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Polygenic Risk Based Detection and Treatment of Subclinical Coronary Atherosclerosis in the PROACT Clinical Trials

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ABSTRACT

BACKGROUND Coronary artery disease (CAD) polygenic risk scores (PRS) may identify individuals at elevated genetic risk "flying under the radar" in contemporary practice. The aims of the PROACT (Polygenic Risk Based Detection and Treatment of Subclinical Coronary Atherosclerosis) trials are to prospectively identify these individuals, quantify subclinical coronary plaque, and slow its progression with pharmacologic interventions.

OBJECTIVES The aim of this study is to report interim feasibility and implementation findings from PROACT, a genotype-first, biobank-enabled trial, characterizing eligibility yield, callback engagement, and subclinical coronary atherosclerosis on coronary computed tomographic angiography among individuals with high CAD PRS.

METHODS Within a hospital-based biobank, adults 40 to 75 years of age with high CAD PRS, without cardiovascular disease, and not on lipid-lowering therapy were invited. The authors characterize 2,495 eligible individuals with high CAD PRS, report on the feasibility and early operational outcomes of a genotype-first callback strategy for a clinical trial in the first 1,314 invited, and describe plaque prevalence by age and sex in the first 204 participants using coronary computed tomographic angiography.

RESULTS Among 64,092 genotyped participants, 2,495 (3.9%) were eligible and had high CAD PRS despite low clinical risk (median 10-year pooled cohort equations risk for atherosclerotic cardiovascular disease 3%; Q1-Q3: 1%-8%). Recruitment showed high engagement: among 1,314 invited individuals, 283 (21.5%) opted in, and 204 (15.5%) completed baseline imaging. Compared with participants who did not opt in, those who opted in had higher specialty care engagement and lived closer to the study site. Analysis of the first 204 participants enrolled by January 31, 2025 (mean age 56.3 ± 8.5 years, 69% women), showed that despite the low clinical risk and favorable cardiovascular health (mean Life's Essential 8 score 73.3 ± 11.5 vs the U.S. average of ∼65), one-half the participants (102 of 204) had subclinical plaque. Subclinical plaque prevalence was 76.2% in men and 38.3% in women and was high across age groups.

CONCLUSIONS These exploratory findings highlight the feasibility of implementing genotype-first recruitment for prevention trials and reveal a large proportion of "silent" high-genetic risk individuals with subclinical plaque for whom pharmacotherapy could be beneficial but who remain undetected by standard clinical assessments. (Polygenic Risk Based Detection of Subclinical Coronary Atherosclerosis and Change in Cardiovascular Health [PROACT 1], NCT05819814; Polygenic Risk Based Detection of Subclinical Coronary Atherosclerosis and Intervention With Statin and Colchicine [PROACT 2], NCT05850091) (JACC. 2026;■:■-■) © 2026 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ASCVD = atherosclerotic cardiovascular disease

CAC = coronary artery calcium

CAD = coronary artery disease

CMP = complete metabolic panel

CTA = computed tomographic angiography

CVD = cardiovascular disease

eGFR = estimated glomerular filtration rate

hsCRP = high-sensitivity C-reactive protein

LDL-C = low-density lipoprotein cholesterol

LE8 = Life's Essential 8

MGB = Mass General Brigham

NHANES = National Health and Nutrition Examination Survey

PCE = pooled cohort equations

PCP = primary care provider

PRS = polygenic risk score(s)

Conventional clinical risk factor–based models leave a critical blind spot in coronary artery disease (CAD) prevention, failing to detect individuals at high genetic risk who might silently develop subclinical atherosclerosis.[1-5]

Most acute coronary events occur among individuals classified as low to intermediate risk according to the pooled cohort equations (PCE), highlighting an important gap in our current approach to prevention.[6] This underestimation is particularly pronounced among younger adults and women, whose clinical risk profiles might remain "normal" until advanced disease stages.[7-12] Current guidelines do not routinely recommend preventive medications among seemingly healthy individuals. This leaves significant numbers of at-risk individuals "flying under the radar" during a critical window when early initiation of prevention is important, given the cumulative nature of most risk factors such as "cholesterol-years."[6,13]

CAD polygenic risk scores (PRS) quantify genetic susceptibility to CAD and serve as a single lifelong metric that could identify about 20% of the population at 3-fold increased risk.[14,15] Analysis of large retrospective data made the case for the potential clinical utility of CAD PRS on the basis of their ability to identify people at high genetic risk but who fall under the clinical risk thresholds in practice.[1,16-19] Post hoc analyses of clinical trials also demonstrated that individuals with high CAD PRS derive a disproportionately higher benefit from lipid-lowering therapy, highlighting the value of CAD PRS in enriching clinical trials.[20-24] Early studies also suggest that disclosure of CAD PRS can have a positive impact on care, such as improved medication adherence and control of low-density lipoprotein cholesterol (LDL-C).[25-27] However, prospective data on the feasibility, implementation, and clinical impact of genome-first prevention strategies in cardiovascular disease (CVD) remain limited.[28,29]

In contrast, oncology has already begun to operationalize genome-based risk stratification at scale. For example, the landmark BARCODE1 (The Use of Genetic Profiling to Guide Prostate Cancer Targeted Screening) trial invited >40,000 men from primary care for prostate cancer screening using a PRS-based stratification strategy.[29] Among men in the highest genetic risk strata who underwent targeted magnetic resonance imaging and biopsy, prostate cancer was detected in 40% of participants, with 55% of these cancers classified as clinically significant. Notably, nearly three-quarters (72%) of these clinically significant cancers would have been missed by conventional prostate-specific antigen–based screening pathways, underscoring the ability of PRS to identify individuals with otherwise silent, high-risk disease.[29] This landmark trial marked a pivotal moment for genome-first cancer prevention, establishing a proof of concept for integration of polygenic risk into population screening.

Cardiovascular prevention has not yet fully replicated this approach. Realizing the clinical utility of CAD PRS will require feasible, pragmatic models for identifying, engaging, and phenotyping individuals at high genetic risk and integrating genomic information into preventive workflows. Coronary computed tomographic angiography (CTA) offers a complementary tool by enabling early visualization of subclinical atherosclerosis. Unlike traditional imaging methods such as coronary artery calcium (CAC) scoring, which detects only calcifications and frequently returns zero in younger adults or those with early-stage disease, coronary CTA quantifies both calcified and noncalcified plaque.[12,30-33] This comprehensive plaque assessment allows earlier detection and precise characterization of atherosclerotic pathology at stages at which interventions are more likely to be effective.[34] Importantly, evidence indicates that plaque progression is a strong

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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 Author Center.

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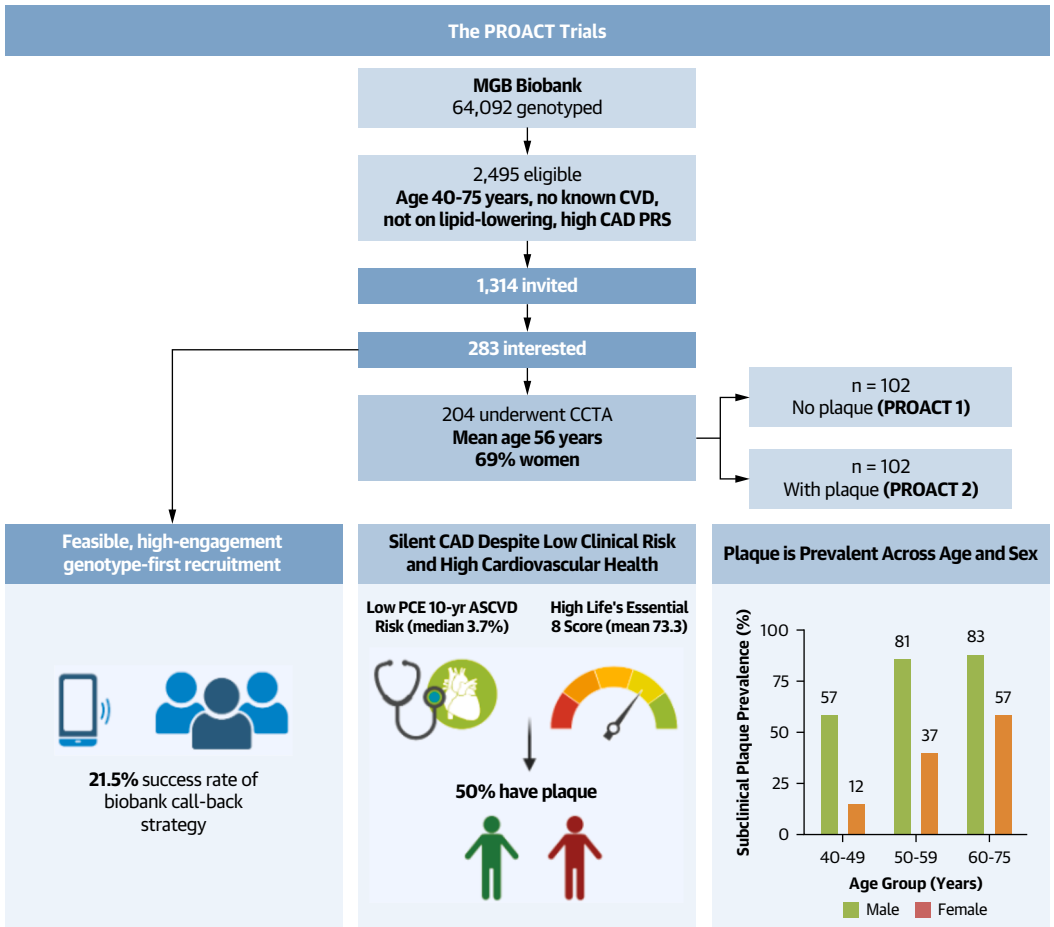
CENTRAL ILLUSTRATION **A Genotype-First Strategy Reveals a Large "Silent" High-Genetic Risk Population With Subclinical CAD, Creating an Opportunity for Earlier Prevention**



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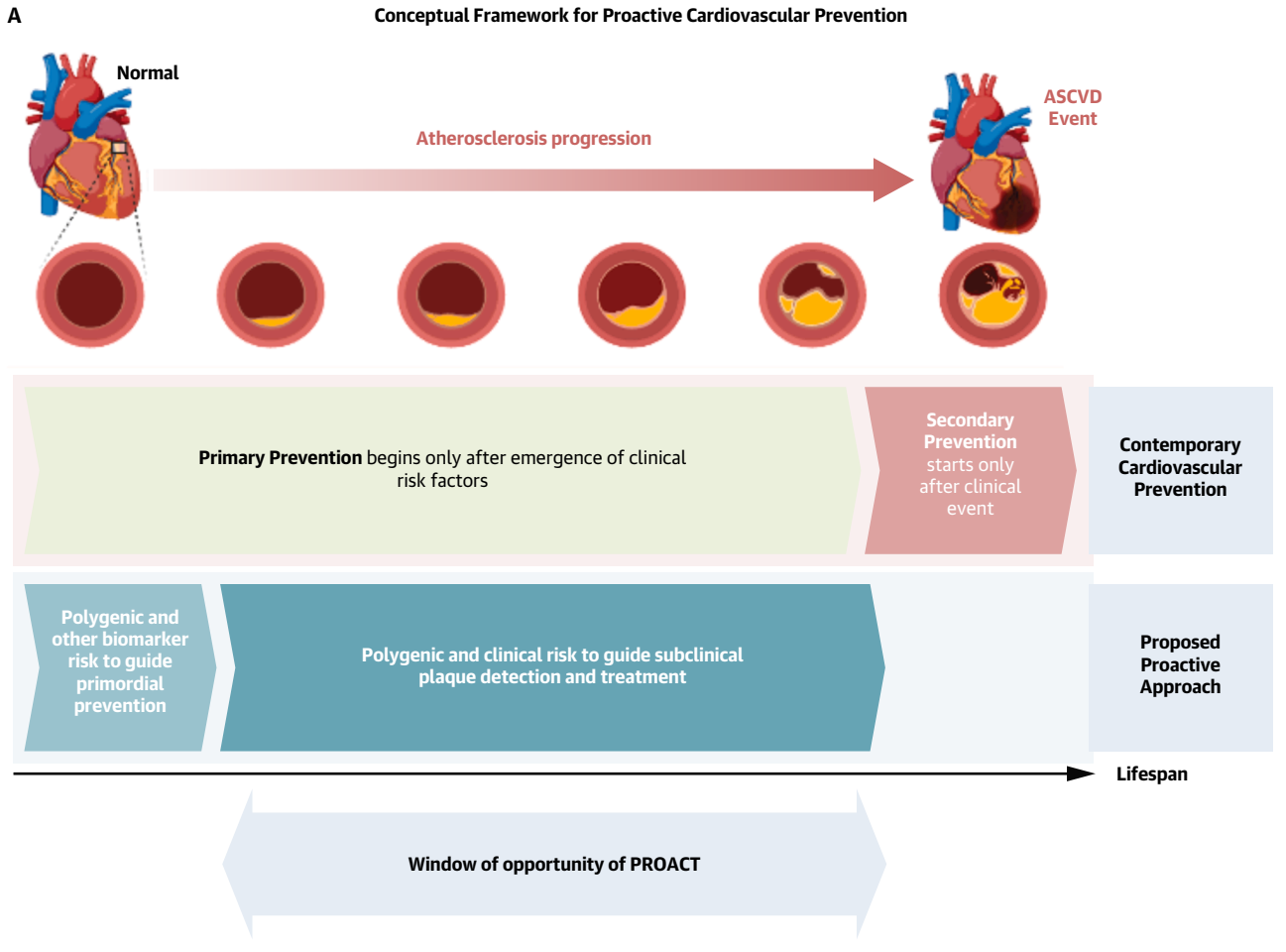
The PROACT (Polygenic Risk Based Detection and Treatment of Subclinical Coronary Atherosclerosis) trials establish a proof of concept for a biobank-enabled, genetically enriched strategy for a primary prevention clinical trial. There were 3.9% eligible, and 21.5% of those invited opted in. Among 204 participants who underwent coronary computed tomographic angiography (CTA), despite low clinical risk and favorable cardiovascular health, 50% had subclinical plaque, including 76.2% of men and 38.3% of women. These interim findings from PROACT highlight a substantial "silent" high-risk population identified using genetics that could qualify for targeted prevention.
ASCVD = atherosclerotic cardiovascular disease; CAD = coronary artery disease; CVD = cardiovascular disease; MGB = Mass General Brigham; PCE = pooled cohort equations; PROACT 1 = Polygenic Risk Based Detection of Subclinical Coronary Atherosclerosis and Change in Cardiovascular Health; PROACT 2 = Polygenic Risk Based Detection of Subclinical Coronary Atherosclerosis and Intervention With Statin and Colchicine; PRS = polygenic risk score.

predictor of cardiovascular events, highlighting a critical preventive "window of opportunity" when proactive plaque identification and treatment to slow progression can prevent future events.[35]

Here, we describe the feasibility, implementation, and interim findings of the PROACT (Polygenic Risk Based Detection and Treatment of Subclinical Coronary Atherosclerosis) clinical trials, which are designed to operationalize this 2-step paradigm: genotype-first risk identification using CAD PRS, followed by targeted imaging to detect subclinical coronary disease (Central Illustration, Figure 1A). This paper presents: 1) a proof-of-concept demonstration of the yield from a genomic-enriched primary prevention trial using biobank data; and 2) the prevalence and characterization of subclinical coronary

FIGURE 1 **PROACT Framework and Study Design for Genomic-Guided Cardiovascular Prevention**



(A) Contemporary cardiovascular prevention begins only after the emergence of clinical risk factors. We propose a more proactive approach whereby polygenic and clinical risk enrichment can guide subclinical plaque detection and treatment. (B) Participants with high coronary artery disease (CAD) polygenic risk scores (PRS) undergo coronary computed tomographic angiography (CTA) and are randomized according to plaque presence into 2 parallel trials. PROACT 1 (Polygenic Risk Based Detection of Subclinical Coronary Atherosclerosis and Change in Cardiovascular Health) tests the impact of genetic risk disclosure on change in cardiovascular health. PROACT 2 (Polygenic Risk Based Detection of Subclinical Coronary Atherosclerosis and Intervention With Statin and Colchicine) tests the impact of single vs dual targeting of low-density lipoprotein (LDL) cholesterol lowering and inflammation on plaque progression over 1 year. ASCVD = atherosclerotic cardiovascular disease; PROACT = Polygenic Risk Based Detection and Treatment of Subclinical Coronary Atherosclerosis.

plaque among the first 204 participants who underwent coronary CTA. These findings provide early operational insights to inform future large-scale preventive trials.

METHODS

STUDY SETTING AND POPULATION. Participants were identified from the Mass General Brigham (MGB) Biobank, a hospital-based research repository of >140,000 consented adults with linked electronic health records and genome-wide array-based genotyping data.[36] Among 64,092 genotyped individuals, we calculated CAD PRS using a commercially available multiancestry score.[18] Adults 40 to 75 years of age, without prior CVD, not on lipid-lowering therapy, and with high CAD PRS were screened for eligibility. A total of 2,495 individuals met all inclusion criteria (Supplemental Table 1) and were eligible for recruitment. All procedures were approved by the MGB Institutional Review Board, and both trials were registered at ClinicalTrials.gov (PROACT 1 [Polygenic Risk Based Detection of Subclinical Coronary Atherosclerosis and Change in Cardiovascular Health], NCT05819814; PROACT 2 [Polygenic Risk Based Detection of Subclinical Coronary Atherosclerosis and Intervention With Statin and Colchicine], NCT05850091).

RECRUITMENT AND CALLBACK WORKFLOW. Eligible participants (n = 2,495) identified from the MGB Biobank are invited in sequential batches of 100 to 200. Each receives an Institutional Review Board-approved invitation letter cosigned by the study principal investigator and the biobank director (Supplemental Figure 1) that explains the study, highlights the voluntary nature of participation, and offers 2 options: 1) opt in by contacting the study team directly via phone; or 2) opt out using a simple mechanism described in the letter (Supplemental Figure 1). If there is no response after 2 weeks, participants are engaged through a structured omnichannel outreach strategy that includes phone calls (Supplemental Figure 2) at different times of day, an email containing a short, prerecorded video from the from the principal investigator explaining the study (Supplemental Figure 3), and a message via the patient's secure online health portal (Patient Gateway) (Supplemental Figure 4). Each contact attempt was logged and tracked to monitor efficiency and participant preferences for communication mode. A recruitment waterfall (**Figure 2A**) and participant journey schematic (**Figure 2B**) summarize the overall callback process and attrition at each step, from biobank identification through randomization.

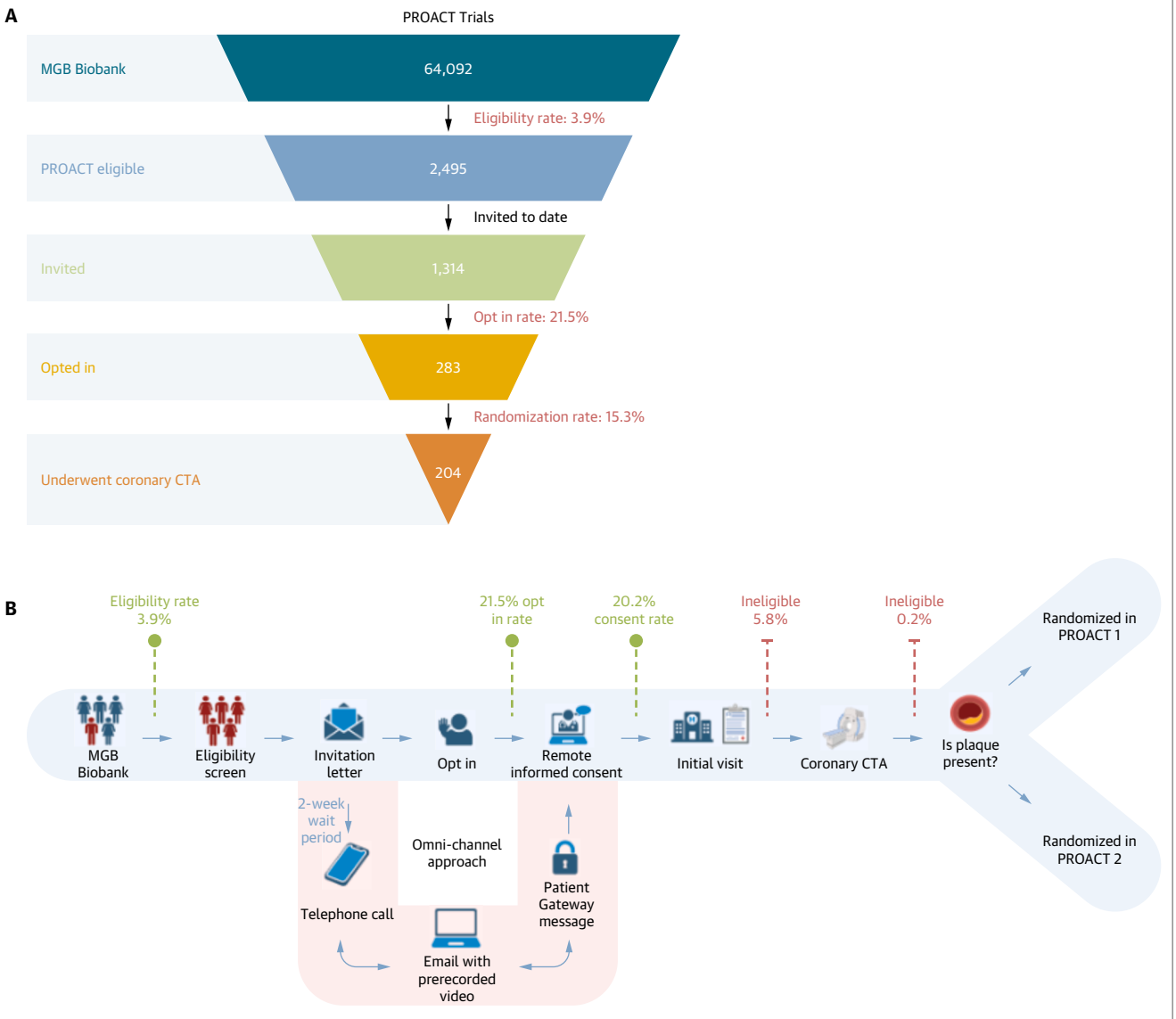
Individuals expressing interest were contacted by study staff members for a brief eligibility confirmation and then scheduled for a virtual informed-consent discussion with a study physician. Participants who consented were subsequently invited for an in-person baseline visit and coronary CTA at Massachusetts General Hospital.

TRIAL DESIGN AND PROCEDURES. All participants undergo a standardized baseline evaluation before randomization into 1 of 2 parallel clinical trials, PROACT 1 and PROACT 2, according to findings on coronary CTA (**Figure 1B**). Both trials share a common enrollment pipeline and measurement framework. Following informed consent, participants complete a remote previsit survey to capture behavioral components of the American Heart Association's Life's Essential 8 (LE8): diet, physical activity, nicotine exposure, and sleep.[37] Validated instruments are used for each domain, including the Mediterranean Eating Pattern for Americans questionnaire for diet, weekly minutes of moderate to vigorous activity for physical activity, average nightly sleep duration, and self-reported tobacco or nicotine exposure.[37,38]

Participants then attend an in-person baseline visit at which study staff members verify eligibility, collect medical history, and obtain anthropometric and hemodynamic measures (height, weight, and blood pressure). Blood is drawn for complete blood count, lipid panel, basic metabolic panel, liver function, glycated hemoglobin, high-sensitivity C-reactive protein (hsCRP), and creatine kinase, as well as for additional samples for biobanking. Samples are stored for measurement of apolipoprotein B, lipoprotein(a), interleukin-6, and interleukin-1 beta and to support future multiomics analyses. The LE8 health factor components (body mass index, blood pressure, blood glucose, and blood lipids) are derived from clinical measures and laboratory results, with a total LE8 score computed on a scale ranging from 0 to 100 (higher scores indicate better cardiovascular health). LE8 category cutoffs are defined as low (<50), moderate (50-79), and high (≥80).[37] A saliva sample is obtained for confirmatory CAD PRS in Clinical Laboratory Improvement Amendments-certified laboratory. Participants also undergo resting electrocardiography, which will be interpreted for a prespecified substudy of ECG2CAD, an artificial intelligence algorithm that leverages machine learning of electrocardiography to detect subclinical CAD.[39]

All participants undergo coronary CTA on dual-source SOMATOM Force scanners (Siemens Healthineers) following Society of Cardiovascular

FIGURE 2 Recruitment Funnel and Participant Journey in the PROACT Clinical Trials



(A) Recruitment funnel illustrating participant enrollment from the Mass General Brigham (MGB) Biobank into the PROACT clinical trials. Of 64,092 genotyped biobank participants, 2,495 (3.9%) met eligibility criteria on the basis of a high coronary artery disease polygenic risk score. In this report, we present the data on the first 1,314 eligible individuals who have been invited to participate, with 283 (21.5%) opting in. Among those who consented, 204 participants (15.5%) underwent coronary CTA, and 201 (15.3%) were randomized. Three participants were withdrawn prior to randomization because of severe stenosis, a severe allergic reaction to contrast, and initiation of statin therapy outside the study. (B) Flow diagram illustrating the participant journey from the MGB Biobank through randomization in PROACT 1 or PROACT 2. Individuals with existing genotyping data underwent eligibility screening, followed by a 2-week opt-out period after receiving an invitation letter. Eligible participants were recontacted through an omnichannel outreach strategy consisting of telephone calls, a prerecorded educational video sent via email, and Patient Gateway messages. Participants who opted in completed remote informed consent and an initial study visit before coronary CTA. Rates of eligibility, opt-in, and consent are displayed at each step, along with the proportion of ineligible participants before and after imaging. Participants with any nonobstructive coronary plaque on coronary CTA were randomized into PROACT 2, whereas those without plaque were randomized into PROACT 1. Abbreviations as in **Figure 1**.

Computed Tomography guidelines.[40,41] The protocol includes a noncontrast calcium scoring scan and a contrast-enhanced angiographic acquisition, with sublingual or transdermal nitroglycerin administered for coronary vasodilation. Coronary computed tomographic angiographic images are analyzed using the Society of Cardiovascular Computed Tomography segment model for the

presence, extent, and composition of atherosclerotic plaque, classified as calcified, noncalcified, or mixed.[40,41] Stenosis severity is graded as no plaque (0%), minimal (1%-24%), mild (25%-49%), moderate (50%-69%), severe (≥50% in the left main coronary artery, 70%-99% in other vessels), or total (100% occlusion). High-risk plaque features were defined as any of the following: positive remodeling (remodeling index >1.1), low attenuation (<30 HU), napkin-ring sign, or spotty calcification (<3 mm).[40] The CAC score was quantified using the modified Agatston method. Participants with severe stenosis are excluded from randomization and referred for clinical care.

Following baseline coronary CTA, participants are assigned to 1 of 2 parallel randomized clinical trials according to the presence or absence of subclinical plaque. Participants with no quantifiable coronary atherosclerosis continue with PROACT 1 and are randomized 1:1 to either: 1) an intervention arm receiving their clinical CAD PRS test results through a web-based report and a 30-minute genetic counseling session; or 2) a control arm receiving standard of care with deferred CAD PRS disclosure until study completion at 12 months (**Figure 1B**). The trial evaluates whether disclosing a high CAD PRS result can improve cardiovascular health over 1 year. The primary outcome is the change in LE8 score from baseline to 12 months, derived from repeat surveys and clinical assessments.[37]

Participants with nonobstructive coronary atherosclerosis are enrolled in PROACT 2, a double-blind, 4-arm, randomized controlled trial. Eligible participants are randomized in equal proportions to 1 of 4 daily regimens: 1) placebo; 2) rosuvastatin 20 mg; 3) colchicine 0.6 mg; or 4) a combination of rosuvastatin 20 mg and colchicine 0.6 mg. Randomization is conducted using permuted blocks by the Massachusetts General Hospital Clinical Trials Pharmacy, which also oversees blinding and dispensing. Follow-up includes monthly phone calls for safety and adherence, an in-person visit at 3 months with laboratory assessments, and 12-month repeat coronary CTA and biomarker assessments. The primary outcome is the change in total noncalcified plaque volume from baseline to 1 year, measured in cubic millimeters. Secondary outcomes include a comparison of the change in low attenuation plaque volume, total plaque volume, total calcified plaque volume, total low attenuation plaque volume, maximal luminal stenosis, calcium score, number of high-risk features, and fat attenuation index, with additional nonimaging endpoints including change in circulating biomarkers (LDL-C, hsCRP, interleukin-6, and interleukin-1β) and safety endpoints (clinical adverse events or significant increase in creatinine or CPK requiring study drug discontinuation).[42,43]

PROACT aims to enroll 400 participants with high CAD PRS (approximately 200 in each of PROACT 1 and PROACT 2), reflecting the observed 50% prevalence of subclinical plaque at baseline. Sample size assumptions were derived from prior imaging studies, providing >90% power for the prespecified primary endpoints.[44-46] The Supplemental Appendix Expanded Methods details randomization algorithms, visit schedules, safety monitoring procedures, and power calculations.

SUBCLINICAL CORONARY PLAQUE ANALYSIS AND STATISTICAL METHODS. We analyzed the first 204 PROACT participants who underwent coronary CTA to assess the prevalence of subclinical coronary plaque and describe demographic, clinical, and cardiovascular characteristics in this group with low clinical but high genetic risk. Participants were stratified by plaque status (any plaque vs no plaque) to characterize differences in age, sex, cardiometabolic factors, and laboratory values. We further examined cardiovascular health using the American Heart Association's LE8 score. LE8 components and total scores (ranging from 0 to 100, with higher values indicating better cardiovascular health) were computed.[37] Between-group comparisons of LE8 scores were conducted.

This paper is exploratory in nature, and the analyses are primarily descriptive. Graphical methods and summary statistics were used to characterize the data. Continuous variables are expressed as mean ± SD or as median (Q1-Q3), while categorical variables are expressed as frequencies and percentages. Depending on the distribution of the data, either the 2-sample Student's *t*-test or the Wilcoxon rank sum test was used to compare continuous outcomes between 2 groups. For within-group comparisons, the paired Student's *t*-test or the Wilcoxon signed rank test was applied, as appropriate. Normality was assessed using the Shapiro-Wilk test.

For categorical outcomes, the Pearson chi-square test or the Fisher exact test was used, depending on expected cell counts. Multivariable logistic regression was performed to estimate the predicted probability of plaque across the age spectrum. Subjects with missing outcomes were excluded only when comparing the variable with missingness between groups.

All statistical analyses were conducted using R version 4.4.1 (R Foundation for Statistical Computing) using the dplyr and gtsummary packages

TABLE 1 Comparison of Candidate Characteristics by Opt-In Status

	Opted In (n = 283)	Did Not Opt In (n = 1,031)	*P* Value
Age, y	55 ± 8	54 ± 9	0.20
Female	188 (66)	665 (65)	0.50
Race			0.20
White	266 (94)	932 (90)	
Black	5 (1.8)	24 (2.3)	
Asian	9 (3.2)	59 (5.7)	
Hispanic	2 (0.7)	4 (0.4)	
Other	1 (0.4)	12 (1.2)	
Health care engagement			
Insurance type			0.12
Government	39 (14)	189 (18)	
Private	243 (86)	840 (81)	
None	1 (0.4)	2 (0.2)	
Social deprivation index	30 ± 26	32 ± 26	0.50
Specialty clinic frequency	54 ± 63	37 ± 50	<0.001
PCP frequency	2 ± 8	2 ± 9	0.90
Emergency frequency	0 ± 1	0 ± 1	0.13
Clinical measures and comorbidities			
SBP, mm Hg	126 ± 16	125 ± 16	0.50
DBP, mm Hg	76 ± 10	76 ± 10	0.60
Total cholesterol, mg/dL	202 ± 37	199 ± 34	0.60
HDL-C, mg/dL	67 ± 22	64 ± 19	0.30
LDL-C, mg/dL	116 ± 31	114 ± 29	0.70
BMI, kg/m^2	27.1 ± 5.3	27.1 ± 5.2	0.90
Current smoking	2 (0.7)	23 (2.2)	0.10
Study engagement-related variables			
Days since biobank enrollment	3,088 ± 716	3,058 ± 728	0.50
Distance, miles	14.3 ± 12.4	17.5 ± 16.6	<0.001

Values are mean ± SD or n (%). *P* values are based on Wilcoxon rank sum tests for continuous variables and Pearson chi-square or Fisher exact tests for categorical variables, as appropriate. Sample sizes vary slightly because of missing data: social deprivation index (n = 1,038), SBP and DBP (n = 1,298), total cholesterol (n = 914), HDL-C (n = 905), LDL-C (n = 599), BMI (n = 1,312), and days since biobank enrollment (n = 1,031). Distance was calculated as the great-circle (Haversine) distance between each participant's residential ZIP code centroid and central Boston (42.3601°N, 71.0589°W).

BMI = body mass index; DBP = diastolic blood pressure; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; PCP = primary care provider; SBP = systolic blood pressure.

for data wrangling and tabulation and ggplot2 and cowplot for visualization. All reported *P* values are 2-sided, with *P* values <0.05 considered to indicate statistical significance.

RESULTS

GENETIC RISK ENRICHMENT IN CLINICALLY LOW-RISK ADULTS. Our analysis of genetic and clinical data from 64,092 MGB Biobank participants illustrates the limitation of the traditional risk factor-based models in identifying individuals with low clinical but high genetic risk. As expected, participants with established CVD on lipid-lowering therapy (n = 8,838) were older compared with those without CVD (n = 26,015) (65.63 ± 7.25 years vs 58.88 ± 9.30 years; $P < 0.0001$), were predominantly men (59% vs 47%; $P < 0.0001$), had lower treated LDL-C (81.03 ± 37.44 mg/dL vs 108.27 ± 34.77 mg/dL; $P < 0.0001$), and were more likely to have high CAD PRS (27% vs 21%; $P < 0.0001$). Among the primary prevention cohort, there were 7,991 patients (30.7%) on lipid-lowering therapy. Also as expected, participants receiving lipid-lowering therapy without established CVD (n = 7,991) had an overall higher clinical risk profile compared with those not on lipid-lowering therapy (n = 18,024) (median American Heart Association PCE 10-year atherosclerotic CVD [ASCVD] risk 11.45 [Q1-Q3: 5.77-19.07] vs 3.07 [Q1-Q3: 1.13-7.61]). However, there was no difference in the prevalence of high polygenic risk between the 2 groups (22% vs 21%; $P = 0.08$) (Supplemental Table 2).

The 18,024 biobank participants with no established CVD and not on lipid-lowering therapy had a mean age of 56.14 ± 9.84 years, and 66.18% were women. Those included 3,696 participants with high CAD PRS and as such "flying under the radar" with high genetic risk despite their apparently low clinical risk. The PROACT trials aimed to target this population of participants in the MGB Biobank. These are middle-aged individuals (mean age 56.09 ± 9.62 years), 67% of whom are women, with mean LDL-C of 110 ± 31 mg/dL and among whom 1,843 (88.4%) were at low or borderline risk according to the PCE 10-year risk calculator (Supplemental Table 2).

OPERATIONAL FEASIBILITY AND RECRUITMENT OUTCOMES. Large biobanks consented for callback such as the MGB Biobank provide an exceptional opportunity to identify and recruit individuals for genetically enriched clinical trials.[47,48] However, the feasibility and effectiveness of such an approach in CVD prevention have not been fully demonstrated.

Among 64,092 genotyped MGB Biobank participants, 2,495 met eligibility criteria (eligibility yield 3.9%; 95% CI: 3.7%-4.0%) for the PROACT trials (Supplemental Table 1). Between November 2023 and January 2025, 1,314 eligible individuals were invited to participate via an omnichannel callback strategy that combines mailed invitations, follow-up phone calls, secure emails, Patient Gateway messages, and a brief informational video (**Figure 2B**). Of these, 283 (21.5%; 95% CI: 19.4%-23.8%) expressed interest in participating. As of this writing, among this cohort, 266 participants (20.2%; 95% CI: 18.2%-22.5%) provided informed consent and 204 (15.5%; 95% CI: 13.6%-17.6%) completed comprehensive clinical assessments and coronary CTA, and 201 (15.3%; 95% CI: 13.4%-17.4%) have been randomized in PROACT1 or PROACT2 (**Figure 2A**).

To explore drivers of study engagement, we compared the 283 candidates who opted in and had complete data with the 1,031 who declined or did not respond to understand potential drivers of interest in biobank callback studies (Table 1). Clear differences emerged in health care engagement and geographic proximity to the study site, whereas demographics or clinical characteristics were broadly similar between groups.

Participants who opted in exhibited higher specialty clinic use at MGB over the past 3 years (54.20 ± 62.83 visits vs 37.35 ± 50.04 visits; $P < 0.001$), and lived significantly closer to central Boston (mean distance 14.30 ± 12.39 miles vs 17.52 ± 16.60 miles; $P < 0.001$). These variables were the primary factors associated with opting in. Geographic patterns further supported the association with proximity, with spatial mapping (Supplemental Figures 5 and 6) demonstrating that opt-in rates were highest in regions closest to central Boston.

In contrast, demographics, clinical risk factors, primary care and emergency visit frequency, insurance type, time since biobank enrollment, and social deprivation index (a neighborhood-level measure of socioeconomic disadvantage) showed no meaningful differences between those who opted in and those who did not; detailed comparisons are provided in Table 1.

TABLE 2 Participant Demographics and Clinical Characteristics by Coronary Plaque Status

	Total (N = 204)	No Plaque (n = 102)	Plaque (n = 102)
Demographic characteristics			
Age, y	56.3 ± 8.5	53.7 ± 8.4	59.0 ± 7.7
Female	141 (69)	87 (85)	54 (53)
Race			
White	189 (92.6)	95 (93.1)	94 (92.2)
Black	4 (2.0)	2 (2.0)	2 (2.0)
Asian	6 (2.9)	2 (2.0)	4 (3.9)
Hispanic	3 (1.5)	2 (2.0)	1 (1.0)
Other	2 (1.0)	1 (1.0)	1 (1.0)
Clinical measures and comorbidities			
SBP, mm Hg	125.62 ± 15.69	123.20 ± 16.91	128.05 ± 14.02
DBP, mm Hg	81.83 ± 9.35	81.22 ± 9.36	82.45 ± 9.35
LDL-C, mg/dL	120.46 ± 29.57	116.58 ± 28.02	124.41 ± 30.71
HDL-C, mg/dL	62.80 ± 18.17	66.09 ± 18.06	59.52 ± 17.76
Triglycerides, mg/dL	131.10 ± 75.42	123.68 ± 73.21	138.52 ± 77.22
BMI, kg/m^2	26.87 ± 4.69	26.24 ± 4.35	27.50 ± 4.96
HbA_{1c}, %	5.47 ± 0.48	5.42 ± 0.34	5.53 ± 0.59
Non-HDL cholesterol, mg/dL	143.34 ± 34.10	137.46 ± 33.14	149.23 ± 34.19
hsCRP, mg/L	2.50 ± 3.21	2.73 ± 3.63	2.26 ± 2.72

Values are mean ± SD or n (%). Between the "plaque" and "no plaque" groups, comparisons used Student's *t*-test for normally distributed measures and the Wilcoxon rank sum test when distributions departed from normality; the Pearson chi-square test was used for categorical variables (the Fisher exact test was applied if any cell count was <5). *P* values refer only to the 2-group comparison ("no plaque" vs "plaque"); the "Total" column is shown for descriptive purposes and was not tested. HbA_{1c} was missing in 17 participants (n = 187 analyzed).

HbA_{1c} = hemoglobin A_{1c}; hsCRP = high-sensitivity C-reactive protein; other abbreviations as in Table 1.

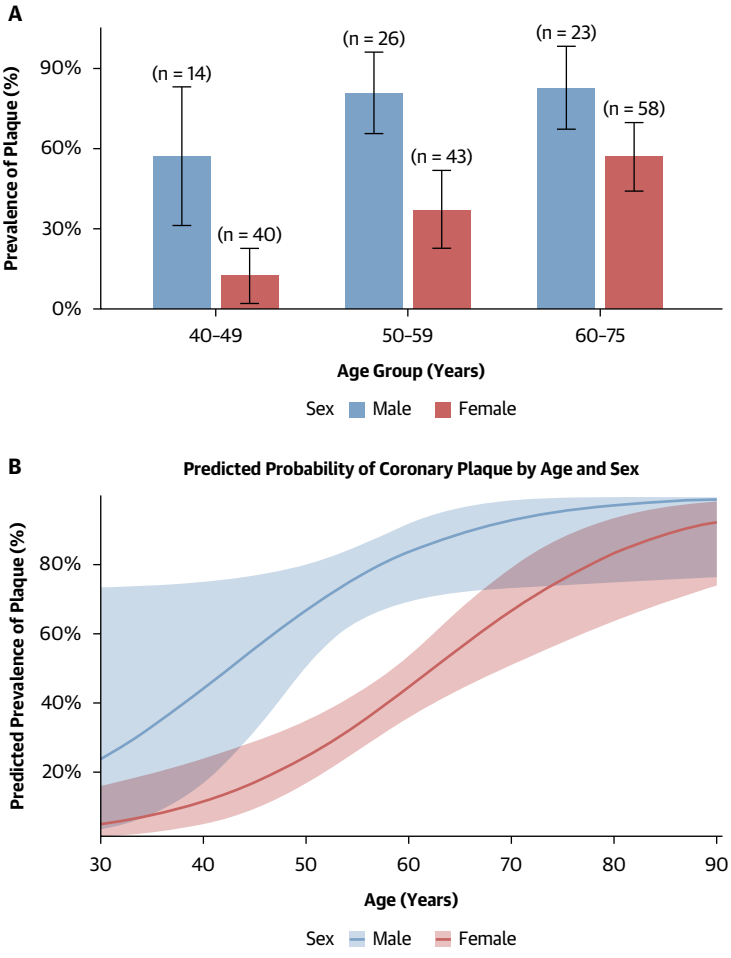
SUBCLINICAL CORONARY PLAQUE AMONG PEOPLE WITH LOW CLINICAL AND HIGH GENETIC RISK. The analyses of coronary plaque prevalence and associated risk factors among enrolled PROACT participants are exploratory and based on an interim subset of the first 204 participants who completed coronary CTA. These findings are primarily descriptive; formal multivariable modeling will be conducted upon full study completion to better assess independent predictors of plaque and treatment effects.

Among 204 participants who underwent coronary CTA, 69% were women, with a mean age of 56.3 ± 8.5 years (Table 2). Coronary plaque was identified in 102 (50%), including 1 individual with severe 3-vessel CAD who was excluded from randomization and referred for coronary artery bypass grafting (Central Illustration). Participants with plaque were older (59.0 ± 7.7 years vs 53.7 ± 8.4 years; $P < 0.001$) and more likely to be men (n = 48 [47%] vs n = 15 [15%]). Race distribution was similar across groups (92% White in both groups; $P = 0.83$).

Subclinical plaque prevalence differed significantly by age and sex (Central Illustration). More than three-quarters of men (76.2%) and 38.3% of women had subclinical plaque. Among participants 40 to 49 years of age, plaque was present in 57% of men (n = 8) and 12% (n = 5) of women (Figure 3A). This gap narrowed with age: among 50- to 59-year-olds, 81% of men (n = 21) and 37% of women (n = 16) had plaque; by 60 to 75 years, 83% of men (n = 19) and 57% of women (n = 33) had plaque (Figure 3B).

Detailed plaque characteristics for all participants (n = 204) are summarized in Table 3. Among participants with plaque (n = 102), 9 (8.8%) had calcified plaque only, 77 (75.5%) had mixed calcified and noncalcified plaque, and 16 (15.7%) had noncalcified plaque only (Figure 4A). High-risk plaque features were present in 28 of these participants (27.5%), most commonly positive remodeling (n = 26 [25.5%]) and spotty calcification (n = 17 [16.7%]) (Figure 4B). Plaque stenosis severity, as defined using the Coronary Artery Disease Reporting and Data System 2.0 classification, revealed that most participants had minimal (n = 77 [75.5%]) or mild (n = 21 [10.3%]) stenosis, while 3 (1.5%) had moderate and 1 (0.5%) had severe stenosis. Similarly, plaque burden scores were distributed as mild (n = 65 [63.7%]), moderate (n = 21 [20.6%]), severe (n = 13 [12.7%]), and extensive (n = 3 [2.9%]). Calcium scores among participants with plaque were as follows: 17 (16.7%) had CAC scores of

FIGURE 3 Prevalence of Subclinical Coronary Plaque by Age and Sex



(A) Bar chart showing the prevalence of subclinical coronary plaque among the first 204 PROACT (Polygenic Risk Based Detection and Treatment of Subclinical Coronary Atherosclerosis) participants enrolled before January 31, 2025, stratified by sex and age groups (40-49, 50-59, and 60-75 years). Plaque prevalence was calculated as the percentage of individuals with detected plaque within each stratum, with error bars indicating 95% CIs. (B) Predicted probability of coronary plaque by age and sex, on the basis of a logistic regression model including an age × sex interaction. Solid lines show a model-estimated prevalence for men (blue) and women (red) across ages 20 to 80 years; shaded ribbons represent 95% CIs (computed on the logit scale and back-transformed to the probability scale). The x-axis spans from 20 to ≥80 years of age, and the y-axis shows predicted plaque prevalence from 0% to 100%. Continuous curves and their uncertainty bands allow comparison of how plaque risk evolves with age in each sex.

0, 58 (56.9%) had CAC scores of 1 to 99, 17 (16.7%) had CAC scores of 100 to 299, and 10 (9.8%) had CAC scores ≥300. For participants who had nonzero CAC scores and were older than 45 years (n = 83), we calculated the MESA (Multi-Ethnic Study of Atherosclerosis) adjusted percentiles and found that 36 of the 83 (43.4%) had MESA percentiles below 75, the guideline-accepted cutoff for statin initiation (Supplemental Figure 7).[6] Complete plaque and Coronary Artery Disease Reporting and Data System distributions for the total cohort (n = 204) are reported in Table 3 and Figure 4.

We also conducted a sensitivity analysis limited to the 153 participants classified as "low" or "borderline" risk according to the PCE (10-year ASCVD risk <7.5%).[49] Even in this group, the prevalence of subclinical plaque remained substantial at 39.9% (95% CI: 32.1%-48.1%). These individuals were predominantly women (78%), with a mean age of 53.6 ± 7.1 years. Sex-specific plaque

TABLE 3 Comparison of Subclinical Plaque Characteristics by ASCVD Risk Score Categories

	All Participants (N = 204)	Low (<5%) (n = 129)	Borderline (5%-<7.5%) (n = 24)	Intermediate (7.5%-<20%) (n = 43)	High (≥20%) (n = 8)
Plaque score categories					
0 segments with plaque	102 (50.0)	82 (63.6)	10 (41.7)	9 (20.9)	1 (12.5)
1 or 2 segments with plaque	66 (32.4)	37 (28.7)	9 (37.5)	16 (37.2)	4 (50.0)
≥3 segments with plaque	36 (17.6)	10 (7.8)	5 (20.8)	18 (41.9)	3 (37.5)
Participants with high-risk plaque features	28 (13.7)	13 (10.1)	3 (12.5)	10 (23.3)	2 (25.0)
Stenosis					
CAD-RADS 0: no plaque or stenosis	102 (50.0)	82 (63.6)	10 (41.7)	9 (20.9)	1 (12.5)
CAD-RADS 1: 1%-24% stenosis	77 (37.7)	39 (30.2)	11 (45.8)	23 (53.5)	4 (50.0)
CAD-RADS 2: 25%-49% stenosis	21 (10.3)	8 (6.2)	3 (12.5)	8 (18.6)	2 (25.0)
CAD-RADS 3: 50%-69% stenosis	3 (1.5)	0 (0.0)	0 (0.0)	3 (7.0)	0 (0.0)
CAD-RADS 4A: 70%-99% stenosis	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)
CAD-RADS 4B: left main coronary artery ≥50% or 3-vessel ≥70% stenosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
CAD-RADS 5: 100% occlusion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Plaque burden					
P0	102 (50.0)	82 (63.6)	10 (41.7)	9 (20.9)	1 (12.5)
P1: mild	65 (31.9)	36 (27.9)	9 (37.5)	17 (39.5)	3 (37.5)
P2: moderate	21 (10.3)	9 (7.0)	3 (12.5)	8 (18.6)	1 (12.5)
P3: severe	13 (6.4)	2 (1.6)	2 (8.3)	8 (18.6)	1 (12.5)
P4: extensive	3 (1.5)	0 (0.0)	0 (0.0)	1 (2.3)	2 (25.0)
CAC score					
0	119 (58.3)	90 (69.8)	13 (54.2)	14 (32.6)	2 (25.0)
1-99	58 (28.4)	32 (24.8)	6 (25.0)	17 (39.5)	3 (37.5)
100-299	17 (8.3)	5 (3.9)	4 (16.7)	7 (16.3)	1 (12.5)
≥300	10 (4.9)	2 (1.6)	1 (4.2)	5 (11.6)	2 (25.0)

Values are n (%). Percentages reflect the proportion of participants within each ASCVD risk stratum. "High-risk plaque features" denote the presence of at least 1 high-risk characteristic on coronary computed tomographic angiography. ASCVD risk categories are based on pooled cohort equation 10-year risk: low (<5%), borderline (5%-7.4%), intermediate (7.5%-19.9%), and high (≥20%). Percentages may not total 100% because of rounding.

ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; CAD-RADS = Coronary Artery Disease Reporting and Data System.

prevalence in this group was 69.7% in men and 31.7% in women.

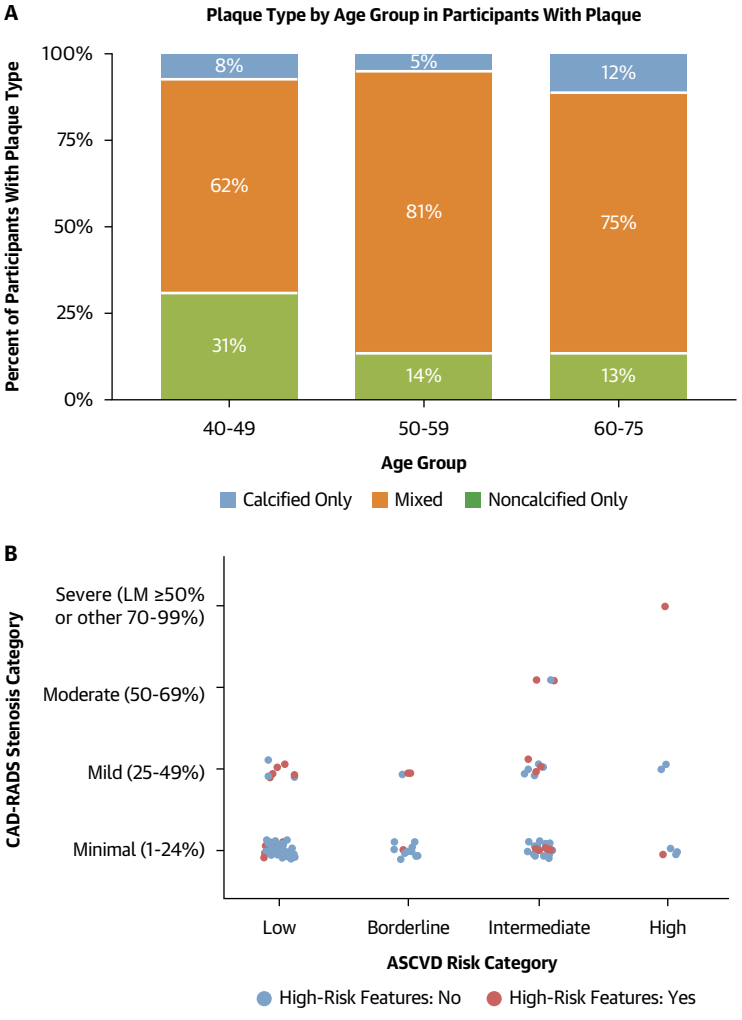
CLINICAL RISK FACTORS AND CARDIOVASCULAR HEALTH AMONG PARTICIPANTS WITH AND WITHOUT PLAQUE. Clinical characteristics were broadly similar between participants with and without plaque. Modestly higher LDL-C (124.4 ± 30.7 mg/dL vs 116.6 ± 28.0 mg/dL), body mass index (27.50 ± 4.96 kg/m^2 vs 26.24 ± 4.35 kg/m^2), and systolic blood pressure (128.05 ± 14.02 mm Hg vs 123.20 ± 16.91 mm Hg) were observed among those with plaque. Other risk factors such as diastolic blood pressure, glycated hemoglobin, non-high-density lipoprotein cholesterol, and hsCRP were similar (Table 3).

The high prevalence of subclinical coronary plaque was observed despite favorable overall cardiovascular health (mean LE8 score 73.3 ± 11.5) (Figure 5A, Supplemental Table 3), which is nearly 1 SD higher than the U.S. adult average (64.7) and is substantially higher than international cohorts.[50,51] LE8 distribution showed that 67 participants (32.8%) had "high," 132 (64.7%) had "moderate," and only 5 (2.5%) had "low" cardiovascular health (Figure 5B). LE8 scores were lower among those with plaque compared with those without plaque, and this was driven primarily by less favorable sleep, blood pressure, and body mass index subscores (Figure 5).

In this interim analysis of a subset PROACT participants selected with high genetic risk but not on lipid-lowering therapy, CAD PRS appears to be the dominant driver of plaque presence (Central Illustration); however, larger sample size at the conclusion of the study, along with multivariable modeling, is likely to provide better understanding of the role of conventional risk factors in this group.

PARTICIPANT VIGNETTES. To contextualize these findings, 2 representative cases highlight how CAD PRS stratification can reveal subclinical disease in

FIGURE 4 Distribution and Severity of Coronary Plaque by Age and ASCVD Risk Category



(A) Stacked bar chart showing the distribution of plaque composition among participants with any detectable plaque (n = 102), stratified by age group (40-49, 50-59, and 60-75 years). Bars represent the proportion of participants within each age group with noncalcified, mixed, or calcified plaque. (B) Scatterplot of individual participants by atherosclerotic cardiovascular disease (ASCVD) (pooled cohort equations) risk category (low, borderline, intermediate, and high) vs Coronary Artery Disease Reporting and Data System (CAD-RADS) stenosis category (category 1, 1%-24%; category 2, 25%-49%; category 3, 50%-69%; category 4A, 70%-99% or left main stenosis ≥50%). Each point represents 1 participant. Red points indicate the presence of ≥1 high-risk plaque feature; gray indicates no high-risk plaque features.

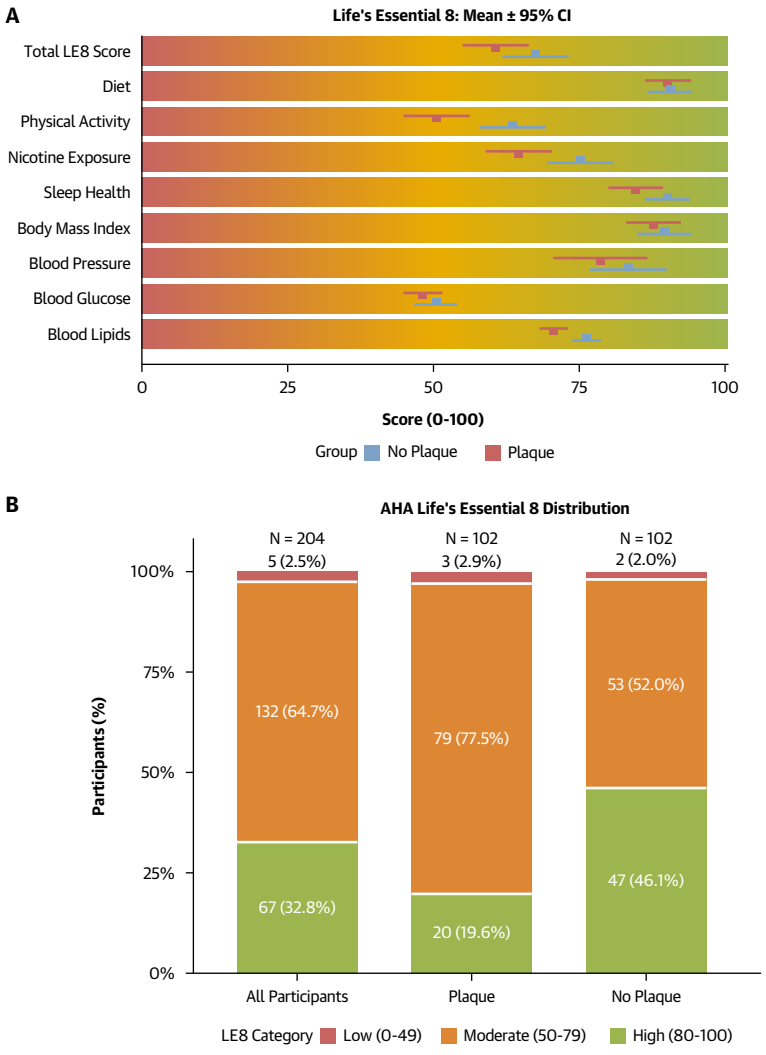
individuals otherwise considered low risk by conventional measures (Figure 6).

Figure 6A depicts a 46-year-old man with a PCE 10-year ASCVD risk of 2.3% and a CAD PRS in the 99th percentile, yet coronary CTA revealed a noncalcified mid left anterior descending coronary artery plaque causing mild stenosis despite a CAC score of 0. Figure 6B shows a 51-year-old woman with a PCE risk of 1.2% and CAD PRS in the 82nd percentile. Coronary CTA showed mixed plaque in the mid left anterior descending coronary artery segment, with a CAC score of 38.

DISCUSSION

We report interim findings from the first genotype-first, biobank-enabled clinical trial that leverages CAD PRS for proactive cardiovascular prevention. This description and analysis of the early findings from PROACT offers 3 preliminary insights. First,

FIGURE 5 Distribution of AHA LE8 Scores by Subclinical Coronary Plaque Status

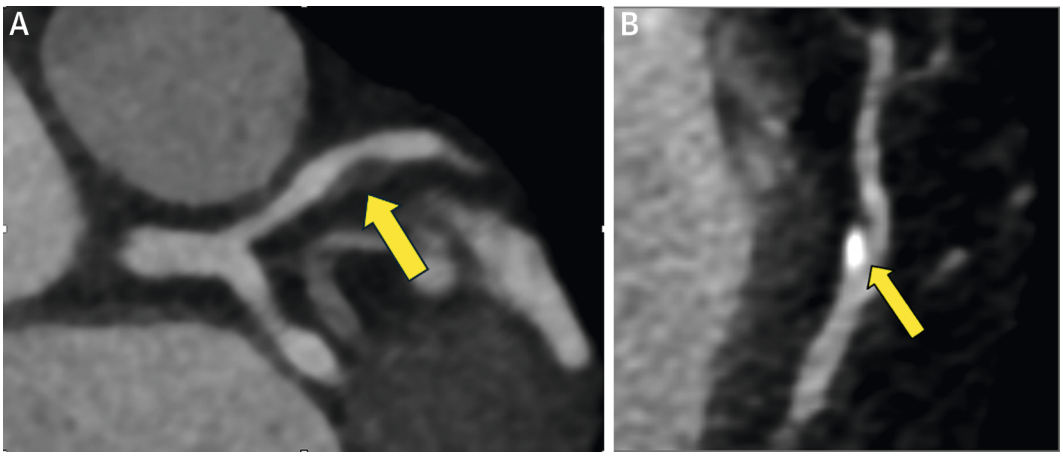


(A) Mean American Heart Association (AHA) Life's Essential 8 (LE8) component and total scores (range: 0-100) are overlaid on a graded background, with blue bars showing the no-plaque group and black bars the plaque group. Thick segments mark group means, and thin horizontal whiskers show 95% CIs. All estimates are based on 102 individuals per group. The gradient beneath each row provides a visual scale from poor (0 = red) to ideal (100 = green) cardiovascular health. Continuous variables are plotted side by side using horizontal dodge for direct comparison. Corresponding numerical values and *P* values are provided in Supplemental Table 2. (B) Stacked bar chart showing the distribution of AHA LE8 cardiovascular health categories—low (0-49), moderate (50-79), and high (80-100)—among all participants and stratified by plaque status. Bars represent the percentage of individuals in each category, with totals displayed above each bar.

conventional risk factor-based models miss a substantial proportion of individuals "flying under the radar" who have subclinical plaque. Second, biobank participants are receptive to genetic testing and identifying subclinical disease. Third, a polygenic risk-enriched strategy to detect subclinical coronary atherosclerosis can uncover silent CAD in at least one-half the population screened despite low clinical risk and favorable cardiovascular health profile (**Central Illustration**).

Conventional risk factor-based models depend on the presence of clinical risk factors that emerge late in the disease trajectory. In our biobank analysis of a lipid lowering-naive cohort without CAD, 21% met the high CAD PRS threshold despite low clinical risk. Prior studies have shown that CAD PRS reclassifies

FIGURE 6 Subclinical Coronary Plaque in Apparently Low-Risk Individuals



Representative participants with low atherosclerotic cardiovascular disease pooled cohort equation (PCE) scores were found to have coronary plaque on coronary computed tomographic angiography. (A) A 46-year-old man (PCE 2.3%, coronary artery calcium [CAC] score = 0, polygenic risk score [PRS] 99th percentile) with noncalcified mid left anterior descending coronary artery (LAD) plaque causing mild stenosis. (B) A 51-year-old woman (PCE 1.2%, CAC score = 38, PRS 82nd percentile) with mixed plaque in the mid LAD segment. These cases highlight how genotype-first imaging can identify silent atherosclerosis missed by traditional risk models.

about 15% of future events out of the "low-risk" category and projects the greatest relative and absolute benefit of statin therapy for primary prevention in the high PRS groups.[19,23,52] By leveraging a fixed, lifelong genetic measure rather than transient clinical biomarkers and middle age clinical risk factors, PROACT may identify high-risk individuals while disease trajectories are potentially still modifiable. One-half of participants had subclinical coronary plaque despite risk factor profiles that mostly do not support lipid-lowering treatment following current guidelines, as well as above the U.S. average profile of cardiovascular health.

PROACT also provides proof of concept for the feasibility of genotype-first recruitment for clinical trials. To our knowledge, this is the first PRS-enriched clinical trial for a drug trial. PRS enrichment holds a strong promise for prognostic and predictive enrichment of clinical trials that could markedly reduce the cost and timeline of clinical development; however, feasibility has never been developed.[53] Any PRS-based enrichment strategy for clinical trials requires large numbers of individuals with available genotyping data who are willing to engage in clinical trials. In this study, we illustrate the rate of eligibility for a typical PRS-enriched primary prevention clinical trial from a contemporary hospital-based biobank in the United States, which was <4% (2,495 of 64,092). Once potentially eligible individuals are identified, the advantage of biobank-based enrollment is the ability to enroll participants relatively quickly rather than serially and to maximize enrollment rates once contacted. The omnichannel approach in PROACT yielded more than 20% of people interested in the study, which exceeds most published estimates of callback studies from biobanks or electronic medical records.[54] Interest correlated with previous specialty clinic engagement (a marker of health system familiarity) and proximity to the imaging site, but not with traditional risk factors or social deprivation index. These operational insights may inform future pragmatic implementation, for example, exploring whether embedding genetic testing within existing specialty pathways may boost uptake. Most important, although the yield of eligibility was low, the enrollment rates were high. This suggests that a key barrier in future PRS-enriched trials is likely to be the availability of genotypes on larger numbers of people who are consented for callback.

These interim findings from PROACT also demonstrate the feasibility and potential clinical utility of a 2-step approach to cardiovascular prevention that consists of biomarker enrichment followed by screening for subclinical coronary plaque (**Figure 1A**). This proactive approach is particularly interesting in PROACT because of the nature of CAD PRS, which despite the potential clinical utility and availability,

has not yet penetrated practice at scale. Our exploratory findings build on prior studies, such as the REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV) trial, which assessed a large cohort of HIV-positive individuals undergoing coronary CTA and revealed that 49% had coronary plaque, and the Miami Heart Study, which similarly reported 49% plaque prevalence in a population already triggering clinical concern and often on statins or aspirin.[55-57] Prior imaging cohorts, including MESA, the Miami Heart Study, and REPRIEVE, were generally enrolled older, more comorbid, predominantly male, and often enriched for individuals already warranting clinical evaluation.[55-58] In contrast, PROACT is the first trial to prospectively assess subclinical coronary plaque in a primary prevention cohort that has low clinical risk and favorable cardiovascular health. Participants were younger, were predominantly women, were not on lipid-lowering therapy, exhibited favorable cardiovascular health with a mean LE8 score 1 SD higher than the national average, and had clinical risk factors that were mostly within reassuring ranges per guidelines. Yet despite these reassuring profiles, one-half harbored subclinical plaque (76.2% of men and 38.3% of women), suggesting that many individuals with high CAD PRS remain undetected by conventional risk stratification and are effectively "flying under the radar."

In addition to enrolling symptomatic or higher clinical risk participants, most prior studies of coronary imaging relied on CAC scoring, which identifies only late-stage calcified plaque and misses noncalcified plaque. In contrast, coronary CTA captures both calcified and lipid-rich noncalcified plaque, the hallmark of early atherosclerosis, and enables full visualization of plaque and its features in the coronary tree, which prior to this technology relied on invasive intravascular imaging. Coronary CTA represents a promising noninvasive alternative suitable for primary prevention, enabling detailed plaque phenotyping including plaque volume, plaque composition, high-risk plaque features associated with vulnerability to rupture, and perivascular fat attenuation index, a measure of residual inflammation associated with cardiovascular outcomes.[59-66] Ongoing advances in artificial intelligence–based plaque quantification promise automated risk stratification and longitudinal monitoring that could further streamline precision prevention pipelines.[67-69] Our interim findings support the potential of a 2-step proactive prevention paradigm: first, genotype-based triage to identify the approximately 20% of adults at 3-fold lifetime risk and, second, targeted coronary CTA to detect subclinical disease and inform therapeutic decision-making. This approach may balance the growing demand for earlier intervention with the practical constraints of mass coronary computed tomographic angiographic screening.

Although PRS are not diagnostic tools themselves, they can play a pivotal role in stratifying individuals for preventive screening and targeted interventions. Similar to how age and smoking history guide the allocation of low-dose computed tomographic scans in lung cancer screening programs, PRS can be integrated into risk-based triaging to refine preventive strategies and prioritize individuals who may benefit from further evaluation.[70] The BARCODE1 trial for prostate cancer demonstrated that genome-first stratification can detect clinically significant disease missed by traditional pathways.[29] Analogous to BARCODE1, PROACT illustrates how genomic information available from birth can uncover risk not captured by current clinical frameworks and can help inform proactive, 2-step prevention paradigm: first, genotype-based triage to identify high-risk individuals and, second, targeted coronary CTA to detect subclinical disease and guide early therapeutic decision-making.

PROACT is approaching enrollment completion of 400 participants, who will be followed for 1 year. The planned readout of PROACT 1 and PROACT 2 is in 2027. PROACT 1 will answer whether disclosure of CAD PRS compared with standard of care results in improved cardiovascular health. PROACT 2 will determine whether single and dual targeting of LDL-C (with high-intensity statin) and inflammation (with low-dose colchicine) reduce noncalcified plaque progression compared with placebo. Analysis of biomarkers and plaque characteristics will provide mechanistic insights on the association of biomarkers with plaque and impact of low-dose colchicine and statin therapy on plaque among people with high polygenic risk. To our knowledge, PROACT 2 constitutes the first PRS-enriched clinical trial of a drug therapy, and we hope that upon its completion, it will usher in a new era of genomically enriched clinical trials and more proactive prevention for CAD.

STUDY LIMITATIONS. First, the findings reflect an interim, exploratory analysis of the first 204 participants, and current associations of plaque with clinical risk factors are not powered for definitive inference. Second, participants are enrolled from a single U.S.-based hospital biobank and are a predominantly White and highly engaged population, which may limit generalizability.

Third, apolipoprotein B and lipoprotein(a) were not routinely measured at baseline; assays are

planned on stored specimens. Fourth, the genotype-first callback design may introduce selection bias, as participants who engage with specialty care or live closer to the imaging center may be more likely to participate.

Fifth, quantitative plaque volume and perivascular fat attenuation analyses are planned once all imaging data are complete. Additional studies are needed to confirm similar feasibility and operations in other contexts, but we hope that this study provides a proof of concept that supports initiating such studies.

CONCLUSIONS

This interim analysis from PROACT demonstrates the feasibility of implementing a genome-first, biobank-enabled strategy for primary prevention trials. PROACT is the first PRS-enriched clinical trial to prospectively evaluate subclinical coronary disease using coronary CTA in a clinically low-risk population, suggesting that CAD PRS can identify individuals who would otherwise fly under the radar in contemporary practice. These interim findings support the potential for a 2-step prevention strategy, genotype-based triage followed by targeted imaging, that may enable earlier intervention. This proof-of-concept report provides an illustration of how cardiovascular prevention could be shifted decades earlier in the disease course and might help align preventive cardiology with the proactive, precision approaches already transforming oncology and other fields.

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KEY WORDS atherosclerosis, coronary artery disease, coronary computed tomography angiography, polygenic risk score, primary prevention

APPENDIX For supplemental methods, references, tables, figures, and trial protocols, please see the online version of this paper.