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Original Investigation

Potential Effects of Reclassifying CKD as a Coronary Heart Disease Risk Equivalent in the US Population

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Background: Persons with chronic kidney disease (CKD) are at high risk for cardiovascular disease events, but are not classified as such in current US cholesterol treatment guidelines. We examined potential effects of modified guidelines in which CKD was considered a "coronary heart disease (CHD) risk equivalent" for risk stratification.

Study Design: Nationally representative cross-sectional study.

Setting & Participants: 4,823 adults 20 years or older from the 2007-2010 National Health and Nutrition Examination Survey.

Predictors: Cardiovascular risk stratification based on current US cholesterol treatment guidelines and 2 simulated scenarios in which CKD stages 3-5 or CKD stages 1-5 were considered a CHD risk equivalent.

Outcomes & Measurements: Proportion of persons with low-density lipoprotein (LDL) cholesterol at levels above treatment targets and above the threshold for lipid-lowering therapy initiation, based on current guidelines and the 2 simulated scenarios.

Results: Under current guidelines, 55.1 million adults in 2010 did not achieve the target LDL cholesterol goal. Of these, 25.2 million had sufficiently elevated levels to meet recommendations for initiating lipid-lowering therapy; 12.1 million were receiving this therapy but remained above goal. When CKD stages 3-5 were considered a CHD risk equivalent, 59.2 million persons were above target LDL cholesterol goals, with 28.5 million and 13.3 million meriting therapy initiation and intensification, respectively. When CKD stages 1-5 were considered a CHD risk equivalent, 65.2 million adults were above goal, with 33.9 million and 14.4 million meriting therapy initiation and intensification, respectively.

Limitations: CKD and LDL cholesterol defined using a single laboratory value.

Conclusions: Many adults in the United States currently do not meet recommended goals for LDL cholesterol levels. Modifying the current cholesterol guidelines to include CKD as a CHD risk equivalent would lead to a substantial increase in both the number of persons with levels above LDL cholesterol treatment targets and those recommended to initiate lipid-lowering therapy.

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Under current US cholesterol treatment guidelines,[1,2] patients with prevalent coronary heart disease (CHD) or a "CHD risk equivalent" are classified as high risk for cardiovascular events and are recommended for aggressive cardiovascular risk reduction with lower target low-density lipoprotein (LDL) cholesterol goals. Conditions considered CHD risk equivalents include noncoronary clinical atherosclerotic disease, diabetes, an abdominal aortic aneurysm, or a combination of 10-year Framingham CHD risk > 20% and 2 of the following risk factors: older

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age, low high-density lipoprotein (HDL) cholesterol level, hypertension, family history of premature CHD, and smoking.

Chronic kidney disease (CKD) is common in the United States and is associated with a high burden of cardiovascular disease. Both reductions in estimated glomerular filtration rate (eGFR) and increases in albuminuria are associated with increased risk of cardiovascular mortality,[3,4] and recent work suggests that CKD carries a myocardial infarction risk similar to that for diabetes.[5] However, CKD is not considered a CHD risk equivalent in the current US cholesterol treatment guidelines; this omission of CKD in cholesterol treatment guidelines has been a point of discussion for several years.[6-8] Both the National Kidney Foundation and the American Heart Association have recommended that patients with CKD be targeted for intensive cardiovascular risk factor control.[6,7] In Europe, cholesterol guidelines formally recommend that adults with CKD be considered at high or very high cardiovascular risk and that LDL cholesterol level reduction be a primary therapy target in adults with moderate to severe CKD.[9]

The goal of this study was to evaluate the potential population-level impact of defining CKD as a CHD risk equivalent in cholesterol guidelines in a US nationally representative population-based sample. We simulated 2 scenarios: one in which CKD stages 3-5 were considered a CHD risk equivalent, and a second in which CKD stages 1-5 were considered a CHD risk equivalent. We then estimated the proportion of US adults failing to meet LDL cholesterol level treatment targets under each of these scenarios, as well as the proportion with sufficiently elevated LDL cholesterol levels that they would be recommended for the initiation or intensification of lipid-lowering therapy, comparing our results with those estimated using the current cholesterol guidelines.

METHODS

Study Population

The 2007-2010 NHANES (National Health and Nutrition Examination Survey) was a cross-sectional, multistage, stratified, clustered probability sample of the US civilian noninstitutionalized population conducted by the National Center for Health Statistics (NCHS).[10] Our study sample included 4,823 adults 20 years or older who attended the mobile examination center visit and were fasting for at least 9 hours prior to their examination and blood draw (the morning fasting subsample) and who were not pregnant or missing urinary albumin or creatinine measurements. The NHANES was approved by the NCHS Research Ethics Review Board, and all participants provided informed consent.[11-13]

Assessment of CKD and Definitions

Serum creatinine was measured in serum samples using the Jaffé rate method. Urinary albumin and creatinine were measured using an enzymatic method in random urine samples collected during the mobile examination center visit.[14,15] We used the 2009 CKD-EPI (CKD Epidemiology Collaboration) creatinine equation to estimate eGFR.[16] Urinary albumin-creatinine ratio (ACR) was calculated from urinary albumin level divided by urinary creatinine level and was expressed in milligrams per gram. We defined CKD stages 1-5 as the presence of decreased eGFR (GFR categories G3a-G5) or moderately to severely increased ACR (albuminuria categories A2 or A3), and CKD stages 3-5, as the presence of decreased eGFR (GFR categories G3a-G5) at any level of albuminuria (A1-A3).[6,17] We did not account for the persistence of albuminuria based on repeated ACR measurements, which may lead to overestimates in the overall prevalence of CKD.

Cardiovascular Risk Stratification and LDL Cholesterol Goals Based on Current Guidelines

We approximated current national cholesterol guidelines[1,2] by stratifying participants into 5 categories of cardiovascular risk. These risk categories, their specific target LDL cholesterol goals, and the LDL cholesterol levels at which to consider lipid-lowering therapy are summarized in Table 1. We defined CHD risk factors and CHD risk equivalents as follows: CHD risk factors included current smoking (self-report), low HDL cholesterol level ($<$40 mg/dL), older age ($\geq$45 years in men and $\geq$ 55 years in women), hypertension (systolic blood pressure $\geq$ 140 mm Hg, diastolic blood pressure $\geq$ 90 mm Hg, or self-reported physician diagnosis of hypertension), family history of premature CHD (self-report of a heart attack in a close relative before age 50 years), and high HDL cholesterol level ($\geq$60 mg/dL; a negative risk factor).[1,2] CHD risk equivalents included: (1) diabetes (hemoglobin $A_{1c} \geq 6.5\%$, self-reported physician diagnosis, or self-reported use of insulin or antidiabetic pills), (2) history of stroke based on self-report, and (3) the presence of 2 or more risk factors with a 10-year risk of a CHD event $>$ 20%, calculated based on the Framingham Risk Score.

Alternative Guideline Scenarios

Two different modifications to the current national cholesterol guidelines were evaluated (Table 1). The first classified CKD stages 3-5 as a CHD risk equivalent (scenario 1), and the second classified CKD stages 1-5 as a CHD risk equivalent (scenario 2). Under the 2 simulated scenarios, adults with CKD classified under current guidelines in 1 of the 3 lowest risk stratification groups (moderately high, moderate, or lower risk) were reclassified as high risk. Adults with CKD classified as high risk under current guidelines would be reclassified as very high risk were they also to have prevalent cardiovascular disease.

Definition of Dyslipidemia and Lipid-Lowering Medication Use

We defined dyslipidemia as: (1) serum LDL cholesterol level above goal based on National Cholesterol Education Program Adult Treatment Panel III (ATP III) criteria and the modified ATP III guidelines,[1,2] or (2) self-reported use of lipid-lowering therapy. Use of therapy was self-reported as part of the home visit questionnaire; type of therapy was assessed during the home visit, during which medication bottles for prescription medications used in the 30 days prior to the home visit were reviewed. We classified lipid-lowering therapy type into 3 groups: (1) statin monotherapies, (2) statin combination therapies (statins in combination with nonstatin antihyperlipemic agents), and (3) other (nonstatin) lipid therapies. We assessed the reliability of self-reported lipid-lowering therapy use by comparing it to prescription medication use collected from medication containers for drugs used in the past 30 days at the NHANES household visit. Concordance between these 2 definitions was high (total agreement = 92.3%; $\kappa = 0.75$).

Statistical Analyses

Analyses were performed using weights for the morning fasting subsample that account for oversampling in the complex survey