Prevention and Treatment of Diabetic Nephropathy: The Program for Irbesartan Mortality and Morbidity Evaluation

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Aggressive treatment of hypertension is effective in reducing both microvascular and macrovascular complications in type 2 diabetes, with target BP <130/80 mmHg being recommended. Angiotensin-converting enzyme inhibitors were found to be more effective than the other traditional agents in reducing the onset of clinical proteinuria in individuals with both type 1 and type 2 diabetes and incipient nephropathy. However, small trials on patients with type 2 diabetes and overt nephropathy failed to demonstrate a specific renoprotective role for this class of drugs. The aim of the Program for Irbesartan Mortality and Morbidity Evaluation was to ascertain whether angiotensin II receptor blockers are effective in both preventing the development of clinical proteinuria and delaying the progression of nephropathy in type 2 diabetes. The Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA) Study showed that, as compared with conventional therapy, irbesartan is better at preventing the development of clinical proteinuria and at restoring normoalbuminuria for comparable BP control in patients with incipient nephropathy. The Irbesartan Diabetic Nephropathy Trial showed that irbesartan is more effective than traditional antihypertensive therapies in reducing the progression toward ESRD in patients with type 2 diabetes and overt nephropathy regardless of changes in BP. Moreover, secondary analysis of the Irbesartan Diabetic Nephropathy Trial showed that the achieved systolic pressure as well as baseline and current proteinuria significantly predict renal outcomes. In conclusion, the results of the Program for Irbesartan Mortality and Morbidity Evaluation demonstrate that irbesartan significantly prevents the development of clinical proteinuria in individuals with microalbuminuria and delays the progression of nephropathy in individuals with proteinuria. Moreover, the renoprotective effects of irbesartan go beyond its effect on BP.


The Program for Irbesartan Mortality and Morbidity Evaluation (PRIME) is the most comprehensive angiotensin receptor blocker (ARB) study on patients with type 2 diabetes. It consists of two large trials, the Irbesartan Diabetic Nephropathy Trial (IDNT) and the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA), which evaluated the renal and cardiovascular effects of irbesartan on hypertensive patients with diabetes (1,2). In particular, these two large trials addressed the question of whether ARB can prevent the development of clinical proteinuria (IRMA) or delay the progression of nephropathy (IDNT) in type 2 diabetics.

There is evidence that BP reduction (3,4) and intensive antihypertensive treatment (5,6) are effective in reducing both the microvascular and the macrovascular complications of type 2 diabetes. Indeed, target BP levels <130/80 mmHg are now recommended for hypertensive patients with diabetes (7–14).

Taking into account that the renin angiotensin aldosterone system (RAAS) seems to play an essential role in the pathophysiology of hypertension and diabetes-related complications, a rationale exists for RAAS blockade. Angiotensin-converting enzyme inhibitors (ACE-I) are deemed to provide the greatest renal protection in type 1 diabetes, whereas available data on the major end points in type 2 diabetes were scanty before PRIME.

Several studies performed on normotensive, microalbuminuric patients with type 2 diabetes showed that ACE-I markedly reduce the incidence of overt nephropathy (relative risk reduction [RRR], approximately 70 to 100%), regardless of BP levels (15–17). These data are consistent with results obtained in type 1 diabetes (18–22). In hypertensive, microalbuminuric patients with type 2 diabetes, the MicroHOPE study (23) and two other smaller studies (24,25) demonstrated the efficacy of ACE-I in reducing the incidence of overt nephropathy as compared with other treatments. On the contrary, this effect was not found in two other studies (26,27). Thus, ACE-I seem to be less clearly effective in hypertensive patients than in normotensive ones. On the average, the weighted risk reduction is only 23%. In patients with type 2 diabetes and overt nephropathy, four of five small trials that evaluated the effects of various classes of drugs failed to demonstrate a specific renoprotective role for ACE-I at this stage of nephropathy (24,26,28–30). Last, ARB could theoretically provide to patients with diabetes an even greater benefit than ACE-I because of the more complete RAAS blockade.

The IRMA study, a multicenter, randomized, double-blind, placebo-controlled trial, evaluated the effect of irbesartan in preventing the onset of clinical proteinuria in patients with type 2 diabetes and hypertension and microalbuminuria (2). A total of 590 patients were randomized to receive therapy with irbe-
sartan 150 mg, irbesartan 300 mg, or placebo. Additional antihypertensive agents (excluding ACE-I, ARB, and dihydropyridine calcium-channel blockers) were allowed in each arm of the study to achieve the target BP of <135/85 mmHg. The primary end point of the study was the onset of overt nephropathy, defined as the occurrence of a urinary albumin excretion rate >200 μg/min and at least 30% higher than baseline. Secondary outcomes were the regression to normoalbuminuria and changes in albuminuria and renal function.

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. Although the difference in systolic pressure between the irbesartan 300-mg group and the placebo group was only 3 mmHg, it was statistically significant. It is interesting that although all patients were hypertensive by definition, only 56% of the patients in the placebo group received antihypertensive therapy. With respect to the primary end point, irbesartan 150 and 300 mg showed an adjusted RRR (aRRR) of 44 and 68%, respectively, versus usual care (placebo group). Moreover, albuminuria was reduced by 38% in the 300-mg group, was reduced by 24% in the 150-mg group, and remained unchanged in the usual care group. In this last group, the reduction in BP from 153/90 to 144/83 mmHg resulted in the stabilization of albuminuria. In addition, regression to normoalbuminuria was more frequent in the patients who were treated with the higher dose of irbesartan (17, 12, and 10.5/100 patient-years in the 300-mg, 150-mg, and placebo group, respectively; Figure 1). On the basis of these data, irbesartan seems to be much more effective in preventing the development of clinical proteinuria and in favoring the regression to normoalbuminuria than conventional therapy. The renoprotective, dose-dependent effect of irbesartan seems to be independent of its BP-lowering effect, even though the 3-mmHg difference in systolic pressure may have played a role. Other confounding factors can be ruled out because the glycated hemoglobin levels and the administration of lipid-lowering agents and aspirin were similar in the three groups at the end of the study.

The IDNT was a large, randomized, double-blind, placebo-controlled, multicenter study that evaluated the efficacy of irbesartan in slowing the progression of overt diabetic nephropathy in 1715 hypertensive patients with type 2 diabetes (1). Patients were followed up for approximately 2.6 yr after being randomized to receive up to 300 mg/d irbesartan, up to 10 mg/d amlodipine, or matched placebo. Additional antihypertensive agents other than ACE-I, ARB, and calcium-channel blockers were allowed in each arm of the study to achieve the target BP <135/85 mmHg. Primary outcome was the composite of a doubling of serum creatinine, ESRD, or death.

The achieved BP was similar in the irbesartan and amlodipine group and slightly higher in the placebo group (140/77, 141/77, and 144/80 mmHg, respectively). On average, patients required three additional nonstudy drugs; however, only 30% of them achieved the target BP. Proteinuria was reduced by 50% in the irbesartan group and by 20% in the other two arms. In these last two arms, the 15-mmHg reduction in systolic BP and 10-mmHg reduction in diastolic BP were associated with a significant decrease in proteinuria. Unlike previous reports, proteinuria was also reduced in the amlodipine group, thus emphasizing the antiproteinuric effect of the reduction in BP itself.

Treatment with irbesartan was associated with a significantly lower risk for the primary composite end point as compared with the placebo (aRRR, 19%) or amlodipine groups (aRRR, 24%; Figure 2). No differences were found between the amlodipine and conventional treatment (placebo) arms. The risk for doubling serum creatinine levels was lower in the irbesartan group than in the conventional treatment (aRRR, 29%) or amlodipine groups (aRRR, 39%). It is interesting that the benefit of the ARB exceeded what is attributable to changes in BP. Indeed, the RRR is adjusted for the achieved BP, and no substantial differences were observed in BP behavior between the irbesartan and the amlodipine groups. However, the 4-mmHg difference in systolic BP and the 3-mmHg difference in diastolic BP between irbesartan and conventional treatment, respectively, likely had some confounding effect. By contrast, glycated hemoglobin levels were similar in the three arms during the

Figure 1. Renoprotection in 590 hypertensive microalbuminuric patients with type 2 diabetes: Effect of angiotensin receptor blocker (ARB) in the Irbesartan in Patients with Type 2 Diabetes and Microalbuminurias Study (2). Conv.th, conventional therapy; NDCCB, non–dihydropyridine calcium channel blockers; aRRR, adjusted relative risk reduction. *P = 0.005 for the comparison of mean BP between the 300-mg irbesartan group and the conventional treatment group.
study. Results obtained in the RENAAL trial (31), that compared losartan to usual care, confirmed the results obtained in IDNT. Taken together, the results of these two large trials clearly demonstrate that ARB, unlike ACE-I, are more effective in halting the progression of renal damage in type 2 diabetes than conventional therapy. Last, an important finding of the IDNT trial, which is consistent with data from a report on the nondiabetic population (32), is that amlodipine proved to be less renoprotective than the RAAS-blocking agents. The database from the IDNT also provided the opportunity to evaluate what the optimal BP is to slow the progression of renal damage and how baseline proteinuria and its changes influence the renoprotective effects of antihypertensive therapy.

The impact that the achieved systolic BP at 12 mo has on the time to subsequent doubling of creatinine is shown in Figure 3. The best renal outcome was observed in patients who achieved systolic BP <132 mmHg. By multivariate linear regression analysis, the 12-mo achieved systolic BP proved to be an independent predictor of renal risk. Overall, a 20-mmHg decrease in systolic BP was associated with a nearly 50% decrease in the risk for doubling serum creatinine (33).

Baseline proteinuria is an important risk factor for renal failure and provides a means for identifying patients who are at greatest risk. The doubling of proteinuria was associated with the doubling of the risk for renal end point (doubling of serum creatinine or ESRD) in 1608 patients in the IDNT (34). The benefit of treatment with irbesartan was maintained after adjusting for differences in baseline proteinuria among the treatment groups. A greater reduction in proteinuria was observed in patients who were assigned to irbesartan than in those who were assigned to either amlodipine or conventional therapy (ratio 12 mo/baseline proteinuria: irbesartan, 0.45; amlodipine, 0.83; conventional therapy, 0.76; P < 0.0001). The change in proteinuria was a strong predictor of the risk of renal end points. Indeed, for each halving of proteinuria at 12 mo of treatment, the risk for renal end point was reduced by one half (RR, 0.52; P < 0.0001) (34). Thus, the IDNT supports the conclusion that both reducing urinary protein excretion and lowering BP are specific renoprotective goals in the management of type 2 diabetes nephropathy, consistent with the results of the RENAAL study (35,36).

The clinical impact of the PRIME is remarkable, because treating 10 hypertensive, microalbuminuric patients with type 2 diabetes with irbesartan would prevent one patient from developing overt nephropathy over 2 yr, and treating 10 hypertensive patients with type 2 diabetes and overt nephropathy would prevent one patient from developing a doubling of serum creatinine, ESRD, or death over 3 yr. Moreover, a major improvement in life expectancy as a result of a delay in the onset of ESRD is associated with a reduction in overall costs per patient. On the basis of the results of the IDNT trial, several financial analyses performed in the United States and in Europe demonstrated that treating patients with type 2 diabetes nephropathy and hypertension with irbesartan led to greater cost savings after 3 yr of treatment, compared with administering amlodipine or standard antihypertensive therapy (37,38). Irbesartan was associated with 10-yr net cost savings of $23,817 and $16,026 per patient in the United States, €14,949 and €9205 in Belgium, and €20,128 and €13,337 in France, versus amlodipine and usual care, respectively (37,38). In Italy, irbesartan led to 10-yr net cost savings of €13,530 and €8133 per patient versus amlodipine and usual care, respectively (39).

In conclusion, PRIME is a comprehensive morbidity and mortality program in hypertensive patients with type 2 diabetes showing that:

1. in IRMA 2, irbesartan markedly slows the progression from microalbuminuria to overt nephropathy;
2. in IDNT, irbesartan protects against further renal disease progression and death in later stages;
3. achieved BP and baseline and achieved proteinuria significantly and independently influence renal outcomes in type 2 diabetes, consistent with results obtained in nondiabetic nephropathies (40);
4. the renoprotective effects of irbesartan go beyond its effect on BP.
However, even taking these important results into account, neither ARB nor ACE-I provide total protection for both renal and cardiovascular events. Further strategies are necessary for both micro- and macrovascular protection in patients with type 2 diabetes, and a multifactorial therapeutic approach (e.g., dual blockade, addition of antialdosterone drugs and statins) might be a promising strategy.

References


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