SUPPLEMENTAL MATERIAL

Predictive Value of Coronary Artery Calcium Score Categories for Coronary Events versus Strokes: Impact of Sex and Race
The Multi-Ethnic Study of Atherosclerosis (MESA) and Dallas Heart Study (DHS)

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Cardiovascular risk factors

The MESA study enrolled 6,814 participants and the DHS enrolled 2,971 participants. In MESA and DHS information about age, sex, race/ethnicity, smoking, medical history, and medication use was obtained using questionnaires.(1, 2) In MESA, diabetes was defined as a fasting glucose ≥126mg/dL or hypoglycemic medication use and in DHS as a fasting glucose ≥126mg/dL, a non-fasting blood glucose level ≥200 mg/dL, or hypoglycemic medication use.(2, 3) MESA participants had resting blood pressure measured three times in the seated position using a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Tampa, Florida), and the average of the second and third readings was recorded.(2) In DHS, five blood pressure measurements were taken in the seated position using a Series #52,000 oscillometric device (Welch Allyn, Inc., Arden, North Carolina) and their average was recorded.(1) Hypertension was defined similarly in both studies as a systolic blood pressure ≥140mmHg, or diastolic blood pressure ≥90mmHg, or antihypertensive medication use. For both MESA and DHS participants, total and high-density lipoprotein cholesterol (HDL-C) and triglyceride levels were measured from blood samples obtained after an overnight fast and low-density lipoprotein cholesterol (LDL-C) levels were calculated with the Friedewald equation.(1, 2) Family history of myocardial infarction (FHx) in first-degree relatives was ascertained using self-report in both studies.(4, 5)

Coronary artery calcium scanning procedures

Three of the six MESA field centers used an electron-beam CT (EBCT) scanner (Chicago, Los Angeles, and New York) and the remaining three (Baltimore, Forsyth County, and St. Paul) used a multidetector CT (MDCT) scanner as previously described.(6) Radiographic phantoms containing identical and known concentrations of calcium were placed beneath the thorax of each participant and certified technologists then scanned each participant two times. A radiologist or cardiologist read CT scans at a single center (Los Angeles Biomedical Research Institute at Harbor–University of California Los Angeles Medical Center, Torrance, California). CAC score was calculated for each scan using the Agatston method and the mean of the two scans was used in analyses. Intraobserver and interobserver agreement was excellent (kappa statistics, 0.93 and 0.90, respectively). (6) In DHS, an EBCT scanner was utilized and was prospectively gated to the electrocardiogram to acquire image slices of the heart during a single inspiratory breath-hold as previously described.(7) Duplicate CT scans were performed while the subject remained supine and the two CAC scores obtained were averaged. EBCT and MDCT scans are known to have high concordance for CAC scores.(8)

Definition of atherosclerotic cardiovascular disease events:

ASCVD was defined as a composite of nonfatal MI, coronary death, nonfatal stroke or fatal stroke in this study. This definition was used for both cohorts. All nonfatal MI, coronary death, nonfatal and fatal stroke events were reviewed and adjudicated by members of the MESA mortality and morbidity review committee, and the DHS clinical endpoints committee, as mentioned previously. The criteria used by MESA and DHS are described below:

1. Nonfatal MI:

1A. MESA. The criteria for nonfatal MI was adapted from the Atherosclerosis Risk in Communities (ARIC) study and include information about chest pain, cardiac enzymes, and ECG changes. These criteria are described in Table 1 and the MESA algorithm to classify cardiac enzymes into abnormal, equivocal, and normal is described in Table 2. The tables are listed in the MESA clinical events manual of operations (https://www.mesa-nhlbi.org/manuals.aspx) in Section 4, Page 2 and 4, respectively.

Table 1 – MESA diagnostic criteria for MI

A. Cardiac Pain Present **Cardiac Enzymes**

ECG Pattern *	Abnormal	Equivocal	Incomplete	Normal
Evolution of Major Q-Wave	Definite MI	Definite MI	Definite MI	Definite MI
Evolution of ST Elevation with or without Q- wave Or New LBBB	Definite MI	Probable MI	Probable MI	No MI
Evolution of ST-T Depression/inversion alone Or Evolution of Minor Q-waves alone	Definite MI	Probable MI	No MI	No MI
Single ECG with Major Q-Wave Or Single ECG with LBBB, described as new	Definite MI	Probable MI	No MI	No MI
Normal, Absent, Uncodable, other	Probable MI	No MI	No MI	No MI

B. Cardiac Pain Absent **Cardiac Enzymes**

ECG Pattern	Abnormal	Equivocal	Incomplete or Missing	Normal
Evolution of Major Q-Wave	Definite MI	Definite MI	Definite MI	Definite MI
Evolution of ST Elevation with or without Q- wave Or New LBBB	Definite MI	Probable MI	No MI	No MI
Evolution of ST-T Depression/inversion alone Or Evolution of Minor Q-Wave alone	Probable MI	No MI	No MI	No MI
Single ECG with Major Q- Wave Or Single ECG with LBBB, described as new	Probable MI	No MI	No MI	No MI
Normal, Absent, Uncodable, other	Probable MI	No MI	No MI	No MI

Table 2 – MESA diagnostic criteria for MI

Enzyme Value	There is (a) no known muscle trauma/ hemolysis and (b) no PTCA or CABG in past 48 hours*	Muscle trauma/ liver/ hemolytic disease exists
CK-MB = present where present or absent	Abnormal	Equivocal
CK-MB ≥ 2x ULN (upper limit of normal)	Abnormal	Equivocal
CK-MB** ≥ 10%Total CK, if no ULN is given	Abnormal	Equivocal
Total CK ≥ 2xULN and LDH ≥ 2xULN	Abnormal	Equivocal
LDH1 : LDH2 > 1	Abnormal	Equivocal

LDH1 ≥ 2x ULN if LDH2 is missing	Abnormal	Equivocal
Total CK ≥ 2x ULN or LDH ≥ 2x ULN	Equivocal	Normal
Normal < Total CK < 2x ULN and Normal < LDH < 2x ULN	Equivocal	Normal
5% Total CK < CK-MB** < 9% Total CK or CK-MB "weakly present"	Equivocal	Equivocal
Normal < CK-MB < 2x ULN	Equivocal	Equivocal
Normal < LDH1 < 2x ULN	Equivocal	Equivocal
Data present, but insufficient for above criteria	Incomplete	Incomplete
Normal < Troponins < 2x ULN	Equivocal	Equivocal
Troponins > 2x ULN	Abnormal	Abnormal
Troponins < ULN	Normal	Normal
CK-MB < ULN	Normal	Normal
All other results	Normal	Normal

*PTCA–abnormal in first 48 hours requires Troponins or LDH1 or CK or CK-MB > 3x ULN; equivocal requires 1-3x ULN. CABG–abnormal in first 48 hours requires Troponins or LDH1 or CK-MB > 5x ULN; equivocal requires 1-5x ULN

**CK and CK-MB must be in same units for this criterion.

1B. DHS. Nonfatal MI criteria are based upon chest pain, cardiac enzymes, and ECG changes as well. The criteria are summarized below:

Criteria for MI (in the absence of revascularization procedure) include:

- abnormal cardiac enzymes AND
- diagnostic chest pain OR

- ECG changes

Criteria for Post percutaneous coronary intervention (PCI) MI include:

- new pathologic Q waves on ECG OR
- cardiac enzymes within 24 hours of the procedure of ≥3x upper limit of normal (ULN) and ≥50% above last measurement if last measure was ≥ULN

Criteria for Post CABG MI include:

- new pathologic Q waves on ECG OR
- CK-MB within 24 hours of the procedure ≥5x ULN and ≥50% above last measurement if last measure was ≥ULN

CHEST PAIN	**(pain, dyspnea, pressure) at rest or accelerated ischemic symptoms, either of which lasts ≥ 10 minutes**
ECG CRITERIA	ECG changes consistent with injury or ischemia: - new significant Q waves (or R waves in V1-V2) in two contiguous leads in the absence of LVH or conduction abnormalities - ST segment or T wave abnormality consistent with ischemia or injury in two or more contiguous leads - development of new left bundle branch block
ENZYME CRITERIA* (CK-MB or Troponin)	Cardiac Enzymes Abnormal: - Marker ≥ ULN and ≥ 50% above last measurement if last measure was ≥ ULN

2. <u>Coronary death:</u>

<u>2A. MESA.</u> Coronary death is defined as atherosclerotic coronary heart disease death that comprises of definite fatal MI, definite fatal CHD, and possible fatal CHD. This also requires the absence of known non-atherosclerotic or non-cardiac causes of death. The definitions for definite fatal MI, definite fatal CHD, and possible fatal CHD are listed below:

Definite Fatal MI:

- Any in-hospital death that meets criteria for MI OR
- Out-of-hospital death with a documented MI within previous 28 days
-

Definite Fatal CHD:

- Does not qualify as a "definite fatal MI" AND
- Chest pain within previous 72 hours OR
- History of CHD

Possible Fatal CHD:

- Does not qualify as "definite fatal MI" or "definite fatal CHD" AND
- Underlying cause of death included in ICD-10 codes I20–I25, I46, I51.6, R96, or R98–R99

2B. DHS. Coronary death is defined as fatal coronary heart disease using criteria that comprise of definite fatal MI, definite fatal CHD, and probable fatal CHD. The criteria for definite fatal MI, definite fatal CHD, and probable fatal CHD are described below:

Definite Fatal MI:

- Hospitalized MI within 4 weeks of death AND
- No obvious non-ischemic cause of death

Definite Fatal CHD:

- Not meet criteria for fatal myocardial infarction AND
- A history of chest pain within 72 hours of death OR
- A history of ischemic heart disease including angina or myocardial infarction AND
- No obvious non-ischemic cause of death

Probable Fatal CHD:

- ICD 10 cause of death I20-I25, I46,151.6 (ICD9 codes 410-414, 427.5, 429.2) with corresponding information on death certificate

3. Nonfatal stroke:

3A. MESA. Nonfatal stroke was defined using the following criteria:

- Rapid onset of neurologic deficit, headache, or meningismus AND
- Neurologic deficits not secondary to brain trauma (closed head injury), tumor, infection (e.g., encephalitis or meningitis), or other non-vascular cause. Clinical evidence or suspicion of embolic stroke secondary to SBE (bacterial endocarditis) would be counted as stroke AND
- Clinically relevant lesion on brain imaging OR Duration greater than 24 hours OR Death within 24 hours. Clinically relevant lesion on brain imaging: Imaging finding judged to be consistent with signs and symptoms regardless of timing of brain imaging (i.e., less or greater than 24 hours), regardless of stroke type (i.e., with or without blood), and regardless of imaging technique (i.e., cranial competed tomography [CT scan] or cranial magnetic resonance imaging [MRI]).

3B. DHS. The criteria for nonfatal stoke in DHS was similar to MESA:

- Rapid onset of neurologic deficit, headache, or meningismus AND
- Neurologic deficits not secondary to brain trauma (closed head injury), tumor, infection (e.g., encephalitis or meningitis), or other non-vascular cause. Clinical evidence or suspicion of embolic stroke secondary to SBE (bacterial endocarditis) would be counted as stroke AND
- Clinically relevant lesion on brain imaging OR Duration greater than 24 hours OR Death within 24 hours. Clinically relevant lesion on brain imaging: Imaging finding judged to be consistent with signs and symptoms regardless of timing of brain imaging (i.e., less or greater than 24 hours), regardless of stroke type (i.e., with or without blood), and regardless of imaging technique (i.e., cranial competed tomography [CT scan] or cranial magnetic resonance imaging [MRI]).

4. Fatal Stroke:

4A. MESA. The criteria for fatal stroke include:

- Stroke occurrence and type determined by stroke event adjudication: subarachnoid hemorrhage, intraparenchymal hemorrhage, other hemorrhage, brain infarction, other stroke type, or unknown stroke type
- Mechanism of death is recorded as due to critical brain injury or as secondary to complications such as infections (lungs, urine, skin), pulmonary embolism, or arrhythmia. Critical brain injury can be lethal either because of the size of the infarct or bleed with herniation, or because of the location in the brain stem

4B. DHS. The criteria for fatal stroke comprise of definite and probable fatal stroke which are defined as:

Definite Fatal Stroke:

- Criteria for stroke AND
- Mechanism of death recorded as due to critical brain injury or secondary to complications such as infections or pulmonary embolism

Probable Fatal Stroke:

- ICD 10 cause of death I60-I66, I67.2, 167.8, I69 (ICD9 codes 430-435, 437.0, 437.1) with corresponding information on death certificate

Online Table 1A Baseline characteristics of study participants stratified by sex

Participant Characteristics	Women (n=3,826)	Men (n=3,216)	p-value
Age (years)	56.6 (12.7)	56.9 (12.6)	0.406
Black race	1460 (38.2)	1106 (34.4)	0.001
Hispanic race	886 (23.2)	762 (23.7)	0.596
Smoking	642 (16.8)	627 (19.5)	0.003
Diabetes	393 (10.3)	373 (11.6)	0.107
Systolic blood pressure (mm Hg)	126.4 (21.2)	127.1 (18.4)	<0.001
Diastolic blood pressure (mm Hg)	71.2 (10.6)	76.2 (9.5)	<0.001
Antihypertensive use	1314 (34.3)	982 (30.5)	<0.001
Total cholesterol (mg/dL)	193.8 (37.4)	186.8 (36.1)	0.002
High density lipoprotein-cholesterol (mg/dL)	55.6 (15.2)	45.4 (12.1)	<0.001
Low density lipoprotein-cholesterol (mg/dL)	114.5 (33.6)	115.4 (32.8)	0.140
Family history of myocardial infarction	1874 (49.0)	1359 (42.3)	<0.001
Statin use	476 (12.4)	404 (12.6)	0.003
Dallas Heart Study	1244 (32.5)	960 (29.9)	0.016
CAC score (Agatston units)	0.0 [0.0-14.9]	4.7 [0.0-119.2]	<0.001
CAC score category			<0.001
Zero	2204 (57.6)	1239 (38.5)	
1 to 99 Agatston units	1110 (29.0)	1122 (24.9)	
≥100 Agatston units	512 (13.4)	855 (26.6)	
ASCVD event	238 (6.2)	336 (10.5)	<0.001
CHD event	110 (2.9)	223 (6.9)	<0.001
Stroke event	128 (3.4)	113 (3.5)	0.694

Values shown are mean (standard deviation) or median [25^{th}-75^{th} percentile] and number (proportion) depending on variable type.
Abbreviations – CAC = coronary artery calcium, ASCVD = atherosclerotic cardiovascular disease, CHD = coronary heart disease.

Online Table 1B Baseline characteristics of study participants stratified by race

Participant Characteristics	White (n=2,828)	Black (n=2,566)	Hispanic (n=1,648)	p-value
Age (years)	58.3 (12.4)	55.2 (12.6)	56.7 (12.9)	<0.001
Women	1480 (52.3)	1460 (56.9)	886 (53.4)	0.003
Smoking	438 (15.5)	584 (22.8)	247 (15.0)	<0.001
Diabetes	154 (5.5)	371 (14.5)	241 (14.6)	<0.001
Systolic blood pressure (mm Hg)	124.0 (19.0)	130.7 (20.0)	125.1 (20.6)	<0.001
Diastolic blood pressure (mm Hg)	72.3 (10.1)	76.7 (10.3)	72.3 (10.0)	<0.001
Antihypertensive use	821 (29.0)	1011 (39.4)	464 (28.2)	<0.001
Total cholesterol (mg/dL)	193.2 (34.8)	185.6 (38.1)	193.8 (38.0)	<0.001
High density lipoprotein-cholesterol (mg/dL)	51.4 (15.5)	52.5 (15.0)	47.6 (12.6)	<0.001
Low density lipoprotein-cholesterol (mg/dL)	115.9 (31.4)	112.8 (34.9)	116.7 (33.6)	<0.001
Family history of myocardial infarction	1528 (54.0)	1073 (41.8)	632 (38.4)	<0.001
Statin use	420 (14.9)	295 (11.5)	165 (10.0)	<0.001
Dallas Heart Study	770 (27.2)	1059 (41.3)	375 (22.8)	<0.001
CAC score (Agatston units)	2.0 [0.0-106.5]	0.0 [0.0-25.2]	0.0 [0.0-31.3]	<0.001
CAC score category				<0.001
Zero	1261 (44.6)	1284 (50.0)	898 (54.5)	
1 to 99 Agatston units	835 (29.5)	906 (35.3)	491 (29.8)	
≥100 Agatston units	732 (25.9)	376 (14.7)	259 (15.7)	
ASCVD event	212 (7.5)	215 (8.4)	147 (8.9)	0.213
CHD event	130 (4.6)	121 (4.7)	82 (5.0)	0.846
Stroke event	82 (2.9)	94 (3.7)	65 (3.9(	0.125

Values shown are mean (standard deviation) or median [25th-75th percentile] and number (proportion) depending on variable type.
Abbreviations: CAC = coronary artery calcium, ASCVD = atherosclerotic cardiovascular disease, CHD = coronary heart disease.

Online Table 2 10-year cumulative incidence of atherosclerotic cardiovascular disease, coronary heart disease, and stroke events in the overall study cohort along with sex and race groups across CAC score categories

CAC group	Demographic group	ASCVD events	CHD events	Stroke events
All CAC groups	**Overall cohort**	6.67 (6.09-7.30)	3.78 (3.35-4.27)	2.82 (2.45-3.25)
	Men	8.70 (7.74-9.76)	5.71 (4.94-6.61)	2.87 (2.32-3.54)
	Women	4.99 (4.32-5.75)	2.18 (1.75-2.71)	2.78 (2.29-3.37)
	Whites	5.95 (5.12-6.91)	3.62 (2.98-4.40)	2.27 (1.77-2.91)
	Blacks	7.05 (6.09-8.15)	3.63 (2.95-4.47)	3.25 (2.61-4.05)
	Hispanics	7.36 (6.15-8.79)	4.31 (3.39-5.46)	3.12 (2.35-4.13)
CAC score zero	**Overall cohort**	2.70 (2.20-3.32)	1.17 (0.85-1.61)	1.48 (1.11-1.95)
	Men	2.75 (1.95-3.87)	1.38 (0.85-2.24)	1.29 (0.78-2.13)
	Women	2.68 (2.06-3.46)	1.05 (0.70-1.60)	1.58 (1.12-2.21)
	Whites	2.03 (1.37-2.99)	0.89 (0.49-1.60)	1.06 (0.61-1.81)
	Blacks	3.44 (2.54-4.65)	1.36 (0.83-2.20)	2.01 (1.35-2.99)
	Hispanics	2.66 (1.76-4.01)	1.33 (0.74-2.40)	1.33 (0.74-2.39)
CAC score 1 to 99	**Overall cohort**	7.04 (6.02-8.22)	3.59 (2.87-4.48)	3.39 (2.70-4.27)
	Men	8.42 (6.90-10.27)	5.24 (4.04-6.77)	3.15 (2.25-4.40)
	Women	5.65 (4.40-7.24)	1.93 (1.24-2.97)	3.64 (2.66-4.97)
	Whites	6.00 (4.56-7.89)	3.03 (2.04-4.49)	2.99 (2.02-4.44)

	Blacks	7.17 (5.62-9.12)	3.54 (2.49-5.03)	3.43 (2.39-4.89)
	Hispanics	8.65 (6.39-11.65)	4.64 (3.05-7.04)	4.08 (2.58-6.40)
CAC score ≥100	**Overall cohort**	16.52 (14.56-18.72)	11.07 (9.44-12.98)	5.46 (4.31-6.90)
	Men	18.07 (15.52-20.99)	12.97 (10.78-15.57)	4.96 (3.61-6.79)
	Women	13.94 (11.10-17.45)	7.91 (5.77-10.81)	6.29 (4.41-8.95)
	Whites	13.10 (10.76-15.91)	9.33 (7.36-11.79)	3.71 (2.49-5.49)
	Blacks	19.75 (15.84-24.48)	12.20 (9.08-16.29)	7.41 (5.02-10.87)
	Hispanics	21.72 (16.94-27.62)	14.68 (10.64-20.07)	7.74 (4.93-12.04)

Values shown are 10-year cumulative event incidence (95% confidence interval). Abbreviations: CAC = coronary artery calcium, ASCVD = atherosclerotic cardiovascular disease, CHD = coronary heart disease.

Online Table 3 CHD-to-stroke incidence ratio across CAC score categories and 10-year ASCVD risk groups

	CAC score zero	**CAC score 1-99**	**CAC score ≥100**
10-y ASCVD risk <7.5%	0.85 (0.43-1.45)	0.90 (0.48-1.50)	4.26 (1.56-10.47)
10-y ASCVD risk 7.5-20%	0.99 (0.49-1.61)	0.95 (0.60-1.42)	2.26 (1.38-3.48)
10-y ASCVD risk ≥20%	0.69 (0.27-1.29)	1.63 (0.96-2.58)	1.86 (1.36-2.56)

Values shown are 10-year CHD-to-stroke cumulative incidence ratio (95% Confidence Interval).

Abbreviations: CAC = coronary artery calcium, ASCVD = atherosclerotic cardiovascular disease, CHD = coronary heart disease.

Online Table 4 Association of coronary artery calcium score with incident atherosclerotic cardiovascular disease, coronary heart disease, and stroke events in MESA and DHS cohorts

	ASCVD events		**CHD events**		**Stroke events**	
	HR (95%CI)	**p-value**	**HR (95%CI)**	**p-value**	**HR (95%CI)**	**p-value**
MESA						
CAC score ≥100	2.66 (2.05-3.44)	**<0.001**	4.05 (2.81-5.83)	**<0.001**	1.49 (1.01-2.19)	**0.044**
CAC score 1 to 99	1.51 (1.15-1.97)	**0.003**	1.87 (1.27-2.75)	**0.002**	1.23 (0.84-2.19)	0.291
CAC score >0	1.98 (1.57-2.50)	**<0.001**	2.75 (1.96-3.85)	**<0.001**	1.34 (0.96-1.88)	0.086
DHS						
CAC score ≥100	3.60 (1.86-6.97)	**<0.001**	5.16 (2.13-12.49)	**<0.001**	2.19 (0.96-4.97)	0.061
CAC score 1 to 99	2.36 (1.33-4.17)	**0.003**	2.40 (1.08-5.34)	**0.033**	1.81 (0.63-5.23)	0.274
CAC score >0	2.57 (1.47-4.49)	**0.001**	2.87 (1.32-6.25)	**0.008**	2.13 (0.94-4.81)	0.069

Referent group is participants with a zero CAC score. Cox proportional hazards regression models adjusted for age, sex, race, smoking, diabetes, systolic blood pressure, antihypertensive use, total cholesterol, high density lipoprotein-cholesterol level, family history of myocardial infarction, statin use, and educational attainment. Abbreviations: HR = hazard ratio, CI = confidence interval, ASCVD = atherosclerotic cardiovascular disease, CHD = coronary heart disease. Bold values indicate statistically significant association (two-sided p-value <0.05).

Online Table 5 Association of coronary artery calcium score with incident atherosclerotic cardiovascular disease, coronary heart disease, and stroke events in MESA after further adjustment for educational attainment

	ASCVD events		**CHD events**		**Stroke events**	
	HR (95%CI)	**p-value**	**HR (95%CI)**	**p-value**	**HR (95%CI)**	**p-value**
CAC score ≥100	2.63 (2.03-3.41)	**<0.001**	3.81 (2.68-5.42)	**<0.001**	1.45 (1.00-2.12)	0.051
CAC score 1 to 99	1.51 (1.15-1.997)	**0.003**	1.73 (1.19-2.53)	**0.004**	1.21 (0.84-1.76)	0.306
CAC score >0	1.98 (1.57-2.50)	**<0.001**	2.59 (1.87-3.59)	**<0.001**	1.32 (1.05-1.83)	**0.047**

Referent group is participants with a zero CAC score. Cox proportional hazards regression models adjusted for age, sex, race, smoking, diabetes, systolic blood pressure, antihypertensive use, total cholesterol, high density lipoprotein-cholesterol level, family history of myocardial infarction, statin use, and educational attainment. Abbreviations: HR = hazard ratio, CI = confidence interval, ASCVD = atherosclerotic cardiovascular disease, CHD = coronary heart disease. Bold values indicate statistically significant association (two-sided p-value <0.05).

Online Table 6 Association of coronary artery calcium score with incident atherosclerotic cardiovascular disease, coronary heart disease, and stroke events assessed using Fine and Gray competing risk regression models

		ASCVD events		CHD events		Stroke events	
	Group	**sHR (95%CI)**	**p-value**	**sHR (95%CI)**	**p-value**	**sHR (95%CI)**	**p-value**
CAC score >0	**Overall**	2.01 (1.63-2.47)	**<0.001**	2.67 (1.98-3.59)	**<0.001**	1.42 (1.05-1.93)	**0.023**
	Men	2.54 (1.86-3.45)	**<0.001**	3.56 (2.30-5.51)	**<0.001**	1.48 (0.93-2.34)	0.096
	Women	1.63 (1.12-2.20)	**0.001**	1.93 (1.24-3.00)	**0.004**	1.40 (0.94-2.10)	0.101
	Whites	2.25 (1.52-3.31)	**<0.001**	3.52 (2.01-6.15)	**<0.001**	1.32 (0.76-2.30)	0.327
	Blacks	1.80 (1.32-2.46)	**<0.001**	2.25 (1.45-3.48)	**<0.001**	1.36 (0.86-2.15)	0.195
	Hispanics	1.97 (1.30-3.00)	**0.002**	2.40 (1.28-4.50)	**0.006**	1.55 (0.84-2.86)	0.163
CAC score 1 to 99	**Overall**	1.63 (1.30-2.05)	**<0.001**	1.92 (1.38-2.67)	**<0.001**	1.40 (1.01-1.93)	**0.043**
	Men	2.04 (1.46-2.84)	**<0.001**	2.67 (1.68-4.25)	**<0.001**	1.42 (0.87-2.32)	0.157
	Women	1.34 (0.96-1.89)	0.087	1.24 (0.72-2.12)	0.442	1.41 (0.91-2.16)	0.123
	Whites	1.91 (1.25-2.91)	**0.002**	2.31 (1.23-4.33)	**0.009**	1.61 (0.92-2.84)	0.099
	Blacks	1.31 (0.92-1.85)	0.130	1.54 (0.95-2.51)	0.082	1.10 (0.66-1.81)	0.725
	Hispanics	1.79 (1.14-2.81)	**0.012**	2.05 (1.05-4.00)	**0.035**	1.56 (0.82-2.98)	0.180
CAC score ≥100	**Overall**	2.66 (2.08-3.40)	**<0.001**	4.02 (2.86-5.65)	**<0.001**	1.46 (1.003-2.134)	**0.048**
	Men	3.32 (2.35-4.69)	**<0.001**	5.02 (3.12-8.08)	**<0.001**	1.55 (0.90-2.68)	0.118
	Women	2.18 (1.51-3.14)	**<0.001**	3.39 (1.99-5.78)	**<0.001**	1.40 (0.84-2.34)	0.199
	Whites	2.72 (1.74-4.25)	**<0.001**	5.56 (2.98-10.39)	**<0.001**	1.02 (0.53-1.95)	0.963
	Blacks	2.90 (1.99-4.23)	**<0.001**	3.78 (2.26-6.34)	**<0.001**	1.93 (1.08-3.44)	**0.027**
	Hispanics	2.31 (1.41-3.81)	**0.001**	3.05 (1.48-6.30)	**0.003**	1.53 (0.72-3.22)	0.268

Referent group is participants with zero CAC score. Fine and Gray competing risk regression models adjusted for age, sex, race, smoking, diabetes, systolic blood pressure, antihypertensive use, total cholesterol, high density lipoprotein-cholesterol level, family history of myocardial infarction, and statin use. The competing event in ASCVD models was non-cardiovascular death, in CHD models was non-CHD death or stroke event, and in stroke models was non-stroke death or CHD event. Abbreviations: sHR = sub-distribution hazard ratio, CI = confidence interval, ASCVD = atherosclerotic cardiovascular disease, CHD = coronary heart disease. Bold values indicate statistically significant association (two-sided p-value <0.05).

Online Table 7 Association of coronary artery calcium score with incident atherosclerotic cardiovascular disease, coronary heart disease, and stroke events among participants that qualify for coronary artery calcium scanning as per 2018 cholesterol guidelines (N=1,252)

		ASCVD events		CHD events		Stroke events	
	Group	**HR (95%CI)**	**p-value**	**HR (95%CI)**	**p-value**	**HR (95%CI)**	**p-value**
CAC score >0	**Overall**	1.91 (1.26-2.89)	**0.002**	2.69 (1.47-4.94)	**0.001**	1.24 (0.69-2.25)	0.472
	Men	2.29 (1.29-4.07)	**0.005**	4.16 (1.72-10.1)	**0.002**	1.08 (0.48-2.42)	0.854
	Women	1.65 (0.86-3.20)	0.135	1.58 (0.61-4.12)	0.346	1.60 (0.64-3.99)	0.316
	Whites	2.27 (1.04-4.94)	**0.039**	4.06 (1.21-13.64)	**0.024**	1.08 (0.37-3.20)	0.887
	Blacks	2.30 (1.15-4.59)	**0.019**	2.44 (0.94-6.34)	0.067	1.99 (0.71-5.60)	0.189
	Hispanics	1.36 (0.64-2.88)	0.429	2.20 (0.68-7.05)	0.186	0.82 (0.28-2.37)	0.702
CAC score 1 to 99	**Overall**	1.55 (0.97-2.47)	0.068	2.02 (1.02-3.97)	**0.043**	1.15 (0.59-2.23)	0.680
	Men	1.91 (1.01-3.61)	**<0.001**	3.27 (1.26-8.46)	**0.015**	1.03 (0.42-2.55)	0.944
	Women	1.28 (0.60-2.70)	0.526	1.00 (0.32-3.16)	0.993	1.47 (0.54-3.96)	0.452
	Whites	1.79 (0.74-4.34)	0.195	2.96 (0.78-11.22)	0.111	1.04 (0.30-3.58)	0.949
	Blacks	1.73 (0.80-3.75)	0.165	1.68 (0.57-4.98)	0.350	1.67 (0.54-5.18)	0.373
	Hispanics	1.53 (0.67-3.53)	0.314	2.21 (0.62-7.91)	0.223	0.99 (0.31-3.19)	0.984
CAC score ≥100	**Overall**	2.42 (1.52-3.84)	**<0.001**	3.64 (1.89-7.00)	**<0.001**	1.37 (0.69-2.73)	0.368
	Men	2.76 (1.48-5.15)	**0.001**	5.25 (2.08-13.30)	**<0.001**	1.14 (0.45-2.87)	0.789
	Women	2.50 (1.15-5.47)	**0.022**	2.93 (0.95-8.97)	0.060	1.87 (0.61-5.71)	0.273
	Whites	2.66 (1.18-6.00)	**0.018**	4.95 (1.43-17.18)	**0.012**	1.12 (0.34-3.63)	0.855
	Blacks	3.30 (1.53-7.13)	**0.002**	3.76 (1.32-10.70)	**0.013**	2.55 (0.80-8.11)	0.114
	Hispanics	1.13 (0.43-2.96)	0.811	2.18 (0.53-8.46)	0.261	0.56 (0.11-2.77)	0.477

Referent group is participants with a zero CAC score. Cox proportional hazards regression models adjusted for age, sex, race, smoking, diabetes, systolic blood pressure, antihypertensive use, total cholesterol, high density lipoprotein-cholesterol level, and family history of myocardial infarction.

Online Table 8A Cardiovascular risk reclassification in the overall cohort after adding CAC score categories to a baseline risk prediction model

ASCVD Events	**Event**			**No Event**		
	Baseline Model + CAC			**Baseline Model + CAC**		
Baseline Model	<7.5%	≥7.5%	Total	<7.5%	≥7.5%	Total
<7.5%	138	53	191	4308	319	4627
≥7.5%	33	350	383	429	1412	1841
Total	171	403	574	4737	1731	6468
Net Effect of CAC						
Increased Risk	53			319		
Decreased Risk	33			429		
Net Correctly Reclassified	0.035 (p=0.031)			0.017 (p<0.001)		
NRI = 0.052 (p=0.002)						

CHD Events	**Event**			**No Event**		
	Baseline Model + CAC			**Baseline Model + CAC**		
Baseline Model	<7.5%	≥7.5%	Total	<7.5%	≥7.5%	Total
<7.5%	134	65	199	5510	323	5833
≥7.5%	20	114	134	274	596	870
Total	154	179	333	5784	919	6703
Net Effect of CAC						
Increased Risk	65			323		
Decreased Risk	20			274		
Net Correctly Reclassified	0.135 (p<0.001)			-0.007 (p=0.045)		
NRI = 0.128 (p<0.001)						

Stroke Events	**Event**			**No Event**		
	Baseline Model + CAC			**Baseline Model + CAC**		
Baseline Model	<7.5%	≥7.5%	Total	<7.5%	≥7.5%	Total
<7.5%	188	12	200	6309	79	6388
≥7.5%	5	36	41	64	342	406
Total	193	48	241	6373	421	6794
Net Effect of CAC						
Increased Risk	12			79		
Decreased Risk	5			64		
Net Correctly Reclassified	0.029 (p=0.090)			-0.002 (p=0.210)		
NRI = 0.027 (p=0.119)						

Baseline 10-year risk prediction models comprised of age, sex, race, diabetes, smoking, systolic blood pressure, antihypertensive use, total cholesterol, HDL-C level, family history, and statin use at baseline. Abbreviations: ASCVD = atherosclerotic cardiovascular disease, CAC = coronary artery calcium, NRI = net reclassification index

Online Table 8B Cardiovascular risk reclassification in men after adding CAC score categories to a baseline risk prediction model

ASCVD Events	**Event**			**No Event**		
	Baseline Model + CAC			**Baseline Model + CAC**		
Baseline Model	<7.5%	≥7.5%	Total	<7.5%	≥7.5%	Total
<7.5%	47	23	70	1553	197	1750
≥7.5%	24	242	266	262	868	1130
Total	71	265	336	1815	1065	2880
Net Effect of CAC						
Increased Risk	23			197		
Decreased Risk	24			262		
Net Correctly Reclassified	-0.003 (p=0.884)			0.023 (p=0.002)		
NRI = 0.020 (p=0.367)						

CHD Events	**Event**			**No Event**		
	Baseline Model + CAC			**Baseline Model + CAC**		
Baseline Model	<7.5%	≥7.5%	Total	<7.5%	≥7.5%	Total
<7.5%	60	46	106	2043	199	2242
≥7.5%	12	105	117	205	543	748
Total	72	151	223	2248	742	2990
Net Effect of CAC						
Increased Risk	46			199		
Decreased Risk	12			205		
Net Correctly Reclassified	0.153 (p<0.001)			0.002 (p=0.765)		
NRI = 0.154 (<0.001)						

Stroke Events	**Event**			**No Event**		
	Baseline Model + CAC			**Baseline Model + CAC**		
Baseline Model	<7.5%	≥7.5%	Total	<7.5%	≥7.5%	Total
<7.5%	92	4	96	2887	34	2921
≥7.5%	2	15	17	20	157	177
Total	94	19	113	2907	191	3098
Net Effect of CAC						
Increased Risk	4			34		
Decreased Risk	2			20		
Net Correctly Reclassified	0.018 (p=0.414)			-0.005 (p=0.057)		
NRI = 0.013 (p=0.546)						

Baseline 10-year risk prediction models comprised of age, sex, race, diabetes, smoking, systolic blood pressure, antihypertensive use, total cholesterol, HDL-C level, family history, and statin use at baseline. Abbreviations: ASCVD = atherosclerotic cardiovascular disease, CAC = coronary artery calcium, NRI = net reclassification index

Online Table 8C Cardiovascular risk reclassification in women after adding CAC score categories to a baseline risk prediction model

ASCVD Events	**Event**			**No Event**		
	Baseline Model + CAC			**Baseline Model + CAC**		
Baseline Model	<7.5%	≥7.5%	Total	<7.5%	≥7.5%	Total
<7.5%	89	17	106	2778	106	2884
≥7.5%	14	118	132	168	536	704
Total	103	135	238	2946	642	3588
Net Effect of CAC						
Increased Risk	17			106		
Decreased Risk	14			168		
Net Correctly Reclassified	0.013 (p=0.590)			0.017 (p<0.001)		
NRI = 0.030 (p=0.210)						

CHD Events	**Event**			**No Event**		
	Baseline Model + CAC			**Baseline Model + CAC**		
Baseline Model	<7.5%	≥7.5%	Total	<7.5%	≥7.5%	Total
<7.5%	76	21	97	3432	113	3545
≥7.5%	1	12	13	70	98	168
Total	77	33	110	3502	211	3713
Net Effect of CAC						
Increased Risk	21			113		
Decreased Risk	1			70		
Net Correctly Reclassified	0.182 (p<0.001)			-0.012 (p=0.001)		
NRI = 0.170 (p<0.001)						

Stroke Events	**Event**			**No Event**		
	Baseline Model + CAC			**Baseline Model + CAC**		
Baseline Model	<7.5%	≥7.5%	Total	<7.5%	≥7.5%	Total
<7.5%	87	5	92	3379	61	3440
≥7.5%	4	32	36	47	209	256
Total	91	37	128	3426	270	3696
Net Effect of CAC						
Increased Risk	5			61		
Decreased Risk	4			47		
Net Correctly Reclassified	0.008 (p=0.739)			-0.004 (p=0.178)		
NRI = 0.004 (p=0.845)						

Baseline 10-year risk prediction models comprised of age, sex, race, diabetes, smoking, systolic blood pressure, antihypertensive use, total cholesterol, HDL-C level, family history, and statin use at baseline. Abbreviations: ASCVD = atherosclerotic cardiovascular disease, CAC = coronary artery calcium, NRI = net reclassification index

Online Table 8D Cardiovascular risk reclassification in Whites after adding CAC score categories to a baseline risk prediction model

ASCVD Events	**Event**			**No Event**		
	Baseline Model + CAC			**Baseline Model + CAC**		
Baseline Model	<7.5%	≥7.5%	Total	<7.5%	≥7.5%	Total
<7.5%	60	22	82	1830	120	1950
≥7.5%	5	125	130	113	553	666
Total	65	147	212	1943	553	2616
Net Effect of CAC						
Increased Risk	22			120		
Decreased Risk	5			113		
Net Correctly Reclassified	0.080 (p=0.001)			-0.003 (p=0.647)		
NRI = 0.078 (p=0.002)						

CHD Events	**Event**			**No Event**		
	Baseline Model + CAC			**Baseline Model + CAC**		
Baseline Model	<7.5%	≥7.5%	Total	<7.5%	≥7.5%	Total
<7.5%	47	35	82	2199	164	2363
≥7.5%	10	38	48	96	238	334
Total	57	73	130	2295	402	2697
Net Effect of CAC						
Increased Risk	35			164		
Decreased Risk	10			96		
Net Correctly Reclassified	0.192 (p<0.001)			-0.025 (p<0.001)		
NRI = 0.167 (p=0.001)						

Stroke Events	**Event**			**No Event**		
	Baseline Model + CAC			**Baseline Model + CAC**		
Baseline Model	<7.5%	≥7.5%	Total	<7.5%	≥7.5%	Total
<7.5%	63	2	65	2589	30	2619
≥7.5%	3	14	17	27	99	126
Total	66	16	82	2616	129	2745
Net Effect of CAC						
Increased Risk	2			30		
Decreased Risk	3			27		
Net Correctly Reclassified	-0.012 (p=0.655)			-0.001 (p=0.691)		
NRI = -0.013 (p=0.628)						

Baseline 10-year risk prediction models comprised of age, sex, race, diabetes, smoking, systolic blood pressure, antihypertensive use, total cholesterol, HDL-C level, family history, and statin use at baseline. Abbreviations: ASCVD = atherosclerotic cardiovascular disease, CAC = coronary artery calcium, NRI = net reclassification index

Online Table 8E Cardiovascular risk reclassification in Blacks after adding CAC score categories to a baseline risk prediction model

ASCVD Events	**Event**			**No Event**		
	Baseline Model + CAC			**Baseline Model + CAC**		
Baseline Model	<7.5%	≥7.5%	Total	<7.5%	≥7.5%	Total
<7.5%	52	19	71	1532	97	1629
≥7.5%	16	128	144	209	513	722
Total	68	147	215	1741	610	2351
Net Effect of CAC						
Increased Risk	19			97		
Decreased Risk	16			209		
Net Correctly Reclassified	0.014 (p=0.612)			0.048 (p<0.001)		
NRI = 0.062 (p=0.031)						

CHD Events	**Event**			**No Event**		
	Baseline Model + CAC			**Baseline Model + CAC**		
Baseline Model	<7.5%	≥7.5%	Total	<7.5%	≥7.5%	Total
<7.5%	57	20	77	2038	122	2160
≥7.5%	9	35	44	130	151	281
Total	66	55	121	2168	273	2441
Net Effect of CAC						
Increased Risk	20			122		
Decreased Risk	9			130		
Net Correctly Reclassified	0.091 (p=0.041)			0.003 (p=0.614)		
NRI = 0.094 (p=0.036)						

Stroke Events	**Event**			**No Event**		
	Baseline Model + CAC			**Baseline Model + CAC**		
Baseline Model	<7.5%	≥7.5%	Total	<7.5%	≥7.5%	Total
<7.5%	74	7	81	2237	78	2315
≥7.5%	5	8	13	50	101	151
Total	79	15	94	2287	179	2466
Net Effect of CAC						
Increased Risk	7			78		
Decreased Risk	5			50		
Net Correctly Reclassified	0.021 (p=0.564)			-0.011 (p=0.013)		
NRI = 0.010 (p=0.789)						

Baseline 10-year risk prediction models comprised of age, sex, race, diabetes, smoking, systolic blood pressure, antihypertensive use, total cholesterol, HDL-C level, family history, and statin use at baseline. Abbreviations: ASCVD = atherosclerotic cardiovascular disease, CAC = coronary artery calcium, NRI = net reclassification index

Online Table 8F Cardiovascular risk reclassification in Hispanics after adding CAC score categories to a baseline risk prediction model

ASCVD Events	**Event**			**No Event**		
	Baseline Model + CAC			**Baseline Model + CAC**		
Baseline Model	<7.5%	≥7.5%	Total	<7.5%	≥7.5%	Total
<7.5%	31	4	35	1002	63	1065
≥7.5%	7	105	112	83	353	436
Total	38	109	147	1085	416	1501
Net Effect of CAC						
Increased Risk	4			63		
Decreased Risk	7			83		
Net Correctly Reclassified	-0.020 (p=0.366)			0.013 (p=0.098)		
NRI = -0.007 (p=0.768)						

CHD Events	**Event**			**No Event**		
	Baseline Model + CAC			**Baseline Model + CAC**		
Baseline Model	<7.5%	≥7.5%	Total	<7.5%	≥7.5%	Total
<7.5%	31	6	37	1253	60	1313
≥7.5%	3	42	45	48	204	252
Total	34	48	82	1301	264	1565
Net Effect of CAC						
Increased Risk	6			60		
Decreased Risk	3			48		
Net Correctly Reclassified	0.037 (p=0.317)			-0.008 (p=0.248)		
NRI = 0.029 (p=0.437)						

Stroke Events	**Event**			**No Event**		
	Baseline Model + CAC			**Baseline Model + CAC**		
Baseline Model	<7.5%	≥7.5%	Total	<7.5%	≥7.5%	Total
<7.5%	36	4	40	1421	29	1450
≥7.5%	1	24	25	15	118	133
Total	37	28	65	1436	147	1583
Net Effect of CAC						
Increased Risk	4			29		
Decreased Risk	1			15		
Net Correctly Reclassified	0.046 (p=0.180)			-0.009 (p=0.035)		
NRI = 0.037 (p=0.282)						

Baseline 10-year risk prediction models comprised of age, sex, race, diabetes, smoking, systolic blood pressure, antihypertensive use, total cholesterol, HDL-C level, family history, and statin use at baseline. Abbreviations: ASCVD = atherosclerotic cardiovascular disease, CAC = coronary artery calcium, NRI = net reclassification index

REFERENCES

1. Victor RG, Haley RW, Willett DL, Peshock RM, Vaeth PC, Leonard D, Basit M, Cooper RS, Iannacchione VG, Visscher WA, Staab JM, Hobbs HH, Dallas Heart Study I. The Dallas Heart Study: a population-based probability sample for the multidisciplinary study of ethnic differences in cardiovascular health. Am J Cardiol. 2004;93(12):1473-80.
2. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, Greenland P, Jacob DR, Jr., Kronmal R, Liu K, Nelson JC, O'Leary D, Saad MF, Shea S, Szklo M, Tracy RP. Multi-Ethnic Study of Atherosclerosis: objectives and design. Am J Epidemiol. 2002;156(9):871-81.
3. Paixao AR, Ayers CR, El Sabbagh A, Sanghavi M, Berry JD, Rohatgi A, Kumbhani DJ, McGuire DK, Das SR, de Lemos JA, Khera A. Coronary Artery Calcium Improves Risk Classification in Younger Populations. JACC Cardiovasc Imaging. 2015;8(11):1285-93.
4. Nasir K, Budoff MJ, Wong ND, Scheuner M, Herrington D, Arnett DK, Szklo M, Greenland P, Blumenthal RS. Family history of premature coronary heart disease and coronary artery calcification: Multi-Ethnic Study of Atherosclerosis (MESA). Circulation. 2007;116(6):619-26.
5. Paixao AR, Berry JD, Neeland IJ, Ayers CR, Rohatgi A, de Lemos JA, Khera A. Coronary artery calcification and family history of myocardial infarction in the Dallas heart study. JACC Cardiovasc Imaging. 2014;7(7):679-86.
6. Carr JJ, Nelson JC, Wong ND, McNitt-Gray M, Arad Y, Jacobs DR, Jr., Sidney S, Bild DE, Williams OD, Detrano RC. Calcified coronary artery plaque measurement with cardiac CT in population-based studies: standardized protocol of Multi-Ethnic Study of Atherosclerosis (MESA) and Coronary Artery Risk Development in Young Adults (CARDIA) study. Radiology. 2005;234(1):35-43.
7. Jain T, Peshock R, McGuire DK, Willett D, Yu Z, Vega GL, Guerra R, Hobbs HH, Grundy SM, Dallas Heart Study I. African Americans and Caucasians have a similar prevalence of coronary calcium in the Dallas Heart Study. J Am Coll Cardiol. 2004;44(5):1011-7.
8. Daniell AL, Wong ND, Friedman JD, Ben-Yosef N, Miranda-Peats R, Hayes SW, Kang X, Sciammarella MG, de Yang L, Germano G, Berman DS. Concordance of coronary artery calcium estimates between MDCT and electron beam tomography. AJR Am J Roentgenol. 2005;185(6):1542-5.