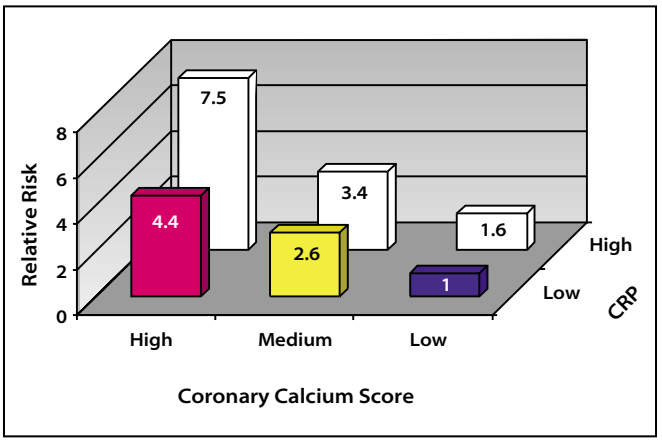

Figure 2. *Relative risks of nonfatal myocardial infarction, coronary death, coronary bypass surgery, or stroke (composite end point) associated with high (≥75th percentile = 4.05 mg/L) and low (<4.05 mg/L) levels of C-reactive protein (CRP) and high (>142.1), medium (3.7–142.1), and low (<3.7) tertiles of coronary calcium scores.*

cant and independent predictor of acute myocardial infarction or coronary death or a composite of cardiovascular events that included myocardial infarction, death, stroke, and revascularization ($P < .005$), whereas elevated CRP was a marginal predictor of myocardial infarction or coronary death ($P = .09$), but a significant predictor of the composite end point ($P = .03$). The subjects were divided into tertiles for coronary calcium scores: < 3.7, tertile 1; 3.7–142.1, tertile 2; and > 142.1, tertile 3. Within each tertile, those with elevated CRP (≥75th percentile of CRP level) had a higher relative risk for myocardial infarction as well as the composite end point (Figures 1 and 2). A lack of interaction between CRP and coronary calcium scores, along with the complementary predictive power of these two variables, suggests that these factors assess different aspects or mechanisms responsible for clinical events. Calcium likely reflects atherosclerosis, whereas CRP reflects the activity (ie, inflammatory activity) of the disease and, therefore, indicates a propensity to complications of atherosclerosis (plaque disruption and thrombosis), in which inflammation has been causally implicated. ■

A lack of interaction between CRP and coronary calcium scores, along with the complementary predictive power of these two variables, suggests that these factors assess different aspects or mechanisms responsible for clinical events.

Hypertension

Angiotensin Receptor Blockers Versus Angiotensin Converting Enzyme Inhibitors and the Treatment of Hypertension in Diabetic Patients

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With U.S. Food and Drug Administration approval of losartan, angiotensin receptor blockers (ARBs) have been available for use as a treatment for hypertension. The ability of these agents to selectively block the angiotensin receptor differs from the mechanism of the angiotensin converting enzyme (ACE) inhibitors, which block the conversion of angiotensin$_1$ to angiotensin$_2$ and inhibit the breakdown of bradykinin. The distinct differences in the mechanisms of these compounds have fueled an ongoing debate regarding the relative benefits of one over the other (or the combination of the two) for more effective treatment of hypertension in special populations, such as for diabetic patients or for the treatment of congestive heart failure.

We will review the findings of three important articles and their implications for the treatment of type 2 diabetics with nephropathy or microscopic albuminuria.

Effects of Losartan on Renal and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Nephropathy

Brenner B, Cooper M, De Zeeuw D, et al.
N Engl J Med. 2001:345:861–869.

In a double-blind trial, Brenner and colleagues randomized 1513 patients to losartan (50–100 mg/d) or placebo in addition to conventional anti-hypertensive therapies except for ACE inhibitors. Patients included those who had been diagnosed with diabetic nephropathy. Nephropathy was defined as the presence on two occasions of a ratio of urinary albumin (mg/L) to creatinine

(g/L) from a first morning specimen of at least 300 and serum creatinine levels of 1.5–3.0 mg/dL. Patients who had type 1 diabetes or renal artery stenosis were excluded. The trial was designed to follow patients for 3.5 years. The study was discontinued prematurely by the steering committee as evidence emerged of a protective effect of losartan. The primary end point of this trial was the composite end point of a doubling of the baseline serum creatinine, end-stage renal disease (long-term dialysis or renal transplant), and death.

Baseline characteristics of the study population included a mean age of 60 years, 61% male, mean blood pressure of 152/82 mm Hg, serum creatinine of 1.9 mg/dL, median urinary albumin/creatinine ratio of 1237–1261, low-density lipoprotein cholesterol of 142 mg/dL, and glycosylated hemoglobin of 8.5%.

A reduction of the composite end point of 16% ($P = .02$) was observed with the use of losartan. There was no reduction in mortality in the losartan group compared with the placebo group (6.8% and 6.6%, respectively; $P = .88$). Treatment with losartan resulted in a 28% reduction of end-stage renal disease compared with placebo (19.6% vs 25.5%; $P = .002$) and a 25% reduction of the doubling of serum creatinine compared with placebo (21.6% vs 26%; $P = .006$).

A secondary end point of first hospitalization for congestive heart failure was reduced by 32% ($P = .005$) with losartan treatment. No difference was observed in the morbidity or mortality from cardiovascular causes. Approximately one third of all patients experienced a fatal or nonfatal myocardial infarction during the study period; this is attributable to the high-risk population that constitutes patients with type 2 diabetes and nephropathy. There are no data comparing global left ventricular function or chamber dimensions before or after treatment. Because there was no reduction in the incidence of myocardial infarctions, the reduction of progression to heart failure may be explained by either a direct protective effect of ARBs on ventricular diastolic or systolic function or enhanced fluid and sodium balance in those patients who do not progress to end-stage renal disease.

The major findings of this study support the use of the ARBs in type 2 diabetic patients with nephropathy to prevent the progression to end-stage renal insufficiency. Though there was a reduction of first-time hospitalizations for congestive heart failure, there was no reduction of cardiovascular death or myocardial infarction. The benefits observed accrued on top of other conventional anti-hypertensive therapies. Previous trials comparing the addition of ACE inhibitors to conventional therapies have shown its superiority in reducing the progression of proteinuria compared with other treatments but not the progression of the more important end point of end-stage renal failure.[1–3] The ARBs may therefore be considered the agents of choice in patients with diabetic nephropathy to prevent the progression of end-stage renal disease and perhaps slow the development of congestive heart failure in this population.

Renoprotective Effect of the Angiotensin Receptor Antagonist Irbesartan in Patients with Nephropathy Due to Type 2 Diabetes

Lewis E, Hunsicker L, Clarke W, et al.
N Engl J Med. 2001:345:851–860.

In Lewis and associates' trial, the potential renoprotective effects of another ARB, irbesartan, was evaluated in patients with diabetic nephropathy. In this trial, 1715 patients were randomized to receive irbesartan (300 mg/d), amlodipine (10 mg/d), or placebo to reach a target blood pressure of 135/85 mm Hg or less. Subjects included those with a documented diagnosis of diabetes mellitus and proteinuria with >900 mg of urinary protein excretion per day who had blood pressures greater than 135/85 mm Hg. Just as in the study by Brenner and colleagues, the primary end point was the composite of death from any cause, development of end-stage renal disease, and doubling of the serum creatinine from baseline levels. Baseline characteristics included the following: mean age of 59 years, blood pressure of 158–160/87 mm Hg, 57%–59% of patients receiving insulin, 27%–30% of patients with a history of stroke, serum creatinines around 1.7 mg/dL, 1.6–1.8 grams of urinary protein excretion over 24 hours, and glycosylated hemoglobin of about 8.2%.

Irbesartan was renoprotective in diabetic patients with nephropathy.

After follow-up for a mean of 2.6 years, irbesartan was associated with a 20% reduction of the primary composite end point compared with placebo ($P = .02$). There was a slight trend for an increase in the composite event rate in the amlodipine group compared with placebo (41.1% vs 39.0%; P = ns). The risk of a doubling of the serum creatinine concentration was 33% lower in the irbesartan group compared with the placebo group (16.9% vs 23.7%; $P = .003$) and higher in the amlodipine group (25.4%). The risk of developing end-stage renal disease

was 14.2% in the irbesartan group, 18.3% in the amlodipine group, and 17.8% in the placebo group, resulting in a strong trend toward improvement in the irbesartan group compared with placebo and amlodipine ($P = .07$). Proteinuria decreased by 33% in the irbesartan group, 10% in the placebo group, and 6% in the amlodipine group. There was no significant reduction in death rates. There was no difference in the mean arterial blood pressure between the irbesartan and amlodipine groups.

Irbesartan was renoprotective in type 2 diabetic patients with nephropathy. The renoprotective effects may be related to the reduction of intrarenal angiotensin activity. Whether this renoprotective effect of ARBs extends to ACE inhibitors in type 2 diabetics is certainly questionable. Data from the Ramipril Efficacy in Nephropathy study showed that patients treated with ramipril lost renal function faster than those assigned to other blood pressure treatments.[4] The United Kingdom Prospective Diabetes Study showed that treatment with ACE inhibitors was no better than with β-blockers in preventing the progression of nephropathy.[5] Another study did show a slowing of the progression of diabetic renal disease in patients treated with an ACE inhibitor.[6] The ability of alternate pathways in the kidneys to convert angiotensin$_1$ to angiotensin$_2$ independent of the ACE pathway and the ability of the ARBs to block the effect of angiotensin at the receptor level may explain any possible differential effect in diabetic patients with nephropathy.

The Effect of Irbesartan on the Development of Diabetic Nephropathy in Patients with Type 2 Diabetes

Parving H, Lehnert H, Mortensen J, et al.
N Engl J Med. 2001:345:870–878.

In the multinational, placebo-controlled study by Parving and colleagues, 590 patients with type 2 diabetes and microalbuminuria were randomized to irbesartan, 150 mg/d or 300 mg/d, or placebo and followed for 2 years. This trial enrolled patients aged 30–70 years with type 2 diabetes and microalbuminuria (albumin excretion rate of 20–200 μg/min) and serum creatinine of no more than 1.5 mg/dL in men and 1.1 mg/dL in women. The primary end point was the development of overt nephropathy, defined as a urinary albumin excretion greater than 200 μg/min and at least 30% higher than the baseline rate.

During the 2-year study, the risk of nephropathy was reduced by 44% in the irbesartan 150-mg group ($P = .05$) and by 68% in the irbesartan 300-mg group ($P < .001$) compared with placebo. Irbesartan reduced the level of urinary albumin by 24% in the 150-mg group and 38% in the 300-mg group, with a 2% decline in the placebo group. Nonfatal cardiovascular events occurred in 8.7% of patients in the placebo group and 4.5% of those in the 300-mg irbesartan group ($P = .11$). The authors' conclusion is that irbesartan is renoprotective independent of its blood pressure lowering effect in hypertensive patients with type 2 diabetes and microalbuminuria.

Diabetes is the most common cause of end-stage renal disease, accounting for 40% of cases.[7] The increasing incidence and prevalence of end-stage renal disease in the United States is creating a major health care burden. The three trials reviewed here provide evidence of the renoprotective and, to a lesser extent, cardioprotective properties of the ARBs irbesartan and losartan in patients with diabetic nephropathy. Losartan and irbesartan were both found to reduce the progression of diabetic nephropathy. In addition, irbesartan was found to reduce the development of frank diabetic nephropathy in patients with microalbuminuria. These studies certainly create a solid case for the use of losartan and irbesartan to prevent the progression of renal disease in type 2 diabetic patients. Whether this effect is specific to these two agents or represents a class effect is open to question. The larger question is identifying the superior antihypertensive agent for use in the diabetic patient with or at risk for the development of nephropathy. Despite the lack of consistent favorable data, there seems to be a prevailing opinion among practitioners that ACE inhibitors offer a renoprotective effect in type 2 diabetics. Any confusion may be the result of generalizing the results with type 1 diabetics to the very different results with type 2 diabetics. At the present time, there are no data assessing the efficacy of an ACE inhibitor compared with an ARB (or their combination) in patients with type 2 diabetes to prevent the progression of nephropathy.

The trials reviewed here provide evidence of the renoprotective and, to a lesser extent, the cardioprotective properties of irbesartan and losartan in patients with diabetic nephropathy.

An evidence-based contemporary approach to renal preservation would entail the use of an ACE inhibitor to prevent progression of renal dysfunction in patients with type 1 diabetes mellitus and nondiabetic renal dysfunction and an ARB, such as irbesartan or losartan, to prevent progression in patients with type 2 diabetes. ■

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Cardiovascular Disease

Does the Lysyl Oxidase Gene *Lox* Play a Critical Role in Cardiovascular Disease?

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Inactivation of Lysyl Oxidase Gene *Lox* Leads to Aortic Aneurysms, Cardiovascular Dysfunction, and Perinatal Death in Mice

Mäki JM, Räsänen J, Tikkanen H, et al.

Circulation. 2002;106:2503–2509.

The pathophysiology of the formation of an aortic aneurysm involves the degradation of elastin. The cross-linking of elastin and collagen is an important determinant of tensile strength, and this cross-linking is mediated by a family of five isoenzymes, called lysyl oxidases.

The study investigators from Finland created a mouse model in which one of the lysyl oxidase genes, called *Lox*, was knocked out. These mice died at birth, and a detailed examination showed fragmentation of elastin lamellae in the aorta, as well as aortic aneurysms and diaphragmatic hernias, in some of the mice. The aortic pulsatility index, as measured by Doppler ultrasonography, was significantly higher in *Lox*-null mice.

These observations suggest that the reduced cross-linking of elastin and collagens causes a reduction in the resilience and tensile strength of the arterial walls, which gives rise to abnormalities of aortic structure and cardiovascular function. It is of interest to note that the mottled blotchy mice that died of aortic rupture before 6 months of age also had a partial deficiency of lysyl oxidase activity resulting from an abnormal copper metabolism. Similarly, in lathyrism, there is an irreversible inhibition of lysyl oxidase, caused by β-aminopropionitrile in peas, in which there is evidence for aortic dissection and the formation of aortic aneurysms, besides other musculoskeletal abnormalities. Taken together, these observations suggest the possibility that *Lox* activity may play a critical role in human cardiovascular disease. ■

Myocardial Infarction

Anticoagulation Post-MI: Are Warfarin and ASA Superior to Aspirin Alone?

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It is well established that thrombosis plays a central role in the pathophysiology of acute myocardial infarction (AMI) and that treatment with thrombolytic agents, anticoagulants, and antiplatelet drugs significantly reduces mortality and morbidity.[1] It is also well known that a significant proportion of recovering MI patients will have reinfarction during the following 2–5 years.[2] Over the past 35 years, the optimal antithrombotic regimen to prevent reinfarction has remained unclear. Currently, there are two common treatments: 81–325 mg of aspirin daily or coumadin with an international normalized ratio (INR) of 2 to 3. Although both regimens have been shown to reduce mortality and morbidity in patients with AMI, it is most common in the United States to treat patients with acetylsalicylic acid (ASA), largely because of its ease of use and relative safety. In a meta-