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THE PRESENT AND FUTURE

JACC REVIEW TOPIC OF THE WEEK

Primary Prevention of Subclinical Atherosclerosis in Young Adults

JACC Review Topic of the Week

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ABSTRACT

There is growing evidence that the atherosclerotic process that leads to symptomatic cardiovascular disease (CVD) starts at an early age. In young adults, exposure to low-density lipoprotein-cholesterol and other cardiovascular risk factor (CVRF) mediators, even at levels considered within normal limits, increases the prevalence of subclinical atherosclerosis and is associated with greater risk of cardiovascular events later in life. The optimal CVRF targets to prevent CVD in asymptomatic young individuals (<40 years) are unknown. The randomized controlled PRECAD (Prevent Coronary Artery Disease) trial has been developed to assess the potential benefit of an aggressive control of CVRF in otherwise healthy young adults. The hypothesis of PRECAD is that in subjects aged 20 to 39 years without known CVD, maintaining low-density lipoprotein-cholesterol <70 mg/dL and strict control of blood pressure and glucose will prevent the onset of atherosclerosis and/or its progression. The primary endpoint will be the change in total atherosclerosis burden, a surrogate for CVD. (J Am Coll Cardiol 2023;82:2152–2162) © 2023 by the American College of Cardiology Foundation.

Cardiovascular disease (CVD) is the leading cause of death and disability in the world.[1] The atherosclerotic process leading to CVD is complex, with evidence that this process begins at very young ages.[2] Longitudinal studies have demonstrated that the presence of cardiovascular risk factors (CVRFs) at young ages accelerates the development of CVD in late adulthood.[3] In this paper, we review the implications of CVRFs in young adults, even at levels considered "normal," on the subsequent development of subclinical atherosclerosis (SA). We revisit the link between CVRF exposure, SA extent and progression, and the risk of later cardiovascular events. Furthermore, we introduce the design and rationale for the PRECAD (Prevent Coronary Artery Disease) trial, a randomized controlled trial that aims to determine whether an intense CVRF intervention starting at young ages can reduce atherosclerotic burden and future cardiovascular events.

SA STARTS AT A YOUNG AGE

Population-based studies have shown that SA starts at a young age. In a cohort of >4,000 healthy subjects between 40 and 54 years of age, the PESA

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HIGHLIGHTS

- In young adults, modifiable cardiovascular risk factors, even when at conventional target levels, are associated with subclinical atherosclerosis and cardiovascular events over long-term follow-up.
- A randomized trial will evaluate whether controlling cardiovascular risk factors to more aggressive targets in adults aged 20 to 39 years reduces atherosclerosis.
- The results may form the basis for new targets for cardiovascular risk modification for primary prevention of atherosclerosis in young adults.

(Progression of Early Subclinical Atherosclerosis) study demonstrated that 63% of asymptomatic participants aged 40 to 54 years had SA in 1 or more vascular territories (carotid, aorta, femoral, and coronary arteries).[4] Interestingly, 60% of the participants classified as low risk by the traditional risk scores had SA, some with involvement of multiple vascular territories. Indeed, the PESA study showed that generalized atherosclerosis (ie, affecting ≥4 vascular territories) can be present as early as age 40 years in healthy subjects, particularly in men, and that at least 50% of subjects after 45 to 49 years have atherosclerosis in ≥2 vascular territories (**Figure 1**).[4] Furthermore, plaque progression was observed in 41.5% of these asymptomatic subjects after only 3 years of follow-up.[4,5]

The presence of SA contributes to prognostic stratification of long-term risk in young adults; in subjects from the MESA (Multi-Ethnic Study of Atherosclerosis) (44-50 years of age) and CARDIA (Coronary Artery Risk Development in Young Adults) study (37-50 years of age) with low 10-year risk, the SA burden and rate of progression at 2, 3, and 5 years were greater in individuals with high lifetime risk compared with low lifetime risk.[6] The number of vascular territories affected with atherosclerosis has also been suggested as an additional metric to improve risk classification in asymptomatic subjects.[4]

CVRFs EVEN AT "NORMAL" LEVELS ARE ASSOCIATED WITH SA

Low-density lipoprotein cholesterol (LDL-C), even at levels currently considered within normal limits, is independently associated with the presence and extent of SA.[7] The PESA study showed that participants with LDL-C as low as 70 mg/dL had SA, in some cases affecting multiple vascular territories (**Figure 2**).[7] Higher levels of LDL-C (but less than thresholds currently considered abnormal in this group) were associated with an increasing risk in the prevalence of SA, from 11% in the 60 to 70 mg/dL group to 64% in the 150 to 160 mg/dL group.[7] Triglyceride levels ≥150 mg/dL have also been associated with higher risk of SA in different vascular territories, after adjusting for other CVRFs.[8]

Similar associations have been observed between other CVRFs within normal limits and SA. Glycated hemoglobin A1c (HbA1c), which is not included in the traditional cardiovascular risk scores,[9,10] has been suggested as an additional biomarker for early cardiovascular risk assessment. Prediabetes is a frequent condition that is defined by HbA1c levels between 5.7% and 6.4%,[11] and even lower HbA1c levels have been associated with SA. In a subgroup of the PESA cohort, a linear association was observed between HbA1c levels (range: 4.9%-6.8%) and SA (**Figure 2**); indeed, even small elevations in HbA1c were associated with a higher prevalence of SA in this cohort of apparently healthy middle-aged individuals.[12] Thus, more effective glycemic control might be beneficial for primary prevention.

Blood pressure has also been studied as an independent risk factor for SA. Previous studies have reported an association between increases in systolic blood pressure (SBP) and coronary artery calcium (CAC), a well-known marker for coronary atherosclerosis.[13] In the MESA study, every 10 mm Hg increase in SBP was associated with a higher prevalence and greater extent of CAC in subjects without traditional CVRF, starting at an SBP level as low as 90 mm Hg.[14] Overall, the high prevalence of SA in subjects with "normal" values for conventional CVRF brings into question the definition of normal in primary prevention.[15]

EXPOSURE TO CVRFs AT AN EARLY AGE INCREASES THE RISK OF CARDIOVASCULAR EVENTS

Not only has LDL-C been linked with SA, but greater exposure to elevated LDL-C has been associated with increased risks of CVD in a concentration-dependent fashion, independent from other CVRFs.[16] In the CARDIA study, among adults aged 18 to 30 years with a median 16-year follow-up, incident CVD risk

ABBREVIATIONS AND ACRONYMS

3DVUS = 3D vascular ultrasound

ACC/AHA = American College of Cardiology/American Heart Association

CAC = coronary artery calcium

CVD = cardiovascular disease

CVRF = cardiovascular risk factors

FH = familial hypercholesterolemia

HbA1c = glycated hemoglobin A1c

LDL-C = low-density lipoprotein-cholesterol

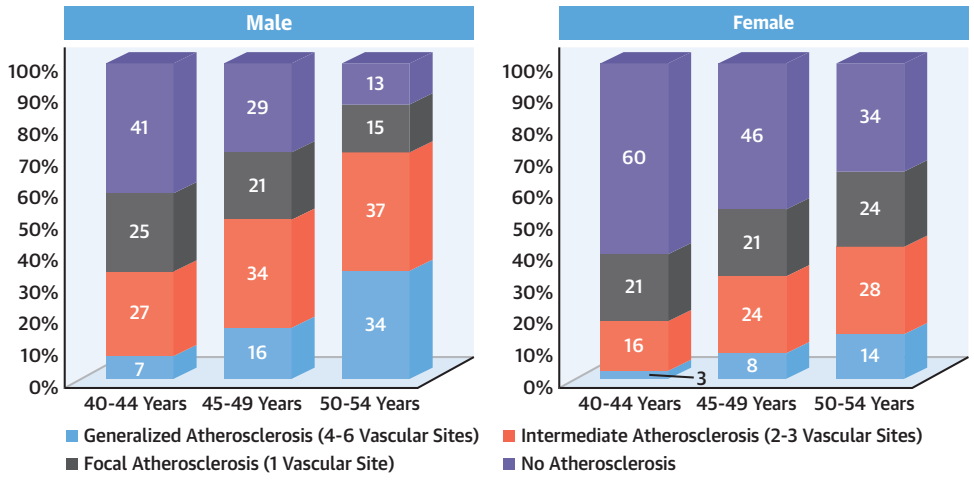
Lp(a) = lipoprotein (a)

PCSK9 = proprotein convertase subtilisin-lexin type 9

SA = subclinical atherosclerosis

SBP = systolic blood pressure

FIGURE 1 SA Starts at a Young Age



The graph shows the distribution of the extent of subclinical atherosclerosis (SA) in multiple vascular territories according to age and sex. Generalized atherosclerosis (ie, affecting ≥4 vascular territories) can be present in subjects as young as 40 years of age. Reproduced with permission from Fernandez-Friera et al.[4]

increased with the total cumulative exposure to LDL-C (calculated as the area under the LDL-C vs age curve from 18 to 40 years) (**Figure 3**).[16] Moreover, the same cumulative LDL-C exposure reached at a younger age resulted in a greater risk increase, emphasizing the potential benefits of early intervention.[16,17] These observations support studying more effective LDL-C lowering for primary prevention, even in individuals conventionally considered at low risk.

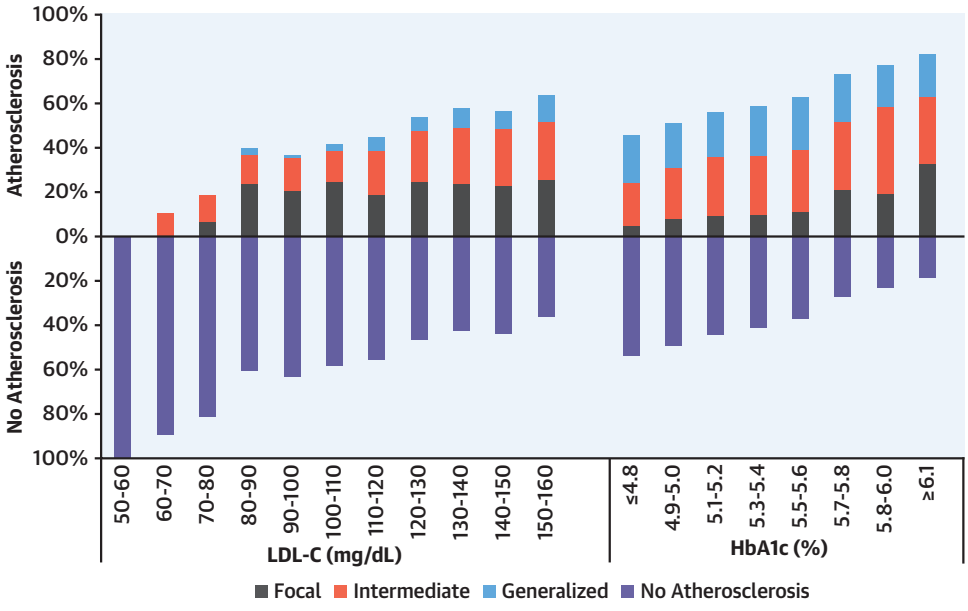
Furthermore, the 30-year follow-up results of the CARDIA study have recently shown that not only does cumulative LDL-C exposure increase incident CVD risk, but similar relationships were demonstrated for exposure to triglycerides, mean arterial pressure, and pulse pressure exposure.[18] Similarly, in the MESA, increasing SBP levels starting at a level of 90 mm Hg were associated with an increased risk of incident CVD in this cohort,[14] emphasizing the potential impact of early intervention across the different CVRF domains, as soon in adult life as possible.

In addition, a strong association between SA and subsequent cardiovascular events has been consistently demonstrated in different population studies. In MESA, among more than 6,000 individuals between 45 and 84 years of age, both the carotid intima-media thickness and the CAC were found to be strong predictors for CVD after adjustment for CVRF.[19,20] In the CAFES-CAVE (Carotid-Femoral morphology and Cardiovascular Events) study, which included more than 13,000 individuals between 35 and 65 years of age, subclinical carotid and femoral atherosclerosis were associated with CVD during 10-year follow-up.[21] The BioImage study, performed in >5,000 asymptomatic adults aged 55 to 80 years, reported that the CAC and carotid plaque burden assessed by 3-dimensional vascular ultrasound (3DVUS) improved risk reclassification and were independently associated with CVD during long-term follow-up.[22,23] Moreover, in a subgroup of individuals aged 45 to 64 years from the ARIC (Atherosclerosis Risk In Communities) study, carotid intima-media thickness and the presence of carotid plaque improved risk prediction when added to traditional risk factors.[24] Based on these data, it is reasonable to hypothesize that preventing the development and progression of SA in young adults (<40 years of age) without known heart or vascular disease may reduce the future risk of CVD.

3DVUS TECHNOLOGY: ATHEROSCLEROSIS BURDEN AS A SURROGATE ENDPOINT FOR CARDIOVASCULAR EVENTS

3DVUS has been shown to accurately measure atherosclerotic plaque volumes, including those of small plaques.[25] Global plaque burden assessed by 3DVUS correlates with CVRF and reflects estimated cardiovascular risk more accurately than plaque detection alone.[26] Because greater atherosclerotic burden has been associated with higher clinical event rates,[20-22] atherosclerotic plaque burden could be used

FIGURE 2 SA With Normal Levels of LDL-C and HbA1c



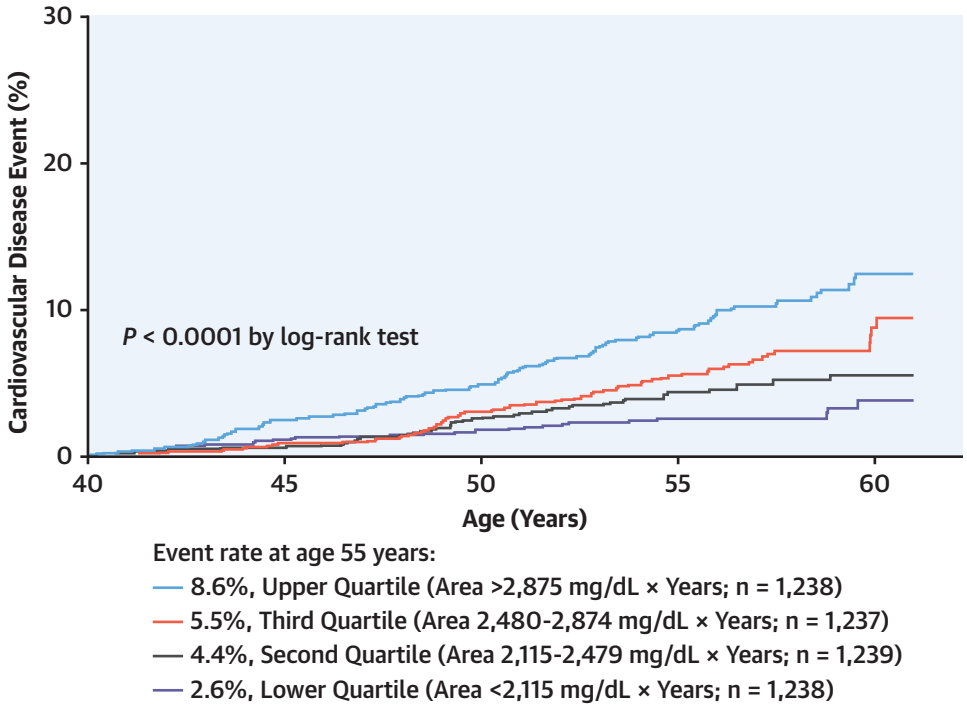
In the PESA (Progression of Early Subclinical Atherosclerosis) study, even "normal" levels of low-density lipoprotein-cholesterol (LDL-C) and glycated hemoglobin A1c (HbA1c) were associated with the presence of subclinical atherosclerosis (SA) in middle-aged adults.[7,12] As LDL-C increases (but remains within normal limits), the prevalence of SA also is significantly greater; similarly, even small increases in HbA1c are associated with a higher prevalence of atherosclerosis. Adapted with permission from Fernandez-Friera et al[7] and Rossello et al.[12]

as a surrogate endpoint for CVD. Moreover, 3DVUS can be used to assess the presence of atherosclerosis in multiple vascular territories.[4,22,26] In the PESA score,[4] the extent of SA is defined by the presence of plaque and CAC. Based on comprehensive imaging of the aorta, right and left carotid and femoral arteries, and coronary arteries, subjects are classified into 1 of 4 groups: 1) no disease, when no evidence of atherosclerosis is detected; 2) focal disease, when 1 site is affected; 3) intermediate disease, when 2 to 3 sites are involved; and 4) generalized disease, when 4 to 6 sites demonstrate atherosclerosis.[4]

HIGH-RISK GROUPS IN YOUNG ADULTS

Among young adults, groups requiring special attention include those with familial hypercholesterolemia (FH) and with elevated levels of lipoprotein (a) (Lp[a]). LDL-C is 2 times higher in patients with heterozygous FH and 4 to 5 times higher in patients with homozygous FH compared with the general population; lowering LDL-C to optimal levels in this latter group can be especially challenging.[27] Currently, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend intensifying lipid-lowering therapies if the LDL-C remains ≥100 mg/dL in patients with FH without clinical CVD.[28,29] High-dose statins are not always sufficient nor tolerated by patients with FH, and new treatments have been explored for this population. Proprotein convertase subtilisin-lexin type 9 (PCSK9) inhibitors have demonstrated effective reductions in LDL-C in the FH population.[30-34] When a certain threshold of cumulative LDL-C exposure is reached, CVD is more likely to occur[35]; this threshold is reached in childhood or early adulthood in patients with FH, and later in life in non-FH individuals.[35] Individuals with loss-of-function mutations in PCSK9 have lower LDL-C levels and reach this threshold much later (**Figure 4**).[36,37] Thus, the use of a PCSK9 inhibitor from an early age may allow the cumulative LDL-C exposure threshold to be reached later in life, delaying or preventing the onset of CVD.[35,38] Inclisiran, a double-stranded small interfering RNA that suppresses PCSK9 translation in the liver, has been shown to be a safe, effective, and well-tolerated treatment to lower LDL-C in adults with FH, when administered subcutaneously twice yearly in addition to maximally tolerated statin therapy with or without other LDL-C-lowering agents.[39] Regarding

FIGURE 3 LDL-C Exposure and Incident Risk of Cardiovascular Disease



Accumulation of exposure to low-density lipoprotein-cholesterol (LDL-C) (calculated as area under the LDL-C vs age curve from 18 to 40 years) is associated with increased risk of an incident event following the landmark age of 40 years.[16] Reproduced with permission from Domanski et al.[16]

Lp(a), PCSK9 inhibitors lower Lp(a) modestly, with clinical trial evidence limited to subgroup analyses.[40,41] New therapies have been developed that markedly reduce Lp(a) and may prove effective in patients at risk.[42-46]

THE NEED FOR RANDOMIZED TRIALS IN YOUNG ADULTS

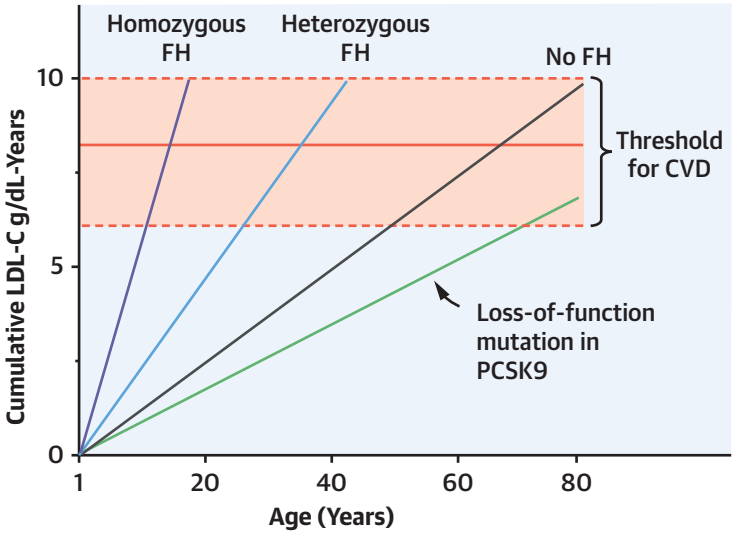
Although the fact that atherosclerosis starts at a young age is no longer questioned,[4] and that SA is linked to CVD later in life,[16,20,22] there is a lack of randomized controlled trials to support primary prevention strategies for young adults (aged <40 years). A recent document summarizes the ACC/AHA[9,29] and the European Society of Cardiology[10] guidelines recommendations that can be applied to adults between 20 and 39 years.[47] As noted in this review, few recommendations are specific for otherwise healthy adults between 20 and 39 years of age, other than those with multiple CVRFs at particularly high-risk.

Moreover, whether effectively controlling CVRF at young ages would prevent or delay the development of SA and overt CVD is unknown. The optimal CVRF targets in adults younger than 40 years of age to avoid the development of atherosclerosis and CVD later in life must be established, and therapies known to reduce these CVRFs must be shown to be effective in this age group. This knowledge can be achieved only through randomized controlled trials. A specific limitation to conducting studies in this age group is the need for very long-term follow-up to detect clinical events due to CVD[42]; assessing the atherosclerotic burden progression as a surrogate endpoint for CVD risk could help reduce the follow-up period and increase study feasibility.

THE PRECAD TRIAL

The PRECAD trial is a randomized controlled trial that aims to evaluate whether maintaining LDL-C lower than 70 mg/dL in addition to strict control of CVRFs in young adults (20-39 years) decreases

FIGURE 4 Early Introduction of a PCSK9 Inhibitor May Delay CVD



Cardiovascular disease (CVD) occurs at a certain threshold of cumulative low-density lipoprotein-cholesterol (LDL-C) exposure. Patients with familial hypercholesterolemia (FH), particularly those with homozygous FH, achieve this threshold earlier in life compared with non-FH individuals. The use of a proprotein convertase subtilisin-lexin type 9 (PCSK9) inhibitor starting early in life could replicate the natural experiment that occurs in individuals with loss-of-function mutations in PCSK9, causing the LDL-C threshold and symptomatic CVD to be reached later in life. Adapted with permission from Horton et al.[35]

the atherosclerotic burden, a surrogate for cardiovascular events, compared with contemporary guideline-directed medical treatment. Because the risk of developing atherosclerosis (and subsequent CVD) with LDL-C <70 mg/dL is very low,[7] and there is evidence of plaque regression at LDL-C levels lower than 70 mg/dL,[48-50] this value was established as the cutoff point.

HYPOTHESIS

The hypothesis of the PRECAD trial is that, compared with usual care, maintaining LDL-C <70 mg/dL beginning in the early adult years, in addition to strict control of other CVRFs (maintaining SBP <120 mm Hg and HbA1c <6.5%), will reduce the progression of total atherosclerotic burden.

STUDY ENDPOINTS

The primary endpoint is the progression of atherosclerosis burden measured by change in global plaque volume by 3DVUS from baseline to 5 years after randomization. Computed tomography angiography is a very useful tool to predict future CVD events; however, the radiation exposure in young populations is questionable.[51-53] Thus, 3DVUS will be used for the evaluation of SA, because atherosclerotic plaque burden assessed by 3DVUS has also been identified as an independent predictor for CVD events.[22]

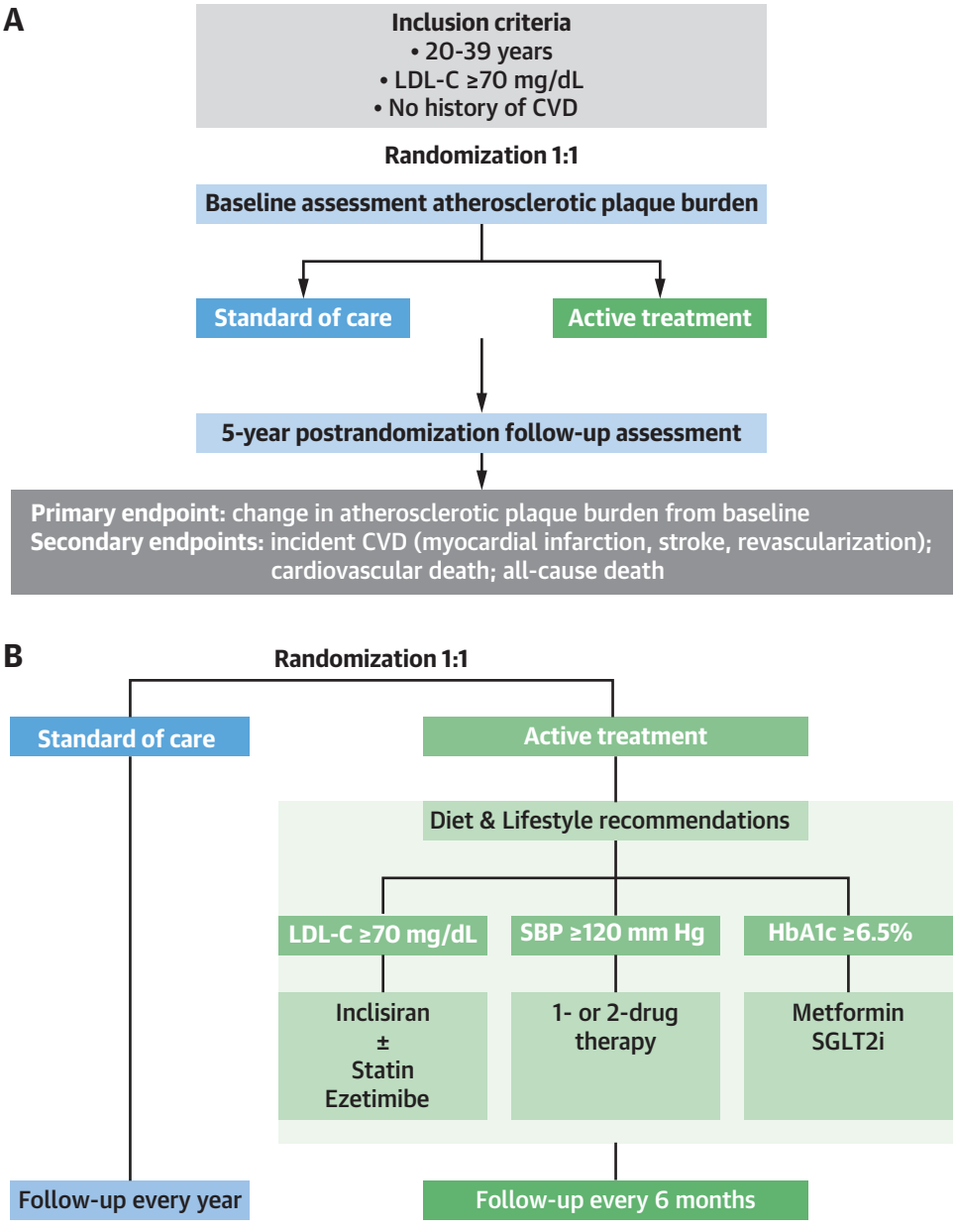
Secondary endpoints include the following: 1) change in global plaque volume by 3DVUS from baseline to 2.5 years after randomization; 2) change in PESA score from baseline to 2.5 and 5 years after randomization; 3) CVD events, including coronary revascularization, myocardial infarction, stroke, and cardiovascular death; and 4) all-cause death.

STUDY POPULATION

Detailed inclusion and exclusion criteria are provided in the Supplemental Material. Eligible subjects are between 20 and 39 years of age, with no previous history of coronary artery disease or cerebrovascular disease, and with LDL-C ≥70 mg/dL. Exclusion criteria include: 1) contraindications to lipid-lowering therapies; 2) conditions with survival <5 years; and 3) pregnancy at the time of randomization.

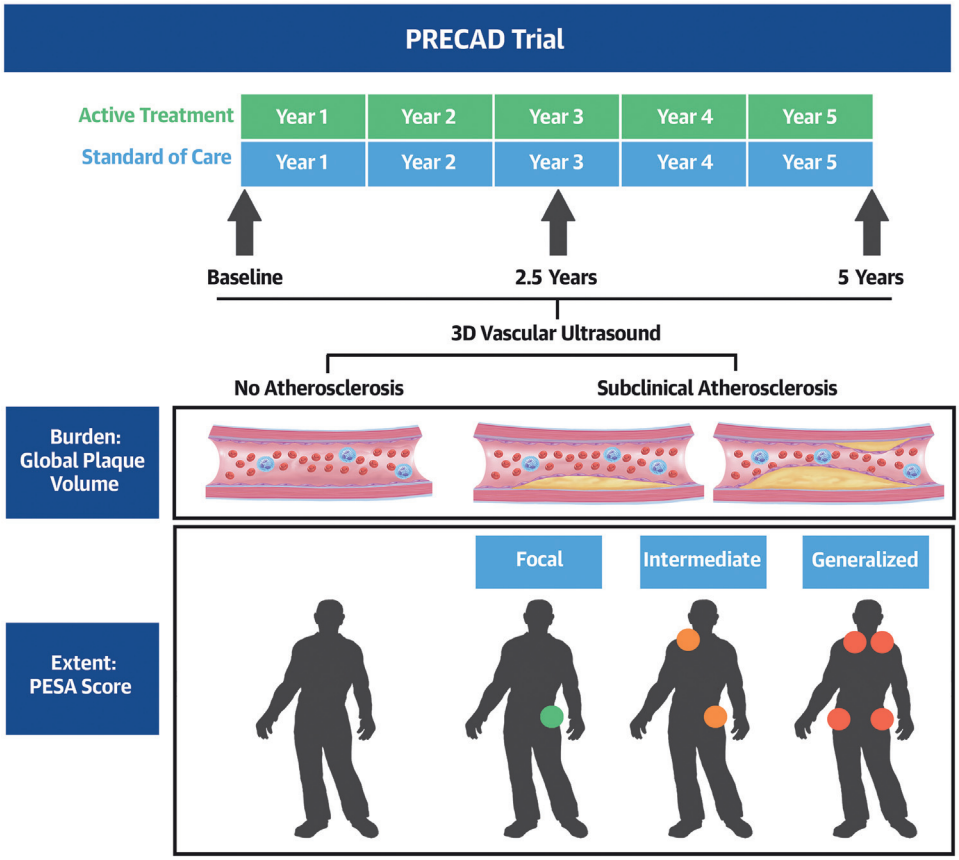
Patients will be recruited for the PRECAD trial from up to 5 sites in New York, New York. Individuals who meet the inclusion criteria and who do not meet any exclusion criterion will be randomized, one-to-one, to the intervention group (active treatment strategy) or to the control group (guideline-directed medical therapy) (**Figure 5A**).

FIGURE 5 The PRECAD Trial



(A) Study design. Eligible subjects are between 20 and 39 years of age, with no previous history of coronary artery disease or cerebrovascular disease, and with low-density lipoprotein-cholesterol (LDL-C) ≥70 mg/dL. Randomization will be 1:1, to the intervention group (active treatment strategy) or to the control group (guideline-directed medical therapy). The primary endpoint is the change in atherosclerosis burden between baseline and 5 years. (B) Treatment arms. In the active treatment group, specific measures will be implemented to achieve the following goals: LDL-C <70 mg/dL, systolic blood pressure (SBP) <120 mm Hg, and glycated hemoglobin A1c (HbA1c) <6.5%. Diet and lifestyle recommendations will be initiated in all patients as a first step; if the goal is not achieved, specific therapies will be implemented. Subjects randomized to standard of care will receive contemporary guideline-directed medical treatment. CVD = cardiovascular disease; PRECAD = Prevent Coronary Artery Disease; SGLT2i = sodium-glucose cotransporter-2 inhibitors.

CENTRAL ILLUSTRATION **Preventing Atherosclerosis in the Young: The Prevent Coronary Artery Disease Trial**



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In the PRECAD (Prevent Coronary Artery Disease) trial, young adults 20 to 39 years of age will be randomized to standard of care or to active treatment arm to aggressively control cardiovascular risk factors (CVRFs). Atherosclerotic burden and extent will be assessed by 3-dimensional (3D) vascular ultrasound of the right and left carotid and femoral arteries at baseline, and at 2.5-year and at 5-year follow-up. Atherosclerotic burden will be defined as global plaque volume (sum of plaque volumes in each of the 4 explored vascular sites). Atherosclerosis extent will be defined according to the presence of plaque and will be categorized according to the PESA (Progression of Early Subclinical Atherosclerosis) score on a 4-point scale as absent, vs focal disease if present in 1 site, vs intermediate disease if present in 2 to 3 sites, vs generalized disease if present in 4 sites. The primary endpoint of the trial is the change in atherosclerosis burden between baseline and 5 years.

TREATMENTS

The treatments in each group are summarized in Figure 5B.

ACTIVE TREATMENT. Specific measures will be implemented to achieve the following goals: LDL-C <70 mg/dL, SBP <120 mm Hg, and HbA1c <6.5%. Diet and lifestyle recommendations will be initiated in all patients as a first step; if the goal is not achieved, specific therapies will be implemented. To achieve the LDL-C target of <70 mg/dL, inclisiran, a PCSK9 inhibitor that has been shown to be safe and effective with biannual subcutaneous injections after the first 2 doses, will be provided. Biannual administration is expected to increase adherence in this group of young participants, and the effects of PCSK9 inhibition starting at a young age may delay or prevent the onset of symptomatic CVD (Figure 4). Inclisiran (Novartis) will be distributed to participating sites and dispensed directly by local clinic staff. If the LDL-C target is not achieved with inclisiran, a statin, with or without ezetimibe, will be introduced and titrated progressively. For the SBP target

of <120 mm Hg, if not achieved by diet and lifestyle recommendations, a standard drug regimen (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, calcium-channel blockers, and/or thiazide diuretic) will be used. For the HbA1c target of <6.5%, metformin and sodium-glucose cotransporter-2 inhibitors may be used if lifestyle and dietary modifications are insufficient.

CONTROL GROUP. Subjects randomized to standard of care will receive contemporary guideline-directed medical treatment according to ACC/AHA guidelines.[9,29]

Further details on the study procedures are provided in the Supplemental Material.

STUDY FLOW

All participants will undergo a baseline visit that will include a 3DVUS of the right and left carotid and femoral arteries to assess the atherosclerosis burden (global plaque volume) and extent (PESA score - number of sites involved). Atherosclerosis burden and extent will be reassessed in all participants at 2.5 years and at 5 years (**Central Illustration**). Further details on follow-up procedures are provided in the Supplemental Material.

ANALYTIC PLAN AND SAMPLE SIZE

Progression of atherosclerosis in PRECAD is defined as a ≥100% increase in global plaque volume assessed by 3DVUS, as previously described.[5] Global plaque volume is defined as the sum of plaque volumes in each of the 4 explored vascular sites (right and left carotid and femoral arteries) per participant.[5] Assuming a progression rate from baseline to 5 years of 23% in the intervention group vs 30% in the control group (an estimate based on unpublished data from the BioImage study),[22] randomizing 1,043 patients in each arm (2,086 patients in total) and assuming follow-up imaging is performed in 80% of patients provides 90% power to demonstrate that the active treatment strategy is superior to the control strategy at a 2-sided alpha = 0.05. Further details on the analytic plans are provided in Supplemental Table 1.

YOUNG AGE AS A WINDOW OF OPPORTUNITY TO ADDRESS CARDIOVASCULAR PREVENTION

The high socioeconomic burden of CVD demands new, effective, and efficient approaches.[54] The best opportunity lies in the young population, because a lifelong reduction in progressive atherosclerosis that accumulates from early adulthood offers the greatest potential for the largest impact on CVD over the life of the individual. The main barriers to early intervention are: 1) the lack of awareness of the need to intervene early in the young population; 2) the low short-term risk in young individuals, which to date has received more attention in the guidelines and practice pathways even if the lifetime risk is high; and 3) the lack of randomized trials demonstrating that strict control of CVRFs in young adults reduces progression of SA and ultimately manifests CVD. The PRECAD trial is a step toward generating evidence to fill these knowledge gaps. PRECAD may provide actionable support for early and aggressive CVRF intervention to improve long-term cardiovascular prognosis in a healthy but potentially vulnerable segment of the population.

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APPENDIX For supplemental material and a table, please see the online version of this paper.