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REVIEW ARTICLE

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Treatment of diabetic nephropathy with angiotensin II receptor antagonist

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Abstract
Type 2 diabetes is an ever-growing problem worldwide. Approximately 40% of the patients with type 2 diabetes will develop diabetic kidney disease. In the United States, diabetes has become the most common single cause of endstage renal disease defined by the need for dialysis or transplantation. Patients with type 2 diabetes and diabetic nephropathy have a dramatically increased cardiovascular risk. The Irbesartan Diabetic Nephropathy Trial was designed to determine whether the use of irbesartan or a calcium channel blocker would provide protection against the progression of nephropathy due to type 2 diabetes beyond that attributable to the lowering of blood pressure. In that study, 1715 hypertensive patients with nephropathy due to type 2 diabetes were randomly assigned to irbesartan 300 mg/day or amlodipine 10 mg/day, or placebo. All patients randomized in this trial had more than 900 mg of protein in their urine and serum creatinines between 1.0 mg/dl and 3.0 mg/dl. The target blood pressure was 135/85 mmHg or less in all groups. The primary outcome was time to a combined endpoint of doubling of their baseline serum creatinine concentration, the development of endstage renal disease, or death from any cause. The mean duration of follow-up was 2.6 years. Treatment with irbesartan was associated with a risk of the primary composite endpoint that was 20% lower than that in the placebo group ($P = 0.02$) and 23% lower than that in the amlodipine group ($P = 0.006$). The risk of doubling of the serum creatinine concentration was 33% lower in the irbesartan group than in the placebo group ($P = 0.003$) and 37% lower in the irbesartan group than in the amlodipine group ($P < 0.001$). Treatment with irbesartan was associated with a relative risk of endstage renal disease that was 23% lower than that in both other groups. These differences were not accounted for by differences in the blood pressures that were achieved. Proteinuria was reduced on average by 33% in the irbesartan group as compared with 6% in the amlodipine group and 10% in the placebo group. The angiotensin II receptor blocker irbesartan was shown to be effective in protecting against the progression of nephropathy due to type 2 diabetes. In a study done in patients with type 2 diabetes and early nephropathy as manifested by microalbuminuria, 590 hypertensive patients with type 2 diabetes and microalbuminuria were randomized to receive either irbesartan 150 mg/day or irbesartan 300 mg/day and followed for 2 years. The primary outcome in that trial was the time to the onset of diabetic nephropathy, defined by persistent albuminuria in overnight specimens, with a urinary albumin excretion rate that was more than 200 mg/min or at least 30% higher than the baseline level. The irbesartan 150 mg/day group demonstrated a 39% relative risk reduction versus the control group in the development of overt proteinuria. The irbesartan 300 mg/day group demonstrated a highly significant 70% risk reduction versus the control group ($P < 0.001$). The albumin excretion rate was reduced in the two irbesartan groups throughout the study (−11% and −38% at 24 months compared with baseline in the irbesartan 150-mg and 300-mg groups, respectively). The albumin excretion rate remained unchanged in the control group. Irbesartan was demonstrated in the above study to be renoprotective, independent of its blood pressure-lowering effect, in patients with type 2 diabetes and microalbuminuria. Thus, irbesartan, an angiotensin receptor blocker, was demonstrated to be significantly renoprotective in patients with type 2 diabetes with either early nephropathy (microalbuminuria) or late nephropathy (proteinuria). The renoprotective effects of irbesartan were above and beyond the effects irbesartan had on systemic blood pressure. Patients with type 2 diabetes and either early or late diabetic nephropathy should be treated with the angiotensin II receptor blocker irbesartan.

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Introduction

Type 2 diabetes mellitus has become epidemic worldwide. By the year 2025 it is projected that there will be 300 million patients worldwide with type 2 diabetes.[1] Without effective intervention, approximately 40% of these patients will develop renal disease. Currently, there are few therapeutic interventions of demonstrated benefit in altering the inexorable progression of type 2 diabetic nephropathy. These include glycemic control, control of hypertension, and the use of angiotensin II receptor blockers. This review will specifically focus on the recent studies which support the use of angiotensin II receptor blocking agents for renoprotection in early and in overt nephropathy.

Many studies in patients with type 1 diabetes have demonstrated the clear benefit of blood pressure control on the rate of progression of renal disease.[2–4] Early studies examining the rate of decline in renal function before and after blood pressure control showed a marked decrease in the rate of decline in renal function in individual patients. In a more recent study of 129 patients with type 1 diabetic nephropathy, patients were randomly assigned to a mean arterial blood pressure goal of less than 92 mmHg or to a mean arterial blood pressure goal of 100–107 mmHg.[5] All patients received varying doses of ramipril as the primary therapeutic antihypertensive agent and patients were followed for a minimum of 2 years. The patients randomized to the less than 92 mmHg mean arterial blood pressure goal had a significant decrease in their urinary total protein excretion compared with the 100- to 107-mmHg group ($P = 0.02$). Over 25% of the patients randomized to the intensive blood pressure control group, and receiving higher doses of angiotensin-converting enzyme (ACE) inhibitor, completed the 2-year study with less than 500 mg of proteinuria. That is, they no longer had clinical evidence of overt nephropathy. This study indicates that in patients with type 1 diabetic nephropathy, the mean arterial blood pressure goal should be 92 mmHg or less for optimal renoprotection if the definition of renoprotection is to include decreased proteinuria. The regression of proteinuria to levels no longer measurably positive by the clinical dipstick method and the stabilization of loss of renal function which accompanied this change in proteinuria strongly support the argument that specific renoprotection was achieved in these patients, to the point of clinical remission of renal disease.

Multiple epidemiologic and cross-sectional studies have demonstrated that small sustained increases in blood pressure increased the risk of kidney failure.[6,7] Patients with hypertension have 22 times the risk of endstage renal disease (ESRD) when compared with patients with normal blood pressure.[6,7] In an analysis of multiple longterm (>3 years) follow-up studies in patients with type 2 diabetes and diabetic nephropathy, it was reported that patients who achieved lower blood pressures had a slower rate of decline in renal function.[8] The patients in these studies were not randomized to different blood pressure goals and these analyses were based on achieved blood pressures. The rate of decline in renal function appeared to be a continuous function of these achieved arterial blood pressure levels.

In the ABCD study, there were 480 normotensive patients with type 2 diabetes who were randomized to moderate (diastolic 80–90 mmHg) versus intensive (diastolic decrease of 10 mmHg) blood pressure control.[9,10] The patients in the moderate group received placebo, whereas the patients in the intensive group were randomized to receive either nisoldipine or enalapril in a blinded manner. Mean blood pressure in the intensive group was 128/75 mmHg, vs 137/81 mmHg in the moderate group ($P = 0.0001$). Over a 5-year follow-up period, intensive blood pressure control slowed the progression to incipient and overt diabetic nephropathy. The progression from normal albumin excretion to microalbuminuria was decreased ($P = 0.012$), as well as the progression from microalbuminuria to overt albuminuria ($P = 0.028$). There was however, no statistically significant difference in alteration in renal function as measured by creatinine clearance between the groups. In this population of type 2 diabetic patients there was no difference in outcome between patients receiving the ACE inhibitor enalapril versus nisoldipine.

The recent UK Prospective Diabetes Study Group (UKPDS) had, embedded within it, a study designed to determine whether tight blood pressure control reduced morbidity and mortality in hypertensive patients with type 2 diabetes.[11] Seven hundred and fifty-eight patients were allocated to tight blood pressure control with the goal of less than 150/85 mmHg, and 390 patients were allocated to less tight control of blood pressure, aiming initially for a target of less than 200/105 mmHg, which was, in the course of the study, modified to a target of less than 180/105 mmHg. During the course of the study, the mean difference in systolic blood pressure was 10 mmHg, and for diastolic blood pressures it was 5 mmHg between the two groups. Reductions in risk in the group assigned to tighter control of blood pressure compared with that assigned to less tight control included a 24% decrease in diabetes-related endpoints, a 32% decrease in deaths related to diabetes, a 44% decrease in strokes, and a 37% decrease in microvascular endpoints (primarily a decreased risk of retinal vasculopathy). Approximately 17% of patients at baseline had microalbuminuria (urinary albumin concentrations >50 mg/l) and only 3.5% had overt clinical proteinuria (urinary albumin concentrations >300 mg/l). By 6 years of follow-up, there was a significant reduction in microalbuminuria in the lower blood pressure group compared with the conventional treatment group (20.3% vs 28.5%; $P < 0.009$). However, in the 9-year follow-up, this beneficial effect was no longer apparent, with the reduction in urinary albumin concentrations being 28.8% and 33.1%, respectively ($P = 0.33$). This discrepancy may be due to the smaller sample size in the 9-year follow-up group. There was no significant difference in plasma creatinine concentration or in the proportion of patients who had a twofold increase in creatinine concentration between the two groups. A subanalysis carried out

during this study revealed that patients receiving ACE inhibitors did not appear to have a more benign course than those who primarily received beta-blockers. Once again ACE inhibitors appeared to be disappointing in this population. However, the small sample size and variable blood pressure goals make this observation insubstantial.[16]

Overall, the evidence supports blood pressure control as an important intervention in slowing the progression of diabetic nephropathy in patients with type 2 diabetes. The precise level of blood pressure control which would provide maximum benefit for the patient with type 2 diabetic nephropathy has not been determined by clinical studies. Systolic hypertension can be extremely difficult to treat in this older population of patients who tend to have advanced vascular disease. Currently, there have been no reports of a "J-curve" phenomenon, indicating increased mortality and morbidity associated with more intense efforts at blood pressure lowering. However, orthostatic hypertension is a practical concern in this population that tends to have peripheral autonomic neuropathy. In light of current information, one can, in general, support the recommended goals of 135 mmHg systolic and 85 mmHg diastolic blood pressures. However, these recommendations must be individualized according to the medical condition of any given patient. These very stringent goals are extremely difficult to meet, particularly in the older population, and specifically with respect to systolic pressure. It is important to avoid setting the goal to an unattainable level which could discourage the patient and the medical staff from complying with the blood pressure regimen altogether.

As discussed, in stark contrast to the strong evidence supporting the use of ACE inhibitors to slow the progression of type 1 diabetic nephropathy, there is a meager amount of data addressing the effect of these agents in type 2 diabetes. However, three recent large clinical trials have concluded that angiotensin II receptor blockers prevent the progression of early (microalbuminuria) and late (proteinuria) diabetic nephropathy in patients with type 2 diabetes. In the Irbesartan and Diabetic Nephropathy Trial (IDNT), 1715 hypertensive patients with type 2 diabetes and 900 mg or more of urinary protein excretion were enrolled.[12] The baseline serum creatinine concentration was required to be between 1.0 and 3.0 mg/dl in women and between 1.2 and 3.0 mg/dl in men. The patients were randomized to receive either irbesartan (300 mg/daily), amlodipine (10 mg/daily), or placebo. The target blood pressure was 135/85 mmHg or less in all groups. Other antihypertensives, excluding calcium channel blockers, ACE inhibitors, or angiotensin II receptor blockers, were used to achieve these blood pressure goals in all three groups. Patients entered into this study would receive on average at least three medications for their blood pressure control. The primary outcome was time to a composite endpoint of doubling of the baseline serum creatinine concentration, the development of endstage renal disease, or death from any cause (Fig. 1). The mean duration of follow-up was 2.6 years. The blood pressure control achieved during the study was comparable in the three groups. In fact, the irbesartan group and the amlodipine group both achieved identical mean blood pressures, of 140 mmHg systolic and 77 mmHg diastolic. Blood

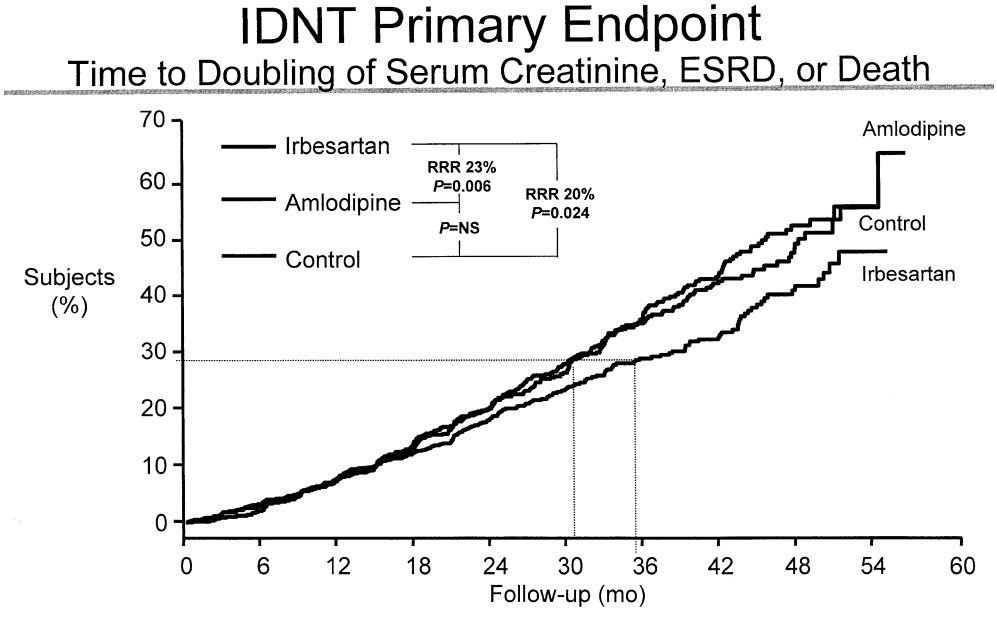

Fig. 1. The primary endpoint for the Irbesartan Diabetic Nephropathy Trial (*IDNT*) was a combination of the time to the events of either: (1) doubling of serum creatinine, (2) endstage renal disease (*ESRD*; defined as serum creatinine >6 mg/dl, dialysis or transplantation), or (3) death. The risk of developing one of these three events is noted in the Fig., with a relative risk reduction (*RRR*) of 23% for irbesartan versus amlodipine and 20% for irbesartan versus control. It is noteworthy that the mortality rate was equivalent in all three groups. Hence, the renal events in this study revealed a more dramatic renoprotective effect than did the triple composite endpoint. *The dotted line* reveals that the patients, time to reaching the composite endpoint was delayed by approximately 6 months if they were in the irbesartan group. *NS*, not significant; *mo*, months. From reference 12, with permission

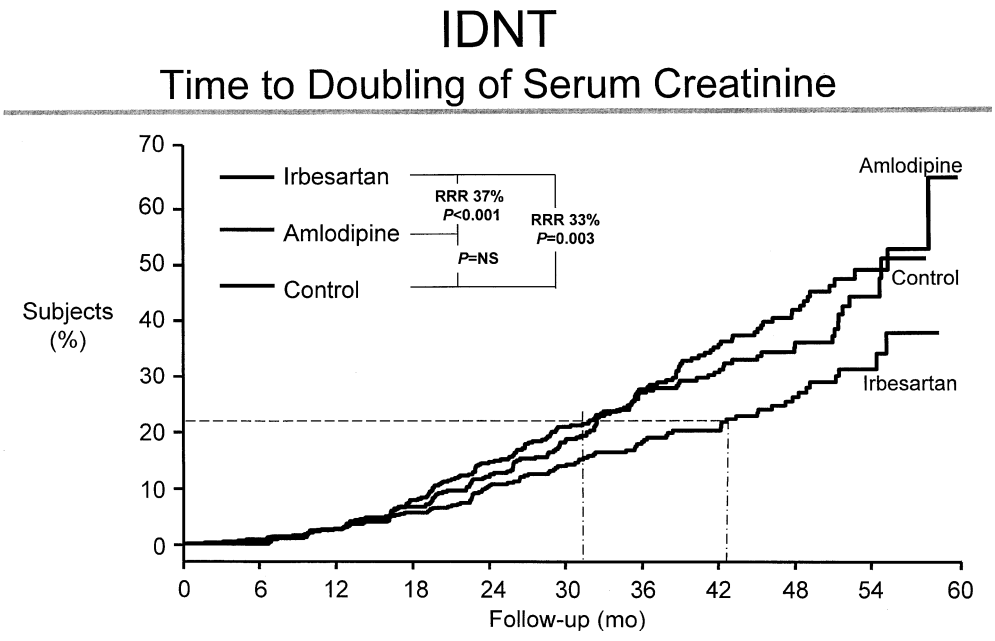

Fig. 2. Time to the doubling of serum creatinine in the Irbesartan Diabetic Nephropathy Trial (*IDNT*) was the most robust of the endpoints. The likelihood of a patient doubling the serum creatinine; hence, halving the glomerular filtration rate, during the course of follow-up was diminished by 37% in the irbesartan-versus-amlodipine comparison and by 33% in the irbesartan-versus-control comparison. *The dotted line* reveals that, among those patients who did reach this endpoint, the likelihood of halving their glomerular filtration rate was delayed by a little over 1 year. From reference 12, with permission

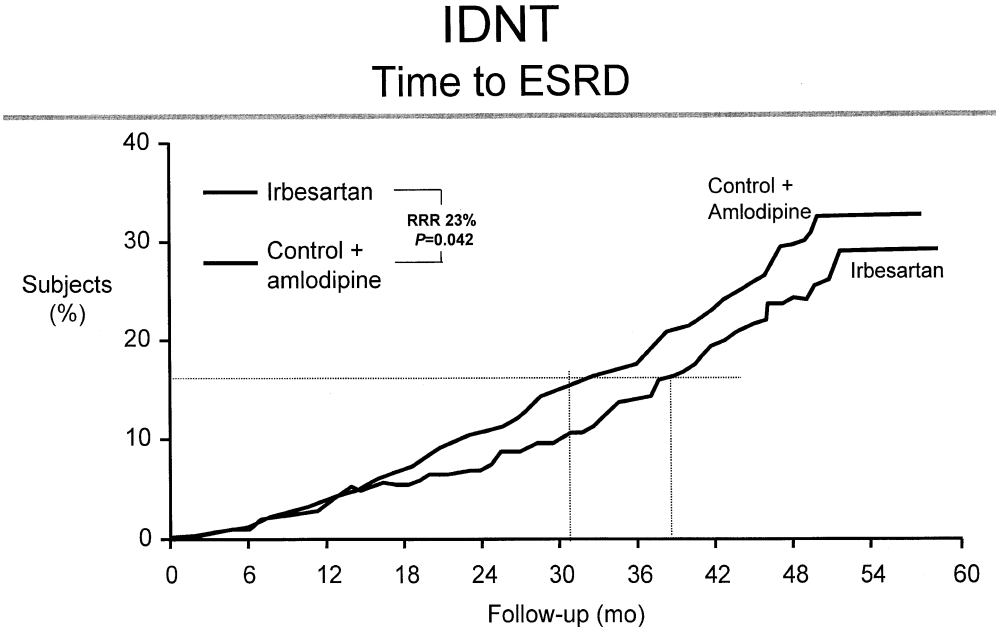

Fig. 3. Time to endstage renal disease (*ESRD*) in the Irbesartan Diabetic Nephropathy Trial (*IDNT*) was delayed when irbesartan was compared with both the control and the amlodipine groups. In fact, the control and amlodipine groups performed identically, as noted in the text. The fact that patients reaching a doubling of the serum creatinine endpoint were removed from the coded study medication and could be placed on angiotensin receptor blockade therapy probably decreased the likelihood of a robust result with respect to endstage renal failure during the limited period of follow-up of patients in the study. Again, it is noteworthy that the time to this event, among those patients who reached endstage renal failure, was delayed by approximately 8 months. From reference 12, with permission

pressure control in the placebo group was slightly higher, at 144/80 mmHg. It is noteworthy that the initial baseline blood pressures were 160/87 mmHg, not unusual in this difficult-to-manage population of patients. Treatment with irbesartan was associated with a risk of the primary composite endpoint that was 20% lower than that in the placebo group ($P = 0.02$) and 23% lower than that in the amlodipine group ($P = 0.006$) (Fig. 1). The doubling of the serum creatinine endpoint is assumed to approximate halving of the glomerular filtration rate during the course of the study. The risk of a doubling of the serum creatinine concentration was 33% lower in the irbesartan group than in the placebo group ($P = 0.003$) and 37% lower in the irbesartan group than in the amlodipine group ($P < 0.001$; Fig. 2). Doubling of the serum creatinine level is an important milestone in the course of the patient with diabetic nephropathy. The time from doubling of the serum creatinine to death or endstage renal failure was less than 1 year in this study. On average, patients who had a doubling of the serum creatinine event took over 1 year longer to reach this point in their course. The angiotensin receptor blocker effectively slowed the loss of renal function, even in those whose renal disease was progressing. Treatment with irbesartan was also associated with a relative risk of ESRD that was 23% lower than that in both other groups ($P = 0.07$ for both comparisons) (Fig. 3). However, it must be noted that the coded medications were stopped when the serum creatinine doubled. Hence, it is likely that some ESRD was prevented because angiotensin

II receptor blockers could be started after the doubling of the serum creatinine event. There was no difference among the three groups in the rate of death from all causes. Proteinuria was reduced on average by 33% in the irbesartan group as compared with 6% in the amlodipine group and 10% in the placebo group. Thus, the angiotensin II receptor blocker irbesartan was demonstrated to be renoprotective; that is, it was effective in protecting against the progression of nephropathy due to type 2 diabetes, and this protection was independent of reduction of the systemic blood pressure.

In the IDNT, one-third of the patients were randomized to receive the calcium channel blocker amlodipine. There was no demonstrated beneficial effect of amlodipine on renal outcomes. The patients randomized to amlodipine had renal outcomes similar to those in patients randomized to placebo (Figs. 2, 3). The overall cardiovascular outcome was not worse in the amlodipine group. All the patients in the trial were receiving additional antihypertensive agents (on average approximately three other antihypertensives or diuretics) in addition to the study drug. Hence, amlodipine was observed to be an effective antihypertensive agent in this patient population. Despite earlier studies in small numbers of patients, which demonstrated that dihydropyridine calcium antagonists, such as amlodipine, caused increased urinary protein excretion, implying a potential danger to longterm renal outcomes, urinary protein excretion, on average, decreased in the IDNT patients randomized to amlodipine. This result could be due to improved overall blood pressure control in the IDNT. Thus, despite previous reports, this agent appears to be a safe antihypertensive agent in the type 2 diabetic nephropathy population, although it is not, in itself, renoprotective.

In another similar study (RENAAL), 1513 patients with type 2 diabetes and 500 mg or more of urinary protein excretion were randomized to receive either losartan (50–100 mg once daily) or placebo.[13] The patient population was similar in demographics and baseline entry blood pressure and renal function. The results of this study were close to identical to the those of the IDNT (Table 1). Treatment with losartan was associated with the risk of the primary endpoint (which was virtually identical to the primary composite endpoint in the irbesartan trial) of 16% lower than that in the placebo group ($P = 0.02$). The risk of doubling of the serum creatinine concentration was 25% lower in the losartan group than in the placebo group ($P = 0.006$), and there was a risk reduction for ESRD of 28% ($P = 0.002$; Table 1). There was no effect on the rate of death from all causes. The level of proteinuria declined by 35% with losartan compared with placebo ($P < 0.001$).

Table 1. Angiotensin II receptor blockers in type 2 diabetic nephropathy

Data	Irbesartan Study	Losartan Study
Sample size	1715	1513
Baseline age (years)	59	60
Baseline median albuminuria	1.9 g/day	1.25 g/g Cr
Baseline serum creatinine	1.7 mg/dl	1.9 mg/dl
Risk reduction: composite outcome	20%	16%
Risk reduction: doubling of serum creatinine	26%	21%
Risk reduction: endstage renal disease	23%	28%

The Irbesartan Study (IDNT) and the Losartan Study (RENAAL) were similar in their patient inclusion criteria and experimental design. The primary outcome in both studies was the time to the first event of either doubling of serum creatinine, endstage renal disease, or death. The results of the two studies were comparable, emphasizing the value of angiotensin receptor blockade in this patient population

In summary, these two studies in essentially identical patient populations, and with similar clinical protocols, both clearly demonstrate a beneficial effect of inhibition of the renal angiotensin system with angiotensin II receptor blockers on slowing the progression of renal disease in patients with type 2 diabetes, proteinuria, and declining renal function (Table 1). In both studies, few adverse outcomes were noted in association with the use of angiotensin II receptor blockers. These significant improvements in renal outcomes were beyond what could be attributed to blood pressure control alone, and demonstrate a specific beneficial renoprotective effect of this class of agents in preserving renal function in patients with type 2 diabetes, proteinuria, and declining renal function.

In the losartan (RENAAL) trial in diabetic nephropathy, patients were allowed to receive other antihypertensive agents, including a variety of calcium channel blockers, in addition to their randomized study drug. There was no reported demonstrable detrimental effect on the beneficial effects of losartan ascribable to the addition of a calcium channel blocker agent to the patient's regimen. Nor was there an apparent renoprotective advantage to the combination of these agents. Data from these two studies, in combination, suggest that calcium channel blockers appear to be not specifically beneficial to the kidney, but they are not harmful either, when compared with other antihypertensive agents.

In the natural course of diabetic nephropathy in both type 1 and type 2 patients, there is a period of years during which pathology develops in the glomeruli; however no change is seen in the glomerular filtration rate or in the presence of overt proteinuria. In fact, a pilot biopsy study carried out before the IDNT revealed that patients satisfying the criteria for overt nephropathy had evidence of advanced glomerulopathy (Fig. 4). Hence, the logical goal of interrupting the course of type 2 diabetic nephropathy at an early stage of the disease process implies that the patient be treated at a time when there is evidence of glomerular malfunction, but before there is overt nephropathy, that is, the stage of microalbuminuria (daily urine albumin excretion >30 mg [20 mg/min] to <300 mg [<200 mg/min]).

A study was done using irbesartan to examine the potential benefits of angiotensin II receptor blockers in patients with type 2 diabetes, microalbuminuria, and well-preserved renal function (Irbesartan in Microalbuminuria: Type 2 Diabetes Trial; IRMA-2).[14] A total of 590 hypertensive patients with type 2 diabetes and microalbuminuria were randomly assigned to irbesartan, either 150 mg daily or 300 mg daily, or placebo.[17] The patients were followed for 2 years.

The primary outcome was time to the onset of persistent overt clinical proteinuria (urinary albumin excretion rate greater than 200 mg/min, or at least 30% higher than the baseline level). The relative risk reduction for the development of overt proteinuria was 39% for the irbesartan 150-mg group vs the control group ($P = 0.08$) and, remarkably, 70% for the irbesartan 300-mg group vs the control group ($P < 0.001$; Fig. 5). A secondary endpoint in the IRMA-2 was change in the overnight urinary albumin excretion rate. The albumin excretion rate was reduced in the two irbesartan groups throughout the study (−24% and −38% at 24 months, compared with baseline in the irbesartan 150-mg and 300-mg groups, respectively). The albumin excretion rate remained unchanged in the control group (−2% at 24 months compared with baseline). The apparent stabilization in the control group is probably the result of much improved blood pressure control. Creatinine clearances remained in the normal range in all three groups throughout the study, as would be expected in these patients with early diabetic nephropathy manifested only by the permeability defect of microalbuminuria. Thus, importantly, this study demonstrated that, in addition to the patients with established diabetic nephropathy with overt proteinuria and declining renal function studied in the IDNT and RENAAL, patients with type 2 diabetes and early nephropathy, manifested only by microalbuminuria, responded well to inhibition of the renal angiotensin system with angiotensin II receptor blockers, with the progression of renal disease dramatically altered. These studies clearly demonstrated that patients with type 2 diabetes and nephropathy manifested by either microalbuminuria or proteinuria and declining renal function should be treated with angiotensin II receptor blockers for renoprotection independent of, but in addition to, the important measure of control of the blood pressure.

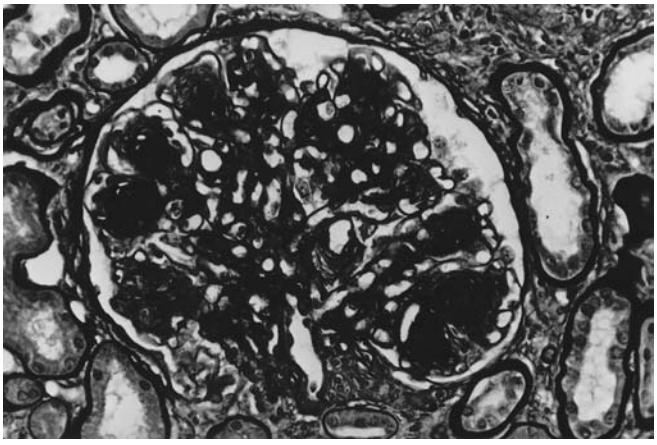

Fig. 4. A pilot study was carried out prior to the Irbesartan Diabetic Nephropathy Trial, utilizing the entry criteria that would be applied by the Collaborative Study Group. Patients entering into this pilot trial, which tested the shortterm effectiveness of irbesartan and amlodipine, had undergone percutaneous renal biopsy. The results revealed that this population of patients generally had advanced diabetic glomerulosclerosis. The glomerulus depicted above is a representative example. This patient entered the study with a blood pressure of 159/72 mm Hg, serum creatinine of 2.1 mg/dl, and 24-h urine protein of 3.0 g/day (clinical features which were characteristic of patients who would ultimately enter the IDNT). This finding emphasizes the need for treating patients with type 2 diabetes mellitus with a renoprotective agent prior to the development of an elevated serum creatinine level or high urine protein excretion (patient S95-150). Methenamine silver, ×100

An important question is whether or not ACE inhibitors have a beneficial effect similar to that of angiotensin II receptor blockers in patients with type 2 diabetes and diabetic nephropathy. The question of whether inhibition of the renal effects of angiotensin II by ACE inhibition and by angiotensin receptor blockade are clinically equivalent has practical ramifications. Clearly, these are two distinct classes of drugs with known differences in pharmacologic effects. One of the best known examples of these differences is the ability of ACE inhibitors to slow the enzymatic catabolism of bradykinin. Angiotensin II receptor blockers, on the other hand, specifically block angiotensin II binding to type 1 angiotensin receptors, but not type 2, with the possible implication of beneficial effects of angiotensin II binding to the latter class of receptors. In a practical sense, based upon the proven effectiveness of ACE inhibitors in type 1 diabetic nephropathy, many patients had been receiving these agents. This therapeutic pattern has been

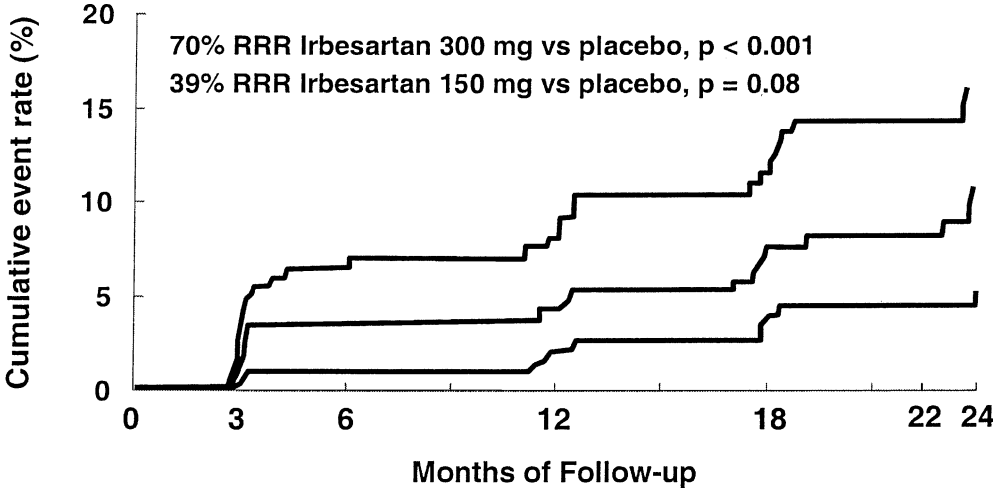

Fig. 5. The results of the Irbesartan in Microalbuminuria: Type 2 Diabetes Trial (IRMA-2) reveal a marked decrease in the likelihood of the patient reaching overt nephropathy, defined as a urine albumin excretion rate of more than 200 mg/min. The *upper curve* represents those patients who received placebo; the *lower curve*, those who received 300 mg of irbesartan; and the *middle curve*, those who received 150 mg of irbesartan. Blood pressure control was essentially equivalent in all three groups

reinforced by the Heart Outcomes Prevention Evaluation (HOPE) Study, which demonstrated improved cardiovascular outcomes in patients with type 2 diabetes when treated with the ACE inhibitor ramipril.[15] It is, therefore, not surprising that there has been reticence on the part of some physicians to replace ACE inhibitor therapy with angiotensin receptor blockers. It must be stated, however, that, as robust as the current evidence is for the use of angiotensin receptor blockers in type 2 diabetic nephropathy, clear evidence for the equivalent therapeutic efficacy of ACE inhibition in the patient population is correspondingly weak. Reference has already been made to the results of the ABCD and UKPDS trials.[9–11]

In a small study testing the value of ACE inhibition, Australian investigators randomized 24 patients with type 2 diabetes, hypertension, and microalbuminuria to either the ACE inhibitor perindopril or the calcium channel blocker nifedipine.[16] Twelve months of treatment with either agent significantly reduced urinary albumin excretion and preserved renal function, suggesting equivalent beneficial effects from blood pressure control with either ACE inhibitors or calcium channel blockers. Results were not dissimilar from those of the UKPDS trial, where the group randomized to tight blood pressure control was also randomized to either receive atenolol, a beta blocker, or captopril, an ACE inhibitor.[11,17] Blood pressure-lowering with captopril or atenolol was similar effective in reducing the incidence of diabetic complications, including renal complications, in this study.[17] These results contrast with the renoprotective effect of irbesartan and losartan when compared with standard antihypertensive therapy in the IDNT and RENAAL trials.[12,13]

In the GISEN study, 352 patients with proteinuria and chronic renal insufficiency were randomized to either ramipril or placebo.[18] This study demonstrated a marked beneficial effect of randomization to ramipril for the group as a whole. However, in the 27 patients with type 2 diabetes and diabetic nephropathy in this trial, there was a statistically significant decrement in renal function in those patients randomized to ramipril when compared with patients in the control group. Clearly, this is subgroup analysis in a small sample of patients.

In contrast to the above, in a multicenter study by Ravid and coworkers,[19] 94 patients with type 2 diabetes and microalbuminuria were randomized to the ACE inhibitor enalapril 10 mg/day or placebo and followed for 5 years. More patients in the placebo group received longacting nifedipine for blood pressure control compared with the enalapril group. Compared with placebo, enalapril decreased the number of patients who progressed from microalbuminuria to proteinuria. Renal function, measured by reciprocal creatinine, was also reported to be better preserved in patients receiving enalapril.

Thus, given the data regarding ACE inhibitors having a beneficial effect in patients with nephropathy secondary to type 1 diabetes,[20] one might have assumed that inhibition of the renin angiotensin system with either ACE inhibitors or angiotensin II receptor blockers would be equally beneficial to patients with type 2 diabetic nephropathy with respect to renoprotection. Disappointingly, the sparse data available are unconvincing. A beneficial renoprotective effect of ACE inhibition has not been established in patients with type 2 diabetic nephropathy.[16–18] In contrast, the beneficial effects of angiotensin II receptor antagonists in patients with type 2 diabetes and nephropathy have been conclusively demonstrated in three large clinical trials.[12–14]

The clear benefit of drugs which interrupt the renin-angiotensin-aldosterone system in type 1 and type 2 diabetic nephropathy must be measured in the context of potential risks to the patient. Certainly, and particularly in the type 2 diabetes population, the effect of these agents upon potassium metabolism deserves examination. While neither irbesartan nor losartan were associated with any apparent sudden deaths due to hyperkalemia, it must be emphasized that, unsurprisingly, both of these agents were associated with significantly more hyperkalemia than occurred in the respective control groups in these studies.[12] These findings emphasize the need for careful monitoring of patients with type 2 diabetes for evidence of elevation of the serum potassium. The use of furosemide, or other loop diuretic agents, in this patient population is valuable in order to increase renal potassium excretion. Neither the IDNT nor the RENAAL studies, encompassing a total of over 1250 patients who received angiotensin II receptor blockers, reported the occurrence of acute renal failure associated with bilateral renal artery stenosis.[12,13] While serious vascular disease would be anticipated in this patient population, the phenomenon of acute renal failure due to angiotensin II inhibition would appear to be an uncommon event. Nevertheless, monitoring of the serum creatinine during the initial weeks of angiotensin II receptor blocker or ACE inhibitor therapy is judicious.

In summary, the devastating complication of endstage renal disease in patients with type 2 diabetic nephropathy can be delayed with blood sugar control, blood pressure control, and the use of angiotensin II receptor blockers for specific renoprotection. While it is important to recognize the specific renoprotective effect of the angiotensin receptor blockers, it is also equally important to emphasize the concurrent requirement that blood pressure be well controlled in this difficult and complex population of patients.

References

1. The World Health Report. Concurring, suffering, enriching humanity. Geneva: WHO; 1997.
2. Mogensen CE. Long-term antihypertensive treatment inhibiting progression of diabetic nephropathy. BMJ 1982;285:685–8.
3. Parving HH, Andersen AR, Smidt UM, Hommel E, Mathiesen ER, Svendsen PA. Effect of antihypertensive treatment on kidney function in diabetic nephropathy. BMJ 1987;294:1443–7.
4. Bjorck S, Nyberg G, Mulec H, Granerus G, Herlitz H, Aurell M. Beneficial effects of angiotensin converting enzyme inhibition on renal function in patients with diabetic nephropathy. BMJ 1986;293:471–4.
5. Lewis JB, Berl T, Bain RP, Lewis EJ. Effect of intensive blood pressure control on the course of type I diabetic nephropathy. Am J Kidney Dis 1999;34:809–17.
6. Ritz E, Stefanski A. Diabetic nephropathy in type II diabetes. Am J Kidney Dis 1996;27:167–94.

7. Klag MJ, Whelton PK, Randall BL, Neaton JD, Brancati FL, Ford CE, et al. Blood pressure and end-stage renal disease in men. N Engl J Med 1996;334:13–18.
8. Bakris GL. Progression of diabetic nephropathy. A focus on arterial pressure level and methods of reduction. Diabetes Res Clin Pract 1998;39(Suppl):S35–42.
9. Estacio RO, Jeffers BW, Gifford N, Schrier RW. Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. Diabetes Care 2000;23:B54–64.
10. Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. Kidney Int 2002;61:1086–97.
11. UK Prospective Diabetes Study group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998;517:709–12.
12. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851–60.
13. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861–9.
14. Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 2001;345:870–8.
15. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin converting enzyme inhibitor, ramipril on cardiovascular events in high risk patients. N Engl J Med 2000;342:145–53.
16. Melbourne Diabetic Nephropathy Study Group. Comparison between perindopril and nifedipine in hypertensive and normotensive diabetic patients with microalbuminuria. BMJ 1991;302: 210–16.
17. UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. BMJ 1998;317:713–20.
18. The GISEN Group. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. Lancet 1997;349:1857–63.
19. 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 1993;118:577–81.
20. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effects of angiotensin-converting enzyme inhibition on diabetic nephropathy. N Engl J Med 1993;329:1456–62.