Optimizing Therapy in the Diabetic Patient with Renal Disease: Antihypertensive Treatment

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Abstract. Hypertension, impaired renal function, and proteinuria are commonly associated to the presence of diabetes. They play a major role in the development of cardiovascular and renal damage. Effective antihypertensive treatment reduces the progression of diabetic nephropathy and improves cardiovascular prognosis. Accordingly, tight BP control (<130/80 mmHg) is currently recommended in diabetic patients. Achieving BP targets represents the most important determinant of cardiovascular and renal protection. However, it has been suggested that specific classes of antihypertensive drugs may exert additional organ protection beyond their BP control. The pharmacologic blockade of the renin-angiotensin-aldosterone system has been shown to convey greater renal and cardiovascular protection compared with other classes of drugs. In particular, studies focusing on renal end point suggest that angiotensin-converting enzyme inhibitors (ACEI) are the first-choice drugs in type 1 diabetes. Both ACEI and angiotensin II receptor blockers prevent the progression from microalbuminuria to clinical proteinuria in type 2 diabetes, but angiotensin blockers provide better renoprotection in patients with overt nephropathy. Regarding cardiovascular protection, several studies (but not all) have shown that ACEI exert a protective effect on diabetic patients. Recently, interesting results in favor of angiotensin receptor blockers have been reported in the IDNT, RENAAL, and LIFE studies. It should be noted that to achieve maximal renal and cardiovascular protection, most diabetic patients require integrated therapeutic intervention, including not only several antihypertensive drugs, but statins and antiplatelet therapy as well.

Diabetes, hypertension, impaired renal function, and proteinuria are commonly associated conditions that act as a guilty company. They are, in fact, responsible for an increase in the risk of development and/or progression of cardiovascular disease, nephropathy, and retinopathy.

Arterial BP plays a very important role in the development of renal damage and presents a complex relationship with diabetic nephropathy, with nephropathy raising BP, and with BP accelerating the course of nephropathy (1). Furthermore, as shown by epidemiologic studies, hypertension is responsible for increased cardiovascular morbidity and mortality associated with diabetes mellitus (1). Effective antihypertensive treatment reduces the risk of development and progression of nephropathy and, as is especially evident with angiotensin-converting enzyme (ACEI) inhibitors (ACEI) and angiotensin receptor blockers (ARB), it lowers cardiovascular morbidity and mortality (2,3). Accordingly, current consensus groups have recommended tight BP control (<130/80 mmHg) in diabetic patients (2,4–7).

Proteinuria is considered a predictor of renal disease progression. Proteinuria acts on tubular cells by inducing inflammation and consequently interstitial fibrosis. In addition, proteinuria favors dyslipidemia, which aggravates renal damage and increases cardiovascular risk. A direct correlation exists between the degree of proteinuria and the progression rate to end-stage renal disease (ESRD) in diabetic nephropathy as well as in other glomerular diseases. Lastly, proteinuria also predicts cardiovascular morbidity and mortality in both diabetic and nondiabetic patients (8).

Overactivity of the renin-angiotensin system (RAS) has been described in diabetic nephropathy (9). Angiotensin II (AngII) acts in synergy with hyperglycemia, contributing to glomerular hypertension and co-stimulating the synthesis of extracellular matrix proteins by means of transforming growth factor–β (TGF-β) induction, which consequently causes renal hypertrophy. A rationale for the RAS blockade therefore exists. ACEI and ARB improve glomerular hypertension and partially prevent renal hypertrophy in diabetes. ACEI suppress the RAS but do not block the production of non–ACE-mediated AngII. On the other hand, ARB provide a more complete blockade of AngII effects by selectively binding to the AT1 receptors and offering better tolerance. Furthermore, by stimulating AT2 receptors, the ARB may help prevent hypertrophic effects and could provide organ protection.

Retinopathy is a common and potentially devastating complication in diabetic patients. Yet ophthalmologic evaluation has shown that about 30% of type 2 diabetic patients who have biopsy-proven diabetic nephropathy do not have diabetic retinopathy.
nopathy (10). In these patients, the presence of retinopathy is associated with an increased risk of progressive renal disease as well as of cardiovascular events and death. Therefore, retinopathy also represents a predictor of renal and cardiovascular outcomes in diabetic patients (11).

Renal Protection

Hypertension is an important determinant of the progression of diabetic renal disease from microalbuminuria to overt nephropathy (12). Several studies performed on normotensive, microalbuminuric patients with either type 1 or type 2 diabetes have shown that ACEI are very effective in reducing the incidence of overt proteinuria (secondary prevention) regardless of the BP levels (approximate risk reduction ratio [aRRR], 70% to 100%) (13–16). The MicroHOPE Study (17), which was performed on a large population, as well as two other smaller studies (18,19) confirm the efficacy of ACEI compared with other types of treatment in hypertensive, microalbuminuric, type 2 diabetic patients, in secondary prevention (aRRR, 23 to 68%). However, the same effect was not observed in two other studies (20,21). ACEI, therefore, seem to be more effective on microalbuminuric, normotensive patients than on hypertensive ones. The IRMA study, a multicentric, randomized, double-blind, placebo-controlled trial that evaluated the effect of irbesartan in secondary prevention, conferred an important renoprotective role to ARB in type 2 hypertensive diabetic patients (22). In this trial, 590 patients were followed up for 2 yr after being randomized to receive 150 mg of irbesartan, or 300 mg of irbesartan, or placebo, together with additional antihypertensive agents (excluding ACEI, ARB, and dihydropyridine calcium channel blockers [CCB]), to achieve the goal BP of less than 135/85 mmHg. The primary end point of the study was the onset of overt nephropathy. The mean achieved BP was 143/83 in the 150-mg group, 141/83 in the 300-mg group, and 144/83 in the placebo group. With respect to the primary end point, treatment with 150 mg of irbesartan or 300 mg of irbesartan appeared to be much more effective than conventional therapy (CT) (aRRR, 44% and 68% versus CT). Furthermore patients treated with the higher dose of irbesartan more frequently regressed to normoalbuminuria (17/100 in the 300-mg group, 12/100 in the 150-mg group, and 10.5/100 patients per year in the control group).

Hypertension is the main factor leading to the decline in renal function and the consequent progression to end-stage renal disease (ESRD) in patients with overt nephropathy. Our meta-analysis of nine longitudinal studies that used various antihypertensive drugs in proteinuric patients with type 1 diabetes shows that achieved BP values play an overwhelming role in determining the decline in GFR. The curve shows that there is a fourfold reduction in the decline of GFR when the mean arterial pressure values are below 100 mmHg. Various types of treatment provided similar efficacy in slowing the progression of nephropathy, regardless of the drug that was used (23). The results of the Irbesartan Diabetic Nephropathy Trial (IDNT) were analyzed to determine the optimal level of achieved BP that is required to slow the nephropathy progression rate in type 2 diabetes. It was found that the level of systolic BP is strongly correlated to the risk of progressing to a renal event. After adjusting for systolic BP, diastolic BP did not appear to be a predictor of renal outcome in this analysis (24). Both analyses show that tight BP control is therefore an essential part of managing patients with overt nephropathy to prevent renal complications.

The renoprotective role of ACEI, beyond what can be attributed to BP reduction, has been shown in only 2 of 5 studies that compared these drugs to either CT or to CCB (25–29) in type 1 diabetic patients with overt nephropathy. In type 2 diabetic patients who also have overt nephropathy, 4 of 5 small trials that evaluated the effects of various classes of drugs failed to demonstrate that ACEI play any specific renoprotective role (20,30–33).

Recently, two large randomized, blinded clinical trials showed that ARB are very effective in protecting against the progression of nephropathy caused by type 2 diabetes (34,35). The design of these two trials was similar, although the baseline characteristics of the study populations were somewhat different (baseline BP values, degree of proteinuria, and prevalence of white, European subjects were all slightly higher in the IDNT study than in the RENAAL study). In the IDNT trial, the 1715 patients who were randomized to irbesartan, amlodipine, or placebo, together with CT (excluding ACEI, ARB, or CCB) were followed up for approximately 2.6 yr. The achieved BP in the irbesartan group was similar to what was observed in the amlodipine group, but it was slightly higher in the CT group (140/77, 141/77, and 144/80 mmHg, respectively). The risk of primary composite end point (doubling of serum creatinine, ESRD, or death) in subjects treated with irbesartan was significantly lower compared with subjects who received placebo (aRRR, 19%) and those who received amlodipine (aRRR, 24%). The risk of doubling serum creatinine was lower in the irbesartan group than in both the placebo group (aRRR, 29%) and the amlodipine group (aRRR, 39%) (34). In the RENAAL study, 1513 patients were followed-up for approximately 3.4 yr after being randomized to either losartan or placebo, along with non-ACEI or non-ARB therapy. The BP values achieved at the end of the study were 140/74 and 142/74 mmHg in the losartan and in the CT groups, respectively. Treatment with losartan resulted in a reduction (aRRR, 15%) in the risk of the primary composite end point (doubling of serum creatinine, ESRD, or death). Lastly, the risk of doubling serum creatinine in the losartan group was 25% lower than in the placebo group (35). In both studies, the benefits of ARB clearly exceeded what might be attributable to changes in BP alone. Finally, by analyzing the IDNT study results to examine the factors associated with progressive renal disease in type 2 diabetes, we can see that proteinuria predicts poor renal outcome in these patients and that treatment with irbesartan is associated with a greater reduction in proteinuria than treatment with amlodipine or placebo (36). Thus, ARB are currently considered the treatment of choice in hypertensive, type 2 diabetic patients for the tertiary prevention of ESRD.

Some interest in the use of other antihypertensive therapeutic strategies to prevent poor renal outcome in diabetic patients has now emerged. Short studies, aimed at assessing the effi-
cacy of the combined treatment of ACEI plus ARB in patients with diabetic or nondiabetic renal disease, have shown promising results regarding both the anti-proteinuric effects and the antihypertensive efficacy of these combinations (37,38). In a recent trial that was followed-up for 2.9 yr, 263 nondiabetic patients were randomly assigned to receive 100 mg/d losartan, 3 mg/dtrandolapril, or a combination of both drugs at equivalent dose. The risk of primary composite end point (doubling of serum creatinine or ESRD) was significantly lower in the combination therapy group than in the monotherapy groups (RR = 0.52) (39). At present further studies on diabetic patients are needed.

A recent study reported that aldosterone escape is observed in 40% of the type 2 diabetes patients with early nephropathy, despite the use of ACEI (40). In this trial, administering spironolactone (25 mg-d) together with an ACEI (trandolapril, 1.5 mg/d) to patients with aldosterone escape led to a significant decrease in urinary albumin excretion and left ventricular mass index, with no changes in either BP or serum potassium levels at the end of a 24-wk study period. This study suggests that the aldosterone blockade may represent the optimal therapy for diabetic patients with microalbuminuria or overt proteinuria who show aldosterone escape during ACEI treatment and who no longer benefit from the maximal antiproteinuric effects of ACE inhibition

Retinal Protection

The UKPDS (41) and the normotensive-Appropriate Blood Pressure Control in Diabetes (ABCD) trial (42) showed that a reduction in BP (144/82 versus 154/87 in the former study, and 128/75 versus 137/81 in the latter) in patients with type 2 diabetes results in a risk reduction for the progression of diabetic retinopathy (UKPDS, RR = 34%; normotensive-ABCD, RR = 26%). However, the same result was not found in the hypertensive-ABCD trial (20).

Cardiovascular Protection

The presence of arterial hypertension increases the risk of cardiovascular disease associated with diabetes mellitus by at least two times compared with subjects with either diabetes or hypertension alone (1).

Evidence from two placebo-controlled trials, i.e. the Systolic Hypertension in the Elderly Program and the Systolic Hypertension in Europe Trial (43,44) showed that active treatment of arterial hypertension prevented major clinical complications in patients with type 2 diabetes. Indeed, a 9 and 10 mmHg decrease in mean systolic BP was associated with a 34% and 62% reduction, respectively, in the relative risk of cardiovascular events.

Furthermore, randomized clinical trials have demonstrated that intensive BP control is more effective in reducing cardiovascular complications compared with moderate BP control (20,41,45,46). Data from the UKPDS showed that a 10 mmHg decrease in systolic BP was associated with a 29% reduction in relative risk of cardiovascular events. Moreover, considering that no threshold for arterial pressure was identified in this study, we may conclude that with regards to this subset of patients, the lower the systolic BP, the lower the risk of complications. In the HOT study, significant reductions in major cardiovascular events were observed despite relatively small differences in the achieved BP (RRR in cardiovascular events of 24% and 51% for differences in systolic BP of 3 and 4 mmHg, respectively). The ABCD trial, which included cardiovascular events only as a secondary end point, demonstrated that the intensive BP control in hypertensive patients was associated with a significantly lower incidence of cardiovascular complications compared with moderate BP control, whereas no differences were observed in the normotensive group (20,42,46). Thus, current guidelines for treating hypertensive patients with diabetes recommend a target BP below 130/85, or even below 130/80 mmHg (2,4–7).

The additional cardiovascular protection conferred by ACEI, beyond their BP effect, is currently controversial (Table 1). Some recent trials, indeed, have shown that ACEI-based antihypertensive regimens are more effective in reducing the risk of cardiovascular complications in hypertensive type 2 diabetic patients than CT (17,47,48) or CCB (20,46,49). By contrast, other comparative trials have failed to show any clear-cut superiority of ACEI in reducing cardiovascular morbidity and mortality in hypertensive or normotensive diabetics over CT (50,51) or CCB (42,51). Lastly, the recent ALLHAT trial did not demonstrate any differences in cardiovascular outcomes in a large cohort of type 2 diabetic patients randomized to a diuretic, a CCB, or an ACEI (52).

As far as the use of CCB is concerned, some trials have demonstrated that the effects of this class of drugs are similar to those observed with CT (51,53,54). Since it was believed that CCB are responsible for a greater percentage of cardiovascular events, these findings could allow us to rule out this hypothesis with regards to hypertensive patients with type 2 diabetes. Recent studies demonstrated a significant reduction in cardiovascular morbidity and mortality when losartan, an angiotensin II receptor antagonist, was compared with CT in a large cohort of diabetic patients with hypertension and left ventricular hypertrophy, with an average follow-up of 5 yr (4). Moreover, results from the IDNT and RENAAL trials showed that treatment with both irbesartan and losartan resulted in a significant reduction in hospitalization for heart failure compared with the placebo-treated group in type 2 diabetic patients with overt nephropathy. By contrast, no significant differences were detected in either study between the ARB-treated group and the controls with regard to the aggregate end point of death from cardiovascular causes, nonfatal myocardial infarction, stroke, or heart failure resulting in hospitalization. This possibly reflects the higher risk for diabetic patients with clinical proteinuria (34,35).

Lastly, an integrated therapeutic intervention, not only with antihypertensive medication, but also with statins, antiplatelet therapy, and optimal glycemic control, has been shown to reduce macrovascular complications in diabetic subjects (55).
Table 1. The effect of various drugs on cardiovascular events in diabetes

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number of Patients</th>
<th>Follow-Up (yr)</th>
<th>BP (mmHg)</th>
<th>Risk Reduction (%)</th>
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<tr>
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<td>New Drugs</td>
<td>Old Drugs</td>
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<td>ACEI versus CT</td>
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<tr>
<td>UKPDS, 1998 (41)</td>
<td>758</td>
<td>8.4</td>
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<tr>
<td>CAPPP, 1999, 2001 (48)</td>
<td>572</td>
<td>6.1</td>
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<td>4.5</td>
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<td>143/77</td>
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<tr>
<td>STOP-2, 2000 (51)</td>
<td>488</td>
<td>4.5</td>
<td>161/80</td>
<td>161/81</td>
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<tr>
<td>ACEI versus CCB</td>
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<td>FACET, 1998 (49)</td>
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<tr>
<td>STOP-2, 2000 (51)</td>
<td>466</td>
<td>4.5</td>
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<td>ABCD-HT, 1998, 2000 (46,20)</td>
<td>470</td>
<td>5.3</td>
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<tr>
<td>ABCD-NT, 2002 (42)</td>
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<td>CCB versus CT</td>
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<td>4.5</td>
<td>162/89</td>
<td>161/81</td>
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<td>ARB versus CT</td>
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<td>LIFE, 2002 (3)</td>
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<td>144/80</td>
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<td>RENAAL 2001 (35)</td>
<td>1513</td>
<td>3.4</td>
<td>140/74</td>
<td>142/74</td>
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<sup>a</sup> ACEI, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; ARB, Angiotensin II receptor blocker; CT, conventional therapy.

<sup>b</sup> Differences between old and new drugs, P < 0.05.

References


