Angiotensin Receptor Blockers in Diabetic Nephropathy: Renal and Cardiovascular End Points

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The activity of the renin–angiotensin-aldosterone system (RAAS) is elevated both in the circulation and in the renal tissue of diabetic and nondiabetic nephropathies. The increased RAAS activity plays an important role in the hemodynamic and nonhemodynamic pathogenetic mechanisms involved in kidney disease. Previous studies have demonstrated that albuminuria is not only a marker of glomerular lesions, but also a progression promoter, and finally a powerful predictor of the long-term beneficial effect of blood pressure-lowering therapy. Randomized crossover and parallel blind studies in patients with diabetic nephropathy have demonstrated that angiotensin II receptor blockers (ARB) induce favorable changes in systemic blood pressure, renal hemodynamics, and proteinuria similar to those induced by angiotensin-converting enzyme (ACE) inhibition. Studies have revealed the optimal renoprotective dose for some ARBs; however, additional dose titration studies are urgently needed to obtain the maximum benefit of this valuable new class of compounds. The combination of ARB and ACE inhibition is well tolerated and even more effective than monotherapy in reducing systemic blood pressure and albuminuria in diabetic nephropathy. In addition, dual RAAS blockade is safe and well tolerated. Impaired autoregulation of glomerular filtration rate (GFR); demonstrated with some blood pressure-lowering agents implies disturbances in the downstream transmission of the systemic blood pressure into the glomerulus, leading to capillary hypertension or hypotension depending of the level of blood pressure. ARB does not interfere with GFR autoregulation in hypertensive diabetic patients. In contrast to previous observational studies with ACE inhibition, long-term treatment with ARB has similar beneficial renoprotective effect on progression of diabetic kidney disease in hypertensive diabetic patients with ACE II and DD genotypes. ARB can prevent/delay development of diabetic nephropathy independently of its beneficial blood pressure-lowering effect in patients with type 2 diabetes and microalbuminuria. Recently, two landmark studies led to the following conclusion: "Losartan and Irbesartan conferred significant renal benefit in patients with type 2 diabetes and nephropathy. This protection is independent of the reduction in blood pressure it causes. The ARB is generally safe and well tolerated." A recent metaanalysis indicates that ARBs reduce cardiovascular events mainly because of reduction in first hospitalization for congestive heart failure in hypertensive type 2 diabetic patients with albuminuria. The studies mentioned here suggest that ARB represents a beneficial treatment of hypertension and proteinuria in incipient and overt diabetic nephropathy.

THROUGH DECADES, diabetic nephropathy has been regarded as an irreversible and rapidly progressive disease with high morbidity and mortality.[1,2] The natural history of diabetic nephropathy, that is, without antihypertensive treatment, is characterized by arterial blood pressure elevation, increasing albuminuria, and a relentless decline in glomerular filtration rate (GFR) of, on average, 10 to 12 mL/min/year.[3,4] Diabetic nephropathy has become the leading cause (25-47%) of end-stage renal disease (ESRD) in Europe, the United States, and Japan. Unfortunately, the proportion of ESRD patients with diabetes is expected to increase considerably because the number of diabetic patients (mainly type 2) in the world is expected to double within the next 15 years, and because the individual diabetic patient lives longer and is therefore at greater risk of developing late complications, including diabetic nephropathy. An early onset of diabetes will furthermore add to the burden of diabetic nephropathy. The relative mortality from cardiovascular disease is nearly 40-fold increased in type 1 patients with proteinuria[5] and ninefold increased in type 2 patients with overt nephropathy[6] as compared with the background population. In addition to the high cardiovascular mortality, the incidence of nonfatal stroke, myocardial infarction, and peripheral vascular disease is also enhanced and the prognosis is much worse than in the nondiabetic population. The average survival time from onset of proteinuria was only 5 to 7 years before the introduction of antihypertensive treatment in these patients.[7] The prognosis has improved over the last decade mainly because of aggressive antihypertensive treatment.[7-10] During recent years, even further improvement in the prognosis and in the course of the disease and its

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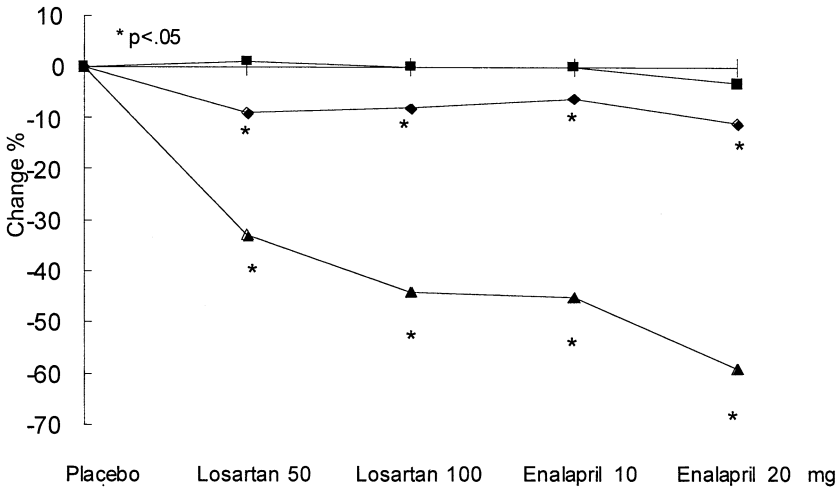

Fig 1. Relative changes in glomerular filtration rate (■), mean arterial blood pressure (◆), and albuminuria (●) compared with placebo in 16 type 1 diabetic patients with diabetic nephropathy. Reprinted from Kidney International with permission.[29] *P <0.05. Each treatment period lasted 2 months.

associated vascular complications have been observed by the use of drugs blocking the renin angiotensin aldosterone system (RAAS).[10-14]

The objective of this review is to analyze the short-term and long-term renoprotective effects of specific intervention in the renin–angiotensin system by angiotensin II subtype 1 receptor blockade (ARB) in diabetic patients with microalbuminuria and overt nephropathy. In addition, the impact of RAAS blockade using these new compounds on cardiovascular events in type 2 patients with incipient and overt nephropathy are analyzed.

SHORT-TERM RENOPROTECTION WITH ANGIOTENSIN RECEPTOR BLOCKADES

Originally, Remuzzi and Bertani[15] described that albuminuria is not only a marker of underlying glomerular damage, but also a risk factor/marker in relation to initiation and progression of diabetic and nondiabetic kidney disease. Their concept has been supported in several animal and human studies as recently reviewed by Rossing.[16] Furthermore, several studies in patients with and without diabetic kidney disease have demonstrated first that the severity of baseline proteinuria is an important predictor of the rate of loss of renal function.[17-20] Second, the reduction in proteinuria when patients with nephropathy are being treated with antihypertensive treatments predicts the efficacy of subsequent renoprotection—the greater the reduction, the better the efficacy.[20-24] Third, the residual proteinuria during treatment with antihypertensive drugs is proportional to the rate of loss in renal function in both diabetic and nondiabetic kidney disease.[25,26] Consequently, de Jong et al.[26] suggested that titration against albuminuria should be a major goal in renoprotective therapy. Most recent data from the Reduction of End points in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study has clearly demonstrated that the reduction of proteinuria over the entire study period accounts for approximately half of the treatment effect of losartan on the risk reduction for end-stage renal failure.[13] If the primary composite end point of RENAAL was taken into consideration (doubling of serum creatinine, development of ESRD, or death), proteinuria explained nearly 100% of the treatment effect of this ARB. On this background, it seems important to suggest that proteinuria must be regarded as a valid surrogate end point in renal trials.

Short-term double-blind, randomized parallel or crossover studies carried out in type 1 and type 2 diabetic patients with microalbuminuria or overt nephropathy have demonstrated that ARBs and angiotensin-converting enzyme (ACE) inhibition have similar beneficial effect on proteinuria, blood pressure, and renal hemodynamics (Fig 1).[27-29] These findings indicate that the reduction in albuminuria and blood pressure during ACE inhibition are primarily caused by interfering in the RAAS. Furthermore, the initial time course of the reduction in arterial blood pressure and albuminuria are concordant, which suggests that systemic and renal hemodynamic mechanisms are of primary importance in the reduction of albuminuria.[30,31] In addition, other studies have clearly documented that

part of the reduction in proteinuria during treatment with ARBs is independent of the beneficial blood pressure-lowering effect.[11] Interestingly, patients who respond favorably to one class of antiproteinuric drugs (eg, ARBs) also respond favorably to other classes of antiproteinuric drugs, supporting a main role for individual patients factors in responsiveness or resistance to antiproteinuric intervention.[32] Studies in animals and man have revealed that the following factors play a role in the transglomerular passage of proteins: glomerular capillary size and charge selectivity, the transglomerular hydraulic pressure, nephrin concentration in the filtration slit membrane, and podocyte number and function.[2] Studies in man have documented that ARB is capable of reducing the abnormal size selectivity in early diabetic kidney disease.[33] Furthermore, blockade of the RAAS system in man leads to a reduction in the estimated glomerular capillary pressure.[34] Animal and human biopsy studies have documented that ARBs can normalize the content of nephrin in the filtration slit membrane and finally that this compound is capable of reducing loss of podocytes.[35,36] In conclusion, ARBs reduce proteinuria by hemodynamic and nonhemodynamic mechanisms. Proteinuria reduction must be regarded as a surrogate end point for renoprotection.

OPTIMAL DOSE OF ANGIOTENSIN RECEPTOR BLOCKADES FOR RENOPROTECTION

Although drugs blocking the RAAS system have an important renoprotective effect, the optimal dosing for renoprotection for such compounds has not been evaluated in the past. Previously, investigators have chosen the dose of ACE inhibitor (ACEI) or ARB by measurement of maximal beneficial effect on blood pressure, usually in patients with essential hypertension. Animal studies have clearly documented a discrepancy between the hemodynamic effect of these compounds and the nonhemodynamic benefits on various growth factors and cytokines.[37] Furthermore, as already mentioned, ARB has a lot of beneficial effects that are independent of the systemic blood pressure effect. Consequently, studies of dose-related efficacy of ACEI or ARB with dose titration based on the maximal antiproteinuric effect for optimal renoprotection are needed. In the irbesartan in patients with type 2 diabetes and microalbuminuria (IRMA 2)[11] study, increasing doses of irbesartan were applied in 590 type 2 patients with microalbuminuria. Irbesartan at a dosage of 300 mg once daily was superior in lowering albuminuria as compared with 150 mg irbesartan daily. Blood pressure levels were identical in the two arms. Furthermore, both arms show a benefit compared with blood pressure lowering to a similar level using compounds that are not blocking the RAAS system. However, it should be stressed that the study did not reveal the optimal dosing of irbesartan (eg, 600/900 mg daily); such studies are ongoing.

In type 2 patients with overt nephropathy, a dose-escalation study has revealed that the optimal dose of another ARB, candesartan, is 16 mg daily for renoprotection as reflected by short-term reduction in albuminuria.[38] The highest dose used in that study was 32 mg candesartan daily. Finally, we investigated 50 consecutive hypertensive type 1 patients with diabetic nephropathy receiving increasing doses of 50, 100, and 150 mg losartan once daily in three periods, each lasting 2 months.[39] This study revealed that the optimal dose of losartan is 100 mg daily for renoprotection and blood pressure reduction in such patients. It should be stressed that this dose was actually the dose used in the RENAAL study.

In conclusion, renoprotective dose for ARBs is being evaluated; however, additional dose-titration studies are urgently needed to obtain the maximum benefit of this valuable new class of compounds.

RENOPROTECTION WITH DUAL RENIN–ANGIOTENSIN SYSTEM BLOCKADE

The rationale for a combination therapy with ARBs and ACEI is based on the assumption that nonclassic pathways of the RAAS produce a substantial amount of angiotensin II. The chymase conversion of angiotensin I to angiotensin II appears to be activated in disorders such as the failing heart and kidney.[40] Second, during long-term ACEI treatment, the phenomenon of "CE-escape" evolves, that is, plasma levels of angiotensin II and aldosterone returning to pretreatment levels.[40] Third, the beneficial effect of ARB can be reduced if stimulation of the AT_2 receptor contributes substantially as recently suggested in animal studies,[41] clearly documenting that specific blockade of the AT_2 receptor has a beneficial effect on kidney function and structure. Finally, combining both drug classes could simply provide a higher degree of blockade of the classic RAAS pathway, and

thereby the tissue activity of the system as demonstrated in animals studies.[42]

Originally, Mogensen and coworkers[43] described that 16 mg candesartan once daily is as effective as 20 mg lisinopril once daily in reducing blood pressure and microalbuminuria in hypertensive patients with type 2 diabetes. Combination treatment with both drugs in the same doses as mentioned here was well tolerated and more effective in reducing blood pressure and microalbuminuria. However, Agarwal[44] reported that combination therapy was not superior to ACE inhibition (40 mg lisinopril) alone in decreasing proteinuria in a small group of hypertensive proteinuric black patients with advanced renal failure of different origin. Surprisingly, the study showed a lowered plasma renin activity and enhanced GFR during treatment with 50 mg losartan daily on top of 40 mg lisinopril. Because many patients with diabetic nephropathy have levels of albuminuria >1 g/day and blood pressure $>135/85$ mm Hg, despite antihypertensive combination therapy, including the recommended dose of ACE inhibitors, eg, 20 mg lisinopril/enalapril daily, we evaluated the concept that such patients might benefit from dual blockade of the renin angiotensin system.[45,46] In type 2 diabetes, we performed a randomized, double-blind, crossover study of 2 months treatment with 8 mg candesartan cilexetil once daily or placebo on top of ACEI, diuretics, and in most cases a calcium channel blocker.[45] Our study revealed a 25% reduction in albuminuria and a 35% reduction in fractional clearance of albumin in addition to a significant reduction in systemic blood pressure. In a similar group of albuminuric type 1 diabetic patients[46] responding insufficiently to antihypertensive treatment with recommended doses of ACE inhibitors and diuretics, we tested the effect of dual RAAS blockade by performing a randomized, double-blind, crossover study with 2 months with 300 mg irbesartan once daily or placebo added on top of previous antihypertensive treatment (three drugs, including ACEI). Irbesartan treatment reduced albuminuria by 37% and caused a reduction in blood pressure of 8/5 mm Hg, whereas GFR remained unchanged. The study thus suggests that dual blockade of the RAAS could offer additional renal and cardiovascular protection in type 1 diabetic patients with diabetic nephropathy responding insufficiently to conventional antihypertensive therapy, including recommended dose of ACEI and diuretics. In another double-blind, randomized, crossover trial,[47] we evaluated 8 weeks treatment with placebo, 20 mg benazepril once daily, 80 mg valsartan once daily, and the combination of 20 mg benazepril and 80 mg valsartan daily. The study revealed that dual blockade induced an additional reduction in albuminuria of 43% compared with any type of monotherapy and a reduction in systemic 24-hour blood pressure of 7/7 mm Hg compared with both monotherapies. GFR was reversibly reduced on dual blockade compared with monotherapy and placebo. Treatments were safe and well tolerated. However, until now, all studies in diabetic nephropathy have compared dual blockade of the RAAS with submaximal doses of monotherapy and, as a consequence, beneficial effect could have been overestimated.[43,45-47] Therefore, we tested if the addition of the maximal recommended dose of ARB offers more complete blockade of the RAAS in type 1 diabetic patients with diabetic nephropathy receiving maximal recommended dose of ACE inhibitors (eg, 40 mg enalapril once daily).[48] We performed a crossover trial with 8 weeks treatment with placebo or 300 mg irbesartan daily added on top of a maximal enalapril dose (40 mg). Our study revealed that dual blockade of the RAAS induces a reduction in albuminuria of 25% and a significant reduction in 24-hour systolic and diastolic blood pressure of 8/4 mm Hg (Table 1). GFR and plasma potassium remained unchanged during both treatment regimes. Dual blockade was still safe and well tolerated. Finally, we evaluated the same concept in type 2 diabetic patients with hypertension and diabetic nephropathy treated with 40 mg lisinopril/enalapril.[49] During dual blockade of the RAAS by addition of 16 mg candesartan daily for 8 weeks, there was a mean reduction in albuminuria of 28% compared with ACEI alone. There was a modest reduction in 24-hour systolic/diastolic blood pressure of 3/2 mm Hg. No significant change in GFR occurred. Long-term studies evaluating doubling of serum creatinine/development of ESRD/death in patients with diabetic nephropathy are urgently needed. Data from nondiabetic kidney disease, as discussed elsewhere, has demonstrated that dual blockade induces an additional long-term renoprotective effect as compared with monotherapy.[50]

In conclusion, dual blockade of the RAAS is superior to the maximal recommended dose of ACE inhibitors with regard to lowering of protein-

Table 1. Dual Blockade of the Renin–Angiotensin System With 300 mg Irbesartan Once Daily in 24 Type 1 Patients With Diabetic Nephropathy Treated With 40 mg Enalapril Once Daily

	40 mg Enalapril + Placebo	40 mg Enalapril + 300 mg Irbesartan	Mean Difference (95% confidence interval)	*P*
Albuminuria (mg/24 hour)*	519 (342,789)	373 (224,622)	−25% (−34,−15)	<0.001
24-hour blood pressure (mm Hg)	131 (3)/74(1)	123 (3)/70(2)	−8 (−12,−4)/−4 (−7,−2)	0.002/0.003
GFR (mL/min/1.73 m^2)	65 (5)	63 (5)	−3 (−1,7)	0.222
Plasma renin concentration (mU/L)*	177 (86,364)	283 (133,602)	64% (8,150)	0.031

* Geometric mean (95% confidence interval)
Abbreviation: GFR, glomerular filtration rate.
NOTE. Values represented are mean (standard error of mean).

uria and blood pressure in diabetic patients with nephropathy. Long-term trials are needed to further establish the role of dual blockade of the RAAS system in renal and cardiovascular protection.

RENAL AUTOREGULATION AND ANGIOTENSIN RECEPTOR BLOCKADE

Normal renal autoregulation enables the kidney to maintain a fairly constant renal blood flow and GFR as the mean blood pressure varies between 80 and 160 mm Hg.[51] This process can be linked to mechanisms that are intrinsic to the kidney: a myogenic reflex in the afferent arteriole and tubuloglomerular feedback. We have previously demonstrated that autoregulation of GFR is impaired or abolished in type 1 and type 2 diabetic patients with diabetic nephropathy.[52,53] Impaired autoregulation of GFR implies disturbances in the downstream transmission of the systemic blood pressure into the glomerulus that lead to capillary hypertension or hypotension, depending on the level of systemic blood pressure. Treatment of hypertension in patients with normal renal function does not generally cause renal dysfunction; however, in patients with hypertension and nephropathy, it is not uncommon for serum creatinine concentration to rise as blood pressure is lowered. Many physicians decrease the dose of antihypertensive medication as a result of this initial response to blood pressure reduction. Unfortunately, such an approach is not optimal for long-term renoprotection and consequently should be discouraged. The initial decline in renal function during blood pressure lowering is hemodynamic in origin and not the result of structural damage to the kidney. On the contrary, the reduction should be viewed as an indication that the intraglomerular pressure has been successfully reduced.

The impact on renal autoregulation of different antihypertensive drugs in animals has been elucidated, whereas information in humans is scanty, as reviewed by Palmer.[51] Recently, we demonstrated that the ARB candesartan can reduce blood pressure without adversely altering the preserved ability to autoregulate GFR in hypertensive type 2 patients without nephropathy.[54] By contrast, in similar patients treated with the dihydropyridine calcium antagonist isradipine, GFR autoregulation is impaired in a sizable proportion of hypertensive type 2 diabetic patients.[55] In some patients, the impairment is so severe that a completely pressure–passive vasculature is present in which any change in the mean arterial blood pressure is matched by a proportional change in the GFR. Consequently, it is of major importance to keep the blood pressure well controlled within narrow limits when using a calcium antagonist alone.

In conclusion, ARB reduces blood pressure without adversely affecting the renal autoregulation of GFR.

RENOPROTECTIVE EFFECT OF RAAS BLOCKADE IN DIABETIC NEPHROPATHY: INTERACTION WITH ANGIOTENSIN-CONVERTING ENZYME INSERTION/DELETION GENOTYPE?

The beneficial short- and long-term renoprotective effect of ACE inhibition is reduced in albuminuric diabetic patients homozygous for the deletion allele compared with the insertion allele of the ACE/ID gene polymorphism.[56-59] In an attempt to overcome this harmful interaction, we evaluated the short-term renoprotective effect in diabetic nephropathy of the ARB losartan in patients homozygous for the insertion (II) or the deletion (Dd) allele.[60] After 4 weeks of

washout, patients received 50 mg losartan daily followed by 100 mg daily in two treatment periods, each lasting 2 months. Both doses of Losartan significantly lowered blood pressure, albuminuria, and GFR. Losartan at a dosage of 100 mg was more effective than 50 mg in reducing albuminuria, 51% versus 33%, respectively. No differences in the impact of losartan between the insertion and the deletion groups were observed. Consequently, the data suggest that losartan offers similar short-term renoprotective and blood pressure-lowering effects in albuminuric hypertensive type 1 patients with ACE II and DD genotypes. The study was continued for a mean follow-up period of 3 years[61] with GFR, albuminuria, and 24-hour blood pressure measurements carried out every 6 months (Fig 2). At baseline, the previously mentioned variables were similar in the two genotype groups, and during the study, the rate of GFR decline was 2.9 versus 3.4 mL/min/year in II versus DD, respectively nonsignificant by difference. Albuminuria and blood pressure were significantly reduced during the study with no differences noted between genotypes. During follow up, albuminuria was decreased by 75% in both genotype groups. In conclusion, in contrast to previous observational studies with ACE inhibitors, long-term treatment with ARB has similar beneficial renoprotective effect on progression of diabetic nephropathy in patients with ACE II and DD genotypes. From a renoprotective treatment point of view, this finding suggests equal benefit to all patients irrespective of the ACE/I/D genotype.

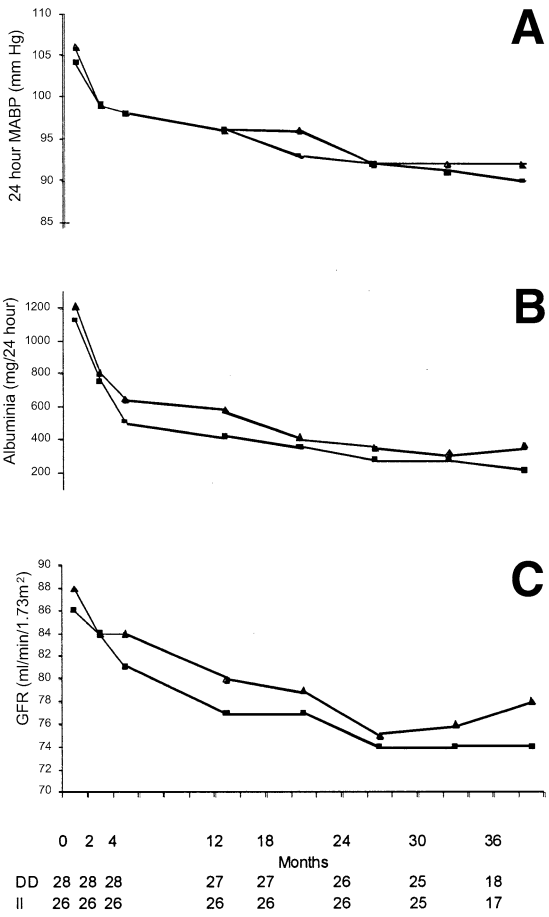

Fig 2. Impact of losartan (100 mg/day) on 24-hour mean arterial blood pressure (MABP; A), albuminuria (B), and glomerular filtration rate (GFR; C) in II (■) and DD (◆) type 1 diabetic patients with diabetic nephropathy. Copyright © 2002 American Diabetes Association. From Diabetes Care 26:1503, 2002. Reprinted with permission from The American Diabetes Association.[29]

PREVENTION OF DIABETIC NEPHROPATHY WITH ANGIOTENSIN RECEPTOR BLOCKADE

Antihypertensive treatment has a renoprotective effect in hypertensive patients with type 2 diabetes and microalbuminuria as reviewed by Parving.[62] However, there has been conflicting evidence regarding the existence of a specific renoprotective effect, that is, a beneficial effect on kidney function beyond the hypotensive effect, of agents such as ACE inhibitors in patients with type 2 diabetes and microalbuminuria.

Therefore, we evaluated the renoprotective effect of an ARB irbesartan in hypertensive patients with type 2 diabetes and microalbuminuria.[11] A total of 590 hypertensive patients with type 2 diabetes and microalbuminuria were enrolled in this multinational, randomized, double-blind, placebo-controlled study of irbesartan, at a dose of either 150 mg daily or 300 mg daily and followed for 2 years.

The primary outcome was time to onset of diabetic nephropathy, defined by persistent albuminuria in overnight specimens, with a urinary albumin excretion rate greater than 200 μg/min and at least 30% higher than the baseline level. The baseline characteristics in the three groups were similar. Ten patients in the 300-mg group (5.2%) and 19 patients in the 150-mg group (9.7%) reached the primary end point, as compared with 30 patients in the placebo group (14.9%) (hazard ratios, 0.30 (95% confidence interval [CI], 0.14-0.61; $P < 0.001$) and 0.61 (95% CI, 0.34-1.08; $P = 0.08$)

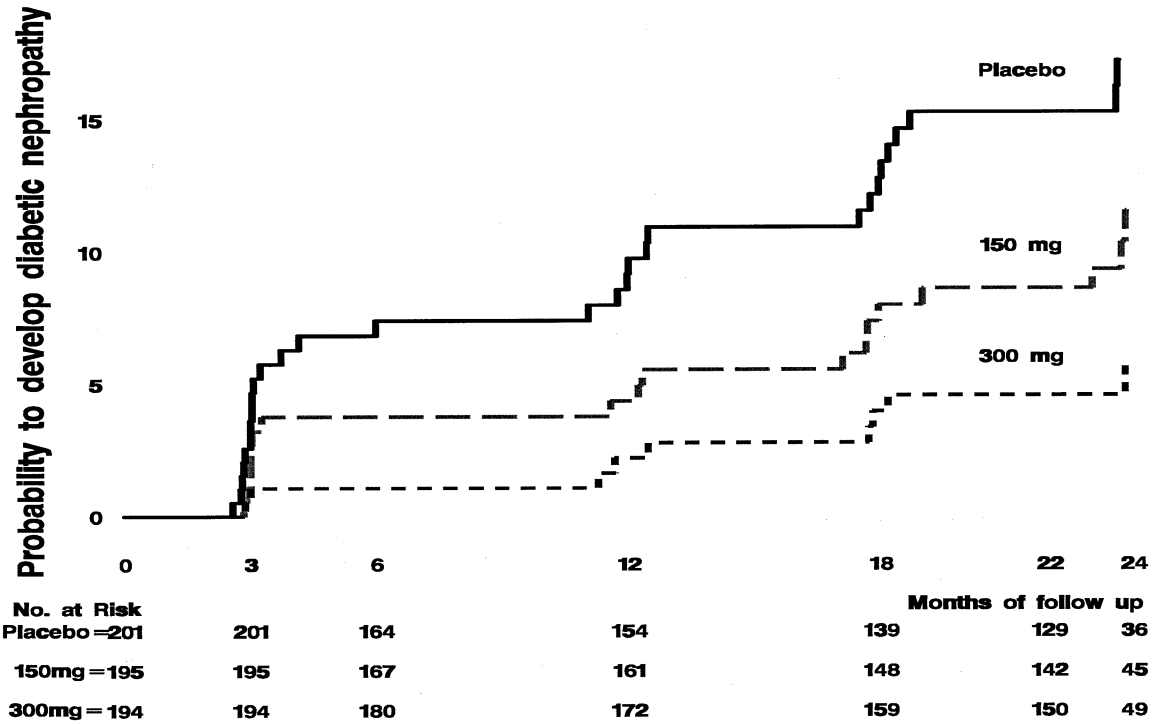

Fig 3. Incidence of progression to diabetic nephropathy during treatment with 150 mg irbesartan daily, 300 mg irbesartan daily, or placebo in hypertensive patients with type 2 diabetes and persistent microalbuminuria. The difference between the placebo group and the 150-mg group was not significant ($P = 0.08$ by the log-rank test), but the difference between the placebo group and the 300-mg group was significant ($P < 0.001$ by the log-rank test). Reprinted from the New England Journal of Medicine with permisssion.[11] © 2001 Massachusetts Medical Society.

for the two Irbesartan groups, respectively (Fig 3). Mean blood pressure was lowered to 103 mm Hg in the placebo and in the 150 mg irbesartan group, whereas mean blood pressure was 102 mm Hg in the 300 mg irbesartan group ($P = 0.004$). Importantly, a substudy of 24-hour blood pressure levels revealed no differences between the three arms.[63] In the placebo group, there was a 2% reduction, 150 mg irbesartan had a 24% reduction, and the 300 mg irbesartan group had a 38% reduction in urinary albumin excretion during the whole study period. The rapid and sustained response to irbesartan and the continuing divergence in renal outcomes between the 300-mg group and the placebo group in our study suggest that longer-term therapy could result in an even better prognosis. The rate of progression to diabetic nephropathy in the placebo group in our study corresponds with other studies conducted in similar populations. Nonfatal cardiovascular events were slightly more frequent in the placebo group (8.7% vs. 4.5% in the 300-mg group; $P = 0.11$). Recently, we evaluated whether the reduction in microalbuminuria is reversible (hemodynamic) or persistent (structural/biochemical normalization) after prolonged antihypertensive treatment. After 2 years, all antihypertensive treatment was stopped for a month in the three arms of IRMA 2.[64] Compared with baseline, the urinary albumin excretion rate was increased in the placebo group and the 150 mg irbesartan daily group, but persistently reduced by 47% (24-73%) in the 300 mg irbesartan daily group. This could suggest that high-dose irbesartan treatment confers long-term renoprotective effects.

In conclusion, ARB can prevent/delay development of diabetic nephropathy independent of its beneficial blood pressure-lowering effect in patients with type 2 diabetes and microalbuminuria.

PROTECTION AGAINST END-STAGE RENAL DISEASE WITH ANGIOTENSIN RECEPTOR BLOCKADE

Interruption of the RAAS slows the progression of renal disease in patients with type 1 diabetes, but

Table 2. RENAAL and IDNT Results: Comparison of Primary Composite End Point and Components

	Risk Reduction (% [95% CI])			
Composite End Point	Losartan vs. Placebo (80)	Irbesartan vs. Placebo (81)	Irbesartan vs. Amlodipine (81)	Amlodipine vs. Placebo (81)
DsCr, ESRD, death	16 (2, 28)	20 (3, 34)	23 (7, 37)	−4 (14, −25)
Doubling of s-Cr	25 (8, 39)	33 (13, 48)	37 (19, 52)	−6 (16, −35)
ESRD	28 (11, 42)	23 (−3, 43)	23 (−3, 43)	0 (−32, 24)
Death	−2 (−27, 19)	8 (−31, 23)	−4 (23, 40)	12 (−19, 34)
ESRD or death	20 (5, 32)	—	—	—

Abbreviations: RENAAL, Reduction of End points in NIDDM with the Angiotensin II Antagonist Losartan study; IDNT, Irbesartan Diabetic Nephropathy Trial; CI, confidence interval; DsCr, doubling of serum creatinine; ESRD, end-stage renal disease.

until recently, similar data is not available for patients with type 2 diabetes as reviewed by Parving.[62] Against this background, two large multinational, double-blind, randomized, placebo-controlled trials with ARBs were carried out in comparable populations of hypertensive patients with type 2 diabetes, proteinuria, and elevated serum creatinine levels.[12,13] In both trials, the primary outcome was the composite of a doubling of baseline serum creatinine concentration, ESRD, or death. A comparison of the benefits obtained in the RENAAL (Reduction of end points in NIDDM with the Angiotensin II Antagonist Losartan) study versus the IDNT (Irbesartan Diabetic Nephropathy Trial) is shown in Table 2. Side effects were low, and less than 2% of the patients had to stop ARB because of severe hyperkalemia. The number of sudden deaths in the different groups was alike. The two landmark studies led to the following conclusion: "Losartan and Irbesartan conferred significant renal benefits in patients with type 2 diabetes and nephropathy. This protection is independent of the reduction in blood pressure it causes. The ARB's are generally safe and well tolerated."

Finally, treatment with ARBs in patients with type 2 diabetes and nephropathy not only reduces incidence of ESRD, but also results in substantial cost savings.[65]

IMPACT OF ANGIOTENSIN RECEPTOR BLOCKADES ON CARDIOVASCULAR EVENTS

Proteinuria is an established risk marker for cardiovascular morbidity and mortality.[2,62] The relative cardiovascular mortality in young type 1 diabetic patients with proteinuria is nearly 40-fold increased as compared with the background population.[5] In proteinuric type 2 patients, the yearly rate of cardiovascular death or major cardiovascular events such as stroke, myocardial infarction, heart failure, and reduced peripheral perfusion leading to foot ulcers and amputations are approximately 7% to 12% yearly.[6] The relative mortality compared with the background population is six- to ninefold increased in type 2 patients with overt nephropathy.[6] Recently, we evaluated if proteinuria not only is a marker of cardiovascular disease in type 2 diabetic patients, but also a target to monitor the therapeutic cardioprotective efficacy of renin–angiotensin system intervention. We analyzed data from the RENAAL study, a double-blind, randomized trial to examine the effect of Losartan on the composite end point of doubling of serum creatinine, ESRD, or death and cardiovascular morbidity and mortality in 1513 type 2 diabetic patients with nephropathy.[13] Losartan reduced albuminuria by 28%, whereas in the placebo group, proteinuria increased by 4% during the first 6 months of therapy. Modeling of the initial 6 months change in different risk parameters for predicting the long-term cardiac risk showed that the initial albuminuria reduction is the strongest independent predictor of cardiovascular outcome: hazard ratio for a cardiovascular end point of 1.13 (95% CI, 1.04-1.23) and for heart failure 1.21 (95% CI, 1.8-1.36).[66] Every 50% reduction in albuminuria during the first 6 months halved the risk for cardiovascular end points and heart failure during the 3-year follow-up period. The study thus indicates that reduction in proteinuria affords cardiovascular protection: the more reduction, the

Table 3. Losartan and Cardiovascular Events in Type 2 Diabetes

	Relative Risk Reduction (%)	
	RENAAL (N = 1513)	LIFE (N = 1195)
Cardiovascular morbidity/mortality	10 (−8,24)	24 (2,24)
Myocardial infarction	28 (−4,50)	17 (−25,45)
Stroke	5 (−41,36)	21 (−14,45)
Heart failure	32 (11,38)	41 (8,42)
Total mortality*	20 (5,32)	39 (16,55)

* Kidney death and all-cause mortality.

Abbreviations: RENAAL, Reduction of End points in NIDDM with the Angiotensin II Antagonist Losartan Study, LIFE, Losartan Intervention For Endpoint reduction in hypertension study.

NOTE. (95% confidence interval).

more protection. This specific cardiovascular protective effect of therapy in that study overlaps the renoprotective effect and appears to be marked link to its antiproteinuric potential. Consequently, proteinuria should not only be considered a risk marker for cardiovascular morbidity, but also a target for therapy in type 2 patients with nephropathy.

The RENAAL study showed an insignificant reduction in myocardial infarction (28%) but a significant reduction in first hospitalization for heart failure with 32% ($P = 0.0005$). Similar data has been presented in the other major landmark study dealing with kidney protection applying the ARB, Irbesartan (Irbesartan Diabetic Nephropathy Trial [IDNT]).[12,67] Furthermore, a metaanalysis based on these two studies and the previously mentioned IRMA 2 revealed a relative risk reduction of 15% for cardiovascular events comparing receptor blockade with conventional blood pressure-lowering therapy.[68] There was a similar trend for death with a risk reduction of 11% but this was not statistically significant. The impact of treatment with ARB on cardiovascular events in hypertensive type 2 diabetic patients with[13] and without diabetic nephropathy[69] is presented in Table 3.

Recently, we have demonstrated that long-term, intensified intervention aimed at multiple risk factors in patients with type 2 diabetes and microalbuminuria reduces the risk of cardiovascular and microvascular events by approximately 50%.[70] The intensively treated patients all received ACEI or ARBs and in 30% of the patients dual RAAS blockade.

In conclusion, ARBs reduce cardiovascular events mainly because of a reduction in first hospitalization for congestive heart failure in hypertensive type 2 diabetic patients with albuminuria.

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