Elevated Blood Pressure and Risk of End-stage Renal Disease in Subjects Without Baseline Kidney Disease

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Background: Many cases of end-stage renal disease (ESRD) are ascribed to hypertension. However, because renal disease itself can raise blood pressure, some investigators argue that ESRD seen in patients with hypertension is due to underlying primary renal disease. Previous cohort studies of the relationship between blood pressure and ESRD did not uniformly screen out baseline kidney disease.

Methods: We conducted a historical cohort study among members of Kaiser Permanente of Northern California, a large integrated health care delivery system. The ESRD cases were ascertained by matching with the US Renal Data System registry.

Results: A total of 316,675 adult Kaiser members participated in the Multiphasic Health Checkups from 1964 to 1985. All subjects had estimated glomerular filtration rates of 60 mL/min per 1.73 m² or higher and negative dipstick urinalysis results for proteinuria or hematuria. During 8,210,431 person-years of follow-up, 1149 cases of ESRD occurred. Compared with subjects with a blood pressure less than 120/80 mm Hg, the adjusted relative risks for developing ESRD were 1.62 (95% confidence interval [CI], 1.27-2.07) for blood pressures of 120 to 129/80 to 84 mm Hg, 1.98 (95% CI, 1.55-2.52) for blood pressures of 130 to 139/85 to 89 mm Hg, 2.59 (95% CI, 2.07-3.25) for blood pressures of 140 to 159/90 to 99 mm Hg, 3.86 (95% CI, 3.00-4.96) for blood pressures of 160 to 179/100 to 109 mm Hg, 3.85 (95% CI, 2.82-5.34) for blood pressures of 180 to 209/110 to 119 mm Hg, and 4.25 (95% CI, 2.63-6.86) for blood pressures of 210/120 mm Hg or higher. Similar associations between blood pressure level and ESRD risk were seen in all subgroup analyses.

Conclusions: Even relatively modest elevation in blood pressure is an independent risk factor for ESRD. The observed relationship does not appear to be due to confounding by clinically evident baseline kidney disease.

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tively wide.\textsuperscript{19,20} To clarify the relationship between blood pressure and subsequent risk of ESRD, we conducted a historical cohort study in a large, diverse sample of persons without clinical evidence of baseline renal disease.

**METHODS**

**STUDY POPULATION**

We studied persons who received care within Kaiser Permanente of Northern California who participated in the Multiphasic Health Testing Service Program between 1964 and 1985.\textsuperscript{21} Kaiser Permanente of Northern California is a large, integrated health care delivery system that currently provides care for approximately one third of the insured adult population in the greater San Francisco Bay Area. The Multiphasic Health Checkups Program was a voluntary health assessment offered at initial and yearly open enrollment periods.\textsuperscript{21} Analyzable data on measured blood pressure, serum creatinine level, and dipstick urinalysis were available for 3 of the 4 Multiphasic Health Checkups periods: June 1964 to August 1973, September 1973 to December 1977, and January 1978 to March 1985.

Among 386,652 individuals who participated in the Multiphasic Health Checkups from 1964 to 1985, 377,601 (98\%) had at least 1 concurrent (ie, performed at the same checkup visit) measurement of blood pressure, serum creatinine, and dipstick urinalysis. We did not further analyze 11,674 individuals younger than 18 years or with a baseline serum creatinine level greater than 10 mg/dL (884 \(\mu\)mol/L) (and therefore might have already had ESRD).

**MEASUREMENT OF BLOOD PRESSURE**

Systolic and diastolic blood pressure were measured based on the acoustic detection of the onset (systolic point) and disappearance (diastolic point) of Korotkoff sounds.\textsuperscript{21} To allow direct comparison with previously published studies,\textsuperscript{20} we categorized blood pressure using the earlier Fifth Joint National Committee Report classification:\textsuperscript{20} “normal” (systolic blood pressure <120 mm Hg and diastolic blood pressure <80 mm Hg); “high normal” (systolic blood pressure of 120 to 129 mm Hg and diastolic blood pressure <80 to 84 mm Hg); “stage 1 hypertension” (systolic blood pressure of 130 to 139 mm Hg and diastolic blood pressure <90 mm Hg or diastolic blood pressure of 85 to 89 mm Hg and systolic blood pressure <140 mm Hg); “stage 1 hypertension” (systolic blood pressure of 140 to 159 mm Hg and diastolic blood pressure <100 mm Hg or diastolic blood pressure of 90 to 99 mm Hg and systolic blood pressure <160 mm Hg); “stage 2 hypertension” (systolic blood pressure of 160 to 179 mm Hg and diastolic blood pressure <110 mm Hg or diastolic blood pressure of 100 to 109 mm Hg and systolic blood pressure <180 mm Hg); “stage 3 hypertension” (systolic blood pressure of 180 to 209 mm Hg and diastolic blood pressure <120 mm Hg or diastolic blood pressure of 110 to 119 mm Hg and systolic blood pressure <210 mm Hg); and “stage 4 hypertension” (systolic blood pressure ≥210 mm Hg or diastolic blood pressure ≥120 mm Hg).

**ASSESSMENT OF BASELINE RENAL DISEASE**

The glomerular filtration rate (GFR) was estimated from serum creatinine using the abbreviated Modification of Diet in Renal Disease study formula.\textsuperscript{21,22} Dipstick urinalysis quantified urinary protein (negative, trace, 1-2+, or 3-4+) and urine hemoglobin (negative, small, moderate, or large).\textsuperscript{21} We classified subjects as having no baseline renal disease if they had an estimated GFR of 60 ml/min per 1.73 m\(^2\) or higher and tested negative for dipstick proteinuria or hematuria.\textsuperscript{23}

**COVARIATES**

Information regarding relevant covariates (such as history of myocardial infarction) was obtained from self-completed questionnaires administered within 45 days of corresponding blood tests. Medical history data were not available in an electronic format for participants from September 1973 to December 1977; therefore, these subjects were classified as missing those data elements. Race was classified as white, black, Asian, and other by self-report. Diabetes mellitus was defined as self-report of a physician diagnosis or random blood glucose level of greater than 200 mg/dL (11.10 mmol/L). Education level was categorized as high school or less, some college, and college graduate or higher. Cigarette smoking status was classified as never, former, and current. Total fasting serum cholesterol level and height and weight were measured using standardized methods.\textsuperscript{21}

**IDENTIFICATION OF ESRD AND DEATH**

We defined ESRD as receipt of renal transplantation or maintenance dialysis. We identified cases of ESRD by matching our cohort against the nationally comprehensive US Renal Data System (USRDS) registry data.\textsuperscript{20} Matching was performed blinded to exposure status using subjects’ Social Security number, first and last names, sex, and date of birth. We chose as our outcome all-cause ESRD rather than only ESRD ascribed to hypertension, because previous studies\textsuperscript{9,13} have shown that the diagnosis of “ESRD due to hypertension” is highly unreliable. Deaths were ascertained using the California Automated Mortality Linkage System, which has a sensitivity of 97% compared with the National Death Index.\textsuperscript{26} Both ESRD and death were assessed through December 31, 2000; the most recent date data were available for both outcomes. Person-years were calculated as years elapsed from baseline (date of Multiphasic Health Checkup) until death, development of ESRD, or the end of follow-up on December 31, 2000, whichever occurred first. Institutional review boards at the collaborating institutions approved the study.

**STATISTICAL ANALYSIS**

All analyses related outcome to data gathered at 1 baseline Multiphasic Health Checkups examination for each patient. Age-adjusted rates of ESRD were calculated using Poisson regression adjusted to median age. The relationship between blood pressure category and subsequent risk of ESRD was analyzed using time-to-event methods. Multivariable analyses were conducted using Cox proportional hazards models. In multivariable analyses, we adjusted for phase of multiphasic study during which baseline assessment occurred, as well as age, sex, race, education level, smoking status, diabetes mellitus, history of myocardial infarction, serum cholesterol level, height, and weight. All models included a missing data category, if applicable. We checked the proportional hazards assumption by comparing estimated log (−log[survivor function]) vs time (person-years) survivor curves. Preplanned subgroup analyses included stratification by sex, race, and diabetes mellitus.

Since it is possible that the national registry’s completeness in capturing ESRD cases nationwide improved through the 1970s, observations might be subject to left truncation. Several left truncation dates were used in sensitivity analyses along with elimination of observed ESRD events before those times.\textsuperscript{22} We chose the truncation dates December 31, 1973, December
31, 1977, and December 31, 1987, to reflect, respectively, when the US Congress gave patients with ESRD Medicare entitlement, when what is now the Center for Medicare and Medicaid Services began to administer the registry, and when the registry became a core component of the then new USRDS. All analyses were conducted using SAS statistical software (SAS Institute Inc, Cary, NC).

RESULTS

Among 365 927 eligible study subjects, 49 252 (13%) had baseline estimated GFRs less than 60 mL/min per 1.73 m², trace or more dipstick proteinuria, and/or small or greater dipstick hematuria and were therefore excluded. The characteristics of the remaining 316 675 subjects with estimated GFRs of 60 mL/min per 1.73 m² or higher and no proteinuria or hematuria who composed the study population are given in Table 1.

Among the 316 675 individuals without baseline clinical evidence of kidney disease, 1149 cases of ESRD (and 48 561 deaths) were identified during 8 210 431 person-years of follow-up. We observed a strong graded relationship between higher blood pressure and higher risk of ESRD that persisted after adjusting for age (Table 2).

The age-adjusted association between blood pressure and risk of ESRD was seen in all strata examined, although the absolute risk of ESRD varied considerably (Figures 1, 2, and 3). For example, among those with blood pressure less than 120/80 mm Hg, the age-adjusted rate of ESRD was only 2.8 per 100 000 person-years for white subjects compared with 14.0 per 100 000 person-years for black subjects and only 3.8 per 100 000 person-years among persons without diabetes vs 12.7 per 100 000 person-years among persons with diabetes.

In the overall population, the strength of the relationship between blood pressure and risk of ESRD was attenuated but persisted after adjusting for phase of multiphasic study, age, sex, race, education level, smoking status, diabetes mellitus, history of myocardial infarction, serum cholesterol level, height, and weight (Table 2). Compared with subjects with a blood pressure less than 120/80 mm Hg, the adjusted relative risk of developing ESRD increased 1.6-fold for subjects with blood pressures of 120 to 129/80 to 84 mm Hg, 2.0-fold for subjects with blood pressures of 130 to 139/85 to 89 mm Hg, 2.6-fold for subjects with blood pressures of 140 to 159/90 to 99 mm Hg, 3.5-fold for subjects with blood pressures of 160 to 179/100 to 109 mm Hg, 3.9-fold for subjects with blood pressures of 180 to 209/110 to 119 mm Hg, and 4.2-fold for subjects with blood pressures of 210/120 mm Hg or higher (Table 2). Only minimal changes occurred in the risk estimates after further adjusting for baseline serum creatinine concentration (Table 2). Results were similar in all left truncated models (data not shown).

Similar results were seen in all subgroup analyses. For example, the corresponding adjusted relative risks for higher blood pressure categories (compared with blood pressure <120/80 mm Hg) were 1.5, 2.1, 2.2, 4.2, 3.9, and 4.2 among white subjects; 1.5, 1.8, 2.4, 4.2, 3.7, and 4.7 among nondiabetic subjects; and 1.6, 1.6, 2.6, 3.2, 3.5, and 5.9 among those with GFRs greater than 90 mL/min per 1.73 m² (P<.05 for all).

COMMENT

We demonstrated in this large cohort a graded association between blood pressure and risk of ESRD among subjects without baseline clinical evidence of kidney disease. This study extends our understanding of the relationship between blood pressure and renal failure in several important ways.
In contrast to the much stronger evidence that malignant hypertension causes kidney damage, there are surprisingly few rigorous studies to support the widely and strongly held belief that nonmalignant hypertension is an important cause of ESRD.\(^1\) Establishing the detrimental effect of lesser degrees of blood pressure elevation on the kidneys is difficult chiefly because kidney disease itself can elevate blood pressure. Some investigators\(^1\) argue that ESRD seen in patients with hypertension is due to underlying primary renal disease such as focal segmental glomerulosclerosis. Previous cohort studies\(^1\) of the relationship between blood pressure and ESRD did not uniformly screen out kidney disease at baseline so were unable to address this potential critical confounder.

In the current study, we were able to overcome this limitation because all 316,675 subjects in this study had baseline estimated GFRs of 60 mL/min per 1.73 m\(^2\) or higher and no dipstick proteinuria or hematuria. Other strengths of this study included the large number of person-years and observed cases of ESRD, inclusion of subjects with normal blood pressure, equal representation of men and women, and broad racial and ethnic diversity. We were able to extend prior reports\(^2\) to show that at any given level of blood pressure there is a higher risk of ESRD among diabetic patients and among black patients even in the absence of baseline renal disease. Our study had sufficient power to demonstrate that the risk of ESRD is increased even with relatively modest elevations of blood pressure. Specifically, we found that compared with those with blood pressures less than 120/80 mm Hg, individuals with blood pressure of 120 to 129/80 to 84 mm Hg were 62\% more likely and those with blood pressure of 130 to 139/85 to 89 mm Hg were 98\% more likely to develop ESRD. These data are consistent with other studies\(^3\) that show that the risk of hypertensive end-organ damage begins with a blood pressure below 140/90 mm Hg. Our findings, therefore,

### Table 2. Age-Adjusted Rates of ESRD and Multivariable Risk of ESRD for Each Category of Blood Pressure

<table>
<thead>
<tr>
<th>Blood Pressure Category</th>
<th>No. of Persons</th>
<th>Mean Systolic/Diastolic Blood Pressure, mm Hg</th>
<th>No. of ESRD Events</th>
<th>Age-Adjusted Rate per 100 000 Person-Years (95% CI)</th>
<th>RR (95% CI)</th>
<th>Multivariable Risk† Adjusted Further for Serum Creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal</td>
<td>89,774</td>
<td>109/66</td>
<td>106</td>
<td>4.5 (3.6-5.8)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Normal, not optimal</td>
<td>72,192</td>
<td>122/73</td>
<td>182</td>
<td>9.3 (7.5-11.5)</td>
<td>1.61 (1.27-2.05)</td>
<td>1.62 (1.27-2.07)</td>
</tr>
<tr>
<td>High normal</td>
<td>56,078</td>
<td>132/77</td>
<td>192</td>
<td>12.9 (10.3-16.0)</td>
<td>1.97 (1.54-2.51)</td>
<td>1.98 (1.55-2.52)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>69,083</td>
<td>143/83</td>
<td>379</td>
<td>19.5 (15.8-24.1)</td>
<td>2.57 (2.06-3.22)</td>
<td>2.59 (2.07-3.25)</td>
</tr>
<tr>
<td>Stage 2</td>
<td>21,340</td>
<td>161/92</td>
<td>199</td>
<td>31.7 (24.6-41.0)</td>
<td>3.82 (2.97-4.92)</td>
<td>3.86 (3.00-4.96)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>66,26</td>
<td>177/101</td>
<td>70</td>
<td>34.5 (24.7-48.0)</td>
<td>3.88 (2.82-5.33)</td>
<td>3.88 (2.82-5.34)</td>
</tr>
<tr>
<td>Stage 4</td>
<td>158,21</td>
<td>189/122</td>
<td>21</td>
<td>43.7 (26.9-71.1)</td>
<td>4.18 (2.59-6.76)</td>
<td>4.25 (2.63-6.86)</td>
</tr>
<tr>
<td>Total</td>
<td>316,675</td>
<td></td>
<td>1149</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Blood pressure categories are based on the Fifth Joint National Committee Report\(^2\) (JNC V) classification. Note that JNC V “optimal” is equivalent to “normal” in JNC 7; JNC V “normal, not optimal” and “high normal” are now “prehypertension” in JNC 7; JNC V “stage 1 hypertension” is the same “stage 1 hypertension” as JNC 7, and JNC V “stages 2-4 hypertension” are now all combined as “stage 2 hypertension” in JNC 7.

†Adjusted for phase of multiphasic study, age, sex, race, education level, smoking status, diabetes mellitus, history of myocardial infarction, serum cholesterol level, height, and weight.
support the latest Joint National Committee Report re-classification of individuals with systolic blood pressure of 120 to 139 mm Hg or diastolic blood pressure of 80 to 89 mm Hg as having “prehypertension” rather than being “normal.”

Our study complements recent investigations that showed that subtle blood pressure elevation precedes subtle evidence of kidney disease. For example, it was noted among 75 normotensive subjects with type 1 diabetes mellitus that increased nocturnal systolic blood pressure occurred before the development of microalbuminuria.

Overall, the incidence of ESRD in our population was low at 14.3 cases per 100,000 person-years, which is similar to the 15.6 cases per 100,000 years previously reported among men screened for the MRFIT study. Even among subjects with blood pressure of 149/90 mm Hg or higher, the incidence of ESRD is 1 or 2 orders of magnitude lower than the incidence of cardiovascular disease, such as myocardial infarction, ischemic stroke, or chronic heart failure.

This finding has important implications. First, given such low incidence rates of ESRD, it may not be feasible to conduct an adequately powered randomized clinical trial to demonstrate that blood pressure lowering among those without baseline renal disease would reduce the incidence of ESRD in the way this has been shown for stroke and other cardiovascular diseases. (This is a distinct question from whether blood pressure lowering among patients with established renal parenchymal disease reduces risk of ESRD.) Hence, proof that elevated blood pressure is a causal risk factor of ESRD by observing the effect of interrupting this risk factor cannot be easily accomplished using a randomized trial approach. Intriguingly, in randomized trials, antihypertensive therapy did not appear to reduce the incidence of less severe cases of renal dysfunction.

Second, because of the large differences between the absolute risk of ESRD and absolute risk of cardiovascular disease, in a competing mortality paradigm, modest absolute reductions in cardiovascular mortality through implementation of available cardiovascular therapies may contribute to significant relative increases in ESRD incidence because patients survive longer and therefore develop kidney failure. This may explain the paradoxical observation that despite the average blood pressure decrease among the US population from the 1960s to the 1990s, the incidence of ESRD and “hypertension-related ESRD” continues to rise. A troubling implication of this is that blood pressure reduction alone may be insufficient to stem the rising tide of ESRD.

The limitations of this study include lack of information on therapies that affect blood pressure and lack of follow-up measures of renal function and blood pressure. Prior cohort studies of blood pressure and risk of ESRD also shared similar shortcomings. The observed relative attenuation of the graded increase in risk of ESRD in subjects with a baseline blood pressure higher than 160 to 179/100 to 109 mm Hg may reflect the fact that those subjects were more likely to have had their hypertension treated subsequently, since they were all members of an integrated health care delivery system who volunteered to undergo screening. As in prior cohort studies, blood pressure, serum creatinine level, and urinalysis, when and if measured, were only measured once. Various methods were used to measure blood pressure in different phases of the Multiphasic Health Check-ups examinations. We used clinically common but relatively crude assays to evaluate for the presence of baseline kidney disease but were unable to assess more subtle kidney damage. In addition, we cannot address recent data that support the hypothesis that patients with essential hypertension may be born with fewer nephrons, which would provide a unifying pathophysiologic explanation for any observed link between early elevated blood pressure and late development of ESRD.

This study provides the strongest epidemiologic evidence to date that nonmalignant hypertension is indeed an independent risk factor for ESRD. Risk is increased even with relatively modest elevations in blood pressure. Notably, the observed relationship does not appear to be due to confounding by clinically evident baseline kidney disease. Improved control of blood pressure and better understanding of other contributors to the worsening epidemic of ESRD are needed to reduce the worldwide burden of kidney disease.

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