Prognostic Value of Serum Creatinine and Effect of Treatment of Hypertension on Renal Function

Results From the Hypertension Detection and Follow-up Program

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The Hypertension Detection and Follow-up Program followed up 10,940 persons for 5 years in a community-based, randomized, controlled trial of treatment for hypertension. Participants were randomized to one of two treatment groups, stepped care and referred care. The primary end point of the study was all-cause mortality, with morbid events involving the heart, brain, and kidney as secondary end points. Loss of renal function, ascertained by a change in serum creatinine, was among these secondary events. Baseline serum creatinine concentration had a significant prognostic value for 8-year mortality. For persons with a serum creatinine concentration greater than or equal to 1.7 mg/dl, 8-year mortality was more than three times that of all other participants. The estimated 5-year incidence of substantial decline in renal function was 21.7/1,000 in the stepped-care group and 24.6/1,000 in the referred-care group. Among persons with a baseline serum creatinine level between 1.5 and 1.7 mg/dl, the 5-year incidence of decline was 113.3/1,000 (stepped care) and 226.6/1,000 (referred care) (p<0.01). The incidence of decline in renal function was greater in men, blacks, and older adults, as well as in those with higher entry diastolic blood pressure. Among persons with a baseline serum creatinine level greater than or equal to 1.7 mg/dl, serum creatinine concentration declined by 25% or more in 28.6% of stepped-care and 25.2% of referred-care participants. Although the incidence of clinically significant hypercreatininemia in a hypertensive population is low, an elevated serum creatinine concentration is a very potent independent risk factor for mortality. The slightly lower rate of development of hypercreatininemia and the higher rate of improvement in stepped-care compared with referred-care participants is consistent with the belief that aggressive treatment of hypertension may reduce renal damage and the associated increased risk of death. (Hypertension 1989;13(suppl I):I-80-I-93)

Hypertension is one of the most common adult chronic diseases for which treatment is available. The disease affects all race, sex, and age groups but has a markedly higher prevalence among blacks and a concomitantly higher mortality from its sequelae. The risk associated with hypertension includes fatal and nonfatal outcomes involving the brain, heart, and kidneys. Although the development of cerebrovascular and cardiovascular complications of hypertension have been described frequently, in recent years, less attention has been directed toward concomitant renal disease.

The kidney is one of the principal target organs of hypertension, and most diseases of the kidney are...
associated with blood pressure elevation.5-9 The mechanism by which hypertension damages the kidney and the relative contribution of high blood pressure to the progression of renal insufficiency remain incompletely defined. In general, large-scale, prospective, randomized trials of treatment for hypertension have not focused on renal function, possibly because of the relatively low incidence of renal disease in hypertensive subjects and because the lack of premonitory symptoms makes ascertainment of renal disease difficult even in the general population. Except for urinalysis and serum creatinine concentration, tests to accurately measure renal function or detect new renal disease are often difficult to conduct.

The clinical quantification of renal function to provide early evidence of disease is usually thought to require determination of the plasma clearance rate of endogenous creatinine,10 a procedure requiring a 24-hour urine collection. In general, it is difficult to obtain an accurate 24-hour urine collection from patients being treated on an outpatient basis, thus making this procedure an impractical test for epidemiological evaluation. For this reason, elevated serum creatinine concentration has frequently been used as a criterion for renal morbidity in clinical trials of hypertension.11-15

This article reports the prevalence of hypercreatininemia at baseline, its use as a prognostic marker, and the longitudinal change of serum creatinine concentration in participants of the Hypertension Detection and Follow-up Program (HDFP). The data base of the HDFP provides a source of information to examine renal function and its course during 5 years in a large cohort of persons with hypertension. The HDFP used a central laboratory and standardized procedures to routinely monitor serum creatinine in its stepped-care (SC) cohort during the 5-year treatment trial (1973-1979) and on three specific occasions in its referred-care (RC) cohort. In addition, the HDFP data base contains follow-up data on 8-year mortality, thereby providing an opportunity to examine the mortality risk associated with serum creatinine.

Subjects and Methods

Trial Design

The design and methods of the HDFP have been described in detail in previous articles.16,17 Briefly, participants were recruited through a two-stage, community-based, screening program for high blood pressure that was performed in 14 US communities between 1973 and 1974.18 From a base population of 159,000 people, aged 30-69 years, a cohort of 10,940 persons with hypertension was identified. (Only bedfast and institutionalized persons were excluded.) Each participant was randomly assigned to either the SC or the RC group; 5,485 persons to the SC group and 5,455 persons to the RC group. Randomization was stratified by clinical center and by three ranges of diastolic blood pressure (DBP): 90-104 mm Hg (stratum 1), 105-114 mm Hg (stratum 2), and greater than or equal to 115 mm Hg (stratum 3). The two treatment groups were comparable with regard to age, race, sex, and risk factors at entry into the study.17 The mean age was 50.8 years, and the percentages of white men, black men, white women, and black women were 34.3%, 21.4%, 19.6%, and 24.6%, respectively. The percentages of participants in the three DBP strata were 71.5%, 18.8%, and 9.7%, respectively. Participants with known primary parenchymal renal disease like chronic glomerulonephritis or diabetic nephropathy were not excluded, but the prevalence of such disease was less than 1%.19

At entry into the study, a physical examination, chest X-ray, 12-lead electrocardiogram, and blood and urine tests were performed. A similar examination in the clinic was repeated at the end of Years 2 and 5. In addition, all SC and RC participants were seen at home (or place of employment at one clinic) at the end of Years 1, 2, 4, and 5 for interval health history and blood pressure measurement. The SC participants were seen at intervals dictated by clinical judgment but at least every 4 months.

Stepped Care

The SC program was designed to treat hypertension by a standardized drug protocol. Therapy was increased stepwise to achieve and maintain a reduction of DBP to or below set goals. Goal DBP was defined as 90 mm Hg for those entering the trial with a DBP of 100 mm Hg or greater or who were already receiving antihypertensive drug therapy; goal DBP was defined as a 10 mm Hg decrease for those with a DBP of 90-99 mm Hg. Drug treatment included the use of diuretic agents, adrenergic receptor blocking agents, and vasodilators. Seventy-five percent of SC participants received either the diuretic agent, chlorthalidone, alone or in combination with an antidiurenergic agent like reserpine or methyldopa.17

Serum Creatinine Determination

Serum creatinine concentration was determined for each participant at baseline and at the end of Years 2 and 5. For SC participants, serum creatinine was determined at 4-month intervals throughout the 5 years of follow-up. Blood samples were analyzed at a central laboratory with consistent methodology throughout the course of the study. Frozen samples were shipped by priority mail or air freight to the central laboratory where the samples were thawed, remixed, and analyzed within 24 hours.

The analysis of serum creatinine was performed with a Technicon SMA 12/60 multichannel analyzer (Technicon Corp., Tarrytown, New York) by Jaffe's reaction between alkaline picrate and creatinine.20 After color development, the absorbance was measured at 505 nm.

The sensitivity for creatinine analysis was expanded by standardizing the SMA 12/60 for the
range 0.0–5.00 mg/dl (0–442 μmol/l) creatinine instead of 0.00–10.00 mg/dl (0–884 μmol/l). Specimens with creatinine values greater than 5.0 mg/dl were diluted and reanalyzed. The reference standard was analyzed by a manual method. Appro- priate careful calibration and quality control procedures were followed. The target value for the creatinine concentration of the calibrator serum was determined by the reference laboratories of the Centers for Disease Control (CDC) in Atlanta, Georgia. The control serum and the calibrator serum were prepared in 50-liter pools by a commercial laboratory. Four lots each of calibrator and control sera were used in staggered fashion during the course of the trial. Results were read directly from the SMA 12/60 into the laboratory computer and were subsequently transferred to computer magnetic tapes that were mailed to the HDFP Coordinating Center.

Overall analytic drift was monitored by one blinded and two unblinded techniques. The blind surveillance used pools of sera prepared by the CDC and shipped to the central lab from selected HDFP clinics in containers identical to those containing patient samples. The data from these pools were monitored by the HDFP laboratory aspects committee, which periodically apprised the director of the central lab of any concerns. In addition, the central lab maintained unblinded records of the means of the control sera data for 30 days before and 30 days after a switch in control or calibrator sera. Finally, at the end of the study, duplicate patient samples that had been stored at −85°C since the onset of the study were thawed, analyzed, and compared with corresponding values obtained at baseline. These three methods revealed an analytic drift for creatinine that was judged insignificant.

**Baseline Serum Creatinine Strata**

Cutpoints for the stratified analysis of baseline serum creatinine concentration approximate selected percentiles. Because the distribution of serum creatinine is right-skewed and the upper range of values is generally viewed as indicative of renal damage, attention was focused on the distribution’s right tail. The cutpoints at 1.5, 1.7, 2.0, and 2.5 mg/dl (132.6, 150.3, 176.8, and 221.0 μmol/l) approximate the 95th, 97th, 98th, and 99th percentiles, respectively, of the distribution. The 0.8 mg/dl (70.7 μmol/l) cutpoint approximately marks the lower 10% of the distribution, and the 0.7 mg/dl (61.9 μmol/l) cutpoint, the lower 5%. The remainder of the distribution was divided into three intervals by cutpoints at 1.0 and 1.2 mg/dl (88.4 and 106.1 μmol/l), representing the approximate 40th and 75th percentiles.

The marker for baseline evidence of kidney damage in the HDFP was defined as a serum creatinine concentration of greater than or equal to 1.7 mg/dl, and this value has been used in the present analysis to define clinically significant hypercreatininemia. Borderline hypercreatininemia was defined as a serum creatinine concentration in the range 1.5–1.7 mg/dl.

**End Points**

Mortality from all causes was the primary end point of the HDFP. Every effort was made to ascertain the vital status of each participant, and only 0.95% of the participants were considered “lost” to 8-year follow-up. Cause-specific mortality and morbid events involving the heart, brain, and kidney were designated secondary end points. Differences in the frequency of observation of SC and RC participants introduced potential bias due to differential ascertainment, evaluation, and validation of nonfatal events. Because differences in the degree of ascertainment can affect observed differences in morbid event rates between the SC and RC groups, findings on nonfatal events must be interpreted with some caution.

The development of renal insufficiency was one of the secondary outcomes specified in the HDFP protocol. Development of a serum creatinine concentration greater than or equal to 2.0 mg/dl and twice the baseline value was originally specified in the protocol. This latter restriction has been relaxed in the present analysis, partly because such a large increase in serum creatinine was rare.

**Statistical Methods**

The analysis of mortality data was performed by standard life table methods to compute cumulative all-cause mortality rates, overall and stratified by baseline serum creatinine concentration. Specifically, the estimated cumulative proportion dying was computed as one minus the cumulative proportion surviving with the Cutler-Ederer estimator for the probability of surviving successive 3-month intervals. The Cutler-Ederer estimator, which does not take into account exact survival time, assumes that, on average, participants lost to or withdrawn from the study survive one half the interval in which they withdraw. More than 95% of the survivors experienced a full 8 years of follow-up for mortality. Less than 1% were considered lost to 8-year follow-up.

Cause-specific mortality rates were directly adjusted for distributional differences in age, race, and sex. A common standard population consisting of all HDFP trial participants was used to provide comparable rates in the various strata examined. Cause of death was assigned by nosologists with only death certificate information and with all personal and study identifying information masked.

The multiple logistic regression analysis was performed with the Walker-Duncan procedure. The relative odds ratio was calculated from $\exp^{\beta}$, where e is the number for which the Napierian logarithm is one, $\beta$ is the logistic coefficient, and $X$ is either one for the discrete variables or is the difference between the high- and low-risk value for continuous variables like age.
The tests of significance for the differences between SC and RC are based on the standard normal distribution for the comparison of two proportions (SC vs. RC). Because the subgroup analyses presented here involve multiple comparisons, a difference at the $p<0.05$ level may have occurred by chance in one of 20 comparisons. No adjustment for multiple comparisons was done.

**Results**

**Baseline Distribution of Serum Creatinine Concentration**

Table 1 presents baseline serum creatinine sample means and standard deviations, overall and by selected baseline characteristics. Also shown are the respective percentages and numbers of participants with concentrations greater than or equal to 1.5 mg/dl (132.6 $\mu$mol/l) and greater than or equal to 1.7 mg/dl (150.3 $\mu$mol/l) at baseline. In this sample of 10,768 persons with hypertension, the mean serum creatinine level was significantly higher for men than for women and for blacks than whites ($p<0.01$). These sex-race differences remained after adjustment for body mass index, age, level of blood pressure, use of antihypertensive medication at trial entry, an elevated fasting blood sugar level or a history of diabetes, a history of cancer, serum cholesterol level, and cigarette use. For the HDFP hypertensive population as a whole, 2.76% of the participants had a serum creatinine concentration greater than or equal to 1.7 mg/dl. Among black men, 5.17% had a serum creatinine concentration greater than or equal to 1.7 mg/dl compared with 2.53% of white men, 2.57% of black women, and 1.13% of white women. No differences in baseline mean creatinine levels were noted between the SC and RC groups, but a slightly higher percentage of SC participants had hypercreatininemia at trial entry. The frequency and cumulative distributions of serum creatinine concentration at entry into the HDFP are depicted in Figure 1 by race and sex.

As shown in Table 1, the baseline prevalence of serum creatinine concentrations greater than or equal to 1.5 mg/dl generally increased with age, blood pressure, serum uric acid, and proteinuria. Nearly 40% of all participants with a proteinuria level of 3+ or greater had a baseline serum creatinine value in this range, and 24.3% had a concentration greater than or equal to 1.7 mg/dl.

**Prognostic Value of Serum Creatinine Concentration**

The baseline level of serum creatinine was an important and significant risk factor for 8-year mortality among HDFP participants. As shown in Figure 2, the risk of death increased progressively with the concentration of creatinine, starting with creatinine levels between 0.80 and 0.99 mg/dl. There was nearly a fivefold increase in the 8-year mortality risk between the lowest and the highest risk strata of creatinine. As depicted by the cumulative 8-year life table mortality curves in Figure 3, the absolute risk of death associated with hypercreatininemia began in the 1st year of the study and became more marked in those with higher baseline creatinine concentrations as time passed. The absolute mortality risk generally was higher in blacks than in whites at all levels of serum creatinine, but the relative increase in risk associated with higher concentrations was similar.

The independent contribution of hypercreatininemia (creatinine $\geq 1.7$ mg/dl) at baseline to the risk of 8-year mortality was examined by multiple logistic regression analysis. The results, summarized in Table 2, suggest that the risk associated with hypercreatininemia was similar to the other variables considered except age and body mass index. The relative odds of dying in 8 years, after adjusting for all other factors examined, was more than twice as great for those with hypercreatininemia than for those with lower concentrations. When the analysis was restricted to those with mild hypertension (90–104 mm Hg diastolic without drug therapy for hypertension at entry), the risk of death associated with hypercreatininemia remained two times greater than in its absence.

Cause-specific 8-year mortality among SC and RC participants is presented in Table 3. Overall, death from renal disease in this cohort was rare; only 43 (3.1%) of the 1,393 deaths with a known cause were attributed to renal disease. However, the mean annual death rate from renal disease was approximately 5/10,000 persons—roughly 10 times the 1976 rate for the general US population in this age range. Most frequently, the cause of death among those with hypercreatininemia was attributed to cardiovascular rather than renal causes. Death from renal disease was much more likely in the presence of an elevated baseline serum creatinine concentration than in its absence. The mortality rates for neoplastic diseases were similar for those with and without hypercreatininemia.

**Change in Serum Creatinine Concentration**

Mean serum creatinine concentrations during the course of the HDFP trial are shown in Figure 4 by race-sex group. Throughout follow-up, the mean concentration of creatinine in women remained about 0.2 mg/dl (17.7 $\mu$mol/l) below that of men and remained higher in blacks than in whites for both sexes. For SC participants whose creatinine concentration was measured every 4 months, there was a gradual rise of about 0.2 mg/dl (17.7 $\mu$mol/l) in the mean concentration of serum creatinine during the first 2 years, which was followed by a leveling off for the next 3 years. The mean and standard deviation of the paired difference between the 60-month and baseline serum creatinine concentrations was $0.20\pm0.40$ mg/dl ($17.2\pm35.4$ $\mu$mol/l) for SC black men, $0.16\pm0.35$ mg/dl ($14.1\pm30.9$ $\mu$mol/l) for SC white men, $0.17\pm0.41$ mg/dl ($15.0\pm36.2$ $\mu$mol/l) for
### TABLE 1. Baseline Serum Creatinine of Hypertension and Detection Follow-up Program Participants, Overall and Stratified by Selected Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>Sample size</th>
<th>Mean±SD</th>
<th>≥1.50 % (n)*</th>
<th>≥1.70 % (n)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All randomized persons</td>
<td>10,768†</td>
<td>1.08±0.38</td>
<td>5.79 (623)</td>
<td>2.76 (297)</td>
</tr>
<tr>
<td>Treatment group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stepped care</td>
<td>5,402</td>
<td>1.08±0.40</td>
<td>6.00 (324)</td>
<td>2.94 (159)</td>
</tr>
<tr>
<td>Referred care</td>
<td>5,366</td>
<td>1.08±0.36</td>
<td>5.57 (299)</td>
<td>2.57 (138)</td>
</tr>
<tr>
<td>Sex-race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black men</td>
<td>2,107</td>
<td>1.22±0.37</td>
<td>11.58 (244)</td>
<td>5.17 (109)</td>
</tr>
<tr>
<td>White men</td>
<td>3,716</td>
<td>1.15±0.31</td>
<td>5.97 (222)</td>
<td>2.53 (94)</td>
</tr>
<tr>
<td>Black women</td>
<td>2,641</td>
<td>1.00±0.48</td>
<td>4.09 (108)</td>
<td>2.57 (68)</td>
</tr>
<tr>
<td>White women</td>
<td>2,304</td>
<td>0.92±0.23</td>
<td>2.13 (49)</td>
<td>1.13 (26)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30–34</td>
<td>685</td>
<td>1.02±0.26</td>
<td>3.36 (23)</td>
<td>2.04 (14)</td>
</tr>
<tr>
<td>35–39</td>
<td>930</td>
<td>1.03±0.26</td>
<td>3.23 (30)</td>
<td>2.15 (20)</td>
</tr>
<tr>
<td>40–44</td>
<td>1,323</td>
<td>1.05±0.37</td>
<td>4.38 (58)</td>
<td>2.94 (27)</td>
</tr>
<tr>
<td>45–49</td>
<td>1,779</td>
<td>1.03±0.38</td>
<td>4.10 (73)</td>
<td>1.45 (23)</td>
</tr>
<tr>
<td>50–54</td>
<td>2,013</td>
<td>1.08±0.32</td>
<td>5.91 (119)</td>
<td>2.33 (47)</td>
</tr>
<tr>
<td>55–59</td>
<td>1,698</td>
<td>1.10±0.49</td>
<td>7.48 (127)</td>
<td>3.65 (62)</td>
</tr>
<tr>
<td>60–64</td>
<td>1,360</td>
<td>1.12±0.38</td>
<td>7.28 (99)</td>
<td>3.38 (46)</td>
</tr>
<tr>
<td>65–69</td>
<td>980</td>
<td>1.15±0.42</td>
<td>9.59 (94)</td>
<td>5.41 (53)</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90–94</td>
<td>2,899</td>
<td>1.06±0.36</td>
<td>5.04 (146)</td>
<td>2.10 (61)</td>
</tr>
<tr>
<td>95–99</td>
<td>2,683</td>
<td>1.06±0.28</td>
<td>4.36 (117)</td>
<td>1.83 (49)</td>
</tr>
<tr>
<td>100–104</td>
<td>2,126</td>
<td>1.08±0.38</td>
<td>5.32 (113)</td>
<td>2.68 (57)</td>
</tr>
<tr>
<td>105–109</td>
<td>1,308</td>
<td>1.08±0.44</td>
<td>6.80 (89)</td>
<td>2.98 (39)</td>
</tr>
<tr>
<td>110–114</td>
<td>716</td>
<td>1.11±0.49</td>
<td>8.66 (62)</td>
<td>4.75 (34)</td>
</tr>
<tr>
<td>115–119</td>
<td>488</td>
<td>1.12±0.45</td>
<td>7.17 (35)</td>
<td>4.30 (21)</td>
</tr>
<tr>
<td>≥120</td>
<td>548</td>
<td>1.16±0.50</td>
<td>11.31 (61)</td>
<td>6.57 (36)</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;120</td>
<td>80</td>
<td>1.12±0.47</td>
<td>8.75 (7)</td>
<td>6.25 (5)</td>
</tr>
<tr>
<td>120–139</td>
<td>2,025</td>
<td>1.08±0.36</td>
<td>5.14 (104)</td>
<td>2.27 (46)</td>
</tr>
<tr>
<td>140–159</td>
<td>4,078</td>
<td>1.06±0.28</td>
<td>4.51 (184)</td>
<td>1.74 (71)</td>
</tr>
<tr>
<td>160–179</td>
<td>2,782</td>
<td>1.06±0.37</td>
<td>6.04 (168)</td>
<td>2.70 (75)</td>
</tr>
<tr>
<td>180–199</td>
<td>1,188</td>
<td>1.11±0.54</td>
<td>6.99 (83)</td>
<td>4.29 (51)</td>
</tr>
<tr>
<td>≥200</td>
<td>615</td>
<td>1.17±0.58</td>
<td>12.52 (77)</td>
<td>7.97 (49)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>&lt;23.89</td>
<td>2,156</td>
<td>1.04±0.41</td>
<td>6.08 (131)</td>
</tr>
<tr>
<td>23.89–26.42</td>
<td>2,140</td>
<td>1.07±0.32</td>
<td>5.14 (110)</td>
<td>2.15 (46)</td>
</tr>
<tr>
<td>26.43–28.78</td>
<td>2,161</td>
<td>1.10±0.31</td>
<td>5.46 (118)</td>
<td>2.45 (53)</td>
</tr>
<tr>
<td>28.79–32.25</td>
<td>2,144</td>
<td>1.12±0.48</td>
<td>6.58 (141)</td>
<td>3.36 (72)</td>
</tr>
<tr>
<td>≥32.26</td>
<td>2,141</td>
<td>1.06±0.34</td>
<td>5.65 (121)</td>
<td>2.43 (52)</td>
</tr>
<tr>
<td>Entry BP medication status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated</td>
<td>7,971</td>
<td>1.05±0.28</td>
<td>4.29 (342)</td>
<td>1.88 (150)</td>
</tr>
<tr>
<td>Treated</td>
<td>2,797</td>
<td>1.15±0.57</td>
<td>10.05 (281)</td>
<td>5.26 (147)</td>
</tr>
<tr>
<td>History of diabetes or FBS≥140 mg/dl</td>
<td>9,704</td>
<td>1.08±0.36</td>
<td>5.56 (540)</td>
<td>2.58 (250)</td>
</tr>
<tr>
<td>No</td>
<td>1,064</td>
<td>1.10±0.53</td>
<td>7.80 (83)</td>
<td>4.42 (47)</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Negative</td>
<td>8,394</td>
<td>1.06±0.27</td>
<td>4.62 (388)</td>
<td>1.82 (153)</td>
</tr>
<tr>
<td>Trace</td>
<td>738</td>
<td>1.09±0.34</td>
<td>5.28 (39)</td>
<td>2.71 (20)</td>
</tr>
<tr>
<td>1+</td>
<td>367</td>
<td>1.18±0.48</td>
<td>13.35 (49)</td>
<td>8.45 (31)</td>
</tr>
<tr>
<td>2+</td>
<td>183</td>
<td>1.29±0.63</td>
<td>20.77 (38)</td>
<td>15.30 (28)</td>
</tr>
<tr>
<td>3+</td>
<td>102</td>
<td>1.79±1.46</td>
<td>43.14 (44)</td>
<td>25.49 (28)</td>
</tr>
<tr>
<td>4+</td>
<td>38</td>
<td>1.71±1.40</td>
<td>26.32 (10)</td>
<td>21.05 (8)</td>
</tr>
<tr>
<td>Serum uric acid (mg/dl)</td>
<td>&lt;4.90</td>
<td>2,258</td>
<td>0.92±0.22</td>
<td>1.20 (27)</td>
</tr>
<tr>
<td>4.90–5.69</td>
<td>2,102</td>
<td>1.02±0.38</td>
<td>2.52 (53)</td>
<td>1.09 (23)</td>
</tr>
<tr>
<td>5.70–6.49</td>
<td>2,336</td>
<td>1.07±0.26</td>
<td>3.64 (85)</td>
<td>1.67 (39)</td>
</tr>
<tr>
<td>6.50–7.29</td>
<td>1,864</td>
<td>1.13±0.30</td>
<td>6.97 (130)</td>
<td>2.52 (47)</td>
</tr>
<tr>
<td>≥7.30</td>
<td>2,196</td>
<td>1.26±0.55</td>
<td>14.94 (328)</td>
<td>7.88 (173)</td>
</tr>
</tbody>
</table>

BP, blood pressure and FBS, fasting blood sugar.
*Values denote percentage and number (n) of participants with values at or above specific levels.
†There were 172 participants who did not have serum creatinine measurements at baseline.
SC black women, and 0.14±0.25 mg/dl (12.4±22.1 μmol/l) for SC white women. RC participants had serum creatinine levels measured only at baseline and at 24 and 60 months of follow-up. At 60 months, there was little difference between SC and RC mean serum creatinine concentrations. First-line SC therapy was diuretic agents for all race-sex groups, and the slight rise in serum creatinine concentration after the initiation of diuretic-based therapy probably represents hemoconcentration.

The shift in the baseline distribution of serum creatinine that was observed at 60 months was not uniform for the range of baseline values. The change in serum creatinine was examined by linear regression analyses, and the results for the four race-sex subgroups are shown in Table 4. Of the 10,940 participants, 78.4% had valid observations for all the analyzed variables. The estimated quadratic regression curves for the subgroups are depicted in Figure 5, where the predicted 60-month creatinine change has been plotted against baseline serum creatinine. The graph indicates that, for each race-sex subgroup after adjustment for subgroup differences in the included baseline variables, the greatest increase in serum creatinine was generally among participants with baseline values below their respective sample means. When the change in mean creatinine concentration was stratified by the base-

![Figure 1](image1.png)

**FIGURE 1.** Plots of baseline distribution of serum creatinine concentration (mg/dl) by race and sex. The sigmoidal curve represents the cumulative percent distribution.

![Figure 2](image2.png)

**FIGURE 2.** Stacked bar graph of all-cause 8-year mortality (%) among 10,768 participants in the Hypertension Detection and Follow-up Program stratified by baseline serum creatinine concentration (mg/dl). The lower densely shaded portion of each column represents 5-year mortality. The percentage of participants in each creatinine stratum is shown at the base of the columns.
line creatinine level, this predicted pattern was observed in all strata except for those with concentrations greater than or equal to 2.0 mg/dl (176.8 μmol/l). This subgroup, 1.4% of the cohort, had the greatest increase over time despite a death rate of more than 30% in 5 years. In the regression analyses, age at entry had a significant positive relation with change in creatinine concentration for all race-sex groups as did baseline diastolic blood pressure; diabetes was positively associated in all but white men. A significant treatment group difference was found only among black women, a difference which is also apparent in Figure 5.

**Development of Clinically Significant Hypercreatininemia**

For the great majority of HDFP participants, the 5-year increase in serum creatinine concentration was relatively small for SC and RC groups. However, among the 8,683 participants for whom the 5-year change in creatinine concentration was ascertained, 200 (2.3%) experienced a progressive rise in serum creatinine concentration to levels that were considered indicative of possible renal insufficiency and that posed considerable risk of future mortality. Table 5 presents data on the incidence and progression of clinically significant hypercreatininemia,
### TABLE 3. Age-Adjusted, Cause-Specific, 8-Year Mortality Rates* per 1,000 for Participants Stratified by Baseline Serum Creatinine Concentration

<table>
<thead>
<tr>
<th>Cause of death (ICDA codes)†</th>
<th>Treatment group</th>
<th>Serum creatinine concentration (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SC</td>
<td>Rate±SEM/l,000 (No.)</td>
</tr>
<tr>
<td>All causes</td>
<td></td>
<td>(n=5,243 SC)</td>
</tr>
<tr>
<td></td>
<td>SC</td>
<td>112.4±4.3 (587)†</td>
</tr>
<tr>
<td>All cardiovascular causes</td>
<td></td>
<td>321.9±35.8 (56)</td>
</tr>
<tr>
<td>(390–458, 746)</td>
<td>SC</td>
<td>58.6±3.2 (306)‡</td>
</tr>
<tr>
<td></td>
<td>RC</td>
<td>174.7±27.8 (32)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td></td>
<td>7.9±1.2 (41)‡</td>
</tr>
<tr>
<td>(430–438)</td>
<td>SC</td>
<td>28.9±11.5 (6)</td>
</tr>
<tr>
<td></td>
<td>RC</td>
<td>100.4±22.8 (18)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td></td>
<td>39.3±2.7 (205)</td>
</tr>
<tr>
<td>(410–414)</td>
<td>SC</td>
<td>147.3±28.4 (24)</td>
</tr>
<tr>
<td></td>
<td>RC</td>
<td></td>
</tr>
<tr>
<td>Noncardiovascular causes</td>
<td></td>
<td>52.8±3.1 (276)</td>
</tr>
<tr>
<td>Renal disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(580–599)</td>
<td>SC</td>
<td>2.9±0.7 (15)</td>
</tr>
<tr>
<td></td>
<td>RC</td>
<td>56.4±18.7 (9)</td>
</tr>
<tr>
<td>Neoplastic diseases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(140–239)</td>
<td>SC</td>
<td>25.1±2.2 (131)</td>
</tr>
<tr>
<td></td>
<td>RC</td>
<td>27.5±12.4 (5)</td>
</tr>
</tbody>
</table>

SC, stepped care and RC, referred care.
*Rates have been adjusted for distributional differences in age between the SC and RC groups. The combined SC and RC population was used as the standard.
†International Classification of Diseases, Adapted; eighth revision.
‡p<0.01, based on the approximate standard normal test of no difference between RC–SC rates.

### FIGURE 4. Plot of change in mean serum creatinine concentration (mg/dl) in Hypertension Detection and Follow-up Program black and white men and women during 60 months of follow-up. The mean values for the stepped-care (SC) group, which had serum creatinine determinations every 4 months, have been connected to give an indication of trend. For the referred-care (RC) group, which had serum creatinine levels measured only at baseline and at 24 and 60 months, the means have been left unconnected. The numbers of SC participants with creatinine measurements at baseline, 24 months, and 60 months are as follows: black men—1,046, 912, and 853; white men—1,868, 1,696, and 1,643; black women—1,318, 1,159, and 1,139; white women—1,170, 1,007, and 998. Similarly for RC, the numbers are: black men—1,061, 850, and 774; white men—1,848, 1,561, and 1,486; black women—1,318, 1,159, and 1,139; white women—1,170, 1,007, and 998. Similarly for SC, the numbers are: black men—1,061, 850, and 774; white men—1,848, 1,561, and 1,486; black women—1,323, 1,077, and 1,035; white women—1,134, 922, and 863.
which is arbitrarily defined as a 5th-year serum creatinine concentration level of greater than or equal to 2.0 mg/dl (176.8 μmol/l) and greater than or equal to 1.25 times the baseline concentration. Imposition of this latter restriction required the most than one standard deviation of the baseline creatinine. Thus, for a participant with a baseline serum creatinine level of greater than or equal to 1.25 times the baseline concentration.

Among participants with a baseline creatinine concentration level of greater than or equal to 1.8 mg/dl (159.1 μmol/l), creatinine concentration had to rise by at least 0.45 mg/dl equal to 1.25 times the baseline concentration. Imposition of this latter restriction required the most than one standard deviation of the baseline creatinine. Thus, for a participant with a baseline serum creatinine level of greater than or equal to 1.25 times the baseline concentration.

Overall, there was only a small difference in the rate of loss of renal function between the SC and RC groups, 21.7/1,000 in SC survivors and 24.6/1,000 in RC survivors, an 11.8% relative difference. The 95% confidence limits for this absolute difference included zero (-3.40, 9.20). The 5-year incidence was significantly greater in blacks than in whites and in men than in women (p<0.01), was significantly greater for those with higher diastolic blood pressures at trial entry compared with those with lower blood pressures (p<0.05), and was also greater for older than younger persons (p<0.01). Table 6 presents data on the 5-year incidence and progression of clinically significant hypercreatininemia stratified by baseline creatinine concentration. Among participants with a baseline creatinine concentration less than 1.7 mg/dl, there was a 22.7% relative difference in favor of SC, but the 95% confidence interval for this difference included zero (-1.05, 10.25). Only among participants with baseline serum creatinine concentrations signifying borderline hypercreatininemia—in the range 1.50–1.69 mg/dl—was there a significant difference between the SC and RC groups (p<0.01), a 50% relative difference in favor of SC. In this small subgroup

<table>
<thead>
<tr>
<th>Baseline covariate</th>
<th>Value</th>
<th>SD</th>
<th>t value</th>
<th>Value</th>
<th>SD</th>
<th>t value</th>
<th>Value</th>
<th>SD</th>
<th>t value</th>
<th>Value</th>
<th>SD</th>
<th>t value</th>
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</thead>
<tbody>
<tr>
<td>Overall mean</td>
<td>0.67375</td>
<td>0.2351</td>
<td>2.87*</td>
<td>0.13619</td>
<td>0.1580</td>
<td>0.86</td>
<td>-0.02506</td>
<td>0.1566</td>
<td>-0.16</td>
<td>-0.07911</td>
<td>0.0851</td>
<td>-0.93</td>
</tr>
<tr>
<td>Treatment group</td>
<td>0.01511</td>
<td>0.0121</td>
<td>1.25</td>
<td>0.00467</td>
<td>0.0065</td>
<td>0.71</td>
<td>-0.02689</td>
<td>0.0109</td>
<td>-2.47</td>
<td>-0.00918</td>
<td>0.0056</td>
<td>-1.65</td>
</tr>
<tr>
<td>DBP change (mm Hg)</td>
<td>-0.00092</td>
<td>0.0010</td>
<td>-0.93</td>
<td>-0.00083</td>
<td>0.0007</td>
<td>-1.24</td>
<td>0.00154</td>
<td>0.0009</td>
<td>1.69</td>
<td>-0.00120</td>
<td>0.0006</td>
<td>-2.09*</td>
</tr>
<tr>
<td>Baseline Cr (mg/dl)*</td>
<td>-0.13902</td>
<td>0.0500</td>
<td>-2.78</td>
<td>-0.22547</td>
<td>0.0283</td>
<td>-7.96</td>
<td>-0.00272</td>
<td>0.0465</td>
<td>-0.06</td>
<td>-0.48479</td>
<td>0.0299</td>
<td>-16.19*</td>
</tr>
<tr>
<td>Squared baseline Cr†</td>
<td>0.33565</td>
<td>0.0355</td>
<td>9.45§</td>
<td>0.06152</td>
<td>0.0436</td>
<td>1.41</td>
<td>0.13319</td>
<td>0.0315</td>
<td>4.23§</td>
<td>0.16039</td>
<td>0.0328</td>
<td>4.89§</td>
</tr>
<tr>
<td>Baseline DBP (mm Hg)*</td>
<td>0.00273</td>
<td>0.0013</td>
<td>2.03§</td>
<td>0.00261</td>
<td>0.0010</td>
<td>2.64</td>
<td>0.00667</td>
<td>0.0012</td>
<td>5.40§</td>
<td>0.00270</td>
<td>0.0008</td>
<td>3.19</td>
</tr>
<tr>
<td>Age at entry (years)</td>
<td>0.00348</td>
<td>0.0012</td>
<td>3.00§</td>
<td>0.00316</td>
<td>0.0007</td>
<td>4.69</td>
<td>0.00394</td>
<td>0.0011</td>
<td>3.73§</td>
<td>0.00159</td>
<td>0.0006</td>
<td>2.65§</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>-0.04386</td>
<td>0.0147</td>
<td>-2.99§</td>
<td>-0.00514</td>
<td>0.0099</td>
<td>-0.52</td>
<td>0.00717</td>
<td>0.0089</td>
<td>0.81</td>
<td>0.00768</td>
<td>0.0051</td>
<td>1.49</td>
</tr>
<tr>
<td>Squared body mass index</td>
<td>0.00075</td>
<td>0.0002</td>
<td>3.07§</td>
<td>0.00005</td>
<td>0.0002</td>
<td>0.29</td>
<td>-0.00011</td>
<td>0.0001</td>
<td>-0.84</td>
<td>-0.00010</td>
<td>0.0001</td>
<td>-1.20</td>
</tr>
<tr>
<td>Rx X baseline Cr</td>
<td>-0.07462</td>
<td>0.0468</td>
<td>-1.60</td>
<td>0.11646</td>
<td>0.0275</td>
<td>4.23§</td>
<td>-0.30711</td>
<td>0.0450</td>
<td>-6.83§</td>
<td>-0.02771</td>
<td>0.0295</td>
<td>-0.94</td>
</tr>
<tr>
<td>Rx X squared baseline Cr</td>
<td>-0.14810</td>
<td>0.0355</td>
<td>-4.22§</td>
<td>-0.03049</td>
<td>0.0437</td>
<td>-0.70</td>
<td>0.16116</td>
<td>0.0314</td>
<td>5.13</td>
<td>0.12912</td>
<td>0.0325</td>
<td>3.97§</td>
</tr>
</tbody>
</table>

Variables coded Yes/no (1/0)

<table>
<thead>
<tr>
<th></th>
<th>Black men</th>
<th>White men</th>
<th>Black women</th>
<th>White women</th>
</tr>
</thead>
<tbody>
<tr>
<td>On antihyp med‡</td>
<td>0.00795</td>
<td>0.0153</td>
<td>0.52</td>
<td>0.00686</td>
</tr>
<tr>
<td>Major EOD</td>
<td>0.01057</td>
<td>0.0156</td>
<td>0.68</td>
<td>0.03708</td>
</tr>
<tr>
<td>Cigarette use</td>
<td>0.00937</td>
<td>0.0115</td>
<td>0.81</td>
<td>0.00448</td>
</tr>
<tr>
<td>History of high BP</td>
<td>0.01299</td>
<td>0.0129</td>
<td>1.01</td>
<td>0.00925</td>
</tr>
<tr>
<td>Diabetes or</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FBS≥140 mg/dl</td>
<td>0.11884</td>
<td>0.0186</td>
<td>6.39</td>
<td>-0.00478</td>
</tr>
<tr>
<td>History of cancer</td>
<td>-0.03479</td>
<td>0.0666</td>
<td>-0.52</td>
<td>0.02419</td>
</tr>
</tbody>
</table>

SC, stepped care; RC, referred care; DBP, diastolic blood pressure; Cr, serum creatinine; Rx, treatment group; EOD, end-organ damage (history of myocardial infarction, stroke, left ventricular hypertrophy, major Q-QS electrocardiographic abnormalities, serum Cr ≥1.7 mg/dl, or intermittent claudication); and FBS, fasting blood sugar.

*Sample mean has been subtracted.
†Squared deviation about the mean.
‡ p<0.05.
§ p<0.01.
(n=238), the incidence of clinically significant hypercreatininemia was 113/1,000 among SC compared with 226/1,000 among RC participants.

The subsequent 3-year mortality experience of participants who developed clinically significant loss of renal function during the 5-year trial period was four times that of other participants. There were 54 deaths among the 200 participants who developed possible renal insufficiency; 27.2% were from the SC group and 28.4% from the RC group. For participants without evidence of clinically significant renal function loss, the adjusted 3-year mortality rates were 6.92% for SC and 7.83% for RC.

Regression of Hypercreatininemia

Regression of preexisting hypercreatininemia among 5-year survivors was greater in SC than in RC participants. Of 106 SC participants who had a baseline serum creatinine concentration greater than or equal to 1.7 mg/dl, 21.7% had a 5-year value that was below 1.7 mg/dl and that was at least 25% lower than their baseline level. Among the corresponding 71 RC participants, 16.9% experienced a similar improvement in serum creatinine concentration. (The difference between these percentages was not significant.) Only two (5.9%) of the 34 participants with such improvement died during the succeeding 3 years compared with the deaths of 15 (31.3%) of the 48 whose condition worsened between baseline and their 5th-year examination, that is, those who had a 5th-year serum creatinine level 1.25 times greater than or equal to their baseline value.

Discussion

The risk factors for the development of cerebrovascular and cardiovascular complications of hypertension have been well defined during the past 2 decades. However, there is a paucity of data on the natural history of the development and progression of renal disease in hypertensive patients. This lack of information is probably related to the relatively lower prevalence of renal disease compared with the prevalence of cardiovascular or cerebrovascular disease in hypertensive patients. In addition, progression of renal disease does not cause symptoms until late in its course.

Large-scale, prospective, randomized trials have clearly shown the impact of antihypertensive treatment in significantly reducing the risk of death, stroke, congestive heart failure, left ventricular hypertrophy, worsening of the level of blood pressure, and possibly, of coronary heart disease. To demonstrate the effectiveness of antihypertensive drug therapy in reducing the incidence and progression of renal disease would require a large study population and a long study period. In addition, the
### Table 5. Five-Year Incidence and Progression of Clinically Significant Hypercreatininemia*

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Treatment group</th>
<th>Size</th>
<th>Sample cases</th>
<th>Rate/1,000±SEM</th>
<th>95% Confidence limits for RC-SC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>SC</td>
<td>4,581</td>
<td>99</td>
<td>21.7±2.1</td>
<td>(-3.40, 9.20)</td>
</tr>
<tr>
<td></td>
<td>RC</td>
<td>4,102</td>
<td>101</td>
<td>24.6±2.4</td>
<td>p=0.36</td>
</tr>
<tr>
<td>Baseline DBP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90–104</td>
<td>SC</td>
<td>3,273</td>
<td>56</td>
<td>13.2±2.0</td>
<td>(-0.59, 11.79)</td>
</tr>
<tr>
<td></td>
<td>RC</td>
<td>2,979</td>
<td>43</td>
<td>18.8±2.5</td>
<td>p=0.08</td>
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<tr>
<td>105–114</td>
<td>SC</td>
<td>886</td>
<td>30</td>
<td>34.4±6.1</td>
<td>(-16.75, 18.95)</td>
</tr>
<tr>
<td></td>
<td>RC</td>
<td>752</td>
<td>26</td>
<td>35.5±6.8</td>
<td>p=0.90</td>
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<tr>
<td>≥115</td>
<td>SC</td>
<td>422</td>
<td>26</td>
<td>63.7±11.8</td>
<td>(-44.31, 20.31)</td>
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<tr>
<td></td>
<td>RC</td>
<td>371</td>
<td>19</td>
<td>51.7±11.5</td>
<td>p=0.46</td>
</tr>
<tr>
<td>Race-sex</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>White men</td>
<td>SC</td>
<td>1,626</td>
<td>30</td>
<td>18.6±3.3</td>
<td>(-6.31, 13.51)</td>
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<tr>
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<td>RC</td>
<td>1,478</td>
<td>33</td>
<td>22.2±3.8</td>
<td>p=0.48</td>
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<tr>
<td>White women</td>
<td>SC</td>
<td>992</td>
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<td>8.0±2.8</td>
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<tr>
<td></td>
<td>RC</td>
<td>856</td>
<td>9</td>
<td>10.7±3.3</td>
<td>p=0.55</td>
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<tr>
<td>Black men</td>
<td>SC</td>
<td>837</td>
<td>40</td>
<td>47.7±7.3</td>
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<td>RC</td>
<td>757</td>
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<td>35.6±6.7</td>
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<td>Black women</td>
<td>SC</td>
<td>1,126</td>
<td>21</td>
<td>18.7±4.0</td>
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<tr>
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<td>RC</td>
<td>1,011</td>
<td>32</td>
<td>32.0±5.6</td>
<td>p=0.05</td>
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<tr>
<td>Age at entry (years)</td>
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<td></td>
<td></td>
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<tr>
<td>30–49</td>
<td>SC</td>
<td>2,079</td>
<td>23</td>
<td>11.0±2.3</td>
<td>(-6.69, 6.29)</td>
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<tr>
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<td>RC</td>
<td>1,864</td>
<td>20</td>
<td>10.8±2.4</td>
<td>p=0.95</td>
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<td>50–59</td>
<td>SC</td>
<td>1,572</td>
<td>34</td>
<td>22.0±3.7</td>
<td>(-5.91, 16.11)</td>
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<tr>
<td></td>
<td>RC</td>
<td>1,454</td>
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<td>27.1±4.2</td>
<td>p=0.36</td>
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<tr>
<td>60–69</td>
<td>SC</td>
<td>930</td>
<td>42</td>
<td>45.7±6.8</td>
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<td>RC</td>
<td>784</td>
<td>41</td>
<td>52.2±7.9</td>
<td>p=0.53</td>
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</tbody>
</table>

Values are reported for SC and RC participants with baseline and 5th-year serum creatinine concentration measurements. Rates have been adjusted for distributional differences between SC and RC in age, race, and sex.  
RC, referred care; SC, stepped care; and DBP, diastolic blood pressure.  
*Clinically significant hypercreatininemia is defined as a 5th-year serum creatinine concentration ≥2.0 mg/dl and at least 1.25 times the baseline concentration. SI units can be obtained from the metric units of creatinine by the conversion factor 88.4 μmol/l per mg/dl.

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Tests to monitor renal function meticulously or to detect new renal disease are often expensive and time-consuming for the physician and the patient. Hence, the level of serum creatinine has become the standard marker for renal function in the hypertensive population treated in office practice. However, this measurement is imperfect because its level is also altered by muscle mass or age.  

This analysis offers data on two topics, namely, elevated serum creatinine as a risk factor and the natural history of the development and progression of hypercreatininemia in a hypertensive population. The conventional cardiovascular risk factors include high blood pressure, elevated serum cholesterol, and cigarette smoking. The risk markers include electrocardiogram abnormalities and cardiac enlargement. The data presented here show that elevated serum creatinine should also be considered an equally important marker of risk. In the HDFP, hypercreatininemia was a potent predictor of mor-

### Table 6. Five-Year Incidence and Progression of Clinically Significant Hypercreatininemia*

<table>
<thead>
<tr>
<th>Baseline creatinine concentration</th>
<th>Treatment group</th>
<th>Sample size</th>
<th>Cases</th>
<th>Rate/1,000±SEM</th>
<th>95% Confidence limits for RC-SC</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.50 mg/dl</td>
<td>SC</td>
<td>4,354</td>
<td>55</td>
<td>12.7±1.7</td>
<td>(-3.56, 6.36)</td>
</tr>
<tr>
<td></td>
<td>RC</td>
<td>3,914</td>
<td>55</td>
<td>14.1±1.9</td>
<td>p=0.58</td>
</tr>
<tr>
<td>1.50–1.69 mg/dl</td>
<td>SC</td>
<td>121</td>
<td>15</td>
<td>113.3±25.5</td>
<td>(28.83, 197.75)</td>
</tr>
<tr>
<td></td>
<td>RC</td>
<td>117</td>
<td>27</td>
<td>226.6±34.7</td>
<td>p=0.01</td>
</tr>
<tr>
<td>&lt;1.70 mg/dl</td>
<td>SC</td>
<td>4,475</td>
<td>70</td>
<td>15.7±1.8</td>
<td>(-1.05, 10.25)</td>
</tr>
<tr>
<td></td>
<td>RC</td>
<td>4,031</td>
<td>82</td>
<td>20.3±2.2</td>
<td>p=0.11</td>
</tr>
<tr>
<td>≥1.70 mg/dl</td>
<td>SC</td>
<td>106</td>
<td>29</td>
<td>286.4±39.9</td>
<td>(-161.19, 92.79)</td>
</tr>
<tr>
<td></td>
<td>RC</td>
<td>71</td>
<td>19</td>
<td>252.2±51.0</td>
<td>p=0.60</td>
</tr>
</tbody>
</table>

Values are reported for SC and RC participants stratified by baseline serum creatinine concentration. Rates have been adjusted for distributional differences between SC and RC in age, race, and sex.  
*Clinically significant hypercreatininemia is defined as a 5th-year serum creatinine concentration ≥2.0 mg/dl and at least 1.25 times the baseline concentration. SI units can be obtained from the metric units of creatinine by the conversion factor 88.4 μmol/l per mg/dl.
tality, as indicated by the fivefold increase in mortality risk between the lowest and highest risk strata. As shown in Table 2, the risk contributed by elevated serum creatinine persisted when the former was examined by multiple logistic regression analysis, thereby implying that the risk is not due solely to the fact that various groups that are at increased risk (like elderly men and blacks) may also have increased creatinine levels. It is important to note that the cause of death was usually cardiac or cerebrovascular rather than renal. Of the HDFP patients with a baseline serum creatinine concentration greater than or equal to 1.7 mg/dl, 16.8% died of a stroke or coronary heart disease within 8 years. This represents 44.2% of the 8-year deaths in this subgroup of HDFP participants.

The most likely explanation for the association of elevated serum creatinine and increased mortality risk is that the elevated creatinine represents the influence of generalized vascular disease on the kidney, which, in turn, influences mortality. The elevated mortality associated with hypertensive cardiovascular disease is felt to be due primarily to accelerated atherosclerosis as well as cerebral hemorrhage. However, it is possible that diffuse arteriosclerosis, which is associated with hypertension, can have a direct influence on the kidney to decrease filtration and an indirect influence on the kidney by way of decreased perfusion, which can result in elevated creatinine level and increased risk.

Few data exist on the long-term impact of antihypertensive therapy on preventing, arresting, or reversing hypertensive renal disease. This report gives some information on the natural history of renal disease as manifested by elevated serum creatinine, as well as information on the effect of therapy on this natural history. If no real change occurs in the level of the substance being studied, then regression to the mean will lower those values at the upper end of the distribution and raise those values at the lower end. This pattern was noted in the creatinine data examined in this report, with the exception of participants whose baseline concentrations were greater than or equal to 2.0 mg/dl. Those participants in this subgroup had the greatest creatinine increase over time and experienced much higher mortality than those with creatinine values below that level. The observed 5-year increase in serum creatinine concentration in those entering the study with already elevated creatinine concentrations was probably muted by selected mortality. Perhaps selected mortality is the reason that only a small overall difference was noted in the progression rates of clinically significant hypercreatininemia between SC and RC groups, 2.17% of SC survivors and 2.46% of RC survivors, an 11.8% relative difference. When the analysis was stratified by baseline serum creatinine level, a 22.7% relative difference was found in favor of SC among participants in the borderline range from 1.5 to 1.7 mg/dl. Our analyses suggest that aggressive antihypertensive therapy was beneficial for the hypertensive kidney, thus slowing the progression of renal function loss and perhaps completely thwarting such loss in participants whose kidneys remained relatively intact. It can be argued that the favorable effect of aggressive antihypertensive therapy is considerably greater than implied by these figures because of two factors: 1) a number of the RC participants were treated, probably quite effectively, and therefore received the benefits of antihypertensive therapy; and 2) the volume contraction produced by thiazide-type diuretic agents causes an immediate increase in serum creatinine of about 0.2 mg/dl.

Together, the data presented here have one important message: serum creatinine is an independent predictor of mortality in a hypertensive population. The data were inadequate to conclusively assess the role of antihypertensive therapy in decreasing the progressive loss of renal function. However, the results of subgroup analyses were consistent with the hypothesis that aggressive treatment of hypertension may prevent progression of renal insufficiency. Additional data are required to provide strong evidence for this belief.

These findings are particularly relevant for chronic renal failure. The annual incidence of end-stage renal disease in the United States is estimated at 100 per million among whites and 250 per million among blacks.31-33 This incidence, coupled with the availability of routine renal dialysis, has resulted in about 85,000 patients on chronic dialysis in the United States today and an increasing number of kidney transplants at a cost approaching $3 billion dollars annually.36-39 The average cost for medical care of patients on dialysis is $25,000/yr, and the cost of treatment for persons with functioning kidney grafts is about one third of this expense.39 As many as 20% of chronic dialysis and transplant patients may have hypertension as the primary cause of their renal failure.32,34,35,40 A better understanding of the various therapeutic considerations relating to hypertension and the impact of its treatment on renal disease may help to curtail the morbid consequences of kidney failure. The billions of dollars being spent to treat patients with end-stage renal disease should justify further research in this area.

Acknowledgments

The 14 clinical centers and four coordination and service centers of the Hypertension Detection and Follow-up Program Cooperative Group, their institutions, investigators, and principal staff contributed to this report as follows:

Neil Shulman, MD and Elbert Tuttle Jr., MD (Atlanta-Emory University);
George Entwisle, MD and A.Y. Apostolides, DVM, PhD (Baltimore-University of Maryland);
Albert Oberman, MD and Harold W. Schnaper, MD (Birmingham-University of Alabama); Edward H. Kass, MD, PhD; James O. Taylor, MD; and B. Frank Polk, MD (deceased) (Boston-B Brigham and Women's Hospital and Harvard Medical School); Jeremiah Stamler, MD; Rose Stamler, MA; and Flora Gosch, MD (Chicago-Northwestern University); Nemat O. Borhani, MD; Beth Newman, PhD; and Marshall Lee, MD (Davis-University of California); John W. Jones, MD and Sandra A. Daugherty, MD, PhD (East Lansing-Michigan State University); H.A. Tyro勒, MD and Curtis G. Hames, MD (Evans County Health Department-Georgia); Lawrence M. Slotkoff, MD, PhD (deceased) (Georgetown, DC-Georgetown University); Herbert G. Langford, MD and John Abernathy, MD (Jackson-University of Mississippi Medical School); Morton H. Maxwell, MD and Roger Detels, MD (Los Angeles-Cedars-Sinai and UCLA Medical Centers); Reuben Berman, MD and Ronald J. Prineas, MB, BS, PhD, (Minneapolis-Mt. Sinai Hospital and University of Minnesota); M. Donald Blaufox, MD, PhD and Sylvia Wassertheil-Smoller, PhD (New York-Albert Einstein College of Medicine); C. Hilmon Castle, MD and Josephine Kasteller, PhD (Salt Lake City-University of Utah); C. Morton Hawkins, ScD; Charles E. Ford, PhD; and Barry B. Davis, MD, PhD (East Lansing-Michigan State University); John W. Jones, MD and Sandra A. Daugherty, MD, PhD (East Lansing-Michigan State University); Barry R. Davis, MD, PhD (Coordinating Center, Salt Lake City-University of Utah); Herbert G. Langford, MD and John Abernathy, MD (Jackson-University of Mississippi Medical School); Morton H. Maxwell, MD and Roger Detels, MD (Los Angeles-Cedars-Sinai and UCLA Medical Centers); Reuben Berman, MD and Ronald J. Prineas, MB, BS, PhD, (Minneapolis-Mt. Sinai Hospital and University of Minnesota); M. Donald Blaufox, MD, PhD and Sylvia Wassertheil-Smoller, PhD (New York-Albert Einstein College of Medicine); C. Hilmon Castle, MD and Josephine Kasteller, PhD (Salt Lake City-University of Utah); C. Morton Hawkins, ScD; Charles E. Ford, PhD; and Barry B. Davis, MD, PhD (Coordinating Center, Houston-The University of Texas School of Public Health); Agostino Molteni, MD, PhD and Kenneth A. Schneider, MD (Central Laboratory, Chicago-Northwestern Memorial Hospital); Ronald J. Prineas, MB, BS, PhD (ECG Center, Minneapolis-University of Minnesota); Gerald H. Payne, MD, MPH; Thomas P. Blaszkowski, PhD; and William J. Zuckel, MD (National Heart, Lung, and Blood Institute, NIH, Bethesda, Maryland).  

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KEY WORDS • cardiovascular risk factors • epidemiology • renal insufficiency • prevalence • incidence • prognosis • serum creatinine concentration
Prognostic value of serum creatinine and effect of treatment of hypertension on renal function. Results from the hypertension detection and follow-up program. The Hypertension Detection and Follow-up Program Cooperative Group.

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Hypertension. 1989;13:I80
doi: 10.1161/01.HYP.13.5_Suppl.I80

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