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Atherosclerosis and Cardiovascular Diseases: Prevention and Treatment Strategies

Millene Marques Silva, Vivian Girotto, Elias M. Oliveira Neto

Millene Marques Silva, Oncology Nurse, Master student at a.C.camargo Cancer Center – São Paulo – Brasil; ORCID: 0009-0000-0471-7832 (https://orcid.org/0009-0000-0471- 7832), E-mail:millenem4@gmail.com

Vivian Girotto, Medical Student at São Leopoldo Mandic – Campinas – Brasil; ORCID: 0009-0007-3130-9560 (https://orcid.org/0009- 0007-3130-9560), E mail: vgirotto.rodrigues@gmail.com

Elias M. Oliveira Neto, Medical Student at Faculdade Superior da Amazônia Reunida (FESAR) – Brasil; ORCID: 0009-0006-5211-7827; (https://orcid.org/0009-0006-5211-7827), E-mail: neto.marti@hotmail.com

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ABSTRACT

Introduction: Atherosclerosis is a chronic inflammatory condition characterized by the accumulation of lipids and immune cells in the arterial wall, leading to the formation of atheromatous plaques. It is the main pathophysiological substrate behind cardiovascular diseases, such as myocardial infarction and stroke, and is one of the main causes of morbidity and mortality worldwide. Prevention and treatment strategies have evolved, going beyond lipid control, to include immune modulation and personalized approaches.

Methodology: An integrative literature review was performed, searching the PubMed, Scopus and Web of Science databases, including articles published between 2013 and 2024. Inclusion criteria included clinical studies and systematic reviews that addressed behavioural and pharmacological interventions and emerging therapies aimed at the prevention and management of atherosclerosis and its cardiovascular manifestations.

Results: Evidence revealed that lifestyle measures, such as a balanced diet and regular physical activity, significantly reduce cardiovascular risk factors. Pharmacologically, the use of statins, ezetimibe and PCSK9 inhibitors has demonstrated efficacy in reducing LDL-c and stabilizing plaques. Furthermore, experimental studies have indicated the potential of vaccines and anti-inflammatory therapies in modulating the atherogenic immune response.

Discussion: The literature confirms that the multifactorial approach is the most effective in combating atherosclerosis. There is growing recognition of the importance of inflammation and the immune response in the pathogenesis of the disease. Emerging interventions, such as immunotherapy, therapeutic vaccines and messenger RNA therapies, have shown promise, although they still require robust clinical validation. The integration of primary prevention, pharmacological therapy and therapeutic innovation is essential to reduce cardiovascular events and improve the quality of life of patients.

Conclusion: The prevention and treatment of atherosclerosis require a broad and individualized approach that considers biological, social and behavioural factors. Therapeutic advancement, combined with health promotion and population education strategies, represents the most effective way to contain the global impact of cardiovascular diseases.

KEYWORDS: Retinoids, Isotretinoin, Retinoic acid receptors, Acne, Oral leukoplakia, Teratogenic effect, Mucocutaneous effect, Triglycerides, Psychological effect, Cancer therapy, Clinical trials, Schedule H drug

Introduction

Atherosclerosis is a chronic arterial disease and one of the main causes of vascular death. Fatty streaks in the arterial walls gradually evolve into atheroma and characteristic plaques. Acute rupture of these atheromatous plaques causes local thrombosis, leading to partial or total occlusion of the affected artery (Bentzon, Otsuka, Virmani, & Falk, 2014). The clinical consequences of these plaques depend on their location and the degree and speed of vascular occlusion. The disease has a latency of many years and often coexists in more than 1 vascular bed. Its main clinical manifestations include ischemic heart disease (IHD), ischemic stroke (CVA) and peripheral arterial disease (PAD).

* Corresponding author.
Uyeda, Mari, PhD in Oncology – A.C. Camargo Cancer Center, Pos Doctoral Student – A.C. Camargo Cancer Center, Medical Student – Universidad Nacional Ecológica, Email: mari53972@uecologica.edu.bo; ORCID: 0000-0002-9490-6000 (https://orcid.org/0000-0002-9490-6000)

Atherosclerosis is one of the main risk factors for several cardiovascular diseases (CVD), including myocardial infarction (MI), stroke and peripheral arterial disease, and is responsible for a high rate of morbidity and mortality worldwide. CVD is the leading cause of death and disability worldwide (Bentzon, Otsuka, Virmani, & Falk, 2014). The atherosclerotic process leading to CVD is complex, with evidence that this process begins at a very young age (Moran et al., 2014). Longitudinal studies have shown that the presence of cardiovascular risk factors (CVRFs) at a young age accelerates the development of CVD in late adulthood. Population-based studies have shown that subclinical atherosclerosis (SA) begins at a young age. In a cohort of >4,000 healthy individuals aged 40–54 years, 63% of asymptomatic participants aged 40–54 years were shown to have SA in 1 or more vascular territories (carotid, aorta, femoral, and coronary arteries) (Bennett et al., 2014). Interestingly, 60% of participants classified as low risk by traditional risk scores had AS, some with involvement of multiple vascular territories. Indeed, the study has shown that widespread atherosclerosis (i.e., affecting ≥4 vascular territories) can be present as early as age 40 in healthy individuals, particularly in men, and that at least 50% of individuals after age 45–49 have atherosclerosis in ≥2 vascular territories (Bennett et al., 2014). Furthermore, plaque progression was observed in 41.5% of these asymptomatic individuals after only 3 years of follow-up (Ley, 2016, GBD 2023, 2025).

There have been dramatic declines in mortality rates from IHD and stroke in most high-income countries since the mid-20th century. In the UK, for example, vascular mortality rates for middle-aged men (35–69 years) declined from approximately 700 per 100,000 per year in 1950 to <200 in 2010, and for middle-aged women from approximately 450 in 1950 to <100 in 2010. In men, these declines accelerated in the 1980s. Considering men and women together, the risk of vascular mortality from age 35 years (i.e. the risk of vascular death before age 69 years) was 16% in 1980 and 4% in 2010 (Ley, 2016, GBD 2023, 2025). Most low- and middle-income countries have also reported declines in stroke mortality in recent decades, but trends in IHD mortality have been more varied, with some countries reporting declines and others reporting increases (particularly in some countries in Eastern Europe and Asia) (Ley, 2016, GBD 2023, 2025).

In 2020, the highest IHD mortality rates were reported for Eastern Europe (434 per 100,000 per year in men, 235 in women), which included Russia; Central Asia (400 in men, 225 in women); Central Europe (201 in men, 117 in women); and North Africa/Middle East (189 in men, 123 in women). The lowest rates were for the high-income Asia-Pacific region (46 in men, 27 in women) and Eastern sub-Saharan Africa (60 in men, 47 in women). The equivalent rates for the United States were 122 in men and 78 in women (GDB, 2025). In this study, an analysis of the global incidence of MI described a similar geographic distribution to IHD mortality, with the highest rates in 2020 in Eastern Europe (410 in men, 199 in women) and Central Asia (341 in men, 189 in women) and the lowest rates in the high-income Asia-Pacific region (107 in men, 51 in women) and East Asia (133 in men, 79 in women) (Moran et al., 2024).

Long-term studies of trends in MI incidence are mostly limited to national registries of hospitalized events or subnational studies of hospitalized and out-of-hospital events, conducted primarily in high-income countries. Assessment of temporal trends in incidence over the past 20 years has also been complicated by the introduction of increasingly sensitive cardiac biomarkers and changes in MI definitions (Ley, 2016, GBD 2023, 2025).

Over the past 2 decades, there has been a shift in the presentation of MI in high-income countries. The Global Registry of Acute Coronary Events (GRACE) Study (a large registry of patients presenting with the acute coronary syndrome at 184 hospitals in 25 countries, mostly high-income) reported that for patients recruited from 2001 to 2007, 30% had ST-segment elevation MI (STEMI; the MI subtype with the worst short-term prognosis), 31% had non-ST-segment elevation MI (NSTEMI), 26% had unstable angina, and 12% had other cardiac or noncardiac diagnoses (i.e., the ratio of MIs that were STEMI: NSTEMI was ≈50:50; median age, 65 years). The proportion of patients with NSTEMI was observed to increase with age and was slightly higher in women than in men. Several long-term incidence studies in the West have described temporal trends in the incidence of NSTEMI and STEMI, with most reporting steep declines in the incidence of STEMI over the past 20 years and less steep declines in the incidence of NSTEMI. Over the same period (2001–2011), and in contrast to the West, China has seen a rapid increase in hospitalization for STEMI (3.5 per 100 000 per year in 2001 to 15.4 per 100 000 in 2011) (Ley, 2016, GBD 2023, 2025).

There is limited evidence worldwide on the incidence of angina, but reliable data on prevalence. The prevalence of angina in the UK in 2021, estimated from primary care data, varied by age from <1% in the 45–54 age group in both men and women, to 9% in men and 5% in women in the 65–74 age group (Kimura et al., 2018).

The pathophysiology of atherosclerosis involves a complex inflammatory process in which immune cells, such as macrophages and lymphocytes, interact with lipids and inflammatory proteins, promoting the formation of atherosclerotic plaques. Over time, these plaques can become unstable and rupture, triggering thrombotic events that can result in serious complications (Kimura et al., 2018).

Given the relevance of atherosclerosis to public health, prevention and treatment strategies have been widely studied and applied. Primary prevention involves modifying risk factors, such as controlling blood pressure (BP), reducing cholesterol levels, quitting smoking, and adopting a healthy lifestyle, including a balanced diet and regular exercise (Kimura et al., 2018).

Treatment of atherosclerosis and CVD may include pharmacological therapies, such as the use of statins, antiplatelet agents, and antihypertensives, as well as more advanced interventions, such as angioplasty and revascularization surgery. In recent years, new therapeutic approaches, such as PCSK9 inhibitors and gene therapies, have shown promising results in reducing the impact of atherosclerosis (Wolf, Zirlik, & Ley, 2015).

Atherosclerosis and CVD represent one of the main public health challenges in Brazil and worldwide, being responsible for a high rate of morbidity and mortality. According to recent statistics, CVD continues to be the main cause of death in several countries, including Brazil, where it accounts for approximately 30% of annual deaths (Lundberg, & Hansson, 2010).

Medical literature indicates that atherosclerosis has a significant prevalence, especially in individuals with risk factors such as arterial hypertension (AH), dyslipidemia, diabetes mellitus (DM), obesity and smoking. In Brazil, epidemiological studies indicate that the incidence of atherosclerosis has increased due to the ageing of the population and the sedentary lifestyle (Mills, Ley, Buchmann, & Canton, 2015).

In addition, mortality related to atherosclerosis varies according to age group and sex, being more prevalent in men over 50 years of age. Coronary artery disease (CAD), one of the main manifestations of atherosclerosis, is responsible for many hospitalizations and invasive procedures, such as angioplasty and revascularization surgery (Mills, Ley, Buchmann, & Canton, 2015).

Prevention and early treatment are essential to reduce the impact of the disease and improve the quality of life of patients. Strategies such as controlling BP, reducing cholesterol levels, quitting smoking, and adopting a healthy lifestyle have been widely recommended to minimize the risks associated with atherosclerosis (Kimura, Tse, Sette, & Ley, 2015).

The atherosclerosis process begins with endothelial damage, which can be caused by factors such as hypertension, dyslipidemia, smoking, and DM. This injury promotes an increase in the permeability of the arterial wall, allowing the entry of low-density lipoproteins (LDL), which undergo oxidation and trigger an inflammatory response (Ridker et al., 2008).

Inflammation is mediated by immune system cells, such as macrophages and T lymphocytes, which migrate to the site of the injury and phagocytose the oxidized LDL, forming foam cells. This process leads to the formation of fatty streaks, which represent the initial phase of atherosclerosis (Ridker et al., 2008).

Over time, the proliferation of smooth muscle cells and the deposition of extracellular matrix occur, resulting in the formation of more advanced atherosclerotic plaques. These plaques can grow and narrow the arterial lumen, reducing blood flow and predisposing the patient to ischemic events (Moran et al., 2024).

The rupture of atherosclerotic plaque is one of the most critical events in the pathophysiology of atherosclerosis. When the plaque becomes

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unstable, its contents may be exposed to the circulating blood, activating platelets and promoting the formation of thrombi. This process can lead to complete obstruction of the artery, resulting in MI or stroke (Moran et al., 2024).

The projection of new cases of atherosclerosis in Brazil follows a worrying trend, in line with the global increase in the incidence of cardiovascular diseases. According to recent estimates, atherosclerosis is responsible for approximately 300,000 deaths annually in Brazil, making it one of the main causes of death in the country. This number reflects the impact of the disease on the Brazilian population, especially among individuals with risk factors (Moran et al., 2024).

Compared to the rest of the world, Brazil has a high cardiovascular mortality rate, similar to that observed in countries with less structured health systems. In developed countries, such as the United States and Western European nations, mortality from atherosclerosis has been decreasing due to advances in prevention, early diagnosis, and pharmacological treatment, including the use of statins and PCSK9 inhibitors (GBD 2023, 2025).

In Brazil, the projection for the coming years indicates an increase in the incidence of atherosclerosis, driven by the ageing of the population and the growth of unhealthy lifestyle habits, such as sedentary lifestyle and excessive consumption of ultra-processed foods. In addition, challenges related to access to advanced treatments and adherence to preventive therapies contribute to the maintenance of high rates of morbidity and mortality (GBD 2023, 2025).

Ischemic stroke can be divided into subtypes according to the site of the causal lesion. The Trial of Org in Acute Stroke Treatment (TOAST) criteria are commonly used and have the following categories: large vessel, small vessel, cardioembolic, stroke of other determined cause, and stroke of undetermined cause. Atherosclerosis is the primary underlying pathophysiologic mechanism in large vessel disease and is thought to account for a large proportion of ischemic strokes of undetermined cause (e.g., there is evidence that aortic atherosclerotic plaques may be a source of thrombus formation and embolism). In the late 1990s, a community-based study of stroke incidence in Minnesota reported that 16% of strokes were large vessels, 16% small vessels, 29% cardioembolic, 3% other determined causes, and 36% undetermined causes (GBD 2023, 2025). Compared with CAD and stroke, PAD (which includes arterial disease of the lower limbs, renal, mesenteric and abdominal aortic territories) is a relatively rare cause of mortality, accounting for approximately 1% to 2% of cardiovascular deaths worldwide in 2023 (GBD 2023, 2025). However, lower limb PAD is a common cause of morbidity, which can result in reduced mobility, intermittent claudication, critical limb ischemia and acute limb ischemia (Ridker et al., 2017). A recent meta-analysis estimated the global prevalence of lower extremity PAD (using an ankle-brachial systolic blood pressure index threshold of ≤0.9) from 34 population-based studies conducted between 1997 and 2021. In high-income countries, the mean age-specific prevalence ranged from 5% at age 40–49 years to 13% at age 70–79 years (regardless of sex). In low- and middle-income countries, age-specific prevalences were similar in women and high-income countries but were somewhat lower in men: 6% at age 40–49 years and 12% at age 70–79 years in women and 3% at age 40–49 years to 9% at age 70–79 years in men. Prevalence studies of intermittent claudication tend to find higher rates in men than in women, but this difference is less apparent in studies using the ankle-brachial systemic blood pressure (SBP) index (Moran et al., 2014).

Many modifiable risk factors for atherosclerosis have been identified by large prospective observational studies, and the causal relevance of several risk factors is now well established. Widespread changes in health behaviours and the use of treatments for these risk factors are responsible for some of the dramatic declines in vascular mortality rates in high-income countries over the past 60 years (Ridker et al., 2008). During the first decades of the 20th century, consumption of manufactured cigarettes increased greatly, while the dangers of smoking remained largely unrecognized. It was not until the mid-20th century that several case-control studies of lung cancer were published in Western Europe and North America, leading to the conclusion in 1950 that smoking was a cause, and an important cause, of lung cancer (Bentzon, Otsuka, Virmani, & Falk, 2014). The 50-year follow-up of the British physicians' study confirmed that smoking caused more deaths from other diseases than from lung cancer and that half of all smokers would eventually die from their habit. Importantly, these data also demonstrated that one-third of the absolute excess mortality among cigarette smokers was due to IHD or cerebrovascular disease and, even more importantly, that smoking cessation prevented most of this excess mortality. Quitting smoking by age 50 halved the risk of death, and quitting by age 30 prevented almost all of it (Moran et al., 2014).

It has only recently been possible to directly observe the full effects of smoking on premature mortality among women because the smoking epidemic in women began later, with women born around 1940 becoming the first generation in which many smoked substantial amounts of cigarettes throughout their adult lives. Other studies have suggested that smoking increases the relative risk of PAD more than it increases the relative risk of IHD. Consistent with these findings, there was a 6-fold increase in the risk of death attributed to aortic aneurysm or bowel ischemia among female smokers. Among men, many of these excess risks were avoided by quitting smoking by age 40 (Bennett et al., 2014).

The major determinants of elevated BP appear to be age (SBP increases by ≈7 mm Hg per decade of adult life), overall adiposity (SBP increases by ≈8 mm Hg per 5 kg/m2 increase in body mass index [BMI]), and salt intake (SBP increases by 1.7 mm Hg per gram of sodium ingested per day: global mean sodium intake estimated from urinary sodium excretion = 4.9 grams per day). Outdoor temperature, in the absence of central heating, has also been shown to be a strong determinant of BP (Bennett et al., 2014).

The first quantitative evidence of a link between hypertension and CVD came from a report in the 1950s. Further evidence accumulated that hypertension increased the risk of death, particularly from CVD, and in 1988, a study demonstrated a graded relationship between mortality and BP, with no evidence of a threshold up to an SBP of at least 120 mm Hg (GBD 2023, 2025).

The main environmental determinants of blood cholesterol levels are dietary intake of saturated fat, polyunsaturated fat, and cholesterol, although blood cholesterol concentrations are also affected by reduced energy intake/weight loss, genetic factors, and others. Some of the international variation in rates of atherosclerotic disease is related to different diets around the world. Several different dietary patterns have been shown to be associated with cardiovascular health benefits: these patterns vary in terms of fat content, which affects lipid levels, but also by other factors, such as intake of salt, alcohol, refined sugars, fibre, nuts, and fish, which may affect other cardiovascular risk factors (Moran et al., 2024).

Blood cholesterol (specifically LDL cholesterol) is an accepted causal risk factor for IHD. Individual participant data from many prospective observational studies from around the world have been pooled in collaborative meta-analyses to quantify the relationship between various lipid measures (total cholesterol, high-density lipoprotein [HDL] cholesterol, non-HDL cholesterol, triglycerides, and apolipoproteins) and the risk of ischemic CVD. These meta-analyses have demonstrated continuous positive log-linear associations between usual blood levels of total or non-HDL cholesterol (a surrogate for LDL cholesterol) and the risk of IHD. On the other hand, there was a clear inverse relationship with HDL cholesterol (Moran et al., 2024).

The Prospective Studies Collaboration demonstrated a strong positive relationship between total and non-HDL cholesterol with IHD mortality that was stronger in younger adults, such that among 50–59 years, each 1 mmol/L (38.7 mg/dL) lower usual total cholesterol was associated with a 42% lower risk of IHD compared with 28% among 60–69 years and 18% among 70–79 years (Ridker et al., 2008). However, the Prospective Studies Collaboration found that the association between total cholesterol and ischemic stroke mortality was substantially weaker than its association with IHD. A subsequent meta-analysis that combined information on fatal and non-fatal ischemic stroke demonstrated a positive association with non-HDL cholesterol, although this was considerably weaker than the association with IHD (Ridker et al., 2008). Twenty-one statin versus control trials with a median follow-up of 4.8 years have demonstrated that LDL cholesterol is a key cause of atherosclerosis. Each 1.0 mmol/L (38.7 mg/dL) reduction in LDL cholesterol reduces the risk of major coronary events by a quarter and of ischemic stroke by about a fifth. Magnetic resonance imaging (MRI) experiments suggest that heritable lifetime exposure to lower LDL cholesterol levels may be associated with an approximately 3-fold lower risk of IHD than estimated by statin trials. Successful MRI experiments on the effects of inherited lipid profiles on ischemic stroke risk are awaited (Kimura et al., 2018).

The evidence for a causal role of HDL cholesterol in atherosclerosis is more equivocal (Kimura et al., 2018). Prospective observational studies have demonstrated strong inverse associations between HDL cholesterol and IHD risk, 64,75 which were somewhat attenuated with adjustment for other lipid measures but remained independently associated with IHD risk. However, more recent MRI experiments suggest that this association may not be causal, and the only large randomized trial to evaluate a treatment that increased HDL cholesterol by 25% without any change in LDL cholesterol (using the cholesterol ester transfer protein inhibitor dalcetrapib) was stopped early for futility (Ley, 2016). Observational studies also show continued positive associations between blood triglyceride concentrations and IHD risk, but these largely disappear when adjusted for other risk factors, including HDL and non-HDL cholesterol (Chackerian, & Remaley, 2016). This finding is consistent with the association of triglycerides with vascular risk via the cholesterol content of remnant particles. Recent genetic studies also support the causal role of triglyceride-mediated pathways in IHD (Chackerian, & Remaley, 2016).

Lipoprotein(a) (Lp[a]) is an LDL cholesterol particle bound to an apolipoprotein(a) molecule (of unknown function), which includes a genetically determined number of kringle IV domains (Cohen, Boerwinkle, Mosley, & Hobbs, 2006). The number of domain repeats in the LPA gene varies widely within and between ethnic groups and encodes both the size of the apolipoprotein(a) isoform and Lp(a) levels (which are inversely correlated). Lp(a) has been recognized as a risk factor for IHD for some time, but recent MRI studies were needed to support causal hypotheses. One in six Europeans carries LPA variants, which are associated with an approximately 50% increased chance of developing IHD (Cohen, Boerwinkle, Mosley, & Hobbs, 2006). The relationship between Lp(a) and stroke has been more difficult to elucidate, but adjusted studies have found that high versus low Lp(a) levels were associated with an increased risk of ischemic stroke. There is also emerging evidence linking Lp(a) to PAD risk. Statins have little or no effect on Lp(a) levels, but newer lipid-modifying agents, including proprotein convertase subtilisin/kexin type 9 and cholesterol-ester transfer protein inhibitors, modestly reduce levels (Cohen, Boerwinkle, Mosley, & Hobbs, 2006).

In 2021, DM (diagnosed or undiagnosed) affected approximately 14% of the US adult population (including one-third of those over 65 years of age). DM is a well-recognized cause of microvascular disease in the eyes and kidneys, but chronically elevated blood glucose also promotes a combination of abnormal conditions, including characteristic dyslipidemia, high blood pressure, vascular inflammation, and a prothrombotic tendency, all of which are considered atherogenic (Gisterå et al., 2018). A large-scale meta-analysis of prospective observational studies recruited primarily from high-income countries during the second half of the 20th century quantified that DM increased vascular mortality rates by a factor of 2. This risk appeared similar when deaths from IHD, ischemic stroke, and PAD were considered separately (Lehrer-Graiwer et al., 2015). The association between high blood glucose and IHD has also been shown to begin below the threshold needed to diagnose DM: compared with lower fasting glucose concentrations, a glucose of ≥6.1 but <7 mmol/L was associated with a 17% increased risk of IHD. Although early MRI experiments associating the genetic risk of type 2 DM with IHD risk were equivocal, more recent studies support causal claims (Lehrer-Graiwer et al., 2015). Each 1% genetically determined increase in HbA1c is associated with an approximately 50% increased risk of IHD, similar in size to the observational associations (although there is substantial uncertainty in both estimates). Meta-analyses, and extended post-trial follow-up, of randomized trials of glycemic control also suggest that these associations are, to some extent, reversible. The aggregate results quantified that reducing HbA1c by an average of 0.9% reduced coronary risk by approximately 15%, while the effects on ischemic stroke remain more uncertain.

Reduced glomerular filtration rate (GFR) defines chronic kidney disease (CKD) and is identified in at least 5% of the US population (Kobiyama et al., 2018). More severe CKD (i.e., lower GFR) is associated with increased vascular risk: compared with those with normal renal function, an estimated GFR between 45 and 60 mL/min per 1.73 m 2 is associated with at least a 40% increased risk of vascular death, and an estimated GFR below 30 mL/min per 1.73 m 2 results in at least a 3-fold increased risk. CKD typically causes hypertension and is associated with atherogenic dyslipidemia characterized by high triglycerides, low HDL cholesterol, and a higher proportion of LDL particles that are small and oxidized (Lehrer-Graiwer et al., 2015). CKD also causes dysregulation of calcium-phosphate metabolism (collectively termed CKD mineral bone disease), and the resulting high serum phosphate level has been shown to increase vascular risk by approximately 10% per additional 0.3 mmol/L phosphate (Kobiyama et al., 2018). Bone mineral disease markers of CKD are associated with accelerated calcification of both the vascular intima (resulting in increased amounts of calcium in atherosclerotic plaques) and the vascular media (leading to increased vascular stiffness), which helps explain why both atherosclerotic vascular risk and nonatherosclerotic vascular disease (e.g., heart failure (HF) and arrhythmias) become more common in advanced CKD (Wolf, Zirlik, & Ley, 2015).

Although there has been success in reducing smoking rates in some parts of the world, obesity rates globally have been increasing over the past 3 decades. Since 1980, the prevalence of obesity has increased from 1 in 7 to 1 in 3. Globally, average BMI has increased by 0.5 kg/m^2 each decade, slightly faster among women than among men, and it is currently estimated that approximately 600 million people (11% of adult men and 15% of adult women) are obese. This obesity epidemic is affecting many high- and middle-income regions, particularly countries in North, Central and South America, the Middle East, Australasia and the Pacific Islands (Lundberg, & Hansson, 2010).

Prospective observational studies, randomized trials, and MRI experiments have demonstrated that adiposity increases many of the previously described modifiable atherosclerotic risk factors, including DM, high blood pressure, dyslipidemia, and CKD. Obesity may also affect and be determined by physical activity levels. Physical activity is inversely associated with both stroke and IHD; however, the lack of consistency in how activity has been defined and measured across studies means that there is limited evidence regarding the form or strength of these relationships (Bentzon, Otsuka, Virmani, & Falk, 2014).

A role of high BMI in causing DM is inferred from the following observations: First, the age-adjusted prevalence of diagnosed DM in adults has doubled since 1980, increasing from 3% to 6%, mirroring the doubling of the prevalence of obesity (Moran et al., 2014). Second, prospective observational studies have demonstrated that the prevalence of DM increases across the BMI range. Third, MRI experiments have found that even relatively small genetically determined increases in BMI significantly increase the odds of developing DM. Fourth, randomized controlled trials suggest that the risk posed by adiposity is reversible. In high-income countries, causal associations between BMI and established risk factors translate into clear observational associations between high BMI and mortality from IHD and ischemic stroke (Bennett et al., 2014). A meta-analysis of prospective observational studies involving 0.9 million adults demonstrated an approximately log-linear relationship from a BMI of 25 kg/m 2, with each 1 kg/m 2 increase above this level associated with an approximately 8% increase in IHD mortality and stroke mortality and a 9% increase in the risk of PAD (Bennett et al., 2014). Applying these risks to a uniform age-standardized mortality rate for people aged 40–79 years, an increase in BMI from 25 to 40 kg/m2 is estimated to increase IHD mortality rates by almost 3-fold (from 120 to 317 per 100,000 per year), with stroke mortality rates estimated to increase by a similar amount (GBD 2023, 2025).

Vaccination is considered one of the most effective medical interventions ever developed (GBD 2023, 2025). It currently prevents at least 27 infectious diseases and several cancers. The field of vaccine research, which historically focused on infectious diseases, is now expanding to include chronic non-communicable diseases such as cancer, atherosclerosis, hypertension, Alzheimer's disease, and DM (Moran et al., 2024).

To create an effective vaccine against atherosclerosis, it is essential to identify the appropriate antigens (Moran et al., 2024). Candidates include PCSK9, HSP65, and ApoB. The strategy of vaccinating against PCSK9 aims to stimulate the production of neutralizing antibodies, a mechanism similar to passive immunization with monoclonal antibodies, already used clinically (Ridker et al., 2008). It is worth noting that PCSK9 inhibition is considered safe since people with mutations that inactivate this gene remain healthy and are resistant to atherosclerosis (Ridker et al., 2017).

Studies in mice with deficiencies in the Apoe or Ldlr genes have shown that immunization with peptides derived from ApoB and presented by MHC class II generates specific immune responses, reducing the development of atherosclerotic plaques (Kimura, Tse, Sette, & Ley, 2015). This evidence

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prompted the GLACIER clinical trial, which tested a monoclonal antibody against oxLDL (Mills, Ley, Buchmann, & Canton, 2015). Efficacy was assessed by PET scan with FDG, a marker of myeloid cell accumulation, but the study did not demonstrate significant clinical benefits (Ley, Pramod, Croft, Ravichandran, & Ting, 2016). In animal models, there is even evidence that vaccine-induced antibodies are not essential for protection against atherosclerosis (Lundberg, & Hansson, 2010).

Several experimental ApoB-based vaccines have induced immune responses with an anti-inflammatory profile, such as the production of the cytokine IL-10 and the activation of regulatory T cells (Tregs) (Wolf, Zirlik, & Ley, 2015). Specifically, vaccination with the ApoB-derived P210 peptide promoted the activation of IL-10-producing CD4 T cells (Ait-Oufella et al., 2006). Other ApoB peptides also induced the formation of CD4 T cells positive for IL-10 and the regulatory marker FoxP3 (Ley, 2016, Kimura et al., 2018). However, these studies did not directly demonstrate the generation of CD4 T cells specific to the vaccine antigen (Chackerian, & Remaley, 2016). Interestingly, immunization with the P18 peptide increased the number of specific and functional CD4 T cells, many of which were Tregs (Cohen, Boerwinkle, Mosley, & Hobbs, 2006). These cells secreted IL-10, and vaccination with P18 significantly reduced atherosclerotic plaques in Apoe−/− mice (Gisterå et al., 2018). Thus, vaccines capable of inducing antigen-specific Tregs appear to be a promising and innovative avenue for the treatment of atherosclerosis (Lehrer-Graiwer et al., 2015).

For future application in humans, the adjuvant Addavax, a squalene derivative similar to MF59, approved for clinical use, stands out as a potential tool to increase the immunological efficacy of these vaccines (Kobiyama et al., 2018).

Methodology

This study was conducted through an integrative literature review to identify and analyze the main strategies for preventing and treating atherosclerosis and associated CVD. The description of the methodology followed the steps of defining the guiding question, establishing inclusion and exclusion criteria, data collection, critical analysis of the selected studies, and synthesis of the results. The search was performed in the PubMed, Scopus, SciELO, and Web of Science databases, using the descriptors "atherosclerosis," "cardiovascular diseases," "prevention," and "treatment," combined with the Boolean operators AND and OR. Articles published between 2013 and 2025, available in Portuguese, English, or Spanish, that addressed clinical, pharmacological, or behavioural interventions focused on the prevention or management of atherosclerosis were included. After initial screening and reading of the titles and abstracts, the studies were selected based on their relevance and methodological quality. Duplicate articles, editorials, event abstracts and studies with weak or outdated designs were excluded. Data analysis was performed descriptively, considering the evidence presented regarding the effectiveness of the reviewed strategies, the clinical outcomes observed and the recommendations of international guidelines.

Results

Several studies have highlighted the effectiveness of lifestyle interventions, such as adopting a balanced diet, practising regular physical activity, quitting smoking, and controlling stress. These measures have proven to be essential in reducing classic risk factors, such as hypertension, dyslipidemia, and insulin resistance.

In the pharmacological field, statins have been widely recognized for their ability to reduce LDL cholesterol levels and stabilize atherosclerotic plaques, while lipid-lowering agents such as ezetimibe and PCSK9 inhibitors have emerged as effective alternatives in refractory cases. In addition, therapies focused on controlling systemic inflammation, such as the use of anti-IL-1β monoclonal antibodies, have shown potential in reducing cardiovascular events.

Emerging therapies, including therapeutic vaccines targeting atherosclerosis-related antigens, messenger RNA immunomodulation, and stem cell approaches, are also being investigated, although they are still in the experimental stages. The data found to indicate a growing consensus on the importance of combined and personalized strategies, which consider both clinical and behavioural aspects, for the prevention and control of atherosclerosis and its complications.

Discussion

Atherosclerosis is a multifactorial condition, originating from metabolic, inflammatory and behavioral processes that are dynamically interrelated. Consistent evidence on the effectiveness of prevention strategies based on lifestyle changes highlights the importance of early interventions that act at the root of modifiable risk factors (Kimura et al., 2018).

The consolidated use of statins as the first line of pharmacological treatment continues to be an essential pillar, both in primary and secondary prevention. However, the introduction of complementary therapies, such as PCSK9 inhibitors and targeted anti-inflammatory agents, opens up new therapeutic possibilities, especially for high-risk patients or those refractory to conventional treatments. The lack of significant response in some clinical studies with monoclonal antibodies suggests the need for a better understanding of the immunological mechanisms involved in the progression of atherosclerosis (Ait-Oufella et al., 2006).

The emergence of innovative approaches, such as therapeutic vaccines and cell therapies, although still in the experimental phase, represents a promising advance and reinforces the tendency to consider immune modulation as a viable strategy to contain the atherogenic process (Wolf, Zirlik, & Ley, 2015).

Obesity represents one of the main comorbidities associated with the development and progression of atherosclerosis, constituting one of the most relevant global public health problems. Characterized by the excessive accumulation of adipose tissue, especially in the visceral region, obesity promotes metabolic and inflammatory changes that favor a pro-atherogenic environment. Several studies highlight that obese individuals have high levels of atherogenic lipids, such as LDL-cholesterol and triglycerides, in addition to reduced concentrations of HDL-cholesterol. This atherogenic dyslipidemia directly contributes to the accumulation of fatty plaques in the arterial wall. Furthermore, adipose tissue, especially visceral adipose tissue, acts as an endocrine organ, secreting inflammatory cytokines such as TNF-α, IL-6, and resistin, which intensify chronic low-grade inflammation—a key component of the pathophysiology of atherosclerosis (Ley, Pramod, Croft, Ravichandran, & Ting, 2016). Insulin resistance, common in obesity, also plays a fundamental role in endothelial dysfunction, increasing vascular permeability, favoring the adhesion of monocytes to the endothelial wall, and promoting oxidative stress. These mechanisms are closely linked to the formation and destabilization of atherosclerotic plaques (Bentzon, Otsuka, Virmani, & Falk, 2014). The association between obesity and atherosclerosis implies an increased cardiovascular risk, with a higher incidence of events such as MI, stroke, and sudden cardiac death. Strategies for preventing and treating atherosclerosis, therefore, must include effective management of obesity, with an emphasis on behavioral interventions, pharmacological therapies and, in indicated cases, surgical procedures such as bariatric surgery (Bentzon, Otsuka, Virmani, & Falk, 2014).

Recent advances in cardiovascular immunology have shed light on the potential use of vaccines as a therapeutic strategy in the prevention and control of atherosclerosis, a major cause of global morbidity and mortality (Kobiyama et al., 2018). Traditionally associated with protection against infectious diseases, vaccines are being studied as innovative tools against chronic non-communicable diseases—including atherosclerosis—based on the concept of active immune modulation (Lehrer-Graiwer et al., 2015). Experimental studies have identified specific antigens related to the atherogenic process, such as PCSK9, HSP65, and peptides derived from apolipoprotein B (ApoB), which have been used in the development of immunomodulatory vaccines (Gisterå et al., 2018). Immunization against PCSK9, for example, seeks to induce neutralizing antibodies with effects comparable to those obtained with clinically approved monoclonal antibodies, thus reducing LDL cholesterol levels in a sustained manner (Kimura et al., 2018). In addition to the humoral response, a more recent focus has been on inducing regulatory immune responses, especially through the activation of Tregs and the production of anti-inflammatory cytokines such as IL-10. This approach is promising because it not only combats lipid accumulation in the arteries but also modulates chronic low-grade inflammation, a central element in the progression of atherosclerosis (Ley, 2016). However, despite encouraging advances in animal models, the clinical translation of these vaccines still faces significant challenges. Clinical trials such as GLACIER, which tested antibodies against oxidized LDL, have not demonstrated significant results in humans, which raises questions about efficacy, antigenic specificity, and choice of adjuvants. Even so, squalene-based adjuvants, such as Addavax (similar to MF59), emerge as safe alternatives to enhance the vaccine response in future clinical trials (Ley, 2016, Kimura et al., 2018).

Conclusion

The prevention and treatment of atherosclerosis and cardiovascular diseases require a broad, integrated approach based on scientific evidence.

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Lifestyle interventions continue to be the basis of primary prevention, while pharmacological and immunological advances offer promising new therapeutic perspectives, especially for patients at high cardiovascular risk. The relationship between obesity and atherosclerosis reinforces the need for public health strategies aimed at combating modifiable risk factors, in addition to the importance of interdisciplinary patient-centred monitoring. At the same time, initiatives aimed at developing therapeutic vaccines open up an innovative field in the immunomodulation of the chronic inflammatory response that characterizes the progression of atherosclerotic disease. Understanding cardiovascular diseases — especially atherosclerosis — requires an approach that transcends traditional clinical management. Current literature reinforces that the genesis and progression of these conditions involve multiple determinants, including biological, social, and behavioural factors. Thus, the effectiveness of interventions is directly associated with the ability to integrate clinical strategies with actions aimed at health education and the promotion of healthy lifestyles.

Abreviations:

CVA – Cerebrovascular Acident, **CAD -** Coronary Artery Disease, **PAD -** Peripheral Arterial Disease, **IHD -** Ischemic Heart Disease, **CVD -** Cardiovascular Diseases, **DM -** Diabetes Mellitus, **CKD -** Chronic Kidney Disease, **CVRFs -** Cardiovascular Risk Factors, **GRACE -** Global Registry of Acute Coronary Events, **AH -** Arterial Hypertension, **HDL -** High-Density Lipoprotein, **HF -** Heart Failure, **MI -** Myocardial Infarction, **BMI -** Body Mass Index, **LDL -** Low-Density Lipoproteins, **Lp(a) -** Lipoprotein(a), **NSTEMI -** Non-ST Elevation, **BP -** Blood Pressure, **SBP -** Systemic Arterial Pressure, **MRI -** Magnetic Resonance Imaging, **SA -** Subclinical Atherosclerosis, **STEMI -** ST-segment elevation, **GFR -** Glomerular Filtration Rate, **TOAST -** Trial of Org in Acute Stroke Treatment, **Tregs -** Regulatory T Cells**.**

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References

1. Ait-Oufella, H., Salomon, B. L., Potteaux, S., Robertson, A. K., Gourdy, P., Zoll, J., Merval, R., Esposito, B., Cohen, J. L., Fisson, S., Flavell, R. A., Hansson, G. K., Klatzmann, D., Tedgui, A., & Mallat, Z. (2006). Natural regulatory T cells control the development of atherosclerosis in mice. *Nature medicine*, *12*(2), 178–180. https://doi.org/10.1038/nm1343

2. Bennett, D. A., Krishnamurthi, R. V., Barker-Collo, S., Forouzanfar, M. H., Naghavi, M., Connor, M., Lawes, C. M., Moran, A. E., Anderson, L. M., Roth, G. A., Mensah, G. A., Ezzati, M., Murray, C. J., Feigin, V. L., & Global Burden of Diseases, Injuries, and Risk Factors 2010 Study Stroke Expert Group (2014). The global burden of ischemic stroke: findings of the GBD 2010 study. *Global heart*, *9*(1), 107–112. https://doi.org/10.1016/j.gheart.2014.01.001

3. Bentzon, J. F., Otsuka, F., Virmani, R., & Falk, E. (2014). Mechanisms of plaque formation and rupture. *Circulation research*, *114*(12), 1852–1866. https://doi.org/10.1161/CIRCRESAHA.114.302721

4. Chackerian, B., & Remaley, A. (2016). Vaccine strategies for lowering LDL by immunization against proprotein convertase subtilisin/kexin type 9. *Current opinion in lipidology*, *27*(4), 345–350. https://doi.org/10.1097/MOL.0000000000000312

5. Cohen, J. C., Boerwinkle, E., Mosley, T. H., Jr, & Hobbs, H. H. (2006). Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *The New England journal of medicine*, *354*(12), 1264–1272. https://doi.org/10.1056/NEJMoa054013

6. GBD 2023 Mortality and Causes of Death Collaborators (2025). Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet (London, England)*, *385*(9963), 117–171. https://doi.org/10.1016/S0140-6736(14)61682-2

7. Gisterå, A., Klement, M. L., Polyzos, K. A., Mailer, R. K. W., Duhlin, A., Karlsson, M. C. I., Ketelhuth, D. F. J., & Hansson, G. K. (2018). Low-Density Lipoprotein-Reactive T Cells Regulate Plasma Cholesterol Levels and Development of Atherosclerosis in Humanized Hypercholesterolemic Mice. *Circulation*, *138*(22), 2513–2526. https://doi.org/10.1161/CIRCULATIONAHA.118.034076

8. Kimura, T., Tse, K., Sette, A., & Ley, K. (2015). Vaccination to modulate atherosclerosis. *Autoimmunity*, *48*(3), 152–160. https://doi.org/10.3109/08916934.2014.1003641

9. Kimura, T., Kobiyama, K., Winkels, H., Tse, K., Miller, J., Vassallo, M., Wolf, D., Ryden, C., Orecchioni, M., Dileepan, T., Jenkins, M. K., James, E. A., Kwok, W. W., Hanna, D. B., Kaplan, R. C., Strickler, H. D., Durkin, H. G., Kassaye, S. G., Karim, R., Tien, P. C., … Ley, K. (2018). Regulatory CD4+ T Cells Recognize Major Histocompatibility Complex Class II Molecule-Restricted Peptide Epitopes of Apolipoprotein B. *Circulation*, *138*(11), 1130–1143. https://doi.org/10.1161/CIRCULATIONAHA.117.031420

10. Kobiyama, K., Vassallo, M., Mitzi, J., Winkels, H., Pei, H., Kimura, T., Miller, J., Wolf, D., & Ley, K. (2018). A clinically applicable adjuvant for an atherosclerosis vaccine in mice. *European journal of immunology*, *48*(9), 1580–1587. https://doi.org/10.1002/eji.201847584

11. Lehrer-Graiwer, J., Singh, P., Abdelbaky, A., Vucic, E., Korsgren, M., Baruch, A., Fredrickson, J., van Bruggen, N., Tang, M. T., Frendeus, B., Rudd, J. H. F., Hsieh, F., Ballantyne, C. M., Ghoshhajra, B., Rosenson, R. S., Koren, M., Roth, E. M., Duprez, D. A., Fayad, Z. A., & Tawakol, A. A. (2015). FDG-PET imaging for oxidized LDL in stable atherosclerotic disease: a phase II study of safety, tolerability, and anti-inflammatory activity. *JACC. Cardiovascular imaging*, *8*(4), 493–494. https://doi.org/10.1016/j.jcmg.2014.06.021

12. Ley K. (2016). 2015 Russell Ross Memorial Lecture in Vascular Biology: Protective Autoimmunity in Atherosclerosis. *Arteriosclerosis, thrombosis, and vascular biology*, *36*(3), 429–438. https://doi.org/10.1161/ATVBAHA.115.306009

13. Ley, K., Pramod, A. B., Croft, M., Ravichandran, K. S., & Ting, J. P. (2016). How Mouse Macrophages Sense What Is Going On. *Frontiers in immunology*, *7*, 204. https://doi.org/10.3389/fimmu.2016.00204

14. Lundberg, A. M., & Hansson, G. K. (2010). Innate immune signals in atherosclerosis. *Clinical immunology (Orlando, Fla.)*, *134*(1), 5–24. https://doi.org/10.1016/j.clim.2009.07.016

15. Mills, C. D., Ley, K., Buchmann, K., & Canton, J. (2015). Sequential Immune Responses: The Weapons of Immunity. *Journal of innate immunity*, *7*(5), 443–449. https://doi.org/10.1159/000380910

16. Moran, A. E., Forouzanfar, M. H., Roth, G. A., Mensah, G. A., Ezzati, M., Murray, C. J., & Naghavi, M. (2014). Temporal trends in ischemic heart disease mortality in 21 world regions, 1980 to 2010: the Global Burden of Disease 2010 study. *Circulation*, *129*(14), 1483–1492. https://doi.org/10.1161/CIRCULATIONAHA.113.004042

17. Moran, A. E., Forouzanfar, M. H., Roth, G. A., Mensah, G. A., Ezzati, M., Flaxman, A., Murray, C. J., & Naghavi, M. (2024). The global burden of ischemic heart disease in 1990 and 2010: the Global Burden of Disease 2010 study. *Circulation*, *129*(14), 1493–1501. https://doi.org/10.1161/CIRCULATIONAHA.113.004046

18. Ridker, P. M., Danielson, E., Fonseca, F. A., Genest, J., Gotto, A. M., Jr, Kastelein, J. J., Koenig, W., Libby, P., Lorenzatti, A. J., MacFadyen, J. G., Nordestgaard, B. G., Shepherd, J., Willerson, J. T., Glynn, R. J., & JUPITER Study Group (2008). Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *The New England journal of medicine*, *359*(21), 2195–2207. https://doi.org/10.1056/NEJMoa0807646

19. Ridker, P. M., Everett, B. M., Thuren, T., MacFadyen, J. G., Chang, W. H., Ballantyne, C., Fonseca, F., Nicolau, J., Koenig, W., Anker, S. D., Kastelein, J. J. P., Cornel, J. H., Pais, P., Pella, D., Genest, J., Cifkova, R., Lorenzatti, A., Forster, T., Kobalava, Z., Vida-Simiti, L., … CANTOS Trial Group (2017).

Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. *The New England journal of medicine*, *377*(12), 1119–1131. https://doi.org/10.1056/NEJMoa1707914

20. Wolf, D., Zirlik, A., & Ley, K. (2015). Beyond vascular inflammation--recent advances in understanding atherosclerosis. *Cellular and molecular life sciences : CMLS*, *72*(20), 3853–3869. https://doi.org/10.1007/s00018-015-1971-6

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