The Prevalence of Reduced Glomerular Filtration Rate in Older Hypertensive Patients and Its Association With Cardiovascular Disease

A Report From the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial

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Background: The prevalence of reduced glomerular filtration rate (GFR) in older hypertensive patients and the relationship between level of GFR and cardiovascular disease (CVD) and its risk factors are not well known.

Methods: We evaluated baseline renal function in 40,514 hypertensive patients 55 years or older who were enrolled in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). We used the simplified Modification of Diet in Renal Disease study equation to estimate GFR and examined the prevalence of CVD in patients with different levels of GFR.

Results: Fifty-seven percent of patients had mild (60-89 mL/min per 1.73 m²), 17.2% had moderate (30-59 mL/min per 1.73 m²), and 0.6% had severe (<29 mL/min per 1.73 m²) reductions in GFR. Compared with patients with normal or mildly reduced GFR, patients with moderate or severe reductions in GFR were more likely to have had a prior myocardial infarction or stroke (19.2% and 23.4% vs 28.7% and 26.9%, respectively), have ischemic changes on electrocardiography (ECG) (16.0% and 18.9% vs 24.6% and 34.1%, respectively), and have left ventricular hypertrophy on ECG (ECG-LVH) (3.9% and 4.2% vs 6.0% and 11.2%, respectively). A decrease in GFR of 10 mL/min per 1.73 m² was independently associated with a 6% higher risk for CVD and 14% higher risk for ECG-LVH. The increase in risk was marked at a GFR of approximately 60 to 70 mL/min per 1.73 m².

Conclusions: The prevalence of reduced GFR is high in older hypertensive patients. Patients with moderate or severe reduction in GFR are more likely to have a history of CVD and ECG-LVH. Even modest reductions in GFR are independently associated with a higher prevalence of CVD and ECG-LVH.

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Approximately 8 million adults (4.5% of the US population) are estimated to have moderate or severe reductions in glomerular filtration rate (GFR; <60 mL/min per 1.73 m²). However, few large-scale epidemiological studies have been performed to determine the prevalence of decreased GFR in older patients, racial/ethnic minorities, and patients who are at high risk for cardiovascular disease (CVD). Accurate estimation of the prevalence of decreased GFR in previous studies has been limited by the variability of serum creatinine measurements between laboratories and the lack of sensitivity of serum creatinine level used as a sole measure of renal function. The National Kidney Foundation Kidney Disease Outcome Quality Initiative (K/DOQI) Clinical Practice Guidelines on Chronic Kidney Disease (CKD) now recommend the use of equations, such as those derived from the Modification of Diet in Renal Disease (MDRD) study, that incorporate age, race, and sex in addition to serum creatinine level for estimation of GFR. Early identification of patients with decreased GFR has important clinical and research implications. In addition, it is well recognized that the prevalence of CVD is very high in patients with end-stage renal disease (ESRD). However, the epidemiology of CVD in patients with earlier stages of chronic renal disease and the relationship of GFR to CVD are not well documented. It is also not clear whether the increased risk for CVD seen in patients with renal disease is due to the coexistence of multiple traditional cardiovascular risk factors (eg, hypertension, diabetes, or smoking) or independently related to the decrement in GFR.

We evaluated baseline renal function in patients enrolled in the Antihypertens-
At baseline, participants underwent measurement of serum potassium, glucose, creatinine, total cholesterol, HDL cholesterol, triglyceride, and alanine aminotransferase levels from fasting blood samples. An ECG was performed if there was no existing tracing within the prior year, and read in a central ECG laboratory. The clinical center study coordinator was instructed to complete a questionnaire listing the inclusion criteria, checking all conditions that were known and documented to apply to the participant. In addition, the questionnaire included items about race, ethnicity, sex, years of education, current estrogen use, current regular aspirin use, cigarette smoking (past or current), and the presence of CHD. The presence or absence of CHD was ascertained as a single yes/no question and defined as a history of MI (including silent MI), primary cardiac arrest, coronary revascularization, angina, angiographically defined coronary stenosis greater than 50%, or reversible coronary perfusion defect on results of noninvasive cardiac testing.

In addition, history of CVD was also defined as 1 or more of the following: (1) old (>6 months) or age-indeterminate MI or stroke; (2) history of a revascularization procedure, angina pectoris, or transient ischemic attack; and (3) other documented atherosclerotic CVD, which included history of intermittent claudication, gangrene, ischemic ulcers, documented (eg, by angiography, intermittent claudication, ankle-brachial index, or Doppler imaging) atherosclerotic peripheral and/or carotid disease (>50% occlusion, or ankle-arm index <0.9), or presence of abdominal aortic aneurysm or carotid bruits. A detailed operations manual standardizing these definitions was provided to all the sites. The LVH reported herein was defined by Minnesota code 3-1 or 3-3 with ST/T-wave changes (Minnesota codes 4 and 5) as determined by the central ECG laboratory.

The double-blind, randomized, active-controlled design of ALLHAT has been described in detail previously. In brief, ALLHAT has 2 components. The antihypertensive component is a randomized double-blind trial designed to determine whether the combined incidence of fatal CHD and nonfatal MI differs between diuretic treatment (chlorthalidone, 12.5-25 mg/d) and each of the following 3 alternative antihypertensive therapies: a calcium channel blocker (amlodipine besylate, 2.5-10 mg), an angiotensin-converting enzyme inhibitor (lisinopril, 10-40 mg), and an α-adrenergic blocker (doxazosin mesylate, 2-8 mg). The component for lowering of lipid levels is a randomized, open-label trial designed to determine in 10,356 moderately hypercholesterolemic adults (a subset of the hypertension trial) whether lowering serum cholesterol levels with a hydroxymethylglutaryl–coenzyme A reductase inhibitor (pravastatin sodium) and a cholesterol-lowering diet (National Cholesterol Education Program Step I Diet) will reduce all-cause mortality compared with a control group receiving dietary counseling and usual care. The participants in ALLHAT are high-risk hypertensive patients 55 years or older, recruited at 623 clinical sites in the United States, Canada, Puerto Rico, and the US Virgin Islands between February 14, 1994, and January 31, 1998. Patient recruitment techniques used in the study have been published in detail previously. All participants gave written informed consent, and all centers obtained institutional review board approval. The trial ended in March 2002, after a mean follow-up of 5 years. Eligibility for participation in ALLHAT required the participant to have at least 1 other risk factor for CVD in addition to hypertension. These include the presence of underlying atherosclerosis, as evidenced by prior MI, stroke, vascular surgical repair or bypass, abnormal ECG, or vascular stenosis as detected by ultrasound; a history of diabetes; current smoking; ECG-LVH or LVH confirmed by echocardiography; or 2 high-density lipoprotein (HDL) cholesterol values less than 35 mg/dL (<0.9 mmol/L) on 2 separate readings within a 5-year period. Because there was limited acceptance of equations to estimate GFR when the study was designed, a serum creatinine level greater than 2 mg/dL (>176.8 µmol/L) as reported by the investigator was used as the criterion to exclude patients with advanced renal dysfunction. However, if the serum creatinine level drawn at the time of randomization was found to exceed 2 mg/dL (>176.8 µmol/L), these patients were maintained in the trial and followed up according to the study protocol.

The participation of more than 40,000 patients and the measurement of serum creatinine levels in a single central laboratory presented a good opportunity to study the prevalence of decreased GFR and the relationship between GFR and CVD and its risk factors in this population.

The purpose of this report is to (1) determine the prevalence of decreased GFR at baseline in ALLHAT participants, (2) describe the association between GFR and history of CVD, and (3) describe the association between GFR and left ventricular hypertrophy on electrocardiography (ECG-LVH).
Table 1. Prevalence of Decreased GFR at Baseline in ALLHAT Participants

<table>
<thead>
<tr>
<th>GFR Definitions</th>
<th>Estimated GFR, mL/min per 1.73 m²</th>
<th>No. (%) of Patients (N = 40514)</th>
<th>Serum Creatinine Level, Mean ± SD, mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal or increased</td>
<td>102.7 ± 13.0</td>
<td>9734 (24.1)</td>
<td>0.8 ± 0.1</td>
</tr>
<tr>
<td>Mild reduction</td>
<td>75.1 ± 8.1</td>
<td>22965 (56.7)</td>
<td>1.0 ± 0.2</td>
</tr>
<tr>
<td>Moderate reduction</td>
<td>51.2 ± 7.2</td>
<td>6952 (17.2)</td>
<td>1.4 ± 0.3</td>
</tr>
<tr>
<td>Severe reduction</td>
<td>≤29 mL/min per 1.73 m²</td>
<td>223 (0.6)</td>
<td>2.8 ± 1.0</td>
</tr>
</tbody>
</table>

Abbreviations: ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

SI conversion factor: To convert creatinine to micromoles per liter, multiply by 88.4.

Table 3

Baseline serum creatinine levels were available in 40514 of 42418 ALLHAT participants. The prevalence of decreased GFR in ALLHAT participants at baseline is shown in Table 1. Of the participants with available creatinine levels, 22965 (56.7%) had a mild reduction in GFR (60-89 mL/min per 1.73 m²), 6952 (17.2%) had a moderate reduction (30-59 mL/min per 1.73 m²), and 223 (0.6%) had a severe reduction (≤29 mL/min per 1.73 m²). The mean estimated GFR and serum creatinine level in each group is listed in Table 1.

Patients with moderate and severe reductions in GFR were older and included a higher proportion of women compared with patients with a mild reduction in or a normal GFR (P < .05, Table 2). The majority of patients with a moderate reduction in GFR were white non-Hispanic (57.6%), whereas black non-Hispanic patients were the largest racial/ethnic group among the patients with a severe reduction of GFR (42.2%) and with a normal or a high GFR (43.0%). Level of education was low in the study population as a whole, with more than 70% of patients reporting 12 or fewer years of education. The mean BMI was lower in patients with severe and moderate reductions in GFR (P < .05). Approximately 90% of patients in all groups were taking antihypertensive medications, and mean baseline systolic blood pressure was higher in patients with a severe reduction in GFR (Table 2).

Patients with moderate (28.7%) and severe (26.9%) reductions in GFR were more likely to have a history of old or age-indeterminate MI or stroke than patients with a mild reduction (23.4%) or a normal or increased GFR (19.2%; P < .05; Figure 1). A higher proportion of patients with moderate (17.2%) and severe (14.4%) reductions in GFR had undergone coronary artery bypass grafting, coronary angioplasty, or another revascularization procedure compared with patients with a mild reduction in GFR or with a normal or a high GFR (13.6% and 9.2%, respectively; P < .05). More patients with moderate (31.3%) and severe (28.7%) reductions in GFR had a history of CHD compared with patients with a mild reduction or a normal or high GFR (26.4% and 21.2%, respectively; P < .05). Patients with moderate (24.6%) and severe (34.1%) reductions in GFR were more likely to have major ST-segment depression or T-wave inversion on the baseline ECG compared with the other groups (18.9% and 16.0%, respectively; P < .05). In addition, the prevalence of ECG-LVH was higher in patients with moderate (6.0%) and severe (11.2%) reductions in GFR than those with a normal GFR (3.9%) or a mild reduction (4.2%; P < .05 for differences between groups).

Given the higher prevalence of CVD in patients with moderate and severe reductions in GFR, additional analyses focused on traditional risk factors for atherosclerosis in these patients (Table 3). Patients with moderate and severe reductions in GFR had significantly higher total and LDL cholesterol levels, higher triglyceride levels, and lower HDL cholesterol levels (P < .05 for differences between groups). In addition, they were more likely to have high total and LDL cholesterol profiles and low HDL cholesterol profiles as defined by the current National Cholesterol Education Program guidelines (Figure 2).11 The prevalence of type 2 diabetes was 44.0%...
in patients with a severely reduced GFR, 32.4% in patients with a moderately reduced GFR, 32.8% in patients with a mildly reduced GFR, and 45.2% in patients with a normal or high GFR (Table 3). A significant number of patients with moderate and severe reductions in GFR were current smokers (17.3% and 24.2%, respectively), as were those with a mild reduction in GFR and a normal GFR (20.9% and 27.1%, respectively; *P < .05*).

Finally, the prevalence of obesity was lower in patients with moderate and severe reductions in GFR.

Multiple logistic regression analyses were used to determine the independent effects of estimated GFR on prevalent CVD. After adjustment for age, race, sex, body mass index, baseline blood pressure, LDL and HDL cholesterol and triglyceride levels, diabetes, and smoking, estimated GFR was independently associated with CVD. A 10-mL/min per 1.73 m² decrease in GFR was associated with a 6% higher risk for CVD (odds ratio [OR], 1.06 per 10 mL/min per 1.73 m²; moderate reduction, 60-89 mL/min per 1.73 m²; severe reduction, less than or equal to 29 mL/min per 1.73 m²; *P < .001*). When GFR was categorized according to the cut points previously defined, patients with severe reduction in GFR were almost twice as likely to have CVD at baseline (OR, 1.99; *P < .001*), compared with the reference group (normal or increased GFR). Patients with a mild reduction in GFR had a slightly increased risk (OR, 1.09; *P = .004*). When GFR was categorized into deciles, patients in the lowest decile of GFR (≤53.6 mL/min per 1.73 m²) had the highest likelihood of having prevalent CVD (OR, 1.55; *P < .001; Figure 3*) compared with patients in the highest decile of GFR. The increased risk appeared to begin at GFR values approximating 60 mL/min per 1.73 m².

Similar logistic regression models were used to determine the relationship between estimated GFR and the presence of ECG-LVH. After adjustment for the covariates listed in the preceding paragraph, estimated GFR was independently associated with the presence of ECG-LVH. A 10-mL/min per 1.73 m² decrease in GFR was associated with a 14% higher risk of LVH (OR, 1.14 per 10 mL/min per 1.73 m²; *P < .001*). When GFR was categorized according to the cut points previously defined, patients with a severe reduction in GFR had more than a 3-fold increase (OR, 3.19; *P < .001*) in the prevalence of ECG-LVH, compared with the reference group (normal or increased GFR). Patients with a mild reduction

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### Table 2. Baseline Demographic Characteristics of ALLHAT Participants Stratified by Estimated GFR

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal or Increased (n = 10,374)</th>
<th>Mild Reduction (n = 22,965)</th>
<th>Moderate Reduction (n = 6,952)</th>
<th>Severe Reduction (n = 223)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y†</td>
<td>63.3 ± 6.4</td>
<td>67.3 ± 7.5</td>
<td>70.7 ± 7.8</td>
<td>70.6 ± 9.0</td>
</tr>
<tr>
<td>Women, No. (%)†</td>
<td>4,828 (46.5)</td>
<td>10,167 (44.3)</td>
<td>3,613 (52.0)</td>
<td>137 (61.4)</td>
</tr>
<tr>
<td>Race/ethnicity, No. (%)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White non-Hispanic</td>
<td>3,512 (33.9)</td>
<td>11,792 (51.4)</td>
<td>4,007 (57.6)</td>
<td>79 (35.4)</td>
</tr>
<tr>
<td>Black non-Hispanic</td>
<td>4,463 (43.0)</td>
<td>6,413 (27.9)</td>
<td>1,745 (25.1)</td>
<td>94 (42.2)</td>
</tr>
<tr>
<td>White Hispanic</td>
<td>1,131 (10.9)</td>
<td>3,124 (13.6)</td>
<td>823 (11.8)</td>
<td>32 (14.4)</td>
</tr>
<tr>
<td>Black Hispanic</td>
<td>710 (6.8)</td>
<td>551 (2.4)</td>
<td>79 (1.1)</td>
<td>9 (4.0)</td>
</tr>
<tr>
<td>Other</td>
<td>558 (5.4)</td>
<td>1,086 (4.7)</td>
<td>286 (4.3)</td>
<td>9 (4.0)</td>
</tr>
<tr>
<td>BMI, mean ± SD†</td>
<td>30.4 ± 6.4</td>
<td>29.8 ± 5.9</td>
<td>29.1 ± 5.9</td>
<td>28.4 ± 6.6</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%) with ≤12 y†</td>
<td>7,069 (72.6)</td>
<td>15,384 (70.8)</td>
<td>4,822 (73.7)</td>
<td>163 (80.3)</td>
</tr>
<tr>
<td>Treated for hypertension, No. %†</td>
<td>9,229 (89.0)</td>
<td>20,635 (89.9)</td>
<td>6,479 (93.2)</td>
<td>208 (93.3)</td>
</tr>
<tr>
<td>Baseline systolic BP, mm Hg, mean ± SD†</td>
<td>145 (15.3)</td>
<td>146.3 ± 15.6</td>
<td>146.6 ± 16.3</td>
<td>150.7 ± 17.0</td>
</tr>
<tr>
<td>Baseline diastolic BP, mm Hg, mean ± SD†</td>
<td>84.9 ± 9.8</td>
<td>84.1 ± 10.0</td>
<td>82.5 ± 10.4</td>
<td>83.1 ± 11.1</td>
</tr>
</tbody>
</table>

Abbreviations: See Table 1; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); BP, blood pressure; SD, conversion factor: To convert creatinine to micromoles per liter, multiply by 88.4.

*Mild or increased GFR is defined as greater than or equal to 90 mL/min per 1.73 m²; mild reduction, 60-89 mL/min per 1.73 m²; moderate reduction, 30-59 mL/min per 1.73 m²; and severe reduction, less than or equal to 29 mL/min per 1.73 m².

†*P < .05*, between the 4 groups.
in GFR also had a significantly increased risk (OR, 1.26; P=.001). When GFR was categorized into deciles, patients in the lowest decile of GFR had the highest likelihood of having ECG-LVH (OR, 2.51; P<.001; Figure 3) compared with patients in the highest decile of GFR. The likelihood of ECG-LVH seemed to increase at a GFR below approximately 70 mL/min per 1.73 m² (Figure 3). Since ECG may be less accurate in the diagnosis of LVH obtained (data not presented).

This report demonstrates a high prevalence of reduced GFR in older hypertensive patients. Patients with moderate or severe reduction in GFR in this population are more likely to have a history of CVD and ECG-LVH. Although most traditional risk factors for CVD are common, dyslipidemia is particularly severe in patients with moderate and severe reduction in GFR. After adjustment for several known risk factors for CVD, even modest reductions in GFR are independently associated with a higher prevalence of clinical CVD and ECG-LVH.

Few studies have documented the prevalence of reduced GFR in large populations, and recent published estimates have been derived from analyses of the NHANES database. Since we documented that measurement of serum creatinine level in the NHANES and ALLHAT laboratories was comparable, use of the modified MDRD equation allows for valid comparisons between the 2 populations. Although patients with known serum creatinine levels greater than 2 mg/dL (>176.8 µmol/L) were excluded, the prevalence of reduced GFR (<60 mL/min per 1.73 m², defined as CKD by the National Kidney Foundation K/DOQI guidelines) is much higher in ALLHAT participants (approximately 18%) compared with the general adult population (4.6%). This is likely due to the fact that the ALLHAT population was older and had multiple risk factors for chronic renal disease.

### Table 3. Risk Factors for CVD at Baseline in ALLHAT Patients Stratified by Estimated GFR

<table>
<thead>
<tr>
<th>GFR*</th>
<th>Normal or Increased</th>
<th>Mild Reduction</th>
<th>Moderate Reduction</th>
<th>Severe Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 10 374)</td>
<td>(n = 22 965)</td>
<td>(n = 6952)</td>
<td>(n = 223)</td>
</tr>
<tr>
<td>Lipid profile, mean ± SD, mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol†</td>
<td>214.5 ± 43.2</td>
<td>215.1 ± 41.7</td>
<td>220.2 ± 46.7</td>
<td>226.9 ± 59.2</td>
</tr>
<tr>
<td>LDL cholesterol†</td>
<td>134.4 ± 37.4</td>
<td>135.6 ± 36.2</td>
<td>138.0 ± 38.5</td>
<td>143.4 ± 45.3</td>
</tr>
<tr>
<td>HDL cholesterol†</td>
<td>48.1 ± 15.0</td>
<td>46.6 ± 14.5</td>
<td>45.7 ± 14.6</td>
<td>45.3 ± 15.2</td>
</tr>
<tr>
<td>Fasting triglyceride†</td>
<td>167.8 ± 139.2</td>
<td>169.5 ± 126.6</td>
<td>186.8 ± 147.2</td>
<td>194.2 ± 148.2</td>
</tr>
<tr>
<td>Receiving treatment with lipid-lowering agents at baseline, No. (%)†</td>
<td>1157 (11.3)</td>
<td>3269 (14.4)</td>
<td>1128 (16.4)</td>
<td>24 (10.8)</td>
</tr>
<tr>
<td>Patients with BMI &gt;30, No. (%)†</td>
<td>4785 (46.3)</td>
<td>9277 (40.5)</td>
<td>2540 (36.6)</td>
<td>75 (33.6)</td>
</tr>
<tr>
<td>Current cigarette smoker, No. (%)†</td>
<td>2807 (27.1)</td>
<td>4789 (20.9)</td>
<td>1201 (17.3)</td>
<td>54 (24.2)</td>
</tr>
</tbody>
</table>

Abbreviations: See Tables 1 and 2; CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Si conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113.

*Mild or increased GFR is defined as greater than or equal to 90 mL/min per 1.73 m²; mild reduction, 60-89 mL/min per 1.73 m²; moderate reduction, 30-59 mL/min per 1.73 m²; and severe reduction, less than or equal to 29 mL/min per 1.73 m².

†P<.05 between groups.
It is important for primary care physicians to appreciate that a significant percentage of their older hypertensive patients may have at least a moderate reduction in GFR. Rather than relying on serum creatinine measurements alone, use of the MDRD study equation allows for recognition of these patients. The clinician can then intervene on manifestations of CKD such as anemia and bone disease, which are often established in the GFR range of 30 to 60 mL/min per 1.73 m². In addition, better blood pressure and glycemic control and inhibition of the renin-angiotensin axis, particularly in proteinuric patients, should be instituted to slow the rate of decline of GFR.

A second important finding in our study was the high prevalence of CVD in patients with moderate and severe reduction in GFR. Forty percent of US patients undergoing hemodialysis have coronary artery disease, and CVD mortality is approximately 15 times greater in dialysis patients than in the general population. The fact that significant morbidity and mortality due to CVD occur soon after the onset of ESRD suggests that the atherosclerotic vascular disease begins during the earlier stages of chronic renal disease. Despite the plethora of evidence in patients with ESRD, the epidemiology of CVD in patients with earlier stages of chronic renal disease is not well delineated. It is in this often hard-to-capture population that this report makes important observations about the prevalence of CVD and its risk factors. We confirm that patients with reduced GFR were more likely to have a history of CVD and ischemic changes on ECG. We used information about the history of CVD provided by the clinician at the time of study entry, which was validated by review of source documentation at site visits. In addition, the more objective findings of ischemic changes on ECG read in a central laboratory showed similar results. Thus, these data demonstrate the high prevalence of CVD in patients with reduced GFR and underscore the need for early recognition and aggressive risk factor management in these patients.

The reason why patients with reduced GFR are at such high risk for CVD is an area of active investigation and is thought to be related to 2 issues. First, the prevalence of traditional risk factors for CVD such as smoking, diabetes, and hypertension may be higher in patients with reduced GFR. Second, there may be factors unique to the altered homeostatic milieu in patients with CKD that increase risk for CVD. This report provides important data supporting both concepts. Hypertension and diabetes were common in patients with reduced GFR. Hypertension in particular was more severe in patients with reduced GFR. Patients with moderate and severe reduction in GFR had lower HDL cholesterol levels and higher total and LDL cholesterol levels. However, patients with reduced GFR were less likely to be current smokers and less likely to be obese than patients with preserved GFR. Although it is possible that the level of control of cardiovascular risk factors in the years before entry in the study may have differed between the GFR groups, data to confirm or refute this possibility are not available in our study participants.

The fact that GFR remained independently associated with prevalence of CVD in our study following adjustment for traditional risk factors lends support to the concept that there may be other factors that predispose patients with reduced GFR to atherosclerotic disease. For example, altered homocysteine levels, vascular calcifications associated with renal osteodystrophy, poor nutrition, and increased levels of inflammatory markers are some of the factors thought to play a role in this process. Additional research is clearly needed to define the role of these and other factors that increase risk of CVD in patients with reduced GFR. The newly launched National Institutes of Health-sponsored prospective cohort study of chronic renal insufficiency will be an important resource in this area of investigation. In addition, the relationship of baseline levels of GFR to incidence of CVD and ECG-LVH will be the subject of another report.

The third important finding in our study is the high prevalence of ECG-LVH in patients with moderate and severe reductions in GFR. Left ventricular hypertrophy is well documented as an independent marker for CVD in the general population. In a study of Framingham participants, Cullen et al. reported that the prevalence of ECG-LVH in patients with mild CKD (defined by a serum creatinine level of 1.4-3.0 mg/dL [123.8-265.2 μmol/L]) was significantly higher compared with the rest of the population. Echocardiographic LVH has also been shown to be higher in patients with creatinine clearance less than or equal to 30 mL/min (38%) than in those with a creatinine clearance greater than 30 mL/min (16%). Our findings in this large and representative sample of patients confirm the high prevalence of ECG-LVH in patients with reduced GFR. In fact, fairly modest reductions in GFR (less than approximately 70 mL/min per 1.73 m²) are associated with a significant increase in the prevalence of LVH.

The reasons why patients with CKD have a higher prevalence of LVH have not been completely elucidated. Clearly, as we demonstrate in this study, patients with CKD often have several traditional risk factors for LVH (eg, hypertension, diabetes, and older age). However, the fact that estimated GFR remained independently associated with LVH after adjustment for several traditional risk factors suggests that the altered homeostatic milieu in CKD may also predispose to the development of LVH. For example, the effect of anemia on LVH has been extensively studied, and a strong association between hemoglobin levels and progressive left ventricular growth has been demonstrated in patients with CKD. In addition, extracellular fluid volume expansion and abnormalities of calcium/phosphate homeostasis may promote development of LVH in patients with CKD. Therefore, early recognition of LVH in patients with CKD may provide an opportunity for intervention with correction of anemia, control of blood pressure, optimization of fluid status, and balance of calcium phosphate. Future prospective studies will be needed to document the impact of these interventions on left ventricular geometry and cardiovascular outcomes.

A strength of this study is its large and diverse patient population, drawn from across the United States, Canada, and Puerto Rico from a variety of health care providers, allowing for generalizability of the results. Al-
though the level of health care before entry into the study may have differed between the sites, it is unlikely to have an impact on the relationship between GFR and CVD/LVH reported herein. In addition, the use of a single central laboratory and careful calibration with the MDRD study assay enhances the validity of the findings. A limitation, however, was our inability to identify patients at the earliest stages of chronic renal disease, based on markers of kidney damage such as proteinuria. According to the National Kidney Foundation K/DOQI Clinical Practice Guidelines on CKD, patients with a normal or increased GFR (≥90 mL/min per 1.73 m²) or a mild reduction in GFR (60-89 mL/min per 1.73 m²) are defined as having CKD if they also have a marker of kidney damage. Therefore, it is possible that some of the ALLHAT participants with a GFR greater than or equal to 60 mL/min per 1.73 m² may also have CKD, and that our data may have underestimated the prevalence of CKD in this population.

Finally, this cohort of more than 7000 well-characterized patients with GFR less than 60 mL/min per 1.73 m² provides an important opportunity to study the progression of renal insufficiency in high-risk hypertensive patients. Although the primary aim of the antihypertensive arm of ALLHAT is to determine the incidence of fatal CHD and nonfatal MI, change in renal function and development of ESRD are prespecified secondary outcomes of the study. Serum creatinine measurements are obtained periodically during follow-up, and development of ESRD is captured as a study event. Future analyses of these data can provide hypothesis-generating information about comparative effects on renal outcomes in each of the randomized antihypertensive and lipid-lowering drug groups. In addition, ALLHAT can be an important resource for epidemiological data. For example, despite the increased prevalence of CVD, there have been conflicting reports from the NHANES data whether renal insufficiency has an independent influence on cardiovascular mortality. Long-term follow-up of the ALLHAT participants may provide additional understanding about the effects of baseline renal insufficiency on cardiovascular outcomes.

CONCLUSIONS

We have demonstrated that the prevalence of reduced GFR in older hypertensive patients is high. Patients with a moderate or a severe reduction in GFR in this population are more likely to have a history of CVD and ECG-LVH. Even modestly low GFR levels are independently associated with a higher prevalence of clinical CVD and ECG-LVH.

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