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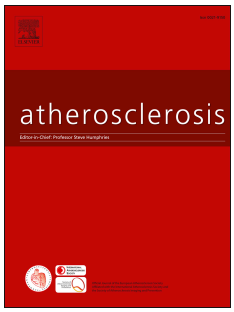

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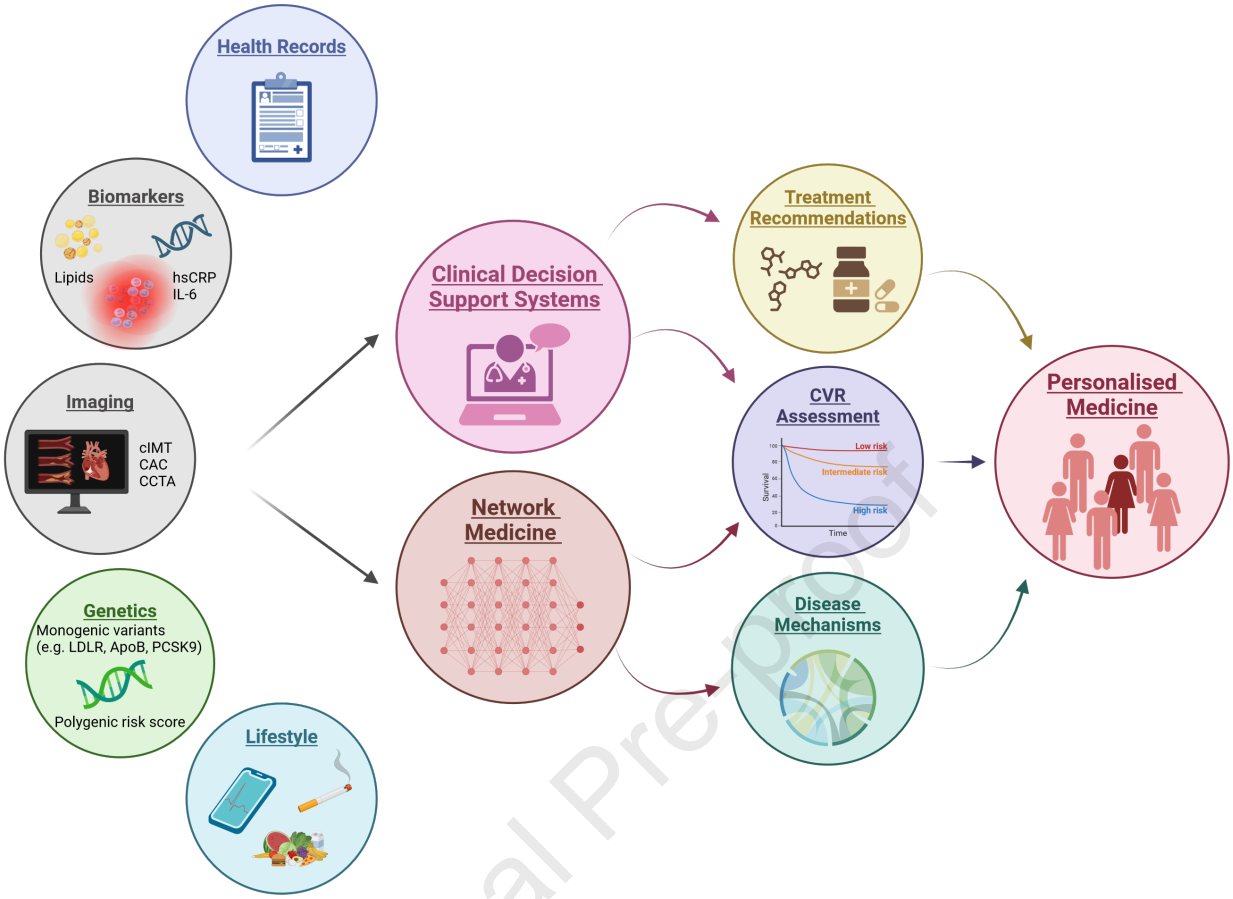

Advancements in risk stratification and management strategies in primary cardiovascular prevention

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Abstract

Atherosclerotic cardiovascular disease (ASCVD) remains a leading cause of morbidity and mortality worldwide, highlighting the urgent need for advancements in risk assessment and management strategies. Although significant progress has been made recently, identifying and managing apparently healthy individuals at a higher risk of developing atherosclerosis and those with subclinical atherosclerosis still poses significant challenges.

Traditional risk assessment tools have limitations in accurately predicting future events and fail to encompass the complexity of the atherosclerosis trajectory. In this review, we describe novel approaches in biomarkers, genetics, advanced imaging techniques, and artificial intelligence that have emerged to address this gap. Moreover, polygenic risk scores and imaging modalities such as coronary artery calcium scoring, and coronary computed tomography angiography offer promising avenues for enhancing primary cardiovascular risk stratification and personalised intervention strategies. On the other hand, interventions aiming against atherosclerosis development or promoting plaque regression have gained attention in primary ASCVD prevention. Therefore, the potential role of drugs like statins, ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, omega-3 fatty acids, antihypertensive agents, as well as glucose-lowering and anti-inflammatory drugs are also discussed. Since findings regarding the efficacy of these interventions vary, further research is still required to elucidate their mechanisms of action, optimise treatment regimens, and determine their long-term effects on ASCVD outcomes.

In conclusion, advancements in strategies addressing atherosclerosis prevention and plaque regression present promising avenues for enhancing primary ASCVD prevention through personalised approaches tailored to individual risk profiles. Nevertheless, ongoing research efforts are imperative to refine these strategies further and maximise their effectiveness in safeguarding cardiovascular health.

Keywords: cardiovascular disease, atherosclerosis, risk stratification, plaque regression, primary prevention

I. Introduction

While there have been notable advancements in the management of atherosclerotic cardiovascular disease (ASCVD), a crucial gap remains in identifying and managing apparently healthy individuals at elevated risk of developing atherosclerosis. More importantly, there is a need to address also individuals who already exhibit early-stage atherosclerotic lesions, detectable by imaging modalities, but have not yet experienced a clinical event (i.e., subclinical atherosclerosis)[1]. The notion that atherosclerosis often remains asymptomatic until advanced stages poses a major challenge for early detection and intervention[2]. While traditional risk factors such as hypertension, dyslipidaemia, diabetes and smoking are well-established, a substantial proportion of individuals with subclinical atherosclerosis may go undetected using conventional risk assessment tools[3]. Current clinical risk algorithms, including the Framingham risk score (FRS), the Systematic COronary Risk Evaluation 2 (SCORE2) system, and the Second Manifestations of ARTerial disease 2 (SMART2), rely purely on traditional risk factors for cardiovascular disease[4-8]. However, these algorithms have limitations in accurately predicting future events, as the included traditional risk factors fail to encompass the complexity of pathophysiological processes underlying atherosclerosis and do not consider plaque vulnerability[9]. This highlights the urgent need for innovative approaches to identify and manage subclinical atherosclerosis in apparently healthy individuals.

Here, we review novel tools enhancing risk stratification including biomarkers, genetics, imaging techniques, and artificial intelligence (AI) for personalised intervention strategies. By examining these innovative approaches, this review

seeks to provide insights into current strategies and future directions in primary cardiovascular risk assessment and management of apparently healthy individuals with or without subclinical atherosclerosis.

II. Subclinical atherosclerosis: histological progression and implications

Subclinical atherosclerosis is the presence of atherosclerosis without clinically manifested ASCVD events and represents a critical phase in ASCVD development. It may be characterised by a broad range of lesions, starting from early plaques to high-risk thin cap fibroatheromas (TCFAs) or even calcified plaques. This chronic inflammatory process commences shortly after birth, and persists throughout an individual's lifespan[10] where it is further modulated by a spectrum of disease drivers including apolipoprotein-B (apoB)-containing lipoproteins, hypertension, smoking, and diabetes mellitus[11]. Histopathological examination has delineated the subclinical stages of atherosclerosis into several categories depending on severity and instability. Among these categories are i) pathologic intimal thickening, ii) fibroatheroma, iii) healed plaque ruptures, and iv) fibrocalcific plaques, representing distinct stages in the continuum of atherosclerosis development[12].

The earliest manifestation of subclinical atherosclerosis, pathologic intimal thickening, is characterised by the presence of a lipid pool within the arterial wall, often accompanied by microscopic calcification[13, 14]. Infiltration of macrophages, as well as adaptive responses mediated by T and B cells[15, 16] are distinctive characteristics of the progression from the pathologic intimal thickening stage into a fibroatheroma[17]. This phase is marked by increased

macrophage apoptosis and a reduction in the uptake of apoptotic bodies, leading to the formation of a necrotic core covered by a thick fibrous cap[18]. Over time, degradation of the extracellular matrix by matrix metalloproteinases together with smooth muscle cell apoptosis contributes to the gradual thinning of the fibrous cap, rendering the plaque more vulnerable to rupture[18].

Plaque rupture, whether symptomatic or silent, represents a critical juncture in the natural history of atherosclerosis, often precipitating acute cardiovascular events[19]. While some ruptures manifest clinically, others occur without overt symptoms, thus evading detection through conventional means[19]. Microscopic examination of healed plaque ruptures reveals breaks in the fibrous cap surrounded by a reparative environment rich in proteoglycans, collagen type III, and interspersed smooth muscle cells[20, 21]. These healed ruptures may progress into fibrocalcific plaques, characterised by increased calcification within the necrotic core and surrounding tissue, ultimately contributing to luminal narrowing and ischaemic sequelae[22]. Despite advancements in imaging technology, the prevalence of silent ruptures within the clinical population remains uncertain, highlighting the ongoing challenges in accurately assessing subclinical atherosclerotic burden [23]. Notably, superficial erosion of matrix-rich, lipid- and macrophage-poor plaques is increasingly recognised as an important driver of acute coronary syndromes particularly in patients receiving lipid-lowering therapy[24]. While plaque rupture continues to be the most extensively studied underlying mechanism of acute coronary syndrome (ACS), plaque erosion has gained recognition as a distinct aetiology. Plaque erosion can be discerned using advanced imaging technology, notably optical coherence

tomography (OCT), and its prevalence has been estimated to be as high as 20-30% in ACS patients[25].

III. Identifying elevated risk of developing atherosclerosis and subclinical atherosclerosis in apparently heathy individuals

The primary challenge lies in identifying apparently healthy individuals who are actually at a higher risk of developing atherosclerosis, as well as those with subclinical atherosclerosis. These individuals would benefit from intensified monitoring and therapeutic prevention beyond standard lifestyle recommendations. Notably, while screening approaches have been shown to be successful in identifying cardiovascular risk factors, the effects on cardiovascular outcomes is less clear, and potential trade-offs with regards to cost effectiveness need to considered[26-28].

Current guidelines rely particularly on cardiovascular risk scores such as SCORE2 or SCORE2-Older Persons for individuals aged >70 years (SCORE2-OP) that aid in identifying individuals predicted to be at higher risk of developing major cardiovascular events who should be considered for further diagnostic evaluation and preventative measures. SCORE2, which estimates the 10-year risk for fatal and non-fatal CVD, is based on risk factors including age, sex, non-HDL cholesterol, smoking status and systolic blood pressure (SBP) as well as geographical “risk” regions calibrated to local incidence and mortality rates[29]. Additionally, risk modifiers including psychosocial factors, family history, genetics, environmental factors and comorbidities with predicted effects on ASCVD development, such as type 1 and type 2 diabetes mellitus (T1DM,

T2DM), chronic kidney disease (CKD), obesity, metabolic dysfunction-associated steatotic liver disease (MASLD), atrial fibrillation, inflammatory/autoimmune conditions and emerging risk factors like clonal haematopoiesis of indeterminate potential (CHIP) should be taken into account[30]. In addition, epidemiological observational studies have consistently identified an association between elevated immune cell blood counts, in particular neutrophils, and increased CVD risk[31-33]. Importantly, although aging is one of the strongest drivers of cardiovascular risk, lifetime risk should also be considered particularly in younger persons who may benefit from early risk management.

Although traditional risk factors are valuable for identifying individuals at elevated risk of developing major ASCVD events in the future, additional approaches have emerged to further characterise and monitor such individuals, but also those with subclinical atherosclerosis, particularly in biomarkers and imaging. Recently, these efforts have been bolstered by AI. AI holds the potential to enhance risk stratification by leveraging complex algorithms to analyse large datasets and identify subtle patterns or associations that may not be apparent through traditional methods alone. For example, radiomics, a branch of medical imaging analysis that extracts quantitative features from radiographic images, has shown promise in predicting cardiovascular outcomes. By incorporating AI-driven analyses of biomarkers and imaging data, we can move towards a more personalized approach to preventive and therapeutic measures in cardiovascular medicine[34]

1. Biomarkers

Atherogenic lipoproteins

Since lipids, particularly low-density lipoprotein cholesterol (LDL-C) and other apoB-containing lipoproteins, play a pivotal and causal role in the initiation and progression of atherosclerosis, these lipoproteins have become a focal point for early detection and therapeutic intervention in preventing atherosclerosis development and halting atherosclerotic plaque regression[35, 36]. Besides a major role as biomarker and predictor of risk[37], LDL-C is also a primary target for lipid-lowering therapy[38]. The identification of proprotein convertase subtilisin/kexin type 9 (PCSK9) as major regulator of LDL-C opened up novel avenues for both detection and therapeutic intervention. However, the potential of circulating PCSK9 levels as biomarker for predicting ASCVD events remains inconclusive so far[39-41].

Another emerging approach to assess cardiovascular risk beyond LDL-C is the measurement of non-high density lipoprotein cholesterol (non-HDL-C). Non-HDL-C holds particular significance as a marker [42], especially in individuals with a high burden of triglyceride-rich lipoproteins (TRL) and their remnants, as frequently noted in diabetes or obesity[43]. Given the common occurrence of hypertriglyceridemia in these conditions, which is a significant contributor to residual risk, it is pivotal to consider this aspect in primary prevention[44].

Besides measuring lipids themselves, Mendelian randomisation studies suggest that overall apoB levels correlate strongly with ASCVD development[37]. Strikingly, apoB has a superior ability and accuracy to predict atherogenic risk compared to traditional lipid markers, especially in individuals with obesity,

metabolic syndrome and diabetes[37, 45]. Accordingly, guidelines now also advocate for apoB measurements to define the targets and evaluate the efficacy of lipid-lowering therapy[43].

Therefore, a pragmatic shift towards assessing atherogenic particle number, preferably through apoB measurements, or alternatively, through estimation of total atherogenic cholesterol content (non-HDL-C; now also included in SCORE-2), could enhance primary ASCVD risk assessment, regardless of the undertaken therapeutic approach. It is important to acknowledge, however, that there are barriers limiting the routine use of apoB measurement compared to LDL-C or non-HDL-C determination, such as costs and limited availability[46, 47]. Hence, where appropriate laboratory facilities exist, apoB may be considered as the default measure of total atherogenic lipid burden. However, conventional lipid parameter (LDL-C, non-HDL-C) highly correlate with apoB levels, and measurement of ApoB levels only modestly improve CVD risk prediction in most patients[48, 49]. Therefore, in resource-constrained environments, efforts should prioritise making some form of cholesterol testing accessible as an initial step towards ultimately achieving optimal practice[47].

Ultimately, a significant lipid-related risk factor is lipoprotein(a) (Lp(a)), which demonstrates proatherogenic, proinflammatory, and potentially antifibrinolytic properties, establishing Lp(a) as being potentially more atherogenic than LDL particles[50-52]. Elevated Lp(a) concentrations are strongly associated with increased ASCVD risk[53], with epidemiological studies demonstrating near-linear associations between Lp(a) concentrations and CVD risk. Therefore, the introduction of a threshold with the Lp(a) consensus statement in 2022 aims to facilitate its practical application in clinical settings[53]. As Lp(a) levels are

relatively stable throughout an individual's lifetime, it is recommended to measure levels once and consider Lp(a) in estimations of global ASCVD risk, particularly in individuals at low or moderate ASCVD risk[53].

Inflammation

While lipids have traditionally dominated cardiovascular risk prediction guidelines, inflammation also plays a central role in the initiation and progression of atherosclerosis. Therefore, the role of inflammation-related biomarkers in predicting ASCVD and preventing atherosclerotic plaque regression is gaining recognition within clinical practice. Particularly C-reactive protein (CRP) and interleukin-6 (IL-6) have emerged as prominent candidates[54]. CRP is primarily synthesised by the liver in response to inflammatory cytokines as part of the systemic acute phase response[55, 56] and serves as a crucial marker of the inflammatory response associated with atherosclerosis[57], although it is unlikely to be causally involved[58]. However, elevated levels of CRP can signify the presence and severity of inflammation related to atherosclerosis. The JUPITER trial was the first trial to cast attention on CRP, where normolipidemic patients with elevated high-sensitivity CRP (hsCRP) levels experienced significantly reduced cardiovascular events when treated with rosuvastatin, despite having LDL-C levels <130 mg/dL[59]. Subsequent analyses of recent lipid-lowering trials revealed that residual inflammatory risk, measured by hsCRP levels, is strongly associated with future cardiovascular events and often outperforms LDL-C in predicting major adverse cardiovascular events (MACE) in patients receiving statins[60]. Furthermore, inflammation-related biomarkers like CRP and IL-6 offer insights into treatment response and therapeutic efficacy, especially in the context of emerging anti-

inflammatory therapies[61, 62]. In line with this, the CANTOS trial demonstrated that patients achieving significant reductions in hsCRP or IL-6 levels experienced reduced MACE following interleukin-1β inhibition, highlighting the utility of these biomarkers in stratifying patients who may benefit from specific treatments[63]. However, because of a higher incidence of fatal infection and sepsis associated with canakinumab compared to placebo[63], canakinumab has not been approved or further investigated for ASCVD prevention.

Genetics

The role of genetic biomarkers in atherosclerosis development and plaque progression is increasingly recognised, with individual genetic background playing a significant role in susceptibility to the development of major ASCVD events[64]. Estimates suggest that coronary artery disease (CAD) heritability ranges from 40% to 60%[64]. Genetic factors contributing to ASCVD encompass both monogenic and polygenic risk variants.

Monogenic risk factors include rare pathogenic variants causing monogenic dyslipidaemias, affecting genes such as LDL receptor (*LDLR*), *PCSK9*, ATP-Binding cassette subfamily G member 8 (*ABCG8*), as well as variants in Tet methylcytosine dioxygenase 2 (*TET2*) and janus kinase 2 (*JAK2*) associated with CHIP, and Lp(a)-increasing variants[65-68]. These variants are linked to early-onset ASCVD and/or heightened risk of developing subclinical atherosclerosis, underscoring the complexity of genetic testing and its role in diagnosis and treatment stratification[65, 69].

Familial hypercholesterolaemia (FH) arises from one or more pathogenic variants in three primary genes responsible for LDL-C clearance. The

predominant gene involved in over 90% of cases is the *LDLR*, followed by *APOB* in approximately 5% of cases, and *PCSK9* in less than 1% of cases. FH manifests in two main categories among the affected persons, depending on the affected alleles: heterozygous FH (HeFH) and homozygous FH (HoFH). HeFH is the most prevalent genetic disorder, associated with a significant risk of ASCVD, with an estimated prevalence of 1 in 311 in the general population and 1 in 17 among ASCVD patients. Without treatment, individuals with HeFH typically experience their first cardiovascular events around the age of 45 years. Conversely, HoFH is considered an orphan disease, with an estimated prevalence ranging from 1 in 160,000 to 300,000 in the general population. In untreated cases, cardiovascular events usually occur by the age of 35 years, although there are reports of ASCVD manifestations in children as young as 10 years old[70].

Genetic testing enables the differentiation of phenotypically similar conditions associated with increased cholesterol levels and elevated ASCVD risk, as seen in FH, sitosterolemia and elevated Lp(a)[71]. Genetic testing can also unravel the complex interplay between different variants and the phenotype in specific inherited conditions[72]. FH individuals, for instance, exhibit significantly increased ASCVD risk compared to non-genetic hypercholesterolemic cases[73]. Furthermore, specific genetic variants may confer varying degrees of ASCVD risk and response to lipid-lowering therapy in this population[65, 74, 75]. Finally, genetic diagnosis not only facilitates therapy initiation and adherence but also enables the identification of at-risk family members through cascade screening[69].

Apart from variants associated with increased LDL-C and elevated ASCVD risk, compelling evidence has firmly established the link between TRL and the initiation or regression of the atherosclerotic plaque, as well as the occurrence of major ASCVD events[76]. Variants in genes encoding proteins that lower triglycerides via lipoprotein lipase (LPL), apolipoprotein CIII (ApoCIII), apolipoprotein AV (ApoAV), angiopoietin like 3 protein (ANGPTL3) and angiopoietin-like protein 4 (ANGPTL4), as well as LDL-C-lowering variants are linked to a comparable reduction in CAD risk per unit difference in ApoB[77]. Hence, genetic testing that encompasses all variants involved in the metabolism of total ApoB-containing lipoproteins could offer a more comprehensive approach to identifying individuals at elevated risk of developing atherosclerosis or those with subclinical atherosclerosis.

Polygenic predisposition to ASCVD, evidenced by over 150 genomic loci significantly associated with CAD, underscores the importance of assessing susceptibility through polygenic risk scores (PRS)[78]. Key clinical traits contributing to the increased cardiovascular risk related to PRS include elevated levels of LDL-C, triglycerides, non-HDL-C, high blood pressure, diabetes, obesity, and a family history of premature cardiovascular events. Other risk factors such as smoking, physical inactivity, and unhealthy dietary habits may also interact with genetic predispositions captured by PRS to further increase cardiovascular risk[79, 80]. Hence, PRS, aggregating numerous common variants identified through genome-wide association studies can strongly predict subclinical atherosclerosis and CAD development[81, 82], offering a higher predictive value than traditional clinical tools particularly in high-risk patients[83, 84]. PRS use in apparently healthy young adults may also prompt early, intensive

treatment and lifestyle modifications, leading to significant reduction in the risk of developing atherosclerosis or facilitating atherosclerotic plaque regression[85]. Although the addition of CAD-PRS to established clinical tools improves the prediction of ASCVD events in apparently healthy adults, its cost-effectiveness remains questionable, while its implementation raises ethical, legal, and regulatory concerns warranting further discussion[86].

2. Imaging of atherosclerotic plaque

Imaging merits a crucial role in the early detection and characterisation of atherosclerotic plaques, utilising non-invasive and invasive techniques to visualise plaque morphology and composition (*Table 1, Supplementary Table 1*). Non-invasive methods, such as vascular ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI), are particularly suitable for primary prevention and screening purposes. While intravascular ultrasound (IVUS), alone or in combination with techniques like virtual histology and OCT, provides the most accurate representation of plaque morphology[87], its invasive nature limits its use to interventional procedures.

Non-invasive imaging

In the evaluation of coronary arteries, technological advancements and the advent of deep-learning algorithms have significantly improved the efficiency and accuracy of cardiovascular imaging, allowing for the assessment of plaque volume and composition, like for example with CT imaging[88]. Modern CT scanners can stratify plaques based on density, providing valuable insights into plaque composition and vulnerability in addition to the degrees of stenosis. Specific features such as low-attenuation plaque volume (LAPV), positive

remodelling, and spotty calcification on coronary CT angiography (CCTA) are associated with a high risk of plaque rupture, indicating vulnerable plaques[89-91]. Indeed, LAPV has been demonstrated to be superior in predicting myocardial infarction in patients with stable chest pain to other CCTA-based measures or cardiovascular risk scores[92]. In primary prevention, the evaluation of coronary atherosclerosis has been significantly enhanced by coronary artery calcium (CAC) scoring, which can be routinely performed as part of thorax investigations without the use of contrast agents and CCTA[93]. It is worth noting that the initiation of statin therapy in primary prevention is likely to result in an increase of the CAC score over time. However, it is important to recognise that this increase is typically indicative of lesion stabilisation rather than an increase in ASCVD risk[94]. CCTA may be even further improved with emerging ultra-high resolution photon-counting CT technologies (UHR-CCTA), allowing for the accurate assessment of even highly calcified plaques[95]. Studies utilising CCTA have corroborated the notion that lesions exhibiting minimal progression over time are less likely to result in acute coronary events, irrespective of their baseline characteristics or degree of luminal stenosis[96-98]. This underscores the importance of considering plaque dynamics and progression when assessing an individual's cardiovascular risk. Thereby the total coronary plaque burden, as assessed by CAC or segment involvement score (SIS), serves as a prognosticator of MACE, even in asymptomatic persons[89, 99].

Carotid and femoral plaques can be routinely visualised using imaging, enabling the assessment of basic plaque characteristics such as echogenicity, surface morphology, and neovascularisation. Ultrasound is commonly used to assess carotid intima media thickness (cIMT), a marker of arterial injury. High-

resolution carotid MRI further enhances plaque characterisation by identifying features like intraplaque haemorrhages and lipid-rich necrotic cores, aiding in risk stratification for future cardiovascular events[100]. In the same context, femoral ultrasonography has gained interest for imaging peripheral subclinical atherosclerosis, particularly in conjunction with carotid imaging, as it offers superior predictive value for MACE[101, 102].

Additionally, functional vascular tests such as ankle-brachial index (ABI), flow-mediated dilation (FMD), carotid-femoral pulse wave velocity (cfPWV), and arterial resistive index provide valuable information on vascular function and arterial stiffness, aiding in risk stratification for cardiovascular events (*Table 2*)[103-106]. Nevertheless, with the exception of carotid plaque detection, measures such as cIMT and functional testing are not recommended for routine cardiovascular risk assessment in most guidelines, including the current ESC prevention guidelines[8].

Invasive imaging

Traditional invasive coronary angiography primarily evaluates the vessel lumen to detect significant stenoses visually that may necessitate revascularisation. However, it offers limited insight into plaque burden or composition. IVUS has been the mainstay for atherosclerotic plaque imaging, recognised as the gold standard for plaque quantification[107]. Various postprocessing methods, including virtual histology-IVUS (VH-IVUS) and integrated backscatter-IVUS (IB-IVUS), differentiate plaque composition[107]. While OCT, using light instead of ultrasound, provides higher resolution images compared to IVUS, the delineation of the outer vessel boundary is limited[108]. Additionally, OCT enables

direct visualisation of thin-cap fibroatheromas, while quantitative plaque volume assessment is less reliable due to reduced penetrance[108]. Other invasive techniques include intracoronary near-infrared spectroscopy (NIRS) for plaque lipid measurement and emerging methods like intracoronary laser speckle imaging, Raman spectroscopy, and fluorescence spectroscopy[109].

These imaging modalities may provide valuable tools for improving prediction of major ASCVD events, though careful consideration of each imaging modality's possibilities and limitations is necessary (*Table 1*).

3. Artificial intelligence

AI is increasingly recognised as a valuable tool in healthcare, including in primary ASCVD prevention and subclinical atherosclerosis (*Figure 1*). By employing machine-learning algorithms and predictive models, AI can analyse complex multimodal data from various sources, including patient health records, imaging, genetic information, and lifestyle factors. Such analyses can unveil patterns and risk factors that are not easily discernible to physicians, enabling early detection and intervention of subclinical atherosclerosis[110]. The capacity to process extensive amounts of data and detect subtle patterns allows for a more personalised, predictive, and proactive approach for primary prevention. For example, the AutoPrognosis model, an automated machine learning framework, surpassed traditional risk prediction models in forecasting ASCVD risk among 423,064 participants from the UK Biobank by utilising 473 predictor variables[111].

Clinical decision support systems (CDSS) are computer-based programs aiding physicians by analysing electronic health records against domain knowledge or

evidence-based guidelines[112]. CDSS can provide patient-tailored prompts, reminders, and recommendations for atherosclerosis preventive services, risk factor detection, assessment, and treatment protocols. While CDSS have been shown to be promising in improving guideline implementation and physician workflows, recent systematic reviews report inconclusive evidence regarding their impact on cardiovascular risk factors, physician performance, and patient outcomes due to variability in features and study heterogeneity[113]. Nonetheless, emerging data suggests the potential of CDSS to enhance specific cardiovascular risk factor management, improve overall cardiovascular risk profiles, and potentially reduce sex disparities in healthcare[114].

One promising approach is network medicine, which integrates complex biological networks and systems-level analyses to identify disease mechanisms and therapeutic targets[115, 116]. Additionally, network medicine facilitates personalised risk factor assessment and the development of tailored prevention strategies based on an individual's unique network profile[117, 118]. While challenges persist, the potential benefits of AI in prevention and management of atherosclerosis, leading to improved patient outcomes and quality of life, are undeniable.

III. Preventive strategies

The 2021 ESC guidelines on cardiovascular disease prevention recommend an individualised, stepwise approach in the setting of primary prevention[8]. Lifestyle modifications, including smoking cessation, physical activity and dietary recommendations, as well as the maintenance of SBP <160 mmHg, represent

the first step in primary prevention that is recommended for all individuals, including apparently healthy persons even with low estimated 10-year CVD risk. Additional preventative strategies, including pharmacological measures, should be considered particularly in persons with increased estimated 10-year CVD risk, as assessed by scoring systems such as the SCORE2 and risk modifiers[8]. Notably, patient adherence may be a particular issue in primary prevention, which may be further impacted by socioeconomic factors, educational level, cognitive and emotional factors as well as gender-associated differences in CVD risk perception.

Besides early detection and identification of apparently healthy individuals at elevated risk of developing atherosclerosis, it is also of major importance to implement proper preventive strategies to avoid the development and further progression of subclinical atherosclerosis.

3.1 Lifestyle modifications

3.1.1 Diet

Since lipids are a major driving factor of atherosclerosis, it is not a surprise that dietary interventions are associated with a lower ASCVD risk. For example, diets emphasising plant-based and Mediterranean diet principles, coupled with heightened intake of fruits, nuts, vegetables, legumes, wholegrain and lean protein from either plants or animals (preferably fish), have shown a consistent association with a lower risk of all-cause mortality compared to standard or control diets[119]. In line with this, the consumption of trans-fat has been shown to increase the risk of ASCVD and all-cause mortality and hence, the replacement of saturated and trans-fats with unsaturated fats is

recommended[120]. Furthermore, reducing dietary sodium has been shown to lower blood pressure and decrease cardiovascular events[121]. Diets aiming at promoting weight reduction may also be beneficial in decelerating ASCVD progression among overweight or obese individuals by improving cardiometabolic risk factors such as insulin resistance, dyslipidaemia, and hypertension. However, for individuals who are not overweight or obese, adopting a diet conducive to cardiovascular health is certainly advisable, though it may not necessarily involve a hypocaloric diet aiming at weight loss[122, 123].

Although these studies suggest dietary intervention as a promising approach, evidence supporting plaque regression with diet intervention alone is limited. While some studies have demonstrated a reduction in coronary atherosclerosis progression of noncalcified plaque volumes with intensive lifestyle changes, these findings have not consistently been translated into significant regression of overall plaque burden[124, 125].

A nutraceutical is defined as a food or component of food that offers medical or health benefits, including prevention and treatment of illnesses. This category also encompasses natural ingredient-based pharmaceuticals. Various classes of nutraceuticals have been proposed to provide potential advantages in cardiovascular prevention, as recently reviewed elsewhere[126, 127]. For instance, consumption of plant phytosterols has been linked to reduced LDL-C levels without significantly affecting HDL-C and triglyceride levels[128]. Polyphenols, found in vegetables, fruits, cereals, and plant-based beverages, including those derived from grape, cocoa, and tea, have also been suggested to have beneficial effects on cardiometabolic parameters that warrant further investigation, particularly at higher doses [126, 127, 129-131]. While nutraceuticals

may hold particular potential in primary prevention as an adjuvant to pharmacotherapy or in those persons who do not qualify for pharmacotherapy, further randomised controlled trials assessing the effects of nutraceuticals on cardiovascular parameters and outcomes are needed[132].

3.1.2 Exercise

The manifold health advantages of regular physical activity are firmly established, with physical activity serving as a cornerstone for maintaining and enhancing cardiovascular health. Current guidelines recommend at least 150-300 minutes of moderate-density aerobic physical activity (e.g. jogging, cycling, walking) per week with added resistance exercise on two days spread throughout the week[30]. Although these recommendations need to be adjusted to patients' abilities, it is important to note that there is a dose-dependent relationship between physical activity and all-cause mortality and that even shorter bouts of physical activity have been proven to be beneficial[133, 134]. Therefore, any reduction in sedentary behaviour should be encouraged, as physically inactive individuals benefit the most from exercise[134, 135].

3.1.3 Smoking cessation

Current and former cigarette smoking is widely recognised as risk factor for ischaemic events, subclinical atherosclerosis, and coronary calcification[136]. Smoking cessation is arguably the most important, cost-effective preventive measure and is associated with a reduction in CVD-associated and all-cause mortality in patients with established ASCVD[137]. In several studies, supportive measures such as nicotine-replacement therapy or electronic cigarettes have been shown to be effective in encouraging smoking cessation, although the

tobacco content in the latter should not be discerned and cardiovascular effects should be further studied[138, 139].

3.2. Pharmacological Interventions

3.2.1 Lipid-lowering medications

Lipid-lowering is the cornerstone in primary and secondary ASCVD prevention, as the reduction in LDL-C is proportional to the relative decrease in CVD risk and generally no detrimental outcomes have been observed with aggressive LDL-C lowering[140 141]. LDL-C levels are generally recommended to be <100mg/dL (<2.6mmol/L), but treatment goals for LDL-C<70mg/dL (<1.8mmol/L) or LDL-C<55mg/dL (<1.4mmol/L) are recommended for high-risk and very high-risk patients respectively, with liberal treatment intensification to higher tolerated doses of statin therapy advocated by ESC/EAS dyslipidaemia guidelines[132, 142]. Of note, although epidemiological evidence links levels of other lipid and lipoprotein subclasses to ASCVD risk, no treatment goals are recommended for HDL or triglycerides. However, triglyceride-lowering drugs should be considered in high-risk patients with hypertriglyceridemia (TG>200mg/dL, >2.3mmol/L) [132, 142].

Several lipid-lowering drugs are available. Statins serve as the cornerstone in primary prevention by effectively reducing cholesterol synthesis and resulting in significant LDL-C reductions by 30-50%[143]. Additionally, they demonstrate other pleiotropic effects, such as lowering inflammation[59]. Numerous studies indicate that statins promote plaque regression in a dose-dependent manner, correlating with reductions in LDL-C levels[144]. Clinical trials such as JUPITER and WOSCOPS have also demonstrated the efficacy of statins in reducing

cardiovascular mortality and events in individuals without prior symptomatic ASCVD (*Supplementary Table 2*) [59, 141, 145].

The cholesterol absorption inhibitor ezetimibe is generally used in combination with statins or other lipid-lowering therapy. Addition of ezetimibe has shown benefits particularly in patients with acute coronary syndrome[146], while in high-risk patients with chronic kidney disease in the setting of primary prevention, a combination of statin and ezetimibe resulted in reduced cardiovascular events compared to placebo[147]. However, trials investigating the impact of adding ezetimibe to statins on plaque regression assessed by IVUS have reported controversial results[144]. Given that ezetimibe is well tolerated, addition of ezetimibe to treatment regimens is recommended in a primary prevention setting if treatment goals are not achieved[8, 132, 146].

Since some patients are intolerant to statins, bempedoic acid, an orally active drug selectively inhibiting hepatic cholesterol biosynthesis by antagonizing ATP citrate-lyase upstream of HMG-CoA reductase, offers a promising alternative that has been shown to effectively reduce LDL-C levels, particularly in combination with ezetimibe, while also exhibiting anti-inflammatory properties[148, 149]. In the CLEAR Outcomes trial, bempedoic acid demonstrated a significant reduction in major cardiovascular events[150], with even greater benefit in a primary prevention subgroup of patients at elevated CV risk but without clinically manifested ASCVD[151]. Thus, bempedoic acid is a promising candidate for primary prevention.

PCSK9 inhibitors in the form of monoclonal antibodies or inclisiran, an RNA interference-based, long-acting hepatic PCSK9 synthesis inhibitor, represent effective options for reducing LDL-C levels, particularly when added to statin

therapy with or without ezetimibe[152-154]. It is important to underline that the available evidence demonstrating the efficacy of these drugs in reducing MACE or slowing down the progression of coronary atherosclerotic plaque primarily pertains to patients with established ASCVD[152, 153, 155, 156].

Oral PCSK9 inhibitor compounds have been developed and have shown significant reductions in PCSK9 levels in phase II trials. The results of phase III studies are eagerly awaited, with the anticipation that access to PCSK9 inhibition will increase due to the lower cost and ease of use associated with oral PCSK9 inhibitors[157, 158]. Additionally, PCSK9 gene editing using CRISPR technology has shown promising results in non-human primates, demonstrating significant reductions in PCSK9 levels. However, the first human trial raised concerns due to reported heart attacks following drug administration[159, 160].

Adnectins, artificial proteins constructed around the structure of the 10th type III domain of human fibronectin, offer a novel approach. These small proteins possess changeable loops that can be engineered to selectively and strongly bind to specific medicinal sites. One such adnectin, BMS-962476, targets PCSK9 and prevents its binding to the epidermal growth factor precursor homology domain-A (EGFA), resulting in a remarkable 91.9% reduction in free PCSK9 levels. The phase III trial of BMS-962476 is currently ongoing[161].

In patients with persistent hypertriglyceridemia, even after reaching LDL-C treatment goals, further pharmacological measures in addition to those outlined above should be considered. Drugs of this class include fibrates that have yielded mixed results with regard to cardiovascular event reduction[162]. The recent PROMINENT trial revealed that pemafibrate, a selective peroxisome proliferator-activated receptor α modulator, significantly lowered triglyceride

levels but did not demonstrate a reduction in cardiovascular events among patients with diabetes and atherogenic dyslipidaemia[163]. Another potential strategy is to use 3-polyunsaturated fatty acids (3-PUFA, omega-3 fatty acids), particularly the highly purified, stable eicopentaeonoic acid (EPA)-derivative icosapent ethyl. However, it is noteworthy that while the REDUCE-IT trial demonstrated cardiovascular benefits, these benefits were not statistically significant in the primary prevention subgroup[164]. Conversely, the STRENGTH trial failed to show a significant reduction in MACE among high-risk patients treated with EPA, leading to a downgrading of the recommendation for EPA use to class IIb in the 2021 ESC prevention guidelines[8, 165]. On the other hand, several studies report plaque regression or increased stability following EPA use in patients with coronary atherosclerosis (*Supplementary Table 2*)[166-170].

3.2.2 Anti-hypertensive therapies

ESC Prevention guidelines recommend that the first step in all treated patients should achieve a treated SBP <140 mmHg and diastolic BP (DBP) <80 mmHg. For younger patients (aged 18-69 years), the recommended ultimate treatment target range for SBP is 120-130 mmHg. However, some patients may safely achieve lower SBP levels, and if these levels are well tolerated, there is no need to reduce treatment. For patients aged >70 years, the ultimate SBP target is <140 mmHg, with the possibility of lowering it to 130 mmHg if well tolerated[8]. Five major drug classes are recommended for the treatment of hypertension: angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers (BBs), calcium-channel blockers (CCBs), and diuretics. All these drug classes, beyond having proven ability to reduce BP, also have evidence from randomised controlled trials and meta-analyses that they reduce

cardiovascular events in individuals without established ASCVD depending on the magnitude of BP reduction achieved[171-173]. ACE inhibitors and ARBs have similar effectiveness in the primary prevention of MACE and mortality outcomes[171-173]. CCBs have similar efficacy as other major drug classes in the primary prevention of MACE and mortality outcomes[171-173]. Among CCBs, dihydropyridines (e.g., amlodipine) and nondihydropyridines (e.g., verapamil and diltiazem) do not show substantial differences in efficacy[172, 173]. Notably, CCBs have a greater effect on stroke reduction than expected for the BP reduction achieved[171].

Several IVUS studies have explored the impact of antihypertensive agents on plaque volumes, with most showing no significant improvement in plaque regression[144]. The CAMELOT trial compared amlodipine, enalapril, and placebo, revealing slightly reduced plaque progression with amlodipine (*Supplementary Table 2*)[174]. However, other trials assessing perindopril, ramipril, and aliskiren did not show significant reductions in plaque progression compared to controls[144].

3.2.3 Glucose-lowering drugs

Patients with T1DM or T2DM, who are at elevated risk for macro- and microvascular complications, are recommended to maintain target glycated haemoglobin (HbA1c) levels of at least <7% (<53 mmol/mol)[8]. Several classes of medications effectively lower blood glucose levels, yet their impact on ASCVD risk varies[175, 176]. While robust evidence predominantly pertains to patients with established ASCVD, data in apparently healthy individuals without known atherosclerosis remain limited and contentious[177, 178] . Although

observational studies and clinical trials suggest potential benefits of metformin, thiazolidinediones, and dipeptidyl-peptidase-4 (DPP4) inhibitors in regressing subclinical atherosclerosis[179], only metformin is regarded as first-line therapy for glycaemic control in individuals free of ASCVD. This is based on the finding of the UKPDS trial showing reduced rates of macrovascular complications including MI in metformin-treated patients without known ASCVD compared to standard-of-care[180]. Notably, this benefit may not extend to patients with T1DM[181].

The efficacy of sodium-glucose co-transporter-2 (SGLT-2) inhibitors in primary prevention remains debated and may depend on patient characteristics as well as drug type. Ipragliflozin did not improve cIMT in T2DM patients within 1 or 2 years after treatment[182, 183]. Tofogliflozin and dapagliflozin have shown mixed results in altering cIMT and FMD[184, 185]. Empagliflozin has demonstrated improvements in arterial stiffness and BP[186-188]. A meta-analysis of RCTs investigating SGLT2 inhibitors in patients without prior ASCVD event revealed reductions in MACE, but significant benefits were restricted to patients with T2DM and concomitant CKD[189]. Further research is essential to comprehend the impact of SGLT-2 inhibition on subclinical atherosclerosis and primary prevention.

Finally, several cardiovascular outcome trials have shown beneficial effects of glucagon-like peptide-1 (GLP-1) receptor agonists on cardiometabolic parameters including reductions in lipid levels, BP, body weight and hyperglycaemia. Multiple studies have demonstrated reduced MACE in patients with prior ASCVD event and T2DM[190-194], but notably also in normoglycemic persons with obesity[195]. Given that most subjects in these

studies had pre-existing cardiovascular disease, the effect of GLP-1 receptor agonists in a primary prevention setting is less firmly established. However, 70% of T2DM patients did not have prior ASCVD event in the REWIND trial, which demonstrated similarly reduced MACE, particularly stroke, as well as decreased microvascular renal complications in both primary and secondary prevention subgroups (*Supplementary Table 2*)[190]. Semaglutide has been recently approved for cardiovascular event prevention in individuals with obesity or overweight and comorbidities[196] .

The novel dual GLP-1/GIP (glucose-dependent insulinotropic polypeptide) agonist tirzepatide, often referred to as 'twincretin,' exhibits a range of beneficial effects, including improvements in lipid profile, reduction in BP, body weight, and inflammatory markers[197]. Notably, tirzepatide has been associated with decreased MACE and cardiovascular mortality in patients with diabetes at high and very high cardiovascular risk[198].

Furthermore, the triple GLP-1/GIP/glucagon receptor agonist, retatrutide, developed for obesity treatment, has demonstrated its cardiovascular safety in a phase II trial[199]. Both dual and triple GLP-1 receptor agonists show promise in the setting of ASCVD prevention. However, further research is warranted, particularly in the primary prevention setting.

3.2.4 Antithrombotic treatment

While antithrombotic therapy such as low-dose aspirin are generally recommended in secondary prevention, the use of antithrombotics in primary prevention remains a topic of contention. Although several individual studies have demonstrated limited benefit with aspirin use compared to placebo, meta-

analyses report reduced incidence of ASCVD with aspirin use. However, this generally did not translate to reductions in mortality, which may be partially due to the significantly increased risk of bleeding complications *(Supplementary Table 2)*[200-203]. Thus, the use of aspirin in a primary prevention setting may be considered in selected very-high-risk patients without contraindications such as elevated bleeding risk [8].

3.2.5 Anti-inflammatory drugs

There is increasing evidence regarding the relationship between the use of immunomodulating drugs and favourable cardiovascular outcomes, mainly in patients with established ASCVD. The first anti-inflammatory therapy approved for secondary ASCVD prevention is low-dose colchicine, which is a broad anti-inflammatory drug. Trials like COLCOT and LoDoCo2 have demonstrated reduced MACE in CAD patients treated with low-dose colchicine compared with those on placebo[204, 205]. In this setting, colchicine may also promote plaque stabilisation. A recent study has demonstrated reductions in LAPV, a measure of plaque stability, as assessed by CCTA in patients receiving colchicine on top of optimal treatment compared to those receiving standard-of-care treatment; of note, overall atheroma plaque volume was not different between groups[206]. According to current guidelines low-dose colchicine (0.5 mg daily) may be considered for secondary prevention especially in patients with recurrent CV events under optimal medical therapy or insufficiently controlled risk factors after acute coronary syndrome episodes[207]. However, data on the impact of colchicine use on primary prevention is still lacking. Similarly, while methotrexate and canakinumab have shown promising results in secondary ASCVD prevention, their efficacy remains uncertain, and benefit may be

restricted to selected patients such as patients with heightened inflammation (hsCRP>2mg/ml) or TET2-driven CHIP[208, 209]. The ongoing ZEUS trial (NCT05021835) investigating IL-6 inhibition in ASCVD patients with CKD may provide further valuable insights into immunomodulatory approaches for ASCVD management[210].

IV. Conclusion

Recent years have seen remarkable progress in managing ASCVD, notably in identifying individuals at heightened risk of atherosclerosis development and those with subclinical atherosclerosis. Additionally, effective strategies for preventing atherosclerosis and promoting plaque regression are rigorously investigated. Despite the well-established association of the traditional risk factors with subclinical atherosclerosis and development of major ASCVD events[211-213], it is important to recognise that a clinical ASCVD event can occur in individuals without obvious risk factors or at low-risk as well[214]. In this context, the recognition of subclinical atherosclerosis and plaque progression as a critical determinant of cardiovascular risk suggests the need for a paradigm shift in primary preventive approaches. Rather than solely targeting traditional risk factors, there is growing recognition of the importance of intervening early in the process of plaque development and progression to prevent adverse cardiovascular events[35]. The advent of personalised medicine, coupled with advances in imaging modalities and biomarker research as well as the continuously expanding toolbox of therapeutic options, offer new opportunities to refine primary ASCVD risk stratification and tailor preventive strategies to

individual patients. Moving forward, a comprehensive approach that integrates genetic, imaging, and biomarker data holds great promise in optimising primary cardiovascular risk assessment and management in apparently healthy individuals with or without subclinical atherosclerosis. Such approaches are being further supported by the fast-developing AI tools, and the expanding use of various -omics approaches like proteomics and lipidomics [9]. By tailoring interventions to individual risk profiles and addressing the underlying pathophysiological processes driving atherosclerosis, we can move closer to achieving the ultimate goal of preserving cardiovascular health.

Conflict of Interest

F.B. has received honoraria and grants from Novartis, Novo Nordisk, Sanofi, and Viatris, outside the scope of the submitted work. All other authors declare to have no conflict of interest.

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Figure Legends

Figure 1. Schematic visualisation of the various cardiovascular risk assessment parameters and therapeutic options towards personalised medicine.

Cardiovascular risk (CVR) assessment is supported by various biomarkers, imaging and artificial intelligence. Based on this assessment lifestyle recommendations can be made and/or treatments can be started and optimized, enabling a personalised medicine. Limited or controversial data exists regarding the role of the drugs underlined with italics in primary prevention. ACE: Angiotensin-converting enzyme; ApoB: Apolipoprotein-B; ARB: Angiotensin receptor blocker; BB: Beta-blocker; CAC: Coronary artery calcium; CCB: Calcium-channel blocker; CCTA: Coronary CT angiography; GIP: Glucose-dependent insulinotropic polypeptide; GLP-1: Glucagon-like peptide-1; HsCRP: High-sensitivity CRP; IL-6: Interleukin-6; LDL-C: Low density lipoprotein cholesterol; Lp(a): Lipoprotein(a); MRI: Magnetic resonance imaging; Non-HDL-C: Non-high density lipoprotein cholesterol; PCSK9: Proprotein convertase subtilisin/kexin type 9; SGLT-2: Sodium-glucose co-transporter-2.

Table 1: Imaging techniques for subclinical ASCVD detection

Method	Description	Advantages	Limitations
Non-invasive methods			

Coronary artery calcium score (CAC score)[89, 93, 215-219]	Low-dose non-contrast CT of the heart showing the amount of calcium in the coronary arteries	Easy-to-access Non-invasive Low-cost Low-dose CT Low inter-observer variability Can be easily performed as part of other thorax CT examinations	Radiation dose (limited in low-dose CT) CAC score does not rule out the presence of non-calcified plaques
Coronary CT angiography (CCTA)[89, 90, 99, 220-223]	High-dose contrast CT of the coronary arteries providing detailed analysis of the presence (quantity) and composition (quality) of atherosclerotic plaques in the whole coronary tree	Non-invasive Detailed analysis of coronary arteries Assessment of calcified and non-calcified plaques Detection of high-risk plaque features Low inter-observer variability Low-dose radiation with newer CT machines	High costs Time-demanding Contrast agent required Expert analysis required (potentially AI-supported) Heavily calcified plaques may result in overestimation of degree of stenosis (improved with newer, e.g. ultra-high resolution photon-counting CT machines)
Carotid MRI[100]	High-resolution magnetic resonance imaging of the carotid arteries providing detailed information about plaque presence (quantity) and composition (quality)	Non-invasive Detailed analysis of carotid arteries High soft tissue plaque resolution Detection of high-risk plaque features Low inter-observer variability	High costs Time-demanding Limited availability Flow and motion artifacts

Carotid ultra-sound[224]	2D/3D vascular ultrasound of the carotid arteries enabling assessment of plaque presence (quantity) and composition (quality) Measurements include carotid intima media thickness (cIMT)	Easy-to-access Non-invasive Low-costs Portable No contrast agent required No radiation	High inter-observer variability Strongly calcified plaques with large acoustic reverb artifact Limited number of views Limited information on plaque quality
Femoral ultra-sound[102, 225, 226]	2D/3D vascular ultrasound of the femoral arteries enabling assessment of plaque presence (quantity) and composition (quality)	Easy-to-access Non-invasive Low-costs Portable No contrast agent required No radiation	High inter-observer variability Not routinely used in clinical practice Time-consuming
Invasive methods			
Intravascular ultrasound (IVUS)[107]	A catheter-based imaging technique used to visualise and assess atherosclerosis within coronary arteries with ultrasound.	High-resolution, cross-sectional images of the coronary artery wall and plaque morphology Detailed assessment of plaque characteristics, including composition, burden, and distribution Precise measurements of lumen diameter, vessel diameter, plaque area, and plaque burden Facilitates assessment of procedures during percutaneous coronary intervention	Invasive procedure Requires specialised equipment Time-consuming Radiation Limited availability and higher cost Variability in measurements May not provide complete visualization of plaque extent and composition in heavily calcified lesions or behind stents

Optical Coherence Tomography (OCT)[108]	A catheter-based imaging technique used to visualise and assess atherosclerosis within coronary arteries with light	High-resolution, cross-sectional images of the coronary artery wall and plaque microstructure Detailed assessment of plaque morphology, composition, and luminal dimensions Precise measurements of lumen diameter, vessel diameter, plaque burden, and stent dimensions Facilitates accurate identification of vulnerable plaques and assessment of stent apposition, expansion, and coverage Helps procedures during percutaneous coronary intervention	Invasive procedure Specialised equipment Time-consuming Radiation Limited availability and higher cost Variability in measurements Limited depth penetration, restricting visualisation to superficial layers of the vessel wall and potentially missing deeper plaque components. Cannot assess distal segments or vessels with significant tortuosity due to limitations in catheter navigation.

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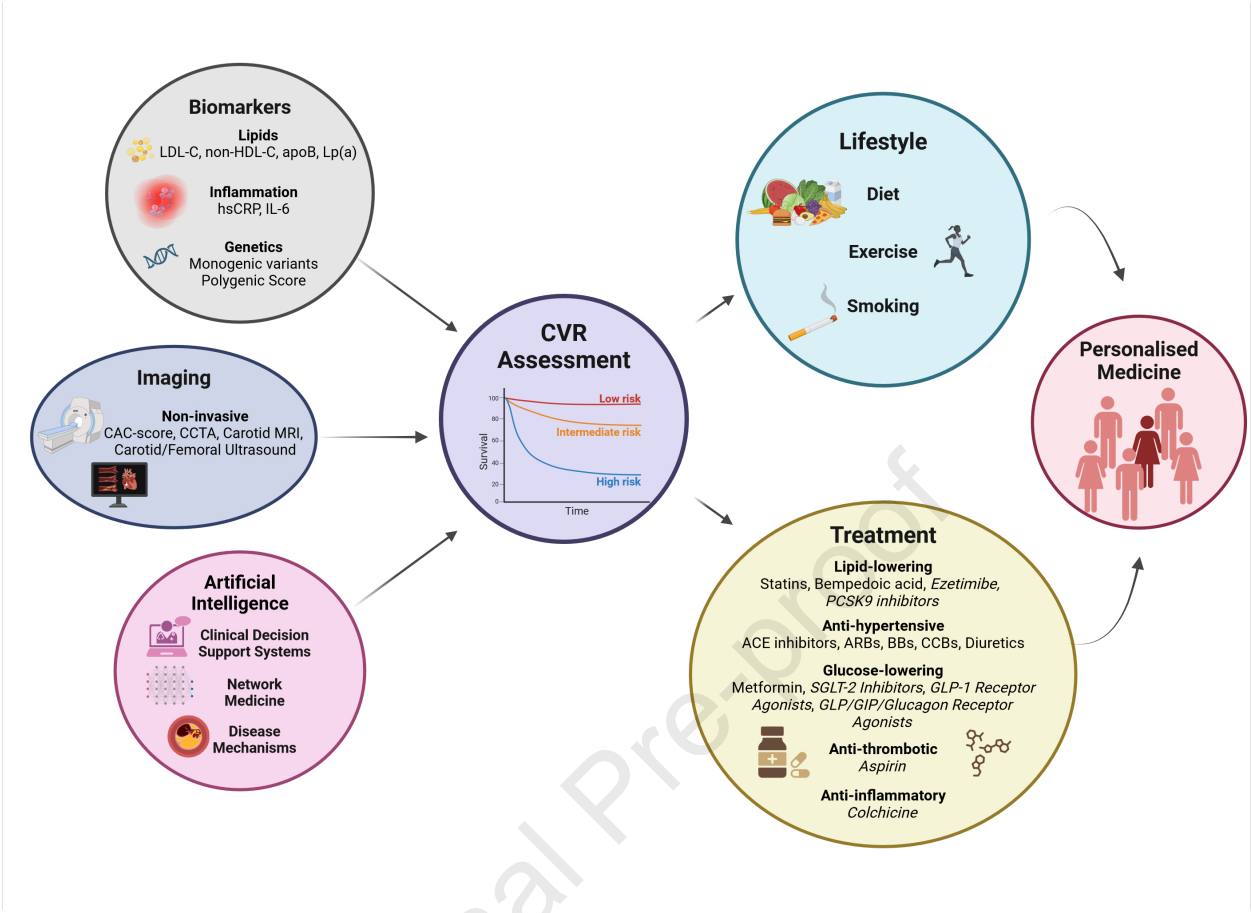
Table 2: Imaging-based functional tests for subclinical ASCVD detection

Method	Description	Advantages	Limitations
Ankle-brachial index (ABI)[103, 227-229]	Ratio of systolic ankle pressure measured by Doppler-ultrasound to brachial systolic pressure. Mainly a measure for peripheral artery disease (PAD)	Easy-to-access Non-invasive No radiation No contrast agent required	High inter-observer variability Elevated ABI can be observed in other co-morbidities
Flow-mediated dilation (FMD)[105, 230, 231]	Ultrasound-based measurement of changes in brachial artery diameter in response to reactive hyperemia. A measure of endothelial function.	Gold standard measurement of peripheral endothelial function Non-invasive No radiation No contrast agent required	High inter-observer variability High degree of expertise required
Carotid-femoral pulse wave velocity (Cf-PWV)[104, 106, 232]	An applanation tonometer is placed over the carotid artery simultaneously with a leg cuff to capture blood pressure waveforms at both sites to derive the PWV. A measure of arterial stiffness.	Gold-standard marker of arterial stiffness Non-invasive No radiation No contrast agent required	Lack of precision in measuring the path length between the carotid and femoral arteries Excludes aorta and aortic arch
Renal resistive index (RRI)[233-235]	The ratio between the difference of peak systolic and diastolic velocities to peak systolic velocity derived from pulse wave Doppler ultrasound measurements of the renal arteries. Generally thought to reflect overall vascular characteristics (not kidney-specific).	Easy-to-access Non-invasive No radiation No contrast agent required	High level of expertise required High inter-observer variability RRI is affected by the presence of hypotension, arrhythmias, and kidney diseases



- Recent advancements in ASCVD management focus on identifying at-risk individuals and plaque regression strategies.
- ASCVD can manifest without traditional risk factors, necessitating a paradigm shift in preventive approaches.
- Targeting plaque progression rather than just traditional risk factors is crucial for preventing adverse events.
- Personalized medicine, advanced imaging, and biomarker research offer new avenues for refining risk stratification.
- Integrating genetic, imaging, and biomarker data, alongside AI tools, promises to optimize cardiovascular risk management.

Conflict of Interest

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