

## BLOOD PRESSURE AND END-STAGE RENAL DISEASE IN MEN

MICHAEL J. KLAG, M.D., M.P.H., PAUL K. WHELTON, M.D., BRYAN L. RANDALL, M.S.,  
JAMES D. NEATON, PH.D., FREDERICK L. BRANCATI, M.D., M.H.S., CHARLES E. FORD, PH.D.,  
NEIL B. SHULMAN, M.D., AND JEREMIAH STAMLER, M.D.

**Abstract Background.** End-stage renal disease in the United States creates a large burden for both individuals and society as a whole. Efforts to prevent the condition require an understanding of modifiable risk factors.

**Methods.** We assessed the development of end-stage renal disease through 1990 in 332,544 men, 35 to 57 years of age, who were screened between 1973 and 1975 for entry into the Multiple Risk Factor Intervention Trial (MRFIT). We used data from the national registry for treated end-stage renal disease of the Health Care Financing Administration and from records on death from renal disease from the National Death Index and the Social Security Administration.

**Results.** During an average of 16 years of follow-up, 814 subjects either died of end-stage renal disease or were treated for that condition (15.6 cases per 100,000 person-years of observation). A strong, graded relation between both systolic and diastolic blood pressure and end-stage renal disease was identified, independent of associations between the disease and age, race, income, use of medication for diabetes mellitus, history of my-

ocardial infarction, serum cholesterol concentration, and cigarette smoking. As compared with men with an optimal level of blood pressure (systolic pressure <120 mm Hg and diastolic pressure <80 mm Hg), the relative risk of end-stage renal disease for those with stage 4 hypertension (systolic pressure  $\geq$ 210 mm Hg or diastolic pressure  $\geq$ 120 mm Hg) was 22.1 ( $P < 0.001$ ). These relations were not due to end-stage renal disease that occurred soon after screening and, in the 12,866 screened men who entered the MRFIT study, were not changed by taking into account the base-line serum creatinine concentration and urinary protein excretion. The estimated risk of end-stage renal disease associated with elevations of systolic pressure was greater than that linked with elevations of diastolic pressure when both variables were considered together.

**Conclusions.** Elevations of blood pressure are a strong independent risk factor for end-stage renal disease; interventions to prevent the disease need to emphasize the prevention and control of both high-normal and high blood pressure. (N Engl J Med 1996;334:13-8.)

©1996, Massachusetts Medical Society.

IN 1991, about 190,000 persons in the United States either underwent dialysis or received a renal transplant for end-stage renal disease.<sup>1</sup> Hypertension was judged to be the underlying cause of the condition in 29 percent of these patients, second only to diabetes mellitus (36 percent).<sup>1</sup> A striking association between malignant hypertension and the development of renal disease has been recognized since the 19th century, but the risk of renal failure associated with less severe hypertension is less certain.<sup>2</sup> Because of the relatively low incidence of end-stage renal disease in the general population, prospective epidemiologic studies of blood pressure and the disease have not been performed.

To determine the risks of renal failure associated with a wide range of blood-pressure levels, we prospectively studied 332,544 men screened for the Multiple Risk Factor Intervention Trial (MRFIT) from 1973 to 1975. In this large cohort, followed for 16 years, 814 cases of end-stage renal disease were identified. Mortal-

ity data from the MRFIT study also gave us an opportunity to identify subjects in the cohort who died of end-stage renal disease without having received dialysis or a renal transplant.

### METHODS

MRFIT was a randomized, multicenter, primary-prevention trial designed to study the effects on the incidence of coronary heart disease of an intervention program to control high blood pressure, lower serum cholesterol concentrations, and reduce cigarette smoking.<sup>3,4</sup> Between 1973 and 1975, 361,662 men from 35 to 57 years of age in 18 U.S. cities were screened for entry into the trial, of whom 12,866 eventually enrolled. Men with evidence of end-organ damage noted in a medical history or physical examination or with a serum creatinine concentration  $\geq$ 2.0 mg per deciliter (177  $\mu$ mol per liter) were excluded from the trial. Of the group screened for MRFIT, 3 men already being treated for end-stage renal disease at the time of screening and 29,115 men for whom information about systolic blood pressure or income was not available were excluded from our study, leaving 332,544 men for our analysis. Details concerning the recruitment and screening procedures in MRFIT have been published elsewhere.<sup>5,6</sup>

### Measurement

At screening for MRFIT, blood pressure was measured by trained personnel according to a standardized protocol.<sup>7</sup> Phases I and V of the Korotkoff sounds were used to determine systolic and diastolic blood pressure, respectively. Three readings were taken with a standard mercury sphygmomanometer; the mean of the last two readings was the blood-pressure measurement that we used in our analysis. In MRFIT, the serum cholesterol concentration was measured once in each participant at 1 of 14 laboratories that met standardization requirements set by the Centers for Disease Control.<sup>8</sup> A one-page questionnaire was administered to determine the number of cigarettes smoked per day and to record demographic characteristics. Information was also elicited concerning the following criteria for exclusion from the trial: expected geographic relocation, previous hospitaliza-

From the Departments of Medicine and Epidemiology (M.J.K., P.K.W., F.L.B.) and the Department of Health Policy and Management (M.J.K.), Johns Hopkins University School of Medicine and Johns Hopkins University School of Hygiene and Public Health, Baltimore; the Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis (B.L.R., J.D.N.); the University of Texas Health Science Center at Houston, Houston (C.E.F.); the Department of Medicine, Emory University, Atlanta (N.B.S.); and the Department of Preventive Medicine, Northwestern University Medical School, Chicago (J.S.). Address reprint requests to Dr. Klag at the Welch Center for Prevention, Epidemiology, and Clinical Research, 2024 E. Monument St., Suite 2-600, Baltimore, MD 21205-2223.

Supported by grants (RO1 DK41837 and RO1 HL28715) from the National Institutes of Health. Dr. Klag is an Established Investigator of the American Heart Association.

tion lasting more than two weeks due to heart attack (so termed), and the current use of any medication for diabetes mellitus. For the purposes of our analysis, we estimated subjects' socioeconomic status, using the median family incomes for black and white heads of family for each subject's ZIP Code of residence.

### Outcome

The principal outcome examined in this analysis was end-stage renal disease due to any cause, defined by treatment for end-stage renal disease or death due to renal failure. Treated cases of end-stage renal disease were ascertained from the national registry of the Health Care Financing Administration (HCFA). The Medicare End-Stage Renal Disease Program was initiated on January 1, 1973, and contains records for 93 percent of all persons in the United States who have received treatment for the condition since that date.<sup>9</sup> Patients enrolled in the registry from 1973 through 1990 were identified as having been screened for MRFIT through matching of Social Security numbers and then by last names and dates of birth.

Data on death from renal failure were derived from the ongoing follow-up of the MRFIT cohort. This information was compiled from the National Death Index (1979 to 1990) and the Social Security Administration (1973 to 1990).<sup>10</sup> Death certificates were collected and coded by a trained nosologist using the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM).<sup>11</sup> Deaths were classified as being due to renal failure if one of the ICD-9-CM codes listed in Table 1 was given on the death certificate as the underlying cause. Hypertensive end-stage renal disease was specifically examined as an outcome in our study and was considered to be present in cases of either entry into the HCFA registry, with an assigned underlying cause of hypertensive renal disease, or death from hypertensive renal disease.

### Statistical Analysis

The relation of blood pressure to end-stage renal disease was investigated with time-to-event methods, including Kaplan-Meier estimation and proportional-hazards regression, stratified according to MRFIT center, with age, race, income, use of medication for diabetes mellitus, history of heart attack, serum cholesterol concentration, and cigarette smoking as covariates.<sup>12,13</sup> Time elapsed from screening for MRFIT until either entry into the HCFA registry or death from renal

disease was examined as an outcome. The incidence of outcomes per 100,000 person-years of observation was calculated and adjusted for age by the direct method on the basis of the age distribution of all men screened. Because the analyses that considered treated end-stage renal disease and death from renal disease as separate outcomes yielded similar results, only those for the combined end point are presented here.

Blood pressure was categorized according to criteria for adults 18 years of age and older modified from the Fifth Joint National Committee Report on Detection, Evaluation, and Treatment of High Blood Pressure.<sup>14,15</sup> The categories were as follows: optimal: systolic blood pressure <120 and diastolic blood pressure <80 mm Hg; normal, not optimal: systolic 120 to 129 mm Hg and diastolic <84 mm Hg or diastolic 80 to 84 mm Hg and systolic <130 mm Hg; high normal: systolic 130 to 139 mm Hg and diastolic <90 mm Hg or diastolic 85 to 89 mm Hg and systolic <140 mm Hg; stage 1 hypertension: systolic 140 to 159 mm Hg and diastolic <100 mm Hg or diastolic 90 to 99 mm Hg and systolic <160 mm Hg; stage 2 hypertension: systolic 160 to 179 mm Hg and diastolic <110 mm Hg or diastolic 100 to 109 mm Hg and systolic <180 mm Hg; stage 3 hypertension: systolic 180 to 209 mm Hg and diastolic <120 mm Hg or diastolic 110 to 119 mm Hg and systolic <210 mm Hg; and stage 4 hypertension: systolic  $\geq$ 210 mm Hg or diastolic  $\geq$ 120 mm Hg.

The comparative strength of the association of end-stage renal disease from any cause with systolic, as compared with diastolic, blood pressure was also examined. The relation between blood pressure and end-stage renal disease from any cause was also investigated in the subgroup of screened men who actually entered the MRFIT study and whose blood pressure therefore was deemed unlikely to be elevated as a consequence of preexisting renal disease. The availability of serum creatinine measurements and dipstick measurements of urinary protein excretion for these men at entry into MRFIT enabled us to analyze the relation of blood pressure to the incidence of end-stage renal disease while taking into account renal function at base line.

## RESULTS

The characteristics of the men in this analysis are shown in Table 2. During the follow-up period (average length, 16 years), 814 men either entered the Medicare End-Stage Renal Disease Program or died of renal disease (Table 1). Of these, 649 entered the Medicare treatment program between the time of their screening for MRFIT and December 31, 1990, and 234 men died of renal disease, 165 of whom did not receive long-term dialysis or a transplant. The cumulative percentages of men who either entered the registry or died of renal disease after 5, 10, and 15 years of follow-up were 0.02 percent, 0.08 percent, and 0.22 percent, respectively.

Figure 1 shows the cumulative incidence during follow-up of end-stage renal disease due to any cause, according to the seven blood-pressure categories. The crude differences in the rates for the blood-pressure categories were reduced somewhat by adjustment for age and other covariates. The reduction occurred because all the factors considered were associated with a significantly increased risk of end-stage renal disease ( $P < 0.001$  for each adjustment factor in the multivariate analysis) and, except for cigarette smoking, were positively correlated with blood pressure. The risk of end-stage renal disease associated with higher blood pressure was strong, positive, and statistically significant in all subgroups defined by age and other base-line covariates. However, the positive associations were weaker among older men, blacks, and men with diabetes (data not shown).

The age-adjusted incidence of end-stage renal disease and the estimated relative risk (adjusted for seven

Table 1. Crude Rates of End-Stage Renal Disease in 332,544 Men Screened for MRFIT.

EVENT AND CAUSE (ICD-9-CM CODE)*	NO. OF MEN	RATE PER 100,000 PERSON-YEARS
Entry into Medicare registry		
Diabetes mellitus (250)	149	2.93
Hypertension (401, 403, 404)	173	3.40
Glomerulonephritis (580-583)	159	3.13
Congenital anomalies (753.1, 759.8)	50	0.98
Pyelonephritis (590)	13	0.26
Other or unknown	105	2.07
Total	649	12.77
Death from end-stage renal disease		
Hypertensive renal disease (403, 404)	31	0.61
Diabetes mellitus with nephropathy (250.4)	0	0.00
Gouty nephropathy (274.1)	0	0.00
Nephrocalcinosis (275.4)	2	0.04
Nephritis, nephrotic syndrome, and nephrosis (580-589)	153	3.01
Infection of the kidney (590)	12	0.24
Hydronephrosis (591)	1	0.02
Calculus of the kidney and ureter (592)	0	0.00
Other kidney disorders (593.3, 593.4, 593.5, 593.7, 593.8, 593.9)	25	0.49
Bladder-neck obstruction (596)	0	0.00
Hyperplasia of prostate (600)	2	0.04
Cystic kidney disease (753.1)	8	0.16
Total	234	4.60
Entry into registry or death from end-stage renal disease	814	16.01

\*Entry into the registry and death from end-stage renal disease are not mutually exclusive.

Table 2. Age, Race, Income, and Risk Factors in 332,544 Men Screened for MRFIT.\*

CHARACTERISTIC AT SCREENING	VALUE
Age (yr)	46±6
Race (%)	
White	90.4
Black	6.1
Other	3.5
Family income <\$25,000 (%)	58.4
Cigarette smoker (%)	36.0
Cigarettes/day	26±13
History of heart attack (%)	1.5
Medication for diabetes mellitus (%)	1.5
Blood pressure (mm Hg)	
Systolic	130.0±15.8
Diastolic	83.7±10.5
Serum cholesterol (mg/dl)†	214±39

\*Plus-minus values are means ±SD.

†To convert values for serum cholesterol to millimoles per liter, multiply by 0.026.

base-line factors) according to the seven blood-pressure categories are shown in Table 3. The risk of end-stage renal disease in men with hypertension, as compared with men with optimal levels of blood pressure, increased with each of the four successively more severe stages of hypertension. Of the cases observed, 49 percent were attributable to hypertension of stage 1 or higher. Among men who survived the first 10 years after MRFIT screening without end-stage renal disease, the relative risks of eventually having the condition in men with hypertension as compared with men with optimal blood pressure were 2.8 (stage 1 hypertension), 5.0 (stage 2), 8.4 (stage 3), and 12.4 (stage 4).

The combined effects of various levels of systolic and diastolic pressure on the age-adjusted incidence of end-stage renal disease are shown in Figure 2. The differences in incidence attributable to differences in diastolic blood pressure were far less marked than the steep risk gradient apparent for systolic blood pressure. For example, among the men in whom the diagnosis of stage 1 hypertension was based on systolic blood pressure (140 to 159 mm Hg), the rates of end-stage renal disease for the four lower categories of diastolic blood pressure were similar. In contrast, for the men whose diagnosis of stage 1 hypertension was based on high diastolic blood pressure (90 to 99 mm Hg), the incidence rates rose sharply from 9.8 to 16.4 per 100,000 person-years, even across the three categories of systolic blood pressure within the normotensive range. Overall, the rates of end-stage renal disease were markedly higher for men with hypertensive levels of both systolic and diastolic blood pressure.

To compare systolic blood pressure with diastolic blood pressure in relation to the relative risk of end-stage renal disease, we divided the ranges of these blood-pressure variables into quintiles (Table 4). Risk was not significantly increased in the next-to-lowest quintile of either measure of blood pressure, as compared with the lowest quintile. For the third, fourth,

and highest quintiles of both systolic and diastolic pressure, however, the relative risk rose progressively. After adjustment for age, race, serum cholesterol concentration, number of cigarettes smoked per day, use of medication for diabetes mellitus, and previous myocardial infarction, the relative risk of end-stage renal disease associated with a base-line blood pressure higher by 1 SD (systolic, 15.8 mm Hg; diastolic, 10.5 mm Hg) was similar for systolic pressure (1.7; 95 percent confidence interval, 1.7 to 1.8) and diastolic pressure (1.7; 95 percent confidence interval, 1.6 to 1.8). However, when systolic and diastolic pressure were considered together in the same proportional-hazards model, with adjustment for all other variables, a base-line systolic pressure higher by 1 SD had more predictive power (relative risk, 1.6; 95 percent confidence interval, 1.5 to 1.7) than a similar increase in diastolic pressure (relative risk, 1.2; 95 percent confidence interval, 1.1 to 1.2).

The patterns of risk associated with blood-pressure levels were similar for hypertensive end-stage renal disease and for end-stage renal disease due to any cause; 193 men had hypertensive end-stage renal disease. After adjustment for the covariates listed above, the relative risk of end-stage renal disease attributed to hypertension that was associated with a blood pressure higher by 1 SD was 2.0 (95 percent confidence interval, 1.8 to 2.1) for systolic blood pressure and 1.9 (95 percent confidence interval, 1.8 to 2.2) for diastolic blood pressure.

#### Men Who Entered the MRFIT Study

Too few cases of end-stage renal disease (a total of 35) occurred among the 12,866 men who entered MRFIT to permit classification in the seven blood-pressure categories. Therefore, for these men, blood pressure was entered as a continuous variable in the multivariate model. Among men who entered MRFIT, a systolic blood pressure higher by 1 SD was associated with a doubling of the risk of end-stage renal disease ( $P<0.001$ ); for those not in the trial the risk increased by a factor of 1.8 ( $P<0.001$ ). The results for diastolic

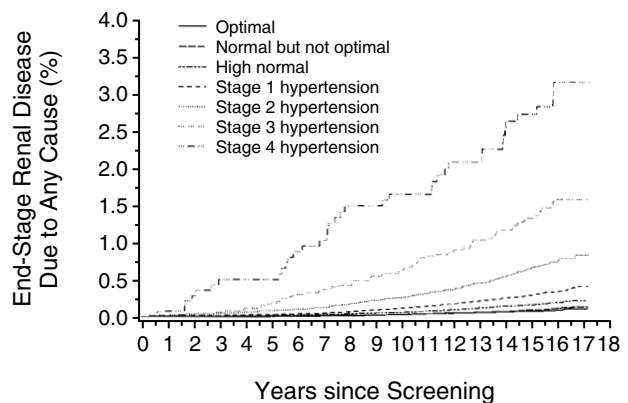


Figure 1. Cumulative Incidence of End-Stage Renal Disease Due to Any Cause, According to Blood-Pressure Category in 332,544 Men Screened for MRFIT.

blood pressure were similar. For men who entered MRFIT, a diastolic blood pressure higher by 1 SD was associated with a 2.5-fold increase in the risk of end-stage renal disease ( $P < 0.001$ ); for men not in the trial, the risk was increased 1.7-fold ( $P < 0.001$ ). When the serum creatinine concentration and urinary protein excretion at entry into the trial were included as covariates in multivariate models, the relative risks of end-stage renal disease associated with a blood pressure higher by 1 SD did not change (for systolic blood pressure: 2.0; 95 percent confidence interval, 1.5 to 2.7; for diastolic pressure: 2.5; 95 percent confidence interval, 1.4 to 4.3). Moreover, when the analysis was confined to the 7817 men who entered MRFIT with a serum creatinine concentration of less than 1.2 mg per deciliter (106  $\mu\text{mol}$  per liter) and a urinary protein excretion of less than 1+, among whom end-stage renal disease developed in 19, estimates of relative risk associated with a blood pressure higher by 1 SD (for systolic blood pressure: 1.8; 95 percent confidence interval, 1.2 to 2.7; for diastolic pressure: 1.7; 95 percent confidence interval, 0.8 to 3.4) were not significantly different from those for the total MRFIT cohort of 12,866 men.

### DISCUSSION

Our study extends knowledge of the link between blood pressure and renal disease in several ways. Higher blood pressure, as measured carefully on a single occasion, was a strong independent risk factor for end-stage renal disease. The increase in risk associated with higher blood pressure was graded and continuous throughout the distribution of blood-pressure readings above the optimal level. Our results demonstrate the validity of using the Joint National Committee's categories in the predic-

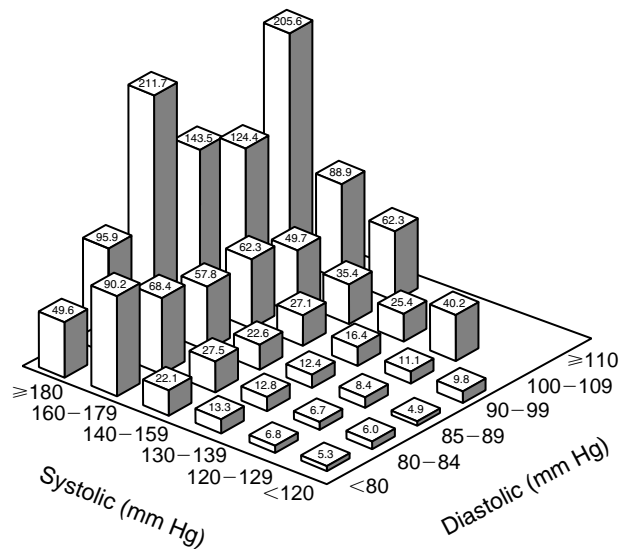


Figure 2. Age-Adjusted Rate of End-Stage Renal Disease Due to Any Cause per 100,000 Person-Years, According to Systolic and Diastolic Blood Pressure in 332,544 Men Screened for MRFIT.

Data on men with stage 3 and stage 4 hypertension were combined because of their small number.

tion of end-stage renal disease. Risk estimates were graded for both systolic and diastolic blood pressure considered separately, but systolic pressure was the stronger predictor of subsequent disease when both variables were considered together. These relations, including the pattern of interactions with age and diabetes mellitus, are very similar to those between coronary heart disease or stroke and blood pressure.<sup>15-17</sup> Older age, lower income, higher serum cholesterol concentrations, cigarette smoking, diabetes mellitus, a history of hypertension, and black race were also associated with an increased risk of end-stage renal disease.

Accelerated and malignant hypertension have long been known to be linked with an increased risk of renal failure, and clinical trials studying patients with this diagnosis have demonstrated that antihypertensive-drug therapy prolongs survival and slows the progression of renal disease.<sup>18-21</sup> The risk of renal failure associated with less severe hypertension has been investigated only recently.<sup>2</sup> In an analysis of 26 geographic areas in Maryland, the incidence of hypertensive end-stage renal disease correlated closely with the prevalence of hypertension, especially severe hypertension.<sup>22</sup> During a 15-year follow-up of 11,912 hy-

Table 3. Base-Line Blood Pressure and the Incidence of End-Stage Renal Disease Due to Any Cause in 332,544 Men Screened for MRFIT.

BLOOD-PRESSURE CATEGORY*	NO. OF MEN	NO. WITH END-STAGE RENAL DISEASE	AGE-ADJUSTED RATE PER 100,000 PERSON-YEARS†	ADJUSTED RELATIVE RISK (95% CI)‡
Optimal	61,089	51	5.3	1.0
Normal but not optimal	81,621	86	6.6	1.2 (0.8-1.7)
High normal	73,798	134	11.1	1.9 (1.4-2.7)§
Hypertension				
Stage 1 (mild)	85,684	275	21.0	3.1 (2.3-4.3)§
Stage 2 (moderate)	23,459	158	43.6	6.0 (4.3-8.4)§
Stage 3 (severe)	5,464	73	96.1	11.2 (7.7-16.2)§
Stage 4 (very severe)	1,429	37	187.1	22.1 (14.2-34.3)§
Total	332,544	814	15.6	—

\*Blood pressure was categorized as follows: optimal: systolic  $< 120$  mm Hg and diastolic  $< 80$  mm Hg; normal, not optimal: systolic 120 to 129 mm Hg and diastolic  $< 84$  mm Hg or diastolic 80 to 84 mm Hg and systolic  $< 130$  mm Hg; high normal: systolic 130 to 139 mm Hg and diastolic  $< 90$  mm Hg or diastolic 85 to 89 mm Hg and systolic  $< 140$  mm Hg; stage 1 hypertension: systolic 140 to 159 mm Hg and diastolic  $< 100$  mm Hg or diastolic 90 to 99 mm Hg and systolic  $< 160$  mm Hg; stage 2 hypertension: systolic 160 to 179 mm Hg and diastolic  $< 110$  mm Hg or diastolic 100 to 109 mm Hg and systolic  $< 180$  mm Hg; stage 3 hypertension: systolic 180 to 209 mm Hg and diastolic  $< 120$  mm Hg or diastolic 110 to 119 mm Hg and systolic  $< 210$  mm Hg; and stage 4 hypertension: systolic  $\geq 210$  mm Hg or diastolic  $\geq 120$  mm Hg.

†Adjusted by the direct method for the age distribution of all men screened.

‡Relative risks, with men with optimal blood pressure as the reference category, were estimated with use of a proportional-hazards regression model, with stratification according to clinic and adjustment for age, race, income, serum cholesterol concentration, number of cigarettes smoked per day, use of medication for diabetes mellitus, and previous myocardial infarction. CI denotes confidence interval.

§ $P < 0.001$ .

Table 4. Adjusted Relative Risk of End-Stage Renal Disease Due to Any Cause According to Quintile of Blood Pressure in 332,544 Men Screened for MRFIT.

BLOOD-PRESSURE QUINTILE	SYSTOLIC			DIASTOLIC		
	RANGE	MEAN	ADJUSTED RELATIVE RISK (95% CI)*	RANGE	MEAN	ADJUSTED RELATIVE RISK (95% CI)*
	<i>mm Hg</i>			<i>mm Hg</i>		
Lowest	<117	110.2	1.0	<75	69.4	1.0
Second	117–123	120.1	1.0 (0.7–1.4)	75–79	77.2	1.3 (0.9–1.8)
Third	124–130	127.2	1.5 (1.1–2.2)†	80–85	82.2	1.4 (1.1–1.9)‡
Fourth	131–140	135.4	2.2 (1.6–3.1)§	86–91	88.4	2.0 (1.5–2.7)§
Highest	>140	153.2	5.0 (3.7–6.7)§	>91	98.9	4.0 (3.0–5.2)§

\*Relative risks, with men in the lowest quintile as the reference category, were estimated with use of a proportional-hazards regression model, with stratification according to clinic and adjustment for age, race, income, serum cholesterol concentration, number of cigarettes smoked per day, use of medication for diabetes mellitus, and previous myocardial infarction. CI denotes confidence interval.

†P=0.009.

‡P=0.02.

§P<0.001.

pertensive male veterans, systolic blood pressure before treatment was a stronger predictor of end-stage renal disease than was diastolic pressure.<sup>23</sup> The results of our study are consistent with observational studies of blood pressure in patients with mild-to-moderate impairment of renal function.<sup>24-30</sup> Observational studies and clinical trials involving patients with established renal insufficiency have also demonstrated that lowering blood pressure preserves renal function.<sup>31-36</sup>

The most important barrier to studying the relation of blood pressure to end-stage renal disease is the low incidence of end-stage disease. The large size of the MRFIT screening cohort and the 15-to-17-year follow-up period produced a large number of cases for study. The availability of comprehensive data on death from renal disease and treatment for end-stage disease means that differences in the incidence of the disease according to blood-pressure levels are unlikely to be due to systematic differences either in the assessment of outcome or in the subjects' access to care. Likewise, our use of end-stage renal disease due to any cause as the primary outcome precludes the possibility of misclassifying the causes of the condition.<sup>37,38</sup>

Our study, however, has several limitations. No women were included. Blood pressure was measured on only one occasion, resulting in an underestimation of the strength of the association of end-stage renal disease with blood pressure.<sup>39</sup> A more precise measure — for example, an average of blood-pressure readings from several visits made over a longer period — would yield greater differences in the incidence of end-stage renal disease associated with higher blood pressure. We also collected no information on antihypertensive therapy. Misclassification of a treated hypertensive person as normotensive or less severely hypertensive would also tend to weaken the estimated risk associated with higher blood pressure. Most of the men were studied before the widespread use of angiotensin-converting-enzyme inhibitors, a class of antihypertensive drugs that may offer special renal protection.

An additional limitation of our study is that renal

function was not assessed at base line except in the subgroup of men who entered the MRFIT trial. Thus, for the majority of men screened, we do not know whether renal insufficiency was already present in those in whom end-stage renal disease later developed. The similar relation in the two groups — all men screened for MRFIT and those who actually entered that study — between blood pressure and end-stage renal disease due to any cause; the independence of that relation from base-line serum creatinine concentrations and urinary protein excretion in the men entering the MRFIT trial; and the

persistence of the relation after 10 years of follow-up in the group of all screened men argue against viewing preexisting renal disease as an important contributor to the observed associations. However, the early increase in the incidence of end-stage renal disease in men with the highest blood pressures (Fig. 1) may reflect preexisting renal disease in this subgroup. The lack of information on renal function, both at base line and during follow-up, does mean, however, that we cannot say definitively whether the strong association between blood pressure and the incidence of end-stage renal disease was due to the initiation of renal disease or to the accelerated progression of preexisting disease.

The costs of end-stage renal disease to the individual and to society make the identification of modifiable risk factors for the condition an important public health priority. Interventions to prevent end-stage renal disease need to emphasize the prevention and control of high blood pressure. The importance of the primary prevention of hypertension, by slowing or stopping the increase in blood pressure from youth to middle age, has received widespread recognition as one means of addressing the epidemic of cardiovascular disease<sup>40,41</sup>; primary prevention also has the potential to prevent a large proportion of cases of end-stage renal disease. In addition, the need to prevent end-stage renal disease dictates continued efforts to achieve the early identification of persons with hypertension and to provide them with effective antihypertensive therapy.

We are indebted to Dr. Paul Eggers and Dr. Marshall McBean of the Health Care Financing Administration for their assistance in the study and to Ms. Barbara Pawloski for editorial help.

## REFERENCES

1. Renal Data System. USRDS 1994 annual data report. Bethesda, Md.: National Institute of Diabetes and Digestive and Kidney Diseases, 1994. (NIH publication no. 94-3176.)
2. Whelton PK, Klag MJ. Hypertension as a risk factor for renal disease: review of clinical and epidemiological evidence. *Hypertension* 1989;13:Suppl 1:1-19-1-27.
3. Multiple Risk Factor Intervention Trial Research Group. Multiple Risk Factor Intervention Trial: risk factor changes and mortality results. *JAMA* 1982;248:1465-77.

4. The Multiple Risk Factor Intervention Trial Research Group. Statistical design considerations in the NHLI Multiple Risk Factor Intervention Trial (MRFIT). *J Chronic Dis* 1977;30:261-75.
5. Sherwin R, Kaelber CT, Kezdi P, Kjelsberg MO, Thomas HE Jr. The Multiple Risk Factor Intervention Trial (MRFIT) II: the development of the protocol. *Prev Med* 1981;10:402-25.
6. Neaton JD, Grimm RH Jr, Cutler JA. Recruitment of participants for the Multiple Risk Factor Intervention Trial (MRFIT). *Control Clin Trials* 1987;8:Suppl:41S-53S.
7. Dischinger P, DuChene AG. Quality control aspects of blood pressure measurements in the Multiple Risk Factor Intervention Trial. *Control Clin Trials* 1986;7:Suppl:137S-157S.
8. National Heart and Lung Institute. Manual of laboratory operations: Lipid Research Clinics Program. Washington, D.C.: Government Printing Office, 1974. (DHEW publication no. (NIH) 75-628.)
9. Health Care Financing Administration. Research report: end stage renal disease, 1985. Washington, D.C.: Government Printing Office, 1987. (HCFA publication no. 03274.)
10. Wentworth DN, Neaton JD, Rasmussen WL. An evaluation of the Social Security Administration master beneficiary record file and the National Death Index in the ascertainment of vital status. *Am J Public Health* 1983;73:1270-4.
11. Department of Health and Human Services. The international classification of diseases, 9th rev., clinical modification: ICD-9-CM. Vol. 1. Diseases: tabular list. Washington, D.C.: Government Printing Office, 1980. (DHHS publication no. (PHS) 80-1260.)
12. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-81.
13. Cox DR. Regression models and life-tables. *J R Stat Soc [B]* 1972;34:187-202.
14. The fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). *Arch Intern Med* 1993;153:598-615.
15. Stamler J, Stamler R, Neaton JD. Blood pressure, systolic and diastolic, and cardiovascular risks: U.S. population data. *Arch Intern Med* 1993;153:598-615.
16. Neaton JD, Wentworth D. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease: overall findings and differences by age for 316,099 white men: Multiple Risk Factor Intervention Trial Research Group. *Arch Intern Med* 1992;152:56-64.
17. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993;16:434-44.
18. Kincaid-Smith P, McMichael J, Murphy EA. The clinical course and pathology of hypertension with papilloedema (malignant hypertension). *Q J Med* 1958;27:117-53.
19. Perera GA. Hypertensive vascular disease; description and natural history. *J Chronic Dis* 1955;1:33-42.
20. Mroczek WJ, Davidov M, Gavrilovich L, Finnerty FA Jr. The value of aggressive therapy in the hypertensive patient with azotemia. *Circulation* 1969;40:893-904.
21. Mamdani BH, Lim VS, Mahurkar SD, Katz AI, Dunea G. Recovery from prolonged renal failure in patients with accelerated hypertension. *N Engl J Med* 1974;291:1343-4.
22. Whittle JC, Whelton PK, Seidler AJ, Klag MJ. Does racial variation in risk factors explain black-white differences in the incidence of hypertensive end-stage renal disease? *Arch Intern Med* 1991;151:1359-64.
23. Perry HM Jr, Miller JP, Fornoff JR, et al. Early predictors of 15-year end-stage renal disease in hypertensive patients. *Hypertension* 1995;25:587-94.
24. Shulman NB, Ford CE, Hall DW, et al. Prognostic value of serum creatinine and effect of treatment of hypertension on renal function: results from the Hypertension Detection and Follow-up Program. *Hypertension* 1989;13:Suppl 1:1-80-1-93.
25. Perneger TV, Nieto FJ, Whelton PK, Klag MJ, Comstock GW, Szklo M. A prospective study of blood pressure and serum creatinine: results from the "Clue" Study and the ARIC Study. *JAMA* 1993;269:488-93.
26. Rosansky SJ, Hoover DR, King L, Gibson J. The association of blood pressure levels and change in renal function in hypertensive and nonhypertensive subjects. *Arch Intern Med* 1990;150:2073-6.
27. Ravid M, Savin H, Lang R, Jutrin I, Shoshana L, Lishner M. Proteinuria, renal impairment, metabolic control, and blood pressure in type 2 diabetes mellitus — a 14-year follow-up report on 195 patients. *Arch Intern Med* 1992;152:1225-9.
28. Rostand SG, Brown G, Kirk KA, Rutsky EA, Dustan HP. Renal insufficiency in treated essential hypertension. *N Engl J Med* 1989;320:684-8.
29. Tierney WM, McDonald CJ, Luft FC. Renal disease in hypertensive adults: effect of race and type II diabetes mellitus. *Am J Kidney Dis* 1989;13:485-93.
30. Walker WG, Neaton JD, Cutler JA, Neuwirth R, Cohen JD. Renal function change in hypertensive members of the Multiple Risk Factor Intervention Trial: racial and treatment effects. *JAMA* 1992;268:3085-91.
31. Klahr S, Schreiner G, Ichikawa I. The progression of renal disease. *N Engl J Med* 1988;318:1657-66.
32. Pettinger WA, Lee HC, Reisch J, Mitchell HC. Long-term improvement in renal function after short-term strict blood pressure control in hypertensive nephrosclerosis. *Hypertension* 1989;13:766-72.
33. Parving HH, Andersen AR, Smidt UM, Svendsen PA. Early aggressive antihypertensive treatment reduces rate of decline in kidney function in diabetic nephropathy. *Lancet* 1983;1:1175-9.
34. Brazy PC, Fitzwilliam JF. Progressive renal disease: role of race and antihypertensive medications. *Kidney Int* 1990;37:1113-9.
35. Zucchelli P, Zuccala A, Borghi M, et al. Long-term comparison between captopril and nifedipine in the progression of renal insufficiency. *Kidney Int* 1992;42:452-8.
36. Bergstrom J, Alvestrand A, Bucht M, Gutierrez A. Progression of chronic renal failure in man is retarded with more frequent clinical follow-ups and better blood pressure control. *Clin Nephrol* 1986;25:1-6.
37. Perneger TV, Whelton PK, Klag MJ, Rossiter KA. Diagnosis of hypertensive end-stage renal disease: effect of patient's race. *Am J Epidemiol* 1995;141:10-5.
38. Perneger TV, Brancati FL, Whelton PK, Klag MJ. End-stage renal disease attributable to diabetes mellitus. *Ann Intern Med* 1994;121:912-8.
39. MacMahon S, Peto R, Cutler J, et al. Blood pressure, stroke, and coronary heart disease. I. Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990;335:765-74.
40. National Heart, Lung, and Blood Institute. Report on the Task Force on Research in Epidemiology and Prevention of Cardiovascular Diseases. Bethesda, Md.: Department of Health and Human Services, 1994.
41. National High Blood Pressure Education Program Working Group. National High Blood Pressure Education Program Working Group report on primary prevention of hypertension. *Arch Intern Med* 1993;153:186-208.