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REVIEW

Targeting Inflammation in Coronary Artery

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ABSTRACT: Atherosclerosis (AS) is a key contributor to ischemic heart disease, resulting in significant cardiovascular (CV) morbidity and mortality worldwide. Despite advancements in managing conventional risk factors, including the utilization of statins, recurrent adverse cardiovascular events remain prevalent, emphasizing the need for novel therapeutic strategies. This review explores the critical role of inflammation in the pathogenesis of coronary artery disease (CAD) and highlights potential atheroprotective approaches targeting inflammatory pathways. We discuss the multifaceted interplay between immune responses and AS, detailing the contributions of myeloid cells, T lymphocytes, and various cytokines in plaque formation and instability. Recent research suggests that inflammatory biomarkers, particularly high-sensitivity C-reactive protein (hs-CRP), serve as valuable predictors for CV events. Innovative therapies, including interleukin (IL)-1 and IL-6 inhibitors, colchicine, and statins, exhibit promise in mitigating inflammation-associated cardiovascular risks. Furthermore, emerging agents such as sodium-glucose transport protein 2 (SGLT2) inhibitors and natural compounds like Brazilian green propolis may enhance treatment outcomes. This review aims to highlight the central role of inflammation in CAD management and to outline future research directions focused on novel anti-inflammatory therapies that may improve clinical outcomes in patients at risk for cardiovascular events.

KEYWORDS: Coronary artery disease; inflammation; atherosclerosis; cardiovascular disease; cytokines; C-reactive protein

1 Introduction

Coronary artery disease (CAD) is a major global health concern, representing the leading cause of cardiovascular (CV) morbidity and mortality worldwide. It significantly contributes to healthcare expenditures and remains a prevalent condition despite advances in management strategies. Although there has been a notable reduction in the incidence of myocardial infarction due to radical alterations in conventional risk factors, such as the use of statins that inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase—which can decrease CV event risk by 20%–25% for every mmol/L drop in low-density lipoprotein cholesterol (LDL-C) [1,2]—the recurrence of adverse cardiovascular events following myocardial infarction continues to be a major challenge.

Emerging evidence underscores the critical role of inflammation in the pathogenesis of CAD. Epidemiological studies conducted since the 1990s have demonstrated a strong association between inflammatory processes and the risk of CV events in both primary and secondary prevention settings. Conditions

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characterized by significant inflammation, such as rheumatoid arthritis (RA), are particularly burdened by atherosclerosis, exemplifying the intricate link between inflammatory pathways and cardiovascular risk [3,4].

The innate and acquired immune responses are increasingly recognized as pivotal in the development and progression of atherosclerosis, influencing both plaque formation and stability. Given this understanding, there is an urgent need for novel therapeutic strategies targeting inflammation as a means to improve patient outcomes in CAD. This review aims to explore the impact of inflammatory processes on CAD and atheroprotective therapeutic approaches, including strategies for targeting inflammatory pathways [5,6].

2 The Central Role of Inflammation in CAD

2.1 Atherosclerosis as an Immune-Inflammatory Disease

Atherosclerotic (AS) lesions develop from lipid-immune inflammatory disorder, which is a chronic condition that has an impact on multiple body systems. Immune inflammatory disease affects the inner layer of blood vessels called the tunica intima. This disorder is linked to such widely known CV risk factors as diabetes mellitus (DM), tobacco use, high blood pressure, and high cholesterol [7,8]. The development of AS disease is conventionally explained by the deposition of lipids in the vessel walls. Aggregation of foam cells and consequent buildup of the lipid layer is, in fact, the first phase of the disease. However, this condition is often found in young subjects and not necessarily elderly patients. Further changes of this condition are difficult to predict, since it may equally likely stay unchanged or develop into an atherosclerotic plaque [9,10].

Studies suggest that there is evidence indicating the diverse roles of immune cells in various atherosclerosis patients, particularly through the concept of immune profiling. Innate immune cells, such as macrophages and neutrophils, contribute to plaque initiation and progression through inflammatory cytokine release and lipid uptake, while adaptive immune cells, including T and B lymphocytes, modulate chronic inflammation and plaque stability. Dendritic cells also participate by presenting antigens and shaping T cell responses within the vascular environment. Importantly, these immune cells display functional heterogeneity, with their activity and phenotype varying among patients depending on clinical status, metabolic conditions, and other individual factors [11]. It highlights how emerging single-cell data reveal specific tissue specialization of innate and adaptive immune cells within plaques compared to blood, suggesting that immune cell functions may differ among patients with distinct clinical statuses [12,13]. This variability points to the influence of factors such as age, sex, and accompanying metabolic diseases on immune cell roles in atherosclerosis, even though these relationships are not explicitly detailed [8].

Moreover, the discussion underlines the necessity of personalized treatment strategies grounded in patients' specific immune profiles. It emphasizes the importance of identifying new treatments tailored to restore immune cell functions for individual patients. The integration of immune monitoring in early-phase clinical trials and the selection of appropriate patient groups based on immune responses further reinforce the idea that personalized medicine approaches could enhance treatment efficacy for those with atherosclerosis [14]. In summary, while specific details about how immune cell functions vary with age, sex, or metabolic conditions are not provided, the complexity of immune responses in this condition and the vital need for personalized treatments based on individual immune profiles are underscored [15,16].

2.2 Immunological Mechanisms across Disease Stages

2.2.1 Early-Stage Immune Activation

In the context of atherosclerosis, specific immune molecules and pathways do indeed play varying roles at different stages of disease progression. In the early stages, modified endogenous molecules such as oxidized low-density lipoprotein (oxLDL) become crucial, providing antigens for antigen-presenting cells

and promoting the activation of adaptive immunity, particularly through T helper cells that release pro-inflammatory cytokines like interferon (IFN)-γ [17]. Cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-6 also play significant roles in early inflammation, facilitating the recruitment of immune cells to the plaque site. As atherosclerosis advances, macrophages become dominant in the lesions, and their function shifts depending on the local microenvironment and the type of signals they receive, influencing plaque stability or vulnerability [18,19]. In Fig. 1, we summarized the stages and key features of these stages of atherosclerosis development.

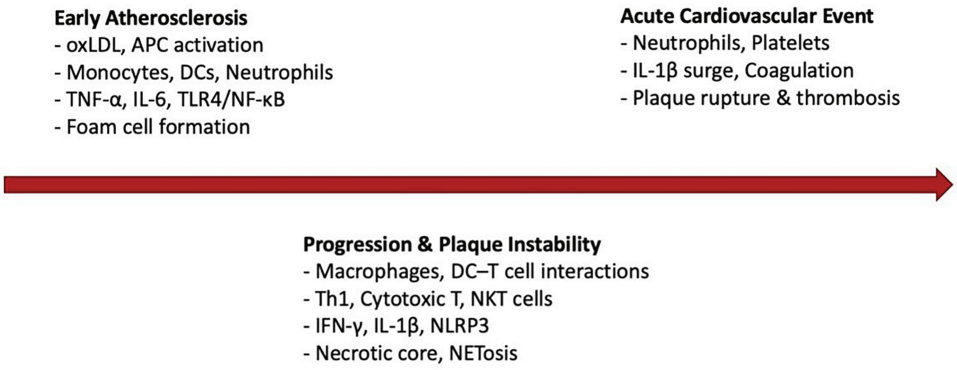

Figure 1: Key features of atherosclerosis development through the stages. oxLDL: Oxidized Low-Density Lipoprotein; APC: antigen-presenting cells; DCs: Dendritic Cells; TNF-α: Tumor Necrosis Factor-α; IL-6: Interferon-6; TLR4: Toll-like receptor 4; NF-κB: Nuclear Factor kappa-B; Th1: helper T cell 1; NKT: Natural killer T cell; IFN-γ: Interferon-gamma; NLRP3: NOD-like receptor family pyrin domain containing 3; NET: Neutrophil Extracellular Trap

2.2.2 Progression and Plaque Instability

During plaque rupture and cardiovascular events, the dynamics change as other immune cells, including T lymphocytes and neutrophils, contribute to the inflammatory milieu and can promote lesion instability [20,21]. For instance, cytotoxic T cells and natural killer T (NKT) cells release pro-atherogenic cytokines and participate in apoptosis within the plaque, reinforcing the risk of rupture. Neutrophils, while contributing to early endothelial dysfunction, are implicated in late-stage events, such as thrombosis and inflammation at the site of ruptured plaques, through mechanisms including the formation of neutrophil extracellular traps (NETs) [22,23].

The TLR4/NF-κB pathway plays a stage-specific role in atherosclerosis. During early disease, TLR4 activation promotes pro-inflammatory signaling, monocyte recruitment, and foam cell formation, accelerating plaque development. However, in later stages, controlled NF-κB activity may also contribute to tissue repair and resolution of inflammation. These dual roles suggest that TLR4/NF-κB inhibition may need to be phased or context-specific, with early suppression likely beneficial, whereas late-stage broad inhibition could impair healing, indicating the need for targeted or time-dependent approaches [24].

2.2.3 Acute Cardiovascular Events

Cytokines such as IL-1β also gain prominence in later stages, as the immune response can pivot toward a more destructive path, culminating in acute cardiovascular events. Thus, the interplay of cytokines and immune cells reflects a complex balance where specific immunological factors are pivotal at various stages, emphasizing the need for targeted therapeutic strategies that take into account the stage of atherosclerosis when addressing immune involvement [25,26].

3 Myeloid Cells

Myeloid cells are cells that are critical for the progression of AS disease. Among them are macrophages, dendritic cells (DC), monocytes, and granulocytes. After being recruited via an injured endothelial layer, monocytes are differentiated into DC and pro-inflammatory macrophages in the sub-endothelial layer [27,28]. DCs serve as a connective element between the first immunity response and the following acquired immunity response, stimulated by exposure to antigens located inside the atheromatous plaque.

3.1 Monocytes and DCs

In the initiation stage of atherosclerosis, DCs contribute to lipid retention in the endothelium and facilitate the formation of foam cells, which accelerates necrotic core expansion. As the disease progresses, activated DCs migrate to lymph nodes to present antigens to T cells, bridging innate and adaptive immunity and promoting T cell activation, notably stimulating cytotoxic T cells and polarizing CD4+ T cells into Th1 cells [29]. In advanced stages, different subtypes of DCs (cDC1s and cDC2s) interact closely with T cells in the aortic wall, driving chronic inflammation and enhancing foam cell formation, while pDCs exhibit dual pro- and anti-atherogenic effects depending on their interactions. Ultimately, during regression, DCs reverse their roles by migrating out of plaques, indicating their pivotal function in both disease progression and resolution [30].

3.2 Macrophages

Macrophages can also facilitate the development of atherosclerosis by generating proteolytic enzymes, aggregating fats within cells, and releasing cytokines. Aggregation of macrophages, which have not undergone phagocytosis, facilitates the necrotic core formation that was detected in atheromatous plaques [31,32]. Such processes drive the plaques to be more vulnerable to ruptures. In atherosclerosis, macrophages play distinct roles at various disease stages. Early in the disease, resident macrophages contribute to plaque formation by transforming into foam cells and promoting necrotic core formation through the accumulation of modified lipoproteins [19,33]. As the disease progresses, inflammatory macrophages exacerbate plaque instability by releasing pro-inflammatory cytokines and degrading extracellular matrix components, leading to plaque rupture. Additionally, different macrophage subsets exhibit unique functions; while some drive inflammation, others promote plaque stability through fibrosis, highlighting the complex interplay of macrophage phenotypes in atherosclerosis [20,34,35].

3.3 Neutrophils

Neutrophils also contribute to the development of atherosclerotic lesions, instability, and thrombosis. Neutrophils are releasing NETs and secreting reactive oxygen species (ROS), which facilitate the adverse effects. Neutrophils are also able to recruit pro-inflammatory monocytes to the vessel walls, which would contribute to the AS development [36,37].

Neutrophil extracellular trap (NET) burden—commonly estimated using circulating cell-free DNA (cf-DNA), myeloperoxidase–DNA complexes or citrullinated histone H3—correlates with infarct size, microvascular injury and worse outcomes after myocardial infarction, suggesting it could be a predictive biomarker for NET-directed therapy [38]. Therapeutic strategies fall into two categories: (1) *NET-degraders*—recombinant DNase-I (dornase alfa) enzymatically cleaves extracellular DNA and has been repurposed and tested in thrombo-inflammatory conditions (promising proof-of-concept data in COVID-19 and ongoing trials in ischemic stroke), while preclinical MI models show reduced infarct size after DNase treatment; clinical data in acute coronary syndrome are still limited [39]. (2) *NET-formation inhibitors*—agents that

block NETosis upstream, including PAD4 inhibitors (e.g., GSK484, JBI-589) that prevent histone citrullination, and repurposed drugs such as colchicine (which suppresses NET release in ACS patients) and SYK inhibitors (fostamatinib/R406) that reduce NET formation *in vitro* and in disease models. Most PAD4 inhibitors remain at the preclinical or early-development stage, whereas colchicine has large outcome trials (LoDoCo/COLCOT) consistent with an anti-NET mechanism and is already in clinical use for secondary prevention [40]. Other candidates (neutrophil elastase inhibitors, MPO inhibitors, calpain inhibitors and autophagy modulators) have shown NET-reducing activity in preclinical studies but limited cardiovascular trial data to date [41].

Clinical efficacy of NET-dismantling (DNase) or NET-inhibiting therapies is plausibly greater in patients with high baseline NET burden; therefore, biomarker-enriched trials (selecting patients with elevated cf-DNA/citH3/MPO-DNA) are recommended to test whether NET burden predicts therapeutic benefit [38].

Neutrophils serve a pivotal role in the inflammatory response during atherosclerosis, initially promoting inflammation through the release of ROS and chemokines that recruit monocytes, leading to foam cell formation. Early in the disease, they primarily exhibit pro-inflammatory functions, exacerbating arterial damage and necrotic core expansion while also facilitating plaque instability through mechanisms that promote rupture and erosion [28,36]. As the disease progresses, a shift occurs where neutrophils begin to show anti-inflammatory characteristics, aiding in tissue healing and remodeling by activating macrophages to clear dead cells. Throughout the stages of atherosclerosis, neutrophils balance their roles between driving inflammation and supporting repair, reflecting their complex involvement in cardiovascular disease pathology [42,43].

3.4 Inflammasome Activation

Furthermore, in the past years, one more pathway was identified and researched. That pathway is the cryopyrin inflammasome, which is formed in macrophages following the altered fats. This results in the generation of mature interleukin 1 beta, which is an important stage of inflammation signaling [44,45].

4 T Cells

4.1 Th1 Cells

T cells are responsible for the regulation of a major step of the immune response in atheromatous plaque, which they carry out via a type 1 helper T cell response. That response is featured by the genesis of IFN-γ and TNF-α, which trigger activation of macrophages and the secretion of nitric oxide (NO) and other vasoactive agents, as well as proinflammatory mediators.

4.2 Other T Cell Subtypes

Several more types of T lymphocytes take part in the development of AS, such as type 2 helper T cells, type 17 helper T cells, and regulatory T cells. Although their impact is not as elucidated [46–49].

In atherosclerosis, Th1 cells are predominantly pro-inflammatory, releasing cytokines like IFN-γ and TNF-α that drive lesion formation and plaque instability. Th2 cells exhibit a mixed role; while IL-4 they produce may promote atherogenesis, other cytokines like IL-5 and IL-13 can offer protective effects by countering Th1 responses and stabilizing plaques [50,51]. Th17 cells contribute to atherosclerosis progression through pro-inflammatory actions, but also aid in collagen production that can enhance plaque stability. Regulatory T cells (Tregs) are crucial for maintaining immune balance, suppressing inflammation, and promoting plaque

stability; however, their depletion or dysfunction during disease progression can exacerbate atherosclerosis and diminish their protective effects [52,53].

5 Cytokines as Mediators of Plaque Development

Cytokines are very important in the atheroma development process as well. Numerous immunity cells (ICs), which are named above, are able to release proinflammatory cytokines, e.g., IFN-γ, IL-1β, and TNF-α, after their activation. Such cytokines can promote the genesis of considerable concentrations of IL-6 [54]. Then, IL-6 makes its environment conductive to the hepatic acute phase reactants (APRs) genesis. Among such acute-phase reactants are fibrinogen, serum amyloid A (SAA), and C-reactive protein (CRP). Moreover, subjects with adiposity and metabolic syndrome frequently show an elevated adipokine generation that is able to facilitate the organism's inflammation response as well. This aggressive inflammation environment may have an adverse impact on atheromatous plaques, resulting in plaque instability, rupture, as well as thrombosis and following cardiovascular events [55–57].

6 Inflammatory Pathways and Therapeutic Approaches

A summary of the main anti-inflammatory therapeutic classes and representative agents used in atherosclerosis is provided in Table 1.

Table 1: Overview of anti-inflammatory treatments for atherosclerosis

Treatment class	Example agents	Mechanism of action	Main findings	Side effects	Contraindications
IL-1 Inhibitors	Canakinumab, Anakinra	Neutralizes IL-1 signaling	Reduces major adverse cardiovascular events (CANTOS study)	Increased risk of infections, elevated liver enzymes, and gastrointestinal perforations	Active infections, severe hypersensitivity to components
IL-6 Inhibitors	Tocilizumab	Blocks IL-6 receptors	Decreases inflammation, CRP levels, potential benefit in STEMI	Increased risk of infections, elevated liver enzymes, and gastrointestinal perforations	Active infections, liver disease, hypersensitivity to tocilizumab
Colchicine	–	Inhibits IL-1β synthesis	Lowers CV events in stable CAD (LoDoCo trials)	Gastrointestinal disturbances (diarrhea, nausea), myelosuppression	Severe renal impairment, hypersensitivity to colchicine
Statins	Atorvastatin	Reduces cholesterol, has anti-inflammatory effects	Lowers hs-CRP, reduces ischemic events (AVERT trial)	Muscle pain, liver enzyme elevation, gastrointestinal symptoms	Active liver disease, pregnancy, hypersensitivity to statins

(Continued)

Table 1 (continued)

Treatment class	Example agents	Mechanism of action	Main findings	Side effects	Contraindications
SGLT2 Inhibitors	Empagliflozin	Reduces glucose reabsorption, has anti-inflammatory properties	Lowers inflammatory markers, improves cardiovascular outcomes	Genital mycotic infections, dehydration, hypotension	Severe renal impairment, active bladder cancer
Methotrexate	–	Suppresses cytokine production	Effective in conditions like RA; mixed results in CAD prevention	Hepatotoxicity, myelosuppression, nausea, mucositis	Pregnancy, liver disease, blood dyscrasias
Natural Compounds	Brazilian green propolis	Antioxidant, anti-inflammatory	Reduces proinflammatory cytokines; emerging evidence in CAD treatment	Generally well-tolerated; potential allergic reactions	Known allergies to bee products, active allergies

Note: Abbreviation: CANTOS—Canakinumab Anti-Inflammatory Thrombosis Outcomes Study; IL-6—interleukin 6; CRP—C-reactive protein; STEMI—ST-segment elevation myocardial infarction; IL-1—interleukin 1; CAD—coronary artery disease; CV—cardiovascular; LoDoCo—Low Dose Colchicine; hs-CRP—high-sensitivity C-reactive protein; AVERT—Atorvastatin Vs. Revascularization Treatments; SGLT2—sodium-glucose transport protein 2.

6.1 Targeting IL-1 Pathway

6.1.1 Canakinumab: IL-1β Inhibition

Canakinumab is a human monoclonal Ab that is used in auto-immune disorders for neutralization of IL-1β signaling. CANTOS study investigated the hypothesis that this drug can considerably decrease the occurrence of detrimental CV events in subjects with a history of heart attack [58,59]. The CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study) was a landmark clinical trial designed to investigate the role of inflammation in cardiovascular disease, specifically targeting IL-1β with the monoclonal antibody canakinumab. This randomized, double-blind, placebo-controlled study enrolled 10,061 patients who had a history of myocardial infarction and elevated levels of high-sensitivity C-reactive protein (hs-CRP), indicative of ongoing inflammation [60,61]. Participants were randomly assigned to receive either canakinumab or placebo, with treatment administered in three different doses (50, 150, or 300 mg) every three months over an average follow-up period of approximately 4 years. The primary outcome was the occurrence of major adverse cardiovascular events (MACE), which included non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death [62,63]. The findings were significant; canakinumab treatment was associated with a 15% reduction in MACE compared to placebo, particularly demonstrating a 24% reduction in cardiovascular death among those in the higher dose groups. These results not only underscored the role of inflammation in atherosclerosis but also suggested that targeting inflammatory pathways could provide a novel approach to reducing cardiovascular risk, marking a critical shift in the management of coronary artery disease and challenging traditional risk factor-based treatment paradigms [6,64].

While the CANTOS study underscores the significant benefits of the IL-1β inhibitor canakinumab in reducing cardiovascular events, it is essential to consider the limitations that may impact its clinical applicability. The study demonstrated a 15% reduction in major adverse cardiovascular events (MACE) among patients with a history of myocardial infarction and elevated high-sensitivity C-reactive protein levels when treated with canakinumab [59]. This reduction included a notable 24% decrease in cardiovascular deaths, highlighting its potential as a groundbreaking therapy for targeting inflammation in coronary artery disease. However, the practical use of canakinumab is constrained by several notable drawbacks. Firstly, the high cost associated with canakinumab may limit accessibility for many patients, particularly given that long-term treatment could be necessary for optimal benefit [65]. Secondly, the treatment was associated with an increased risk of serious infections, as IL-1β plays a critical role in the body's immune response. Patients receiving canakinumab may experience heightened susceptibility to infections, which necessitates careful patient selection and monitoring. Thus, while canakinumab offers promising therapeutic potential, its cost and safety profile must be balanced against the benefits to ensure responsible and effective clinical application [66,67].

The major adverse CV events involve such harmful conditions as heart attack (MI), ischemic stroke, CV death, as was reported by Ridker and colleagues [68]. Moreover, Everett and colleagues revealed that the subjects who were treated with canakinumab showed a reduction in hospital admission as well as in CV mortality related to cardiac failure [69]. Although therapy with this drug has a high cost. It is also connected to an elevated risk of various infections by different pathogens, which can turn out to be peripheral or systemic.

6.1.2 Anakinra: IL-1α and IL-1β Inhibition

Furthermore, as was found by Morton and colleagues, anakinra is a suppressant of IL-1α and IL-1β [70]. Anakinra efficiently inhibits the IL-1α and IL-1β signaling, thus reducing the genesis of C-reactive protein and decreasing the occurrence of major adverse CV events [71].

Canakinumab and Anakinra are IL-1 inhibitors that play a significant role in modulating inflammation associated with CAD. Canakinumab is a human monoclonal antibody that selectively inhibits IL-1β, a key pro-inflammatory cytokine involved in the inflammatory response. By neutralizing IL-1β, canakinumab effectively dampens the inflammatory cascade that contributes to atherosclerosis [72,73]. Anakinra works similarly by blocking both IL-1α and IL-1β, preventing their signaling through the IL-1 receptor. Clinical studies have demonstrated that these therapies can significantly reduce levels of CRP and other inflammatory markers, resulting in a decreased incidence of MACE in patients with elevated hs-CRP levels following myocardial infarction [74,75].

6.2 Targeting IL-6 Pathway

Recent research by Markousis-Mavrogenis and colleagues showed that most part of subjects with cardiac failure demonstrate increased IL-6 concentrations in plasma [76].

Tocilizumab: IL-6 Receptor Blockade

Tocilizumab is a humanized monoclonal Ab that binds to membrane membrane-soluble form of IL-6 R. Jones and colleagues reported that inhibition of IL-6 receptor can reduce the concentrations of C-reactive protein as well as multiple proinflammatory mediators [77]. Protogerou and colleagues reported that tocilizumab was approved for RA treatment [78]. As was discovered by Bacchiega [79] and Ruiz-Limon and colleagues [80], this drug ameliorates the functioning of the endothelium, decreases OS, and decreases pro-inflammation and pro-thrombotic characteristics of monocytes. A double-blind, placebo-controlled study

evaluated the effect of a tocilizumab dose on subjects with non-ST-elevation myocardial infarction (non-STEMI) who were expected to undergo a coronary angiogram. A short suppression of IL-6 with this drug resulted in decreased inflammation and a significant reduction in the expression of troponin associated with percutaneous coronary intervention (PCI) [81,82]. The safety profile was also proven to be acceptable, as was reported by Kleveland and colleagues [83]. Another trial assessed the tocilizumab impact on myocardial salvage in subjects with STEMI [84]. The cohort of subjects who received tocilizumab showed a higher myocardial salvage index (MSI) and not as high microvascular obstruction (MVO) as the control cohort. Although a considerable distinction in the infarction size between the tocilizumab cohort and the control cohort was not detected (7.2% and 9.1%). Although the *p*-value is almost significant (0.08). The two cohorts showed close results regarding the occurrence of MACE. Broch and colleagues concluded that this drug is able to elevate MSI in STEMI subjects [85–87].

Tocilizumab, an IL-6 inhibitor, is another important agent in the context of CAD. This humanized monoclonal antibody binds to the membrane-bound and soluble forms of the IL-6 receptor, inhibiting IL-6 signaling. IL-6 is a pro-inflammatory cytokine that plays a significant role in the immune response and is associated with the progression of atherosclerosis [88–90]. By blocking IL-6, tocilizumab lowers levels of inflammation markers like hs-CRP, improves endothelial function, and potentially stabilizes atherosclerotic plaques. Studies have shown reductions in troponin levels and enhanced myocardial salvage in patients after acute coronary events when treated with tocilizumab [91,92].

Interestingly, Tocilizumab, an IL-6 receptor antagonist, reduces systemic inflammation as reflected by decreased hs-CRP levels but can paradoxically elevate lipoprotein(a) [Lp(a)] levels. This effect is likely due to IL-6 inhibition relieving inflammatory suppression of hepatic Lp(a) production. In patients with elevated baseline Lp(a) or high residual cardiovascular risk, concomitant Lp(a)-lowering therapies may be considered to optimize outcomes, although further studies are needed to clarify long-term benefits [93].

6.3 Broad-Spectrum Anti-Inflammatory Agents

6.3.1 Methotrexate

Methotrexate, a drug traditionally used in the treatment of malignancies and autoimmune diseases, has garnered attention for its potential role in preventing and treating CAD. Its effectiveness in this context largely stems from its anti-inflammatory properties, which target mechanisms that contribute to the progression of atherosclerosis and cardiovascular events [94]. Methotrexate suppresses the pro-inflammatory cytokines. Among such cytokines are TNF-α, IL-1β, and IL-6. These pro-inflammatory cytokines play a huge role in the progression of AS and other inflammatory diseases mediated by immunity, as was reported by Van Breukelen-van der Stoep and colleagues [95].

Methotrexate, originally used for cancer and autoimmune diseases, serves as another therapeutic option by suppressing the production of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β. These cytokines play a pivotal role in the progression of atherosclerosis [96–98]. Methotrexate has also been shown to have effects on the adenosine A2A receptor (ADORA2A), promoting reverse cholesterol transport and preventing atherogenesis. Although studies on methotrexate's efficacy in CAD have shown mixed results, it has potential atheroprotective effects, particularly in patients with inflammatory conditions such as rheumatoid arthritis [99].

Methotrexate works by inhibiting the production of pro-inflammatory cytokines, such as TNF-α and IL-6. By suppressing these inflammatory mediators, methotrexate helps reduce the inflammatory response that can exacerbate vascular pathology. This effect is particularly relevant in patients with conditions

characterized by systemic inflammation, such as rheumatoid arthritis, who have a notably higher risk of cardiovascular disease [100,101].

Clinical studies investigating the efficacy of methotrexate in CAD have yielded mixed results. Some trials suggest that low-dose methotrexate can lower levels of inflammatory markers like hs-CRP, which is a biomarker associated with an increased risk of cardiovascular events. For instance, the Cardiovascular Inflammation Reduction Trial (CIRT) studied the impact of methotrexate on patients with a history of myocardial infarction and elevated hs-CRP levels [102–104]. While the trial found that methotrexate treatment did not significantly reduce major adverse cardiovascular events compared to placebo, it did succeed in lowering hs-CRP levels, suggesting some anti-inflammatory efficacy [105].

Moreover, the potential atheroprotective effects of methotrexate may also arise from its capability to enhance reverse cholesterol transport, a process crucial for removing excess cholesterol from arterial walls. This mechanism, combined with its ability to stabilize existing plaques and reduce their vulnerability to rupture, posits methotrexate as a beneficial therapy in patients at high risk of acute coronary events [106]. Treatment strategies that involve methotrexate, methotrexate with etanercept, or methotrexate with sulfasalazine and hydroxychloroquine demonstrated amelioration in the high-density lipoprotein profile of RA subjects, as was reported by Charles-Schoeman and colleagues [107]. Furthermore, methotrexate showed an ability to exert atheroprotective effects via activation of ADORA2A. Upon activation, the ADORA2A can curb the foam cell formation, as was reported by Reiss and colleagues [108]. Besides, monotherapy with this drug, as well as this drug in combination with TNF-α suppressants, can decrease the lipoprotein A Lp(a) and endothelial leucocyte adhesion molecule-1 (ELAM-1) concentrations in serum. In comparison to other disease-modifying antirheumatic drugs in randomized clinical trials (RCTs), this drug can control the stiffness of arteries and the increase in blood pressure related to it [109,110]. These findings indicate that methotrexate's efficiency is likely higher than that of other disease-modifying antirheumatic drugs in the disruption of inflammation pathways, as was reported by Woodman and colleagues [111]. Another double-blind RCT established the efficacy of this drug at low dosage in decreasing the occurrence of CV events in subjects with stable AS. That trial has been terminated after an average observation period of 2.3 years. Although its results demonstrated that this drug was not able to decrease the concentrations of such markers as IL-1, IL-6, and C-reactive protein [112,113]. Occurrence of detrimental CV events was not reduced either in comparison to the placebo group. Furthermore, methotrexate showed such adverse side effects as increased concentrations of hepatic enzymes, decreased number of leukocytes, decreased hematocrit level, and a higher rate of non-basal cell carcinoma (BCC) cancer occurrence in comparison to the placebo group, as was reported by Ridker and colleagues [114].

Despite the complexities in its application, methotrexate embodies a promising avenue in the broader landscape of anti-inflammatory therapies aimed at reducing cardiovascular risk. As the field continues to evolve, its integration into treatment regimens for patients with coronary artery disease may become clearer, particularly for those with underlying inflammatory conditions. Overall, while methotrexate may not represent a definitive solution for CAD management, its potential to modulate inflammation offers valuable insights into the intricate interplay between immune responses and cardiovascular health [115].

6.3.2 Statins

Statins exert pleiotropic effects against inflammation. Statins, such as atorvastatin, are widely prescribed as cholesterol-lowering agents but also exhibit significant anti-inflammatory properties that contribute to cardiovascular risk reduction. They work by inhibiting HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis, which not only reduces lipid levels but also decreases the production of pro-inflammatory cytokines. Statins improve endothelial function and have been shown to stabilize

atherosclerotic plaques. In clinical trials, statin therapy has resulted in reductions in hs-CRP levels and improved cardiovascular outcomes among patients, showcasing their role beyond traditional lipid management [116–118].

They also show fat-decreasing properties. Numerous studies indicated that statins are able to suppress the activation of T lymphocytes that depend on antigens. Statins are also capable of reducing the inflammatory cell count and of stimulating the synthesis of nitric oxide by the endothelium, as was reported by Kwak and colleagues [119–121]. Ridker and colleagues conducted a series of studies that showed the ability of statins to decrease the high-sensitivity C-reactive protein concentrations in plasma in subjects without MACE history [122]. Hereby, statins seem to be able to help down-regulate inflammatory processes, both vascular and systemic. However, further research is necessary since now any evident therapeutic benefits achieved by lowering high-sensitivity C-reactive protein levels are difficult to distinguish from the fat-reducing activity of statins [123,124]. It was reported that in the AVERT trial, atorvastatin therapy resulted in reduced occurrence of hospital admission and ischemic events in subjects with angina pectoris and CAD [125]. Statin usage for CV event prevention could be helpful in subjects with hypertension, DM, tobacco use, coronary artery disease family history, or in subjects with elevated CV risk assessed with the Framingham risk score (FRS). Subjects treated with statins are generally advised to have their C concentrations and hepatic functioning monitored regularly [126].

Statins exert multiple cardiovascular benefits beyond lipid-lowering, including improvement of endothelial function and inhibition of platelet activation. These effects are partly independent of their anti-inflammatory actions, as they can enhance nitric oxide bioavailability and reduce platelet aggregation directly. Additionally, variations exist among statins in anti-inflammatory potency; for instance, rosuvastatin and atorvastatin both reduce hs-CRP, but rosuvastatin may exhibit slightly greater anti-inflammatory efficacy at equivalent lipid-lowering doses [127].

Statins, widely prescribed for lowering cholesterol, are increasingly recognized for their anti-inflammatory properties that contribute to cardiovascular risk reduction. They exert their effects by inhibiting HMG-CoA reductase, leading to reduced cholesterol synthesis, which in turn decreases the production of pro-inflammatory cytokines and improves endothelial function. Statins have been shown to lower levels of hs-CRP, a marker of inflammation, independently of their cholesterol-lowering effects [116,128]. Clinical evidence supporting the anti-inflammatory benefits of statins comes from numerous large-scale trials, such as the JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) trial, which demonstrated that rosuvastatin significantly reduced cardiovascular events in individuals with elevated hs-CRP but normal LDL levels. Additionally, statins are associated with stabilization of atherosclerotic plaques, making them less likely to rupture and lead to acute cardiovascular events. The clinical implications of statin therapy extend beyond lipid management; their ability to modulate the immune response suggests a role in the comprehensive management of patients at high cardiovascular risk, particularly those with inflammatory conditions like rheumatoid arthritis or metabolic syndrome [129,130].

6.3.3 Colchicine

Colchicine is a drug that exhibits activity directed against inflammation. It is applied in cases of gout for prophylaxis and therapy [131]. Imazio and colleagues conducted trials on the application of colchicine for AS cardiac disorders management [132]. Given the anti-inflammation effect of this drug, it suppresses the synthesis of IL-1β and inhibits ELAM-1 expression, which is required for adhesion of neutrophils in endothelial cells (ECs). Furthermore, this drug abolishes cryopyrin inflammasome complex (NLRP3

inflammasome) activation, inhibiting the expression of IL-1β and IL-6 synthesized after the signals of danger [72,133].

Colchicine, a drug traditionally used for gout, has emerged as a promising therapy for CAD due to its anti-inflammatory properties. Colchicine inhibits microtubule polymerization, which is essential for the inflammatory response, particularly in inhibiting the activation and migration of neutrophils. It also directly suppresses the synthesis of IL-1β by inhibiting the activation of the inflammasome complex, particularly the cryopyrin inflammasome. These actions lead to a significant reduction in MACE, especially in stable CAD patients, by lowering inflammatory markers and resulting in decreased risk of unstable angina and myocardial infarctions [134–136].

Huang et al. discovered that administration of this drug to rats with elevated cholesterol levels considerably decreased concentrations of C-reactive protein and Lp-related phospholipase A2 (PLA2) in blood [137]. Moreover, this therapy has been proven to enhance the synthesis of NO, which implies that there has been a significant amelioration of the functioning of the endothelium. Results of a proteomics research showed that subjects with coronary artery disease who received colchicine therapy showed notably decreased expression of cryopyrin pathway cascade (IL-18, IL-6) as well as the acquired immunity response via suppression of CCL17, CD-40 [138,139]. Silvis and colleagues reported that median concentrations of high-sensitivity C-reactive protein and EV cryopyrin were considerably decreased as well after treatment with colchicine [140].

The RCT LoDoCo (Low-Dose Colchicine), which was focused on the secondary prevention of CV events, involved 532 subjects with stable CAD, as was reported by Nidorf and colleagues [141]. Following a median of 3 years, the observation demonstrated that therapy with colchicine was able to considerably decrease the occurrence of CV mortality, noncardioembolic stroke, acute coronary syndrome (ACS), and sudden cardiac arrest (SCA). The decrease in ACS was seventy-two percent, where more than fifty percent of the decrease was accounted for by the decreased incidence of unstable angina pectoris [142,143]. Nidorf and colleagues indicated that the LoDoCo-2 study has validated these discoveries, demonstrating a remarkable reduction in MACE in subjects with stable CAD following the colchicine therapy [141]. The median follow-up time in this study was reported to be 28.6 months.

The COLCOT (COLchicine Cardiovascular Outcomes Trial) trial was large-scale and involved investigation of the positive effects of colchicine therapy for secondary prevention of adverse CV events [144]. This trial involved 4745 subjects who had previously had ischemic stroke or myocardial infarction (MI) not long before the trial. These subjects were divided into two groups, where the first group was administered colchicine at a low dosage and the second group received a placebo. According to Tardif and colleagues, the results from the first group showed that the colchicine therapy decreased the adverse CV events by 23%, e.g., MI, ischemic stroke, SCA with resuscitation, hospital admission for angina resulting in re-vascularisation, and CV mortality [145]. Bouabdallaou and colleagues discovered that early administration of this drug within the first three days of MI showed notable positive effects, with a forty-eight percent relative risk decrease in the primary outcome [144]. These discoveries indicate that administration of this drug in hospitals to subjects with MI has great potential and exhibits a powerful positive impact.

Colchicine has emerged as a promising anti-inflammatory therapy for the secondary prevention of cardiovascular events, as highlighted in the LoDoCo and COLCOT trials. In the LoDoCo trial, colchicine significantly reduced the occurrence of major adverse cardiovascular events (MACE) by 72%, primarily by lowering the risk of unstable angina pectoris, while the COLCOT trial demonstrated a 23% reduction in cardiovascular events among patients who had experienced a recent myocardial infarction [146]. These findings underscore colchicine's potential to exert beneficial effects by modulating inflammatory pathways involved in atherosclerosis and thrombosis. However, the clinical utility of colchicine must be tempered by

an awareness of its potential side effects, which can include gastrointestinal disturbances, such as diarrhea, nausea, and abdominal pain. More seriously, colchicine has the potential to cause myelosuppression, which could lead to leukopenia and increase the risk of infections [147,148]. Furthermore, colchicine's narrow therapeutic index means that careful dosing and monitoring are required to avoid toxicity, especially in patients with renal impairment or those taking medications that can interact with colchicine and affect its metabolism. Therefore, while colchicine offers a novel approach to managing cardiovascular risk through inflammation reduction, clinicians must consider both its efficacy and safety profile in order to optimize patient outcomes and minimize adverse effects [149,150].

6.4 Combination and Adjunct Therapies

The combination of immune suppression therapy with traditional lipid-lowering drugs like statins holds potential for enhancing cardiovascular outcomes, particularly in patients at high risk for cardiovascular events. The literature indicates that therapies such as Tocilizumab and Canakinumab, which target inflammatory pathways, can effectively reduce cardiovascular inflammation. This anti-inflammatory effect is crucial since inflammation plays a significant role in the progression of atherosclerosis and other cardiovascular diseases [103,151,152].

6.4.1 Synergy of Immune Suppression and Lipid-Lowering Therapy

Evidence suggests that integrating immune suppression with statin therapy can amplify the overall effects on cardiovascular health. Studies have demonstrated that statins not only lower lipid levels but also possess pleiotropic effects, including anti-inflammatory properties. Combining these with targeted immune suppressors may provide a dual mechanism: statins can reduce lipid accumulation and stabilize plaques, while immune suppressors can mitigate the inflammatory processes that contribute to plaque instability and cardiovascular events [153,154].

However, while there are promising preliminary findings regarding the benefits of such combination therapies, comprehensive clinical data specifically targeting high-risk groups are still emerging. Some studies, such as those examining Canakinumab, have shown reductions in cardiovascular events in patients with elevated hs-CRP levels, suggesting that targeting inflammation can be beneficial in addition to standard lipid management. Yet, more extensive clinical trials are needed to provide robust evidence and clarify long-term outcomes, safety, and optimal treatment protocols for combining these therapies [155–157].

In summary, while there is a rationale for combining immune suppression therapies with lipid-lowering drugs to further reduce cardiovascular risks, particularly in high-risk patients, further research is necessary to establish conclusive clinical guidelines and evidence supporting this approach. This combination could ultimately lead to more effective strategies for managing cardiovascular disease [158,159].

6.4.2 Challenges and Considerations

The potential of immune suppressors like Tocilizumab and Canakinumab in reducing cardiovascular risk has garnered significant interest, particularly due to their anti-inflammatory properties. Long-term data supporting the effectiveness of these drugs in cardiovascular risk reduction is still emerging. For example, the CANTOS trial demonstrated that Canakinumab reduced the risk of cardiovascular events in patients with a history of myocardial infarction and elevated hs-CRP levels [160,161]. However, while these findings are promising, the duration of follow-up in such studies may not yet be sufficient to fully assess the long-term benefits and risks associated with these therapies. Further studies are needed to evaluate the long-term cardiovascular outcomes and overall safety of these agents across diverse populations [162–164].

Assessing the risks associated with long-term use of immune suppressors is crucial, particularly in elderly patients who may present with multiple comorbidities. Immune suppressive therapy can increase the risk of infections, malignancies, and other adverse effects due to its mechanism of action, which dampens the immune response. For elderly patients, who often have age-related immune senescence and may already be at heightened risk for infections, this aspect is particularly concerning. Moreover, the use of these medications can complicate the management of existing health conditions and may interact with other medications, potentially affecting patient safety and adherence to therapy [165,166].

Patient compliance is another significant factor in the long-term use of these drugs. Adherence to treatment regimens can be influenced by the complexity of medication schedules, potential side effects, and the perceived benefits of therapy. Ensuring that patients understand the rationale behind the treatment, the importance of adherence for cardiovascular risk reduction, and the management of any arising side effects is critical. Regular follow-up and monitoring can help address concerns and modify treatment as necessary, improving compliance and overall satisfaction with the treatment plan [167,168].

In summary, while there is emerging evidence on the effectiveness of immune suppressors like Tocilizumab and Canakinumab in reducing cardiovascular risk, long-term data is still required to substantiate their use, particularly concerning safety in elderly patients. Careful risk assessment, patient education, and ongoing monitoring are vital to optimize therapy and enhance adherence to treatment in this vulnerable population [169,170].

7 Emerging Therapies and Natural Compounds

7.1 Xanthine Oxidase (XO) Inhibitors

7.1.1 Mechanism of Action

Allopurinol (ALP) and oxipurinol serve as a substrate for the enzyme xanthene oxidase. Xanthene oxidase contributes to the conversion of hypoxanthine into xanthine, which is followed by the xanthine transformation into uric acid (UA). Suppressants of xanthene oxidase notably decrease oxidative stress (OS) and downregulate the synthesis of UA [171,172]. Research has suggested that allopurinol's effects on oxidative stress and endothelial function may contribute to its protective role in CAD, although further studies are warranted to better understand its efficacy in this context. Hereby, they contribute to the decrease of the risk of endothelium function impairment as well as of the inflammatory process, which facilitate the development of atheromatous plaques and CV disease.

7.1.2 Clinical Evidence

ALP was proved to exert 3 major effects which account for its powerful CV activity. The first is the ability to decrease circulating UA concentrations since it has proinflammatory properties. The second is its capacity of suppressing the synthesis of ROS, which stimulates endothelium function impairment and affects the stability of atheromatous lesions. The third is the ability to curb AS, as well as to protect from ischemia/reperfusion injury (IRI) [173–175].

The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation trial group of authors performed a trial on subjects with stable coronary artery disease. The authors discovered that even though the subjects received optimal treatment and re-vascularization, they showed life quality reduction and exhibited symptoms [176,177]. Weintraub and colleagues concluded that it should be advised that ALP and similar agents are better used as an additional treatment of angina because of their capacity of alleviating endothelium function impairment by reducing the synthesis of UA and free radicals [178].

Another research was performed by Baldus and colleagues on subjects with coronary artery disease with no history of ALP therapy [179]. The subjects were administered with acetylcholine (ACh). The researchers assessed the coronary vaso-constrictor response of the subjects to this compound as well as alterations of coronary artery circulation following administering of ALP metabolite oxipurinol. Oxipurinol did not influence ACh-dependent alterations in subjects with preserved functioning of the coronary endothelium. Although in subjects with endothelium functioning impairment, administering oxipurinol led to a considerable amelioration in artery MLD and coronary artery circulation. The trial results showed that free radicals obtained from XO diminished the availability of NO. Suppression of oxipurinol might ameliorate the functioning of the endothelium in coronary vessels in subjects with coronary artery disease [180,181].

Another research of angina pectoris involved sixty subjects. The subjects had stable angina and received treatment with pentaerythritol tetranitrate (PETN) and ALP. The results showed that this combined treatment is much more efficient than the PETN treatment alone. After the treatment, the subjects showed a considerable decrease in serum and urine concentrations of UA [182,183]. Kaliakin and Mit'kin observed that this therapy resulted in a reduction of lipid peroxidation (LPO) and anti-oxidative system functioning as well as in a significant amelioration of central haemodynamics [184].

Another RCT evaluated the application of ALP in the elevation of the exercise ability of sixty-five subjects with CAD, stable angina pectoris, and positive exercise tolerance. The results of the trial showed that ALP therapy was able to considerably decrease concentrations of UA as well as to elevate the St depression time, time of the physical activity, as well as time to angina pectoris. The results resemble those of several presently used anti-anginal agents [185,186]. The researchers indicated that ALP has a good safety profile, is sufficiently tolerated, and has acceptable cost as an antiischemic compound for subjects with angina. Noman and colleagues theorized that endogenous XO action might account for the coronary ischemia caused by exercise [185].

ALP upregulates synthesis of adenosine triphosphate and elevates exercise ability, retaining the supply of oxygen to the myocardium even at the peaks of exercise. ALP was also proved to ameliorate the functioning of the endothelium and to decrease coronary artery vasoconstriction parameters, as was reported by Stone and colleagues [187]. Recent research was performed on eighty subjects with CAD. The results showed that ALP therapy considerably ameliorated vasorelaxation depending on the endothelium, as well as inhibited OS in subjects with CAD [188].

7.2 Agents Targeting Lipid Rafts

7.2.1 Mechanism of Action

Lipid rafts play a prominent role in the pathogenesis of inflammation associated with cardio-metabolic diseases. These cholesterol- and sphingolipid-rich membrane microdomains act as organizing centers for many signaling molecules and are crucial in the initiation and propagation of inflammatory responses [189]. Rafts host a wide range of receptors that regulate innate and adaptive immunity. Toll-like receptor 4 (TLR4), tumor necrosis factor receptor 1 (TNFR1), integrin CD11b, and antigen receptors such as BCR and TCR are recruited into lipid rafts during activation [189]. CD36, a scavenger receptor implicated in the uptake of oxLDL, also localizes to rafts, where it drives foam cell formation and contributes to metabolic inflammation [190]. Given this role, raft abundance strongly influences inflammatory signaling. Augmentation of rafts enhances receptor clustering, potentiates downstream signaling, and promotes cytokine secretion [191], whereas raft disruption attenuates these responses, demonstrating an anti-inflammatory effect [192].

7.2.2 Therapeutic Strategies

Therapeutic targeting of lipid rafts has therefore emerged as a promising strategy to modulate inflammation in atherosclerosis as well as in other inflammatory diseases [193]. Because rafts depend on cholesterol and sphingolipids for their stability, agents that alter lipid composition or interfere with raft-associated receptors can attenuate pro-inflammatory signaling. Statins not only reduce systemic LDL cholesterol but also disrupt raft cholesterol, thereby reducing TLR4 and TNFR1 signaling in vascular cells [124,194]. MβCD and hydroxypropyl-β-cyclodextrin (HPβCD) extract cholesterol from rafts, reduce foam cell formation, and lower atherosclerotic burden in animal models, though systemic toxicity limits their translational potential [195,196]. Agents targeting sphingolipids, such as inhibitors of sphingomyelin synthesis (e.g., myriocin) or sphingomyelinase inhibitors, destabilize ceramide-rich raft domains and prevent clustering of death and inflammatory receptors [197]. Another therapeutic strategy is to block raft-resident receptors directly: monoclonal antibodies or small molecules targeting CD36 and TLR4 reduce ligand binding, prevent receptor clustering, and inhibit foam cell formation and cytokine release [198]. Novel small molecules and natural compounds also show promise; synthetic oxysterols such as Oxy210 redistribute raft cholesterol and attenuate macrophage inflammation [199], while polyphenols like resveratrol and curcumin weaken raft integrity and reduce inflammatory signaling, though their bioavailability remains a limitation [200,201]. Another promising agent, apolipoprotein A-I binding protein (AIBP), was shown to reduce lipid rafts content, inhibit inflammatory responses to LPS, and confer protection against atherosclerosis in a mouse model [202]. Finally, nanoparticle-based therapeutics are emerging as highly specific approaches to modulate raft composition and signaling. Lipid- and protein-decorated nanoparticles designed to selectively target raft domains reduce systemic toxicity and hold translational potential in cardiovascular disease [203].

Overall, lipid rafts act as central hubs for inflammatory receptor signaling in atherosclerosis, and their abundance and composition directly influence disease progression. Multiple therapeutic classes, including cholesterol modulators, raft disruptors, sphingolipid-targeting agents, receptor-specific inhibitors, oxysterols, natural compounds, and nanoparticles, demonstrate preclinical efficacy, but the challenge remains to translate these raft-targeted therapies into safe and effective treatments for cardiovascular disease.

7.3 Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors

7.3.1 Mechanism of Action

Suppression of SGLT2 is unanimously acknowledged as an important part of managing DM, cardiac failure, and renal disorders, as was reported by Carnicelli and Mentz [204], Padda [205], Vaduganathan and colleagues [206]. Suppression of sodium-glucose transport protein 2 shows pleiotropic impact, which may be explained by different factors, such as powerful activity directed against inflammation, as was reported by Elrakaybi [207], La Grotta and colleagues [208]. Theofilis and colleagues conducted a number of RCT and revealed a remarkable efficacy of the treatment of cardiac failure with decreased left ventricular ejection fraction (LVEF) [209]. In case of elevated LVEF, the effect of the treatment is yet to be fully discovered. Novel medications, e.g., angiotensin receptor/neprilysin inhibitor (ARNI) and finerenone, might be able to alleviate the burden associated with cardiac failure [210,211].

SGLT2 inhibitors, such as empagliflozin, have gained attention not only for their glucose-lowering effects in diabetes management but also for their anti-inflammatory and cardioprotective benefits. These agents promote urinary glucose excretion, which can reduce body weight and improve glycemic control. In addition to their metabolic effects, SGLT2 inhibitors have been shown to exert favorable effects on inflammation and oxidative stress, both of which are critical in the pathogenesis of cardiovascular disease [212,213].

7.3.2 Clinical Evidence

Clinical trials demonstrate that SGLT2 inhibitors significantly lower the risk of hospitalization for heart failure and reduce MACE among patients with existing cardiovascular disease or those at high risk [214].

Recent research involved thirty studies which were focused on the impact of sodium-glucose transport protein 2 suppressants on inflammation biomarkers. The results of this research showed that sodium-glucose transport protein 2 suppressants therapy considerably decreased concentrations of IL-6, C-reactive protein, TNF-α, and monocyte chemoattractant protein 1 [215,216]. When empagliflozin was applied, the reduction of C-reactive protein and TNF-α was not as pronounced. Whereas in this trial, mild-to-significant heterogenous property has been observed and publication bias is probable, these results stayed unaltered following sensitivity analysis [217,218]. The trial results indicated that suppression of sodium-glucose transport protein 2 is able to decrease inflammation biomarkers in animals, confirming the theory of anti-inflammation properties of sodium-glucose transport protein 2 suppressants, as was reported by Theofilis and colleagues [18]. Kondo et al. investigated the characteristics of canagliflozin, which has a greater affinity to sodium-glucose transport protein 1 than to sodium-glucose transport protein 2 [219]. This drug showed remarkable anti-oxidant activity. Canagliflozin was able to decrease the activity of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase, making tetrahydrobiopterin more available and ameliorating NO synthase un-coupling via sodium-glucose transport protein 1/AMP activated protein kinase/RAC-1 pathway. This process leads to alleviation of inflammation and inhibition of apoptosis [220,221]. Although more research is necessary to establish the main cause of these positive effects of these agents on CVD occurrence (sodium-glucose transport protein 1 or sodium-glucose transport protein 2). That is a subject of particular interest, as recent trial indicated that nonselective suppression of sodium-glucose transport protein 2 could turn out to be more efficient in decreasing the risk of hospital admission for heart failure and CV mortality [222–224].

SGLT2 inhibitors have garnered attention not only for their glucose-lowering effects in diabetes management but also for their anti-inflammatory and cardioprotective benefits. These agents promote urinary glucose excretion, which has been shown to reduce body weight and improve glycemic control [225]. In addition to these metabolic effects, SGLT2 inhibitors also exert favorable effects on inflammation and oxidative stress, mechanisms that are critical in the pathogenesis of cardiovascular disease. Studies such as EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure and a Reduced Ejection Fraction) and DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) have demonstrated that SGLT2 inhibitors significantly lower the risk of hospitalization for heart failure and reduce major cardiovascular events among patients with existing cardiovascular disease or at high risk [226–229]. The cardiovascular benefits of SGLT2 inhibitors extend beyond their diuretic and antihypertensive effects. Evidence suggests they exert distinct anti-inflammatory and antifibrotic actions, including reduction of pro-inflammatory cytokines (e.g., IL-6, TNF-α) and attenuation of myocardial fibrosis. Moreover, SGLT2 inhibitors modulate myocardial energy metabolism by promoting ketone utilization, improving mitochondrial efficiency, and enhancing ATP production, which collectively contribute to improved cardiac function and reduced heart failure risk [230]. The anti-inflammatory effects of SGLT2 inhibitors may be linked to reduced levels of circulating inflammatory markers and improved myocardial oxygenation. Clinically, the implications of using SGLT2 inhibitors extend beyond glycemic control; they represent a paradigm shift in the management of patients with heart failure and chronic kidney disease, highlighting the importance of a multi-faceted approach that addresses inflammation and cardiovascular risk concurrently [213].

7.4 Natural Compounds

Brazilian Green Propolis

The extract of Brazilian green propolis is a natural substance obtained from different biologically active plants, synthesized by the bees *Apis mellifera*. This compound protects against oxidative stress and inflammation, as well as exhibits immunity modulating effects. Recent researches showed that propolis is able to decrease inflammation markers and symptoms of various disorders associated with inflammation [231,232]. Research indicates that Brazilian green propolis can lower inflammatory markers and improve endothelial function, presenting a potential adjunct therapy for CAD management.

For example, in subjects with CKD who are going through haemodialysis, 4-week propolis therapy resulted in a notable decrease in concentrations of such proinflammatory cytokines as TNF-α, IFNγ, and IL-1. Moreover, an RCT in subjects with COVID-19 who underwent hospital admission showed that the subjects that were administered with from four hundred to eight hundred mg of propolis daily for 1 week stayed hospitalized for a shorter time period in comparison to the placebo group. These findings imply that the propolis doses in the RCTs were safe, which enables its application in the next trials [233,234].

The ability of propolis to protect against inflammation and to enhance the immune system was detected in these randomized controlled trials, which involved ILs. The results of these trials show promising perspectives for the application of propolis in subjects with CAD, since the inflammatory process is critical in the progression of atheromatous plaques. A review was published recently which emphasized the impact of green propolis on CVD, pronouncing its effects in maintaining of endothelium and myocardium functioning, and its anti-angiogenic characteristics. Moreover, another group of researchers investigated multiple propolis samples and detected its ability to affect thrombocyte aggregation testing, which implies that this substance could have antiplatelet characteristics [235,236].

Natural products like propolis exhibit significant potential in regulating immune responses through specific molecular mechanisms, as evidenced by various studies illustrating their antioxidant, anti-inflammatory, and immunomodulatory properties. Propolis, particularly the Brazilian green and red varieties, demonstrates anti-atherosclerotic effects by modulating the serum lipoprotein profile, suppressing macrophage apoptosis, and inhibiting matrix metalloproteinase activity, all of which relate to its role in immune response regulation [17,231]. Moreover, the therapeutic effects of propolis appear to stem from the combined actions of numerous compounds that engage multiple signaling pathways, suggesting that further investigation could elucidate the precise molecular mechanisms involved [237].

As for the combination of these natural products with existing drugs, the literature indicates promising avenues. The multifaceted bioactivities of propolis may enhance the efficacy of traditional anti-inflammatory medications or potentially reduce their side effects. For instance, propolis's ability to modulate vascular inflammation and oxidative stress could complement therapies aimed at cardiovascular conditions, thereby improving overall treatment outcomes. This integrative approach could leverage the benefits of both natural and synthetic pharmacological agents [231,238,239].

Additionally, clinical research supporting the effectiveness and safety of propolis in treating cardiovascular diseases is still needed. Current studies predominantly focus on preclinical models, which establish a foundation for studying propolis's cardiovascular benefits. However, to translate these findings into clinical practice, extensive trials confirming the therapeutic profiles of propolis, including dosage, safety, and long-term effects, are essential. Overall, while propolis shows great promise, particularly in cardiovascular health, ongoing research is crucial to clarify its clinical applications and mechanisms of action fully [237].

Key clinical trials evaluating anti-inflammatory strategies in coronary artery disease are summarized in Table 2.

Table 2: Comparative summary table of key clinical studies on inflammation and CAD

Study name	Treatment/Agent	Study design	Patient population	Key findings	Limitations/ Comments
CANTOS	Canakinumab	RCT	10,061 post-MI patients with elevated hs-CRP	15% reduction in major adverse cardiovascular events (MACE); 24% reduction in cardiovascular death with higher doses	High cost; increased risk of serious infections
LoDoCo	Colchicine	RCT	532 patients with stable CAD	72% reduction in MACE, significant decrease in unstable angina	Long-term safety and efficacy data required
COLCOT	Colchicine	RCT	4745 post-MI patients	23% reduction in MACE, including myocardial infarction and ischemic stroke	Limited generalizability to diverse populations
AVERT	Atorvastatin	RCT	CAD patients with ischemic symptoms	Reduced ischemic events; beneficial effect on hs-CRP levels	Focused on statin use, not specifically on inflammation
EMPEROR-Reduced	Empagliflozin	RCT	Patients with heart failure and CAD	Lowered risk of hospitalization for heart failure; anti-inflammatory effects observed	Majority of patients had diabetes, limiting generalizability
Methotrexate Trials	Methotrexate	Multiple studies (RCTs)	Variable populations (RA, CAD)	Mixed results; potential to lower inflammatory markers but uncertainties in CV event reduction	Higher rates of adverse effects; requires close monitoring
Tocilizumab	IL-6 Inhibitor	DBPC Study, RCTs	Non-STEMI patients	Reduced inflammation, lower CRP levels; potential benefit in myocardial salvage	Safety profile includes risk of infections; specific patient group studied
Brazilian Green Propolis	Natural Compound	Various trials (RCTs)	Patients with inflammatory conditions	Decreased inflammatory markers in multiple settings; potential atheroprotective effects	Further studies needed to confirm clinical impact in CAD

Note: Abbreviation: RCT: randomized clinical trial; CAD: coronary artery disease; EMPEROR: Empagliflozin Outcome Trial in Patients with Chronic Heart Failure; RA: rheumatoid arthritis; CV: cardiovascular.

8 Biomarkers and Risk Stratification

8.1 Hs-CRP

8.1.1 Mechanism and Role

There is growing interest in researching the utilization of markers to evaluate inflammation, and that interest has been increasing for many years now. Elevated concentrations of high-sensitivity CRP and IL-6 were proved to be closely connected to the adverse cardiovascular events. Although C-reactive protein is generated by the liver. C-reactive protein possibly reflects the result of the pathway of activation of IL-1/IL-6 [114,240]. Hereby, it probably does not facilitate the appearance of such harmful conditions as acute coronary syndrome directly. However, high-sensitivity C-reactive protein seems to be a major marker and is being closely investigated as a predictor of the risk of detrimental CV events.

8.1.2 Clinical Evidence

Recent research has demonstrated that in groups of subjects with elevated risk of AS, high-sensitivity C-reactive protein could be used to predict cardiovascular disease, CV mortality, and overall mortality [241,242]. High-sensitivity C-reactive protein proved to be better as a predictor of such events than residual C risk (as evaluated by LDL-C). This emphasizes the possible perspectives of utilizing C-reactive protein for prediction in evaluation of the risk of adverse CV events in coronary artery disease. Although it is noteworthy that whereas assessable blood markers, e.g., C-reactive protein, give useful information, their usefulness is still restricted since they are not providing information on the atheromatous plaques' location and degree [243,244].

Inflammatory biomarkers, such as hs-CRP and IL-6, have gained traction as predictive factors for cardiovascular events, providing critical insights into an individual's risk profile. Elevated levels of these markers are associated with a higher likelihood of adverse cardiovascular outcomes, making them valuable tools in both primary and secondary prevention strategies. For instance, routine measurement of hs-CRP can be employed in clinical practice to stratify risk among patients, particularly for those with elevated cholesterol levels but no apparent traditional risk factors [245,246]. Monitoring hs-CRP levels can help guide treatment decisions, as a significant reduction in hs-CRP following interventions—such as statin therapy or anti-inflammatory treatments like canakinumab—may indicate a favorable response and reduced cardiovascular risk. Clinicians can utilize point-of-care testing and laboratory assessments to routinely measure these biomarkers, integrating them into risk assessment algorithms [247,248]. Moreover, clinical guidelines suggest using hs-CRP measurements to aid in the decision-making process for statin therapy, especially in individuals with intermediate cardiovascular risk. Maintaining awareness of inflammatory markers and their dynamics can enhance patient care by enabling more personalized and proactive management of cardiovascular disease, ultimately striving for better outcomes through targeted interventions [249].

8.1.3 Limitations and Considerations

hs-CRP is recognized as a significant biomarker for predicting cardiovascular events, but its predictive accuracy can be influenced by several factors, including obesity, diabetes, infections, and metabolic syndrome. These conditions can lead to elevated levels of hs-CRP due to their association with chronic inflammation, which complicates the interpretation of hs-CRP as an isolated risk marker [250,251]. For example, the presence of obesity and metabolic syndrome can result in persistently elevated hs-CRP levels, thereby masking an individual's true cardiovascular risk. Similarly, acute infections can cause marked spikes in hs-CRP, making it challenging to assess long-term cardiovascular risk reliably.

To improve the prediction of cardiovascular events using hs-CRP, several strategies can be employed. First, it is essential to interpret hs-CRP levels in the context of the patient's overall health status, particularly during periods of chronic inflammation or acute illness [252,253]. Measuring hs-CRP when the patient is in a stable condition can yield more reliable readings. Additionally, integrating hs-CRP with other biomarkers or clinical risk factors could enhance its predictive power. For instance, using hs-CRP alongside traditional lipid profiles, like LDL-C, and other inflammatory markers could provide a more comprehensive assessment of cardiovascular risk [254,255].

Furthermore, considering the individual characteristics such as ethnicity, age, sex, and comorbidities when establishing hs-CRP thresholds is vital. Given the variation in hs-CRP levels among different populations and health conditions, a one-size-fits-all approach may not be appropriate. Personalized risk assessment strategies that account for these factors can lead to more accurate predictions. Lastly, utilizing hs-CRP

measurements over time rather than relying on a single measurement can capture the dynamic nature of inflammation and provide better risk stratification [256,257].

In conclusion, while obesity, diabetes, infections, and metabolic syndrome can indeed interfere with the accuracy of hs-CRP as a cardiovascular risk predictor, a holistic and personalized approach to its interpretation, along with the use of complementary biomarkers, can substantially enhance its utility in predicting cardiovascular events. This strategy can help clinicians make more informed decisions and ultimately improve patient outcomes in cardiovascular health [258].

8.2 Other Inflammatory Biomarkers

While hs-CRP serves as a crucial biomarker for predicting cardiovascular events, several other inflammatory biomarkers, such as IL-6, TNF-α, fibrinogen, and serum amyloid A (SAA), have also shown significant predictive value in assessing cardiovascular risk [259].

8.2.1 IL-6, TNF-α, Fibrinogen

Research indicates that these biomarkers, individually and in combination, can enhance the prediction of cardiovascular events, particularly among patients categorized as "intermediate risk." For example, studies have demonstrated a robust association between elevated levels of IL-6 and TNF-α with increased atherosclerotic risk, suggesting that these pro-inflammatory cytokines can provide insights into the inflammatory processes underlying cardiovascular disease [260,261].

Combining multiple inflammatory biomarkers may yield a more accurate risk assessment, as different markers reflect various aspects of the inflammatory response involved in atherogenesis. This multifactorial approach can improve risk stratification and potentially help identify individuals who may benefit most from preventive interventions.

8.2.2 Combined Biomarker Approach

For instance, a combined evaluation of hs-CRP, IL-6, fibrinogen, and other inflammatory markers could offer a more precise picture of cardiovascular risk and support more tailored treatment approaches [262,263].

8.3 Clinical Implications

Additionally, the integration of these biomarkers into current cardiovascular disease prevention strategies could optimize management approaches. By identifying patients at higher risk through comprehensive inflammatory profiling, clinicians could implement earlier and more aggressive treatment regimens, including lifestyle modifications, pharmacotherapy, and anti-inflammatory interventions. The interplay of these biomarkers with established cardiovascular risk factors—such as hypertension, obesity, and diabetes—also underscores the importance of addressing inflammation as a pivotal component in managing cardiovascular health [264–266].

In summary, while hs-CRP is a widely recognized biomarker, incorporating a panel of inflammatory markers can enhance predictive accuracy for cardiovascular events, particularly in patients at intermediate risk, and help refine and optimize current cardiovascular disease prevention strategies. By recognizing the multifaceted nature of cardiovascular risk, clinicians can better tailor interventions to improve patient outcomes.

9 Future Directions and Research Focus

As we look to the future of cardiovascular disease management, particularly in the context of atherosclerosis, several promising avenues of research warrant attention. These focus areas include cytokine targeting, immune response regulation, the exploration of natural compounds, inflammasome modulation, and the development of combination therapies. Each of these directions holds the potential to provide novel therapeutic strategies that not only aim to reduce inflammation but also improve clinical outcomes for patients at risk of cardiovascular events [267,268]. Major future research directions and representative ongoing clinical trials are summarized in Table 3.

Table 3: Future directions in anti-inflammatory research for atherosclerosis

Research focus	Potential targets	Ongoing studies/Clinical trials	Expected outcomes
Cytokine targeting	Interleukin 1 beta, Interleukin 6	NCT05021835: Ziltivekimab vs. placebo in CKD patients	Decreased cardiovascular events in high-risk patients
Regulation of immune response	T-regulatory cells	LILACS trial: IL-2 in CVD patients	Enhanced T-reg function, improved plaque stability
Natural compounds	Brazilian green propolis	N/A	Reduced inflammatory markers, potential atheroprotective effects
Inflammasome modulation	Cryopyrin inflammasome	N/A	New treatments targeting inflammasome components
Combination therapies	Statins, IL-1, IL-6 inhibitors	N/A	Improved efficacy in reducing CV events through multi-target approach
Biomarker validation	High-sensitivity CRP, IL-6	Ongoing studies on predictive values of inflammatory markers	Better risk stratification and monitoring of treatment outcomes

Note: Abbreviation: LILACS: Lymphadenectomy in locally advanced cervical cancer study; N/A: Not Applicable.

9.1 Cytokine Targeting

Research into the selective inhibition of pro-inflammatory cytokines continues to be a pivotal area of focus. Inhibitors of IL-1β and IL-6 have demonstrated success in clinical trials, where they have shown the ability to significantly reduce major adverse cardiovascular events. For instance, ongoing trials such as NCT05021835 are investigating the efficacy of ziltivekimab against placebo in chronic kidney disease (CKD) patients, aiming to elucidate its impact on cardiovascular outcomes. Targeting these cytokines not only aims to directly mitigate inflammation but may also stabilize atherosclerotic plaques and prevent rupture, thereby reducing the risk of acute cardiovascular incidents [269,270].

9.2 Immune Response Regulation

The regulation of immune responses, particularly through the enhancement of T-regulatory (Treg) cells, represents another promising frontier in AS research. Trials like the Lymphadenectomy in locally advanced cervical cancer study (LILACS) study, which evaluates the effects of IL-2 on cardiovascular disease patients,

aim to enhance Treg function and improve plaque stability. The role of Tregs in controlling inflammation and autoimmunity could make them crucial players in the prevention of atherosclerosis progression. If successful, such therapies could lead to novel interventions that restore balance within the immune system, benefiting patients with CAD [271–273].

9.3 Natural Compounds

The investigation of natural compounds for their potential atheroprotective effects has gained momentum, particularly with agents such as Brazilian green propolis. Research indicates that these natural substances can lower inflammatory markers and exhibit cardioprotective properties. Future studies are anticipated to clarify their mechanisms of action and validate their efficacy in clinical settings, providing alternative or adjunctive options for managing AS and its inflammatory components [274].

9.4 Inflammasome Modulation

Modulating the cryopyrin inflammasome (NLRP3 inflammasome) is an emerging area of interest that could unveil new therapeutic strategies targeting the innate immune system's contribution to AS. Research is ongoing to explore how targeting components of this inflammasome can influence inflammatory cytokine release and subsequent atherosclerotic development. Successful interventions in this domain may lead to innovative drugs aimed specifically at interrupting harmful inflammatory cascades in AS progression [275,276].

9.5 Combination Therapies

The adoption of combination therapies, integrating established drugs such as statins with novel anti-inflammatory agents like IL-1 and IL-6 inhibitors, represents a strategic approach to enhance therapeutic efficacy. Ongoing trials are assessing how these multi-target strategies can synergistically reduce cardiovascular events, leveraging different mechanisms of action to combat inflammation and atherosclerosis more effectively. The potential for combination therapies to address multiple facets of AS could result in improved patient outcomes and a reduction in recurrent cardiovascular incidents [277–279].

9.6 Biomarker Validation

Finally, the validation of inflammatory biomarkers, including hs-CRP and IL-6, for risk stratification and monitoring treatment efficacy is critical for advancing cardiovascular care. Ongoing studies are exploring their predictive values, which can help tailor interventions based on individual inflammatory profiles, ultimately enhancing personalized medicine approaches in CAD management [280,281].

10 Conclusion

In conclusion, the substantial burden of atherosclerosis and its complications underscores the urgent need for improved strategies in cardiovascular disease prevention and management. This review highlights the intricate relationship between inflammatory processes and the progression of coronary artery disease, illustrating how immune system dysregulation can exacerbate atherogenesis and plaque instability. Emerging evidence supports the pivotal role of inflammatory biomarkers, such as high-sensitivity C-reactive protein, in predicting adverse cardiovascular events and monitoring treatment efficacy.

Current therapeutic approaches, including targeted inhibition of pro-inflammatory cytokines and the use of statins, demonstrate promise in reducing cardiovascular risk associated with inflammation. Additionally, novel agents like sodium-glucose transport protein 2 inhibitors and natural products like

Brazilian green propolis may offer new avenues for anti-inflammatory intervention. Future research should focus on the mechanistic understanding of inflammation in cardiovascular pathology, the development of tailored anti-inflammatory therapies, and the optimization of existing treatments to mitigate recurrent cardiovascular events.

By advancing our insights into the inflammatory underpinnings of atherosclerosis, we can enhance the standard of care for patients with coronary artery disease, ultimately improving their quality of life and reducing the burden of cardiovascular morbidity and mortality.

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