CJASN

Clin J Am Soc Nephrol. 2008 Jan; 3(Suppl 1): S3–S10. PMCID: PMC3152266
doi: 10.2215/CJN.03250807

Slowing Nephropathy Progression: Focus on Proteinuria Reduction

George L. Bakris

Hypertensive Diseases Unit, Section of Endocrinology, Diabetes and Metabolism, Pritzker School of Medicine, University of Chicago, Chicago, Illinois

Correspondence: Dr. George L. Bakris, University of Chicago, Pritzker School of Medicine, 5841 S. Maryland Avenue, MC 1027, Chicago, IL 60637. Phone: 773-702-7936; Fax: 773-834-0486; E-mail: gbakris@earthlink.net

Abstract

Blood pressure control reduces decline of kidney function. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers offer renoprotection to a small extent beyond that attributable to blood pressure lowering. These agents also reduce proteinuria, a risk marker for renal disease progression. Accumulating evidence indicates that their antiproteinuric effect correlates with their additional renal benefits.

The content is based on an official American Society of Nephrology continuing medical education luncheon symposium held November 16, 2006, in San Diego, California.

Faculty:

George L. Bakris, MD, Hypertensive Diseases Unit, Section of Endocrinology, Diabetes and Metabolism, Pritzker School of Medicine, University of Chicago, Chicago, Illinois

Stuart L. Linas, MD, Department of Internal Medicine, Division of Renal Diseases and Hypertension, University of Colorado Health Sciences Center, Denver, Colorado

Raymond R. Townsend, MD, Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

Credit Designation Statement: The American Society of Nephrology designates this educational activity (entire supplement) for a maximum of 2.0 *AMA PRA Category 1 Credits*™. Physicians should only claim credit commensurate with the extent of their participation in the activity. Study the education content, and complete the examination; 80% correct is required for full credit on first submission. Continuing medical education credit eligible through November 2008.

Learning Objectives:

1. To examine the epidemiology and pathophysiology of stroke and cardiovascular disease in the

chronic kidney disease population
2. To evaluate the efficacy of current therapies for the treatment of cardiovascular risk in patients with renal disease
3. To apply new clinical insights for the identification and treatment of cardiovascular risk to improve outcomes for patients with chronic kidney disease

Target audience: Physicians in internal medicine, nephrology, endocrinology, and other health care providers who are interested in the treatment of hypertension and kidney disease.

Categories: Chronic kidney disease, proteinuria, renoprotection, risk reduction

BP control is essential to slow the progression of nephropathy in patients who are at risk for or have developed chronic kidney disease (CKD). Proteinuria also is another important therapeutic target, because it is a major risk factor for renal disease progression (1–4).

Patients with hypertension typically require multiple agents to control BP (5). Therapies that target the renin-angiotensin system (RAS) offer particular benefit to hypertensive, proteinuric patients with kidney disease because these agents reduce proteinuria as well as BP (6,7). Reduction of proteinuria by >30% of baseline within the first 6 to 12 mo of treatment in patients with kidney disease has been shown to predict long-term renal (2) and cardiovascular (CV) outcomes (8).

The management of albuminuria in normotensive or hypertensive patients with diabetes is outlined in the Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease (9). Reduction in albuminuria levels may slow progression of diabetic kidney disease and improve clinical outcomes, even in normotensive patients; therefore, albuminuria may be identified as a target for treatment in diabetic kidney disease (9). In hypertensive patients with diabetes and CKD stages 1 through 4, the treatment guidelines recommend the use of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB), in combination with a diuretic, to reach a target BP of <130/80 mmHg (9). ACEI or ARB should be used to treat macroalbuminuria in normotensive patients with diabetes and should be considered to treat microalbuminuria in normotensive patients with diabetes (9).

It should be noted that nephropathy progression can occur in the absence of albuminuria, and multiple examples in the literature show large samples of patients who have type 2 diabetes and for whom this is true (10,11). In these studies, patients with clear advanced nephropathy (*e.g.*, stage 3 or higher) progressed and had no obvious evidence of albuminuria. Hence, although the majority of patients do have albuminuria and it is relevant and important to monitor, it is not absolutely clear that only those with albuminuria will progress (10,11).

ACEI have decreased the risk for nephropathy progression in patients without diabetes (12,13). In patients with both diabetes and high CV risk, ACEI therapy has reduced the risk for nephropathy and CV events (14). ARB have decreased the risk for End Stage Renal Disease (ESRD) and nephropathy progression in people with diabetes-related nephropathy (15,16). Some evidence suggests that a combination of ACEI and ARB therapy can slow renal disease progression more than can monotherapy with either drug class in patients with non–diabetes-related nephropathy (17). This article summarizes clinical evidence regarding the role of ACEI and ARB in people with non–diabetes- and diabetes-related nephropathy.

ACE Inhibition, Proteinuria, and Renoprotection in Patients without Diabetes

Several trials have demonstrated the renoprotective benefits of controlling proteinuria as well as BP in people with moderate to severe renal disease. These investigations have attempted to separate the impact of reductions in proteinuria from that of reductions in BP. Table 1 summarizes their findings (1,12,13,18–20).

Higher Proteinuria Linked to Faster Decline in GFR

One of the early clinical trials supporting the concept of proteinuria as an independent risk factor for renal disease progression was the Modification of Diet in Renal Disease (MDRD) (1). Patients were grouped by higher or lower baseline GFR and were assigned to either a normal or low BP goal. Patients with higher baseline proteinuria experienced a relatively faster rate of GFR decline and benefited more from the lower BP goal (1). Numerous analyses have since confirmed this observation (21–23). Thus, the selection of BP-lowering medications for patients with renal disease should be based on the efficacy of these agents in reducing proteinuria (1).

ACE Inhibition Slows Renal Disease Progression in Patients with Mild Renal Insufficiency and High Proteinuria

Among the first prospective clinical studies to demonstrate that ACE inhibition has a renoprotective benefit in patients with hypertensive nephropathy was the Angiotensin-Converting-Enzyme Inhibitor in Progressive Renal Insufficiency (AIPRI) study. Therapy with benazepril significantly reduced the risk for a composite renal outcome (doubling of baseline serum creatinine or need for dialysis) compared with placebo. This reduction in risk was attenuated but remained significant after adjustment for benazepril's effect on diastolic BP (DBP) and urinary protein excretion (18).

After adjustment for DBP and proteinuria changes, the benefit of benazepril remained significant in the subgroup of patients with mild renal impairment at baseline (risk reduction 65 to 66%) and those with baseline urinary protein excretion ≥3 g/d (risk reduction 52 to 56%). However, the benefit was no longer significant in those with moderate renal impairment or lower levels of urinary protein excretion (18).

ACE Inhibition Reduces the Risk for ESRD in Patients with CKD and Proteinuria

In the Ramipril Efficacy in Nephropathy (REIN) study, ramipril therapy prevented the need for dialysis when used for 3 to 4 yrs in patients with proteinuria and CKD (19,20). These and other results were consistent with a renoprotective effect exceeding that attributable to BP lowering alone (13,20).

The trial was stopped early in patients with higher baseline proteinuria (≥3 g/d), because ramipril was associated with a significantly slower rate of GFR decline per month, the primary outcome (13). Ramipril also reduced the risk for a combined secondary end point (doubling of baseline serum creatinine or development of ESRD) in this stratum of patients ($P = 0.02$). This relationship remained significant after adjustment for changes in BP ($P = 0.04$), suggesting a mechanism other than BP lowering (13).

Findings in both strata of patients suggested that proteinuria reduction accounted for at least some of the renoprotection. In the higher proteinuria stratum, proteinuria was the only time-dependent variable that predicted ramipril's renoprotective effect (13). In the ramipril group, early (1 mo after randomization) percentage reduction in urinary protein excretion from baseline was inversely correlated with long-term

(≥6 mo) change in GFR ($P = 0.035$; Figure 1) (13). Percentage reduction from baseline in urinary protein excretion during the entire treatment period predicted the risk for reaching the combined end point ($P = 0.04$) (13).

ACEI Therapy Slows GFR Decline in African Americans

The incidence of ESRD is 3.7-fold higher in African Americans than in Caucasians (24). The African American Study of Kidney Disease (AASK) was the first outcome trial to demonstrate a renoprotective effect with an ACEI in an African American population (12).

When used with a diuretic to achieve BP control, ramipril significantly reduced the risk for a composite renal outcome (reduced GFR, development of ESRD, or death) when compared with either metoprolol or amlodipine given concurrently with a diuretic (12). The risk for the composite outcome did not differ significantly between patients who received amlodipine and those who received metoprolol, although the risk for ESRD and death was significantly lower with metoprolol than with amlodipine (12). Change in GFR slope, another primary outcome, showed no consistent significant differences among agents (12).

Patients were randomly assigned not only to an antihypertensive agent but also to a normal or lower mean arterial pressure (MAP) goal (12). The mean BP achieved were 141/85 mmHg in the normal group and 128/78 mmHg in the lower BP group (12). The lower MAP goal did not significantly affect the rate of the composite renal outcome or the change in GFR slope (12).

Use of ACEI on renal disease progression has not been tested in patients with type 2 diabetes, and, likewise, ARB have not been tested in patients with type 1 diabetes; however, on the basis of their mechanism of action of inhibiting of the RAS, it is logical to hypothesize that the protective effects will be similar. Moreover, the Diabetics Exposed to Telmisartan and Enalapril (DETAIL) trial supports this concept in type 2 diabetes (25,26).

Impact of ACE Inhibition, ARB Therapy, BP, and Proteinuria on Renal and CV Risk in Diabetes

Diabetes is the leading cause of ESRD in the United States (24). Studies in populations with diabetes support the renoprotective effects of RAS inhibition (Table 2) (14–16).

ACE Inhibition Reduces Proteinuria in Patients with Diabetes-Related Nephropathy

Early data demonstrated that captopril could reverse proteinuria in patients with diabetes-related nephropathy. Captopril therapy led to remission of nephrotic proteinuria (>3.5 g/d) in 16.5% of patients, compared with 1.5% of those who received placebo ($P = 0.005$). This finding comes from a *post hoc* analysis of the subset of patients who entered the Captopril Study with this condition ($n = 108$) (27). Remission of proteinuria was associated with achieving a lower systolic BP (126 ± 8 *versus* 140 ± 13 mmHg; $P = 0.002$).

Intensive DBP Control Decreases CV Risk

The UK Prospective Diabetes Study Group (UKPDS) further evaluated the effect of tight BP control on diabetes-related outcomes in hypertensive patients with type 2 diabetes ($n = 1,148$; median follow-up 8.4 yr) (28). First-choice antihypertensive therapy was captopril or atenolol (28). Intensive BP control

(<150/85 mmHg) significantly reduced rates of diabetes-related disease and death and of CV disease when compared with less stringent control (<180/105 mmHg) (28). The reduction in risk for fatal and nonfatal renal failure was NS (28). The lower BP target group showed a reduced risk for urinary albumin concentration ≥50 mg/L after 6 yrs of therapy (risk reduction 29%; $P = 0.009$) (28).

ACEI Therapy Favorably Reduces CV Risk When Compared with Calcium Channel Blockers

The Appropriate Blood Pressure Control in Diabetes trial was powered to detect differences in renal outcomes between two different BP-lowering strategies but failed to reach its primary end point. This occurred in part because renal function was well preserved at baseline, BP control was superb, and no proteinuria was present. Early in this trial, however, enalapril was associated with a reduced risk for CV events compared with nisoldipine in a subgroup of patients with both hypertension and type 2 diabetes ($n = 470$) (29). This finding comes from analysis of a secondary end point (29).

ACEI Therapy Reduces Risk for CV Events and Nephropathy in High-Risk Patients with Diabetes

The impact of ACEI therapy (ramipril) on CV risk in patients with diabetes was a primary outcome in the Heart Outcomes Prevention Evaluation (HOPE) (14). Ramipril significantly lowered the risk for the combined primary CV end point by 25% (14). Adjustment for change in BP did not alter this result. Ramipril also significantly reduced the risk for overt nephropathy and lowered albuminuria (14).

ARB Therapy Slows Renal Disease and Reduces ESRD in Hypertensive Patients with Nephropathy Resulting from Type 2 Diabetes

ARB therapy also has demonstrated a renoprotective effect in hypertensive patients with diabetes-related nephropathy. Irbesartan significantly lowered the risk for a primary composite renal end point by 19% compared with placebo and 24% compared with amlodipine after adjustment for MAP during treatment (16). Proteinuria fell by an average of 33% with irbesartan therapy, compared with 6% with amlodipine and 10% with placebo (16).

In a similar study population, losartan significantly reduced the risk not only for the primary composite outcome (time to doubling of baseline serum creatinine concentration, development of ESRD, or death) but also for ESRD alone when compared with placebo (15). These findings persisted after adjustment for BP (15). Losartan also decreased estimated GFR decline by 15.2% (4.4 *versus* 5.2 ml/min per 1.73 m^2; $P = 0.01$) and lowered the risk for first heart failure–related hospitalization by 32% ($P = 0.005$) (15).

ACEI and ARB Therapy Provide Equivalent Renal and CV Protection for Hypertensive Patients with Diabetes and Early Nephropathy

No large outcome trial has compared the renal effects of ACEI and ARB therapy. One small ($n = 250$) trial of patients with type 2 diabetes, hypertension, and early nephropathy (mean GFR 91.4 to 94.3 ml/min per 1.73 m^2) demonstrated that telmisartan was not inferior to enalapril in GFR change from baseline over 5 yrs (26).

Early Changes in Proteinuria Predict Long-Term Renal and CV Outcome

Multiple studies that demonstrated renoprotection with ACEI or ARB therapy also reported reduction in proteinuria (2–4). An analysis of trials in patients with hypertension and diabetes-related nephropathy

(2,3,15) and in patients without diabetes and with hypertension and nephropathy (4) revealed that initial changes in proteinuria showed a roughly inverse relationship to the degree of long-term renal deterioration.

Every 50% decrease in proteinuria during the first 6 mo of losartan or placebo treatment was associated with a 36% reduction in risk for the composite renal end point, a 45% reduction in risk for ESRD, and an 18% reduction in risk for CV events during subsequent follow-up (2,8). Losartan reduced average proteinuria by 35% from baseline during the 3.4-yr follow-up period (15). Much of this occurred in the first 6 mo of therapy, when proteinuria fell by 28% (2). Patients with a 15-mmHg decrease in systolic BP but a >30% increase in proteinuria had a four-fold elevated risk for ESRD (30).

Analysis of irbesartan's effects identified a similar pattern. For every 50% reduction in proteinuria in the first 12 mo of ARB therapy, risk for the combined renal outcome (doubling of baseline serum creatinine, serum creatinine = 6.0 mg/dl, or development of ESRD) fell by more than half (hazard ratio 0.44; 95% confidence interval [CI] 0.40 to 0.49; $P < 0.001$) (3). Proteinuria decreased by an average of 41% during the first year of irbesartan therapy, compared with an 11% reduction with amlodipine and a 16% reduction with placebo (3). Most of the reduction in proteinuria associated with ARB treatment occurred during the first 12 mo of the study (3).

Data from AASK demonstrate this relationship in patients without diabetes. Change in proteinuria at 6 mo predicted subsequent risk for ESRD (Figure 2) (4). This relationship extended to patients with baseline urinary protein excretion <300 mg/d. A 50% reduction in proteinuria at 6 mo was associated with a 72% reduction in risk for ESRD at 5 yrs (4). This was the first analysis to demonstrate that changes in low levels of proteinuria predict ESRD in patients with nondiabetic renal disease (4).

Role of ACEI and ARB Therapy in Management of Chronic Renal Disease Progression

On the basis of the previously summarized trials, treatment guidelines state that ACEI and ARB delay progression of renal disease and advise their use in hypertensive patients with kidney disease (5). Still, some researchers have questioned whether ACEI and ARB offer renoprotection independent of BP effects (31). A meta-analysis of 13 trials ($n = 37,089$) that compared the effect of ACEI or ARB with that of other antihypertensive agents found that ACEI or ARB therapy was associated with a small reduction in risk for ESRD (risk reduction 0.87; 95% CI 0.75 to 0.99; $P = 0.04$). This benefit was not observed in an analysis that was restricted to trials of patients with diabetes (four trials; $n = 14,437$) (31). These authors found that ACEI and ARB therapy did not reduce the risk for doubling serum creatinine or slowing GFR decline when compared with other antihypertensive agents (31).

ACEI or ARB therapy reduced daily albumin excretion in patients without diabetes (−15.73 mg/d; 95% CI −24.72 to −6.74; $P = 0.001$; 44 trials; $n = 5,266$) and in patients with diabetes (−12.21 mg/d; 95% CI −21.68 to −2.74) (31). These findings were clouded by evidence of small-study bias ($P < 0.001$) and significant study heterogeneity ($P < 0.0001$) (31). Authors of the meta-analysis concluded that BP lowering is more important than the drug class prescribed (31). Still, the significant reduction in risk for ESRD is noteworthy.

Renoprotection with ACEI Plus ARB Therapy

Some people develop ESRD even with ACEI or ARB therapy. This suggests a need for further reduction of renal progression than is possible with either agent alone. Investigators therefore compared the effect of ACEI (trandolapril) and ARB (losartan) therapy separately and in combination in 263 patients without diabetes and with moderately reduced renal function (mean calculated GFR 37.5 to 38.4 ml/min per 1.73 m^2). Most patients (≥90%) were hypertensive (17). The combined primary end point was time to doubling of serum creatinine concentration or development of ESRD (17). Patients were followed for a median of 2.9 yrs (17).

The trial was stopped early because of the benefit of combination therapy. Combination therapy favorably reduced the risk for reaching the combined end point when compared with either losartan (risk reduction 23 *versus* 11% for losartan; hazard ratio 0.40; 95% CI 0.17 to 0.69; $P = 0.016$) or trandolapril (reduction 23 *versus* 11% for trandolapril; hazard ratio 0.38; 95% CI 0.18 to 0.63; $P = 0.018$; Figure 3) (17). Change in proteinuria was independently associated with outcome (for every 10% proteinuria reduction: hazard ratio 0.58; 95% CI 0.24 to 0.88; $P = 0.022$) (17). BP reductions were similar across all three treatment groups (17).

Efficacy results were stratified on the basis of baseline proteinuria. Combining ACEI and ARB therapy significantly slowed renal disease progression in all three patient strata (<1 g/d, $P = 0.049$; 1 to <3 g/d, $P = 0.029$; ≥3 g/d, $P = 0.033$) (17). Urinary protein excretion decreased in all treatment groups but demonstrated the greatest reduction with combination therapy (maximum median reduction 42.1% with losartan, 44.3% with trandolapril, and 75.6% with combination therapy). In the combination-therapy group, patients with higher proteinuria (≥3 g/d) had greater reductions in proteinuria than did those with lower levels (<1 g/d) (17).

Ongoing Investigations

More information about the benefit of ACEI and ARB therapy will come from two major trials that are in progress. The Ongoing Telmisartan Alone and in Combination with Ramipril Global End-point Trial (ONTARGET) is a large ($n = 25,620$), double-blind, parallel-group trial that includes patients from 40 countries and is comparing ramipril, telmisartan, and combination treatment with both agents (32). The study population is similar to that for the HOPE trial (≥55 yr of age with a history of coronary artery disease, peripheral vascular disease, cerebrovascular disease, or diabetes with end-organ damage) (32). The end point is a composite of CV mortality, myocardial infarction, stroke, or hospitalization for heart failure. Patients will be followed for 3.5 to 5 yrs (32).

A similarly designed trial (Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease [TRANSCEND]) compares the effect of telmisartan and placebo on the same primary end point and in patients with the same profile as those in ONTARGET except for their intolerance of ACEI ($n = 6,000$) (32). Results of both trials are expected in 2008.

In addition to these studies, there is a large VA cooperative study planned to compare ACEI therapy alone *versus* combinations of ACEI and ARB on renal disease progression. It is believed that the study will start in 2008.

Conclusions

Results of multiple trials point to the renal benefits of ACEI and ARB therapy beyond those attributable to BP lowering. Evidence strongly suggests that these effects derive from a reduction in proteinuria. Most hypertensive patients require multiple-drug treatment to achieve target BP goals (5). Patients with hypertension and proteinuric renal disease should receive an ACEI or an ARB as an integral part of their therapy.

Disclosures

G.L.B. has served as a consultant to Abbott, Boehringer Ingelheim, BMS/Sanofi-Aventis, Forest, Glaxo Smith Kline, Merck, Novartis, Walgreen's formulary committee, Gileada, and Sankyo and has received research funding from National Institutes of Health (National Institute of Diabetes and Digestive and Kidney Disease/National Heart, Lung, and Blood Institute), Glaxo Smith Kline, Gileada, Forest, and Sanofi. He is also a member of the American Society of Nephrology Hypertension Executive Committee; editorial board member of *Kidney International*, *Diabetes Care*, *Hypertension*, *Journal of Clinical Hypertension*, *Translational Medicine*, *Journal of Clinical Pharmacology*, and *Nephrology, Dialysis, Transplantation*; and editor of *American Journal of Nephrology*.

Acknowledgments

This activity is supported by an independent educational grant from Boehringer Ingelheim.

Eileen A. McCaffrey, MA, Clarus Health, provided writing support.

Notes

Activity Production: Each author was provided with the final edited manuscript, which was transcribed by a medical writer from the author's original presentation, for final approval. The posttest questions were written on the basis of the supplement content and reviewed by the continuing medical education accreditor.

References

1. Peterson JC, Adler S, Burkart JM, Greene T, Hebert LA, Hunsicker LG, King AJ, Klahr S, Massry SG, Seifter JL: Blood pressure control, proteinuria, and the progression of renal disease. The Modification of Diet in Renal Disease Study. Ann Intern Med 123 :754 –762,1995 [PubMed: 7574193]

2. de Zeeuw D, Remuzzi G, Parving HH, Keane WF, Zhang Z, Shahinfar S, Snappin S, Cooper ME, Mitch WE, Brenner BM: Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: Lessons from RENAAL. Kidney Int 65 :2309 –2320,2004 [PubMed: 15149345]

3. Atkins RC, Briganti EM, Lewis JB, Hunsicker LG, Braden G, Champion de Crespigny PJ, DeFerrari G, Drury P, Locatelli F, Wiegmann TB, Lewis EJ: Proteinuria reduction and progression to renal failure in patients with type 2 diabetes mellitus and overt nephropathy. Am J Kidney Dis 45 :281 –287,2005 [PubMed: 15685505]

4. Lea J, Greene T, Hebert L, Lipkowitz M, Massry S, Middleton J, Rostand SG, Miller E, Smith W, Bakris GL: The relationship between magnitude of proteinuria reduction and risk of end-stage renal disease: Results of the African American Study of Kidney Disease and hypertension. Arch Intern Med 165

Clin J Am Soc Nephrol
Clin J A

:947 –953,2005 [PubMed: 15851648]

5. Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7). National High Blood Pressure Education Program, Bethesda, National Heart, Lung, and Blood Institute, National Institutes of Health, August2004. , NIH Publication No. 04-5230

6. Palmer BF: Proteinuria as a therapeutic target in patients with chronic kidney disease. Am J Nephrol 27 :287 –293,2007 [PubMed: 17457028]

7. Williams ME: Diabetic nephropathy: The proteinuria hypothesis. Am J Nephrol 25 :77 –94,2005 [PubMed: 15746541]

8. de Zeeuw D, Remuzzi G, Parving HH, Keane WF, Zhang Z, Shahinfar S, Snapinn S, Cooper ME, Mitch WE, Brenner BM: Albuminuria, a therapeutic target for cardiovascular protection in type 2 diabetic patients with nephropathy. Circulation 110 :921 –927,2004 [PubMed: 15302780]

9. KDOQI clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. Am J Kidney Dis 49[Suppl 2] :S1 –S179,2007

10. Retnakaran R, Cull CA, Thorne KI, Adler AI, Holman RR, for the UKPDS Study Group: Risk factors for renal dysfunction in type 2 diabetes: UK Prospective Diabetes Study 74. Diabetes 55 :1832 –1839,2006 [PubMed: 16731850]

11. Kramer HJ, Nguyen QD, Curhan G, Hsu C: Renal insufficiency in the absence of albuminuria and retinopathy among adults with type 2 diabetes mellitus. JAMA 289 :3273 –3277,2003 [PubMed: 12824208]

12. Wright JT, Bakris G, Greene T, Agadoa LY, Appel LJ, Charleston J, Cheek D, Douglas-Baltimore JG, Gassman J, Glassock R, Hebert L, Jamerson K, Lewis J, Phillips RA, Toto RD, Middleton JP, Rostand SG, for the African American Study of Kidney Disease and Hypertension Study Group: Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: Results from the AASK trial. JAMA 288 :2421 –2431,2002. [published erratum appears in *JAMA* 295: 2726, 2006] [PubMed: 12435255]

13. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia): Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. Lancet 349 :1857 –1863,1997 [PubMed: 9217756]

14. Heart Outcomes Prevention Evaluation (HOPE) Study Investigators: Effects of ramipril on cardiovascular and microvascular outcome in people with diabetes mellitus: Results of the HOPE study and the MICRO-HOPE substudy. Lancet 355 :253 –259,2000 [PubMed: 10675071]

15. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S, for the RENAAL Study Investigators: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 345 :861 –869,2001 [PubMed: 11565518]

16. Lewis EJ, Hunsicker LC, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I, for the Collaborative Study Group: Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 345 :851 –860,2001 [PubMed: 11565517]

17. Nakao N, Yoshimura A, Morita H, Takada M, Kayano T, Ideura T: Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): A randomised controlled trial. Lancet 361 :117 –124,2003 [PubMed: 12531578]

18. Maschio G, Alberti D, Janin G, Locatelli F, Mann JF, Motolese M, Ponticelli C, Ritz E, Zucchelli P, for the Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study Group: Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. N Engl J Med 334 :939 –945,1996 [PubMed: 8596594]

19. Ruggenenti P, Perna A, Gherardi G, Gaspari F, Benini R, Remuzzi G: Renal function and requirement for dialysis in chronic nephropathy patients on long-term ramipril: REIN follow-up trial. Gruppo Italiano di Studi Epidemiologici in Nefrologia (GISEN). Ramipril Efficacy in Nephropathy. Lancet 352 :1252 –1256,1998 [PubMed: 9788454]

20. Ruggenenti P, Perna A, Gherardi G, Garini G, Zoccali C, Salvadori M, Scolari F, Schena FP, Remuzzi G: Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. Lancet 354 :359 –364,1999 [PubMed: 10437863]

21. Chua DC, Bakris GL: Is proteinuria a plausible target of therapy? Curr Hypertens Rep 6 :177 –181,2004 [PubMed: 15128468]

22. Mann JF, Yi QL, Gerstein HC: Albuminuria as a predictor of cardiovascular and renal outcomes in people with known atherosclerotic cardiovascular disease. Kidney Int Suppl 92 :S59 –S62,2004 [PubMed: 15485420]

23. Yuyun MF, Dinneen SF, Edwards OM, Wood E, Wareham NJ: Absolute level and rate of change of albuminuria over 1 year independently predict mortality and cardiovascular events in patients with diabetic nephropathy. Diabetes Med 20 :277 –282,2003

24. US Renal Data System: USRDS 2006 Annual Data Report: Atlas of End-Stage Renal Disease in the United States, Bethesda, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health,2006

25. Bakris GL, Weir M: ACE inhibitors and protection against kidney disease progression in patients with type 2 diabetes: What's the evidence? J Clin Hypertens 4 :420 –423,2002

26. Barnett AH, Bain SC, Bouter P, Karlberg B, Madsbad S, Jervell J, Mustonen J, for the Diabetics Exposed to Telmisartan and Enalapril Study Group: Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. N Engl J Med 351 :1952 –1961,2004 [PubMed: 15516696]

27. Hebert LA, Bain RP, Verme D, Cattran D, Whittier FC, Tolchin N, Rohde RD, Lewis EJ: Remission of nephrotic range proteinuria in type 1 diabetes. Collaborative Study Group. Kidney Int 46 :1688 –

1693,1994 [PubMed: 7700028]

28. UK Prospective Diabetes Study Group: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes. UKPDS 38. BMJ 317 :703 –713,1998. [published erratum appears in *BMJ* 318: 29, 1999] [PMCID: PMC28659] [PubMed: 9732337]

29. Estacio RO, Schrier RW: Antihypertensive therapy in type 2 diabetes: Implications of the appropriate blood pressure control in diabetes (ABCD) trial. Am J Cardiol 82 :9R –14R,1998

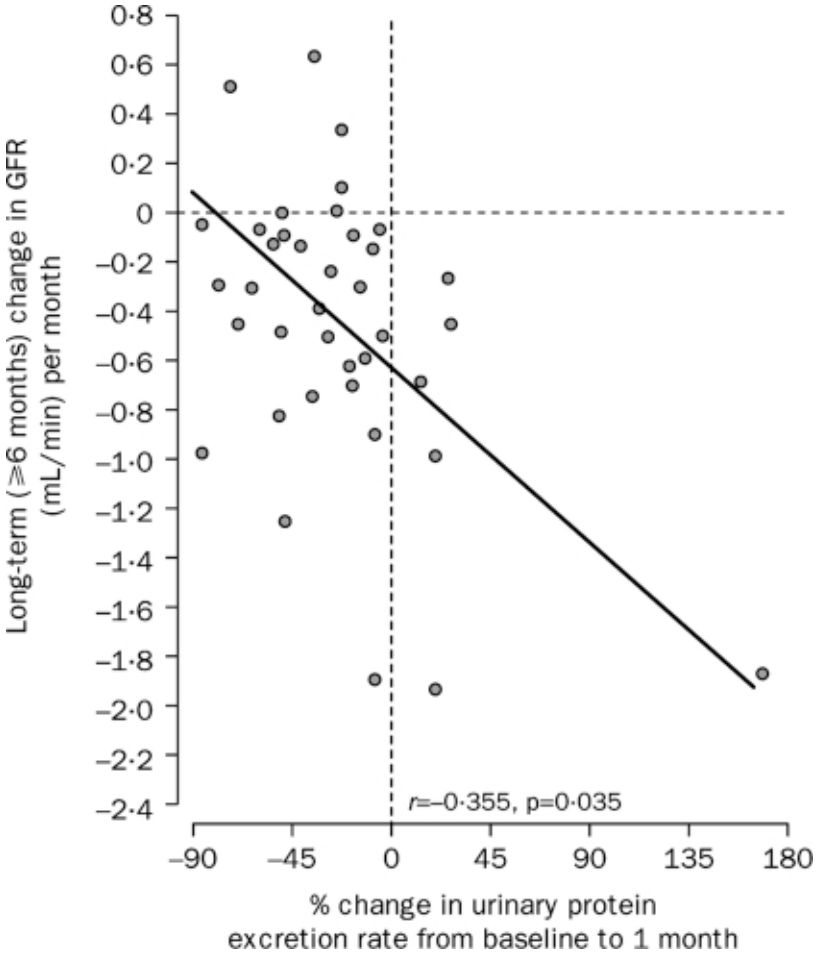
30. Eijkelkamp WB, Zhang Z, Remuzzi G, Parving HH, Cooper ME, Keane WF, Shahinfar S, Gleim GW, Weir MR, Brenner BM, de Zeeuw D: Albuminuria is a target for renoprotective therapy independent from blood pressure in patients with type 2 diabetic nephropathy: Post hoc analysis from the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial. J Am Soc Nephrol 18 :1540 –1546,2007 [PubMed: 17409317]

31. Casas JP, Chua W, Loukogeorgakis S, Vallance P, Smeeth L, Hingorani AD, MacAllister RJ: Effect of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: Systematic review and meta-analysis. Lancet 366 :2026 –2033,2005 [PubMed: 16338452]

32. Teo K, Yusuf S, Sleight P, Anderson C, Mookadam F, Ramos B, Hilbrich L, Pogue J, Schumacher H, for the ONTARGET/TRANSCEND Investigators: Rationale, design, and baseline characteristics of 2 large, simple, randomized trials evaluating telmisartan, ramipril, and their combination in high-risk patients: The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (ONTARGET/TRANSCEND) trials. Am Heart J 148 :52 –61,2004 [PubMed: 15215792]

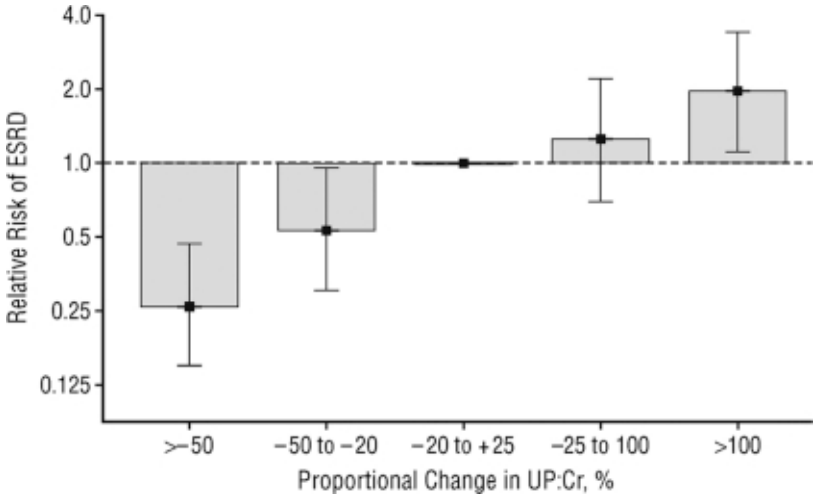
Figures and Tables

Figure 1.



Early proteinuria change predicts long-term renal decline. Correlation between early (1 mo after randomization) percentage change in urinary protein excretion from baseline and long-term (>6 mo after randomization) rate of GFR decline among 36 patients who received ramipril in the high-proteinuria (baseline ≥3 g/d) group. Reprinted from reference (13), with permission.

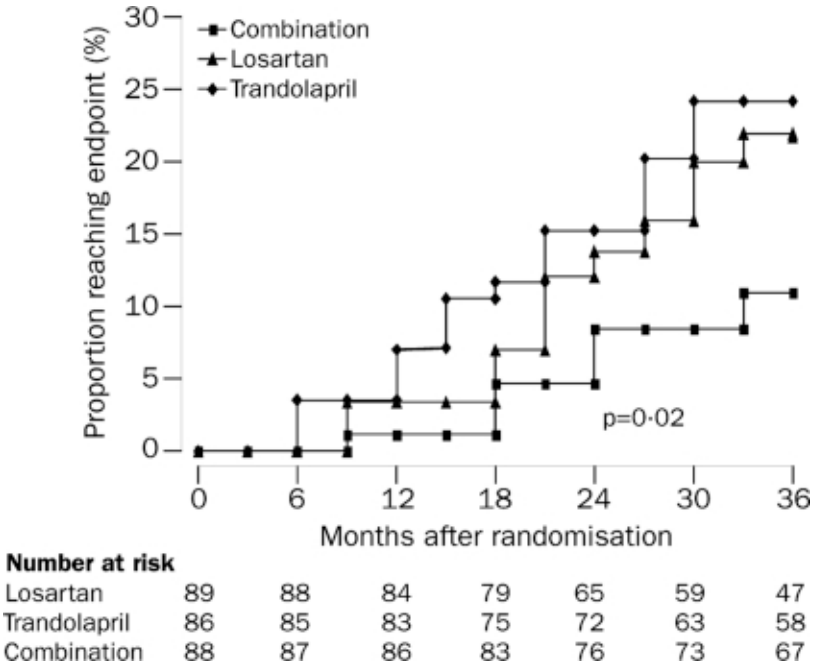
Figure 2.



Six-month change in proteinuria predicts risk for ESRD. Relationship between the risk for ESRD and initial change in

proteinuria. The relative risk for ESRD during follow-up for different subgroups, defined by the change in the urine protein-to-creatinine ratio (UP:Cr) from baseline to 6 mo and controlling for randomized treatment group and the initial level of proteinuria, is shown. The reference group ranges from a 20% reduction in UP:Cr to a 25% increase. The cutoff values that define the change-in-proteinuria subgroups correspond to percentage changes that are symmetric on the log scale. Error bars represent SE. Reprinted from reference (4), with permission.

Figure 3.



Combination angiotensin-converting enzyme inhibitor (ACEI)/angiotensin II receptor blocker (ARB) reduced risk for renal end point *versus* ACEI or ARB. Effect of losartan plus trandolapril compared with the effect of either agent alone on end point (time to doubling of serum creatinine or ESRD). Patients did not have diabetes and had hypertension and chronic nephropathy. Reprinted from reference (17), with permission.

Table 1.

Renoprotection in patients without diabetes[a]

Study, Study Design, Subjects	Outcome Measure(s)	Findings
Peterson *et al.* (1)		
Randomized; n = 840; stratified by BL GFR: Higher GFR = 25 to 55 ml/min per 1.73 m^2 (n = 585), lower GFR = 13 to 24 ml/min per 1.73 m^2 (n = 255)	Effect of normal (MAP ≤107 mmHg if ≤60 yr or ≤113 mmHg if ≥61 yr) *versus* low BP goal (≤92 mmHg if ≤60 yrs or ≤98 mmHg if ≥61 yrs) on GFR, and relationship to baseline proteinuria; any antihypertensive agent allowed, ACEI suggested as first choice; mean follow-up 2.2 yrs	GFR declined faster in those with higher BL proteinuria (>0.25 g/d if higher GFR [P = 0.02] or >1 g/d if lower GFR [P = 0.01]); higher BL proteinuria was associated with greater benefit of low MAP goal.

Maschio *et al.* (18)		
Prospective, double-blind; patients randomly assigned to benazepril or placebo (n = 583)[b]; renal function: mild (CrCl = 46 to 60 ml/min) or moderate (CrCl = 30 to 45 ml/min) renal disease; 81 to 83% hypertensive	Composite outcome: time to doubling of BL SC or ESRF; duration 3 yrs	ACEI reduced risk by 53% (95% CI 27 to 70%) in overall population; RR 38% (95% CI 3 to 61%) when adjusted for DBP; RR 39% (95% CI 5 to 61%) when adjusted for change in proteinuria
GISEN group (13); Ruggenenti *et al.* (19,20)		
Prospective, double-blind; patients randomly assigned to ramipril or placebo (n = 352)[b]; 79 to 86% hypertensive; renal function: CrCl = 20 to 70 ml/min per 1.73 m^2; patients stratified by BL proteinuria	Primary outcome if proteinuria ≥3 g/d (n = 166): Rate of GFR decline; secondary outcomes: composite of time to doubling of BL SC or ESRF, change in proteinuria; trial stopped earlyPrimary outcome if proteinuria = 1 to 2.9 g/d (n = 186): Rate of GFR decline, time to ESRF, time to proteinuria ≥3 g/d; median follow-up 31 mo	Proteinuria ≥3 g/d: ACEI slowed rate of GFR decline: 0.53 (SE 0.08) *versus* 0.88 (SE 0.13) ml/min (P = 0.03); reduced risk for secondary composite outcome (P = 0.02); reduced urinary protein excretion *versus* BL (median 55% at 36 mo)[c]Proteinuria 1 to 2.9 g/d: ACEI reduced risk for ESRF (RR 2.72; 95% CI 1.22 to 6.08) and of proteinuria ≥3 g/d (RR 2.40; 95% CI 1.27 to 4.52)
Wright *et al.* (12)		
Prospective, 3 × 2 factorial trial; patients randomly assigned to ramipril, metoprolol, or amlodipine and to a normal (102 to 107 mmHg) or low (≤92 mmHg) MAP goal (n = 1,094)[b]	Composite outcome: ≥50% reduction in GFR *versus* BL or ≥25 ml/min per 1.73 m^2, ESRD, or death; follow-up ≤4 yrs	ACEI reduced risk *versus* metoprolol by 22% (95% CI 1 to 38%; P = 0.04) and *versus* amlodipine by 38% (95% CI 14 to 56; P = 0.004); metoprolol *versus* amlodipine NS; lower MAP goal, NS effect

[a]ACEI, angiotensin-converting enzyme inhibitor; BL, baseline; CI, confidence interval; CrCl, creatinine clearance; CV, cardiovascular; DBP, diastolic BP; ESRF, end-stage renal failure; MAP, mean arterial pressure; RR, relative risk; SC, serum creatinine.
[b]Other antihypertensive therapy allowed as needed; roughly two thirds of patients received diuretic therapy.
[c]Urinary protein excretion did not change significantly in the placebo group (13).

Table 2.

Renoprotection in patients with diabetes[a]

Study, Study Design, Subjects	Outcome Measure(s)	Findings
HOPE Study (14)		
Prospective; patients randomly assigned to ramipril or placebo (n = 3,577); diabetes; ≥55 yrs of age; previous CV event or ≥1 other CV risk factor; no clinical proteinuria[b]; 56% hypertensive	Combined primary end point: MI, stroke, CV death; secondary end point: overt nephropathy (defined as clinical proteinuria); follow-up 4.5 yrs	ACEI reduced risk for primary end point by 25% (95% CI 12 to 36%; P = 0.0004); ACEI reduced risk for overt nephropathy by 24% (95% CI 3 to 40%; P = 0.027); ACEI reduced albumin/creatinine ratio at 1 yr (P = 0.001) and at study end (P = 0.02).
Lewis *et al.* (16)		
Prospective; patients randomly assigned to irbesartan, amlodipine, or placebo[c] (n = 1,715); hypertension, type 2 diabetes, nephropathy (SC 1 to 3 mg/dl; urinary protein excretion ≥900 mg/d)	Primary outcome: time to doubling of BL SC, ESRD, or death; outcomes adjusted for MAP during follow-up; mean follow-up 2.6 yrs	ARB reduced risk for primary end point by 19% (adjusted RR 0.81; 95% CI 0.67 to 0.99; P = 0.03) *versus* placebo and by 24% (adjusted RR 0.76; 95% CI 0.63 to 0.92; P = 0.005) *versus* amlodipine
Brenner *et al.* (15)		
Prospective; patients randomly assigned to losartan or placebo[c] (n = 1,513); hypertension, type 2 diabetes, nephropathy	Primary outcome: time to doubling BL SC, ESRD, or death; outcomes adjusted for BP; mean follow-up 3.4 yrs	ARB reduced risk for primary end point by 15% (P = 0.03) *versus* placebo; ARB reduced risk for ESRD by 26% (P = 0.007)

[a]ARB, angiotensin II receptor blocker; CV, cardiovascular; MI, myocardial infarction.
[b]Total protein excretion ≥500 mg/d, urine albumin ≥300 mg/d, or albumin-to-creatinine ratio >36 mg/mmoL.
[c]Other antihypertensive therapy allowed as needed.