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REVIEW ARTICLE

Inflammation and cardiovascular disease – Part II: Anti-inflammatory therapy in cardiovascular disease

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Abstract

Inflammation plays a central role in the pathogenesis of atherosclerotic cardiovascular diseases (ASCVDs), contributing to plaque progression, instability, and thrombosis. Chronic systemic inflammation exacerbates endothelial dysfunction, promotes oxidative stress, and accelerates atherogenesis, necessitating targeted interventions. This review explores established and emerging strategies for modulating inflammation to improve cardiovascular outcomes. Statin therapy remains foundational, with trials, such as JUPITER, demonstrating significant reductions in cardiovascular events through high-sensitivity C-reactive protein modulation, independent of low-density lipoprotein lowering. Non-statin lipid-lowering therapies, including proprotein convertase subtilisin/kexin type 9 inhibitors, ezetimibe, and bempedoic acid, have shown additional anti-inflammatory benefits and further reduce inflammation-driven cardiovascular risk. In addition, triglyceride-lowering agents targeting apolipoprotein C-III and angiopoietin-like protein pathways offer promising avenues for reducing metabolic inflammation and residual ASCVD risk. Anti-inflammatory pharmacotherapy has gained traction, with trials such as canakinumab anti-inflammatory thrombosis outcomes study, colchicine cardiovascular outcomes trial, and low-dose colchicine underscoring the efficacy of canakinumab and colchicine in reducing cardiovascular events. Emerging interleukin (IL) pathways (e.g., IL-17, IL-33, and IL-36) and novel therapeutic targets (e.g., cluster of differentiation 47 inhibitors, serum/glucocorticoid-regulated kinase 1 modulation, and P-selectin blockade) present future opportunities for precision cardiovascular medicine. However, residual inflammatory risk persists despite optimal lipid control, highlighting the need for a multimodal approach integrating lipid-lowering, anti-inflammatory, and targeted immunomodulatory therapies. The expanding role of inflammation in ASCVD suggests a paradigm shift toward inflammation-guided treatment strategies. Further research is warranted to refine patient selection, personalize therapy, and optimize long-term outcomes for inflammation-driven cardiovascular disease.

Keywords: Cardiovascular inflammation; Cardiovascular disease; Chronic kidney disease; Inflammation-targeted therapies; Lipid-lowering therapy; PCSK9 inhibitors and inflammation reduction; ApoC-III and triglyceride-lowering therapies

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1. Introduction: Managing inflammation as a key factor in atherosclerotic cardiovascular disease (ASCVD)

ASCVD is a leading global cause of mortality, responsible for over 17 million deaths annually.[1] Traditional risk factors, such as hyperlipidemia, hypertension, diabetes, and obesity, are well established, but increasing evidence highlights the pivotal role of systemic inflammation in disease progression and plaque instability.

The references cited in this review were identified through a structured literature search of PubMed and ClinicalTrials.gov from January 2000 to March 2025 using keywords such as "inflammation," "atherosclerosis," "cardiovascular disease," "interleukin," "ApoC-III," and "anti-inflammatory therapy." Additional studies were identified by manually reviewing the reference lists of relevant articles. Only peer-reviewed studies published in English were included, with priority given to randomized clinical trials, large cohort studies, and landmark translational investigations.

2. Evidence with statin therapy, low-density lipoprotein (LDL) reduction, and cardiovascular disease (CVD) prevention

Pravastatin has been studied extensively in the West of Scotland Coronary Prevention Study (WOSCOPS) and the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trials.[2] WOSCOPS showed a 26% reduction in LDL levels and a 28% reduction in cardiac mortality with pravastatin. The PROSPER trial showed a 34% reduction in LDL levels and a 24% reduction in cardiac outcomes in elderly patients. The Heart Protection Study evaluated the benefits of simvastatin in 20,000 patients with no prior coronary events and found an 18% reduction in cardiac mortality and a 26% reduction in coronary events in the simvastatin 40 mg daily group compared to the placebo group.[2]

Building upon prior evidence, the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin trial further evaluated statins in primary prevention, specifically in individuals with LDL levels <130 mg/dL but elevated high-sensitivity C-reactive protein levels (hs-CRP; ≥2.0 mg/L).[3] The trial enrolled 17,802 participants, who were randomized to receive either rosuvastatin 20 mg daily or placebo. Rosuvastatin therapy resulted in a 50% reduction in LDL levels, a 37% reduction in hs-CRP levels, and a 44% reduction in major cardiovascular events. The trial was terminated early due to significant cardiovascular risk reduction.

3. Beyond statins for LDL reduction

While statins remain the primary therapy for dyslipidemia, gene therapy offers emerging alternatives. Approaches include gene addition, inactivation, and editing of target hepatocytes to restore cholesterol metabolism. In pre-clinical studies, adeno-associated virus-mediated gene therapy has demonstrated a 98% reduction in cholesterol levels, showing promise for the treatment of familial hypercholesterolemia (Figure 1).[4]

Beyond statins, novel agents, such as ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, and bempedoic acid, have emerged to effectively treat dyslipidemia (Figure 2). Ezetimibe inhibits Niemann–Pick C1-like protein 1, a transporter of food cholesterol from the intestinal lumen into enterocytes, reducing LDL levels by 15 – 20%.[5] In the Improved Reduction of Outcomes: Vytorin Efficacy International Trial, adding ezetimibe to simvastatin resulted in a 24% reduction in LDL levels and a 2% decrease in cardiovascular events.[6] PCSK9 inhibitors (e.g., alirocumab and evolocumab) enhance LDL receptor recycling by preventing LDL receptor degradation and have resulted in >60% reduction in LDL levels in the Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy (ODYSSEY)[7] and the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trials.[8] Bempedoic acid, an ATP citrate lyase inhibitor, showed a 21% reduction in LDL levels in the Cholesterol Lowering through Bempedoic Acid (ECT1002), an ACL-Inhibiting Regimen (CLEAR) Outcomes trial, particularly benefiting statin-intolerant patients.[9] A subgroup analysis of patients with baseline hs-CRP levels >2 mg/L in the bempedoic acid group showed a median decrease of 1.66 mg/L in hs-CRP levels at the 12-week follow-up.[10]

4. Reduction of triglycerides and its impact on CVD

Genetic and pharmacological approaches targeting apolipoprotein C-III (ApoC-III), angiopoietin-like protein 3 (ANGPTL3), ANGPTL4, and related pathways show promise for reducing triglycerides. ApoC-III inhibition, initially observed in Amish populations with loss-of-function mutations, correlates with a 39% reduction in triglyceride levels and a 40% decrease in ASCVD risk.[11] ApoC-III also upregulates inflammatory cytokines (e.g., interleukin-6 [IL-6] and tumor necrosis factor-alpha [TNF-α]), contributing to endothelial dysfunction; therefore, inhibiting ApoC-III also reduces systemic inflammation, potentially preventing CVD progression.[12]

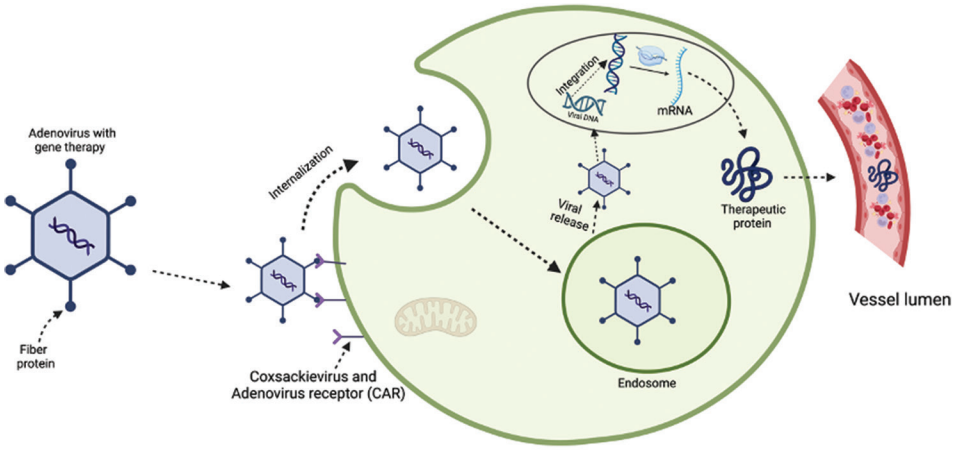

Figure 1. Adenovirus vector application in gene therapy. This method involves using a modified adenovirus to deliver a therapeutic gene into target cells. The virus facilitates cell entry and enables the integration of the targeted gene into the host genome. This leads to the desired production of therapeutic protein using the host cellular system at the molecular level. Image created by the authors with BioRender.com. Vipanpreet chahil (2025) https://app.biorender.com/illustrations/679fedb6b4efdea982d4ae03.

ApoC-III-mediated lipid dysregulation is a key driver of metabolic syndrome, a condition characterized by hypertriglyceridemia, low high-density lipoprotein (HDL) level, hypertension, and insulin resistance, affecting 35% of adults and half of those over 60 in the United States.[13] Metabolic syndrome significantly elevates CVD risk and contributes to nonalcoholic fatty liver disease (NAFLD), the leading cause of chronic liver disease, which impacts 30% of the global population. NAFLD is closely linked to obesity, insulin resistance, obstructive sleep apnea, and genetic predisposition.[14]

Hypertriglyceridemia management requires a multidisciplinary approach, emphasizing lifestyle interventions (e.g., diet control, exercise, and weight loss) and lipid-lowering agents. The class I recommendation advises identifying patients aged ≥20 years with hypertriglyceridemia and encouraging lifestyle changes.[15] Patients aged 40 – 75 years with moderate-to-severe hypertriglyceridemia (≥175 mg/dL) and ASCVD risk ≥7.5% should be reassessed after lifestyle modification. If triglyceride levels remain elevated, statin therapy is recommended. For high-risk patients with persistent triglyceride levels >200 mg/dL despite optimal treatment, the 2019 European Society of Cardiology and European Atherosclerosis Society guidelines support fibrates, PCSK9 inhibitors, and omega-3 fatty acids as add-on therapy.

5. Evidence of HDL modification and its impact on CVD

The primary functions of HDL include facilitating cholesterol efflux to the liver, delivering cholesterol to steroidogenic tissues, and mediating lipid exchange with apolipoprotein B (ApoB)-containing particles.[16] Beyond its lipid-modulating effects, HDL actively regulates inflammation, a key driver of atherosclerosis. HDL is typically anti-inflammatory but can exhibit transient pro-inflammatory properties, as observed in animal and human studies where its inflammatory activity peaks 3-day post-inflammation.[17] Under normal conditions, HDL suppresses vascular adhesion molecules and mitigates endothelial dysfunction, reinforcing its protective effects against atherogenesis.[18]

Examples of HDL-modifying agents are niacin, statins, cholesteryl ester transfer protein (CETP) inhibitors, and fibrates. Niacin effectively raises HDL levels but is limited by side effects, such as flushing. It reduces the levels of triglycerides, LDL, and total cholesterol while increasing HDL levels through inhibition of hepatocyte microsomal diacylglycerol acyltransferase-2 and selective inhibition of apolipoprotein A1 (ApoA1) uptake.[18] Fibrates are another option commonly used with statins, as they decrease triglyceride levels through hepatic synthesis of ApoA1 and ApoA2. However, targeting triglyceride levels reduction and increasing HDL levels has not demonstrated significant cardiovascular risk reduction.[18]

Cholesteryl esters are transferred by CETP from HDL to larger lipoproteins, lowering HDL levels.[18] Despite initial interest, CETP inhibitors have not demonstrated ASCVD risk reduction in major trials due to safety concerns or a lack of LDL-lowering effects. The Randomized Evaluation of the Effects of Anacetrapib through Lipid Modification trial showed that anacetrapib increased HDL levels by 104% but did not reduce cardiovascular mortality or the incidence of major cardiac events.[18]

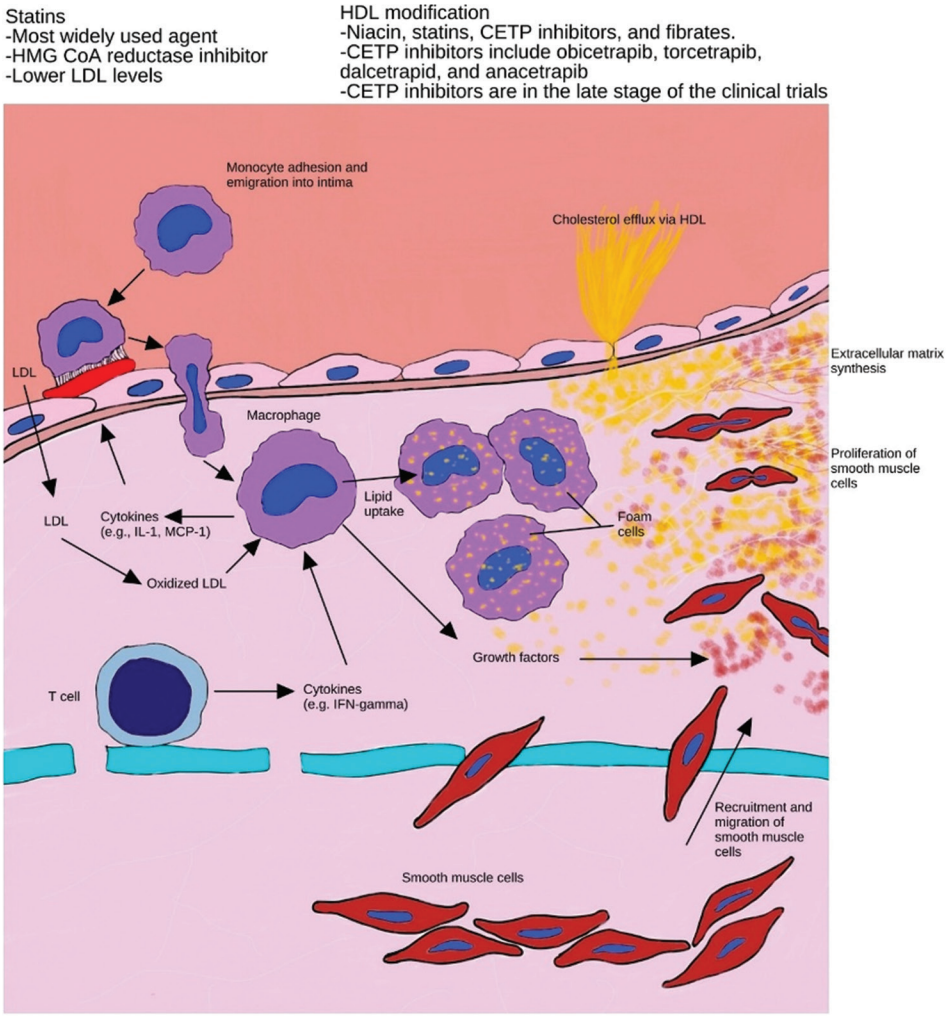

Figure 2. Pathophysiology and pharmacological interventions in atherosclerosis. This detailed diagram illustrates the key mechanisms in the development of atherosclerosis, highlighting the role of lipid accumulation, immune cell activation, and smooth muscle proliferation in plaque formation. It also presents various therapeutic strategies, including statins, HDL modification, gene therapy, bempedoic acid, eicosapentaenoic acid (EPA), and newer medications, such as ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. Image created by the authors with notability.
Abbreviations: CETP: Cholesteryl ester transfer protein; HDL: High-density lipoprotein; HMG-CoA reductase: 3-hydroxy-3-methylglutaryl-coenzyme A reductase; IFN-gamma: Interferon-gamma; IL: Interleukin; LDL: Low-density lipoprotein; MCP-1: Monocyte chemoattractant protein 1; NF-κB: Nuclear factor kappa B; NPC1L1: Niemann–Pick C1-like protein 1; TNF-alpha: Tumor necrosis factor-alpha.

Obicetrapib, a newer CETP inhibitor, has shown improved safety and efficacy compared to previous agents. It significantly lowers the levels of LDL, non-HDL, ApoB, and lipoprotein (Lp[a]) while increasing the levels of pre-β HDL, mature HDL particles, and ApoA1. In phase 2 trials, the 10 mg obicetrapib group showed a 45% median reduction in LDL levels, a 34% reduction in ApoB levels, and a 33% decrease in Lp(a) levels.[19] Obicetrapib's clinical

program includes pivotal trials, such as the BROADWAY trial, which showed a 33% reduction in LDL levels and a 21% reduction in major adverse cardiovascular events (MACE) after 1 year.[20] The BROOKLYN trial demonstrated a 41.5% reduction in LDL levels in heterozygous familial hypercholesterolemia patients at 1 year.[20]

6. Eicosapentaenoic acid (EPA) and its anti-inflammatory benefits

EPA is crucial to cardiovascular health due to its anti-inflammatory and cardioprotective properties. It integrates into cell membranes, replacing arachidonic acid, a precursor to pro-inflammatory eicosanoids, such as prostaglandins and leukotrienes.[21] This shift reduces the production of inflammatory molecules and promotes the synthesis of anti-inflammatory mediators, such as resolvins, which are essential for resolving chronic inflammation. In addition, EPA downregulates key inflammatory cytokines, including TNF-α, IL-1, and IL-6, by inhibiting the nuclear factor kappa B (NF-κB) pathway, a major regulator of inflammation.

The Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial showed that high-dose icosapent ethyl led to a 25% reduction in MACE, including a 20% decrease in cardiovascular mortality and a 31% reduction in myocardial infarction incidence.[21] The trial also showed a significant reduction in inflammatory marker levels, with hs-CRP levels decreasing by 19% and IL-6 levels by 10%.

7. Clinical trials using anti-inflammatory agents in CVD prevention (CURT > low-dose colchicine [LODOCO], colchicine cardiovascular outcomes trial [COLCOT], canakinumab anti-inflammatory thrombosis outcomes study [CANTOS], stabilization of plaques using darapladib-thrombolysis in myocardial infarction [SOLID TIMI], and losmapimod in myocardial infarction 60 [LATITUDE TIMI])

Key clinical trials, including the Cardiovascular Inflammation Reduction Trial (CIRT), the LODOCO, the COLCOT, the CANTOS, the SOLID-TIMI 52, and the LATITUDE-TIMI 60 trials, have explored various inflammatory pathways in atherosclerosis and their impact on cardiovascular outcomes (Table 1).

The CIRT, a randomized placebo-controlled trial, examined low-dose methotrexate (15 – 20 mg weekly) in patients with prior myocardial infarction or multivessel coronary artery disease with metabolic syndrome or diabetes.[22] Despite its established role in autoimmune disease, methotrexate failed to reduce IL-1β, IL-6, or CRP levels and had no significant impact on cardiovascular outcomes. The primary endpoint occurred in an incidence rate of 4.13 versus 4.31/100 person-years in the methotrexate and placebo groups, respectively (hazard ratio [HR]: 0.96; 95% confidence interval [CI]: 0.79 – 1.16). These findings suggest that non-specific immunosuppression may not be effective in atherosclerosis.

In contrast, in post-myocardial infarction patients, the LODOCO trial demonstrated a 24% reduction in MACE with colchicine 0.5 mg daily treatment (HR: 0.76; 95% CI: 0.61 – 0.95).[23] Building on this, the COLCOT assessed colchicine's efficacy when initiated within 30-day post-myocardial infarction, showing a 23% reduction in cardiovascular events (HR: 0.77; 95% CI: 0.61 – 0.96), particularly in stroke and urgent revascularization, reinforcing its role in post-myocardial infarction management.[23]

The CANTOS trial explored anti-inflammatory therapy using canakinumab, a monoclonal antibody against IL-1β. In patients with elevated hs-CRP levels following myocardial infarction, treatment with canakinumab at 150 mg every 3 months reduced cardiovascular events by 15% (HR: 0.85; 95% CI: 0.74 – 0.98; p=0.021) and cardiovascular mortality by 21% (HR: 0.79; 95% CI: 0.67 – 0.93; p=0.005).[24] However, it did not reduce all-cause mortality (HR: 0.94; 95% CI: 0.83 – 1.06) and was associated with an increased risk of fatal infections, raising concerns about the safety of broad immune suppression.

The ZEUS trial is a randomized, double-blind cardiovascular outcomes study evaluating ziltivekimab, a monoclonal antibody that selectively inhibits IL-6, in patients with chronic kidney disease and ASCVD with elevated hsCRP levels ≥2 mg/L.[25] Given the high cardiovascular risk in this population, particularly for those who cannot tolerate colchicine, the trial aims to determine whether monthly subcutaneous ziltivekimab 15 mg treatment can reduce MACE. Secondary endpoints assess kidney function decline, dialysis initiation, and mortality related to cardiovascular or renal causes. With more than 6,200 participants and a target of 1,044 primary outcomes, the ZEUS trial is powered to detect a 20% relative risk reduction in MACE. This study builds on prior evidence linking IL-6 to atherogenesis and inflammation, potentially establishing ziltivekimab as a novel anti-inflammatory strategy for high-risk patients.

The SOLID-TIMI 52 trial evaluated darapladib, a selective inhibitor of lipoprotein-associated phospholipase A2, hypothesizing that reducing plaque necrosis would lower cardiovascular risk. Despite its mechanistic rationale,

Table 1. Comprehensive overview of significant clinical trials exploring the relationship between anti-inflammatory treatments and cardiovascular disease

Trial name	Description	Key findings
CIRT	Investigated low-dose methotrexate for cardiovascular outcomes in patients with prior myocardial infarction or coronary artery disease and metabolic conditions.	Methotrexate did not significantly reduce inflammatory markers or cardiovascular events compared to placebo. The final primary endpoint occurrence was similar between the methotrexate and placebo groups.
LODOCO	Assessed the efficacy of low-dose colchicine in reducing cardiovascular events post-myocardial infarction.	Significant reduction in MACE with colchicine treatment compared to placebo, highlighting its potential in reducing future cardiovascular incidents.
COLCOT	Evaluated colchicine's role in post-myocardial infarction care, focusing on a broad spectrum of cardiovascular outcomes.	Demonstrated a robust reduction in cardiovascular events, advocating for colchicine integration into post-myocardial infarction therapeutic regimens.
CANTOS	Explored the effects of canakinumab on patients with a history of myocardial infarction and a persistent inflammatory response.	Canakinumab significantly reduced the risk of cardiovascular events, particularly at the 150 mg dose, independent of lipid-lowering effects, suggesting benefits in cardiovascular-specific morbidity and mortality.
ZEUS	Evaluate ziltivekimab, an IL-6 inhibitor, for reducing inflammation and MACE in patients with CKD and ASCVD with elevated hsCRP levels.	The trial is enrolling >6,200 participants to assess whether ziltivekimab 15 mg monthly reduces MACE by 20%. Secondary endpoints include kidney function decline and cardiovascular or renal mortality. Expected completion in 2026.
SOLID-TIMI 52	Investigated darapladib's role in stabilizing atherosclerotic plaques post-acute coronary syndrome.	No significant reduction in primary or secondary endpoints, indicating that darapladib did not confer significant cardiovascular protection post-acute coronary syndrome.
Latitude-TIMI 60	Assessed the efficacy and safety of losmapimod in patients with acute myocardial infarction.	Despite reducing early inflammatory markers, losmapimod did not significantly improve long-term clinical outcomes, challenging the efficacy of p38 MAPK inhibition in post-myocardial infarction recovery.

Abbreviations: ASCVD: Atherosclerotic cardiovascular disease; CKD: Chronic kidney disease; IL: Interleukin; MACE: Major adverse cardiovascular events; MAPK: Mitogen-activated protein kinase.

darapladib failed to improve outcomes, with an HR of 1.00 for major coronary events and 0.99 for cardiovascular death, myocardial infarction, or stroke.[26] Similarly, the LATITUDE-TIMI 60 trial investigated losmapimod, a p38 mitogen-activated protein kinase (MAPK) inhibitor, in acute coronary syndrome patients. While losmapimod reduced inflammatory marker levels, it did not translate into improved cardiovascular outcomes (HR: 0.99; 95% CI: 0.91 – 1.08), reinforcing the challenges of targeting single inflammatory pathways in atherosclerosis.[27]

8. Newer targets in IL signaling

ILs are cytokines produced by leukocytes that regulate immune responses by modulating inflammation, cell proliferation, and differentiation. They bind to specific receptors, triggering signaling cascades, such as the Janus kinase signal transducer and activator of transcription (JAK/STAT), MAPK, and NF-κB, influencing immune cell function and inflammatory gene expression.[28] Their dual ability to activate or suppress immune responses makes them central to autoimmune diseases, cancers, and cardiovascular pathologies. Dysregulation of IL signaling can lead to chronic inflammation and contribute to disease progression, making them attractive therapeutic targets.

The JAK/STAT pathway is pivotal in converting IL signals into gene expression changes that drive immune processes. Upon receptor binding, ILs activate JAK kinases, leading to STAT phosphorylation and nuclear translocation, where they regulate genes involved in inflammation and immune cell differentiation.[29] IL-6 and IL-10, for example, modulate both pro- and anti-inflammatory responses through this pathway. Dysregulation of the JAK/STAT pathway contributes to autoimmune disorders and malignancies, making it a key target for therapeutic intervention. The MAPK pathway, activated by ILs, governs cell proliferation, apoptosis, and cytokine production, influencing immune responses in acute and chronic inflammation.[30] Meanwhile, the NF-κB pathway, critical in immune modulation, is triggered by cytokines such as IL-1 and TNF. Upon activation, NF-κB translocates to the nucleus, promoting the transcription of pro-inflammatory genes essential for immune defense but also implicated in chronic inflammatory diseases, such as atherosclerosis.[31]

Several ILs play crucial roles in cardiovascular inflammation. IL-1, IL-6, and IL-18 contribute to vascular damage and plaque instability, accelerating atherosclerosis. Emerging cytokines, such as IL-17F, IL-33, IL-34, and

IL-36, offer new insights into vascular inflammation. IL-17F amplifies inflammatory cytokine and chemokine production, promoting neutrophil recruitment and endothelial dysfunction.[32] IL-33, released upon cellular injury, interacts with the ST2 receptor to activate myeloid differentiation primary response protein 88 and NF-κB, triggering pro-inflammatory cascades that drive immune cell recruitment.[33] IL-34 binds to macrophage colony-stimulating factor 1 receptor, sustaining monocyte and macrophage survival in inflamed tissues and exacerbating vascular pathology.[34] IL-36, a member of the IL-1 family, is activated by neutrophil-derived enzymes, amplifying immune cell adhesion and endothelial dysfunction, perpetuating chronic inflammation in vascular tissues.[35]

Advancements in monoclonal antibody therapies have provided targeted approaches to modulating vascular inflammation. In the CANTOS trial, canakinumab, an IL-1β inhibitor, demonstrated a 15% reduction in major cardiovascular events, validating IL-1β as a therapeutic target in atherosclerosis. Tocilizumab, an IL-6 receptor antagonist, improved myocardial salvage and significantly reduced inflammatory markers in the Assessing the Effect of Anti-IL-6 Treatment in Myocardial Infarction (ASSAIL-MI) trial, suggesting a role in acute coronary syndromes.[35,36] Secukinumab, targeting IL-17A, and ustekinumab, inhibiting IL-12/23, have demonstrated robust anti-inflammatory effects in autoimmune diseases and may provide cardiovascular benefits by reducing systemic inflammation.[37,38] Bimekizumab, which inhibits both IL-17A and IL-17F, showed a 91% reduction in the Psoriasis Area and Severity Index response rate in the BE READY trial, underscoring its potent anti-inflammatory properties.[39] Spesolimab, an IL-36 receptor antagonist, and astegolimab targeting IL-33/ST2 offer promising strategies to reduce endothelial activation and immune-driven vascular injury.[40,41]

9. Emerging therapeutic targets in CVD

Cluster of differentiation 47 (CD47), a transmembrane glycoprotein known as the "don't eat me" signal, prevents the clearance of apoptotic and damaged cells by macrophages, leading to persistent inflammation in atherosclerotic plaques. Inhibition of CD47-signal regulatory protein-alpha (SIRPα) signaling enhances macrophage-mediated efferocytosis, reducing necrotic core size, inflammation levels, and plaque burden.[42] Experimental studies have shown that CD47 blockade with monoclonal antibodies or SIRPα-Fc fusion proteins facilitates the clearance of apoptotic debris while improving endothelial function and neovascularization.[42] However, since CD47 inhibition also plays a role in immune surveillance, careful consideration is required to balance its cardiovascular benefits with potential risks, such as unintended immunosuppression and thrombosis.[42] Dual targeting of CD47 and vascular endothelial growth factor has been explored to enhance the resolution of inflammation while preventing excessive angiogenesis within unstable plaques.

Serum/glucocorticoid-regulated kinase 1 (SGK1), a kinase that regulates sodium retention, fibrosis, and cellular survival, is pivotal in cardiovascular remodeling and arrhythmogenesis. Upregulation of SGK1 has been implicated in myocardial hypertrophy, ischemia-reperfusion injury, and ion channel dysfunction.[43] Pharmacologic inhibition of SGK1 with small-molecule inhibitors, such as GSK650394 and EMD638683, has shown promise in mitigating hypertrophic signaling and reducing cardiac fibrosis. In addition to its role in cardiac remodeling, SGK1 inhibition has been explored as a potential strategy to modulate arrhythmogenic substrates by influencing $NaV_{1.5}$ and K^+ channel activity, reducing the likelihood of prolonged action potentials and arrhythmias. Moreover, SGK1 inhibition may provide cardioprotective effects against oxidative stress, particularly in conditions such as doxorubicin-induced cardiomyopathy.

P-selectin, an adhesion molecule stored in platelet α-granules and endothelial Weibel–Palade bodies, is a key driver of thromboinflammation. P-selectin contributes to platelet aggregation, endothelial dysfunction, and vascular inflammation by mediating leukocyte rolling and adhesion. Pharmacologic strategies targeting P-selectin include monoclonal antibodies, glycomimetic inhibitors, and small-molecule antagonists.[44] Crizanlizumab, a monoclonal antibody targeting P-selectin, has demonstrated clinical efficacy in reducing vaso-occlusive episodes in sickle cell disease and is now being investigated for cardiovascular applications to mitigate thrombosis-related complications.[44] In addition, PSI-697, an orally available P-selectin inhibitor, has shown potential in reducing atherogenesis and vascular injury in preclinical models.[44]

Growth/differentiation factor 15 (GDF-15), a member of the transforming growth factor-beta superfamily, has gained attention both as a biomarker and a therapeutic target in CVD. Elevated GDF-15 levels correlate with adverse outcomes in heart failure, myocardial infarction, and atrial fibrillation, reflecting its role in cellular stress responses and inflammation.[45] Therapeutically, modulation of GDF-15 signaling has been explored to mitigate maladaptive inflammatory responses and vascular dysfunction. GDF-15 influences leukocyte integrin activation and endothelial function, suggesting that targeting its signaling axis could provide cardioprotective effects, particularly in conditions characterized by excessive vascular inflammation and

remodeling.[45] Although GDF-15's role in metabolic regulation has made it a target in obesity and diabetes, its application in CVD remains an area of active investigation.

10. Conclusion

The therapeutic intervention of CVD has evolved, recognizing inflammation as a critical driver of disease progression and treatment response. While statins remain central to lipid-lowering therapy, advances in gene-based treatments, triglyceride-targeting agents, and novel anti-inflammatory strategies have expanded therapeutic options. Future research should prioritize optimizing combination therapies, refining patient selection, and addressing residual inflammatory risk to improve cardiovascular outcomes.

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Ethics approval and consent to participate

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Consent for publication

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Availability of data

Not applicable.

Further disclosure

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