Type 2 Diabetes: RENAAL and IDNT—The Emergence of New Treatment Options

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The Reduction in End Points in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study and the Irbesartan Diabetic Nephropathy Trial (IDNT) are two recently reported trials with hard end points, conducted in patients in advanced stages of diabetic nephropathy. Two other studies—the Irbesartan Microalbuminuria Study (IRMA)-2 and the Microalbuminuria Reduction with Valsartan study (MARVAL)—were trials conducted in patients with type 2 diabetes with microalbuminuria, a cardiovascular risk factor associated with early-stage diabetic nephropathy. These trials all had a common theme—that is, does an angiotensin receptor blocker (ARB) interfere with the natural history of diabetic nephropathy in a blood pressure-independent fashion? Without question, the results of these trials legitimatize the use of the ARB class in forestalling the deterioration in renal function, which is almost inevitable in the patient with untreated diabetic nephropathy. These data can now be added to the vast array of evidence supporting angiotensin-converting enzyme (ACE) inhibitor use in patients with nephropathy associated with type 1 diabetes. It now appears a safe conclusion that the patient with diabetic nephropathy should receive therapy with an agent that interrupts the renin-angiotensin system. These studies have not resolved the question as to whether an ACE inhibitor or an ARB is the preferred agent in people with nephropathy from type 1 diabetes, though the optimal doses of these drugs remain to be determined. Head-to-head studies comparing ACE inhibitors to ARBs in diabetic nephropathy are not likely to occur, so it is unlikely that comparable information will be forthcoming with ACE inhibitors. An evidence-based therapeutic approach derived from these trials would argue for ARBs to be the foundation of therapy in the patient with type 2 diabetes and nephropathy. (J Clin Hypertens. 2002;4:52–57)

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Diabetes mellitus is rapidly increasing in prevalence worldwide and is currently estimated to affect more than 7.3% of the US population.[1] In the not-so-distant past, type 2 diabetes mellitus was viewed as a relatively benign condition, at least in the elderly, with relatively little effect on life expectancy or renal function.[2] It has now become obvious that type 2 diabetes must be taken every bit as seriously as type 1 diabetes, in part because of its renal complications.[3] Diabetes is now the most common cause of end-stage renal disease (ESRD) in this country, accounting for 40% of the cases of ESRD with chronic renal failure having developed in over 90,000 people in 2000.[4] Both the prevalence and the incidence of ESRD are approximately twice what they were 10 years ago.[4] If the trends of the past two decades persist, approximately 175,000 new cases of ESRD will be diagnosed in 2010. The proportion of ESRD patients suffering from diabetes is expected to increase considerably because the number of patients with diabetes is expected to double within the next 15 years and because the individual diabetic patient now has a longer life expectancy and is therefore at greater risk of developing late complications, including diabetic nephropathy. Caring for patients with ESRD already consumes more than $18 billion per year in the United States. The cost associated with the management of ESRD is expected to surpass $28 billion by 2010.[4]

THE TRIALS

Microalbuminuria

The Irbesartan Microalbuminuria (IRMA)-2 trial addressed the question of whether an angiotensin receptor blocker (ARB), irbesartan, would delay or prevent the development of clinical proteinuria in patients with type 2 diabetes mellitus, microalbuminuria, and a normal serum creatinine level (1.3 mg/dL for men and 1.1 mg/dL for women).[5] Type 2 diabetic patients whose overnight urinary albumin excretion rate (UAER) was 20–200 μg per minute on two of three consecutive samples were randomized to receive placebo or irbesartan 150 or 300 mg once daily. Goal blood pressure (BP) was <135/85 mm Hg 3 months after randomization; additional antihypertensive agents, except angiotensin-converting enzyme (ACE) inhibitors and dihydropyridine calcium channel blockers (CCBs), were permitted to achieve that goal. The primary end point of the study was defined as the occurrence of a UAER of >200 μg/min and/or a UAER at least 30% higher than baseline on at least two consecutive measurements. Average BP values were slightly lower in the two groups treated with irbesartan than in the placebo group during the first 6 months of the study, but this small difference disappeared during the last 12 months of the study. Patients were followed for an average of 2 years. In the irbesartan 150-mg vs. the placebo group, there was a 39% reduction (p=0.08; ns) in the development rate of clinical proteinuria, while in the irbesartan 300-mg treatment group there was a 70% reduction in the primary end point (p<0.001). Return to a normal UAER, defined as a UAER of <20 μg/min, was 34% more frequent among patients treated with irbesartan 300 mg than among patients in the placebo group (p=0.006). The results of this study demonstrate that the ARB irbesartan, at a dose of 300 mg daily, can importantly delay the progression of microalbuminuria to clinical proteinuria in patients with type 2 diabetes.

Microalbuminuria Reduction with Valsartan (MARVAL) was a smaller multicenter, double-blind, randomized, parallel study of 332 type 2 diabetes patients aged 35–75 with microalbuminuria and normal or high BP.[6] Patients were randomized to receive valsartan 80 mg once daily or amlodipine 5 mg once daily over 24 weeks. A target BP of 135/85 mm Hg was aimed for by dose doubling and the addition of bendrofluazide and doxazosin therapy. The study was designed to assess the BP-independent effects of valsartan vs. amlodipine on the UAER. The geometric means (lower and upper quartiles) in UAER (mg/min) from baseline to the end of the study were, for the valsartan group, 57.97 (33.0, 102.3) to 32.3 (18.2, 59.7) and for amlodipine, 55.4 (34.3, 84.6) to 50.7 (31.8, 85.6) (p<0.001). In addition, more patients returned to normal albuminuric status after 24 weeks with valsartan (29.9%) vs. amlodipine (14.5%) (p<0.001). These differences were observed in association with equivalent BP-lowering effects for valsartan and amlodipine.

Diabetic Nephropathy

Both the Irbesartan Diabetic Nephropathy Trial (IDNT) and the Reduction in End Points in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study were designed to have sufficient statistical power to detect an approximate 25% difference in the primary outcome measure between the specific intervention and the placebo group in patients with type 2 diabetic nephropathy.[7,8] The RENAAL and IDNT trials involved 1513 and 1715 patients, respectively. Each trial had a placebo treatment limb, which, in fact, was a conventional therapy treatment limb with placebo added. RENAAL patients randomized to the placebo group were treated with antihypertensive agents as needed (primarily diuretics, CCBs, β blockers, and peripheral α antagonists) to a goal BP of <140/<90 mm Hg. In both the losartan-treated and placebo groups, approximately 90% of patients required a CCB to achieve BP control, which in most cases was a dihydropyridine CCB. In the RENAAL trial, losartan was given in a dose of either 50 or 100 mg/day.

IDNT had three treatment limbs: placebo, amlodipine, and irbesartan. Patients randomized to the placebo group were treated with antihypertensive agents as needed (primarily diuretics, β blockers, and centrally acting agents), with CCBs disallowed in all treatment limbs. The irbesartan dose in the IDNT trial was titrated from 75 to 300 mg/day. The dose of amlodipine was titrated from 2.5 to 10 mg in the IDNT trial. The goal systolic BP was ≤135 mm Hg (or 10 mm Hg lower than the value at screening if it was more than 145 mm Hg) and a diastolic BP of ≤85. These goal BP values were somewhat lower than those in the RENAAL trial.

Each study was designed to maintain comparable BP values among treatment arms; the study results demonstrate that, in fact, comparable average BP values were achieved in the treatment and placebo arms of each trial and, in the IDNT trial, in the amlodipine treatment arm as well. To approach BP goals in these studies, multiple antihypertensive medications were required. In RENAAL, there was a 16% reduction in the number of losartan-treated patients who reached the primary end point vs. those randomized to the placebo group, and a 20% reduction in patients reaching the primary end point in the irbesartan treatment vs. placebo arm of the IDNT trial. This was despite comparable reductions in BP in each

treatment limb. Although patients in the IDNT trial randomized to receive amlodipine as initial therapy achieved reductions in BP comparable to those in the irbesartan and placebo groups, the percentage of patients who reached the primary end point in this arm (41%) was slightly higher than the percentage of patients in the placebo arm (39%) and significantly greater than in the irbesartan arm.

In each clinical trial, a secondary composite cardiovascular end point was pre-specified. In RENAAL, this composite end point was mortality and morbidity from cardiovascular causes, including myocardial infarction, stroke, first hospitalization for heart failure or unstable angina, coronary or peripheral revascularization, or any death from cardiovascular causes. A slightly different composite cardiovascular secondary end point was specified in IDNT, which incorporated death from cardiovascular causes, nonfatal myocardial infarction, heart failure leading to hospitalization, stroke causing permanent neurologic deficit, and/or below-the-knee/above-the-ankle amputation. Although there were no differences in ARB-treated vs. placebo-treated patients in the composite cardiovascular end point in either trial, there was a 32% reduction in hospitalizations for heart failure when losartan was compared to placebo in the RENAAL trial and a reduction of 23% when irbesartan was compared to placebo in the irbesartan group in the IDNT trial. Moreover, there was a trend, albeit not significant (p=0.07), toward a reduction in myocardial infarction in the losartan group of the RENAAL trial. Interestingly, in the IDNT trial, the amlodipine treatment group had a significantly higher rate of congestive heart failure (CHF) than the placebo or irbesartan groups. Important in terms of this finding is that patients were not permitted ACE inhibitor therapy at any time during the study and, if they had been receiving an ACE inhibitor prior to active treatment, it was to have been discontinued. In both the RENAAL and IDNT trials, hyperkalemia was uncommon as a reason for study drug discontinuation. Lastly, it should be acknowledged that these trials were not powered for cardiovascular end points.

ARE THE IDNT AND RENAAL FINDINGS A CLASS EFFECT?

This poses a difficult question. Acceptance of the concept of a class effect requires a denial of the fact that ARBs are structurally and physicochemically distinct, with differing potency, pharmacokinetics, and tissue penetration characteristics.[9–11] Although the concept of class effect is now under consideration for ARBs, a true operational definition of "class effect" does not exist for ARBs or, for that matter, any class of drugs. Instead, a related term, "class labeling," is preferred by the Food and Drug Administration. Further confusing the issue is the inherent difficulty in identifying dose equivalence for the various positive effects of ARBs, such as renal protection, BP reduction, and/or an antiproteinuric effect. True dose equivalence for BP control has never been determined among the various ARBs. The impression that equivalent doses are readily identifiable in the hypertensive patient is merely an outgrowth of the unique dose-response relationships of ARBs. ARBs have a steep dose response at low doses; however, when they are given in higher doses, a relatively shallow dose response emerges. This dose-response pattern readily lends itself to the concept of class effect. The issue of class effect is more dubious when renal protection is sought with an ARB. The dosages for ARBs in nephropathic states and the variable renal handling of these drugs[12,13] make it highly doubtful that a "renal equivalent" ARB dose could be identified for other ARBs unless the ARB in question had been specifically submitted to testing.

WHAT IS THE BEST DRUG COMBINATION FOR DIABETIC NEPHROPATHY?

Both the IDNT and RENAAL trials required three drugs in addition to the study medication in order to reach the per-protocol BP goals.[7,8] Moreover, in all trials to date that have focused on achieving lower BP values, some 3.2 different antihypertensive medications have been required.[14] In each study, certain medications were proscribed. In the IDNT trial, CCBs and ACE inhibitors were not allowed. In the RENAAL trial, only ACE inhibitor use was not permitted. Consequently, the RENAAL trial provides the best data on the types of medication that effect BP control when added to an ARB. Moreover, there was little difference between the losartan and the placebo-treated limbs in which secondary agents were selected. In the RENAAL trial, approximately 85% of the subjects received a diuretic, which was most commonly a loop diuretic. The selection of a loop diuretic was in large measure predicated on the need for more aggressive volume reduction than could be achieved with a thiazide-type diuretic. Eighty percent of the patients were given a CCB, which in 60% of cases was a dihydropyridine CCB. The data set from the RENAAL trial unfortunately does not allow for a distinction to be made between dihydropyridine and nondihydropyridine CCB-treated patients, since the majority of patients received dihydropyridine CCBs.

At least in theory, the use of a nondihydropyridine CCB with an ARB is likely to be the preferred method of treatment because the combination of a nondihydropyridine CCB with an ACE inhibitor further reduces urinary protein excretion beyond what is seen with an ACE inhibitor alone.[15] This en-

hanced antiproteinuric effect seems not to occur to the same degree—if at all—when a dihydropyridine CCB is added to either an ARB or an ACE inhibitor in the proteinuric patient.[16] In 45% and 35% of subjects, respectively, a peripheral α antagonist and a β blocker were also added. The use of peripheral α blockers in the RENAAL study raises the question of whether their use compromised the effect of losartan—at least as relates to the development of CHF. This is a question of some relevance, given the recent results from the Antihypertensive and Lipid-Lowering Treatment To Prevent Heart Attack Trial (ALLHAT), in which doxazosin increased the risk of CHF.[17] No such information concerning peripheral α antagonism is available at this time from the RENAAL trial.

ARE ACE INHIBITORS SUPERIOR TO ARBS IN PATIENTS WITH DIABETIC NEPHROPATHY?

In one of the biggest dilemmas facing cardiovascular clinical research, clinical trials are increasingly being required to show benefits on clinical end points rather than surrogate end points, while at the same time the incremental benefits of newer treatments are shrinking. ACE inhibitors and ARBs appear to be little different in their BP-reducing ability. Although the initial major end point of interest was simply BP, many head-to-head studies of these two drug classes have now used more elaborate primary renal outcome measures, such as differences in albuminuria and/or changes in renal function, as was the case in the RENAAL and IDNT trials. Unfortunately, there are currently no plans, at least for the foreseeable future, to specifically compare ACE inhibitors to ARBs regarding their individual effect(s) on diabetic nephropathy.

The last decade has provided us with a wealth of information, which indicates that ACE inhibitors are renoprotective, with the exception that there has not been a hard end point study of ACE inhibitors in type 2 diabetic nephropathy. The results of the RENAAL and IDNT trials now provide just such evidence for the ARBs.[7,8] Does the absence of hard end point data for ACE inhibitors in type 2 diabetic nephropathy matter? Common sense would suggest that these drugs, if anything, are quite similar in their renoprotective mechanisms. On the surface, neither class can therefore be viewed as superior. If a physician believes therapy should be strongly influenced by clinical trial findings, then the preferred treatment in this patient population should be an ARB, now that studies are available; otherwise, the selection of a drug class—as has often been the case—is predicated on a physician's past experience and individual perspective on the literature.

SLOWING DIABETIC NEPHROPATHY: ACE INHIBITOR/ARB COMBINATION VS. MONOTHERAPY

The combination of an ACE inhibitor and an ARB has been occasionally used in progressive renal disease, particularly as relates to an antiproteinuric effect beyond that seen with a single agent.[18–25] For example, in an early study of normotensive patients with biopsy-proved immunoglobulin A nephropathy and non-nephrotic proteinuria, the combination of losartan with an ACE inhibitor produced an average 73% greater reduction in proteinuria than either agent alone (ACE inhibitor, 38%; losartan, 30%). In this study, no further reduction in proteinuria was observed by doubling the dose of either the ACE inhibitor or losartan. The observed changes could not be explained by either changes in systemic BP or the glomerular filtration rate. It is noteworthy that the additive antiproteinuric effect with the combination of an ACE inhibitor and losartan was observed within 4 weeks of combination therapy.[21]

Similar observations were made in the recent Candesartan and Lisinopril Microalbuminuria (CALM) trial, a randomized study of the effect of combining the ARB candesartan and the ACE inhibitor lisinopril on microalbuminuria in 199 type 2 diabetic patients. This was a 12-week combination therapy trial, with 12 weeks of prior monotherapy with either candesartan or lisinopril.[20] In this study, the reduction in the urinary albumin:creatinine ratio in those receiving candesartan (16 mg/day) and lisinopril (20 mg/day) was significantly greater (50% reduction) than that observed with either agent alone (24% for candesartan and 39% for lisinopril). As is often the case with combination therapy, BP values were lower than with the individual agent, which makes interpretation of the findings difficult. After 24 weeks of therapy, diastolic BP was reduced to a greater degree with combination therapy (–16.3 mm Hg) than with either candesartan (–10.4 mm Hg) or lisinopril (–10.7 mm Hg) alone. The importance of BP reduction in the additive antiproteinuric effects of combination therapy cannot be overemphasized.[18–20,22] The relationship between BP and the antiproteinuric effect of combination therapy may go undetected if office-based BP readings are exclusively used. A recent study by Russo et al.[22] found no relationship between trough BP and the antiproteinuric effect of combination therapy with enalapril and losartan. Alternatively, in this same study, there was a significant and highly correlated relationship between mean ambulatory BP and the fall in urinary protein excretion.

As of this writing there is no strong evidence to support the combination of these agents as yielding additional benefits when the dose of one of the

components has yet to be fully maximized. Without question, additional studies will be required to determine whether long-term cardiovascular and renal outcome measures are more favorably influenced by combination therapy. Moreover, the optimal dose relationship for combination therapy remains ill-defined.[26]

SLOWING DIABETIC NEPHROPATHY: WHAT DRUG EFFECTS ARE CONTRIBUTORY?

In both the RENAAL and IDNT trials, the control groups achieved similar levels of BP control; thus, within the limits of how BP control was determined in these studies, the observed renal benefits were likely to be BP-independent. A variety of neurohumoral and cellular systems are activated in progressive diabetic nephropathy, one of the more important changes being increased urinary protein excretion. For some time now, it has been clear that the progression rate in chronic renal failure correlates with the level of proteinuria.[27,28] The converse seemingly applies—that is, the degree to which proteinuria is reduced correlates with the rate of slowing of progressive renal failure. In both the RENAAL and IDNT trials, in the losartan and irbesartan treatment limbs, proteinuria was markedly reduced compared to the other treatment limbs. For example, in the RENAAL trial, there was a 35% average reduction in the level of proteinuria, a finding that persisted throughout the study.[7] Likewise, in the IDNT trial, proteinuria was reduced, on average, by 33% in the irbesartan treatment limb, as compared with 6% in the amlodipine group and 10% in the placebo group.[8] These reductions in proteinuria were also maintained throughout the follow-up period. The reduction in proteinuria in these trials is a starting point for the presumed renoprotection of these compounds. Invoking other, unmeasured parameters as the basis for the positive findings of these trials is pure speculation at this time.

WILL IDNT AND MARVAL AFFECT THE USE OF AMLODIPINE IN DIABETIC NEPHROPATHY?

As was originally hypothesized over a decade ago,[29,30] a growing body of evidence, particularly in proteinuric patients, now suggests that dihydropyridine CCBs are not as renoprotective as either ACE inhibitors[31] or ARBs.[7,8] The CCB studied in most of these cases has been amlodipine. The MARVAL trial in microalbuminuric diabetic nephropathy patients[6] and the IDNT trial in patients with more overt nephropathy[8] both showed a substantial benefit in the active treatment limb, which compared valsartan (MARVAL) or irbesartan (IDNT) with amlodipine. Similarly, the recently concluded African American Study of Kidney Disease (AASK) trial showed that a ramipril-based regimen was substantially better than an amlodipine-based regimen in forestalling progressive renal disease in nondiabetic blacks with hypertensive nephrosclerosis, an observation particularly evident in the portion of the study population with protein excretion in excess of 300 mg/day.[31] Taken together, these trials suggest strongly that patients with proteinuria of diverse etiologies should not receive an amlodipine-based regimen without the simultaneous administration of an ACE inhibitor or an ARB. The appropriate amount of ACE inhibitor or ARB that should be combined with a dihydropyridine CCB remains poorly defined. On a practical note, it is reasonable to use the highest dose of ACE inhibitor or ARB together with the lowest dose of dihydropyridine CCB that still achieves goal BP. It is currently unknown as to what degree the renoprotective effects of an ACE inhibitor or an ARB are attenuated by coadministration of a dihydropyridine CCB—if at all—although if BP is sufficiently reduced in the process, this may counterbalance any possibility of negative effects.

DOSES OF IRBESARTAN AND LOSARTAN IN DIABETIC NEPHROPATHY

Neither the IDNT nor RENAAL trial specifically studied a full dose range of irbesartan or losartan.[7,8] Instead, each study was designed to evaluate the response to losartan and irbesartan at doses currently indicated for the treatment of hypertension. The results of both studies were BP-independent, thereby suggesting a mechanistic benefit derived from tissue-based, nonvasodepressor effects of these drugs. Accordingly, it can be speculated that higher doses might have provided additional benefit. Some indication of this can be gleaned from the IRMA-2 trial,[5] in which 150- and 300-mg doses of irbesartan were studied in patients with microalbuminuria. Urinary albumin decreased 24% in the 150-mg group, 38% in the 300-mg group, and 2% in the placebo group. Moreover, 70% and 39% of those in the 150- and 300-mg treatment groups progressed to overt nephropathy, respectively. These differences were independent of any change in BP. In consideration of the above, the optimal dose of losartan or irbesartan in diabetic nephropathy is not known.

For now, the top-end dose of either medication should be the one employed in the studies: 300 mg for irbesartan and 100 mg for losartan. In the patient with diabetic nephropathy, multidrug therapy is typically required for BP control. Thus, there is generally a considerable margin to allow a *maximal dose* of an ARB, and every effort should be made to employ these top-end doses, up to and including a downward titration and/or elimination of other

drugs in the antihypertensive regimen of a patient with diabetic nephropathy.

CONCLUSIONS

Diabetic nephropathy is a global problem of significant economic consequence. To date, there is not an established means to predictably reduce the primary rate of development of diabetic nephropathy; rather, current practice typically addresses diabetic nephropathy when it is already present, either in the form of microalbuminuria or as the more advanced disease state characterized by macroproteinuria and declining renal function. Important elements of the treatment plan for diabetic nephropathy include meticulous BP control and reduction in urine protein excretion to below 1 g/day. In this regard, ACE inhibitors and/or ARBs are of considerable importance. Currently, in type 1 diabetic nephropathy, ACE inhibitors remain the initial agents of choice and if this class of drugs is poorly tolerated, ARBs can be substituted. In the instance of type 2 diabetic nephropathy, the available evidence supports the preferential use of ARBs. This latter position is one recently adopted by the American Diabetes Association in a newly published guidelines paper on diabetic nephropathy treatment.[32] This sentiment is based on the strength of the clinical trial evidence with both losartan and irbesartan in type 2 diabetes.[7,8] How these data relate to the use of the ARB class in the hypertensive diabetic patient without increased urinary protein excretion remains to be determined.

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