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THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Personalized Intervention Based on Early Detection of Atherosclerosis

JACC State-of-the-Art Review

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ABSTRACT

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide and challenges the capacity of health care systems globally. Atherosclerosis is the underlying pathophysiological entity in two-thirds of patients with CVD. When considering that atherosclerosis develops over decades, there is potentially great opportunity for prevention of associated events such as myocardial infarction and stroke. Subclinical atherosclerosis has been identified in its early stages in young individuals; however, there is no consensus on how to prevent progression to symptomatic disease. Given the growing burden of CVD, a paradigm shift is required—moving from late management of atherosclerotic CVD to earlier detection during the subclinical phase with the goal of potential cure or prevention of events. Studies must focus on how precision medicine using imaging and circulating biomarkers may identify atherosclerosis earlier and determine whether such a paradigm shift would lead to overall cost savings for global health. (J Am Coll Cardiol 2024;83:2112–2127)

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HIGHLIGHTS

- Early-stage subclinical atherosclerosis can be identified in young individuals, but evidence-based strategies are needed to prevent progression of disease and clinical events.
- Precision medicine using imaging and circulating biomarkers could facilitate early identification of atherosclerosis and the development of curative interventions.
- A paradigm shift based on these principles could reduce the global burden of CVD with enormous implications for population health.

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide. An estimated 621 million people are living with CVD, and 18.6 million people die of the disease every year, primarily due to ischemic heart disease and ischemic stroke.[1-3] As the prevalence and mortality related to CVD continues to rise globally, this condition challenges the capacity of health care systems.[1,4] Despite extensive knowledge regarding its pathobiology and clinical manifestations of later-stage disease, an extensive, robust, and sustainable solution to prevent CVD is lacking.[1,5]

Atherosclerosis is the underlying pathophysiological entity in two-thirds of patients with CVD.[1,6,7] Although subclinical atherosclerosis is prevalent in children and young adults, there is no consensus on the most rational approach to prevent its progression from a subclinical phase to symptomatic phase, beyond lifestyle management such as diet and physical inactivity.[8-11] However, there is now growing recognition that to halt the increase of atherosclerotic cardiovascular disease (ASCVD) globally, a new standard of care targeting atherosclerosis in its subclinical phase, including in younger asymptomatic individuals (ie, perhaps younger than 50 years) needs to be defined.[12-15] Atherosclerosis usually develops over decades, with heterogeneous intervening phases, before leading to an event, leaving ample opportunity for prevention.[11] Atherosclerosis is described to debut as fatty streaks already in early childhood.[11,16] This suggests that a paradigm shift from management of clinical manifestations of ASCVD in its late stages to earlier detection and intervention, leading to prevention and delay of its clinical consequences, is needed.[17,18]

The international research initiative REACT (Reversal of Early Atherosclerosis through personalized Curative Treatment) strives to apply a precision medicine-based approach paving the way for personalized prevention and treatment of ASCVD. This initiative, established in 2022, brought together a group of multidisciplinary global experts to address the scientific basis for earlier detection of discrete subsets of atherosclerosis and prevention of clinical events. The group envisioned a large global initiative and defined the parameters of a novel precision medicine-driven screening program that will include studies and trials of innovative imaging and circulating biomarkers for early detection of atherosclerosis. Further, knowledge about psychosocial factors is warranted, because lifestyle (smoking, diet, sedentary lifestyle), sleeping patterns, anxiety, and depression are driving forces for atherosclerosis progression.

ABBREVIATIONS AND ACRONYMS

ASCVD = atherosclerotic cardiovascular disease

CAC = coronary artery calcium

CT = computed tomography

CTCA = computed tomography coronary angiography

CVD = cardiovascular disease

CVH = cardiovascular health

LDL-C = low-density lipoprotein cholesterol

PRS = polygenic risk scores

REACT = Reversal of Early Atherosclerosis through personalized Curative Treatment

LACK OF PRECISION IN EXISTING RISK FACTOR–BASED ASCVD RISK ASSESSMENT

At present, no country appears to have a national, standardized approach to systematically screen the population for primary prevention of ASCVD. Such strategies appear to be used sporadically among some regions[19,20] and are based on conventional risk stratification tools that are calculated from the presence of traditional, modifiable risk factors (low-density lipoprotein cholesterol [LDL-C], systolic blood pressure, and smoking status), in addition to age and sex.[21,22] Although these tools may be useful at the

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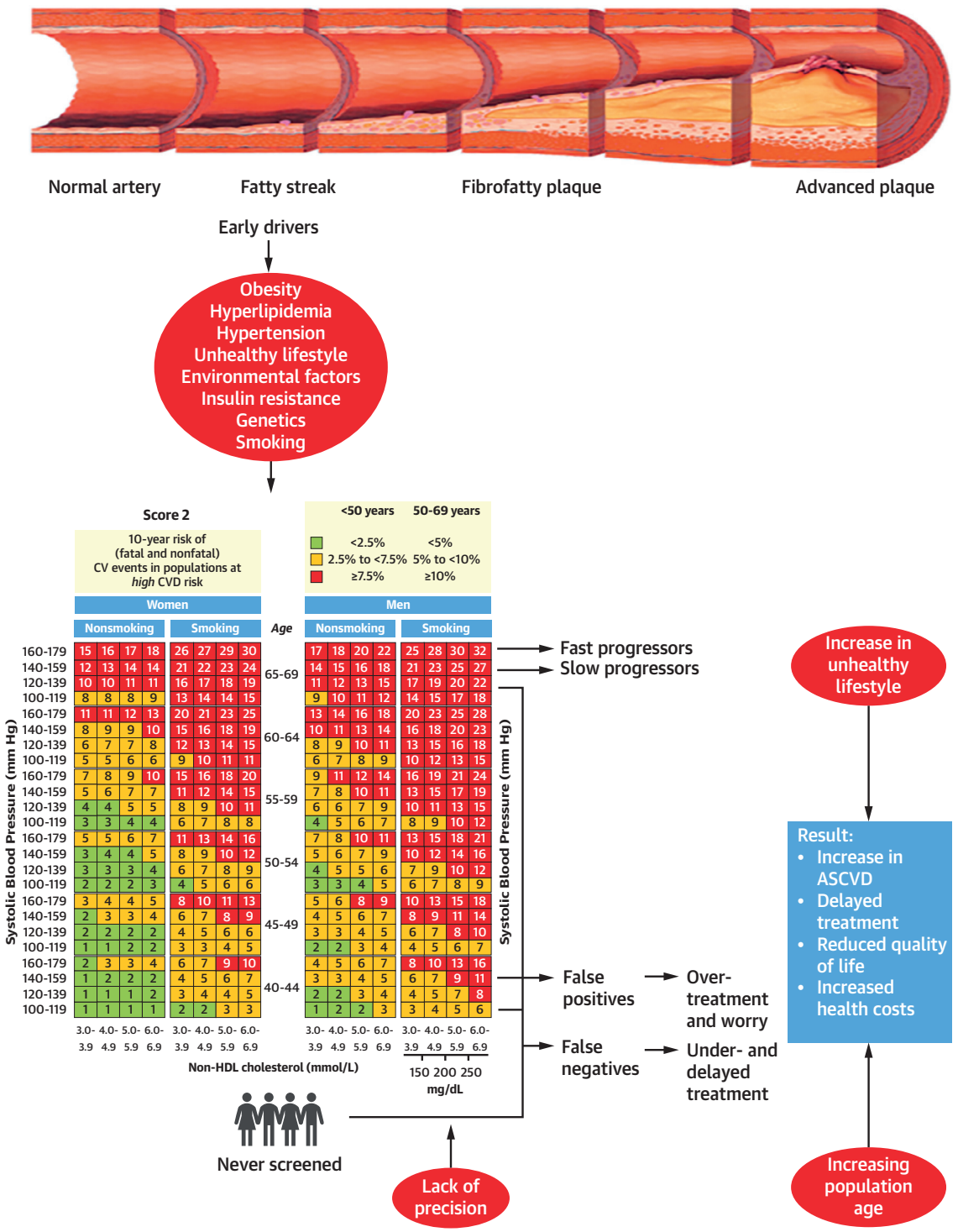
population level, their predictive capacity is more variable at the individual level (Figure 1).[23-26] According to these scores, initiation of interventions to control modifiable risk factors are recommended for subjects with a calculated risk exceeding a certain threshold. Because the relative incidence of ASCVD events is much higher in older adults (ie, when the underlying pathophysiological mechanism of atherosclerosis is well advanced), most young to middle-aged individuals do not fulfil criteria for initiating interventions and their risk factors such as levels of LDL-C are often left untreated.[27,28] Most of these risk equations are based on traditional risk factors and do not calculate the risk for young individuals. Very recently, a new risk equation that includes subjects as young as 30 years old has been presented by the American Heart Association (PREVENT [Predicting Risk of Cardiovascular Disease EVENTs]).[29] This new risk equation includes traditional risk factors and estimated glomerular filtration rate. Models included in the newly proposed PREVENT score are sex-specific, race-free, developed on the age-scale, and adjusted for competing risk of non-CVD death.[29] The implications of this new risk calculator are still to be determined.

The general approach of all these risk equations is suboptimal, because it is known that the relative risk reduction of future ASCVD clinical events is much higher when control for risk factors (LDL-C levels, blood pressure, smoking, and potentially blood glucose and obesity) is started early in life, that is, when the atherosclerotic process is incipient or subclinical.[30-34] In addition, existing risk stratification calculators fall short in providing individual precision, as the propensity to develop atherosclerosis varies distinctly from person to person. This variation in susceptibility is influenced by a complex interplay of factors, including genetic predispositions, environmental exposures, and social determinants of health, making some individuals more vulnerable to risk factors than others. Social determinants of health, which include economic, environmental, and psychosocial factors that influence health, play a significant role in the development of ASCVD and are influential in moderating ASCVD risk trajectories. However, further studies of the full impact are warranted.[35] Furthermore, the presence of important risk enhancers, such as comorbid inflammatory diseases, are common but not included in conventional risk scores.[36] The conventional risk scores also fall short of monitoring whether atherosclerosis progresses slowly or fast, as this may vary among individuals.[37] For these reasons, more direct detection of the presence of the early atherosclerosis process than can be provided by risk scores, may more precisely identify which patients are at risk of events, and those who are not.[38] Imaging tools are currently the only methods to directly identify the presence of atherosclerosis and may be aided by biomarkers to increase prediction of atherosclerosis and ASCVD risk. Compared with population-based risk assessment, imaging has the advantage of directly demonstrating atherosclerosis, and the incorporation of imaging parameters in the risk assessment has been shown to substantially improve the prediction of CVD.[39] Although at the population level the impact of modifiable risk factors on the development of atherosclerosis is robust, at the individual level there is imprecision, such that there are individuals scored to be at low long-term ASCVD risk who in fact may have very advanced atherosclerosis, and other individuals scored high risk in the short term, who have not developed any atherosclerosis.[36,40] It is important to note that the risk factors incorporated into quantitative risk scores are linked to future adverse events through an intermediary process: the progression of atherosclerosis. Both ultrasound of peripheral artery plaque and computed tomography (CT) measuring coronary artery calcification (CAC) (a hallmark of advanced stages of atherosclerosis) have been proven useful when imaging findings lead to treatment and personalized intervention.[41-50] Yet there is no guide on how the presence of this underlying mechanistic driver of ASCVD events affects risk scores or how the detection of subclinical atherosclerosis may tailor risk factor interventions more precisely to the individual.

THE RATIONALE FOR EARLY INTERVENTION OF ATHEROSCLEROSIS

The current recommendation from the World Health Organization (WHO) states that "It is important to detect CVD as early as possible so that management with counselling and medicines can begin,"[7] in agreement with many other recent statements.[12-14] These statements represent an important shift in emphasis from a secondary to a primary prevention paradigm, in recognition of the increasing global prevalence of ASCVD and its attendant risk factors. A growing body of evidence now supports the rationale for earlier intervention in subclinical atherosclerosis analogous to the approach taken for prevention of other chronic disease states such as kidney disease and diabetes, as sequela of preclinical abnormal values detected early on in disease progression.[13] There is little or no controversy regarding measures to control smoking, obesity, and hyperglycemia in young individuals, but there continues to be

FIGURE 1 Lack of Precision in Existing Risk Factor–Based CVD Risk Assessment



The figure illustrates the development of plaque throughout life. Early drivers will lead to progression of plaque. The risk of a CVD event can be estimated using existing risk calculators; however, these are not used systematically in health care systems, leaving many unscreened. Further, the risk calculators fall short in providing individual precision and therefore lead to both false positives and false negatives as well as lack the ability to stratify fast and slow progressors. This leads to both under- and overtreatment. With the increase in unhealthy lifestyle and population age it is predicted that ASCVD and the derived health costs will continue to increase. ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease.

uncertainty regarding how lipid levels should be assessed and controlled earlier in life.[51] Just as it is not clinically acceptable to delay managing hyperglycemia until patients develop diabetic complications, it needs to be explored if progression of atherosclerosis and ASCVD events can be reduced by treating subclinical atherosclerosis earlier.[49,52] There are now calls to consider addressing even mild elevations of cholesterol and atherosclerosis before a heart attack or a stroke occurs.[15,53,54] One prospective study included 4,958 asymptomatic adults aged 18 to 30 years and found that the same area under the LDL-C curve, meaning exposure accumulated at a younger age, compared with older age, resulted in a greater CVD risk increase, emphasizing the importance of optimal LDL-C control starting early in life.[55] Guidelines for treatment of familial hypercholesteremia already advocate early treatment, however not based on imaging, and the question remains as to whether this earlier treatment approach should also extend to the general population without fundamental abnormalities of cholesterol metabolism.

Despite the WHO recommendations, many countries do not systematically evaluate asymptomatic individuals for their overall ASCVD risk before the age of 50 to 60 years. The problem is that at this age, the prevalence of silent atherosclerosis is already high,[10] and the disease can be advanced.[1,6] Overall, in people aged 30 to 79 years in 2020, the global prevalence of carotid artery atherosclerosis is estimated to be 21%, equivalent to 815 million affected people.[6] However, several newer studies indicate that the prevalence is even higher, even though data on age groups younger than 50 years is sparse.[9,10,31,56-58] In the VIPVIZA (Visualization of asymptomatic atherosclerotic disease for optimum cardiovascular prevention) trial,[49] researchers have recently discovered a carotid plaque prevalence as high as 28% in the participants aged 40 to 47 years old on baseline, and 3- and 6-year follow-up combined (Ulf Näslund, 2023). This issue is highlighted by evidence demonstrating that preventing cardiovascular events through lifestyle modifications and medication is markedly more effective in individuals younger than 50 years, compared with older individuals.[10] For example, it has been shown that in high-risk populations such as those with early onset of high LDL-C levels (familial hypercholesterolemia), as well as in other high-risk groups of children such as those with diabetes, lifestyle and pharmacologic intervention in childhood and adolescence reduces the risk of early morbidity and mortality.[33,59-61] The safety and efficacy of several interventions, including pharmacotherapy, in such children and young adults are increasingly being demonstrated.[53,62,63] Another striking illustration of the profound impact of early LDL-C control is evident from studies on individuals with loss-of-function mutations in the *PCSK9* gene. Carriers of these mutations exhibit an approximate 30% reduction in LDL-C levels.[64] Such moderate but sustained reductions over a lifetime lead to a significant decrease in lifetime exposure to LDL-C. This is associated with a substantial reduction in the incidence of major ASCVD clinical events.[64]

However, there remains some paucity in the literature with respect to studies and randomized controlled trials explicitly evaluating the health and economic benefits of screening for and treating ASCVD risk in young people,[65] in part because of the hesitation surrounding the implication of potential lifetime pharmacologic therapy. Thus, there clearly is a need to evaluate the effect of detecting and managing subclinical atherosclerosis in asymptomatic younger individuals—the overall vision of the REACT initiative.

THE FUTURE OF ASCVD PREVENTION

The REACT initiative aims to test an atherosclerosis screening solution. The structure suggested is a precision medicine-based[38] approach to screening for subclinical atherosclerosis by imaging, circulating biomarkers, traditional risk factors (lipid levels, hypertension, smoking, age, sex), and psychosocial and potential other phenotypical risk factors, accompanied by a new and more precise atherosclerosis risk calculator. Genomics may in the future be used to predict when to undertake more detailed screening. This should facilitate personalized early treatment of atherosclerosis and a reduction in clinical ASCVD events (**Central Illustration**).[38]

LESSONS FROM POPULATION STUDIES IN YOUNG TO MIDDLE-AGED INDIVIDUALS

In the Bogalusa Heart Study, a long-term community study of a rural biracial (Black/White) population, it was found that increased lipid levels in childhood as well as distinct lipid trajectories over the course of life are associated with midlife carotid intima-media thickness. The findings suggest that screening for dynamic changes in lipid profiles from early life may potentially improve identification of high-risk individuals for prevention of CVD.[30]

The Cardiovascular Risk in Young Finns Study has followed a cohort of initially 3- to 18-year-old Finnish children and adolescents since 1980. The 21- and 27-year follow-ups included left carotid intima-media

assessment and plaque measurement by ultrasound. The reported prevalence of carotid plaque at the mean age of 36 years was 3.3%.[31] However, in the most recent follow-up study, using an imaging protocol that included all 3 carotid arterial segments: common carotid, bifurcation, and internal carotid, bilaterally, a much higher plaque prevalence was observed, starting from 20% at age 40 years and being about 50% in individuals older than 50 years. In the offspring of the original study participants, including children, adolescents, and young adults between ages 3 and 36 years, the presence of carotid plaques was found to occur as early as 18 years of age (Olli T. Raitakari, 2023). The Young Finns Study has demonstrated that childhood dyslipidemia, even if resolved by adulthood, is a risk factor for the development of adult carotid plaque. In addition, childhood lipids were associated with plaque size among individuals with carotid plaque.[31] These findings highlight the importance of further exploring the effect of early prevention of dyslipidemia in childhood to reduce atherosclerosis development.[66]

The CARDIA (Coronary Artery Risk Development in Young Adults) study similarly found that early intervention and continued risk factor control was important for the prevention of coronary calcium, which in turn correlated to events. This group developed an ASCVD score, consisting of cardiovascular health (CVH) points, assigned for risk factors. They examined the association between baseline and early adulthood changes in CVH points, and the risk of subclinical atherosclerosis measured by CAC and intima-media thickness. Improvement in the CVH point score at baseline or a change of 1 point over time, was associated with a decrease in CAC or intima-media thickness. For participants with a moderate CVH class at baseline (which was most of the young population in this study) altering CVH class was associated with a reduction of midlife risk of subclinical atherosclerosis.[32]

In the PESA (Progression of Early Subclinical Atherosclerosis) study involving a healthy cohort of adults aged 40 to 55 years (mean age 46 years), ultrasound of several territories demonstrated plaque in the peripheral arteries of 60% of the participants (56% in men, 31% in women).[10] Importantly, peripheral artery plaque was detected in approximately 40% of participants with a CAC score of 0.[37] Moreover, lifestyle factors were found to influence subclinical atherosclerosis and predict potential regression of plaque in the young subjects studied, further motivating early intervention. Interestingly and importantly a substantial number of subjects with plaques in either the carotid or femoral arteries at baseline seemed to have complete remission of atherosclerosis at 6 years follow-up.[37] Participants exhibiting a lower total burden of atherosclerotic plaque were more likely to experience regression, indicating that the disease may be more amenable to modification in its early stages. This finding reinforces the value and potential benefits of initiating interventions at an earlier stage in the disease's progression and should be explored further. **Table 1** summarizes the studies.

Thus, there are strong indications for the benefit of both the identification of subclinical atherosclerotic disease and early intervention on risk factors to reduce events later in life. The true prevalence of atherosclerosis in the younger middle-aged cohort remains unsettled and an important focus of future attention. Furthermore, the acceptability of screening and adhering to preventive initiatives in younger populations as well as the direct and psychological costs of this type of intervention must be investigated.

SHIFTING THE FOCUS IN ATHEROSCLEROSIS CARE: THE POTENTIAL OF IMAGING

Advanced imaging techniques, such as ultrasound, CT, and magnetic resonance imaging, directly visualize atherosclerosis in the arteries, that is, the combined result of genetic disposition and exposure to both known and unknown risk factors. Given that imaging is the only method to identify and quantitate plaque, it plays a critical role in atherosclerosis research and potentially in precision medicine via screening, early diagnosis, guiding treatment, and in monitoring the response to therapy.[41,48,49,68,69]

Vascular ultrasound can identify early (noncalcified and calcified) atherosclerotic plaque in a noninvasive, radiation-free manner.[10,70] Initial studies using peripheral artery ultrasound as a means for identifying atherosclerosis relied on carotid intima-media thickness. However, intima-media thickness is a suboptimal surrogate for atherosclerosis, and it does not provide clear incremental value for risk stratification over classical risk factors.[71] In contrast, identification of atherosclerotic plaque by vascular ultrasound demonstrated incremental benefit and to re-stratify subjects deemed to be intermediate risk by conventional risk scores.[42,72,73] Vascular ultrasound has evolved significantly in recent years, moving from a very imprecise initial approach to an analysis of the actual presence and burden of plaque and plaque composition.[48,70,74-76] In addition, vascular ultrasound can provide information on the spatial extent of the disease in different peripheral large arterial territories (ie, carotid and

CENTRAL ILLUSTRATION **Reversal of Early Atherosclerosis Through Personalized Curative Treatment Vision: A Precision Medicine Approach for Prevention of Atherosclerotic Cardiovascular Disease**

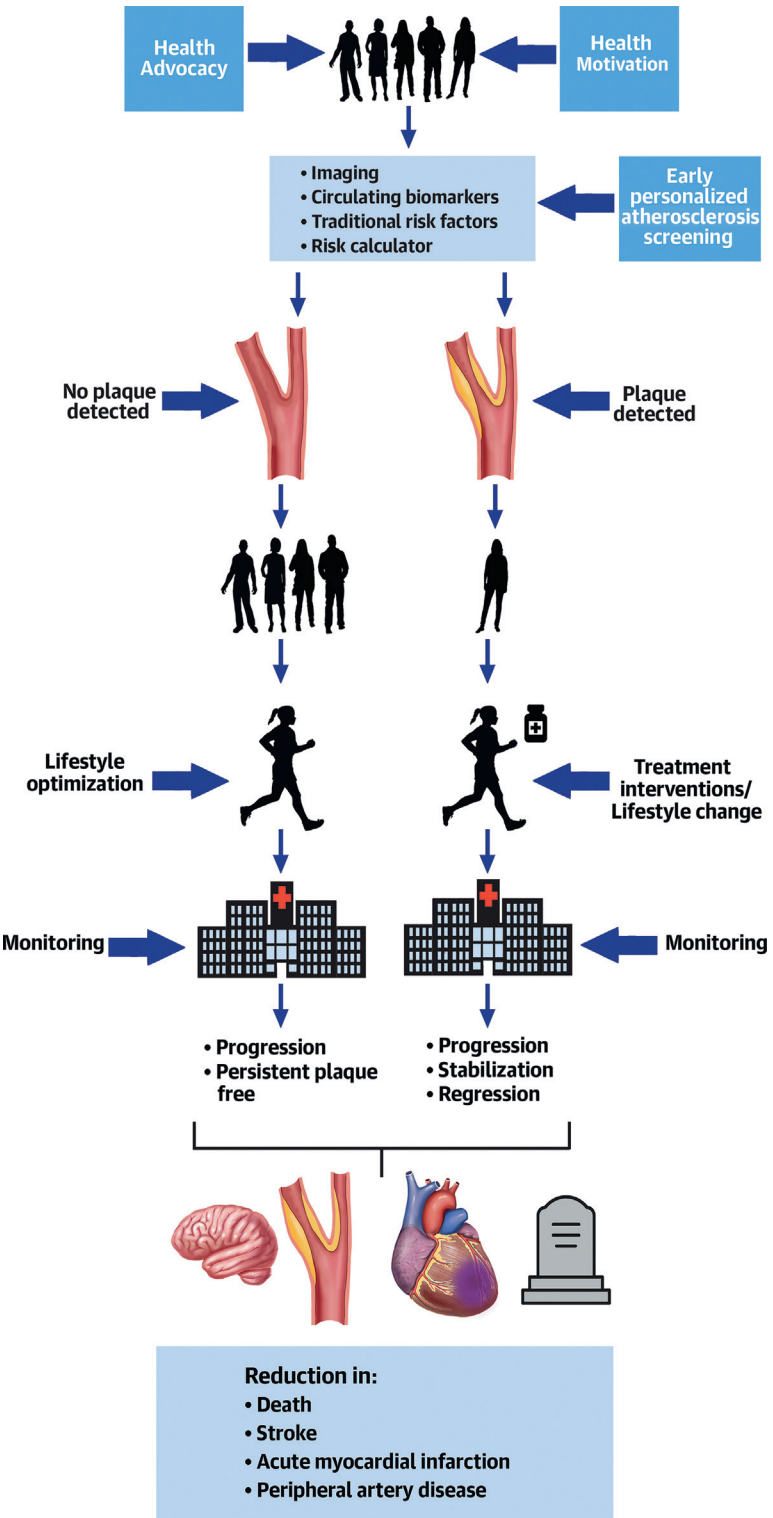


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TABLE 1 Summary of Population Studies Assessing Subclinical Atherosclerosis in Young to Middle-Aged Individuals (ie, Mean Age <50 Years)

	Bogalusa Heart Study (n = 914)	Young Finns Study (n = 2,062)	CARDIA Study (n = 2,935)	PESA Study (n = 4,184)
Mean follow-up, y	36.8	39	20	6
Mean age, y	46	48	45	46
Female, %	58	55	56	37
BMI, kg/m^2, mean	31	28	29	26
Imaging modality	Ultrasound	Ultrasound	Ultrasound	Ultrasound
Imaging measurement	Intima-media thickness	Plaque thickness	Intima-media thickness	Plaque volume / thickness
Detection site, artery	Carotid arteries	Carotid arteries	Carotid arteries	Carotid, femoral and aorta arteries
Plaque prevalence, %	8-14	40	4	60

Intima-media thickness is a measurement of the thickness of tunica intima and tunica media, the innermost 2 layers of the artery wall. Plaque is defined as a focal structure encroaching into the arterial lumen of at least 0.5 mm or 50% of the surrounding intima-media thickness value or demonstrates a thickness >1.5 mm as measured from the media-adventitia interface to the intima-lumen interface, in accordance with the Mannheim criteria.[67]

BMI = body mass index; CARDIA = Coronary Artery Risk Development in Young Adults; PESA = Progression of Early Subclinical Atherosclerosis.

femoral arteries). Importantly, it has recently been demonstrated that the use of 3-dimensional ultrasound technology and plaque quantification software provides accurate plaque volume measurements, while reducing time of analysis.[77] Three-dimensional ultrasound of carotid plaque was also found to correlate well with angiographic coronary artery stenosis.[78] Therefore, vascular ultrasound could be an ideal tool for a personalized prevention strategy in which LDL-C lowering (and other) therapy is guided by the presence and quantity of atherosclerotic plaque. This approach has, heretofore, not been tested. To make this vascular ultrasound-guided approach widely applicable in an ambulatory clinical environment, there are important aspects that need to be developed, such as making acquisition simple for nonexperts and providing a rapid and automatic analysis.

Coronary artery calcification identification by CT has been used as a surrogate for noninvasive arterial imaging of atherosclerosis.[44,75,79-81] In the United States, CAC scoring in accordance with guidelines, is used in some centers to improve risk classification and help decide on statin initiation in adults older than 40 years.[21,79,82] There are also good data on individuals aged 30 to 45 years old.[47] Many studies have shown that CAC assessment is a diagnostic test with a high negative predictive value to exclude coronary artery disease.[83-85] CAC scoring has a low sensitivity and specificity in young ages because of the inability to diagnose noncalcified atherosclerotic plaques that have a higher propensity to rupture, and the imaging modality has not been calibrated for individuals younger than 30 years.[86,87] The appearance of coronary calcification is a late process in the course of atherosclerotic disease. Thus, the high negative predictive value of a CAC score of 0 has in some individuals with CAC score of 0 been challenged by findings of noncalcified coronary atherosclerosis (demonstrated with CT angiography), established with varying frequency (prevalence 4% to 40%) and associated with an increased risk of cardiovascular events.[10,88] CAC testing is associated with a small amount of ionizing radiation (approximately 1 mSv). The harm vs benefit discussion for this modality remains when considering suitability as a mass screening tool for primary prevention and the focus on early disease in young individuals.[89] If follow-up imaging to track progression of early atherosclerosis is considered as part of a screening program, the

CENTRAL ILLUSTRATION Continued

Health motivation and health advocacy should be applied to the entire population as early as possible. Early personalized atherosclerosis screening may include tools such as imaging, circulating biomarkers, traditional risk factors, and a risk calculator. Depending on whether plaque is detected or not, individuals will go into different trajectories with different interventions and monitoring frequency. Treatment interventions may include pharmacotherapy for low-density lipoprotein-cholesterol lowering, hypertension, and smoking cessation. Lifestyle interventions may include education and support for dietary change, exercise, and smoking cessation. Such an atherosclerosis screening program is expected to reduce death from atherosclerotic cardiovascular disease, acute myocardial infarction, stroke, and peripheral artery disease.

associated costs and the small but incremental dose of radiation from serial imaging also become relevant.

Computed tomography coronary angiography (CTCA) has emerged as a noninvasive, patient-friendly diagnostic modality to assess the full spectrum of coronary artery health and disease. The diagnostic potential of CTCA is high because it allows not only the detection of significant coronary artery stenoses but also the presence of nonobstructive coronary plaques and plaque composition, in addition to the pericoronary adipose tissue and fat attenuation index.[90,91] Early subclinical coronary artery disease diagnosed with this noninvasive tool might therefore have a role in refining risk on an individual basis beyond conventional risk factors or algorithms. However, the lack of evidence for the impact of CTCA on patient outcomes in asymptomatic populations must be addressed. The SCOT-HEART 2 (Computed Tomography Coronary Angiography for the Prevention of Myocardial Infarction; NCT03920176) trial and the DANE-HEART (Computed Tomography Coronary Angiography for Primary Prevention; NCT05677386) trial, currently recruiting, will provide a direct comparison between CTCA and a validated cardiovascular risk score (ASSIGN Cardiovascular Risk Score, used routinely in Scotland) in 6,000 middle-aged individuals at risk of CVD. It may help answer the key remaining question regarding whether the benefits of CTCA over and above CACS (coronary artery calcium score) and/or current multivariate risk scores also result in meaningful restratification of management in the asymptomatic population and are associated with clinical benefit.

There are potential drawbacks to CTCA that require consideration, especially in the asymptomatic population.[92] The ongoing work to reduce radiation exposure is important, as current CTCA techniques remain at 1 to 5 mSv for CTCA compared with for example the annual background radiation of 2.5 to 6 mSv.[93,94] For context, exposure to 100 mSv is believed to increase lifetime cancer risk by 0.5%. No studies have directly assessed the impact of low doses of radiation in adults, so the impact of a single 1 mSv scan is unknown. Contrast reaction rates are very low, especially those for severe adverse reactions.[95] However, the importance of both radiation and contrast reactions increases with a population-based approach, particularly in asymptomatic individuals in whom the risk-benefit ratio differs from that of symptomatic patients. In the future, better methods may become available, as the development of noncontrast CT angiography is being investigated.

In addition to visualizing atherosclerosis and perhaps identifying high-risk individuals, imaging of subclinical atherosclerosis may also improve clinician-patient risk communication. A recent review and meta-analyses demonstrated that patient visualization of subclinical atherosclerosis is associated with motivation and ASCVD risk reduction.[96]

To target the optimal imaging modality for population-based screening, it is necessary to determine if peripheral and coronary plaque are interchangeable or tightly correlated in the younger population[95,97] and if they follow a parallel trajectory albeit initiated earlier in one vascular territory. Further, the choice of imaging modality applicable to population-based strategies requires several considerations regarding feasibility. The requirements for the technology are easy access use by nonexperts and low cost, and ideally outside the expert-environment of hospitals, preferably at the health care center level. In addition, quantification of disease should be simple (at the best, automated). Because of the young population addressed in this newly proposed personalized prevention strategy, they must be approached during regular check-ups (eg, in occupational health services of companies, other community touch points) and thus the imaging modality must ideally be portable and applicable in those locations.

IMAGING-ONLY GUIDED INTERVENTION: POTENTIAL RISK OF OVERTREATMENT

The prevalence of subclinical atherosclerosis has been shown to be high in middle-aged individuals;[37] however, not all of these subjects will develop an ASCVD clinical event in their lifetime. Thus, a pure imaging-guided approach for early treatment might come with overtreatment. Yet, substantial reductions in overtreatment have been described with the use of CAC score.[98] Overtreatment is an inherent risk to most interventions in medicine, even those in secondary prevention. As an example, after a myocardial infarction, antithrombotic and cholesterol-lowering treatment is recommended to prevent future ischemic events, but a significant proportion of untreated individuals will never develop a second event. This is also true for primary prevention of other diseases, such as screening for prostate cancer. Contrary to other screening programs, the present proposal is based on direct visualization of the disease by ultrasound, and noninvasive, inexpensive interventions (eg, lipid lowering) with proven safety profiles.[99] The

risk of overtreatment is expected to be less using imaging combined with other biomarkers, than with current risk scores and recommendations for CVD prevention.

BLOOD-BASED BIOMARKERS

Circulating biomarkers may hold promise to identify asymptomatic individuals who most likely exhibit early atherosclerosis independently of their age or conventional cardiovascular risk profile and would benefit the most from vascular imaging screening and early intervention. Furthermore, biomarkers of subclinical atherosclerosis may be particularly valuable in situations in which vascular imaging is scarce or unavailable. However, much work is needed in this setting, as the presently applied biomarkers of atherosclerosis for use in clinical practice need to be expanded to improve precision. A clinically available measure is high-sensitivity C-reactive protein, a circulating inflammatory biomarker associated with risk of CVD events but not atherosclerosis.[100] However, high-sensitivity C-reactive protein is a nonspecific acute-phase response protein that may inform of the overall inflammatory status of an individual but lacks a causal link to atherosclerosis.[101-103] Moreover, inconsistent findings have been reported regarding the association between high-sensitivity C-reactive protein and subclinical atherosclerosis.[84,104-108] Other biomarkers that have been shown to reclassify risk of ASCVD include lipoprotein(a), high-sensitivity troponin, and N-terminal pro-B-type natriuretic peptide.[109]

In this context, quantitative proteomics and metabolomics analyses have identified various circulating proteins and metabolites that are correlated with imaging evidence of subclinical atherosclerosis and therefore show promise as biomarkers.[108,110-114] Additional epidemiological and clinical studies are necessary to confirm the accuracy and reliability of measuring these molecules, which may also have unrecognized dynamics. Another limitation to consider is that existing biomarkers have typically been examined in the context of cross-sectional measurements of subclinical atherosclerosis burden.[110] There is a paucity of biomarkers predictive of adverse progression of the disease during its preclinical stages. Emerging longitudinal data from observational human cohorts with comprehensive imaging phenotyping at multiple time points offer a unique opportunity to identify new predictive and prognostic biomarkers.[37]

EXPLORING THE IMPACT OF POLYGENIC RISK SCORES: PRESENT INSIGHTS AND FUTURE EXPECTATIONS

With expanding knowledge of the genetic basis of ASCVD, especially from monogenic familial hypercholesteremia, there is increased interest in exploring the potential clinical applicability of genetic predictors that might improve CVD risk management. Besides the role of age-related acquired somatic mutations,[115,116] more than 240 independent inherited genetic variants have been associated to date with a higher risk of ASCVD, particularly coronary artery disease.[117-120] Building on this knowledge and the increasing availability of genomic data from large cohorts, several polygenic risk scores (PRS) have been developed to quantify the cumulative genetic susceptibility to ASCVD conferred by multiple inherited variants across the genome.[121] Exhibiting a high PRS for coronary artery disease is associated with a rate of events comparable to an individual with several conventional risk factors, suggesting that these composite metrics may offer substantial value for the precise and personalized assessment of ASCVD risk.[122-127] Nonetheless, the actual clinical utility of PRS for population-wide ASCVD prevention remains a matter of debate, as available PRS may provide a limited improvement on ASCVD risk discrimination when added to existing clinical predictors and are particularly limited in the prediction of incident events.[121,122,125,128-130] In this context, a potentially more pertinent clinical application of PRS may lie in its ability to guide preventive imaging or other screening tests for subclinical atherosclerosis among asymptomatic young or middle-aged individuals, including those categorized as low risk based on conventional risk scores. Reinforcing this concept, studies[131-134] have demonstrated a correlation between polygenic predictors of clinically apparent ASCVD and subclinical atherosclerosis, including among young adults in the CARDIA study.[132] Moreover, emerging evidence suggests that the predictive power of PRS for ASCVD is greater in younger individuals and could be used to identify patients who would benefit from cholesterol-lowering therapy despite not meeting the typical criteria for intervention based on their conventional risk profile.[135] Therefore, although much work lies ahead, PRS may significantly facilitate the implementation of earlier and more targeted imaging-based assessments or other screening tools that inform the timing of pharmacological or lifestyle intervention against ASCVD.

TABLE 2 Renewed Version of the Original *Principles and Practice of Screening for Disease*

• The screening program should respond to a recognized need.
• The objectives of screening should be defined at the outset.
• There should be a defined target population.
• There should be scientific evidence of screening program effectiveness.
• The program should integrate education, testing, clinical services, and program management.
• There should be quality assurance, with mechanisms to minimize potential risks of screening.
• The program should ensure informed choice, confidentiality, and respect for autonomy.
• The program should promote equity and access to screening for the entire target population.
• Program evaluation should be planned from the outset.
• The overall benefits of screening should outweigh the harm.

Synthesis of emerging screening criteria proposed over the past 40 years.[65]

FRAMEWORK FOR RANDOMIZED CONTROLLED TRIALS

There is an undeniable challenge in assessing hard clinical endpoints for the methods suggested: does early screening lead to treatment and improved outcomes? Randomized controlled trials intervening on younger populations would require a several-decades-long follow-up period to obtain an improvement in hard endpoints such as major adverse cardiovascular events or death. Such trials are indeed necessary, but their feasibility remains challenging.[13] Alternatively, surrogate outcomes in younger populations may include the sustained stabilization or even regression of plaque, as evidenced by imaging techniques.[45,136] Further, a significant lowering of LDL-C early in life may be a highly relevant outcome as studies show people who have low lifetime levels of LDL-C have remarkably low ASCVD event rates.[54,64,137-141] Supporting this methodology, regulatory agencies have expressed the potential for reviewing imaging outcomes if they can be linked to data on ASCVD events.[137,142,143]

TABLE 3 Knowledge Gaps to Be Addressed Moving Toward Early Prevention and Treatment of Atherosclerosis

Issue	Action
Paradigm shift from ASCVD management to cure	Reframing atherosclerosis as a disease in itself that is treatable and potentially curable if addressed at very early stages.
Accurate data overview on global ASCVD prevalence and outcome	In-depth review of current evidence including reanalysis of existing data sets to better clarify the prevalence of atherosclerosis and the capabilities of existing tools.
Uncovering the current prevalence of subclinical atherosclerosis in the younger population	A large prevalence study demonstrating the prevalence of subclinical atherosclerosis assessed with state-of-the-art imaging modalities covering both coronary and peripheral arteries in the younger populations, optimally with diverse ethnicities and risk profile.
The effect of early intervention on ASCVD outcome	Randomized controlled trial on the effect of early detection of atherosclerosis with a precision medicine method. Outcome should be as closely associated with hard clinical endpoints as feasible.
Health advocacy	Governments: dialogue on the cost-benefit of early screening. Scientific societies: supporting research and education of physicians on the rationale for this approach. Population: information, education, and motivation of the younger population educating on the long-term potential of early screening.

ASCVD = atherosclerotic cardiovascular disease.

HEALTH PROMOTION

A major challenge in the paradigm of primary prevention of ASCVD will require changing the mindset of the (young) population and many stakeholders, such as policy makers, experts, and their scientific societies. The concept that needs to be introduced and accepted is that atherosclerosis is a disease that can be halted or cured if tackled early.

The importance of bottom-up health advocacy approaching the population and communities cannot be overstated. There is a crucial gap in the opportunity for early detection of atherosclerosis in young adults, as these individuals often do not have regular visits to their general practitioners, especially younger men who do not have medical contacts as women do with routine gynecologic care or during pregnancy.[27] Therefore, it is crucial to explore the opportunities and create evidence for tools that could potentially be suitable to use if a strategy of approaching young adults during regular check-ups such as educational institutions, workplace, etc were to be desired. Health promotion programs starting in early childhood have the potential to reduce the global burden of CVD. These interventions need to be explored further and advertised at a population level and through governmental health advocacy.[144] Further, motivation to enroll in a screening program and adherence to potential lifestyle changes and pharmacological treatment, if indicated, must be investigated in younger populations. The position of screening programs in prevention and early detection of disease is growing. Optimizing screening strategies enables potential intervention earlier in disease pathways to improve patient outcomes and reduce health care burden. Criteria outlined in the Wilson and Jungner[145] WHO report *Principles and Practice of Screening for Disease*, issued in 1968, have long been considered the gold standard in assessing the appropriateness of a screening tool. A suggested modified version was issued in 2008[65] (Table 2). CVD as a whole, and atherosclerosis specifically, evidently meets many of both the original and emerging screening criteria. However, importantly, the most cost-efficient

screening method needs to be determined. The cost implication to the individual and the health care system is important and will need weighing against the overall current impact of ASCVD on patients and the health economy. The current explorations on CVD screening have been conducted on older populations, finding that early detection and prevention of asymptomatic ASCVD can be beneficial and cost-effective, but not in older individuals.[52,146] Thus, data demonstrating improved prognosis in asymptomatic younger groups following appropriate management based on these new (bio)imaging markers are needed.[147] Further psychosocial and mental health considerations also need to be studied, such as the impact on young individuals of learning that they have disease (even if it is early and subclinical) as well as the impact that such findings may have on their lifestyle, diet, exercise, and occupational and family choices, short and long term.

FUTURE DIRECTIONS

The future agenda of the REACT group, from now until 2030, envisions a strong focus on studying and promoting the value of the detection of subclinical atherosclerosis before ASCVD events. In the short term, we recognize a need for an international initiative to first define the true prevalence of plaque across age groups, and further, defining the proportion of those younger than 40 to 45 years of age with plaque or elevated lipid levels who do not have familial hypercholesteremia. In the medium term, we propose intervention trials to determine the impact of early screening on outcomes. Finally, we plan to establish a pathway toward advocating for both the societal health and economic benefits of large-scale early atherosclerosis screening, driving a precision- and personalized medicine-based approach to management and prevention of ASCVD events (**Table 3**).

CONCLUSIONS

Subclinical atherosclerosis, analogous to the preclinical markers of hyperglycemia that lead to diabetes, is now considered the precursor to important ASCVD outcomes. The detection and monitoring of this silent, preclinical stage of disease have been inadequately addressed in clinical practice. However, it is gaining critical importance because of the escalating global prevalence of ASCVD and risk factors for this disease group. Detecting the presence of atherosclerosis in otherwise asymptomatic individuals is now possible with noninvasive imaging tools, such as vascular ultrasound, CTCA, and CAC, which now have enhanced image resolution and stratification capabilities to detect atherosclerotic lesions. Further development of such novel imaging biomarkers, along with how they may integrate with other blood markers, may be the key to precisely identifying individuals who would benefit from early detection, monitoring, and management of subclinical atherosclerosis.

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