JACC: CARDIOVASCULAR IMAGING VOL. ■, NO. ■, 2020

PUBLISHED BY ELSEVIER

CLINICAL RESEARCH

# Coronary Artery Calcium to Improve the Efficiency of Randomized Controlled Trials in Primary Cardiovascular Prevention

Miguel Cainzos-Achirica, MD, MPH, PHD,[a,b,c] Marcio Sommer Bittencourt, MD, MPH, PHD,[d] Albert D. Osei, MD, MPH,[c] Waqas Haque, MPHIL, MPH,[c] Deepak L. Bhatt, MD,[e] Roger S. Blumenthal, MD,[c] Ron Blankstein, MD,[e] Kausik K. Ray, MD, MPHIL,[f] Michael J. Blaha, MD, MPH,[c,g,h,*] Khurram Nasir, MD, MPH, MSc[a,b,c,*]

## ABSTRACT

**OBJECTIVES** This study sought to assess the value, in terms of sample size and cost, of using the coronary artery calcium (CAC) score to enrich the study population of primary prevention randomized controlled trials (RCTs) with participants at high absolute risk of atherosclerotic cardiovascular disease (ASCVD) events.

**BACKGROUND** The feasibility of RCTs assessing the efficacy of novel add-on therapies for primary prevention among high-risk individuals treated with statins may be limited by sample size and cost.

**METHODS** We evaluated 3,075 statin-naive participants from the Multi-Ethnic Study of Atherosclerosis with estimated 10-year ASCVD risk of ≥7.5%. CAC of >100, CAC of >400, high sensitivity C-reactive protein levels of >2 and >3 mg/l, ankle-brachial index of <0.9, and triglyceride levels of >175 mg/dl were each evaluated as enrichment criteria on top of estimated ASCVD risk of ≥7.5%, ≥10%, ≥15% and ≥20%. For each criterion, using the observed 5-year incidence of CVD, we projected the incidence of CVD assuming a 28% relative risk reduction with high-intensity statin therapy and after addition of novel therapy with additive relative risk reductions of 15% and 25%. Sample size and cost of a hypothetical primary prevention 5-year RCT of a novel therapy on top of statins versus statins alone were then computed by using the projected incidences. Yearly costs per included participant of $6,000 to $9,000 and of $500/$600 per screened nonparticipant were assumed.

**RESULTS** CAC of >400, present in 15% to 23% participants, consistently identified the subgroups with highest 5-year incident events and outperformed the other features yielding the smallest projected sample size, ranging 33% to 58% lower than using risk estimations alone for participant selection. CAC of >400 also yielded the lowest projected RCT costs, at least $40 million lower than using risk estimations alone. CAC of >100 showed the second-best performance in most scenarios.

**CONCLUSIONS** High CAC scores used as study entry criteria can improve the efficiency and feasibility of primary prevention RCTs evaluating the incremental efficacy of novel add-on therapies. (J Am Coll Cardiol Img 2020;■:■-■)
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From the [a]Division of Cardiovascular Prevention and Wellness, Department of Cardiology, Houston Methodist DeBakey Heart & Vascular Center, Houston, Texas; [b]Center for Outcomes Research, Houston Methodist, Houston, Texas; [c]Johns Hopkins Ciccarone Center for the Prevention of Cardiovascular Disease, Johns Hopkins University School of Medicine, Baltimore, Maryland; [d]Center for Clinical and Epidemiological Research, University Hospital, University of São Paulo, São Paulo, Brazil; [e]Division of Cardiovascular Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; [f]Imperial Centre for Cardiovascular Disease Prevention, Department of Primary Care and Public Health, Imperial College London,

ISSN 1936-878X/$36.00 https://doi.org/10.1016/j.jcmg.2020.10.016

**ABBREVIATIONS AND ACRONYMS**

**ABI** = ankle-brachial index

**ASCVD** = atherosclerotic cardiovascular disease events

**CAC** = coronary artery calcium

**hsCRP** = high sensitivity C-reactive protein

**CVD** = cardiovascular disease

**FDA** = U.S. Food and Drug Administration

**MESA** = Multi-Ethnic Study of Atherosclerosis

**NNS** = number needed to screen

**PCSK9i** = proprotein convertase subtilisin/kexin type 9 inhibitor(s)

**RCT** = randomized controlled trial

**RRR** = relative risk reduction

Significant interest currently exists for exploring the potential value of novel therapies such as proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) (1) or icosapent ethyl (2) for primary prevention of cardiovascular disease (CVD) among individuals free of established disease but at high risk of events. However, designing an appropriate randomized controlled trial (RCT) is challenging, because overall event rates in primary prevention cohorts are relatively low, and there is marked risk heterogeneity, even among those estimated to be at highest risk (3). These challenges are further compounded by the fact that novel therapies are tested on top of the current standard of care (i.e., statins), which confers significant reduction in risk (4,5), thus requiring a large sample size to detect any potential benefit.

Considering the shifting health care system focus on value (6), even when considering therapies that have a beneficial outcome, an unfavorably small absolute risk reduction and, thus, a high number needed to treat would prevent their adoption in primary prevention populations. Identifying appropriate high-risk populations to be included in future trials may facilitate evidence generation and allocation of novel add-on therapies to patients likely to derive benefit. Addressing these issues, the U.S. Food and Drug Administration (FDA) has encouraged personalized strategies to recruit in RCTs for emerging therapies the study populations most likely to benefit. Recommendations include decreasing heterogeneity by excluding individuals less likely to have the disease or event studied, and predictive enrichment with high-risk participants (7).

The coronary artery calcium (CAC) score is a guideline-recommended tool for risk refinement among borderline/intermediate risk individuals in primary prevention settings (8–10). A high CAC score is associated with an almost 10-fold higher risk of adverse CVD events as compared to a CAC of 0, which in asymptomatic adults indicates very low risk of future cardiovascular events (3,11–16). However, the ability of CAC to guide patient selection for primary prevention RCTs of novel add-on therapies is unknown.

The aim of the present study was to evaluate the implications, in terms of sample size and trial cost, of using a CAC-based study entry enrichment strategy in a hypothetical primary prevention RCT of a novel add-on therapy on top of statins. For reference, these calculations were also computed for other guideline-endorsed tests (8–10).

## METHODS

**SETTING.** We used data from the Multi-Ethnic Study of Atherosclerosis (MESA), an ongoing, community-based, prospective cohort study of 6,814 men and women of 4 races/ethnicities recruited in 6 U.S. sites (17). Participants were 45 to 84 years of age and free of overt CVD at baseline. Recruitment and initial assessment took place between the years 2000 and 2002. All participants provided written informed consent at study entry, and the protocol was approved by the local ethics committees of each of the 6 sites. Further details on the MESA study methods have been described elsewhere (11,12,15–18).

**STUDY POPULATION.** For the present analysis, all MESA participants who had baseline data on CAC and information on incident events during follow-up were considered for inclusion. To be able to model the effect of background therapy with high-intensity statins in the study population, participants using statins at baseline (approximately 15%) were excluded. We estimated 10-year atherosclerotic CVD (ASCVD) risk in each participant using the pooled cohort equations (8,9), and participants with missing data on any of the risk factors included in the pooled cohort equations were also excluded.

**BASELINE EVALUATION.** Information on sociodemographic factors, medical history, tobacco use, and medication use was collected at baseline with questionnaires (17). Blood samples were drawn from all participants after a 12-hour fast, and levels of triglycerides and high-sensitivity C-reactive protein (hsCRP) were measured in a central laboratory (University of Vermont, Burlington, Vermont), among

London, England; [g]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland; and the [h]Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins University, Baltimore, Maryland. *Drs. Blaha and Nasir contributed equally to this work. Todd Villines, MD, served as Guest Editor for this paper.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Cardiovascular Imaging* author instructions page.

Manuscript received August 17, 2020; revised manuscript received October 8, 2020, accepted October 14, 2020.

**TABLE 1 Baseline Characteristics of the Study Participants**

| | | 10-Year Estimated ASCVD Risk, %* | | | | |
|---|---|---|---|---|---|---|
| | Overall (5,777 [100.0]) | <7.5 (2,702 [46.8]) | 7.5-10 (521 [9.0]) | 10-15 (797 [13.8]) | 15-20 (533 [9.2]) | ≥20 (1,224 [21.2]) |
| Age, yrs | 61.5 ± 10.3 | 53.9 ± 6.4 | 60.9 ± 6.6 | 64.4 ± 7.2 | 68.6 ± 6.5 | 73.5 ± 6.6 |
| Women | 3,049 (52.8) | 1,808 (66.9) | 237 (45.5) | 337 (42.3) | 220 (41.3) | 447 (36.5) |
| Race/ethnicity | | | | | | |
| Non-Hispanic White | 2,173 (37.6) | 1,100 (40.7) | 179 (34.4) | 263 (33.0) | 196 (36.8) | 435 (35.5) |
| African American | 1,590 (27.5) | 593 (22.0) | 175 (33.6) | 291 (36.5) | 194 (36.4) | 337 (27.5) |
| Hispanic | 1,315 (22.8) | 648 (24.0) | 117 (22.5) | 155 (19.5) | 91 (17.1) | 304 (24.8) |
| Chinese American | 699 (12.1) | 361 (13.4) | 50 (9.6) | 88 (11.0) | 52 (9.8) | 148 (12.1) |
| Education (n = 5,690) | | | | | | |
| Less than college | 2,950 (51.9) | 1,217 (45.6) | 264 (51.3) | 423 (54.1) | 302 (56.9) | 744 (62.5) |
| Technical school/associate's degree | 707 (12.4) | 369 (13.8) | 65 (12.6) | 91 (11.6) | 58 (10.9) | 124 (10.4) |
| Bachelor's degree or greater | 2,033 (35.7) | 1,085 (40.6) | 186 (36.1) | 268 (34.3) | 171 (32.2) | 323 (27.1) |
| Family history of CHD (n = 5,408) | 2,221 (41.1) | 1,002 (39.0) | 208 (41.8) | 327 (43.7) | 211 (42.8) | 473 (43.0) |
| BMI, kg/m$^2$ | 28.2 ± 5.5 | 28.2 ± 5.9 | 28.4 ± 5.2 | 28.5 ± 5.4 | 28.5 ± 5.3 | 27.9 ± 4.9 |
| Tobacco use (n = 5,756) | | | | | | |
| Current | 785 (13.6) | 283 (10.5) | 89 (17.2) | 148 (18.7) | 81 (15.2) | 184 (15.1) |
| Former | 2,065 (35.9) | 887 (32.9) | 194 (37.4) | 296 (37.3) | 199 (37.4) | 489 (40.1) |
| Never | 2,906 (50.5) | 1,523 (56.6) | 236 (45.5) | 349 (44.0) | 252 (47.4) | 546 (44.8) |
| Hypertension | 2,592 (44.9) | 629 (23.3) | 237 (45.5) | 421 (52.8) | 342 (64.2) | 963 (78.7) |
| Diabetes | 443 (7.7) | 58 (2.2) | 27 (5.2) | 57 (7.2) | 46 (8.6) | 255 (20.8) |
| LDL cholesterol, mg/dl | 120 ± 31 | 118 ± 31 | 122 ± 31 | 122 ± 32 | 120 ± 32 | 121 ± 32 |
| HDL cholesterol, mg/dl | 51 ± 15 | 53 ± 15 | 50 ± 14 | 49 ± 15 | 50 ± 15 | 48 ± 14 |
| Aspirin use at baseline (n = 5,538) | 952 (17.2) | 249 (9.7) | 91 (18.5) | 141 (18.3) | 142 (27.4) | 329 (27.9) |
| Statin use at MESA visit 2 (n = 5,052) | 469 (9.3) | 137 (5.8) | 48 (10.7) | 85 (11.9) | 52 (11.0) | 147 (14.2) |
| Statin use at MESA visit 3 (n = 4,961) | 727 (14.7) | 252 (10.4) | 74 (16.8) | 121 (17.2) | 74 (16.7) | 206 (21.7) |

Values are n (%) or mean ± SD. *Estimated using the pooled cohort equations.

ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; CHD = coronary heart disease; HDL = high-density lipoprotein; LDL = low density lipoprotein; MESA = Multi-Ethnic Study of Atherosclerosis.

other measurements. All MESA participants had their CAC score assessed at the baseline visit using non-contrast cardiac-gated computed tomography and the Agatston score (19). Details on the scanning protocol used in MESA have been reported before (11,12,15-18). MESA participants also underwent measurement of the ankle-brachial index (ABI) at baseline (17,18).

**STUDY OUTCOMES.** Consistent with FDA guidance for pivotal cardiovascular outcome trials, we used an expanded 5-point major adverse cardiovascular event study outcome (from now on, "CVD events") for this analysis. This included fatal/nonfatal myocardial infarction, definite angina and probable angina followed by revascularization, fatal/nonfatal stroke, resuscitated cardiac arrest, and CVD death, all of which were adjudicated by a committee (17). To emulate 5-year-outcome RCTs, for the present analysis, follow-up was censored at 5 years.

**STATISTICAL ANALYSES.** We defined 4 subpopulations of potential candidates for novel add-on therapies on top of statins using increasingly stringent baseline estimated 10-year ASCVD risk thresholds: ≥7.5%, ≥10%, ≥15%, and ≥20% (8,9). The calculations described were conducted for each of these subpopulations.

First, the prevalence of increasingly higher baseline CAC scores (0, >0, >100, and >400) was calculated and, using the reciprocal, the number needed to screen (NNS) to identify 1 participant with each CAC score was derived.

Using the reciprocal of observed 5-year Kaplan-Meier cumulative survivor function for CVD events and assuming a 28% relative risk reduction (RRR) with high-intensity statin therapy in a statin-naive population with mean baseline low-density lipoprotein cholesterol levels of 120 to 122 mg/dl (**Table 1** and Supplemental Appendix) (5,8,9), we projected the incidence of the study outcome in populations treated with high-intensity statin therapy. Then, assuming additional RRRs of 15% and 25%, with a hypothetical novel therapy added on top of statins (1,2,20), we projected the updated incidence of CVD events.

The incidence projections with statins alone and statins plus a novel add-on therapy were then used to compute the sample size of a hypothetical 5-year primary prevention RCT of a novel add-on therapy

**TABLE 2** Baseline Prevalence of CAC, Observed 5-Year Incidence of CVD Events, and Estimated Incidence With Statins Alone and With Statins Plus Novel Add-On Therapy, by Estimated 10-Year ASCVD Risk and Baseline CAC Burden

| 10-Year Estimated ASCVD Risk* | Baseline CAC | | | Observed 5-Year Incidence, % | Estimated 5-Year Incidence with Statins‡, % | Estimated 5-Year Incidence With Novel Add-On Therapy on Top of Statins,§ % | |
|---|---|---|---|---|---|---|---|
| | Groups | Prevalence % | NNS† | | | RRR 15% | RRR 25% |
| ≥7.5% | All | 100 | – | 8.1 | 5.86 | 4.98 | 4.40 |
| | =0 | 35.4 | 2.8 | 3.5 | 2.48 | 2.11 | 1.86 |
| | >0 | 64.6 | 1.5 | 10.7 | 7.73 | 6.57 | 5.80 |
| | >100 | 34.6 | 2.9 | 13.5 | 9.74 | 8.28 | 7.31 |
| | >400 | 14.8 | 6.8 | 17.9 | 12.88 | 10.95 | 9.66 |
| ≥10% | All | 100 | – | 9.0 | 6.50 | 5.53 | 4.88 |
| | =0 | 31.8 | 3.1 | 3.8 | 2.70 | 2.30 | 2.03 |
| | >0 | 68.3 | 1.5 | 11.5 | 8.29 | 7.05 | 6.22 |
| | >100 | 38.1 | 2.6 | 14.2 | 10.22 | 8.68 | 7.66 |
| | >400 | 16.4 | 6.1 | 18.3 | 13.19 | 11.21 | 9.89 |
| ≥15% | All | 100 | – | 10.4 | 7.48 | 6.36 | 5.61 |
| | =0 | 26.1 | 3.8 | 4.8 | 3.48 | 2.96 | 2.61 |
| | >0 | 73.9 | 1.4 | 12.4 | 8.91 | 7.58 | 6.69 |
| | >100 | 44.3 | 2.3 | 14.3 | 10.28 | 8.74 | 7.71 |
| | >400 | 20.4 | 4.9 | 16.9 | 12.20 | 10.37 | 9.15 |
| ≥20% | All | 100 | – | 12.2 | 8.76 | 7.44 | 6.57 |
| | =0 | 23.2 | 4.3 | 6.7 | 4.82 | 4.09 | 3.61 |
| | >0 | 76.8 | 1.3 | 13.8 | 9.96 | 8.46 | 7.47 |
| | >100 | 48.6 | 2.1 | 15.5 | 11.12 | 9.46 | 8.34 |
| | >400 | 23.2 | 4.3 | 17.6 | 12.67 | 10.77 | 9.50 |

CVD events included fatal/nonfatal myocardial infarction, definite angina and probable angina followed by revascularization, fatal/nonfatal stroke, resuscitated cardiac arrest, and CVD death. *Estimated using the pooled cohort equations. †Number of individuals who would have to be screened to detect 1 with a given CAC score. ‡Assuming a 28% 5-yr RRR with maximally tolerated statin therapy. §Assuming additional 5-yr RRRs of 15% and 25% with novel add-on therapy on top of statins.

ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; CVD = cardiovascular disease; NNS = number needed to screen; RRR = relative risk reduction.

on top of statins compared to statins alone, in which the study entry strategy would combine increasing baseline estimated 10-year ASCVD risk thresholds plus additional enrichment criteria: CAC of >100 and CAC of >400. The RCT was assumed to have 2 arms, 2-sided analysis, alpha error of 0.05, and statistical power of 80% and 90% (1,2,20). The calculations can be easily replicated with widely available calculators (21).

Using the estimated sample size and the respective NNS for CAC of >100 and CAC of >400, we also estimated the cost of the hypothetical RCT. Specifically, 2 RCT cost components were computed: 1) related to screening, inclusion, and follow-up (up to 5 years) of participants who would be included in the study because they would fulfill the study entry enrichment criterion (e.g., CAC of >100) and 2) related to single-time screening of potential RCT participants who would not be included in the study population because they would not fulfill the enrichment criterion (e.g., CAC score of ≤100). For the first component, we defined a priori 2 hypothetical cost scenarios ($6,000 and $9,000 per participant per year) based on published cardiovascular RCT costs per participant (22,23). For screened nonparticipants, using the mean cost of recruitment activities per recruited RCT participant ($409) reported by Speich et al. (22), we assumed a priori a cost of screening of non-participants of $500 for non-CAC-based screening and of $600 for CAC-based screening. More details on these calculations are described in the Supplemental Appendix.

For reference, all calculations were also performed for the following guideline-endorsed tests/features: hsCRP of >2 mg/l, hsCRP of >3 mg/l, triglyceride level of ≥175 mg/dl, and ABI of <0.9 (8-10). In a sensitivity analysis, calculations were repeated after excluding interim statin users. All statistical analyses were performed with Stata, version 15 (StataCorp, College Station, Texas).

## RESULTS

**STUDY PARTICIPANTS.** Of the 6,814 MESA participants, 6,809 had information on incident events during follow-up. Of them, a total of 1,006 used

**TABLE 3 Estimated Sample Size of a Hypothetical Primary Prevention RCT of Novel Add-On Therapy on Top of Statins Compared to Statins Alone Using Estimated ASCVD Risk Plus Additional Study Entry Criteria**

| | RRR 15% | | | | RRR 25% | | | |
|---|---|---|---|---|---|---|---|---|
| **Estimated ASCVD* Risk** | **≥7.5%** | **≥10%** | **≥15%** | **≥20%** | **≥7.5%** | **≥10%** | **≥15%** | **≥20%** |
| ASCVD risk alone | 20,780 | 18,860 | 16,118 | 13,410 | 7,166 | 6,418 | 5,490 | 4,630 |
| ASCVD risk plus | | | | | | | | |
| CAC >100 | 12,072 | 11,326 | 11,390 | 10,516 | 4,144 | 3,898 | 3,888 | 3,566 |
| CAC >400 | 8,844 | 8,576 | 9,384 | 8,996 | 3,026 | 2,940 | 3,216 | 3,076 |
| hsCRP >2 mg/l | 19,204 | 16,636 | 13,764 | 10,868 | 6,590 | 5,752 | 4,754 | 3,740 |
| hsCRP >3 mg/l | 17,784 | 15,890 | 12,804 | 9,906 | 6,076 | 5,374 | 4,330 | 3,418 |
| TG ≥175 mg/dl | 14,632 | 13,608 | 11,722 | 10,546 | 5,020 | 4,626 | 4,012 | 3,612 |
| ABI <0.9 | 10,216 | 10,236 | 10,030 | 10,062 | 3,482 | 3,524 | 3,452 | 3,438 |

Values are n. The RCT was assumed to be 2-sided, with an alpha error of 0.05 and statistical power of 80%. *Estimated using the pooled cohort equations.
ABI = ankle-brachial index; hsCRP = high sensitivity C-reactive protein; N = number; RCT = randomized controlled trial; TG = triglycerides; other abbreviations as in Table 2.

statins at baseline, and 26 participants were excluded because of missing risk factor data. Of the resulting 5,777 statin-naive participants with complete data, 3,075 had an estimated 10-year ASCVD risk of ≥7.5%.

Higher baseline estimated risk was associated with older age, higher frequency of male sex, and higher prevalence of traditional risk factors such as diabetes and hypertension (Table 1). Aspirin use at baseline and interim statin use over time also increased with baseline risk, with a high of 28% baseline aspirin users and of 22% interim statin users in the ≥20% ASCVD risk group at MESA visit 3.

**NUMBER NEEDED TO SCREEN.** In all 4 subpopulations defined by increasing estimated ASCVD risk thresholds, the higher the CAC burden >0, the higher the NNS to detect a participant with such a CAC score (Table 2). Comparing NNS of CAC across ASCVD risk thresholds, the highest NNSs for CAC scores >0 were observed by using a ≥7.5% risk cutoff (NNS of 1.5, 2.9, and 6.8 to detect CAC of >0, >100, and >400, respectively), and the lowest were observed with a ≥20% risk cutoff (NNS of 1.3, 2.1, and 4.3, respectively). A CAC of 0 was more frequent the lower the ASCVD risk threshold used. Still, 23% of individuals with estimated % ≥20ASCVD risk had a CAC equal to 0.

For the other tests evaluated, in all estimated risk strata, hsCRP of >2.0 mg/l had the lowest NNS (2), followed by hsCRP of >3.0 mg/l (Supplemental Table 1). Conversely, ABI of <0.9 was the least prevalent feature (NNS range 11 to 18).

**OBSERVED AND PROJECTED INCIDENCE OF CVD EVENTS.** Overall, the higher the ASCVD risk threshold used, the higher the observed 5-year incidence of CVD events (Table 2). In all 4 subpopulations defined by increasing estimated ASCVD risk, higher CAC burden was associated with greater 5-year incidence of CVD events, which remained fairly stable across subpopulations. Conversely, CAC of 0 was consistently associated with the lowest incidence of CVD events, ranging from 3.5% to 6.7%.

In all 4 subpopulations, high CAC scores consistently identified the subgroups of participants who would derive the largest absolute benefit from novel add-on therapy compared to statins alone, and CAC of 0 identified those who would derive the smallest absolute benefit (Table 2). For example, in individuals with baseline estimated ASCVD risk of ≥20%, treatment with high-intensity statins plus an add-on therapy with RRR 15% would reduce the incidence from an estimated 12.7% to 10.8% among those with CAC of >400, whereas the absolute change would be 4.8% to 4.1% (-0.7%) in participants with CAC of 0.

For the other tests, ABI of <0.9 identified the subgroups with the highest incidence of CVD if the estimated risk was ≤20%, whereas hsCRP of >3 mg/l did so among individuals with estimated ASCVD risk of ≥20% (Supplemental Table 2). ABI also identified the subgroups who would derive the largest absolute benefit from novel add-on therapy.

**SAMPLE SIZE.** There was a trend toward smaller sample sizes with higher estimated ASCVD risk thresholds in both RRR scenarios and regardless of the statistical power specified (Tables 3 and Supplemental Table 3). In all, CAC of >400 as an RCT entry criterion yielded the smallest estimated sample size, ranging 33% to 57% smaller compared to using estimated ASCVD risk alone (assuming a 15% RRR with novel add-on therapy) and 34% to 58% smaller assuming a 25% RRR. The smallest sample sizes after CAC of >400 were observed for ABI of <0.9 for ASCVD risk thresholds up to ≥15% and for hsCRP of >3.0 mg/l for ASCVD risk of ≥20%.

**TABLE 4** Cost Projections for a Hypothetical Primary Prevention RCT of Novel Add-On Therapy on Top of Statins Compared to Statins Alone Using Estimated ASCVD Risk Plus Additional Study Entry Criteria, by Estimated Cost per Included Participant and RRR

| | RRR 15% | | | | RRR 25% | | | |
|---|---|---|---|---|---|---|---|---|
| Estimated ASCVD Risk* | ≥7.5% | ≥10% | ≥15% | ≥20% | ≥7.5% | ≥10% | ≥15% | ≥20% |
| **Estimated costs per included participant of $6,000/yr** | | | | | | | | |
| ASCVD risk alone | 623.4 | 565.8 | 483.5 | 402.3 | 215.0 | 192.5 | 164.7 | 138.9 |
| ASCVD risk plus | | | | | | | | |
| CAC >100 | 375.9 | 350.7 | 350.6 | 322.4 | 129.0 | 120.7 | 119.7 | 109.3 |
| CAC >400 | **296.1** | **283.5** | **303.5** | **287.7** | **101.3** | **97.2** | **104.0** | **98.4** |
| hsCRP >2 mg/l | 585.7 | 507.4 | 419.8 | 331.5 | 201.0 | 175.4 | 145.0 | 114.1 |
| hsCRP >3 mg/l | 547.7 | 489.4 | 395.0 | 306.1 | 187.1 | 165.5 | 133.6 | 105.6 |
| TG ≥175 mg/dl | 465.3 | 432.7 | 372.8 | 333.8 | 159.6 | 147.1 | 127.6 | 114.3 |
| ABI <0.9 | 395.4 | 385.9 | 358.6 | 350.7 | 134.8 | 132.9 | 123.4 | 119.8 |
| **Estimated costs per included participant of $9,000/yr** | | | | | | | | |
| ASCVD risk alone | 935.1 | 848.7 | 725.3 | 603.5 | 322.5 | 288.8 | 247.1 | 208.4 |
| ASCVD risk plus | | | | | | | | |
| CAC >100 | 557.0 | 520.5 | 521.4 | 480.2 | 191.2 | 179.2 | 178.0 | 162.8 |
| CAC >400 | **428.8** | **412.2** | **444.2** | **422.6** | **146.7** | **141.3** | **152.2** | **144.5** |
| hsCRP >2 mg/l | 873.8 | 756.9 | 626.3 | 494.5 | 299.8 | 261.7 | 216.3 | 170.2 |
| hsCRP >3 mg/l | 814.5 | 727.8 | 587.1 | 454.7 | 278.3 | 246.1 | 198.5 | 156.9 |
| TG ≥175 mg/dl | 684.8 | 636.9 | 548.6 | 492.0 | 234.9 | 216.5 | 187.8 | 168.5 |
| ABI <0.9 | 548.6 | 539.4 | 509.0 | 501.6 | 187.0 | 185.7 | 175.2 | 171.4 |

Values are millions of U.S. dollars. Results presented in millions of U.S. dollars. The RCT was assumed to be 2-sided, with an alpha error of 0.05 and statistical power of 80%. Two scenarios for cost per included participant/year were considered: $6,000 and $9,000. The cost of screening nonparticipants was assumed to be $500 for strategies not involving CAC testing and $600 for strategies involving CAC testing. *Estimated using the pooled cohort equations. **Bold** identifies the study enrichment strategy with the lowest cost.

Abbreviations as in Tables 2 and 3.

**COSTS.** In all cost scenarios, a strategy using CAC of >400 yielded the least expensive study in terms of costs related to included participants and related to screening (**Table 4** and Supplemental Table 4). For example, assuming a 15% RRR with novel add-on therapy, 80% power, and costs of $6,000/year per included participant and $500 to $600 per screened nonparticipant, the cost of an RCT using CAC of >400 as an inclusion criterion on top of estimated ASCVD risk of ≥20% would be $115 million less than that of a study including all individuals with such estimated risk. Costs associated with the screening of nonparticipants represented a small proportion of the total estimated costs (**Figure 1**). CAC of >100 showed the second-best performance in 8 out of 16 scenarios evaluated.

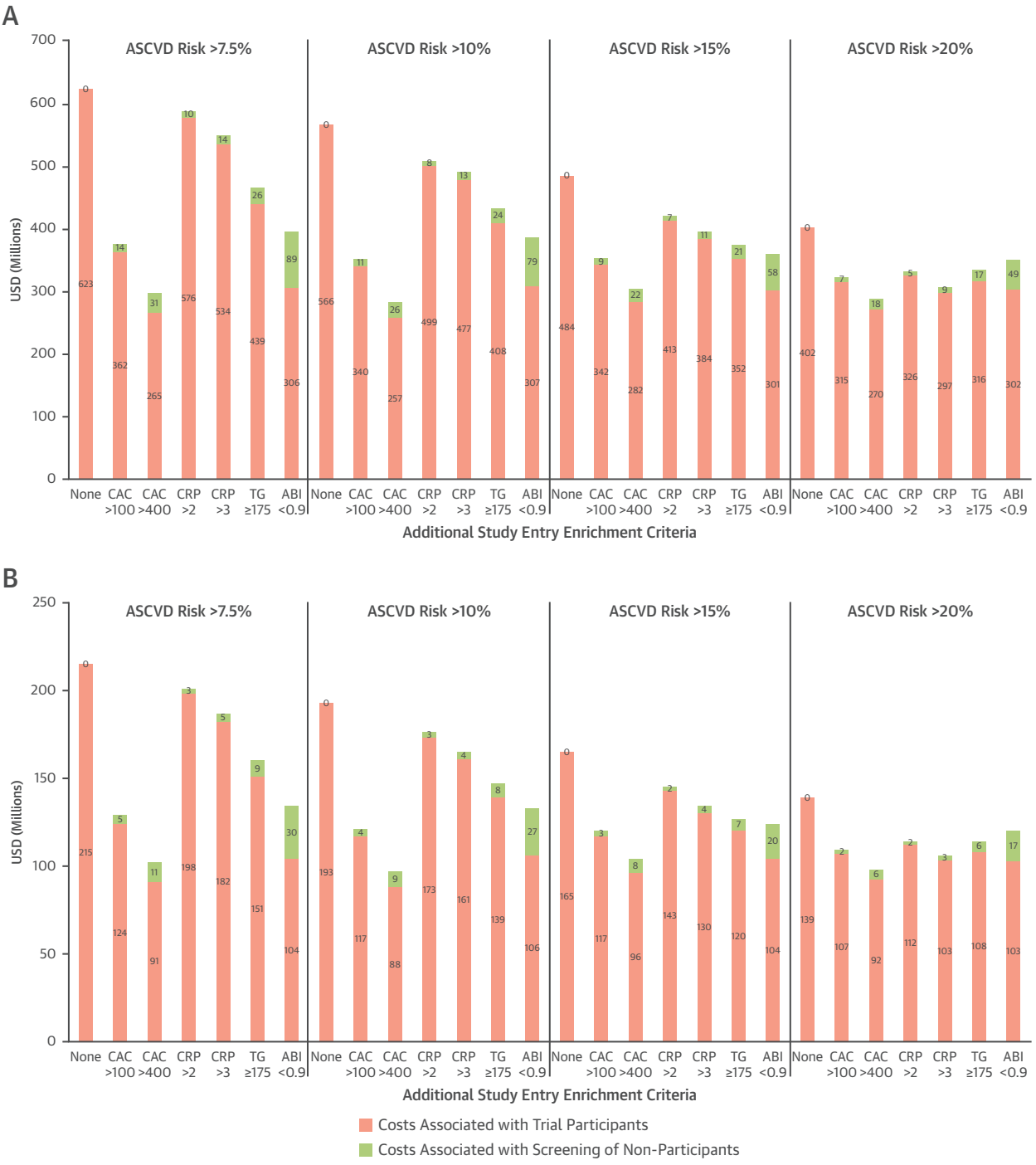
The results of the analysis excluding interim statin users were qualitatively consistent with those of the main analyses (Supplemental Tables 5 and 6).

## DISCUSSION

Multiple evidence-based novel add-on therapies have become available for patients with clinically overt ASCVD, such as PCSK9i or icosapent ethyl (1,2,20). Given the marked reductions in CVD events observed with these drugs in symptomatic high-risk patients, there is growing interest in evaluating their potential use for a more timely, improved primary prevention of ASCVD among persons without a history of clinical ASCVD but at highest risk. In this context, our findings have implications for the design of future RCTs. Specifically, our results suggest that use of CAC as an entry criterion can enrich the study population with individuals at increased risk of events (CAC of >100, CAC of >400) and/or facilitate the exclusion of participants at lower risk of events (CAC of 0) (24). The increase in cost associated with CAC screening would be offset by substantial improvement in trial efficiency by more accurately identifying those at higher risk, thus reducing the sample size required. Compared to other tests/features, CAC would allow for the largest improvement in trial feasibility, providing an opportunity to generate RCT scientific evidence in the most efficient, least expensive manner (**Central Illustration**).

Such a strategy would align with the FDA recommendation for designing efficient clinical studies, according to which the main goal of enrichment is to focus on population (demographic, pathophysiological, or diagnostic) characteristics that will favorably affect study efficiency, that is, increasing the chance of study success, preferably also leading to a smaller sample size (7). This approach would also overcome some of the challenges and costs of targeting a broad population by reducing costs associated with treating

**FIGURE 1** **Cost Projections for a Hypothetical Primary Prevention Trial of a Novel Therapy on Top of Statins Compared to Statins Alone Using Estimated ASCVD Risk Plus Additional Study Entry Criteria, by Cost Components**




**(A)** Assuming a 15% RRR with novel add-on therapy on top of statins. **(B)** Assuming a 25% RRR with novel add-on therapy on top of statins. Results are presented in millions of U.S. dollars. A statistical power of 80% and costs of $6,000/year per included participant and of $500 per screened nonparticipant ($600 for CAC-based enrichment strategies) were assumed. ABI = ankle-brachial index; ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; CRP = C-reactive protein; RRR = relative risk reduction; TG = triglycerides; USD = U.S. dollars.

**CENTRAL ILLUSTRATION Test-Based Approaches for the Selection of the Study Population of a Randomized Controlled Trial of a Novel Therapy for Primary Cardiovascular Disease Prevention on Top of Statins and Implications for Sample Size, Cost, and Feasibility**

| Approaches to the selection of the study population of an RCT of a novel add-on therapy for primary ASCVD prevention in highest risk individuals | Sample size[a] (number) | Estimated cost[b] (millions) | Implications for RCT feasibility | Implications for patients |
|---|---|---|---|---|
| **A.** Include all primary prevention **statin users** | Largest | Highest | **Lower** feasibility, might preclude evidence generation | **Limited** therapeutic options for primary prevention high risk patients |
| **B.** Include all primary prevention statin users with **estimated 10-year ASCVD risk above a specified threshold** (e.g., >7.5%) | 20,780 | $623.4 | | |
| **C.** Include all primary prevention statin users with 10-year ASCVD risk above a specified threshold **plus additional clinical/analytic study enrichment criteria** | | | | |
| **C1.** HsCRP >2 mg/L | 19,204 | $585.7 | | |
| **C2.** HsCRP >3 mg/L | 17,784 | $547.7 | | |
| **C3.** Triglycerides ≥175 mg/dL | 14,632 | $465.3 | | |
| **C4.** Ankle-brachial index <0.9 | 10,216 | $395.4 | | |
| **D.** Include all primary prevention statin users with 10-year ASCVD risk above a specified threshold **plus additional CAC score study enrichment criteria** | | | **CAC** can be used as study entry criterion to enrich RCTs with highest-risk participants. This can facilitate evidence generation for novel add-on therapies | Potential to result in **more therapeutic options for high-risk primary prevention patients** |
| **D1.** CAC score >100 | 12,072 | $375.9 | | |
| **D2. CAC score >400** | **8,844** (Smallest) | **$296.1** (Lowest) | | |

**Cainzos-Achirica, M. et al. J Am Coll Cardiol Img. 2020;■(■):■–■.**

[a]The randomized controlled trial was assumed to be 2-sided, with an alpha error of 0.05 and statistical power of 80%, with a relative risk reduction with novel add-on therapy of 15%, and using an estimated atherosclerotic cardiovascular disease risk threshold of ≥7.5%, which is the American College of Cardiology/American Heart Association guideline threshold for statin eligibility. [b]Assuming costs of $6,000/year per included participant and of $500 per screened nonparticipant ($600 for coronary artery calcium-based enrichment strategies).

those who benefit the least, as suggested by the Professional Society for Health Economics and Outcomes Research Personalized Medicine Special Interest Group (6). Cardiovascular trials of primary prevention therapies are costly, and the present findings suggest that trial enrichment with CAC could lead to marked (up to 58%) reductions in sample size and large cost reductions compared to using estimated ASCVD risk alone.

Our results for CAC are consistent with a wealth of studies portraying CAC as a powerful prognostic tool for the prediction of ASCVD events (3,11-16), with a better performance in risk prediction than multiple other tests and biomarkers (16). In those studies, the ability of high CAC scores to identify truly high-risk individuals was independent of traditional risk factor burden and score-based risk estimations. Consistent with this, in our study, the incidence of CVD observed in participants with CAC of >400 was highest and remained fairly stable across estimated risk thresholds. This provides further support to the notion of coronary plaque burden being a more precise predictor of incident events compared to prediction tools reliant solely on traditional risk factors (11,12,15,16,25). Also, CAC of 0 identified individuals at lowest risk of events, which is consistent with the notion of CAC of 0 being a strong negative risk marker (13,14,26-28) and suggests that it may be useful identifying individuals who could be excluded from RCTs expected to include truly high-risk participants.

Importantly, even though in our cost calculations we assumed that CAC would have to be measured de novo in all potential RCT participants, increased adoption by recent guidelines (8,9) may expand the use of CAC scoring in routine cardiovascular primary prevention. A key quality of CAC compared to hsCRP, which was used to enrich landmark trials such as JUPITER (Justification for the Use of Statins in

Prevention: an Intervention Trial Evaluating Rosuvastatin) or CANTOS (Canakinumab Antiinflammatory Thrombosis Outcome Study) (29–31), is that CAC scores tend to increase over time, even in the presence of lipid-lowering therapy (32). Therefore, once a patient has had a CAC score above a given threshold (e.g., >400), in most cases, it will be safe to assume that this will remain true later in time. Use of already existing CAC data (e.g., recorded in the patient's electronic medical record) would reduce the cost associated with the screening component of eventual CAC-enriched RCTs.

The present findings also have implications for clinical decision making. In primary prevention patients in whom the addition of other therapies beyond statins is considered for further risk reduction, CAC scoring can be a valuable tool to inform the effective, safe allocation of add-on pharmacotherapies such as low-dose aspirin (33) and other medications (34). The use of CAC to inform shared decision making would be particularly useful if pivotal trials of novel add-on therapies incorporated CAC scoring as part of their study entry criteria.

A CAC-based RCT enrichment paradigm could result in relatively narrow target populations in the product labels of add-on therapies when used in primary prevention. Although this could be interpreted as a barrier for sponsors when pursuing RCTs in primary prevention, the alternative (inclusion of participants at heterogeneous risk) may result in a larger barrier—failure to demonstrate any benefit in primary prevention. Moreover, a CAC enrichment paradigm would inform a more precise allocation of preventive medications, some of which are costly and/or have potential side effects. Consistent with a trial enrichment approach, in REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial), the primary prevention study arm comprised participants with diabetes mellitus and 2 additional cardiovascular risk factors/markers, including high hsCRP levels and abnormal ABI (2). Although REDUCE-IT did not use CAC, it is important to note that CAC has demonstrated the ability to stratify risk even among individuals with 3 or more traditional risk factors, as well as within hsCRP strata (3,15). In the ongoing VESALIUS-CV (Effect of Evolocumab in Patients at High Cardiovascular Risk Without Prior Myocardial Infarction or Stroke) trial, CAC together with other markers of subclinical atherosclerosis is being used to enrich the study population with high-risk participants (35).

**STUDY LIMITATIONS.** We excluded baseline statin users from the main analyses; however, interim use of statins during follow-up may have affected the calculations. Nevertheless, a sensitivity analysis further excluding interim statin users yielded qualitatively consistent observations. Exclusion of statin users resulted—together with MESA baseline characteristics—in a study population with relatively low event rates. This likely inflated the sample size and cost projections, both of which would be expected to be lower in populations with higher rates of events. Of note, by excluding statin users, the distribution of CAC at baseline (and of other tests such as hsCRP) was that of a statin-naive population. This may differ among individuals using statins, which is the population in whom novel add-on therapies such as PCSK9i would be considered. Further studies in large primary prevention populations of high-intensity statin users are needed. In the meantime, available studies confirm that CAC is also strongly associated with CVD events in high-risk populations with high rates of statin use (36,37).

The RRRs used for the theoretical novel add-on therapy in primary prevention were based on those reported for PCSK9i and icosapent ethyl in secondary prevention settings (1,2,20). In REDUCE-IT, there was no statistically significant effect modification between primary/secondary prevention study arms and CVD reduction with icosapent ethyl (2). Consistent with this, and for the sake of simplicity, we also assumed a constant effect of novel-add on therapies across CAC strata. Nonetheless, effect modification by CAC burden is indeed a possibility, as observed for statins in both the Walter Reed cohort and the St. Francis Trial (38,39). Importantly, if this were the case, the constant effect assumption would have introduced a conservative bias when estimating the reductions in sample size and cost with a CAC-based enrichment strategy, both of which would actually be larger.

Our cost calculations were based on published cost data; nevertheless, these entailed important assumptions. For example, the cost associated with the screening of primary prevention individuals with specific estimated ASCVD risks was assumed to be captured by the participant/screening costs included in the calculations. This cost would be very low in a pragmatic trial using large health care databases and automated procedures to identify individuals above a certain estimated ASCVD risk and/or treated with certain medications, such as statins. However, the cost of this screening would be higher in environments in which these approaches would not be possible. Still, as observed in **Figure 1**, the cost of screening would have to be exceedingly high to attenuate the savings associated with a CAC-based enrichment paradigm.

Finally, the racial and ethnic distribution in MESA may not be generalizable to other populations. Similarly, MESA is a U.S. cohort, and the sample size and cost projections may not apply to other countries. In addition, the MESA baseline occurred 18 to 20 years ago, and event rates may be lower in 2020. For these and the reasons described earlier, the cost projections presented in this study are intended to facilitate comparisons between test-based enrichment approaches using a well-characterized, multiethnic study population. On the other hand, they should not be used to inform the actual cost of future RCTs in primary prevention.

## CONCLUSIONS

CAC can be a valuable tool to refine the study population of RCTs evaluating the efficacy of novel add-on therapies in primary prevention patients at highest ASCVD risk already treated with statins. CAC has the potential to enrich study populations with high-risk individuals and to identify individuals less likely to have events who could be excluded from study populations to reduce risk heterogeneity. The modest cost of CAC screening would be offset through reductions in sample size, thereby reducing overall trial costs and improving feasibility. This could facilitate the generation of novel scientific evidence in primary prevention patients at highest risk.

**ACKNOWLEDGMENTS** The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

## AUTHOR DISCLOSURES

This research was supported by contracts HHSN268201500003I and N01-HC-95159 through N01-HC-95169 from the National Heart, Lung, and Blood Institute and by grants UL1-TR-000040, UL1-TR-001079, UL1-TR-001420, and UL1-TR-001881 from the National Center for Advancing Translational Sciences. Dr. Ray acknowledges support from the National Institute for Health Research (NIHR) Imperial Biomedical Research Centre and Imperial College London is grateful for support from the NIHR Applied Research Collaboration for North West London. Dr. Bhatt has served on the Advisory Board of Cardax, Cereno Scientific, Elsevier Practice Update Cardiology, Medscape Cardiology, PhaseBio, and Regado Biosciences; has served on the Board of Directors for Boston Veterans Affairs Research Institute, Society of Cardiovascular Patient Care, and TobeSoft; has served as chair of the American Heart Association Quality Oversight Committee; has served on the Data Monitoring Committee for the Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), and Population Health Research Institute; has received honoraria from the American College of Cardiology (senior associate editor, *Clinical Trials and News*, ACC.org; vice chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (editor-in-chief, *Harvard Heart Letter*), Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (editor-in-chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (guest editor, associate editor), Medtelligence/ReachMD (continuing medical education [CME] steering committees), Population Health Research Institute (for the COMPASS operations committee, publications committee, and steering committee and U.S. national coleader, funded by Bayer), Slack Publications (chief medical editor, *Cardiology Today's Intervention*), Society of Cardiovascular Patient Care (secretary/treasurer), WebMD (CME steering committees); reports the following roles: *Clinical Cardiology* (deputy editor), National Cardiovascular Data Registry (NCDR)-ACTION Registry Steering Committee (chair), Veteran Affairs Clinical Assessment, Reporting and Tracking Program (VA CART) Research and Publications Committee (chair); has received research funding from Abbott, Afimmune, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Chiesi, CSL Behring, Eisai, Ethicon, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Idorsia, Ironwood, Ischemix, Lilly, Medtronic, PhaseBio, Pfizer, PLx Pharma, Regeneron, Roche, Sanofi Aventis, Synaptic, The Medicines Company; has received royalties from Elsevier (editor, *Cardiovascular Intervention: A Companion to Braunwald's Heart Disease*) has served as site coinvestigator for Biotronik, Boston Scientific, CSI, St. Jude Medical (now Abbott), Svelte; has served as trustee for the American College of Cardiology; and has performed unfunded research for FlowCo, Merck, Novo Nordisk, and Takeda. Dr. Ray reports personal fees from Aegerion, grants and personal fees from Amgen, Sanofi/Regeneron, Pfizer, and Merck Sharp & Dohme Corp. (MSD), personal fees from AstraZeneca, Cerenis, Akcea, The Medicines Company, Kowa, Novartis, Cipla, Lilly, Algorithm, Takeda, Boehringer Ingelheim, AbbVie, and Silence Therapeutics. Dr. Reddy's has received personal fees from Bayer, Daiichi Sankyo, Esperion, AbbVie, Zuelling Pharma, and Resverlogix, outside the submitted work. Dr. Nasir is on the Advisory Boards of Amgen, Novartis, and The Medicine Company; and his research is partly supported by the Jerold B. Katz Academy of Translational Research. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

**ADDRESS FOR CORRESPONDENCE:** Dr. Miguel Cainzos-Achirica, MD, MPH, PhD, Division of Cardiovascular Prevention and Wellness, Department of Cardiology, Houston Methodist DeBakey Heart & Vascular Center, 6565 Fannin Street, Brown Building 5-019, Houston, Texas 77030. E-mail: mcainzosachirica@houstonmethodist.org.

## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** Use of CAC as a study entry criterion in primary prevention RCTs can enrich study populations with individuals at high risk of events (CAC of >100, CAC of >400) and/or facilitate the exclusion of participants at low risk (CAC of 0), reducing risk heterogeneity and improving overall trial efficiency.

**COMPETENCY IN PATIENT CARE:** CAC testing can help inform add-on therapy allocation in routine primary prevention care, and CAC may be particularly informative for this purpose should relevant trials incorporate CAC scoring as part of their study entry criteria.

**TRANSLATIONAL OUTLOOK 1:** The present findings may be used to inform the design of primary prevention RCTs of novel add-on therapies that had been considered unfeasible because of the estimated sample size and cost.

**TRANSLATIONAL OUTLOOK 2:** Further studies are needed in large cohorts of primary prevention patients using high-intensity statin therapy to confirm these findings, as well as studies evaluating the performance of higher CAC score thresholds (e.g., CAC of >1,000).

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**KEY WORDS** cardiovascular disease, coronary artery calcium, cost, prevention, randomized controlled trials

**APPENDIX** For an expanded Methods section and supplemental tables, please see the online version of this paper.