Usefulness of Coronary Artery Calcium to Identify Adults of Sufficiently High Risk for Atherothrombotic Cardiovascular Events to Consider Low-Dose Rivaroxaban Thromboprophylaxis (from MESA)

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Low-dose rivaroxaban was effective in secondary prevention of atherosclerotic cardiovascular disease (ASCVD) in the COMPASS trial. There is no established role, however, for oral anticoagulants in primary prevention. We evaluated whether coronary artery calcium (CAC) scoring identifies a high-risk primary prevention adult population who may benefit from low-dose rivaroxaban to prevent ASCVD events. We modeled expected outcomes of low-dose rivaroxaban in 5,196 Multiethnic Study of Atherosclerosis (MESA) cohort participants not already on antiplatelet or anticoagulant therapy. We applied relative risk ratios from COMPASS to absolute MESA event rates in order to estimate number needed to treat (NNT) to avoid a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, as well as number needed to harm (NNH) to cause 1 hospitalized bleed; with both NNT and NNH stratified by calculated ASCVD risk and by baseline CAC. MESA participants with CAC ≥300 had crude ASCVD event rate of 20 per 1000 patient-years, which is comparable to that observed in the COMPASS control-arm. CAC was independently associated with the composite ASCVD outcome (p <0.001 for trend). However, CAC was not independently associated with adjusted hazard ratio for hospitalized major bleeding. Predicted 5-year NNT (modeled from COMPASS) was 75 in persons with CAC 100-299 and 45 with CAC ≥300 despite NNH values of 252 and 98, respectively. In conclusion, CAC helps to distinguish estimated ASCVD benefit from estimated bleeding harm, thereby identifying very high-risk primary prevention adults without established cardiovascular disease who may derive net-benefit from low-dose rivaroxaban. **(Am J Cardiol 2019;124:1198−1206)**

Myocardial infarction (MI) represents a thrombotic event on the background of unstable atherosclerotic coronary artery plaque. Though most clinical trials have focused on antiplatelet therapy to prevent atherosclerotic cardiovascular disease (ASCVD), the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial suggested a role for low-dose anticoagulants in stable ischemic heart disease.[1] Up to 70% of ST-elevation MIs, however, occur in those without previously identified ASCVD.[2] We propose that the COMPASS secondary prevention strategy could potentially be of benefit in the primary prevention setting if a population of comparable atherosclerotic risk is identified.[3−5] However, achieving clinical benefit in primary prevention centers around appropriate risk stratification, particularly when therapy is associated with potential for harm, such as bleeding on anticoagulant therapy. Coronary Artery Calcium (CAC) scoring provides a window into true atherosclerotic burden and offers refined risk stratification beyond traditional risk calculators.[6−8] Our goal was to determine whether individualized assessment, using both CAC and traditional risk estimation, might identify a high-risk population who are predicted to achieve overall net benefit from low-dose oral antithrombotic therapy as primary ASCVD prevention.

Methods

We modeled the effect of low-dose rivaroxaban in the Multiethnic Study of Atherosclerosis (MESA), a prospective,

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multicenter, multiethnic population free of clinical ASCVD at baseline. The MESA cohort of 6,814 individuals was recruited between July 2000 and September 2002. Full details regarding the MESA study design were published previously.[9] Six US communities were chosen as field centers based on broad ethnic diversity: New York, NY, Baltimore, MD, St. Paul, MN, Chicago, IL, Los Angeles, CA, and Forsyth County, NC. Participants were between ages 45 and 84 at enrollment and self-identified with 1 of 4 ethnic groups: white, black, Hispanic, and Chinese. All provided written informed consent. The institutional review board at all participating institutions approved the study protocol.

Baseline examination included assessment of cardiovascular risk factors. Smoking status and family history of MI or stroke were self-reported. Resting blood pressure was measured as the mean of the last 2 of 3 recordings after a minimum 5 minutes seated using a Dinamap Pro-100 automated oscillometric sphygmomanometer. Blood for laboratory testing was collected and processed at field centers and analyzed at the central MESA laboratory (University of Vermont, Burlington, Vermont). Diabetes mellitus was defined as either self-reported diagnosis, use of hypoglycemic medications, or fasting blood glucose ≥126 mg/dl. Fasting low-density lipoprotein cholesterol level was calculated using the Friedewald equation. Ten-year ASCVD risk was calculated using the Pooled Cohort Equations (PCE).[10] Consistent with previous MESA analyses, Hispanic and Chinese participants were classified as white for the purpose of this calculator.[10]

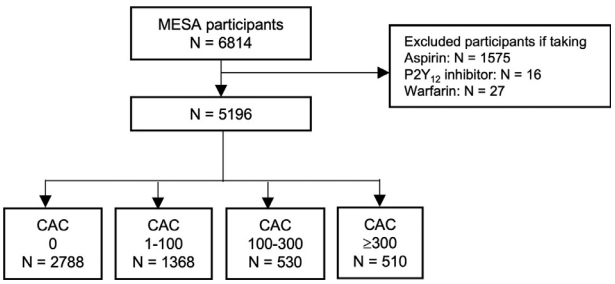

Figure 1. Patient selection from the MESA primary prevention cohort. CAC = coronary artery calcium; MESA = Multiethnic Study in Atherosclerosis.

Cardiac computed tomography (CT) was performed at baseline using either cardiac-gated electron-beam CT scanner (Chicago, Los Angles, New York) or multidetector CT system (Baltimore, Forsyth County, St. Paul, North Carolina). Full protocols for scanning and interpretation have been reported.[11] Images were interpreted at the MESA CT reading center (Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, California). All patients were scanned twice. CAC score was calculated by the Agatston method. The CAC score for each participant was recorded as the mean of both scores, with high intra- and interobserver agreement ($\kappa = 0.93$ and $\kappa = 0.90$, respectively).[6]

Our primary study population was the MESA primary prevention cohort. We excluded those who were prescribed anticoagulant or antiplatelet therapy at baseline (Figure 1). In a sensitivity analysis, we modeled the effect of adding low-dose rivaroxaban to aspirin monotherapy. To do so, we also identified a second exploratory study subsample of MESA participants who were on aspirin monotherapy at study enrollment. To facilitate more direct comparison to COMPASS outcomes, we further limited this second subsample to individuals who met all criteria for inclusion

Table 1
Baseline demographic and clinical characteristics of the primary study population

Variable	Study population (N = 5,196)	CAC 0 (N = 2,788)	CAC 1 to <100 (N = 1,368)	CAC 100 to <300 (N = 530)	CAC ≥300 (N = 510)	p Value
Age (years)	61 ± 10	57 ± 9	63 ± 10	67 ± 9	70 ± 8	<0.001
Men	2337 (45%)	992 (36%)	709 (52%)	296 (56%)	340 (67%)	<0.001
Race/Ethnicity						<0.001
White	1770 (34%)	823 (30%)	478 (35%)	224 (42%)	245 (48%)	
Chinese	682 (13%)	358 (13%)	199 (15%)	79 (15%)	46 (9%)	
African American	1499 (29%)	888 (32%)	372 (27%)	124 (23%)	115 (23%)	
Hispanic	1245 (24%)	719 (26%)	319 (23%)	103 (19%)	104 (20%)	
Diabetes mellitus	589 (11%)	241 (9%)	174 (13%)	83 (16%)	91 (18%)	<0.001
Body mass index (kg/m^2)	28.3 ± 5.6	28.3 ± 5.7	28.2 ± 5.4	28.3 ± 5.7	28.5 ± 5.1	0.82
Systolic blood pressure (mm Hg)	126 ± 21	122 ± 20	128 ± 21	132 ± 22	135 ± 22	<0.001
Antihypertensive medication use	1731 (33%)	737 (26%)	512 (37%)	219 (41%)	263 (52%)	<0.001
Current smoker	714 (14%)	373 (13%)	199 (15%)	73 (14%)	69 (14%)	<0.001
Creatinine (mg/dl)*	0.9 (0.8–1.0)	0.9 (0.8–1.0)	0.9 (0.8–1.1)	0.9 (0.8–1.1)	1.0 (0.9–1.1)	<0.001
Low-density lipoprotein cholesterol (mg/dl)	118 ± 32	117 ± 31	121 ± 33	121 ± 32	118 ± 33	0.001
Lipid-lowering medication use	665 (13%)	246 (9%)	203 (15%)	100 (19%)	116 (23%)	<0.001
High-sensitivity C-reactive protein (mg/dl)*	1.9 (0.8–4.3)	1.9 (0.8–4.4)	2.0 (0.9–4.3)	1.9 (0.9–4.5)	1.9 (0.8–4.1)	0.69
Family history of myocardial infarction	1991 (41%)	960 (36%)	555 (43%)	221 (45%)	255 (55%)	<0.001

Results are stratified by CAC. Categorical variables are summarized as count (percentage). Continuous variables are summarized as mean (±standard deviation) or median (interquartile range). *CAC = Coronary Artery Calcium.

* Depending on the normality of the data.

in the COMPASS trial with the exception of established atherosclerotic disease, given MESA is a primary prevention study (Supplemental Figure 1). Specifically, we included participants on aspirin monotherapy who also met any of the following criteria: (1) age ≥65 with 1 additional risk factor: CAC >0, carotid intimal medial thickness greater than population median, or ankle-brachial index ≤0.9 or ≥1.4; (2) age <65 and any 2 additional risk factors listed above; or (3) age <65 and 1 additional risk factor listed above, plus any of the following co-morbid conditions: current smoking, diabetes mellitus, or estimated GFR (eGFR) <60 ml/min per 1.73 m^2. Individuals with recent stroke or any history of hemorrhagic or lacunar stroke, severe heart failure (ejection fraction <30% or New York Heart Association class III or IV symptoms), evidence of liver dysfunction, or advanced stable kidney disease (eGFR <15 ml/min) were excluded from this subsample in accordance with COMPASS eligibility.[1]

Incidences of ASCVD events in MESA were documented at intervals of 9 to 12 months. Trained personnel called each subject or a family member to inquire about interim hospital admissions, outpatient diagnoses of ASCVD, and deaths. 92% of living participants completed telephone interviews. Medical records were successfully collected for 98% of hospital admissions and for 95% of reported outpatient ASCVD encounters. Two members of the MESA mortality and morbidity review committee independently reviewed each reported event with adjudication by the full committee in the event of disagreement.

To align with the primary COMPASS outcome, we defined ASCVD as a composite of cardiovascular death, nonfatal MI, or nonfatal stroke. To capture bleeding events, medical records of participants were searched for ICD-9 and ICD-10 codes indicative of fatal bleed or hospitalization for bleeding event (Supplemental Table 1).[12,13] Additional details about MESA follow-up methods and event reporting are available at http://www.mesa-nhlbi.org.

Count and percentage were calculated for categorical variables. For continuous variables, either mean ± standard deviation or median ± interquartile range was determined in the case of normal or non-normal distributions, respectively. Continuous variables were compared using analysis of variance or Kruskal Wallis test as appropriate. Categorical variables were compared using the chi-squared test. Study participants were stratified based on CAC score, with subgroups delineated at CAC 0, CAC 1 to <100, CAC 100 to <300, and CAC ≥300.[6] We further stratified our analytic sample based on calculated 10-year ASCVD risk using the PCE into 3 groups: those with 10-year estimated risk <10%, 10% to ≤20%, and ≥20%.

Table 2
Composite atherosclerotic cardiovascular disease outcomes and hospitalized major bleeding events in the Multiethnic Study in Atherosclerosis study population

CAC	n (%)	ASCVD event		Major bleeding event	
		Event rate	HR (95% CI)*	Event rate	HR (95% CI)*
Overall study population (N = 5,196)					
0	2788 (54%)	2.7	1 (ref)	1.8	1 (ref)
1 to <100	1368 (26%)	7.7	1.8 (1.29,2.43)	3.3	1.4 (0.91,2.02)
100 to <300	530 (10%)	14.5	2.7 (1.88,3.86)	3.6	1.2 (0.70,2.08)
≥300	510 (10%)	20.1	2.9 (2.03,4.25)	5.4	1.5 (0.88,2.56)
p-value	–	<0.001	<0.001	<0.001	0.16
ASCVD <10% (N = 2,908)					
0	2047 (70%)	1.3	1 (ref)	1.3	1 (ref)
1 to <100	634 (22%)	3.0	1.7 (0.91,3.04)	2.0	1.2 (0.64,2.22)
100 to <300	143 (5%)	8.1	3.9 (1.89,8.15)	3.8	1.9 (0.77,4.79)
≥300	84 (3%)	7.2	3.3 (1.28,8.48)	0.9	0.5 (0.06,3.74)
p value	–		<0.001	0.048	0.64
ASCVD 10-20% (N = 1,159)					
0	451 (39%)	6.6	1 (ref)	2.5	1 (ref)
1 to <100	393 (34%)	9.8	1.5 (0.89,2.46)	3.9	1.6 (0.74,3.31)
100 to <300	174 (15%)	11.4	2.0 (1.05,3.72)	1.0	0.5 (0.10,2.05)
≥300	141 (12%)	18.8	2.3 (1.19,4.39)	2.6	0.9 (0.24,3.55)
p value	–	0.001	0.01	0.21	0.65
ASCVD ≥20% (N = 1,129)					
0	290 (26%)	8.1	1 (ref)	4.4	1 (ref)
1 to <100	341 (30%)	15.5	1.7 (0.97,2.97)	5.6	1.4 (0.65,3.03)
100 to <300	213 (19%)	22.2	2.7 (1.50,4.72)	5.8	1.5 (0.62,3.42)
≥300	285 (25%)	25.4	3.2 (1.83,5.53)	8.6	2.0 (0.90,4.24)
p value	–	<0.001	<0.001	0.18	0.09

Results are reported for the primary study population (not on aspirin or anticoagulant at baseline). Results are stratified by CAC and 10-year ASCVD risk calculated by the Pooled Cohort Equations. Outcomes are expressed as event rates (per 1000 person-years) and hazard ratios (95% CI).

ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; HR = hazard ratio; MESA = Multiethnic Study in Atherosclerosis.

* Model is adjusted for age, sex, body mass index, race/ethnicity, education, MESA site, diabetes status, baseline systolic blood pressure, antihypertensive therapy use, tobacco use, creatinine, baseline low-density lipoprotein cholesterol, lipid-lowering medication, high-sensitivity C-reactive protein, and family history of myocardial infarction.

Absolute 2-year composite ASCVD outcome and major bleeding event rates were calculated for comparison to the COMPASS population event rates. Cox regression modeling was used to obtain multivariable-adjusted hazard ratios for the composite ASCVD outcome in each group with further determination of Kaplan-Meier estimates of cumulative event-free survival in each group. Models were adjusted for age, sex, body mass index, race/ethnicity, MESA site, presence of diabetes mellitus, baseline systolic blood pressure, antihypertensive therapy, smoking status, creatinine, baseline low-density lipoprotein cholesterol, lipid-lowering medication, high-sensitivity C-reactive protein, and family history of MI or stroke.

The number-needed-to-treat (NNT) to prevent 1 ASCVD outcome at 5 years was calculated according to the Bland-Altman method using survival probability of ASCVD at 5 years in each MESA subgroup and expected relative risk reduction for ASCVD.[14] Expected relative risk reduction was extrapolated from the independent effect of low-dose rivaroxaban in the COMPASS trial: 24%.[1] We also reported NNT at 2 years to align with the COMPASS trial duration. Using the same methods, we performed sensitivity analyses in the COMPASS-eligible subsample.

Within each risk subgroup, we used identical methods to those used for NNT to determine number-needed-to-harm (NNH) for 1 hospitalized major bleeding event. We extrapolated absolute risk increase by multiplying the observed absolute risk for bleeding within each subgroup by the relative risk increase for major bleeding attributable to the addition of low-dose rivaroxaban reported in COMPASS: 70%.[1] We then used the same method to calculate net clinical benefit within each risk subgroup, defined as the avoidance of composite ASCVD outcome or hospitalized major bleeding event. This number was derived from absolute baseline ischemic and bleeding risks and relative change in net clinical benefit with addition of rivaroxaban therapy in the COMPASS trial: 20%.[1]

Results

Baseline characteristics of the overall MESA study sample are displayed in Table 1. There was a crude association between higher CAC scores and other known co-morbid ASCVD risk factors: older age, male sex, white race, need for antihypertensive or lipid-lowering medications, and family history of MI ($p < 0.001$ for each).

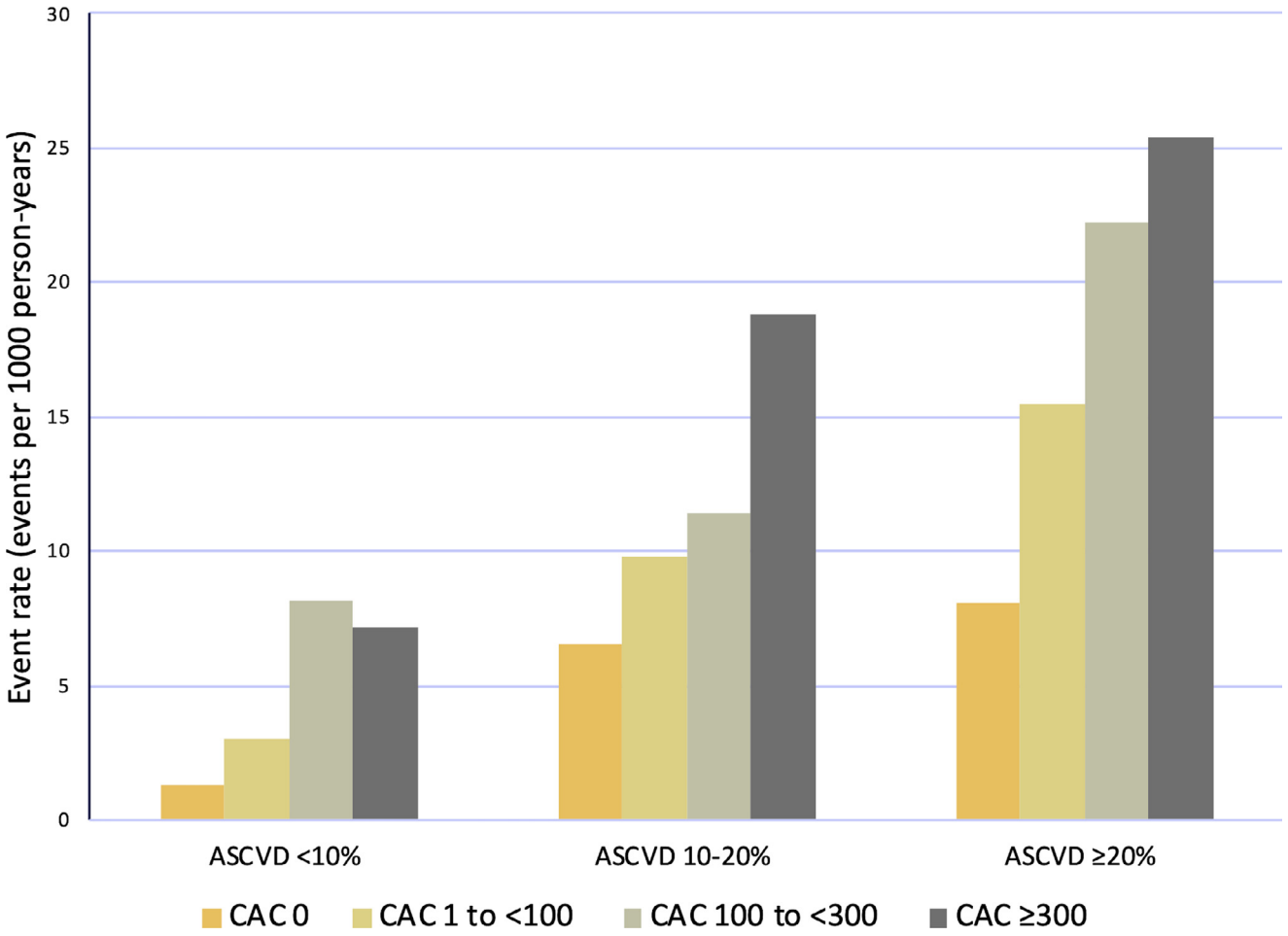

Figure 2. Event rate for the composite ASCVD outcome in MESA participants, stratified by ASCVD risk prediction score by PCE and further stratified by CAC. ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; MESA = Multiethnic Study in Atherosclerosis; PCE= pooled cohort equations.

In our primary study sample, CAC score was independently associated with observed ASCVD events (Table 2). The composite ischemic outcome occurred at a rate of 20.1 events/1000 person-years with CAC ≥300, compared with 2.7/1000 person-years with CAC 0, resulting in a nearly 3-fold adjusted hazard ratio in the highest CAC subset. Within each PCE-estimated ASCVD risk subgroup, CAC provided further risk information (Figure 2). For example, in the MESA subgroup with estimated ASCVD risk of ≥20% but CAC 0, ischemic events were less frequent than would have been predicted, compared with the substantial ASCVD event rate in the subgroup with calculated risk ≥20% and CAC ≥300.

Table 3 demonstrates the 2-year and 5-year NNT predicted by our modeling to prevent 1 composite ASCVD event if low-dose rivaroxaban were used as antithrombotic therapy in the MESA population. Higher CAC was correlated with lower 5-year NNT to prevent the composite ischemic outcome of cardiovascular death, nonfatal MI, or nonfatal stroke. Notably, estimated 5-year NNT to avoid 1 ASCVD event reached 75 with CAC 100 to <300 and 45 with CAC ≥300.

Although higher CAC was associated with hospitalized major bleeding in crude analyses, after adjustment there was no independent association between CAC level and the bleeding outcome (Table 2). When modeling the effect of low-dose rivaroxaban therapy, higher CAC was also correlated with estimated 5-year NNH (an unadjusted parameter) for bleeding risk (Table 3). However, at higher CAC score strata, there was a greater relative gain in estimated ischemic benefit compared to concurrent excess bleeding risk for low-dose rivaroxaban. Indeed, when considering the ratio between estimated NNT and NNH at each CAC level, the ischemic benefit and hemorrhagic risk were essentially equivalent with CAC 0, compared with a 2-3-fold ratio of higher predicted NNH compared to NNT with CAC ≥100. Risk stratification by CAC led to greater separation of observed risk curves in the high-risk subset when compared with risk stratification by PCE (Figure 3).

Using the relative risk reduction of 20% for net-clinical-benefit achieved by addition of low-dose rivaroxaban therapy in the COMPASS trial, the greatest 2-year and 5-year net benefit in the MESA population was predicted in those with CAC ≥100 (Table 4). Estimated 5-year net benefit reached 85 with CAC 100 to <300 and 49 with CAC ≥300.

In a sensitivity analysis, CAC score also predicted observed event rate for the primary ischemic outcome in the second MESA subsample analyzed who were prescribed aspirin for primary prevention and who meet the modified COMPASS eligibility criteria (Table 5). There were 19.8 events/1000 person-years with CAC ≥300 compared with

Table 3
Estimated number needed to treat for composite atherosclerotic cardiovascular disease outcome and number needed to harm for hospitalized major bleeding event with very low dose rivaroxaban as primary prevention in Multiethnic Study in Atherosclerosis participants

CAC	Estimated 5-year NNT	Estimated 5-year NNH	Estimated 2-year NNT	Estimated 2-year NNH
Overall study population (N = 5,196)				
0	387	388	1,043	1,356
1 to <100	118	170	370	470
100 to <300	75	252	219	643
≥300	45	98	84	174
ASCVD <10% (N = 2,908)				
0	1,390	610	8,335	2,440
1 to <100	317	298	870	763
100 to <300	119	172	198	349
≥300	87	–	117	–
ASCVD 10%-20% (N = 1,159)				
0	180	263	614	1,109
1 to <100	79	117	229	317
100 to <300	89	–	240	–
≥300	63	326	143	326
ASCVD ≥20% (N = 1,129)				
0	88	136	168	354
1 to <100	74	131	272	414
100 to <300	55	169	220	509
≥300	35	60	65	114

Results are stratified by baseline CAC and further stratified by 10-year ASCVD risk calculated using the Pooled Cohort Equations. Calculations were based on baseline absolute ASCVD risk and bleeding risk and relative risk derived from the COMPASS trial outcome. Participants in the primary analysis were not on aspirin or anticoagulants at baseline.

ASCVD = Atherosclerotic Cardiovascular Disease; CAC = Coronary Artery Calcium; NNH = number needed to harm; NNT = number needed to treat.

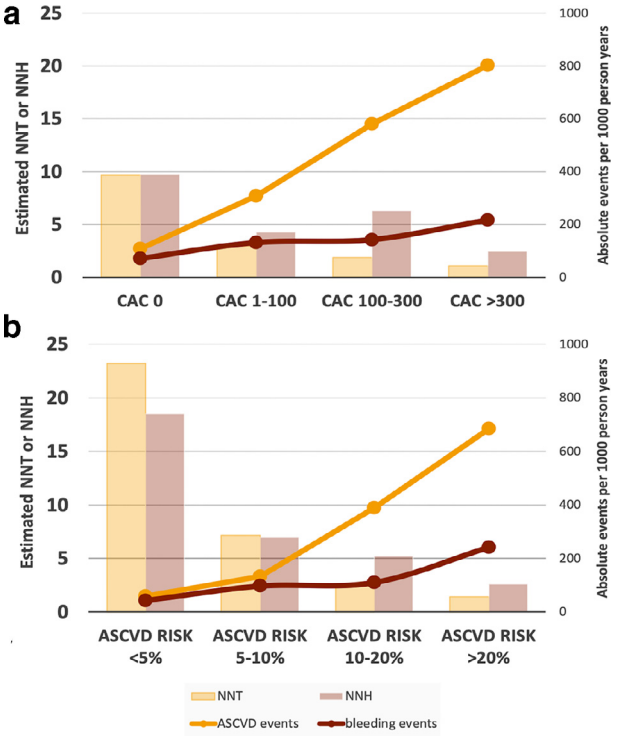

Figure 3. Comparison between event rate for composite ASCVD outcome and event rate for hospitalized major bleeding event (*right axis*) in MESA participants and comparison between predicted 5-year NNT to prevent 1 ischemic event and 5-year NNH to cause 1 bleeding event with rivaroxaban (*left axis*), stratified by (*A*) baseline CAC and (*B*) ASCVD risk prediction score by PCE. ASCVD = atherosclerotic cardiovascular disease; CAC = Coronary Artery Calcium; MESA = Multiethnic Study in Atherosclerosis; NNH = number needed to harm; NNT = number needed to treat; PCE = pooled cohort equations.

Table 4
Estimated net clinical benefit with use of very low dose rivaroxaban as primary prevention in Multiethnic Study in Atherosclerosis participants

CAC	Estimated 5-year NCB	Estimated 2-year NCB
Overall study population (N = 5,196)		
0	338	1,066
1 to <100	114	354
100 to <300	85	262
≥300	49	97
ASCVD <10% (N = 2,908)		
0	835	3,335
1 to <100	278	783
100 to <300	103	179
≥300	138	210
ASCVD 10-20% (N = 1,159)		
0	167	737
1 to <100	76	241
100 to <300	106	288
≥300	69	138
ASCVD ≥20% (N = 1,129)		
0	92	203
1 to <100	74	236
100 to <300	66	349
≥300	37	75

Results are stratified by baseline CAC and further stratified by 10-year ASCVD risk calculated by the Pooled Cohort Equations. Net clinical benefit is defined as the avoidance of composite ASCVD outcome or hospitalized major bleeding event; number is derived from absolute baseline ischemic and bleeding risks and relative change in net clinical benefit with addition of rivaroxaban therapy in the COMPASS trial. Participants in the primary analysis were not on aspirin or anticoagulants at baseline.

ASCVD = Atherosclerotic Cardiovascular Disease; CAC = Coronary Artery Calcium; NCB = net clinical benefit.

4.8 events/1000 person-years with CAC 0. The use of both CAC and PCE risk stratification provided further differentiation of observed risk in this subsample just as in the primary study group. Similar to the primary study sample, 5-year NNT and 5-year NNH predicted by our modeling for the addition of low-dose rivaroxaban were each progressively lower at higher CAC. A more favorable NNH:NNT ratio was also predicted at higher CAC, as described above, with estimated NNH:NNT ratio of 2 to 2.5 for those with nonzero CAC.

Discussion

Using outcome rates observed in the primary prevention MESA cohort and then modeling the potential effect of low-dose rivaroxaban therapy, we demonstrate that combined risk stratification using CAC and PCE can identify a subpopulation at sufficiently high ASCVD risk to consider further investigation of low-dose thromboprophylaxis as primary prevention.

Modeling outcome data from MESA participants with CAC ≥100 and an expected 24% ASCVD relative risk reduction extrapolated from the COMPASS trial, we estimate that treating <75 high-risk individuals (e.g., those with CAC ≥100 and calculated ASCVD risk ≥10%) with low-dose antithrombotic therapy for 5 years would prevent 1 ischemic event. In the highest CAC category (score ≥300), estimated NNT-5 reached as low as 45 with a favorable ratio of benefit compared with attributable hospitalized major bleeding events.

Event rates in MESA participants either with CAC ≥300 (irrespective of ASCVD risk level) or with both CAC ≥100 and ASCVD risk ≥10%, approached those observed in the COMPASS control group (5.4% over mean 23 months of follow up, equivalent to 28.4 events/1000 person-years). Consequently, the estimated 2-year NNT of 84 to prevent ischemic event with addition of low-dose rivaroxaban in participants with CAC ≥300 is comparable to the 2-year NNT for the addition of low-dose rivaroxaban to aspirin in the COMPASS secondary prevention population: 76.9.[1]

A noteworthy finding of our analysis was that the margin of modeled ASCVD benefit to modeled bleeding harm with low-dose rivaroxaban improved in higher CAC groups. Furthermore, CAC was not independently associated with major bleeding. Therefore, CAC appeared superior to the PCE in identifying those more likely to benefit from low-dose rivaroxaban than to experience harm in the form of major bleeding. A potential explanation is that age is a key driver of risk in the PCE, a factor also associated with increased incidence and morbidity of bleeding events.[15] Though age-based modeling is outside the scope of this study, further refining traditional scores by measuring subclinical disease (i.e., CAC) may identify a population most likely to gain net benefit from interventions with bleeding risk.

Table 5
Estimated number needed to treat for composite atherosclerotic cardiovascular disease outcome and number needed to harm for hospitalized major bleeding event with the addition of very low dose rivaroxaban to aspirin monotherapy in the subpopulation of Multiethnic Study in Atherosclerosis participants prescribed aspirin at baseline and meeting modified COMPASS trial eligibility criteria

CAC	n	Event rate	HR (95% CI)*	Estimated 5-year NNT	Estimated 5-year NNH	Estimated 2-year NNT	Estimated 2-year NNH
0	223	4.8	1 (ref)	459	176	928	543
1 to <100	350	6.9	1.2 (0.57,2.66)	103	207	161	842
100 to <300	197	15.6	2.3 (1.09,5.00)	62	153	270	461
≥300	286	19.8	2.5 (1.17,5.17)	56	107	163	678
p value		<0.001	0.003				

Results are stratified by baseline CAC.

ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; HR = hazard ratio; NNH = number needed to harm; NNT = number needed to treat.

* See footnote to Table 2 for adjustment variables included in model.

Currently, antithrombotic therapy does not have a widely established clinical role for either primary or secondary prevention, with early secondary prevention trials limited by high rates of major bleeding with use of either full-dose anticoagulants or low-dose anticoagulants added to dual antiplatelet therapy.[16−19] The COMPASS trial used low-dose rivaroxaban added to low dose aspirin in an effort to more appropriately balance competing ischemic and hemorrhagic outcomes.[1] This lower-dose strategy has, in fact, been previously evaluated in those without established heart disease. In the Thrombosis Prevention Trial, combined aspirin and low dose warfarin (mean INR 1.47) led to a 34% reduction in ischemic events compared with placebo, with a 21% relative risk reduction attributed to warfarin in the factorial design, similar to the 24% risk reduction observed with addition of warfarin to aspirin monotherapy in COMPASS.[20] However, high absolute bleeding risk was felt to be unacceptable in the Thrombosis Prevention Trial in the setting of lower baseline event rates.

The utility of CAC for allocating preventive thereapies based on refined ASCVD risk stratification has been previously established.[21−23] Our results add to this evidence by showing that CAC appears useful for identifying those with the highest ASCVD event rates but who do not also have excessively high bleeding rates—thereby potentially enabling the identification of persons who have more to gain from low-dose rivaroxaban than have to lose in terms of absolute bleeding risk. Furthermore, CAC may also identify persons at lower risk for bleeding on low-dose rivaroxaban than the typical NNH reported for aspirin in primary prevention. The estimated NNH-2 to cause a major bleed in the high-risk subgroups of our MESA analysis (e.g., CAC $\geq$100 and calculated ASCVD risk $\geq$10%) ranged from 114 to 509. For indirect comparison, in a decision analysis study for the US Preventive Services Task Force, the NNH to cause 1 nonfatal gastrointestinal bleed or intracranial hemorrhage for individuals recommended aspirin therapy ranged from as low as 32 to 47.[24]

If the clinical benefit predicted by our modeling data is confirmed in a trial setting, low-dose rivaroxaban may find a role in primary prevention of ASCVD events in those felt to be at very high risk (defined using CAC quantification) despite addressing other risk factors. The newest American College of Cardiology/American Heart Association prevention guidelines feature stepwise risk stratification to determine statin eligibility.[25] It may be possible that, using traditional atherosclerotic and bleeding risk profiles in combination with CAC, those estimated to have very high ASCVD risk with favorable risk: benefit ratio will in the future be recommended low-dose rivaroxaban in addition to statin for primary prevention.

Limitations

We assumed relative risk reduction from therapeutic intervention (in this case low-dose rivaroxaban) to be preserved across the categories of baseline CAC. Nonetheless, it is well-established that relative risk is stable across different categories of baseline absolute risk,[14,26] and previous studies in MESA using this assumption have demonstrated that CAC may inform NNT estimation for primary prevention therapies.[21−23] Furthermore, COMPASS subgroup analyses revealed that relative risk reduction achieved with rivaroxaban was consistent across demographic subgroups, irrespective of baseline risk.[1,27,28] Nonetheless, the next logical step after this hypothesis-generating study is design of a controlled clinical trial evaluating the effect of low-dose antithrombotic therapy as primary prevention among very high risk individuals.

Our relative risks were derived from the relative risks associated with addition of rivaroxaban to aspirin monotherapy. We interpreted this as the additional benefit gained exclusively from the rivaroxaban component of combined therapy, though we cannot exclude the possibility of effect modification.

As MESA was designed to capture ASCVD events, major bleeding events were not adjudicated. Therefore, potential exists for incomplete recording of bleeding events, which would overestimate net benefit of intervention. However, use of ICD codes to track bleeding on anticoagulant therapy has been shown to have high negative predictive value at the expense of potential over-reporting.[12,13] Indeed, our rate of 4.7 events/1000 person-years is slightly higher than rates in other primary prevention trial control groups (aspirin trials).[29,30]

Conclusion

In individuals without known ASCVD, assessment of subclinical atherosclerosis using CAC, in combination with traditional risk estimation, identified a high-risk population who may gain net benefit from low-dose oral antithrombotic therapy in the primary prevention setting. This study contributes evidence suggesting that, as investigation into the role of preventive antithrombotic therapy progresses, the high-risk primary preventive population should be given consideration for study, in addition to those with known previous atherosclerotic events.

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Disclosures

The authors state that there are no relevant financial relationships to disclose.

Supplementary materials

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