Hypertension as a Risk Factor for Renal Disease

Review of Clinical and Epidemiological Evidence

Paul K. Whelton and Michael J. Klag

Renal failure is a well-recognized complication of accelerated and malignant hypertension that can be prevented by appropriate antihypertensive therapy. The risk of renal disease in patients with milder forms of hypertension is less certain. Death certificate, insurance industry, and community-based observational studies provide little information with respect to the risk of kidney damage in the hypertensive patient. Randomized controlled trials of antihypertensive drug therapy provide equivocal results. The strongest evidence in support of the hypothesis that mild hypertension increases the risk of subsequent renal disease comes from analyses of the Hypertension Detection and Follow-up Program and the Medicare End-Stage Renal Disease (ESRD) Program. The risk of blood pressure–related ESRD appears to be especially high in blacks, independent of age, sex, and prevalence of hypertension. Although these results need to be confirmed, the data raise the possibility that the effects of high blood pressure on the kidney are different in blacks than in whites. Based on current trends, it is projected that the number of beneficiaries in the Medicare ESRD Program will continue to increase during the next 30–40 years and that the diagnosis of hypertensive ESRD will become increasingly common. Additional studies to characterize the relation between mild hypertension and subsequent risk of renal disease and to confirm the corresponding benefits of antihypertensive therapy are urgently needed. (Hypertension 1989;13[suppl I]:I-19–I-27)

In 1836, Bright noted an association between hypertrophy of the heart and contraction of the kidneys. However, modern understanding of the relation between high blood pressure and the kidney can be traced to the classic treatise by Volhard and Fahr published in 1914. The concepts presented in this document formed the basis for subsequent definitions of malignant and essential hypertension as well as the foundation for our comprehension of the pathophysiology of both forms of high blood pressure. Since this landmark publication, many authors have reported that high blood pressure increases the risk of developing renal disease. However, most of the available literature is based on the experience of patients with severe hypertension. Little has been written with respect to the risk of renal disease in the much larger number of persons with mild forms of high blood pressure. This article reviews the evidence concerning a relation between high blood pressure and the subsequent risk of developing renal disease. In addition, suggestions are made to identify areas of uncertainty that need further examination.

Renal Disease Mortality Statistics

National mortality statistics provide a vast reservoir of information that is not only representative of the entire population but is also helpful in supporting the hypothesis of an association between a putative risk factor and a disease of interest. In many countries, mortality statistics reports provide information detailing the number of deaths and corresponding rates of mortality from a variety of presumed underlying causes of death including hypertensive renal disease. In the United States, the reported mortality from hypertensive renal disease has declined dramatically during the past 2 decades. This is true for men and women and for age-specific as well as age-adjusted rates. Figure 1 provides an illustration of the pattern for US residents between the ages of 65 and 84 years. Although the decline is impressive, such information must be interpreted with extreme caution. A variety of commonly recognized difficulties, includ-
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Deaths per 100,000

Calendar Year

I-20

Impressive evidence documents a causal relation between severe forms of hypertension and the occurrence of renal disease. In the era preceding the availability of effective antihypertensive drug therapy, approximately 90% of patients with accelerated and malignant hypertension were dead within 12 months of their initial presentation. The vast majority died from uremia, and their prognosis was closely related to the level of renal function at the time of their initial presentation. The advent of drugs like the thiazide diuretic agents and the ganglion blocking agents revolutionized the treatment of patients with severe hypertension. These agents made it possible to reduce not only blood pressure but also the risk of uremia and other sequelae of accelerated and malignant hypertension. With time, the spectrum of available antihypertensive drug therapy broadened, and it became increasingly clear that prognosis could be radically improved, even in those who had advanced renal insufficiency. In 1969, Mroczek et al reported the effects of therapy in 25 patients with accelerated hypertension and renal insufficiency. The 12-month survival of this group was 88%, and the average blood urea nitrogen of the 22 survivors declined from 76 to 28 mg/dl during the first 12 months of treatment. Subsequent reports have identified even more dramatic instances of improvement after antihypertensive therapy. Indeed, most nephrologists can cite examples of patients who initially required dialysis but who eventually normalized their renal function with prolonged antihypertensive drug therapy. Thus, there is little doubt that severe hypertension increases an individual’s risk of developing renal disease and that appropriate treatment will reduce the risk. However, severe hypertension is uncommon, and the incidence of death from malignant hypertension has declined dramatically in recent years. For this reason, demonstration of an increased risk of renal disease in patients with mild-to-moderate hypertension would have far greater therapeutic and public health implications.

Renal Disease in Mild-to-Moderate Hypertension

In contrast to the relatively large body of literature relating mild and moderate hypertension to an increased risk of stroke and coronary heart disease, surprisingly little information is available with respect to the corresponding risk of developing renal disease. Insurance industry reports are a potential source of such information. Relevant results from the 1979 Blood Pressure Study are presented in Table 1. For hypertension and nephritis mortality, increasing levels of blood pressure tend to be associated with a progressively higher standardized mortality ratio. However, the category of overall mortality from hypertension includes deaths from hypertensive heart disease as well as from hypertensive renal disease. The former are far more common than the latter. As such, the category of overall hypertension mortality is predominantly a reflection of deaths from hypertensive heart disease and does not adequately reflect the pattern of mortality from hypertensive renal disease. Likewise, the category of mortality from nephritis includes death from a variety of renal disease.

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diseases but predominantly reflects the experience of those with intrinsic renal disease and not those with renal disease secondary to hypertension. Overall, insurance industry reports provide limited opportunities to explore the possibility of a relation between hypertension and the risk of subsequently developing renal disease.

Another potential source of useful information might be community-based longitudinal cohort studies. Although studies such as those in Framingham and Evans County have generated an extensive body of literature on the relation between blood pressure and cardiovascular disease, little of substance has emanated from these sources concerning the influence of blood pressure on renal function. An exception to this rule is the Baltimore Longitudinal Study on Aging (BLSA). Surprisingly, no association could be demonstrated between blood pressure and creatinine clearance in the BLSA despite the fact that both variables were independently related to age. This may reflect the highly selective nature of the BLSA sample, which is predominantly composed of white middle-class professionals. Moreover, systematic exclusions reduced the participation rate in the creatinine clearance studies to 48% of the sample.

Hypertension treatment trials represent a third source of potentially useful information. If hypertension is a risk factor for the development of renal disease, one might expect that the risk would be

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**Table 1.** Percent Ratio of Observed-Expected Hypertension and Nephritis Mortality

<table>
<thead>
<tr>
<th>Initial blood pressure (mm Hg)</th>
<th>Percent observed-expected mortality ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic</td>
<td></td>
</tr>
<tr>
<td>&lt;128</td>
<td>108</td>
</tr>
<tr>
<td>128–137</td>
<td>202</td>
</tr>
<tr>
<td>138–147</td>
<td>246</td>
</tr>
<tr>
<td>148–157</td>
<td>402</td>
</tr>
<tr>
<td>&gt;158–167</td>
<td>(453)</td>
</tr>
<tr>
<td>&gt;168</td>
<td>(&gt;828)</td>
</tr>
<tr>
<td>Diastolic</td>
<td></td>
</tr>
<tr>
<td>&lt;83</td>
<td>68</td>
</tr>
<tr>
<td>78–87</td>
<td>137</td>
</tr>
<tr>
<td>83–92</td>
<td>(139)</td>
</tr>
<tr>
<td>88–97</td>
<td>(171)</td>
</tr>
<tr>
<td>93–102</td>
<td>(...)</td>
</tr>
<tr>
<td>&gt;98</td>
<td>(...)</td>
</tr>
</tbody>
</table>

*Rates enclosed in parentheses are based on 10–34 deaths. Ellipses enclosed in parentheses indicate that fewer than 10 persons in this category died during the period of follow-up.


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**Table 2.** Renal Events During Treatment in Six Randomized Placebo-Controlled Trials of Antihypertensive Drug Therapy. Because the Criteria for Assessable Events in Each Trial Differ Considerably, This Information Is Best Used for Within-Trial Comparisons.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Diastolic blood pressure at entry (mm Hg)</th>
<th>Number of patients studied</th>
<th>Patient-years of follow-up</th>
<th>BUN or creatinine*</th>
<th>Proteinuria†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wolff and Lindeman (1966)</td>
<td>&gt;100 (80% on medications)</td>
<td>87</td>
<td>125</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Veterans Administration Study (1967)</td>
<td>115–129</td>
<td>143</td>
<td>217</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Veterans Administration Study (1970)</td>
<td>90–114</td>
<td>380</td>
<td>1,475</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>US Public Health Service Study (1977)</td>
<td>95–114</td>
<td>389</td>
<td>2,723</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Australian National Study (1980)</td>
<td>95–109</td>
<td>3,427</td>
<td>13,859</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

*Blood urea nitrogen (BUN) or creatinine criteria are BUN >5 mg/dl in Wolff and Lindeman study; BUN >70 mg/dl or doubled in 1967 Veterans Administration Study; "progressive azotemia" and creatinine persistently >2 mg/dl in 1970 Veterans Administration Study; "renal insufficiency" in 1977 US Public Health Service Study; "renal failure" in the 1980 Australian National Study; and fatal or nonfatal "renal" events in 1985 European Working Party on High Blood Pressure in the Elderly Study.

†Proteinuria measurements are "proteinuria" in Wolff and Lindeman study and "proteinuria, persistent, >1 + " in 1970 Veterans Administration Study.

Data are adapted from References 17–22.
reduced by effective antihypertensive drug therapy. Table 2 presents relevant information from six randomized placebo-controlled trials of treatment of patients with hypertension. Each trial has reported morbidity outcome information related to the changes in the level of creatinine, blood urea nitrogen, or proteinuria. Because the criteria for assessable renal events differed considerably from trial to trial, the information presented is best used for within-study comparisons. Four of the six trials that have provided information on blood urea nitrogen or creatinine outcome measures identified a smaller number of events during active therapy. However, the difference in absolute numbers of patients affected was small. The two trials with the largest number of events had more patients with an increase in blood urea nitrogen or creatinine during active rather than during placebo therapy. However, in the Wolff and Lindeman trial, more patients in the active-therapy group than in the control group experienced a decline in blood urea nitrogen of greater than 5 mg/dl. Two of the six trials reported proteinuria as an outcome measure and, in both trials, proteinuria was less common during active therapy. In addition, Wolff and Lindeman reported a decrease in preexisting proteinuria in nine active-therapy patients as opposed to only one placebo control participant. In summary, while a majority of the relevant trials have suggested that antihypertensive drug therapy reduces the risk of renal disease, the evidence is imperfect, and trials with the greatest number of renal disease events have failed to confirm the benefit of treatment.

Renal disease morbidity and mortality (8th revision International Classification of Diseases, Adapted, codes 580–599) results are available for the Hypertension Detection and Follow-up Program (HDFP). With respect to mortality, more renal disease deaths were reported during special- than referred-care treatment. This was true for the entire study (15 vs. 10 deaths) and for the stratum 1 group with an initial diastolic blood pressure between 90 and 104 mm Hg (7 vs. 5 deaths). However, the previously mentioned concerns regarding interpretation of renal disease vital statistics applies equally well to an understanding of the HDFP results. Thus, while HDFP mortality results provide a valuable body of data with which to judge the overall benefits of antihypertensive drug therapy, the same data are not very helpful in making judgments concerning the influence of hypertension treatment on the risk of developing renal disease. In contrast, morbidity results from the HDFP provide one of the most compelling arguments in favor of a relation between mild hypertension and an increased risk of renal disease. As indicated in the article by Shulman et al., high blood pressure was one of several factors associated with a reduction in renal function during the 5 years of follow-up in this study. In addition to being more common in those with elevated blood pressure, renal dysfunction was also more common among men, blacks, and those in the highest age groups under study. The incidence of renal dysfunction was lower among special-care participants, suggesting that treatment of hypertension might have reduced the development of renal disease. These results are impressive and provide the strongest single body of evidence supporting a relation between mild hypertension and risk of renal disease.

### Hypertension and End-Stage Renal Disease

An alternative method for exploring the association between high blood pressure and renal disease would be to identify the prevalence of prior hypertension in patients with renal insufficiency. The prevalence of hypertension in the general population is well established. If hypertension were reported as the underlying diagnosis in a disproportionately large percentage of patients with renal insufficiency, this would bolster the argument that high blood pressure is a risk factor for renal disease. As previously mentioned, it is well known that untreated malignant hypertension can rapidly lead to renal failure. However, few patients with renal insufficiency have a history of malignant hypertension. It seems reasonable to assume that any relation between renal failure and a preexisting history of hypertension can be primarily attributed to the effects of mild-to-moderate hypertension.

At present, no prospective data exist on the prevalence of prior hypertension in a complete or random sample of patients with renal insufficiency. However, ESRD registries exist in several countries. Of these, the US Health Care Financing Agency (HCFA) ESRD program is the largest and probably most representative renal failure registry in existence. With enactment of the 1972 Social Security Amendment, Congress extended Medicare coverage to most US residents with ESRD. Under this legislation, physicians are required to provide chronic ESRD treatment to all renal-failure patients with Medicare coverage unless the therapy is medically contraindicated. It is estimated that the Medicare program funds almost 95% of ESRD treatment in the United States. Figure 2 provides a graphic representation of temporal trends in the prevalence rates and corresponding total number of Medicare ESRD program beneficiaries, as well as the incidence rates and corresponding annual number of new enrollees between 1974 and 1983. As shown in the figure, the size of the program has grown dramatically from approximately 16,000 beneficiaries in 1974 to approximately 78,000 in 1983. The corresponding point prevalence rates have increased from 76 per million to 358 per million. Statistics for the most recent year available, 1983, indicate a further expansion of the program to almost 93,000 enrollees. Incidence has also increased, but much of the increase in program size appears to be due to the relatively favorable survivorship experience of those being treated. Although one cannot be cer-
tain, the positive financial incentive to enroll ESRD patients, the widespread availability of dialysis and renal transplant units, and the stability of Medicare ESRD program incidence rates suggest that most US residents who develop ESRD are now being enrolled in the program.

HCFA stipulates that Medicare ESRD providers gather demographic and medical information at specified intervals. These data are collected by regional ESRD Networks, and summary statistics are published annually by the HCFA and the National Forum of ESRD Networks. Information collected at entry into the program includes the health care provider’s diagnosis of an enrollee’s underlying cause of ESRD. Thus, the HCFA ESRD data system provides an opportunity to explore the relation between ESRD and a diagnosis of preexisting hypertension. Unfortunately, the quality and completeness of the data are uncertain. There is limited knowledge of the response rates to individual questions, scanty information on comorbid conditions, and inadequate validation of the data collected by many Networks. Despite these constraints, the HCFA data base is the largest and probably most representative source of information on ESRD associations and treatment outcomes.

Temporal trends in the proportional incidence of provider-reported underlying cause of ESRD are illustrated in Figure 3. For clarity, the information provided is confined to the three most common diagnoses. When the program was initiated, glomerulonephritis was by far the most frequent diagnosis. However, in recent years, the proportion of new ESRD cases attributed to glomerulonephritis has declined. The corresponding proportions attributed to hypertension and diabetes mellitus have increased progressively to the point where each accounts for almost one quarter of all new ESRD patients. For example, in 1983, the overall rate of enrolling new cases into the ESRD program was 92 per million, and the corresponding incidence rates for glomerulonephritis, hypertension, and diabetic nephropathy were 23, 24, and 24 per million, respectively.

Although health care providers report a variety of

**Figure 2.** Plot of temporal trends in Medicare-funded End-Stage Renal Disease Program prevalence and annual incidence rates (rate per million persons). Numbers in parentheses represent corresponding estimates, in thousands, of the total number (prevalence numerator) and the annual number (incidence numerator) of beneficiaries enrolled in the program. The data presented are based on information published in Whelton, Rowland and Roberts, and Eggers et al. 

**Figure 3.** Plot of temporal trends in proportional incidence rates of provider-reported underlying cause of end-stage renal disease (ESRD). Adapted from Health Care Financing Administration, Table 6.
other underlying causes of renal failure, including polycystic kidney disease, interstitial nephritis, obstructive uropathy, and collagen vascular diseases, none of these diagnoses accounts for more than 5-10% of those entering the Medicare ESRD program.

The distribution of ESRD diagnosis changes dramatically with age. This is illustrated in Figure 4, which identifies the pattern for new patients enrolled in the Medicare program during 1980. As shown in Figure 4, glomerulonephritis was the most frequent diagnosis in young adults but became proportionately less common with aging. Diabetic nephropathy was the most frequent diagnosis in middle age but was relatively uncommon at the extremes of life. Hypertension was an infrequent diagnosis early in life but was by far the most common presumptive cause of ESRD in older patients. At each age range illustrated in Figure 4, the proportion of new ESRD patients in whom hypertension was reported as the underlying diagnosis was greater than the corresponding proportion of hypertensive subjects in the general population. If one accepts the representativeness and validity of the Medicare ESRD data base, the findings presented in Figure 4 provide strong evidence in favor of the notion that hypertension is a particularly important risk factor for ESRD in later life. One additional point is worth emphasizing. The median age of those entering the Medicare ESRD program has progressively increased. For example, in 1973, the median was less than 55 years, but by 1985, the median age had increased to greater than 60 years. This phenomenon may reflect both the aging of the US population and physicians' increasing willingness to initiate dialysis in older patients. Based on the trend toward a progressively higher median age and the striking relation between age and proportional incidence of hypertensive ESRD, it seems likely that hypertensive ESRD will account for a progressively larger number of new Medicare program enrollees unless there is some basic alteration in the incidence of hypertensive ESRD. For these reasons, the public health importance of hypertension as a risk factor for ESRD may be far greater than one might initially assume.

Black-White Differences in Hypertensive End-Stage Renal Disease

Further exploration of the Medicare data base reveals that hypertension, as an underlying cause of ESRD, is more commonly reported in black than in white patients. For instance, in 1980, the percent distribution of new enrollees with ESRD thought to be due to hypertension, glomerulonephritis, and diabetes mellitus, respectively, was 43%, 14%, and 22% in blacks and 17%, 21%, and 21% in whites. Several explanations can be advanced for this impressive black-white difference in hypertensive ESRD incidence. One possibility is that the difference is a chance finding. However, this seems improbable, as black-white differences in the incidence of hypertensive ESRD have been noted in several regional US data bases. Another hypothesis is that US physicians are more likely to identify hypertension as an underlying cause of ESRD in black than in white patients. If this is the case, the problem is not confined to the United States, as impressive black-white differences in hypertensive ESRD have also been noted in other countries. For instance, in a South African study, Seedat et al reported that hypertension was the cause of ESRD in 32% of black as opposed to only 10% of white patients referred for evaluation of end-stage renal failure. A third possibility is that black-white differences in the incidence of hypertensive ESRD could be accounted for by corresponding differences in the prevalence of hypertension. Black-white differences in the prevalence of hypertension are well known. For example, in the 1976–1980 National Health and Nutrition Examination Survey (NHANES II), the age-adjusted prevalence of hypertension (subjects with systolic blood pressure >160 mm Hg, with diastolic blood pressure >95 mm Hg, or taking anti-
hypertensive medications) in black men aged 25–74 years was 28% while the corresponding rate for their white counterparts was only 21%.26 For women, blacks had a rate of almost 40% whereas the rate for whites was only 20%. Thus, a black–white difference in hypertension prevalence represents a plausible explanation for the disparity in incidence of hypertensive ESRD. However, McClellan et al35 have reported that adjustment for variations in age, sex, and the prevalence of hypertension does not eliminate the black–white difference in incidence of hypertensive ESRD. Specifically, these authors assessed the influence of race on the risk of developing renal failure due to hypertension among new ESRD patients seen in the state of Georgia during the 5-year period between 1979 and 1984. The overall incidence rates of ESRD due to hypertension were 101.5 per million for black patients and 12.0 per million for their white counterparts. Thus, the overall relative risk of hypertensive ESRD for blacks compared with whites was 8.4. After adjustment for black–white differences in age, sex, and estimated prevalence of hypertension, the relative risk was still impressively elevated at 5.7.

There is another discrepancy between blacks and whites in the prevalence of more severe forms of hypertension that might contribute disproportionately to the incidence of hypertensive ESRD. For example, in the 1971–1974 NHANES survey, the age-adjusted rate of persons aged 18–74 years with a diastolic blood pressure greater than 105 mm Hg was 11.2% for black and 4.1% for white men.25 The corresponding rates for black and white women were 11.1% and 3.4%, respectively. Although McClellan et al35 adjusted for the overall prevalence of hypertension, they did not standardize for the possible effects of a corresponding difference in the prevalence of severe hypertension. In addition, they did not adjust for the effects of duration of hypertension, frequency and quality of antihypertensive treatment, or the presence of other comorbid variables like diabetes mellitus. Thus, their relative-risk estimates may overstate the true situation. However, it seems unlikely that further adjustment would have reduced the relative risk to unity, and these authors' findings argue strongly in favor of a difference in the natural history of hypertension in blacks and whites.

A difference in the choice of drugs that are used to treat black and white patients with high blood pressure represents a final possible explanation for the reported discrepancy in the black–white incidence of hypertensive ESRD. Although this may become an important consideration in the future, there is no evidence that any of the drugs used during the period under discussion have any special renal protective effects.

### Areas for Future Research

The evidence in support of a relation between milder forms of hypertension and risk of subsequent kidney disease is suggestive but inconclusive. For mildly hypertensive individuals, the absolute risk, if any, is low, and only a small proportion of such patients progress to develop chronic renal failure. Despite this situation, the individual and societal implications of any such risk may be substantial. ESRD is an incapacitating illness that frequently leads to a diminution in the individual's economic well-being as well as quality of life.37 In addition, funding of ESRD care is a substantial financial burden for society. Reimbursement for Medicare-supported ESRD care has risen from $229 million in 1974 to a current level of almost $2 billion.27,28 Temporal trends in overall and per capita Medicare ESRD program reimbursement costs and number of beneficiaries are presented in Figure 5. During the 10-year period between 1974 and 1984, reimbursement costs for the overall program rose steeply and progressively. This increase in program cost has primarily resulted from a rapid expansion in the number of patients who are accepted for ESRD...
treatment. Per capita costs have risen more slowly
and even declined slightly in recent years. Indeed,
in the context of the rate of rise in general health
care costs, the Medicare ESRD program per capita
inflation rate has been quite modest.

Reductions in Medicare ESRD program costs can
be achieved by diminishing the payment per patient
provided to ESRD health care providers or by
decreasing the number of patients receiving ESRD
care. Until now, most of the attention has been
focused on regulating health care provider reim-
bursement rates. Given that per capita costs have
not risen substantially since 1974, it seems unlikely
that major gains can be expected from a reduction
in unit costs. A decrease in ESRD program pool
size is more likely to effect the desired reduction in
program costs. In the short-term, this seems improb-
able. Based on expected changes in demographic
patterns and current ESRD Program incidence and
prevalence rates, Eggers et al. have predicted that
the Medicare pool size will grow to more than
150,000 beneficiaries by the year 2020. It is of
interest that their projections suggest that enroll-
m ent of white patients will increase by 118% while
the corresponding figure for nonwhites is 337%.
Because the diagnosis of hypertensive ESRD is
especially common in black patients, this form of
renal failure is likely to become an even more
common entity unless the risk factors for renal
disease can be altered in a radical fashion.

Strategies aimed at the prevention and treatment
of hypertension may be a key step toward a reduc-
tion in the risk of developing ESRD. Despite the
difficulties of achieving this goal, the benefits of
blood pressure-lowering interventions are multi-
faceted, and prevention and treatment of hyperten-
sion is certainly an attractive solution to the current
dilemma of the escalation in ESRD program size
and cost. In addition to the potential benefit to be
derived by those who would otherwise have devel-
oped ESRD on the basis of hypertension per se, this
approach may also substantially benefit those at
risk of developing diabetic nephropathy and other
forms of renal failure. However, much more needs
to be learned regarding the relation between high
blood pressure and the risk of renal disease before
one could confidently predict the magnitude of any
benefits that would result from high blood pressure
prevention and treatment interventions. As a first
step, additional prospective studies to characterize
the relation between mild hypertension and the
subsequent risk of renal disease and to confirm the
renal benefits of antihypertensive therapy are
urgently needed.

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