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.

Condensed abstract
To change cardiovascular disease (CVD) from being the leading cause of mortality and morbidity worldwide, a paradigm shift is needed. Atherosclerosis is the underlying pathophysiological entity in two-thirds of CVD cases. To facilitate a shift, subclinical atherosclerosis must be considered an early asymptomatic CVD stage. This should lead to a clinical change from management and prevention of CVD complications to actual cure of atherosclerosis, as treatment is more effective at earlier stages. A precision medicine-approach is critical as not all individuals benefit from screening or initiation of treatment. This approach is expected to improve life quality and life expectancy.

Keyword (Max. of 6)**:** Atherosclerosis, Cardiovascular disease, Primary prevention, Precision medicine, Imaging.

Abbreviations (Max. of 10)**:**
ASCVD: Atherosclerotic cardiovascular disease
CAC: coronary artery calcium
CARDIA: Coronary Artery Risk Development in Young Adults
CT: Computed tomography
CTCA: Computed tomography coronary angiography
CVD: Cardiovascular disease
CVH: Cardiovascular health
PESA: Progression of Early Subclinical Atherosclerosis
PRS: Polygenic risk scores
REACT: Reversal of Early Atherosclerosis through personalized Curative Treatment

List of 3-4 brief bullet points highlighting the main messages
• 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 cardiovascular disease with enormous implications for population health.

Introduction.

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 from 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 CVD (ASCVD) globally, a new standard of care targeting atherosclerosis in its subclinical phase, including in younger asymptomatic individuals (i.e. perhaps less than 50 years of age) needs to be defined [12-15]. Atherosclerosis usually develops over decades, with heterogenous 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 “Reversal of Early Atherosclerosis through personalized Curative Treatment”, REACT – 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 multi-disciplinary 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 which will include studies and trials of innovative imaging and circulating biomarkers for early detection of atherosclerosis. Further, knowledge about psycho-social factors is warranted, since lifestyle (smoking, diet, sedentary lifestyle), sleeping patterns, anxiety and depression are driving forces for atherosclerosis progression.

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 amongst some regions [19,20], and are based on conventional risk stratification tools that are calculated from the presence of traditional, modifiable risk factors (LDL-cholesterol, systolic blood pressure, and smoking status), in addition to age and gender [21,22]. While these tools may be useful at the 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. Since the relative incidence of ASCVD events is much higher in older adults (i.e. 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-cholesterol 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 which includes subjects as young as 30 years old has been presented by the AHA (Predicting Risk of Cardiovascular Disease EVENTs (PREVENT)).[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, since it is known that the relative risk reduction of future ASCVD clinical events is much higher when control for risk factors (LDL-cholesterol levels, blood pressure, smoking, and potentially blood glucose and obesity) is started early in life i.e. when the atherosclerotic process is incipient or subclinical [30-34]. Additionally, 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 co-morbid 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 to 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]. Though, 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 impacts 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 states that "It is important to detect cardiovascular disease 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 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 LDL-cholesterol 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-cholesterol 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 50-60 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 30–79 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 below 50 years is sparse.[9,10,31,56-58] In the VIPVIZA trial,[49] they have recently discovered a carotid plaque prevalence as high as 28% in the participants aged 40-47 years old on baseline, 3- and 6-year follow-up combined (unpublished data). This issue is highlighted by evidence demonstrating that preventing cardiovascular events through lifestyle modifications and medication is markedly more effective in individuals under the age of 50, compared to older individuals [10]. For example, it has been shown that in high-risk populations such as those with early onset of high LDL-cholesterol 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-cholesterol 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-cholesterol levels.[64] Such moderate but sustained reductions over a lifetime lead to a significant decrease in lifetime exposure

to LDL-cholesterol. 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 due to 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), psycho-social 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 3–18-year-olds 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 three 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 aged over 50 years. In the offspring

of the original study participants including children, adolescents and young adults between ages 3-36 years, the presence of carotid plaques was found to occur as early as 18 years of age (unpublished data). 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. Additionally, 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 Coronary Artery Risk Development in Young Adults (CARDIA) 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 coronary artery calcium (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 40-55 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 zero.[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 upon 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.

Table 1. Summary of population studies assessing subclinical atherosclerosis in young to middle aged individuals (i.e. mean age< 50 years).

	Bogalusa Heart Study	Young Finns Study	CARDIA Study	PESA Study
N	914	2062	2935	4184
Mean follow-up, years	36.8	39	20	6
Mean age, years	46	48	45	46
Female, %	58	55	56	37
BMI, kg/m2, 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

BMI = body mass index; CARDIA = Coronary Artery Risk Development in Young Adults; PESA = Progression of Early Subclinical Atherosclerosis. Intima-media thickness is a measurement of the thickness of tunica intima and tunica media, the innermost two 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]

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, i.e., 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 (non-calcified and calcified) atherosclerotic plaque in a non-invasive, 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 (i.e. carotid- and femoral arteries). Importantly, it has recently been demonstrated that the use of three-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 where LDL cholesterol 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 non-experts and providing a rapid and automatic analysis.

Coronary artery calcification identification by CT has been used as a surrogate for non-invasive arterial imaging of atherosclerosis.[44,75,79-81] In the US, CAC scoring in accordance with guidelines, is used in some centers to improve risk classification and help decide upon statin initiation in adults

older than 40 years[21,79,82] There are also good data on individuals aged 30-45 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 non-calcified atherosclerotic plaques that have a higher propensity to rupture, and the imaging modality has not been calibrated for individuals <30 years of age.[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 non-calcified coronary atherosclerosis (demonstrated with CT angiography), established with varying frequency (prevalence 4-40%) and associated with an increased risk of cardiovascular events.[10,88] CAC testing is associated with a small amount of ionizing radiation (approx. 1 mSv). The harm versus 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 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 non-obstructive 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 non-invasive 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 trial and the DANE-HEART trial, currently recruiting, will provide a direct comparison between CTCA and a validated CV risk score (ASSIGN Cardiovascular Risk Score, used routinely in Scotland) in 6,000 middle-aged individuals at risk of CVD.[92,93] It may help answer the key remaining question regarding whether the benefits of CTCA over and above CACS and/or current multivariate risk scores also result in meaningful re-stratification 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.[94] The ongoing work to reduce radiation exposure is important, as current CTCA techniques remain at 1-5 mSv for CTCA compared to for example the annual background radiation of 2.5-6 mSv.[95,96] 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.[97] However, the importance of both radiation and contrast reactions increases with a population-based approach particularly in asymptomatic individuals where the risk-benefit ratio differs from that of symptomatic patients. In the future better methods may become available, as the development of non-contrast 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.[98]

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[97,99] 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 non-experts and low cost, and ideally outside the expert-environment of hospitals, preferably at health care center level. In addition, quantification of disease should be simple (at the best, automated). Since the young population addressed in this newly proposed personalized prevention strategy, they must be approached during regular check-ups (e.g. 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 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 over treatment have been described with the use of CAC score.[100] Over treatment 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 non-invasive, inexpensive interventions (e.g. lipid lowering with proven safety profiles.[101] The risk of over treatment 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 where 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.[102] However, high-sensitivity C-reactive protein is a non-specific acute phase response protein that may inform of the overall inflammatory status of an individual but lacks a causal link to atherosclerosis.[103-105] Moreover, inconsistent findings have been reported regarding the association between high-sensitivity C-reactive protein and subclinical atherosclerosis.[84,106-110] 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.[111]

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.[110,112-116] 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.[112] 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 timepoints 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,[117,118] over 240 independent inherited genetic variants have been associated to date with a higher risk of ASCVD, particularly coronary artery disease.[119-122] Building upon 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.[123] 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.[124-129] 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.[123,124,127,130-132] 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[133-136] have demonstrated a correlation between polygenic predictors of clinically apparent ASCVD and subclinical atherosclerosis, including among young adults in the CARDIA study.[134] Moreover, emerging evidence suggest that the predictive power of PRS for ASCVD is greater in younger individuals and could be used to identify patients that would benefit from cholesterol-lowering therapy despite not meeting the typical criteria for intervention based on their conventional risk profile.[137] Therefore, while 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.

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.[45,138] Further, a significant lowering of LDL-cholesterol early in life may be a highly relevant outcome as studies show people who have low lifetime levels of LDL-cholesterol have remarkably low ASCVD event rates.[54,64,139-143] Supporting this methodology, regulatory agencies have expressed the potential for reviewing imaging outcomes if they can be linked to data on ASCVD events.[139,144,145]

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 CV disease. These interventions need to be explored further and advertised at a population level and through governmental health advocacy.[146] 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 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.[147] 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 healthcare system are 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 beneficial and cost-effective, but not in the elderly.[52,148] Thus, data demonstrating improved prognosis in asymptomatic younger groups following appropriate management based on these new (bio)imaging markers are needed.[149] Further psychosocial, and mental health considerations also need to be studied, such as the impact upon young individuals of learning that they have disease (even if its 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.

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]

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. Further, defining the proportion of those with plaque or elevated lipid levels under the age of 40-45, who do not have familiar 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 towards 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).

Table 3. Knowledge gaps to be addressed moving towards early prevention and treatment of atherosclerosis.

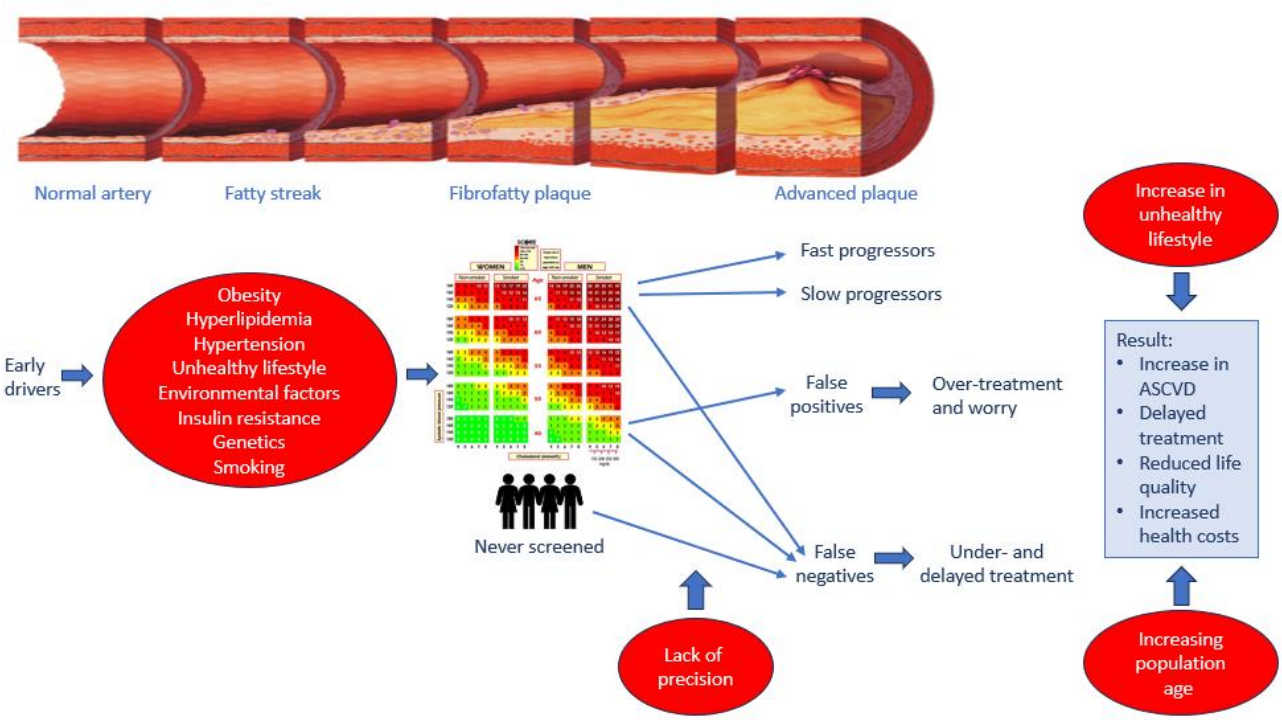
Issue	Action
Paradigm shift from ASCVD management to cure	Reframing atherosclerosis as a disease in itself that is treateble and potentially curable if addressed at very early stages.
Accurate data overview on global ASCVD prevalence and outcome	In depth review of current evidence including reanalysis of existing data sets to better clarify the prevelance of atherosclerosis and the capabilites 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.

Conclusions.

Subclinical atherosclerosis, analogous to the preclinical markers of hyperglycemia which lead to diabetes, is now considered the precursor to important ASCVD outcomes. The detection and monitoring of this silent, pre-clinical stage of disease have been inadequately addressed in clinical practice. However, it is gaining critical importance due to 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 non-invasive 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 that would benefit from early detection, monitoring, and management of subclinical atherosclerosis.

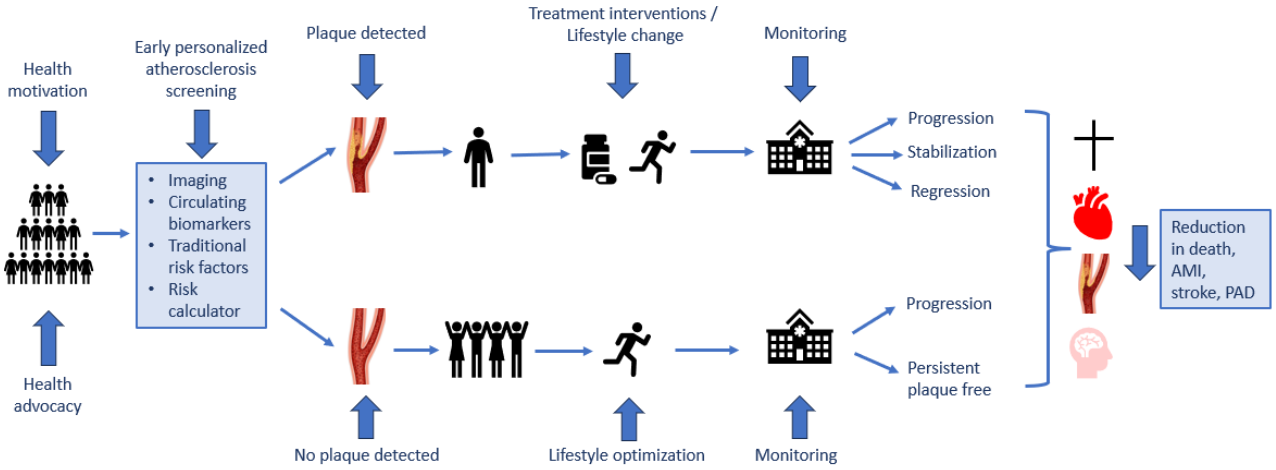
Figure 1. Lack of precision in existing risk-factor based CVD risk assessment.



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 therefor leads 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 over-treatment. 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.

Central Illustration. REACT vision – A precision medicine approach for prevention of ASCVD.



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 LDL-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 ASCVD death, AMI, stroke, and PAD.

AMI = Acute myocardial infarction; ASCVD = Atherosclerotic cardiovascular disease; PAD = Peripheral artery disease; REACT = Reversal of Early Atherosclerosis through personalized Curative Treatment.

References.

1. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, Barengo NC, Beaton AZ, Benjamin EJ, Benziger CP, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. *J Am Coll Cardiol*. 2020;76:2982-3021. doi: 10.1016/j.jacc.2020.11.010
2. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Cheng S, Delling FN, et al. Heart Disease and Stroke Statistics-2021 Update: A Report From the American Heart Association. *Circulation*. 2021;143:e254-e743. doi: 10.1161/CIR.0000000000000950
3. Mensah GA, Roth GA, Fuster V. The Global Burden of Cardiovascular Diseases and Risk Factors: 2020 and Beyond. *J Am Coll Cardiol*. 2019;74:2529-2532. doi: 10.1016/j.jacc.2019.10.009
4. advocacy/burden-report-consumer-report.pdf. AHACdacbfAPthwho-mfg-i.
5. Ford ES, Capewell S. Proportion of the decline in cardiovascular mortality disease due to prevention versus treatment: public health versus clinical care. *Annu Rev Public Health*. 2011;32:5-22. doi: 10.1146/annurev-publhealth-031210-101211
6. Song P, Fang Z, Wang H, Cai Y, Rahimi K, Zhu Y, Fowkes FGR, Fowkes FJI, Rudan I. Global and regional prevalence, burden, and risk factors for carotid atherosclerosis: a systematic review, meta-analysis, and modelling study. *Lancet Glob Health*. 2020;8:e721-e729. doi: 10.1016/S2214-109X(20)30117-0
7. https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds).
8. Webber BJ, Seguin PG, Burnett DG, Clark LL, Otto JL. Prevalence of and risk factors for autopsy-determined atherosclerosis among US service members, 2001-2011. *JAMA*. 2012;308:2577-2583. doi: 10.1001/jama.2012.70830
9. Berry JD, Liu K, Folsom AR, Lewis CE, Carr JJ, Polak JF, Shea S, Sidney S, O'Leary DH, Chan C, et al. Prevalence and progression of subclinical atherosclerosis in younger adults with low short-term but high lifetime estimated risk for cardiovascular disease: the coronary artery risk development in young adults study and multi-ethnic study of atherosclerosis. *Circulation*. 2009;119:382-389. doi: 10.1161/CIRCULATIONAHA.108.800235
10. Fernandez-Friera L, Penalvo JL, Fernandez-Ortiz A, Ibanez B, Lopez-Melgar B, Laclaustra M, Oliva B, Mocoroa A, Mendiguren J, Martinez de Vega V, et al. Prevalence, Vascular Distribution, and Multiterritorial Extent of Subclinical Atherosclerosis in a Middle-Aged Cohort: The PESA (Progression of Early Subclinical Atherosclerosis) Study. *Circulation*. 2015;131:2104-2113. doi: 10.1161/CIRCULATIONAHA.114.014310
11. Skilton MR, Celermajer DS, Cosmi E, Crispi F, Gidding SS, Raitakari OT, Urbina EM. Natural History of Atherosclerosis and Abdominal Aortic Intima-Media Thickness: Rationale, Evidence, and Best Practice for Detection of Atherosclerosis in the Young. *J Clin Med*. 2019;8. doi: 10.3390/jcm8081201
12. Fuster V, Ibanez B. Address Cardiovascular Health in Middle Age: Time to Remove the Blindfold. *J Am Coll Cardiol*. 2023;81:705-707. doi: 10.1016/j.jacc.2023.01.004
13. Makover ME, Shapiro MD, Toth PP. There is urgent need to treat atherosclerotic cardiovascular disease risk earlier, more intensively, and with greater precision: A review of current practice and recommendations for improved effectiveness. *Am J Prev Cardiol*. 2022;12:100371. doi: 10.1016/j.ajpc.2022.100371
14. Williams KJ. Eradicating Atherosclerotic Events by Targeting Early Subclinical Disease: It Is Time to Retire the Therapeutic Paradigm of Too Much, Too Late. *Arterioscler Thromb Vasc Biol*. 2023. doi: 10.1161/ATVBAHA.123.320065
15. Steinberg D, Grundy SM. The case for treating hypercholesterolemia at an earlier age: moving toward consensus. *J Am Coll Cardiol*. 2012;60:2640-2642. doi: 10.1016/j.jacc.2012.09.016
16. Berenson GS, Wattigney WA, Tracy RE, Newman WP, 3rd, Srinivasan SR, Webber LS, Dalferes ER, Jr., Strong JP. Atherosclerosis of the aorta and coronary arteries and cardiovascular risk factors in

persons aged 6 to 30 years and studied at necropsy (The Bogalusa Heart Study). *Am J Cardiol*. 1992;70:851-858. doi: 10.1016/0002-9149(92)90726-f
17. Devesa A, Ibanez B, Malick WA, Tinuoye EO, Bustamante J, Peyra C, Rosenson RS, Bhatt DL, Stone GW, Fuster V. Primary Prevention of Subclinical Atherosclerosis in Young Adults: JACC Review Topic of the Week. *J Am Coll Cardiol*. 2023;82:2152-2162. doi: 10.1016/j.jacc.2023.09.817
18. German CA, Shapiro MD. Charting a Course for Atherosclerosis Regression: Shifting the Paradigm. *J Am Coll Cardiol*. 2023;82:2084-2086. doi: 10.1016/j.jacc.2023.10.003
19. Blomstedt Y, Norberg M, Stenlund H, Nystrom L, Lonnberg G, Boman K, Wall S, Weinehall L. Impact of a combined community and primary care prevention strategy on all-cause and cardiovascular mortality: a cohort analysis based on 1 million person-years of follow-up in Vasterbotten County, Sweden, during 1990-2006. *BMJ Open*. 2015;5:e009651. doi: 10.1136/bmjopen-2015-009651
20. Norberg M, Wall S, Boman K, Weinehall L. The Vasterbotten Intervention Programme: background, design and implications. *Glob Health Action*. 2010;3. doi: 10.3402/gha.v3i0.4643
21. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140:e596-e646. doi: 10.1161/CIR.0000000000000678
22. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Back M, Benetos A, Biffi A, Boavida JM, Capodanno D, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J*. 2021;42:3227-3337. doi: 10.1093/eurheartj/ehab484
23. Dalton JE, Rothberg MB, Dawson NV, Krieger NI, Zidar DA, Perzynski AT. Failure of Traditional Risk Factors to Adequately Predict Cardiovascular Events in Older Populations. *J Am Geriatr Soc*. 2020;68:754-761. doi: 10.1111/jgs.16329
24. Arora S, Qamar A, Gupta P, Hendrickson M, Singh A, Vaduganathan M, Pandey A, Bansal A, Batra V, Mukhopadhyay S, et al. Guideline based eligibility for primary prevention statin therapy - Insights from the North India ST-elevation myocardial infarction registry (NORIN-STEMI). *J Clin Lipidol*. 2022;16:227-236. doi: 10.1016/j.jacl.2021.12.001
25. Singh A, Collins BL, Gupta A, Fatima A, Qamar A, Biery D, Baez J, Cawley M, Klein J, Hainer J, et al. Cardiovascular Risk and Statin Eligibility of Young Adults After an MI: Partners YOUNG-MI Registry. *J Am Coll Cardiol*. 2018;71:292-302. doi: 10.1016/j.jacc.2017.11.007
26. Miedema MD, Garberich RF, Schnaidt LJ, Peterson E, Strauss C, Sharkey S, Knickelbine T, Newell MC, Henry TD. Statin Eligibility and Outpatient Care Prior to ST-Segment Elevation Myocardial Infarction. *J Am Heart Assoc*. 2017;6. doi: 10.1161/JAHA.116.005333
27. Stone NJ, Smith SC, Jr., Orringer CE, Rigotti NA, Navar AM, Khan SS, Jones DW, Goldberg R, Mora S, Blaha M, et al. Managing Atherosclerotic Cardiovascular Risk in Young Adults: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2022;79:819-836. doi: 10.1016/j.jacc.2021.12.016
28. An J, Zhang Y, Zhou H, Zhou M, Safford MM, Muntner P, Moran AE, Reynolds K. Incidence of Atherosclerotic Cardiovascular Disease in Young Adults at Low Short-Term But High Long-Term Risk. *J Am Coll Cardiol*. 2023;81:623-632. doi: 10.1016/j.jacc.2022.11.051
29. Khan SS, Matsushita K, Sang Y, Ballew SH, Grams ME, Surapaneni A, Blaha MJ, Carson AP, Chang AR, Ciemins E, et al. Development and Validation of the American Heart Association's PREVENT Equations. *Circulation*. 2024;149:430-449. doi: 10.1161/CIRCULATIONAHA.123.067626
30. Yan Y, Li S, Liu Y, Guo Y, Fernandez C, Bazzano L, He J, Chen W. Associations Between Life-Course Lipid Trajectories and Subclinical Atherosclerosis in Midlife. *JAMA Netw Open*. 2022;5:e2234862. doi: 10.1001/jamanetworkopen.2022.34862
31. Koskinen JS, Kyto V, Juonala M, Viikari JSA, Nevalainen J, Kahonen M, Lehtimaki T, Hutri-Kahonen N, Laitinen TP, Tossavainen P, et al. Childhood Dyslipidemia and Carotid Atherosclerotic Plaque in Adulthood: The Cardiovascular Risk in Young Finns Study. *J Am Heart Assoc*. 2023;12:e027586. doi: 10.1161/JAHA.122.027586

32. Ye X, Xiong Z, Li J, Lin Y, Xie P, Zhong X, Huang R, Zhuang X, Liao X. Changes in Cardiovascular Health during Young Adulthood and Subclinical Atherosclerosis in Middle Age: The CARDIA Study. *Glob Heart*. 2023;18:14. doi: 10.5334/gh.1179
33. Luirink IK, Wiegman A, Kusters DM, Hof MH, Groothoff JW, de Groot E, Kastelein JJP, Hutten BA. 20-Year Follow-up of Statins in Children with Familial Hypercholesterolemia. *N Engl J Med*. 2019;381:1547-1556. doi: 10.1056/NEJMoa1816454
34. Li Y, Deng S, Liu B, Yan Y, Du J, Li Y, Jing X, Liu Y, Wang J, Du J, et al. The effects of lipid-lowering therapy on coronary plaque regression: a systematic review and meta-analysis. *Sci Rep*. 2021;11:7999. doi: 10.1038/s41598-021-87528-w
35. Mensah GA, Fuster V, Murray CJL, Roth GA, Global Burden of Cardiovascular D, Risks C. Global Burden of Cardiovascular Diseases and Risks, 1990-2022. *J Am Coll Cardiol*. 2023;82:2350-2473. doi: 10.1016/j.jacc.2023.11.007
36. Studzinski K, Tomasik T, Krzyszton J, Jozwiak J, Windak A. Effect of using cardiovascular risk scoring in routine risk assessment in primary prevention of cardiovascular disease: an overview of systematic reviews. *BMC Cardiovasc Disord*. 2019;19:11. doi: 10.1186/s12872-018-0990-2
37. Mendieta G, Pocock S, Mass V, Moreno A, Owen R, Garcia-Lunar I, Lopez-Melgar B, Fuster JJ, Andres V, Perez-Herreras C, et al. Determinants of Progression and Regression of Subclinical Atherosclerosis Over 6 Years. *J Am Coll Cardiol*. 2023;82:2069-2083. doi: 10.1016/j.jacc.2023.09.814
38. Franks PW, Cefalu WT, Dennis J, Florez JC, Mathieu C, Morton RW, Ridderstrale M, Sillesen HH, Stehouwer CDA. Precision medicine for cardiometabolic disease: a framework for clinical translation. *Lancet Diabetes Endocrinol*. 2023;11:822-835. doi: 10.1016/S2213-8587(23)00165-1
39. Winther S, Schmidt SE, Mayrhofer T, Botker HE, Hoffmann U, Douglas PS, Wijns W, Bax J, Nissen L, Lynggaard V, et al. Incorporating Coronary Calcification Into Pre-Test Assessment of the Likelihood of Coronary Artery Disease. *J Am Coll Cardiol*. 2020;76:2421-2432. doi: 10.1016/j.jacc.2020.09.585
40. Lloyd-Jones DM, Wilkins JT. Cardiovascular Risk Assessment and Prevention Across the Life Course: Propensity, Determinants, Risk, Disease. *J Am Coll Cardiol*. 2023;81:633-635. doi: 10.1016/j.jacc.2022.12.007
41. Baber U, Mehran R, Sartori S, Schoos MM, Sillesen H, Muntendam P, Garcia MJ, Gregson J, Pocock S, Falk E, et al. Prevalence, impact, and predictive value of detecting subclinical coronary and carotid atherosclerosis in asymptomatic adults: the BioImage study. *J Am Coll Cardiol*. 2015;65:1065-1074. doi: 10.1016/j.jacc.2015.01.017
42. Sillesen H, Muntendam P, Adourian A, Entrekin R, Garcia M, Falk E, Fuster V. Carotid plaque burden as a measure of subclinical atherosclerosis: comparison with other tests for subclinical arterial disease in the High Risk Plaque BioImage study. *JACC Cardiovasc Imaging*. 2012;5:681-689. doi: 10.1016/j.jcmg.2012.03.013
43. Blankenhorn DH, Hodis HN. George Lyman Duff Memorial Lecture. Arterial imaging and atherosclerosis reversal. *Arterioscler Thromb*. 1994;14:177-192. doi: 10.1161/01.atv.14.2.177
44. Orringer CE, Blaha MJ, Blankstein R, Budoff MJ, Goldberg RB, Gill EA, Maki KC, Mehta L, Jacobson TA. The National Lipid Association scientific statement on coronary artery calcium scoring to guide preventive strategies for ASCVD risk reduction. *J Clin Lipidol*. 2021;15:33-60. doi: 10.1016/j.jacl.2020.12.005
45. Alalawi L, Budoff MJ. Long term prognostic value for a normal CCTA. *J Cardiovasc Comput Tomogr*. 2022;16:531-532. doi: 10.1016/j.jcct.2022.07.006
46. Alalawi L, Budoff MJ. Recent Advances in Coronary Computed Tomography Angiogram: The Ultimate Tool for Coronary Artery Disease. *Curr Atheroscler Rep*. 2022;24:557-562. doi: 10.1007/s11883-022-01029-3
47. Javaid A, Dardari ZA, Mitchell JD, Whelton SP, Dzaye O, Lima JAC, Lloyd-Jones DM, Budoff M, Nasir K, Berman DS, et al. Distribution of Coronary Artery Calcium by Age, Sex, and Race Among Patients 30-45 Years Old. *J Am Coll Cardiol*. 2022;79:1873-1886. doi: 10.1016/j.jacc.2022.02.051

48. Nicolaides AN, Panayiotou AG, Griffin M, Tyllis T, Bond D, Georgiou N, Kyriacou E, Avraamides C, Martin RM. Arterial Ultrasound Testing to Predict Atherosclerotic Cardiovascular Events. *J Am Coll Cardiol*. 2022;79:1969-1982. doi: 10.1016/j.jacc.2022.03.352
49. Naslund U, Ng N, Lundgren A, Fharm E, Gronlund C, Johansson H, Lindahl B, Lindahl B, Lindvall K, Nilsson SK, et al. Visualization of asymptomatic atherosclerotic disease for optimum cardiovascular prevention (VIPVIZA): a pragmatic, open-label, randomised controlled trial. *Lancet*. 2019;393:133-142. doi: 10.1016/S0140-6736(18)32818-6
50. Hollands GJ, Usher-Smith JA, Hasan R, Alexander F, Clarke N, Griffin SJ. Visualising health risks with medical imaging for changing recipients' health behaviours and risk factors: Systematic review with meta-analysis. *PLoS Med*. 2022;19:e1003920. doi: 10.1371/journal.pmed.1003920
51. Raitakari O, Pahkala K, Magnussen CG. Prevention of atherosclerosis from childhood. *Nature reviews*. 2022;19:543-554. doi: 10.1038/s41569-021-00647-9
52. Lindholt JS, Sogaard R, Rasmussen LM, Mejldal A, Lambrechtsen J, Steffensen FH, Frost L, Egstrup K, Urbonaviciene G, Busk M, et al. Five-Year Outcomes of the Danish Cardiovascular Screening (DANCAVAS) Trial. *N Engl J Med*. 2022;387:1385-1394. doi: 10.1056/NEJMoa2208681
53. Ference BA, Yoo W, Alesh I, Mahajan N, Mirowska KK, Mewada A, Kahn J, Afonso L, Williams KA, Sr., Flack JM. Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: a Mendelian randomization analysis. *J Am Coll Cardiol*. 2012;60:2631-2639. doi: 10.1016/j.jacc.2012.09.017
54. Robinson JG, Williams KJ, Gidding S, Boren J, Tabas I, Fisher EA, Packard C, Pencina M, Fayad ZA, Mani V, et al. Eradicating the Burden of Atherosclerotic Cardiovascular Disease by Lowering Apolipoprotein B Lipoproteins Earlier in Life. *J Am Heart Assoc*. 2018;7:e009778. doi: 10.1161/JAHA.118.009778
55. Domanski MJ, Tian X, Wu CO, Reis JP, Dey AK, Gu Y, Zhao L, Bae S, Liu K, Hasan AA, et al. Time Course of LDL Cholesterol Exposure and Cardiovascular Disease Event Risk. *J Am Coll Cardiol*. 2020;76:1507-1516. doi: 10.1016/j.jacc.2020.07.059
56. Enos WF, Holmes RH, Beyer J. Coronary disease among United States soldiers killed in action in Korea; preliminary report. *JAMA*. 1953;152:1090-1093.
57. McNamara JJ, Molot MA, Stremple JF, Cutting RT. Coronary artery disease in combat casualties in Vietnam. *JAMA*. 1971;216:1185-1187.
58. Fuchs A, Kuhl JT, Sigvardsen PE, Afzal S, Knudsen AD, Moller MB, de Knegt MC, Sorgaard MH, Nordestgaard BG, Kober LV, et al. Subclinical Coronary Atherosclerosis and Risk for Myocardial Infarction in a Danish Cohort : A Prospective Observational Cohort Study. *Ann Intern Med*. 2023;176:433-442. doi: 10.7326/M22-3027
59. Prospective Studies C, Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, Halsey J, Qizilbash N, Peto R, Collins R. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. *Lancet*. 2007;370:1829-1839. doi: 10.1016/S0140-6736(07)61778-4
60. de Ferranti SD, Steinberger J, Ameduri R, Baker A, Gooding H, Kelly AS, Mietus-Snyder M, Mitsnefes MM, Peterson AL, St-Pierre J, et al. Cardiovascular Risk Reduction in High-Risk Pediatric Patients: A Scientific Statement From the American Heart Association. *Circulation*. 2019;139:e603-e634. doi: 10.1161/CIR.0000000000000618
61. Wiegman A, Gidding SS, Watts GF, Chapman MJ, Ginsberg HN, Cuchel M, Ose L, Averna M, Boileau C, Boren J, et al. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. *Eur Heart J*. 2015;36:2425-2437. doi: 10.1093/eurheartj/ehv157
62. Gooding HC, de Ferranti SD. Cardiovascular risk assessment and cholesterol management in adolescents: getting to the heart of the matter. *Curr Opin Pediatr*. 2010;22:398-404. doi: 10.1097/MOP.0b013e32833a6e22

63. Heller DJ, Coxson PG, Penko J, Pletcher MJ, Goldman L, Odden MC, Kazi DS, Bibbins-Domingo K. Evaluating the Impact and Cost-Effectiveness of Statin Use Guidelines for Primary Prevention of Coronary Heart Disease and Stroke. *Circulation*. 2017;136:1087-1098. doi: 10.1161/CIRCULATIONAHA.117.027067
64. Cohen JC, Boerwinkle E, Mosley TH, Jr., Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Engl J Med*. 2006;354:1264-1272. doi: 10.1056/NEJMoa054013
65. Andermann A, Blancquaert I, Beauchamp S, Dery V. Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. *Bull World Health Organ*. 2008;86:317-319. doi: 10.2471/blt.07.050112
66. Koskinen JS, Kyto V, Juonala M, Viikari JSA, Nevalainen J, Kahonen M, Lehtimaki T, Hutri-Kahonen N, Laitinen T, Tossavainen P, et al. Childhood risk factors and carotid atherosclerotic plaque in adulthood: The Cardiovascular Risk in Young Finns Study. *Atherosclerosis*. 2020;293:18-25. doi: 10.1016/j.atherosclerosis.2019.11.029
67. Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N, Csiba L, Desvarieux M, Ebrahim S, Hernandez Hernandez R, et al. Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th, 15th and 20th European Stroke Conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011. *Cerebrovasc Dis*. 2012;34:290-296. doi: 10.1159/000343145
68. Mantella LE, Liblik K, Johri AM. Vascular imaging of atherosclerosis: Strengths and weaknesses. *Atherosclerosis*. 2021;319:42-50. doi: 10.1016/j.atherosclerosis.2020.12.021
69. Bengtsson A, Norberg M, Ng N, Carlberg B, Gronlund C, Hultdin J, Lindahl B, Lindahl B, Nordin S, Nyman E, et al. The beneficial effect over 3 years by pictorial information to patients and their physician about subclinical atherosclerosis and cardiovascular risk: Results from the VIPVIZA randomized clinical trial. *Am J Prev Cardiol*. 2021;7:100199. doi: 10.1016/j.ajpc.2021.100199
70. Lopez-Melgar B, Fernandez-Friera L, Oliva B, Garcia-Ruiz JM, Penalvo JL, Gomez-Talavera S, Sanchez-Gonzalez J, Mendiguren JM, Ibanez B, Fernandez-Ortiz A, et al. Subclinical Atherosclerosis Burden by 3D Ultrasound in Mid-Life: The PESA Study. *J Am Coll Cardiol*. 2017;70:301-313. doi: 10.1016/j.jacc.2017.05.033
71. Johri AM, Nambi V, Naqvi TZ, Feinstein SB, Kim ESH, Park MM, Becher H, Sillesen H. Recommendations for the Assessment of Carotid Arterial Plaque by Ultrasound for the Characterization of Atherosclerosis and Evaluation of Cardiovascular Risk: From the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2020;33:917-933. doi: 10.1016/j.echo.2020.04.021
72. Peters SA, den Ruijter HM, Bots ML, Moons KG. Improvements in risk stratification for the occurrence of cardiovascular disease by imaging subclinical atherosclerosis: a systematic review. *Heart*. 2012;98:177-184. doi: 10.1136/heartjnl-2011-300747
73. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, Najjar SS, Rembold CM, Post WS, American Society of Echocardiography Carotid Intima-Media Thickness Task F. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. *J Am Soc Echocardiogr*. 2008;21:93-111; quiz 189-190. doi: 10.1016/j.echo.2007.11.011
74. Inaba Y, Chen JA, Bergmann SR. Carotid plaque, compared with carotid intima-media thickness, more accurately predicts coronary artery disease events: a meta-analysis. *Atherosclerosis*. 2012;220:128-133. doi: 10.1016/j.atherosclerosis.2011.06.044
75. Laclaustra M, Casasnovas JA, Fernandez-Ortiz A, Fuster V, Leon-Latre M, Jimenez-Borreguero LJ, Pocovi M, Hurtado-Roca Y, Ordovas JM, Jarauta E, et al. Femoral and Carotid Subclinical

Atherosclerosis Association With Risk Factors and Coronary Calcium: The AWHS Study. *J Am Coll Cardiol*. 2016;67:1263-1274. doi: 10.1016/j.jacc.2015.12.056
76. Johri AM, Behl P, Hetu MF, Haqqi M, Ewart P, Day AG, Parfrey B, Matangi MF. Carotid Ultrasound Maximum Plaque Height-A Sensitive Imaging Biomarker for the Assessment of Significant Coronary Artery Disease. *Echocardiography*. 2016;33:281-289. doi: 10.1111/echo.13007
77. Lopez-Melgar B, Mass V, Nogales P, Sanchez-Gonzalez J, Entrekin R, Collet-Billon A, Rossello X, Fernandez-Friera L, Fernandez-Ortiz A, Sanz J, et al. New 3-Dimensional Volumetric Ultrasound Method for Accurate Quantification of Atherosclerotic Plaque Volume. *JACC Cardiovasc Imaging*. 2022;15:1124-1135. doi: 10.1016/j.jcmg.2022.01.005
78. Johri AM, Chitty DW, Matangi M, Malik P, Mousavi P, Day A, Gravett M, Simpson C. Can carotid bulb plaque assessment rule out significant coronary artery disease? A comparison of plaque quantification by two- and three-dimensional ultrasound. *J Am Soc Echocardiogr*. 2013;26:86-95. doi: 10.1016/j.echo.2012.09.005
79. Patel J, Pallazola VA, Dudum R, Greenland P, McEvoy JW, Blumenthal RS, Virani SS, Miedema MD, Shea S, Yeboah J, et al. Assessment of Coronary Artery Calcium Scoring to Guide Statin Therapy Allocation According to Risk-Enhancing Factors: The Multi-Ethnic Study of Atherosclerosis. *JAMA Cardiol*. 2021;6:1161-1170. doi: 10.1001/jamacardio.2021.2321
80. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. *JAMA*. 2004;291:210-215.
81. Nasir K, Cainzos-Achirica M. Role of coronary artery calcium score in the primary prevention of cardiovascular disease. *BMJ*. 2021;373:n776. doi: 10.1136/bmj.n776
82. McClelland RL, Jorgensen NW, Budoff M, Blaha MJ, Post WS, Kronmal RA, Bild DE, Shea S, Liu K, Watson KE, et al. 10-Year Coronary Heart Disease Risk Prediction Using Coronary Artery Calcium and Traditional Risk Factors: Derivation in the MESA (Multi-Ethnic Study of Atherosclerosis) With Validation in the HNR (Heinz Nixdorf Recall) Study and the DHS (Dallas Heart Study). *J Am Coll Cardiol*. 2015;66:1643-1653. doi: 10.1016/j.jacc.2015.08.035
83. Shareghi S, Ahmadi N, Young E, Gopal A, Liu ST, Budoff MJ. Prognostic significance of zero coronary calcium scores on cardiac computed tomography. *J Cardiovasc Comput Tomogr*. 2007;1:155-159. doi: 10.1016/j.jcct.2007.10.001
84. Blaha MJ, Rivera JJ, Budoff MJ, Blankstein R, Agatston A, O'Leary DH, Cushman M, Lakoski S, Criqui MH, Szklo M, et al. Association between obesity, high-sensitivity C-reactive protein >/=2 mg/L, and subclinical atherosclerosis: implications of JUPITER from the Multi-Ethnic Study of Atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2011;31:1430-1438. doi: 10.1161/ATVBAHA.111.223768
85. Budoff MJ, Shaw LJ, Liu ST, Weinstein SR, Mosler TP, Tseng PH, Flores FR, Callister TQ, Raggi P, Berman DS. Long-term prognosis associated with coronary calcification: observations from a registry of 25,253 patients. *J Am Coll Cardiol*. 2007;49:1860-1870. doi: 10.1016/j.jacc.2006.10.079
86. Kelly JL, Thickman D, Abramson SD, Chen PR, Smazal SF, Fleishman MJ, Lingam SC. Coronary CT angiography findings in patients without coronary calcification. *AJR Am J Roentgenol*. 2008;191:50-55. doi: 10.2214/AJR.07.2954
87. Sheppard JP, Lakshmanan S, Lichtenstein SJ, Budoff MJ, Roy SK. Age and the power of zero CAC in cardiac risk assessment: overview of the literature and a cautionary case. *Br J Cardiol*. 2022;29:23. doi: 10.5837/bjc.2022.023
88. Bergstrom G, Persson M, Adiels M, Bjornson E, Bonander C, Ahlstrom H, Alfredsson J, Angeras O, Berglund G, Blomberg A, et al. Prevalence of Subclinical Coronary Artery Atherosclerosis in the General Population. *Circulation*. 2021;144:916-929. doi: 10.1161/CIRCULATIONAHA.121.055340
89. Whelton SP, Blaha MJ. Coronary artery calcium: from risk prediction to treatment allocation and clinical trials. *Heart*. 2023;109:1714-1721. doi: 10.1136/heartjnl-2022-321711
90. Mowatt G, Cook JA, Hillis GS, Walker S, Fraser C, Jia X, Waugh N. 64-Slice computed tomography angiography in the diagnosis and assessment of coronary artery disease: systematic review and meta-analysis. *Heart*. 2008;94:1386-1393. doi: 10.1136/hrt.2008.145292

91. McGill HC, Jr., McMahan CA, Zieske AW, Tracy RE, Malcom GT, Herderick EE, Strong JP. Association of Coronary Heart Disease Risk Factors with microscopic qualities of coronary atherosclerosis in youth. *Circulation*. 2000;102:374-379. doi: 10.1161/01.cir.102.4.374
92. Available NDCTCAftPoMITSTS-HIcD.
93. Prevention hcgsNTD-HT-CTCAfP.
94. Williams MC, Stewart C, Weir NW, Newby DE. Using radiation safely in cardiology: what imagers need to know. *Heart*. 2019;105:798-806. doi: 10.1136/heartjnl-2017-312493
95. https://www.epa.gov/radiation/radiation-sources-and-doses.
96. https://www.gov.uk/government/publications/ionising-radiation-dose-comparisons/ionising-radiation-dose-comparisons#:~:text=The 2.7 mSv dose that rihaw.
97. Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K. Adverse reactions to ionic and nonionic contrast media. A report from the Japanese Committee on the Safety of Contrast Media. *Radiology*. 1990;175:621-628. doi: 10.1148/radiology.175.3.2343107
98. Whitmore K, Zhou Z, Chapman N, Huynh Q, Magnussen CG, Sharman JE, Marwick TH. Impact of Patient Visualization of Cardiovascular Images on Modification of Cardiovascular Risk Factors: Systematic Review and Meta-Analysis. *JACC Cardiovasc Imaging*. 2023;16:1069-1081. doi: 10.1016/j.jcmg.2023.03.007
99. Achim A, Peter OA, Cocoi M, Serban A, Mot S, Dadarlat-Pop A, Nemes A, Ruzsa Z. Correlation between Coronary Artery Disease with Other Arterial Systems: Similar, Albeit Separate, Underlying Pathophysiologic Mechanisms. *J Cardiovasc Dev Dis*. 2023;10. doi: 10.3390/jcdd10050210
100. van der Aalst CM, Denissen S, Vonder M, Gratama JWC, Adriaansen HJ, Kuijpers D, Vliegenthart R, van Lennep JER, van der Harst P, Braam RL, et al. Screening for cardiovascular disease risk using traditional risk factor assessment or coronary artery calcium scoring: the ROBINSCA trial. *Eur Heart J Cardiovasc Imaging*. 2020;21:1216-1224. doi: 10.1093/ehjci/jeaa168
101. Vickers A, O'Brien F, Montorsi F, Galvin D, Bratt O, Carlsson S, Catto JW, Krilaviciute A, Philbin M, Albers P. Current policies on early detection of prostate cancer create overdiagnosis and inequity with minimal benefit. *BMJ*. 2023;381:e071082. doi: 10.1136/bmj-2022-071082
102. Ridker PM. A Test in Context: High-Sensitivity C-Reactive Protein. *J Am Coll Cardiol*. 2016;67:712-723. doi: 10.1016/j.jacc.2015.11.037
103. Elliott P, Chambers JC, Zhang W, Clarke R, Hopewell JC, Peden JF, Erdmann J, Braund P, Engert JC, Bennett D, et al. Genetic Loci associated with C-reactive protein levels and risk of coronary heart disease. *JAMA*. 2009;302:37-48. doi: 10.1001/jama.2009.954
104. Zacho J, Tybjaerg-Hansen A, Jensen JS, Grande P, Sillesen H, Nordestgaard BG. Genetically elevated C-reactive protein and ischemic vascular disease. *N Engl J Med*. 2008;359:1897-1908. doi: 10.1056/NEJMoa0707402
105. Dehghan A, Dupuis J, Barbalic M, Bis JC, Eiriksdottir G, Lu C, Pellikka N, Wallaschofski H, Kettunen J, Henneman P, et al. Meta-analysis of genome-wide association studies in >80 000 subjects identifies multiple loci for C-reactive protein levels. *Circulation*. 2011;123:731-738. doi: 10.1161/CIRCULATIONAHA.110.948570
106. Jenny NS, Brown ER, Detrano R, Folsom AR, Saad MF, Shea S, Szklo M, Herrington DM, Jacobs DR, Jr. Associations of inflammatory markers with coronary artery calcification: results from the Multi-Ethnic Study of Atherosclerosis. *Atherosclerosis*. 2010;209:226-229. doi: 10.1016/j.atherosclerosis.2009.08.037
107. Al Rifai M, Martin SS, McEvoy JW, Nasir K, Blankstein R, Yeboah J, Miedema M, Shea SJ, Polak JF, Ouyang P, et al. The prevalence and correlates of subclinical atherosclerosis among adults with low-density lipoprotein cholesterol <70 mg/dL: The Multi-Ethnic Study of Atherosclerosis (MESA) and Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). *Atherosclerosis*. 2018;274:61-66. doi: 10.1016/j.atherosclerosis.2018.04.021

108. Hunt ME, O'Malley PG, Vernalis MN, Feuerstein IM, Taylor AJ. C-reactive protein is not associated with the presence or extent of calcified subclinical atherosclerosis. *Am Heart J*. 2001;141:206-210. doi: 10.1067/mhj.2001.112488
109. Fernandez-Friera L, Fuster V, Lopez-Melgar B, Oliva B, Sanchez-Gonzalez J, Macias A, Perez-Asenjo B, Zamudio D, Alonso-Farto JC, Espana S, et al. Vascular Inflammation in Subclinical Atherosclerosis Detected by Hybrid PET/MRI. *J Am Coll Cardiol*. 2019;73:1371-1382. doi: 10.1016/j.jacc.2018.12.075
110. Lee WY, Allison MA, Kim DJ, Song CH, Barrett-Connor E. Association of interleukin-6 and C-reactive protein with subclinical carotid atherosclerosis (the Rancho Bernardo Study). *Am J Cardiol*. 2007;99:99-102. doi: 10.1016/j.amjcard.2006.07.070
111. Wong YK, Tse HF. Circulating Biomarkers for Cardiovascular Disease Risk Prediction in Patients With Cardiovascular Disease. *Front Cardiovasc Med*. 2021;8:713191. doi: 10.3389/fcvm.2021.713191
112. Nunez E, Fuster V, Gomez-Serrano M, Valdivielso JM, Fernandez-Alvira JM, Martinez-Lopez D, Rodriguez JM, Bonzon-Kulichenko E, Calvo E, Alfayate A, et al. Unbiased plasma proteomics discovery of biomarkers for improved detection of subclinical atherosclerosis. *EBioMedicine*. 2022;76:103874. doi: 10.1016/j.ebiom.2022.103874
113. Martinez-Lopez D, Roldan-Montero R, Garcia-Marques F, Nunez E, Jorge I, Camafeita E, Minguez P, Rodriguez de Cordoba S, Lopez-Melgar B, Lara-Pezzi E, et al. Complement C5 Protein as a Marker of Subclinical Atherosclerosis. *J Am Coll Cardiol*. 2020;75:1926-1941. doi: 10.1016/j.jacc.2020.02.058
114. Amar J, Fauvel J, Drouet L, Ruidavets JB, Perret B, Chamontin B, Boccalon H, Ferrieres J. Interleukin 6 is associated with subclinical atherosclerosis: a link with soluble intercellular adhesion molecule 1. *J Hypertens*. 2006;24:1083-1088. doi: 10.1097/01.hjh.0000226198.44181.0c
115. Wurtz P, Raiko JR, Magnussen CG, Soininen P, Kangas AJ, Tynkkynen T, Thomson R, Laatikainen R, Savolainen MJ, Laurikka J, et al. High-throughput quantification of circulating metabolites improves prediction of subclinical atherosclerosis. *Eur Heart J*. 2012;33:2307-2316. doi: 10.1093/eurheartj/ehs020
116. Tzoulaki I, Castagne R, Boulange CL, Karaman I, Chekmeneva E, Evangelou E, Ebbels TMD, Kaluarachchi MR, Chadeau-Hyam M, Mosen D, et al. Serum metabolic signatures of coronary and carotid atherosclerosis and subsequent cardiovascular disease. *Eur Heart J*. 2019;40:2883-2896. doi: 10.1093/eurheartj/ehz235
117. Jaiswal S, Libby P. Clonal haematopoiesis: connecting ageing and inflammation in cardiovascular disease. *Nat Rev Cardiol*. 2020;17:137-144. doi: 10.1038/s41569-019-0247-5
118. Fuster JJ, Walsh K. Somatic Mutations and Clonal Hematopoiesis: Unexpected Potential New Drivers of Age-Related Cardiovascular Disease. *Circ Res*. 2018;122:523-532. doi: 10.1161/CIRCRESAHA.117.312115
119. Aragam KG, Jiang T, Goel A, Kanoni S, Wolford BN, Atri DS, Weeks EM, Wang M, Hindy G, Zhou W, et al. Discovery and systematic characterization of risk variants and genes for coronary artery disease in over a million participants. *Nat Genet*. 2022;54:1803-1815. doi: 10.1038/s41588-022-01233-6
120. Samani NJ, Erdmann J, Hall AS, Hengstenberg C, Mangino M, Mayer B, Dixon RJ, Meitinger T, Braund P, Wichmann HE, et al. Genomewide association analysis of coronary artery disease. *N Engl J Med*. 2007;357:443-453. doi: 10.1056/NEJMoa072366
121. Schunkert H, Konig IR, Kathiresan S, Reilly MP, Assimes TL, Holm H, Preuss M, Stewart AF, Barbalic M, Gieger C, et al. Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease. *Nat Genet*. 2011;43:333-338. doi: 10.1038/ng.784
122. Consortium CAD, Deloukas P, Kanoni S, Willenborg C, Farrall M, Assimes TL, Thompson JR, Ingelsson E, Saleheen D, Erdmann J, et al. Large-scale association analysis identifies new risk loci for coronary artery disease. *Nat Genet*. 2013;45:25-33. doi: 10.1038/ng.2480
123. Aragam KG, Natarajan P. Polygenic Scores to Assess Atherosclerotic Cardiovascular Disease Risk: Clinical Perspectives and Basic Implications. *Circ Res*. 2020;126:1159-1177. doi: 10.1161/CIRCRESAHA.120.315928

124. Inouye M, Abraham G, Nelson CP, Wood AM, Sweeting MJ, Dudbridge F, Lai FY, Kaptoge S, Brozynska M, Wang T, et al. Genomic Risk Prediction of Coronary Artery Disease in 480,000 Adults: Implications for Primary Prevention. *J Am Coll Cardiol*. 2018;72:1883-1893. doi: 10.1016/j.jacc.2018.07.079
125. Hindy G, Aragam KG, Ng K, Chaffin M, Lotta LA, Baras A, Regeneron Genetics C, Drake I, Orho-Melander M, Melander O, et al. Genome-Wide Polygenic Score, Clinical Risk Factors, and Long-Term Trajectories of Coronary Artery Disease. *Arterioscler Thromb Vasc Biol*. 2020;40:2738-2746. doi: 10.1161/ATVBAHA.120.314856
126. Aragam KG, Dobbyn A, Judy R, Chaffin M, Chaudhary K, Hindy G, Cagan A, Finneran P, Weng LC, Loos RJF, et al. Limitations of Contemporary Guidelines for Managing Patients at High Genetic Risk of Coronary Artery Disease. *J Am Coll Cardiol*. 2020;75:2769-2780. doi: 10.1016/j.jacc.2020.04.027
127. Patel AP, Wang M, Ruan Y, Koyama S, Clarke SL, Yang X, Tcheandjieu C, Agrawal S, Fahed AC, Ellinor PT, et al. A multi-ancestry polygenic risk score improves risk prediction for coronary artery disease. *Nat Med*. 2023;29:1793-1803. doi: 10.1038/s41591-023-02429-x
128. Khera AV, Chaffin M, Aragam KG, Haas ME, Roselli C, Choi SH, Natarajan P, Lander ES, Lubitz SA, Ellinor PT, et al. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nat Genet*. 2018;50:1219-1224. doi: 10.1038/s41588-018-0183-z
129. Lu X, Liu Z, Cui Q, Liu F, Li J, Niu X, Shen C, Hu D, Huang K, Chen J, et al. A polygenic risk score improves risk stratification of coronary artery disease: a large-scale prospective Chinese cohort study. *Eur Heart J*. 2022;43:1702-1711. doi: 10.1093/eurheartj/ehac093
130. Khan SS, Page C, Wojdyla DM, Schwartz YY, Greenland P, Pencina MJ. Predictive Utility of a Validated Polygenic Risk Score for Long-Term Risk of Coronary Heart Disease in Young and Middle-Aged Adults. *Circulation*. 2022;146:587-596. doi: 10.1161/CIRCULATIONAHA.121.058426
131. Mosley JD, Gupta DK, Tan J, Yao J, Wells QS, Shaffer CM, Kundu S, Robinson-Cohen C, Psaty BM, Rich SS, et al. Predictive Accuracy of a Polygenic Risk Score Compared With a Clinical Risk Score for Incident Coronary Heart Disease. *JAMA*. 2020;323:627-635. doi: 10.1001/jama.2019.21782
132. Elliott J, Bodinier B, Bond TA, Chadeau-Hyam M, Evangelou E, Moons KGM, Dehghan A, Muller DC, Elliott P, Tzoulaki I. Predictive Accuracy of a Polygenic Risk Score-Enhanced Prediction Model vs a Clinical Risk Score for Coronary Artery Disease. *JAMA*. 2020;323:636-645. doi: 10.1001/jama.2019.22241
133. Khera AV, Emdin CA, Drake I, Natarajan P, Bick AG, Cook NR, Chasman DI, Baber U, Mehran R, Rader DJ, et al. Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Disease. *N Engl J Med*. 2016;375:2349-2358. doi: 10.1056/NEJMoa1605086
134. Natarajan P, Young R, Stitziel NO, Padmanabhan S, Baber U, Mehran R, Sartori S, Fuster V, Reilly DF, Butterworth A, et al. Polygenic Risk Score Identifies Subgroup With Higher Burden of Atherosclerosis and Greater Relative Benefit From Statin Therapy in the Primary Prevention Setting. *Circulation*. 2017;135:2091-2101. doi: 10.1161/CIRCULATIONAHA.116.024436
135. Severance LM, Contijoch FJ, Carter H, Fan CC, Seibert TM, Dale AM, McVeigh ER. Using a genetic risk score to calculate the optimal age for an individual to undergo coronary artery calcium screening. *J Cardiovasc Comput Tomogr*. 2019;13:203-210. doi: 10.1016/j.jcct.2019.05.005
136. Emdin CA, Xia R, Agrawal S, Rana JS, Lloyd-Jones D, Fornage M, Khera AV. Polygenic Score Assessed in Young Adulthood and Onset of Subclinical Atherosclerosis and Coronary Heart Disease. *J Am Coll Cardiol*. 2022;80:280-282. doi: 10.1016/j.jacc.2022.05.013
137. Marston NA, Pirruccello JP, Melloni GEM, Koyama S, Kamanu FK, Weng LC, Roselli C, Kamatani Y, Komuro I, Aragam KG, et al. Predictive Utility of a Coronary Artery Disease Polygenic Risk Score in Primary Prevention. *JAMA Cardiol*. 2023;8:130-137. doi: 10.1001/jamacardio.2022.4466
138. Finck T, Hardenberg J, Will A, Hendrich E, Haller B, Martinoff S, Hausleiter J, Hadamitzky M. 10-Year Follow-Up After Coronary Computed Tomography Angiography in Patients With Suspected Coronary Artery Disease. *JACC Cardiovasc Imaging*. 2019;12:1330-1338. doi: 10.1016/j.jcmg.2018.07.020

139. Yamashita S, Masuda D, Akishita M, Arai H, Asada Y, Dobashi K, Egashira K, Harada-Shiba M, Hirata K, Ishibashi S, et al. Guidelines on the Clinical Evaluation of Medicinal Products for Treatment of Dyslipidemia. *J Atheroscler Thromb*. 2020;27:1246-1254. doi: 10.5551/jat.CR004
140. Zambon A, Mello ESA, Farnier M. The burden of cholesterol accumulation through the lifespan: why pharmacological intervention should start earlier to go further? *Eur Heart J Cardiovasc Pharmacother*. 2021;7:435-441. doi: 10.1093/ehjcvp/pvaa123
141. Kahn JA, Glueck CJ. Familial hypobetalipoproteinemia. Absence of atherosclerosis in a postmortem study. *JAMA*. 1978;240:47-48. doi: 10.1001/jama.240.1.47
142. Daviglus ML, Liu K, Pirzada A, Yan LL, Garside DB, Feinglass J, Guralnik JM, Greenland P, Stamler J. Favorable cardiovascular risk profile in middle age and health-related quality of life in older age. *Arch Intern Med*. 2003;163:2460-2468. doi: 10.1001/archinte.163.20.2460
143. Lloyd-Jones DM, Leip EP, Larson MG, D'Agostino RB, Beiser A, Wilson PW, Wolf PA, Levy D. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. *Circulation*. 2006;113:791-798. doi: 10.1161/CIRCULATIONAHA.105.548206
144. approval FaDA-UCteft, https://www. ocdabgfi, fda.gov/media/81172/download.
145. version]. EMAGociompittoldce, version-section. hweeeec-i-mp-t-l-d-s-gc-e.
146. Fernandez-Jimenez R, Briceno G, Cespedes J, Vargas S, Guijarro J, Baxter J, Hunn M, Santos-Beneit G, Rodriguez C, Cespedes MP, et al. Sustainability of and Adherence to Preschool Health Promotion Among Children 9 to 13 Years Old. *J Am Coll Cardiol*. 2020;75:1565-1578. doi: 10.1016/j.jacc.2020.01.051
147. Wilson JMG, Jungner G. Principles and practice of screening for disease. World Health Organization. 1968.
148. Lindholt JS, Sogaard R. Population screening and intervention for vascular disease in Danish men (VIVA): a randomised controlled trial. *Lancet*. 2017;390:2256-2265. doi: 10.1016/S0140-6736(17)32250-X
149. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2020;41:407-477. doi: 10.1093/eurheartj/ehz425