Atherosclerotic Cardiovascular Disease Events in Adults With CKD Taking a Moderate- or High-Intensity Statin: The Chronic Renal Insufficiency Cohort (CRIC) Study

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Rationale & Objective: The 2018 American Heart Association/American College of Cardiology (AHA/ACC) cholesterol guideline uses risk stratification to guide the decision to initiate nonstatin lipid-lowering medication among adults with atherosclerotic cardiovascular disease (CVD). We determined atherosclerotic CVD (ASCVD) event rates among adults with chronic kidney disease (CKD) taking statin therapy within 2018 AHA/ACC cholesterol guideline risk categories.

Study Design: Observational cohort study.

Setting & Participants: Adults with CKD not on dialysis in the Chronic Renal Insufficiency Cohort (CRIC) study who were taking a moderate/high-intensity statin 1 year after enrollment (baseline for the current analysis, n = 1,753).

Exposure: 2018 AHA/ACC cholesterol guideline risk categories: without a history of ASCVD, a history of 1 major ASCVD event and multiple high-risk conditions, and a history of ≥2 major ASCVD events.

Outcome: Adjudicated ASCVD events after the year 1 study visit.

Analytical Approach: We calculated age-sex standardized rates for ASCVD events and age-sex adjusted hazard ratios for ASCVD events accounting for the competing risk of death.

Results: There were 394 ASCVD events over a median follow-up period of 8 years. The ASCVD event rates (with 95% CI) per 1,000 person-years among participants without a history of ASCVD, with a history of 1 major ASCVD event and multiple high-risk conditions, and with a history of ≥2 major ASCVD events were 21.7 (18.4-25.1), 45.0 (37.8-52.3), and 73.3 (53.3-93.4), respectively. Compared with participants without a history of ASCVD, the HR (95% CI) rates for ASCVD events among those with a history of 1 major ASCVD event and multiple high-risk conditions, and with a history of ≥2 major ASCVD events were 1.89 (1.52-2.36) and 2.50 (1.85-3.39), respectively.

Limitations: Data on whether participants were taking a maximally tolerated statin dosage were unavailable.

Conclusions: The 2018 AHA/ACC cholesterol guideline identifies adults with CKD who have very high ASCVD risk despite taking a moderate/high-intensity statin.

Visual Abstract included

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Statins reduce the risk for atherosclerotic cardiovascular disease (CVD) events in the general population and among adults with chronic kidney disease (CKD) and not on dialysis.[1-3] The 2018 American Heart Association/American College of Cardiology (AHA/ACC) guideline on the management of blood cholesterol recommends maximally tolerated statin therapy for adults with CKD who have a history of atherosclerotic CVD (ASCVD).[4] This guideline also recommends ezetimibe and/or a proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9I) for adults with ASCVD who have very high ASCVD risk and low-density lipoprotein (LDL) cholesterol levels of ≥70 mg/dL despite taking a maximally tolerated statin dose.[4] Very high ASCVD risk is defined in this guideline as a history of 1 major ASCVD event with multiple high-risk conditions or a history of ≥ 2 major ASCVD events (Table S1).

As CKD is considered a high-risk condition by the 2018 AHA/ACC cholesterol guideline and most adults with CKD have other ASCVD risk factors,[5,6] a high proportion of adults with CKD and a history of a major ASCVD event may meet the definition of very high ASCVD risk. Determining the absolute risk for ASCVD events among adults with CKD taking a moderate- or high-intensity statin who meet the definition of very high ASCVD risk in the 2018 AHA/ACC cholesterol guideline may inform the need for, and potential benefit of, additional interventions to prevent cardiovascular events in this population.

We determined the rates of ASCVD events among adults with CKD taking a moderate- or high-intensity statin who met the definition of very high ASCVD risk according to the 2018 AHA/ACC cholesterol guideline. For comparison, we also calculated the rate of ASCVD events among adults with CKD taking a moderate- or high-intensity statin who did not meet the AHA/ACC guideline definition for very high risk. To accomplish this objective, we analyzed

PLAIN-LANGUAGE SUMMARY

We analyzed the risk for atherosclerotic cardiovascular disease (CVD) events among 1,753 adults with chronic kidney disease (CKD) and not on dialysis taking a moderate- or high-intensity statin according to risk categories in the 2018 AHA/ACC cholesterol guideline. Compared with individuals without a history of ASCVD, those with a history of 1 major ASCVD event and multiple high-risk conditions and with a history of ≥2 major ASCVD events had a higher age-sex adjusted risk for ASCVD events. These results indicate that the risk stratification algorithm in the 2018 AHA/ACC cholesterol guideline identifies adults with CKD who have a very high ASCVD risk despite taking a moderate- or high-intensity statin.

data from the Chronic Renal Insufficiency Cohort (CRIC) study.[7]

METHODS

Study Population

The CRIC study enrolled 3,939 adults aged 21 to 74 years with mild-to-moderate CKD and not on dialysis between May 2003 and August 2008 at 7 centers in the United States.[8] Mild-to-moderate CKD was defined by an estimated glomerular filtration rate (eGFR) of 20-70 mL/min/1.73 m^2 for adults aged 21-44 years, 20-60 mL/min/1.73 m^2 for adults aged 45-64 years, and 20-50 mL/min/1.73 m^2 for adults aged 65-74 years. The CRIC study protocol was approved by the institutional review boards at the participating centers, and all participants provided written informed consent.

All CRIC study participants completed an in-person study visit upon enrollment (ie, the year 0 study visit). Participants were asked to return for annual in-person follow-up study visits.[9] For the current analysis, we included 3,520 CRIC study participants who completed the follow-up study visit conducted 1 year after enrollment (ie, the year 1 study visit), which served as baseline for the current analysis (Fig S1). This restriction was applied so that we could identify participants who had an acute coronary syndrome (ACS) in the prior year (ie, a recent ACS), one of the components of the definition of major ASCVD events in the 2018 AHA/ACC cholesterol guideline (Table S1). We restricted the analysis to CRIC study participants with valid data on statin use and dosage based on the medication inventory conducted at the year 1 study visit (n = 3,400). We excluded 1,425 participants who were not taking a statin and 218 who were taking a low-intensity statin. Finally, we excluded 4 participants who did not have follow-up data for cardiovascular outcomes, resulting in 1,753 participants being included in the current analysis.

Participant Characteristics and Statin Use

Data on the participants' sex, race/ethnicity, education, and self-reported history of myocardial infarction (MI), stroke, and peripheral artery disease (PAD) were collected at the year 0 study visit (ie, their time of enrollment into the CRIC study).[10] We used the data on the participants' age, body mass index, eGFR, and LDL cholesterol obtained at their year 1 follow-up study visit (ie, the baseline for the current analysis). Estimated GFR was assessed using serum creatinine, serum cystatin-C, age, sex, and race and the CRIC-eGFR equation.[11] LDL cholesterol was measured from blood samples using β quantification.[12] We used data on physical activity, serum high-sensitive C-reactive protein, fibroblast growth factor 23, and urinary albumin-to-creatinine ratio obtained through study procedures during the year 0 study visit because these variables were not assessed at the year 1 follow-up study visit. We used data from the medication inventory at the year 1 follow-up study visit to identify the use and intensity of statin therapy (Table S2). We used the medication inventory data of participants who attended follow-up study visits after the year 1 study visit to identify changes in statin use.

Identification of Cardiovascular Hospitalizations and All-Cause Mortality

Participants were asked about hospitalizations possibly related to cardiovascular events, including MI, ischemic stroke, PAD and heart failure, at every annual follow-up study visit and through phone calls at 6-month intervals between visits. Selected hospitals and health care systems were also queried for possible cardiovascular hospitalizations. Medical records were retrieved and adjudicated by at least 2 study clinicians to confirm the occurrence of MI, ischemic stroke, PAD, or heart failure event. For the current analysis, ASCVD events included MI, ischemic stroke, or PAD, and total CVD events included ASCVD events or heart failure. The definitions of these events are provided in Table S3. Deaths were identified from reports of relatives, retrieval of death certificates or obituaries, hospital and outpatient records, and the Social Security Death Master File.

We used CRIC study follow-up between the year 0 and year 1 study visits (ie, before baseline for the current analysis) to define the participants' baseline ASCVD risk categories, as described in the next section. We used data after the year 1 study visit to identify MI, ischemic stroke, PAD, and heart failure hospitalizations and all-cause mortality as outcome events. For this analysis, the participants were censored if they were lost to follow-up observation or on December 31, 2016, whichever occurred first.

Atherosclerotic CVD Risk Assessment

We used data on the participants' characteristics collected at the year 0 and year 1 study visits, and data on adjudicated MI, ischemic stroke, and PAD hospitalizations between the year 0 and year 1 study visits (ie, before baseline for the current analysis) to determine each participant's ASCVD risk category according to the 2018 AHA/ACC cholesterol guideline. The participants were categorized into 3 mutually exclusive groups: (1) not having a history of major ASCVD events; (2) having a history of major ASCVD events (ie, history of coronary heart disease, stroke, or PAD, recent ACS, or an acute ischemic stroke or PAD event, Table S1, top panel) and very high ASCVD risk, including the following 2 groups: having a history of 1 major ASCVD event and multiple (ie, 2 or more) high-risk conditions (ie, CKD and age ≥ 65 years, prior coronary artery bypass grafting, or percutaneous coronary intervention, diabetes, hypertension, current smoking, LDL cholesterol ≥ 100 mg/dL while taking a statin, and history of heart failure [Table S1, bottom panel]); and (3) having a history of ≥ 2 major ASCVD events.

All CRIC study participants eligible for the current analysis with a history of a major ASCVD event met the definition for very high ASCVD risk.

Statistical Analysis

We calculated separately the summary statistics for characteristics and the cumulative incidence of ASCVD events among participants without a history of major ASCVD events, with a history of 1 major ASCVD event and multiple high-risk conditions, and with a history of ≥ 2 major ASCVD events. We also calculated the unadjusted rate and the age-sex adjusted rate, and rate difference and hazard ratio for ASCVD events among participants without a history of major ASCVD events, with a history of 1 major ASCVD event and multiple high-risk conditions, and with a history of ≥ 2 major ASCVD events. Adjusted rates, rate differences, and hazard ratios included adjustment for age and sex as these are non-modifiable risk factors.

The adjusted rates were calculated using direct standardization to represent the age-sex distribution of participants with a history of 1 major ASCVD event and multiple high-risk conditions and with a history of ≥ 2 major ASCVD events combined (ie, those at very high ASCVD risk). Rate differences were calculated using Poisson regression. The analyses described previously were repeated to calculate the cumulative incidence, unadjusted rate and the age-sex adjusted rate, and rate difference and hazard ratio for MI, ischemic stroke, PAD, total CVD events, heart failure hospitalizations, and all-cause mortality, separately. For all outcomes except all-cause mortality, the cumulative incidence and hazard ratio were calculated accounting for the competing risk of death as described by Fine and Gray.[13] No competing risk was considered for the analysis of all-cause mortality.

The calculation of unadjusted rates and age-sex-adjusted rates, rate differences, and hazard ratios for ASCVD, MI, ischemic stroke, PAD, total CVD and heart failure events, and all-cause mortality was repeated within subgroups defined by eGFR (ie, <30, 30 to <45, and ≥45 mL/min/1.73 m^2), and LDL cholesterol (ie, <70, 70 to <100, and ≥100 mg/dL). In a sensitivity analysis, we calculated unadjusted rates and age-sex-adjusted rates, rate differences and hazard ratios in the overall study population censoring CRIC study participants if they down-titrated to a low-intensity statin or discontinued statin therapy during the follow-up period.

RESULTS

Among the participants included in the current analysis, 1,106 (63.1%) did not have a history of major ASCVD events, 488 (27.8%) had a history of 1 major ASCVD event and multiple high-risk conditions, and 159 (9.1%) had a history of ≥2 major ASCVD events. The participants who had a history of 1 major ASCVD event with multiple high-risk conditions or ≥ 2 major ASCVD events were older and more likely to be Black versus their counterparts without a history of major ASCVD events (Table 1). A higher percentage of participants with a history of 1 major ASCVD event and multiple high-risk conditions and with a history of ≥2 major ASCVD events had a prior coronary artery bypass grafting or percutaneous coronary intervention, diabetes, hypertension, or history of heart failure compared with their counterparts without a history of major ASCVD events.

Over a median of 8 years of follow-up observation, there were 394 ASCVD events, including 255 MI events, 89 ischemic strokes, and 120 PAD events. The cumulative incidence and rate of ASCVD events were higher among participants with a history of 1 major ASCVD event and multiple high-risk conditions and among participants with a history of ≥2 major ASCVD events compared with their counterparts without a history of major ASCVD events (Fig 1, Fig S2, and Table 2).

The age-sex-adjusted hazard ratios for ASCVD events among the participants with a history of 1 major ASCVD event and multiple high-risk conditions and a history of ≥2 major ASCVD events compared with those without a history of major ASCVD events were 1.89 (95% CI, 1.52-2.36) and 2.50 (95% CI, 1.85-3.39), respectively. The ASCVD event rates were higher among participants with a history of 1 major ASCVD event and multiple high-risk conditions and with ≥ 2 major ASCVD events versus those without a history of major ASCVD events within each eGFR subgroup (Table 3) and LDL cholesterol subgroup (Table S4) and in a sensitivity analysis that censored participants upon their titrating to a low-intensity statin or discontinuing statin therapy (Table S5).

The total CVD, heart failure, and all-cause mortality event rates and hazard ratios were each higher overall among participants with 1 major ASCVD event and

Table 1. Characteristics of Chronic Renal Insufficiency Cohort Study Participants Included in the Current Analysis

Participant Characteristics[a]	2018 AHA/ACC Blood Cholesterol Guideline ASCVD Risk Category		
	No History of Major ASCVD Events	History of 1 Major ASCVD Event With Multiple High-Risk Conditions[b]	History of ≥2 Major ASCVD Events[b]
No. of participants	1,106	488	159
Age, y	59.4 ± 10.4	62.8 ± 8.0	63.5 ± 6.9
Sex, male	616 (55.7%)	310 (63.5%)	94 (59.1%)
Race/ethnicity			
White	489 (44.2%)	205 (42.0%)	68 (42.8%)
Black	416 (37.6%)	211 (43.2%)	77 (48.4%)
Hispanic	147 (13.3%)	54 (11.1%)	11 (6.9%)
Other	54 (4.9%)	18 (3.7%)	3 (1.9%)
Less than high school education	230 (20.8%)	109 (22.3%)	39 (24.5%)
Body mass index, kg/m^2	32.8 ± 7.8	32.5 ± 7.2	33.4 ± 6.8
Physical activity, total MET score[c,d]	163.5 (110.1, 244.5)	146.5 (97.8, 214.8)	133.4 (94.5, 215.8)
Major ASCVD Events			
History of coronary heart disease[c]	0 (0)	301 (61.7%)	139 (87.4%)
History of stroke[c]	0 (0)	114 (23.4%)	85 (53.5%)
History of PAD[c]	0 (0)	60 (12.3%)	89 (56.0%)
Between year 0 and year 1 study visits			
Recent acute coronary syndrome[e]	0 (0)	7 (1.4%)	10 (6.3%)
Ischemic stroke	0 (0)	5 (1.0%)	9 (5.7%)
Peripheral artery disease	0 (0)	1 (0.2%)	14 (8.8%)
High-Risk Conditions			
Age ≥ 65 y	386 (34.9%)	230 (47.1%)	70 (44.0%)
History of CABG/PCI	78 (7.1%)	216 (44.3%)	107 (67.3%)
Diabetes	646 (58.4%)	332 (68.0%)	111 (69.8%)
Hypertension	1,042 (94.3%)	466 (95.5%)	155 (97.5%)
Current smoking	126 (11.4%)	70 (14.3%)	20 (12.6%)
LDL cholesterol ≥ 100 mg/dL while taking a statin[f]	367 (35.6%)	109 (23.5%)	39 (25.3%)
History of heart failure	81 (7.3%)	102 (20.9%)	64 (40.3%)
Laboratory Measurements			
eGFR, mL/min/1.73 m^2			
<30	279 (26.1%)	135 (28.7%)	61 (38.6%)
30-44	380 (35.6%)	169 (36.0%)	57 (36.1%)
45-59	273 (25.6%)	126 (26.8%)	32 (20.2%)
≥60	136 (12.7%)	40 (8.5%)	8 (5.1%)
High sensitivity C-reactive protein > 3 mg/L[c]	465 (42.2%)	204 (42.0%)	95 (59.8%)
Albuminuria, mg/g[c]			
<30	458 (43.0%)	186 (39.6%)	59 (38.1%)
30-300	261 (24.5%)	128 (27.2%)	42 (27.1%)
>300	347 (32.5%)	156 (33.2%)	54 (34.8%)
FGF-23, RU/mL[c]	144.9 (96.3, 230.2)	161.6 (109.6, 257.1)	184.0 (109.6, 279.0)
Uric acid, mg/dL[c]	7.4 ± 1.9	7.6 ± 1.9	7.7 ± 2.0
LDL cholesterol, mg/dL	88.0 (72.0, 107.0)	82.0 (65.0, 98.0)	83.5 (66.0, 102.0)

(Continued)

Table 1 (Cont'd). Characteristics of Chronic Renal Insufficiency Cohort Study Participants Included in the Current Analysis

Participant Characteristics[a]	2018 AHA/ACC Blood Cholesterol Guideline ASCVD Risk Category		
	No History of Major ASCVD Events	History of 1 Major ASCVD Event With Multiple High-Risk Conditions[b]	History of ≥2 Major ASCVD Events[b]
LDL cholesterol, mg/dL			
<70	220 (21.4%)	148 (31.9%)	45 (29.2%)
70-<100	443 (43.0%)	207 (44.6%)	70 (45.5%)
≥100	367 (35.6%)	109 (23.5%)	39 (25.3%)

The values in the table are number (percentage) or mean ± SD except for physical activity, FGF-23, and LDL cholesterol, which are expressed as median (25th, 75th percentile).
Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CABG, coronary artery bypass grafting; CRIC, Chronic Renal Insufficiency Cohort; eGFR, estimated glomerular filtration rate; FGF, fibroblast growth factor; LDL, low-density lipoprotein; MET, metabolic equivalent of task; PAD, peripheral artery disease; PCI, percutaneous coronary interventions.
[a]Participant characteristics were calculated at the CRIC year 1 study visit (ie, baseline for the current analysis), unless otherwise indicated.
[b]Adults with a history of 1 major ASCVD event with multiple high-risk conditions or with a history of ≥2 major ASCVD events are considered to be at a very high risk for ASCVD events in the 2018 AHA/ACC cholesterol guideline. Major ASCVD events include history of coronary heart disease, stroke or PAD, recent acute coronary syndrome, or an acute ischemic stroke or PAD event. Multiple high-risk conditions include chronic kidney disease and one or more of the following: age ≥ 65 years, history of prior CABG or PCI, diabetes, hypertension, current smoking, low-density lipoprotein cholesterol ≥ 100 mg/dL or history of heart failure.
[c]Calculated at the CRIC year 0 study visit.
[d]Physical activity was assessed using total MET from Typical Week Physical Activity Survey (TWPAS).
[e]Recent acute coronary syndrome is defined by a myocardial infarction hospitalization between year 0 and year 1 study visits (ie, before baseline for the current study).
[f]All the participants included in this analysis were taking a moderate- or high-intensity statin.

multiple high-risk conditions and with a history of ≥2 major ASCVD events versus those without a history of major ASCVD events (Fig S3 and Table S6) and within each subgroup defined by eGFR (Table S7) and LDL cholesterol (Tables S8) levels, and when censoring participants if they titrated to a low-intensity statin or discontinued statin therapy (Table S9).

DISCUSSION

In the current study of adults with CKD taking a moderate- or high-intensity statin, all participants with a history of ASCVD had multiple high-risk conditions or a history of ≥2 major ASCVD events and, therefore, met the 2018 AHA/ACC cholesterol guideline definition of very high ASCVD risk. Despite taking a moderate- or high-intensity statin, the ASCVD event rates were high among participants meeting the definition of very high risk. The ASCVD risk reported in the current study could be used to determine the potential benefit of additional interventions to prevent cardiovascular events among adults with CKD at very high ASCVD risk who are taking a statin.

The 2018 AHA/ACC cholesterol guideline recommends a moderate- or high-intensity statin for adults with a history of ASCVD.[4] The guideline also recommends initiation of ezetimibe or a PCSK9I among adults with a history of ASCVD who meet the definition of very high ASCVD risk and have an LDL cholesterol level of ≥70 mg/dL despite taking a maximally tolerated statin dosage.[4] As ezetimibe is available as generic drug, the guidelines suggest taking into account cost-effectiveness when considering the initiation of a nonstatin lipid-lowering therapy.[4,14]

Prior studies of patients with a history of ASCVD, most of whom did not have CKD, suggest that a high proportion of this population meets the definition of very high ASCVD risk in the 2018 AHA/ACC cholesterol guideline.[15,16] In a study of adults with commercial health insurance and established ASCVD, 55.3% of patients met the definition of very high ASCVD risk.[15] In another study of adults with ACS and dyslipidemia, 63.1% of participants met the definition of very high risk.[16] Results from the current study suggest that the vast majority of adults with CKD who have a history of ASCVD can be expected to meet the definition of very high risk in the 2018 AHA/ACC cholesterol guideline and may be considered for ezetimibe and/or PCSK9I initiation.

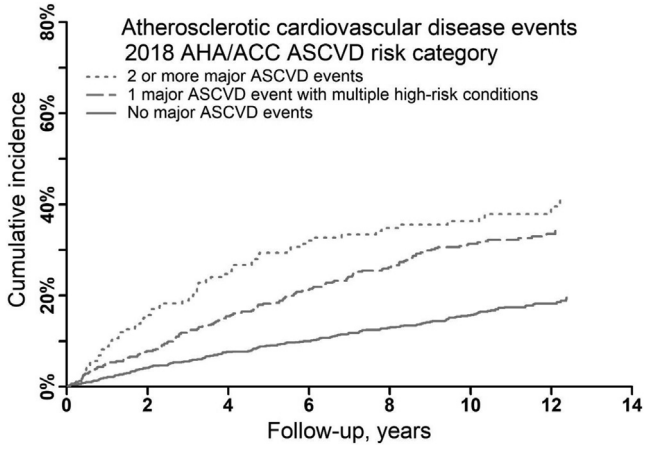

Figure 1. Cumulative incidence of atherosclerotic cardiovascular disease events by the 2018 AHA/ACC atherosclerotic cardiovascular disease risk categories. ASCVD events include myocardial infarction, ischemic stroke, or peripheral artery disease. Cumulative incidence was calculated accounting for the competing risk of death. Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease.

Table 2. Atherosclerotic Cardiovascular Disease Event Rates and Hazard Ratios by the 2018 AHA/ACC Atherosclerotic Cardiovascular Disease Risk Categories

Outcomes	ASCVD Risk Category		
	No History of Major ASCVD Events	History of 1 major ASCVD Event With Multiple High-Risk Conditions	History of ≥2 major ASCVD Events
No. of participants	1,106	488	159
ASCVD events			
Events/person-years	182/9,292	152/3,426	60/900
Unadjusted rate	19.6 (16.7-22.4)	44.4 (37.3-51.4)	66.7 (49.8-83.5)
Adjusted rate	21.7 (18.4-25.1)	45.0 (37.8-52.3)	73.3 (53.3-93.4)
Adjusted rate difference	0.0 (reference)	23.3 (15.4-31.3)	51.6 (31.3-71.9)
Hazard ratio	1.0 (reference)	1.89 (1.52-2.36)	2.50 (1.85-3.39)
Myocardial infarction			
Events/person-years	121/9,519	103/3,631	31/1,029
Unadjusted rate	12.7 (10.4-15.0)	28.4 (22.9-33.8)	30.1 (19.5-40.7)
Adjusted rate	14.5 (11.8-17.3)	28.8 (23.2-34.4)	32.4 (20.3-44.4)
Adjusted rate difference	0.0 (reference)	14.3 (8.0-20.5)	17.9 (5.5-30.2)
Hazard ratio	1.0 (reference)	1.84 (1.40-2.40)	1.72 (1.15-2.58)
Ischemic stroke			
Events/person-years	42/9,875	30/3,863	17/1,071
Unadjusted rate	4.3 (3.0-5.5)	7.8 (5.0-10.5)	15.9 (8.3-23.4)
Adjusted rate	4.4 (3.0-5.8)	7.8 (5.0-10.6)	16.4 (8.1-24.7)
Adjusted rate difference	0.0 (reference)	3.4 (0.2-6.5)	12.0 (3.7-20.4)
Hazard ratio	1.0 (reference)	1.54 (0.96-2.46)	2.71 (1.55-4.74)
Peripheral artery disease			
Events/person-years	49/9,772	48/3,811	23/1,039
Unadjusted rate	5.0 (3.6-6.4)	12.6 (9.0-16.2)	22.1 (13.1-31.2)
Adjusted rate	5.3 (3.7-6.9)	12.8 (9.2-16.4)	25.3 (14.2-36.5)
Adjusted rate difference	0.0 (reference)	7.5 (3.5-11.4)	20.0 (8.7-31.3)
Hazard ratio	1.0 (reference)	2.21 (1.47-3.33)	3.53 (2.10-5.92)

Values between parenthesis indicate 95% CI. Hazard ratios were adjusted for age and sex, and account for the competing risk of death. ASCVD events include myocardial infarction, ischemic stroke, or peripheral artery disease. Rates and rate differences are expressed per 1,000 person-years. Adjusted rates were calculated using direct standardization, with the standard population being all participants with very high ASCVD risk: men <55 years (8.7%), 55-65 years (24.4%), 65-70 years (15.1%), and ≥70 years (14.2%); and women <55 years (5.9%), 55-65 years (14.7%), 65-70 years (8.7%), and ≥70 years (8.3%).
Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval.

The Study of Heart and Renal Protection (SHARP) trial demonstrated a 17% reduction in major vascular events among participants with CKD and not on dialysis randomized to simvastatin plus ezetimibe compared with placebo (risk ratio, 0.83; 95% CI, 0.74-0.94).[17] In a post hoc analysis of the randomized trial IMPROVE-IT, which compared participants randomized to simvastatin and ezetimibe versus simvastatin alone, the hazard ratios for the primary end point of cardiovascular death, major coronary event, or nonfatal stroke were 0.88 (95% CI, 0.82-0.95) and 0.87 (95% CI, 0.78-0.98) at eGFR levels of 60 and 45 mL/min/1.73 m^2, respectively.[18] In the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial, participants taking a statin who were randomized to PCSK9I had a lower risk for the primary end point of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization compared with their counterparts randomized to placebo (hazard ratio, 0.85; 95% CI: 0.79, 0.92).[19] There was no evidence supporting a difference in the hazard ratios between participants with eGFR ≥ 90, 60 to 89, and < 60 mL/min/1.73 m^2: 0.82 (95% CI, 0.71-0.94), 0.85 (95% CI, 0.77-0.94), and 0.89 (95% CI, 0.76-1.05), respectively (P interaction = 0.75).[20] Participants meeting the definition of very high-risk in the current study had a high ASCVD event rate, so the absolute risk reduction conferred by ezetimibe or a PCSK9I in addition to statin therapy in these individuals may be substantial.

Other interventions, in addition to a maximally tolerated statin therapy and nonstatin lipid-lowering medication, may further reduce the risk for ASCVD events in adults with CKD at very high ASCVD risk. According to the 2018 AHA/ACC cholesterol guideline, all adults with a history of ASCVD should engage in healthy lifestyles, including eating a healthy diet, participating in physical activity, and not smoking.[4] Blood pressure control can also reduce the risk for ASCVD events in this population. In a prespecified subgroup analysis of the Systolic Blood Pressure Intervention Trial (SPRINT) among adults with CKD, the hazard ratio for the composite cardiovascular outcome and all-cause mortality with more intensive versus less intensive blood pressure control (ie, systolic blood pressure < 120 versus < 140 mm Hg) was 0.81 (95% CI, 0.63-

Table 3. Atherosclerotic Cardiovascular Disease Event Rates and Hazard Ratios by the 2018 AHA/ACC Atherosclerotic Cardiovascular Disease Risk Categories and Estimated Glomerular Filtration Rate Levels

	ASCVD Risk Category		
Outcomes	**No History of Major ASCVD Events**	**History of 1 Major ASCVD Event With Multiple High-Risk Conditions**	**History of ≥2 Major ASCVD Events**
eGFR<30mL/min/1.73 m²	**n = 279**	**n = 135**	**n = 61**
ASCVD events			
Events/person-years	59/2,017	53/718	22/284
Unadjusted rate	29.3 (21.8-36.7)	73.8 (53.9-93.7)	77.5 (53.9-93.7)
Adjusted rate	38.8 (27.9-49.8)	83.0 (59.5-106.5)	81.8 (41.3-122.3)
Adjusted rate difference	0.0 (reference)	44.2 (18.2-70.1)	43.0 (1.03-84.9)
Hazard ratio	1.0 (reference)	1.85 (1.26-2.72)	1.76 (1.07-2.92)
Myocardial infarction			
Events/person-years	43/2,097	35/783	14/318
Unadjusted rate	20.5 (14.4-26.6)	44.7 (29.9-59.5)	44.0 (20.9-67.0)
Adjusted rate	26.1 (17.5-34.8)	50.9 (33.4-68.4)	49.1 (17.6-80.6)
Adjusted rate difference	0.0 (reference)	24.8 (5.2-44.3)	23.0 (−9.7-55.6)
Hazard ratio	1.0 (reference)	1.56 (0.98-2.49)	1.41 (0.77-2.58)
Ischemic stroke			
Events/person-years	8/2,196	11/867	3/336
Unadjusted rate	3.6 (1.1-6.2)	12.7 (5.2-20.2)	8.9 (0.0-19.0)[a]
Adjusted rate	5.0 (1.2-8.4)	13.2 (5.0-21.5)	16.7 (0.0-42.7)[a]
Adjusted rate difference	0.0 (reference)	8.2 (−0.9-17.3)	11.7 (−14.6-37.9)
Hazard ratio	1.0 (reference)	2.69 (1.03-7.03)	1.64 (0.44-6.16)
Peripheral artery disease			
Events/person-years	20/2,132	19/848	8/317
Unadjusted rate	9.4 (5.3-13.5)	22.4 (12.3-32.5)	25.2 (7.8-42.8)
Adjusted rate	12.0 (6.3-17.8)	24.6 (13.1-36.2)	25.7 (6.7-44.8)
Adjusted rate difference	0.0 (reference)	12.6 (−0.3-25.5)	13.7 (−6.2-33.6)
Hazard ratio	1.0 (reference)	2.07 (1.06-4.03)	2.07 (0.87-4.95)
eGFR 30 to<45mL/min/1.73 m²	**n = 380**	**n = 169**	**n = 57**
ASCVD events			
Events/person-years	61/3,221	57/1,205	20/326
Unadjusted rate	18.9 (14.2-23.7)	47.3 (35.0-59.6)	61.3 (34.5-88.3)
Adjusted rate	20.2 (14.9-25.4)	50.4 (37.0-63.7)	70.7 (37.6-103.8)
Adjusted rate difference	0.0 (reference)	30.2 (15.8-44.6)	50.5 (17.0-84.0)
Hazard ratio	1.0 (reference)	2.18 (1.52-3.14)	2.37 (1.40-4.02)
Myocardial infarction			
Events/person-years	38/3,276	41/1,273	10/374
Unadjusted rate	11.6 (7.9-15.3)	32.2 (22.3-42.1)	26.7 (10.2-43.3)
Adjusted rate	12.9 (8.7-17.1)	34.1 (23.5-44.7)	28.0 (9.9-46.1)
Adjusted rate difference	0.0 (reference)	21.2 (9.8-32.6)	15.1 (−3.5-33.7)
Hazard ratio	1.0 (reference)	2.37 (1.51-3.73)	1.70 (0.82-3.52)
Ischemic stroke			
Events/person-years	21/3,369	13/1,349	5/401
Unadjusted rate	6.2 (3.6-8.9)	9.6 (4.4-14.9)	12.5 (1.5-23.4)
Adjusted rate	6.0 (3.3-8.7)	10.7 (4.7-16.6)	12.2 (1.1-23.3)
Adjusted rate difference	0.0 (reference)	4.7 (−1.8-11.2)	6.2 (−5.2-17.6)
Hazard ratio	1.0 (reference)	1.35 (0.67-2.70)	1.49 (0.57-3.88)
Peripheral artery disease			
Events/person-years	11/3,379	19/1,342	7/384
Unadjusted rate	3.3 (1.3-5.2)	14.2 (7.8-20.5)	18.2 (4.7-31.8)
Adjusted rate	3.9 (1.6-6.3)	15.1 (8.1-22.0)	18.4 (4.0-32.8)
Adjusted rate difference	0.0 (reference)	11.2 (3.8-18.5)	14.5 (−0.1-29.1)
Hazard ratio	1.0 (reference)	3.87 (1.84-8.15)	4.24 (1.60-11.20)

(Continued)

Table 3 (Cont'd). Atherosclerotic Cardiovascular Disease Event Rates and Hazard Ratios by the 2018 AHA/ACC Atherosclerotic Cardiovascular Disease Risk Categories and Estimated Glomerular Filtration Rate Levels

	ASCVD Risk Category		
Outcomes	No History of Major ASCVD Events	History of 1 Major ASCVD Event With Multiple High-Risk Conditions	History of ≥2 Major ASCVD Events
eGFR≥45mL/min/1.73 m²	**n = 409**	**n = 166**	**n = 40**
ASCVD events			
Events/person-years	56/3,782	38/1,387	17/289
Unadjusted rate	14.8 (10.9-18.7)	27.4 (18.7-36.1)	58.8 (30.8-86.6)
Adjusted rate	15.0 (10.6-19.4)	26.6 (17.8-35.5)	67.5 (30.8-104.1)
Adjusted rate difference	0.0 (reference)	11.6 (1.8-21.5)	52.5 (15.6-89.4)
Hazard ratio	1.0 (reference)	1.66 (1.10-2.51)	3.69 (2.10-6.48)
Myocardial infarction			
Events/person-years	36/3,867	25/1,448	7/335
Unadjusted rate	9.3 (6.3-12.4)	17.3 (10.5-24.0)	20.9 (5.4-36.4)
Adjusted rate	10.2 (6.5-13.9)	18.1 (10.7-25.5)	20.7 (4.5-37.0)
Adjusted rate difference	0.0 (reference)	7.9 (−0.3-16.2)	10.5 (−6.1-27.2)
Hazard ratio	1.0 (reference)	1.66 (0.98-2.79)	1.98 (0.85-4.60)
Ischemic stroke			
Events/person-years	12/4,013	6/1,516	9/332
Unadjusted rate	3.0 (1.3-4.7)	4.0 (0.8-7.1)	27.1 (9.4-44.8)
Adjusted rate	2.7 (1.0-4.3)	3.6 (0.6-6.6)	31.1 (8.0-54.2)
Adjusted rate difference	0.0 (reference)	0.9 (−2.5-4.3)	28.4 (5.3-51.6)
Hazard ratio	1.0 (reference)	1.19 (0.46-3.13)	8.30 (3.59-19.22)
Peripheral artery disease			
Events/person-years	14/3,971	8/1,501	7/338
Unadjusted rate	3.5 (1.7-9.0)	5.3 (1.6-9.0)	20.7 (5.4-36.0)
Adjusted rate	3.5 (1.4-5.5)	4.4 (1.3-7.4)	25.4 (4.9-45.8)
Adjusted rate difference	0.0 (reference)	0.9 (−2.8-4.6)	21.9 (1.3-42.5)
Hazard ratio	1.0 (reference)	1.27 (0.54-2.99)	5.34 (2.15-13.28)

Values between parenthesis indicate 95% CI. Rates and rate differences are expressed per 1,000 person-years. Adjusted rates were calculated using direct standardization, with the standard population being all participants with very high ASCVD risk: men <55 years (8.7%), 55 to 65 years (24.4%), 65 to 70 years (15.1%), and ≥70 years (14.2%); women <55 years (5.9%), 55 to 65 years (14.7%), 65 to 70 years (8.7%), ≥70 years (8.3%). Hazard ratios were adjusted for age and sex, and account for the competing risk of death. There were 57 participants with missing eGFR who were not included in this table. ASCVD events include myocardial infarction, ischemic stroke, or peripheral artery disease.

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; eGFR, estimated glomerular filtration rate.

[a]A lower 95% CI <0 was calculated. However, we reported a lower 95% CI of zero instead as rates cannot be negative.

1.05) and 0.72 (95% CI, 0.53-0.99), respectively.[21] The nonsteroidal selective mineralocorticoid receptor antagonist finerenone has also shown to reduce the risk for cardiovascular events in adults with CKD who have diabetes.[22] Sodium-glucose cotransporter-2 inhibitors have been shown to reduce the risk for ASCVD events in adults with CKD, both with and without diabetes.[23,24]

The current study has several strengths. The CRIC study consists of a diverse population with CKD with a broad range of eGFR and LDL cholesterol levels. A long follow-up period was available to ascertain outcomes. The current study used data collected before the publication of the 2018 AHA/ACC blood cholesterol guideline, so the ASCVD event rates could be interpreted as the expected rate without treatment intensification through the addition of nonstatin lipid-lowering therapy, as recommended in the guideline.

Results from this study should be interpreted in the context of some limitations. The CRIC study did not have information on familial hypercholesterolemia, which is one of the very high-risk conditions in the 2018 AHA/ACC cholesterol guideline. Some of the comorbidities assessed were self-reported, and some participant characteristics were only available at the year 0 study visit (ie, 1 year before baseline for the current analysis). The CRIC study included adults with CKD who were 21 to 74 years of age, so results from the current analysis cannot be extrapolated to adults ≥ 75 years of age with CKD. Data on the duration of statin therapy were not available. We could not determine whether participants were taking a maximally tolerated statin dosage as data on statin intolerance were not available. Results from subgroup analyses need to be considered with caution, as some included a small number of events.

In conclusion, in the current study of adults with established CKD taking moderate- to high-intensity statins, the ASCVD event rates were substantially higher among participants with a history of 1 major ASCVD event and multiple high-risk conditions and with a history of ≥2 major ASCVD events compared with those without a history of major ASCVD events. These data support the ASCVD risk stratification algorithm in the

2018 AHA/ACC cholesterol guideline for adults with CKD. Additional interventions to prevent cardiovascular events among adults with CKD at very high ASCVD risk according to the 2018 AHA/ACC cholesterol guideline who are already taking a statin may be warranted.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1: Cascade of Chronic Renal Insufficiency Cohort study participants included in the current analysis.

Figure S2: Cumulative incidence of myocardial infarction, ischemic stroke, and peripheral artery disease by the 2018 AHA/ACC atherosclerotic cardiovascular disease risk categories.

Figure S3: Cumulative incidence of total cardiovascular disease, heart failure, and all-cause mortality by the 2018 AHA/ACC atherosclerotic cardiovascular disease risk categories.

Table S1: Major atherosclerotic cardiovascular disease events and high-risk conditions in the 2018 AHA/ACC cholesterol guideline and their definitions as operationalized using the Chronic Renal Insufficiency Cohort study data.

Table S2: Dosages used to define high-, moderate-, and low-intensity statin therapy by statin type.

Table S3: Definitions of outcome events including myocardial infarction, ischemic stroke, peripheral artery disease, and heart failure.

Table S4: Atherosclerotic cardiovascular disease event rates by the 2018 AHA/ACC atherosclerotic cardiovascular disease risk categories and on-treatment LDL cholesterol levels.

Table S5: Atherosclerotic cardiovascular disease event rates and hazard ratios by the 2018 AHA/ACC atherosclerotic cardiovascular disease risk categories censoring participants when they titrated to a low-intensity statin or discontinued statin treatment.

Table S6: Total cardiovascular disease, heart failure, and all-cause mortality event rates and hazard ratios by the 2018 AHA/ACC atherosclerotic cardiovascular disease risk categories.

Table S7: Total cardiovascular disease, heart failure, and all-cause mortality event rates and hazard ratios by the 2018 AHA/ACC atherosclerotic cardiovascular disease risk categories and on levels of estimated glomerular filtration rate levels.

Table S8: Total cardiovascular disease, heart failure, and all-cause mortality event rates and hazard ratios by the 2018 AHA/ACC atherosclerotic cardiovascular disease risk categories and on-treatment LDL cholesterol levels.

Table S9: Total cardiovascular disease, heart failure, and all-cause mortality event rates and hazard ratios by the 2018 AHA/ACC atherosclerotic cardiovascular disease risk categories censoring participants when they titrated to a low-intensity statin or discontinued statin treatment.

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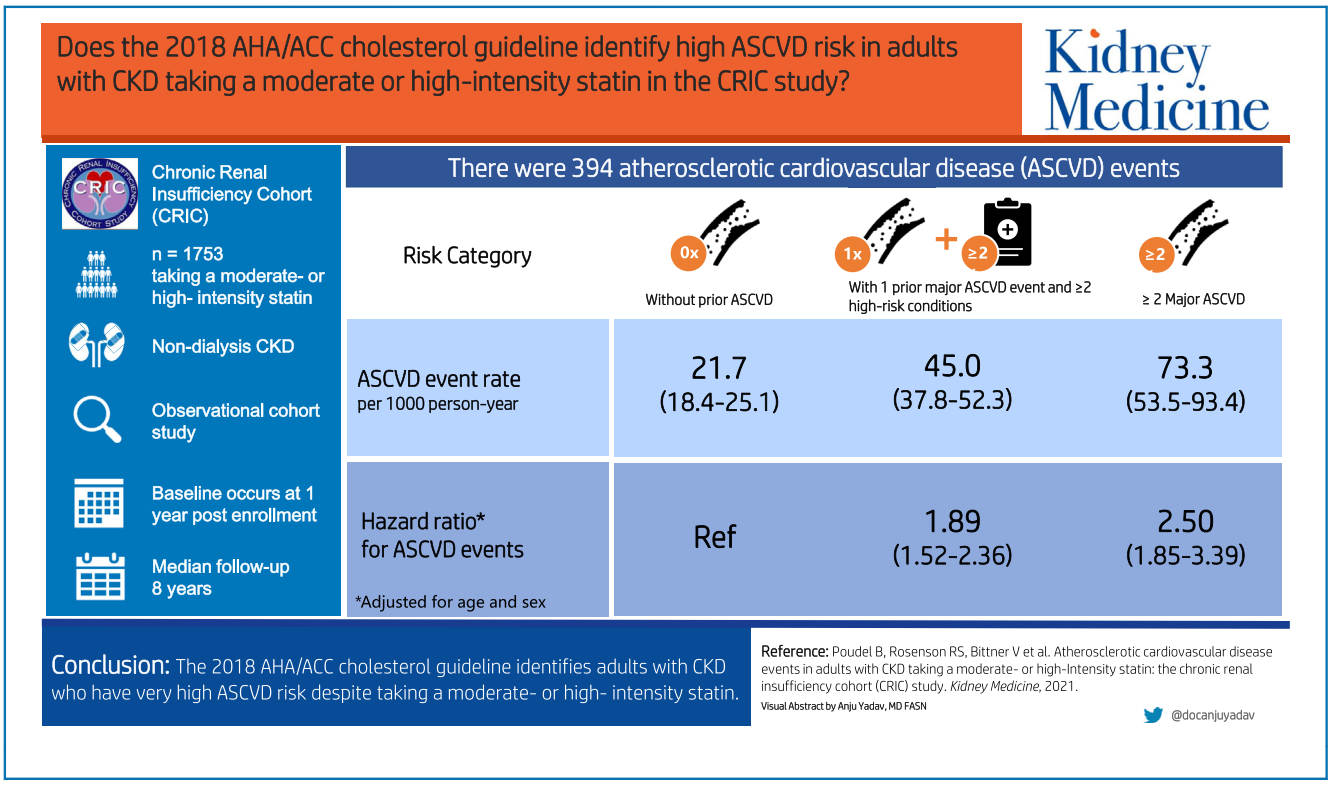
Does the 2018 AHA/ACC cholesterol guideline identify high ASCVD risk in adults with CKD taking a moderate or high-intensity statin in the CRIC study?
Kidney Medicine
Chronic Renal Insufficiency Cohort (CRIC)
n = 1753 taking a moderate- or high- intensity statin
Non-dialysis CKD
Observational cohort study
Baseline occurs at 1 year post enrollment
Median follow-up 8 years
There were 394 atherosclerotic cardiovascular disease (ASCVD) events
Risk Category
0x
Without prior ASCVD
1x
+
≥2
With 1 prior major ASCVD event and ≥2 high-risk conditions
≥2
≥ 2 Major ASCVD
ASCVD event rate per 1000 person-year
21.7 (18.4-25.1)
45.0 (37.8-52.3)
73.3 (53.5-93.4)
Hazard ratio* for ASCVD events
*Adjusted for age and sex
Ref
1.89 (1.52-2.36)
2.50 (1.85-3.39)
Conclusion: The 2018 AHA/ACC cholesterol guideline identifies adults with CKD who have very high ASCVD risk despite taking a moderate- or high- intensity statin.
Reference: Poudel B, Rosenson RS, Bittner V et al. Atherosclerotic cardiovascular disease events in adults with CKD taking a moderate- or high-Intensity statin: the chronic renal insufficiency cohort (CRIC) study. Kidney Medicine, 2021.
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