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Original Investigation

Prevalence and Correlates of Myocardial Scar in a US Cohort

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IMPORTANCE Myocardial scarring leads to cardiac dysfunction and poor prognosis. The prevalence of and factors associated with unrecognized myocardial infarction and scar have not been previously defined using contemporary methods in a multiethnic US population.

OBJECTIVE To determine prevalence of and factors associated with myocardial scar in middle- and older-aged individuals in the United States.

DESIGN, SETTING, AND PARTICIPANTS The Multi-Ethnic Study of Atherosclerosis (MESA) study is a population-based cohort in the United States. Participants were aged 45 through 84 years and free of clinical cardiovascular disease (CVD) at baseline in 2000-2002. In the 10th year examination (2010-2012), 1840 participants underwent cardiac magnetic resonance (CMR) imaging with gadolinium to detect myocardial scar. Cardiovascular disease risk factors and coronary artery calcium (CAC) scores were measured at baseline and year 10. Logistic regression models were used to estimate adjusted odds ratios (ORs) for myocardial scar.

EXPOSURES Cardiovascular risk factors, CAC scores, left ventricle size and function, and carotid intima-media thickness.

MAIN OUTCOMES AND MEASURES Myocardial scar detected by CMR imaging.

RESULTS Of 1840 participants (mean [SD] age, 68 [9] years, 52% men), 146 (7.9%) had myocardial scars, of which 114 (78%) were undetected by electrocardiogram or by clinical adjudication. In adjusted models, age, male sex, body mass index, hypertension, and current smoking at baseline were associated with myocardial scar at year 10. The OR per 8.9-year increment was 1.61 (95% CI, 1.36-1.91; $P < .001$); for men vs women: OR, 5.76 (95% CI, 3.61-9.17; $P < .001$); per 4.8-SD body mass index: OR, 1.32 (95% CI, 1.09-1.61, $P = .005$); for hypertension: OR, 1.61 (95% CI, 1.12-2.30; $P = .009$); and for current vs never smokers: 2.00 (95% CI, 1.22-3.28; $P = .006$). Age-, sex-, and ethnicity-adjusted CAC scores at baseline were also associated with myocardial scar at year 10. Compared with a CAC score of 0, the OR for scores from 1 through 99 was 2.4 (95% CI, 1.5-3.9); from 100 through 399, 3.0 (95% CI, 1.7-5.1), and 400 or higher, 3.3 (95% CI, 1.7-6.1) ($P \leq .001$). The CAC score significantly added to the association of myocardial scar with age, sex, race/ethnicity, and traditional CVD risk factors (*C* statistic, 0.81 with CAC vs 0.79 without CAC, $P = .01$).

CONCLUSIONS AND RELEVANCE The prevalence of myocardial scars in a US community-based multiethnic cohort was 7.9%, of which 78% were unrecognized by electrocardiography or clinical evaluation. Further studies are needed to understand the clinical consequences of these undetected scars.

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Ischemic heart disease is an important public health concern, but a considerable proportion of myocardial infarctions (MIs) are clinically unrecognized. Given the aging of the US population, it is important to understand the prevalence, risk factors, and prognosis of unrecognized MI.[1,2] Previous population-based studies in the United States, using electrocardiography (ECG) criteria, reported that approximately 20% of MIs are silent.[2,3] More recently, clinical[4-6] and population studies[1,7,8] have demonstrated that cardiac magnetic resonance (CMR) imaging with late gadolinium enhancement (LGE) has greater sensitivity than ECG for detecting myocardial scar. Cardiac magnetic resonance can identify myocardial scar related to MI as well as other nonischemic etiologies. Clinical trials use unrecognized myocardial scars detected by CMR as end points[9] because they often lead to major adverse cardiac events.[1,5]

Population studies in Iceland (n = 936 participants[1]) and Sweden (n = 248 participants[7]) have documented that the prevalence of myocardial scar detected by CMR is significantly higher than is detected by clinical assessment, serum biomarkers, and ECG. Equivalent studies are needed in the United States and may stimulate a greater appreciation of the burden of subclinical disease. Given the high prevalence of ischemic heart disease in the United States and globally,[10] it is important to accurately evaluate the burden and correlates of myocardial scar in the population.

The Multi-Ethnic Study of Atherosclerosis (MESA) recruited individuals from 4 different ethnicities from 6 US communities. The purpose of this study was to determine the prevalence of myocardial scar using CMR and to determine the association between cardiovascular disease (CVD) risk factors and myocardial scar in a large population-based study.

Methods

Study Sample

The MESA study design has been previously described.[11] In brief, 6814 men and women who identified themselves as white, black, Hispanic, or Chinese and were aged 45 to 84 years and free of clinically apparent CVD were recruited from 2000 through 2002 from 6 US communities: Baltimore City and Baltimore County, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; northern Manhattan and the Bronx, New York; and St Paul, Minnesota. Consenting participants (n = 3045) underwent CMR from April 2010 until February 2012 (visit 5 of the cohort). Institutional review boards at each center approved the study protocol, and all participants gave written informed consent. Study participants who agreed to participate and who had estimated glomerular filtration rate (eGFR) of 45 mL/min/1.73 m^2 or higher (≥60 mL/min/1.73 m^2 for the Chicago site) and no known allergies to gadolinium (n = 1840) also underwent LGE CMR 15 minutes after administration of a 0.15-mmol/kg dose of a gadolinium-based contrast agent (Magnevist, Bayer Healthcare Pharmaceuticals).

CVD Risk Factors

MESA participants underwent an extensive evaluation including clinical history, physical examination, laboratory tests, and anthropometric measurements. Standard questionnaires were used to obtain information about participant demographics; medical history including smoking, current medications including lipid-lowering, hypoglycemic, and antihypertensive drugs; and physician diagnosis of hypertension and diabetes. Race/ethnicity was assessed as one of the overall aims of the MESA study to provide insights about interactions between ethnicity, risk factors, and subclinical and clinical CVD. Ethnicity was self-identified in fixed categories as white, black, Hispanic, or Chinese.

Centrally trained clinical teams blinded to participant outcome collected information on cardiovascular risk factors. Hypertension was defined as systolic blood pressure of 140 mm Hg or higher, diastolic blood pressure of 90 mm Hg or higher, or self-reported use of antihypertensive medications.[12] Diabetes was defined based on the use of hypoglycemic drugs or insulin or fasting blood glucose 126 mg/dL or higher (to convert glucose from mg/dL to mmol/L, multiply by 0.055).[13] Serum creatinine measurements, eGFR calculation, microalbuminuria, and macroalbuminuria classifications have been described previously.[14,15]

The ECG studies at year 10 were centrally read and classified using the Minnesota code.[16] Silent MIs by ECG were identified based on major Q-wave abnormalities representing old MIs among participants at year 10. Carotid artery intima-media thickness measurements in MESA have been described previously.[17]

Coronary Artery Calcification Score Measurements

The method for acquisition and interpretation of the coronary artery calcification (CAC) score has been reported previously.[18] Briefly, the CAC score was assessed by either a cardiac-gated electron beam CT or a multidetector CT at baseline and year 10 in 6 centers. All images were interpreted at the MESA CT reading center and the Agatston score was calculated.

Assessment of Clinical MI Events

Details of CVD event ascertainment have been published.[19] For this report, clinical MI events were cumulative from the study start to the 10-year examination date. Briefly, definite or probable MI required finding participants' hospital records documenting either abnormal cardiac biomarkers (2 times the upper limits of normal) regardless of pain or ECG findings; evolving Q waves regardless of pain or biomarker findings; or a combination of chest pain, ST-T elevation or new left bundle-branch block, and biomarker levels 1 to 2 times the upper limits of normal.

CMR Imaging and Image Analysis

Cardiac MR imaging was performed using 1.5-T scanners (Avanto and Espree, Siemens Medical Systems and Signa HD, GE) with a 6-channel anterior phased array coil. Cardiac MR protocol was uniform in all centers and all studies were centrally evaluated by readers blinded to all other study data. Left ventricular mass, volumes, and functional parameters were determined by a cine steady-state free precession sequence using CIM software (version 6.2, Auckland MRI Research Group).

Myocardial scar was defined as focal LGE either in 2 adjacent short-axis slices or in 1 short-axis and a long-axis image

at a corresponding location using QMass (version 7.2, Medis). Myocardial scars that involved subendocardium in a coronary artery distribution were defined as "typical" scar. Myocardial scars predominantly affecting midwall or subepicardium without subendocardial involvement in a noncoronary artery distribution were defined as an "atypical" scar.

Statistical Analysis

Participant demographics and characteristics at the year-10 examination are presented as mean (SDs) or as No. (%). Log transformation was applied to variables with skewed distribution. The missing data approach was complete-case analysis, which uses only participants who have all variables observed. Logistic regression models were used to model the log odds of myocardial scar using CAC both continuously and categorically in separate models. For the continuous models, CAC was log-transformed after adding 1 (due to CAC score values of 0). After log transformation, there was no evidence of nonlinearity in the relationship between log (CAC + 1) and the log odds of myocardial scar. For the categorical CAC models, the groups were 0, 1 through 99, 100 through 399, and 400 Agatston units or higher. For each version of CAC, 4 sets of models were fit based on a priori defined sets of covariates both for cross-sectional and longitudinal associations. Model 1 adjusted for age, sex, and race/ethnicity. Model 2 further adjusted for systolic blood pressure, hypertension medication, total and high-density lipoprotein (HDL) cholesterol, lipid medication, smoking status, diabetes, GFR, and household income of more than $50 000. Model 3 additionally added body mass index (BMI) and left ventricular mass, end-diastolic volume, and ejection fraction. Model 4 additionally added the average of the left and right distal mean common carotid artery intima-media thickness. To evaluate the improvement in prediction by adding CAC to the model with traditional risk factors, the area under the curve (AUC) was calculated before and after adding CAC to the adjusted model. Both continuous CAC (log [CAC+1]) and categorical CAC scores were evaluated in a series of models.

Both cross-sectional and longitudinal models were constructed to evaluate the association of age- and sex-adjusted CAC score with the presence of a CMR-defined scar in comparison with clinically adjudicated MI. These models were additionally adjusted for the 10-year Framingham Global Risk score or the 10-year ACC/AHA (American College of Cardiology and American Heart Association) risk score (composite risk scores were used due to the small number of clinically adjudicated MIs).[20,21]

We used SAS 9.2 (SAS Institute Inc) and R 2.13.0 (R Foundation for Statistical Computing) for the analysis. The statistical testing was 2-sided. *P* values ≤.05 were considered statistically significant and are presented for descriptive purposes.

Results

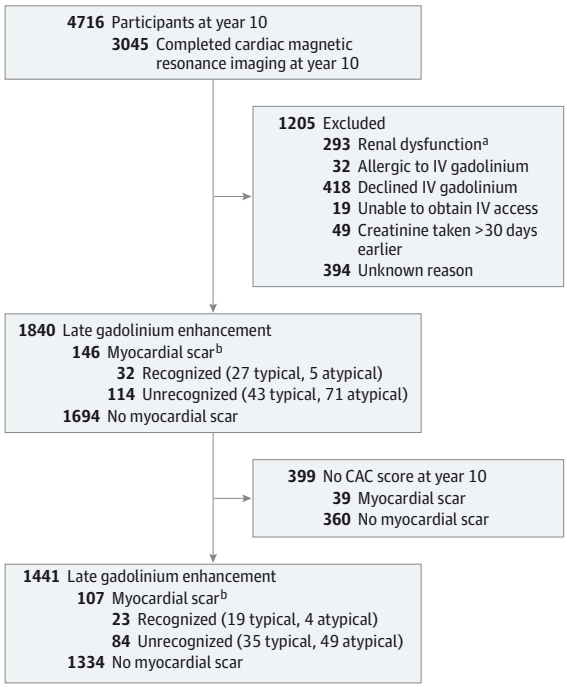
Study Population

During the 10th year, 3045 of 4716 participants underwent CMR examination (**Figure**). The mean age of participants with CMR was 69 years, 47% were men, 40% were white, 10% were Chinese American, 25% were black, and 20% were Hispanic. Of these, 1840 (60%) also completed the LGE CMR examination. Of participants who did not receive LGE CMR, 34.7% declined administration of intravenous (IV) gadolinium, 24.3% were excluded due to low renal function, 4.1% had creatinine measurements more than 30 days ago, 2.6% were allergic to gadolinium, 1.6% did not have IV access, and 32.7% had an unknown reason.

The 2876 participants without an LGE CMR were a mean (SD) age of 71.2 (9.6) years, 43.2% of whom were men, 38.0% were white, 59% were taking antihypertensive medication, 22.4% had diabetes, and they had a mean (SD) Framingham risk score of 16.5% (9.5%) vs the participants with LGE CMR, who were a mean (SD) age of 67.9 (8.8) years (*P* < .001), 52.7% of whom were men (*P* < .001), 45.3% white (*P* < .001), 50% were taking antihypertensive medication (*P* < .001), 16.5% had diabetes (*P* < .001), and they had a Framingham risk score of 15.5% (9.1%) (*P* < .001).

Demographic and clinical characteristics of the 1840 participants who underwent CMR are shown in **Table 1** and **Table 2** and eTable 1 in the Supplement. Compared with participants without CMR myocardial scar at year 10, those with myocardial scar were older, more likely to be male, more

Figure. Study Enrollment and Participation



IV indicates intravenous.

[a] Estimated glomerular filtration rate of 45 mL/min/1.73 m^2.

[b] Recognized myocardial infarction and scars were detected by electrocardiogram or by clinical evaluation. Typical scars, detected by cardiac magnetic resonance (CMR) imaging, involved subendocardium in a coronary artery distribution; atypical scars predominantly affected midwall or subepicardium, usually without subendocardial involvement and in a noncoronary artery distribution.

Table 1. Clinical Characteristics of Participants at Baseline by Presence or Absence of Myocardial Scar at Year 10

	No Scar (n = 1694)	Any Scar (n = 146)	*P* Value[a]
Age, mean (SD), y	58.1 (8.8)	62.5 (9.4)	<.001
Sex, No. (%)			
Women	858 (50.6)	22 (15.1)	<.001
Men	836 (49.4)	124 (84.9)	
Race/ethnicity, No. (%)			
White	758 (44.8)	76 (52.1)	.03
Chinese	165 (9.7)	5 (3.4)	
Black	415 (24.5)	43 (29.5)	
Hispanic	356 (21.0)	22 (15.1)	
Income <$50 000, No. (%)[b]			
No	828 (50.0)	69 (48.9)	.80
Yes	827 (50.0)	72 (51.1)	
BMI, mean (SD)	28.0 (4.9)	28.6 (4.5)	.15
Hypertension, No. (%)[c]			
No	1138 (67.2)	76 (52.1)	.001
Yes	556 (32.8)	70 (48.0)	
Hypertension medication, No. (%)			
No	1236 (73.0)	87 (59.6)	.001
Yes	457 (27.0)	59 (40.4)	
Blood pressure, mean (SD), mm Hg[d]			
Systolic	121.5 (19.1)	128.8 (21.0)	<.001
Diastolic	71.8 (10.1)	76.4 (10.0)	<.001
Cholesterol, mean (SD), mg/dL			
Total	194.4 (35.1)	189.5 (30.9)	.10
HDL	50.6 (14.6)	46.0 (12.4)	<.001
Lipid medication, No. (%)			
No	1443 (85.2)	119 (81.5)	.23
Yes	250 (14.8)	27 (18.5)	
Diabetes, No. (%)			
No	1568 (92.6)	127 (87.0)	.02
Yes	126 (7.4)	19 (13.0)	
Smoking status, No. (%)			
Never	843 (49.9)	62 (42.8)	.02
Former	646 (38.2)	54 (37.2)	
Current	202 (11.9)	29 (20.0)	
GFR, mean (SD), mL/min/1.73 m2	84.0 (15.5)	84.0 (16.3)	.96
Left ventricle, mean (SD)			
Mass, g	145.2 (36.1)	176.2 (42.0)	<.001
End diastolic volume, mL	129.3 (29.9)	139.9 (33.1)	<.001
Stroke volume, mL	88.4 (19.4)	91.5 (22.0)	.07
Ejection fraction, %	68.9 (6.7)	65.8 (7.4)	<.001
Common CIMT, mean (SD), mm	0.7 (0.2)	0.8 (0.2)	<.001
10-y Risk, mean (SD), %			
Framingham global	11.4 (8.4)	18.7 (8.9)	<.001
ACC/AHA	8.6 (8.9)	16.1 (12.2)	<.001
CAC, Agatston units, No. (%)			
0	1006 (59.4)	37 (25.3)	<.001
1-99	420 (24.8)	50 (34.3)	
100-399	179 (10.6)	34 (23.3)	
≥400	89 (5.3)	25 (17.1)	

Abbreviations: ACC/AHA, American College of Cardiology–American Heart Association; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; CAC, coronary artery calcification; CIMT, carotid intima-media thickness; GFR, glomerular filtration rate (Modification Diet in Renal Disease equation); HDL, high-density lipoprotein.

SI conversion factors: To convert cholesterol from mg/dL to mmol/L, multiply by 0.0259.

[a] *P* values from analysis of variance test or χ^2 test as appropriate across myocardial scar group.

[b] Income represents total household annual income.

[c] Defined as systolic blood pressure of 140 mm Hg or higher, diastolic blood pressure of 90 mm Hg or higher, or self-reported use of antihypertensive medications.

[d] Defined by use of hypoglycemic drugs or insulin, or fasting blood glucose of 126 mg/dL or higher (to convert to mmol/L, multiply by 0.0555).

likely to be white, more likely to be hypertensive, had slightly lower cholesterol levels, and had a higher prevalence of current cigarette smoking. The baseline and year 10 demographic and clinical characteristics of the participants with CAC score are shown in eTables 2A and 2B in the Supplement by CAC score categories.

Participants with myocardial scar also had greater common carotid intima-media thickness, higher Framingham risk,

Table 2. Clinical Characteristics of Participants at Year 10 by Presence or Absence of Scar

	No Scar (n = 1694)	Any Scar (n = 146)	*P* Value[a]
Age, mean (SD), y	67.5 (8.7)	71.9 (9.3)	<.001
Sex, No. (%)			
Women	858 (50.6)	22 (15.1)	<.001
Men	836 (49.4)	124 (84.9)	
Race/ethnicity, No. (%)			
White	758 (44.8)	76 (52.1)	.01
Chinese	165 (9.7)	5 (3.4)	
Black	415 (24.5)	43 (29.5)	
Hispanic	356 (21.0)	22 (15.1)	
Income <$50 000, No. (%)[b]			
No	819 (49.7)	67 (47.2)	.56
Yes	829 (50.3)	75 (52.8)	
BMI, mean (SD)	28.4 (5.1)	28.7 (4.8)	.49
Hypertension, No. (%)			
No	791 (46.7)	44 (30.1)	<.001
Yes	903 (53.3)	102 (69.9)	
Hypertension medication, No. (%)[c]			
No	1236 (73.0)	87 (59.6)	.001
Yes	457 (27.0)	59 (40.4)	
Blood pressure, mean (SD), mm Hg			
Systolic	122.0 (19.3)	124.7 (17.9)	.10
Diastolic	68.7 (9.7)	70.1 (9.6)	.10
Cholesterol, mean (SD), mg/dL			
Total	183.5 (36.4)	171.8 (36.9)	<.001
HDL	54.9 (16.3)	51.4 (15.2)	.01
Lipid medication, No. (%)			
No	1061 (62.6)	78 (53.4)	.03
Yes	633 (37.4)	68 (46.6)	
Diabetes, No. (%)[d]			
No	1424 (84.1)	114 (78.1)	.06
Yes	270 (15.9)	32 (21.9)	
Smoking status, No. (%)			
Never	739 (43.8)	50 (34.5)	.003
Former smoker	819 (48.5)	73 (50.3)	
Current smoker	130 (7.7)	22 (15.2)	
GFR, mean (SD), mL/min/1.73 m2	84.8 (18.6)	81.7 (17.2)	.06
Left ventricle, mean (SD)			
Mass, g	123.9 (31.9)	155.7 (37.5)	<.001
End diastolic volume, mL	122.5 (30.4)	138.6 (40.2)	<.001
Stroke volume, mL	75.2 (18.1)	77.0 (21.5)	.25
Ejection fraction, %	61.9 (6.7)	56.6 (9.3)	<.001
Common CIMT, mean (SD), mm	0.8 (0.2)	0.9 (0.2)	<.001
10 y, mean (SD), %			
Framingham global	15.0 (9.0)	21.7 (8.1)	<.001
ACC/AHA	16.4 (15.0)	24.1 (15.4)	<.001
CAC, Agatston units, No. (%)			
0	467 (35.0)	5 (4.7)	<.001
1-99	408 (30.6)	27 (25.2)	
100-399	234 (17.5)	30 (28.0)	
≥400	225 (16.9)	45 (42.1)	

Abbreviations: ACC/AHA, American College of Cardiology–American Heart Association; BMI, body mass index; CAC, coronary artery calcification; CIMT, carotid intima-media thickness; GFR, glomerular filtration rate (Modification Diet in Renal Disease equation); HDL, high-density lipoprotein.

SI conversion factors: To convert cholesterol from mg/dL to mmol/L, multiply by 0.0259.

[a] *P* values from analysis of variance test or χ^2 test as appropriate across myocardial scar group.

[b] Income represents total household annual income.

[c] Defined as systolic blood pressure of ≥140 mm Hg, diastolic blood pressure of ≥90 mm Hg, or self-reported use of antihypertensive medications.

[d] Defined by use of hypoglycemic drugs or insulin, or fasting blood glucose of ≥126 mg/dL (to convert to mmol/L, multiply by 0.0555).

Table 3. Longitudinal Association of CVD Risk Factors at Baseline (n=1840) With the Presence of Myocardial Scar (n=146) at Year 10 After Adjusting for Age and Sex[a]

CVD Risk Factor	Any Myocardial Scar, OR (95% CI)	*P* Value[b]
Age per SD of 8.9 y[c]	1.61 (1.36-1.91)	<.001
Sex[c]		
Women	1 [Reference]	<.001
Men	5.76 (3.61-9.17)	
Race/ethnicity		
White	1 [Reference]	
Chinese	0.31 (0.12-0.78)	.01
Black	1.08 (0.72-1.62)	.73
Hispanic	0.57 (0.34-0.94)	.03
Income > $50 000[d]	0.97 (0.68-1.39)	.87
BMI per SD of 4.8	1.32 (1.09-1.61)	.005
Hypertension[e]		
No	1 [Reference]	.009
Yes	1.61 (1.12-2.30)	
Cholesterol		
Total per SD of 34.8 mg/dL	1.03 (0.86-1.24)	.71
HDL per SD of 14.5 mg/dL	0.93 (0.75-1.15)	.49
Lipid medication		
No	1 [Reference]	.81
Yes	1.06 (0.67-1.67)	.81
Diabetes[f]		
No	1 [Reference]	.13
Yes	1.51 (0.88-2.59)	.13
Smoking status		
Never	1 [Reference]	.21
Former	0.78 (0.52-1.15)	
Current	2.00 (1.22-3.28)	.006
GFR per SD of 15.6 mL/min/1.73m^2	1.06 (0.89-1.27)	.51
Left ventricle		
Mass per SD 37.5 g	1.81 (1.49-2.19)	<.001
End diastolic volume per SD of 30.3 mL	1.24 (1.03-1.49)	.02
Stroke volume per SD of 19.4 mL	1.08 (0.90-1.29)	.40
Ejection fraction per SD of 4.8 %	0.76 (0.64-0.90)	.002
Common CIMT per SD of 0.2	1.24 (1.03-1.50)	.02
Risk[g]		
Framingham global risk per SD of 8.7%	1.48 (1.17-1.86)	.001
ACC/AHA per SD of 9.4%	1.44 (1.18-1.77)	<.001
CAC >0 Agatston units	2.61 (1.73-3.95)	<.001

Abbreviations: ACC/AHA, American College of Cardiology–American Heart Association; BMI, body mass index; CAC, coronary artery calcification; CIMT, carotid intima-media thickness; CVD, cardiovascular disease; GFR, glomerular filtration rate (Modification Diet in Renal Disease equation).

SI conversion factor: To convert cholesterol from mg/dL to mmol/L, multiply by 0.0259.

[a] Separate models, each included 1 CVD risk factor with age and sex.

[b] *P* values from analysis of variance test or χ^2 test across myocardial scar group.

[c] Age is adjusted only for sex, and sex is only adjusted for age.

[d] Income represents total household annual income.

[e] Defined as systolic blood pressure of ≥140 mm Hg, diastolic blood pressure of ≥90 mm Hg, or self-reported use of antihypertensive medications.

[f] Defined as use of hypoglycemic drugs or insulin or fasting blood glucose ≥126 mg/dL (to convert to mmol/L, multiply by 0.0555).

[g] Framingham and ACC/AHA risk scores are not adjusted for age and sex.

ACC/AHA risk, and CAC scores than those without myocardial scar at baseline and at the 10-year follow-up (Table 1 and Table 2).

Prevalence of and Factors Associated With CMR-Defined Myocardial Scar

The overall prevalence of myocardial scar by CMR was 7.9% (146 of 1840) (Figure). The prevalence of previously unrecognized myocardial scar was 6.2% (114 of 1840), whereas 1.7% (32 of 1840) had clinically recognized MI. Thus, 78% (114 of 146) of myocardial scars were unrecognized by clinical or ECG adjudication. Among unrecognized myocardial scars, 38% (43 of 114) were typical and 62% (71 of 114) were atypical scars. Among recognized myocardial scars, 84% (27 of 32) were typical, and 16% were atypical (5 of 32). Men had a higher prevalence of myocardial scar than women (12.9% vs 2.5%, respectively; difference, 10.4%; 95% CI, 8%-13%; *P* < .001).

A total of 1441 participants had LGE CMR and concurrent CAC score. The relative proportions of myocardial scars in the CT cohort were similar to that described above: the prevalence of unrecognized myocardial scar was 5.8% (84 of 1441), whereas 1.6% (23 of 1441) had clinically recognized MI (Figure). Thus, for participants with concurrent LGE CMR and CAC score, 78% (84 of 107) of myocardial scars were unrecognized by clinical adjudication or year 10 ECGs. Only 10 of 107 participants (9.3%) with a scar had evidence of ECG-defined silent MI at year 10.

Table 3 shows minimally adjusted logistic regression models to assess the longitudinal association of individual risk factors at baseline with the presence of myocardial scar at year 10. Older age and male sex were associated with higher odds of having CMR-detected myocardial scar. Also associated with the likelihood of having a myocardial scar were hypertension, higher BMI, and current smoking vs never smokers (Table 3). In a multivariable model including all of these variables, these associations remained significant with slight changes in the magnitude of ORs. Framingham risk score and ACC/AHA risk score were associated positively with myocardial scar (Table 3). Both typical and atypical myocardial scars were associated with age (OR, 1.79; 95 CI, 1.41-2.28 per 8.9 years, *P* < .001) and sex (OR, 1.46; 95% CI, 1.17-1.83 for men; *P* = .001; eTable 3 in the Supplement). Hypertension was significantly associated with typical myocardial scar (OR, 1.66; 95% CI, 1.01-2.74; *P* = .04) but not with atypical myocardial scar (OR, 1.54; 95% CI, 0.95-2.50; *P* = .08; eTable 3 in the Supplement). Calcium score at baseline was associated with typical myocardial scar (OR, 6.05; 95% CI, 2.90-12.61; for CAC >0; *P* < .001) but not atypical myocardial scar (OR, 1.51; 95% CI, 0.90-2.53 for CAC >0; *P* = .12; eTable 3 in the Supplement).

Relationship of CAC Score to Myocardial Scar

Table 4 shows the cross-sectional relationship of CMR-defined myocardial scar and CAC score. The prevalence of myocardial scar increased in relationship to CAC score: 1.1% for scores of 0, 6.2% for scores ranging from 1 through 99, 11.4% for scores ranging from 100 through 399, and 16.7% for scores of 400 or higher, as did the ORs adjusted for age, sex, and race/ethnicity (Table 4). Further stepwise adjustments for CVD risk factors (model 2), left ventricular parameters and BMI (model 3), and

carotid artery intima-media thickness (model 4) did not alter the pattern of association of myocardial scar among CAC score categories but slightly changed the magnitude of ORs (Table 4; receiver operating curve, eFigure 1A in the Supplement).

Table 5 shows the longitudinal relationship of CMR-defined myocardial scar and baseline CAC score. The prevalence of myocardial scar increased in relationship to CAC score: 3.5% for scores of 0, 10.6% for scores ranging from 1 through 99, 11.4% for scores ranging from 100 through 399, and 16.7% for scores of 400 or higher, as did the corresponding ORs adjusted for age, sex, and race/ethnicity(Table 5). Further stepwise adjustments for CVD risk factors (model 2), LV parameters and BMI (model 3), and carotid artery intima-media thickness (model 4) showed similar association of myocardial scar among CAC score categories with slight changes in the magnitude of the ORs (Table 5; receiver operating curve, eFigure 1B in Supplement). The ORs for CAC associations with unrecognized myocardial scars (eTables 4A and 4B in the Supplement) and all myocardial scars (Table 5) were of similar magnitude. CAC score added significantly to the association of myocardial scar over the variables in models 1-3 (*C* statistic, 0.78 vs 0.76, $P = .003$ in model 1; 0.81 vs 0.79 (eFigure 1B in the Supplement), $P = .01$ in model 2; 0.82 vs 0.80, $P = .01$ in model 3, respectively) but not in model 4 (*C* statistic: 0.823 vs 0.81, $P = .08$).

Clinically Adjudicated MI and CMR Scar in Relationship to Cardiovascular Risk and CAC Score

We compared the association of CAC score with CMR-defined scar vs the association of CAC score with clinically adjudicated MI (**Table 6**). In cross-sectional analysis at year 10, age- and sex-adjusted CAC score showed similar association with CMR myocardial scar vs clinically adjudicated MI (OR, 1.28; 95% CI, 1.15-1.42; $P < .001$ vs OR, 1.34; 95% CI, 1.05-1.70; $P = .02$, respectively). Likewise, longitudinally, the CAC score was associated with CMR-detected myocardial scar and clinically adjudicated MI (OR, 1.22; 95% CI, 1.13-1.32; $P < .001$ vs OR, 1.35; 95% CI, 1.14-1.61; $P = .001$, respectively). The addition of Framingham risk score or the ACC/AHA risk score to model with CAC did not substantially change these ORs (Table 6).

Discussion

The most significant long-term outcome of coronary atherosclerosis is MI. In patients who survive MI, normal contractile tissue is replaced by noncontractile fibrosis (scar). Cardiovascular magnetic resonance is considered a standard of reference for defining the presence of myocardial scar. The MESA cohort is ideal to study the long-term sequela of cardiovascular risk factors and coronary atherosclerosis on the myocardium. In this US-based cohort of men and women (mean age, 68 years), the prevalence of CMR-defined myocardial scar was 7.9%; 78% of CMR-identified myocardial scars were unrecognized by clinical adjudication or by ECG. Age- and sex- adjusted calcium score was associated with CMR-defined myocardial scar (OR, 1.2; $P < .001$) without further improvement of the statistical model with the addition of the ACC/AHA or Framingham risk score (OR, 1.21 for ACC/AHA; OR, 1.21 for the Framingham Risk score, $P < .001$ for both).

In MESA, among the 7.9% of study participants with myocardial scars, only 1.7% had clinically recognized MIs, whereas 6.2% had only CMR-detected myocardial scar. The clinical significance of unrecognized myocardial scar remains to be defined, although prior myocardial scar has been noted pathologically in more than 70% of patients with sudden cardiac death but without prior known coronary artery disease.[22] In the ICELAND study[1] involving 936 elderly participants, the prevalence of recognized and unrecognized myocardial scar by CMR (ischemic pattern) was higher than in MESA, at 9.7% and 17%, respectively. Unrecognized myocardial scar in ICELAND was associated with an 8% absolute risk increase in mortality compared with no scar. Of 248 70-year-old participants in the PIVUS study[7] in Uppsala, Sweden, the prevalence of CMR-detected mycoardial scar was 4.4% and the prevalence of unrecognized myocardial scar was 19.8%. The lower prevalence of myocardial scar in MESA compared with the ICELAND and PIVUS studies may be due to differences in the prevalence of cardiovascular risk factors, which were mostly lower in MESA participants, and due to MESA's rigorous exclusion of individuals with baseline cardiovascular disease. Compared with MESA, participants in ICELAND had a higher prevalence of hypertension (67% vs 50%), diabetes (36% vs 17%), and smoking (60% vs 8%). In PIVUS, 73% of participants were hypertensive and 12.5% were diabetic. Moreover, the average age of the ICELAND cohort was 76 years vs 69 years in MESA and 70 years in PIVUS. An additional difference is the multiethnic population composition of MESA compared with the predominant northern European ancestry of both the ICELAND and PIVUS studies.

To our knowledge, this study represents the first US population-based evaluation of myocardial scar by CMR and its relationship with cardiovascular risk factors. The CAC score is an important measure of subclinical atherosclerotic burden and is an independent predictor of coronary heart disease and cardiovascular disease.[23-25] The CAC score has been shown to enhance traditional risk factor–based prediction models[23,26] and individuals with a greater number and degree of risk factors are more likely to have higher CAC scores.[27] In MESA, CAC scores and CVD risk factors were similar between individuals with CMR-defined scars compared with clinically overt MI events. The current study also demonstrates that the CAC score was associated with subclinical myocardial damage.

Of individual risk factors, age, male sex, CAC score, BMI, current smoking, and use of antihypertensive medications at baseline were associated with higher odds of myocardial scar. In addition, Chinese and Hispanic ethnicity had lower odds of myocardial scar than European or African ethnicity. As expected, Framingham and ACC/AHA risk scores were also associated with myocardial scar. On the other hand, established risk factors including serum lipid levels and diabetes showed no significant association with myocardial scar perhaps due to confounding introduced by concurrent medication use. Our results are consistent with previous studies showing age and male sex as risk factors of myocardial scar by CMR. In the ICELAND study,[1] diabetes was also a risk factor for

Table 4. Cross-sectional Association of Coronary Artery Calcification (CAC) Score at Year 10 (n=1441) With the Presence of Myocardial Scar (n=107) at Year 10[a]

	CAC Score													
	0 (n = 472)		1-99 (n = 435)			100-399 (n = 264)			≥400 (n = 270)			Log (CAC+1)		
Models[b]	No. With Scars/ Total[c]	OR (95% CI)	No. With Scars/ Total[c]	OR (95% CI)	*P* Value	No. With Scars/ Total[c]	OR (95% CI)	*P* Value	No. With Scars/ Total[c]	OR (95% CI)	*P* Value	No. With Scars/ Total[c]	OR (95% CI)	*P* Value
1	5/472	1 [Reference]	27/435	4.5 (1.7-11.9)	.003	30/264	7.5 (2.8-20.0)	<.001	45/270	8.4 (3.1-22.7)	<.001	107/1441	1.3 (1.2-1.4)	<.001
2	5/461	1 [Reference]	27/426	4.1 (1.5-10.9)	.005	28/248	6.5 (2.4-17.8)	<.001	44/261	7.1 (2.6-19.7)	<.001	104/1396	1.3 (1.1-1.4)	<.001
3	5/460	1 [Reference]	27/426	4.0 (1.5-10.8)	.007	28/428	6.8 (2.4-19.0)	<.001	44/261	6.4 (2.3-17.9)	<.001	104/1395	1.2 (1.1-1.4)	<.001
4	4/445	1 [Reference]	27/411	4.9 (1.7- 14.8)	.004	27/236	8.5 (2.7-23.9)	<.001	42/247	7.7 (2.5-23.9)	<.001	100/1339	1.3 (1.1-1.4)	<.001

[a] Log (CAC+1): CAC score was log-transformed after adding 1 (due to values of 0 CAC score) for the continuous models: 1, adjusted for age, sex, and race/ethnicity; 2, variables in model 1 plus systolic blood pressure, hypertension medication, total cholesterol, high-density lipoprotein cholesterol, lipid medication, smoking status, diabetes, glomerular filtration rate, and household income more than $50 000; 3, variables in model 2 plus body mass index; and left ventricular mass, end-diastolic volume, and ejection fraction; 4, variables in model 3 plus average of left and right distal mean common carotid artery intima-media thickness.

[b] All adjusted variables were from the year-10, examination 5.

[c] Numerators and denominators include only those participants who have all observed variables.

Table 5. Longitudinal Association of Coronary Artery Calcification (CAC) Score at Baseline (n=1840) With the Presence of Myocardial Scar (n=146) at Year 10

	CAC Score													
	0 (n = 1043)		1-99 (n = 470)			100-399 (n = 213)			≥400 (n = 114)			Log (CAC+1)[b]		
Models[a]	No. With Scars/ Total[c]	OR (95% CI)	No. With Scars/ Total[c]	OR (95% CI)	*P* Value	No. With Scars/ Total[c]	OR (95% CI)	*P* Value	No. With Scars/ Total[c]	OR (95% CI)	*P* Value	No. With Scars/ Total[c]	OR (95% CI)	*P* Value
1	37/1043	1 [Reference]	50/470	2.4 (1.5-3.9)	<.001	34/213	3.0 (1.7-5.1)	<.001	25/114	3.3 (1.7-6.1)	<.001	146/1840	1.2 (1.1-1.3)	<.001
2	36/1010	1 [Reference]	47/460	2.2 (1.4-3.5)	.001	34/209	2.6 (1.5-4.6)	.001	24/112	3.1 (1.6-5.9)	.001	141/1791	1.2 (1.1-1.3)	<.001
3	35/1000	1 [Reference]	47/451	2.2 (1.3-3.6)	.002	34/207	2.5 (1.4-4.5)	.001	24/109	3.2 (1.6-6.2)	.001	140/1767	1.2 (1.1-1.3)	<.001
4	24/766	1 [Reference]	35/335	2.3 (1.3-4.1)	.004	23/156	2.2 (1.1-4.3)	.029	16/82	2.2 (1.0-4.8)	.05	98/1339	1.1 (1.0-1.3)	.009

Abbreviation: OR, odds ratio.

[a] All covariates taken from baseline (examination 1). Model 1 was adjusted for age, sex, and race/ ethnicity; model 2 includes variables in model 1 plus systolic blood pressure, hypertension medication, total cholesterol, high-density lipoprotein cholesterol, lipid medication, smoking status, diabetes, glomerular filtration rate, household income greater than $50 000; model 3 includes variables in model 2 plus body mass index, and left ventricular mass, end-diastolic volume, and ejection fraction; and model 4 includes variables in model 3 plus average of left and right distal mean common carotid artery intima-media thickness.

[b] Log (CAC+1): CAC was log-transformed after adding 1 (due to values of 0 CAC score) for the continuous models.

[c] Numerators and denominators include only those patients who have all observed variables.

Table 6. Association of Coronary Artery Calcification (CAC) Score With the Presence of Myocardial Scar and Clinical Myocardial Infarction at Year 10[a]

	Myocardial Scar by CMR		Clinically Adjudicated Myocardial Infarction	
	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
Covariates at Year 10				
No. of patients	107		20	
Log (CAC+1) at y 10[b]				
Age + sex	1.28 (1.15-1.42)	<.001	1.34 (1.05-1.70)	.02
Age, sex, FRS	1.27 (1.15-1.41)	<.001	1.35 (1.06-1.73)	.02
Age, sex, ACC/AHA	1.28 (1.15-1.42)	<.001	1.36 (1.06-1.73)	.01
Covariates at Baseline				
No. of patients	146		29	
Log (CAC+1) at baseline[b]				
Age + sex	1.22 (1.13-1.32)	<.001	1.35 (1.14-1.61)	.001
Age, sex, FRS	1.21 (1.12-1.31)	<.001	1.35 (1.13-1.60)	.001
Age, sex, ACC/AHA	1.21 (1.12-1.31)	<.001	1.36 (1.14-1.61)	<.001

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association risk score; CMR, cardiac magnetic resonance; FRS, Framingham global cardiovascular disease risk score.

[a] Associations for examination 5 CAC scores include all scars or myocardial infarction events that have both CAC and scar measurements at year 10. Associations for baseline. CAC score include all scars or myocardial infarction events that have both baseline CAC score and year-10 scar measured.

[b] Log (CAC+1): CAC was log-transformed after adding 1 (due to values of 0 CAC score) for the continuous models.

unrecognized MI, perhaps due to a higher prevalence of diabetes in that study than in MESA.

Cardiac magnetic resonance–defined scar has been well-validated in histological studies and is considered a standard of reference in defining the presence and extent of infarction. The ICELAND study showed that participants with unrecognized MI had median CAC scores that were intermediate between those without scar and those with scar and recognized MI, respectively.[1] The PIVUS study found more frequent vascular disease in participants with scar and recognized MI.[28] Christiansen et al[29] reported that 30% of patients with acute chest pain and elevated troponin levels had a previously unrecognized CMR-detected ischemic myocardial scar with no or minimal coronary artery disease at coronary angiography.

In general, CMR-defined scar represents replacement of contractile myocardium by noncontractile, fibrotic tissue but the etiology of myocardial scar is not specific. Myocardial infarction shows late gadolinium enhancement that is subendocardial or transmural in a coronary territory (typical scar). An atypical scar may instead involve the epicardium or midmyocardial wall and does not correspond to any single coronary territory. Atypical myocardial scars are routinely recognized by CMR and are a novel area of investigation.[30] Nonischemic cardiomyopathies, such as hypertrophic cardiomyopathy, sarcoidosis and amyloidosis among others, exhibit atypical myocardial scars, but none of the participants in our study population had CMR or clinical characteristics suggestive of these relatively rare conditions. In MESA, atypical and typical myocardial scar had approximately equal prevalence. Participants with atypical scars were more likely to be older, male, and obese and were less likely to be of Chinese ethnicity (eTable 1 in the Supplement). In addition, unrecognized myocardial scars were more likely to be atypical and recognized myocardial scars were more likely to be typical.

There are several limitations of the current study. The MESA study may not be representative of a general population in the community due to its healthier characteristics. Overall, the MESA cohort had moderate use of antihypertensive (29%) and lipid-lowering medication (15%) at baseline; medication use increased to 51% and 38%, respectively, at year 10. MESA participants who underwent CMR examination had better renal function than the full cohort. Typical and atypical CMR patterns have been defined by animal studies and by patients with clinically overt disease. These scar patterns may represent an oversimplification of scar etiology in asymptomatic individuals and are of unknown clinical significance. Cardiac magnetic resonance is relatively sensitive for detection of myocardial scar, although a minimum scar size of at least 1 g of tissue is generally accepted as the lower limit of detection. The changes in *C* statistics that we observed were also small. The prevalence of myocardial scar is low, resulting in small sample sizes and limited power for comparisons by scar subtype.

Conclusions

The prevalence of myocardial scars in a US community-based multiethnic cohort was 7.9%, of which 78% were unrecognized by electrocardiography or clinical evaluation. Further studies are needed to understand the clinical consequences of these undetected scars.

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