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NARRATIVE REVIEW

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IL-6 in the spotlight: From cardiovascular pathophysiology to therapy

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Abstract

Background: Interleukin-6 (IL-6), a pro-inflammatory cytokine and anti-inflammatory myokine, is involved in immune regulation and metabolic control. Persistent IL-6 activation, particularly via trans-signalling, is implicated in endothelial dysfunction, atherosclerosis, myocardial fibrosis, and adverse remodelling.

Methods: This review summarizes experimental, genetic, and clinical evidence on the role of IL-6 in cardiovascular disease (CVD), focusing on the molecular pathways, prognostic value, and its potential as a therapeutic target. Experimental and genome-wide association studies, as well as clinical trials—including IL-6–targeted interventions—are comprehensively reviewed.

Results: While acute activation of IL-6/STAT signalling, that is, before or during myocardial infarction, is protective, chronic activation leads to maladaptive changes in the myocardium. Mechanistically, IL-6 promotes vascular inflammation, monocyte recruitment, coagulation, and fibrosis. Mendelian randomization implies a causal role of IL-6 signalling in coronary artery disease, stroke, and atrial fibrillation. Simultaneously, elevated IL-6 levels predict adverse outcomes in acute coronary syndromes and heart failure. Pharmacological IL-6 inhibition reduces systemic inflammation, with pilot data implying acceptable safety profiles. Large phase III outcome trials are ongoing, shedding light on the impact of IL-6 blockade in high-risk populations, such as those with chronic kidney disease and heart failure with preserved or mildly reduced ejection fraction.

Conclusions: IL-6 plays a dual role-protective versus pathogenic and acute versus chronic. Chronic IL-6 links inflammation and metabolic dysregulation to structural cardiovascular damage. Chronic IL-6 activation requires therapeutic approaches tailored to disease context, timing and signalling mode. The results of ongoing trials will clarify whether IL-6–targeted interventions can be integrated into cardiovascular prevention and management strategies, complementing established therapies and addressing residual inflammatory risk.

KEYWORDS

cardiovascular disease, chronic kidney disease, heart failure, IL-6, inflammation, monoclonal antibodies

1 | INTRODUCTION

Cardiovascular and cerebrovascular diseases (CVD) cause one of three deaths globally, with a tremendous effect on quality of life and overall morbidity, particularly so in patients with cardiometabolic disease, including renal disease. Therefore, CVD imposes a substantial societal and economic burden. This observation calls for a better understanding of their mechanisms to improve and refine strategies for their prevention and therapy. The intricate pathogenesis of CVD is multifactorial, with chronic inflammatory states accelerating their development, contributing to their high fatality rate.[1–4]

Whereas acute low-grade upregulation of the pro-inflammatory cytokines is described to have cardioprotective roles during acute myocardial infarction, they are potentially harmful if sustained or present at high concentrations.[5,6] Hallmarks of low-grade inflammatory states involved in CVD pathogenesis include the activation of the innate immune system and increased circulating levels of pro-inflammatory mediators, such as interleukins (ILs), tumour necrosis factors (TNFs), as well as the biomarker C-reactive protein (CRP). Among these pro-inflammatory molecules, IL-6 is an immune-mediated cytokine that is elevated in systemic inflammatory states. In the MESA (Multi-Ethnic Study of Atherosclerosis) study, patients with higher IL-6 levels tended to be older, more often female and more frequently had a smoking history.[7] They also had higher rates of hypertension, diabetes, and a family history of coronary heart disease. Additionally, on median, these patients exhibited higher systolic blood pressure, heart rate, and waist circumference, and included a larger proportion of African American and Hispanic individuals compared to those with lower IL-6 levels,[7] highlighting that this molecule may sit at the crossroads of cardiovascular, renal, and metabolic risk pathways.

Anti-inflammatory therapies have been studied for their effectiveness in reducing CV events in patients with established CVD.[8–10] Among these, colchicine gained the Food and Drug Administration (FDA) approval for reducing secondary CV risk, despite a recent trial challenging its effectiveness in patients with a recent acute myocardial infarction (MI) receiving intensive treatment.[10,11] More specific anti-inflammatory drugs including inhibitory antibodies against ILs are being tested. The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) demonstrated that targeted use of IL-1β inhibition substantially reduces CV events.[12] Notably, beneficial effects were most pronounced in those with the largest reduction of IL-6 following anti-IL1β injections.[13]

Consequently, ongoing trials are investigating novel therapies aimed at inhibiting circulating IL-6 to reduce CVD events.[14,15]

This review provides a comprehensive and up-to-date overview of the role of IL-6 in cardio-cerebrovascular diseases (Figure 1), focusing on the molecular pathways through which it contributes to cardiovascular dysfunction and the onset of CVD. Furthermore, it explores the translational relevance of these mechanisms in clinical practice and highlights ongoing trials targeting this pathway.

2 | A COMPLEX MEDIATOR

The journey of IL-6 dates back to 1988, previously known as B cell stimulatory factor 2, hybridoma plasmacytoma growth factor, hybridoma growth factor, or hepatocyte-stimulating factor.[16] Since then, studies have established IL-6 as a pleiotropic cytokine with a central role in inflammation and immune response, haematopoiesis, bone metabolism, the endocrine system, and the development of the central nervous and CV systems.[17,18] Similarly to IL-1β and TNF-α, IL-6 stimulates the synthesis of acute phase proteins; thus, acting as a primary pro-inflammatory cytokine.[19] In addition, it modulates the transition from the acute to the chronic phase of inflammation, enhancing the immune response by promoting end-stage B-cell differentiation, immunoglobulin secretion, and T-cell activation,[20] with potential anti-inflammatory roles.

IL-6 is composed of a single chain phosphorylated glycoprotein, comprising four helix-long α-chain bundles, which are structured in three dimensions to achieve the tertiary shape.[21,22] As a pleiotropic mediator, it is produced by a wide range of cell types across different tissues and physiological contexts. Among immune cells, IL-6 is primarily secreted by monocytes/macrophages, dendritic cells, B cells, and T lymphocytes—particularly Th17 cells—in response to infections and inflammatory stimuli. Within non-immune tissues, adipocytes release IL-6, classifying it as an adipocytokine, while skeletal muscle fibres produce it during physical activity, where it acts as

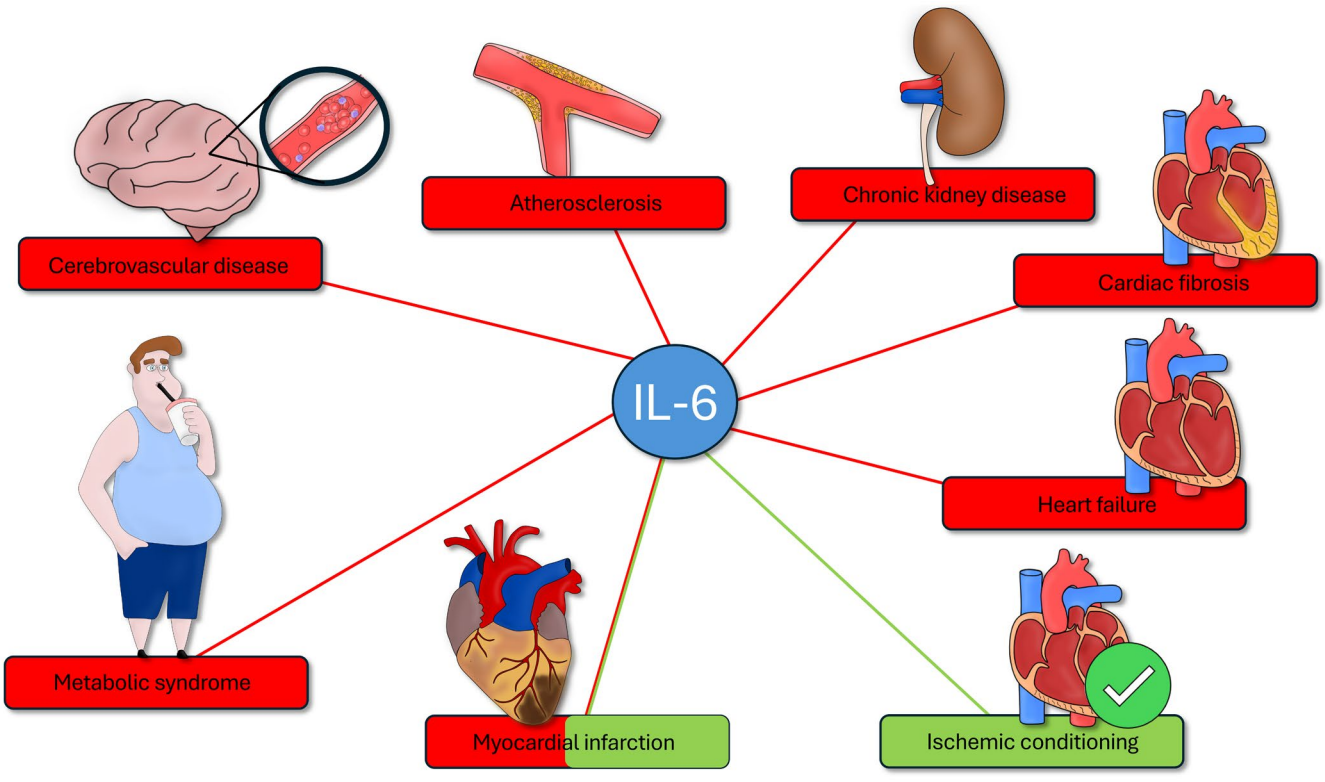

FIGURE 1 Schematic representation of the dual role of interleukin-6 (IL-6). IL-6 promotes endothelial activation, macrophage recruitment, and accelerated atherosclerosis. It alters cardiomyocyte function, increases neurohormonal tone, and contributes to interstitial fibrosis, coronary microvascular dysfunction, and systemic inflammation. IL-6 is also associated with metabolic dysregulation, further amplifying cardiovascular risk. Conversely, transient and localized IL-6 activation can exert protective effects, supporting ischemic preconditioning, tissue repair, and adaptive immune responses during the early phase of myocardial infarction healing. The overall impact of IL-6 thus depends on the balance between acute, reparative activation and chronic, maladaptive inflammation, reflecting its context-dependent role in cardiovascular pathophysiology. IL-6, Interleukin 6.

a myokine. Endothelial cells and vascular smooth muscle cells also generate IL-6 in response to pro-inflammatory signals, contributing to vascular inflammation and remodelling. In the bone microenvironment, osteoblasts are a significant source of IL-6, implicating it in bone metabolism and inflammation. Additionally, fibroblasts, keratinocytes, mesangial cells, and certain epithelial cells—including bronchial and intestinal epithelial cells—can produce IL-6 under specific pathological conditions, further underscoring its multifaceted role in both local and systemic immune responses. IL-6's signalling varies throughout the body and occurs via two primary pathways, defined as classic signalling and trans-signalling, with potential opposite effects (Figure 2). The cytokine binds to cells via a membrane-bound type I cytokine receptor complex composed of a transmembrane glycoprotein called IL-6Rα (or CD126), and a gp130/IL6Rβ (gp130 or CD130) signalling subunit.[23] The complex formation begins with the four alpha-chains of IL-6 capturing the alpha-chain of IL6Rα, creating a five alpha-chain complex, followed by gp130 binding. No signalling can occur until the trimer IL-6/IL-6Rα/gp130 undergoes homodimerization to form a hexameric complex.[24] The effects of IL-6 depend on the localization and expression of its specific receptor, IL-6Rα. While the signal-transducing subunit gp130 is ubiquitously expressed across virtually all cell types, the membrane-bound IL-6 receptor (IL-6Rα) is expressed only by a limited subset of cells, such as hepatocytes and certain leukocyte populations.

A further pathway, known as trans-signalling, has been described. This pathway begins with the cleavage of CD126, mediated by the metalloproteases ADAM10 and ADAM17, producing its soluble form, sIL-6R, which acts as a carrier of IL-6 to the gp130 site in cells lacking IL-6R.[25] A third mode of IL-6 signalling, termed cluster signalling, involves preassembled membrane-bound IL-6–IL-6Rα complexes on one cell engaging gp130 receptors on adjacent target cells. Classical IL-6R signalling likely promotes a stronger anti-inflammatory response, whereas the trans-signalling plays a pro-inflammatory role.[26] Based on this hypothesis, autoimmune disorders and cancer seem to be primarily driven by IL-6 trans-signalling, whereas regenerative and protective activities are mediated by classic IL-6 signalling.[27] The distinct modes of IL-6 receptor

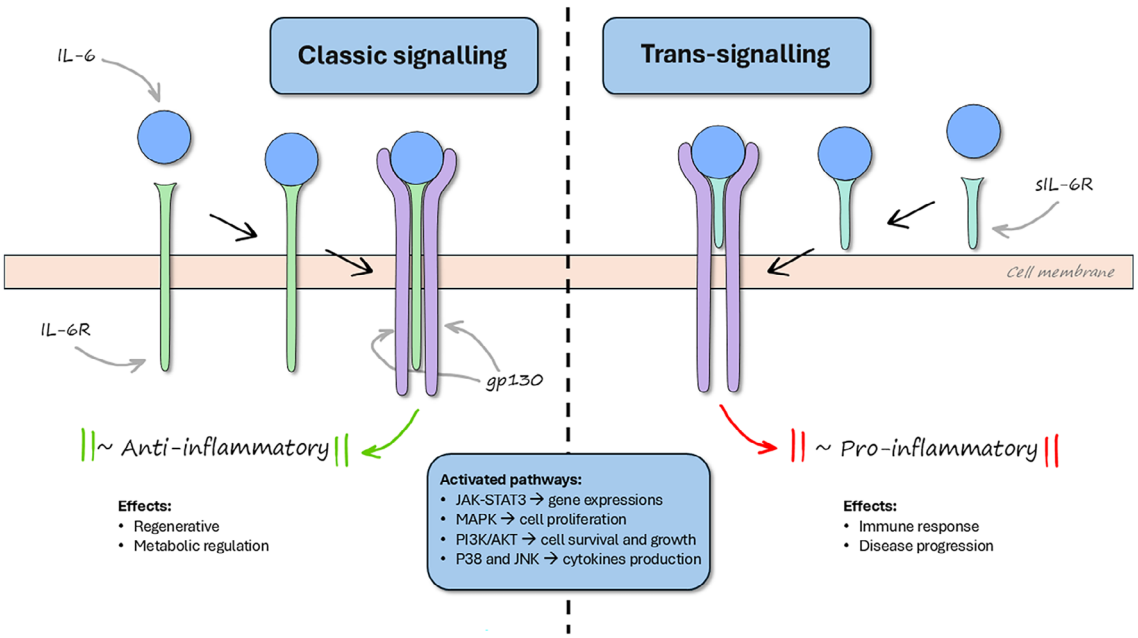

FIGURE 2 IL-6 signalling. IL-6 signalling occurs through two distinct mechanisms: Classic signalling and trans-signalling. Classic signalling involves the binding of IL-6 to its membrane-bound receptor (IL-6R) and is generally associated with anti-inflammatory effects. In contrast, trans-signalling occurs when IL-6 binds to the soluble IL-6 receptor (sIL-6R), which allows IL-6 to act on a broader range of cells, and is primarily linked to pro-inflammatory responses. While both pathways converge on similar downstream cascades, such as JAK-STAT3 and PI3K/AKT, they differ in intensity, duration, and cellular consequences. Classic signalling is limited to cells expressing membrane-bound IL-6R, including hepatocytes and certain leukocytes, whereas trans-signalling can influence a wider array of cell types due to the widespread distribution of sIL-6R. Moreover, the same signalling input can elicit distinct responses depending on the specific transcriptional landscape and co-regulatory factors within different cell types, resulting in varied gene expression profiles and functional outcomes. AKT, Protein kinase B; IL-6, Interleukin 6; IL-6R, Interleukin 6 receptor; JAK, Janus kinase-signal transducer; JNK, C-Jun N-terminal kinase; MAPK, Mitogen-activated protein kinase; PI3K, Phosphoinositide 3-kinase; sIL-6R, Soluble interleukin 6 receptor; STAT3, Activator of transcription 3.

activation lead to the engagement of different intracellular signalling pathways. Depending on the microenvironment and the cell type involved, downstream cascades may include Janus kinases (JAKs), mitogen-activated protein kinases (MAPKs), phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt), with the activation of different transcription factors such as signal transducer and activator of transcription 3 (STAT3) and nuclear factor kappa B (NF-κB), ultimately resulting in specific physiological or pathological outcomes.

3 | A KEY DRIVER OF INFLAMM-AGING AND METAFLAMMATION

From a physiological perspective, IL-6 functions as a key alarm signal, rapidly induced in response to a variety of insults—such as infections, tissue injury, and malignant transformation—and serving as a potent trigger of inflammatory responses.[28] By promoting inflammation, IL-6 plays a pivotal role in the pathogenesis of numerous conditions, including cardiovascular[29] and musculoskeletal diseases,[30] cancer,[31] neurological disorders,[32] anaemia,[33] inflammatory bowel disease,[34] asthma, and other chronic inflammatory pulmonary conditions.[35] IL-6 is also deeply implicated in the development and maintenance of chronic inflammatory states.[36] It has emerged as a central mediator in age-related inflammation, contributing to a process known as *inflammaging*—a state of persistent, low-grade inflammation that develops with aging. This phenomenon is driven by a complex interplay of mechanisms, including immunosenescence, impaired cellular clearance ("garbaging"), chronic infections, dysbiosis, metaflammation, clonal haematopoiesis of indeterminate potential (CHIP), as well as both genetic and epigenetic alterations.[3] IL-6 has been proven to mediate most of such mechanisms. Being produced at high levels by senescent cells, IL-6 is part of the senescence-associated secretory phenotype (SASP) where it further amplifies the inflammatory state and contributes to the development of age-related diseases by promoting tissue remodelling and dysfunction linking cellular aging to systemic inflammatory processes.

Among the contributors to inflammaging, the gut plays a particularly prominent role. As the splanchnic organ with the highest exposure to exogenous pathogens, it harbours a dynamic microbiome that can serve as a continuous source of inflammatory stimuli. Age-related shifts in microbial composition—particularly the replacement of beneficial commensals with facultative anaerobes—have been associated with increased systemic levels of pro-inflammatory cytokines, including IL-6.[37] These changes can significantly impact homeostatic regulation, especially through cardiovascular and neurological pathways, further reinforcing IL-6's role as a molecular link between chronic inflammation, aging, and disease.[38,39]

IL-6 is also a key mediator in *metaflammation*, a chronic, low-grade inflammatory state closely linked to metabolic dysfunction. In metabolic diseases such as obesity, type 2 diabetes, and insulin resistance, IL-6 is produced by adipose tissue and muscle cells, where it plays a dual role. While it contributes to the inflammatory milieu that impairs insulin signalling and promotes insulin resistance, it also has adaptive functions in response to metabolic stress, particularly during exercise, where it acts as a myokine to enhance muscle adaptation and overall energy homeostasis. However, in the context of *metaflammation*, the chronic overproduction of IL-6 exacerbates metabolic disturbances, creating a vicious cycle of inflammation and metabolic dysfunction that accelerates disease progression. In the absence of inflammation, the adipose tissue contributes 10–35% of circulating IL-6[40] with deep implications in body fat modulation. IL-6 gene knockout in mice leads to obesity later in life.[41] Additionally, IL-6 appears to influence fat mass reduction through mechanisms within the central nervous system (CNS).[41,42] Specifically, its anti-obesity effects in rodents are believed to occur primarily in the brain, particularly in the hypothalamus and hindbrain.[43] Research in animal models suggests that IL-6 within the CNS may mediate the reduction of food intake and body weight following activation of glucagon-like peptide-1 (GLP-1) receptors.[44] Beyond the CNS, IL-6 seems to stimulate GLP-1 production in both the endocrine pancreas and the gut.[45] This interaction underscores IL-6's central role in both the regulation of metabolic homeostasis and the pathogenesis of metabolic diseases, linking it to both acute and chronic inflammatory responses in a variety of organ systems.

4 | THE ROLE OF IL-6 DURING THE LIFE CYCLE OF AN ATHEROSCLEROTIC PLAQUE

Atherosclerosis is a chronic inflammatory disease driven by various proinflammatory mediators, which contribute to plaque formation and vulnerability.[46,47] According to a recent meta-analysis, the increase in risk of coronary artery disease per standard deviation of systemic inflammation, defined by either high-sensitivity C-reactive protein (hsCRP) or IL-6, exceeds that of one standard deviation increase in cholesterol or blood pressure.[48] Aligning with this notion, recent murine studies have shown that the alternative pathway of IL-6 by trans-signalling through pg130 substantially contributes to atherosclerosis.[49,50] These data

highlight the significance of low, chronic inflammation in increasing the risk of atherosclerotic diseases, possibly surpassing traditional cardiovascular risk factors.

IL-6 is produced by various cell types in response to inflammation, angiotensin II, oxidative stress, and vascular injury.[51] By promoting smooth muscle cell proliferation and migration, endothelial dysfunction, and the recruitment and activation of inflammatory mediators, IL-6 plays a key role in regulating the downstream inflammatory responses that contribute to the development and destabilization of atherosclerotic plaques.[52,53] IL-6 facilitates macrophage-monocyte activation and migration into the intima, lipid uptake, and low-density lipoprotein (LDL) oxidation.[54] Furthermore, IL-6 plays a crucial role in promoting a procoagulant state. IL-6 induces thrombocytosis[55] and facilitates monocyte procoagulant activity by enhancing their mRNA, protein content, and surface expression of tissue factor.[56,57] Of interest, we recently demonstrated that direct IL-6 inhibition blunts arterial thrombosis by specifically reducing collagen-mediated platelet activation in a mouse model of inflammaging.[58] Also, IL-6 trans-signalling induces plasminogen activator inhibitor type 1 (PAI-1) in endothelial cells,[59] thereby playing a crucial role in stabilizing blood clots. At the vessel wall, IL-6 colocalizes with angiotensin II in aortic atherosclerotic plaques,[60] upregulating cell adhesion molecules,[61] potentiating vascular permeability, and leading to sustained loss of endothelial barrier function.[62] Anti-IL-6 therapy partially reverses the attenuated endothelial-dependent arteriolar dilatation that develops in diabetic mice knockout for TNF-α ($dbTNF^{-}/dbTNF^{-}$).[63] Similarly, treatment with the anti-IL-6 receptor antibody MR16-1 has been shown to downregulate inflammation, and reduce atherosclerotic lesion size in $LDLr^{-/-}$ mice.[64] However, lifetime IL-6 deficiency has been found to be associated with more severe atherosclerosis rather than inhibition of plaque formation, likely due to the disruption of the balance between IL-6 and IL10.[65]

Genome-wide association studies (GWAS) support a potential causal role for the IL-6 pathway in inflammation, atherosclerosis and coronary artery disease. Elevated CRP levels were associated in GWAS with both loci implicated in the immune system (CRP, IL-1 receptor antagonist, IL-6 receptor, IL-1 Family Member 10, Interferon Regulatory Factor 1, and NLRP3) as well as with loci associated with metabolic syndrome (Apolipoprotein C-1, Hepatocyte Nuclear Factor 1, Leptin receptor, Glucokinase Regulatory Protein, Hepatocyte Nuclear Factor 4 Alpha, and Protein Tyrosine Phosphatase, Non-Receptor Type 2).[66–68] The IL-6R locus itself associates with coronary artery disease,[69] while a genetically mediated reduction in IL-6 signalling is associated with longevity and lower risk of atrial fibrillation, stroke and CHD.[70] Furthermore, Mendelian randomization analyses show that genetic variation in IL-6 signalling is positively associated with plasma IL-6 receptor (IL-6R) levels and is correlated with lifelong CRP levels and CV risk.[71,72]

5 | LOOKING AT THE SEQUELAE OF ATHEROSCLEROSIS

5.1 | Acute myocardial infarction

IL-6 plays a highly complex role in the pathophysiology of myocardial infarction (MI), mediating a broad range of inflammatory and cardioprotective/reparative processes that influence cardiac injury, remodelling, and long-term outcomes.

The protective functions of IL-6 are best characterized in ischemia–reperfusion injury and myocardial infarction, both of which induce IL-6 production. Conceptually, cardioprotective cytosolic signalling pathways are divided into three major cardioprotective pathways and one of those is the so-called survival activating factor enhancement (SAFE) pathway.[73] In response to IL-6 and IL-6-like cytokines or tumour necrosis factor alpha (TNF) and through sarcolemmal glycoprotein 130 or TNF receptors, Janus kinase (JAK) is activated and phosphorylates signal transducer and activator of transcription (STAT)3.[74] The strongest and most robust cardioprotective intervention is ischemic conditioning, which is effective in all species tested so far, including humans.[75,76] Cardioprotection by late local and remote ischemic conditioning involves the canonical function of STAT3[77,78] and STAT5.[79] STAT3 is the key protein of the SAFE pathway[73,80,81] and the non-canonical function of STAT3 plays a unique role in acute cardioprotection. STAT3 is the only cytosolic protein whose activation is consistently associated with a reduction in infarct size by all ischemic conditioning procedures. Pharmacological blockade of STAT3 activation proves its causal involvement in cardioprotection. STAT3 activation has been observed in all species, including larger mammals such as pigs.[73,76,80,81] The intracellular targets of the SAFE pathway are mitochondria and preservation of mitochondrial function is central for cardiomyocyte function and viability and thus the reduction of ischemia/reperfusion injury.[82]

Following acute MI, IL-6 levels rise sharply in the plasma, with early elevations detectable upon hospital admission and peaking within the first 48 hours.[83] These levels often remain elevated for several weeks to months, paralleling other inflammatory biomarkers such as hs-CRP.[83] Basic and translational research has shown that this IL-6 surge reflects its role in orchestrating the immune response to ischemic injury and modulating both

deleterious and protective processes in the infarcted myocardium.[84] In murine models, single-cell RNA sequencing has identified cardiac fibroblasts as the principal source of IL-6 in the infarcted heart.[85] These fibroblasts become activated in response to ischemia and hypoxia, and their IL-6 production is finely regulated by purinergic signalling, particularly through adenosine acting on the A2b receptor. Interestingly, this signalling pathway is influenced by T cell-derived adenosine, underscoring a metabolic interplay between immune cells and stromal cells that governs cytokine secretion in the injured heart.[85] Cardiac myocytes, especially those in the border zone of reperfused infarctions, also contribute to the local production of IL-6.[86] In vitro, isolated ventricular myocytes have been shown to upregulate IL-6 mRNA in response to pro-inflammatory cytokines such as TNF-α and IL-1β, as well as postischemic lymph. This response is often accompanied by an increase in intracellular adhesion molecule-1 (ICAM-1) expression, a key mediator in neutrophil-myocyte interactions and subsequent myocyte injury.[86] Therefore, both fibroblasts and cardiomyocytes actively shape the IL-6-mediated microenvironment following MI, modulated by the broader inflammatory milieu. The chronic IL-6 trigger also activates the Janus kinase (JAK)/STAT pathway, which here however activates the canonical function of STAT, which is central for the deleterious effects.[87] Moreover, IL-6 also activates the TGF-β1/Smad3 signalling axis, promoting myocardial fibrosis through enhanced expression of matrix metalloproteinases (MMP-2/9) and collagen deposition.[88] These fibrotic processes contribute to adverse ventricular remodelling and progressive deterioration in cardiac function.

Despite its well-established role in promoting inflammation, the chronic IL-6 also exerts important protective and regenerative effects. Animal studies have shown that IL-6 overexpression can enhance cardiomyocyte proliferation and reduce apoptosis, in part through upregulation of cyclin D1 and Bcl-2.[89] The IL-6/sIL-6R complex has been implicated in mobilizing protective signalling during early reperfusion, possibly attenuating myocyte apoptosis and promoting tissue salvage.[89] These dual roles illustrate the context-dependent nature of IL-6 biology in the heart: while necessary for initiating repair and regeneration, excessive or prolonged IL-6 expression contributes to maladaptive remodelling and functional decline.[90]

In patients, elevated IL-6 levels are associated with poor outcomes following MI, including increased mortality, recurrent infarction, and the development of heart failure.[13,91–96] Studies have shown a strong correlation between IL-6 levels and infarct size, as well as markers of myocardial necrosis and left ventricular (LV) dysfunction. Importantly, persistent elevation of IL-6 beyond the acute phase is a predictor of adverse ventricular remodelling and long-term systolic impairment. These findings have led to considerable interest in IL-6 as a prognostic biomarker and as a potential therapeutic target in acute coronary syndromes. In clinical settings, elevated IL-6 levels are also more frequently observed in patients with traditional cardiovascular risk factors such as smoking and hypertension, suggesting that IL-6 may mediate part of their pathogenic effect on MI risk.[97]

IL-6 was then investigated as a potential therapeutic target. Experimental results displayed mixed results.[98–101] In the ASSAIL-MI trial (Assessing the effect of Anti-IL-6 treatment in Myocardial Infarction), a single dose of the anti-IL-6R antibody tocilizumab, resulted in a modest 6% improvement in myocardial salvage index by cardiac magnetic resonance at 3 to 6 days, without significant benefit at 6 months.[102] Nevertheless, tocilizumab significantly reduced microvascular obstruction and CRP levels during the index hospitalization, without affecting the troponin curve. Furthermore, treatment with tocilizumab lead to modification of five proteins associated with the acute phase response, including monocyte chemoattraction, and neutrophil function, as identified through aptamer-based proteomics.[103] This data began to reinforce the potential importance of the IL-6 blockade in CVDs. Similarly, pre-procedural administration of colchicine has been found to attenuate the increase in IL-6 and hsCRP in 400 individuals undergoing elective percutaneous coronary intervention.[104] However, no benefits on the risk of percutaneous coronary intervention-related myocardial injury were reported.

This therapeutic ambiguity highlights the need for a nuanced, temporally tailored approach to IL-6 modulation. Rather than broad or continuous inhibition, selective targeting of specific IL-6 signalling pathways—such as trans-signalling via the sIL-6R—may offer a more refined strategy that mitigates harmful inflammation while preserving reparative processes. Furthermore, understanding the timing, cellular sources, and receptor dynamics of IL-6 signalling will be crucial for optimizing its therapeutic modulation. This may also involve combining IL-6-targeting therapies with agents that modulate fibrosis, immune cell recruitment, or metabolic responses to injury.

5.2 | Cardiac fibrosis and heart failure

IL-6 is also critically involved in the pathophysiology of cardiac fibrosis (CF) and HF, acting as a potent regulator of inflammatory and remodelling processes in the myocardium.[105] In CF, regardless of aetiology, fibroblast activation and migration, matrix metalloproteinase activation, and accumulation of collagen,

glycoproteins, and proteoglycans lead to scar formation and stabilization.[106,107] IL-6 promotes fibrosis via MAPK- and CAMKII-STAT3–dependent pathways and acts downstream of hypoxia-induced mitogenic factor, with its inhibition preventing fibroblast activation.[108,109] IL-6 overexpression amplifies TGF-β1-mediated MMP2/MMP3 signalling, enhancing myofibroblast proliferation, differentiation, and fibrotic matrix deposition.[110] Experimental models demonstrate that IL-6 knockout mice develop less CF,[111] preserve better cardiac function, and exhibit reduced cardiomyocyte apoptosis in dilated cardiomyopathy through STAT3 inhibition.[112] Fibroblast-derived IL-6 directly activates STAT3 following myocardial infarction,[113] and its genetic deletion attenuates cardiac hypertrophy and fibrosis after angiotensin II stimulation.[114]

In HF, inflammatory biomarkers such as hsCRP and IL-6 predict incident HF, adverse remodelling, and worse outcomes despite optimal medical therapy.[115–119] In the BIOSTAT-CHF cohort, elevated IL-6 levels predicted HF hospitalization, cardiovascular mortality, and all-cause mortality, and correlated with NT-proBNP, procalcitonin, TNF-α, IL-1, and hepcidin,[120] the latter—together with IL-6—being a major regulator of systemic iron metabolism and iron-deficiency anaemia commonly associated with HF.[121] The CANTOS trial provided proof-of-concept that cytokine inhibition can improve HF outcomes: higher baseline IL-6 predicted a two-fold increased risk of HF hospitalization, and canakinumab reduced incident HF events in a dose-dependent manner, with the greatest benefit in patients achieving the largest reductions in inflammation.[122] IL-6 blockade emerges as a promising strategy to attenuate CF across HF phenotypes, including HF with preserved ejection fraction.[123] Furthermore, standard HF therapies—β-blockers, renin–angiotensin–aldosterone system inhibitors, mineralocorticoid receptor antagonists, and sodium–glucose cotransporter 2 inhibitors—possess anti-inflammatory properties that may contribute to their capacity to counteract CF, promote reverse remodelling, improve endothelial barrier function, and reduce inflammatory cell recruitment by modulating NF-κB signalling, monocyte chemoattractant protein-1, TNF-α, IL-6, hsCRP, NLRP3 inflammasome, and adhesion molecules such as ICAM-1, VCAM-1, P- and E-selectin.[124–127]

6 | INTERLEUKIN-6 IN THE CARDIO-RENAL CONTINUUM

The kidney is both a target and a potent amplifier of systemic inflammation, with IL-6 playing a role in the bidirectional cardio-renal interaction. In the setting of chronic kidney disease (CKD), IL-6 is produced locally by mesangial cells, podocytes, and tubular epithelial cells in response to ischemic, metabolic, or hemodynamic stress.[128–132] These cells express both membrane-bound and soluble IL-6 receptors, allowing for classical and trans-signalling activation.[130] The downstream JAK/STAT3, MAPK, and NF-κB pathways drive the expression of adhesion molecules, monocyte chemoattractant protein-1, and profibrotic mediators such as collagen I, PAI-1, and TGF-β, promoting endothelial dysfunction, mesangial proliferation, and tubulointerstitial fibrosis.[133–135] Experimental models of hypertensive, diabetic, and ischemia–reperfusion nephropathy demonstrate that IL-6 blockade or genetic deletion attenuates macrophage infiltration, fibrotic remodelling, and albuminuria, underscoring its causal role in progressive renal injury.[128,136–141]

Clinically, IL-6 levels increase in parallel with the severity of renal dysfunction and independently predict accelerated decline in estimated glomerular filtration rate (eGFR) and progression to end-stage kidney disease.[142–144] In the Chronic Renal Insufficiency Cohort (CRIC) study and other longitudinal cohorts, individuals in the highest IL-6 quartile had approximately 40–60% higher risk of CKD progression and cardiovascular death compared with those in the lowest quartile, even after adjustment for traditional risk factors and CRP.[145–148] IL-6 also contributes to the anaemia of CKD via induction of hepatic hepcidin, which suppresses intestinal iron absorption and promotes iron sequestration within macrophages, further enhancing oxidative stress and tissue hypoxia.[149,150] Elevated IL-6 concentrations in CKD are strongly associated with vascular stiffness, coronary calcification, and left-ventricular hypertrophy, reflecting its capacity to extend renal inflammation to systemic vascular and cardiac compartments.[144,151–153] This mechanistic link defines a “cardio-renal inflammatory loop”, in which renal dysfunction fuels systemic IL-6 production, and IL-6 in turn aggravates vascular injury and cardiac remodelling. The consequence is a state of chronic low-grade inflammation that accelerates atherosclerosis, thrombosis, and progression of heart failure. Importantly, in patients with CKD or on dialysis, IL-6 and hsCRP outperform LDL-cholesterol as predictors of adverse cardiovascular events, highlighting the predominant role of inflammation over lipid burden in this population.[154,155] Furthermore, IL-6 levels predict responsiveness to erythropoiesis-stimulating agents (ESA) and long-term mortality, further supporting its pathophysiological centrality. Indeed, in a phase 1/2 randomized, placebo-controlled trial, ziltivekimab administered intravenously every 2 weeks for 12 weeks led to dose-dependent reductions in ESA usage, ESA resistance index, and increases in serum iron, transferrin saturation, and albumin, without dose-limiting toxicity.[156]

Given this convergence of renal and cardiovascular inflammation, IL-6 signalling has emerged as a compelling therapeutic target in CKD. By interrupting the JAK/STAT3 axis and reducing hepatic acute-phase protein synthesis, IL-6 inhibition could mitigate systemic inflammation, preserve renal function, and reduce atherothrombotic risk. This rationale underpins ongoing trials testing IL-6 blockade in CKD and dialysis populations (detailed in the upcoming paragraph), where suppression of IL-6–mediated inflammation may help to break the vicious cycle linking kidney injury, vascular dysfunction, and cardiovascular death.

7 | THE OLYMPIAN ERA OF ANTI-IL-6 TRIALS

Over the past decade, increasing mechanistic and clinical evidence has positioned IL-6 as a central driver of residual inflammatory risk in cardiovascular disease, with promising implications for targeted therapy. The proof-of-concept that modulating the IL-1β–IL-6 signalling axis can reduce CV event rates was established by CANTOS, which demonstrated that lowering downstream IL-6 levels through IL-1β inhibition significantly reduced major adverse cardiovascular events (MACE).[12,13] However,

TABLE 1 Ongoing Phase III trial for IL-6 inhibiting agents with cardiovascular outcomes.

	NCT ID	Estimated study completion	Estimated enrollment	IL-6 inhibitor	Population	Endpoints
ZEUS	NCT05021835	June 2026	6200	Ziltivekimab	Patients with established atherosclerotic cardiovascular disease, chronic kidney disease and systemic inflammation	Composite endpoint consisting of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke
HERMES	NCT05636176	July 2027	5600	Ziltivekimab	Patients with heart failure with mildly reduced or preserved ejection fraction and systemic inflammation	Composite heart failure endpoint consisting of cardiovascular death, heart failure hospitalization or urgent HF visit
ATHENA	NCT06200207	January 2027	680	Ziltivekimab	Patients with heart failure with mildly reduced or preserved ejection fraction and systemic inflammation	Change in Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score (KCCQ-CSS)
ARTEMIS	NCT06118281	September 2026	10,000	Ziltivekimab	Patients with acute myocardial infarction	Composite endpoint consisting of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke
POSIBIL6ESKD	NCT05485961	August 2029	2310	Clazakizumab (CSL 300)	Patients with end-stage kidney disease undergoing dialysis	Composite endpoint consisting of cardiovascular death or myocardial infarction

IL-1β antagonism is associated with high costs and potential adverse effects, and canakinumab is not approved for CV prevention, which has shifted attention toward directly inhibiting IL-6 as a potentially more efficient and specific strategy (Table 1).

Patients with CKD represent an especially compelling target population for IL-6–directed interventions. CKD confers a high absolute CV risk, is characterized by persistent systemic inflammation, and limits the use of other anti-inflammatory therapies such as colchicine due to renal excretion.[157] In this context, the phase IIb RESCUE trial evaluated the IL-6 ligand–blocking monoclonal antibody ziltivekimab in patients with CKD and elevated hsCRP. Treatment led to an approximately 80% reduction in hsCRP to levels below 2 mg/L, a magnitude of inflammatory lowering nearly double that achieved in CANTOS, without adversely affecting lipid profiles or causing significant cytopenias or injection-site reactions over 24 weeks.[158] Although limited by sample size and duration, these findings provided the rationale for advancing ziltivekimab into multiple phase III cardiovascular outcome trials.

The largest of these, ZEUS (Ziltivekimab Cardiovascular Outcomes Study; NCT05021835), is enrolling 6200 patients with stage 3–4 CKD and elevated hsCRP to determine whether chronic IL-6 inhibition reduces the incidence of MI, stroke, and CV death. Secondary objectives include assessing the effect of ziltivekimab on renal disease progression, measured by estimated glomerular filtration rate decline, changes in urinary albumin-to-creatinine ratio, and development of end-stage renal disease. The trial will also stratify outcomes by baseline left ventricular ejection fraction, enabling analysis of effects across HF phenotypes.

Beyond CKD, IL-6 inhibition is being tested in HF populations with elevated inflammatory activity, where it is hypothesized to mitigate adverse remodelling by reducing CF, microvascular dysfunction, and systemic inflammation.[159] The HERMES trial (A Research Study to Look at How Ziltivekimab Works Compared to Placebo in People With Heart Failure and Inflammation; NCT05636176) is a phase III, randomized, double-blind, placebo-controlled study enrolling approximately 5600 patients with HF with preserved ejection fraction (HFpEF) or mildly reduced ejection fraction (HFmrEF), elevated NT-proBNP, echocardiographic evidence of structural or functional abnormalities, and hsCRP ≥2 mg/L. Participants receive monthly 15 mg ziltivekimab or placebo in addition to standard care, with the primary endpoint being time to first CV death, HF hospitalization, or urgent HF visit.

Two additional phase III studies are expanding the evaluation of ziltivekimab. ATHENA (A Research Study Looking Into How Ziltivekimab Works Compared to Placebo in Participants With Heart Failure and Inflammation, NCT06200207) enrols 680 patients with HFpEF and systemic inflammation (hsCRP ≥2 mg/L) to test whether IL-6 blockade can improve patient-reported quality of life, assessed by the Kansas City Cardiomyopathy Questionnaire clinical summary score over 12 months. Meanwhile, the ARTEMIS trial (A Research Study to Look at How Ziltivekimab Works Compared to Placebo in People With a Heart Attack, NCT06118281) is designed to evaluate the efficacy and safety of ziltivekimab in approximately 10,000 patients with recent ACS. Patients are enrolled within 14 days post-ACS and randomized to receive monthly subcutaneous injections of ziltivekimab at doses ranging from 7.5 to 30 mg, or placebo, in addition to standard of care. The primary endpoint is a composite of MACE, including CV death, nonfatal MI, and stroke. By targeting IL-6–mediated inflammation early in the post-infarction period, ARTEMIS aims to assess whether IL-6 inhibition can reduce residual inflammatory risk and improve long-term CV outcomes in this high-risk population.

While most current phase III programs focus on ziltivekimab, other IL-6–targeting agents are advancing in selected high-risk groups. Clazakizumab, an IL-6 ligand inhibitor, is under investigation in the phase III POSIBIL6ESKD trial (Combined Dose-Finding and CV Outcomes Study With CSL300 (Clazakizumab) in Adult Subjects With ESKD Undergoing Dialysis, NCT05485961), enrolling patients with end-stage kidney disease, diabetes, or established atherosclerotic CVD and elevated hsCRP. The primary endpoint is time to CV death or MI, with long-term follow-up planned to assess safety in this complex and underserved population.

Together, these ongoing phase III studies will address whether direct IL-6 inhibition can safely and effectively reduce CV events across different high-risk groups. If successful, IL-6–targeted therapy could represent the first precision anti-inflammatory approach broadly applicable in CV prevention, offering a new therapeutic pillar alongside lipid-lowering, antithrombotic, and neurohormonal modulation strategies. While most ongoing trials focus on cardiovascular outcomes, IL-6 blockade may have broader implications. Preclinical and translational studies suggest that IL-6 modulation could benefit other organs commonly affected by chronic inflammatory stress, including the kidney and metabolic tissues. Beyond attenuating vascular inflammation, IL-6 inhibition may help preserve renal function and improve metabolic homeostasis through indirect effects on insulin sensitivity, lipid metabolism, and hepatic acute-phase responses. These hypotheses remain to be confirmed in dedicated clinical studies, but collectively they highlight the potential of IL-6–targeted therapy as a strategy to address residual inflammatory risk in a multi-organ context.

8 | CONCLUSION

IL-6 is a prime driver of cardiovascular inflammation, linking systemic inflammation to vascular dysfunction, atherosclerosis, myocardial fibrosis, and adverse cardiac remodelling. Yet, IL-6 signalling exerts context-dependent effects: transient, classic signalling via the membrane-bound IL-6 receptor promotes tissue repair, metabolic adaptation, and cardioprotection in acute injury or infection, whereas persistent or excessive activation (particularly through trans-signalling) triggers endothelial activation, immune cell recruitment, and chronic inflammatory damage. Thus, the net impact of IL-6 depends on timing, receptor engagement, signalling pathway, and cellular context, highlighting its double-edged role in cardiovascular pathophysiology and other organ systems such as the kidney. Epidemiological, genetic, and mechanistic evidence supports a causal role of IL-6 in CV health and disease. Early clinical studies indicate that IL-6 inhibition can substantially lower systemic inflammatory markers with an acceptable short-term safety profile, but the key question remains whether such interventions can translate into improved cardiovascular outcomes, and which patient subgroups are most likely to benefit. Future strategies will need to modulate IL-6 activity with precision, attenuating its pathogenic effects while preserving its homeostatic and reparative functions, to complement existing therapies and address residual inflammatory risk in CVD.

AUTHOR CONTRIBUTIONS

AP, AT, and GL drafted the first version of the manuscript and provided the figures and the table. LL conceptualized the article and revised the first draft. All authors provided critical feedback, helped to shape the manuscript and approved the final version.

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CONFLICT OF INTEREST STATEMENT

LL and GGC are coinventors on the International Patent WO/2020/226993 filed in April 2020; the patent relates to the use of antibodies which specifically bind interleukin-1a to reduce various sequelae of ischemia–reperfusion injury to the central nervous system. LL has received financial support from the Swiss Heart Foundation and the Novartis Foundation for Medical-Biological Research outside of this work. SK declares research grants to the institution from the Cantonal Hospital Baden, the Jubiläumsstiftung SwissLife, the Lindenhof Foundation, the Novartis Foundation for Medical-Biological Research, the Swiss Heart Foundation, the Swiss Society of Cardiology, and the Theodor-Ida-Herzog-Egli Foundation. He has also received speaker fees from Roche Diagnostics and the Foundation for Cardiovascular Research—Zurich Heart House. He has also received equipment and materials from Roche Diagnostics outside the submitted work. Travel support, again unrelated to this work, was received from the European Atherosclerosis Society, the European Society of Cardiology, the European Society of Clinical Investigation, Sphingotec GmbH, the 4TEEN4 Pharmaceuticals GmbH, and PAM Theragnostics GmbH. SK is a consultant to and scientific advisory board member of MDCalc.

DATA AVAILABILITY STATEMENT

No new data is presented in this work.

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