Renal and Cardiovascular Protection in Type 2 Diabetes Mellitus: Angiotensin II Receptor Blockers

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Abstract. Aggressive treatment of hypertension is effective in reducing both microvascular and macrovascular complications in type 2 diabetes, and target BP less than 130/85 or 130/80 mmHg are now recommended. Inhibition of renin angiotensin aldosterone system (RAAS) plays an essential role in the treatment of hypertension and diabetes-related complications. Studies focusing on renal end-points suggest that angiotensin-converting enzyme inhibitors (ACE-I) are more effective than other traditional agents in reducing the onset of clinical proteinuria in both type 1 and type 2 diabetic patients with incipient nephropathy, mainly in normotensive ones (secondary prevention). However, several small trials in type 2 diabetic patients with overt nephropathy (tertiary prevention) failed to demonstrate a specific renoprotective role for ACE-I, at variance with type 1 diabetes. Three recent large trials address the question of whether angiotensin II receptor blockers (ARB) prevent the development of clinical proteinuria or delay the progression of nephropathy in type 2 diabetes. The IRMA study showed that irbesartan is more effective than conventional therapy in preventing the development of clinical proteinuria and in favoring the regression to normoalbuminuria for comparable BP control in patients with incipient nephropathy. The IDNT and RENAAAL trials showed that ARB are more effective than traditional antihypertensive therapies in reducing progression toward end-stage renal failure (ESRF) in type 2 diabetic patients with overt nephropathy independently of changes in BP. Moreover, a reduction in hospitalizations for heart failure was demonstrated for ARB-treated patients compared with placebo. Furthermore, the LIFE study showed that losartan is more effective than conventional therapy in reducing cardiovascular morbidity and mortality in a cohort of diabetic patients with hypertension and left ventricular hypertrophy. In conclusion, ARB seem to be effective in both preventing renal damage and reducing progression toward ESRF in type 2 diabetic patients. Thus, the guidelines for the prevention and treatment of diabetic nephropathy are now changed. In type 1 diabetes ACE-I are the first-choice drug; in type 2 diabetes, ARB are considered first-choice drugs in secondary prevention as well as ACE-I and have been now elected the unique first-choice drug in tertiary prevention of ESRF. Finally, ARB should be considered as the first-choice drug in cardiovascular prevention too, as well as ACE-I.

Hypertension is an extremely common comorbid condition in type 2 diabetes. Its prevalence is higher than in the general population, thus contributing to explain the increased risk of both microvascular and macrovascular complications observed in diabetic patients. Hypertension appears to play an important role in the development and progression of renal damage in type 2 diabetes (1,2). Furthermore, hypertension is a major risk factor for the increased cardiovascular morbidity and mortality associated with diabetes mellitus, as confirmed by epidemiologic studies demonstrating a two or three times increased risk of cardiovascular mortality in hypertensive compared with normotensive type 2 diabetic patients (1,2).

Randomized clinical trials have demonstrated the effectiveness of the BP reduction (3,4) and of the intensive antihypertensive treatment (5,6) in reducing both microvascular and macrovascular complications. Current treatment guidelines recommend a target BP less than 130/85 or 130/80 mmHg for hypertensive patients with diabetes (7–14).

Proteinuria is a well-known marker of glomerular damage, which has recently been considered an independent promoter of renal disease progression too (15). A strict relationship has been demonstrated between the degree of glomerular proteinuria and both the interstitial fibrosis and the rate of progression of chronic renal failure in diabetic nephropathy as well as in other glomerular disease (16). Furthermore, interventions able to slow the progression of diabetic nephropathy are associated with a reduction in proteinuria (17). Finally, proteinuria is a powerful independent predictor of cardiovascular morbidity and mortality (18).

Renin angiotensin aldosterone system (RAAS) plays an essential role in the pathophysiology of hypertension and diabetes-related complications. A physiologic clinical rationale, therefore, exists for RAAS blockade. Although angiotensin-converting enzyme inhibitors (ACE-I) suppress the RAAS, they are not able to block the production of angiotensin II (AngII) by non–ACE-mediated pathways. Furthermore, ACE...
is not a specific enzyme, and its inhibition reduces the degradation of bradykinin, which in turn may amplify the vasodilator effect of this substance and induce the class-specific side effects associated with this drug. On the other hand, the lack of suppression of the degradation of aldosterone seem to be the main drawbacks of AngII receptor blockers (ARB) (19,20). However, ARB appear to have potential advantages over ACE-I. In fact, they can provide a more complete blockade of AngII effects by binding selectively to the AT1 receptors while offering better tolerance. Furthermore, additional benefits of ARB could arise from AT2 receptor stimulation, which could contribute to prevent hypertrophic effects and provide end organ protection (19,20). These findings may have potentially important pathophysiological and clinical implications. A recent study by Hollenberg (20) reported enhanced renal vasodilator response due to RAAS inhibition with ARB relative to that observed with ACE-I in healthy human volunteers maintained on a low-salt diet to activate RAAS. Thus, blocking the system with ARB could provide even a greater efficacy than ACE-I, particularly under conditions of disease, such as diabetes, in which overactivity of RAAS has been described (21).

In the following sections, we will analyze the impact of treatment with ARB compared with the effect of traditional therapy on renal and cardiovascular end points in hypertensive patients with type 2 diabetes.

**Renal Protection**

Three recent large, randomized, blinded, clinical trials addressing the question whether ARB prevent the development of clinical proteinuria in microalbuminuric patients (secondary prevention) (22) or delay the progression of overt nephropathy to end-stage renal failure (ESRF) in proteinuric patients with type 2 diabetes were published (tertiary prevention) (23,24).

Available studies dealing with the role of traditional antihypertensive treatment, including ACE-I, on the same renal end points in type 2 diabetes provide controversial results. Several studies performed in normotensive microalbuminuric patients showed that ACE-I markedly reduce the incidence of overt nephropathy (relative risk reduction [RRR], approximately 70 to 100%) in type 2 diabetes independently of BP levels (25–27), according to results obtained in type 1 diabetes (28–32).

In hypertensive microalbuminuric type 2 diabetic patients, a recent study comparing placebo with an active treatment mainly based on calcium channel blockers (CCB) showed the effectiveness of the active therapy in reducing the incidence of overt nephropathy (33). Moreover, two other studies compared the effect of tight BP control with a moderate one. The intensive treatment reduced, even if not significantly, the incidence of nephropathy in the first study (34); no differences were observed in the second study (5). As far as the role of the individual class of drugs is concerned, the Microhope study (35) on a large population and two other smaller studies (36,37) confirm the efficacy of ACE-I compared with other treatment in reducing the incidence of overt nephropathy. By contrast, this effect was not found in two other studies (34,38). Thus ACE-I seem to be less clearly effective in hypertensive patients than in normotensive ones.

The IRMA study, a multicentric, randomized, double-blind, placebo-controlled trial, evaluated the effect of irbesartan in preventing the onset of clinical proteinuria in type 2 diabetic patients with hypertension and microalbuminuria (22). Five hundred ninety subjects were randomized to receive therapy with 150 mg of irbesartan, 300 mg of irbesartan, or placebo. Additional antihypertensive agents, ACE-I, ARB, and dihydropyridine CCB being excluded, were allowed in each arm of the study to achieve the goal BP of less than 135/85 mmHg. The primary end point of the study was the onset of overt nephropathy, which was defined as the occurrence of a urinary albumin excretion rate greater than 200 μg/min and at least 30% higher than baseline. The mean duration of follow-up was 2 yr. The average BP during the course of the study was 143/83 mmHg in the 150-mg group, 141/83 mmHg in the 300-mg group, and 144/83 mmHg in the placebo group. With respect to the primary end point, 150 and 300 mg of irbesartan showed, respectively, an adjusted RRR of 44% and 68% versus conventional therapy; in addition, the regression to normoalbuminuria was more frequent in the patients treated with the higher dose of irbesartan (17 in the 300-mg group, 12 in the 150-mg group, and 10.5/100 patients per yr in the control group; Figure 1). Taking into account all these data, irbesartan appears much more effective than conventional therapy in preventing the development of clinical proteinuria and in favoring the regression to normoalbuminuria for comparable BP control.

In type 2 diabetic patients with overt nephropathy, a strict control of BP does not seem significantly effective in reducing the decline of GFR, at least in the only study reported in the literature (34), and four out of five small trials evaluating the effects of different classes of drugs failed to demonstrate a specific renoprotective role for ACE-I at this stage of nephropathy (34,36,39–41) (Figure 2). By contrast, in proteinuric patients with type 1 diabetes, a strict BP control was deemed effective in slowing the progression of nephropathy independently of the drug used (42); moreover, ACE-I appear to be clearly more renoprotective than other drugs, at least in two of five studies (RRR, approximately 30 to 60%) (43–47).

In type 2 diabetic patients with overt nephropathy, two recent large trials confer to ARB an important renoprotective role (23,24). Although the baseline characteristics of populations of the two studies were slightly different (in the IDNT study, the prevalence of white and European subjects, the baseline BP values, and the degree of proteinuria were slightly higher than in the RENAAL study), the design of both trials was similar. In the IDNT trial, 1715 patients were followed for approximately 2.6 yr after being randomized to irbesartan,amlodipine, or placebo, each one plus conventional therapy, excluding ACE-I, ARB, and CCB. The achieved BP was similar in the irbesartan and amlodipine group and little higher in the conventional treatment group (140–141/77, 144/80 mmHg, respectively). The treatment with irbesartan was associated with a risk of the primary composite end point (doubling of serum creatinine, ESRF, or death) significantly lower than in the placebo (adjusted RRR [aRRR] = 19%) and
the amlodipine group (aRRR = 24%) (Figure 3A). The risk of a doubling of serum creatinine in the irbesartan group was lower than in the placebo group (aRRR = 29%) and the amlodipine group (aRRR = 39%) (23). In the RENAAL study, 1513 patients randomized to losartan or placebo, both taken in addition to conventional antihypertensive therapy not including RAAS antagonist drugs, were followed for approximately 3.4 yr. Average BP values at the end of the study were 140/74 mmHg in the losartan group and 142/74 mmHg in the conventional treatment group. The treatment with losartan resulted in a reduction (aRRR = 15%) in the risk of the same primary composite end-point as in the IDNT trial (Figure 3B). The risk of a doubling of serum creatinine in the losartan group was 25% lower than in the conventional treatment group (24). Interestingly, the benefit of the ARB exceeded that attributable to changes in BP in both studies.

Finally, an important finding of the IDNT trial was that amlodipine appeared to be less effective than the RAAS blocking agents as far as renal end-points were concerned, which is in keeping with data from a report on a nondiabetic population (48).

Cardiovascular Protection

Some studies on large populations have demonstrated that the reduction of BP is the main factor that is able to decrease the risk of cardiovascular events independently of the class of antihypertensive agent used (3,4). Moreover, tight BP control has been deemed as more effective than moderate control in two other large trials addressing the effects of antihypertensive treatment on the same cardiovascular end points (5,6).

Considering the role of the individual classes of drugs, most studies have demonstrated the superior effectiveness of ACE-I in cardioprotection. Some recent trials have shown that ACE-I–based antihypertensive regimens were more effective in reducing the risk of cardiovascular complications in type 2 diabetes than conventional therapy (35,49) or CCB (34,50,51). By contrast, the UKPDS and STOP 2 studies failed to demonstrate a specific cardiovascular protective role for ACE-I compared with conventional therapy in patients with type 2 diabetes (51,52).

Interesting results were obtained for ARB. The composite cardiovascular end point (death from cardiovascular causes, nonfatal myocardial infarction, stroke, and heart failure resulting in hospitalization) was similar in IDNT and RENAAL.
for the prevention and treatment of diabetic nephropathy have now been changed. In type 1 diabetes ACE-I are the first-choice drugs. In type 2 diabetes, ARB are now considered first-choice drugs in microalbuminuric patients, as are ACE-I (secondary prevention). Furthermore, ARB have been elected the unique first-choice drugs in patients with overt nephropathy (tertiary prevention). Finally, taking into account the results of recent trials, including the LIFE study, ARB should be considered first-choice drugs in cardiovascular prevention too, as should ACE-I. Additional studies are needed to address the role of ARB in lowering the incidence of microalbuminuria in normoalbuminuric subjects.

Conclusions

In conclusion, ARB seem to be effective in both preventing renal damage and reducing progression toward end-stage renal disease in type 2 diabetic patients. According to the new evidence from these three large clinical trials, the guidelines

Figure 3. Time to primary composite end point (doubling of serum creatinine, end-stage renal disease, or death) in the IDNT study (A) and the RENAAL study (B) (23,24).

studies. The treatments with irbesartan and losartan resulted in a 9 and 10% reduction respectively in the risk of the composite cardiovascular end points compared with conventional therapy. These differences were not statistically significant. Nevertheless, a significant reduction in hospitalizations for heart failure was demonstrated for patients on irbesartan compared with placebo or amlodipine in the IDNT study (−23%), and for losartan compared with placebo in the RENAAL study (−32%).

Although the incidence of major cardiovascular events was elevated due to a higher risk for patients with diabetes and overt proteinuria, the absence of any difference in the secondary endpoint in both trials could be mainly the effect of a short follow-up period. The LIFE study showed that losartan was more effective than conventional therapy in reducing cardiovascular morbidity and mortality in a large cohort of diabetic patients with hypertension and left ventricular hypertrophy followed for a long period, approximately 5 yr (53).

References