The treatment of high-risk hypertensive patients with diabetes presents clinicians with challenges and opportunities. The coexistence of hypertension and diabetes dramatically and synergistically increases the risk of microvascular and macrovascular complications. Perhaps most important among these is the increased risk of cardiovascular events in this patient population, an observation that can be best appreciated by the increased number of deaths attributed to cardiovascular-related diseases in diabetic patients aged 45 to 65 years. Consequently, aggressive therapy in this population offers the promise of significantly reducing excess cardiovascular deaths. Despite this opportunity for reducing mortality in these high-risk patients, several challenges to treatment remain. While aggressive blood pressure reduction has been documented to reduce the rate of events in these patients, questions remain as to the level to which blood pressure should be reduced. The recent guidelines from the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure emphasized the importance of treating patients with hypertension and diabetes as if they already have target organ damage. Low blood pressure targets of 130/85 mm Hg, with an optimal goal of 120/80 mm Hg, can reduce the risk of events in hypertensive patients with diabetes, regardless of the pharmacological means used. However, there are physiologic and clinical rationale for renin angiotensin system blockade, with angiotensin-converting enzyme inhibition as the preferential therapy in these patients. In this regard, preliminary data with the new class of angiotensin II receptor blockers suggest that these agents may offer benefits equivalent to those observed with angiotensin-converting enzyme inhibitors while offering better tolerance.

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The coexistence of hypertension and type 2 diabetes mellitus renders a diabetic patient about twice as likely to experience cardiovascular events as a nondiabetic person; in subjects with no history of myocardial infarction (MI), the presence of diabetes elevates the risk of MI to that observed in nondiabetic patients with a history of MI. Numerous studies have shown that diabetes and hypertension are major risk factors for the development of cardiovascular and renal damage. Coexistent hypertension and diabetes increase the risk of microvascular and macrovascular complications, and the effects of blood pressure control have been extensively studied. Indeed, numerous trials have demonstrated that lowering blood pressure in high-risk patients with diabetes can reduce overall mortality, deaths from strokes, cardiovascular disease events, and MI; reduce the increase in proteinuria; prevent the progression of renal disease and the decline in glomerular filtration rate (GFR) in patients with type 1 diabetes mellitus; and slow the progression of renal disease in patients with type 2 diabetes mellitus. Despite these observations, treatment issues remain concerning hypertensive patients with diabetes. Clinicians are often faced with decisions regarding the level to which blood pressure should be lowered in these patients.
patients and discerning the comparative effects of various antihypertensive classes on patients with concomitant hypertension and diabetes. A wealth of recent data, and the entry into the antihypertensive armamentarium of new classes of agents, has begun to yield answers to these important questions.

This review will detail the evidence for blood pressure reduction in high-risk hypertensive patients with diabetes, provide recommendations for the levels to which blood pressure should be reduced, review the evidence for the preferred classes of antihypertensive agents in these patients, and discuss preliminary results and ongoing clinical trials in these patients with the newly developed angiotensin II receptor blockers (ARBs).

PREVALENCE OF ARTERIAL HYPERTENSION IN PATIENTS WITH DIABETES

The Table shows a comparison by Tarnow et al.15 of the prevalence of arterial hypertension in patients with type 1 and type 2 diabetes mellitus according to blood pressure criteria from the World Health Organization (≥160/95 mm Hg) and from the Fifth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (≥140/90 mm Hg). These data are noteworthy not only in that they demonstrate the high prevalence of arterial hypertension in diabetic patients but also as they indicate the relatively low rates of antihypertensive treatment in patients with microalbuminuria and, to some extent, in those with macroalbuminuria.

CARDIOVASCULAR DISEASE

Cardiovascular disease is approximately 2 to 4 times more common in diabetic patients than in nondiabetic persons16 and accounts for about 50% of all diabetes-related deaths. As many as 52% of deaths in diabetic patients aged 45 to 65 years who are undergoing dialysis can be attributed to cardiovascular-related diseases, including cardiac arrest, acute MI, atherosclerotic heart disease, cardiac arrhythmia, and pulmonary edema.17 The Studies of Left Ventricular Dysfunction trials18,20 demonstrated that the presence of diabetes in patients with left ventricular dysfunction increases the risk of morbidity and mortality. The Systolic Hypertension in the Elderly Program1 found a higher rate of cardiovascular events in diabetic patients (6%) than in nondiabetic patients (3.5%).

In a review of the literature on the cardiac effects of coexistent diabetes and hypertension, Grossman and Messerli21 concluded that experimental models and clinical data support hypertension as having a critically important role in the pathogenesis of coronary artery disease (CAD) in diabetic patients. This review documented increased frequency and severity of CAD and its sequelae, including premature congestive heart failure, acute MI, and sudden cardiac death, in these patients.

Whereas the complications of type 1 diabetes mellitus are mostly microvascular, patients with type 2 diabetes mellitus are more susceptible to acceleration of atherosclerosis22; the most important macrovascular complication, coronary heart disease, is responsible for about half of the deaths in these patients.23 The classic risk factors (high cholesterol levels and hypertension) are important in the pathogenesis of coronary heart disease but do not fully explain the high incidence of macrovascular complications in patients with type 2 diabetes mellitus.24 The coexistence of type 2 diabetes mellitus and hypertension may be related to endothelial dysfunction, which has been demonstrated in patients who have these conditions. Endothelial dysfunction and injury begin a cascade of events leading to the formation of fatty streaks and atherosclerotic plaque. Atherosclerotic CAD substantially decreases 1-year survival among patients with type 2 diabetes mellitus and renal disease who are undergoing hemodialysis (72% and 22% in patients without and with cardiovascular disease, respectively). By year 5, the probability of these patients surviving is poor, irrespective of the cardiovascular disease status (2% vs 8% in patients with and without cardiovascular disease, respectively).25 Because hypertension is a major, although not the only, factor contributing to cardiac death, the issue of antihypertensive treatment in these patients is of prime importance.26,27

RENA L DISEASE

Difficulties in determining the onset of diabetes often result in patients having diabetes for perhaps several years before diagnosis. As a result, some patients show signs of incipient diabetic nephropathy, including microalbuminuria and hypertension, when diabetes is initially diagnosed.28

Diabetic nephropathy is the most common cause of end-stage renal disease (ESRD) in the United States.27,29,30 Among patients with diabetic nephropathy, 65% of patients with diabetic nephropathy have type 2 diabetes mellitus, and hypertension is a major risk factor for its development.25,31 The Appropriate Blood Pressure Control in Diabetes trial32 found that both systolic blood pressure and diastolic blood pressure (DBP) were associated with the development of diabetic nephropathy. Because of their high mortality and poor survival rates, patients with type 2 diabetic nephropathy have a poor long-term prognosis.25,29 Many researchers have shown that cardiovascular causes, particularly MI, sudden death, and cardiac death from other causes, account for up to 54% of the mortality rate associated with nephropathy.

MICROALBUMINURIA AND PROTEINURIA

The normal 24-hour urinary protein excretion rate ranges from 50 to 150 mg/d and contains little albumin; the normal daily urinary albumin excretion rate (UAER) is about 8 mg (range, 0-30 mg). It has long been recognized that the UAER is a hallmark of renal disease (Figure 1). Although frank or overt albuminuria has been defined as a UAER of 300 mg/d or more, a UAER of 30 mg/d is also abnormal and is predictive of eventual development of proteinuria, diabetic nephropathy, and increased risk of microvascular and macrovascular complications.
The term microalbuminuria indicates a UAER of 30 to 300 mg/d. The appearance of sustained microalbuminuria is an indicator of diabetic nephropathy and a predictor of cardiovascular disease (Figure 2), specifically CAD.31 A meta-analysis32 of studies on the associations between microalbuminuria and total cardiovascular mortality and morbidity in patients with type 2 diabetes mellitus found an overall odds ratio of 1.8 (95% confidence interval, 1.2-2.8).

Microalbuminuria, the single strongest predictor of the development of coronary events compared with traditional risk factors, can be considered less a risk factor than an indication of an ongoing vascular disease process.31 When the UAER has exceeded the upper limit of normal (30 mg/d), diabetic glomerular disease has begun. Persistent clinical proteinuria at the diagnosis of type 2 diabetes mellitus may indicate the presence of long-standing undiagnosed diabetes or of renal disease unrelated to diabetes.33,34 Microalbuminuria is also correlated with atherosclerosis and endothelial dysfunction and has a role in generalized and glomerular endothelial dysfunction. Concomitant diabetes and hypertension appear to exert a synergistic effect on the development of CAD because coexisting hypertension is associated with a doubling in the rates of microalbuminuria, left ventricular hypertrophy, electrocardiographic signs of MI, and a prior history of other cardiovascular events, even at the initial diagnosis of diabetes.35 Hypertension accelerates the rate of decline in renal function in patients with type 2 diabetes mellitus and proteinuria. Consequently, it is prudent that in patients with type 2 diabetes mellitus, any increase in blood pressure to above 130/85 mm Hg be treated aggressively.31 Indeed, the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI)36 recommends the initiation of drug therapy in patients with a high normal blood pressure (defined as 130-139/85-89 mm Hg) and with diabetes.

Several longitudinal studies37-42 suggest that once microalbuminuria is present, it progresses to proteinuria in anywhere from 22% to 50% of patients over 5 to 10 years. Even among patients without renal involvement, an elevated blood pressure in the preproteurinuric state is related to the risk of subsequently developing persistent proteinuria.33 Once a patient with type 2 diabetes mellitus develops proteinuria, further decline in renal function appears to be inevitable. Results from several studies33,41 in patients with type 2 diabetes mellitus and proteinuria show that GFR declines at an annual rate of 4 to 12 mL/min.

### Prevalence of Arterial Hypertension in Patients With Type 1 and Type 2 Diabetes Mellitus

<table>
<thead>
<tr>
<th>Type of Diabetes Mellitus</th>
<th>No. of Patients</th>
<th>Prevalence of Antihypertensive Treatment, %</th>
<th>World Health Organization†</th>
<th>JNC V†</th>
<th>JNC V Stage 1, 2, 3, and 4‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normoalbuminuria</td>
<td>562</td>
<td>8</td>
<td>15 (12-18)§</td>
<td>42 (38-46)</td>
<td>31, 6, 0, and 0</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>215</td>
<td>12</td>
<td>26 (20-33)§</td>
<td>52 (45-59)</td>
<td>31, 13, 1, and 0</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td>180</td>
<td>48</td>
<td>61 (53-68)§</td>
<td>79 (72-85)</td>
<td>42, 7, 2, and 1</td>
</tr>
<tr>
<td>Total</td>
<td>957</td>
<td>16</td>
<td>26 (23-29)§</td>
<td>51 (48-54)</td>
<td>32, 8, 0 and 1</td>
</tr>
<tr>
<td>Normoalbuminuria</td>
<td>322</td>
<td>30</td>
<td>51 (45-57)§</td>
<td>71 (66-76)</td>
<td>32, 21, 5, and 0</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>151</td>
<td>39</td>
<td>73 (65-81)§</td>
<td>90 (84-95)</td>
<td>33, 33, 15, and 0</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td>75</td>
<td>65</td>
<td>82 (72-90)‖</td>
<td>93 (85-98)</td>
<td>33, 25, 2, and 0</td>
</tr>
<tr>
<td>Total</td>
<td>549</td>
<td>41</td>
<td>61 (57-66)§</td>
<td>80 (76-83)</td>
<td>33, 24, 9, and 0</td>
</tr>
</tbody>
</table>

*Data from Tarnow et al.15 JNC V indicates Fifth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.
†JNC V stageing according to patients not taking antihypertensive medication. Higher staging was used when either the systolic blood pressure or the diastolic blood pressure fell into different categories. Stage 1 indicates a blood pressure of 140 to 159/90 to 99 mm Hg; stage 2, 160 to 179/100 to 109 mm Hg; stage 3, 180 to 209/110 to 119 mm Hg; and stage 4, greater than 210/greater than 120 mm Hg.
§P<.001 vs JNC V.
‖P<.05 vs JNC V.

### Figure 1. Relation between the duration of diabetes and the urinary albumin excretion rate (UAER). DN indicates diabetic nephropathy; MAU, microalbuminuria. Reprinted with permission from René de Cater.37

PREVENTION OF CARDIOVASCULAR OUTCOMES

Several recent clinical trials have documented the efficacy of blood pressure reduction for the prevention of cardiovascular disease events in high-risk hypertensive patients with diabetes. The results of the United Kingdom Prospective Diabetes Study (UKPDS) 38 emphasized the benefits of lowering blood pressure and treating hyperglycemia in diabetic patients. Specifically, the recent report of the UKPDS 38 demonstrated that tight control of blood pressure (defined as <150/85 mm Hg) in patients with type 2 diabetes mellitus and hypertension significantly reduced the risk...
of diabetes-related mortality compared with less stringent blood pressure control (defined as <180/105 mm Hg). This study was done in 20 hospital-based clinics in the United Kingdom with a goal of determining the effect of the level of blood pressure control on macrovascular and microvascular complications. Achieved mean blood pressure in the tight control group was 144/82 mm Hg compared with 154/87 mm Hg in the less tight control group (P < .001). Tight control resulted in a 32% reduction in the risk of mortality from diseases, mostly cardiovascular, usually exacerbated by diabetes (P = .02). The risk of stroke was reduced by 44%; MI, 21%; combined macrovascular diseases, 34%; microvascular disease, 37%; and heart failure, 56%. Thus, for hypertensive patients with type 2 diabetes mellitus, UKPDS 38 offered clear evidence that blood pressure should be controlled rigorously, that it is possible to achieve and maintain therapeutic goals, and that clinicians who had recommended strict control of blood pressure in diabetic patients were using good clinical judgment.23

In the subset of 1501 patients with diabetes at baseline in the Hypertension Optimal Treatment (HOT) study9 (mean blood pressure at baseline was approximately 169/105 mm Hg), aggressive blood pressure control reduced the risk of major cardiovascular events by half in the group with a DBP of 80 mm Hg or lower compared with the group with a DBP of 90 mm Hg or lower; and this difference remained significant when silent MI was included. In the HOT study, the achieved blood pressures in the 3 target groups were as follows: approximately 144/85 mm Hg in the group with a DBP of 90 mm Hg or lower; 141/83 mm Hg in the group with a DBP of 85 mm Hg or lower; and 140/81 mm Hg in the group with a DBP of 80 mm Hg or lower.9 The approximate halving of the risk was also observed for all MIs. All strokes also showed a declining rate with the lower target blood pressure groups, with a risk reduction of about 30%.9 Cardiovascular mortality was also significantly lower in the 80 mm Hg target group.9 Similarly, the Systolic Hypertension in the Elderly Program demonstrated that active antihypertensive therapy significantly decreased the relative risk of stroke in diabetic patients.1

Consequently, data from UKPDS 38 and the HOT study indicate that reducing DBP by as little as 5 mm Hg significantly reduces the risk of adverse outcomes related to diabetes. Perhaps more important, these trials demonstrated that there was no J-shape curve for DBP. Indeed, in the HOT study, there was a direct and statistically significant relation between a reduced risk of major cardiovascular events (P = .005; group with a DBP of ≤90 mm Hg vs group with a DBP of ≤80 mm Hg) and major cardiovascular events, including silent MI (P = .04; group with a DBP of ≤90 mm Hg vs group with a DBP of ≤80 mm Hg), observed with tighter blood pressure control.

Still more evidence regarding the effects of blood pressure reduction in high-risk hypertensive patients with diabetes will come from several ongoing, long-term, randomized trials, such as the Antihypertensive and Lipid Lowering Treatment study, which have enrolled many patients with diabetes.

**PREVENTION OF RENAL OUTCOMES**

The unique sensitivity to blood pressure of the kidney with glomerular disease (diabetic nephropathy or glomerulonephritis) has only recently been appreciated,15 even in patients whose blood pressure values are within the conventional range of normotension as defined by the World Health Organization and JNC VI. Despite this dawning appreciation, the optimal level of blood pressure in patients with diseased kidneys is still a matter of some confusion.

The main goal of treating patients with type 2 diabetic nephropathy should be to prevent the progression from incipient nephropathy to ultimate ESRD. The Modification of Diet in Renal Disease study14 was the first trial to randomize subjects with renal disease, including those with diabetes, to different levels of blood pressure to assess the effects on the progression of renal disease. The Modification of Diet in Renal Disease study found that reducing blood pressure to below 130/85 mm Hg slowed the progression of renal disease in hypertensive patients with type 2 diabetes mellitus. Overwhelming evidence indicates that hypertension accelerates the rate of decline in renal function in patients with type 2 diabetes mellitus and proteinuria.46–47 A study in Israel by Ravid et al40 showed a significant positive correlation between mean blood pressure and the rate of decline in reciprocal creatinine level during a mean follow-up of 13 years. Controlling blood pressure (mean arterial pressure of ≤92 mm Hg) in patients with moderate to severe renal insufficiency and pronounced proteinuria can slow the decline of GFR.12 In that trial, Lewis et al10 showed that captopril was clearly superior to placebo in reducing the rate of end points, defined as doubling of serum creatinine level per 100 patient-years, at achieved mean arterial pressure levels above 95 mm Hg (Figure 3).

The classic observations of Danish researchers11,12 established beyond any doubt that lowering blood pressure in patients with diabetic nephropathy attenuates the rate of decrease of GFR. The observations of Mogensen11 and other researchers12,13 have been confirmed by numerous studies. Many studies12,13 in patients with type 1 diabetes mellitus have conclusively demonstrated the clear benefit of blood pressure control on the rate of progression of renal disease. Less information is available to confirm the benefit of blood pressure con-
control on progressive renal disease in patients with type 2 diabetes mellitus, although available data generally support a beneficial effect of antihypertensive therapy. Although target blood pressure levels and the definition of adequate control remain unresolved, the traditional target blood pressure of 140/90 mm Hg for patients with renal insufficiency and declining renal function may be too high and lower blood pressure may have a more substantial renoprotective effect.

**BLOOD PRESSURE REDUCTION IN HYPERTENSIVE PATIENTS WITH DIABETES**

There is overwhelming evidence from epidemiological data supporting the need for more intensive control of blood pressure to levels below what we have traditionally accepted in hypertensive patients with diabetes. The JNC VI provides an important consensus opinion that blood pressure in hypertensive patients with diabetes—particularly in those with proteinuria—should be reduced to less than 130/85 mm Hg, with an optimal blood pressure being 120/80 mm Hg. Lower blood pressure, regardless of the choice of drug, will help to preserve renal function. This point is evident from the results of the UKPDS 39, which found that within the group randomized to tight control in UKPDS 38, there were no statistically significant differences for blood pressure reduction or any renal and cardiovascular outcome between those randomized to atenolol and those randomized to captopril. For the observed similarity between β blockade and angiotensin-converting enzyme (ACE) inhibition in this population, a few points are notable. Titration of multiple medications was performed for most of the patients in UKPDS, which may explain the lack of difference between the 2 primary therapies on the rate of progression of renal disease. Furthermore, it can be argued that the short-acting ACE inhibitor captopril was ineffectively administered as only 25 to 50 mg was given twice daily. Despite these arguments, lower blood pressure remains the critical factor in delaying renal disease progression. This point can be appreciated from the HOT study results, in which a calcium channel blocker (CCB)–based therapeutic approach significantly reduced events in hypertensive patients with diabetes.

Taking into account the results noted in UKPDS 38 and the HOT study, and the guidelines of the JNC VI, it should be standard practice to reduce blood pressure to at least 130/85 mm Hg in hypertensive patients with diabetes, with every effort made to attain optimal levels of 120/85 mm Hg.

**THERAPEUTIC CONSIDERATIONS IN HYPERTENSIVE PATIENTS WITH DIABETES**

Despite the observations in the HOT study and UKPDS, there are physiologic and clinical rationale for the preferential use of renin angiotensin system (RAS) blockade with ACE inhibitors in hypertensive patients with diabetes. Indeed, this view is reflected in the JNC VI, which categorized RAS-blocking agents, specifically ACE inhibitors, as the preferred therapy for hypertensive patients with type 2 diabetes mellitus and proteinuria. The JNC VI recommendations were based on an impressive array of data on ACE inhibition in high-risk patients, which, viewed in its entirety, demonstrates that blockade of the RAS prevents or delays the progression to the end-organ damage commonly seen in high-risk hypertensive patients with diabetes to a degree that surpasses which would be expected from blood pressure lowering alone. This observation is illustrated in Figure 4, from the meta-analysis by Weidmann et al, which shows that, on average, ACE inhibitors reduce proteinuria in diabetic patients even if blood pressure is not lowered. These results were confirmed in an updated meta-analysis.

The possibility of a renoprotective effect of ACE inhibition comes from studies in diabetic rats showing that increased efferent arteriolar resistance—mediated by angiotensin II—leads to increased glomerular pressure, accelerated decline in renal function, and increased glomerulosclerosis. Kasiske et al demonstrated that ACE inhibitors reduce proteinuria and albuminuria to a significantly greater degree than other classes of antihypertensive agents (Figure 5). Experimental studies in animal blood vessels indicate that ACE inhibition improves endothelial function. These results have been extended to humans with results from the Trial on Reversing Endothelial Dysfunction, which found that 6 months of therapy with the ACE inhibitor...
Quinapril hydrochloride improves epicardial coronary dysfunction in patients with coronary atherosclerosis. By reducing microalbuminuria, ACE inhibitors can help to prevent the progression of microalbuminuria to overt nephropathy. In one trial, captopril significantly lowered the rate of progression from microalbuminuria to overt nephropathy in 92 normotensive patients with type 1 diabetes mellitus. Recently, reviews of the literature have coalesced findings demonstrating the beneficial effects of ACE inhibitors in hypertensive patients with either type 1 or type 2 diabetes mellitus. Angiotensin-converting enzyme inhibitors have been demonstrated to slow the development of end-stage renal failure, and a meta-analysis of published studies of diabetic patients with microalbuminuria or overt proteinuria concluded that ACE inhibitors exert specific antiproteinuric effects even without a change in blood pressure. The evidence supporting the use of ACE inhibitors in high-risk hypertensive patients with diabetes extends to protection from cardiovascular disease. The Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial found that therapy with fosinopril sodium reduced the rate of secondary outcomes (prospectively defined cardiovascular events, including acute MI, stroke, and hospitalized angina) by 50% compared with amlo- dipine. Although not the primary end point of the study, these results were obtained despite equivalent reductions in DBP with both agents and a greater reduction in systolic blood pressure with amlodipine.

Numerous trials already have documented the ability of ACE inhibitors to reduce mortality within a wide range of heart failure, from asymptomatic left ventricular dysfunction to severe heart failure. Nesto and Zarich reviewed the evidence that ACE inhibition is beneficial in diabetic patients with acute MI, and concluded that “ACE inhibitors counteract many of the established and putative mechanisms accounting for the increased mortality of MI in diabetes mellitus.” Evidence of a role for ACE inhibition in the prevention of congestive heart failure and cardiovascular outcomes in high-risk patients with hypertension and type 2 diabetes mellitus continues to accumulate. A significant reduction in mortality of about 45% was found in the study population of patients with persistent clinical signs of severe congestive heart failure (New York Heart Association class IV). The observation that RAS blockade may be superior to other forms of antihypertensive therapy in hypertensive patients with diabetes is not without physiologic rationale. Increased efferent glomerular arteriolar tone is often present in diabetic patients, possibly due to the excessive vascular responsiveness to angiotensin II. Combined with disease of the afferent arteriole, which is common in patients with diabetic renal disease, glomerular capillary pressure is often elevated. Consequently, a therapeutic strategy that reduces systemic blood pressure and efferent glomerular arteriolar tone is ideal.
for limiting glomerular injury in diabetic patients. As the efferent arteriole may be more sensitive than the afferent arteriole to the vasoconstrictive effects of angiotensin II, drugs that block the RAS subsequently lower glomerular capillary pressure as they lower systemic blood pressure. Calcium channel blockers or direct-acting vasodilators preferentially dilate the afferent glomerular arteriole. Thus, if blood pressure is not reduced sufficiently, a paradoxical increase in glomerular capillary pressure could occur.

In a recent review of the literature, Kloe et al observed that dihydropyridine CCBs do not lower urinary protein levels despite a reduction of blood pressure. Furthermore, while studies on the effects of dihydropyridine CCBs on the course of renal function are limited, to our knowledge, available data suggest that this class of CCBs may be less advantageous than other antihypertensive drugs. Information on the effects of the nondihydropyridine CCBs is limited to a few studies in patients with diabetic renal disease.

ANGIOTENSIN II RECEPTOR ANTAGONISTS IN HYPERTENSIVE PATIENTS WITH DIABETES

Insofar as angiotensin II is a major component of the RAS, which is important in the pathophysiological features of essential hypertension and the progression of renal disease and its sequelae, interruption of the RAS at the receptor level may offer several distinct advantages. It is known that ACE inhibitors may not completely block the conversion of angiotensin I to angiotensin II due to activation of alternative pathways. In contrast to ACE inhibitors, ARBs offer more complete and pharmacologically desirable blockade of the RAS, specifically by inhibiting the actions of angiotensin II at the level of the angiotensin tissue receptor subtype 1 (AT₁).

Furthermore, clinical trials with ARBs have demonstrated that they are free from the adverse effect of cough observed with the administration of ACE inhibitors. The precise mechanism of ACE inhibitor-induced cough remains to be elucidated; however, it is likely related to the nonspecific blockade of ACE and the resultant accumulation of endogenous substrates such as bradykinin, substance P, or both.

The superior tolerability profile of the ARBs, therefore, may translate into improved compliance compared with ACE inhibitors. A comparison of the ARB irbesartan with the ACE inhibitor enalapril maleate in patients with severe hypertension demonstrated that irbesartan is associated with a significantly lower rate of cough than is the ACE inhibitor (2.5% vs 13.1%; P = .007). The elevation in bradykinin levels with ACE inhibition and the subsequent stimulated production of nitric oxide, prostacyclin, and endothelial hyperpolarizing factor may contribute to the clinical benefits of ACE inhibitors.

While the base of information regarding ARBs in high-risk hypertensive patients with diabetes is lacking compared with that of ACE inhibitors, preclinical and pilot trial data suggest that the ARBs should provide renoprotection and cardioprotection in these patients to at least the same degree as that provided by ACE inhibitors.

PRECLINICAL STUDIES

Preclinical studies have indicated that the ARBs irbesartan, candesartan, and losartan potassium may diminish glomerulosclerosis in diabetic rat models. Whether the positive effects on renal hemodynamics seen thus far with ARBs are a class effect is not known. In one trial, obese Zucker rats were administered losartan potassium, 100 or 200 mg/L, in drinking water for 18 weeks beginning at the age of 26 weeks. Despite reductions in systolic blood pressure vs untreated controls at the age of 44 weeks, losartan therapy resulted in no significant change in albuminuria or glomerular or tubulointerstitial injury.

A small study in healthy volunteers indicated that ARBs may offer therapeutic advantages over ACE inhibitors when more complete blockade of the RAS is desirable. In this study, young, healthy volunteers who were on a low-salt diet to activate the renin system were examined to gauge the response of renal perfusion to pharmacological interruption of the RAS. This study evaluated the renal vasodilator response to 3 ACE inhibitors, 2 renin inhibitors, and 2 ARBs at the top of their respective dose-response relationships. Based on previous studies, it was likely that if a kinin-independent mechanism contributed to the renal hemodynamic response to ACE inhibition, the renal vasodilator response to ACE inhibition would exceed that of other agents. However, this study documented that renin inhibitors and ARBs induced a renal vasodilator response of 140 to 150 mL/min per 1.73 m², approximately 50% larger than the maximal renal hemodynamic response to ACE inhibition, which was 90 to 100 mL/min per 1.73 m² (Figure 6).

These data demonstrate that in the intact human kidney, virtually all angiotensin II generation is renin dependent, but at least 40% of angiotensin II is converted to angiotensin II by pathways other than ACE, presumably a chymase, although other enzyme pathways also exist. Consequently, ARBs may produce changes in renal plasma flow that are greater than those attained with ACE inhibition.

DIABETIC NEPHROPATHY TRIALS: PILOT DATA

Preliminary studies of ARBs in humans indicate that the agents may have beneficial effects on renal func-
tion. A pilot study \(^8^0\) of irbesartan and amlodipine in 47 patients with type 2 diabetes mellitus and hypertension (DBP of >85 mm Hg and SBP of >135 mm Hg) demonstrated that both agents achieved similar reductions in blood pressure, although patients treated with irbesartan had significantly increased serum creatinine levels and decreased urinary protein excretion rates compared with those receiving amlodipine (Figure 7). Creatinine clearance among patients receiving irbesartan increased by 0.14 mL/s (8.5 mL/min) per 1.73 m\(^2\) but decreased by 0.24 mL/s (14.28 mL/min) per 1.73 m\(^2\) with amlodipine (\(P<.01\)). By week 12, urinary protein excretion decreased with irbesartan by 8.5% and increased with amlodipine by 19.7%. These superior effects on markers of renal protection attained with irbesartan were observed despite similar reductions in DBP, indicating an additive benefit of RAS blockade in the treatment of type 2 diabetes mellitus.

Similar beneficial renal effects have been observed with candesartan and losartan. In 2 small, short-duration trials \(^8^1^,^8^2\) of patients with mild to moderate hypertension, candesartan has been demonstrated to increase renal blood flow while maintaining GFR. In another trial, \(^8^3\) 35 patients with mild hypertension (DBP, 90-100 mm Hg), stable type 2 diabetes mellitus, and microalbuminuria (10-100 mg of protein in an overnight urine sample) were randomized to placebo or candesartan therapy, 8 to 16 mg. The median UAER decreased from 28.5 to 12.2 mg/12 h (57%) while taking candesartan and increased from 30.2 to 32.8 mg/12 h (9%) while taking placebo. A small study \(^8^4\) of losartan therapy in 15 patients with hypertension (mean arterial blood pressure, 123 mm Hg) and nondiabetic renal disease, in which patients were randomized to receive losartan or amlodipine, indicated that the ARBs may have beneficial renal effects. The UAER decreased from 3510 mg/24 h at baseline to 2684 mg/24 h (\(P<.01\)) while taking losartan and increased nonsignificantly to 3748 mg/24 h while taking amlodipine.

Such observations demonstrate the role of the RAS in renal disease and provide the basis for future large trials of ARBs in diabetic patients. Two such trials, each involving more than 1500 patients, the Irbesartan Diabetic Nephropathy Trial (IDNT) and the Losartan Renal Protection Study (RENAAL), are under way. Their objective is to assess the effects of ARBs on the progression of nephropathy in patients who have type 2 diabetes mellitus.

The IDNT and RENAAL will assess the impact of irbesartan and losartan, respectively, on delaying the progression of renal disease and its adverse clinical sequelae in patients with type 2 diabetes mellitus who have hypertension and diabetic nephropathy. \(^8^5\) The principle difference between these trials relates to the comparator groups. In IDNT, subjects are randomized to irbesartan, amlodipine, or placebo (usual care), while in RENAAL, subjects are randomized to only losartan or placebo (usual care). In both clinical trials, additional medications can be added to facilitate reduction of systolic blood pressure to less than 140 mm Hg (RENAAL) and to less than 135 mm Hg (IDNT). The latter study will provide an interesting comparison between the mechanistic effects of an ARB (which dilates the efferent glomerular arteriole like an ACE inhibitor) and a CCB (which dilates the afferent glomerular arteriole) on blood pressure, proteinuria, and renal disease progression.

Trials such as the IDNT and RENAAL will serve to address whether the preliminary evidence suggesting a beneficial role of ARBs is maintained during the long-term. What has already emerged is the remarkable safety of the ARBs. Regarding renal protection, it is of particular interest that hyperkalemia, a short-term initial increase in serum creatinine level (in view of initial concern about occult renal artery stenosis), and hematologic adverse effects were extremely rare.

**SUMMARY**

The public health burden of type 2 diabetes mellitus and of hypertension is significant and rapidly increasing. Diabetes is estimated to affect at least 5% of the population of industrialized countries, with 90% of those with diabetes having type 2 diabetes mellitus. \(^1^7\) These patients are at higher risk of developing cardiovascular-related diseases, which represent the major cause of mortality and morbidity in these patients. Since 1987, the incidence and prevalence of ESRD have more than doubled, and deaths from ESRD also are increasing. \(^1^7\) Most patients with diabetic nephropathy, the major cause of ESRD, tend to have type 2 diabetes mellitus. Therefore, identifying optimal treatments that slow or prevent this disease is essential.
Primary care physicians will manage most hypertensive patients with diabetes. It is of paramount importance that the primary goal of lower blood pressure targets be used when treating this patient population. These goals should be at least 130/85 mm Hg, with an optimal target of 120/80 mm Hg. To achieve this, clinicians must learn from the lessons of the HOT study, in which combination therapy was liberally used to attain the impressive blood pressure reductions noted in that trial. In the HOT study, 68% of all patients were maintained on combination antihypertensive therapy.

Despite some recent data on the efficacy of other classes of antihypertensive agents in this patient population, there is physiologic and clinical rationale for the preferential use of RAS blockade with ACE inhibitors. The newer class of ARBs may offer another option for RAS blockade in these patients. Theoretically, they have the advantages of improved tolerability and more complete RAS blockade compared with ACE inhibitors. There are not enough data on the comparative efficacy of ARBs vs other antihypertensive classes to make definitive recommendations regarding their widespread use as preferred therapy in patients with hypertension and diabetes. Trials such as IDNT and RENAAL will begin to answer the question as to whether ARBs offer equivalent or superior protection in these patients.

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REFERENCES


19. Kimmel M, Kikkaew R, Togawa M, et al. High blood pressure is a risk factor for the development of