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

Maura Ravera, Elena Ratto, Simone Vettoretti, Denise Parodi, and Giacomo Deferrari
Department of Internal Medicine, Section of Nephrology and Dialysis, University of Genoa, Genoa, Italy

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.

J Am Soc Nephrol 16: S48–S52, 2005. doi: 10.1681/ASN.2004110957

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 diabetes.

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-

Address correspondence to: Dr. Giacomo Deferrari, Department of Internal Medicine, Viale Benedetto XV, 6-16123 Genoa, Italy. Phone: +39-010-353-8959; Fax: +39-010-353-8959; E-mail gildaplm@unige.it

ISSN: 1046-6673/1603-0048

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

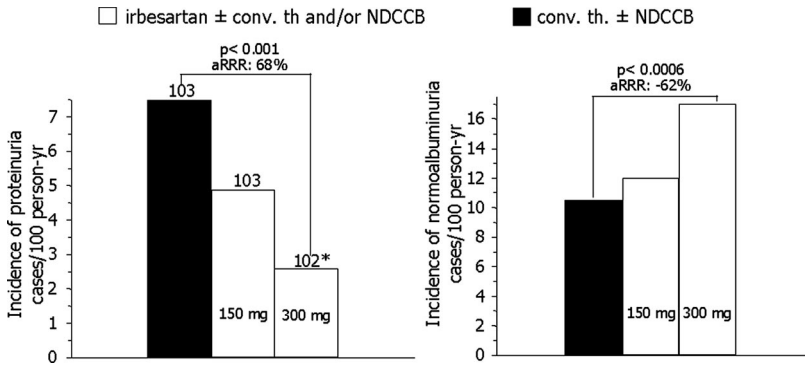

Figure 1. Renoprotection in 590 hypertensive microalbuminuric patients with type 2 diabetes: Effect of angiotensin receptor blocker (ARB) in the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study (2). Conv.th, conventional therapy; NDCCB, non–dihydropyridine calcium channel blockers; 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.

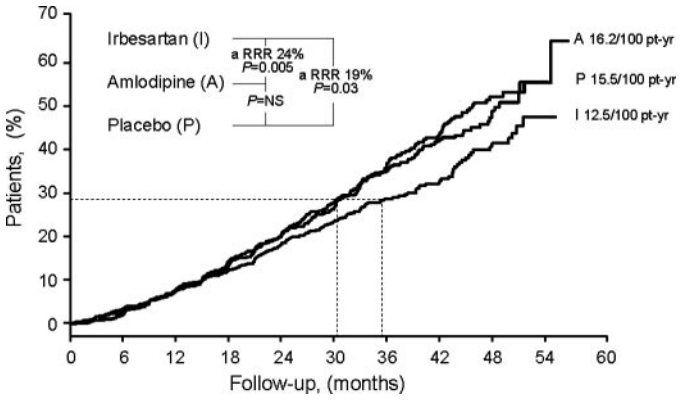

Figure 2. Time to primary composite end point (doubling of serum creatinine, ESRD, or death) in the Irbesartan Diabetic Nephropathy Trial (IDNT) (1).

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).

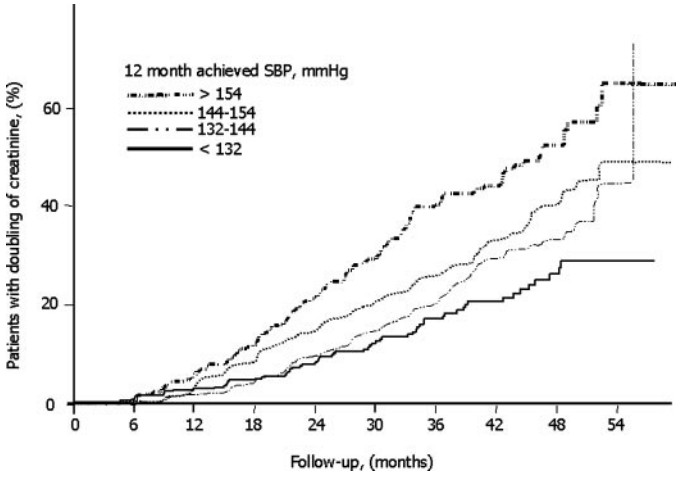

Figure 3. Time to doubling of serum creatinine according to quartiles of achieved systolic BP at 12 mo in the IDNT (33). SBP, systolic BP.

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

1. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I; Collaborative Study Group: Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 345: 851–860, 2001
2. Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P; Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group: The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 345: 870–878, 2001
3. Curb JD, Pressel SL, Cutler JA, Savage PJ, Applegate WB, Black H, Camel G, Davis BR, Frost PH, Gonzalez N, Guthrie G, Oberman A, Rutan GH, Stamler J: Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. Systolic Hypertension in the Elderly Program Cooperative Research Group. *JAMA* 276: 1886–1892, 1996
4. Tuomilehto J, Rastenyte D, Birkenhager WH, Thijs L, Antikainen R, Bulpitt CJ, Fletcher AE, Forette F, Goldhaber A, Palatini P, Sarti C, Fagard R: Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *N Engl J Med* 340: 677–684, 1999
5. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ* 317: 703–713, 1998
6. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, Menard J, Rahn KH, Wedel H, Westerling S: Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: Principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* 351: 1755–1762, 1998
7. Mogensen CE, Keane WF, Bennet PH, Jerums G, Parving HH, Passa P, Steffes MW, Striker GE, Viberti GC: Prevention of diabetic renal disease with special reference to microalbuminuria (Consensus report). *Lancet* 346: 1080–1084, 1995
8. Bakris GL, Williams M, Dworkin L, Elliott WJ, Epstein M, Toto R, Tuttle K, Douglas J, Hsueh W, Sowers J; for the National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group: Preserving renal function in adults with hypertension and diabetes: A consensus approach. *Am J Kidney Dis* 36: 646–661, 2000
9. Kaplan NM: Management of hypertension in patients with type 2 diabetes mellitus. Guidelines based on current evidence. *Ann Intern Med* 135: 1079–1183, 2001
10. American Diabetes Association: Treatment of hypertension in adults with diabetes. *Diabetes Care* 25: 199–201, 2002
11. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 report. *JAMA* 289: 2560–2572, 2003
12. World Health Organization, International Society of Hypertension Writing Group: 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. *J Hypertens* 21:1983–1992, 2003
13. European Society of Hypertension-European Society of Cardiology Committee: 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 21: 1011–1053, 2003
14. Deferrari G, Cavallo Perin P, Di Paolo S, Locatelli R, Nosadini R, Penno G, Piccoli G, Ravera M: Linee guida della nefropatia diabetica [Italian]. *G Ital Nefrol Suppl* 24: S96–S108, 2003
15. Ravid M, Savin H, Jutrin I, Bental T, Katz B, Lishner M: Long-term stabilizing effect of angiotensin-converting enzyme inhibition on plasma creatinine and on proteinuria in normotensive type II diabetic patients. *Ann Intern Med* 118: 577–581, 1993
16. Sano T, Hotta N, Kawamura Tm Matsumae H, Chaya S, Sasaki H, Nakayama M, Hara T, Matsuo S, Sakamoto N: Effects of long-term enalapril treatment on persistent microalbuminuria in normotensive type 2 diabetic patients: Result of a 4-year, prospective, randomized study. *Diabet Med* 13: 120–124, 1996
17. Ahmad J, Siddiqui MA, Ahmad H: Effective postponement of diabetic nephropathy with enalapril in normotensive type 2 diabetic patients with microalbuminuria. *Diabetes Care* 20: 1576–1581, 1997
18. The Microalbuminuria Captopril Study Group: Captopril reduces the risk of nephropathy in IDDM patients with microalbuminuria. *Diabetologia* 39: 587–593, 1996
19. Crepaldi G, Carta Q, Deferrari G, Mangili R, Navalesi R, Santeusanio F, Spalluto A, Vanasia A, Villa GM, Nosadini R, The Italian Microalbuminuria Study Group in IDDM: Effects of lisinopril and nifedipine on the progression to overt albuminuria in IDDM patients with incipient nephropathy and normal blood pressure. *Diabetes Care* 21: 104–110, 1998
20. Penno G, Chaturvedi N, Talmud PJ, Cotroneo P, Manto A, Nannipieri M, Luong L, Fuller J; the Euclid Study Group: Effect of angiotensin-converting enzyme (ACE) gene polymorphism progression of renal disease and the influence of ace inhibition in IDDM patients. Findings from the EUCLID randomized controlled trials. *Diabetes* 47: 1507–1511, 1998
21. Mathiesen ER, Hommel E, Hansen HP, Smidt UM, Parving HH: Randomised controlled trial of long term efficacy of captopril on preservation of kidney function in normotensive patients with insulin dependent diabetes and microalbuminuria. *BMJ* 319: 24–25, 1999
22. The ATLANTIS Study Group: Low dose ramipril reduces

microalbuminuria in type 1 diabetic patients without hypertension. *Diabetes Care* 23: 1823–1829, 2000
23. Heart Outcomes Prevention Evaluation Study Investigators: Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: Results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. *Lancet* 355: 253–259, 2000
24. Lebovitz HE, Wiegmann TB, Cnaan A, Shahinfar S, Sica DA, Broadstone V, Schwartz SL, Mengel MC, Segal R, Versaggi JA: Renal protective effects of enalapril in hypertensive NIDDM: Role of baseline albuminuria. *Kidney Int Suppl* 45: S150–S155, 1994
25. Chan JC, Ko GT, Leung DH, Cheung RC, Cheung MY, So WY, Swaminathan R, Nicholls MG, Critchley JA, Cockram CS: Long-term effects of angiotensin-converting enzyme inhibition and metabolic control in hypertensive type 2 diabetic patients. *Kidney Int* 57: 590–600, 2000
26. Estacio RO, Jeffers BW, Gifford N, Shrier R: Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. *Diabetes Care* 23[Suppl 2]: B54–B64, 2000
27. Baba S; The J-Mind Study Group: Nifedipine and enalapril equally reduce the progression of nephropathy in hypertensive type 2 diabetics. *Diabet Res* 54: 191–201, 2001
28. Bakris GL, Copley JB, Vicknair N, Sadler R, Leurgans S: Calcium channel blockers versus other antihypertensive therapies on progression of NIDDM associated nephropathy. *Kidney Int* 50: 1641–1650, 1996
29. Nielsen FS, Rossing P, Gall MA, Skott P, Smidt UM, Parving HH: Long-term effect of lisinopril and atenolol on kidney function in hypertensive NIDDM subjects with diabetic nephropathy. *Diabetes* 46: 1182–1188, 1997
30. Fogari R, Zoppi A, Corradi L, Mugellini A, Lazzari P, Preti P, Lusardi P: Long-term effects of ramipril and nitrendipine on albuminuria in hypertensive patients with type II diabetes and impaired renal function. *J Hum Hypertens* 13: 47–53, 1999
31. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S; RENAAL Study Investigators: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 345: 861–869, 2001
32. Sica DA, Douglas JG: The African American Study of Kidney Disease and Hypertension (AASK): New findings. *J Clin Hypertens* 3: 244–251, 2001
33. Pohl MA, Blumenthal S, Hunsicker LG, the Collaborative Study Group: Impact of achieved systolic blood pressure on renal function in type 2 diabetic nephropathy [Abstract]. *J Am Soc Nephrol* 13: 644A, 2002
34. Atkins RC, Briganti EM, Wiegmann TB, on Behalf of the Collaborative Study Group: Effect of baseline proteinuria and change in proteinuria with treatment on the risk of renal endpoints in the Irbesartan Diabetic Nephropathy Trial (IDNT) [Abstract]. *J Am Soc Nephrol* 13: 7A, 2002
35. Bakris GL, Weir MR, Shanifar S, Zhang Z, Douglas J, van Dijk DJ, Brenner BM; RENAAL Study Group: Effects of blood pressure level on progression of diabetic nephropathy: Results from the RENAAL Study. *Arch Intern Med* 163: 1555–1565, 2003
36. de Zeeuw D, Remuzzi G, Parving HH, Keane WF, Zhang Z, Shahinfar S, Snapinn S, Cooper ME, Mitch WE, Brenner BM: Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: Lessons from RENAAL. *Kidney Int* 65: 2309–2320, 2004
37. Rodby RA, Chiou CF, Borenstein J, Smitten A, Sengupta N, Palmer AJ, Roze S, Annemans L, Simon TA, Chen RS, Lewis EJ; Collaborative Study Group: The cost-effectiveness of irbesartan in the treatment of hypertensive patients with type 2 diabetic nephropathy. *Clin Ther* 25: 2102–2119, 2003
38. Palmer AJ, Annemans L, Roze S, Lamotte M, Rodby RA, Cordonnier DJ: An economic evaluation of irbesartan in the treatment of patients with type 2 diabetes, hypertension and nephropathy: Cost-effectiveness of Irbesartan in Diabetic Nephropathy Trial (IDNT) in the Belgian and French settings. *Nephrol Dial Transplant* 18: 2059–2066, 2003
39. Palmer AJ, Annemans L, Roze S, Lamotte M, Berto P, Ravera M, Rodby RA: Economic evaluation of irbesartan in patients with type 2 diabetes, hypertension and nephropathy: The Italian perspective. *Pharmacoeconomics* 2005, in press
40. Jafar TH, Stark PC, Schmid CH, Landa M, Maschio G, de Jong PE, de Zeeuw D, Shahinfar S, Toto R, Levey AS; AIPRD Study Group: Progression of chronic kidney disease: The role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: A patient-level meta-analysis. *Ann Intern Med* 139: 244–252, 2003