Supplementary Online Content

Patel J, Pallazola VA, Dudum R, et al. Assessment of coronary artery calcium scoring to guide statin therapy allocation according to risk-enhancing factors: multi-ethnic study of atherosclerosis. *JAMA Cardiol*. Published online July 14, 2021. doi:10.1001/jamacardio.2021.2321

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Coronary Artery Calcium, Risk-Enhancing Factors Assessment, and Ascertainment of Incident ASCVD

Coronary Artery Calcium

At MESA visit 1 (baseline), CAC was quantified using the Agatston scoring method (1). CAC was measured either by electron-beam computed tomography or by multidetector row helical computed tomography, depending on the field center. Interobserver agreement (κ=0.93) and intraobserver agreement (κ=0.90) were high (2).

Risk-Enhancing Factors Assessment

A. Serum and urine laboratory data assessment

Biochemistry assays were performed on serum markers of lipids and lipid metabolism, systemic inflammation, insulin resistance, and on urinary markers of renal function at a central laboratory (University of Vermont, Burlington, VT, USA) (10). High-density lipoprotein cholesterol (HDL-C) level was measured using the cholesterol oxidase method. Low-density lipoprotein-cholesterol (LDL-C) was calculated using the Friedewald equation (3). High-Sensitivity C-reactive protein (hsCRP) was measured using the BNII nephelometer (N hs-CRP and N Antiserum to Human Fibrinogen; Dade Behring). Intra-assay and inter-assay coefficients of variation (CV) ranged from 2.3 to 4.4% and 2.1 to 5.7%, respectively (4).

The calculated LDL-C includes the cholesterol contained in lipoprotein(a) [Lp(a)]. As such, Lp(a) was subtracted [measured using a gradient gel electrophoresis by Health Diagnostics Laboratory (Richmond, VA)] from LDL-C. Lp(a) mass concentration was then measured by a latex-enhanced turbidimetric immunoassay (Denka Seiken, Tokyo, Japan) (5). Apolipoproproetin B (ApoB) was measured at Health Diagnostics Laboratory Inc (Richmond, VA) using Roche reagents and a Roche modular-P analyzer (Roche Diagnostics; Indianapolis, IN). A random urine sample was obtained and analyzed centrally for creatinine [measured using colorimetry with a Johnson & Johnson Vitros 950 analyzer (Johnson & Johnson Clinical Diagnostics Inc.,

Rochester, NY)]; CV were ≤2%. Estimated glomerular filtration rate (eGFR) was calculated using the four-variable Modification of Diet in Renal Disease equation (6).

B. Anthropometric, demographic, medical history, and clinical variables

Age, sex, race/ethnicity, reproductive history, and lifestyle factors were ascertained using validated questionnaires. Body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared. We used the National Cholesterol Education Program/Adult Treatment Panel III definition to classify participants with metabolic syndrome (7). Diabetes mellitus was defined using the 2003 American Diabetes Association criteria: fasting glucose ≥126 mg/dL or use of insulin or oral hypoglycemic medications (8).

Hypertension was defined according to the 2017 Guideline for High Blood Pressure in Adults (≥130-139 or 80-89 mm/Hg), or as a history of physician-diagnosed hypertension, or taking a medication for hypertension (9). Resting seated blood pressure was measured 3 times using a Dinamap automated oscillometric sphygmomanometer (model Pro 100; Critikon, Tampa, FL); an average of the final 2 measurements were used for analysis (10). ABI measurements were obtained with a Doppler probe in the bilateral brachial, dorsalis pedis, and posterior tibial arteries and a value calculated by the ratio of the highest ankle systolic blood pressure divided by the higher systolic blood pressure of the arms (11).

Women were asked if they had or were currently undergoing menopause, with age of onset and date of last menstruation information collected for those who answered 'Yes' (4). MESA pparticipants at visit 2 reported on the presence or absence of FamHx defined as any first-degree relative (mother, father, siblings, or child) with coronary heart disease or heart attack or stroke occurring before the age of 55 years in males and 65 years in females, respectively.[9] Response options were "yes," "no," and "do not know." For the purposes of this analysis, "do not know" responses were counted as "no" responses (4).

Ascertainment of Incident ASCVD

ASCVD included hard coronary heart disease (CHD) events (myocardial infarction, resuscitated cardiac arrest, or CHD death), and fatal or non-fatal hemorrhagic or ischemic stroke, and transient ischemic attack (10).

eTable 1. Prevalence of CAC Among Those With ASCVD Risk-Enhancing Factors

	Definition	**Prevalence (n, %)**			
ASCVD RENF		**CAC=0**	**CAC 1-99**	**CAC ≥100**	**p-value**
FamHx	Premature family history of ASCVD	99 (38)	91 (35)	68 (26)	0.21
CKD, mL/min/1.73 m^2	EGFR 15–59	72 (37)	69 (36)	53 (27)	0.22
MetS*	Require 3 out of 5 factors for diagnosis	247 (42)	190 (32)	157 (26)	0.76
Premature menopause	Menopause before age 40 y	34 (44)	24 (31)	19 (25)	0.96
TG, mg/dL	≥175	133 (40)	109 (33)	87 (26)	0.62
hs-CRP, mg/L	≥2	369 (44)	262 (31)	201 (24)	0.29
Lp(a), mg/dL	>50	180 (49)	105 (29)	79 (22)	0.01†
ApoB100, mg/dL	≥130	307 (39)	257 (32)	228 (29)	0.003†
ABI	<0.9	10 (24)	8 (19)	24 (57)	<0.001†
Combined Renf					
0		70 (40)	60 (34)	45 (26)	0.37
1–2		310 (46)	203 (30)	165 (24)	
≥3		45 (26)	165 (24)	129 (27)	

*Defined when 3 of the following 5 factors are present: 1) waist circumference >40 inches (men) or 35 inches (women); 2) triglycerides >150 mg/dL; 3) blood pressure >140/90 mmHg; 4) fasting blood glucose levels >126 mg/dl); 5) high-density lipoprotein cholesterol <40 mg/dL in men or <50 in women mg/dL.
† – Indicates significant results.

ABI—ankle brachial index ASCVD— atherosclerotic cardiovascular disease; ApoB—apolipoprotein B; CAC—coronary artery calcium; CKD—chronic kidney disease; FamHx—family of history of premature ASCVD; hs-CRP—high sensitivity C-reactive protein; Lp(a)—lipoprotein(a); MetS—metabolic syndrome; RENF—risk-enhancing factor; TG – triglycerides.

eTable 2. Age-Standardized Prevalence of CAC According to Presence of ASCVD Risk-Enhancing Factors

	Definition	Overall (N = 1,688)	Females (N=712)			Males (N=976)		
ASCVD RENF			CAC=0	CAC 1-99	CAC ≥100	CAC=0	CAC 1-99	CAC ≥100
FamHx	Premature family history of ASCVD	19	51	34	15	26	33	41
CKD, mL/min/1.73 m^2	EGFR 15–59	11	49	31	21	30	35	35
MetS*	Require 3 out of 5 factors for diagnosis	35	52	29	19	31	34	35
Premature menopause	Menopause before age 40 y	5	48	28	23	—	—	—
TG, mg/dL	≥175	19	51	31	18	29	35	36
hs-CRP, mg/L	≥2	49	54	29	17	34	33	34
Lp(a), mg/dL	>50	22	54	29	17	45	27	28
ApoB100, mg/dL	≥130	47	51	29	20	30	33	37
ABI	<0.9	2	34	32	34	23	5	72
Combined RENF								
0		13	33	42	25	38	34	28
1–2		51	64	23	13	35	32	34
≥3		36	50	30	20	32	33	35

*Defined when 3 of the following 5 factors are present: 1) waist circumference >40 inches (men) or 35 inches (women); 2) triglycerides >150 mg/dL; 3) blood pressure >140/90 mmHg; 4) fasting blood glucose levels >126 mg/dl); 5) high-density lipoprotein cholesterol <40 mg/dL in men or <50 in women mg/dL.

ABI—ankle brachial index ASCVD— atherosclerotic cardiovascular disease; ApoB—apolipoprotein B; CAC—coronary artery calcium; CKD—chronic kidney disease; FamHx—family of history of premature ASCVD; hs-CRP—high sensitivity C-reactive protein; Lp(a)—lipoprotein(a); MetS—metabolic syndrome; PM – premature menopause; RENF—risk-enhancing factor; TG – triglycerides.

eTable 3. Prevalence of Events and Unadjusted and Multivariable-Adjusted Hazard Ratios (95% CIs) for the Association of Risk-Enhancing Factors With Incident Cardiovascular Disease Stratified by Baseline Coronary Artery Calcium

	CAC = 0 (N=722)		CAC 1-99 (N=532)		CAC ≥100 (N=434)		Overall (N=1,688)	
	Unadjusted	Adjusted*	Unadjusted	Adjusted*	Unadjusted	Adjusted*	Unadjusted	Adjusted*
Individual RENF								
FamHx	1.00 (0.41-2.41)	0.67 (0.26-1.71)	1.45 (0.68-3.10)	1.45 (0.66-3.17)	1.07 (0.51-2.25)	0.91 (0.41-2.03)	1.12 (0.74-1.84)	1.13 (0.71-1.80)
CKD (RENF)	0.75 (0.23-2.42)	0.79 (0.23-2.65)	1.47 (0.68-3.15)	1.39 (0.62-3.15)	0.95 (0.43-2.10)	0.98 (0.44-2.20)	1.10 (0.67-1.80)	1.08 (0.65-1.80)
eGFR (per mL/min)	1.01 (0.99-1.03)	1.01 (0.98-1.03)	0.99 (0.97-1.01)	0.99 (0.97-1.01)	1.01 (0.99-1.03)	1.01 (0.99-1.03)	1.00 (0.99-1.02)	1.00 (0.99-1.02)
MetS	0.94 (0.49-1.83)	0.64 (0.31-1.32)	1.70 (0.94-3.07)	1.42 (0.74-2.73)	1.51 (0.91-2.50)	**1.84 (1.05-3.22)**†	1.37 (0.99-1.91)	1.34 (0.94-1.91)
PM	1.14 (0.28-4.73)	1.11 (0.25-4.87)	1.62 (0.50-5.22)	1.33 (0.37-4.71)	1.35 (0.42-4.31)	1.55 (0.43-5.56)	1.32 (0.65-2.70)	1.33 (0.63-2.81)
TG (RENF)	0.77 (0.32-1.84)	0.46 (0.18-1.20)	0.87 (0.40-1.87)	0.78 (0.35-1.75)	1.15 (0.62-2.12)	1.25 (0.65-2.42)	0.95 (0.63-1.45)	0.86 (0.55-1.34)
TG (per mg/dL)	1.00 (0.99-1.01)	1.00 (0.99-1.00)	1.00 (0.99-1.01)	1.00 (0.99-1.01)	1.00 (0.99-1.01)	1.00 (0.99-1.01)	1.00 (0.99-1.00)	1.00 (0.99-1.00)
hsCRP (RENF)	1.32 (0.71-2.48)	1.36 (0.68-2.72)	1.01 (0.59-1.91)	0.85 (0.45-1.59)	1.12 (0.67-1.85)	0.98 (0.57-1.68)	1.12 (0.81-1.55)	1.06 (0.75-1.49)
hsCRP (per mg/L)	1.12 (0.85-1.47)	1.11 (0.81-1.51)	1.23 (0.94-1.60)	1.12 (0.84-1.49)	1.01 (0.82-1.25)	0.99 (0.79-1.24)	1.10 (0.95-1.27)	1.08 (0.93-1.26)
Lp(a) (RENF)	0.76 (0.35-1.65)	0.86 (0.38-1.92)	1.12 (0.54-2.33)	1.26 (0.57-2.79)	1.59 (0.89-2.85)	1.59 (0.87-2.91)	1.07 (0.72-1.59)	1.19 (0.79-1.80)
Lp(a) (per mg/dL)	0.88 (0.67-1.16)	0.97 (0.72-1.32)	1.02 (0.78-1.33)	1.10 (0.80-1.50)	1.07 (0.85-1.35)	1.06 (0.81-1.38)	0.97 (0.84-1.13)	1.04 (0.88-1.22)
ApoB100 (RENF)	1.32 (0.71-2.45)	1.42 (0.69-2.96)	0.60 (0.32-1.11)	0.55 (0.25-1.22)	1.00 (0.60-1.65)	1.09 (0.58-2.04)	0.99 (0.71-1.37)	1.10 (0.74-1.64)
ApoB100 (per mg/dL)	0.99 (0.98-1.01)	0.98 (0.95-1.01)	1.00 (0.99-1.02)	1.02 (0.99-1.05)	0.99 (0.98-1.01)	1.01 (0.99-1.03)	1.00 (0.99-1.01)	1.00 (0.99-1.02)
ABI (RENF)	2.22 (0.30-16.12)	2.76 (0.35-21.78)	1.99 (0.27-14.46)	2.24 (0.28-18.01)	0.55 (0.13-2.27)	0.32 (0.07-1.36)	1.25 (0.46-3.39)	1.13 (0.41-3.10)
ABI (per 1 unit)	0.39 (0.01-10.34)	0.23 (0.01-9.98)	0.038 (0.002-0.709)	0.015 (0.001-0.392)	1.47 (0.21-10.36)	2.95 (0.40-21.66)	0.42 (0.09-1.93)	0.29 (0.06-1.44)
Composite RENF								
0	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
1–2	2.43 (0.57-10.36)	1.82 (0.40-8.21)	**0.29 (0.11-0.72)**†	**0.25 (0.09-0.64)**†	0.88 (0.35-2.19)	0.80 (0.30-2.15)	0.75 (0.43-1.30)	0.72 (0.41-1.28)
≥3	2.01 (0.45-9.09)	1.15 (0.23-5.84)	0.70 (0.31-1.59)	0.52 (0.20-1.36)	1.01 (0.40-2.57)	0.88 (0.31-2.56)	0.96 (0.55-1.68)	0.87 (0.47-1.62)
Basic	0.79 (0.42-1.46)	0.59 (0.30-1.15)	1.23 (0.67-2.25)	1.03 (0.54-1.98)	1.30 (0.78-2.19)	1.26 (0.72-2.22)	1.12 (0.81-1.56)	1.06 (0.75-1.50)
Advanced	1.33 (0.59-3.01)	1.27 (0.52-3.06)	**0.52 (0.28-0.96)**†	**0.42 (0.21-0.85)**†	1.17 (0.64-2.12)	1.13 (0.57-2.21)	0.88 (0.60-1.28)	0.90 (0.60-1.35)
Number of Events (n)								
Total	40		44		61		145	
Individual RENF								
FamHx	9		9		9		24	
CKD	3		8		7		18	
MetS	13		21		26		60	
PM	2		3		3		8	
TG	6		8		13		27	
hsCRP	23		22		30		75	
Lp(a)	8		9		15		32	
ApoB100	20		16		32		68	
ABI	1		1		2		4	
Composite RENF								
0	2		9		6		17	
1–2	21		9		20		50	
≥3	11		16		17		44	
Basic	19		27		38		84	
Advanced	33		28		47		108	

*Model is adjusted for age, sex, race/ethnicity, MESA site, education, hypertension, statin medication use, low-density lipoprotein cholesterol, cigarette smoking status.
† – Indicates significant results.
ABI—ankle brachial index ASCVD— atherosclerotic cardiovascular disease; ApoB—apolipoprotein B; CAC—coronary artery calcium; CKD—chronic kidney disease; eGFR— estimated glomerular filtration rate; FamHx—family of history of premature ASCVD; hs-CRP—high sensitivity C-reactive protein; LDL-C—low-density lipoprotein cholesterol; Lp(a)—lipoprotein(a); MetS—metabolic syndrome; PM – premature menopause; RENF—risk-enhancing factor; TG – triglycerides; RENF—risk enhancing factor

eTable 4. Adjusted Area Under the Curve (AUC) for Different Models With 95% CIs for the Difference in Adjusted AUC for the Addition of Risk-Enhancing Factors and Coronary Artery Calcium (Modeled as Continuous and Binary) to Traditional Risk Factors

A. Modeled as Continuous		
	C-statistic	**95% Confidence Interval**
Traditional risk factors (base model)	0.633	–
FamHx	–	–
eGFR, mL/min/1.73 m^2	0.633	-0.006,0.005
MetS	–	–
Premature menopause	–	–
TG, mg/dL	0.637	-0.008,0.011
hsCRP*, mg/L	0.633	-0.012,0.012
Lp(a)*, mg/dL	0.638	-0.002,0.012
ApoB100, mg/dL	0.658	-0.027,0.038
ABI	0.641	-0.006,0.030
PCE, ≥12%	0.636	-0.013,0.014
CAC, Agatston units	0.678	**0.015,0.101**

Base model: age, sex, race/ethnicity, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, systolic blood pressure, diabetes mellitus, antihypertensive medication use, cigarette-smoking status, statin medication use.
BOLD indicates significant results

ABI—ankle brachial index ASCVD— atherosclerotic cardiovascular disease; ApoB—apolipoprotein B; CAC—coronary artery calcium; eGFR—estimated glomerular filtration rate; FamHx—family of history of premature ASCVD; hs-CRP—high sensitivity C-reactive protein; LDL-C—low-density lipoprotein cholesterol; Lp(a)—lipoprotein(a); MetS—metabolic syndrome; PM – premature menopause; PCE – Pooled Cohort Equations; RENF—risk-enhancing factor; TG – triglycerides.

B. Modeled as Binary		
	C-statistic	**95% Confidence Interval**
Traditional risk factors (base model)	0.633	–
FamHx	0.613	-0.025,0.020
eGFR, mL/min/1.73 m^2	0.632	-0.006,0.004
MetS	0.642	-0.009,0.027
Premature menopause	0.636	-0.007,0.014
TG, mg/dL	0.631	-0.011,0.007
hsCRP*, mg/L	0.633	-0.002,0.002
Lp(a)*, mg/dL	0.635	-0.011,0.009
ApoB100, mg/dL	0.634	-0.002,0.003
ABI	0.633	-0.001,0.001
PCE ≥12%	0.636	-0.006,0.016
CAC, Agatston units	0.666	-0.003,0.060

Base model: age, sex, race/ethnicity, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, systolic blood pressure, diabetes mellitus, antihypertensive medication use, cigarette-smoking status, statin medication use.
BOLD indicates significant results

ABI—ankle brachial index ASCVD— atherosclerotic cardiovascular disease; ApoB—apolipoprotein B; CAC—coronary artery calcium; eGFR—estimated glomerular filtration rate; FamHx—family of history of premature ASCVD; hs-CRP—high sensitivity C-reactive protein; LDL-C—low-density lipoprotein cholesterol; Lp(a)—lipoprotein(a); MetS—metabolic syndrome; PM – premature menopause; PCE – Pooled Cohort Equations; RENF—risk-enhancing factor; TG – triglycerides.

eTable 5. Reclassification of Incident Cardiovascular Disease Events With Addition of Risk-Enhancing Factors and Coronary Artery Calcium (Modeled as Continuous and Binary) to the Pooled Cohort Equations

A. Modeled as Continuous

	% Reclassified to low risk		% Reclassified to high risk		NRI (95% Confidence Interval)
	Events	Non-events	Events	Non-events	–
Base Model (PCE)	–	–	–	–	–
FamHx	–	–	–	–	–
eGFR, mL/min/1.73 m^2	28.2	61.5	15.5	5.2	0.0005 (-0.0242,0.0252)
MetS	–	–	–	–	–
Premature menopause	–	–	–	–	–
TG, mg/dL	30.5	63.1	15.4	5.2	-0.0083 (-0.0164,-0.0002_
hsCRP, mg/L	28.8	61.5	17.2	5.4	0.006 (-0.025,0.038)
Lp(a), mg/dL	29.9	63.5	15.3	5.0	0.003 (-0.019,0.024)
ApoB100, mg/dL	34.1	66.5	16.3	5.2	0.010 (-0.008,0.027)
ABI	29.7	63.7	17.3	5.3	0.019 (-0.009,0.047)
PCE ≥12%	26.6	60.1	15.0	4.8	0.009 (-0.009,0.027)
CAC, Agatston units	28.9	65.7	18.9	5.4	**0.067 (0.018,0.116)**

BOLD indicates significant results

ABI—ankle brachial index; ASCVD— atherosclerotic cardiovascular disease; ApoB—apolipoprotein B; CAC—coronary artery calcium; eGFR—estimated glomerular filtration rate; FamHx—family of history of premature ASCVD; hs-CRP—high sensitivity C-reactive protein; Lp(a)—lipoprotein(a); MetS—metabolic syndrome; NRI – net reclassification index; PCE – Pooled Cohort Equations; RENF—risk-enhancing factor; TG – triglycerides.

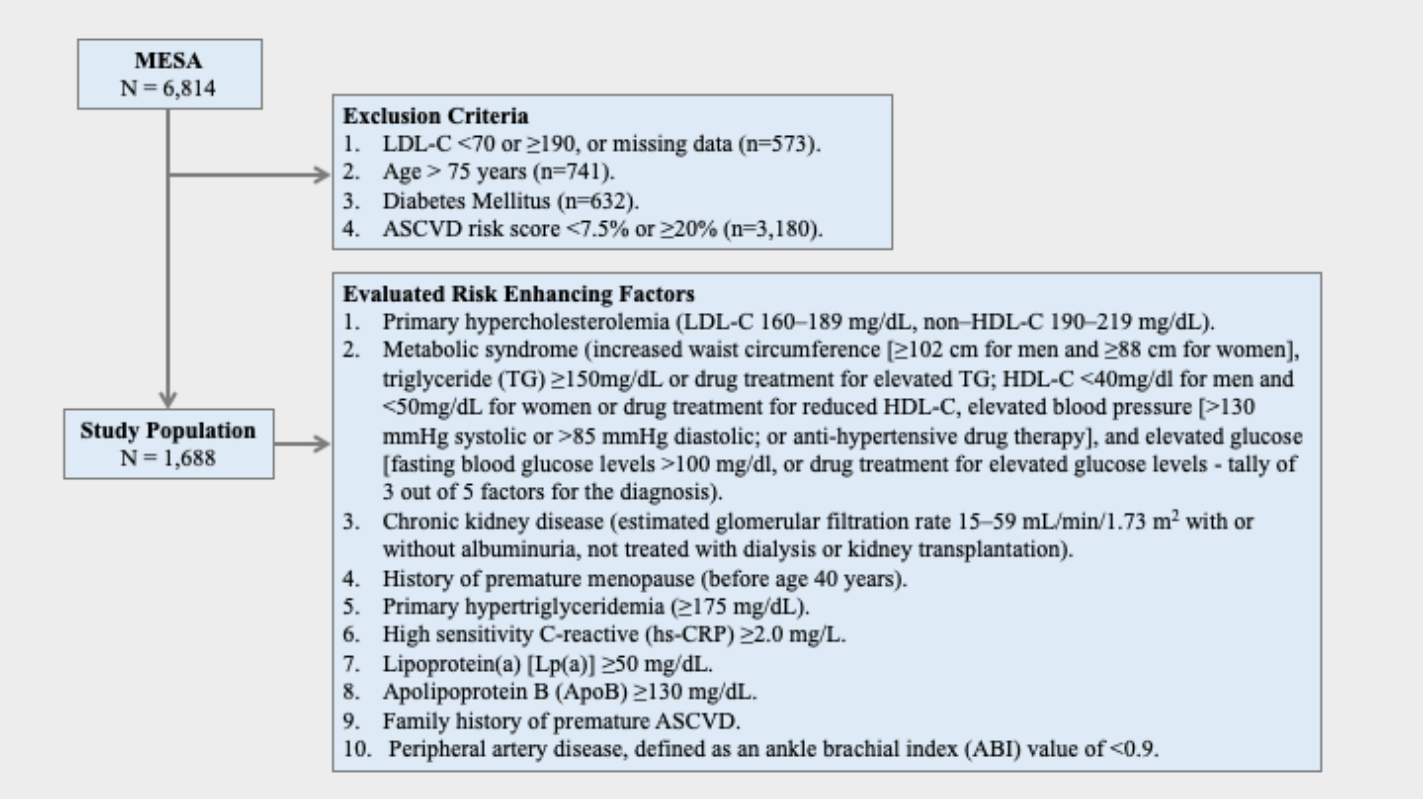
B. Modeled as Binary

	% Reclassified to low risk		% Reclassified to high risk		NRI (95% Confidence Interval)
	Events	**Non-events**	**Events**	**Non-events**	
Base Model (PCE)	–	–	–	–	–
FamHx	37.4	68.9	13.7	4.5	-0.015 (-0.038,0.008)
eGFR, mL/min/1.73 m^2	30.3	63.1	15.7	5.2	-0.003 (-0.008,0.002)
MetS	27.0	59.9	16.6	5.5	0.004 (-0.033,0.042)
Premature menopause	29.3	62.9	15.7	5.2	0.006 (-0.010,0.022)
TG, mg/dL	30.4	63.0	15.5	5.2	-0.006 (-0.021,0.010)
hsCRP, mg/L	28.2	62.2	15.7	5.1	0.010 (-0.016,0.037)
Lp(a), mg/dL	29.8	62.1	16.3	5.3	-0.003 (-0.026,0.020)
ApoB100, mg/dL	30.4	63.1	15.9	5.2	-0.001 (-0.007,0.005)
ABI	30.2	63.4	17.1	5.2	0.017 (-0.001,0.035)
PCE ≥12%	26.6	60.9	15.0	4.8	0.009 (-0.009,0.027)
CAC, Agatston units	21.6	53.9	16.1	4.8	0.0001 (-0.0469,0.0471)

BOLD indicates significant results

ABI—ankle brachial index; ASCVD— atherosclerotic cardiovascular disease; ApoB—apolipoprotein B; CAC—coronary artery calcium; eGFR—estimated glomerular filtration rate; FamHx—family of history of premature ASCVD; hs-CRP—high sensitivity C-reactive protein; Lp(a)—lipoprotein(a); MetS—metabolic syndrome; NRI – net reclassification index; PCE – Pooled Cohort Equations; RENF—risk-enhancing factor; TG – triglycerides.

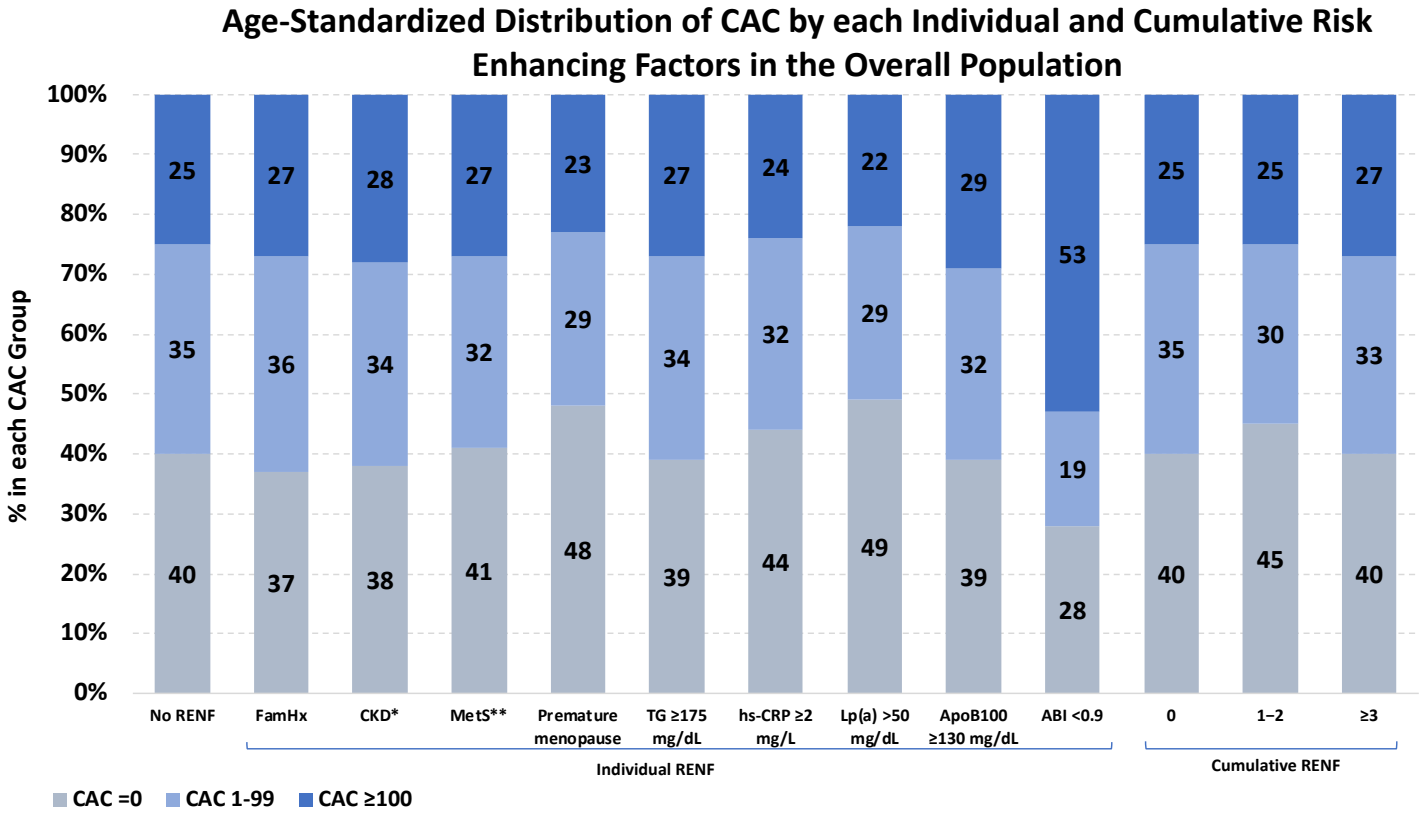
eFigure 1. Derivation of Study Population



Flow chart depicting study population exclusion and inclusion criteria.

ASCVD – atherosclerotic cardiovascular disease; HDL-C: high-density lipoprotein cholesterol LDL-C—low-density lipoprotein cholesterol.

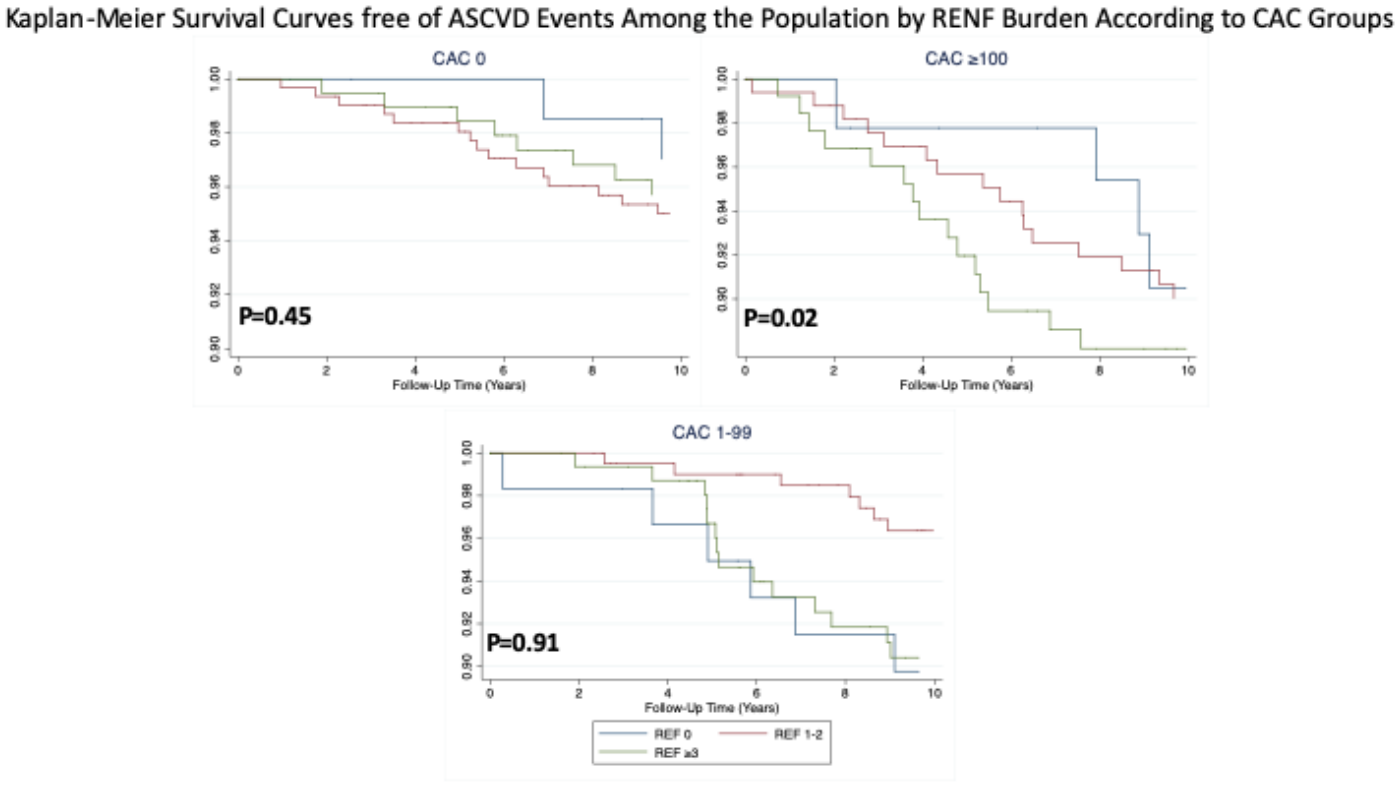
eFigure 2. Age-Standardized Distribution of CAC by Each Individual and Cumulative Risk-Enhancing Factors in the Overall Population



CAC scores at baseline across each individual and cumulative risk enhancing factor according the AHA/ACC Cholesterol Guidelines when standardized for age. The absence of CAC was 45% and 40% among those with 1-2 and ≥3 RENF, respectively.

*eGFR 15-59 mL/min/1.73 m2 **Defined when 3 of the following 5 factors are present: 1) waist circumference >40 inches (men) or 35 inches (women); 2) triglycerides >150 mg/dL; 3) blood pressure >140/90 mmHg; 4) fasting blood glucose levels >126 mg/dl); 5) high-density lipoprotein cholesterol <40 mg/dL in men or <50 in women mg/dL.
ABI—ankle brachial index; *Apo B*—apolipoprotein B; *CAC*—coronary artery calcium; *CKD*—chronic kidney disease; *hs-CRP*—high sensitivity C-reactive protein; *FamHx*—family of history of premature ASCVD; *Lp(a)*—lipoprotein(a); *MetS*—metabolic syndrome; PM – premature menopause; TG – triglycerides.

eFigure 3. Kaplan-Meier Survival Curves Free of ASCVD Events Among the Population by Risk-Enhancing Factor Burden According to CAC Groups



The fewest events were observed over a median 12 year follow up period was in those with CAC=0, irrespective of RENF burden.

ASCVD – atherosclerotic cardiovascular disease*; CAC*—coronary artery calcium; *RENF* – risk enhancing factor

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