Coronary artery calcium testing in young adults

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Purpose of review
To provide a summary of recent literature on coronary artery calcium testing (CAC) for risk stratification in young adults <45 years old.

Recent findings
One of every ten young adults in the general population, and one out of every three young adults with traditional atherosclerotic cardiovascular disease (ASCVD) risk factors, have CAC. While the definition of premature CAC has yet to be formally defined in guidelines, it has become increasingly clear that any prevalent CAC among adults <45 years old should be considered premature. Traditional risk factors are strong predictors of CAC in young adults; however, this association has been found to wane over the life course which suggests that the onset and severity of risk factors for calcific atherosclerosis varies as individuals age. Though CAC is a robust predictor of both ASCVD and cancer-related mortality in old age, CAC in young adults confers a stepwise higher risk uniquely for incident ASCVD mortality, and not for non-ASCVD causes. New tools are available to assist in interpretation of CAC in the young, and for estimating the ideal age to initiate CAC scoring.

Summary
The identification of premature CAC is important because it suggests that calcific plaque can be detected with modern imaging earlier in the natural history than previously thought. Taken together, these findings underline a utility of selective use of CAC scoring on non-contrast computed tomography among at-risk young adults to facilitate timely lifestyle modification and pharmacotherapies for the prevention of later life ASCVD.

Keywords
computed tomography, coronary artery calcium, coronary artery disease, screening, young adult

INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) can originate in youth with the development of fatty streaks in persons as young as two years of age [1]. The first phase of this process occurs when low-density lipoprotein (LDL) cholesterol concentrations are elevated in the periphery (≥70 mg/dL), leading to their movement to and accumulation within the arterial intima [2]. In the setting of continuous exposure to a pro-atherosclerotic and inflammatory milieu, LDL cholesterol particles ultimately congregate to develop extracellular lipid pools and cores, which histologically and formally signifies the initiation of atherosclerosis [2]. The aggregation of extracellular lipids causes cell necrosis leading to arterial intimal remodeling and the development of fibroatheromas and complex lesions, all of which can contain calcified nodules or themselves become calcified at any stage of plaque formation [3].

Historically, plaque calcification has been thought of as the end-stage phase of atherosclerosis. While early fibroatheromas have been consistently identified among individuals in adolescence and their 20–40 s, advancing atheromas were thought to predominantly occur no earlier than 55 years of age [4,5]. However, this long-held schema of atherosclerosis progression has been challenged by recent epidemiological studies of coronary artery calcium (CAC) and thoracic aortic calcium (TAC) in asymptomatic young adults [6–9]. In particular,

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KEY POINTS

- Premature CAC should likely be recognized as any prevalent CAC among persons <45 years old as this generally places individuals above the 90% CAC percentile.
- The role of CAC scanning should be fundamentally different depending on the patient's age.
- The identification of premature CAC is important because it suggests that calcific plaque can be detected with modern imaging earlier in the natural history than previously thought.
- Traditional risk factors are strong predictors of CAC in young adults; however, this association has been found to wane over the life course which suggests that the onset and severity of risk factors for calcific atherosclerosis varies as individuals age.

noncontrast cardiac gated computed tomography (CT) has identified the presence of CAC among persons <45 years old [6,10], which has been associated with a substantially increased risk for ASCVD events and all-cause mortality compared to younger adults who do not have CAC (CAC = 0). This information is important because, (1) it suggests a potential utility of noninvasive imaging on cardiac CT much earlier than recommended by current societal guidelines for ASCVD risk stratification, and that (2) our biological schema and approach to atherosclerosis should be revisited to identify the factors that are associated with premature calcification to help further prevent primary ASCVD events in the general population. In the present review, we summarize recent evidence regarding the prevalence and incidence of premature CAC as well as the utility of CAC scoring in young adults (age 30–45) for ASCVD risk stratification and management.

DEFINITION AND PREVALENCE OF PREMATURE CORONARY ARTERY CALCIUM

Once CAC is identified, an exponential increase in CAC scores is observed over time, regardless of the age of onset of detection [6,11]. Assuming a number needed to scan of four individuals, the predicted age of conversion to CAC >0 among men and women without traditional risk factors is 42 years and 58 years old, respectively [12▪▪]. Several previous investigations have noted the presence of CAC in younger individuals (Table 1); however, the age inclusion criteria have slightly varied across studies, therefore the definition of premature CAC has yet to be formally defined. Less than 10% of adults have detectable CAC by 40 years of age [6], whereas the prevalence of CAC in younger persons aged 33–39 years old is between 5–6% [9]. As such, we believe that it may be reasonable to identify and define premature CAC as CAC $\geq 90^{th}$ percentile for a given age group for all comers, as it correlates with any CAC detectable in young adults (at its earliest stages). Of course, the evolving definition of

Table 1. Association of premature CAC with ASCVD outcomes.

Author	Sample	Age range	Prevalence of premature CAC	Traditional risk factor(s) most strongly associated with premature CAC	Hard Outcomes Studied
Loria *et al.* [9]	CARDIA	18–30 years	10%	Cigarette Smoking, LDL-C	N/A[a]
Osei *et al.* [10]	CAC Consortium	20–30 years	13%	Hyperlipidemia, Family History of CHD	N/A[a]
Mahoney *et al.* [31]	Muscatine Study	29–43 years	22%	HDL-C, Systolic Blood Pressure	N/A[a]
Hartiala *et al.* [32]	Young Finns	40–46 years	19%	LDL-C, Systolic Blood Pressure	N/A[a]
Mortensen *et al.* [33▪▪]	Western Denmark Heart Registry[b]	18–45 years	14%	Diabetes, Family History of CHD	CHD
Kang *et al.* [26]	Korean Young Adults	18–45 years	7%	N/A[c]	ASCVD Mortality, Non-ASCVD Mortality
Javaid *et al.* [7]	Walter Reed Cohort	30–49 years	21%	Hyperlipidemia, Hypertension	MI, MACE
Miedema *et al.* [34]	CAC Consortium	32–45 years	34%	Hyperlipidemia, Family History of CHD	CHD, ASCVD, All-Cause Mortality
Carr *et al.* [6]	CARDIA	32–46 years	10%	N/A[c]	CHD, ASCVD

[a]Only studied premature CAC and traditional risk factors.
[b]Symptomatic patients.
[c]Only studied premature CAC and hard outcomes.
ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CARDIA, coronary artery risk development in young adults; CHD, coronary heart disease.

premature CAC will certainly vary according to sex and major society guidelines have endorsed the utilization of CAC percentiles to assess statin eligibility [13–16]. The identification of an age, sex, and/or race CAC percentile $\geq 75^{th}$ for adults <55 years of age is an important marker that suggests statin pharmacotherapy should be initiated to reduce ASCVD risk [14,17].

A cutoff of 40 years old has been traditionally used by the American College of Cardiology/American Heart Association guidelines to demarcate selective use of cardiac CT, because this is the age at which guidelines recommend initiating risk stratification for the primary prevention of ASCVD, which is most commonly applied to the concept of statin eligibility [17]. In particular, CAC has been found to improve precision in those that will versus those who will not benefit from primary prevention statin pharmacotherapy. Among statin-eligible candidates, the number needed to treat for those with long-term absence of CAC = 0 is more than two-fold greater compared to those with CAC>0, as the presence of CAC=0 is associated with an exceedingly low risk of ASCVD regardless of risk factor burden [18].

Recently, a CAC percentile calculator has been created for young adults aged 30–45 years old to estimate the probability of CAC >0 among individuals without ASCVD [8]. This online risk stratification tool was produced via findings from a combination of clinical-referral and population-based samples, including the CAC Consortium, Walter Reed cohort, and the Coronary Artery Risk Development in Young Adults study. The novelty of this newly developed tool is that it allows clinicians and scientific investigators to define premature CAC because it was not previously well known and/or described. Investigators specifically found that White males had the highest prevalence of premature CAC (26%), followed by Black males, White females (10%), and Black females (7%) [8]. Thus, the yield of a CAC scan in young adults is higher for men versus women and higher for White versus Black individuals. However, women and Black individuals have been found to develop extra-CAC, most notably TAC, prior to CAC, therefore similar percentile studies of TAC are currently ongoing to further sharpen the broader definition of premature vascular calcification [19–21].

Overall, ASCVD risk communication via CAC percentiles in tandem with absolute CAC scores in younger adults is preferred because percentile estimates can (1) predict relative risk versus age, sex, and ethnicity-matched peers, (2) better estimate lifetime risk trajectory, and (3) prioritize early pharmacotherapy treatment intensity (which may not be indicated when considering absolute score alone).

CHANGING ROLES OF CORONARY ARTERY CALCIUM TESTING ACROSS AGE GROUPS

In younger patients where nearly all individuals are deemed to be low-risk by traditional risk equations, CAC scanning can identify premature atherosclerosis and facilitate earlier risk factor reduction with pharmacotherapy when such younger persons may not otherwise qualify under current conventional risk scoring (Fig. 1). Thus the role of CAC is in detecting unheralded risk, not identification of low risk states. This is in contrast with the use of CAC among intermediate risk adults which

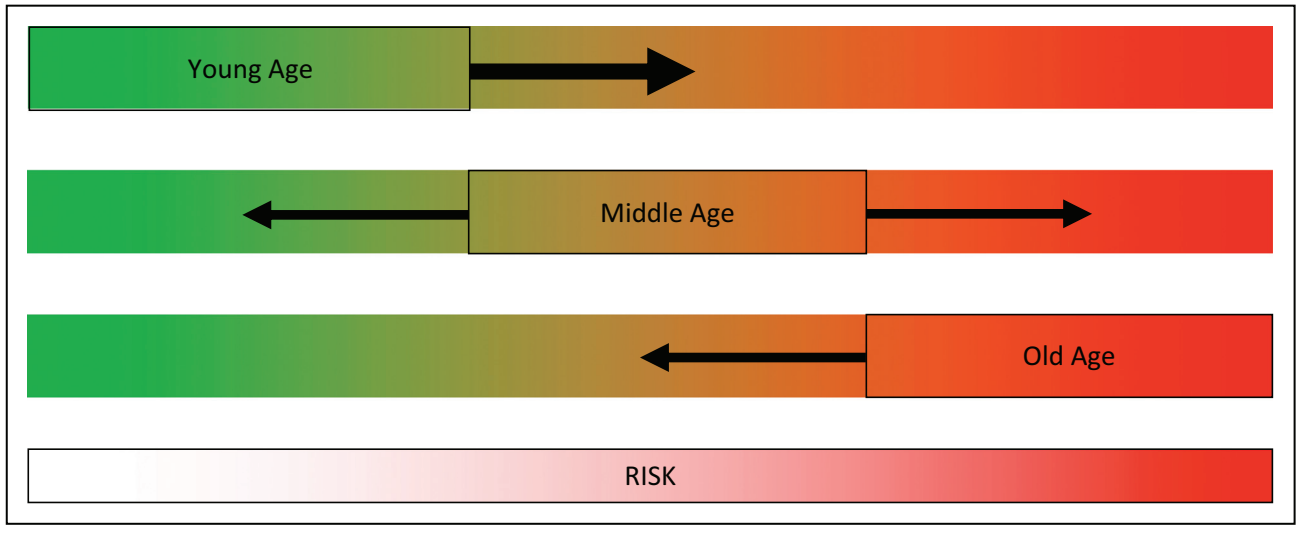


FIGURE 1. Varying roles of CAC across age – focus on identification of unheralded high risk at young age (<45 years old). CAC, coronary artery calcium.

resembles the purest form of ''risk stratification'' as the presence or absence of CAC can define either high risk or low risk groups, respectively. At the other end of the spectrum, CAC scanning in older age may also be beneficial as essentially all older adults are eligible to receive primary prevention pharmacotherapies when using risks scores; here, the absence of CAC or the presence of low CAC may identify an individual who may not derive net benefit from primary prevention pharmacotherapy (identification of otherwise unidentifiable low risk).

DEMOGRAPHICS AND RISK FACTORS ASSOCIATED WITH PREMATURE CORONARY ARTERY CALCIUM

Even while focusing specifically on younger adults, age remains as a powerful risk factor for atherosclerotic calcification. The likelihood of detecting CAC sharply increases as individuals age; however, a selective strategy for identifying the young adults that would derive net benefit of ASCVD risk reduction versus the negative consequences of CT screening is prudent in the era of precision medicine. Similar to middle-aged and older adults, younger adults of nonwhite ethnicity and women are less likely to harbor premature CAC compared to younger adults of white ethnicity and men, respectively [21]. In young adults aged 30 to 49 years there is a 47% lower risk of premature CAC for black versus whites, whereas men are 3.5-fold more likely to have CAC >0 compared to women [21]. Ethnic and sex-specific differences in risk factor profiles have not been able to fully explain such differences, which suggests that the development and burden of premature subclinical atherosclerosis may be different according to demographics. Thus, the approach to leveraging subclinical atherosclerosis imaging in younger adults should likely consider the yield of each test. For example, the prevalence of CAC in the Progression and Early Detection of Atherosclerosis in women (5%) is one-fifth that of men (25%); however, both sexes have nearly an identical burden of abdominal aortic plaque (22% versus 26%, respectively) [22].

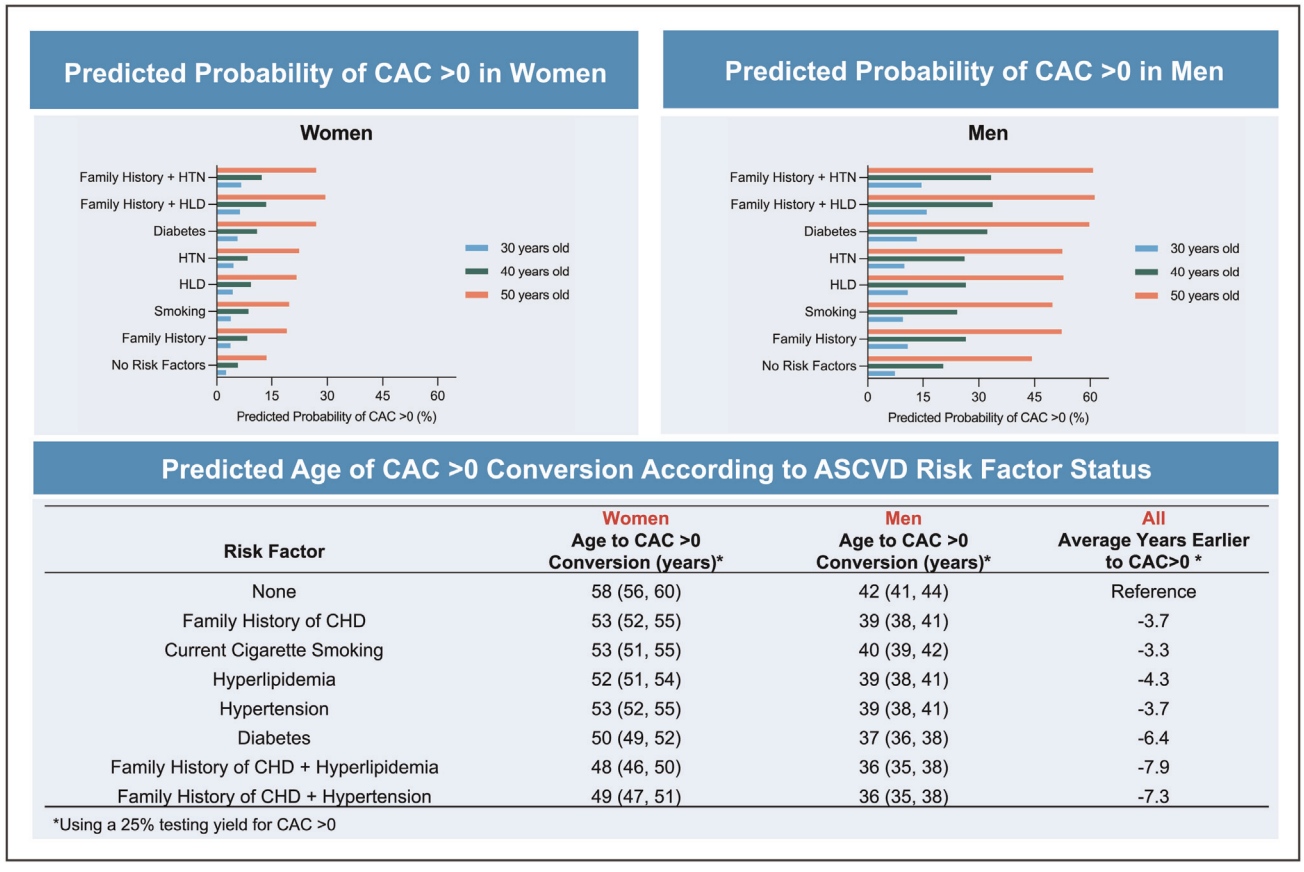
Beyond demographics, there appears to be a stepwise increase in the probability of premature CAC according to modifiable risk factor burden. Among asymptomatic primary prevention patients from the CAC Consortium, diabetes, and hyperlipidemia had the strongest associations with premature CAC and associated with an average 6.4 and 4.3 year earlier CAC offset period, or how far in advance an individual with a specific risk factor would develop CAC >0 compared with the same person with no ASCVD factors [12▪▪] (Table 1). In particular, there is a 30% and 20% increase in risk for premature CAC for every 30 mg/dL higher LDL-C and 15 mg/dL higher blood glucose, respectively [9].

Similar to diabetes and hyperlipidemia, hypertension exhibits a graded association with the incidence of CAC in young adults (Fig. 2). Specifically, there is a 20% higher risk of premature CAC for every 10 mmHg increase in systolic blood pressure and an individual with hypertension is likely to develop CAC >0 approximately 3–4 years earlier compared to an individual without hypertension [9]. Compared to hypertension, an analogous CAC offset period is observed for cigarette smoking, but tobacco use appears to be more strongly associated with premature CAC incidence (over 2-fold higher risk) [12▪▪]. Specifically, a CAC offset period is defined by how much earlier an individual in a higher risk category would develop incident CAC when compared to individuals in the lowest risk group [12▪▪].

It is important to note that the risk factors for the initiation of CAC vary across the life course, such that the association between traditional risk factors and CAC becomes less pronounced as individuals age. All traditional risk factors consistently associate with incident CAC in younger and middle-aged adults, except for diastolic blood pressure, high-density lipoprotein cholesterol, and body mass index in younger adults, and diastolic blood pressure and fasting blood glucose in middle-aged adults [23]. However, no individual traditional risk factor has been found to significantly associate with incident CAC in older adults [23]. Altogether these results suggest that the onset and severity of risk factors for calcific atherosclerosis varies as individuals age.

LONG-TERM PROGNOSTIC IMPLICATIONS OF PREMATURE CORONARY ARTERY CALCIUM

In the past decade, several previous investigations have reported on the association of CAC with both ASCVD and non-ASCVD outcomes in younger adults. With respect to ASCVD outcomes, premature CAC confers a stepwise higher risk for coronary heart disease (CHD) events among both black and white younger adults in a population-based sample [6]. Starting as low as CAC scores between 1 and 19, there is a 2.6 higher risk of CHD events and a graded increase in risk thereafter for CAC 20–99 (hazard ratio (HR)=5.8) and CAC ≥100 (HR=9.8). These results were notably consistent even after excluding events that included coronary artery revascularization without acute symptoms and have been replicated in clinical referral-based samples. However, among younger adults who were specifically



Predicted Age of CAC >0 Conversion According to ASCVD Risk Factor Status

Risk Factor	Women Age to CAC >0 Conversion (years)*	Men Age to CAC >0 Conversion (years)*	All Average Years Earlier to CAC>0 *
None	58 (56, 60)	42 (41, 44)	Reference
Family History of CHD	53 (52, 55)	39 (38, 41)	-3.7
Current Cigarette Smoking	53 (51, 55)	40 (39, 42)	-3.3
Hyperlipidemia	52 (51, 54)	39 (38, 41)	-4.3
Hypertension	53 (52, 55)	39 (38, 41)	-3.7
Diabetes	50 (49, 52)	37 (36, 38)	-6.4
Family History of CHD + Hyperlipidemia	48 (46, 50)	36 (35, 38)	-7.9
Family History of CHD + Hypertension	49 (47, 51)	36 (35, 38)	-7.3

*Using a 25% testing yield for CAC >0

FIGURE 2. Probability of CAC >0 according to age and ASCVD risk factor burden. Adapted from Dzaye *et al.* ''Modeling the Recommended Age for Initiating CAC Testing Among At-Risk Young Adults''. ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium.

referred to undergo early noncontrast CT scanning, the association of CAC with ASCVD mortality has only noted to be significant for CAC scores ≥100, after adjusting for traditional risk factors [24]. Nevertheless, these latter findings have not been upheld across all studies, particularly those examining nonfatal outcomes, suggesting that statistical power may be an important limitation among investigations that have failed to identify an association between premature CAC scores <100 and ASCVD outcomes [25]. Therefore, we affirm that any premature CAC, particularly >10, among younger adults is likely to be prognostic and signify elevated ASCVD risk.

While premature CAC confers a higher risk of ASCVD events, the identification of CAC in younger adults has not consistently associated with all-cause mortality and/or non-ASCVD death, including lung cancer and cancer mortality. In particular, the presence of CAC has only been demonstrated to predict non-ASCVD outcomes in older adults. For example, the presence of CAC ≥300 independently associates with non-ASCVD mortality in persons above but not below 45 years of age [26]. Furthermore, a 2–4 fold higher risk of all-cause mortality has been observed for young adults with CAC ≥100, but not for younger persons with prevalent CAC between 1 and 100.

The strong association between CAC and ASCVD events in younger adults suggests that prevalent CAC in young age is likely a marker of vulnerable plaque. There is limited data on the contributions to CAC in young versus old age, but it is presumed that high CAC scores in young age are likely driven by a large calcific plaque area as opposed to calcium density, whereas CAC in old age is likely driven by a more equal contribution of calcium area and calcium density. Discordance between CAC area and density is a strong risk factor for ASCVD events, beyond traditional risk factors and the Agatston CAC itself [27▪]. Therefore, future studies should be performed to identify anticipated biological differences in the composition of calcific plaque between younger versus older persons for a given Agatston CAC score, which could improve age-specific ASCVD risk prediction. On the other hand, the lack of association between premature CAC and non-ASCVD mortality, including cancer,

is likely reflective of short follow-up time, different pathophysiology of cancers in young versus old age, and the competing risk of ASCVD versus non-ASCVD events across the life course.

GENOMIC RISK PREDICTION OF PREMATURE CORONARY ARTERY CALCIUM

Although the genetic contributions of CAC have been less well studied, their early findings have identified a potential utility of genomic risk prediction for premature CAC and the optimal time for initial CAC testing. Polygenic risk scores for CHD have specifically been found to improve discrimination for the prediction of premature CAC, and the magnitude of C-statistic improvement becomes larger when at higher CAC thresholds. For example, the addition of a CHD PRS to demographics improves the prediction of CAC in younger adults more so for CAC >300 (ΔC-statistic=0.045) versus CAC >20 (ΔC-statistic=0.030) [28]. Although the CHD PRS independently associated with elevated CAC in young adults, improvements in premature CAC discrimination for a CHD PRS have been found to be lower in magnitude compared to traditional risk factors themselves.

A clinical situation that may lend itself most towards the utility of PRS is the recommended initial time to a first CAC scan and subsequent CT scan intervals for those with CAC=0. This affirmation is based upon findings that have shown an association between an elevated PRS and the probability of CAC >0 [29]. For a given equal traditional risk factor burden, persons in with the highest quintile burden of genetic susceptibility to CHD reach a 25% probability of CAC >0 10 years earlier when compared to those in the lowest quintile. Approximately one out of four persons in the latter study were young adults. Overall, these findings highlight a potential utility for measuring polygenic CHD risk early in life to guide the optimal age to initiate CAC scanning and guide the best approach for primary ASCVD risk reduction with lifestyle and pharmacotherapy [30]. Similarly, it is likely that an individual with CAC=0 in the highest category of genomic risk for CHD have a shorter CAC=0 warranty period compared to those with a low inherited risk of CHD, suggesting that they may need to be rescanned earlier to identify prevalent CAC and modify their preventive treatment (Fig. 3).

CONCLUSION

Premature CAC should likely be recognized as any prevalent CAC among persons <45 years old as this generally places individuals above the 90% CAC percentile. The role of CAC scanning should be fundamentally different depending on the patient's age. The utility of CAC screening in the young is to identify any prevalent CAC to gauge relative risk versus peers, estimate lifetime risk trajectory, and guide initial pharmacotherapy treatment intensity that might be considered over a long-time horizon among individuals who are likely to be overlooked by current risk calculators. In coming years, cardiac CT angiography may become increasingly useful to detect noncalcified plaque in younger patients who

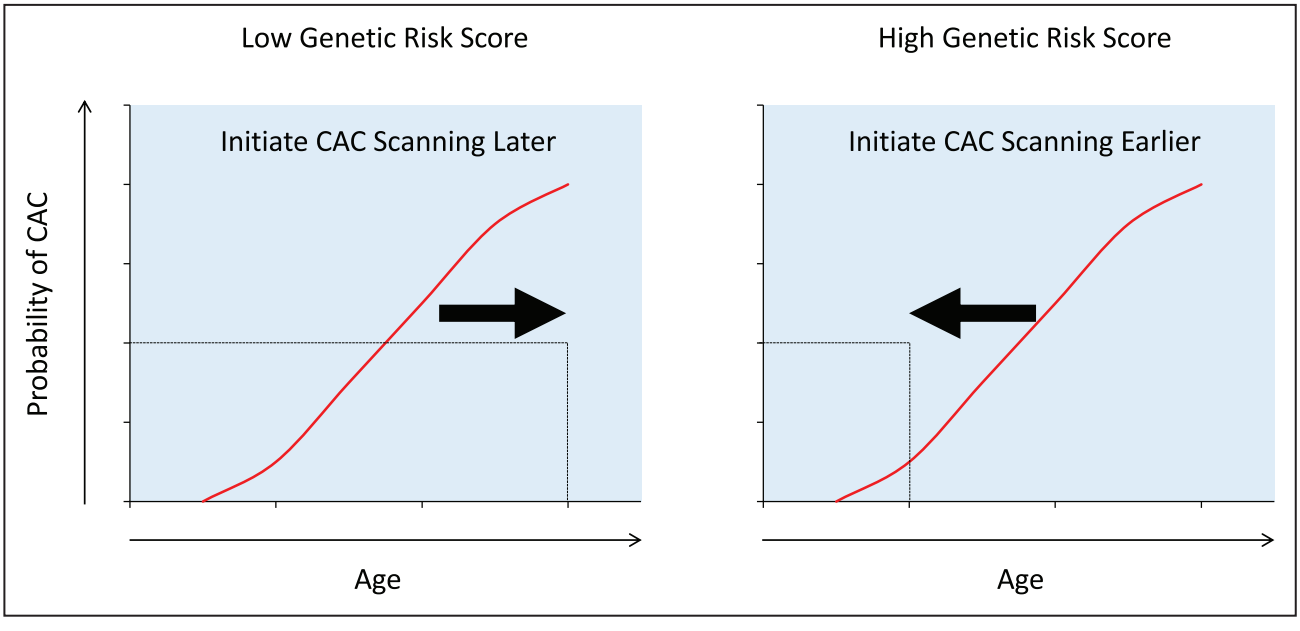


FIGURE 3. Probability of CAC versus age and genetic risk score. CAC, coronary artery calcium

inherently carry higher ASCVD risk, including those with early onset diabetes and familial hypercholesterolemia, although the yield of such testing must be weighed against the high cost compared to CAC.

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Conflicts of interest

The authors have no conflicts of interest.

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