Emerging Trends for Prevention and Treatment of Diabetic Nephropathy: Blockade of the RAAS and BP Control

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ABSTRACT

BACKGROUND: Diabetic nephropathy (DN) is the leading cause of end-stage renal disease (ESRD), and it affects 30% of patients with type 1 diabetes mellitus (DM) and 20% of patients with type 2 DM. Clinical features in both types of DM are similar and are characterized by an underlying abnormality of the microcirculation, manifested by both retinopathy and nephropathy. Clinical hallmarks of DN include elevated blood pressure (BP) and elevated urinary protein excretion. Treatment consists of maintaining BP at <130/85 mm Hg in patients without proteinuria and <125/75 mm Hg in patients with microalbuminuria or overt DN. In addition, agents that inhibit the renin-angiotensin-aldosterone system (RAAS) have been found to be effective in reducing the risk of progression to DN, a result independent of their antihypertensive effect.

SUMMARY: The earlier Collaborative Study Group (CGS) trial demonstrated that the angiotensin-converting enzyme (ACE) inhibitor captopril lowered BP and provided renal protection in type 1 diabetic kidney disease beyond that attributable to the BP change. The Irbesartan Diabetic Nephropathy Trial (IDNT) studied the effect of the angiotensin receptor blocker (ARB) irbesartan on the reduction of BP, urinary protein excretion, and progression to DN. The study end points in the IDNT demonstrated that ARB therapy reduced BP, reduced urinary protein excretion, and provided renal protection against progression to DN. The Reduction of Endpoints in NIDDM With the Angiotensin II Antagonist Losartan (RENAAL) trial demonstrated that the ARB losartan, when combined with conventional antihypertensive agents, decreased urinary protein excretion by 35%. Losartan both lowered BP and provided renal protection against DN. In a study comparing an ACE inhibitor (trandolapril), an ARB (losartan), and a combination of the 2 agents (trandolapril and losartan), data showed that all 3 arms reduced BP to the same degree. However, a combination of the ARB plus the ACE inhibitor produced both a significant reduction in urinary protein excretion beyond that seen with either agent alone and a significantly greater protection against progression to doubling of serum creatinine or ESRD. The reduction in urinary protein excretion and renal progression seen with individual agents were not statistically different from each other.

CONCLUSION: These studies demonstrated that the combination blockade of the RAAS axis with an ARB plus an ACE inhibitor may play an important role in the prevention and treatment of DN and may turn the tide of increasing kidney disease due to DM, improve the overall quality of life of patients with DM, and save the lives of patients with either type 1 or type 2 DM.

KEYWORDS: Diabetic nephropathy, Glomerulosclerosis, Kimmelsteil-Wilson lesion, Microalbuminuria, End-stage renal disease (ESRD), RAAS axis, Angiotensin receptor blocker (ARB), Angiotensin-converting enzyme (ACE) inhibitor, CGS trial, IDNT, RENAAL trial

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Diabetic nephropathy (DN) is the leading cause of end-stage renal disease (ESRD) in developed countries. In 2001, this disorder accounted for 45% of the new cases of ESRD in the United States.[1] Type 1 diabetes mellitus (DM) affects 0.5% of the general population. Type 2 DM is recognized in at least 4% of the population. About one third of patients with type 1 DM and approximately 20% of patients with type 2 DM have diabetic nephropathy (DN). Because of the greater worldwide prevalence of type 2 DM, which accounts for 90% of all cases, most patients with DM and ESRD have type 2 disease. There are several risk factors involved in the etiology of DN, including glomerular hypertension and hyperfiltration, systemic hypertension, hyperglycemia, and, potentially, cigarette smoking, hyperlipidemia, and gene polymorphisms that affect the renin-angiotensin-aldosterone system (RAAS). ESRD from diabetic nephropathy is more prevalent in African Americans with type 2 DM than in whites (4:1 ratio), while the reverse is true for type 1 DM.[2]

Pathophysiology of Diabetic Nephropathy

The clinical features of DN in both type 1 and type 2 DM are similar, although the time from onset of recognized DM to diabetic kidney disease may be shorter in type 2 DM.[2] In type 2 DM, advanced pathologic changes of the kidney may be found at the time of diagnosis of DM.[3] There is an underlying and generalized abnormality of the microcirculation in both types of DM. In particular, the degree of retinopathy (as observed with the ophthalmoscope) can be directly correlated with the degree of renal abnormality (as indicated by proteinuria and renal biopsy). Diabetic kidney disease is characterized pathophysiologically by increased permeability of the glomerular capillary wall to protein leading to clinical proteinuria, with an associated thickening of the basement membrane and abnormalities of the glomerular arterioles. Glycosylation of many proteins occurs with DM, particularly in the collagen of the basement membrane.[4]

DN is generally diagnosed based on clinical grounds without a renal biopsy. Important clues to the early diagnosis, in addition to the presence of clinical DM itself, include the presence of normal-sized or enlarged kidneys, evidence of proliferative diabetic retinopathy, and microalbuminuria or overt albuminuria. Retinopathy is found in 90% of type 1 DM cases and in 60% of patients with type 2 DM who eventually develop nephropathy.[2]

Early abnormal microscopic changes in DN include a thickening of the glomerular basement membrane (GBM) and the expansion of the mesangium due to the accumulation of extracellular matrix. Prominent areas of nodular matrix expansion (Kimmelsteil-Wilson lesions) are seen in microscopic sections along with the thickened GBM. Laminated and

eosinophilic nodules may be seen in the periphery of the glomeruli. In both type 1 and type 2 DM, fibrin caps, capsular drops, and gross hyalinization of the arterioles may be present.[3] Progressive expansion of the mesangium results in the progressive occlusion of the glomerular capillaries, ultimately producing a large acellular mass.[4] Over time, the mesangial matrix becomes diffusely expanded, and the glomerulus becomes sclerotic.[2]

The best treatment for DN is prevention. A comprehensive program of diabetic care should include early detection so that therapies can be initiated effectively.[5] Therapy is aimed at preventing the onset and slowing the progression of DN by controlling blood sugar and systemic blood pressure (BP), and by blockade of the RAAS. Control of glucose levels can be achieved through regulating diet and administering oral hypoglycemic agents and insulin.[2] In addition, a consensus panel of the American Diabetes Association has recommended protein intake reductions in patients with DM with microalbuminuria (0.8 g/kg/day is the Adult Recommended Daily Allowance and about 10% of the daily caloric intake). There is some evidence that protein intake should be restricted to 0.6 g/kg/day in patients with overt DN.[5]

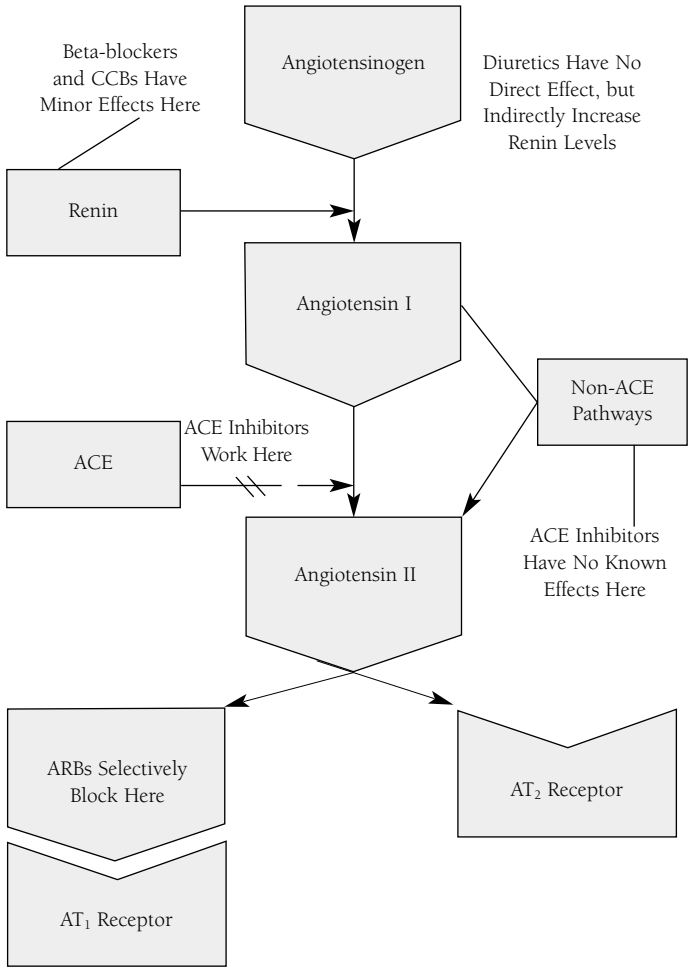
Treatment of Hypertension Associated With Diabetic Nephropathy

The development of hypertension in both type 1 and type 2 DM is a clinical hallmark. Thirty percent of patients with type 2 DM have high blood pressure when they are diagnosed, and about 70% of these patients have hypertension when nephropathy develops. The added problems associated with renal vascular disease contribute to hypertension in about 20% of all patients with type 2 DM and in almost 40% of those patients with overt nephropathy.[6]

Numerous clinical studies in both types of DM have demonstrated the value of strict BP control in reducing albumin excretion and in inhibiting the decline in renal function. In order to preserve renal function, BP should be maintained at <130/85 mm Hg in patients with DM without proteinuria. When patients have shown evidence of microalbuminuria or nephropathy, a slightly lower target blood pressure (125/75 mm Hg) is advised.[5]

Agents blocking the RAAS (angiotensin-converting enzyme [ACE] inhibitors and angiotensin receptor blockers [ARBs]) reduce the progression of overt nephropathy in both type 1 and type 2 DM—both through BP reduction and through mechanisms independent of BP—and should be initiated whenever microalbuminuria or overt proteinuria is detected. Figure 1 shows the role of ACE inhibitors and ARBs in RAAS blockade. If use of an ACE inhibitor produces unmanageable side effects (e.g., allergy, cough, or angioedema), an ARB can be used as an alternative agent, and vice versa. ACE inhibitors and ARBs are the only agents shown to produce a drug-specific benefit in DN independent of BP control.[5]

FIGURE 1 Renin-Angiotensin-Aldosterone System



ACE = angiotensin-converting enzyme; CCBs = calcium channel blockers; ARBs = angiotensin receptor blockers; AT = angiotensin.

Summary

Treatment of Patients With Microalbuminuria

The DM substudy of the Heart Outcomes Prevention Evaluation (HOPE) clinical trial examined patients with type 2 DM and microalbuminuria and demonstrated that treatment with an ACE inhibitor provided a 24% reduction in the rate of progression to overt nephropathy compared with the group receiving placebo, despite similar BPs in both groups.[6] In the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA II) trial, treatment with irbesartan (300 mg/day) decreased the level of urinary albumin secretion by 38% from baseline. Over a 3-year follow-up period, irbesartan also reduced the risk of progression to macroalbuminuria by 70% compared with placebo.[6,7] Irbesartan was less effective when used at the dose of 150 mg/day.[7] Other

clinical trials of patients with type 2 DM and overt nephropathy demonstrated that ACE inhibitors were more effective than other antihypertensive agents in reducing proteinuria. (ARBs were not included in these studies.)[6]

Treatment of Patients With Overt Proteinuria

In an earlier randomized controlled trial conducted by the Collaborative Study Group (CSG), the ACE inhibitor captopril was shown to protect against deterioration of renal function in patients with type 1 DM and nephropathy and to be significantly more effective than BP control alone.[8] In this trial, 207 patients received captopril and 202 received placebo. Inclusion criteria for all patients consisted of type 1 DM with urinary protein excretion >500 mg/day and a serum creatinine concentration of <2.5 mg/dL (220 μmol/L). The goal for BP control was the same (<140/90 mm Hg) in both groups, with BP control achieved using adjunctive agents other than ACE inhibitors. Median follow-up was 3 years. The primary end point was a doubling of the baseline serum creatinine concentration.[8]

The CSG investigators' research supported the proposal that captopril beneficially alters glomerular hemodynamics in patients with DM by a mechanism independent of its antihypertensive properties.[8] ACE inhibitors are known to decrease urinary protein excretion in patients with type 2 DM and other glomerulopathies. In this study, use of captopril also resulted in decreased proteinuria. The beneficial effects of captopril on glomerular hemodynamics and on glomerular pathology were suggested to explain the decrease in proteinuria.[8]

The Irbesartan Diabetic Nephropathy Trial

The CSG investigators designed the Irbesartan Diabetic Nephropathy Trial (IDNT) to determine whether the use of an ARB or a calcium channel blocker (CCB) would provide protection against the progression of nephropathy due to type 2 DM beyond the agents' known antihypertensive effects.[9]

In the IDNT, 1,715 hypertensive patients with nephropathy due to type 2 DM were randomly assigned to 3 treatment arms: (1) irbesartan 300 mg daily, (2) amlodipine 20 mg daily, or (3) placebo. The target BP was 135/85 mm Hg or less in all groups, again with control being achieved with the use of adjunctive antihypertensive agents other than ACE inhibitors, ARBs, or CCBs.[9] The 3 groups were compared with regard to the time to the primary composite end point of a doubling of baseline serum creatinine concentration, the development of ESRD, or death from any cause. All groups were also compared with a secondary cardiovascular end point. The IDNT mean duration of follow-up was 2.6 years.[9]

The investigators found that therapy with irbesartan resulted in a 20% lower risk of the primary end point compared with the placebo group (P = 0.02) and a 23% lower risk than the amlodipine group (P = 0.006). The risk of doubling the serum creatinine concentration was 33% lower in the irbesartan group compared with the placebo group (P = 0.003) and 37% lower in the irbesartan group compared with the amlodipine group (P<0.001).[9]

Data from this trial showed that treatment with irbesartan was associated with better renal outcomes than the other study agents (i.e., amlodipine and placebo). Use of the ARB agent produced a reduction in the rate of progression of the nephropathy, which was reflected in a significant increase in the time to a doubling of the serum creatinine concentration (representing an approximate halving of the glomerular filtration rate [GFR]). At 3 years of follow-up, the absolute reduction in the rate of doubling of serum creatinine was 11.5% (from 27.2% in patients receiving placebo to 15.7% in patients receiving irbesartan). Thus, one prevents 1 patient from doubling by treating 9 patients with irbesartan for a period of 3 years.[9] The mean rate of increase in the serum creatinine concentration and the mean rate of decrease in creatinine clearance were significantly lower in the group of patients receiving irbesartan.[9] The investigators interpreted these results as demonstrating that irbesartan was renoprotective in patients with nephropathy due to type 2 DM.[9] The renoprotective effects were similar to those described previously,[8] when the ACE inhibitor captopril was used in patients with nephropathy due to type 1 DM.[9]

The effect of baseline proteinuria and change in proteinuria was also investigated in the IDNT in patients with DN. Proteinuria has been shown to have a strong correlation with the rate of renal disease progression. In an analysis involving 1,608 patients with baseline 24-h proteinuria, urine protein was seen as a significant predictor of poor outcome with a relative risk (RR) for renal disease of 2.06 for each doubling of proteinuria (P<0.0001). Among 1,261 patients with proteinuria at baseline and at 12 months follow-up, the reduction of urine protein at 12 months was associated with a significant reduction of the risk of renal end point (RR = 0.52) for each halving of the proteinuria value (P<0.0001). The investigators observed that proteinuria was reduced significantly more in those patients who received irbesartan than in those who received either amlodipine or placebo. The beneficial results of irbesartan as protection against the progression of renal failure in DN were found to be strongly correlated with the reduction in proteinuria.[10]

Reduction of Endpoints in NIDDM With the Angiotensin II Antagonist Losartan (RENAAL) Study

The Reduction of End Points in Non-Insulin Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan (RENAAL) Study compared losartan with conventional antihypertensive therapy (without ACE inhibitors). This study found that losartan, when combined with conventional antihypertensive treatment, decreased the level of urinary protein excretion by 35% and reduced the risk of ESRD by 28%.[11]

In the RENAAL study, the primary composite end point of a doubling of the serum creatinine concentration, ESRD, or death was reached in 327 patients (43.5%) compared with 359 patients

enrolled in the placebo arm (47.1%). The investigators concluded that therapy with losartan produced a statistically significant 16% reduction in the risk of the primary composite end point (P = 0.02).[11] The risk of doubling the serum creatinine concentration was 25% lower in the losartan group than in the placebo arm of the trial (P = 0.006). The study found no significant difference in mortality between the 2 groups (P = 0.88), but the risk of the combined end point (i.e., ESRD or death) was 20% lower in the losartan group compared with patients who received placebo.[11] The investigators concluded that losartan, combined with conventional antihypertensive agents as required, provided strong renal protection and reduced BP in patients with type 2 DM and nephropathy.[11] The primary benefit attained from the administration of losartan was a significant improvement in renal outcomes in addition to the effects of its antihypertensive properties in patients with type 2 DM and nephropathy.[11] Table 1 summarizes and compares the results and end points of the IDNT and the RENAAL study.

TABLE 1 Comparison of Major End Points of RENAAL and IDNT Trials

Study End Points	RENAAL[11] Mean Follow-up: 3.4 years	IDNT[9] Mean Follow-up: 2.6 years		
	Losartan Versus Control	Irbesartan Versus Control	Irbesartan Versus Amlodipine	Amlodipine Versus Control
	% RRR	% RRR	% RRR	% RRR
Doubling of creatinine, ESRD*, or death	16 (P = 0.02)	20 (P = 0.02)	23 (P = 0.006)	-4 (P = 0.69)
Doubling of creatinine	25 (P = 0.006)	33 (P = 0.03)	37 (P<0.001)	6 (P = 0.60)
ESRD	28 (P = 0.002)	23 (P = 0.07)	23 (P = 0.07)	0 (P = 0.99)
Death	-2 (P = 0.88)	8 (P = 0.57)	-4 (P = 0.80)	12 (P = 0.40)
CV mortality and mortality	10 (P = 0.26)	9 (P = 0.40)	-3 (P = 0.79)	12 (P = 0.29)

** ESRD = end-stage renal disease. The RENAAL trial defined ESRD as the need for long-term dialysis or transplantation. The IDNT defined ESRD as being indicated by the initiation of dialysis, renal transplantation, or a serum creatinine concentration of at least 6.0 mg/dL.*

RRR = relative risk reduction; RENAAL = Reduction of Endpoints in NIDDM With the Angiotensin II Antagonist Losartan trial; IDNT = Irbesartan Diabetic Nephropathy Trial; CV = cardiovascular.

Lewis EJ et al. N Engl J Med. 2001:345:851-60.[9]

Brenner BM et al. N Engl J Med. 2001:345:861-69.[11]

Angiotensin-converting Enzyme Inhibitor Plus Angiotensin Receptor Blocker Therapy in Renal Disease

A double-blind, randomized clinical trial was conducted to assess the effectiveness and safety of combined therapy with ACE inhibitors plus ARBs compared with monotherapy with each agent at maximum dosage in patients with nondiabetic renal disease.[12]

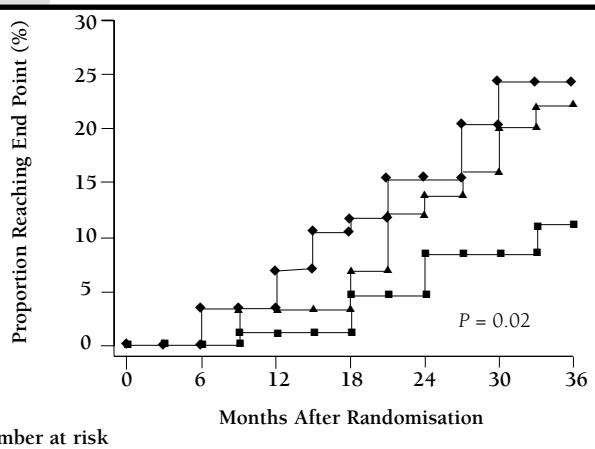
Study enrollment in the Combination Treatment of Angiotensin-II Receptor Blocker and Angiotensin-converting Enzyme Inhibitor in Non-diabetic Renal Disease (COOPERATE) trial consisted of 336 patients with nondiabetic renal disease (primarily IgA nephropathy). The patients were screened, and after an 18-week run-in period, 263 were randomly assigned to an ARB (losartan 100 mg daily), an ACE inhibitor (trandolapril 3 mg daily), or a combination of the drugs at equivalent doses. The 3 arms of the trial were compared using survival analysis on the combined end point of time to doubling of serum creatinine concentration or ESRD. Analysis was performed on an intention-to-treat basis.[12] Inclusion criteria for the study were: 18 to 70 years of age, chronic nephropathy with serum creatinine of 133 to 398 μmol/L, GFR of 20 to 70 mL/min per 1.73 m^2 (with variation of <30% in at least 3 consecutive measurements), diagnosed nondiabetic renal disease, and persistent proteinuria with urinary protein excretion >0.3 g/day (for at least 3 months with no evidence of overt heart failure or urinary tract infection).[12]

Achieved BPs in the 3 arms of the study were identical. Mean systolic and diastolic BP of all study subjects was reduced by antihypertensive agents to a mean of 128/80 mm Hg after randomization.[12] When compared with baseline values, the mean systolic BP fell by 5.2 mm Hg in the trandolapril group, 5.3 mm Hg in the combination therapy group, and 5.1 mm Hg in the losartan group. Mean diastolic BP was reduced by 2.9 mm Hg in the trandolapril arm, 3.0 mm Hg in the combination therapy arm, and 2.9 mm Hg in the losartan arm. There was no statistically significant difference in BP reduction among the 3 study groups (P = 0.109).[12]

Despite the similarity of achieved BPs, the investigators found that 11% (10 of 85) receiving combination therapy (losartan and trandolapril) reached the primary end point, compared with 23% (20 of 85) who received trandolapril monotherapy (P = 0.018). Twenty-three percent (20 of 86) of patients receiving losartan monotherapy reached the combined primary end point (P = 0.016).[12] Figure 2 shows the percentages of patients by treatment group who reached end point. A distinct benefit of combination therapy was observed in the retardation of progression of renal disease for patients with high rates of urinary protein excretion and for those with small amounts of proteinuria.[12]

The rate of urinary protein excretion was significantly reduced in all 3 treatment groups, and the reduction rate was greatest in the combination treatment group (P = 0.01). The greatest median change in daily urinary protein excretion was -42.1% in the losartan group, -44.3% in the trandolapril group, and -75.6% in the combination group. Patients with severe proteinuria (>3 g/day) in the combination group demonstrated a greater reduction after treatment than did patients with less severe proteinuria (<1 g/day). Comparison of the 3 treatment groups in terms of reducing

FIGURE 2 Combination Treatment of Angiotensin-II Receptor Blocker and Angiotensin-converting Enzyme Inhibitor in Non-diabetic Renal Disease (COOPERATE) Trial—Percentages of Patients Reaching End Point by Treatment Group



Number at risk							
Losartan	89	88	84	79	65	59	47
Trandolapril	86	85	83	75	72	63	58
Combination	88	87	86	83	76	73	67

Combination Losartan Trandolapril

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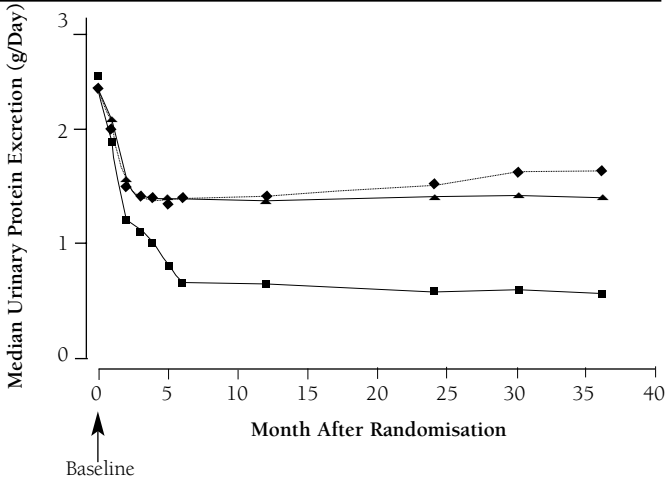
FIGURE 3 Combination Treatment of Angiotensin-II Receptor Blocker and Angiotensin-converting Enzyme Inhibitor in Non-diabetic Renal Disease (COOPERATE) Trial—Median Urinary Protein Excretion by Treatment Group



Combination Losartan Trandolapril

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urinary protein excretion showed that combination therapy was superior to either monotherapy at any range (including <1 g/day). Once maximum antiproteinuric effects had been achieved in the combination group and the losartan group, proteinuria remained constant for the duration of the trial period.[12] Figure 3 shows the median urinary protein excretion by treatment group.[12]

Combination therapy was shown to be significantly better than therapy with the individual agents in renal survival of nondiabetic patients who have moderately reduced renal function and moderate daily protein excretion.[12] The most important difference among the treatment groups appeared to be attributable to the significant antiproteinuric effect of combination therapy. The investigators found that the 3-year renal survival rate in the combination-therapy arm was mainly attributable to that result. The significant antiproteinuric effect (as shown in Figure 3) was demonstrated irrespective of baseline proteinuria and level of renal dysfunction. Moreover, the greater the baseline proteinuria, the more significant the reduction in urinary protein excretion. Reductions in urinary protein were noticed in the monotherapy groups, but combination treatment further reduced proteinuria over any range of the baseline proteinuria and renal dysfunction variables.[12] The study results indicated that combination therapy was well tolerated even in patients with advanced renal insufficiency. The data also support the theory that the RAAS plays a part in the progression of renal disease. Lastly, the trial results indicated that combination ARB/ACE inhibitor therapy may produce different efficacy in various subtypes of renal disease.[12]

Conclusion

The IDNT and RENAAL studies confirm the efficacy of ARBs in slowing the progression of established renal disease in patients with type 2 DM. These studies also provide an opportunity to estimate the optimal targets for BP control in these patients and to determine whether blockade of the RAAS is equally important at all achieved levels of BP control. In the IDNT, a direct correlation was shown between follow-up systolic BP and the risk of an adverse renal outcome (with no lower limit to this relationship). Once the impact of follow-up systolic BP is accounted for, diastolic BP and baseline systolic BP are unrelated to renal outcomes. It appears that the optimal systolic BP goal lies between 120 mm Hg and 130 mm Hg. Importantly, the IDNT analyses also show that RAAS blockade is equally important at all levels of achieved systolic BP, even at the lowest achieved levels. The effect of systolic BP control and RAAS blockade are independent and additive. Irbesartan-treated patients whose BP was reduced by 20 mm Hg (median achieved in the IDNT) from baseline to follow-up had a 63% reduction in risk of an adverse renal outcome. Finally, very recent data suggest that the combination of an ACE inhibitor plus an ARB offers greater protection against progression of kidney disease than either agent alone.

Other analyses of the IDNT and RENAAL study have shown that the strongest baseline predictor of a renal outcome is

proteinuria. Additionally, reduction of proteinuria, which is associated both with ARB therapy and with BP reduction, is strongly predictive of a good outcome. This suggests that the effectiveness of the treatment can be monitored by following the levels of proteinuria. That finding is particularly important in the clinician's approach to the earliest stages of diabetic kidney disease, in which microalbuminuria is the only characteristic and in which the protection of GFR cannot be easily demonstrated within the duration of a typical clinical trial. The combination of blockading the RAAS and aggressively reducing BP provides the means for decreasing the incidence of kidney disease due to DM—thereby saving lives and improving the quality of patients' lives.

DISCLOSURES

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