The Role of Combination Antihypertensive Therapy and the Progression of Renal Disease Hypertension
Looking Toward the Next Millennium
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The importance of the level to which blood pressure is reduced becomes increasingly important when one considers preservation of renal function. It is clear that three major subsets of patients emerge as requiring levels of blood pressure control of < 130/85 mm Hg to preserve renal function. Such individuals include black Americans, those with diabetic nephropathy, and those with renal insufficiency or ≥ 1 g of proteinuria. It is clearly important to achieve such levels of blood pressure control in these high-risk individuals. It is also clear that single-agent therapy will never achieve these levels of blood pressure control. Therefore, multiple antihypertensive agents will be required to achieve such a goal. With increasing numbers of medications, however, there is also, unfortunately, a decrease in compliance. Therefore, fixed-dose combinations emerge as playing a major part both in achieving a level of blood pressure control as well as maintaining levels of compliance. Certain types of angiotensin-converting enzyme inhibitors, as well as calcium channel antagonist combinations, however, appear to have better overall effects than others do. These and related data are reviewed in this paper. Am J Hypertens 1998;11:158S–162S © 1998 American Journal of Hypertension, Ltd.

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Diabetic renal disease is by far the largest-growing problem in the US. This is related to the significant increased incidence of diabetes in the U.S., especially in older individuals.1,2 With the increased prevalence of non–insulin-dependent diabetes (NIDDM), the propensity to develop renal dysfunction also increases. It is estimated that 35% to 40% of people with NIDDM will develop nephropathy.3 Other than blood sugar control the only other factor that has been shown to be of importance in slowing the progression of NIDDM-associated nephropathy is blood pressure reduction.3 Moreover, there are certain high-risk groups that require greater-than-recommended lowering of arterial pressure to achieve comparable preservation of renal function.

To achieve appropriate blood pressure control, especially to the newly recommended levels, single-agent therapy will be inadequate. Moreover, as the numbers of antihypertensive agents are increased, compliance with medication tends to fall. Hence, fixed-dose combinations of various medications may serve to both enhance blood pressure reduction and maintain compliance. These and related issues will be discussed.

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LEVEL OF BLOOD PRESSURE REDUCTION

The timing of therapeutic intervention for hypertension in these patients has been widely discussed. The presence of microalbuminuria is a defined point for initiation of therapy but may be too late. Moreover, there are cases where patients with microalbuminuria and NIDDM progressed to renal failure without further increases in albuminuria. Thus, blood pressure should be an additional surrogate marker to detect disease presence and progression.

A recent consensus report by the High Blood Pressure Education Program of the National Institutes of Health suggests that diabetic patients with a blood pressure of $130/85$ mm Hg should be receiving antihypertensive therapy. This panel of nephrologists and cardiologists concluded that the goal of therapy should be to reduce the blood pressure to levels substantially <$130/85$ mm Hg. This concept is predicated on an analysis of retrospective data from large clinical trials of patients with diabetic nephropathy. It is clear from this analysis that patients with diabetic nephropathy garner the greatest benefit for preservation of renal function by having systolic pressures of $\leq 130$ and diastolic pressures of $\leq 85$ mm Hg.

Other groups at risk include black Americans and patients with renal insufficiency who have greater than 1 g proteinuria. These observations were borne out from a post-hoc analysis of the modification of dietary protein and renal disease (MDRD) trial, which examined the decline in glomerular filtration rate (GFR) over a period of 4 years. Figure 1 illustrates the effects of blood pressure control on progression of renal disease in these high-risk groups. Glomerular filtration rate was unaffected by mean arterial pressure in goals with protein levels less than 1 g per day. However, those with proteinuria in excess of 1 g per day showed a rapid drop in GFR as mean arterial pressures exceeded 98 mm Hg. When black Americans were examined separately it was found that renal decline began at lower levels of mean arterial pressure, i.e., 92 mm Hg. Therefore, in these high-risk groups blood pressure intervention may have to be applied at lower pressure levels to optimally preserve renal function.

Data from a randomized, double-blind, placebo-controlled study also support this concept. In a 1993 study by the Collaborative Study Group, the effects of different antihypertensive therapies on progression to end-stage renal disease (ESRD) in diabetic patients was examined. Those who were administered an angiotensin-converting enzyme (ACE) inhibitor as part of their antihypertensive regimen demonstrated a delay in the development of ESRD compared with those who received a regimen without an ACE inhibitor. The level of blood pressure reduction was similar when those with and without ACE inhibitors were compared. However, when a post-hoc analysis examined patients with the greatest degree of renal insufficiency and proteinuria, only those who had reductions in proteinuria had good renal outcomes. It should be noted, however, that there was a 4-mm Hg difference in blood pressures between these two groups, a difference that was statistically significant. Thus, the level of blood pressure control seems to play a role even when ACE inhibitors are used. Therefore, the benefits of antihypertensive treatment are not maximized in diabetic patients if proteinuria as well as blood pressure is not reduced.

Achieving these desired levels of blood pressure control can never be achieved by single-agent therapy. Generally two or three drugs are needed to achieve a level of blood pressure reduction of $\leq 130/85$ mm Hg. Moreover, based on the recent NHANES III database, physicians and patients are doing a poor job of lowering blood pressure even to levels of 140/90 mm Hg. This is evidenced by the fact that only 27% of the population has achieved blood pressures levels of $\leq 140/90$ mm Hg. One of the main reasons for this
failure to achieve blood pressure control centers around medication compliance and side-effect profiles. Fixed-dose combinations of an ACE inhibitor with a calcium channel antagonist (CCA) are associated with a much lower side-effect profile.8 Thus, fixed-dose combinations are an ideal way to improve compliance by reducing the number of pills that are taken by patients as well as the side effects associated with individual medications.

**RENA L EFFECTS**

The earliest hemodynamic changes in the kidney of a diabetic patient are increased mesangial expansion and increased glomerular capillary pressure, both of which make this without a clinical correlate.10 Mesangial matrix expansion is caused predominantly by an increase in matrix proteins secondary to elevated blood glucose levels and aggravated by increased blood pressures. Once glomerular permeability increases, microalbuminuria becomes evident.

Studies have found that ACE inhibitors and certain classes of CCA can mitigate this expansion of matrix proteins.10–13 Table 1 summarizes the renal hemodynamic effects of both ACE inhibitors and CCA in the diabetic patient. It is clear from Table 1 that a combination of a nondihydropyridine CCA and an ACE inhibitor may be predicted to have relatively greater antiproteinuric effects than a dihydropyridine CCA with an ACE inhibitor.

Although ACE inhibitors generally have positive renal hemodynamic effects, the CCA, in general, do not lower intraglomerular pressure. Moreover, CCA have other effects that account for differences in the renal outcome (Table 1). Griffin and colleagues noted that when nifedipine was compared with enalapril with regard to protection against glomerular scarring nifedipine, in spite of similar levels of blood pressure reduction, failed to protect against glomerular scarring.14 Nifedipine was associated with a loss of renal autoregulation. This observation, coupled with data from other studies that demonstrate a failure of both long- and short-acting dihydropyridine calcium channel antagonist (DHPCCA) to prevent glomerulosclerosis and reduce proteinuria, indicate that they are not useful in preventing renal disease.14–18

One key study examined the differences in antihypertensive effects and glomerular protection in diabetic animals treated with diltiazem, verapamil, felodipine, and amlodipine.16 Blood pressure was controlled with verapamil, felodipine, and amlodipine only. However, a statistically significant reduction in proteinuria was observed only with verapamil and not with any of the dihydropyridines. Moreover, there were reductions in proteinuria observed even in the diltiazem group, where blood pressure was not reduced. Thus, these data, coupled with two recent observations from long-term clinical trials utilizing DHPCCA, ie, the Melbourne Diabetes Group and the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) Trial, further corroborate the fact that DHPCCA are now beneficial to the kidney in spite of blood pressure reduction. In the Melbourne Diabetes Study at 4-year follow-up, the rate of decline in GFR was highest in the nifedipine group with no significant reduction in proteinuria among insulin-dependent diabetic patients.19 In the PRAISE Trial, more than twice as many people randomized to amlodipine had worsening of renal function in spite of a reduction in cardiac events among these heart failure patients.20

**COMBINATION THERAPY**

The role of combination therapy with an ACE inhibitor and a CCA has been extensively examined with respect to renal protection. One of the earliest studies was done by Carmines and Navar, who studied the effects of pretreatment with captopril on afferent and efferent arterioles.21 The authors then added nonhypotensive doses of verapamil or diltiazem. At the doses added neither blood pressure nor renal blood
Moreover, the combination of a nondihydropyridine to a greater extent than either agent alone. While providing the ability to lower blood pressure, it yields an effect similar to that of an ACE inhibitor with a dihydropyridine calcium antagonist. The study randomized the animals to either no therapy, single-agent therapy with low doses of either verapamil or trandolapril, or a fixed-dose combination of the two. Blood pressure was purposely not reduced, with systolic blood pressures of between 255 and 275 mm Hg. At 11 weeks, verapamil and trandolapril both reduced proteinuria but the combination had significantly greater effects on proteinuria reduction compared with either alone. More importantly, single agents produced less scarring than was seen in the control group but the difference was not significant; combination therapy prevented scarring in these animals.

Another study examined the effects of amlodipine, 50 mg/L, and benazapril, 50 mg/L, alone and combined (25 mg/L each) in a rat remnant kidney model. After a period of 2 months our three groups of animals had similar levels of blood pressure reduction as measured by 24-h blood pressure monitoring. Proteinuria was reduced by benazapril and fixed-dose combination to approximately equivalent levels whereas proteinuria was increased in the animal receiving amlodipine alone. With regard to glomerular scarring benazapril and combined therapy had a similar protective effect whereas amlodipine alone failed to reduce the scarring.

In yet another study the effects of either trandolapril or verapamil alone versus their fixed-dose combination were examined on proteinuria changes in patients with NIDDM nephropathy. After 1 year both systolic and diastolic pressures were adequately reduced in all three groups. However, whereas trandolapril and verapamil reduced proteinuria 33% and 27%, respectively, over the 1-year period, the combination of lower doses of the two agents resulted in a significantly greater reduction, 62%, in proteinuria. Interestingly, no significant change in glomerular filtration rate or renal blood flow was observed in these patients.

**DISCUSSION**

To date there are very few well-controlled studies evaluating the effects of combination therapy on progression of renal disease. It is apparent from the available data, however, that a combination of an ACE inhibitor with a dihydropyridine calcium antagonist yields an effect similar to that of an ACE inhibitor alone while providing the ability to lower blood pressure to a greater extent than either agent alone. Moreover, the combination of a nondihydropyridine with an ACE inhibitor not only provides greater utility in lowering blood pressure but has the additive benefit of bringing proteinuria to levels greater than that seen with a dihydropyridine/ACE inhibitor combination.

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