Treating Hypertension in the Patient With Overt Diabetic Nephropathy

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Summary: Arterial blood pressure is a major determinant of renal and cardiovascular outcomes in diabetic nephropathy. There is a proportional relationship between the systolic blood pressure and renal and mortality outcomes. Decreasing the diastolic pressure does not significantly decrease these outcomes. Irrespective of the magnitude of pretreatment systolic hypertension in the patient with type 2 diabetic nephropathy, the systolic pressure achieved with antihypertensive therapy is the important determinant of renal and cardiovascular risk. Achieving a lower systolic pressure down to 120 mm Hg is associated with substantial risk reduction. Although the data are limited, systolic blood pressure less than 120 mm Hg may be associated with increased all-cause mortality in this patient population, increasing the possibility of a J-curve response. A marked decrease in diastolic pressure, which is a danger when undertaking aggressive therapy with the goal of decreasing the systolic pressure to 130 mm Hg, can be associated with an increased risk of cardiac events. The renoprotective and proteinuria-decreasing effects of angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers recommend these agents as the standard of care in type 2 diabetic nephropathy. In addition to angiotensin-converting enzyme inhibitor and angiotensin-receptor blocker therapy, controlling the systolic blood pressure in this difficult to control patient population may require the use of 3 or more antihypertensive agents.
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An increase in the arterial blood pressure is a major risk factor for the progression of renal disease in diabetic nephropathy and an important determinant of cardiovascular outcome in this patient population. Advances in the therapeutic approach to the patient with diabetic nephropathy have led to dramatic improvement in the clinical course of these patients. Only 30 years ago, Kussman et al[1] reported that a cross-section analysis of patients followed-up in his clinic who had type 1 diabetes mellitus revealed that the onset of proteinuria could be expected 17 years after the initial diagnosis of diabetes. Proteinuria presaged a malignant course. The mean serum creatinine level recorded at the time of the onset of proteinuria was 1.2 ± 0.3 mg/dL. A loss of at least 50% of renal function and early renal failure with a mean serum creatinine level of 2.8 ± 0.9 mg/dL was documented within only 2 years after the onset of proteinuria. Death, primarily attributed to renal failure, occurred within 5 years after the onset of proteinuria. Mogensen[2] is credited with the initial report that documented the improvement in outcome associated with stricter blood pressure management. He reported that decreasing the blood pressure from 162/103 mm Hg to 144/95 mm Hg in 6 subjects decreased the rate of loss of glomerular filtration from 1.23 mL/min/mo to 0.49/mL/min/mo. Later, Nyberg et al[3] and Parving et al[4,5] confirmed these observations. Parving et al[4,5] treated 11 patients with aggressive antihypertension management, decreasing the mean blood pressure from 143/96 mm Hg to 129/84 mm Hg. They reported the rate of the glomer-

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ular filtration rate decrease from an initial 0.89 mL/min/mo to 0.22 mL/min/mo.

There have been only a few clinical trials in patients with diabetes in which there was prospective randomization into groups with significantly different blood pressure goals. The UK Prospective Diabetes Study randomized patients to tight control (<150/85 mm Hg) and less tight control (<180/105 mm Hg). They showed that the prevention of macrovascular and microvascular events in type 2 diabetes could be achieved by better blood pressure control. The UK Prospective Diabetes Study showed that despite currently obsolete blood pressure goals, decreasing the mean arterial pressure by approximately 8 mm Hg resulted in a 20% to 30% risk reduction in multiple cardiovascular and diabetes-related end points.[6]

In another study of patients with advanced diabetic renal disease, the effect of tight blood pressure control was investigated in 129 patients who had participated previously in the Collaborative Study Group trial of the effect of angiotensin-converting enzyme (ACE) inhibition on diabetic nephropathy, which used captopril (Capoten; Bristol Myers-Squibb, Princeton, NJ) in a type 1 diabetic population.[7] Patients were assigned randomly to a mean arterial pressure of 92 mm Hg or less or 100 to 107 mm Hg, and were followed-up for 2 years. After 2 years, patients with the lower blood pressure goal had decreased proteinuria from 1,043 mg/d to 535 mg/d, whereas the higher standard therapy group increased from 1,140 mg/d to 1,723 mg/d. Hence, on average, the aggressive treatment group was no longer urine-dipstick–protein positive. This was the first study to claim that a renal remission was possible in diabetic nephropathy. Renal remission was defined as a 24-hour protein excretion of less than 500 mg/d plus a loss of glomerular filtration rate of less than 2 mL/y. It was noteworthy that 6 patients who initially had nephrotic-range proteinuria of 3 g/d or more, which generally is believed to have a very poor renal prognosis, had been observed for 6 to 9 years and satisfied the definition of renal remission at the end of this study. Blood pressure control in this study was undertaken using ramipril (Altace; Monarch, Bristol, TN), which was titrated up to a dose of 20 mg/d before the addition of other antihypertensive agents. Therefore, those patients with the best outcome had better blood pressure control and were also on the highest dose of the ACE inhibitor.

As one might expect, the limited evidence-based data have prompted some controversy with respect to blood pressure management of this patient population. The treating nephrologist must be concerned not only about the best agent to use, but also the ideal blood pressure goal. In view of advanced vascular disease that is seen in the type 2 diabetes population, there is a concern that aggressive treatment can cause the blood pressure to be decreased to the point of increased cardiovascular or renal risk. The systolic blood pressure in patients with diabetic nephropathy is notoriously difficult to control. An aggressive attempt to decrease systolic pressure engenders the potentially dangerous possibility that a concomitant marked decrease in the diastolic pressure could put the patient at increased risk for an adverse cardiac event.

ANGIOTENSIN RECEPTOR ANTAGONIST TRIALS

In recent years, 2 large clinical trials have been performed with the intent of determining whether angiotensin-receptor blockade is associated with retardation of the progression of renal disease in type 2 diabetic nephropathy by a mechanism independent of blood pressure control. The Irbesartan Diabetic Nephropathy Trial (IDNT) (Avapro; Bristol Myers-Squibb)[8] and the Reduction in End-Points in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) (Cozaar; Merck, West Point, PA)[9] were designed to achieve statistical power for renal outcomes. Neither were powered for cardiovascular outcomes. Nevertheless, useful data regarding the determination of optimal targets for the systolic and diastolic components of arterial pressure with respect to renal and cardiovascular outcomes and all-cause mortality have been derived from these studies.

The IDNT was a randomized, double-blind, placebo-controlled trial performed in 209 clinics worldwide.[8] A total of 1,590 hypertensive

patients with type 2 diabetes were enrolled. These patients were randomized to 3 treatment regimens: (1) the angiotensin-receptor blocker (ARB) irbesartan in a dose titrated from 75 to 300 mg/d; (2) the dihydropyridine calcium channel blocker amlodipine (Norvasc; Pfizer, New York, NY), in a dose titrated from 2.5 to 10 mg/d; or (3) placebo control. Antihypertensive agents with the exception of ACE inhibitors, ARBs, and calcium channel blockers were used as needed in each group with a target systolic pressure of 135 mm Hg or less, or a 10 mm Hg decrease when the value at screening was more than 145 mm Hg, and a diastolic pressure of 85 mm Hg or less. Two thirds of this patient population were men, the average age was approximately 60 years, and the average body mass index was 31. Approximately 75% of patients were non-Hispanic white and 13% were non-Hispanic black. The primary outcome was the time to a composite outcome of doubling of the serum creatinine level, end-stage renal (ESRD) disease, or death. The average blood pressure at the time of entry into the study was a systolic pressure of 160 ± 20 mm Hg and a diastolic pressure of 87 ± 11 mm Hg. Over the course of follow-up evaluation in the IDNT, which averaged 2.6 years, the blood pressure achieved in the irbesartan group and the amlodipine group were essentially identical (140/77 mm Hg), whereas that of the placebo group was slightly higher (144/80 mm Hg). As would be expected in this patient population, several antihypertensive agents, in addition to coded medication, were required for blood pressure control. Patients in the placebo group required an average of 3.3 nonstudy drugs for their blood pressure control as compared with 3.0 in patients randomized to the irbesartan and amlodipine groups. The distribution of classes of these nonstudy drugs used to control the blood pressure did not differ among the groups and included diuretics, β-blockers, peripheral α-blockers, and central α-2 agonists.

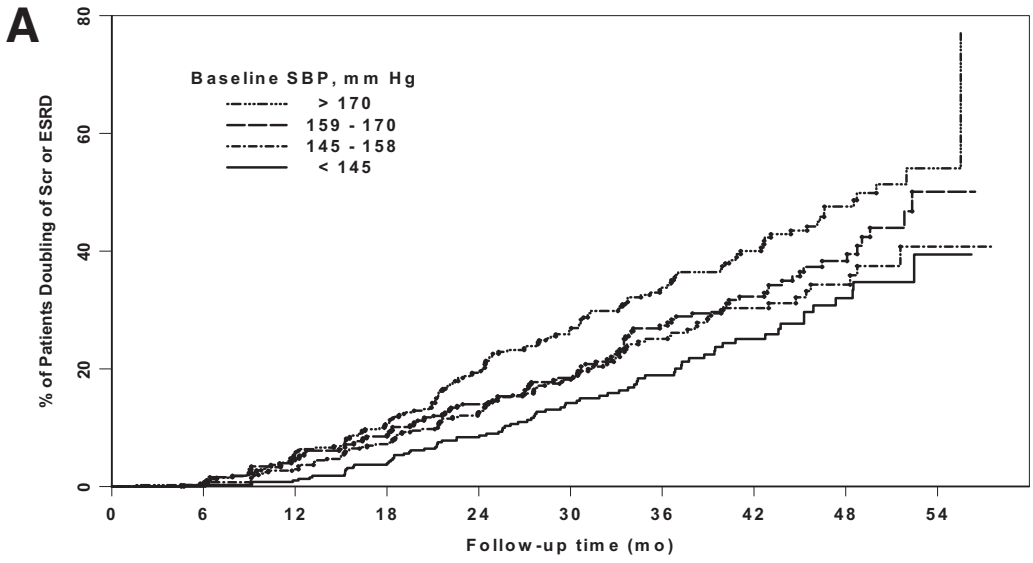
In accord with the aggressive therapeutic approach, the diastolic blood pressure was controlled in 82% of patients entered into this trial. However, only 30% of patients achieved the systolic goal of 135 mm Hg.

THE IMPORTANCE OF SYSTOLIC BLOOD PRESSURE CONTROL

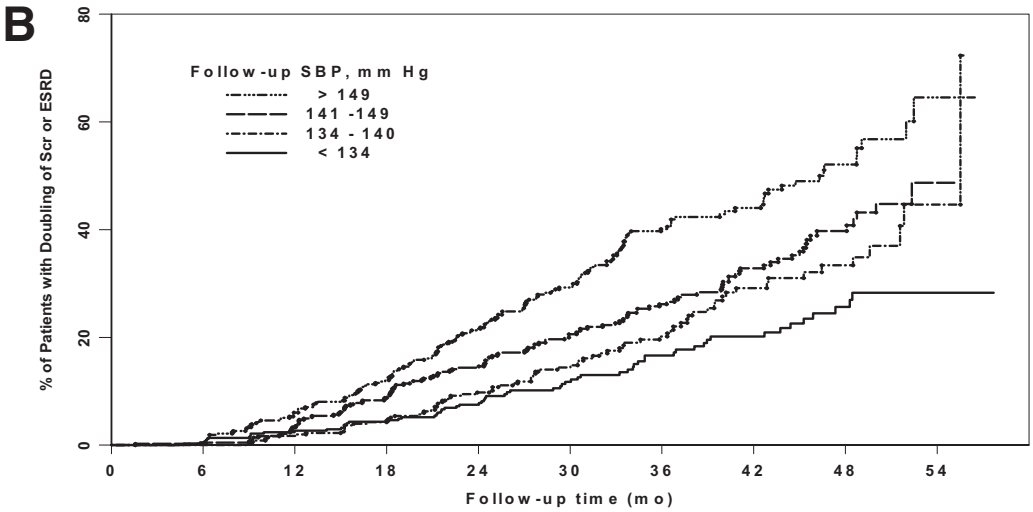
The importance of control of systolic hypertension as a determinant of the course of renal progression was shown in the IDNT. The baseline systolic blood pressure correlated significantly with renal outcomes (doubling of the serum creatinine level or ESRD) (Fig. 1A).[10] The likelihood of reaching a renal end point increased progressively with the higher baseline systolic blood pressures ($P < .0001$). Thirty-six percent of patients in the highest quartile of blood pressure (baseline systolic blood pressure >170 mm Hg) reached a renal end point compared with only 18% of patients in the lowest systolic blood pressure quartile (systolic blood pressure <145 mm Hg) during the 4-year course of the study. In contrast, the baseline diastolic blood pressure weakly correlated with these renal outcomes ($P = .065$).

Perhaps even more importantly, the systolic blood pressure that was achieved during the course of this study was associated with the renal outcome in an even more dramatic manner than that reported for the baseline systolic pressure (Fig. 1B).[10] The best renal outcome was observed in patients who achieved a systolic blood pressure of less than 134 mm Hg. Only 17% of patients in this lowest quartile (63 of 379 patients) reached these renal end points during the course of follow-up evaluation. On the other hand, 38% of patients in the highest quartile with a systolic blood pressure of greater than 149 mm Hg reached renal end points.[10]

Thus, although the baseline systolic blood pressure was an independent predictor of renal outcome in this patient population, this relationship was lost when the achieved systolic blood pressure was taken into account. A decrease of 20 mm Hg in the achieved systolic blood pressure was associated with a 47% decrease in the risk for developing a renal end point. The average follow-up systolic blood pressure was shown to be correlated directly with the relative risk of a renal end point in the IDNT down to an achieved pressure of 130 mm Hg. There was a plateau in the renal outcomes of less than 130 mm Hg (Fig. 2A).[10] This point becomes relevant when one examines the association between the achieved systolic pressure



BP group:										
> 170	405	398	365	336	268	201	145	101	39	4
159-170	383	377	357	335	273	205	140	103	41	2
145-158	411	410	388	364	304	218	142	85	38	4
< 145	391	389	373	351	286	213	143	91	41	2



BP group:										
> 149	426	417	376	346	273	202	129	77	28	2
141-149	428	426	405	373	307	234	168	119	46	3
134-140	357	355	346	331	278	198	124	78	37	3
< 134	379	376	356	336	273	203	149	106	48	4

Figure 1. (A) Cumulative proportions of patients who reached a renal end point (doubling of baseline serum creatinine [SCr] or ESRD, defined as an SCr level of ≥6.0 mg/dL or renal replacement therapy) by quartile of baseline systolic blood pressure (SBP). The number of patients who were at risk for reaching a renal end point is tabulated for each period during the follow-up evaluation. (B) Cumulative proportions of patients who reached a renal end point (doubling of baseline SCr or ESRD, defined as an SCr level of ≥6.0 mg/dL or renal replacement therapy) by quartile of achieved SBP. The number of patients who were at risk for reaching a renal end point is tabulated for each period during the follow-up evaluation. Reproduced with permission from the J Am Soc Nephrol.[10]

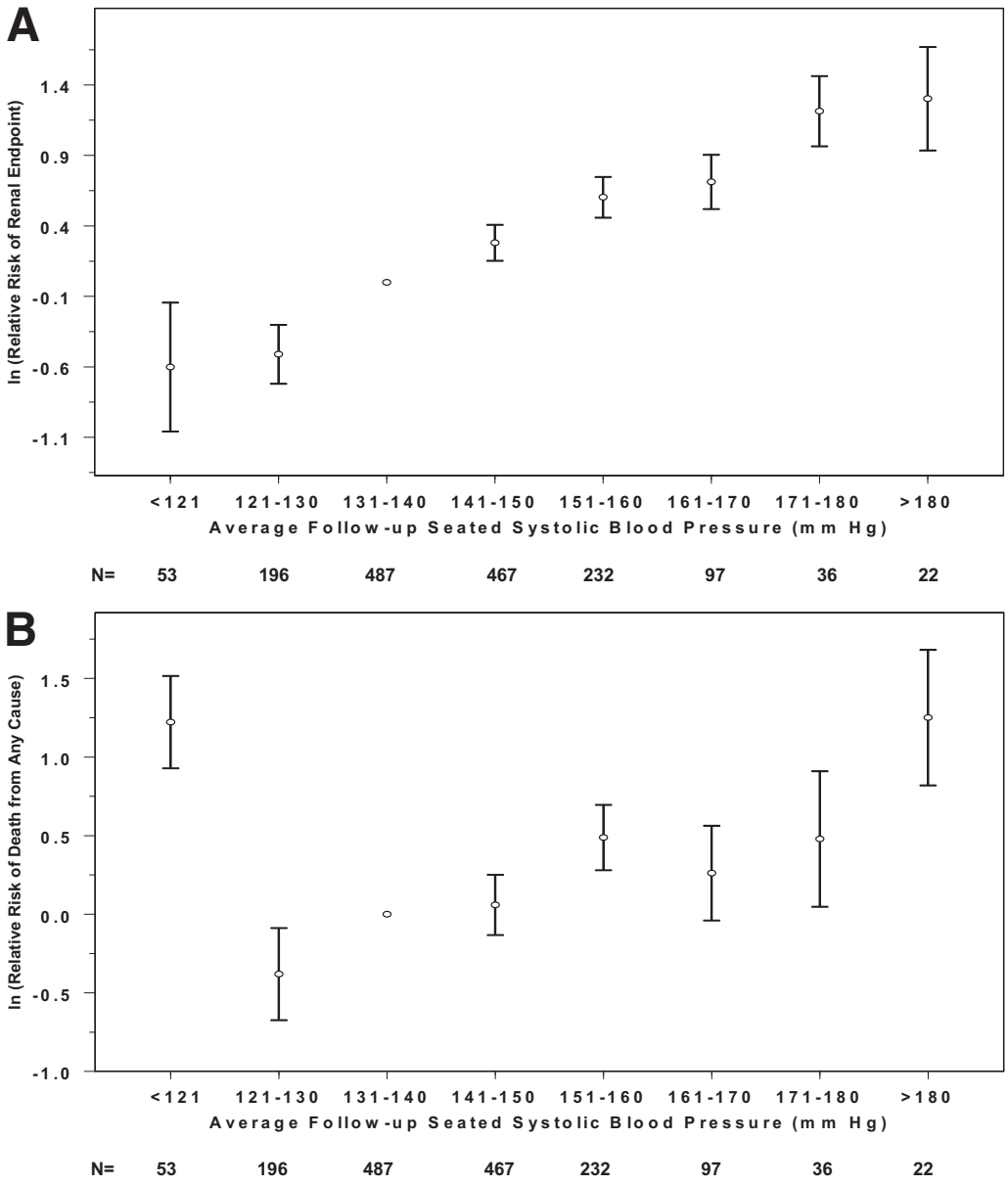


Figure 2. (A) Natural log of the relative risk for reaching a renal end point by level of achieved follow-up systolic blood pressure (SBP). The number of patients who were at risk for reaching a renal end point is tabulated for each level of achieved follow-up SBP. (B) Natural log of the relative risk for all-cause mortality by level of achieved follow-up SBP. The number of patients who were at risk for death by any cause is tabulated for each level of achieved follow-up SBP. Reproduced with permission from the J Am Soc Nephrol.[10]

and all-cause mortality (Fig. 2B)[10] among patients in the IDNT and this is discussed later.

CAN BLOOD PRESSURE CONTROL INVOLVE HAZARD

For almost 2 decades it has been suggested that the relationship between blood pressure control and clinical outcome is not a straight line, but rather has a graphic U- or J-shaped relationship. In 1988, Cruickshank et al[11] observed that death as a result of cardiovascular disease could be diminished by decreasing the blood pressure. However, these investigators noted that there was a definable nadir that could be seen with respect to the effectiveness of blood pressure decrease on cardiac mortality. Further decreasing the diastolic pressure to less than a critical value could thereafter be associated

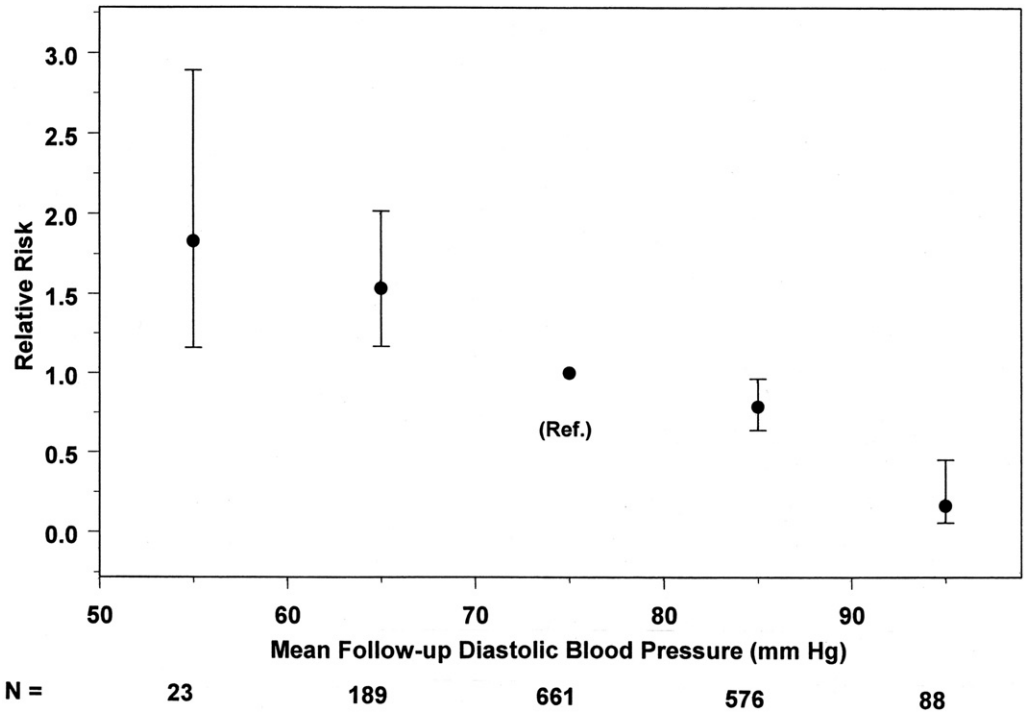


Figure 3. Relative risk of myocardial infarction by level of achieved diastolic blood pressure. The number of patients at risk for death for each level of blood pressure is tabulated at the bottom. Reproduced with permission from the J Am Soc Nephrol.[21]

with a subsequent increase in cardiac mortality. These observations were compatible with the consideration that low diastolic pressures could critically lower coronary perfusion because blood flow to the myocardium occurs during diastole.[12] On the basis of these observations, the concept of the J-curve was introduced.[13] Over the 20 years that have intervened since these reports, there has been a good deal of controversy regarding the existence of a J-curve. Some studies confirmed this concept, others did not.[14-17] However, recent observations do support the contention that a very low diastolic pressure is associated with an increase in adverse cardiac events (Fig. 3).[18,19]

Although underpowered for cardiovascular events and retrospective in the manner of analysis, the IDNT did provide the opportunity to study a specific, well-defined patient population that was of relevance to nephrologists.[10] In this study, the all-cause mortality decreased in a linear fashion relative to an achieved systolic blood pressure from 180 mm Hg to 120 mm Hg. However, patients with a follow-up systolic blood pressure of less than 120 mm Hg had a substantially higher mortality rate that was statistically significant ($P < .001$) (Fig. 2B). This observation appears to indicate a J-curve response in the population under study. Unfortunately, the nature of these observations are confounded by their retrospective nature. Insofar as patients were not randomized to achieve various blood pressure levels and relatively few patients in this study had a decrease in systolic blood pressure of less than 120 mm Hg, one must treat this apparent J-curve as being less than definitive. It is noteworthy that this J-curve phenomenon was evident in all 3 treatment groups and in patients with and without a history of cardiovascular disease at the time of entry into the trial.[10]

INDEPENDENT RENOPROTECTIVE EFFECT OF ARBS

One of the advantages of the IDNT was the ability to compare results achieved with ARB therapy as compared with a dihydropyridine calcium channel blocker or blood pressure management with other agents. When an observer examines the

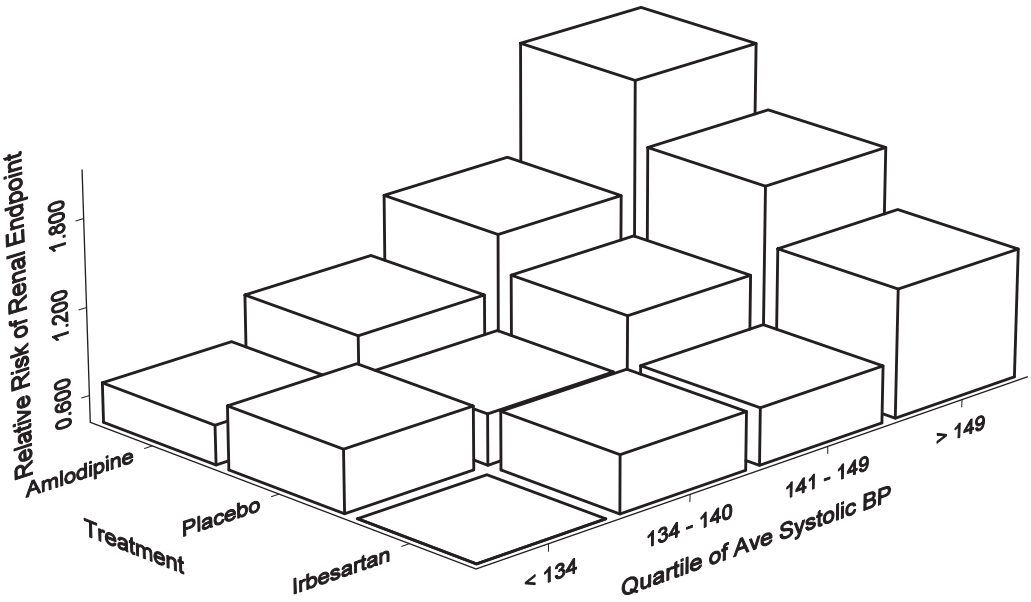


Figure 4. Simultaneous impact of quartile of achieved systolic blood pressure (BP) and treatment modality on the relative risk for reaching a renal end point (doubling of baseline serum creatinine level or ESRD, defined as a serum creatinine level of ≥6.0 mg/dL or renal replacement therapy). Reproduced with permission from the J Am Soc Nephrol.[10]

simultaneous impact of the achieved systolic blood pressure and the randomized treatment modality on the relative risk of reaching a renal end point it is apparent that, in addition to achieved systolic blood pressure, randomization to the ARB was associated independently with improved outcome (Fig. 4).[10] Patients randomized to the amlodipine group performed equally to those receiving placebo. This dihydropyridine calcium channel blocker increased neither renal nor cardiovascular risks.[8,20]

When the patient population in the IDNT was examined to determine whether the results of a specific cardiovascular event were more or less common in 1 of the 3 treatment groups, there appeared to be no difference when cardiovascular death, myocardial infarction, cerebral vascular accident, or cardiac revascularization were examined. Patients randomized to receive irbesartan did have a significant decrease in the requirement for hospitalization for congestive heart failure when compared with either the amlodipine ($P = .004$) or placebo ($P = .048$) groups.[9,10] Similar results were reported in the RENAAL study, which used losartan.[20,21] Although not statistically significant, fewer patients who received amlodipine during IDNT had strokes than those receiving irbesartan or placebo.

In the IDNT, as noted previously, the risk for cardiovascular mortality differed little among the 3 assigned treatment groups. However, there was a linear relationship between the achieved systolic blood pressure and the risk of cardiovascular mortality irrespective of the group assigned. The lower the systolic blood pressure, the lower the risk. Results that were similar to the IDNT also were observed in the RENAAL study.[22] In contrast, the relative risk of myocardial infarction, all-cause, or cardiovascular mortality was increased as the diastolic blood pressure decreased (Fig. 3). The relative risk of having a myocardial infarction during the IDNT was increased 61% for every 10–mm Hg decrease of the diastolic pressure ($P < .0001$).[21] This effect was independent of treatment assignment.

POTENTIAL DANGER OF EXCESSIVE DECREASE OF DIASTOLIC BLOOD PRESSURE

In a post hoc study that was designed to determine whether an aggressive decrease of the diastolic pressure could be associated with increased coronary events,[18,19] Messerli et al analyzed data from the International Verapamil Trandolapril Study and showed all-cause death and myocardial

infarction, but not stroke, increased with low diastolic pressures. The potential danger of excessively decreasing the diastolic pressure can occur easily while trying to control the systolic pressure (Fig. 3). Osher et al[23] force-titrated 257 hypertensive diabetic patients to achieve the blood pressure goal of less than 130/85 mm Hg as recommended by the Joint National Commission on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. They achieved the diastolic goal in 90% of patients and the systolic goal in 33%, numbers similar to those reported in the IDNT. The diastolic pressure was 70 mm Hg or less in 57% of patients. The attainment of a diastolic pressure of less than 70 mm Hg was more likely if the patient had a higher systolic pressure, a history of coronary artery disease, or was older.

EFFECT OF BLOOD PRESSURE MANAGEMENT UPON PROTEINURIA

A further consideration with respect to the treatment of hypertension in patients with diabetic nephropathy is the effect of blood pressure decreases on urine protein excretion and its relationship to outcome. A reduction in either systolic or diastolic blood pressure is associated with a reduction in proteinuria.[24] However, the antihypertensive agent used determines the magnitude of reduction of proteinuria as blood pressure decreases. In the IDNT, the magnitude of proteinuria reduction associated with blood pressure decreases in the irbesartan group was more pronounced than that seen in the amlodipine group after 1 year of treatment (16.3% versus 8.0% reduction in proteinuria for each 10% reduction of systolic pressure). For each 10% reduction in diastolic blood pressure, proteinuria reduction also was decreased more profoundly in the irbesartan group (13.7% versus 6.7% reduction in proteinuria for each 10% reduction).[24]

The decrease in proteinuria associated with blood pressure control takes on increased importance because there is growing evidence that proteinuria may be an independent modifiable risk factor for the prevention of progression of overt diabetic nephropathy.[25] ARBs and ACE inhibitors have been associated independently with a greater reduction in proteinuria when compared with other blood pressure lowering agents that do not act through the inhibition of the renin-angiotensin system. In the IDNT, proteinuria levels decreased on average 41% in the irbesartan group by 12 months as compared with 11% in the amlodipine group and 16% in the control group. Proteinuria reduction attributed to irbesartan has been calculated to account for approximately one third of the renoprotective effect that was observed in the IDNT.[24] These observations confirm previous studies that revealed an association between the severity of proteinuria and progression of nephropathy.[26-30]

LIMITATIONS OF META-ANALYSIS TECHNIQUES

Strong evidence from statistically valid clinical trials indicates that ACE inhibitors and ARBs effectively diminish the rate of progression of both type 1 and type 2 diabetic nephropathy.[8,9,26] Some confusion has resulted from the publication of faulty meta-analyses and post hoc secondary analyses in very large clinical trials that were not originally designed to detect renal events. Meta-analysis is an accepted methodology that can provide valuable information regarding therapeutic efficacy when properly powered large clinical trials have not been undertaken. It is incumbent on the investigator conducting a meta-analysis to be certain that a reasonable homogeneity be required of clinical trials that are to be included in the analysis. This has been referred to as a *face validity test*. The failure of a meta-analysis to use a face validity test can lead the investigator to risk conclusions that can appear egregiously nonsensical relative to existing evidence-based standards of care that have been derived from statistically powerful controlled clinical trials. Some meta-analyses that have attempted to explore the impact of renin-angiotensin system blockade in proteinuric renal diseases have failed to require studies that are to be included have similar patient populations, similar drug interventions, or similar predefined patient outcomes. Strippoli et al[31] reported the efficacy and safety of ACE inhibitors and ARBs in the treatment of diabetic nephropathy. These investigators were led to the flawed conclusion that ARB therapy proposed a potential danger to patients with

diabetic nephropathy because more cardiovascular events were recorded in trials using these agents when compared with trials using ACE inhibitors. They failed to take into account the possibility that their results could be explained by the fact that the majority of trials using ACE inhibitors were performed in patients with type 1 diabetic nephropathy, whose average age would be expected to be approximately 35 years, whereas the treatment trials using ARBs were performed in patients with type 2 diabetic nephropathy, whose average age would be expected to be approximately 60 years. It is not surprising that more cardiovascular events might occur in the older type 2 diabetes population independent of the therapeutic agent used. An examination of the number of cardiovascular complications and deaths that occurred in the placebo group in the trial of the ACE inhibitor captopril in type 1 diabetic nephropathy[26] showed that the likelihood of an event was markedly lower than the cardiovascular events and mortality that occurred in the placebo group in the IDNT.[8] Hence, the difference in cardiovascular events and mortality was driven by the population studied and not the therapeutic agent that was used. This meta-analysis by Strippoli et al[31,32] would not pass the face validity test. In fact, the flawed conclusions are misleading with respect to good clinical practice in the diabetic nephropathy patient population. The 2 large trials that investigated renoprotection in diabetic nephropathy both showed ARBs to be the treatment of choice.[8,9] The pros and cons of whether ARB therapy can indeed increase the risk of myocardial infarction has been debated and, in summary, there seems to be little current evidence that this potential danger actually exists.[33,34]

Another misleading meta-analysis that failed the face validity test was reported by Casas et al,[35] which concluded that ACE inhibitors and ARBs were no more effective than other antihypertensive drugs with respect to renoprotection. Unfortunately, approximately 85% of the patients in this meta-analysis derived from one study, the Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT) trial, which excluded patients with severe renal disease.[36] This trial was designed to determine which antihypertensive agent best prevented mortality and cardiovascular events. End-stage renal disease was not an expected outcome in the ALLHAT trial. Proteinuria was not measured in patients in the ALLHAT trial. There was, in fact, no similarity between the patient population in the ALLHAT trial when compared with the existing statistically valid diabetic nephropathy trials in the literature. Serious questions have been raised regarding the validity of the Casas et al report, which was primarily an analysis of the ALLHAT patient population rather than a meta-analysis.[37]

The ALLHAT trial itself has been the subject of considerable controversy from many points of view. A secondary analysis by Rahman et al[38] concluded that hypertensive patients with a reduced glomerular filtration rate who were entered into the ALLHAT trial were not protected from the development of ESRD by the use of lisinopril (Zestril; AstraZeneca, Wilmington DE) when the group receiving this ACE inhibitor was compared with patients receiving amlodipine or chlorthalidone.

The ALLHAT trial involved more than 33,000 patients, 36% of whom had diabetes. As noted previously, the validity of examining the patient population entered into the ALLHAT trial in a meta-analysis of diabetic nephropathy trials has been questioned. However, an even more important question was posed by Hollenberg,[39] who requested data from the investigators regarding the dose of medications that actually had been achieved in the ALLHAT trial. The response of the ALLHAT investigators revealed a serious weakness in the study.[40] In fact, of 7,814 patients randomized to the lisinopril group, 22% were not taking the drug at the 1-year point and a further 28% were receiving the lowest dose of lisinopril (ie, 10 mg/d). Hence, 50% of patients in the ACE inhibitor group were either not receiving the medication or were receiving a dose so low that renoprotection might not be expected. At year 3, there were 31.5% randomized to the lisinopril group who were not taking the drug and 20% were receiving 10 mg/d, and at year 5 there were 38.5% not taking the drug, and 14% were on 10 mg/d. Similar but somewhat lower percentages of patients in the chlorthalidone and amlodip-

ine groups were not taking their medication. The conduct of a valid clinical trial depends on the assumption that the majority of patients will take the coded medication. Perhaps an intent-to-treat analysis was valid in the determination of the primary outcome of the ALLHAT trial, despite the number of patients who were not taking their coded study drug. However, a valid post hoc study with the aim of determining the renoprotective efficacy of an ACE inhibitor should require that patients are indeed receiving an adequate dose of the prescribed drug. An intent-to-treat analysis would not be valid in this post hoc study because an excessive number of patients were not taking the medication to which they had been randomized. It is difficult to imagine investigators concluding that ACE inhibition is not renoprotective in hypertensive patients with a reduced glomerular filtration rate when half the patients were either not taking the drug or were taking a dose that many would consider inadequate for renoprotection.[38] It is equally difficult to imagine that these ALLHAT data would be included in a meta-analysis that proposed to determine the renoprotective effect of ACE inhibitors.[35]

Another controversy regarding the validity of the primary conclusion was precipitated when the Heart Outcomes Prevention Evaluation (HOPE) study was published. This was a large cardiovascular study that randomized a total of 9,297 patients older than age 55 to either ramipril (10 mg/d) or matching placebo for 5 years, with the primary goal of determining an alteration in cardiovascular event risk. The goal of the study was to determine the likelihood of cardiovascular events in a high-risk population, which certainly would be relevant to patients with diabetic nephropathy. This study concluded that ramipril therapy was associated with a 22% reduction in the composite primary outcome of myocardial infarction, stroke, or death from cardiovascular causes ($P < .001$). These results often are quoted when the question arises of whether to use ACE inhibitors rather than evidence-based standard ARB therapy in type 2 diabetic nephropathy. One of the potentially confusing factors generally overlooked in the HOPE trial was the fact that patients received their study medication at bedtime. Hence, the morning clinic blood pressure difference was only 3 mm Hg systolic and 2 mm Hg diastolic lower in the ramipril group. However, a small substudy of HOPE patients using 24-hour ambulatory blood pressure measurements revealed that overall differences of 11 mm Hg systolic and 4 mm Hg diastolic in favor of ramipril were recorded.[41,42] It is therefore suspected that these substantial differences in achieved blood pressure would be more likely to account for differences in the cardiovascular outcomes reported for the HOPE study rather than any specific cardioprotective effect of the ACE inhibitor. This information weakens the argument that ACE inhibitors should be used preferentially to ARBs in patients with type 2 diabetic nephropathy, who are a population at increased risk for cardiovascular events.

ALBUMINURIA AND CARDIOVASCULAR RISK

Therapeutic measures that decrease systemic blood pressure and decrease albuminuria are associated not only with renoprotection, but also appear to be cardioprotective in patients with type 2 diabetic nephropathy. The RENAAL study was a prospective, double-blinded, randomized trial of 1,513 patients with type 2 diabetes and nephropathy with a protocol similar to that used in the IDNT.[9] A major difference was the randomization to only 2 groups, 1 group receiving the ARB losartan and the other receiving placebo. Calcium channel–blocking agents were allowed in both arms of the study. The results of the RENAAL study duplicated those of the IDNT with respect to renal outcomes.[8,9] These investigators performed a secondary analysis regarding the impact of decreasing albuminuria on cardiovascular end points.[25,43] They reported that albuminuria was the strongest predictor of cardiovascular outcome in that study. There was an 18% reduction in cardiovascular risk for every 50% reduction in albuminuria, and a 27% reduction in heart failure risk for every 50% reduction in albuminuria. These results lend further support to the use of ARBs and blood pressure management in this patient population. Similar results have been reported in a different patient population

in the Losartan Intervention for Endpoint Reduction of Hypertension Study (LIFE) trial.[44]

OTHER STRATEGIES FOR BLOCKING THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

There is growing evidence that several other strategies using agents that inhibit the renin-angiotensin-aldosterone system appear to have independent blood pressure decreasing and renoprotective characteristics. Definitive studies in diabetic nephropathy have yet to be performed. In most of these studies the primary end point has been the determination of diminished proteinuria. Long-term studies to document significant retardation of the progressive loss of renal function or prevention of ESRD are awaited. High doses of ACE inhibitors or ARBs that are in excess of the usual range approved by regulatory agencies such as the Food and Drug Administration have been used to decrease proteinuria to levels that are less than those achieved at approved doses and also concomitantly decrease systemic blood pressure.[45] It has been difficult to discern whether these results can be attributed to specific proteinuria decreasing effects, more effective antihypertensive effects, or other mechanisms promoting renoprotection. The combination of ACE inhibitors and ARBs together in their usual therapeutic doses also have led to reports of decreasing of proteinuria levels beyond that shown by either of these agents alone.[46-54] Once again, conclusions often are confounded by the inability to equalize blood pressure control in the randomized groups. The aldosterone-blocking agents spironolactone[55] and eplerenone[56] have been administered in small trials to patients with proteinuric renal diseases and have effectively decreased the urine protein excretion rate. The decreased protein excretion rate appears to be independent of the antihypertensive effect of these aldosterone-blocking drugs. Because decreased proteinuria is associated with an improved renal outcome, these therapeutic approaches may be promising in terms of renoprotection. The one potential drawback of all of these therapies, particularly in patients with diabetic nephropathy who may have hyporeninemic hypoaldosteronism and a decreasing glomerular filtration rate, is the potential for serious hyperkalemia. Jacobsen et al[49] reported that dual ACE inhibitor/ARB blockade was associated with hyperkalemia in 3%, increased creatinine levels in 8%, and hypotension in 5% of patients so treated. However, even when hyperkalemia tends to be relatively mild and somewhat unusual, it is best to remember that the first evidence of severe hyperkalemia can be sudden death. A more carefully controlled experience to ascertain the risk-benefit of these various approaches is required before a recommendation can be made for their routine clinical use.

The recommendation that agents that block the renin-angiotensin system should be administered for renoprotection is not empiric. The remarkable similarity of the primary results regarding the independent renoprotective effect of ARBs achieved in IDNT and RENAAL make the likelihood that the findings are random infinitesimally small. ARBs and ACE inhibitors should be the first-line therapy in patients who have overt diabetic nephropathy. In addition to blockade of the renin-angiotensin system, blood pressure control, particularly the systolic pressure, clearly is associated with improved renal and cardiovascular outcomes in this complicated patient population.[7,10,22,57] The treatment of systolic blood pressure to achieve a goal of 130 mm Hg, in accord with current guidelines, may be an arduous task. The clinician should be aware that in this patient population, decreasing the systolic pressure to less than 120 mm Hg may be associated with an increased risk of cardiovascular events without improving the renoprotective outcome achieved at 130 mm Hg.[10,57] Decreasing the diastolic pressure to the current guideline of 80 mm Hg is more readily attainable in this patient population. However, increased adverse cardiac events can occur at lower diastolic blood pressures.[18,21]

It is important to realize that although the blood pressure may be poorly controlled for many years before a patient receives proper medical attention, the achievement of better control of the systolic blood pressure is associated with improved renal and mortality outcomes.[10] Despite the concern of a J-curve at systolic pressures less than 120 mm Hg and increased cardiac events at excessively decreased diastolic pressures, a beneficial result can be anticipated through careful blood pressure management by using an ARB

or ACE inhibitor in a therapeutic management approach that is likely to require at least 3 antihypertensive agents.

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