive RRT later than Whites is concerning, but has not been studied sufficiently to separate the effect of race per se from other clinical or health system factors.

Key Question 3: What is the effect of early initiation of RRT (at GFR > 20 ml/min, before development of uremia symptoms) on health and resource utilization outcomes?

Impact of timing on hospitalizations

Morbidity differences have been examined as a function of the timing of referral to a nephrologist rather than the GFR at initiation of RRT, and fail to perform adequate multivariate analyses. Some studies report no difference in hospitalizations (reported as hospital days after 3 months of RRT), whereas others observe differences with patients referred late having more hospital days and duration of hospitalization.

Economic impact of timing

Two studies attempt economic analyses comparing the cost of care for patients referred to a nephrologist early or late. These are limited analyses, focusing on hospital charges. However, both studies suggest that late referral may be associated with increased hospital costs.

Impact of timing on the use of temporary vascular access
Use of temporary vascular access is a of concern as limited evidence indicates that patients dialyzing with a catheter have higher mortality (LE: 4, QS: poor). Using a retrospective ESRD cohort of 178 patients in UK from August 1993 to April 1995, 71.3% of patients required temporary vascular access incident to RRT. Twenty-five of 127 patients with temporary access died in the first 90 days of RRT versus 1 of 51 with permanent vascular access ($p < 0.01$). Notably, the patients' demographics and co-morbid conditions are not reported, so it is difficult to assign the mortality effect to the temporary vascular access.

The impact of timing of referral on the use of a temporary catheter at the initiation of RRT has been explored in four studies. European and American cohorts showed that patients referred late are more likely to require hemodialysis with a temporary catheter rather than an internal vascular access. Conversely, the percentage of patients with an autologous fistula is lower among patients referred late to a nephrologist.

Impact of timing on modality selection for RRT
We identified three studies that examine the relationship between timing of referral and modality selection for RRT.

One large retrospective cohort analysis of Medicare beneficiaries in New Jersey found no relationship between the timing of referral and the selection of peritoneal versus hemodialysis.

Similarly, an analysis of patients in West Virginia and Pennsylvania found no relationships between late and early referral and the percentage of patients switching from hemodialysis to peritoneal dialysis after 4 months of RRT (LE: 2b, QS: fair).

For kidney transplantation, one study reported no difference (LE: 4, QS: fair), and another reported a significant difference, with late-referred patients being less likely to be transplanted in follow-up (LE: 2b, QS: good). Both cohorts are from Europe where transplantation practices may differ from the US. Moreover, neither study performed appropriate adjustments of confounders such as patients' ages, co-morbid conditions, HLA types, insurability, preferences, etc. that will substantially influence transplantation rates.

Impact of timing on kidney transplantation outcomes
In a retrospective cohort analysis of 1,849 kidney transplant recipients from a single center in Minneapolis, Minnesota from January 1984 to June 1998, patients were classified by the type of organ donor (cadaveric ($n = 775$) versus living ($n = 1,074$)). Patient and transplant survival were compared by type of organ donor and by whether or not patients underwent hemodialysis prior to kidney transplantation (LE: 2b, QS: fair). The 5-year post-transplant patient survival was better for patients not dialyzed than those dialyzed regardless of the type of organ donor (92.6% versus 76.6%, respectively, for cadaver donor kidneys; $p = 0.001$ and 93.3% versus 89.5%, respectively, for living donor kidneys; $p = 0.02$). The graft survival rate was at 5 years was no different for

cadaveric kidneys, but for living donor kidneys was greater without dialysis (92.3% versus 84.8%; p = 0.006).

These findings were extended by a retrospective cohort analysis of 8,481 cadaveric kidney transplant recipients from the entire US using a national Medicare kidney transplant registry (LE: 2b, QS: good). Living related kidney transplant donors were excluded from this analysis. In comparison to the 6,662 kidney transplant recipients who underwent dialysis of varying duration before kidney transplants (329 $\pm$ 638 days of dialysis), the 1,819 patients had a 1-year allograft failure (defined as death, repeated kidney transplant, or resumption of dialysis) rate ratio of 0.48 (p = 0.002) and a 2-year failure rate ratio of 0.18 (p = 0.001). The duration of dialysis was positively associated with the occurrence of acute rejection by kidney biopsy (p = 0.001 for the trend).

Overall conclusions:

Studies related to timing of RRT are far from ideal and many caveats apply when considering their implications for clinical practice. Descriptive studies generally failed to identify a representative inception cohort, instead selecting patients from a single or small group of sites at the point of initiation of RRT. They also failed to characterize the reason for initiating RRT, and do not make adequate use multivariate techniques in sorting out the determinants of early versus late timing of RRT. Similarly, studies of the relationship of timing of RRT and outcomes are not based on representative inception cohorts; instead study cohorts are identified at the time of RRT. Although the clinically crucial question relates to timing relative to GFR or some other objective patient characteristic, most of the studies in this area focus on the timing of referral to the nephrologist as the independent variable. As with the question of determinants of timing of RRT, studies of the relationship between timing and outcome infrequently use multivariate statistical tools to adjust for confounders, or fail to include crucial factors in the adjustment.

Although limited, the available literature provides some suggestive findings. First, with regard to current practices, most patients who ultimately have RRT are referred early to a nephrologist and early referral is associated with less severe symptoms at initiation of RRT and less likelihood of requiring emergent dialysis. Nevertheless, many patients initiate RRT with advanced symptoms and signs, regardless of the timing of their first visit with the nephrologist or their future dialysis care center. Despite their better preparation for RRT, one of four patients with early referral required emergent dialysis. While there are statistically significant differences in residual kidney function at initiation of RRT between patients referred to a nephrologist late and early, the magnitude of the differences is very modest. Second, few factors tend to be predictive of timing of RRT, although the finding that Blacks initiate RRT later than Whites is consistent. Third, there is no evidence that earlier initiation of RRT will lead to decreased mortality or morbidity. Although two studies suggest that survival is better when RRT is initiated at higher residual kidney function, one found the opposite result and most studies exploring the impact of timing of referral on survival found no effect on mortality.

Because of significant methodological problems, the available data must be interpreted with care before making clinical and clinical policy decisions. First, with regard to referral to a nephrologist, later referral to a nephrologist is associated with later initiation of RRT as well as with major patient problems. However, it is not clear to what extent the problems could be alleviated by earlier referral to a nephrologist. It is likely that the primary reason that patients referred late have worse outcomes relates to factors preclude early referral such as aggressive kidney failure, lack of access to health care, comorbid conditions that are being poorly managed for the same reasons that nephrology services are delayed, and so on.

Second, with regard to earlier initiation of RRT, serum creatinine concentration does appear to be associated with subsequent survival with RRT, supporting the hypothesis that early RRT is better. However, a variety of factors could confound this simple association and late RRT may be a marker for other factors that impact survival. It is difficult to underestimate the importance of confounders, especially comorbid conditions. Several studies lend strong support to the importance of comorbidity both in survival and in timing of RRT.

Third, the same lack of control for confounders limits the interpretation of studies exploring the impact of timing and/or referral on hospitalizations, modality selection for RRT, or outcomes of kidney transplantation. Some data suggest that patients undergoing kidney transplants may enjoy improved survival and perhaps graft survival if transplantation is not preceded by dialysis. However, much of this effect may be explained by other patient or health service factors. The question may not be easily resolved with a cohort study as patients who undergo transplantation without prior dialysis are fundamentally different from patients who have dialysis first. Because this decision does not even closely approximate a “natural experiment,” a cohort study, even one that applies multivariate adjustment, is unlikely to resolve the issue of whether earlier dialysis induces a risk for later transplantation.

Prospective trials with random allocation to early versus late initiation of RRT would be the ideal approach to resolving the question of optimal timing of RRT. An alternate research approach is large cohort studies that meticulously identify a population of pre-ESRD patients at an early and uniform point in this phase of disease, and follows them forward to RRT. To the extent that the RRT timing decision is a “natural experiment,” i.e., not hopelessly confounded by clinical characteristics, it is possible to gain useful insight into the question of optimal timing of RRT.

7.2 Background

Conventional criteria for the initiation of renal replacement therapy (RRT) are uremia, congestive heart failure, acidosis, hyperkalemia, serositis, neuropathy, and severe azotemia. These criteria can lead to patients being treated only when they are seriously ill and after they have already suffered irreversible cumulative complications from chronic kidney disease (CKD). It has been suggested that initiating dialysis when the

patient has greater residual kidney function (RKF) will result in better outcomes during ESRD.

The proposal that earlier dialysis is better than later dialysis is supported by urea kinetic models.[1] These models are based on evidence from patients with ESRD, reviewed in detail by the K/DOQI Clinical Practice Guidelines on Hemodialysis Adequacy. This evidence lead to the recommendation that patients on hemodialysis receive a minimum dose of Kt/V_{urea} 2.0 (single pool, variable volume model) per treatment three times per week (assuming RKF GFR < 5 mL/min/1.73 m^2).[2] Accepting that patients with advanced CKD should have the same requirement for solute clearance as patients with ESRD, one can calculate the level of RKF that should serve as a target for dialysis. Urea kinetic constructs assume the minimum total weekly Kt/V_{urea} (i.e., Kr [residual renal clearance] + Kp [exogenous clearance]) for patients with advanced CKD should be ≥ 2.0. A weekly Kt/V_r urea of 2.0 would be equivalent to renal urea clearance of 7 mL/min [normalized to V] or renal creatinine clearance of 9-14 mL/min/1.73 m^2 = GFR 10.5 mL/min). A mathematical model indicates that increasing exogenous clearance as residual clearance declines can provide at least this minimum benchmark for total clearance.[3]

Despite the strong logical chain extrapolated from ESRD evidence, this approach has not been validated in actual patients and the underlying assumptions may be highly dependent on the patients' comorbid conditions, anthropometric attributes, or other factors. In this regard, it has been suggested that CKD patients with specific characteristics may benefit from earlier RRT. For example, it has been argued that the elderly and diabetics may benefit from dialysis if provided before the onset of uremic symptoms. Patients intending to receive peritoneal dialysis (PD) as their mode of RRT may benefit from earlier RRT, when residual kidney function is greater. Also, patients undergoing living donor kidney transplantation may benefit from early dialysis and so avoid the complications of dialysis. On the other hand, patients undergoing cadaveric donor kidney transplantation may benefit from avoiding dialysis and its putative immunologic enhancement.

These arguments led the Working Group to formulate three key questions on the timing of initiation of RRT in patients with ESRD. The aim of this chapter is to review the available literature to answer these questions.

7.3 Methods

To address the issue of timing of initiation of RRT in patients with pre-ESRD, three key questions were formulated:

1. When – in terms of GFR, symptoms of uremia, or other complications – is RRT initiated among patients with pre-ESRD?
2. What factors affect the timing of initiation of RRT among patients with pre-ESRD?
3. What is the effect of early initiation of RRT (at GFR > 20 ml/min, before development of uremia symptoms) on health and resource utilization outcomes?

To identify the literature addressing the three questions related to the timing of initiation of RRT, the following search terms were used: "time factors," "survival rate," "timing," "initiation," "referral and consultation," "physicians' practice patterns." Additional references were identified from the bibliographies of included articles, as well as publications suggested by members of the Working Group and by reviewers who examined an initial draft of this report.

Health outcomes of interest were congestive heart failure/pulmonary edema, functional/activity status, quality of life, cognition, death, blood pressure control, and complications.

7.4 Results

One hundred and eighty-two titles and abstracts were screened. Of these, 59 were identified for full-text screening. We were unable to obtain copies of six of these articles.[4-8] Of the remaining 53, 30 were excluded during full-text review for the following reasons: did not meet the criteria for the pre-ESRD population (n=3), small case series/single case report (n = 1), or did not address at least one of the key questions (n = 26). In all, a total of 23 articles were abstracted using a standardized form and are summarized in Evidence Table 6.

Key Question 1: When – in terms of GFR, symptoms of uremia, or other complications – is RRT initiated among patients with pre-ESRD?

The goal here was to describe the patterns of timing of RRT in terms of kidney function, or clinical signs and symptoms to better understand what triggers RRT in the current environment.

An ideal study of the current practices related to initiation of RRT would identify a representative cohort of patients at a uniform point in their progression (an inception cohort selected, say, at the point GFR drops below 30 ml/min/1.73 m^2), follow their natural history to the point of RRT, and identify the reason for initiating dialysis. However, most of the studies we identified select patients at the point of RRT and the reason for dialysis is often not described. Thus, these studies generally address our first question only indirectly.

In an early and small retrospective cohort study of 40 adult patients with ESRD receiving care in Paris, France, from January 1988 to December 1990, patients were stratified into early versus late referral to a nephrologist (early = regularly followed for chronic kidney disease for > 6 months, versus late = followed for CKD for $\leq$ 1 month) (LE: 4, QS: good).[9] Twenty patients were in the early-referral group and 20 in the late-referral group. Clinical parameters differed between the two groups, but it is unclear if these are incident to time of first evaluation by a nephrologist or incident to receiving RRT; pulmonary edema was more common for the late-referral group (late 13 of 20 vs. early 3 of 20; $p < 0.01$) and the systolic blood pressure (BP) was higher in the late-referral group (late 180 $\pm$ 14 vs. early 153 vs. 15 mmHg; $p < 0.001$). At initiation of hemodialysis, the creatinine was higher in the late-referral group, likely a reflection of their lower creatinine clearance (1120 $\pm$ 270 vs. 970 $\pm$ 110 μmol/L and 5.85 $\pm$ 1.87 vs.

6.47 ± 1.67 mL/min, respectively; $p < 0.01$). Late-referral patients initiated hemodialysis for dyspnea with peripheral edema and pedal edema (n = 12) or severe asthenia and wasting (n= 4), whereas the early-referral patients initiated hemodialysis when their creatinine clearance was < 7 mL/min or for asthenia or nausea (n for this group is not provided; no tests for significance were performed). Serum albumin and bicarbonate concentrations were also lower at the time of RRT for the late-referral group (35.3 ± 4.8 vs. 39.7 ±3.4 g/L and 14.2 ± 3.9 vs. 22.5 ±4.2, respectively).

In a more recent and larger retrospective cohort study of 2,236 adult patients with ESRD receiving care in several European countries from 1993 to 1995, a substudy of patients receiving care from January 1996 to December 1997 reported symptoms and signs at the initiation of RRT (hemodialysis and peritoneal dialysis) (LE :4 , QS: fair).[10] The data were captured by survey of the caregivers and were not subject to validation. The number of subjects captured is not reported. Patients were classified based on the timing of the referral to a nephrology unit. A patient was considered as late referral if he was admitted for dialysis in an emergency situation (271 of 781 patients) and was considered early referral if he was known to the dialysis center for at least 1 month prior to RRT (510 of 781 patients). At the initiation of RRT, 71% of all the patients had uremic symptoms and 21% had pulmonary edema. These symptoms were significantly more common for the late-referral patients ($p < 0.003$). In a substudy of Flemish patients, no differences were noted in the hematocrit, serum bicarbonate, and albumin concentrations, or in intact PTH levels between early and late patients (29.7%, 19.9 mEq/L, 3.8 gm/dL, and 285.1 pg/mL, respectively, for the total of 331 Flemish patients) at the time of the initiation of RRT.

Another European report from a single center in Marseille, France, from January 1989 to December 1996 included 270 adult ESRD patients (LE: 2b , QS: good).[11] Using a retrospective analysis, patients were characterized as an early referral if seen by a nephrologist > 4 months before the initiation of RRT; if it was ≤ 4 months, the patient was characterized as a late referral. Most patients were early referrals (n = 177 versus 93). For symptoms and signs, patients with late referral were more likely to have pulmonary edema (29% versus 11.5%), severe hypertension (8.6% versus 0.06%), and require emergent dialysis (57% versus 23%). The serum creatinine clearance was lower in the late referral group (7.01 ± 3 versus 8.02 ± 2.69 mL/min; $p < 0.01$).

In a longitudinal cohort study from Brazil of 184 adult patients with ESRD, the patients were categorized into those having early and late referral (seen > 3 months and < 1 months prior to RRT, respectively) (LE: 2b, QS: good).[12] Patients with a late referral (n = 106) were more likely to start dialysis with higher serum creatinine concentrations and lower creatinine clearance than the early referrals (n = 78) (14.1 ± 0.7 versus 10.7 ± 0.7 mg/dL and 4.4. ± 0.5 and 6.4 ± 0.5 mL/min; $p < 0.01$). The serum albumin and bicarbonate concentrations were not different. The serum potassium concentration was higher for the late referral patients (5.5 ± 0.1 vs. 4.9 ± 0.7 mEq/L; $p < 0.01$).

Similar findings of worse clinical characteristics at the initiation of hemodialysis for a patient group segregated into those engaged with a nephrologist versus those not

engaged with a nephrologist were also reported from the US. First, in a retrospective cohort study of adult patients with ESRD receiving care in four dialysis centers in West Virginia and Pennsylvania between January 1990 and November 1997, the patients were stratified into early and late referral to a nephrologist (early defined as having seen a nephrologist > 1 month prior to RRT and late as ≤ 1 month prior to RRT) (LE: 2b, QS: fair).[13] Of the 180 early cases and 58 late cases, patients referred late were more like to require emergent hemodialysis (90% versus 22%, respectively; $p < 0.0001$). No non-random difference was noted in the need to initiate RRT for uremia/hyperkalemia and/or pulmonary edema between the early- and late-referred patients (36% versus 50% and 64% versus 50%, respectively).

In a retrospective cohort analysis from October 1992 to December 1997 describing a single center experience from Boston, Massachusetts, 135 adult patients with ESRD were categorized by the timing of referral to a nephrologist (LE: 2b, QS: good).[14] If the patient was seen by a nephrologist > 4 months prior to the initiation of RRT, the patient was characterized as an early referral (n = 105). If it was ≤ 4 months, the patient was characterized as a late referral (n = 30). Patients referred late were more likely to initiate RRT (hemodialysis and peritoneal dialysis) with a GFR < 5 ml/min per 1.73 m^2 (43% versus 17%) and with higher creatinine concentrations (9.6 ± 5.7 versus 7.6 ± 3.6 mg/dL, respectively; $p < 0.02$). The serum albumin concentration was lower among the late-referral patients at the initiation of dialysis (2.9 ± 0.7 versus 3.3 ± 0.63g/dL, respectively; $p < 0.01$). The creatinine clearance, BUN, potassium, and bicarbonate concentrations, and hematocrit were no different between subgroups.

In summary, the majority of patients at the time of RRT had an early referral to a nephrologist. Of those referred early to a nephrologist, residual kidney function was modestly better at the initiation of RRT. Nevertheless, a substantial proportion of patients referred early to a nephrologist undergo emergent RRT.

Key Question 2: What factors affect the timing of initiation of RRT among pre-ESRD patients?

An ideal study of factors that affect the timing of initiation of RRT would, as noted for the question of current practice patterns, identify an inception cohort followed prospectively to the point of RRT. Moreover, the resulting data would be analyzed with multivariate techniques in an effort to discern the independent contribution of various factors on kidney function at initiation of RRT. The few studies that examine which factors may affect timing of RRT do not approach this ideal.

In the large retrospective cohort study of 2,236 adult patients with ESRD receiving care in several European countries from 1993 to 1995, the timing of RRT between the late- and early-referral groups was not affected by the diagnosis of diabetes mellitus or the patients' hematocrit, PTH level, or serum bicarbonate and albumin concentrations (LE: 4, QS: fair).[10]

These findings are consistent with the results from the single center experience in New York, New York, from January 1990 to December 1995 (LE: 2b, QS: good).[15] After

adjustments for patients' ages and presence of diabetes mellitus, there was no correlation between the indication for initiation of RRT and the patients' BUN, creatinine, or serum albumin concentration.

One study examined the factors influencing the decision to initiate dialysis based on hypothetical cases. In a survey of physicians in southwest UK and the Channel Islands (n = 203 [18 were nephrologists]) in which vignettes were presented, referral for dialysis was influenced by the patient's and family's wishes, patient's age and comorbid conditions, nephrologist availability, and whether the respondent was a specialist or subspecialist (LE: 5, QS: fair).[16] No similar study was identified in a group of US physicians for whom attitudes and practice patterns are likely to be different.

A retrospective cohort study examined the difference between rates of referrals for RRT and distance from the dialysis center in Wales from April 1985 to March 1994 for 539 patients age 16 or older (LE: 2b, QS: fair).[17] The authors observed that in a multivariate model, for patients $\leq$ 29 years old and > 60 years old, the distance from the dialysis unit inversely affected the likelihood of RRT. The cohort is poorly described, so external validity is further limited. In addition, this study might be of limited applicability to dialysis practices in the US because of substantial differences in reimbursement and physician and patient behaviors.

A single retrospective cohort study of 5,388 incident adult ESRD patients in Maryland and Virginia examined factors associated with level of serum creatinine at the onset of RRT (LE: 2b, QS: fair).[18] Patients who were younger, Black, male, or with fewer co-morbid conditions were more likely to have higher serum creatinine values at initiation of RRT ($p < 0.001$).

The impact of co-morbid conditions on decision-making is given support by a longitudinal cohort study of 304 CKD patients from the Grampian region of UK from January 1989 to June 1992 (LE: 4, QS: poor).[19] CKD patients were stratified by age and co-morbid conditions; the greater the patient's age and co-morbidity, the less likely they were to be referred to a nephrologist.

Because the ESRD Program is disproportionately composed of Black beneficiaries, an examination of racial differences in the initiation of RRT is warranted. In a retrospective cohort study of 220 adult patients with CKD treated in the New York, New York, from January 1987 to December 1994 and stratified by race, Blacks had a higher serum creatinine concentration at the initiation of RRT (hemodialysis) than Whites (12 ± 0.4 mg/dL versus 8.8 ± 0.47 mg/dL, respectively; $p = 0.001$) (LE: 2b, QS: good).[20] Because Blacks had fewer months under the care of a nephrologist than Whites (13 ± 0.8 versus 43.5 ± 4.8; $p = 0.001$), they may be viewed as relatively late referrals. The creatinine clearance (23.4 versus 32.4 ml/min; SD and p-value not reported) for the Black patients was lower than for Whites. As Black and White patients had similar frequency of clinic visits, weight at baseline and albumin concentrations, these characteristics do not explain differences in timing of RRT.

The same authors report additional information evidently from the same population in a second publication (LE: 2b, QS: good).[21] Although the observation period, the treatment center, the size of the population and most of the demographic information were the same in both papers, it is difficult to conclude definitely that these papers describe the same population, as there are discrepancies in mean ages and mean serum creatinine values between the two papers. The second paper offers the added observations that Blacks have lower hematocrit values incident to ESRD than Whites (24% vs. 28%), but the serum albumin and bicarbonate concentrations were the same (3.6 versus 3.7 gm/dL and 24 versus 28 mEq/L, respectively; p-values not reported). More Blacks were diabetic, and diabetics have been reported to have lower serum creatinine concentrations than non-diabetics. The finding of higher serum creatinine values among American Blacks at the time of RRT has also been reported in US Renal Data System data set.[22,23]

Some insight into the variability of criteria for initiating RRT based on laboratory parameters alone is offered by a longitudinal cohort study of 139 adult patients with CKD treated by a single center in New York, New York, from January 1990 to December 1995 (LE: 2b, QS: good).[15] Twenty-eight percent of the predominantly Black patient cohort initiated maintenance hemodialysis for nausea and vomiting; 25% for weakness; 19% for CHF; 6.5% for symptoms and signs like angina, pericarditis, seizures, and hyperkalemia; and 21% with no symptoms. After adjustments for patients' ages and presence of diabetes mellitus, there was no correlation between the indication for initiation of RRT and the patients BUN, creatinine, or serum albumin concentration. It is noteworthy that the cohort was > 90% Black, and, as discussed above, Blacks receive RRT seemingly later than Whites.[20,21]

In summary, available studies do not reveal a consistent pattern to explain the variation in timing of RRT, particularly in laboratory parameters. Two non-US studies highlight the importance of distance to a facility as a limiting factor; however this may not be applicable to the somewhat unique US environment. The finding that Blacks tend to receive RRT later than Whites is concerning, but has not been studied sufficiently to separate the effect of race per se from other clinical or health system factors.

Key Question 3: What is the effect of early initiation of RRT (at GFR > 20 ml/min, before development of uremia symptoms) on health and resource utilization outcomes?

Impact of creatinine clearance/timing on mortality

Three studies have explored the impact of creatinine clearance values at the initiation of dialysis on mortality.[18,24,25]

A post hoc analysis of the CANUSA longitudinal observational trial of 680 ESRD patients treated by peritoneal dialysis (PD) in the US and Canada stratified patients into those with a weekly GFR of $\geq$ 39 L/wk and < 39 L/wk of RRF.[24] Based on an average of the creatinine and urea clearances, the corresponding mean GFR values were 6.2 mL/min and 2 mL/min. The 24-month unadjusted patient survival for the two patient groups was 82.1% and 73.6%, respectively ($P < 0.015$). The applicability of this finding

is uncertain because the patients' characteristics are not well described, and no adjustment is made for important factors such as co-morbid conditions and dose of PD.

A single retrospective cohort study of 5,388 incident adult ESRD patients in Maryland and Virginia examined the relationship between serum creatinine and ESRD patient survival (LE: 2b, QS: fair).[18] Patients were divided into quintiles based on their serum creatinine concentration at initiation of RRT. In a multivariate model, every one mg/dL increase in the serum creatinine concentration was associated with a 4% decrease in death risk ($p = 0.01$). This finding is probably related to differences in comorbid conditions. Lower SCr at incident ESRD was associated with older age, greater prevalence of diabetes and greater prevalence of hypertension. These comorbidities may explain the unexpected direction of the association between SCr and mortality.

Several other studies have examined the effect of the timing of referral on patient mortality.

A study of patients in Bolgna, Italy examined the association between creatinine clearance at initiation of dialysis and mortality for 76 patients seen from December 1965 to June 1974 (LE: 2b, QS: poor).[25] Patients were classified into four groups by creatinine clearance: 0-5 mL/min, 5-15 mL/min, and 15-21 mL/min. While mortality appeared higher for those in the lowest category of creatinine clearance (3-4 year survival 41% for patients with creatinine clearance of 0-5 mL/min versus 83-86% for the others), data were not analyzed using appropriate survival techniques, and no effort was made to adjust for other factors.

Relying on a retrospective cohort analysis of 198 adults with ESRD in UK, a late referral was defined as initiating hemodialysis < 12 weeks after being first seen (n = 64), and early referral as $\geq$ 12 weeks between the first nephrology visit and the start of hemodialysis (n = 134) (LE: 2b, QS: good).[26] No difference was seen in the crude 1-year survival between groups (late 60.5% versus early 72.5%; p = not significant). Co-morbid conditions are not reported, so confounding variables may be present that greatly influence the mortality rate.

Similarly, in a retrospective cohort study of adult ESRD patients receiving care in four dialysis centers in West Virginia and Pennsylvania between January 1990 and November 1997, the unadjusted 4-month mortality was 4% and 7% for the early and late referrals, respectively (p = not significant) (LE: 2b, QS: fair).[13]

In a large retrospective cohort study of 2,236 adult ESRD patients receiving care in several European countries from 1993 to 1995, the unadjusted mortality of the Flemish subgroup at 1 year after RRT was reported as 16.4% and 26.7% for the early- and late-referral patients, respectively ($p < 0.07$) (LE: 4, QS: fair).[10]

In another European report of a single center in Marseille, France, from January 1989 to December 1996 that included 270 adult ESRD patients, Kaplan Meier survival curves presented no difference in survival for the late-referral versus early-referral patient

groups (67 ± 4.9 months versus 58.7 ± 5 months; p = not significant) (LE: 2b, QS: good).[11]
In a longitudinal cohort study from Brazil of 184 adult ESRD patients categorized into those having early and late referral, crude mortality at 6 months differed between the two groups (31% versus 23% for late and early referral, respectively) (LE: 2b, QS: good).[12] However, death risk in a Cox hazards model was no different (0.93-4.54; p = not significant).

In a study of 188 adult ESRD subjects from a single center in Aberdeen, Scotland, the 2-year actuarial survival was no different depending upon whether the patients with chronic kidney disease were followed by nephrologists, by other specialists, or presented within 4 weeks of RRT (LE: 4, QS: poor).[27]

Impact of timing on hospitalizations
Similarly, morbidity differences have been examined as a function of the timing of referral to a nephrologist rather than the GFR at initiation of RRT, and fail to perform adequate multivariate analyses. Some studies report no difference in hospitalizations (reported as hospital days after 3 months of RRT),[11] whereas others observe differences with patients referred late having more hospital days[10] and duration of hospitalization.[9,26 28,29]

Economic impact of timing
Two studies attempt economic analyses comparing the cost of care for patients referred to a nephrologist early or late.[9] These are limited analyses, focusing on hospital charges. However, both studies suggest that late referral may be associated with increased hospital costs. [13]

Impact of timing on the use of temporary vascular access
Use of temporary vascular access is a of concern as limited evidence indicates that patients dialyzing with a catheter have higher mortality (LE: 4, QS: poor).[30] Using a retrospective ESRD cohort of 178 patients in UK from August 1993 to April 1995, 71.3% of patients required temporary vascular access incident to RRT. Twenty-five of 127 patients with temporary access died in the first 90 days of RRT versus 1 of 51 with permanent vascular access ($p < 0.01$). Notably, the patients' demographics and co-morbid conditions are not reported, so it is difficult to assign the mortality effect to the temporary vascular access.

The impact of timing of referral on the use of a temporary catheter at the initiation of RRT has been explored in four studies. European[9,11,30] and American cohorts[14,14] showed that patients referred late are more likely to require hemodialysis with a temporary catheter rather than an internal vascular access. Conversely, the percentage of patients with an autologous fistula is lower among patients referred late to a nephrologist.[10,11]

Impact of timing on modality selection for RRT
We identified three studies that examine the relationship between timing of referral and modality selection for RRT.

One large retrospective cohort analysis of Medicare beneficiaries in New Jersey found no relationship between the timing of referral and the selection of peritoneal versus hemodialysis.[31]

Similarly, an analysis of patients in West Virginia and Pennsylvania found no relationships between late and early referral and the percentage of patients switching from hemodialysis to peritoneal dialysis after 4 months of RRT (LE: 2b, QS: fair).[13]

For kidney transplantation, one study reported no difference (LE: 4, QS: fair),[10] and another reported a significant difference, with late-referred patients being less likely to be transplanted in follow-up (LE: 2b, QS: good).[11] Both cohorts are from Europe where transplantation practices may differ from the US. Moreover, neither study performed appropriate adjustments of confounders such as patients' ages, co-morbid conditions, HLA types, insurability, preferences, etc. that will substantially influence transplantation rates.

Impact of timing on kidney transplantation outcomes
In a retrospective cohort analysis of 1,849 kidney transplant recipients from a single center in Minneapolis, Minnesota from January 1984 to June 1998, patients were classified by the type of organ donor (cadaveric (n = 775) versus living (n = 1,074)). Patient and transplant survival were compared by type of organ donor and by whether or not patients underwent hemodialysis prior to kidney transplantation (LE: 2b, QS: fair).[32] The 5-year post-transplant patient survival was better for patients not dialyzed than those dialyzed regardless of the type of organ donor (92.6% versus 76.6%, respectively, for cadaver donor kidneys; p = 0.001 and 93.3% versus 89.5%, respectively, for living donor kidneys; p = 0.02). The graft survival rate was at 5 years was no different for cadaveric kidneys, but for living donor kidneys was greater without dialysis (92.3% versus 84.8%; p = 0.006).

These findings were extended by a retrospective cohort analysis of 8,481 cadaveric kidney transplant recipients from the entire US using a national Medicare kidney transplant registry (LE: 2b, QS: good).[33] Living related kidney transplant donors were excluded from this analysis. In comparison to the 6,662 kidney transplant recipients who underwent dialysis of varying duration before kidney transplants (329 $\pm$ 638 days of dialysis), the 1,819 patients had a 1-year allograft failure (defined as death, repeated kidney transplant, or resumption of dialysis) rate ratio of 0.48 (p = 0.002) and a 2-year failure rate ratio of 0.18 (p = 0.001). The duration of dialysis was positively associated with the occurrence of acute rejection by kidney biopsy (p = 0.001 for the trend).

7.5 Discussion

The goal of this review was to examine the current state of practice with regard to initiation of RRT (key question 1 and 2) and to determine if the evidence supports earlier RRT for all or for a subgroup of patients with CRF (key question 3).

Studies related to timing of RRT are far from ideal and many caveats apply when considering their implications for clinical practice. Descriptive studies generally failed to identify a representative inception cohort, instead selecting patients from a single or small group of sites at the point of initiation of RRT. They also failed to characterize the reason for initiating RRT, and do not make adequate use multivariate techniques in sorting out the determinants of early versus late timing of RRT. Similarly, studies of the relationship of timing of RRT and outcomes are not based on representative inception cohorts; instead study cohorts are identified at the time of RRT. Although the clinically crucial question relates to timing relative to GFR or some other objective patient characteristic, most of the studies in this area focus on the timing of referral to the nephrologist as the independent variable. As with the question of determinants of timing of RRT, studies of the relationship between timing and outcome infrequently use multivariate statistical tools to adjust for confounders, or fail to include crucial factors in the adjustment.

Although limited, the available literature provides some suggestive findings. First, with regard to current practices, most patients who ultimately have RRT are referred early to a nephrologist and early referral is associated with less severe symptoms at initiation of RRT and less likelihood of requiring emergent dialysis. [10,11,13] Nevertheless, many patients initiate RRT with advanced symptoms and signs, regardless of the timing of their first visit with the nephrologist or their future dialysis care center. Despite their better preparation for RRT, one of four patients with early referral required emergent dialysis. [13] While there are statistically significant differences in residual kidney function at initiation of RRT between patients referred to a nephrologist late and early,[11,12] the magnitude of the differences is very modest. Second, few factors tend to be predictive of timing of RRT, although the finding that Blacks initiate RRT later than Whites is consistent. Third, there is no evidence that earlier initiation of RRT will lead to decreased mortality or morbidity. Although two studies suggest that survival is better when RRT is initiated at higher residual kidney function,[18] one found the opposite result and most studies exploring the impact of timing of referral on survival found no effect on mortality. [10-13,27]

Because of significant methodological problems, the available data must be interpreted with care before making clinical and clinical policy decisions. First, with regard to referral to a nephrologist, later referral to a nephrologist is associated with later initiation of RRT as well as with major patient problems. However, it is not clear to what extent the problems could be alleviated by earlier referral to a nephrologist. It is likely that the primary reason that patients referred late have worse outcomes relates to factors preclude early referral such as aggressive kidney failure, lack of access to health care, comorbid conditions that are being poorly managed for the same reasons that nephrology services are delayed, and so on.

Second, with regard to earlier initiation of RRT, serum creatinine concentration does appear to be associated with subsequent survival with RRT, supporting the hypothesis that early RRT is better. However, a variety of factors could confound this simple association and late RRT may be a marker for other factors that impact survival. It is difficult to underestimate the importance of confounders, especially comorbid conditions. Several studies lend strong support to the importance of comorbidity both in survival and in timing of RRT.

Third, the same lack of control for confounders limits the interpretation of studies exploring the impact of timing and/or referral on hospitalizations, modality selection for RRT, or outcomes of kidney transplantation. Some data suggest that patients undergoing kidney transplants may enjoy improved survival and perhaps graft survival if transplantation is not preceded by dialysis. However, much of this effect may be explained by other patient or health service factors. The question may not be easily resolved with a cohort study as patients who undergo transplantation without prior dialysis are fundamentally different from patients who have dialysis first. Because this decision does not even closely approximate a “natural experiment,” a cohort study, even one that applies multivariate adjustment, is unlikely to resolve the issue of whether earlier dialysis induces a risk for later transplantation.

Prospective trials with random allocation to early versus late initiation of RRT would be the ideal approach to resolving the question of optimal timing of RRT. An alternate research approach is large cohort studies that meticulously identify a population of pre-ESRD patients at an early and uniform point in this phase of disease, and follows them forward to RRT. To the extent that the RRT timing decision is a “natural experiment,” i.e., not hopelessly confounded by clinical characteristics, it is possible to gain useful insight into the question of optimal timing of RRT.

7.6 References

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Evidence Table 6 – Timing the initiation of renal replacement therapy (RRT)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Arora, Obrador, Ruthazer, et al., 1999 **and** **Arora, Kausz, Obrador, et al., 2000**	Design: Cohort study Intervention(s) studied: 1) Early referral to a nephrologist (> 4 months before initiation of dialysis) (n = 105); 2) Late referral to a nephrologist (≤ 4 months before initiation of dialysis) (n = 30). Dates: Patients analyzed began dialysis between Oct 1992 and Dec 1997 Location: Boston, MA Recruitment setting: Hospital; dialysis center; outpatient nephrology clinic	No. of pre-ESRD subjects: 155 incident patients, of whom 153 had information regarding timing of referral; 18 patients with late referral due to irreversible acute renal failure excluded; 135 patients included in final analysis Inclusion criteria: Incident patients age > 18 years who began dialysis between October 1, 1992, and December 31, 1997 Exclusion criteria: Late referral due to irreversible acute renal failure Age at entry (mean ± SD): Early, 61 ± 15; late, 55 ± 17 (p = 0.08) Sex: Early, 47% M, 53% F; late, 54% M, 46% F Race: Early, 54% White; late, 53% White Renal function *at start of dialysis:* Estimated GFR (mean ± SD, in ml/min per 1.73 m^2): Early: 8 ± 4 Late: 7 ± 4 p = 0.33 % with estimated GFR < 5 ml/min per 1.73 m^2: Early: 17% (18/102) Late: 43% (13/30) p = 0.01 SCr (mean ± SD, in mg/dl): Early: 7.6 ± 3.6 Late: 9.6 ± 5.7 p = 0.02	*Key Question 1) When – in terms of GFR, symptoms of uremia, or other complications – is RRT initiated among patients with pre-ESRD?:* Serum albumin higher in early-referral patients (3.3 ± 0.63 g/dl) than in late-referral patients (2.9 ± 0.7 g/dl) at time of initiation of dialysis (p = 0.01). *Key Question 2) What factors affect the timing of initiation of RRT among pre-ESRD patients*?: a) Late-referral patients more likely to initiate dialysis late (i.e., with GFR < 5 ml/min/1.73 m^2) (OR, 4.1; 95% CI, 1.4 to 11.5; multivariate model adjusted for age, sex, race, and cause of ESRD). b) HMO patients significantly more likely to be referred late than Medicare patients (OR, 4.5; 95% CI, 1.3 to 14.6). *Key Question 3) What is the effect of early initiation of RRT (at GFR > 20 ml/min, before development of uremia symptoms) on health and resource utilization outcomes?:* a) Permanent angioaccess for first dialysis significantly more likely in early-referral (48%) than late-referral (4%) patients (p = 0.001). b) EPO used more often in early-referral (40%) than in late-referral (17%) patients (p = 0.016), but no significant difference in Hct at time of initiation of dialysis (29% vs. 27%, respectively; p = 0.13). c) Early referrals had fewer hospital days per patient year at risk during the first 3 months of RRT than did late referrals (24.4 vs. 42.4; p = 0.06). Multivariate analysis showed that the relative risk (RR) of hospital utilization during the first 3 months of dialysis was significantly higher among late referrals (RR, 2.0; 95% CI, 1.2 to 3.4). d) Early referrals had fewer outpatient visits per patient year at risk during the first 3 months of RRT than did *(continued on next page)*	Quality Scoring: 1) Global assessment: Good 2) Validity criteria: Population described: Partially Incl/excl described: Partially Dropouts discussed: Completely Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: < 50% 5) Level of evidence: 2b Notes:

Evidence Table 6 – Timing the initiation of RRT (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
		Blood pressure at entry: NR Co-morbidities at entry: Diabetes as etiology of chronic kidney disease: Early: 36% Late: 40% p = 0.70 Other: Individual disease severity (IDS) index at entry: Early: IDS score 0-1: 8% IDS score 2: 55% IDS score 3: 37% Late: IDS score 0-1: 10% IDS score 2: 56% IDS score 3: 33% p = 0.80	late referrals (21.1 vs. 18.2; no p-value reported). Multivariate analysis showed that the adjusted relative risk (RR) of outpatient utilization during the first 3 months of dialysis was significantly higher among late referrals than among early referrals (RR, 1.4; 95% CI, 1.1 to 2.0).	

Evidence Table 6 – Timing the initiation of RRT (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Bonomini, Albertazzi, Vangelista, et al., 1976	Design: Cohort study (prospective?) Intervention(s) studied: Patients grouped (and assigned treatment ?) according to their residual CrCl at time of initiation of dialysis as follows: 1) CrCl 0-5 ml/min, 2-3 dialysis sessions per week for 1-6 years (n = 22); 2) CrCl 0-5 ml/min, daily dialysis sessions for 1-4 years (n = 9); 3) CrCl 5-15 ml/min, 3 dialysis sessions per week for 1-5 years (n = 38); 4) CrCl 15-21 ml/min, 3 dialysis sessions per week for 1-4 years (n = 7); 5) CrCl 15-21 ml/min, no dialysis (?), low-protein diet (0.3-0.6 g protein/kg/day, 2000-2500 calories/day) for 1-4 years) (n = 27). Dates: Patients began RRT from Dec 1965 to June 1974 Location: Bologna, Italy Recruitment setting: Nephrology clinic/department	No. of pre-ESRD subjects: 103 Inclusion criteria: Age > 18; chronic uremia; on RRT for 1-7 years Exclusion criteria: None specified Age: NR Sex: NR Race: NR Renal function at entry: NR (except to extent that patients grouped according to CrCl at time of initiation of dialysis Blood pressure at entry: NR Co-morbidities at entry: NR	*Key Question 1) When – in terms of GFR, symptoms of uremia, or other complications – is RRT initiated among patients with pre-ESRD?:* Not addressed *Key Question 2) What factors affect the timing of initiation of RRT among pre-ESRD patients?:* Not addressed *Key Question 3) What is the effect of early initiation of RRT (at GFR > 20 ml/min, before development of uremia symptoms) on health and resource utilization outcomes?:* Mortality (see Note at right): 3-4-year survival rates for the five groups of patients described at left were: Group 1: 40.9% Group 2: 83.3% Group 3: 84.2% Group 4: 85.7% Group 5: 37.0%	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: No/not assessable Incl/excl described: Partially Dropouts discussed: No/not assessable Sample size justified: Partially 3) GFR/CrCl: Not assessable 4) % pre-ESRD: 50-75% 5) Level of evidence: 2b Note: Data were not analyzed using appropriate survival techniques; no effort made to adjust for factors other than initial CrCl.

Evidence Table 6 – Timing the initiation of RRT (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Boyle, Kudlac, and Williams, 1996	Design: Cohort study Intervention(s) studied: Renal replacement therapy (dialysis or transplantation) Dates: Patients analyzed began renal replacement therapy between Apr 1985 and Mar 1994 Location: Dyfed and West Glamorgan, Wales, UK Recruitment setting: 2 "renal units"	No. of pre-ESRD subjects: 539 Inclusion criteria: Age ≥ 16; started chronic RRT between Apr 1985 and Mar 1994 Exclusion criteria: None specified Age: Range, 16-89; mean 59 in males and 60 in females Sex: 61% M, 39% F Race: 98% Caucasian Renal function at entry: NR Blood pressure at entry: NR Co-morbidities at entry: NR	*Key Question 1) When – in terms of GFR, symptoms of uremia, or other complications – is RRT initiated among patients with pre-ESRD?:* Not addressed *Key Question 2) What factors affect the timing of initiation of RRT among pre-ESRD patients?:* A Poisson regression model showed that a significant negative relationship existed between referral to a renal unit/initiation of RRT and distance from the renal unit for the following age groups: Age — Model parameter (± SE) 16-29 — -0.4098 ± 0.1676 60-74 — -0.2555 ± 0.0673 ≥ 75 — -0.6042 ± 0.1081 *Key Question 3) What is the effect of early initiation of RRT (at GFR > 20 ml/min, before development of uremia symptoms) on health and resource utilization outcomes?:* Not addressed	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: No/not assessable Incl/excl described: Partially Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Not assessable 4) % pre-ESRD: < 50%/not assessable 5) Level of evidence: 2b Notes:

Evidence Table 6 – Timing the initiation of RRT (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Chesser and Baker, 1999	Design: Cohort study Intervention(s) studied: Dialysis (hemo- or peritoneal) Dates: Patients analyzed began dialysis between Aug 1993 and Apr 1995 Location: London, UK Recruitment setting: Hospital	No. of pre-ESRD subjects: 178 Inclusion criteria: Patients beginning dialysis between Aug 1993 and Apr 1995 Exclusion criteria: Dialysis following failure of renal transplant Age (mean ± SD): 56.7 ± 14.7 Sex: NR Race: NR Renal function at entry: NR Blood pressure at entry: NR Co-morbidities at entry: NR	*Key Question 1) When – in terms of GFR, symptoms of uremia, or other complications – is RRT initiated among patients with pre-ESRD?:* Not addressed *Key Question 2) What factors affect the timing of initiation of RRT among pre-ESRD patients?:* Not addressed *Key Question 3) What is the effect of early initiation of RRT (at GFR > 20 ml/min, before development of uremia symptoms) on health and resource utilization outcomes?:* a) 29% of patients had a permanent angioaccess in place at the time of first dialysis; 71% required temporary access. Reasons for the lack of a permanent access (n = 127) were late referral (37%), late presentation to the medical profession (29%), delays within the renal service (28%), and patient indecisiveness (6%). b) 90-day mortality was significantly higher in the temporary-access group than in the permanent-access group (20% vs. 2%, p < 0.01).	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: No/not assessable Incl/excl described: No/not assessable Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Not assessable 4) % pre-ESRD: < 50%/not assessable 5) Level of evidence: 4 Notes:

Evidence Table 6 – Timing the initiation of RRT (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Ellis, Reddy, Bari, et al., 1998	Design: Cohort study Intervention(s) studied: 1) Early referral to renal unit (> 12 weeks before initiation of RRT) (n = 134); 2) Late referral to renal unit (≤ 12 weeks before initiation of RRT) (n = 64). RRT could be hemodialysis, peritoneal dialysis, hemofiltration, hemodiafiltration, or transplantation. Dates: Patients started RRT between Jan 1996 and Dec 1997 Location: London, UK Recruitment setting: Renal unit	No. of pre-ESRD subjects: 198 Inclusion criteria: ESRD; started RRT between Jan 1996 and Dec 1997 Exclusion criteria: None specified Age (mean, with range): Early, 59.6 (16-88); late, 59.6 (26-88) Sex: Early, 55% M, 45% F; late, 66% M, 34% F Race: Early: 67% White, 22% Black, 5% Asian, 5% other; late: 72% White, 18% Black, 9% Asian, 2% other Renal function: SCr *at initiation of RRT* (mean, with range): Early: 743.4 µmol/l (320-2014) Late: 931.7 µmol/l (386-2200) Blood pressure at entry: NR Co-morbidities at entry: Diabetes: 78/198 (39%) Hypertension (not defined): 159/198 (80%)	*Key Question 1) When – in terms of GFR, symptoms of uremia, or other complications – is RRT initiated among patients with pre-ESRD?:* Not addressed *Key Question 2) What factors affect the timing of initiation of RRT among pre-ESRD patients*?: Not addressed *Key Question 3) What is the effect of early initiation of RRT (at GFR > 20 ml/min, before development of uremia symptoms) on health and resource utilization outcomes?:* a) Hospitalization around the time of starting RRT (4 weeks prior to start through 12 weeks after starting) (means): Early referral: 9.7 days Late referral: 25 days p < 0.001 b) 1-year survival: Early referral: 72.5% Late referral: 60.5% p = not significant	Quality Scoring: 1) Global assessment: Good 2) Validity criteria: Population described: No/not assessable Incl/excl described: Partially Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: SCr 4) % pre-ESRD: > 75% 5) Level of evidence: 2b Note: Only one-third of diabetic patients (26/78) were on an angiotensin-converting-enzyme inhibitor (ACEI) at the time of referral.

Evidence Table 6 – Timing the initiation of RRT (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Feest, Mistry, Grimes, et al., 1990	Design: Prospective cohort study Intervention(s) studied: None (observational study) Dates: Jan 1986 - Mar 1990 Location: Devon and Blackburn, UK Recruitment setting: Hospital; renal unit	No. of pre-ESRD subjects: 210 Inclusion criteria: Advanced chronic renal failure (SCr > 500 µmol/l) diagnosed for the first time between Jan 1986 and Dec 1987 Exclusion criteria: Acute renal failure; renal failure associated with the terminal phase of longstanding myeloma or cancer of the prostate, bladder, cervix, or ovary Age (at time of diagnosis): 0-20: 1% 20-49: 15% 50-59: 12% 60-69: 21% 70-79: 27% ≥ 80: 24% Sex: NR Race: NR Renal function at entry: NR Blood pressure at entry: NR Co-morbidities at entry: NR	*Key Question 1) When – in terms of GFR, symptoms of uremia, or other complications – is RRT initiated among patients with pre-ESRD?:* Not addressed *Key Question 2) What factors affect the timing of initiation of RRT among pre-ESRD patients?:* 113/210 patients (54%) were referred to a nephrologist. The proportion of patients *not* referred to a renal unit increased with increasing age. Among eligible patients aged 60-80, 51% were not referred to a renal unit. *Key Question 3) What is the effect of early initiation of RRT (at GFR > 20 ml/min, before development of uremia symptoms) on health and resource utilization outcomes?:* Not addressed	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: No/not assessable Incl/excl described: Partially Dropouts discussed: Partially Sample size justified: No/not assessable 3) GFR/CrCl: No/not assessable 4) % pre-ESRD: < 50%/not assessable 5) Level of evidence: 4 Notes:

Evidence Table 6 – Timing the initiation of RRT (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Fink, Burdick, Kurth, et al., 1999	Design: Cohort study Intervention(s) studied: Renal replacement therapy (dialysis or transplantation) (n = 5,388) Dates: Patients began RRT between Apr 1995 and Dec 1996; followed up through Oct 1998 Location: Maryland and Virginia Recruitment setting: Not specified/unable to determine	No. of pre-ESRD subjects: 5,388; patients divided into quintiles by incident SCr levels; number in each quintile as follows: 1st (lowest) SCr quintile: 1,080 2nd quintile: 1,068 3rd quintile: 1,115 4th quintile: 1,055 5th (highest) quintile: 1,070 Inclusion criteria: Started RRT between Apr 1995 and Dec 1996; incident SCr recorded on HCFA form 2728 Exclusion criteria: None specified Age (% < 65): 1st (lowest) SCr quintile: 39% 2nd quintile: 46% 3rd quintile: 57% 4th quintile: 67% 5th (highest) quintile: 81% p < 0.001 Sex (% M): 1st (lowest) SCr quintile: 38% 2nd quintile: 46% 3rd quintile: 54% 4th quintile: 59% 5th (highest) quintile: 71% p < 0.001 Race (% White or other [vs. Black]): 1st (lowest) SCr quintile: 68% 2nd quintile: 58% 3rd quintile: 52% 4th quintile: 42% 5th (highest) quintile: 30% p < 0.001 Renal function at entry: SCr (mean ± SEM, in mg/dl): 1st (lowest) quintile: 4.6 ± 2.7	*Key Question 1) When – in terms of GFR, symptoms of uremia, or other complications – is RRT initiated among patients with pre-ESRD?:* Not addressed *Key Question 2) What factors affect the timing of initiation of RRT among pre-ESRD patients?:* Not addressed *Key Question 3) What is the effect of early initiation of RRT (at GFR > 20 ml/min, before development of uremia symptoms) on health and resource utilization outcomes?:* For each 1-mg/dl increment in incident SCr level, there was a 4% decrease in the risk of death (relative risk, 0.96; 95% CI, 0.93 to 0.99; p = 0.01).	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: Partially Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: SCr 4) % pre-ESRD: > 75% 5) Level of evidence: 2b Notes:

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Evidence Table 6 – Timing the initiation of RRT (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
		2nd quintile: 6.6 ± 1.4 3rd quintile: 8.3 ± 1.4 4th quintile: 10.1 ± 2.1 5th (highest) quintile: 16.3 ± 0.2 Blood pressure at entry: NR Co-morbidities at entry (% with none, 1, and ≥ 2): 1st (lowest) quintile: 12%, 14%, 74% 2nd quintile: 14%, 16%, 71% 3rd quintile: 15%, 24%, 62% 4th quintile: 17%, 33%, 50% 5th (highest) quintile: 24%, 35%, 41% p < 0.001 Other: Diabetes as cause of chronic kidney disease: 1st (lowest) SCr quintile: 53% 2nd quintile: 53% 3rd quintile: 40% 4th quintile: 32% 5th (highest) quintile: 20% p < 0.001		

Evidence Table 6 – Timing the initiation of RRT (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Ifudu, Dawood, Homel, et al., 1998 **and** **Ifudu, Dawood, Homel, et al., 1996**	Design: Cohort study (prospective) Intervention(s) studied: Hemodialysis Dates: Patients hospitalized to begin dialysis between Jan 1990 and Dec 1994; follow-up through Dec 1995 Location: Brooklyn, NY Recruitment setting: Hospital	No. of pre-ESRD subjects: 139 Inclusion criteria: Chronic renal failure; admitted to hospital for initiation of RRT between Jan 1990 and Dec 1994; age ≥ 19 Exclusion criteria: AIDS or HIV+; acute renal failure; hospital-acquired renal failure; prior kidney trans-plantation; previous dialysis for ESRD Age: Mean ± SD, 53.6 ± 14.6; range, 19-81 Sex: 45% M, 55% F Race: 83% Black, 11% Hispanic, 6% White Renal function at entry: SCr (mean ± SD): 12.6 ± 5.2 mg/dl Blood pressure at entry: NR Co-morbidities at entry: Diabetes as cause of CKD: 44% Hypertension (no defined) as cause of CKD: 36% "Intravascular volume overload" as indication for dialysis: 19%	*Key Question 1) When – in terms of GFR, symptoms of uremia, or other complications – is RRT initiated among patients with pre-ESRD?:* Major indications for initiation of dialysis were as follows: Nausea/vomiting: 28% Severe weakness: 25% "No major symptoms": 21% Congestive heart failure ("intravascular volume overload"): 19% Miscellaneous (angina, pericarditis, pruritus, seizure, hyperkalemia): 6.5% *Key Question 2) What factors affect the timing of initiation of RRT among pre-ESRD patients?:* Not addressed *Key Question 3) What is the effect of early initiation of RRT (at GFR > 20 ml/min, before development of uremia symptoms) on health and resource utilization outcomes?:* a) Overall mortality: 30% b) Cox regression analyses showed no significant association between mortality and any of the indicators evaluated: Indication for initiation of dialysis (p = 0.2) SCr levels (< 10 vs. ≥ 10 mg/dl; p = 0.8) Blood urea nitrogen concentration (< 100 vs. ≥ 100 mg/dl; p = 0.68) Serum albumin concentration (< 4 vs. ≥ 4 g/dl; p = 0.62). All analyses were adjusted for age and diabetes status. c) A separate analysis of the relationship between the type of medical care received during progression to ESRD (nephrologist, non-nephrologist, none) and outcomes at the time of initiation of RRT (Ifudu, Dawood, Homel, et al., 1996) showed that the mean length of hospital stay was shorter for subjects under the care of a nephrologist (12 ± 23 days; n = 59) than	Quality Scoring: 1) Global assessment: Good 2) Validity criteria: Population described: Completely Incl/excl described: Completely Dropouts discussed: Completely Sample size justified: No/not assessable 3) GFR/CrCl: SCr 4) % pre-ESRD: > 75% 5) Level of evidence: 2b Note: Population consisted of inner-city residents.

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Evidence Table 6 – Timing the initiation of RRT (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			for subjects who received non-nephrologist care (25 ± 21 days; n = 63) or those who received no prior medical care (29 ± 23 days; n = 17) (p = 0.002).	

Evidence Table 6 – Timing the initiation of RRT (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Iofel, Dawood, Valcourt, et al., 1998 **and** **Ifudu, Dawood, Iofel, et al., 1999**	Design: Cohort study (retrospective) Intervention(s) studied: Referral to a nephrologist (n = 220) Dates: Patients referred between Jan 1987 and Dec 1994 Location: Brooklyn, NY Recruitment setting: Hospital nephrology division	No. of pre-ESRD subjects: 220, of whom 61 (28%) were White, 155 (70%) non-White (Black or Hispanic), and 4 (2%) Asian Inclusion criteria: Chronic renal failure; referred to nephrology division between Jan 1987 and Dec 1994; subsequently received hemodialysis Exclusion criteria: AIDS or HIV+; receiving EPO; no health insurance; acute renal failure; hospital-acquired renal failure; prior kidney transplantation; GI bleeding; hemoglobinopathy; previous dialysis for ESRD Age (mean ± SEM): Whites: 51 ± 2.4 Non-Whites: 52 ± 1.1 p = 0.67 Sex: Whites: 43% M, 57% F Non-Whites: 54% M, 46% F Race: 63% Black, 28% White, 7% Hispanic, 2% Asian Renal function *at referral:* SCr (mean ± SEM): Whites: 3.0 ± 0.24 mg/dl Non-Whites: 4.3 ± 0.38 mg/dl p = 0.001 Estimated CrCl (mean): Whites: 32.4 ml/min Non-Whites: 23.4 ml/min Blood pressure at referral (mean ± SEM): Whites: 153 ± 4.4 mmHg	*Key Question 1) When – in terms of GFR, symptoms of uremia, or other complications – is RRT initiated among patients with pre-ESRD?:* a) SCr values at start of dialysis significantly higher in non-Whites than in Whites (mean ± SEM): Whites: 8.8 ± 0.47 mg/dl Non-Whites: 12.0 ± 0.4 mg/dl p = 0.001: b) Hct values at start of dialysis significantly lower in non-Whites than in Whites (mean ± SEM): Whites: 28 ± 4.5% Non-Whites: 24 ± 5.8% p = 0.001 c) Estimated CrCl at start of dialysis lower in non-Whites than in Whites: Whites: 10.82 ml/min/1.73 m^2 Non-Whites: 7.99 ml/min/1.73 m^2 *Key Question 2) What factors affect the timing of initiation of RRT among pre-ESRD patients?:* a) The greater the SCr at referral, the greater the odds of receiving less than 12 months of care from a nephrologist before initiation of dialysis (OR, 1.8; 95% CI, 1.04 to 3.13; p = 0.03). No significant association between receiving less than 12 months of care from a nephrologist before dialysis and other variables tested (age, race, body weight, serum albumin). b) Delayed referral to nephrologist (SCr > 4 mg/dl) more likely in non-Whites than in Whites (OR, 5.6; 95% CI, 1.52 to 20; p = 0.008). c) Delayed referral (SCr > 4 mg/dl) more likely in patients > 55 years old (OR, 4.7; 95% CI, 1.37 to 16; p = 0.01). *Key Question 3) What is the effect of early initiation of RRT (at GFR > 20 ml/min, before development of uremia symptoms) on health and resource utilization outcomes?:*	Quality Scoring: 1) Global assessment: Good 2) Validity criteria: Population described: Partially Incl/excl described: Completely Dropouts discussed: Partially Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by reviewers 4) % pre-ESRD: > 75% 5) Level of evidence: 2b Notes: *(continued on next page)*

Evidence Table 6 – Timing the initiation of RRT (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
		Non-Whites: 156 ± 4.9 mmHg p = 0.47 Co-morbidities at entry: Diabetes as cause of CKD: Whites: 38% Non-Whites: 45% p = 0.36 Hypertension as cause of CKD: Whites: 23% Non-Whites: 32% Other: Body weight at referral (mean ± SEM): Whites: 161 ± 5.2 lbs Non-Whites: 168 ± 7.7 lbs p = 0.24 Serum albumin at referral (mean ± SEM): Whites: 3.7 ± 0.09 g/dl Non-Whites: 3.6 ± 0.09 g/dl	Not addressed *Other outcomes:* Interval from referral to start of dialysis (mean ± SEM): Whites: 43.5 ± 4.8 months Non-Whites: 13 ± 0.8 months p = 0.001 Frequency of clinic visits (mean ± SEM): Whites: 0.85 ± 0.06 Non-Whites: 0.87 ± 0.08 p = 0.63	

Evidence Table 6 – Timing the initiation of RRT (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Jungers, Zingraff, Page, et al., 1993	Design: Case-control study (retrospective) Intervention(s) studied: 1) Early referral (n = 20). Patients had been regularly followed at hospital nephrology department for at least 6 months prior to start of hemodialysis. 2) Late referral (n = 20). Patients referred to hospital nephrology department "in emergency conditions" within 1 month of their first dialysis. Dates: Patients started hemodialysis between Jan 1988 and Dec 1990 Location: Paris, France Recruitment setting: Nephrology department	No. of pre-ESRD subjects: 40, including 20 late-referral "cases" and 20 age- and sex-matched early referral controls. Cases selected randomly from 250 eligible patients. Inclusion criteria: Chronic renal failure due to primary renal disease; started hemodialysis between Jan 1988 and Dec 1990 Exclusion criteria: Systemic or malignant disease; rapidly progressive glomerulonephritis; dialysis after failed transplant Age (mean ± SD): Early, 53.5 ± 11.4; late, 53.9 ± 15.8 Sex: Both groups 60% M, 40% F Race: NR Renal function: CrCl *at time of first dialysis* (mean ± SD): Early: 6.47 ± 1.67 ml/min Late: 5.85 ± 1.87 ml/min p < 0.01 SCr *at time of first dialysis* (mean ± SD): Early: 970 ± 110 µmol/l Late: 1120 ± 270 µmol/l p < 0.01 Blood pressure at entry (mean ± SD): Systolic BP: Early: 153 ± 15 mmHg Late: 180 ± 14 mmHg p < 0.001	*Key Question 1) When – in terms of GFR, symptoms of uremia, or other complications – is RRT initiated among patients with pre-ESRD?:* In early-referral group, decision to start dialysis based on CrCl < 7 ml/min or presence of marked asthenia and/or nausea. In late-referral group, patients referred for dialysis because of dyspnea with peripheral and/or pulmonary edema (12 cases), severe asthenia and vomiting (4 cases), or recently detected high blood pressure (3 cases). *Key Question 2) What factors affect the timing of initiation of RRT among pre-ESRD patients?:* Not addressed *Key Question 3) What is the effect of early initiation of RRT (at GFR > 20 ml/min, before development of uremia symptoms) on health and resource utilization outcomes?:* a) Duration of hospitalization (mean ± SD): Early: 5.7 ± 1.1 days Late: 33.2 ± 13.1 p < 0.001 b) Total cost of hospitalization per treatment group (mean ± SD): Early: 0.78 million FF Late: 4.34 million FF (no p-value reported) c) Need for temporary vascular access: Early: 0/20 Late: 15/20 d) Duration of temporary vascular access (mean ± SD): Early: 0 days Late: 32.1 ± 10.3 days	Quality Scoring: 1) Global assessment: Good 2) Validity criteria: Population described: Partially Incl/excl described: Partially Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 4 Notes:

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Evidence Table 6 – Timing the initiation of RRT (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
		Diastolic BP: Early: 86 ± 7 mmHg Late: 102 ± 10 mmHg p < 0.001 Co-morbidities at entry: Diabetes as cause of CKD: Early: 0 Late: 10% Pulmonary edema: Early: 15% Late: 65% Other: Hgb *at time of first dialysis* (mean ± SD): Early: 9.4 ± 0.9 g/dl Late: 7.1 ± 1.1 g/dl p < 0.001 Albumin *at time of first dialysis* (mean ± SD): Early: 39.7 ± 3.4 g/l Late: 35.3 ± 4.8 g/l p < 0.01		

Evidence Table 6 – Timing the initiation of RRT (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Keshaviah, Emerson, and Nolph, 1999	Design: Mathematical simulation (variable-volume, single-pool, urea kinetic model) Intervention(s) studied: Hemodialysis and continuous ambulatory peritoneal dialysis Dates: NA Location: NA Recruitment setting: NA	No. of pre-ESRD subjects: NA Inclusion criteria: NA Exclusion criteria: NA Age: NA Sex: NA Race: NA Renal function at entry: NA Blood pressure at entry: NA Co-morbidities at entry: NA Other: Assumed that patients modeled have chronic kidney disease with stable decline in GFR	*Key Question 1) When – in terms of GFR, symptoms of uremia, or other complications – is RRT initiated among patients with pre-ESRD?:* Not addressed *Key Question 2) What factors affect the timing of initiation of RRT among pre-ESRD patients?:* Model showed that a gradual increase in Kp (exogenous renal clearance) can maintain total weekly Kt/V_{urea} at a level $\geq$ 2.0 (in accordance with DOQI guidelines) over a period of several years of dialysis in the face of declining Kr (residual renal clearance). *Key Question 3) What is the effect of early initiation of RRT (at GFR > 20 ml/min, before development of uremia symptoms) on health and resource utilization outcomes?:* Not addressed	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: No/not assessable Incl/excl described: Partially Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by reviewers 4) % pre-ESRD: < 50%/not assessable 5) Level of evidence: 5 Notes:

Evidence Table 6 – Timing the initiation of RRT (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Khan, Catto, Edward, et al., 1994	Design: Cohort study (retrospective) Intervention(s) studied: Referral to a nephrologist Dates: SCr ≥ 300 µmo/l measured between July 1989 and June 1990; patients followed up for 2 years Location: Grampian region, UK Recruitment setting: Hospital renal unit	No. of pre-ESRD subjects: 304 Inclusion criteria: SCr ≥ 300 µmol/l during study period; chronic renal failure (defined as persistently elevated SCr, which had not returned to normal 2 years after index assay or at time of death); case notes available Exclusion criteria: On dialysis; acute renal failure; single SCr measure available Age (mean, with range): Referred patients, 62.0 (8-95); non-referred patients, 76.3 (21-96) Sex: 58% M, 42% F Race: NR Renal function at entry: NR Blood pressure at entry: NR Co-morbidities at entry: See at right, under "other outcomes"	Patients were divided into low-, medium-, and high-risk groups, as follows: Low-risk (n = 39): Age < 70 AND no co-morbid illness Medium-risk (n = 70): Age 70-80; OR age < 80 with one of the following: angina, previous MI, cardiac failure, CVA, PVD, COPD, pulmonary fibrosis, or liver disease; OR age < 70 with diabetes mellitus High-risk (n = 195): Age > 80; OR any age with 2+ organ dysfunctions in addition to ESRD; OR any age with diabetes and cardiac/pulmonary disease; OR any age with visceral malignancy *Key Question 1) When – in terms of GFR, symptoms of uremia, or other complications – is RRT initiated among patients with pre-ESRD?:* Not addressed *Key Question 2) What factors affect the timing of initiation of RRT among pre-ESRD patients?:* Significantly more patients in the low-risk group ($p < 0.01$) and significantly fewer patients in the high-risk group ($p < 0.0001$) were referred to a nephrologist: Low-risk: 27/39 (69%) Medium-risk: 41/70 (59%) High-risk: 41/195 (21%) *Key Question 3) What is the effect of early initiation of RRT (at GFR > 20 ml/min, before development of uremia symptoms) on health and resource utilization outcomes?:* 2-year survival: Among *referred* patients: Low-risk: 100% Medium-risk: 63% High-risk: 27% Among *non-referred* patients: Low-risk: 100% Medium-risk: 48% High-risk: 14%	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: Partially Incl/excl described: Completely Dropouts discussed: Completely Sample size justified: No/not assessable 3) GFR/CrCl: SCr 4) % pre-ESRD: < 50%/not assessable 5) Level of evidence: 4 Notes:

Evidence Table 6 – Timing the initiation of RRT (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Lameire and Van Biesen, 1999 **Study 1**	Design: Cohort study (retrospective; data gathered by postal survey) Intervention(s) studied: 1) Early referral (n = 1,653). Patient seen in renal unit for at least 1 month before start of dialysis; assumed to have been offered information on different dialysis modalities. 2) Late referral (n = 583). Patient admitted for dialysis in an emergency; no time to offer information on different dialysis modalities. Dates: Patients admitted for dialysis between 1993 and 1995 Location: 14 sites in Europe Recruitment setting: 14 dialysis centers	No. of pre-ESRD subjects: 2,236 Inclusion criteria: Admitted for dialysis between 1993 and 1995 Exclusion criteria: None specified Age: Mean, 57.3 Sex: 60% M, 40% F Race: NR Renal function at entry: NR Blood pressure at entry: NR Co-morbidities at entry: Diabetes: 17%	*Key Question 1) When – in terms of GFR, symptoms of uremia, or other complications – is RRT initiated among patients with pre-ESRD?:* Overall, 26% of patients (583/2,236) were referred late. There was substantial variability in the timing of referral among the various centers surveyed, including variability among centers in the same country. *Key Question 2) What factors affect the timing of initiation of RRT among pre-ESRD patients?:* Not addressed *Key Question 3) What is the effect of early initiation of RRT (at GFR > 20 ml/min, before development of uremia symptoms) on health and resource utilization outcomes?:* Not addressed	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: No/not assessable Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: 50-75% 5) Level of evidence: 4 Notes:

Evidence Table 6 – Timing the initiation of RRT (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Lameire and Van Biesen, 1999 **Study 2**	Design: Cohort study (retrospective; data gathered by postal survey) Intervention(s) studied: 1) Early referral (n = 510). Patient seen in renal unit for at least 1 month before start of dialysis; assumed to have been offered information on different dialysis modalities. 2) Late referral (n = 271). Patient admitted for dialysis in an emergency; no time to offer information on different dialysis modalities. Dates: Patients admitted for dialysis between Jan 1996 and Dec 1997 Location: 18 sites in Europe (8 in Flemish-speaking Belgium and 10 in rest of Europe) Recruitment setting: 18 nephrology units	No. of pre-ESRD subjects: 781 (331 from 8 Flemish sites and 450 from 10 other European sites) Inclusion criteria: Admitted for RRT between Jan 1996 and Dec 1997 Exclusion criteria: None specified Age (mean ± SD?): Early: 60.5 ± 15.5 Late: 62.1 ± 16.3 Sex: Both groups 57% M, 43% F Race: NR Renal function at entry: CrCl at first visit to renal unit (mean ± SD?): Early: 28.1 ± 23.4 ml/min Late: 6.9 ± 8.8 ml/min p < 0.001 Blood pressure at entry: Diastolic BP (mean ± SD?): Early: 82.4 ± 14.4 mmHg Late: 85.2 ± 19.5 mmHg p = 0.13 Co-morbidities at entry: Diabetes (Flemish patients only): 32% Number of antihypertensive drugs (mean ± SD?): 1.5 ± 1.0	*Key Question 1) When – in terms of GFR, symptoms of uremia, or other complications – is RRT initiated among patients with pre-ESRD?:* a) CrCl at the start of RRT (mean ± SD?): Early: 7.6 ± 3.9 ml/min Late: 7.1 ± 4.6 ml/min p = 0.18 b) Symptoms of uremia: Early: 66% Late: 83% p = 0.001 c) Pulmonary edema: Early: 17% Late: 31% p = 0.003 *Key Question 2) What factors affect the timing of initiation of RRT among pre-ESRD patients?:* Following outcomes measured at the start of dialysis among Flemish patients only (n = 331): a) Hct (mean ± SD?): Early (n = ?): 30.1% ± 5.6% Late (n = ?): 29.5% ± 6.0% p = 0.4 b) Parathyroid hormone level (mean ± SD?): Early: 270.1 ± 3.9 pg/ml Late: 314.7 ± 397.5 pg/ml p = 0.4 c) Bicarbonate levels (mean ± SD?): Early: 20.2 ± 3.9 mEq/l Late: 19.5 ± 4.7 mEq/l p = 0.2 d) Serum albumin (mean ± SD?): Early: 3.8 ± 0.6 g/dl Late: 3.4 ± 0.4 g/dl p = 0.1	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: No/not assessable Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: 50-75% 5) Level of evidence: 4 Note: Study population was subgroup of population described in Study 1 (see preceding entry).

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Evidence Table 6 – Timing the initiation of RRT (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes

Key Question 3) What is the effect of early initiation of RRT (at GFR > 20 ml/min, before development of uremia symptoms) on health and resource utilization outcomes?:

a) Status of patient 1 year after start of RRT (measured among Flemish patients only, n = 331):

Status	Early (n = ?)	Late (n = ?)	p-value
Death	16%	27%	0.07
Transplanted	18%	5%	0.02
On dialysis	65%	67%	0.5
Renal function recovered	<1%	1%	0.4

b) Arteriovenous fistula access for first hemodialysis (measured among Flemish patients only, n = 331):
Early (n = ?): 51%
Late (n = ?): 7%
(no p-value reported)

c) Hospitalization at start of RRT (mean ± SD?):
Early: 15.1 ± 16.0 days
Late: 27.8 ± 23.7 days
$p < 0.001$

Evidence Table 6 – Timing the initiation of RRT (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Mange, Joffe, and Feldman, 2001	Design: Cohort study (retrospective) Intervention(s) studied: 1) Renal transplantation from living donor without prior exposure to dialysis = "preemptive transplantation" (n = 1,819); 2) Renal transplantation from living donor after dialysis initiated (n = 6,662). Dates: Patients underwent transplantation between Jan 1994 and June 1997; follow-up through June 1998 Location: US (nationwide) Recruitment setting: Data obtained from US Renal Data System (nationwide database maintained by the United Network for Organ Sharing)	No. of pre-ESRD subjects: 8,481 Inclusion criteria: Age ≥ 18; first kidney transplant from a living donor in the US between Jan 1994 and June 1997; known date of first treatment for ESRD Exclusion criteria: Prior transplantation Age (median ± SD): Preemptive: 40 ± 12 Non-preemptive: 41 ± 13 Sex: Preemptive: 53% M, 47% F Non-preemptive: 59% M, 41% F Race: Preemptive: 74% White, 21% Black, 6% other Non-preemptive: 76% White, 18% Black, 6% other Renal function at entry: NR Blood pressure at entry: NR Co-morbidities at entry: Diabetes as cause of CKD: Preemptive: 15% Non-preemptive: 24% Hypertension (not defined) as cause of CKD: Preemptive: 5% Non-preemptive: 16% Panel-reactive antibodies (median % positive ± SD): Preemptive: 0 ± 10.4 Non-preemptive: 0 ± 13.5	*Key Question 1) When – in terms of GFR, symptoms of uremia, or other complications – is RRT initiated among patients with pre-ESRD?:* Not addressed *Key Question 2) What factors affect the timing of initiation of RRT among pre-ESRD patients?:* Not addressed *Key Question 3) What is the effect of early initiation of RRT (at GFR > 20 ml/min, before development of uremia symptoms) on health and resource utilization outcomes?:* A multivariable proportional-hazards analysis showed that transplantation from a living donor without previous long-term dialysis was associated with a 52% reduction in the risk of allograft failure during the 1st year after transplantation (rate ratio, 0.48; 95% CI, 0.30 to 0.77; p = 0.002), an 82% reduction during the 2nd year (rate ratio, 0.18; 95% CI, 0.08 to 0.42; p = 0.001), and an 86% reduction during subsequent years (rate ratio, 0.14; 95% CI, 0.06 to 0.30; p = 0.001) when compared to transplantation after dialysis. (Allograft failure was defined as death, repeated transplant, or resumption of dialysis.) A separate logistic-regression analysis showed that there was a significant linear increase in the odds of biopsy-confirmed acute rejection within 6 months of transplantation with increasing duration of dialysis before transplantation (p = 0.001 for all intervals vs. preemptive transplantation).	Quality Scoring: 1) Global assessment: Good 2) Validity criteria: Population described: Partially Incl/excl described: Completely Dropouts discussed: Completely Sample size justified: No/not assessable 3) GFR/CrCl: Not assessable 4) % pre-ESRD: < 50%/not assessable 5) Level of evidence: 2b Notes:

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Evidence Table 6 – Timing the initiation of RRT (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
		Other: Duration of dialysis prior to transplantation (median ± SD): Preemptive: NA Non-preemptive: 329 ± 638 days		
Miura, Kitagami, and Ohta, 1999	Design: Prospective clinical trial (before/after study) Intervention(s) studied: 1) Hemodialysis following emergent introduction (n = 9). Patients suffered sudden renal failure and had not been expecting dialysis. 2) Hemodialysis following ordinary introduction (n = 10). Patients had been followed by medical specialists who decided that dialysis was appropriate when renal function worsened. Dates: NR Location: Nagoya, Japan Recruitment setting: Hospital	No. of pre-ESRD subjects: 19 Inclusion criteria: Renal failure requiring hemodialysis Exclusion criteria: None specified Age: NR Sex: NR Race: NR Renal function at entry: NR Blood pressure at entry: NR Co-morbidities at entry: NR Other: Baseline depression scores (as measured by Zung self-rated depression scale; estimated from graph): Emergent: 53 Ordinary: 38 p < 0.01	*Key Question 1) When – in terms of GFR, symptoms of uremia, or other complications – is RRT initiated among patients with pre-ESRD?:* Not addressed *Key Question 2) What factors affect the timing of initiation of RRT among pre-ESRD patients?:* Not addressed *Key Question 3) What is the effect of early initiation of RRT (at GFR > 20 ml/min, before development of uremia symptoms) on health and resource utilization outcomes?:* Zung self-rated depression scale scores (estimated from graph): Emergent pre-dialysis: 53 Emergent post-dialysis: 46 p < 0.01 Ordinary pre-dialysis: 38 Ordinary post-dialysis: 34 p < 0.05 Ordinary post-dialysis vs. emergent post-dialysis, p < 0.01.	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: No/not assessable Incl/excl described: No/not assessable Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Not assessable 4) % pre-ESRD: < 50%/not assessable 5) Level of evidence: 4 Notes:

Evidence Table 6 – Timing the initiation of RRT (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Papalois, Moss, Gillingham, et al., 2000	Design: Cohort study Intervention(s) studied: 1) Preemptive kidney transplantation (no previous dialysis) using cadaver donor (ND-CAD) (n = 72); 2) Preemptive transplantation using living donor (ND-LD) (n = 313); 3) Non-preemptive transplantation (following dialysis) using cadaver donor (D-CAD) (n = 703); 4) Non-preemptive transplantation using living donor (D-LD) (n = 761). Dates: Patients underwent kidney transplantation between Jan 1984 and June 1998; follow-up assessments made 5 years after transplantation Location: Minneapolis, MN Recruitment setting: University hospital department of surgery	No. of pre-ESRD subjects: 1,849 Inclusion criteria: Primary adult kidney transplantation between Jan 1984 and June 1998 Exclusion criteria: None specified Age (mean): ND-CAD, 39.1; ND-LD, 32.6; D-CAD, 44.5; D-LD, 34.7 Sex: NR Race: NR Renal function at entry: NR Blood pressure at entry: NR Co-morbidities at entry: Diabetes: ND-CAD: 38% ND-LD: 33% D-CAD: 37% D-LD: 34%	*Key Question 1) When – in terms of GFR, symptoms of uremia, or other complications – is RRT initiated among patients with pre-ESRD?:* Not addressed *Key Question 2) What factors affect the timing of initiation of RRT among pre-ESRD patients?:* Not addressed *Key Question 3) What is the effect of early initiation of RRT (at GFR > 20 ml/min, before development of uremia symptoms) on health and resource utilization outcomes?:* a) Quality of life: There were no significant differences between preemptive and non-preemptive transplant patients in quality of life 5 years after transplantation, as assessed by the SF-36 (all 8 concepts/subscales). Mean scores on the general health perception subscale were as follows: ND-CAD: 53 D-CAD: 58 p = not significant ND-LD: 53 D-LD: 58 p = not significant b) Actuarial survival: 5-year actuarial patient survival was significantly higher for preemptive transplant patients than for non-preemptive transplant patients, regardless of donor source: ND-CAD: 93% D-CAD: 77% p = 0.001 ND-LD: 93% D-LD: 90% p = 0.02	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: No/not assessable Incl/excl described: No/not assessable Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Not assessable 4) % pre-ESRD: < 50%/not assessable 5) Level of evidence: 2b Notes:

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Evidence Table 6 – Timing the initiation of RRT (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			c) Death-censored survival: Death-censored 5-year graft survival rates were similar for preemptive and non-preemptive transplant patients receiving transplants from a cadaver (ND-CAD, 83%; D-CAD, 78%; p = not significant), but significantly better for preemptive transplant patients (vs. non-preemptive) receiving transplants from a living donor (ND-LD, 92%; D-LD, 85%; p = 0.006). d) Employment status: There were no significant differences in employment status 5 years after transplantation between preemptive and non-preemptive transplant groups. The proportion of patients working (full- or part-time, or student) in each group was as follows: ND-CAD: 80% D-CAD: 82% p = not significant ND-LD: 89% D-LD: 86% p = not significant e) Chronic rejection rates: There were no significant differences in chronic rejection rates (5 years after transplantation) between preemptive and non-preemptive transplant groups: ND-CAD: 19% D-CAD: 22% p = not significant ND-LD: 16% D-LD: 18% p = not significant	

Evidence Table 6 – Timing the initiation of RRT (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Parry, Crowe, Stevens, et al., 1996	Design: Questionnaire survey Intervention(s) studied: Survey sent to general physicians and elderly care physicians (n = 203) and nephrologists (n = 20). The survey consisted of 14 brief case histories of patients aged 65-87 who were likely to need dialysis to survive. Non-nephrologists were asked if they would refer the patient to a nephrologist for assessment; nephrologists were asked if they would accept the patient in their dialysis program. Further questions were asked about factors that would increase or decrease the probability of a referral/acceptance. Dates: NR Location: Southwest England and Channel Islands, UK Recruitment setting: Not specified/unable to determine	No. of subjects: 223 questionnaires mailed; 156 returned (138 non-nephrologists, 18 nephrologists) Inclusion criteria: General physician, elderly care physician, or nephrologist Exclusion criteria: None specified Age: NR Sex: NR Race: NR Renal function at entry: NA Blood pressure at entry: NA Co-morbidities at entry: NA	*Key Question 1) When – in terms of GFR, symptoms of uremia, or other complications – is RRT initiated among patients with pre-ESRD?:* Not addressed *Key Question 2) What factors affect the timing of initiation of RRT among pre-ESRD patients?:* Results of questionnaire survey were as follows: More patients included in the survey would have been accepted by nephrologists than would have been referred by physicians (median, 13 vs. 10; $p < 0.001$). Most physicians and nephrologists would refer or accept a patient if either the patient or relatives wished treatment. Liver metastases and dementia were both regarded as contraindications to dialysis by most physicians (133 and 129, respectively) and most nephrologists (17 and 16, respectively). Age was not a contraindication, except when the patient was older than 80, which was seen as a relative contraindication by 57% of physicians and 39% of nephrologists. -Myeloma, hemiplegia, fecal incontinence, and being bed bound were thought to be only relative contraindications by most physicians and nephrologists. -Physicians more likely to refer if they had a dialysis unit within their hospital ($p < 0.05$), of if early review by a nephrologist was possible ($p < 0.001$). -Pressure on dialysis services not a contraindication to acceptance by nephrologists. -Fear of a law suit not an important factor for either group. *Key Question 3) What is the effect of early initiation of RRT (at GFR > 20 ml/min, before development of uremia symptoms) on health and resource utilization outcomes?:* Not addressed	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: No/not assessable Incl/excl described: No/not assessable Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Not assessable 4) % pre-ESRD: < 50%/not assessable 5) Level of evidence: 5 Note: Very few quantitative data reported.

Evidence Table 6 – Timing the initiation of RRT (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Roubicek, Brunet, Huiart, et al., 2000	Design: Cohort study (retrospective) Intervention(s) studied: 1) Early referral to nephrologist (n = 177). Patients referred ≥ 16 weeks before start of dialysis. 2) Late referral to nephrologist (n = 93). Patients referred < 16 weeks before start of dialysis. Dates: Patients started hemodialysis between Jan 1989 and Dec 1996; follow-up through Dec 1998 Location: Marseille, France Recruitment setting: Hospital nephrology department	No. of pre-ESRD subjects: 270 Inclusion criteria: ESRD; started dialysis between Jan 1989 and Dec 1996; information available on timing of referral Exclusion criteria: Acute irreversible or rapidly progressing renal failure Age (mean ± SD): Early, 58 ± 16; late, 56 ± 18 Sex: Early, 59% M, 41% F; late, 61% M, 39% F Race: NR Renal function at entry: NR for time of referral; see at right for time of dialysis Blood pressure at entry: NR Co-morbidities at entry: Diabetes: Early, 28%; late, 27% CHF (ejection fraction ≤ 40%): Early, 11%; late, 9% Hypertension (not defined): Early, 84%; late, 77% Peripheral vascular disease: Early, 21%; late, 19% Cerebral vascular disease: Early, 6%; late, 13% Primary renal vascular diseases: Early, 22%; late, 24%	*Key Question 1) When – in terms of GFR, symptoms of uremia, or other complications – is RRT initiated among patients with pre-ESRD?:* The following outcomes were measured at first dialysis: Outcome — Early — Late — p-value SCr (mg/dl) — 9.1 ± 2.5 — 10.9 ± 4.2 — < 0.001 CrCl (ml/min) — 8.0 ± 2.7 — 7.0 ± 3 — < 0.01 Hgb (g/dl) — 8.5 ± 1.5 — 8.34 ± 1.5 — NS Pulmonary edema — 11.5% — 29% — < 0.05 Severe hypertension — 0.06% — 8.6% — < 0.01 Emergent 1st dialysis — 23% — 57% — < 0.001 *Key Question 2) What factors affect the timing of initiation of RRT among pre-ESRD patients?:* Not addressed *Key Question 3) What is the effect of early initiation of RRT (at GFR > 20 ml/min, before development of uremia symptoms) on health and resource utilization outcomes?:* a) Mean survival (± SD; Kaplan-Meier curves): Early: 67 ± 4.9 months Late: 58.7 ± 5 months p = not significant b) Length of initial hospitalization (mean ± SD): Early: 20 ± 21.5 days Late: 33.3 ± 21.8 p < 0.001 c) Days in hospital beyond the 3rd month (mean ± SD): Early: 21.5 ± 33.7 days Late: 21.1 ± 36 days p = not significant d) Need for temporary venous access: Early: 29% *(continued on next page)*	Quality Scoring: 1) Global assessment: Good 2) Validity criteria: Population described: Partially Incl/excl described: Partially Dropouts discussed: No/not assessable Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: < 50%/not assessable 5) Level of evidence: 2b Notes:

Evidence Table 6 – Timing the initiation of RRT (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			Late: 73% p < 0.001 e) Radial fistula: Early: 53% Late: 12% p < 0.001 f) Transplantation: Early: 24% Late: 24%	

Evidence Table 6 – Timing the initiation of RRT (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Schmidt, Domico, Sorkin, et al., 1998	Design: Cohort study (retrospective) Intervention(s) studied: 1) Early referral to nephrologist (n = 180). Patients referred > 1 month before starting dialysis. 2) Late referral to nephrologist (n = 58). Patients referred ≤ 1 month before starting dialysis. Dates: Patients started dialysis between Jan 1990 and Apr 1997; follow-up through Nov 1997 Location: West Virginia (3 sites) and Pennsylvania (1 site) Recruitment setting: Dialysis units	No. of pre-ESRD subjects: 238 Inclusion criteria: Chronic renal failure; began dialysis between Jan 1990 and Apr 1997 Exclusion criteria: No information on timing of referral; acute renal failure; trauma-induced renal loss; renal allograft failure; rapidly progressive glomerulonephritis; malignancy Age (mean ± SD): Early, 59 ± 15; late, 65 ± 15 Sex: Early, 47% M, 53% F; late, 43% M, 57% F Race: Early, 92% White, 8% Black; late, 91% White, 9% Black Renal function at entry: NR Blood pressure at entry: NR Co-morbidities at entry: Diabetes as cause of CKD: Early, 50%; late, 33% Hypertension (not defined) as cause of CKD: Early, 16%; late, 22% Renovascular disease as cause of CKD: Early, 6%; late, 14%	*Key Question 1) When – in terms of GFR, symptoms of uremia, or other complications – is RRT initiated among patients with pre-ESRD?:* Emergent hemodialysis was required in 22% of early-referral patients, compared with 90% of late-referral patients ($p < 0.0001$). Indications for emergent hemodialysis (n = 70/104 patients receiving it) were as follows: Indication — Early — Late — p-value Uremia/hyperkalemia — 36% — 50% — NS Pulmonary edema — 64% — 50% — NS *Key Question 2) What factors affect the timing of initiation of RRT among pre-ESRD patients?:* Not addressed *Key Question 3) What is the effect of early initiation of RRT (at GFR > 20 ml/min, before development of uremia symptoms) on health and resource utilization outcomes?:* a) 4-month mortality: Early: 8/180 (4%) Late: 4/58 (7%) p = not significant b) Initial choice of dialysis modality: Early: 59% hemodialysis, 41% peritoneal dialysis Late: 91% hemodialysis, 9% peritoneal dialysis c) Dialysis modality at 4 months: Early: 47% hemodialysis, 48% peritoneal dialysis Late: 66% hemodialysis, 28% peritoneal dialysis d) Crude cost simulations suggest that early referral is less expensive than late referral, but no firm data presented.	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: Partially Dropouts discussed: Partially Sample size justified: No/not assessable 3) GFR/CrCl: Not assessable 4) % pre-ESRD: < 50%/not assessable 5) Level of evidence: 2b Notes:

Evidence Table 6 – Timing the initiation of RRT (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Sesso and Belasco, 1996	Design: Cohort study (prospective) Intervention(s) studied: 1) Early diagnosis of chronic renal failure (n = 78). Diagnosis made > 3 months prior to start of dialysis. 2) Late diagnosis of chronic renal failure (n = 106). Diagnosis made < 1 month prior to start of dialysis. Dates: Patients started dialysis between Oct 1992 and Mar 1995 Location: Sao Paulo, Brazil Recruitment setting:	No. of pre-ESRD subjects: Inclusion criteria: Began dialysis for ESRD between Oct 1992 and Mar 1995; diagnosis of chronic renal failure made < 1 month or > 3 months prior to start of dialysis Exclusion criteria: Diabetes as cause of CKD; diagnosis of chronic renal failure made 1-3 months prior to start of dialysis Age (median, with range): Early diagnosis: 45 (16-84) Late diagnosis: 47 (16-92) Sex: Both groups 58% M, 42% F Race: Early diagnosis: 44% White, 56% non-White Late diagnosis: 50% White, 50% non-White Renal function at entry: NR Blood pressure at entry: Systolic BP (mean): Early diagnosis: 161 mmHg Late diagnosis: 172 mmHg p < 0.05 Diastolic BP (mean): Early diagnosis: 104 mmHg Late diagnosis: 106 mmHg p = not significant Co-morbidities at entry: Severe hypertension (> 200/120 mmHg): 26% in late-referral group; not reported for early-referral group MI/angina: Early, 8%; late, 4% Cerebral vascular disease: Early,	*Key Question 1) When – in terms of GFR, symptoms of uremia, or other complications – is RRT initiated among patients with pre-ESRD?:* a) CrCl at start of dialysis (mean ± SEM): Early diagnosis: 6.4 ± 0.5 ml/min Late diagnosis: 4.4 ± 0.5 ml/min p < 0.01 b) SCr at start of dialysis (mean ± SEM): Early diagnosis: 10.7 ± 0.7 mg/dl Late diagnosis: 14.1 ± 0.7 mg/dl *Key Question 2) What factors affect the timing of initiation of RRT among pre-ESRD patients?:* Not addressed *Key Question 3) What is the effect of early initiation of RRT (at GFR > 20 ml/min, before development of uremia symptoms) on health and resource utilization outcomes?:* a) 26/78 early-diagnosis patients (33%) had an arteriovenous fistula suitable for use in place at time of first dialysis; 0 late-diagnosis patients did. 100% of late-diagnosis patients had central venous catheter as the initial dialysis access. b) 6-month survival: Early diagnosis: 87% Late diagnosis: 69% p < 0.01 c) Risk of death: Risk of death, late vs. early diagnosis (unadjusted for other risk factors): 2.77 (95% CI, 1.36 to 5.66) Risk of death, late vs. early diagnosis (adjusted for several potential risk factors): 2.05 (95% CI, 0.93 to 4.54 = not significant) d) Initial dialysis modality (hemodialysis vs. continuous ambulatory peritoneal dialysis vs. intermittent peritoneal	Quality Scoring: 1) Global assessment: Good 2) Validity criteria: Population described: Partially Incl/excl described: Partially Dropouts discussed: Partially Sample size justified: No/not assessable 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 2b Notes: *(continued on next page)*

Evidence Table 6 – Timing the initiation of RRT (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
		8%; late, 7% Peripheral vascular disease: Early, 8%; late, 3% Cardiac insufficiency: Early, 13%; late, 10% Malignancy: Early, 6%; late, 9% Pulmonary infection: Early, 6%; late, 18% ($p < 0.01$) Other: Median monthly income (with range): Early diagnosis: US$352 ($0-$3505) Late diagnosis: US$273 ($0-$1667)	dialysis) not significantly different between early- and late-diagnosis groups. e) Multivariate Cox proportional hazards regression model found that patient age, serum albumin, and pulmonary infection were significant and independent predictors of mortality.	

8. Counseling and rehabilitation

8.1 Chapter summary

Education/counseling

We considered evidence related to three questions:

1. Does early systematic education about RRT choices improve patients' satisfaction or compliance with RRT or RRT-related health outcomes, compared with usual care (at time of need; no systematic early education)?
2. Do comprehensive prepared educational programs, multidisciplinary teams or specialty educators educate patients better than usual care (informal, non-specialty educators)?
3. Is there an association between better knowledge about RRT and greater satisfaction, compliance or health outcomes with RRT?

Exercise

1. Is there an association between physical function and outcomes in pre-ESRD patients?
2. Does exercise counseling in pre-ESRD patients result in improved self-reported activity, performance-based measures, or exercise capacity?
3. Does exercise counseling in pre-ESRD patients result in improved health outcomes compared to no exercise counseling?
4. Does supervised exercise therapy improve outcomes compared to no exercise therapy?

Key Question 1: Is there an association between physical function and outcomes in pre-ESRD patients?

We did not identify any studies of pre-ESRD patients that describe the relationship between level of physical functioning and health outcomes such as quality of life, mortality, complications, and deterioration in kidney function. To a certain extent, the intervention studies described under key questions 2 and 3, below, indirectly address this issue, but they fail to report health outcomes, focusing instead on measures of physical functioning.

Conclusions

The body of research testing the effect of exercise counseling or training in pre-ESRD patients is extremely limited, consisting of only a handful of small studies. Although these studies demonstrate that, as in healthy patients or dialysis patients, pre-ESRD patients can increase muscle strength and exercise capacity, the studies are too small to detect potential benefits of exercise on other health outcomes.

Exercise counseling studies suggest that improvements in performance-based measures of physical functioning and exercise capacity can occur without resource-intensive supervised exercise therapy. Furthermore, these studies suggest

improvements in symptoms and quality of life; however, these studies did not report adequate procedures to reduce several important biases. Notably, only one of these studies had random allocation to exercise versus control groups. In the two non-randomized studies that did use control groups, there was no report of masking those measuring outcomes to treatment group, thus 6-minute walk test could have been influenced by differences in coaching or encouragement. Finally, the control group in one study[49] had no attention-placebo intervention, thus improvement in reported quality of life could have reflected differences in the patients' amount of contact with, and desire to please, investigators. Nevertheless, self-reported activity and compliance with exercise regimens was higher in exercise compared to control groups, and this is consistent with observed improvements in performance-based measures of physical functioning.

Employment counseling

Key Question 1: Does employment counseling in pre-ESRD patients result in improved maintenance of employment during RRT?

A single study[58] suggests that predialysis counseling of employed patients, particularly blue-collar workers, improves maintenance of employment; however, this study likely overestimates the strength of this effect because of the retrospective design and long duration of time between surveying employment status and the intervention. The sample of patients in this study is highly selected based upon that fact that at the time of enrollment in the study, they belonged to an HMO, were employed, and had already survived an average of over 4 years after initiating hemodialysis. Were this study performed prospectively, mortality would likely have reduced the observed odds ratio of 2.8 favoring the intervention group.

Evaluation (individualized assessment)

Key Question 1: Does systematic individualized clinical assessment improve outcomes in pre-ESRD patients compared to usual care with no systematic individualized psychosocial or rehabilitation assessment (until dialysis or other RRT)?

We found only one study that described the use of individualized clinical assessment.[21] This study is described in the section on "Education."

Encouragement (emotional support)

Key Question 1: Is there an association between clinician-delivered encouragement and outcomes in pre-ESRD patients?

We found no studies describing clinician-delivered encouragement, broadly defined, offered to pre-ESRD patients. Although encouragement was certainly a component of some of the multidisciplinary interventions involving nurses, social workers, and other

health professionals described in education, its effect or association cannot be determined from the studies described previously.

8.2 Introduction

This chapter of the report addresses rehabilitation and uses the terminology, familiar to renal organizations, of the Life Options Rehabilitation Advisory Council. The Life Options Rehabilitation Advisory Council describes five core principles of a rehabilitation program for ESRD patients: education, exercise, employment, evaluation (individualized assessment), and encouragement.[1] The Results section of this chapter is divided according to these five subtopics.

The purpose of this chapter is to systematically review the available empirical research literature on each of these topics as it pertains to the pre-ESRD population.

8.3 Methods

The key questions addressed are described in each subtopic section below.

To identify the literature addressing the key questions related to all of the five topics considered in this section, the following terms were used: MeSH terms “decision making” (exploded), “counseling,” “patient education,” “choice behavior,” “exercise therapy” (exploded), "physical education and training,” “exercise,” “exercise tolerance,” “social support,” “adaptation, psychological,” “nurse-patient relations,” “professional-patient relations,” “physician-patient relations,” “rehabilitation” (floating subheading), “rehabilitation, vocational” (exploded), “needs assessment,” “nursing assessment,” “patient care planning,” and text-string searching for “encouragement.”

All citations identified by this search were reviewed for inclusion for any of the five subtopics. Citations included at the title-and-abstract screening were coded according to which of the five subtopics they addressed. The subsequent review of the full text occurred separately for each topic.

The outcome measures considered are described below for each subtopic.

Studies identified

Nine hundred and fifty titles and abstracts were screened. Of these, 67 were identified for full-text screening. We were unable to obtain a copy of one article.[2] Thirty-six were excluded during full text review for the following reasons: outcomes not reported separately for the pre-ESRD population (n = 7), did not meet criteria for the pre-ESRD population (n = 8), did not address at least one of the key questions (n =21). Thirty articles were included at the full-text screening stage: three of these were review articles; the remaining 27 were abstracted using a standardized form and are summarized in Evidence Table 7.

8.4 Education/counseling

Background

Patients with pre-ESRD face important decisions regarding which mode of renal replacement therapy (RRT) they will use. The choice is difficult because the treatments are complicated, involving dietary and fluid restrictions, medication schedules, vascular or peritoneal access placement or transplantation. Predialysis education programs often are aimed not only at informing patients of all treatment options, but also at decreasing anxiety for patients and their families and at providing enhanced self-care strategies. Regardless of whether treatment is home based or dialysis center based, patients need to acquire knowledge and skills to participate in their treatment. Thus, patient education is an important component in management of pre-ESRD and may be expected to influence patients' choice of and success with RRT modality.

Evaluation of health education programs relies on the principle that an educational intervention will increase patients' knowledge, resulting in a change in behavior (adherence) and improved health outcomes. While health education programs have been developed and tested in a variety of clinical conditions, the results have been inconsistent. Demonstration of the effectiveness of such programs has been limited by the lack of three factors: (1) a defined core of disease-specific knowledge needed to influence outcomes, (2) reliable and valid instruments to measure disease-specific knowledge, and (3) sufficient size and duration of studies to identify measurable impacts on health outcomes.

In the case of pre-ESRD, most education has focused on choice of modality of RRT (hemodialysis, peritoneal dialysis, or kidney transplant). At least two instruments for measuring knowledge about kidney failure and treatment options have been developed and demonstrate reliability and validity.[3,4]

Methods

Our goal is to describe, for the pre-ESRD population, the current state of research on the association between educational interventions or patient knowledge about RRT and patient satisfaction with or outcomes of care. We considered evidence related to three questions:

1. Does early systematic education about RRT choices improve patients' satisfaction or compliance with RRT or RRT-related health outcomes, compared with usual care (at time of need; no systematic early education)?
2. Do comprehensive prepared educational programs, multidisciplinary teams or specialty educators educate patients better than usual care (informal, non-specialty educators)?
3. Is there an association between better knowledge about RRT and greater satisfaction, compliance or health outcomes with RRT?

The outcomes considered under each question are described below.

Results

Twelve studies, described in 15 publications,[3,5-18] described the association between education and patient satisfaction, knowledge or outcomes. One report described two separate studies,[16] while several studies were described in more than one report.

Key Question 1: Does early systematic education about RRT choices improve patients' satisfaction or compliance with RRT or RRT-related health outcomes, compared with usual care (at time of need; no systematic early education)?

Studies reporting patient satisfaction and desire for information as outcomes.

Klang et al.[14] compared 38 pre-ESRD patients undergoing a comprehensive pre-dialysis education program with 28 dialysis patients (control group) who had received only conventional information. The education program was comprised of a series of 4 group teaching sessions, each 2 hours in length, covering 4 themes: (1) kidney disease and diet, (2) active renal replacement therapies, (3) physical exercise training and (4) possible impact of CKD on finances, family and social life. The control group received conventional information only: they were told by their physicians during a regular outpatient consultation that they would need maintenance dialysis and that their options were hemodialysis (HD) or CAPD. Three months after the patients began dialysis, investigators measured disease specific knowledge, patients' perceived amount of information, and sense of coherence (described in a later section). The education group did not have greater knowledge overall than the control group; however, the education group did demonstrate a significant correlation between their disease-specific knowledge and their perceived amount of information, whereas there was no such correlation in the control group. Fewer patients in the control than in the education group reported they had sufficient knowledge to participate in choosing RRT modality ($p < 0.01$). Sense of coherence (SOC) scores were not correlated with disease-specific knowledge or perceived information in either group; and SOC scores increased from before dialysis to after dialysis in the education group. In the control group, SOC scores (after dialysis began) were similar to pre-dialysis scores of the education group, although these differences were not statistically significant.

In another publication,[15] investigators reported the effect of the educational intervention on a different set of outcomes: symptoms, perceived health (Health Index), functional status (Sickness Impact Profile or SIP), and emotional status (State-Trait Anxiety Inventory, or STAI). Three months after the education group began dialysis, their measures were compared with a control group of dialysis patients who had not received a pre-dialysis educational program. There were no differences between the groups in symptoms or perceived health. However, the education group scored significantly better than the control group in mood, mobility, functional status and anxiety. At 9 months after beginning dialysis, when these measures were taken again, there was no longer any significant difference between the education and control group scores for any of these measures.

Pre-ESRD patients have different expectations regarding the degree of participation in decision-making regarding choice of modality. Breckenridge[7] interviewed patients on

dialysis to assess the decision-making at the time of initiation of RRT. In-depth, semi-structured interviews also assessed patients' satisfaction with the decision-making process. The interview data showed two patterns of decision-making: (1) patients exerted a choice, or (2) selection of treatment modality was made by others, or external circumstances dictated choice. Among patients for whom selection of treatment modality was not the patient's own choice, there was a diversity of satisfaction; "a few informants were upset that they had no choice in the decision but others clearly deferred the decision to the physician." The proportion of the 22 subjects who exerted a choice was not described; neither was the satisfaction of these two groups quantified. Although presumably the only patients who were dissatisfied were those not allowed choice. This study is limited not only by its small size and lack of quantification, but also by the fact that the length of time on dialysis varied, and thus, the decisions on initial RRT modality varied, from 4 months to 19 years. During this time, recall of events may suffer, and health care and physician practices regarding patient education and counseling may have changed.

Ahlmen et al.[5] report a prospective study in which 97 patients with chronic kidney disease (CKD) expected to "be in need of active treatment of uremia within the next 6 months" underwent an educational intervention. Education was delivered during four 90-minute evening discussions on protein-restricted diet and conservative treatment of uremia, hemodialysis treatment, peritoneal dialysis (CAPD, CCPD), and kidney and pancreas transplantation. The sessions involved patient and family, physician, nurse, dietician, and experienced patients. On surveying patients after initiation of dialysis, 88% of patients were satisfied with information they received, and 86% satisfied with modality choice. No data are presented on historical satisfaction rates before the education intervention was begun. Sixty-four of the patients made a choice of RRT: 37 chose CAPD, 23 chose HD, and 4 chose predialytic transplantation. Twenty-nine had not yet made a choice at the time of the study, while four died before choosing. Forty-eight of the patients with "stabilized active treatment of uremia" were sent questionnaires, and 43 questionnaires were returned (response rate, 89.6%). All the patients returning the questionnaires (25 CAPD, 15 HD, 3 transplant) felt that they decided their own therapy and received accurate information before choosing RRT modality. Eighty-six percent did not want to change their chosen therapy, and 88% found the information provided to be adequate.

Another study[9] describes 79 patients' and 12 nephrologists' recollections about pretreatment counseling among ESRD patients on hemodialysis who are "medically suitable for transplant." Patients were identified at five freestanding and three hospital-based chronic HD facilities. The semi-structured questionnaire queried patients about whether their nephrologist encouraged them to seek a kidney transplant or discussed life expectancy. A majority of patients (68%) reported being encouraged to seek a transplant; those patients who were younger, more educated, or had a higher occupational level were more likely to report being encouraged to seek a transplant. Some patients (because of fear) did not desire life expectancy discussions; however, other patients reported they asked for information about life expectancy, but their nephrologists did not provide it.

Coupe[8] describes the results of a survey of 297 patients 2-3 months after beginning dialysis in a single health care region in Wales. Some of the patients had contact with the education nurse in the pre-ESRD phase, while others did not. There is no explanation for why some patients had education nurse contact, and no comparison of the characteristics of patients in these two groups. Patients who did see the education nurse were more likely to express satisfaction with the amount of information they received than those who did not (74% versus 27% satisfaction, respectively). These studies show that there is variability in patients' expressed desire for information.

Studies providing related data on quality of life and psychosocial status of pre-ESRD patients. A body of research in pre-ESRD subjects is aimed at describing patients' symptoms, information needs, knowledge, quality of life, anxiety, functional status, and coping strategies. While these studies do not directly address the questions of effectiveness of education, they are described here because they report on the population of interest and provide data relevant to interpreting the intervention studies.

The necessary content of pre-ESRD education was the subject of two reports[10,11] stemming from semi-structured interviews of 22 RRT patients, 10 nephrologists, and 11 nurses. The patients were carefully selected in consultation with their physicians for their perceived ability to contribute, balance of type of RRT modality, age, and gender. The data collected in semi-structured interviews were classified into domains. Twenty-nine domains were mentioned by at least 25% of the study population, and they were identified by similar proportions of patients, physicians and nurses. Seven domains were mentioned more often by health professionals than patients including, in particular, risks for relatively infrequent complications. Presumably, health professionals were familiar with complications, while the patients were not. No domains were mentioned more often by patients than health professionals. Furthermore, they found that the frequency with which domains were mentioned correlated with direct measures of their importance. The investigators concluded that careful consultation with health professionals is sufficient to determine the content of informational materials that address treatment choice and to anticipate or address patient concerns.

Also pertinent to determining necessary content is a prospective study of 28 pre-ESRD patients who were followed during the transition from pre-ESRD to maintenance dialysis (with HD or CAPD).[12] The most frequently reported symptoms were thirst, sleep disturbances, dry throat, and itching; these symptoms were reported with similar frequency before and after starting dialysis.

Data on expected quality of life changes during pre-ESRD and RRT phases are also pertinent to content of pre-ESRD education programs. We report on several studies describing quality of life, anxiety, and other psychological measures in pre-ESRD populations. Previous studies using the Sickness Impact Profile (SIP), a measure of behavioral health related dysfunctions in 12 areas of activity, in patients on dialysis reported intermediate scores, with means of 10 to 13.9.[19] SIP scores were low (indicating relatively little perceived dysfunction) in one non-US study of pre-ESRD

subjects,[12] but much higher (indicating severe perceived dysfunction) in a US study[20] (see Table 2). The reasons for the discrepancy in SIP scores between the two studies of pre-ESRD subjects is not clear, but may reflect selection bias. Harris et al., in their cross sectional study, found no relationship between creatinine clearance and SIP scores.[20] However, they postulated that their study population may have included severely disabled patients who might either die before dialysis or choose not to undergo dialysis; such a culling of the kidney failure population could lead to improved disability (SIP scores) in a dialysis population. Klang et al.[12] actually addressed this issue by prospectively measuring SIP in pre-ESRD and after-dialysis phases in the same population, finding no significant change in overall SIP scores; however, there was significant decline in eating and work subscales, while recreation and pastime scores improved with the transition from pre-ESRD to dialysis. Although the prospective non-US study was methodologically superior to the cross-sectional US study, the reasons for the differences in findings are not certain, and might be attributed to cultural differences.

Table 2: SIP scores in pre-ESRD patients

SIP Scores	Klang et al., 1997	Harris et al., 1998
N	28	360
SIP - Overall	4 (5)	24.5 (15.6)
Physical dimension	3.1 (8.7)	21.3 (17.8)
Psychosocial dimension	2.3 (4.4)	21.4 (17.0)
Sleep and rest	9.9 (12.3)	NR
Eating	4.3 (4.0)	NR
Recreation and pastime	10.3 (10.9)	NR
Work	9.9 (20.7)	NR
Home management	6.7 (15.0)	NR
Alpha coefficient	0.96	0.87
GFR	12 (3)	34 (10)

NR = Not reported

The State-Trait Anxiety Inventory (STAI), a measure of psychological status that distinguishes between disposition (trait) and transitory (state) types of anxiety, was used in a Swedish study of pre-ESRD patients who were only minimally disabled according to SIP scores.[12] Mean STAI scores were relatively low, with a mean of 38 (SD 12) on the 20-100 scale, where lower scores indicate less anxiety. Furthermore, scores remained low before and after starting dialysis as these patients were followed prospectively.

Another descriptive study of 25 patients with pre-ESRD (matched to 25 dialysis patients for age, sex, and duration of kidney disease) described their coping strategies and sense of coherence (comprehensibility, manageability and meaningfulness). The Jalowiec Coping scale, a 40-item questionnaire that assesses general coping behavior, was used to compare the predialysis and dialysis patients. Of the scale's 40 coping strategies, there were statistically significant differences in seven; five were used more often by patients on dialysis treatment: "Try to maintain some control," "Try to look a the problem objectively" "Actively try to change the situation," "Set specific goals," and "Go

to sleep, things will be better tomorrow." Predialysis patients used the strategies "Worry" and "Getting nervous" more often than dialysis patients. The scale groups strategies according to three coping styles (confrontational, emotive, and palliative); dialysis patients scored higher on the confrontational and palliative coping style scales than predialysis patients.

Also in this study, the sense-of-coherence (comprehensibility, manageability, and meaningfulness) scores were higher in the dialysis patients than predialysis patients. Furthermore, the SOC scores were significantly negatively correlated with the emotive and palliative coping style scores, indicating that the weaker the sense of coherence, the more the emotive and palliative strategies were used.

These data would suggest that it may be necessary to improve patients' knowledge of their health and disease to enable them to adopt the productive confrontational coping style used by dialysis-experienced patients.

Studies reporting RRT-related health outcomes. O'Donnell and Tucker,[17] described a survey of 84 pre-ESRD patients, most of whom went through a multidisciplinary education program incorporating social worker, dietitian, established dialysis patients, and representatives from kidney disease support groups and local kidney disease charities. Of 84 mailed surveys, 61 (72%) returned the satisfaction surveys, most of whom had attended the education program (37, 61%). The investigators reported patients' perceptions of their preparation for dialysis, but did not compare responses for patients who did and did not participate in the education program. Such a comparison was made for length of stay: patients who attended the program had a shorter length of stay compared with those who did not attend (9.2 days versus 4.6 days). No statistical tests were reported for this comparison. Neither was the number of patients among those mailed surveys who had attended the educational program described to allow evaluation of response bias.

Levin et al,[16] described results from a multidisciplinary predialysis program in Toronto involving 141 pre-ESRD subjects. The educational intervention comprised two evening discussions about nutrition, medications, and options; predialysis clinic visits with physician, renal nurse coordinator, and social worker; and a group encounter with a renal dietician. The goals of the intervention were to improve the initiation of dialysis access prior to the first dialysis session, reduce the rates of inpatient dialysis starts, and reduce the length of hospital stay at the initiation of dialysis. When compared to historical data before the initiation of the education program, the intervention was associated with: an increase in initiation of access before first dialysis (86.3% versus 72%); a reduction in length of stay at initiation of dialysis (16.7 days versus 33 days); but an increase in the rate of inpatient dialysis starts (35-40% versus 28%). The authors pointed to a severe constraint on hemodialysis resources that confounded the effect of the education intervention, leading to hemodialysis slots being allocated to patients with the most urgent need.

Levin et al.[16] studied 76 subjects in a prospective non-randomized cohort comparison of 37 patients who received a multidisciplinary clinic-based education and follow-up program and 39 patients who received the usual standard of individualized physician care. The standardized education program consisted of discussions about kidney function, blood pressure, bone disease, and diet therapy, delivered in a stepwise progressive fashion over the course of the multiple visits totaling between 15 and 33 hours per year. Visits included equal time with nurse educator, physician, social worker, and nutritionist. The usual care group had no special education intervention and received individualized physician care during office visits to nephrologists at intervals determined by nephrologist or general practitioner. Estimated contact time was 7-15 hours per year. All patients had formal orientation to dialysis by a nurse educator and a social worker of 2-3 hour duration. The education group received more training for dialysis as outpatients (76% versus 43%, $p < 0.05$) than the usual care group. The study recorded health care utilization outcomes, including the number of urgent dialysis starts, non-elective access creations, total hospital admissions, and hospital admissions for uremia. The patients in the education group had fewer urgent dialysis starts (13% versus 35%, $p < 0.05$), fewer hospital days in the first month of dialysis (6.5 versus 13.5 days; $p < 0.05$), fewer hospitalization for symptomatic uremia (3 versus 11; $p< 0.05$). The education group had favorable but non-statistically significant results for the number of hospital admissions (17 versus 27; p = not significant), and number of non-elective access creations (1 versus 6; p = not significant).

Harris et al.[21] report a randomized controlled trial of a multidisciplinary case management clinic versus usual care involving 437 patients (49 of whom had SCr > 3 md/dL). The clinic allowed evaluation by nephrologist, renal nurse, renal dietitian, and social worker, with frequency of visits depending on the serum creatinine level: patients with SCr < 3 mg/dL were evaluated every 3 months; patients with SCr between 3 and 4 mg/dL were evaluated every 4 months; and patients with SCr > 4 mg/dL were evaluated every 3 months. The intervention was a comprehensive program designed to increase prescription of angiotensin converting enzyme (ACE) inhibiting drugs, improve blood pressure control, decrease use of nephrotoxic drugs, decrease protein intake, and decrease barriers to care. The usual care arm of the study involved primary care from the patients' usual physicians who were free to refer patients to the regular renal clinic located in the same multispecialty outpatient center. The intervention patients had more outpatient visits in all post-enrollment years of the study, most of which were explained by visits to the nephrology case management clinic. However, during the intervention period (2 years) and follow-up period (3 years), there was no difference between intervention and control patients in change in kidney function, mortality, ED visits, hospitalization, or total inpatient days.

Although the study did not specifically describe an education curriculum or goal, or measure changes in patient knowledge, the involvement of a renal nurse, dietitian, and social worker imply a patient education focus. The fact that the trial was negative suggests that none of the components of the program was effective. The investigators attempted to explain the study's negative findings by noting that a substantial portion of patients at enrollment were already taking the drugs that were the focus of much of the

nephrologists' recommendations. However, one might also conclude that there was also no effect from any enhanced education

Key Question 2: Do comprehensive prepared educational programs, multidisciplinary teams, or specialty educators educate patients better than usual care (informal, non-specialty educators)?

Klang et al.[14] compared 38 pre-ESRD patients undergoing a comprehensive predialysis education program with 28 dialysis patients (control group) who had received only conventional information. The education program comprised a series of four group teaching sessions, each 2 hours in length, covering four themes: 1) kidney disease and diet; 2) active renal replacement therapies; 3) physical exercise training; and 4) possible impact of CKD on finances, family, and social life. The control group received conventional information only: they were told by their physicians during a regular outpatient consultation that they would need maintenance dialysis and that their options were HD or CAPD. Three months after the patients began dialysis, investigators measured disease-specific knowledge, patients' perceived amount of information, and sense of coherence (described in previous section). The education group did not have greater knowledge, overall, than the control group; however, the education group did have a significant correlation between their disease-specific knowledge and their perceived amount of information, whereas there was no such correlation in the control group. Fewer patients in the control than education group reported that they had sufficient knowledge to participate in choosing RRT modality ($p < 0.01$).

A randomized controlled trial was performed in Canada to evaluate the effect of an "enhanced patient education program on disease specific knowledge" in 167 pre-ESRD subjects.[6] The education program was a single 1-hour and 15-minute session comprising an individually administered slide-lecture presentation delivered by a trained research assistant concerning normal kidney function, kidney diseases, and current renal replacement therapies. The standard education condition comprised procedures that were available routinely though the treatment facility – any of multiple nephrology clinics participating in the study. Disease-specific knowledge about ESRD and its treatment was measured with the Kidney Disease Questionnaire (KDQ), a valid and reliable instrument that has been shown to be sensitive to the effects of a pre-ESRD education program and knowledge gained in the context of beginning dialysis treatment.[3] The study found that patients who received the enhanced education intervention showed a significant increase in KDQ scores, while the standard patient education patients did not ($p < 0.0001$). The effect of the enhanced education would be to increase KDQ scores from the median (50^{th} percentile) to the 83^{rd} percentile.

At long term follow-up, 4 years later, patients who received predialysis education continued to demonstrate superior KDQ scores as compared with those who received standard education. However, attrition of patients was significant, as only 26 of 179 original patients took part in the longitudinal follow-up.

Although not measuring knowledge gains per se, the study by Breckenridge,[7] described above, provides indirect evidence suggesting that the use of nurse-educators in pre-

ESRD education leads to greater patient satisfaction than routine, or non-personalized pre-ESRD education. While the effect on satisfaction may be related to a social function of nurse visits rather than an educational one, this study is consistent with an enhanced education effect.

Key Question 3: Is there an association between better knowledge about RRT and greater satisfaction, compliance, or health outcomes with RRT?
In the previously cited study by Klang et al.,[15] patients who received a predialysis educational intervention did not show significantly better knowledge than control patients. As described above, the patients who received the educational intervention had similar symptoms and perceived health scores compared with the control group; however, the education group scored significantly better than the control group in mood, mobility, functional status, and anxiety. The discrepancy between knowledge and health status sheds doubt on attributing better outcomes to improvements in knowledge alone. One must suppose that other benefits of the program may have had a greater influence, perhaps through improving patients sense of coherence, and thus affecting their coping strategies and social functioning in the clinical setting.

8.5 Exercise

Background

Physical activity is an important component of health. Physicians are encouraged in several national guidelines to recommend routinely that healthy patients exercise regularly.[22-24] Although physicians do not routinely counsel patients about physical activity,[25] they are more likely to counsel patients at high risk for a disease and patients with a known disease.[26-31] Such counseling has been shown to result in sustained improvements in cardiorespiratory fitness in inactive adults without serious chronic diseases.[32]

In patients on hemodialysis, interventions to increase physical activity have been shown to improve well-being and exercise capacity.[33-37] A recent large controlled study showed that exercise training and encouragement can result in improvements in physical functioning in ESRD patients.[38] Furthermore, even ESRD patients with low levels of physical functioning can benefit from exercise counseling in self-reported and objective measures of physical function.[39] Prospective studies of hemodialysis patients have shown that physical functioning is highly predictive of hospitalization and mortality,[40,41] suggesting that exercise training or counseling may result in improved survival through its effect on physical functioning or other physiologic outcomes. Exercise training has been reported to increase hemoglobin levels in hemodialysis patients.[36,42]

Patients with pre-ESRD may be better able than dialysis patients to undertake increased physical activity because they, in general, have better functional status and less co-morbidity. Furthermore, pre-ESRD patients may benefit more than patients on RRT, as suggested by one study directly comparing effects of exercise in predialysis and dialysis patients (reviewed below).[43]

Methods

In order to determine the effect of physical activity in the pre-ESRD population, we sought published research addressing the following questions:

1. Is there an association between physical function and outcomes in pre-ESRD patients?
2. Does exercise counseling in pre-ESRD patients result in improved self-reported activity, performance-based measures, or exercise capacity?
3. Does exercise counseling in pre-ESRD patients result in improved health outcomes compared to no exercise counseling?
4. Does supervised exercise therapy improve outcomes compared to no exercise therapy?

The outcomes considered under each question are described below.

Results

We identified seven studies of physical activity counseling or exercise therapy in the pre-ESRD population.[43-49] Three of these studies were randomized controlled trials,[43-46] two were non-randomized concurrent cohort comparisons,[48,49] and one was an uncontrolled (before/after) prospective single-subject design trial.[47]

Key Question 1: Is there an association between physical function and outcomes in pre-ESRD patients?

We did not identify any studies of pre-ESRD patients that describe the relationship between level of physical functioning and health outcomes such as quality of life, mortality, complications, and deterioration in kidney function. To a certain extent, the intervention studies described under key questions 2 and 3, below, indirectly address this issue, but they fail to report health outcomes, focusing instead on measures of physical functioning. There are a number of studies of patients on hemodialysis that address this association, which are referenced in the Introduction to this chapter.

Key Question 2: Does exercise counseling in pre-ESRD patients result in improved self-reported activity, performance-based measure, or exercise capacity?

Three studies, all randomized controlled trials, tested the effect of exercise coaching on performance-based measures or exercise capacity (see Table 3).

Table 3: Exercise counseling

Study	N	Intervention	Performance-based measures	Exercise capacity	Other health outcomes
Fitts and Guthrie 1995[46]	20	Exercise coaching in biweekly meetings x 3 mo to encourage home exercise for 30 min, 5 days/wk	↔ 6-min walk (if analysis controlled for perceived exertion, then ↑6-min walk)		
Eidemak, Haaber, Feldt-Rasmussen, et al 1997[45]	30	Home based exercise, coached by physiotherapies, 30 min/day for median 18 months; to 60-70 maximal exercise capacity		↑maximal aerobic work capacity	↔ course of nephropathy, ↔ lipids
Fitts, Guthrie and Blagg, 1999[43]	18	Exercise coaching in regular meetings (1 h/wk mos 1-3; 1 h/mo mos 4-6) to encourage home exercise for 30 min, 5 days/wk	↑ 6-min walk		Improved SIP scores, symptom scores

↑ Statistically significant increase in outcome in exercise compared to control group
↓ Statistically significant decrease in outcome in exercise compared to control group
↔ No statistically significant change in outcome in exercise compared to control group

Eidemak et al.[45] randomized 30 patients with a median glomerular filtration rate (GFR) of 25 ml/min/1.73 m^2) (range 10-43) to physical training (30 minutes of bicycling daily or an equal amount of other physical activities) or to maintenance of the usual lifestyle. The median maximal work capacity increased significantly in the exercise group but remained unchanged in the control group during 18 to 20 months.

Fitts et al.[46] randomized 20 people expected to require dialysis within about 6 months to receive exercise coaching for 3 months or a control group who were told to continue their usual activities. Distance walked in 6 minutes (self-paced) was not significantly different after the exercise training; however, three people changed their perceived exertion by more than one point between pre-and post-training tests. Excluding data for those who changed by more than one point equalized perceived exertion changes in the two groups and resulted in a significant increase in 6-minute walking distance in the exercise group (+21.8 meters) but not in the control group (+1.5 meters).

Fitts, Guthrie, and Blagg[43] studied 18 patients expected to begin dialysis in 6-12 months and 18 patients on dialysis 1-5 years. Patients were randomized to a program of

exercise coaching and rehabilitation counseling for 6 months or a control group. Subjects were tested at the end of the 6-month training period, and again after 6 months without further training. Exercise group patients walked further in 6 minutes at 6 months (+3.9 meters) and 12 months (+4.1 meters) than initially ($p < 0.01$), while control patients had no significant improvement.

Key Question 3: Does exercise counseling in pre-ESRD patients result in improved health outcomes compared to no exercise counseling?

Two of the three RCTs described above reported additional health outcomes beyond measures of physical functioning. Fitts, Guthrie, and Blagg[43] found that the exercise group had better Sickness Impact Profile scores than the control group at 6 months ($p < 0.05$); however, the improvement was no longer statistically significant at 12 months.

Fitts, Guthrie, and Blagg[43] also measured the effect of exercise counseling versus control on the presence of 13 symptoms most commonly reported by dialysis patients: pain, tiring easily or no energy, weakness or lack of strength, aches or swelling or sick feeling, fainting or dizziness, nervousness or tension or anxiety, short of breath or trouble breathing, depression, tremor, muscle weakness, leg cramps, muscle spasms, and shaky hands. Each symptom was rated according to frequency (0 = never, 1 = rarely, 2 = sometimes, 3 = often) and summed for a total score. Symptom scores improved 15% in the exercise group, but worsened 21% in controls. In contrast to the pre-ESRD patients, dialysis patients also enrolled in the study had no differences in symptom scores between groups. There were significant differences in Karnofsky index of disability between exercise and control groups as rated either by patients or physicians.

Key Question 4: Does supervised exercise therapy improve outcomes compared to no exercise therapy?

We identified four studies that examined the effect of supervised exercise therapy among pre-ESRD patients[47-49] (see Table 4). One randomized trial[44] and two non-randomized studies[4948] used no exercise, sham exercise, or low-intensity exercise control groups.

Table 4: Supervised exercise

Study	N	Intervention	Performance-based measures	Exercise capacity	Other outcomes
Castaneda, Gorton, Uhlin et al., 2001[44]	26	Resistance training; physiotherapist supervised; 45 min/session, 3 sessions/wk for 12 weeks	↑Muscle strength		↓Body weight
Heiwe, Tollback, Clyne, 2001[48]	16	Regular muscle endurance exercise training x 12 wks	↑Muscular strength ↑Dynamic endurance +Walking capacity ↑Functional mobility		
Clyne, Ekholm, Jogestrand et al.,1991[49]	10	Physiotherapist-supervised; 45min/session, 3 sessions/wk for 3 mo; to 60-70% maximal exercise capacity	↑Static thigh muscle endurance ↑Dynamic thigh muscle endurance	+Exercise capacity ($p<0.01$)	↔Hgb ↔GFR ↔BP ↔echocardio-graphic variables
Boyce, Robergs, Avasthi et al.,1997[47]	16 (8)	Physiotherapist-supervised, up to 60 min/session, 3 sessions/wk for 4 mo; to 70% maximal exercise capacity	↑Knee flexion peak torque	↑Peak oxygen consumption	↔Hgb ↔GFR ↓BP ↔lipids ↔echocardio-graphic variables

↑ Statistically significant increase in outcome in exercise compared to control group
↓ Statistically significant decrease in outcome in exercise compared to control group
↔ No statistically significant change in outcome in exercise compared to control group

Castaneda et al.[44] studied the effects of resistance training in 26 pre-ESRD patients (17 men, 9 women, mean age 65 years) with mean GFR of 26 ml/min per 1.73 m^2. After a 2-8 week run-in period on a low-protein diet, patients were randomly allocated to resistance training versus sham exercises while continuing a low-protein diet. Exercise sessions were supervised by a physiotherapist 3 times per week, 45 minutes per session for 12 weeks. After training, improvement in muscle strength was significantly greater with resistance training (32% ± 14%) than without (-13% ± 20%) ($P < 0.001$). No other functional outcomes were assessed as the study was concerned primarily with the effects on catabolism.

Clyne et al.[49] examined the effects of physical training in 10 pre-ESRD patients (7 men, 3 women, mean age 47 ± 8 years) with mean GFR of 15 $\pm$ 7 ml/min per 1.73 m^2. This group participated in an exercise program three times per week for 3 months. A concurrent group of nine patients with comparable baseline variables served as controls. The exercise group increased its maximal exercise capacity, measured by standardized exercise test on a bicycle ergometer, from an average 159 ± 49 to 174 ± 57 W ($p < 0.01$), while the control group's exercise capacity remained unchanged (171 ± 60 and 171 ± 65 W, respectively; p = not significant). Total hemoglobin, blood volume, GFR, blood pressure, and echocardiographic variables remained unchanged. Measures of muscle function (static endurance of thigh and dynamic endurance) showed similar improvement in the exercise group, but not in the control group. The authors conclude that physical training improves exercise capacity in pre-ESRD patients, and that this effect is mainly due to improved muscular function.

Heiwe et al.[48] studied the effect of individual muscle endurance exercises for the thigh on muscle function, walking capacity, and functional mobility among elderly predialysis patients. The interventions consisted of 12 weeks of individual muscle endurance exercises for the thigh and a control low-intensity group program. Pre-ESRD patients included 16 in the thigh endurance exercise group (age 76 ± 7 years, GFR 18 ± 5 ml/min/1.73m^2) and nine patients in the low-intensity exercise group (age 72 ± 6 years, GFR 16 ± 5 ml/min/1.73 m^2), respectively. Muscular strength, dynamic endurance, walking capacity, and functional mobility increased significantly in the pre-ESRD group after 12 weeks of regular muscle endurance exercise training, whereas there was no significant change in static muscle endurance and quality of life. None of the values changed in the low-intensity exercise group.

Boyce et al.[47] studied the effects of 4 months of exercise training on cardiorespiratory function and endurance, blood pressure, muscle strength, hematology, blood lipids, and kidney function in pre-ESRD patients. Sixteen subjects began, but only eight (50%) completed the study. Subjects were evaluated before and after a 2-month baseline, after 4 months of exercise training, and again 2 months after stopping training (detraining). Peak oxygen consumption (pVO_2) changed significantly during the study (1.3 ± 0.3 L/min, 1.5 ± 0.3 L/min, and 1.4 ± 0.3 L/min for baseline, post-exercise training, and detraining, respectively; $P < 0.02$), as did the VO_2 at the ventilatory threshold (0.65 ± 0.18 L/min, 0.92 ± 0.19 L/min, and 0.68 ± 0.23 L/min for baseline, post-exercise training, and detraining, respectively; $P < 0.01$). Knee flexion peak torque increased after exercise training (43.4 ± 25.6 Nm to 51.0 ± 30.5 Nm; $P < 0.02$). GFR, as measured by creatinine clearance, declined during the course of the study (25.3 ± 12.0 mL/min, 21.8 ± 13.2 mL/min, and 21.8 ± 13.2 mL/min for baseline, post-exercise training, and detraining, respectively; $P < 0.001$). Exercise training did not change hematology, blood lipids, or echocardiographic measurements of left ventricular function and mass. Resting systolic and diastolic blood pressures decreased significantly from baseline after the exercise training (146 ± 15.7/87 ± 9 mm Hg to 124 ± 17.5/78 ± 9.5 mm Hg; $P < 0.02$), and then increased significantly after detraining (139 ± 14.7 mm Hg and 87 ± 9.9 mm Hg; $P < 0.01$).

Conclusions

The body of research testing the effect of exercise counseling or training in pre-ESRD patients is extremely limited, consisting of only a handful of small studies. Although these studies demonstrate that, as in healthy patients or dialysis patients, pre-ESRD patients can increase muscle strength and exercise capacity, the studies are too small to detect potential benefits of exercise on other health outcomes.

Exercise counseling studies suggest that improvements in performance-based measures of physical functioning and exercise capacity can occur without resource-intensive supervised exercise therapy. Furthermore, these studies suggest improvements in symptoms and quality of life; however, these studies did not report adequate procedures to reduce several important biases. Notably, only one of these studies had random allocation to exercise versus control groups. In the two non-randomized studies that did use control groups, there was no report of masking those measuring outcomes to treatment group, thus 6-minute walk test could have been influenced by differences in coaching or encouragement. Finally, the control group in one study[49] had no attention-placebo intervention, thus improvement in reported quality of life could have reflected differences in the patients' amount of contact with, and desire to please, investigators. Nevertheless, self-reported activity and compliance with exercise regimens was higher in exercise compared to control groups, and this is consistent with observed improvements in performance-based measures of physical functioning.

8.6 Employment counseling

Background

Maintenance of employment after RRT has never reached the level of 60% projected when the US government began insuring dialysis care under the Medicare Act of 1973.[50] In fact, the proportion of dialysis patients that continue to work is less than half the level projected, ranging from 23% to 31%.[51] Work disability increases significantly after initiation of dialysis, although functional disability for recreation and pastime may actually decrease.[12] Several factors have been associated in descriptive studies with greater likelihood of maintaining employment: home dialysis versus in-center hemodialysis,[52] kidney transplant,[53] higher educational status (white-collar workers),[54-56] and attitudes toward working.[57] However, studies testing whether health care providers can improve maintenance of employment are few. There is little evidence that vocational rehabilitation after initiation of RRT is effective.[52]

Methods

We sought to answer the following question: Does employment counseling in pre-ESRD patients result in improved maintenance of employment during RRT?

Results

We identified two studies of predialysis programs aimed at maintaining employment, both retrospective studies comparing program participants. One was a controlled study

among patients on in-center hemodialysis,[58] and the other was an uncontrolled study among patients on home dialysis[59]

Rasgon et al.[58] assessed the employment status of 102 hemodialysis patients enrolled in a large HMO, some of whom had a multidisciplinary predialysis education and orientation program conducted by a social worker. Those patients receiving in-center hemodialysis at the HMO regional dialysis center had received the intervention, while patients at community dialysis centers under contract with the HMO had not. Patients were identified and surveyed at least 6 months after beginning HD, and patients in the study were required to be employed prior to beginning dialysis. The intervention was directed specifically at blue-collar workers (because previous research has shown blue-collar workers are more likely to cease working after beginning HD), but the study was not limited to blue-collar workers. A social worker met with each patient at least twice before beginning HD, conducting an interview and assessment, to evaluate impact of illness, coping skills, and learning ability, followed by education and counseling sessions for discussion of treatment options and strategies for maintaining current employment. The intervention and control patients were similar in sex distribution, ethnicity, marital status, age, functional status, and time on dialysis. Education level showed no statistically significant differences, but there were substantially more patients with "some high school" in the treatment group than in the control group (38.7% versus 19.3%), and more patients with "some college" in the control group than in the treatment group (43.9% versus 22.7%).

The total number of patients working at the time of the interview (mean of 50 months after initiation of RRT) was not statistically different between groups, but there was a trend toward a higher percentage of patients in the treatment group (46.7%) continuing working after beginning dialysis than patients in the control group (33.3%) (OR 1.8; $p = 0.085$, one-tailed). Among blue-collar workers, for whom the program was designed, significantly more patients in the treatment group (46.7%) continued working after beginning dialysis than patients in the control group (23.5%) (OR 2.8; $p < 0.05$, one-tailed). However, there were no differences in employment among white-collar workers. Approximately 50% of white-collar workers remained employed in both treatment and control groups.

The findings are of marginal statistical significance because the blue-collar worker subgroup analysis was not specified a priori and a one-tailed statistical test was used (ignoring the possibility that the intervention was less effective among blue-collar workers). Furthermore, the lengthy time since the intervention (average of more than 4 years) and retrospective nature of inquiry may have lead to overestimating the effect of the intervention since more severely ill patients, in whom one would expect counseling to have little effect on maintaining employment, may have died.

A subsequent study described the effects of the same intervention among 30 patients on home dialysis (28 on CAPD and 2 on home HD), but lacked a contemporaneous control group.[59] The 30 patients who participated in predialysis counseling were referred approximately 6 months prior to initiation of dialysis. Eleven of them became

disabled prior to beginning RRT. Of 19 patients who continued working until RRT was initiated, 14 continued to work while on RRT. Of the five who stopped working after RRT, one retired after 24 months of RRT and four became disabled after 12, 22, and <1 month, respectively. Although there was no formally identified control group in this study, the percentage of patients who maintained employment (74%) was high compared to historical data of in-center hemodialysis patients from same institution.

Conclusions

A single study[58] suggests that predialysis counseling of employed patients, particularly blue-collar workers, improves maintenance of employment; however, this study likely overestimates the strength of this effect because of the retrospective design and long duration of time between surveying employment status and the intervention. The sample of patients in this study is highly selected based upon that fact that at the time of enrollment in the study, they belonged to an HMO, were employed, and had already survived an average of over 4 years after initiating hemodialysis. Were this study performed prospectively, mortality would likely have reduced the observed odds ratio of 2.8 favoring the intervention group.

8.7 Evaluation (individualized assessment)

The question addressed under this heading was as follows: Does systematic individualized clinical assessment improve outcomes in pre-ESRD patients compared to usual care with no systematic individualized psychosocial or rehabilitation assessment (until dialysis or other RRT)? We found only one study that described the use of individualized clinical assessment.[21] This study is described above in the section on "Education."

8.8 Encouragement (emotional support)

Background

Encouragement, in the Life Options Rehabilitation Advisory Council recommendations, involves fostering hope and facilitating independence among patients.[1] It is specifically recommended that dialysis facilities use a team approach; encourage patients to learn about all aspects of dialysis; foster patient and staff commitment to rehabilitation; and promote maintained employment, exercise, and fitness. While anxiety and coping strategies might be expected targets of counseling among pre-ESRD patients, the concept of encouragement goes beyond emotional support, extending to the way staff interact with patients and even to the atmosphere within the facility. We took a broad view of encouragement, but attempted to identify studies that could measure an effect of any of these psychosocial interventions.

Methods

The question addressed in this section is the following: Is there an association between clinician-delivered encouragement and outcomes in pre-ESRD patients?

Results

We found no studies describing clinician-delivered encouragement, broadly defined, offered to pre-ESRD patients. Although encouragement was certainly a component of some of the multidisciplinary interventions involving nurses, social workers, and other health professionals described in education, its effect or association cannot be determined from the studies described previously.

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Evidence Table 7 – Counseling and Rehabilitation

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Ahlmén, Carlsson, and Schönborg, 1993	Design: Uncontrolled prospective trial (before-after study) Intervention(s) studied: Educational intervention consisting of four 90-minute evening discussions on protein-restricted diet and conservative treatment of uremia, hemo-dialysis (HD) and peritoneal dialysis (CAPD, CCPD), and kidney and pancreas transplantation. Dates: Mar 1988 - Mar 1992 Location: Skövde, Sweden Recruitment setting: Outpatient nephrology clinic	No. of pre-ESRD subjects: 97 Inclusion criteria: Expected to need active treatment of uremia within 6 months Exclusion criteria: None specified Age: Range, 16-81 Sex: 61% M, 39% F Race: NR Renal function at entry: NR Co-morbidities at entry: NR	*Education* *Key Question 1) Does early systematic education about RRT choices improve patients' satisfaction or compliance with RRT or RRT-related health outcomes compared with usual care (at time of need; no systematic early education)?* Not addressed *Key Question 2) Do comprehensive prepared educational programs, multidisciplinary teams, or specialty educators educate patients better than usual care (informal, non-specialty educators)?* Not addressed *Key Question 3) Is there an association between better knowledge about RRT and greater satisfaction, compliance, or health outcomes with RRT?* 37/97 chose CAPD 23/97 chose HD 4 chose predialysis transplantation 29 had not yet made choice 4 died before choice Of 48 questionnaires sent, 43 were returned. Patients returning the questionnaires (25 CAPD, 15 HD, 3 transplant) felt that they decided their own therapy and received accurate information before choosing RRT modality. 86% did not want to change their chosen therapy, and 88% found the information provided to be adequate.	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: Partially Incl/excl described: Completely Dropouts discussed: Completely Sample size justified: No 3) GFR/CrCl: Not assessable 4) % pre-ESRD: > 75% 5) Level of evidence: 4 Note: No control group

Evidence Table 7 – Counseling and Rehabilitation (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Boyce, Robergs, Avasthi, et al., 1997	Design: Uncontrolled trial (before-after), single-subject reversal design Intervention(s) studied: Exercise program for 4 months, 3 times weekly, supervised by exercise physiologist, nephrologist, and cardiologist. Training began at 50%-60% maximal HR as established by pretraining exercise testing. Exercise gradually increased to 60 min at 70% of PMHR at individually determined phases of the training program. Dates: NR Location: Albuquerque, NM Recruitment setting: Academic research facility	No. of pre-ESRD subjects: 16 entered (8 completed) Inclusion criteria: Sedentary (no regular physical activity); chronic renal failure; SCr 2.2-3.4 mg/dl Exclusion criteria: Claudication; previous TIAs; poorly controlled hypertension (> 250/120 mmHg) during exercise; COPD; asthma; uncontrolled CHF; uncontrolled symptoms of CAD (exertional or unstable angina and chronic ventricular compromising dysrhythmias); EF < 30% Age: Mean (± SD), 50.4 ± 6.8; range, 37-55 or 57 Sex: 62.5% M, 37.5% F (of 8 who completed study) Race: NR Renal function at entry: SCr: Range, 2.2 to 3.4 mg/dl Co-morbidities at entry: Hypertension: 100% Diabetes: 50% Hyperlipidemia: 50%	*Exercise* *Key Question 1) Is there an association between physical function and outcomes in pre-ESRD patients?* Not addressed *Key Question 2) Does exercise counseling in pre-ESRD patients result in improved self-reported activity, performance-based measures or exercise capacity?* Not addressed *Key Question 3) Does exercise counseling in pre-ESRD patients result in improved health outcomes compared to no exercise counseling?* Not addressed *Key question 4) Does supervised exercise therapy improve outcomes compared to no exercise therapy?* Compliance with training (total no. sessions attended divided by total no. sessions possible): 82% (range, 25% to 98%) Peak exercise intensity (VO_2) was significantly higher (12%) after exercise training compared with baseline, then decreased significantly (9%) after "detraining." Ventilation threshold was similarly significantly higher after exercise training compared with baseline, then decreased significantly after "detraining." Left ventricular function showed no significant change for EF, LV mass, LVEDV, or LVESV. Thigh muscular strength showed significant increases in knee flexion torque (hamstrings), but no change in knee extension torque (quadriceps).	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: No Incl/excl described: Completely Dropouts discussed: Completely Sample size justified: Partially 3) GFR/CrCl: Not assessable 4) % pre-ESRD: < 50% 5) Level of evidence: 4 Note: 50% dropout rate – only 8 subjects completed of 16 starting the study.

Evidence Table 7 – Counseling and Rehabilitation (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Brecken-ridge, 1997b **and** **Brecken-ridge, 1997a**	Design: Case series (retrospective) Intervention(s) studied: Individual, focused, semi-structured, in-depth interview using Patient Perception Interview Guide, which contains six open-ended questions. 1. Please tell me about the way the decision that you would be on [RRT] was made 2. Have you ever been on another type of dialysis? 3. What caused you to switch from one to the other? 4. Which modality do you prefer? 5. What do you like about your preferred choice? 6. Are there any drawbacks to your preferred choice? Described by investigators as a "naturalistic method of inquiry employing a qualitative, grounded approach." Dates: NR Location: Philadelphia, PA Recruitment setting: Four renal diaysis units at a large urban tertiary care center	No. of pre-ESRD subjects: 22 subjects with dialysis Inclusion criteria: Receiving RRT at one of study sites Exclusion criteria: None specified Age (mean, with range): 53.8 (29-69) Sex: 59% M, 41% F Race: 77% Black, 23% White Renal function at entry: All patients on RRT Co-morbidities at entry: NR	*Education* *Key Question 1) Does early systematic education about RRT choices improve patients' satisfaction or compliance with RRT or RRT-related health outcomes compared with usual care (at time of need; no systematic early education)?* The results showed two patterns of decision-making: a) Patient's choice of treatment modality (7 themes): Self-decision – Patient's own choice of modality Significant other decision – family member had a major influence on modality choice To live decision – dialysis necessary to live Independence versus dependence decision – Pt wanted to take care of self on modality chosen. To be cared for decision – Pt is cared for by another on modality chosen. Patient preference/choice Switching modality due to patient preference/choice b) Selection of patient's treatment modality (4 themes): Access-rationing decision – choice based on factors such as availability of space at a center Physiologically dictated decision – Patient's physiological limitations dictated modality choice. No patient choice in making decision Expert decision – Patient stated that health care provider made modality choice. Another way of looking at the data is to separate the choice issues into three questions: 1) How was choice made? 2) Why was choice made? 3) By whom was choice made? "A few informants were upset that they had no choice in the decision but others clearly deferred the decision to the physician." There is a diversity among patients regarding their value of choice. *Key Question 2) Do comprehensive prepared educational programs, multidisciplinary teams or specialty educators educate patients better than usual care (informal, non-specialty educators)?*	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: Partially Incl/excl described: No Dropouts discussed: NA Sample size justified: Completely 3) GFR/CrCl: NA 4) % pre-ESRD: > 75% 5) Level of evidence: 4 Note: Varied length of time on dialysis of 4 months to 19 years may threaten validity of data, since patient recall of events occurring years previously may be inaccurate. Also the health care system and physician practice patterns may have changed.

(continued on next page)

Evidence Table 7 – Counseling and Rehabilitation (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			Not addressed *Key Question 3) Is there an association between better knowledge about RRT and greater satisfaction, compliance or health outcomes with RRT?* Not addressed	

Evidence Table 7 – Counseling and Rehabilitation (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Castaneda, Gordon, Uhlin, et al., 2001	Design: RCT Intervention(s) studied: 1) Exercise – resistance training program – 3 times per week for 12 weeks, 45 min per session, supervised by physiotherapist. Pt performed 3 sets of 8 repetitions on each of 5 resistance training machines with intensity adjusted to 80% of repetition maximum – plus low-protein diet; 2) Control group – Sham exercises plus low-protein diet. Dates: NR Location: Boston, MA Recruitment setting: Hospital-based outpatient nephrology clinics	No. of pre-ESRD subjects: 26 Inclusion criteria: Chronic renal failure (SCr between 133 and 442 µmol/l [1.5 and 5.0 mg.dl]); age > 50 Exclusion criteria: Myocardial infarction within the past 6 months; any unstable chronic condition; dementia; alcoholism; dialysis or previous renal transplantation; current resistance training; recent weight change (± 2 kg); albumin level < 30 g/l; proteinuria > 10 g/d, abnormal stress test result at screening. Age (mean): 65 Sex: 65% M, 35% F Race: 77% White, 19% African-American, 4% Hispanic Renal function at entry: GFR: Mean, 26.0 ml/min x 1.73m^2 Co-morbidities at entry: No patients had diabetes 19/26 had hypertension diagnosis	*Exercise* *Key Question 1) Is there an association between physical function and outcomes in pre-ESRD patients?* Not addressed *Key Question 2) Does exercise counseling in pre-ESRD patients result in improved self-reported activity, performance-based measures or exercise capacity?* Not addressed *Key Question 3) Does exercise counseling in pre-ESRD patients result in improved health outcomes compared to no exercise counseling?* Not addressed *Key question 4) Does supervised exercise therapy improve outcomes compared to no exercise therapy?* Adherence to training sessions was 91% ± 9% for resistance training and 90% ± 10% for sham exercise. Resistance training showed a trend toward increased in mid-thigh muscle area (p = 0.113). Considering other measurements associated with muscle mass, resistance training significantly increased total body potassium and hypertrophied type I and type II muscle-fiber areas by 4% ± 8%, 24% ± 31% , and 22% ± 29%, respectively. During the run-in period patients in both groups lost weight; however, during the intervention period, resistance training subjects maintained body weight and sham exercise subjects experienced substantial additional loss.	Quality Scoring: 1) Global assessment: Excellent 2) Validity criteria: Population described: Completely Incl/excl described: Completely Dropouts discussed: Completely Sample size justified: No 3) GFR/CrCl: Measured by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 1b Notes:

Evidence Table 7 – Counseling and Rehabilitation (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Clyne, Ekholm, Jogestrand, et al., 1991	Design: Prospective concurrent cohort comparison Intervention(s) studied: 1) Exercise training program – 3 times a week for 3 months, 45 min exercise, 15 min relaxation, supervised by physiotherapist, with intensity adjusted to 60-70% of max exercise capacity; 2) Control group – no change in sedentary life style. Dates: NR Location: Stockholm, Sweden Recruitment setting: Hospital-based outpatient nephrology clinics	No. of pre-ESRD subjects: 19 Inclusion criteria: Predialytic, uremic patients; age < 60 Exclusion criteria: None specified Age (mean ± SD): 47 ± 8 Sex: 74% M, 26% F Race: NR Renal function at entry: GFR: Mean, 14 ml/min x 1.73m^2; range, 5 to 29 Co-morbidities at entry: No patients had diabetes 18/19 had BP > 150/90 mm Hg or were taking antihypertensive drugs	*Exercise* *Key Question 1) Is there an association between physical function and outcomes in pre-ESRD patients?* Not addressed *Key Question 2) Does exercise counseling in pre-ESRD patients result in improved self-reported activity, performance-based measures or exercise capacity?* Not addressed *Key Question 3) Does exercise counseling in pre-ESRD patients result in improved health outcomes compared to no exercise counseling?* Not addressed *Key question 4) Does supervised exercise therapy improve outcomes compared to no exercise therapy?* Exercise group showed changes (from baseline to post-12 weeks of exercise training) in: Exercise capacity (increased) ($p < 0.01$) Maximal heart rate during exercise at equal load (decreased) ($p < 0.05$) Thigh muscular function assessed by static endurance ($p < 0.002$) and dynamic endurance ($p < 0.001$) Control group showed no changes in any outcome measures. The following outcomes did not show any significant changes from baseline to 12 weeks in either exercise or control groups: Vital capacity and maximal voluntary ventilation Total hemoglobin and blood volume Blood pressure remained unchanged in both groups. The study did not report statistical comparisons of exercise versus sedentary control group.	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: No Dropouts discussed: No Sample size justified: No 3) GFR/CrCl: Measured by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 2b Notes: Non-random assignment to groups based on geographic location. Study under-powered to detect differences between exercise and sedentary groups.

Evidence Table 7 – Counseling and Rehabilitation (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Coupe, 1998	Design: Cohort study Intervention(s) studied: Pre-dialysis education and support including home visits, visits to the dialysis units, written, visual and audio education material and patient information day. Dates: Apr 1994 - Jan 1996 Location: Wales, UK Recruitment setting: Outpatient nephrology clinic affiliated with university hospital	No. of pre-ESRD subjects: 297 Inclusion criteria: New referrals to renal unit Exclusion criteria: None Age: NR Sex: NR Race: NR Renal function at entry: SCr: 571 µmol/l Co-morbidities at entry: NR	*Education* *Key Question 1) Does early systematic education about RRT choices improve patients' satisfaction or compliance with RRT or RRT-related health outcomes compared with usual care (at time of need; no systematic early education)?* Not addressed *Key Question 2) Do comprehensive prepared educational programs, multidisciplinary teams or specialty educators educate patients better than usual care (informal, non-specialty educators)?* Not addressed *Key Question 3) Is there an association between better knowledge about RRT and greater satisfaction, compliance or health outcomes with RRT?* Of those patients who presented at end-stage or with acute on chronic renal failure, the ratio of patients opting for HD and PD was 80:20 in favor of HD. In a postal questionnaire administered 2 to 3 months after beginning HD, pts were asked about the level of information they had been given re: How the kidneys work, what happens when they fail, hemodialysis, peritoneal dialysis, medication, access, etc. Patients felt they didn't receive enough information about tests and investigations and adaptation to everyday life on dialysis. 74% of patients who had contact with the education nurse were satisfied with the amount of information they received. Of those who did not have contact with the education nurse, only 27% were satisfied.	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: Partially Incl/excl described: No Dropouts discussed: Completely Sample size justified: No 3) GFR/CrCl: Serum creatinine 4) % pre-ESRD: > 75% 5) Level of evidence: 4 Note: Unclear why some patients were not seen by nurse. If this is related to acuity of presentation then the findings may be confounded.

Evidence Table 7 – Counseling and Rehabilitation (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Devins, Binik, Mandin, et al., 1990 **and** **Binik, Devins, Barre, et al., 1993** **and** **Devins, Hollomby, Barre, et al., 2000**	Design: RCT to develop and assess an instrument (the Kidney Disease Questionnaire [KDQ]) to reliably and validly assess patient knowledge about ESRD and its treatment Intervention(s) studied: 1) Enhanced patient education. Individually administered slide-lecture presentation concerning normal kidney function, kidney diseases, and current renal replacement therapies. Delivered by a trained research assistant in one session, 1-¼ hour duration. 2) Standard patient education. Procedures that were available routinely though their treatment facility. Dates: Aug 1983 - Jan 1988 Location: Multiple sites in Canada Recruitment setting: Nephrology clinics	No. of pre-ESRD subjects: 167 Inclusion criteria: Consecutive new patients expected to require RRT within 6-12 months, Exclusion criteria: None specified Age: 49 years Sex: 66% M, 34% F Race: NR Renal function at entry: SCr: 655 mmol/l Co-morbidities at entry: NR	*Education* *Key Question 1) Does early systematic education about RRT choices improve patients' satisfaction or compliance with RRT or RRT-related health outcomes compared with usual care (at time of need; no systematic early education)?* Not addressed *Key Question 2) Do comprehensive prepared educational programs, multidisciplinary teams or specialty educators educate patients better than usual care (informal, non-specialty educators)?* Patients who received the enhanced education intervention showed a significant increase in KDQ scores, while the standard patient education patients did not ($p < 0.0001$). Effect size 0.97 indicating the effect of the enhanced education would be to increase KDQ scores from the median (50^{th} percentile) to the 83rd percentile. At long term follow-up, patients who received predialysis education demonstrated superior Kidney Disease Questionnaire scores as compared with those who received standard education. Patients identified after the initiation of RRT and who received standard education, however, demonstrated the same level of knowledge retention as produced by enhanced education. The results were identical across the longitudinal and cross-sectional samples. *Key Question 3) Is there an association between better knowledge about RRT and greater satisfaction, compliance or health outcomes with RRT?* Not addressed	Quality Scoring: 1) Global assessment: Good 2) Validity criteria: Population described: Partially Incl/excl described: Partially Dropouts discussed: Completely Sample size justified: Completely 3) GFR/CrCl: Serum creatinine 4) % pre-ESRD: > 75% 5) Level of evidence: 1b Notes: Enhanced educational intervention was minimal; even so, it showed an effect. These reports suggest that QOL measures were collected but have thus far not been reported in the literature. Highly variable amount and kind of educational information and material was used in multiple control sites comprising standard education condition.

Evidence Table 7 – Counseling and Rehabilitation (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Eidemak, Haaber, Geldt-Rasmussen, et al., 1997	Design: RCT Intervention(s) studied: 1) Physical training (30 min of bicycling daily or an equal amount of other physical activities) individually designed to match each patient's physical capacity. Exercise duration and intensity gradually increased to 60-75% of maximal exercise capacity. 2) Usual lifestyle. Dates: Jan 1991 - June 1992 Location: Herlev, Denmark Recruitment setting: Outpatient clinic of academic hospital	No. of pre-ESRD subjects: 30 Inclusion criteria: Moderate progressive chronic renal failure with at least some worsening over the past year Exclusion criteria: Diabetes Age: 45 (range, 22-70) Sex: 18 men, 13 women Race: NR Renal function at entry: GFR: Median, 25 ml/min; range, 10-43 Co-morbidities at entry: Diabetics excluded	*Exercise* *Key Question 1) Is there an association between physical function and outcomes in pre-ESRD patients?* Not addressed *Key Question 2) Does exercise counseling in pre-ESRD patients result in improved self-reported activity, performance-based measures or exercise capacity?* Not addressed *Key Question 3) Does exercise counseling in pre-ESRD patients result in improved health outcomes compared to no exercise counseling?* Not addressed *Key question 4) Does supervised exercise therapy improve outcomes compared to no exercise therapy?* The median maximal work capacity increased significantly in the exercise group (from 25 ml O_2/(min*kg BW) to 27 ml O_2/(min*kg BW)) and remained unchanged in the control group (21 to 19 ml O_2/(min*kg BW)) over 20 months. There was no beneficial effect on progression of chronic renal failure.	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: Partially Dropouts discussed: No Sample size justified: No 3) GFR/CrCl: Measured by investigators 4) % pre-ESRD: 50-75% 5) Level of evidence: 2b Notes: Total cholesterol increased in exercise group ($p < 0.05$) possibly caused by a higher caloric intake. BP levels were same at baseline and end of the study in both groups.

Evidence Table 7 – Counseling and Rehabilitation (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Fitts and Guthrie, 1995	Design: RCT Intervention(s) studied: 1) Exercise coaching in biweekly meetings to clarify goals, develop individual programs, practice measurement and experience of target heart rate (75% maximum), demonstrate exercises, review exercise diaries and discuss motivational literature. Individual programs emphasized aerobic exercise (usually walking), but also included stretching and strengthening components as needed. The goal was to exercise for 30 min, 5 days/wk. 2) Control patients were told to continue their usual activities. Dates: NR Location: Seattle, Washington Recruitment setting: Outpatient nephrology clinics	No. of pre-ESRD subjects: 20 Inclusion criteria: Chronic renal failure expected to require dialysis within about 6 months Exclusion criteria: Any serious comorbidity including diabetes, cancer, or cardiac, orthopedic, or neurologic conditions Age: 44.8 (range 2-67) Sex: 55% M, 45% F Race: NR Renal function at entry: NR (all pts were expected by their nephrologists to require dialysis within about 6 months) Co-morbidities at entry: Pts with serious co-morbid conditions were excluded	*Exercise* *Key Question 1) Is there an association between physical function and outcomes in pre-ESRD patients?* Not addressed *Key Question 2) Does exercise counseling in pre-ESRD patients result in improved self-reported activity, performance-based measures or exercise capacity?* The exercise compared to control patients showed no statistically significant differences in change in 6-minute walk, perceived exertion or heart rate change from before to after the exercise intervention. However, 3/10 control group patients had a > 1 point change in perceived exertion, which, the investigators claim, obscured the effect of exercise training. After excluding these 3 patients from the control group, the exercise group increased distance walked significantly more than the control group. *Key Question 3) Does exercise counseling in pre-ESRD patients result in improved health outcomes compared to no exercise counseling?* Not addressed *Key question 4) Does supervised exercise therapy improve outcomes compared to no exercise therapy?* Not addressed	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: No Dropouts discussed: Completely Sample size justified: No 3) GFR/CrCl: Not assessable 4) % pre-ESRD: > 75% 5) Level of evidence: 2b Notes:

Evidence Table 7 – Counseling and Rehabilitation (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Fitts, Guthrie, and Blagg, 1999	Design: RCT Intervention(s) studied: 1) Exercise coaching and rehabilitation counseling for up to 1 hr/wk for months 1-3, then up to 1 hr/mo for months 4-6 for a total of 16 hr. 14 low-intensity stretching and strengthening exercises. Goal was to exercise for 30 min 5 days/ week for 26-week program. 2) Control. No rehabilitation services provided during 6-month follow-up period. Dates: NR Location: Seattle, WA Recruitment setting: Nephrology outpatient clinic associated with urban academic hospital	No. of pre-ESRD subjects: 17 Inclusion criteria: Expected to begin dialysis in 6-12 months; employed within the last year Exclusion criteria: Serious coexisting disease (e.g., diabetes) Age: 47 (range 18-60) Sex: 9 men, 9 women Race: NR Renal function at entry: NR Co-morbidities at entry: No serious co-morbidities	*Exercise* *Key Question 1) Is there an association between physical function and outcomes in pre-ESRD patients?* Not addressed *Key Question 2) Does exercise counseling in pre-ESRD patients result in improved self-reported activity, performance-based measures or exercise capacity?* Not addressed *Key Question 3) Does exercise counseling in pre-ESRD patients result in improved health outcomes compared to no exercise counseling?* Not addressed *Key question 4) Does supervised exercise therapy improve outcomes compared to no exercise therapy?* Exercise patients improved 6-min walk by 3.9 m at 6 months and 4.1 m at 12 months ($p < 0.05$), but not control. Hematocrit increased ($p < 0.05$) in exercise group, but not in controls. SIP scores improved in exercise group compared to controls at 6 months ($p < 0.05$). Symptom scores (13 symptoms rated 0-3 according to frequency and summed for a total score) improved in the exercise group by 15%, but worsened in controls by 21% (difference between groups, $p < 0.01$ at 6 mo, $p < 0.05$ at 12 mo).	Quality Scoring: 1) Global assessment: Good 2) Validity criteria: Population described: Partially Incl/excl described: Completely Dropouts discussed: Completely Sample size justified: No 3) GFR/CrCl: Not assessable 4) % pre-ESRD: > 75% 5) Level of evidence: 2b Note: Parallel study among long-term HD patients showed little or no effect from exercise.

Evidence Table 7 – Counseling and Rehabilitation (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Gordon and Sehgal, 2000	Design: Descriptive study using semi-structured questionnaire about encouragement from nephrologists to seek a transplant and discussions about life expectancy. Intervention(s) studied: Counseling about choice of RRT modality. Nephrologists interviewed regarding 1) timing of discussions of ESRD treatment options; 2) order of presentation of treatment options; 3) encouragement of patients to seek a transplant; and 4) discussions about life expectancy. Dates: NR Location: Northeast Ohio Recruitment setting: 5 free-standing and 3 hospital-based chronic hemodialysis facilities	No. of pre-ESRD subjects: 79 Inclusion criteria: Age > 18 years, medically suitable for transplantation according to their nephrologists Exclusion criteria: Previous kidney transplant, mentally incompetent Age: 48 years (range 19-73) Sex: 49% M, 51% F Race: 65% African-American, 30% White, 5% other Renal function at entry: On hemodialysis Co-morbidities at entry: Hypertension as cause of CRF: 33% Diabetes as cause of CRF: 32% Other: Nephrologist sample (n = 12) Age: 46 (35-57) Sex: 83% men Race: 92% White, 8% other	*Education* *Key Question 1) Does early systematic education about RRT choices improve patients' satisfaction or compliance with RRT or RRT-related health outcomes compared with usual care (at time of need; no systematic early education)?* Not addressed *Key Question 2) Do comprehensive prepared educational programs, multidisciplinary teams or specialty educators educate patients better than usual care (informal, non-specialty educators)?* Not addressed *Key Question 3) Is there an association between better knowledge about RRT and greater satisfaction, compliance or health outcomes with RRT?* a) Nephrologist data: All reported giving information about treatment options gradually over a period of time. All reported presenting the option of HD first, then PD, then transplantation. 3 patient factors influenced information-giving: 1) acute medical issues, such as active infection, delayed discussion of transplantation; 2) 44% of nephrologists would exclude options based on initial patient response (example given involved dropping PD option if patient responded "Well, I don't want that thing with tubes in my belly!"); 3) patient knowledge. All nephrologists reported that they encourage all patients to seek a transplant; 42% volunteered that they are especially encouraging to younger and healthier patients. Nephrologists were reluctant to discuss life expectancy. b) Patient data: 68% of patients reported being encouraged to seek a *(continued on next page)*	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: Completely Dropouts discussed: Completely Sample size justified: No 3) GFR/CrCl: Not assessable 4) % pre-ESRD: > 75% 5) Level of evidence: 4 Note: Nephrologist counseling data are self-reported and may overestimate actual performance in practice.

Evidence Table 7 – Counseling and Rehabilitation (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			transplant by nephrologists. Being encouraged was associated with 1) younger age, 2) increased education, and 3) higher occupational level, but not with transplant suitability. Only higher socioeconomic status (combination of increased education or higher occupational level) was independently associated with being encouraged on multivariable analysis (1.5 points on a 5-point Likert scale). Some patients were reluctant to learn about life expectancy (because of fear); but some reported they asked for information about life expectancy, but were not provided with this information by their nephrologists.	

Evidence Table 7 – Counseling and Rehabilitation (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Groome, Hutchinson, and Tousignant, 1994 **and** **Groome, Hutchinson, and Prichard, 1991**	Design: Descriptive study using semi-structured interview Intervention(s) studied: None Dates: NR Location: Montreal, Quebec, Canada Recruitment setting: Academic hospital-based outpatient nephrology clinic	No. of pre-ESRD subjects: 22 RRT patients (12 HD, 4 CAPD, 6 post-transplant); 10 physicians; 11 nurses Inclusion criteria: Chosen in consultation with their physicians for their perceived ability to contribute, for balance of RRT modality and age and gender variation. Exclusion criteria: None specified Age: NR Sex: NR Race: NR Renal function at entry: NR Co-morbidities at entry: NR	*Education* *Key Question 1) Does early systematic education about RRT choices improve patients' satisfaction or compliance with RRT or RRT-related health outcomes compared with usual care (at time of need; no systematic early education)?* Not addressed *Key Question 2) Do comprehensive prepared educational programs, multidisciplinary teams or specialty educators educate patients better than usual care (informal, non-specialty educators)?* Not addressed *Key Question 3) Is there an association between better knowledge about RRT and greater satisfaction, compliance or health outcomes with RRT?* Information domains identified by physician, nurses or RRT patients include 29 items mentioned by at least 25% of study population -Details about treatment schedule -Need for a helper for home HD -Travel to dialysis center for treatment versus home treatment -How much responsibility patient has for his/her own treatment -Amount of time each treatment takes -Degree of patient's control over his/her treatment -Energy level, strength -Initiation of treatment, what is involved -Patient's ability to work -Degree of freedom -Sense of well-being, quality of life -Needling -Risk of infection -Availability and quality of nursing and physician care -Effect on family of home hemodialysis or CAPD -Patient's appearance, body image -Degree of independence -Restriction of movement and ability to do other activities while on treatment	Quality Scoring: 1) Global assessment: Fair 2) Validity criteria: Population described: Partially Incl/excl described: Partially Dropouts discussed: No Sample size justified: No 3) GFR/CrCl: Not assessable 4) % pre-ESRD: > 75% 5) Level of evidence: 4 Notes: Patients had less familiarity with complications (which formed 3 of 7 items that differed in frequency of endorsement between health professionals and patients). Lifestyle considerations ranked as being more important than medical consequences, in general. However, peritonitis ranked highly, and is presumably the greatest deterrent to choosing CAPD. There is general agreement between health professionals and patients, and there are discrepancies

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Evidence Table 7 – Counseling and Rehabilitation (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			-Symptoms resulting from treatment -Ability to carry on with a normal life -Other medical effects -Patient's mental status, happiness -Consequences of the uncertainty and the wait for a transplant The following 7 items were mentioned in different proportions by health professionals and patients. Each was cited more often by health professionals than patients. No items were mentioned more often by patients than health professionals -Temporary and/or permanent loss of access with hemodialysis and CAPD -Risk of rejection of transplanted kidney -Treatment survival -Hepatitis on HD, peritonitis on CAPD, septicemia with transplant -Efficiency of the treatment method for reversing the uremic state and minimizing comorbid disease -Ability to travel -Diet and fluid restrictions	

Evidence Table 7 – Counseling and Rehabilitation (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Grumke and King, 1994	Design: Retrospective case series Intervention(s) studied: Comprehensive pre-dialysis education comprising kidney disease introduction, modes of RRT, nutrition, and financial counseling. Dates: 1983-1993 Location: Columbia, St Louis and Kansas City, Missouri Recruitment setting:	No. of pre-ESRD subjects: 1,141 (approximately 80% of whom were pre-ESRD; rest had just begun dialysis) Inclusion criteria: All patients participating in Missouri Kidney Program's Patient Education Program Exclusion criteria: None specified Age: Mean, 52.3 Sex: 51% M; 49% F Race: 69% White; 28% Black; 3% other Renal function at entry: NR Co-morbidities at entry: NR	*Education* *Key Question 1) Does early systematic education about RRT choices improve patients' satisfaction or compliance with RRT or RRT-related health outcomes compared with usual care (at time of need; no systematic early education)?* Not addressed *Key Question 2) Do comprehensive prepared educational programs, multidisciplinary teams or specialty educators educate patients better than usual care (informal, non-specialty educators)?* 99% of patients rated them as "helpful." Knowledge assessment surveys improved form 68% before attending class to 87% after attending class. Changes were observed in attitudes toward RRT, with fewer patients undecided ($p = 0.00001$) and more patients choosing peritoneal dialysis ($p = 0.001$) after attending class. Also fewer patients were undecided about transplant ($p = 0.001$)and more were not willing to undergo transplant ($p = 0.02$) *Key Question 3) Is there an association between better knowledge about RRT and greater satisfaction, compliance or health outcomes with RRT?* Not addressed	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: Partially Incl/excl described: Partially Dropouts discussed: Partially Sample size justified: NA 3) GFR/CrCl: Not assessable 4) % pre-ESRD: > 75% 5) Level of evidence: 4 Note: High baseline knowledge scores were observed in this population.

Evidence Table 7 – Counseling and Rehabilitation (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Harris, Luft, Rudy, et al., 1998	Design: RCT Intervention(s) studied: 1) Multidisciplinary case management through nephrology case management clinic, including evaluation by nephrologist, renal nurse, renal dietitian and social worker every 3 months (SCr < 3mg/dl), every 4 months (SCr 3-4), or every 3 months (SCr > 4mg/dl). Comprehensive program designed to increase ACEI Rx, improve BP control, decrease use of nephrotoxic drugs, decrease protein intake, and decrease barriers to care. 2) Usual care. Primary care from usual physicians who were free to refer patients to the regular renal clinic located in the same multispecialty outpatient center. Dates: June 1989-June 1996 Location: Indianapolis, IN Recruitment setting: General medicine practice of urban public teaching hospital multispecialty outpatient facility	No. of pre-ESRD subjects: 437 total; 49 patients with SCr > 3mg/dl Inclusion criteria: Est CrCl < 50 ml/min on two occasions ≥ 6 months apart; SCr > 1.4 mg/dl Exclusion criteria: Institutionalized, inability to speak and understand English, impaired communication due to neurologic deficit Age: 69 ± 11 years Sex: 34% M, 66% F Race: 80% Black, 20% other Renal function at entry: SCr: 2.1 ± 0.9 mg/dl CrCl: 34 ± 10 ml/min Co-morbidities at entry: Hypertension: 99% Diabetes mellitus: 43% Ischemic heart disease: 58% CHF: 40% Prior MI: 37% Prior stroke: 20%	*Evaluation* *Does systematic individualized clinical assessment improve outcomes in pre-ESRD patients compared to usual care with no systematic individualized psychosocial, rehab assessment (until dialysis or other RRT)?* During the intervention period (2 years) or follow-up period (3 years) there were no differences between intervention and control patients in: Change in renal function Mortality ED visits Hospitalization Total inpatient days Among the subset of patients with SCr > 3 mg/dl, there were also no differences. Intervention patients had more outpatient visits in all post-enrollment years, most of which were explained by visits to the nephrology case management clinic	Quality Scoring: 1) Global assessment: Excellent 2) Validity criteria: Population described: Yes Incl/excl described: Yes Dropouts discussed: Yes Sample size justified: No 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: < 50% 5) Level of evidence: 1 Notes: Unable to determine how many patients in each group required dialysis. Study could not assess whether intervention patients were referred for intravascular access in a timelier manner or whether there was improved management of anemia or secondary hyperparathyroidism. A substantial portion of patients at enrollment was already taking the drugs that were the focus of many of the nephrologists' recommendations.

Evidence Table 7 – Counseling and Rehabilitation (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Heiwe, Tollbäck, Clyne, 2001	Design: Prospective nonrandomized concurrent cohort comparison Intervention(s) studied: 1) Exercise – regular exercise training program 3 times a week for 12 weeks. Individual strength and dynamic and static endurance training was followed by low intensity group exercise for 30 min and relaxation for 10 min. 2) Control – maintain sedentary lifestyle. Dates: NR Location: Stockholm, Sweden Recruitment setting: Outpatient nephrology clinic	No. of pre-ESRD subjects: 37 began study; 12 were subsequently excluded (4 started HD, 1 cardiac arrhythmia, 2 orthopedic, 1 control pt began regular exercise) Inclusion criteria: Age ≥ 60; GFR ≤ 25 ml/min; serum potassium ≤ 5.5 mmol/l; standard bicarbonate ≥ 21 mmol/l; Hgb ≥ 10 g/dl; stable medical condition Exclusion criteria: Orthopedic disability and/or neurological symptoms or disease which might affect ability to participate in exercise program Age: Mean, 74 Sex: 57% M, 43% F Race: NR Renal function at entry: GFR: Mean, 17 ml/min Co-morbidities at entry: NR	*Exercise* *Key Question 1) Is there an association between physical function and outcomes in pre-ESRD patients?* Not addressed *Key Question 2) Does exercise counseling in pre-ESRD patients result in improved self-reported activity, performance-based measures or exercise capacity?* Not addressed *Key Question 3) Does exercise counseling in pre-ESRD patients result in improved health outcomes compared to no exercise counseling?* Not addressed *Key question 4) Does supervised exercise therapy improve outcomes compared to no exercise therapy?* Exercise group showed increases (from baseline to post-12 weeks of exercise training) in: Quadriceps muscle strength ($p < 0.0001$); Dynamic muscular endurance ($p < 0.004$) ; 6-minute walking distance ($p < 0.002$); Functional mobility ($p < 0.004$). There were no significant changes in: Static thigh muscle endurance; SIP scores. There were no changes from baseline to 12 weeks in the control group. The study did not report statistical comparisons of exercise versus sedentary control group.	Quality Scoring: 1) Global assessment: Good 2) Validity criteria: Population described: Completely Incl/excl described: Completely Dropouts discussed: Completely Sample size justified: No 3) GFR/CrCl: Measured 4) % pre-ESRD: > 75% 5) Level of evidence: 2b Note: Patient self-selection of exercise or control group likely biased results. Study under-powered to detect differences between exercise and sedentary groups.

Evidence Table 7 – Counseling and Rehabilitation (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Klang, Björvell, and Clyne, 1999 **and** **Klang, Björvell, Berglund, et al., 1998**	Design: Comparative historical cohort study Intervention(s) studied: 1) Comprehensive pre-dialysis education program (series of 4 group teaching sessions, 2 hours each, covering 4 themes: renal disease and diet; active renal replacement therapies; physical exercise training; and possible impact of CRF on finances, family and social life. 2) Control group. Conventional information only, i.e., told by MD during a regular outpatient consultation that they would need maintenance dialysis and that the options were HD or CAPD. Dates: 1991-1993 Location: Stockholm, Sweden Recruitment setting: Outpatient nephrology clinic at academic hospital	No. of pre-ESRD subjects: 56 *Experimental group (n = 28):* Inclusion criteria: CRF with GRF < 20 ml/min Exclusion criteria: Active RRT Age: 54 years (range, 30-80) Sex: 50% M, 50% F Race: NR Renal function at entry: GFR: 12 ml/min ± 3 (range, 7-18) SCr: 547 ± 152 mmol/l (range, 218 to 831) *Control group (n = 28):* Inclusion criteria: Active RRT, received conventional pre-dialysis education only Exclusion criteria: None specified Age: 58 ± 14 (range, 29-78) Sex: 75% M, 25% F Race: NR Renal function at entry: On HD or CAPD	*Education* *Key Question 1) Does early systematic education about RRT choices improve patients' satisfaction or compliance with RRT or RRT-related health outcomes compared with usual care (at time of need; no systematic early education)?* Not addressed *Key Question 2) Do comprehensive prepared educational programs, multidisciplinary teams or specialty educators educate patients better than usual care (informal, non-specialty educators)?* Not addressed *Key Question 3) Is there an association between better knowledge about RRT and greater satisfaction, compliance or health outcomes with RRT?* All patients in the Education group stated that they had had sufficient knowledge to participate in choosing RRT modality, compared with 22/28 patients in the Control group ($p < 0.01$). There were no significant differences between Education and Control groups in knowledge, overall information, specific knowledge on renal disease in general, medication, diet, progress, dialysis, transplant, other patients experiences or in Sense of Coherence. Education group had significantly better mood, less mobility problems (HI), less functional disabilities (SIP) and lower levels of anxiety (STAI) compared to the control group. There were no significant differences between the groups in symptoms or overall health. These differences were observed during the first 6 months of dialysis treatment, after which the differences disappeared. Younger patients benefited from education program more than older patients.	Quality Scoring: 1) Global assessment: Good 2) Validity criteria: Population described: Partially Incl/excl described: Partially Dropouts discussed: Completely Sample size justified: No 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 2b Note: Experimental group described in Klang and Clyne, 1997. Control group described in Klang, Björvell, and Cronqvist, 1996.

Evidence Table 7 – Counseling and Rehabilitation (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Klang, Björvell, and Cronqvist, 1996	Design: Descriptive study of consecutive patients Intervention(s) studied: Comprehensive pre-dialysis education program (series of 4 group teaching sessions, 2 hours each, covering 4 themes: renal disease and diet; active renal replacement therapies; physical exercise training; and possible impact of CRF on finances, family and social life. Dates: 2-year period (assumed 1993-1995) Location: Stockholm, Sweden Recruitment setting: Outpatient clinic at university hospital	No. of pre-ESRD subjects: 25 selected from a group of 38 pre-dialysis patients to match 25 dialysis patients for age, sex, and duration of kidney disease Inclusion criteria: GFR < 25 ml/min Exclusion criteria: Dialysis Age: 58 ± 14 (range, 30-83) Sex: NR Race: NR Renal function at entry: NR Co-morbidities at entry: NR	*Education* *Key Question 1) Does early systematic education about RRT choices improve patients' satisfaction or compliance with RRT or RRT-related health outcomes compared with usual care (at time of need; no systematic early education)?* Not addressed *Key Question 2) Do comprehensive prepared educational programs, multidisciplinary teams or specialty educators educate patients better than usual care (informal, non-specialty educators)?* Not addressed *Key Question 3) Is there an association between better knowledge about RRT and greater satisfaction, compliance or health outcomes with RRT?* On the Jalowiec Coping Scale (JCS-40), predialysis patients, compared with dialysis, patients were more likely to use an emotive coping style ("get nervous" or "worry"). Dialysis patients were more likely to use a confrontational coping style ("try to maintain some control"; "try to look at the problem objectively"; "actively try to change the situation"; "set specific goals"). On the Sense of Coherence Scale (SOC), the weaker the sense of coherence, the more the emotive and the palliative strategies were used. The older the patients, the less the confrontational and emotive strategies were used.	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: Partially Incl/excl described: Partially Dropouts discussed: Completely Sample size justified: Partially 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: 4 Notes:

Evidence Table 7 – Counseling and Rehabilitation (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Klang and Clyne, 1997	Design: Prospective series Intervention(s) studied: Education program (4 group sessions) Dates: 2-year period (assumed 1994-1996) Location: Stockholm, Sweden Recruitment setting: University hospital	No. of pre-ESRD subjects: 28 Inclusion criteria: GFR < 20 ml/min Exclusion criteria: RRT Age: 54 (range, 30-80) Sex: 50% M, 50% F Race: NR Renal function at entry: GFR: 12 ml/min ± 3 (range, 7-18) SCr: 547 ± 152 mmol/l (range, 218-831) Co-morbidities at entry: NR Other: Employed: 14/28 (50%) Hgb: 11.0 ± 1 (range, 8.2-14.7)	*Education* *Key Question 1) Does early systematic education about RRT choices improve patients' satisfaction or compliance with RRT or RRT-related health outcomes compared with usual care (at time of need; no systematic early education)?* This study illustrates how symptoms, subjective health, anxiety and functional ability are affected during transition from pre-ESRD care to maintenance dialysis. a) Disease-specific symptoms and perceived health (HI): Thirst, sleep disturbances, dry throat and itching were the most frequently reported symptoms. There were no significant differences in frequency of symptoms prior to and after having started dialysis. b) Sickness Impact Profile (SIP) and STAI: The highest levels of dysfunction were in the areas of recreation and pastime, work, sleep and rest. There was no significant difference in anxiety scores before and after starting dialysis. c) Choice of dialysis modality (CAPD or HD): Did not affect the frequency of symptoms, perception of health, functional or emotional status. *Key Question 2) Do comprehensive prepared educational programs, multidisciplinary teams or specialty educators educate patients better than usual care (informal, non-specialty educators)?* Not addressed *Key Question 3) Is there an association between better knowledge about RRT and greater satisfaction, compliance or health outcomes with RRT?* Not addressed *Employment* *Does employment counseling in pre-ESRD patients result in improved maintenance of employment during RRT?*	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: Partially Incl/excl described: Partially Dropouts discussed: Completely Sample size justified: No 3) GFR/CrCl: Calculated by investigators 4) % pre-ESRD: > 75% 5) Level of evidence: Notes:

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Evidence Table 7 – Counseling and Rehabilitation (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
			Functional disability decreased significantly for recreation and pastime ($p < 0.05$) after starting dialysis, and work disability increased significantly ($p < 0.05$). More patients stated that they worked shorter hours after starting dialysis than before.	

Evidence Table 7 – Counseling and Rehabilitation (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Levin, Lewis, Mortioy, et al., 1997 **Study 1**	Design: Prospective, nonrandomized cohort study Intervention(s) studied: 1) Multidisciplinary clinic-based education and follow-up program (n = 37). Standardized education program consisting of discussions about renal function, blood pressure, bone disease, and diet therapy, delivered in a stepwise progressive fashion over the course of multiple visits. Initial visit 3 hours in duration; subsequent visits 1.5 hrs and included equal time with nurse educator, physician, social worker and nutritionist. Total time between 15 and 33 hours per year. 2) Usual standard of individualized physician care (n = 39). Office visits to nephrologists at intervals determined by nephrologist or general practitioner. Estimated time: 7-15 hours per year. All patients had formal orientation to dialysis by nurse educator and social worker. 2-3 hr duration. Dates: Sept 1992 - Feb 1995 Location: Vancouver, British Columbia, Canada Recruitment setting: Academic nephrology facilities	No. of pre-ESRD subjects: 76 Inclusion criteria: All pts who began dialysis Exclusion criteria: Referred to nephrologist less than 4 months before beginning dialysis, pts who changed dialysis modality, pts with failed transplants, pts with unresolved acute renal failure Age: NR Sex: NR Race: NR Renal function at entry: NR Co-morbidities at entry: NR	*Education* *Key Question 1) Does early systematic education about RRT choices improve patients' satisfaction or compliance with RRT or RRT-related health outcomes compared with usual care (at time of need; no systematic early education)?* Fewer urgent dialysis starts (13% vs. 35%, $p < 0.05$) More outpatient training (76% vs. 43%, $p < 0.05$) No hospital admissions: 17 vs. 27 (p = NS) Fewer hospital days in the 1st mo of dialysis (6.5 d vs. 13.5 d; $p < 0.05$) Non-elective access creation: 1 vs. 6 (p = NS) Hospitalization for symptomatic uremia: 3 vs. 11 ($p < 0.05$) Training for dialysis as opt: 76% vs. 43% ($p < 0.05$) *Key Question 2) Do comprehensive prepared educational programs, multidisciplinary teams or specialty educators educate patients better than usual care (informal, non-specialty educators)?* Not addressed *Key Question 3) Is there an association between better knowledge about RRT and greater satisfaction, compliance or health outcomes with RRT?* Not addressed	Quality Scoring: 1) Global assessment: Good 2) Validity criteria: Population described: Completely Incl/excl described: Completely Dropouts discussed: Completely Sample size justified: No 3) GFR/CrCl: Not assessable 4) % pre-ESRD: > 75% 5) Level of evidence: 2b Notes:

Evidence Table 7 – Counseling and Rehabilitation (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Levin, Lewis, Mortioy, et al., 1997 **Study 2**	Design: Retrospective historical cohort comparison (before-after study) Intervention(s) studied: Multidisciplinary predialysis program comprising 2 evening discussions about nutrition, medications, and options; predialysis clinic visits with physician, renal nurse coordinator, and social worker; group session with renal dietician. Dates: Nov 1991 - Dec 1993 Location: Toronto, Ontario, Canada Recruitment setting: Academic nephrology facility	No. of pre-ESRD subjects: 141 Inclusion criteria: All predialysis patients known to institution; historical data collected immediately prior to the initiation of the predialysis program Exclusion criteria: NR Age: 53.7 yrs Sex: 60% M, 40% F Race: NR Renal function at entry: NR Co-morbidities at entry: NR	*Education* *Key Question 1) Does early systematic education about RRT choices improve patients' satisfaction or compliance with RRT or RRT-related health outcomes compared with usual care (at time of need; no systematic early education)?* Not addressed *Key Question 2) Do comprehensive prepared educational programs, multidisciplinary teams or specialty educators educate patients better than usual care (informal, non-specialty educators)?* Not addressed *Key Question 3) Is there an association between better knowledge about RRT and greater satisfaction, compliance or health outcomes with RRT?* Predialysis access creation: 86.3% of patients	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: Partially Incl/excl described: Partially Dropouts discussed: Partially Sample size justified: No 3) GFR/CrCl: Not assessable 4) % pre-ESRD: > 75% 5) Level of evidence: 4 Notes: PD selected by 89/134 patients (66%). Access created before 1st dialysis in 86.3%. AVF created in 68% of those choosing HD.

Evidence Table 7 – Counseling and Rehabilitation (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
O'Donnell and Tucker, 1999	Design: Practice audit (outcomes research) using semi-structured questionnaire; retrospective case series Intervention(s) studied: Multidisciplinary education program incorporating social worker; dietitian; established dialysis patients; and representatives from renal support groups and local renal charities. Dates: Apr 1996 - Sep 1997 Location: Brighton, England, UK Recruitment setting: Local public health care system	No. of pre-ESRD subjects: 61 patients who returned satisfaction surveys (72% of 84 mailed surveys) Inclusion criteria: All patients involved in existing education program – generally includes pts referred by GP, nephrologist or other consultants when SCr ≥ 250 mmol/l Exclusion criteria: None specified Age: NR Sex: NR Race: NR Renal function at entry: NR Co-morbidities at entry: NR	*Education* *Key Question 1) Does early systematic education about RRT choices improve patients' satisfaction or compliance with RRT or RRT-related health outcomes compared with usual care (at time of need; no systematic early education)?* Not addressed *Key Question 2) Do comprehensive prepared educational programs, multidisciplinary teams or specialty educators educate patients better than usual care (informal, non-specialty educators)?* Not addressed *Key Question 3) Is there an association between better knowledge about RRT and greater satisfaction, compliance or health outcomes with RRT?* 61% of patients surveyed had received pre-dialysis education 48 (80%) of patients felt that they had been given sufficient information to choose between different types of treatment. 56 (92%) felt that they had been given a choice of modality. 46 (77%) reported having seen a social worker. 52 (87%) reported having seen a dietitian. 48 (79%) reported having spoken to someone already on dialysis. Some comments indicated that the educational material was biased toward CAPD. 86% received written information about their condition. 47 (92%) considered the information useful. 22 (36%) said that they were unprepared for some events that occurred to them, unexpected complications (n=112) being the most common. *Patients who attended the program had a shorter length of stay compared with those patients who did not attend (9.2 d versus 4.6 days).*	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: Partially Incl/excl described: Partially Dropouts discussed: Partially Sample size justified: No 3) GFR/CrCl: Not assessable 4) % pre-ESRD: > 75% 5) Level of evidence: 4 Note: Comparisons with those not attending the program are likely confounded by differences in acuity and severity.

Evidence Table 7 – Counseling and Rehabilitation (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Rasgon, Schwankovsky, Jamer-Rogers, et al., 1993	Design: Nonrandomized controlled trial Intervention(s) studied: 1) Multidisciplinary predialysis program consisting of: psychosocial assessment; education about dialysis and choice of modalities; orientation to dialysis unit; and counseling sessions with patient, family and others conducted by licensed social worker. 2) Control – usual care, no special predialysis program Dates: NR Location: Southern California Recruitment setting: Large HMO	No. of pre-ESRD subjects: 102 Inclusion criteria: Receiving in-center HD at one of several centers in a large HMO age 18-65; employed prior to beginning HD Exclusion criteria: None specified Age: 50 Sex: 62% M, 38% F Race: 40% African-American, 30% Hispanic, 20% White, 10% Asian Renal function at entry: On dialysis Co-morbidities at entry: NR Other: Mean Karnofsky score: 76	*Employment* *Does employment counseling in pre-ESRD patients result in improved maintenance of employment during RRT?* Treatment group patients were significantly more likely to meet with a social worker prior to beginning dialysis than control group patients. Total number of patients working at the time of the interview (50 months after initiation of RRT) was not statistically different between groups, but there was a trend toward a higher percentage of patients in the treatment group (46.7%) continuing working after beginning dialysis than patients in the control group (33.3.%) (OR 1.8; p = 0.085, one-tailed). Among the subpopulation of blue-collar workers, who were the primary target group of the program, significantly more patients in the treatment group (46.7%) continued working after beginning dialysis than patients in the control group (23.5.%) (OR 2.8; p < 0.05, one-tailed). There were no differences in employment among white-collar workers. Approximately 50% of white-collar workers remained employed in both treatment and control groups.	Quality Scoring: 1) Global assessment: ?? 2) Validity criteria: Population described: Completely Incl/excl described: Completely Dropouts discussed: Completely Sample size justified: No 3) GFR/CrCl: Not assessable 4) % pre-ESRD: > 75% 5) Level of evidence: 2b Notes: Marginal statistical significance given subgroup analysis not specified a priori and one-tailed test used. Lengthy time of retrospective nature of inquiry may lead to overestimation of effect since many ill patients may have died.

Evidence Table 7 – Counseling and Rehabilitation (continued)

Study	Design and Interventions	Patient Population	Results (by Key Question)	Quality Scoring/Notes
Rasgon, Chemleski, Ho, et al., 1996	Design: Case series Intervention(s) studied: 1) Multidisciplinary predialysis program consisting of: psychosocial assessment; education about dialysis and choice of modalities; orientation to dialysis unit; and counseling sessions with patient, family and others conducted by licensed social worker. 2) Historical control – usual care, no special predialysis program. Dates: Mar 1995 - Dec 1995 Location: Southern California Recruitment setting: Large HMO	No. of pre-ESRD subjects: 30 Inclusion criteria: Receiving home dialysis in a large HMO; age 18-65 Exclusion criteria: None specified Age: 46.8 (range, 28-63) Sex: NR Race: NR Renal function at entry: On dialysis Co-morbidities at entry: Diabetes: 43%	*Employment* *Does employment counseling in pre-ESRD patients result in improved maintenance of employment during RRT?* 11 patients were disabled prior to beginning RRT. Of 19 patients working before beginning RRT, 14 continued to work after beginning RRT. Of the 5 who stopped working, 1 retired after 24 months of RRT and 4 became disabled after 12, 22, < 1, and < 1 month. The percentage of patients who maintained employment (74%) is high compared to historical data from same institution of in-center hemodialysis patients.	Quality Scoring: 1) Global assessment: Poor 2) Validity criteria: Population described: Completely Incl/excl described: Partially Dropouts discussed: Completely Sample size justified: No 3) GFR/CrCl: Not assessable 4) % pre-ESRD: > 75% 5) Level of evidence: 4 Note: Sample size small; low power.

9. Future Research

The available literature regarding management of pre-ESRD patients is quite limited. Current practice and guidelines for this population are likely based on extrapolation of data from patients with a broader range of kidney failure severity, or in some cases, data from patients with normal renal function. The lack of research on the pre-ESRD population as opposed to the hemodialysis population seems to be one of access. Although the number of patients with pre-ESRD is substantial and comparable to the number of patients on hemodialysis, pre-ESRD patients are not as easily accessible for inclusion in research studies. The prevalence in the general population is low – too low for population-based studies to be a feasible way to identify this subpopulation. Within health care systems, access to pre-ESRD patients has been problematic because of great variability in consulting behavior. Pre-ESRD patients often do not present to nephrologists until they require RRT. Increasingly, computerized patient record systems are available which should allow identification of patients with severe CKD based on estimates of creatinine clearance from integrated laboratory (serum creatinine course over time), clinical (body weight) and demographic data (age). Systematic identification of such patients could allow entry into trials comparing individual interventions or comprehensive disease management approaches, which may be tested for whether they modify clinical outcomes before or after RRT.

Each of the topics covered in this report suffers from a lack of data linking interventions in the pre-ESRD phase to improved health outcomes. The relatively short time patients spend in the pre-ESRD phase makes for limited time for interventions to exert an effect that would be measurable. This is a particular problem for conditions that develop over a protracted period of time, such as atherosclerotic disease and its clinical manifestations or metabolic bone disease. Thus, intermediate outcomes are routinely substituted. Whether the link between intermediate outcomes (blood pressure, serum lipid levels, etc.) and important clinical health outcomes is the same as in other more well-studied populations is somewhat uncertain in pre-ESRD patients. Demonstrating these relationships will require large studies, with sufficient numbers of patients followed for sufficiently long to accrue enough clinical events for statistical power, while controlling for potential confounders such as comorbid conditions. Identification of large numbers of incident ESRD patients may be feasible in large heath care systems with integrated medical record systems.

Appendixes

Appendix 1

Sample full-text screening form

PREPARATION FOR RRT
FULL-TEXT SCREENING FORM
TOPIC = ANEMIA

Reviewer_____First Author_____Year_____Pro-Cite #_____

1) Does the study include *only* RRT patients?

_____ If "yes," skip to question 4f)

_____ If "no," proceed to question 2)

Final decision (circle one):

INCLUDE EXCLUDE

2) Does the study include *both* RRT *and* non-RRT patients?

_____ If "yes," proceed to question 3)

_____ If "no" (i.e., if only non-RRT patients), skip to question 4)

3) Are outcomes reported separately for the non-RRT subgroup?

_____ If "yes," proceed to question 4)

_____ If "no," EXCLUDE and stop here

4) Does the article describe a pre-ESRD study population or subgroup?

4a) Is the mean (or median) GFR between 10 and 30 ml/min per 1.73 m^2?

_____ If "yes," skip to question 5)

_____ If GFR reported, but not within specified range, skip to question 4e)

_____ If GFR not reported, proceed to question 4b)

4b) Is the estimated mean or median CrCl between 10 and 30 ml/min per 1.73 m^2 using the modified Cockroft-Gault formula? (See below)

Est CrCl = [140 - (Age)]*{(Wt in kg (default = 72))/[(Scr)*72]}*Gender Correction Factor (GCF - see box at right)

(Note: To convert SI to conventional units, umol/L = mg/dL*88.4)

Men (%)	Wmn (%)	GCF
5	95	0.8575
10	90	0.8650
15	85	0.8725
20	80	0.8800
25	75	0.8875
30	70	0.8950
35	65	0.9025
38	62	0.9070
40	60	0.9100
42	58	0.9130
44	56	0.9160
46	54	0.9190
48	52	0.9220
50	50	0.9250
52	48	0.9280
54	46	0.9310
56	44	0.9340
58	42	0.9370
60	40	0.9400
62	38	0.9430
65	35	0.9475
70	30	0.9550
75	25	0.9625
80	20	0.9700
85	15	0.9775
90	10	0.9850
95	5	0.9925

_____ If “yes,” skip to question 5)

_____ If possible to estimate CrCl, but not within specified range, skip to question 4e)

_____ If not possible to estimate CrCl, proceed to question 4c)

4c) Is the mean (or median) Scr > 2.5?

_____ If “yes,” skip to question 5)

_____ If Scr reported, but not within specified range, proceed to question 4e)

_____ If Scr not reported, proceed to question 4d)

4d) Even if no quantitative data are reported on GFR, CrCl, or Scr, is the population described as pre-ESRD?

_____ If “yes,” skip to question 5)

_____ If “no,” proceed to question 4e)

4e) Is this a prospective study in which a population is followed as GFR declines to pre-ESRD range?

_____ If “yes,” skip to question 5)

_____ If “no,” proceed to question 4f)

4f) Is this a retrospective study in which an RRT population had data collected on pre-ESRD phase?

_____ If “yes,” proceed to question 5)

_____ If “no,” EXCLUDE and stop here

5) What is the study design?

_____ RCT – proceed to question 6)

_____ Prospective clinical trial (before/after study or non-randomized controlled trial) – proceed to question 6)

_____ Cohort study – proceed to question 6)

_____ Large case series (n ≥ 10) – proceed to question 6)

_____ Review article – proceed to question 6)

_____ Small case series (n < 10) – EXCLUDE and stop here (except for AEs of hypertension meds)

_____ Case report (n = 1) – EXCLUDE and stop here (except for AEs of hypertension meds)

_____ Other – please specify: _____ – proceed to question 6)

6) Key questions – check all that apply, then proceed to question 7:

_____a) What is the prevalence of anemia in pre-ESRD?

_____b) What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion?

(Note that this question can be addressed by studies documenting the proportion of anemic patients with low

nutritional

parameters, or by studies describing the proportion of patients who respond to nutritional repletion.)

_____c) What proportion of patients without nutritional deficiencies are resistant to EPO?

_____d) What proportion of pre-ESRD patients have low EPO levels?

_____e) What is the efficacy of EPO in improving intermediate and ultimate outcomes? …by dose?

_____f) None of the above – EXCLUDE from consideration *for this topic* (proceed to question 7)

7) Please indicate whether this article should be considered for another topic:

_____ Yes – please circle topic(s): Hypertension Counseling Nutrition Bone Lipids Timing

_____ No

Appendix 2

Sample data abstraction form

PREPARATION FOR RRT
DATA ABSTRACTION FORM
TOPIC = ANEMIA

Reviewer:_____First Author:_____Year:_____Procite #:_____

STUDY DESIGN (check one):

_____Randomized controlled trial (RCT)

_____Prospective clinical trial (before/after study or non-randomized controlled trial)

_____Cohort study

_____Case series, concomitant controls

_____Case series, historical controls

_____Case series, no controls

_____Not specified or unable to classify

EXCLUDE THIS ARTICLE (give reason[s]):

NUMBER OF *PRE-ESRD* SUBJECTS AT START OF STUDY:_____

DATES AND LOCATION:

Inclusive dates of data collection (month and year): from_____to_____

Multicenter study? (circle one): Yes / No If "Yes," no. of sites:_____

Geographic location (city and state [US] or city and country):_____

RECRUITMENT SETTING (check all that apply):

_____Dialysis center

_____Nephrology clinic or department

_____Hospital

_____Primary care

_____Community population

_____Not specified or unable to determine

_____Other – describe:_____

If inclusion and/or exclusion criteria are implied, but not clearly described, please indicate this.

INCLUSION CRITERIA:	EXCLUSION CRITERIA:

INTERVENTIONS

Describe the interventions used in each study group. Include all information necessary to reproduce the treatment protocol/algorithm (dosing, route of administration, length of treatment, length of follow-up, etc.). Indicate which intervention (if any) served as a control.

Intervention A =

Intervention B =

("Interventions" continued on next page)

Intervention C =

DEMOGRAPHIC CHARACTERISTICS OF STUDY POPULATION:
1) Identify interventions A, B, and C, and give N's.
2) Use "NR" to indicate "Not reported"

	Intervention A = **N =**	**Intervention B =** **N =**	**Intervention C =** **N =**	**Overall** **N =**
AGE (specify summary statistic [mean, median] and measure of dispersion [standard deviation, range, etc.]; if age not described in these terms, then enter as reported):				
Mean:				
Median:				
SD:				
Range:				
SEX:				
Male:	n = / %	n = / %	n = / %	n = / %
Female:	n = / %	n = / %	n = / %	n = / %
RACE:				
White:	n = / %	n = / %	n = / %	n = / %
Black:	n = / %	n = / %	n = / %	n = / %
Hispanic:	n = / %	n = / %	n = / %	n = / %
Other:	n = / %	n = / %	n = / %	n = / %

CLINICAL CHARACTERISTICS AT BASELINE:
1) Identify interventions A, B, and C, and give N's.
2) Use "NR" to indicate "Not reported"

	Intervention A = **N =**	**Intervention B =** **N =**	**Intervention C =** **N =**	**Overall** **N=**
GFR at entry into study (specify either summary statistic [mean, median] and measure of dispersion [SD, SEM, range] or proportion of patients in various categories):				
Estimated CrCl at entry into study (specify either summary statistic [mean, median] and measure of dispersion [SD, SEM, range] or proportion of patients in various categories):				
Scr at entry into study (specify either summary statistic [mean, median] and measure of dispersion [SD, SEM, range] or proportion of patients in various categories):				
Hgb at entry into study:				
Mean or median, with SD, SEM, or range (please specify measures used)				
% of patients with anemia (please specify threshold Hgb level used to define "anemia")				
Hct at entry into study:				
Mean or median, with SD, SEM, or range (please specify measures used)				
% of patients with anemia (please specify threshold Hct level used to define "anemia")				

("Clinical characteristics at baseline" continued on next page)

	Intervention A = N =	Intervention B = N =	Intervention C = N =	Overall N=
EPO levels at entry into study:				
Mean or median, with SD, SEM, or range (please specify measures used)				
% of patients with low EPO levels (please specify threshold used to define "low" levels)				
Nutritional parameters at entry into study (specify either summary statistic [mean, median] and measure of dispersion [SD, SEM, range] or proportion of patients in various categories):				
Iron measures: **Serum iron:**				
Total iron-binding capacity:				
Serum transferrin saturation:				
Serum ferritin:				
Folate:				
B12:				
Serum albumin:				

("Clinical characteristics at baseline" continued on next page)

	Intervention A = N =	Intervention B = N =	Intervention C = N =	Overall N=
Significant co-morbidities at entry into study (give % of patients with each):				
Diabetes:				
Hypertension (indicate how defined):				
Coronary artery disease:				
CHF:				
Other (please specify):				

RESULTS (Key Questions)
Please report quantitative data for Questions 2 (second part) and 5 in the table on the next page. Report all other results under the appropriate question below.

1. **What is the prevalence of anemia in pre-ESRD? (Use study population characteristics if anemia was not among selection criteria, and indicate how anemia was defined.):**

2. **What proportion of anemic pre-ESRD patients have deficiencies treatable by nutritional repletion (primarily iron, but also B-12, folate, protein, etc)? (See table below for second part of this question.)**

3. **What proportion of patients without nutritional deficiencies are resistant to EPO? (Please indicate how EPO resistance was defined.)**

4. **What proportion of pre-ESRD patients have low EPO levels?**

5. **What is the efficacy of EPO in improving intermediate and ultimate outcomes? …by dose? (Use table below for quantitative data.)**

("Results" continued on next page)

RESULTS TABLE – QUANTITATIVE OUTCOMES DATA ON FOLLOWING TWO QUESTIONS:

Question 2: Does nutritional repletion improve anemia or intermediate (Hgb, Hct) or ultimate (angina, CHF, activity/function, quality of life, cognition, mortality) outcomes?

Question 5: Does EPO improve intermediate (BP, Hgb, Hct) or ultimate (angina, CHF, activity/function, quality of life, cognition, mortality) outcomes? (For BP, please report mean arterial pressure if available; if not, then report systolic and diastolic.)

Outcome Measured (Describe)	How measured, (e.g., scale/units used, %)	Intervention A/ Study Period 1 =	Intervention B/ Study Period 2 =	Intervention C/ Study Period 3 =	P value
1)					
2)					
3)					

NOTES – Please report any significant information not captured on the preceding pages. If the study was not designed to answer the questions of interest to us, please provide a brief description of the study's aims.

QUALITY SCORING:

	Excellent	Good	Fair	Poor
1. Global subjective judgement of quality (check one):				

	Criterion fulfilled?		
2. Validity criteria (check one response for each criterion):	**Completely (2 points)**	**Partially (1 point)**	**No/Not assessable (0 points)**
a) The total population from which the sample is taken is well described.			
b) The inclusion/exclusion criteria are well described.			
c) It is stated that there were no dropouts/exclusions *OR* there is a clear discussion or description of any study patients not included in the analysis (including reasons for dropout or exclusion, and descriptions of loss to follow-up and missing data).			
d) The sample size is well justified.			

	Measured by investigators (4 points)	**Calculated by investigators (3 points)**	**Calculated by reviewers (2 points)**	**Serum creatinine (1 point)**	**Not assessable (0 points)**
3. Method used to assess GFR/CrCl (check one):					
			> 75% (2 points)	**50-75% (1 point)**	**< 50% /not assessable (0 points)**
4. Proportion of study patients who meet pre-ESRD criteria (check one):					

5. Level of Evidence	**Articles on Therapy/Prevention or Aetiology/Harm**	**Level of Evidence**	**Articles on Prognosis/Natural History**
1a	Systematic Review (with homogeneity) of RCTs	1a	SR (with homogeneity) of inception cohort studies or a CPG validated on a test set.
1b	Individual RCT (with narrow Confidence Interval)	1b	Individual inception cohort study with at least 80% f/u
1c	All or none	1c	All or none case series
2a	Systematic Review (with homogeneity*) of cohort studies	2a	SR (with homogeneity) of either retrospective cohort studies or untreated control groups in RCTs
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	2b	Retrospective cohort study or f/u of untreated control patients ina n RCT; or CPG not validated in a test set.
2c	"Outcomes" Research	2c	"Outcomes" Research
3a	Systematic Review (with homogeneity*) of case-control studies	3a	
3b	Individual Case-Control Study	3b	
4	Case-series (and before/after studies and poor quality cohort and case-control studies)	4	Case-series (and poor quality prognostic cohort studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Adapted from: Levels of Evidence and Grades of Recommendations. Ver17 Sep 1998. Chris Ball, Dave Sackett, Bob Phillips, Brian Haynes, and Sharon Straus Available from http://cebm.jr2.ox.ac.uk/docs/levels.html#notes. Accessed 1/15/99.