Save Your Kidneys—Part 1
The Hard Way, with Medications

(This is a technical article, but very important to anyone with kidney disease or taking any of the anti-angiotensin medications—ACE-I or ARB.)

The prevalence of chronic kidney disease in the US adult population is estimated to be 10.8% (approximately 19.2 million people). In 1999 in the USA 357,000 people had end-stage kidney disease and the annual cost of dialysis and kidney transplant exceeded $15.6 billion. Almost 70% of new cases of end-stage kidney disease are due to hypertension, diabetes or glomerulonephritis—and these common conditions are in most cases a direct result of foods consumed on the Western diet.

Protein found in the urine in amounts of 30 mg/day or greater, is the hallmark sign for the beginnings of chronic kidney disease. Over 300 mg/day is considered serious kidney disease. In general, the more protein in the urine, the worse the kidney disease. Not only does the protein in the urine reflect the health of the kidneys, but this is a reliable sign of the health of the rest of the body, including the blood vessels of the heart, brain, and eyes. Lowering the amount of protein in the urine in some cases reflects an improvement in the kidneys and a person's overall health.

Medications to Prevent Progressive Kidney Disease

There are four classes of medications that are believed to slow the progression of kidney disease: antihypertensive agents, drugs that have a blockade effect on the renin-angiotensin-aldosterone system, cholesterol-lowering agents (usually statins), and blood-sugar lowering medications.

Common recommendations are to reduce the blood pressure levels to 130/85 mmHg for people with high blood pressure and kidney disease from diabetes. However, blood pressures of 140/90 mmHg may be low enough and lowering the blood pressure too much is considered detrimental.[1] For example, in one recent study of patients with coronary heart disease treated with sustained-release verapamil (a calcium channel blocker) or atenolol to lower blood pressure, the risk of death and heart attack was increased when the diastolic pressure (the lower number) was reduced below 70 to 80 mm Hg.[2] The harmful effects of lowering blood pressure were greater for people with diabetes and/or elevated cholesterol. The incidence of heart attacks, death, and/or stroke was three times higher for patients treated with medications with a diastolic blood pressure (the lower number) of 60 mmHg compared to a person with a pressure of 80 to 90 mmHg.[2] (A lower blood pressure for people *not on medication* is, in contrast, healthy.)

Recommendations are to lower cholesterol levels with statins to below 150 mg/dl and LDL choles-

terol below 77 mg/dl.[3] Decreases in blood sugars over the long-term (as measured by Hgb A1c levels) have also been shown to slow kidney disease in people with type-1 diabetes.

Two Categories of Anti-angiotensin Medications

ACE-I: Accupril (quinapril), Aceon (perindopril), Altace (ramipril), Capoten (Captopril), Lotensin (benazepril), Mavik (trandolapril), Monopril (fosinopril), Prinivil (lisinopril), Univasc (moexipril), Vasotec (enalapril), Zestril (lisinopril)

ARB: Cozaar (losartan), Atacand (candesartan), Teveten (eprosartan), Avapro (irbesartan), Micardis (telmisartan), Benicar (olmesartan), Hyzaar (losartan) and Diovan (valsartan).

Renal Protective Anti-Angiotensin Drugs

Medications used to slow the progression of kidney disease are referred to as "renal-protective" (or renoprotective) and the most popular of these are a class of blood pressure lowering medications which inhibit the activity of an adrenal hormone called angiotensin. (I will refer to these as anti-angiotensin medications.)

These medications fall into two general classes: The kinds that block the production of angiotensin by the adrenal gland are known as *angiotensin-converting enzyme inhibitors* (ACE-I) and those that block the activity of this hormone at the places where it works in the body (the receptor sites) are called *angiotensin receptor blockers (*ARB*).* Research has found the more severe the kidney damage, as reflected by a larger amount of protein in the patient's urine, the greater the benefits from these medications.

Disease Mongering with Proteinuria

The bulk of the research on the medications that modify the effects of angiotensin is funded by the pharmaceutical companies, so the real truths about the benefits of these drugs are hard to know for certain. The amount of protein in the patient's urine (proteinuria) is the "end point" most often measured to determine a drug's benefit. However, the "end points" most meaningful to the patient are staying alive, healthy, and off a dialysis machine. Research has clearly established that these medications will decrease the amount of protein in the urine, but their benefits for improved health are seriously questioned.

An example of the lack of a direct connection between reducing proteinuria with medication and a patient's improved health is the diabetic medication Avandia. (Avandia is also known as rosiglitazone.) Rosiglitazone combined with metformin has been proven to provide a greater reduction in proteinuria than other oral antidiabetic combinations.[4] Yet, the *New England Journal of Medicine* on June 2007 published the results of diabetics taking rosiglitazone—they found a 43% increased risk of

a heart attack and a 64% increased risk of death from all cardiovascular causes.[5] Thus, diabetic patients using Avandia will be more likely to die, but they will die with less protein in their urine.

Renal-protective Effects of Anti-Angiotensin Drugs Questioned

A study recently published in the Lancet concluded, "…claims that ACE inhibitors and ARBs are renoprotective in diabetes seem to derive from small placebo-controlled trials that provide uncertain evidence of the existence of any true advantage over and above blood-pressure control… There seems to be little justification for ACE inhibitors or ARBs to be first-line choices for renoprotection in diabetes on the basis of efficacy, and residual uncertainty still exists about the inherent value of these drugs in other renal disorders. In view of the present analysis, treatment decisions for hypertension in renal disease should be based on the blood-pressure-lowering effect, comparative tolerability, and cost of antihypertensive treatment."[6]

Not only may these two categories of anti-angiotensin medications (ACE-I and ARB) have no special benefits, they may actually be more harmful than other antihypertensive medications. There is good evidence from one very large study that ACE-I drugs result in a higher risk of stroke and cardiovascular disease (like heart failure and heart surgery) when compared to the use of inexpensive diuretics (chlorthalidone) for the treatment of hypertension.[7]

ARB Increase the Risk of Stroke and Heart Disease[8]

The VALUE trial showed the angiotensin receptor blocker valsartan produced a statistically significant 19% relative increase in myocardial infarction (fatal and non-fatal) compared with amlodipine and a 13% increase in the incidence of stroke in patients taking valsartan.

The CHARM-alternative trial showed a significant 36% increase in myocardial infarction with candesartan (versus placebo) despite a reduction in blood pressure (4.4 mm Hg systolic and 3.9 mm Hg diastolic) vs. placebo treatment.

The SCOPE study, candesartan was associated with a non-significant 10% increase in fatal plus non-fatal myocardial infarction despite lower blood pressure (3.2 mm Hg systolic and 1.6 mm Hg diastolic) for candesartan vs. placebo.

Patients with Diabetes without Proteinuria

A common practice by almost all doctors these days is to treat all diabetics, with or without hypertension, with ACE-I and/or ARB drugs, even when they have no protein in their urine. The highly respected Cochrane review of diabetic patients, many with hypertension, but no protein in their urine, found the future development of protein in the urine was reduced by ACE-I medications, but this had no effect on progression of kidney disease or risk of death.[9] Another recent review of the current evidence concluded: "Until more evidence accumulates on the alleged renoprotection associated with RAS inhibition (inhibition of the renin-angiotensin system), it seems reasonable for clinicians to not use pharma-

cologic intervention with ACE inhibitors or ARBs in normotensive patients with diabetes. For hypertensive patients with diabetes, prescribing a thiazide diuretic would also seem to represent the practice of evidence-based medicine."[10] In addition, patients with kidney disease from causes other than diabetes with low levels of protein in their urine (500 mg/day or less) have not been shown to benefit from ACE-I or ARB medications.[11]

What To Do?

Kidney disease is a serious problem and people with diabetes are at especially high risk of losing the function of their kidneys. Treating high blood pressure, cholesterol, and blood sugar with medications will be of some benefit. However, these medications are associated with serious side effects and financial costs. ACE-I and ARB medications are highly profitable for the pharmaceutical industry and as a result they have spent billions of dollars for research that favors their products and marketing to their sales division, the medical doctors. As discussed above, the real benefits for the patient of using these medications, over less expensive ones, are in doubt. Based on available research, a diuretic, such as chlorthalidone, would be the drug of first choice for treating hypertension in patients with kidney disease. People with diabetes and no protein in their urine should not routinely receive so-called "renal-protective" medications in the form of ACE-I or ARB. In addition, people with kidney disease from non-diabetic causes and no protein in their urine should not take these medications for "renal-protection." For people with diabetes and significant kidney disease, given a choice between use of an ACE-I and ARB, the ACE-I are more effective with fewer risks that the ARB.[12]

Hypertension, elevated cholesterol, and type-2 diabetes are due to the Western diet. Likewise, the health of the heart, kidneys, arteries, and the rest of the body is dependent on a healthy diet. What is missing in the current treatment of people with kidney disease is diet-therapy. For almost seventy years doctors have been aware of the profound effect that a healthy diet has on preserving kidney function, and even reversing some of the kidney damage. Next month's newsletter will continue with a discussion of the most effective form of renal-protection: a healthy, cost-free, low-protein vegan diet.

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