The Effect of Blood Pressure Reduction on End Stage Renal Disease

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In the past 20 years, clinicians have clearly demonstrated that antihypertensive therapy is very effective in reducing the incidence of myocardial infarction and stroke. However, little is known about the effects of blood pressure reduction on end stage renal disease (ESRD). Data from major clinical studies has clearly shown that patients with hypertension have an increased risk of developing ESRD. Black men and women with hypertension are at the greatest risk; however, the incidence of ESRD is increasing in all racial groups. Because patients with hypertensive ESRD often require dialysis, the cost of treating this increasing common disorder has the potential to deplete the Medicare system. The primary effect of blood pressure reduction in patients with ESRD has not been adequately addressed in any trial that has been completed to date. Results from some studies suggest that blood pressure reduction may improve renal function and that angiotensin converting enzyme inhibitors and calcium channel blockers may have renoprotective effects.

Currently in progress are two large scale clinical trials that may provide more information on the effects of antihypertensive therapy on preventing ESRD in hypertensive patients. These are the African American Study of Kidney Disease and Hypertension (AASK), and a substudy of the Hypertension Optimal Treatment (HOT) Study. Data from the HOT study is expected to be available 5 years prior to that of the ASK Study, which is expected to be completed by the year 2002. Am J Hypertens 1996; 9: 605–645

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A n important unresolved issue in the treatment of hypertension is the effect of blood pressure reduction on end stage renal disease (ESRD). Currently, there is little information available on the mechanisms through which hypertension leads to ESRD, or the effects of antihypertensive therapy on renal function. The objective of this discussion is to provide a general overview of what is currently known about hypertensive ESRD and the steps that are being taken to expand the knowledge base of this vitally important subject.

ESRD is a major consequence of chronic hypertension. However, large clinical trials for the treatment of hypertension have focused mainly on the effects of antihypertensive therapy on the prevention of stroke and myocardial infarctions, with little attention given to the effects of blood pressure reduction on renal function. Over the past two decades, clinicians have made tremendous strides in controlling hypertension and in reducing the incidence of coronary heart disease and stroke in hypertensive patients. However, over this same period of time, the incidence of hypertensive ESRD has actually increased (Figure 1).

The increased risk of ESRD is clearly demonstrated...
by data from the Multiple Risk Factor Intervention Trial (MRFIT). A participant with a diastolic blood pressure of 120 mm Hg was 30-times more likely to develop ESRD than was a participant with diastolic blood pressure of 70 mm Hg. A similar correlation was seen for systolic blood pressure. Furthermore, a racial analysis of the 23,000 blacks and over 300,000 whites in the MRFIT Screened Study revealed that blacks are three times more likely to develop ESRD than are their age- and sex-matched white counterparts with hypertension. Furthermore, the incidence of ESRD among blacks was much higher at every level of blood pressure.

The United States Renal and Data Registry confirms that ESRD occurs at a relatively young age in black men and women. In the white population, ESRD usually occurs in the fifth or sixth decade of life. However, it is not uncommon for this disease to develop in blacks under the age of 35. In fact, blacks between the ages of 20 to 35 have almost a 18-fold increase in ESRD when compared to whites, although the reason for this is unknown.

Hypertension is disproportionately the etiology for ESRD in blacks, while diabetes mellitus continues to be the most frequent cause of ESRD. When etiologies are examined among the various racial groups, the primary cause of ESRD is hypertension in black patients, diabetes mellitus in Native Americans, and a slightly higher trend in glomerular nephrology in Asian-Americans (Figure 2).

The desperate impact of ESRD on blacks is more evident when it is considered that although blacks make up only 12% of the US population, they account for up to 31% of patients on dialysis (Figure 3). Dialysis is an extremely expensive procedure with estimated costs about $9 billion a year in the United States. Because the incidence of ESRD is increasing in all racial groups, the cost of dialysis has the potential to threaten the solvency of the Medicare system.

Beyond the monetary issue, there is a human cost. To understand this, consider that the average 49-year-old can expect to live another 30 years. However, if the 49-year old is a man and is unfortunate enough to develop prostate cancer, his life expectancy is cut in half to 15 years. If the 49-year old develops lung cancer instead, life expectancy is drastically reduced to <5 years. Patients with ESRD not only have markedly reduced survival (5 to 7 years), but their quality of life is drastically affected by their need for dialysis.

The key questions, then, are these: What are the mechanisms whereby hypertension causes ESRD, and why is there a predilection for blacks? Does antihypertensive therapy actually protect against ESRD? If antihypertensive agents do have renoprotective properties, what is the optimal level to which blood pressure should be lowered?

### PREVIOUS CLINICAL INVESTIGATIONS

The primary effect of lowering blood pressure on renal function has not been adequately addressed in any clinical trial completed to date. However, data from several important clinical investigations have provided some insights into the renoprotective effects of antihypertensive therapy on the prognosis of renal insufficiency.

The Multiple Risk Factor Intervention Trial (MRFIT) An analysis of the over 5,000 blacks versus white participants suggest that similar strategies for reducing blood pressure may have dissimilar effects on the progression of renal insufficiency. Renal function (serum creatinine levels were the marker of renal function), declined five times faster in blacks than in whites over the period of follow-up during the study. These findings suggest that blood pressure reduction improved renal function in whites but did not in blacks.

However, further analysis of the MRFIT data has led some investigators to question whether antihypertensive therapy had any significant beneficial effect on renal function in any racial group. Over the course of 6 years of therapy, creatinine levels decreased somewhat in white patients, but at the end of this period these levels had virtually returned to baseline (Table 1). Black patients started off with higher levels of creatinine and had a continuous rise over the same period.
of time. However, the difference in creatinine levels between blacks and white was very minor, despite the fact that most patients were controlled to approximately equal levels of blood pressure.

These results suggest that blood pressure reduction does not improve renal function in any racial group. However, it is important to stress that MRFIT was not designed to study renal function and investigators should use caution when trying to use data from this study to draw definitive conclusions about the effect of antihypertensive therapy on this important parameter.

Medical Diet and Renal Study (MDRD) The best currently available data as to the effect of blood pressure control on the progression of renal insufficiency is from the Medical Diet and Renal Study (MDRD), which included 53 black patients and 500 white patients. The marker of renal function was determined by glomerular filtration rate (GFR) via iothalamate clearance. Investigators found that over a 3-year period, the loss or decline in GFR was 18 mL/min in blacks compared to 11 mL/min in whites. Despite similar levels of BP control and identical medical therapy, blacks had a significantly greater loss in renal function when compared to their white counterparts (Table 2).

Although the primary hypothesis of the MDRD Study regarded the effect of diet on renal function, there was a blood pressure arm in the study. Diastolic blood pressure was controlled to two levels; the first was to a mean arterial pressure (MAP) of 102 to 107 mm Hg and the other was a MAP of 92 mm Hg. The results after 3 years of follow-up showed that the lower blood pressure group had a slower decline in GFR than did the usual blood pressure control group (Table 2). These findings provided a hint that blood pressure reduction may actually improve renal function.

CLINICAL TRIALS WITH ANTIHYPERTENSIVE AGENTS POSSESSING PUTATIVE RENOPROTECTIVE PROPERTIES

The concept of a renoprotective antihypertensive regimen (ie, the selective ability of specific antihypertensive agents to reverse, restitute, or prevent the pathophysiologic progression of hypertensive renal disease when compared to an equally effective alternative antihypertensive regimen) offers a potentially useful therapeutic strategy to ameliorate hypertensive renal disease. This consideration is particularly relevant to blacks, in whom effective control of systemic hypertension may not translate into protection from renal parenchymal disease. A substantial body of evidence indicates that two main classes of pharmacological agents, angiotensin converting enzyme inhibitors (ACEIs) and some calcium channel blockers (CCBs), may have renoprotective effectiveness under experimental conditions.7,8 ACEIs have been demonstrated to decrease post-glomerular capillary resistance and normalize glomerular capillary pressure and thus protect the kidney from the development of arteriolar nephrosclerosis.8,9 An additional non-renin-mediated renoprotective effect of ACEIs may be the destruction of bradykinin and cellular vasodilatory prostaglandin biosynthesis.10 Experimental evidence also indicates that CCBs may protect the glomerular microcirculation from hypertensive injury by way of afferent arteriolar dilatation and reduction of glomerular capillary pressure.11,12 The experimental evidence of the renoprotective action of ACEIs and CCBs is compelling.

TABLE 1. SUMMARY STATEMENT OF THE RESULTS OF THE MULTIPLE RISK FACTOR INTERVENTION TRIAL—6 YEAR FOLLOW-UP

| 463 blacks v 5,061 nonblacks |
| Blood pressure control was the same in both groups |
| Renal function declined 5x faster in blacks |
| Blacks: 1/Cr = −0.0090 ± 0.0013 |
| Nonblacks: 1/Cr = 0.0018 ± 0.0004 |
| Good BP control (diastolic BP < 95 mm Hg) |
| Improved renal function in whites |
| Did not help blacks |

Cr, creatinine; BP, blood pressure. Summarized from Walker et al.1

TABLE 2. SUMMARY STATEMENTS OF THE RESULTS OF THE MDRD STUDY

| 53 Blacks v 532 Nonblacks |
| Renal function loss |
| Faster in blacks (18 mL/min/3 years) than in whites (11 mL/min/3 years) |
| Lower than usual BP control may help preserve renal function |
| Low BP lost 10 mL/min/3 years |
| Usual BP lost 25 mL/min/3 years |
| Not statistically significant (too few patients) |

The protective effects of ACEIs and CCBs has been supported by several clinical trials that have demonstrated a reversal, stabilization, or slowing of the progression of renal function in diverse hypertensive patient populations with varying degrees of renal insufficiency.\textsuperscript{11,13-18} Unfortunately, most of these clinical studies suffer from one or more methodological deficiencies relating to inadequate sample size, inappropriate patient selection criteria, relatively short follow-up period, defective control group or lack of control, and the use of suboptimal measures of renal function.\textsuperscript{18} An important limitation of the available clinical studies is the inclusion of few or no blacks, the subgroup with the highest incidence of hypertensive renal parenchymal disease. Bauer et al\textsuperscript{19} reported a clinical trial of 23 patients with one of the longest follow-up periods. After 3 years of follow-up, patients with essential hypertension and moderately impaired renal function (inulin clearance <80 mL/min) treated with enalapril showed a 33\% higher inulin clearance compared to placebo. Sundera\textsuperscript{20} demonstrated a mean 62\% improvement in GFR at 16 months in a group of 18 patients with pretreatment GFR =80 mL/min/1.73 m\textsuperscript{2}. There, however, remains a clear and urgent need for clinical trials to delineate the possible renoprotective properties of antihypertensive medications.

The most compelling data from studies in humans that show that there are specific renal protective properties of certain antihypertensive medications is provided by a study by Lewis et al that provides the most complete human data on the effects of antihypertensive effects on renal function.\textsuperscript{21} This data indicates that certain antihypertensive agents do indeed have specific renal protective effects. When captopril was used to treat blood pressure in patients with type 1 diabetes mellitus, it was shown to significantly reduce the doubling of creatinine when compared to the placebo group. Interestingly, captopril had no effect on subjects with normal creatinine, but the effect was appreciated in patients with impaired renal function. Thus, this study showed that type 1 diabetics with renal insufficiency can reduce the likelihood of doubling creatinine levels with the drug captopril.

**CURRENT CLINICAL INVESTIGATIONS**

There are important limitations in each of the trials that have been discussed thus far. One of the more striking limitations is the fact that black patients, who have the highest incidence of ESRD, are underrepresented in these studies. There was also an inadequate comparison of the effects of different classes of drugs on renal function. Last but certainly not least, investigators are still not sure which blood pressure level to aim for in hypertensive patients with renal insufficiency. In an attempt to address these crucial concerns, investigators have launched two large scale clinical trials, both of which are currently in progress.

The African American Study of Kidney Disease and Hypertension (AASK). The AASK Study, is a long-term multicentered, prospective, double-blinded, randomized trial that is sponsored by the National Institute of Diabetes, Digestive and Kidney Disease (Bethesda, MD). The expected duration of the study is 4 to 7 years.

The AASK Study has a three-by-two factorial design: two levels of blood pressure control, and three drug treatment arms. The two levels of blood pressure are a MAP of <92 mm Hg, and a MAP between 102 and 107 mm Hg. Patients have been randomized to a specific target blood pressure level, and will be randomized to a medication limb with subsequent drug therapy with a \( \beta \)-blocker, an ACEI, or a calcium channel blocker.

The purpose of the AASK Study is to observe the rate of decline in glomerular filtration, as measured by inhaledate clearance, within each of the drug groups, and as a function of BP decline in the two different blood pressure groups. The second aim is a time event analysis to assess the rate of severe reduction in GFR (50\% or loss of 25 mL/min), ESRD, dialysis, transplantation, and death. The AASK Study began in March 1995 and is expected to be completed by the year 2002.

The Hypertension Optimal Treatment Study (HOT) The HOT Study is an ongoing international trial that was designed to determine the target level of diastolic blood pressure that clinicians should aim for to minimize the risk of cardiovascular disease and death in patients with hypertension. There is a substudy of the HOT Study that has been designed to compare the effects of blood pressure reduction on renal function. In contrast to the AASK Study, this substudy will assess the effect of blood pressure control in both black and white patients. The focus will be on the effect of blood pressure reduction, rather than the effects of any specific class of antihypertensive.

In the HOT renal substudy, patients will have measurements of creatinine and microalbumin dose centrally and glomerular filtration measured locally (by inhaledate clearance). These measures will be obtained at baseline, 1 to 2 years follow-up, and at the end of the study. Presently, 200 subjects will be measured for creatinine clearance, 110 will have measures of GFR, and about 4,000 individuals will have creatinine measured by a control laboratory.

The data from the renal sub-study of the HOT investigation is expected to be available 5 years prior to the AASK Study. These substudy results will provide vital information about the etiology of ESRD in all racial groups, and the effect of antihypertensive therapy in preventing or this extremely serious consequence of hypertension.
REFERENCES


