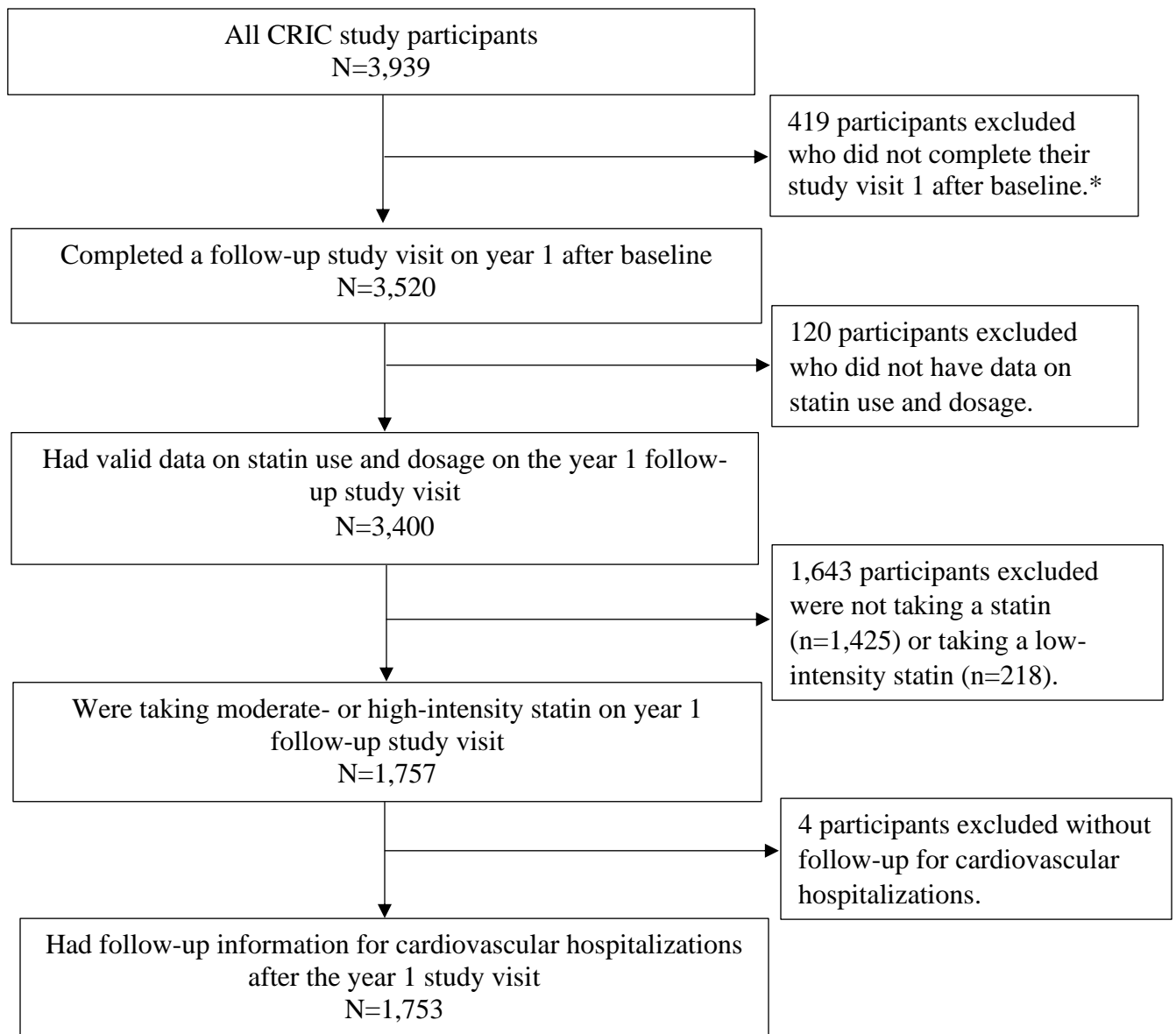


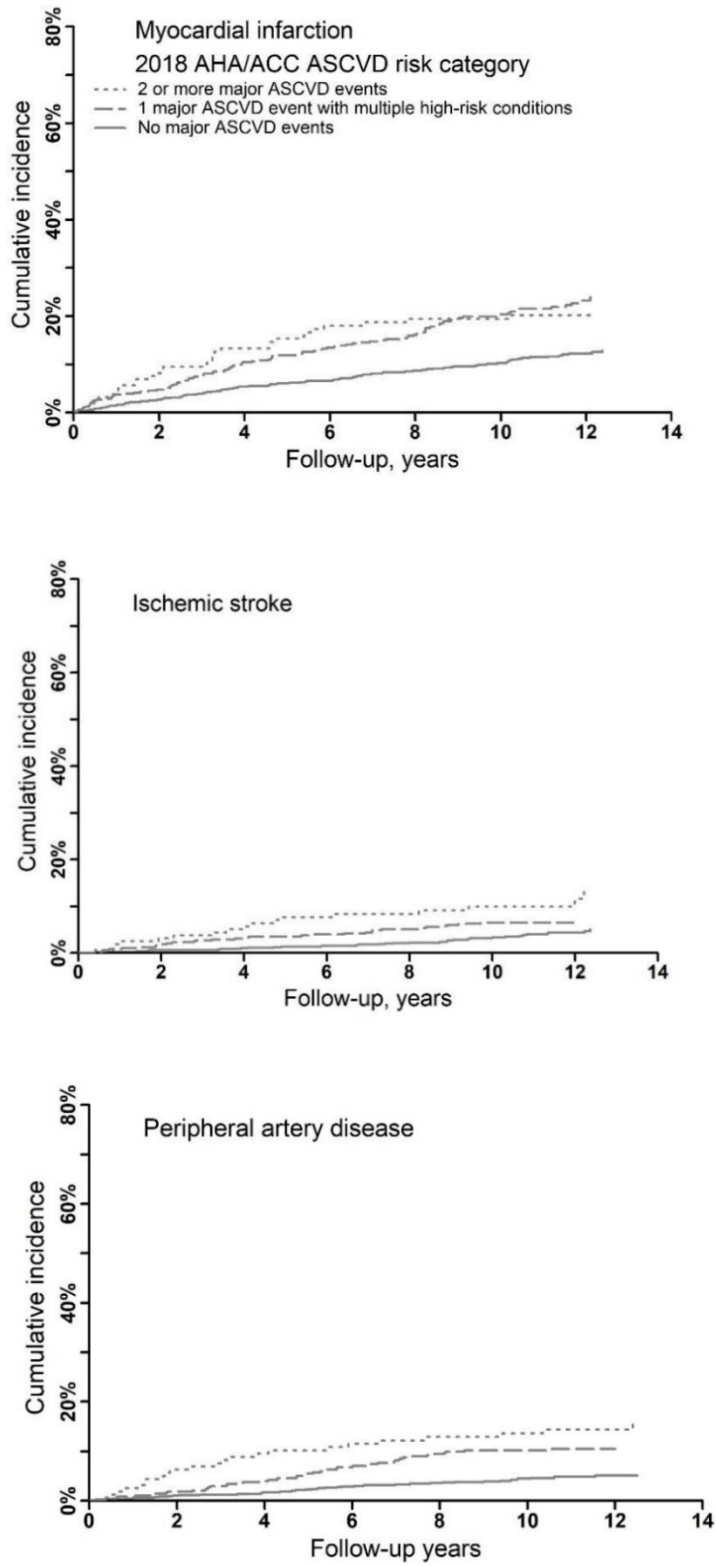
Figure S1. Cascade of Chronic Renal Insufficiency Cohort study participants included in the current analysis.



CRIC: Chronic Renal Insufficiency Cohort.

* Of the 419 participants excluded because they did not attend the year 1 study visit, 70 (16.7%) died before the year 1 study visit, and 214 (51.1%) completed at least 1 follow-up study visit or phone call after the year 1 study visit. The remaining 135 (32.2%) participants did not die before the year 1 study visit and did not complete any of the follow-up study visits or phone calls after the year 1 study visit.

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

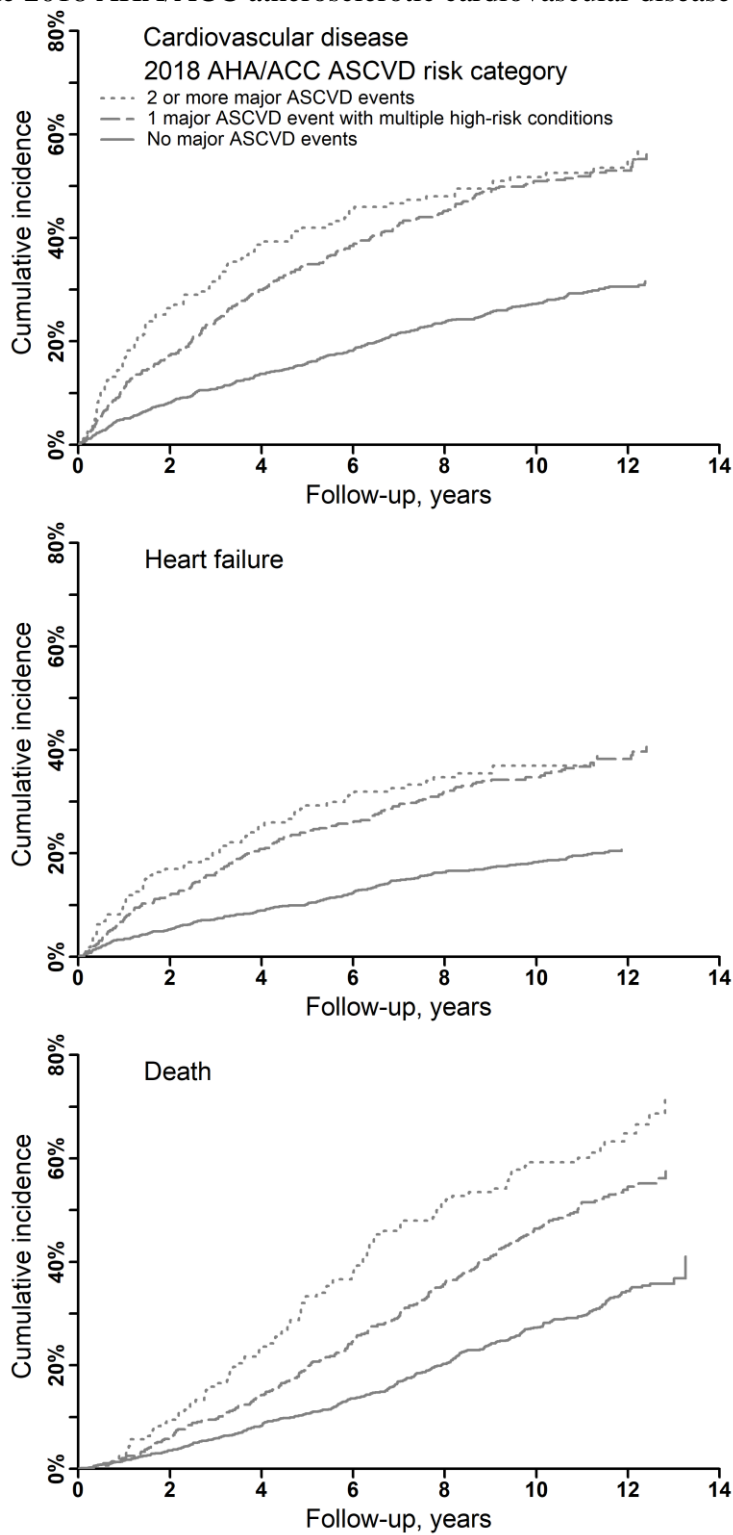


ACC: American College of Cardiology; AHA: American Heart Association; ASCVD: Atherosclerotic cardiovascular disease.

Atherosclerotic cardiovascular disease events include myocardial infarction, ischemic stroke or peripheral artery disease.

Cumulative incidence was calculated accounting for the competing risk of death.

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



ACC: American College of Cardiology; AHA: American Heart Association; ASCVD: Atherosclerotic cardiovascular disease.

Cardiovascular disease events include ASCVD events or heart failure.

Cumulative incidence was calculated accounting for the competing risk of death except for all-cause mortality. No competing risk was considered for the analysis of all-cause mortality.

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.

Major ASCVD events or high-risk conditions	Definition in the CRIC study
<i>Major ASCVD events</i>	
History of coronary heart disease	Defined by self-report of a prior diagnosis of heart attack or angina by a doctor or other health professional using data collected at the year 0 study visit.
History of stroke	Defined by self-report of a prior diagnosis of stroke by a doctor or other health professional using data collected at the year 0 study visit.
History of PAD	Defined by self-report of a prior diagnosis of claudication by a doctor or other health professional, or an amputation or an artery revascularization procedure in arms or legs using data collected at the year 0 study visit.
Recent acute coronary syndrome event	Defined by an MI hospitalization between the year 0 and year 1 study visits which was adjudicated by study clinicians. For participants with multiple confirmed MI hospitalizations, each hospitalization was counted as an event.
Acute ischemic stroke event	Defined by an ischemic stroke hospitalization between the year 0 and year 1 study visits which was subsequently confirmed by study clinicians. For participants with multiple confirmed ischemic stroke hospitalizations, each hospitalization was counted as an event.
Acute PAD event	Defined by a PAD hospitalization between the year 0 and year 1 study visits which was subsequently confirmed by study clinicians. For participants with multiple confirmed PAD hospitalizations, each hospitalization was counted as an event.
<i>High-risk conditions</i>	
Age ≥ 65 years old	Defined at the year 1 follow-up study visit.
Prior coronary artery bypass grafting or percutaneous coronary intervention	Defined by self-report of a prior coronary artery bypass grafting or percutaneous coronary intervention during the year 0 or year 1 study visits.
Diabetes	Defined by a plasma glucose ≥ 126 mg/dL after fasting for a minimum of 8 hours, a plasma glucose ≥ 200 mg/dL after fasting for less than 8 hours, hemoglobin A1c $\geq 6.5\%$, or self-reported use of insulin or glucose-lowering medication using data collected at the year 1 follow-up study visit.

Hypertension	Defined by a systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg or self-reported use of antihypertensive medication using data collected at the year 1 follow-up study visit. For this analysis, systolic and diastolic blood pressure were calculated as the average of the three study blood pressure measurements conducted by trained staff.
Current smoking	Defined by reporting having smoked more than 100 cigarettes in the lifetime and currently smoking, even occasionally using data collected at the year 1 follow-up study visit.
LDL cholesterol ≥ 100 mg/dL while taking a statin	Defined by an LDL cholesterol ≥ 100 mg/dL and taking a statin using data collected at the year 1 follow-up study visit.
History of heart failure	Defined by self-report of prior diagnosis of heart failure by a doctor or other health professional using data collected at the year 0 study visit, or by a heart failure hospitalization between the year 0 and year 1 study visits which was subsequently confirmed by CRIC study clinicians.

ACC: American College of Cardiology; AHA: American Heart Association; ASCVD: atherosclerotic cardiovascular disease; CRIC: Chronic Renal Insufficiency Cohort; LDL: low-density lipoprotein; MI: myocardial infarction; PAD: peripheral artery disease.

According to the 2018 AHA/ACC guideline on the management of blood cholesterol a very high risk for ASCVD is defined as having a history of one major ASCVD event with multiple high-risk conditions or ≥ 2 major ASCVD events.

Reproduced and adapted from: Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC, Jr., Sperling L, Virani SS, Yeboah J. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Journal of the American College of Cardiology*. 2019;73(24): 3168-3209.¹

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

Statin type	High-intensity	Moderate-intensity	Low-intensity
Atorvastatin	40-80 mg	10-20 mg	-
Rosuvastatin	20-40 mg	5-10 mg	-
Simvastatin	80 mg	20-40 mg	10 mg
Fluvastatin	-	80 mg (or 40 mg BID)	20-40 mg
Pitavastatin	-	1-4 mg	-
Pravastatin	-	40-80 mg	10-20 mg
Lovastatin	-	40-60 mg	10-20 mg

BID: Bis In Die (twice a day).

Adapted from: Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC, Jr., Sperling L, Virani SS, Yeboah J. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Journal of the American College of Cardiology*. 2019; 73(24): 3168-3209.¹

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

Outcome events	Definition
Myocardial infarction	A myocardial infarction was defined based on symptoms, cardiac biomarker levels, and electrocardiograms consistent with acute myocardial ischemia. ²
Ischemic stroke	An ischemic stroke was defined by a sudden or rapid onset of one major or two minor neurologic signs or symptoms within a cerebrovascular distribution lasting for more than 24 hours or until the patient died, without evidence of hemorrhage on computed tomography or magnetic resonance imaging performed within 24 hours of the onset of symptoms. ^{3,4}
Peripheral artery disease	A peripheral artery disease hospitalization was defined by a hospitalization resulting in a peripheral revascularization procedure (surgical bypass or angioplasty) or major amputation as adjudicated by a trained research nurse. ^{5,6}
Heart failure	A heart failure hospitalization was defined based on clinical symptoms, physical examination of the heart and lungs, radiographic evidence of pulmonary congestion, and, when available, central venous hemodynamic monitoring data, and echocardiographic imaging. ⁷

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

Outcomes	ASCVD risk category		
	No history of major ASCVD events	History of one major ASCVD event with multiple high-risk conditions	History of ≥ 2 major ASCVD events
LDL cholesterol < 70 mg/dL			
	N=220	N=148	N=45
ASCVD events			
Events/person-years	46/1,805	46/1,045	15/290
Unadjusted rate (95% CI)	25.5 (18.1, 32.9)	44.0 (33.3, 56.7)	51.7 (25.6, 78.0)
Adjusted rate (95% CI)	26.7 (18.6, 34.8)	44.7 (31.5, 58.0)	55.5 (25.8, 85.2)
Adjusted rate difference (95% CI)	0 (ref)	18.0 (2.5, 33.6)	28.8 (-2.0, 59.6)
Hazard ratio (95% CI)	1 (ref)	1.40 (0.93, 2.11)	1.55 (0.86, 2.78)
Myocardial infarction			
Events/person-years	26/1,848	29/1,108	7/328
Unadjusted rate (95% CI)	14.1 (8.7, 19.5)	26.2 (16.6, 35.7)	21.3 (5.5, 37.2)
Adjusted rate (95% CI)	15.0 (8.9, 21.0)	25.4 (15.9, 34.9)	22.8 (4.2, 41.4)
Adjusted rate difference (95% CI)	0 (ref)	10.4 (-0.8, 21.7)	7.8 (-11.8, 27.4)
Hazard ratio (95% CI)	1 (ref)	1.45 (0.86, 2.46)	1.16 (0.50, 2.70)
Ischemic stroke			
Events/person-years	10/1,917	8/1,171	3/334
Unadjusted rate (95% CI)	5.2 (2.0, 8.5)	6.8 (2.1, 11.6)	9.0 (0.0, 19.1)*
Adjusted rate (95% CI)	5.6 (2.0, 9.3)	7.1 (2.1, 12.1)	11.5 (0.0, 25.8)*
Adjusted rate difference (95% CI)	0 (ref)	1.5 (-4.7, 7.7)	5.9 (-8.9, 20.6)
Hazard ratio (95% CI)	1 (ref)	1.22 (0.48, 3.07)	1.28 (0.36, 4.54)
Peripheral artery disease			
Events/person-years	17/1,898	19/1,130	6/312
Unadjusted rate (95% CI)	9.0 (4.7, 13.2)	16.8 (9.3, 24.4)	19.2 (3.8, 34.6)
Adjusted rate (95% CI)	9.0 (4.5, 13.5)	16.4 (8.8, 24.1)	20.8 (4.1, 37.6)
Adjusted rate difference (95% CI)	0 (ref)	7.4 (-1.4, 16.3)	11.8 (-1.4, 16.3)
Hazard ratio (95% CI)	1 (ref)	1.49 (0.77, 2.88)	1.83 (0.71, 4.68)
LDL cholesterol 70 to <100 mg/dL			
	N=443	N=207	N=70
ASCVD events			
Events/person-years	67/3,735	66/1,469	32/349
Unadjusted rate (95% CI)	17.9 (13.6, 22.2)	44.9 (34.1, 55.8)	91.7 (59.9, 123.4)
Adjusted rate (95% CI)	19.9 (14.9, 24.8)	46.5 (35.2, 57.8)	97.2 (61.5, 132.9)
Adjusted rate difference (95% CI)	0 (ref)	26.6 (14.3, 39.0)	77.3 (41.3, 113.4)
Hazard ratio (95% CI)	1 (ref)	2.15 (1.53, 3.03)	3.64 (2.34, 5.67)
Myocardial infarction			
Events/person-years	47/3,823	48/1,559	16/418
Unadjusted rate (95% CI)	12.3 (8.8, 15.8)	30.8 (22.1, 39.5)	38.3 (19.5, 57.0)
Adjusted rate (95% CI)	13.8 (9.8, 17.9)	32.2 (23.0, 41.4)	39.6 (18.8, 60.4)
Adjusted rate difference (95% CI)	0 (ref)	18.4 (8.3, 28.4)	25.8 (4.6, 47.0)
Hazard ratio (95% CI)	1 (ref)	2.18 (1.44, 3.29)	2.28 (1.27, 4.09)

Ischemic stroke			
Events/person-years	17/3,976	10/1,675	8/446
Unadjusted rate (95% CI)	4.3 (2.2, 6.3)	6.0 (2.3, 9.7)	17.9 (5.5, 30.3)
Adjusted rate (95% CI)	4.6 (2.4, 6.9)	6.3 (2.4, 10.3)	20.7 (5.6, 35.7)
Adjusted rate difference (95% CI)	0 (ref)	1.7 (-2.9, 6.3)	16.1 (0.8, 31.3)
Hazard ratio (95% CI)	1 (ref)	1.15 (0.53, 2.48)	2.90 (1.23, 6.84)
Peripheral artery disease			
Events/person-years	17/3,936	19/1,640	15/439
Unadjusted rate (95% CI)	4.3 (2.3, 6.4)	11.6 (6.4, 17.0)	34.2 (16.9, 51.5)
Adjusted rate (95% CI)	4.7 (2.4, 7.1)	11.7 (6.5, 17.0)	40.0 (16.9, 63.2)
Adjusted rate difference (95% CI)	0 (ref)	7.0 (1.2, 12.8)	35.3 (12.1, 58.5)
Hazard ratio (95% CI)	1 (ref)	2.47 (1.26, 4.83)	6.13 (2.91, 12.91)
LDL cholesterol \geq 100 mg/dL			
	N=367	N=109	N=39
ASCVD events			
Events/person-years	51/3,187	32/757	13/226
Unadjusted rate (95% CI)	16.0 (11.6, 20.4)	42.3 (27.6, 56.9)	57.5 (26.2, 88.7)
Adjusted rate (95% CI)	16.9 (11.6, 22.1)	43.7 (27.8, 59.6)	91.3 (23.1, 159.5) [†]
Adjusted rate difference (95% CI)	0 (ref)	26.8 (10.1, 43.6)	74.4 (6.1, 142.8)
Hazard ratio (95% CI)	1 (ref)	2.21 (1.40, 3.48)	2.71 (1.44, 5.10)
Myocardial infarction			
Events/person-years	34/3,276	20/804	8/248
Unadjusted rate (95% CI)	10.4 (6.9, 13.9)	24.9 (14.0, 35.8)	32.3 (9.9, 54.5)
Adjusted rate (95% CI)	11.8 (7.3, 16.3)	24.9 (13.4, 36.5)	28.1 (6.6, 49.6)
Adjusted rate difference (95% CI)	0 (ref)	13.1 (0.8, 25.5)	16.3 (-5.7, 38.2)
Hazard ratio (95% CI)	1 (ref)	1.86 (1.04, 3.32)	2.11 (0.96, 4.64)
Ischemic stroke			
Events/person-years	12/3,382	11/847	6/255
Unadjusted rate (95% CI)	3.5 (1.5, 5.6)	13.0 (5.3, 20.7)	23.5 (4.7, 42.3)
Adjusted rate (95% CI)	3.0 (1.1, 4.9)	13.7 (5.3, 22.1)	27.1 (0.0, 54.9)*
Adjusted rate difference (95% CI)	0 (ref)	10.7 (2.0, 19.3)	24.1 (-3.7, 51.9)
Hazard ratio (95% CI)	1 (ref)	3.33 (1.48, 7.45)	5.53 (2.11, 14.46)
Peripheral artery disease			
Events/person-years	13/3,338	7/871	2/254
Unadjusted rate (95% CI)	3.9 (1.8, 6.0)	8.0 (2.1, 14.0)	7.9 (0.0, 18.8)*
Adjusted rate (95% CI)	3.4 (1.4, 5.4)	8.7 (2.0, 15.4)	10.7 (0.0, 27.8)*
Adjusted rate difference (95% CI)	0 (ref)	5.3 (-1.7, 12.3)	7.3 (-9.9, 24.5)
Hazard ratio (95% CI)	1 (ref)	1.99 (0.77, 5.11)	1.67 (0.37, 7.65)

ACC: American College of Cardiology; AHA: American Heart Association; ASCVD: Atherosclerotic cardiovascular disease; CI: confidence interval; LDL: low-density lipoprotein.

ASCVD events include myocardial infarction and 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%), men 55 to 65 years (24.4%), men 65 to 70 years (15.1%), men \geq 70 years (14.2%), women <55 years (5.9%), women 55 to 65 years (14.7%), women 65 to 70 years (8.7%), and women \geq 70 years (8.3%).

Hazard ratios were adjusted for age and sex, and account for the competing risk of death.

There were 105 participants with missing LDL cholesterol and were not included in this table.

* A lower 95% confidence limit <0 was calculated. However, we reported a 95% confidence limit of zero instead as rates cannot be negative.

†Some age-sex groups used for direct standardization of rates included a very small number of events and participants. Therefore, caution is needed when interpreting adjusted rates.

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.

Outcomes	ASCVD risk category		
	No history of major ASCVD events	History of one major ASCVD event with multiple high-risk conditions	History of ≥ 2 major ASCVD events
	n=1,106	n=488	n=159
ASCVD events			
Events/person-years	136/7,002	115/2,752	47/713
Unadjusted rate (95% CI)	19.4 (16.2, 22.7)	41.8 (34.2, 49.4)	65.9 (47.1, 84.8)
Adjusted rate (95% CI)	21.7 (17.9, 25.6)	42.4 (34.6, 50.3)	70.2 (48.7, 91.8)
Adjusted rate difference (95% CI)	0 (ref)	20.7 (12.0, 29.4)	48.5 (26.6, 70.4)
Hazard ratio (95% CI)	1 (ref)	1.81 (1.41, 2.33)	2.53 (1.79, 3.57)
Myocardial infarction			
Events/person-years	94/7,125	80/2,900	23/801
Unadjusted rate (95% CI)	13.2 (10.5, 15.9)	27.6 (21.5, 33.6)	28.7 (17.0, 40.4)
Adjusted rate (95% CI)	15.3 (12.1, 18.6)	28.1 (21.9, 34.4)	30.5 (17.0, 44.0)
Adjusted rate difference (95% CI)	0 (ref)	12.8 (5.8, 19.8)	15.2 (1.3, 29.0)
Hazard ratio (95% CI)	1 (ref)	1.74 (1.28, 2.37)	1.61 (1.01, 2.58)
Ischemic stroke			
Events/person-years	32/7,408	24/3,070	14/831
Unadjusted rate (95% CI)	4.3 (2.8, 5.8)	7.8 (4.7, 10.9)	16.8 (8.0, 25.7)
Adjusted rate (95% CI)	4.5 (2.9, 6.2)	7.8 (4.7, 11.0)	17.2 (7.7, 26.8)
Adjusted rate difference (95% CI)	0 (ref)	3.3 (-0.2, 6.9)	12.7 (3.0, 22.4)
Hazard ratio (95% CI)	1 (ref)	1.53 (0.90, 2.60)	2.87 (1.54, 5.34)
Peripheral artery disease			
Events/person-years	30/7,358	33/3,049	18/809
Unadjusted rate (95% CI)	4.1 (2.6, 5.5)	10.8 (7.1, 14.5)	22.2 (12.0, 32.5)
Adjusted rate (95% CI)	4.2 (2.6, 5.8)	11.0 (7.2, 14.8)	26.2 (13.1, 39.3)
Adjusted rate difference (95% CI)	0 (ref)	6.8 (2.7, 10.9)	22.0 (8.8, 35.2)
Hazard ratio (95% CI)	1 (ref)	2.42 (1.47, 4.00)	4.62 (2.51, 8.52)

ACC: American College of Cardiology; AHA: American Heart Association; ASCVD: Atherosclerotic cardiovascular disease; CI: confidence interval.

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%), men 55 to 65 years (24.4%), men 65 to 70 years (15.1%), men ≥ 70 years (14.2%), women <55 years (5.9%), women 55 to 65 years (14.7%), women 65 to 70 years (8.7%), and women ≥ 70 years (8.3%).

Hazard ratios were adjusted for age and sex, and account for the competing risk of death.

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.

Outcomes	ASCVD risk category		
	No history of major ASCVD events	History of one major ASCVD event with multiple high-risk conditions	History of ≥ 2 major ASCVD events
	n=1,106	n=488	n=159
Total CVD events			
Events/person-years	307/8,704	247/2987	84/777
Unadjusted rate (95% CI)	35.3 (31.3, 39.2)	82.7 (72.4, 93.0)	108.1 (85.0, 131.2)
Adjusted rate (95% CI)	38.1 (33.5, 42.6)	84.8 (74.1, 95.5)	115.2 (88.4, 141.9)
Adjusted rate difference (95% CI)	0 (ref)	46.7 (35.1, 58.3)	77.1 (49.9, 104.3)
Hazard ratio (95% CI)	1 (ref)	2.08 (1.76, 2.47)	2.30 (1.78, 2.96)
Heart failure			
Events/person-years	204/9,137	176/3,349	59/934
Unadjusted rate (95% CI)	22.3 (19.3, 25.4)	52.6 (44.8, 60.3)	63.2 (47.1, 79.3)
Adjusted rate (95% CI)	24.0 (20.5, 27.5)	54.2 (46.1, 62.3)	63.7 (46.6, 80.8)
Adjusted rate difference (95% CI)	0 (ref)	30.2 (21.4, 39.1)	39.7 (22.3, 57.1)
Hazard ratio (95% CI)	1 (ref)	2.12 (1.73, 2.60)	2.22 (1.65, 3.00)
All-cause mortality			
Events/person-years	343/10,604	246/4,138	98/1,165
Unadjusted rate (95% CI)	32.3 (28.9, 35.8)	59.4 (52.0, 66.9)	84.1 (67.5, 100.8)
Adjusted rate (95% CI)	37.5 (33.3, 41.8)	61.7 (53.9, 69.5)	90.2 (71.2, 109.2)
Adjusted rate difference (95% CI)	0 (ref)	24.2 (15.3, 33.0)	52.7 (33.2, 72.1)
Hazard ratio (95% CI)	1 (ref)	1.68 (1.42, 1.98)	2.38 (1.89, 2.98)

ACC: American College of Cardiology; AHA: American Heart Association; ASCVD: Atherosclerotic cardiovascular disease; CI: confidence interval; CVD: cardiovascular disease.

Total CVD events include ASCVD events or heart failure. 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%), men 55 to 65 years (24.4%), men 65 to 70 years (15.1%), men ≥ 70 years (14.2%), women <55 years (5.9%), women 55 to 65 years (14.7%), women 65 to 70 years (8.7%), and women ≥ 70 years (8.3%).

Hazard ratios were adjusted for age and sex, and account for the competing risk of death except for all-cause mortality. No competing risk was considered for the analysis of all-cause mortality.

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 estimated glomerular filtration rate levels.

Outcomes	ASCVD risk category		
	No history of major ASCVD events	History of one major ASCVD event with multiple high-risk conditions	History of ≥ 2 major ASCVD events
eGFR < 30 mL/min/1.73 m²			
	N=279	N=135	N=61
Total CVD events			
Events/person-years	112/1,765	83/559	36/225
Unadjusted rate (95% CI)	63.5 (51.7, 75.2)	148.5 (116.6, 180.5)	160.0 (107.5, 211.9)
Adjusted rate (95% CI)	75.7 (59.8, 91.6)	162.3 (125.2, 199.4)	193.0 (106.5, 279.6)*
Adjusted rate difference (95% CI)	0 (ref)	86.6 (46.2, 127.0)	117.3 (29.3, 205.3)
Hazard ratio (95% CI)	1 (ref)	1.82 (1.35, 2.44)	1.70 (1.16, 2.50)
Heart failure			
Events/person-years	86/1,883	64/655	30/248
Unadjusted rate (95% CI)	45.7 (36.0, 55.3)	97.7 (73.7, 121.6)	121.0 (77.8, 164.5)
Adjusted rate (95% CI)	51.4 (39.1, 63.8)	104.1 (77.0, 131.2)	149.2 (77.4, 221.1)*
Adjusted rate difference (95% CI)	0 (ref)	52.7 (22.9, 82.5)	97.8 (24.9, 170.7)
Hazard ratio (95% CI)	1 (ref)	1.72 (1.22, 2.40)	1.80 (1.18, 2.75)
All-cause mortality			
Events/person-years	135/2,329	94/934	47/359
Unadjusted rate (95% CI)	58.0 (48.2, 67.7)	100.6 (80.3, 121.0)	130.9 (93.6, 168.6)
Adjusted rate (95% CI)	70.1 (56.8, 83.3)	104.9 (82.7, 127.2)	146.9 (98.2, 195.5)*
Adjusted rate difference (95% CI)	0 (ref)	34.8 (8.9, 60.7)	76.8 (26.4, 127.2)
Hazard ratio (95% CI)	1 (ref)	1.56 (1.19, 2.04)	2.22 (1.58, 3.11)
eGFR 30 to <45 mL/min/1.73 m²			
	N=380	N=169	N=57
Total CVD events			
Events/person-years	106/3,028	89/1,074	26/298
Unadjusted rate (95% CI)	35.0 (28.3, 41.7)	82.9 (65.7, 100.1)	87.2 (53.6, 120.6)
Adjusted rate (95% CI)	36.8 (29.5, 44.1)	88.7 (69.9, 107.4)	95.1 (53.6, 136.6)
Adjusted rate difference (95% CI)	0 (ref)	51.9 (31.8, 72.0)	58.3 (16.2, 100.4)
Hazard ratio (95% CI)	1 (ref)	2.21 (1.67, 2.92)	1.85 (1.16, 2.95)
Heart failure			
Events/person-years	70/3,136	66/1,205	19/359
Unadjusted rate (95% CI)	22.3 (17.1, 27.6)	54.8 (41.5, 68.0)	52.9 (29.1, 76.7)
Adjusted rate (95% CI)	22.8 (17.2, 28.3)	58.0 (43.8, 72.2)	55.7 (28.6, 82.8)
Adjusted rate difference (95% CI)	0 (ref)	35.2 (20.0, 50.5)	32.9 (5.3, 60.6)
Hazard ratio (95% CI)	1 (ref)	2.32 (1.66, 3.24)	1.92 (1.14, 3.24)
All-cause mortality			
Events/person-years	127/3,627	91/1,457	36/421
Unadjusted rate (95% CI)	35.0 (28.9, 41.1)	62.5 (49.6, 75.3)	85.5 (57.5, 113.4)
Adjusted rate (95% CI)	39.7 (32.6, 46.9)	66.1 (52.3, 80.0)	120.8 (34.2, 207.4)*
Adjusted rate difference (95% CI)	0 (ref)	26.4 (10.8, 42.0)	81.1 (-5.8, 167.9)

Hazard ratio (95% CI)	1 (ref)	1.70 (1.29, 2.22)	2.21 (1.52, 3.20)
eGFR \geq45 mL/min/1.73 m²			
	N=409	N=166	N=40
Total CVD events			
Events/person-years	78/3,666	67/1,261	21/253
Unadjusted rate (95% CI)	21.3 (16.6, 26.0)	53.1 (40.4, 65.9)	83.0 (47.6, 118.6)
Adjusted rate (95% CI)	22.4 (16.9, 28.0)	79.0 (23.2, 134.9)	94.7 (49.1, 140.4)*
Adjusted rate difference (95% CI)	0 (ref)	56.6 (0.5, 112.7)	72.3 (26.3, 118.3)
Hazard ratio (95% CI)	1 (ref)	2.35 (1.69, 3.26)	3.60 (2.18, 5.95)
Heart failure			
Events/person-years	39/3,863	41/1,387	10/326
Unadjusted rate (95% CI)	10.1 (6.9, 13.3)	29.6 (20.5, 38.6)	30.7 (11.7, 49.7)
Adjusted rate (95% CI)	11.7 (7.6, 15.9)	56.3 (1.4, 111.2)	36.1 (7.9, 64.2)
Adjusted rate difference (95% CI)	0 (ref)	44.6 (-10.5, 99.6)	24.4 (-4.1, 52.8)
Hazard ratio (95% CI)	1 (ref)	2.69 (1.73, 4.19)	2.71 (1.33, 5.52)
All-cause mortality			
Events/person-years	65/4,322	54/1,603	14/384
Unadjusted rate (95% CI)	15.0 (11.4, 18.7)	33.7 (24.7, 42.7)	36.5 (17.3, 55.5)
Adjusted rate (95% CI)	18.4 (13.4, 23.4)	44.9 (18.7, 71.0)	41.0 (18.2, 63.8)
Adjusted rate difference (95% CI)	0 (ref)	26.5 (-0.2, 53.1)	22.6 (-0.7, 46.0)
Hazard ratio (95% CI)	1 (ref)	2.00 (1.39, 2.88)	2.10 (1.17, 3.77)

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

Total CVD events include ASCVD events or heart failure. 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%), men 55 to 65 years (24.4%), men 65 to 70 years (15.1%), men \geq 70 years (14.2%), women <55 years (5.9%), women 55 to 65 years (14.7%), women 65 to 70 years (8.7%), and women \geq 70 years (8.3%).

Hazard ratios were adjusted for age and sex, and account for the competing risk of death except for all-cause mortality. No competing risk was considered for the analysis of all-cause mortality.

There were 57 participants with missing estimated glomerular filtration rate and were not included in this table.

*Some age-sex groups used for direct standardization of rates included a very small number of events and participants. Therefore, caution is needed when interpreting adjusted rates.

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.

Outcomes	ASCVD risk category		
	No history of major ASCVD events	History of one major ASCVD event with multiple high-risk conditions	History of ≥ 2 major ASCVD events
LDL cholesterol < 70 mg/dL			
N	220	148	45
Total CVD events			
Events/person-years	74/1,672	74/917	25/252
Unadjusted rate (95% CI)	44.3 (34.2, 54.3)	80.7 (62.3, 99.1)	99.2 (60.3, 138.0)
Adjusted rate (95% CI)	48.1 (36.4, 59.8)	87.0 (66.0, 107.9)	107.0 (62.1, 152.0)
Adjusted rate difference (95% CI)	0 (ref)	38.9 (14.8, 62.9)	58.9 (12.5, 105.4)
Hazard ratio (95% CI)	1 (ref)	1.60 (1.16, 2.22)	1.76 (1.12, 2.76)
Heart failure			
Events/person-years	48/1,736	56/1,012	18/287
Unadjusted rate (95% CI)	27.6 (19.8, 35.5)	55.3 (40.9, 69.8)	62.7 (33.8, 91.7)
Adjusted rate (95% CI)	30.9 (21.5, 40.3)	58.5 (42.4, 74.5)	66.1 (33.2, 99.0)
Adjusted rate difference (95% CI)	0 (ref)	27.6 (8.9, 46.2)	35.2 (0.9, 69.4)
Hazard ratio (95% CI)	1 (ref)	1.77 (1.20, 2.62)	1.88 (1.09, 3.24)
All-cause mortality			
Events/person-years	74/2,081	80/1,235	25/356
Unadjusted rate (95% CI)	35.6 (27.5, 43.7)	64.8 (50.6, 79.0)	70.2 (42.7, 97.8)
Adjusted rate (95% CI)	39.7 (30.1, 49.2)	65.1 (50.5, 79.7)	68.1 (39.7, 96.5)
Adjusted rate difference (95% CI)	0 (ref)	25.4 (8.0, 42.9)	28.4 (-1.6, 58.4)
Hazard ratio (95% CI)	1 (ref)	1.65 (1.20, 2.27)	1.72 (1.09, 2.72)
LDL cholesterol 70 to <100 mg/dL			
N	N=443	N=207	N=70
Total CVD events			
Events/person-years	111/3,559	108/1,284	38/310
Unadjusted rate (95% CI)	31.2 (25.4, 37.0)	84.1 (68.2, 100.0)	122.6 (83.6, 161.5)
Adjusted rate (95% CI)	33.8 (27.2, 40.4)	86.1 (69.7, 102.4)	123.8 (81.9, 165.7)
Adjusted rate difference (95% CI)	0 (ref)	52.3 (34.6, 69.9)	90.0 (47.6, 132.4)
Hazard ratio (95% CI)	1 (ref)	2.46 (1.88, 3.20)	2.85 (1.91, 4.26)
Heart failure			
Events/person-years	73/3,767	79/1,435	22/414
Unadjusted rate (95% CI)	19.4 (14.9, 23.8)	55.1 (42.9, 67.2)	53.1 (30.9, 75.3)
Adjusted rate (95% CI)	21.5 (16.3, 26.7)	56.0 (43.5, 68.3)	52.5 (28.0, 77.1)
Adjusted rate difference (95% CI)	0 (ref)	34.5 (20.9, 47.9)	31.0 (5.9, 56.1)
Hazard ratio (95% CI)	1 (ref)	2.60 (1.88, 3.58)	2.15 (1.30, 3.55)
All-cause mortality			
Events/person-years	141/4,242	105/1,779	43/501
Unadjusted rate (95% CI)	33.2 (27.8, 38.7)	59.0 (47.7, 70.3)	85.8 (60.2, 111.5)
Adjusted rate (95% CI)	37.6 (31.2, 44.0)	60.1 (48.5, 71.6)	92.5 (62.5, 122.6)
Adjusted rate difference (95% CI)	0 (ref)	22.5 (9.2, 35.6)	54.9 (24.2, 85.6)

Hazard ratio (95% CI)	1 (ref)	1.66 (1.28, 2.13)	2.44 (1.73, 3.44)
LDL cholesterol \geq 100 mg/dL			
N	N=367	N=109	N=39
Total CVD events			
Events/person-years	94/2,947	53/663	19/188
Unadjusted rate (95% CI)	31.9 (25.4, 38.3)	79.9 (58.4, 101.4)	101.1 (55.7, 146.7)
Adjusted rate (95% CI)	33.2 (25.4, 40.9)	88.2 (62.6, 113.9)	198.5 (44.8, 352.1)*
Adjusted rate difference (95% CI)	0 (ref)	55.0 (28.3, 81.9)	165.2 (11.4, 319.2)
Hazard ratio (95% CI)	1 (ref)	2.25 (1.59, 3.20)	2.43 (1.45, 4.06)
Heart failure			
Events/person-years	67/3,087	34/766	17/205
Unadjusted rate (95% CI)	21.7 (16.5, 26.9)	44.4 (29.5, 59.3)	82.9 (43.4, 122.0)
Adjusted rate (95% CI)	21.7 (15.7, 27.7)	48.4 (30.7, 66.1)	76.5 (34.4, 118.8)
Adjusted rate difference (95% CI)	0 (ref)	26.7 (8.0, 45.3)	54.8 (12.2, 97.4)
Hazard ratio (95% CI)	1 (ref)	1.85 (1.22, 2.81)	2.96 (1.71, 5.12)
All-cause mortality			
Events/person-years	104/3,624	52/925	26/273
Unadjusted rate (95% CI)	28.7 (22.2, 34.2)	56.2 (40.9, 71.5)	95.2 (58.6, 131.7)
Adjusted rate (95% CI)	35.5 (27.5, 43.4)	60.4 (43.1, 77.7)	121.0 (63.6, 178.4)*
Adjusted rate difference (95% CI)	0 (ref)	24.9 (5.9, 44.0)	85.5 (27.6, 143.5)
Hazard ratio (95% CI)	1 (ref)	1.79 (1.28, 2.52)	3.08 (1.97, 4.79)

ACC: American College of Cardiology; AHA: American Heart Association; ASCVD: Atherosclerotic cardiovascular disease; CI: confidence interval; CVD: cardiovascular disease; LDL: low-density lipoprotein.

Total CVD events include ASCVD events or heart failure. 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%), men 55 to 65 years (24.4%), men 65 to 70 years (15.1%), men \geq 70 years (14.2%), women <55 years (5.9%), women 55 to 65 years (14.7%), women 65 to 70 years (8.7%), and women \geq 70 years (8.3%).

Hazard ratios were adjusted for age and sex, and account for the competing risk of death except for all-cause mortality. No competing risk was considered for the analysis of all-cause mortality.

There were 105 participants with missing low-density lipoprotein cholesterol and were not included in this table.

*Some age-sex groups used for direct standardization of rates included a very small number of events and participants. Therefore, caution is needed when interpreting adjusted rates.

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.

Outcomes	ASCVD risk category		
	No history of major ASCVD events	History of one major ASCVD event with multiple high-risk conditions	History of ≥ 2 major ASCVD events
	n=1,106	n=488	n=159
Total CVD events			
Events/person-years	230/6,634	207/2,419	73/628
Unadjusted rate (95% CI)	34.7 (30.2, 39.2)	85.6 (73.9, 97.2)	116.2 (89.5, 142.8)
Adjusted rate (95% CI)	37.6 (32.4, 42.8)	88.3 (76.1, 100.5)	122.8 (92.6, 153.1)
Adjusted rate difference (95% CI)	0 (ref)	50.7 (37.5, 64.0)	85.2 (54.6, 115.9)
Hazard ratio (95% CI)	1 (ref)	2.25 (1.86, 2.72)	2.92 (2.24, 3.81)
Heart failure			
Events/person-years	152/6,926	149/2,710	49/737
Unadjusted rate (95% CI)	21.9 (18.5, 25.4)	55.0 (46.1, 63.8)	66.5 (47.9, 85.1)
Adjusted rate (95% CI)	24.0 (19.9, 28.1)	57.5 (48.1, 66.8)	66.4 (46.9, 85.9)
Adjusted rate difference (95% CI)	0 (ref)	33.5 (23.3, 43.7)	42.4 (22.5, 62.3)
Hazard ratio (95% CI)	1 (ref)	2.31 (1.84, 2.91)	2.67 (1.93, 3.69)
All-cause mortality			
Events/person-years	237/7,934	174/3,298	72/894
Unadjusted rate (95% CI)	29.9 (26.1, 33.7)	52.8 (44.9, 60.6)	80.5 (61.9, 99.1)
Adjusted rate (95% CI)	34.2 (29.6, 38.8)	55.0 (46.8, 63.3)	86.4 (64.9, 107.8)
Adjusted rate difference (95% CI)	0 (ref)	20.8 (11.4, 30.3)	52.2 (30.2, 74.1)
Hazard ratio (95% CI)	1 (ref)	1.58 (1.30, 1.93)	2.45 (1.88, 3.20)

ACC: American College of Cardiology; AHA: American Heart Association; ASCVD: Atherosclerotic cardiovascular disease; CI: confidence interval; CVD: cardiovascular disease.

Total CVD events include ASCVD events or heart failure. 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%), men 55 to 65 years (24.4%), men 65 to 70 years (15.1%), men ≥ 70 years (14.2%), women <55 years (5.9%), women 55 to 65 years (14.7%), women 65 to 70 years (8.7%), and women ≥ 70 years (8.3%).

Hazard ratios were adjusted for age and sex, and account for the competing risk of death except for all-cause mortality. No competing risk was considered for the analysis of all-cause mortality.

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