The Impact of Reclassifying Moderate CKD as a Coronary Heart Disease Risk Equivalent on the Number of US Adults Recommended Lipid-Lowering Treatment

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Background: The Third National Cholesterol Education Program Adult Treatment Panel (ATP-III) guidelines recommend consideration of lipid-lowering therapy at lower low-density lipoprotein cholesterol levels (≥100 mg/dL [≥2.59 mmol/L]) for adults with coronary heart disease risk equivalents. Chronic kidney disease is associated with increased coronary heart disease risk but is not included as a risk equivalent in these guidelines.

Methods: The impact of including moderate chronic kidney disease (estimated glomerular filtration rate, 30 to 59 mL/min/1.73 m² [0.50 to 0.98 mL/s]) as a coronary heart disease risk equivalent on the percentage and number of US adults with chronic kidney disease recommended lipid-lowering therapy was estimated by using data from the Third National Health and Nutrition Examination Survey.

Results: Of adults with moderate chronic kidney disease, 53.0% had a history of coronary heart disease or a risk equivalent, 24.7% reported a history of myocardial infarction or stroke, 17.7% had diabetes, 9.6% had angina, and 26.9% had a 10-year coronary heart disease risk greater than 20%. Using current ATP-III guidelines, lipid-lowering therapy is recommended for 61.4% of adults with moderate chronic kidney disease. If moderate chronic kidney disease was reclassified as a coronary heart disease risk equivalent, this percentage would increase to 87.7%, representing an increase in number of adults with moderate chronic kidney disease recommended lipid-lowering treatment from 4.5 to 6.5 million adults.

Conclusion: This analysis shows that a majority of adults with moderate chronic kidney disease have coronary heart disease or risk equivalents. Nonetheless, a substantially greater proportion of US adults with moderate chronic kidney disease would be recommended lipid-lowering therapy through its reclassification as a coronary heart disease risk equivalent.


INDEX WORDS: Chronic kidney disease (CKD); coronary heart disease; Third National Cholesterol Education Program Adult Treatment Panel (ATP-III); low-density lipoprotein (LDL) cholesterol.

Chronic kidney disease (CKD) is a major public health problem in the United States and around the world. Overall, 7.4 million adults in the United States are estimated to have stage 3 CKD (estimated glomerular filtration rate, 30 to 59 mL/min/1.73 m² [0.50 to 0.98 mL/s]). A chief concern for individuals with CKD is the incidence of cardiovascular disease events, including coronary heart disease, cerebrovascular disease, and peripheral vascular disease. A recent meta-analysis provided strong evidence...
that individuals with renal insufficiency experience increased cardiovascular mortality risk.\textsuperscript{9} Compared with their counterparts without renal insufficiency, persons with renal insufficiency experienced a 1.4- to 3.7-fold increased risk for cardiovascular disease mortality.\textsuperscript{9}

Because of the high burden of coronary heart disease among patients with CKD, the National Kidney Foundation Task Force on Cardiovascular Disease and the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention recommend including patients with CKD in the “highest risk group” for treatment and prevention of cardiovascular disease.\textsuperscript{10-12} However, the National Cholesterol Education Program Adult Treatment Panel (ATP-III) guidelines do not classify CKD as a coronary heart disease risk equivalent for high blood cholesterol treatment recommendations.\textsuperscript{13,14}

Coronary heart disease, stroke, and diabetes mellitus, a coronary heart disease risk equivalent in the ATP-III guidelines, are common in individuals with CKD.\textsuperscript{7,8} Because most individuals with CKD already may be classified as having coronary heart disease or a risk equivalent, reclassifying CKD as a coronary heart disease risk equivalent may affect the treatment recommendation for only a limited number of adults with CKD. Conversely, given the large number of US adults with CKD, a change affecting even a small percentage of adults with CKD may alter treatment recommendations for a large number of persons. The primary aim of the present analysis is to determine the percentage and number of adults with CKD in the United States for whom the recommendation for lipid-lowering treatment would be modified if moderate CKD were reclassified as a coronary heart disease risk equivalent in the National Cholesterol Education Program ATP-III guidelines.

**METHODS**

**Study Population**

The Third National Health and Nutrition Examination Survey (NHANES III), conducted in 1988 to 1994 by the National Center for Health Statistics of the Centers for Disease Control and Prevention, included a sample of the noninstitutionalized civilian US population identified through a stratified multistage probability sampling design. Participants were asked to complete an in-home interview, followed by a visit to a mobile examination center for the administration of additional questionnaires, a medical evaluation, and collection of a blood sample.

In NHANES III, a total of 7,167 adult participants aged 20 years and older completed the in-home interview and had a blood sample collected after a 9-hour or longer fast during a morning visit to the medical examination center. Individuals with a triglyceride level greater than 400 mg/dL (\(>10.34 \text{ mmol/L}\)) or missing lipoprotein values were excluded from the current analysis (\(n = 400\)), as were participants with missing covariable information (\(n = 100\)). Individuals with an estimated glomerular filtration rate less than 30 mL/min/1.73 m\(^2\) (\(<0.50 \text{ mL/s; ie, stages 4 and 5 CKD; n = 118}\) were excluded because the sample size to examine risk for coronary heart disease associated with this subset of NHANES III participants was limited. After these exclusions were made, data for 6,549 adults from NHANES III were available for analysis. The NHANES III morning laboratory sampling weight was used in the current analysis to provide results representative of the US adult population.

**ATP-III Guidelines**

**ATP-III Treatment Recommendations**

ATP-III guidelines classify adults into coronary heart disease risk categories based on the presence of coronary heart disease, risk equivalents, and risk factors. These guidelines define high low-density lipoprotein (LDL) cholesterol level warranting therapeutic lifestyle changes and consideration of pharmacological lipid-lowering therapy as an LDL cholesterol level of 100 mg/dL or greater (\(\geq 2.59 \text{ mmol/L}\)) for those with coronary heart disease and/or a risk equivalent(s). For adults without coronary heart disease or a risk equivalent(s), high LDL cholesterol level is defined as 130 mg/dL or greater (\(\geq 3.36 \text{ mmol/L}\)) for those with 2 or more coronary heart disease risk factors and a 10-year coronary heart disease risk of 10% to 20%, 160 mg/dL or greater (\(\geq 4.14 \text{ mmol/L}\)) for those with 2 or more coronary heart disease risk factors and a 10-year coronary heart disease risk less than 10%, and 190 mg/dL or greater (\(\geq 4.91 \text{ mmol/L}\)) for those with 0 or 1 coronary heart disease risk factors.

**ATP-III–Defined Major Coronary Heart Disease Risk Factors**

Major coronary heart disease risk factors in the ATP-III guidelines include cigarette smoking, hypertension, low high-density lipoprotein (HDL) cholesterol level (\(<40 \text{ mg/dL} \ (<1.03 \text{ mmol/L})\), family history of premature coronary heart disease (in a first-degree male relative < 55 years of age or a first-degree female relative < 65 years of age), and older age (men \(\geq 45\) years; women \(\geq 55\) years). An HDL cholesterol level of 60 mg/dL or greater (\(\geq 1.55 \text{ mmol/L}\) is considered protective and offsets the presence of 1 other risk factor.
**ATP-III–Defined Coronary Heart Disease and Coronary Heart Disease Risk Equivalents**

The ATP-III guidelines define coronary heart disease as a history of myocardial infarction, angina, and/or coronary procedures. Coronary heart disease risk equivalents include stroke, other clinical atherosclerotic diseases (eg, peripheral arterial disease), diabetes mellitus, and 2 or more coronary heart disease risk factors in the presence of a 10-year coronary heart disease risk greater than 20%, calculated by using the Framingham risk equation.15

**Data Collection**

Questionnaires were used to collect information on demographics, cigarette smoking, family history of coronary heart disease, antihypertensive medication use, and history of coronary heart disease, stroke, angina, and diabetes mellitus. NHANES III participants who reported having smoked 100 or more cigarettes during their lifetime were classified as current smokers if they answered affirmatively to the question “Do you now smoke cigarettes?” Participants were classified as having hypertension if, based on the average of 3 blood pressure measurements during the in-home interview and 3 blood pressure measurements during the medical examination center visit, they had a systolic blood pressure of 140 mm Hg or greater and/or diastolic blood pressure of 90 mm Hg or greater and/or they reported currently using antihypertensive medication. Documentation of a family history of coronary heart disease from NHANES III is limited to a participant-reported history of myocardial infarction or angina before age 50 years among first-degree relatives; therefore, this definition was used to identify family history of premature coronary heart disease. In line with ATP-III guidelines, the presence of coronary heart disease in NHANES III was defined as a history of myocardial infarction and/or angina pectoris. A history of myocardial infarction was assessed through self-report and angina was assessed through the Rose questionnaire.16 Coronary heart disease risk equivalents in the current analysis included a history of stroke (self-reported), diabetes mellitus (self-reported and/or plasma glucose ≥126 mg/dL [≥7.0 mmol/L] after a 9-hour or longer fast at the NHANES visit), and, for individuals with 2 or more major coronary heart disease risk factors, a 10-year coronary heart disease risk greater than 20%.

Blood samples collected in NHANES III were stored at −20°C and shipped weekly to the Lipoprotein Analytical Laboratory at Johns Hopkins University, Baltimore, MD, for lipid analyses and the University of Missouri, Columbia, MO, for glucose analyses. Resulting laboratory values, provided in the public release of the NHANES III data set, were used in the current analysis.17 Total and HDL cholesterol and triglycerides were measured using the Hitachi 704 Analyzer, and serum creatinine was measured using the Hitachi 737 Analyzer (Hitachi, Indianapolis, IN), with all reagents purchased from Roche/Boehringer Mannheim Diagnostics, Indianapolis, IN. LDL cholesterol level was calculated by using the Friedewald equation16:

\[
\text{LDL cholesterol} \text{[mg/dL]} = \text{total cholesterol} \text{[mg/dL]} - \text{HDL cholesterol} \text{[mg/dL]} - \text{triglycerides} \text{[mg/dL]} / 5
\]

**Definition of Moderate CKD**

Serum collected during the NHANES III mobile examination center visit was sent to the White Sands Research Center at Alamogordo, NM, for creatinine measurement. After applying the calibration correction to the measured serum creatinine as recommended by Coresh et al,19 glomerular filtration rate estimation was performed using the Modification of Diet in Renal Disease equation.19,20

Estimated glomerular filtration rate = \(\exp(5.228 - 1.154 \times \log(\text{serum creatinine} - 0.23) - [0.299 \text{ if female}] + [0.192 \text{ if African American}] - 0.203 \times \log(\text{age}))\)

Based on National Kidney Foundation CKD staging criteria, participants with an estimated glomerular filtration rate of 30 or greater and less than 60 mL/min/1.73 m² (≥0.50 and <1.00 mL/s) were defined as having moderate CKD.21 Those with an estimated glomerular filtration rate of 60 mL/min/1.73 m² or greater (≥1.00 mL/s) were categorized as not having moderate CKD.

The protocol for NHANES III was approved by the National Center for Health Statistics of the Centers for Disease Control and Prevention Institutional Review Board. Informed consent was obtained from each NHANES III participant.

**Statistical Analysis**

The prevalence of ATP-III–defined categories of total cholesterol (<200, 200 to 239, and ≥240 mg/dL [<5.17, 5.17 to 6.18, and ≥6.21 mmol/L]), LDL cholesterol (<100, 100 to 129, 130 to 159, 160 to 189, and ≥190 mg/dL [<2.59, 2.59 to 3.34, 3.36 to 4.11, 4.14 to 4.89, and ≥4.91 mmol/L]), HDL cholesterol (<40, 40 to 59, and ≥60 mg/dL [<1.03, 1.03 to 1.53, and ≥1.55 mmol/L]), and triglycerides (<150 and ≥150 mg/dL [<3.88 and ≥3.88 mmol/L]) was calculated for participants with and without moderate CKD. Next, the prevalence of coronary heart disease, risk equivalents, and risk factors was determined, and the distribution of ATP-III risk categories was computed for persons with and without moderate CKD, separately. Percentages of persons with and without moderate CKD recommended lipid-lowering therapy were calculated, first using the current ATP-III guidelines and subsequently after reclassifying moderate CKD as a coronary heart disease equivalent. These analyses were conducted for the overall population and for persons without coronary heart disease or risk equivalents. Using these percentages and previously published estimates of moderate CKD,2 the number of participants with moderate CKD recommended for pharmacological lipid-lowering therapy was estimated before and after its simulated reclassification as a coronary heart disease risk equivalent.

Data management was conducted using SAS (SAS Institute Inc, Cary, NC), and analyses were performed using SUDDAN (Research Triangle Institute, Research Triangle Park, NC) to account for the complex sampling design of NHANES III.
Table 1. Lipid Levels by Presence of Moderate CKD for Participants in NHANES III

<table>
<thead>
<tr>
<th>Lipid Profile</th>
<th>No Moderate CKD (%)</th>
<th>Moderate CKD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200</td>
<td>49.6 ± 1.4</td>
<td>26.9 ± 3.5</td>
</tr>
<tr>
<td>200-239</td>
<td>32.9 ± 1.2</td>
<td>36.7 ± 3.7</td>
</tr>
<tr>
<td>≥240</td>
<td>17.5 ± 0.8</td>
<td>36.4 ± 3.7</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100</td>
<td>23.8 ± 1.0</td>
<td>12.5 ± 2.0</td>
</tr>
<tr>
<td>100-129</td>
<td>31.9 ± 1.2</td>
<td>26.1 ± 3.7</td>
</tr>
<tr>
<td>130-159</td>
<td>27.3 ± 1.1</td>
<td>31.1 ± 3.2</td>
</tr>
<tr>
<td>160-189</td>
<td>12.0 ± 0.6</td>
<td>15.7 ± 2.7</td>
</tr>
<tr>
<td>≥190</td>
<td>5.0 ± 0.4</td>
<td>14.6 ± 3.1</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>23.3 ± 1.1</td>
<td>30.1 ± 4.0</td>
</tr>
<tr>
<td>40-59</td>
<td>53.4 ± 1.2</td>
<td>50.3 ± 3.5</td>
</tr>
<tr>
<td>≥60</td>
<td>23.3 ± 1.0</td>
<td>19.6 ± 2.8</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;150</td>
<td>72.3 ± 1.3</td>
<td>49.3 ± 4.2</td>
</tr>
<tr>
<td>≥150</td>
<td>27.7 ± 1.3</td>
<td>50.7 ± 4.2</td>
</tr>
</tbody>
</table>

Note: Values expressed as percentage ± SE. To convert cholesterol in mg/dL to mmol/L, multiply by 0.02586; triglycerides in mg/dL to mmol/L, multiply by 0.01129.

RESULTS

Lipid Profile

US adults with, compared with their counterparts without, moderate CKD were more likely to have greater levels of total and LDL cholesterol and lower levels of HDL cholesterol (Table 1). Additionally, the presence of high triglyceride levels was more common among adults with moderate CKD.

Prevalence of ATP-III Coronary Heart Disease Risk Factors, Risk Equivalents, and Risk Categories

The prevalence of coronary heart disease and risk equivalents was significantly greater in adults with moderate CKD compared with their counterparts without moderate CKD (53.0% and 13.8%, respectively; Table 2; Fig 1). The prevalence of a history of myocardial infarction, stroke, diabetes, angina, and a 10-year coronary heart disease risk greater than 20% were each greater in adults with moderate CKD. For adults without coronary heart disease or risk equivalents, those with moderate CKD were substantially more likely than their counterparts without moderate CKD to have 2 or more coronary heart disease risk factors (70.7% compared with 31.7%). Adults with moderate CKD were more likely to have hypertension and be older, but less likely to be current cigarette smokers compared with their counterparts without moderate CKD. Only 22.2% of adults with moderate CKD were free of coronary heart disease and risk equivalents and had 0 or 1 coronary heart disease risk factors.

Impact of Reclassifying Moderate CKD as a Coronary Heart Disease Risk Equivalent

Applying the current ATP-III cutoff values, 61.4% of US adults with moderate CKD are recommended pharmacological treatment to decrease their LDL cholesterol levels (Fig 2). If moderate CKD were reclassified as a coronary heart disease risk equivalent, 87.7% of adults with moderate CKD would be recommended pharmacological lipid-lowering therapy. Also, based on their coronary heart disease risk profile

Table 2. Prevalence of Coronary Heart Disease or Risk Equivalents and Coronary Heart Disease Risk Factors for Patients With and Without Moderate CKD

<table>
<thead>
<tr>
<th>Coronary heart disease or risk equivalents</th>
<th>No Moderate CKD (%)</th>
<th>Moderate CKD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>13.8 ± 0.8</td>
<td>53.0 ± 4.0</td>
</tr>
<tr>
<td>History of myocardial infarction/stroke</td>
<td>3.6 ± 0.3</td>
<td>24.7 ± 2.7</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5.8 ± 0.4</td>
<td>17.7 ± 2.6</td>
</tr>
<tr>
<td>Angina</td>
<td>4.1 ± 0.5</td>
<td>9.6 ± 1.8</td>
</tr>
<tr>
<td>10-y risk for coronary heart disease &gt; 20%</td>
<td>2.9 ± 0.4</td>
<td>26.9 ± 3.4</td>
</tr>
<tr>
<td>Coronary heart disease risk factors†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 or more coronary heart disease risk factors†</td>
<td>31.7 ± 1.2</td>
<td>70.7 ± 6.0</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>26.8 ± 1.2</td>
<td>NA</td>
</tr>
<tr>
<td>Hypertension</td>
<td>16.1 ± 0.8</td>
<td>62.2 ± 5.2</td>
</tr>
<tr>
<td>Older age‡</td>
<td>27.6 ± 1.4</td>
<td>87.2 ± 5.5</td>
</tr>
<tr>
<td>Low HDL§</td>
<td>20.6 ± 1.2</td>
<td>20.9 ± 4.9</td>
</tr>
<tr>
<td>High HDL§</td>
<td>24.6 ± 1.1</td>
<td>31.4 ± 4.8</td>
</tr>
</tbody>
</table>

Note: Values expressed as percentage ± SE. Abbreviation: NA, sample size too small (n < 20) for reliable estimate.

†In those without myocardial infarction or angina and in the presence of 2 or more coronary heart disease risk factors.
‡Among participants without coronary heart disease or risk equivalents.
§High HDL cholesterol level is a protective coronary heart disease risk factor and offsets the presence of 1 other risk factor.
and LDL cholesterol level, 31.6% of adults with moderate CKD and without coronary heart disease or risk equivalents currently are recommended pharmacological lipid-lowering therapy. This percentage would increase to 87.6% recommended lipid-lowering treatment if moderate CKD were included as a coronary heart disease risk equivalent in the ATP-III guidelines.

A greater percentage of adults younger than 65 years, females, and non-Hispanic whites would be impacted by the reclassification of moderate CKD as a coronary heart disease risk equivalent.

Figure 1. Distribution of persons with and without moderate CKD into ATP-III risk categories.

Figure 2. Percentages of persons with and without moderate CKD recommended lipid-lowering therapy for the (left) overall population and (right) persons without coronary heart disease or a risk equivalent by using cutoff values from the ATP-III guidelines. Cutoff values for ATP-III guidelines recommend consideration of drug therapy for patients with LDL cholesterol levels of 100 mg/dL or greater for patients with coronary heart disease or risk equivalents and, for patients without coronary heart disease or a risk equivalent, 130 mg/dL or greater for those with 2 or more coronary heart disease risk factors and a 10-year coronary heart disease risk of 10% to 20%, 160 mg/dL or greater for patients with 2 or more coronary heart disease risk factors and a 10-year coronary heart disease risk less than 10%, and 190 mg/dL or greater for patients with 0 or 1 coronary heart disease risk factors, respectively. Error bars represent 95% confidence intervals. To convert cholesterol in mg/dL to mmol/L, multiply by 0.02586.
Specifically, for adults with moderate CKD currently not recommended lipid-lowering therapy, its reclassification as a coronary heart disease risk equivalent would result in lipid-lowering therapy being recommended for 44.8% of adults younger than 65 years, 21.6% of adults 65 years and older, 33.6% of females, 17.2% of males, 27.9% of non-Hispanic whites, and 20.1% of non-Hispanic blacks. Also, for those with moderate CKD, 66.9% of participants with 0 or 1 coronary heart disease risk factors versus only 17.5% of participants with 2 or more coronary heart disease risk factors would be impacted by this change in classification.

Using the ATP-III guidelines, 4.5 million adults with moderate CKD are recommended for pharmacological lipid-lowering therapy. With the reclassification of moderate CKD as a coronary heart disease risk equivalent, pharmacological lipid-lowering therapy would be recommended for 6.5 million adults with moderate CKD.

DISCUSSION

Using the most recently published lipid-lowering treatment guidelines from the US National Cholesterol Education Program, 61.4% of adults with moderate CKD (4.5 million adults) are recommended lipid-lowering therapy. We found that reclassification of moderate CKD as a coronary heart disease risk equivalent would increase the number of adults with moderate CKD recommended for pharmacological treatment by 2 million to a total of 6.5 million, nearly a 50% increase. Based on our estimates, if moderate CKD were reclassified as a coronary heart disease risk equivalent, almost 9 of every 10 adults with moderate CKD (87.7%) would be recommended for consideration of pharmacological lipid-lowering therapy. Although there is substantial evidence showing that moderate CKD is associated independently with increased cardiovascular risk, the ATP-III guidelines do not include it as a coronary heart disease risk equivalent. Results of the current study indicate that such a change would affect a substantial proportion of patients with moderate CKD.

The current study determined the population-level impact on lipid-lowering treatment of reclassifying moderate CKD as a coronary heart disease risk equivalent. In 2002, the National Kidney Foundation defined stage 3 CKD as an estimated glomerular filtration rate between 30 and 59 mL/min/1.73 m² (0.50 and 0.98 mL/s). This level of renal function was used in the current study because it represents a decrease by more than half of normal kidney function and is associated with biochemical abnormalities and increased cardiovascular disease risk. Also, a scientific statement published in 2003 by the American Heart Association Councils on Kidney and Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention suggested “the National Cholesterol Education Program and other groups include CKD in the highest-risk group for recommendations for prevention, detection, and treatment of cardiovascular disease risk factors.” At least 1 study evaluated the risk equivalency of CKD and coronary heart disease. In that study, coronary heart disease incidence rates were compared directly between persons with stage 3 CKD without prior myocardial infarction and their counterparts without stage 3 CKD with prior myocardial infarction. The investigators reported a significantly lower risk for coronary heart disease and cardiovascular mortality in those with stage 3 CKD without prior myocardial infarction compared with those without stage 3 CKD with prior myocardial infarction. The rationale for including type 2 diabetes as a coronary heart disease risk equivalent in the ATP-III guidelines was provided in a recent editorial. Although only a small proportion of studies found a similar risk in persons with diabetes and established coronary heart disease, the decision to include diabetes as a risk equivalent was based on a consideration of the average 10-year coronary heart disease risk for patients with diabetes, the efficacy and cost-effectiveness of using lipid-lowering therapy in this patient population, and the increased coronary heart disease case-fatality rate in the context of diabetes. Among NHANES III participants, 28.8% of adults with moderate CKD had a 10-year coronary heart disease risk greater than 20% compared with only 14.5% among adults with diabetes and 2.5% among those without moderate CKD or diabetes. It should be noted that this sharp difference likely is driven by the older age of individuals with moderate CKD compared with diabetes. It also is worthwhile to note that in many studies, diabetes is associated with a greater
relative risk for cardiovascular disease compared with CKD.\textsuperscript{29-33} However, in a recent study that directly compared rates of atherosclerotic vascular disease, congestive heart failure, renal replacement therapy, and mortality among persons with (1) no diabetes and no CKD, (2) diabetes and no CKD, (3) CKD and no diabetes, and (4) both CKD and diabetes, unadjusted rates of these outcomes were all greater in persons with CKD and no diabetes compared with those with diabetes and no CKD.\textsuperscript{22} Also, after multivariate adjustment for age, race, sex, hospital days, and comorbid conditions, hazard ratios of cardiovascular disease were greater in those with diabetes and no CKD, whereas risks for renal replacement therapy and all-cause mortality were greater among their counterparts with CKD and no diabetes. Although several studies noted that patients with moderate CKD had increased cardiovascular disease risk,\textsuperscript{4-9,12,34} to our knowledge, the case-fatality rates of cardiovascular outcomes have not been reported in patients with, compared with their counterparts without, CKD. Future studies are needed to directly evaluate the coronary heart disease risk equivalency of moderate CKD, cost-effectiveness of lipid-lowering therapy, and case-fatality rates from coronary heart disease and stroke among patients with moderate CKD.

Clear benefits of statins on intermediate outcomes, including decreases in LDL cholesterol levels and progression of renal disease, were shown in individuals with moderate CKD.\textsuperscript{35,36} In a meta-analysis including 13 prospective randomized controlled trials examining lipid level reduction and renal disease progression, use of lipid-lowering treatment was associated with a slower decrease in estimated glomerular filtration rate ($P = 0.008$).\textsuperscript{36} The investigators also noted a possible decrease in proteinuria associated with statin therapy, but this result was of borderline significance.

Few randomized trials have been adequately powered to examine the benefits of statins on coronary heart disease and mortality risk reduction in the context of CKD. The Pravastatin Pooling Project reported a significantly decreased risk for total mortality and a combined outcome of myocardial infarction, coronary death, and coronary revascularization associated with statin use in individuals with moderate CKD.\textsuperscript{37} However, in the Deutsche Diabetes Dialyse Studie, including patients with type 2 diabetes undergoing hemodialysis, no significant reductions in cardiac death, myocardial infarction, and stroke during the study period were observed in the group randomly assigned to statin administration.\textsuperscript{38} However, this study was restricted to dialysis patients, and these results may not represent those expected in patients with stage 3 or 4 CKD. Results from randomized trials of statins including adults with varying degrees of CKD, such as the ongoing Study of Heart and Renal Protection, are needed to sufficiently investigate the efficacy and cost-effectiveness of lipid-lowering therapy to reduce coronary heart disease in these individuals.\textsuperscript{39}

The findings of the current study must be interpreted in the context of its limitations. Data used in the current analysis were collected in 1988 to 1994, rather than the more recent NHANES 1999 to 2002 data set. This decision was undertaken because of the lack of adequate sample size for studying moderate CKD in the subgroup of participants with fasting LDL cholesterol measurements in NHANES 1999 to 2002.\textsuperscript{2} However, it was reported that the prevalence of CKD did not change substantially between NHANES III and NHANES 1999 to 2002. A second limitation is that coronary heart disease, some risk equivalents, and coronary heart disease risk factors were identified by self-report, and a family history of premature coronary heart disease was defined differently from the ATP-III guidelines in the NHANES III data set, potentially resulting in misclassification of participants into risk category groupings. Additionally, the definition of moderate CKD in the current analysis relied on estimated glomerular filtration rate measured at a single time, rather than decrease estimated glomerular filtration rate for 3 months, as outlined in the Kidney Disease Outcomes Quality Initiative.\textsuperscript{11} Use of an estimated glomerular filtration rate from a single point may have resulted in misclassification of participants into CKD categories.

Despite these limitations, the current study has several strengths. These include use of a large nationally representative sample of the US adult population and calculation of the absolute number of adults with moderate CKD who would be impacted if CKD were reclassified as a coronary disease risk equivalent.
heart disease risk equivalent in the ATP-III guidelines.

The current study defines the impact of reclassifying moderate CKD as a coronary heart disease risk equivalent in the National Cholesterol Education Program ATP-III guidelines on lipid-lowering therapy for US adults. Although two thirds of US adults with moderate CKD are already categorized in the highest risk group by using current ATP-III guidelines, inclusion of moderate CKD as a coronary heart disease risk equivalent would change the lipid-lowering treatment recommendation for 2 million patients. Reclassification of moderate CKD as a coronary heart disease risk equivalent has implications for a large number of US adults and should not be undertaken without evidence of benefits to these patients.

REFERENCES


