Contrasting Cholesterol Management Guidelines for Adults with CKD

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ABSTRACT
The Kidney Disease Improving Global Outcomes Lipid Work Group recommends statins for adults ≥50 years old with CKD. The American College of Cardiology/American Heart Association endorses statins for adults with atherosclerotic cardiovascular disease, adults with LDL cholesterol ≥190 mg/dl, and adults 40–79 years old with LDL cholesterol=70–189 mg/dl and diabetes or a 10-year predicted risk for atherosclerotic cardiovascular disease ≥7.5% estimated using the Pooled Cohort risk equations. Using data from the Reasons for Geographic and Racial Differences in Stroke Study, we calculated the agreement for statin treatment between these two guidelines for adults 50–79 years old with CKD (eGFR, 60 ml/min per 1.73 m² or albuminuria ≥30 mg/g) not on dialysis. We assessed the validity of the Pooled Cohort risk equations in individuals with CKD. Study participants were enrolled between 2003 and 2007, and we report incident cardiovascular disease events (stroke and coronary heart disease) through December of 2010. Among 4726 participants with CKD, 2366 (50%) were taking statins, and 1984 (42%) were recommended statins by the American College of Cardiology/American Heart Association guideline but not taking them. Overall, 376 (8%) participants did not meet the American College of Cardiology/American Heart Association criteria for initiating statin treatment. Cardiovascular disease incidence was low (3.0/1000 person-years; 95% confidence interval, 0.1 to 5.9) among these participants. The Pooled Cohort risk equations were well calibrated (Hosmer–Lemeshow chi-squared=2.7, P=0.45) with moderately good discrimination (C index, 0.71; 95% confidence interval, 0.65 to 0.77). In conclusion, these guidelines show high concordance for statin treatment for adults with CKD.


Over the past 15 years, a number of studies have shown CKD to be associated with an increased risk for atherosclerotic cardiovascular disease (ASCVD).1–5

Data from randomized trials have shown that statins reduce the risk for ASCVD events and cardiovascular mortality among individuals with CKD not on dialysis.6–9 On the basis of the high absolute risk for ASCVD among individuals with CKD in conjunction with results from clinical trials, the 2013 Kidney Disease Improving Global Outcomes (KDIGO) Foundation Clinical Practice Guideline for Lipid Management in CKD recommended that all adults 50 years of age or older with CKD not on dialysis should be taking a statin.10

In 2013, the American College of Cardiology/American Heart Association (ACC/AHA) published a treatment guideline for serum cholesterol management for both primary and secondary ASCVD prevention.11 According to this guideline, four groups of
adults are recommended statins: (1) adults with a history of ASCVD, (2) adults with LDL cholesterol (LDL-C)=190 mg/dl, (3) adults age 40–79 years with LDL-C=70–189 mg/dl and diabetes, and (4) adults with a 10-year predicted risk for ASCVD events ≥7.5% using the Pooled Cohort risk equations published by Stone et al.\textsuperscript{11} and Goff et al.\textsuperscript{12}

All adults ≥50 years of age with CKD are recommended statins according to the 2013 KDIGO Lipid Management guideline. However, the 2013 ACC/AHA cholesterol treatment guideline found no evidence of the contribution of CKD to ASCVD risk assessment, and CKD was not considered when defining recommendations for discussing initiation of statin therapy. Although the average ASCVD risk among the population ≥50 years of age with CKD is high, some individuals with CKD may not meet the criteria for considering the initiation of statins according to the ACC/AHA guideline.\textsuperscript{11} We analyzed data from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study to estimate the discordance in statin therapy recommendations between the 2013 ACC/AHA and KDIGO cholesterol treatment guidelines. Because the Framingham coronary heart disease (CHD) risk score has been found to be poorly calibrated among individuals with CKD,\textsuperscript{13} we also assessed the performance of the ASCVD Pooled Cohort risk equations among participants with CKD. Finally, to determine whether individuals with CKD and a low predicted ASCVD risk actually have low risk, we calculated ASCVD incidence rates among participants with CKD in the REGARDS Study by strata of 10-year predicted ASCVD risk.

RESULTS

**Indications for Statin Use**

In total, 4726 REGARDS participants 50–79 years old with CKD not on dialysis met the inclusion criteria for this analysis (Supplemental Figure 1), including 2250 participants with eGFR<60 ml/min per 1.73 m\textsuperscript{2} and 3276 participants with albumin-to-creatinine ratio (ACR)≥30 mg/g. Among participants with CKD, 50.0% were taking statins, 35.5% had a history of ASCVD, 39.9% had diabetes, and 3.2% had an LDL-C≥190 mg/dl (Table 1). Overall, 72.2% of participants were taking statins or were not taking statins but had ASCVD, LDL-C≥190 mg/dl, or LDL-C=70–189 mg/dl and diabetes and are recommended statins by the ACC/AHA guideline (Figure 1, left panel). In addition, 19.8% of participants were free of these conditions but had LDL-C=70–189 mg/dl and a predicted 10-year ASCVD risk≥7.5%. In total, the 2013 ACC/AHA cholesterol treatment guideline recommends statins for 92.0% of participants with CKD, leaving 8.0% of participants with CKD who do not meet the criteria for statins. When participants with eGFR<60 ml/min per 1.73 m\textsuperscript{2} and participants with ACR≥30 mg/g were evaluated separately, 5.5% and 8.6%, respectively, did not meet the criteria for statins.

**ASCVD Pooled Cohorts Risk Equations and ASCVD Risk**

There were 1110 participants with CKD not taking statins who were free of ASCVD and diabetes and had an LDL-C between 70 and 189 mg/dl for whom the decision to initiate statins is recommended by the ACC/AHA guideline to be informed by 10-year ASCVD risk (Table 2). Among this subset of participants, 24.1% of participants had a 10-year predicted ASCVD risk<7.5% (Figure 1, right panel). When participants with eGFR<60 ml/min per 1.73 m\textsuperscript{2} and ACR≥30 mg/g were analyzed separately, 17.6% and 25.7%, respectively, had a 10-year predicted ASCVD risk<7.5%. Supplemental Tables 1–3 show characteristics for participants with CKD with either eGFR<60 ml/min per 1.73 m\textsuperscript{2} or ACR≥30 mg/g stratified by 10-year predicted ASCVD risk. Among individuals with CKD, those with a 10-year ASCVD predicted risk<7.5% were younger, less likely to be black, men, current smokers, or taking antihypertensive medication compared with their counterparts with a 10-year ASCVD predicted risk≥7.5%.

We observed 78 incident ASCVD events over 5 years of follow-up among participants with CKD for whom the decision to initiate statins is recommended by the ACC/AHA guideline to be informed by 10-year ASCVD risk. The ASCVD Pooled Cohort risk equations were well calibrated among participants with CKD (Hosmer–Lemeshow chi-squared test=2.7, \(P=0.45\)), eGFR<60 ml/min per 1.73 m\textsuperscript{2} (chi-squared test=4.9, \(P=0.18\)), and ACR≥30 mg/g (chi-squared test=5.4, \(P=0.15\)) (Figure 2, Supplemental Table 4). The C-index values among participants with CKD, eGFR<60 ml/min per 1.73 m\textsuperscript{2}, and ACR≥30 mg/g were 0.71 (95% confidence interval [95% CI], 0.65 to 0.77), 0.73 (95% CI, 0.65 to 0.82), and 0.71 (95% CI, 0.64 to 0.77), respectively.

The incidence rates for ASCVD among participants with CKD, eGFR<60 ml/min per 1.73 m\textsuperscript{2}, and ACR≥30 mg/g were 14.1 (95% CI, 11.0 to 17.2), 14.3 (95% CI, 9.4 to 19.2), and 15.8 (95% CI, 11.7 to 19.7) per 1000 person-years, respectively (Supplemental Table 5). Among participants with 10-year

Table 1. Statin use and prevalence of indications for statin use among REGARDS Study participants with CKD

<table>
<thead>
<tr>
<th>Participants Subgroups</th>
<th>eGFR&lt;60 ml/min per 1.73 m\textsuperscript{2} or ACR≥30 mg/g</th>
<th>eGFR&lt;60 ml/min per 1.73 m\textsuperscript{2}</th>
<th>ACR≥30 mg/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total participants, n</td>
<td>4726</td>
<td>2250</td>
<td>3276</td>
</tr>
<tr>
<td>Taking statins, n (%)</td>
<td>2366 (50.0)</td>
<td>1262 (56.1)</td>
<td>1566 (47.8)</td>
</tr>
<tr>
<td>History of ASCVD, n (%)</td>
<td>1676 (35.5)</td>
<td>902 (40.1)</td>
<td>1145 (35.0)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>1857 (39.3)</td>
<td>825 (36.7)</td>
<td>1440 (44.0)</td>
</tr>
<tr>
<td>LDL-C≥190 mg/dl, n (%)</td>
<td>153 (3.2)</td>
<td>75 (3.3)</td>
<td>112 (3.4)</td>
</tr>
</tbody>
</table>
ASCVD predicted risk <7.5%, the ASCVD incidence rates were 3.0 (95% CI, 0.1 to 5.9), 0.0 (95% CI, 0.0 to 7.5), and 4.0 (95% CI, 0.1 to 7.9) per 1000 person-years for participants with CKD, eGFR <60 ml/min per 1.73 m², and ACR ≥30 mg/g, respectively (Figure 3).

### DISCUSSION

In this study, 50.0% of participants with CKD were taking statins. Statins were underused, because 42.0% of participants with CKD were not taking statins, despite having a history of ASCVD, LDL-C ≥190 mg/dl, or LDL-C ≤70–189 mg/dl and either diabetes or a 10-year predicted ASCVD risk ≥7.5%. Overall, 92.0% of participants 50–79 years of age with CKD not on dialysis were taking statins or are recommended statin therapy by the 2013 ACC/AHA cholesterol treatment guideline.10,11 Only 8.0% of individuals 50–79 years of age with CKD did not meet the 2013 ACC/AHA criteria for statin initiation. These results indicate a high concordance for the recommendations of statin therapy between the ACC/AHA guideline and the KDIGO guideline, which recommends universal statin treatment for adults ≥50 years of age.

Over the past 15 years, studies have reported CKD to be associated with an increased risk for ASCVD.1–5 Tonelli et al.14 reported that, among individuals without a history of previous
myocardial infarction (MI), having CKD without diabetes is associated with a higher incidence rate of hospitalized MI (6.9/1000 person-years; 95% CI, 6.6 to 7.2) compared with having diabetes without CKD (5.4/1000 person-years; 95% CI, 5.2 to 5.7). In addition, the observed incidence rate for coronary death or nonfatal MI among individuals ≥50 years of age with CKD from the Alberta Kidney Disease cohort (which includes >1 million patients) was 17.3/1000 person-years (95% CI, 17.0 to 17.7). On the basis of these results, the KDIGO Lipid Work Group concluded that all individuals with CKD ≥50 years of age should be considered in the highest risk group for future coronary events and treated with statins.

Statins have been shown to reduce the occurrence of ASCVD events among individuals with CKD not on dialysis. The Third Report of the National Cholesterol Education Program, Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) recommended consideration of statin therapy for individuals with elevated LDL-C combined with an increased risk for CHD defined on the basis of a history of CHD, the presence of CHD risk equivalents, or a high predicted risk estimated using an equation derived from the Framingham Health Study. However, CKD was not considered a risk equivalent in the ATP III guideline, and prior studies have reported that adding CKD as a CHD risk equivalent in ATP III would significantly increase the proportion of individuals with CKD recommended statin therapy. The 2013 ACC/AHA cholesterol treatment guideline has increased the number of United States adults who are now recommended statin therapy. As documented in this study.

Figure 2. The ASCVD Pooled Cohort risk equations show good calibration among study participants with CKD, eGFR < 60 ml/min per 1.73 m² and ACR ≥ 30 mg/g. Good calibration is determined by similar observed and predicted rates.

Figure 3. The incidence of ASCVD is low among REGARDS Study participants with CKD and a 10-year predicted ASCVD risk < 7.5%. The dotted line represents the 10-year ASCVD predicted risk considered by the ACC/AHA Task Force as the threshold for initiation of statins.
analysis, the vast majority of individuals 50–79 years of age with CKD not on dialysis are recommended statin therapy by the 2013 ACC/AHA cholesterol treatment guideline.

Weiner et al.\textsuperscript{13} reported that the Framingham CHD risk prediction equation used in ATP III was not well calibrated for predicting CHD events among individuals with CKD and was not suitable to guide a therapeutic decision among these individuals without recalibration. Specifically, in an analysis pooling data from the Atherosclerosis Risk In Communities Study and the Cardiovascular Health Study, the 10-year observed and predicted risks for CHD among individuals 45–74 years old with CKD were 13.9% and 8.2%, respectively.\textsuperscript{13} The 2013 Pooled Cohort risk equations for estimating ASCVD risk were developed using data from several United States cohorts.\textsuperscript{12} A prior study has shown that these equations are well calibrated and have moderately good discrimination among the general population, for whom they are recommended to guide the decision to initiate statins.\textsuperscript{22} In this study, the ASCVD Pooled Cohort risk equations were well calibrated and had moderately good discrimination among individuals with CKD. Data from this study suggest that these equations can be used to inform clinical decisions among individuals with CKD.

The 2013 ACC/AHA cholesterol treatment guideline found limited evidence to support initiation of statin therapy in primary prevention for individuals ≥80 years old.\textsuperscript{11} However, the 2013 KDIGO Lipid Management guideline recommended statin use for individuals with CKD≥80 years of age.\textsuperscript{10} Older individuals with CKD have a reduced life expectancy, high competing risk for other CKD-related outcomes, and a higher risk for statin-related adverse events and drug-drug interactions.\textsuperscript{23–25} These factors can reduce the potential benefit of statin initiation among the very old with CKD. Given the high prevalence of CKD among individuals ≥80 years of age,\textsuperscript{26} studies are needed to identify the benefits of statins for this high-risk group.

The results from this study suggest that the 2013 KDIGO Lipid Management guideline could lead to unnecessary treatment for only a small percentage of individuals with CKD. Although these individuals have a low ASCVD risk, the more straightforward recommendation in the KDIGO guideline (i.e., treating all individuals with CKD≥50 years of age) could lead to an increase in the percentage of individuals with CKD taking statins. This result is important considering that >40% of participants with CKD in this study were recommended statins by the 2013 ACC/AHA guideline but not taking them. Statin use increased markedly after the universal recommendation of statins for individuals ≥60 years old with CKD (i.e., eGFR<60 ml/min per 1.73 m\(^2\) or ACR≥30 mg/g) not on dialysis. We restricted the analysis to participants <80 years of age, because the ACC/AHA guideline does not recommend initiation of statin therapy for primary prevention in people ≥80 years old.\textsuperscript{11} Participants were excluded if they were missing information on baseline serum creatinine, ACR, history of ASCVD, diabetes, or variables used in the Pooled Cohort risk equations or had no follow-up information on the occurrence of ASCVD events. The REGARDS Study protocol was approved by the Institutional Review Boards governing research in human subjects at the participating centers, and all participants provided written informed consent.

**Baseline Assessment**

Computer-assisted telephone interviews were administered by trained staff and used to collect information on participants’ age, race, sex, smoking status, prior diagnosed comorbid conditions (e.g., MI, stroke, diabetes, and atrial fibrillation [AF]) and history of vascular interventions (e.g., coronary and lower extremity revascularization procedures and aortic aneurysm repair surgery), dialysis therapy, and use of antihypertensive, antidiabetes, and lipid-lowering medications.

After the interview, trained health professionals conducted in-home examinations using standardized protocols. Procedures included two BP measurements, which were averaged, an electrocardiogram, collection of blood and urine samples, and a review of bottles of prescription and over-the-counter medications used during the 2-week period before the study visit. Serum total cholesterol, HDL-cholesterol (HDL-C), triglycerides, and glucose were measured by colorimetric
reflectance spectrophotometry. For participants with fasting serum triglycerides <400 mg/dl, LDL-C was calculated using the Friedewald equation. For participants who did not fast before their study visit (n=802) or had triglycerides ≥400 mg/dl (n=83), non–HDL-C was calculated as total cholesterol–HDL-C.

History of ASCVD at baseline was defined as a self-report of a prior diagnosis of MI or stroke; a prior coronary artery bypass, coronary angioplasty, or stenting; a lower extremity revascularization procedure or an aortic aneurysm repair surgery; or evidence of a previous MI on the study electrocardiogram. Diabetes was defined as fasting glucose ≥126 mg/dl (≥200 mg/dl for nonfasting participants) or self-report of a prior diagnosis of diabetes with current use of insulin or oral hypoglycemic medications. AF was defined using the baseline electrocardiogram or self-report. Information on heart failure (HF) was not ascertained at baseline. Therefore, we defined prevalent HF as treatment with digoxin on the basis of the in-home review of bottles for medications. We defined current statin therapy through the review of pill bottles or self-reported use of lipid-lowering medications. We estimated the 10-year ASCVD predicted risk using the Pooled Cohort risk equations (Supplemental Table 6).

Serum creatinine was measured using an isotope-dilution mass spectrometry traceable method. eGFR was calculated using information on age, race, sex, and serum creatinine along with a published equation from the Chronic Kidney Disease Epidemiology Collaboration. Urinary albumin and creatinine were measured using a BN ProSpec Nephelometer (Dade Behring, Marburg, Germany) and a rate-blanked Jaffé procedure using a Modular-P Analyzer (Roche/Hitachi, Indianapolis, IN), respectively, and these values were used to calculate ACR. As described above, CKD was defined as eGFR <60 ml/min per 1.73 m² or ACR ≥30 mg/g.

Data Collected during Follow-Up
Living REGARDS participants or proxy respondents were contacted every 6 months by telephone to assess incident stroke or CHD events. When nonfatal events were reported, medical records were retrieved for adjudication. Stroke events were confirmed by a panel of experts using the World Health Organization definition. Events not meeting this definition but characterized by symptoms lasting <24 hours with neuroimaging consistent with acute infarct or hemorrhage were also classified as strokes. Nonfatal MIs were adjudicated by trained clinicians following published guidelines. When stroke or CHD-related deaths were reported, interviews with the next of kin or a proxy, medical records in the last 1 year of life, death certificates, and autopsy reports were used to determine if a stroke or a CHD event was the main underlying cause of death. We defined incident ASCVD as an incident nonfatal or fatal stroke, nonfatal MI, or CHD death. Adjudication of both stroke and CHD events in the REGARDS Study is currently available through December 31, 2010.

Statistical Analyses
We calculated the percentage of REGARDS Study participants with CKD taking statins with ASCVD, diabetes, and LDL-C ≥190 mg/dl. Also, we calculated the distribution of the population with CKD taking statins, not taking statins but recommended statins by the 2013 ACC/AHA cholesterol treatment guideline (i.e., with history of ASCVD, LDL-C ≥190 mg/dl, or LDL-C = 70–189 mg/dl and either diabetes or a 10-year predicted ASCVD risk ≥7.5%), and not taking statins and not recommended statins by the 2013 ACC/AHA cholesterol treatment guideline.

Next, we assessed the validity of the Pooled Cohort risk equations for participants with CKD. These analyses were limited to participants with CKD for whom the calculation of 10-year ASCVD risk is recommended by the ACC/AHA guideline to inform the decision to initiate statins. Specifically, we excluded participants already taking statins or those who had a history of ASCVD, diabetes, AF, HF, LDL-C ≥190 mg/dl, or LDL-C <70 mg/dl (or non–HDL-C ≥220 or <100 mg/dl for those without valid LDL-C). For calibration, observed and predicted numbers of events at 5 years were calculated by quintile of 10-year predicted risk. We used a 5-year period, because the REGARDS Study participants have not yet been followed for 10 years. Participants were censored at the time that the first of the following events occurred: (1) incident ASCVD, (2) death, (3) last REGARDS Study interview, (4) 5 years of follow-up, or (5) December 31, 2010. The observed number of ASCVD events was calculated adjusting for follow-up time using the Kaplan–Meier estimate. The predicted number of ASCVD events was estimated on the basis of the mean 5-year ASCVD risk on the Pooled Cohort risk equations for each quintile estimated using the survival constant [S(t)] at 5 years provided by the ACC/AHA Guideline on the Assessment of Cardiovascular Risk Working Group (S. Coady, personal communication). We evaluated the calibration of the ASCVD Pooled Cohort risk equations using a modified Hosmer–Lemeshow chisquared statistic. A chi-squared >20 or P value <0.05 indicates poor calibration. We evaluated the discrimination of the ASCVD Pooled Cohort risk equations using the C index. A C index between 0.70 and 0.80 is considered moderately good, and a C index ≥0.80 is considered excellent. Finally, we calculated the ASCVD incidence rate (overall and separately) for REGARDS Study participants with CKD and 10-year predicted ASCVD risk <7.5% and ≥7.5%. An incidence rate of 7.5/1000 person-years approximates a 10-year risk of 7.5%. All analyses were repeated for REGARDS Study participants with eGFR <60 ml/min per 1.73 m² and ACR ≥30 mg/g separately. Data management and analysis were conducted using SAS, version 9.3 (SAS Institute, Cary, NC).

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A full list of participating REGARDS investigators and institutions and additional information about the study can be found at http://www.regardsstudy.org.

DISCLOSURES

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REFERENCES


