Cardiovascular Disease Risk Factors in Chronic Kidney Disease

Overall Burden and Rates of Treatment and Control

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Background: Mild to moderate chronic kidney disease (CKD) is associated with increased risk for cardiovascular disease. The burden of cardiovascular disease risk factors in this setting is not well described.

Methods: We compared the age- and sex-adjusted prevalence of cardiovascular disease risk factors and their treatment and control among persons with and without CKD in 3258 Framingham offspring cohort members who attended the seventh examination cycle (1998-2001). Glomerular filtration rate (GFR) was estimated using the simplified Modification of Diet in Renal Disease Study equation. We defined CKD as a GFR of less than 59 mL/min per 1.73 m² in women and less than 64 mL/min per 1.73 m² in men.

Results: Those with CKD were older, more likely to be obese (33.5% vs 29.3%; P=.02), and more likely to have low levels of high-density lipoprotein cholesterol (45.2% vs 29.4%; P<.001) and high triglyceride levels (39.9% vs 29.8%; P=.001). Those with CKD had a higher prevalence of hypertension (71.2% vs 42.7%; P<.001) and hypertension treatment (86.0% vs 72.5%; P=.001), but were less likely to achieve optimal blood pressure control (27.0% vs 45.5%; P<.001). Participants with CKD had a higher prevalence of elevated low-density lipoprotein cholesterol levels (60.3% vs 44.7%; P=.06) and lipid-lowering therapy (57.1% vs 42.6%; P=.09), although this was not statistically significant. A greater proportion of individuals with CKD than those without had diabetes (23.5% vs 11.9%; P=.02) and were receiving diabetes treatment (63.6% vs 46.9%; P=.05), but were less likely to achieve a hemoglobin A1c level of less than 7% (43.8% vs 59.4%; P=.03).

Conclusions: Chronic kidney disease is associated with a significant burden of cardiovascular disease risk factors in the community. The diagnosis of CKD should alert the practitioner to look for potentially modifiable cardiovascular risk factors.

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Chronic Kidney Disease (CKD) is a risk factor for cardiovascular disease (CVD) and is associated with an increase in all-cause mortality. Nineteen million US adults are affected by CKD, including more than 25% of the population 70 years and older. Among those with end-stage renal disease, 50% of all deaths are due to CVD, and the risk of CVD is 10 to 20 times higher than in the general population.

The etiology of the increased risk of CVD in CKD is unknown, but may in part be due to shared CVD risk factors, including diabetes, hypertension, obesity, lipid abnormalities, and smoking. The burden of CVD risk factors among patients who have not undergone dialysis and those who have is extremely high. Data from nephrology clinics demonstrate prevalence rates of hypertension as high as 40%, of left ventricular hypertrophy of 20%, and of cigarette smoking of 30% to 60%. Patients with CKD are generally undertreated with respect to cardioprotective medications (including β-blockers, aspirin, angiotensin-converting enzyme inhibitors, and lipid-lowering medications), even in settings of congestive heart failure, prior myocardial infarction, and coronary artery bypass surgery.

Less is known regarding the CVD risk factor burden among individuals with earlier stages of CKD, many of whom are not necessarily treated for CKD or do not manifest clinical CVD. Moderate CKD is an independent risk factor for CVD, suggesting a need to better understand CVD risk factor burden and rates of risk factor treatment and control in this group. Thus, the aim of this study was to evaluate the burden of CVD risk factors among those with CKD in an unselected, community-based setting. We also sought...
to determine rates of treatment and control of CVD risk factors among those with and without CKD.

METHODS

STUDY SAMPLE

The Framingham Heart Study is a community-based prospective cohort study that began in 1948, consisting of 5209 men and women in the original cohort. In 1971, 5124 men and women enrolled in the Framingham Heart Study offspring cohort, which included the children and spouses of the children of the original cohort. Participant examinations for the offspring cohort occurred approximately every 4 years; the design and methodology have been described elsewhere. The present investigation includes the participants in the offspring cohort who attended the seventh examination cycle (1998-2001).

Of 3337 members of the offspring cohort who attended the seventh examination, 229 were excluded for missing creatinine values and 50 for missing covariate data, resulting in a final study sample of 3258 participants.

MEASUREMENTS AND DEFINITIONS

Kidney function was estimated by glomerular filtration rate (GFR), calculated using the simplified Modification of Diet in Renal Disease (MDRD) Study equation. Our definition of CKD was based on the National Kidney Foundation Disease Outcome Quality Initiative Working Group definition of kidney disease, which defines CKD as a GFR of less than 60 mL/min per 1.73 m². However, we have found that the use of this cut point classifies approximately 50% more women as having kidney disease than men; therefore, we modified the definition of CKD as a GFR of less than 59 mL/min per 1.73 m² in women or less than 64 mL/min per 1.73 m² in men.

Serum creatinine was measured using the modified Jaffe method. Because the measurement of creatinine level can vary, creatinine level was calibrated using a 2-step process. First, creatinine values from the Third National Health and Nutrition Examination Survey were calibrated to the Cleveland Clinic laboratory values, requiring a correction factor of 0.23 mg/dL (20.3 µmol/L). Then, age- (20-39, 40-59, 60-69, and ≥70 years) and sex-specific creatinine values were aligned with the corresponding corrected Third National Health and Nutrition Examination Survey age- and sex-specific mean values, as previously described.

CVD AND RISK FACTOR ASSESSMENT

Each examination included a CVD assessment and blood testing. Participants with a fasting blood glucose level of at least 126 mg/dL (≥7.0 mmol/L) or who were receiving insulin and/or oral hypoglycemic treatment for diabetes were defined as having diabetes. Participants with a systolic blood pressure of at least 140 mm Hg or a diastolic blood pressure of at least 90 mm Hg (the mean of 2 readings taken by an examining physician) or who were receiving medication for treatment of hypertension were defined as having hypertension. Cholesterol levels were measured after an overnight fast. Low levels of high-density lipoprotein cholesterol (HDL-C) were defined as less than 40 mg/dL (<1.0 mmol/L) in men and less than 50 mg/dL (<1.3 mmol/L) in women. High triglyceride levels were defined as at least 150 mg/dL (>1.7 mmol/L). Hemoglobin A₁c level was measured by means of high-performance liquid chromatography; assay coefficient variances were less than 2.5%. Our hemoglobin A₁c assay is calibrated against the Diabetes Control and Complications Trial standard hemoglobin A₁c assay. Smoking status was defined as smoking 1 or more cigarettes a day in the year preceding the examination. Body mass index was defined as weight in kilograms divided by the square of height in meters. Central obesity was defined as a waist circumference of more than 88 cm in women and more than 102 cm in men. Left ventricular hypertrophy with strain was determined by a physician-interpreted electrocardiogram finding. Framingham risk score values were calculated to predict 10-year CVD risk in participants free of CVD. Prevalent coronary heart disease included recognized or unrecognized myocardial infarction, coronary insufficiency, and angina pectoris. Prevalent CVD was defined as coronary heart disease, stroke, transient ischemic attack, or intermittent claudication. The criteria for diagnosis of these cardiovascular events have been described elsewhere.

TREATMENT AND CONTROL OF CVD RISK FACTORS

Rates of treatment of hypertension were calculated by taking the proportion of those receiving antihypertensive medications among all participants with hypertension. Rates of hypertension control among participants with CKD were calculated by taking the proportion of individuals with a blood pressure of greater than 130/80 mm Hg among all participants with CKD and hypertension, and by taking the proportion of participants with a blood pressure of greater than 140/90 mm Hg among all participants with hypertension but without CKD. Hypertension control cut points were defined according to the guidelines defined in the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Rates of elevated low-density lipoprotein cholesterol (LDL-C) levels were calculated by taking the proportion of those with elevated LDL-C levels according to LDL-C treatment goals set by the National Cholesterol Education Program Adult Treatment Panel III or those receiving lipid-lowering agents. Lipid control was assessed using the National Cholesterol Education Program Adult Treatment Panel III guidelines for cholesterol level management and was calculated by taking the proportion of individuals with LDL-C levels above their specified goal among all individuals with elevated LDL-C levels. The guidelines of the National Cholesterol Education Program Adult Treatment Panel III recommend a target LDL-C level of less than 160 mg/dL (<4.1 mmol/L) for persons with no or 1 cardiac risk factor, less than 130 mg/dL (<3.4 mmol/L) for persons with 2 or more cardiac risk factors, and less than 100 mg/dL (<2.6 mmol/L) for those with CVD, diabetes mellitus, or other cardiac risk factor equivalents. Rates of control of diabetes were calculated by taking the proportion of individuals with a hemoglobin A₁c level of less than 7% of all individuals with diabetes.

STATISTICAL ANALYSIS

Prevalence of CVD risk factors and rates of treatment and control were compared among individuals with and without CKD. In descriptive analyses, we looked at the rates of those participants with each risk factor (hypertension, elevated LDL-C level, and diabetes) and assessed whether risk factors in these individuals were untreated, treated but not controlled, or treated and controlled using the criteria described in the previous sections. These rates were adjusted via multivariable logistic regression. Because prevalence rates and the treatment and control of CVD risk factors can differ by age and clinical CVD status, secondary analyses were performed with stratification of participants into groups younger than 65 years or 65 years or older and by excluding participants with clinically recognized CVD (recognized myocardial infarction, coronary insufficiency, congestive heart failure, or stroke; n=60 among participants with
The prevalence of CKD in the study sample was 8.6%. Among those with CKD, 96.1% had stage 3 CKD (n = 270) (GFR, ≥ 30 mL/min per 1.73 m² and < 59 mL/min per 1.73 m² in women or < 64 mL/min per 1.73 m² in men). The remaining 3.9% of participants with CKD had stage 4 (n = 8) (GFR, 15–29 mL/min per 1.73 m²) or stage 5 (n = 3) (GFR, < 15 mL/min per 1.73 m²). The participants with CKD were older than those without CKD (Table 1). The participants with CKD had lower mean diastolic blood pressure, higher mean fasting blood glucose and serum triglyceride values, and lower mean serum HDL-C values than those without CKD. The participants with CKD had higher prevalence of CVD, myocardial infarction, congestive heart failure, and coronary heart disease than those without CKD (P < 0.001). Those with CKD were more likely to be obese (Table 1) and to have low HDL-C and high triglyceride levels than those without CKD. The percentage of participants without prevalent CVD but with a Framingham 10-year risk of CVD of 10% or greater was 4 times higher in those with CKD compared with those without CKD. Smoking status did not differ according to CKD status. Rates of hypertension were 71.2% among those with CKD, compared with 65.5% among those without CKD (P < 0.001) (Table 2). Overall, more participants with CKD had elevated HDL-C levels as defined by the guidelines of the National Cholesterol Education Program Adult Treatment Panel III than those without CKD (60.5% vs 44.7%), although this difference was not statistically significant (P = 0.06). Diabetes was nearly twice as common among participants with CKD compared with those without CKD (23.5% vs 11.9%; P = 0.02). The number of CVD risk factors among partici-
pants with and without CKD is displayed in Figure 1. Among participants with CKD, 73.0% had 2 or more CVD risk factors, compared with 51.4% of those without CKD.

**TREATMENT AND CONTROL OF HYPERTENSION**

Most participants were receiving treatment for hypertension, although there was a significantly greater proportion of participants with CKD treated for hypertension than participants without CKD (86.0% vs 72.5%; P<.001) (Table 2). Control of hypertension was lower among participants with CKD (27.0%) compared with those without CKD (45.5%; P<.001) (Figure 2A), even though hypertensive participants with CKD received a higher median number of antihypertensive medications compared with participants without CKD (2 vs 1 antihypertensive medication).

**TREATMENT AND CONTROL OF ELEVATED LDL-C LEVELS**

Participants with CKD were more likely to be treated with lipid-lowering agents than were participants without CKD (57.1% vs 42.6%), although this difference was not statistically significant (P=.09). Rates of control of elevated LDL-C levels were poor in both groups (41.8% vs 31.1%; P=.19) (Table 2), and nearly half of participants with and without CKD were untreated (Figure 2B).

**TREATMENT AND CONTROL OF DIABETES**

More participants with diabetes and CKD were receiving hypoglycemic treatment than those without CKD (63.6% vs 46.9%; P=.05). Nonetheless, participants with CKD were less likely to have optimal hemoglobin A1c levels (43.8% vs 59.4%; P=.03) (Table 2). Among participants treated for diabetes, there was a greater prevalence of suboptimal hemoglobin A1c in those with compared with those without CKD (Figure 2C).

**SECONDARY ANALYSES**

In an analysis excluding participants with clinical CVD (recognized myocardial infarction, coronary insufficiency, and stroke), rates of treatment and control for hypertension, elevated LDL-C levels, and diabetes did not materially differ from the overall analysis (data not shown).

In analyses stratified by age (Table 3), hypertension was more prevalent in both age groups among participants with CKD. Differences in rates of treatment and control of hypertension among those with and without CKD were more pronounced among those 65 years or older. Higher rates of elevated LDL-C levels among those with CKD were observed among older individuals, but differences in treatment and control of elevated LDL-C levels were not evident in age-stratified analyses. In contrast, differences in the prevalence of diabetes by CKD status were more evident among younger individuals.
COMBINATIONS OF RISK FACTOR CONTROL

Among participants without diabetes, dual control of hypertension and elevated LDL-C levels occurred less in participants with (13.1%; 95% confidence interval [CI], 7.1%-22.8%) than in those without (22.5%; 95% CI, 17.3%-28.7%) CKD, although this difference was not statistically significant (P=.10). Among participants with diabetes, rates of successful triple control of hypertension and LDL-C and hemoglobin A1c levels were low and did not differ among those with (7.5%; 95% CI, 2.5%-20.9%) and without (8.9%; 95% CI, 4.4%-17.6%) CKD (P=.61).

RATES OF CARDIOPROTECTIVE MEDICATION AND DIURETIC USE

Overall use of cardioprotective medications is shown in Table 1. A greater proportion of hypertensive participants with CKD were treated with angiotensin-converting enzyme inhibitors than persons without CKD (57.6% vs 47.0%; P=.005) and were more likely to take diuretic medications (28.5% vs 12.8%; P<.001). Among participants with prevalent coronary heart disease, there was no difference in aspirin use (83.3% vs 76.8%; P=.30) or β-blocker use (60.0% vs 64.7%; P=.90) among those with and without CKD.

Table 3. Age- and Sex-Adjusted Rates of CVD Risk Factors, Stratified by Age

<table>
<thead>
<tr>
<th>CVD Risk Factors</th>
<th>Participants Aged &lt;65 y, % (95% CI)</th>
<th>Participants Aged ≥65 y, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without CKD (n = 995)</td>
<td>With CKD (n = 216)</td>
</tr>
<tr>
<td></td>
<td>Without CKD (n = 1982)</td>
<td>With CKD (n = 65)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>33.9 (30.6-37.4)</td>
<td>58.5 (46.2-69.8)</td>
</tr>
<tr>
<td></td>
<td>70.8 (64.8-76.2)</td>
<td>84.2 (68.5-92.9)</td>
</tr>
<tr>
<td></td>
<td>51.4 (45.2-57.8)</td>
<td>31.6 (18.5-48.4)</td>
</tr>
<tr>
<td>Elevated LDL-C levels</td>
<td>40.7 (37.2-44.2)</td>
<td>43.1 (31.6-55.3)</td>
</tr>
<tr>
<td></td>
<td>36.1 (30.8-41.8)</td>
<td>46.4 (28.9-64.9)</td>
</tr>
<tr>
<td></td>
<td>26.6 (21.8-32.0)</td>
<td>35.7 (20.1-55.1)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8.7 (6.9-11.9)</td>
<td>20.0 (11.7-31.9)</td>
</tr>
<tr>
<td></td>
<td>41.6 (30.3-54.1)</td>
<td>61.5 (33.0-83.9)</td>
</tr>
<tr>
<td></td>
<td>59.9 (46.9-71.6)</td>
<td>46.2 (21.2-73.2)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

OVERALL FINDINGS

There is a significant burden of CVD risk factors among participants with CKD in the community. Participants with CKD are more likely to be treated for hypertension, elevated LDL-C levels, and diabetes, but rates of control are uniformly low in those with and without CKD. In general, when we stratified our analysis using an age cutoff of 65 years, older individuals demonstrated more significant differences in hypertension prevalence, treatment, and control.

HYPERTENSION

The prevalence of hypertension was significantly higher among those with compared with those without CKD. These differences were more evident among older individuals, consistent with previously published data demonstrating lower rates of blood pressure control (<130/80 mm Hg) among older individuals with mild to moderate CKD. Participants with CKD had higher rates of hypertension treatment than participants without CKD, leading us to question whether the treatment modalities themselves might increase serum creatinine levels moderately enough to classify these participants with CKD. Indeed, hypertensive participants with CKD were more likely to be treated with angiotensin-converting enzyme inhibitors and diuretics, which can increase serum creatinine levels. This increase does not significantly further the progression of renal dysfunction in patients with mild to moderate CKD. The CKD participants with hypertension in our study, despite increased use of antihypertensive therapy, were less likely to achieve recommended treatment goals.

Hypertension is a well-established independent risk factor for the development of end-stage renal disease and CKD progression. However, it is unclear whether patients with CKD benefit from tighter blood pressure control targets. Three recent studies of tight vs usual blood pressure control have reported conflicting results regarding outcomes of end-stage renal disease and GFR.
Individuals with stage 3 CKD. In addition, 2 post hoc analyses of the Systolic Hypertension in the Elderly Program demonstrated a 30% to 40% reduction in CVD events via systolic blood pressure reduction among elderly persons with mild renal dysfunction. Additional studies specifically examining effects of hypertension control on CVD outcomes among those with CKD are needed to expand on these findings.

ELEVATED LDL-C LEVELS

Among all participants, levels of elevated LDL-C did not significantly differ according to CKD status, although older individuals with CKD had higher prevalence rates of elevated LDL-C levels. Participants with CKD were more likely to have elevated triglyceride values and lower HDL-C values, consistent with prior analyses of adverse lipid profiles associated with CKD. We chose to focus our analysis primarily on management of LDL-C levels because of clear guidelines regarding management.

There is evidence that the treatment of hyperlipidemia may reduce the rate of kidney function decline in individuals with stage 3 CKD. In addition, 2 post hoc analyses of clinical trials with gemfibrozil and pravastatin sodium have shown beneficial effects of lipid-lowering medications on CVD outcomes among patients with moderate CKD (GFR, 30-70 mL/min per 1.73 m²). However, a recent randomized clinical trial in patients with diabetes undergoing hemodialysis demonstrated no protective benefit of lipid-lowering medication on CVD end points, although the generalizability of these findings to patients with CKD who are not undergoing hemodialysis is uncertain. Taken together, these data suggest that lipid-lowering therapy among individuals with moderate CKD has beneficial effects on renal and CVD outcomes. Additional clinical trials are necessary to examine the effects of lipid-lowering agents on both CKD progression and CVD risk reduction.

DIABETES MELLITUS

The rates of diabetes control were significantly lower among participants with CKD. This is surprising in light of evidence from the United Kingdom Prospective Diabetes Study and the Diabetes Control and Complications Trial, which demonstrated that tight glycemic control is associated with reduced progression of nephropathy and doubling of serum creatinine levels. Recent data suggest that tight control of glucose levels among patients with type 1 diabetes reduces long-term CVD risk; however, clinical trial data in those with type 2 diabetes remain inconclusive. Whether subgroups of patients with diabetes and CKD would experience a reduction in CVD outcomes with tight glycemic control requires further research.

STRENGTHS AND LIMITATIONS

There are several strengths to our study design. The Framingham Heart Study is a community-based sample not selected for CKD, reducing the risk of referral or selection bias. We have excellent assessment and documentation of CVD risk factors and treatment. Several limitations exist as well. Our study sample is limited geographically and ethnically because our participants are primarily white individuals. Nevertheless, the relation between CVD risk factor outcomes observed in the Framingham data set has been validated in 6 ethnically and geographically diverse populations, suggesting that our findings are applicable in other populations. We used guidelines for treatment that were not necessarily in place at the time of data collection. Because the MDRD equation that we used to estimate GFR has been validated in subjects with GFR of less than 90 mL/min per 1.73 m², values outside of this range are extrapolated. A recent study showed that the MDRD equation underestimates GFR by 29% in healthy persons, but by only 6.2% among patients with CKD. However, given that we did not use GFR as a continuous variable in our analysis, it remains unclear how this would affect the determination of CKD in our sample. Our definition of CKD as a disease trait falls within the range that has been validated for the MDRD equation, improving the robustness of our results for our dichotomous analysis. Our definition of CKD is limited to a single measurement of serum creatinine level on one occasion, not measured during a period of 3 months or longer as has been defined by the National Kidney Foundation. We measured risk factors on a single occasion, which could have led to outcome misclassification, thus biasing our results toward the null value. Furthermore, we used the simplified MDRD study equation to estimate GFR, instead of measuring it directly. To improve the validity and accuracy of the MDRD equation, we indirectly calibrated our creatinine values. We were unable to account for albuminuria, which may have led to an underestimation of CKD in our study. Although cross-sectional study designs are generally considered to be limiting in that they cannot determine the directionality of our reported relations, our primary aim was to characterize CVD risk factor burden, treatment, and control at a given point in time, therefore making the cross-sectional design the most favorable for this analysis.

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

Individuals with CKD had higher Framingham risk scores and low rates of optimization of all risk factors. Understanding barriers to effective risk factor modification in CKD is essential. Health care practitioners may not be aware of the relatively low creatinine values that corre-
spond to CKD; among non-Hispanic white individuals aged 60 years, the mean creatinine cut point corresponding to a GFR in the CKD range is only 1.0 mg/dL (88.4 μmol/L) in women and 1.3 mg/dL (114.9 μmol/L) in men.23 Efforts should focus on educating health care providers about the need to manage CVD risk factors in patients with CKD, with the ultimate aim of preventing CKD progression and promoting reductions in cardiovascular morbidity and mortality. Given the high prevalence of CVD risk factors and the relatively low levels of risk factor control, there may be a need to more aggressively manage CKD in this specific subgroup of individuals.

Chronic kidney disease, with its high burden of vascular disease risk factors and associated risk of adverse CVD outcomes, represents an important public health concern. The identification of an individual with CKD should alert the practitioner to a large underlying burden of potentially modifiable CVD risk factors.

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