State-of-the-Art
by EuroIntervention

Targeting inflammation in atherosclerosis: overview, strategy and directions

Ron Waksman[1]*, MD; Ilan Merdler[1], MD, MHA; Brian C. Case[1], MD; Ori Waksman[1], MD;
Italo Porto[2,3], MD, PhD

*Corresponding author: MedStar Washington Hospital Center, 110 Irving St. NW, Suite 4B-1, Washington, D.C., 20010, USA.
E-mail: ron.waksman@medstar.net
The authors' affiliations can be found at the end of this article.

ABSTRACT

Atherosclerosis is a chronic condition characterised by the build-up of plaque in the inner lining of the blood vessels and it is the main underlying cause of cardiovascular disease. The development of atherosclerosis is associated with the accumulation of cholesterol and inflammation. Although effective therapies exist to lower low-density lipoprotein cholesterol (LDL-C) levels, some patients still experience cardiovascular events due to persistent inflammation, known as residual inflammatory risk (RIR). Researchers have conducted laboratory and animal studies to investigate the measurement and targeting of the inflammatory cascade associated with atherosclerosis, which have yielded promising results. In addition to guideline-directed lifestyle modifications and optimal medical therapy focusing on reducing LDL-C levels, pharmacological interventions targeting inflammation may provide further assistance in preventing future cardiac events. This review aims to explain the mechanisms of inflammation in atherosclerosis, identifies potential biomarkers, discusses available therapeutic options and their strengths and limitations, highlights future advancements, and summarises notable clinical studies. Finally, an evaluation and management algorithm for addressing RIR is presented.

While reduction of low-density lipoprotein cholesterol (LDL-C) remains the mainstay of secondary atherosclerotic cardiovascular disease (ASCVD) treatment, the prevention and attenuation of systemic inflammation have emerged as targets of interest in patients with recurrent events[1]. The association between heightened systemic inflammation and increased ASCVD risk is supported by large clinical, observational and epidemiological studies. Furthermore, landmark randomised control trials exploring the use of anti-inflammatory agents to attenuate systemic inflammation have demonstrated significant reductions in secondary ASCVD events[2].

Despite this evidence, preventative guidelines and commonly used ASCVD risk algorithms remain unclear regarding the clinical utility of inflammatory biomarkers in routine practice, and a significant proportion of patients continue to experience adverse cardiac events despite optimised LDL-C levels[3]. The significant impact of inflammation on the development of atherosclerosis implies the existence of an additional mechanism and an overlooked residual inflammatory risk (RIR). This review summarises the relevant mechanisms of atherosclerosis and provides an assessment of current increased inflammatory risk biomarkers, RIR enhancers, and therapies. Additionally, emerging therapeutic agents, future perspectives and suggested strategies are discussed.

Mechanism of atherosclerosis and inflammation

Atherosclerotic lesions, often referred to as plaques, develop within the arterial intima. Inflammation plays a pivotal role in all stages of atherosclerosis (Figure 1) and involves various immune cells in the body[4,5]. Macrophages can be categorised as M1 (proinflammatory) or M2 (anti-inflammatory) and maintaining a balance between the two is crucial for disease progression or regression[6,7]. Monocyte chemoattractant protein-1 (MCP-1), vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) play significant roles by recruiting monocytes and macrophages[8,9]. T and B lymphocytes also contribute to atherosclerosis, with abnormal numbers of lymphocytes being an independent risk factor. Different subsets of T cells, such as Th1, Th2, and Th17, release specific cytokines with proinflammatory or regulatory effects. CD8+ cells have a protective effect by limiting Th1 cells and macrophages. B cells regulate inflammation through interleukin (IL)-10 production, and decreased IL-10+ B cells are associated with inflammation in atherosclerosis patients[10,11]. Neutrophils form neutrophil-extracellular-traps (NETs) and contribute to inflammation through cholesterol crystal-induced release of NETs[12-14]. The nod-like receptor family pyrin domain containing 3 (NLRP3) inflammasome plays a crucial role in the initiation and progression of atherosclerosis by promoting vascular inflammation and interfering with lipid metabolism[15]. Mast cells, natural killer cells, and dendritic cells also have roles in promoting atherosclerosis through various mechanisms, including enzymatic degradation, foam cell formation, and cytokine production[16-18]. It is also worth mentioning that inflammation and the thrombotic cascade are closely connected, where inflammation triggers and amplifies the thrombotic response, resulting in blood clot formation in specific pathological conditions.

Identifying inflammatory risk

Elevated biomarker levels may identify patients who could benefit from inflammation reduction therapy. Additionally, biomarkers can be used to assess treatment response. Regarding the identification of inflammatory risk, some biomarkers are currently used in clinical practice, while others are still primarily utilised in research studies (Table 1).

HIGH-SENSITIVITY C-REACTIVE PROTEIN

C-reactive protein (CRP) is probably the most promising biomarker and has the largest amount of investigated data. CRP is an acute-phase protein produced by the liver and it can be detected in the blood. CRP synthesis is induced by IL-1, IL-6, and tumour necrosis factor (TNF)-α. High-sensitivity CRP (hs-CRP) assays have been developed to detect minor changes in plasma CRP concentrations, and elevated levels of hs-CRP have been associated with a higher incidence of cardiovascular events. Studies usually refer to hs-CRP ≥2 mg/L as the cutoff for increased risk for cardiovascular disease[19]. Several cardiovascular prediction algorithms (such as the Reynolds Risk Score) showed promising results when adding hs-CRP to a clinical risk prediction model[20]. Very high and very low CRP values were shown to be clinically useful for risk prediction[21]. The JUPITER trial suggested 15 years ago that elevated hs-CRP levels, rather than other factors, are responsible for high cardiovascular event rates[22]. According to guidelines, hs-CRP is not currently indicated for decision-making, and there is limited information on hs-CRP distribution. The downside of this marker is the lack of specificity[23-25]. There is no established cutoff to indicate the value which might be linked to infection rather than atherosclerosis, but the suggested values in the literature are more than 10 times higher than the 2 mg/L usually referred to[26]. A combined analysis from the PROMINENT, REDUCE-IT, and STRENGTH trials examined hs-CRP and LDL-C as predictors of major adverse cardiovascular events, cardiovascular death, and all-cause death[27]. The study concluded that, for patients taking statins, inflammation assessed by hs-CRP might be a better marker than LDL-C levels to predict the risk of future cardiovascular events and death.

OTHER INFLAMMATORY MARKERS

Fibrinogen influences clotting, platelets, and blood health and thickness, while elevated levels hinder circulation and

Abbreviations

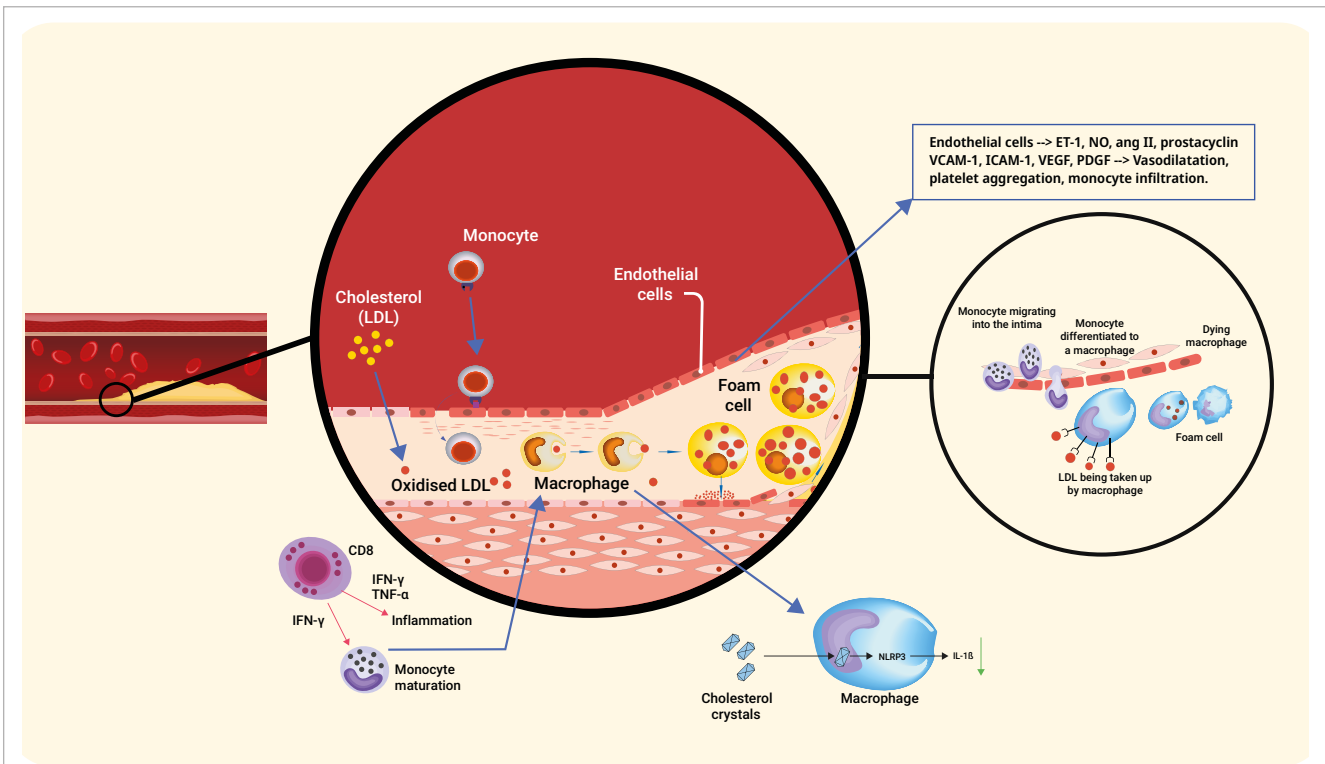|	
ASCVD	atherosclerotic cardiovascular disease
CRP	C-reactive protein
hs-CRP	high-sensitivity C-reactive protein
LDL-C	low-density lipoprotein cholesterol
MI	myocardial infarction
RIR	residual inflammatory risk

Figure 1. *Mechanism of inflammation in atherosclerosis. ang II: angiotensin II; CD8: cluster of differentiation 8; ET-1: endothelin-1; ICAM-1: intercellular adhesion molecule-1; IFN: interferon; IL: interleukin; LDL: low-density lipoprotein; NLRP: nod-like receptor family pyrin; NO: nitric oxide; PDGF: platelet-derived growth factor; TNF: tumour necrosis factor; VCAM-1: vascular cell adhesion molecule-1; VEGF: vascular endothelial growth factor*

contribute to artery hardening. Uric acid, from purine breakdown, is associated with hypertension, heart disease, and strokes, and is common in gout and kidney disease[28].

Lipoprotein(a) [Lp(a)], an apolipoprotein (Apo) B-100, independently increases the risk of ASCVD by promoting atherosclerosis, inflammation, and thrombosis. Lp(a) shares structural similarities with plasminogen and tissue plasminogen activators, interfering with fibrinolysis and promoting coagulation. Additionally, Lp(a) carries cholesterol particles that contribute to atherosclerosis and binds proinflammatory oxidised phospholipids, attracting inflammatory cells and leading to smooth muscle cell proliferation[29]. Lp(a) holds significant relevance in assessing residual risk and warrants a dedicated review, beyond the scope of this review.

Promising novel biomarkers include oxidised LDL-C (linked to atherosclerosis)[30], midkine (linked to atherosclerosis)[31], specific microRNAs (associated with atherosclerosis and ischaemic events)[32], pentraxins such as PTX3 (linked to inflammation and coronary stenosis)[31], adrenomedullin (related to cardiovascular processes)[33], cystatin C (linked to subclinical atherosclerosis)[34], lipoprotein-associated phospholipase A2 (Lp-PLA2; indicative of intravascular inflammation)[35], and matrix metalloproteinases, particularly stromelysin-2 (linked to atherosclerosis)[36].

Inflammatory risk enhancers

Certain comorbidities independently contribute to inflammation and increased risk of ASCVD, regardless of LDL-C levels.

Table 1. Inflammatory markers.

Biomarker	Mechanism
High-sensitivity C-reactive protein	Acute phase protein, produced by the liver
	Its synthesis is induced by IL-1, IL-6 and TNF-α
	Studies usually refer to hs-CRP ≥2 mg/L as the cutoff
	Influenced by infection, general tissue damage, obesity, old age, hypertension, diabetes mellitus, and smoking
Fibrinogen	Affects platelet aggregation, endothelial function and is a major determinant of plasma viscosity
Uric acid	Independent risk factor for atherosclerotic cardiovascular disease and binds atherogenic proinflammatory oxidised phospholipids which, in turn, attract inflammatory cells
Lipoprotein(a)	Associated with the development of hypertension, coronary artery disease, and stroke
Novel biomarkers	Oxidised MDA-modified LDL-C, midkine, microRNAs, pentraxins, adrenomedullin, cystatin C, Lp-PLA2, matrix metalloproteinases

hs-CRP: high-sensitivity C-reactive protein; IL: interleukin; LDL-C: low-density lipoprotein cholesterol; Lp-PLA2: lipoprotein-associated phospholipase A2; MDA: malondialdehyde; RNA: ribonucleic acid TNF-α: tumour necrosis factor alpha

Type 2 diabetes mellitus is a well-established example involving a complex mechanism that includes atherogenic LDL-C, hyperglycaemia, oxidative stress, and heightened inflammation[37]. Hypertension is another recognised cardiac risk factor, with studies supporting an independent association between inflammatory markers and hypertension, although the temporal relationship is challenging to determine[38]. Systemic inflammatory conditions such as systemic lupus erythematosus and rheumatoid arthritis have been investigated and were shown to carry an elevated risk of cardiovascular disease and plaque rupture[39].

Smoking has been extensively studied and is known to induce endothelial dysfunction, macrophage recruitment, cytokine secretion, thrombosis, insulin resistance, dyslipidaemia, vascular inflammation, abnormal vascular growth, and angiogenesis. The Multi-Ethnic Study of Atherosclerosis (MESA) demonstrated that tobacco smoking is associated with early markers of cardiovascular injury, and smokers tend to have high levels of hs-CRP[40]. High or acute alcohol intake can augment nuclear factor kappa B (NF-κB) activation and TNF-α production and inhibit IL-10 levels[41]. A sedentary lifestyle can enhance inflammatory responses by reducing the numbers of circulating IL-10-secreting regulatory T cells and increasing proinflammatory monocytes[42]. Epidemiological studies have provided evidence linking air pollution to ASCVD. Inhaled small particles have been shown to contribute to endothelial dysfunction, thrombosis, vasoconstriction, and plaque instability[43]. Additionally, factors such as race, gender, and ethnicity play a significant role in risk enhancement[44]. It is often the less traditional risk factors that have the greater inflammatory-atherosclerotic predilection.

Anti-inflammatory intervention for atherosclerosis

The traditional approach of treating atherosclerosis focuses on controlling dyslipidaemia. This is usually done by lifestyle modifications and lipid-lowering medications. However, even when dyslipidaemia is well controlled, other risk factors need to be addressed. Several risk factors for atherosclerosis are non-modifiable, such as gender, race, advanced age, or family history of premature cardiovascular disease, while some are modifiable, such as diabetes mellitus, hypertension, and tobacco use. Despite optimal therapy to address the modifiable risk factors, many patients remain at increased risk of cardiac events due to persistent inflammation. This is referred to as the RIR, which could be a pharmacological target[45-47]. This topic is vast, and we will focus on lipid-lowering and anti-inflammatory medications **(Table 2)**. We summarise the available therapeutic options, their correlation to inflammation, and the available clinical data **(Central illustration)**.

Lifestyle modification

Lifestyle management – focusing on diet, smoking cessation, and exercise – is key in preventing ASCVD. Recommended diets include those that are low in saturated fats, sugar, alcohol, and sodium and high in polyunsaturated fats, potassium, vitamins, and fibre. Weight loss alone may not significantly reduce atherosclerosis, so exploring antioxidant-rich foods is worthwhile. While dietary regimens have limited impact on LDL-C reduction, the Dietary Approaches to Stop

Table 2. Prominent anti-inflammatory interventions.

Treatment	Mechanism
Lifestyle modifications	Fruits, vegetables, whole grains, fibre, probiotics, sleep, stress decrease and exercise have been linked to inflammation reduction by inhibiting the production of proinflammatory cytokines, limiting neutrophil migration, and positively influencing phagocytosis Physical activity can stimulate anti-inflammatory responses by increasing circulating numbers of IL-10-secreting regulatory T cells and reducing circulating numbers of proinflammatory monocytes
Lipid-lowering medications	
Statins	1. Inhibit chemokine release and Th1-type chemokine receptors on T cells 2. Inhibit NF-κB, TNF-α and IL-1β 3. Decrease the number of inflammatory cells in atherosclerotic plaques
Ezetimibe	1. Decreases macrophage content and monocyte chemoattractant protein-1 expression in atherosclerotic lesions 2. Reduces the activity of NF-κB
PCSK9 inhibitors	Possible decrease in stimulation and translocation of NF-κB
Anti-inflammatory medications	
Colchicine	Inhibits cytoskeletal microtubule polymerisation, leading to inhibition of vesicular secretion of inflammatory signals and preventing activation of the NLRP3 inflammasome by cholesterol crystals and reducing the release of IL-1β
Canakinumab	Anti-IL-1β monoclonal antibody
Tocilizumab	A monoclonal antibody against IL-6 receptor
Ziltivekimab	Antibody directed against IL-6 ligand

IL: interleukin; NF-κB: nuclear factor kappa B; NLRP3: nod-like receptor family pyrin domain containing 3 inflammasome; PCSK9: proprotein convertase subtilisin/kexin type 9; TNF: tumour necrosis factor

Hypertension (DASH) and Mediterranean diets have anti-inflammatory effects[48,49]. Specific elements such as alpha-lipoic acid, arachidonic acid[50], resolvins[51], and long-chain n-3 polyunsaturated fatty acids can reduce inflammation[52]. Physical activity also reduces inflammation and positively affects atherosclerosis and cardiac health[53]. Smoking cessation is a well-established lifestyle change for ASCVD prevention[54].
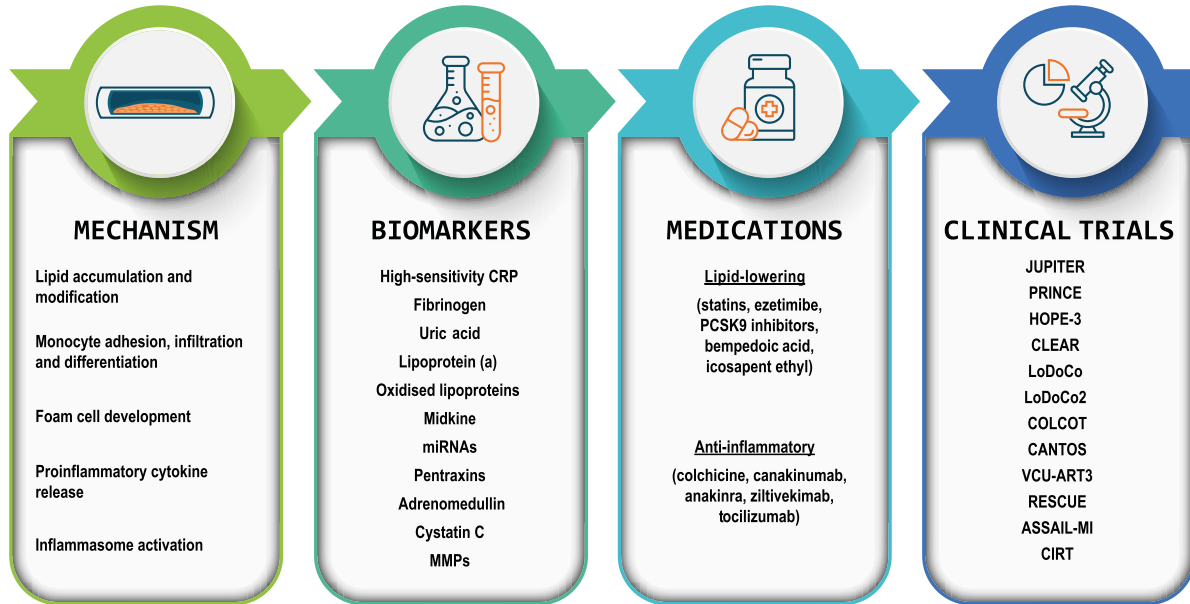
Lipid-lowering drugs
STATINS
Statins are also known as 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors and have long been used as a treatment for atherosclerosis[55]. The mechanism of this class of medications is to inhibit HMG-CoA reductase and block the intracellular mevalonic acid metabolism pathway, reducing intracellular cholesterol synthesis. This leads to an increase in the number and activity of LDL-C receptors on the cell membrane surface, which clears serum cholesterol.

Statins are mainly used in the treatment of atherosclerosis due to their cholesterol-lowering action, which not

Mechanisms of inflammation in atherosclerosis, biomarkers of inflammation in atherosclerosis, potential treatments, and prominent clinical trials.

Targeting residual inflammatory risk in atherosclerosis

MECHANISM	BIOMARKERS	MEDICATIONS	CLINICAL TRIALS
Lipid accumulation and modification	High-sensitivity CRP	**Lipid-lowering** (statins, ezetimibe, PCSK9 inhibitors, bempedoic acid, icosapent ethyl)	JUPITER
	Fibrinogen		PRINCE
Monocyte adhesion, infiltration and differentiation	Uric acid		HOPE-3
	Lipoprotein (a)		CLEAR
Foam cell development	Oxidised lipoproteins		LoDoCo
	Midkine		LoDoCo2
	miRNAs	**Anti-inflammatory** (colchicine, canakinumab, anakinra, ziltivekimab, tocilizumab)	COLCOT
Proinflammatory cytokine release	Pentraxins		CANTOS
	Adrenomedullin		VCU-ART3
	Cystatin C		RESCUE
Inflammasome activation	MMPs		ASSAIL-MI
			CIRT

Proposed strategy for diagnosis and management of residual inflammatory risk
Atherosclerosis → Lifestyle changes and optimal medical therapy → Measure hs-CRP
hs-CRP >2 mg/L → Consider anti-inflammatory therapy (colchicine)

Ron Waksman *et al.* • *EuroIntervention* 2023;19:e32-e44 • DOI: 10.4244/EIJ-D-23-00606

hs-CRP: high sensitivity C-reactive protein; IL: interleukin; miRNA: microRNA; MMPs: matrix metalloproteinases; PCSK9: proprotein convertase subtilisin/kexin type 9

only reduces total cholesterol (TC) and LDL levels but also reduces triglyceride (TG) levels and improves high-density lipoprotein (HDL) levels. In addition, statins have anti-inflammatory properties, which are exhibited by a reduction in the release of C-reactive peptide, chemokines, cytokines, and adhesion molecules and modulation of T-cell activity. Statins inhibit the migration of leukocytes due to a decrease in the expression of adhesion molecules ICAM-1, lymphocyte function-associated antigen-1, and monocyte chemotactic protein-1; they also inhibit NF-κB, TNF-α, and IL-1β, thus decreasing the number of inflammatory cells in atherosclerotic plaques[56].

The relationship between statin therapy and hs-CRP is important when discussing RIR. In the PROVE-IT TIMI 22 study, subjects who achieved hs-CRP levels <2 mg/L had fewer cardiovascular events, independent of LDL-C reduction[57]. The combination of simvastatin and ezetimibe yielded comparable results in the IMPROVE-IT study[58]. In the JUPITER study, the magnitude of hs-CRP reduction achieved with rosuvastatin was proportional to the reduction in cardiovascular risk[22]. Statins may be categorised by intensity and dose[59]. Zhang et

al published a meta-analysis examining CRP levels in various types and doses of statins and showed that simvastatin 40 mg/day might be the most effective therapy; atorvastatin 80 mg/day showed the best long-term effect[60]. The Pravastatin Inflammation/CRP Evaluation (PRINCE) trial demonstrated that pravastatin 40 mg/day significantly reduced plasma CRP levels independent of any changes in LDL-C levels, and the HOPE-3 (Heart Outcomes Prevention Evaluation-3) study on intermediate-risk participants without cardiovascular disease supported the hs-CRP-lowering effect of rosuvastatin regardless of CRP and lipid levels at baseline[56,61].

EZETIMIBE
Ezetimibe inhibits intestinal cholesterol absorption by selectively blocking the Niemann-Pick C1-Like 1 (NPC1L1) protein in the jejunal brush border, affecting the uptake of intestinal lumen micelles into the enterocyte. Ezetimibe might decrease macrophage content and monocyte chemoattractant protein-1 expression[62]. Morrone et al reported higher levels of hs-CRP reduction with a combination therapy of ezetimibe and statins than for monotherapy with statins[63].

PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9 INHIBITORS

Proprotein convertase subtilisin/kexin type 9 (PCSK9) binds to LDL receptors and targets them for lysosomal degradation. PCSK9 inhibitors (PCSK9-i) prevent this process, and the first two types of PCSK9-i approved by the U.S. Food and Drug Administration (FDA) were alirocumab and evolocumab (both monoclonal antibodies). These therapies are recommended for patients with high LDL-C levels despite statin therapy and to treat patients who cannot tolerate statins because of adverse side effects. A relatively new approach to block PCSK9 synthesis includes inclisiran, a double-stranded small-interfering RNA that specifically targets and induces PCSK9 messenger RNA (mRNA) degradation. PCSK9-i have shown a significant reduction in cardiovascular events in clinical trials[64].

An analysis from the FOURIER trial showed that LDL-C reduction with evolocumab reduces cardiovascular events across all hs-CRP strata, with greater absolute risk reductions in patients with higher baseline hs-CRP levels[65]. However, in a *post hoc* analysis of the SPIRE trials in a stable outpatient population, evidence of residual inflammatory risk persisted among patients treated with both statin therapy and PCSK9-i[66]. Animal models have shown PCSK9 to have structural homology to a domain on resistin, an adipocyte-specific hormone, which manages proinflammatory stimulation and nuclear translocation of NF-κB, and this might add anti-inflammatory properties[67]. Rosenson and Goonewardena revealed immune-modulating properties of this group of medications by profiling immune cells and examining specific changes[68]. PCSK9-i have been shown to reduce monocyte levels of intracellular lipids and improve monocyte phenotypes with decreased monocyte migration[69]. This contradicts clinical trials that have not shown changes in inflammatory markers, suggesting that ASCVD event reduction by PCSK9-i is solely because of LDL-C lowering. Another important study to highlight is the PACMAN-AMI trial, which demonstrated that, in patients with acute myocardial infarction, the inclusion of subcutaneous biweekly alirocumab, alongside high-intensity statin therapy, led to significantly greater coronary plaque regression in non-infarct-related arteries after 52 weeks when compared to the placebo group[70].

OTHER LIPID-LOWERING THERAPIES

Bempedoic acid (BA) reduces LDL-C and hs-CRP, similarly to statins, potentially addressing both inflammatory and cholesterol risks without replacing statins[71]. Lomitapide and mipomersen have potential anti-inflammatory effects for familial hypercholesterolaemia[72,73]. Icosapent ethyl, used for severe hypertriglyceridaemia and ASCVD, may have anti-inflammatory properties by inhibiting IL-1β and IL-6[74]. HDL may have anti-inflammatory properties, reversing LDL-C effects, and high hs-CRP levels are linked to HDL dysfunction[75].

Targeting inflammatory pathways

The ongoing research in this rapidly evolving field continues to identify potential new medications and biomarkers. We will focus on known medications and relevant prominent studies with significant clinical outcomes **(Table 3)**.

Table 3. Summary of prominent clinical trials.

Name of study	Medication	Inflammatory results	Clinical outcomes
CANTOS[2] (2017)	canakinumab	Reduced hs-CRP values compared to baseline and placebo	Patients with hs-CRP levels that dropped below 2 mg/L had a significant 25% reduction in major events
VCU-ART3[83] (2020)	anakinra	Hs-CRP was significantly lower in patients receiving anakinra versus placebo	The incidence of death or new-onset heart failure or of death and hospitalisation for heart failure was significantly lower with anakinra versus placebo
ASSAIL-MI[106] (2021)	tocilizumab	A significant difference was seen in hs-CRP area under the curve in tocilizumab patients compared to placebo	There was a 21% difference between the final infarct size at 6 months in the tocilizumab and placebo groups, but this difference was not statistically significant
RESCUE[84] (2021)	ziltivekimab	Median hs-CRP levels were significantly reduced compared to the placebo group	The medication was well tolerated, did not affect the total cholesterol to HDL cholesterol ratio, and there were no serious injection-site reactions
LoDoCo[78] (2013)	colchicine	N/A	Colchicine 0.5 mg/day administered in addition to statins and other standard secondary prevention therapies appeared effective for the prevention of cardiovascular events in patients with stable coronary disease
LoDoCo2[79] (2020)	colchicine	N/A	A composite of cardiovascular death, myocardial infarction, ischaemic stroke, or ischaemia-driven coronary revascularisation occurred less in patients taking colchicine
COLCOT[80] (2019)	colchicine	N/A	Time to first cardiovascular event in MI patients was better in patients on colchicine versus placebo
Combined analysis from the PROMINENT, REDUCE-IT, and STRENGTH trials[27] (2023)	-	Hs-CRP reduction was significantly associated with major adverse cardiovascular events	Inflammation-assessed hs-CRP might be a better marker than LDL-C levels to predict the risk of future cardiovascular events and death

HDL: high-density lipoprotein; hs-CRP: high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol; MI: myocardial infarction; N/A: not applicable

COLCHICINE

Colchicine works by inhibiting cytoskeletal microtubule polymerisation, leading to the inhibition of vesicular secretion of inflammatory signals and preventing activation of the NLRP3 inflammasome by cholesterol crystals and reducing the release of IL-1β[76]. In animal models, therapy with colchicine showed lower plasma CRP levels than therapy with atorvastatin, and a pilot study of 200 patients with clinically stable coronary artery disease (CAD) already receiving atorvastatin showed that 4 weeks of colchicine therapy led to a 60% decrease in hs-CRP levels[77].

The LoDoCo Trial (The effect of low dose colchicine on the natural history of patients with stable CAD) was a prospective, randomised, observer-blinded endpoint trial. A total of 532 patients with stable CAD receiving aspirin and/or clopidogrel and statins were randomly assigned colchicine 0.5 mg/day or no medication and were followed for a median of 3 years[78]. The primary outcome was defined as the composite incidence of acute coronary syndrome (ACS), out-of-hospital cardiac arrest, or ischaemic stroke. The primary outcome occurred in 5.3% of patients who received colchicine and in 16.0% of those who did not. In a secondary analysis that excluded 32 patients assigned to colchicine who withdrew within 30 days because of intestinal intolerance and 7 patients who did not start treatment, the primary outcome occurred in 4.5% versus 16.0% (p<0.001). The study concluded that colchicine 0.5 mg/day administered in addition to statins and other standard secondary prevention therapies appeared effective for the prevention of cardiovascular events in patients with stable coronary disease.

The LoDoCo2 Study was an investigator-initiated, double-blind, placebo-controlled trial that randomised 5,552 patients who had chronic coronary disease to take either colchicine 0.5 mg daily or a placebo[79]. The primary endpoint was defined as a composite of cardiovascular death, myocardial infarction, ischaemic stroke, or ischaemic-driven coronary revascularisation. The median follow-up was about 30 months. The primary endpoint occurred in 6.8% of patients in the colchicine group and 9.6% of patients in the placebo group (p<0.001). When the components of the primary endpoint were analysed separately, a consistent trend was seen with all endpoints, and myocardial infarction and ischaemia-driven coronary revascularisation were both significantly less frequent in the colchicine group. In this study, more than 90% of patients tolerated colchicine, with no significant side effects. The study concluded that colchicine might be a good choice for long-term prevention of cardiovascular events in patients with chronic coronary disease.

The Colchicine Cardiovascular Outcomes Trial (COLCOT) included a total of 4,745 patients who had experienced a myocardial infarction (MI) within the previous 30 days and were randomised to 0.5 mg colchicine or placebo (patients with stable coronary artery disease were not included in COLCOT, unlike in the LoDoCo trials). The primary composite endpoint was defined as the time to first event of one of the following: cardiovascular death, cardiac arrest, MI, stroke, or urgent hospitalisation for angina requiring coronary revascularisation[80]. All patients received guideline-directed medical therapy and percutaneous coronary intervention (PCI), if indicated, before randomisation. The follow-up length was only 23 months. The rate of the primary composite endpoint was significantly lower in the colchicine group than in the placebo group (5.1% vs 7.1%; p=0.004). Other adverse events were similar between the two groups except for nausea, flatulence, and pneumonia, all of which had rates that were significantly higher in the colchicine arm. The study implied that colchicine effectively reduces the risk of first ischaemic cardiovascular events compared to a placebo. The recently published MACT Pilot Study results focused exclusively on individuals with ACS undergoing PCI. The findings revealed that discontinuing aspirin one day after PCI and administering low-dose colchicine, alongside either ticagrelor or prasugrel, is not only safe but also linked to beneficial effects on platelet function and inflammatory profiles[81].

INTERLEUKINS AND CHEMOKINE INHIBITORS

Canakinumab is a human anti-IL-1β monoclonal antibody, and its mode of action is based on the neutralisation of 1β signalling, resulting in the suppression of inflammation. This medication has mostly been used for the treatment of autoimmune disorders.

The Canakinumab Anti-Inflammatory Thrombosis Outcome Study (CANTOS) was the first study to prove the benefit of targeting inflammation (published in 2017). The study evaluated the usage of three different doses of canakinumab (50 mg, 150 mg, and 300 mg) compared to placebo; the drug was administered subcutaneously every three months[2]. The primary endpoint of cardiovascular events, defined as non-fatal MI, non-fatal stroke, and cardiovascular death, was evaluated at 24 months. Over 17,000 patients were screened from 39 countries, with 10,061 patients successfully randomised. At 24 months, all three canakinumab arms showed a significant reduction in hs-CRP values as compared to baseline and the placebo arm. Both the 150 mg and 300 mg arms demonstrated a significant reduction in cardiovascular events as compared to the placebo arm. When combining the 150 mg and 300 mg arms together in comparison to the placebo arm, patients receiving canakinumab demonstrated a 39% relative risk reduction in hs-CRP values and a 15% relative risk reduction in the primary endpoint. Additionally, when looking at patients with hs-CRP levels above and below the median at enrolment, those with a higher hs-CRP at baseline benefitted more.

A subanalysis of the study looked at the group of CANTOS patients who achieved hs-CRP levels below 2 mg/L and compared them with subjects who had smaller reductions[82]. The reduction in hs-CRP after a single dose of canakinumab was a strong predictor of canakinumab efficacy. Those with hs-CRP levels that dropped below 2 mg/L had a significant 25% reduction in major events (p<0.0001). This finding suggests that a goal of less than 2 mg/L of hs-CRP is needed to adequately reduce RIR. The major side effect of canakinumab in CANTOS was a small increase in fatal infections. Criticism was mainly directed at the lack of a clear dose response, the increased risk for a fatal complication due to infection, the need for an injection, and the high cost of the medication.

Another interleukin inhibitor is anakinra, which is an IL-1 receptor antagonist. The Virginia Commonwealth University Anakinra Remodeling Trial 3 (VCU-ART3) was a randomised, placebo-controlled, double-blind, clinical trial that included 99 patients with ST-elevation myocardial infarction

(STEMI)[83]. The patients were assigned to 2 weeks of treatment with either anakinra once daily, anakinra twice daily, or placebo. The levels of hs-CRP were significantly lower in patients receiving anakinra versus placebo. The incidences of death or new-onset heart failure or of death and hospitalisation for heart failure were significantly lower with anakinra versus placebo (9.4% vs 25.7%; p=0.046 and 0% vs 11.4%; p=0.011). The incidence of serious infection was not different between the anakinra and placebo groups. Injection site reactions occurred more often in patients receiving anakinra versus placebo. The study concluded that in STEMI patients, an anti-inflammatory medication such as anakinra might reduce the inflammatory response and, thus, lead to better outcomes.

Ziltivekimab is a novel human antibody directed against the IL-6 ligand. The Trial to Evaluate Reduction in Inflammation in Patients with Advanced Chronic Renal Disease Utilizing Antibody Mediated IL-6 Inhibition (RESCUE) was a randomised, double-blind, phase 2 trial of participants (n=264) with moderate to severe chronic kidney disease and high-sensitivity CRP levels of at least 2 mg/L[84]. Subjects were randomly allocated to subcutaneous administration of placebo or ziltivekimab (at different doses) every 4 weeks for 24 weeks. The study compared the change in hs-CRP levels after 12 weeks of treatment as the primary outcome. At 12 weeks, median hs-CRP levels were reduced by 77% for the 7.5 mg group, 88% for the 15 mg group, and 92% for the 30 mg group, compared with 4% for the placebo group. Dose-dependent reductions were also seen for inflammatory markers. The medication was well tolerated, and there were no serious side effects. This study's outcomes are extremely strong, with considerable prognostic potential, and this IL-6 inhibitor might be considered as effective as canakinumab.

Tocilizumab and sarilumab are both monoclonal antibodies against the IL-6 receptors. Endothelial function was shown to be improved by tocilizumab in patients at high risk for CAD, despite increasing LDL-C. The trial ASSessing the Effect of Anti-IL-6 Treatment in Myocardial Infarction (ASSAIL-MI) was a double-blind, placebo-controlled, randomised study in patients with acute STEMI[85,86]. The participants were randomised to receive either a single infusion of 280 mg tocilizumab or placebo. The primary endpoint was the myocardial salvage index, which was measured by magnetic resonance imaging 3 to 7 days post-event. The tocilizumab group had higher myocardial salvage index scores, and a significant difference was seen in the CRP area under the curve, at a median of 1.9 mg/L/h (interquartile range [IQR] 0.9 to 4.9) in the tocilizumab patients compared to 8.6 mg/L/h (IQR 5.0 to 17.9) in the placebo group (p<0.001). There was a 21% difference between the final infarct size at 6 months in the tocilizumab and placebo groups, but this difference was not statistically significant (p=0.08). There was no difference in serious events (MI, coronary artery bypass grafting, subarachnoid haemorrhage, resuscitated ventricular fibrillation, ventricular tachycardia, chest pain, and ischaemic stroke) between the two groups (p=0.57).

MLN1202, a neutralising monoclonal antibody against CCR2, led to a notable reduction in hs-CRP, compared to placebo, in a preliminary study[87].

METHOTREXATE

Methotrexate inhibits lymphocyte proliferation and inflammatory cytokine production via adenosine binding with the A2 receptor. The Cardiovascular Inflammation Reduction Trial (CIRT) was a randomised, double-blind trial of low-dose (15-20 mg weekly) methotrexate or placebo in 4,786 patients with earlier MI or multivessel coronary disease who had either type 2 diabetes or metabolic syndrome[88]. This anti-inflammatory agent, which is available in a generic form, is considered safe at low doses. Methotrexate had no impact on the primary endpoint of major adverse cardiovascular events, compared with placebo. This was true for the original composite of non-fatal MI, non-fatal stroke, or cardiovascular death and for the final endpoint, which added hospitalisation for unstable angina leading to urgent revascularisation. Mortality was higher with low-dose methotrexate, both from cardiovascular causes and overall, and this was why the trial was stopped after a median follow-up of 2.3 years. Methotrexate did not reduce levels of CRP, IL-1β, or IL-6.

HYDROXYCHLOROQUINE, ALLOPURINOL, AND SALICYLATES

Hydroxychloroquine is used for inflammatory rheumatic diseases, altering lysosomal pH and reducing inflammation by inhibiting TLR7 and TLR9[89]. Allopurinol treats hyperuricaemia in gout, potentially reducing atherosclerosis-related inflammation in mice, but its clinical effectiveness remains inconclusive[90]. Salicylates inhibit NF-κB activity but did not reduce inflammation in atherosclerosis patients in the TINSAL-T2D and TINSAL-FMD trials[91].

OTHER MEDICATIONS UNDER INVESTIGATION

Dapansutrile, an NLRP3 inflammasome inhibitor, had no significant effect on CRP levels[92]. Succinobucol, an antioxidant, did not reduce cardiovascular events in a phase III trial[93]. Darapladib, an Lp-PLA2 inhibitor, showed conflicting results in clinical studies[94]. Losmapimod (p38 inhibitor) and inclacumab (P-selectin inhibitor) are currently being investigated. Antithrombotic medications in CAD patients may offer additional benefits beyond their primary purpose due to the relationship between inflammation and thrombosis[95].

Strategy: assessment and treatment

The presence of local and systemic inflammation in patients with atherosclerosis is well established. Targeted reduction of inflammation is crucial for preventing cardiovascular events in patients already receiving optimal medical therapy. Biomarkers are available to detect and measure the inflammation process, with hs-CRP being the most widely investigated and accessible biomarker for this purpose. Several anti-inflammatory medications, including colchicine, have shown improvement in both inflammation and clinical outcomes in cardiac patients. Recently, colchicine was even widely approved for this purpose by the FDA[96].

To tailor therapies effectively, clinicians need to evaluate the overall risk/benefit ratio for their patients. There are two main patient phenotypes: those with residual cholesterol risk and elevated LDL-C levels despite medical therapy and those with RIR. The first group should receive additional

LDL-C-lowering treatment according to guidelines, such as the European Society of Cardiology (ESC) or American College of Cardiology/American Heart Association recommendations[49]. The second group consists of patients with LDL-C at target levels but still experiencing RIR. While ESC guidelines suggest lowering LDL-C to less than 40 mg/dL or adding colchicine for patients with recurrent cardiac events despite optimal medical therapy, these indications are primarily based on secondary prevention after an event has occurred.

The data presented in this review support using a biomarker to diagnose RIR and treat inflammation proactively before an event occurs. Non-invasive or invasive imaging techniques, such as coronary computed tomography, carotid ultrasound, positron emission tomography, intravascular ultrasound, near-infrared spectroscopy, and optical coherence tomography, can show atherosclerotic arteries, while risk scores can identify patients at high risk of atherosclerosis even without visual evidence of plaque. Once a patient reaches the target LDL-C level, we propose using a biomarker to assess the presence of RIR rather than adopting a watchful waiting approach for a new event **(Figure 1)**.

Hs-CRP levels have been proven to independently predict cardiovascular events (both new and recurrent) in multiple, prospective epidemiological cohorts. Stable hs-CRP levels over time, excluding acute infection, are typically below the commonly used cutoff value of 2 mg/L. If a patient has elevated hs-CRP levels despite LDL-C control, consideration should be given to using an anti-inflammatory medication. While no single medication has been proven superior, considering previous studies, experience, affordability, and recent FDA approval[97], colchicine appears to be the best available option. Therefore, we join in recommending hs-CRP as the biomarker of choice and colchicine as the preferred drug[98]. However, several questions need to be addressed to establish this protocol, such as the timing and frequency of hs-CRP testing after reaching target LDL-C levels, management of patients with renal failure or gastrointestinal intolerance, duration of colchicine prescription, and follow-up strategies after treating RIR. Furthermore, the suggested protocol does not address the potential treatment of patients with both low hs-CRP and LDL-C levels.

Future perspectives

The future of atherosclerosis and RIR treatment lies in personalised medicine and novel medications. Ongoing research is focused on promising anti-inflammatory strategies and exploring new possibilities for atherosclerosis treatment[99]. One intriguing avenue is targeting efferocytosis, a process in which macrophages clear apoptotic tissue from plaques. Dysregulation of this process leads to increased inflammation and atherosclerosis. Additionally, advancements in nanotechnology offer potential breakthroughs by improving drug delivery, reducing systemic toxicity, and enhancing circulation time for drugs, including water-insoluble ones. *In vitro* and animal studies have already evaluated anti-atherosclerotic nanotherapeutic approaches. Personalised medicine represents a therapeutic approach that takes into account an individual's medical history, environmental factors, genetic background, and molecular defects. A particularly promising avenue lies in mRNA-based therapeutics, which enables precise targeting of specific genes and holds great potential for the future of medical treatment.

Two crucial advancements worth considering to enhance established risk assessment methods are the use of updated models that incorporate the latest imaging technologies and the integration of artificial intelligence algorithms. In future trials related to colchicine in ACS, there will be a heightened focus on incorporating optical coherence tomography imaging guidance for secondary endpoints, as well as leveraging technologies such as cardiac magnetic resonance imaging, nuclear medicine, and sodium fluoride positron emission tomography/computed tomography[100,101]. Furthermore, it is essential to underscore the importance of integrating hs-CRP into both existing and new cardiac risk algorithms.

Several key clinical trials are currently underway **(Table 4)** to examine the effects of different medications on RIR. For example, the ZEUS trial aims to evaluate the impact of ziltivekimab on reducing cardiovascular events in individuals with established ASCVD, chronic kidney disease, and inflammation[102]. The CONVINCE trial focuses on evaluating the use of colchicine in adults who have suffered an ischaemic stroke or transient ischaemic attack[103]. The CLEAR SYNERGY trial investigates the efficacy and safety of colchicine and spironolactone in patients with MI who underwent primary PCI[104]. Lastly, the GOLDILOX-TIMI 69 trial is a phase IIB study evaluating the anti-inflammatory potential of MEDI6570, a monoclonal antibody, and its effect on atherosclerotic and heart failure events in patients with a history of MI[105]. These clinical trials represent important efforts in advancing our understanding and treatment of atherosclerosis and RIR.
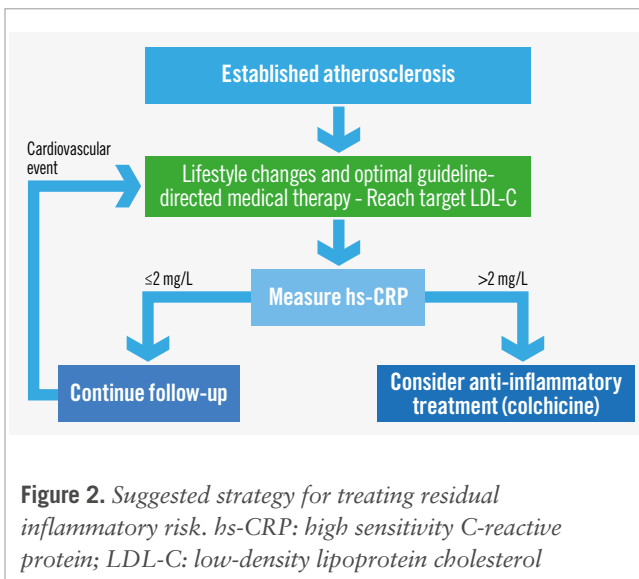
Table 4. Ongoing trials.

Name of study	Aim
ZEUS[102]	Evaluating the impact of ziltivekimab on reducing cardiovascular events in individuals with established ASCVD
CONVINCE[103]	Evaluating the use of colchicine in adults who have suffered an ischaemic stroke or transient ischaemic attack
CLEAR SYNERGY[104]	Investigating the efficacy and safety of colchicine and spironolactone in patients with MI who underwent primary percutaneous coronary intervention
GOLDILOX-TIMI 69[105]	Phase IIB study evaluating the anti-inflammatory potential of MEDI6570, a monoclonal antibody, and its effect on atherosclerotic and heart failure events in patients with a history of MI

ASCVD: atherosclerotic cardiovascular disease; MI: myocardial infarction

Conclusions

Active primary prevention of RIR in atherosclerosis is crucial, as shown by extensive data. The convergence of biological evidence highlighting inflammation in atherosclerosis, the availability of biomarkers, and the effectiveness of anti-inflammatory medications demonstrated in clinical trials all call for their integration into future guidelines. We contend that the current evidence is substantial enough to advocate

Figure 2. *Suggested strategy for treating residual inflammatory risk. hs-CRP: high sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol*

for the use of hs-CRP to assess patients with established atherosclerosis and the addition of colchicine to their medication regimen as a preventive measure, rather than waiting for a recurrent event to occur **(Figure 2)**.

Authors' affiliations

1. MedStar Heart & Vascular Institute, MedStar Washington Hospital Center, MedStar Georgetown University Hospital, Washington, D.C., USA; 2. Department of Internal Medicine, University of Genoa, Genoa, Italy; 3. Cardiovascular Disease Unit, IRCCS Ospedale Policlinico San Martino – Italian IRCCS Cardiology Network, Genoa, Italy

Funding

Conflict of interest statement

R. Waksman reports serving on the advisory boards of Abbott, Boston Scientific, Medtronic, Philips IGT, and Pi-Cardia Ltd.; being a consultant for Abbott Vascular, Biotronik, Boston Scientific, Cordis, Medtronic, Philips IGT, Pi-Cardia Ltd., Swiss Interventional Systems/SIS Medical AG, Transmural Systems Inc., and Venus MedTech; receiving institutional grant support from Amgen, Biotronik, Boston Scientific, Chiesi, Medtronic, and Philips IGT; and being an investor in MedAlliance and Transmural Systems Inc. I. Porto reports consultant or speaker fees from SysMedical, Medtronic, Abbott, Edwards Lifesciences, Abiomed, Terumo, Philips, Sanofi, Amgen, Daiichi Sankyo, AstraZeneca, Bayer, and Pfizer; and a department grant (minor) from Chiesi, Bayer, Medtronic, and Abbott. The other authors have no conflicts of interest to declare.

References

1. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation.* 2002;105:1135-43.

2. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, Kastelein JJP, Cornel JH, Pais P, Pella D, Genest J, Cifkova R, Lorenzatti A, Forster T, Kobalava Z, Vida-Simiti L, Flather M, Shimokawa H, Ogawa H, Dellborg M, Rossi PRF, Troquay RPT, Libby P, Glynn RJ; CANTOS Trial Group. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. *N Engl J Med.* 2017;377:1119-31.

3. Miedema MD, Garberich RF, Schnaidt LJ, Peterson E, Strauss C, Sharkey S, Knickelbine T, Newell MC, Henry TD. Statin Eligibility and Outpatient Care Prior to ST-Segment Elevation Myocardial Infarction. *J Am Heart Assoc.* 2017;6:e005333.

4. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, Mehran R, McPherson J, Farhat N, Marso SP, Parise H, Templin B, White R, Zhang Z, Serruys PW; PROSPECT Investigators. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med.* 2011;364:226-35.

5. Erlinge D, Maehara A, Ben-Yehuda O, Bøtker HE, Maeng M, Kjøller-Hansen L, Engstrøm T, Matsumura M, Crowley A, Dressler O, Mintz GS, Fröbert O, Persson J, Wiseth R, Larsen AI, Okkels Jensen L, Nordrehaug JE, Bleie Ø, Omerovic E, Held C, James SK, Ali ZA, Muller JE, Stone GW; PROSPECT II Investigators. Identification of vulnerable plaques and patients by intracoronary near-infrared spectroscopy and ultrasound (PROSPECT II): a prospective natural history study. *Lancet.* 2021;397:985-95.

6. Barrett TJ. Macrophages in Atherosclerosis Regression. *Arterioscler Thromb Vasc Biol.* 2020;40:20-33.

7. Moore KJ, Sheedy FJ, Fisher EA. Macrophages in atherosclerosis: a dynamic balance. *Nat Rev Immunol.* 2013;13:709-21.

8. Aukrust P, Halvorsen B, Yndestad A, Ueland T, Øie E, Otterdal K, Gullestad L, Damås JK. Chemokines and cardiovascular risk. *Arterioscler Thromb Vasc Biol.* 2008;28:1909-19.

9. Simon TG, Trejo MEP, McClelland R, Bradley R, Blaha MJ, Zeb I, Corey KE, Budoff MJ, Chung RT. Circulating Interleukin-6 is a biomarker for coronary atherosclerosis in nonalcoholic fatty liver disease: Results from the Multi-Ethnic Study of Atherosclerosis. *Int J Cardiol.* 2018;259:198-204.

10. Grivel JC, Ivanova O, Pinegina N, Blank PS, Shpektor A, Margolis LB, Vasilieva E. Activation of T lymphocytes in atherosclerotic plaques. *Arterioscler Thromb Vasc Biol.* 2011;31:2929-37.

11. Sage AP, Tsiantoulas D, Binder CJ, Mallat Z. The role of B cells in atherosclerosis. *Nat Rev Cardiol.* 2019;16:180-96.

12. Döring Y, Drechsler M, Soehnlein O, Weber C. Neutrophils in atherosclerosis: from mice to man. *Arterioscler Thromb Vasc Biol.* 2015;35:288-95.

13. Silvestre-Roig C, Braster Q, Ortega-Gomez A, Soehnlein O. Neutrophils as regulators of cardiovascular inflammation. *Nat Rev Cardiol.* 2020;17:327-40.

14. Soehnlein O. Multiple roles for neutrophils in atherosclerosis. *Circ Res.* 2012;110:875-888.

15. Grebe A, Hoss F, Latz E. NLRP3 Inflammasome and the IL-1 Pathway in Atherosclerosis. *Circ Res.* 2018;122:1722-40.

16. Bot I, Shi GP, Kovanen PT. Mast cells as effectors in atherosclerosis. *Arterioscler Thromb Vasc Biol.* 2015;35:265-71.

17. Kovanen PT, Bot I. Mast cells in atherosclerotic cardiovascular disease - Activators and actions. *Eur J Pharmacol.* 2017;816:37-46.

18. Selathurai A, Deswaerte V, Kanellakis P, Tipping P, Toh BH, Bobik A, Kyaw T. Natural killer (NK) cells augment atherosclerosis by cytotoxic-dependent mechanisms. *Cardiovasc Res.* 2014;102:128-37.

19. Carrero JJ, Andersson Franko M, Obergfell A, Gabrielsen A, Jernberg T. hsCRP Level and the Risk of Death or Recurrent Cardiovascular Events in Patients With Myocardial Infarction: a Healthcare-Based Study. *J Am Heart Assoc.* 2019;8:e012638.

20. Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. *JAMA.* 2007;297:611-9.

21. Ridker PM, Cook N. Clinical usefulness of very high and very low levels of C-reactive protein across the full range of Framingham Risk Scores. *Circulation.* 2004;109:1955-9.

22. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med.* 2008;359:2195-207.

23. Jezovnik MK, Poredos P. Inflammation and atherosclerosis: Clinical utility of the C-reactive protein. ESC E-Journal of Cardiology Practice. 2007;5:15. https://www.escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-5/Inflammation-and-atherosclerosis-Clinical-utility-of-the-C-reactive-protein (Last accessed 30 March 2023).

24. Aday AW, Ridker PM. Targeting Residual Inflammatory Risk: A Shifting Paradigm for Atherosclerotic Disease. *Front Cardiovasc Med.* 2019;6:16.

25. Quispe R, Michos ED, Martin SS, Puri R, Toth PP, Al Suwaidi J, Banach M, Virani SS, Blumenthal RS, Jones SR, Elshazly MB. High-Sensitivity C-Reactive Protein Discordance With Atherogenic Lipid Measures and Incidence of Atherosclerotic Cardiovascular Disease in Primary Prevention: The ARIC Study. *J Am Heart Assoc.* 2020;9:e013600.

26. Pereira J, Ribeiro A, Ferreira-Coimbra J, Barroso I, Guimarães JT, Bettencourt P, Lourenço P. Is there a C-reactive protein value beyond which one should consider infection as the cause of acute heart failure? *BMC Cardiovasc Disord.* 2018;18:40.

27. Ridker PM, Bhatt DL, Pradhan AD, Glynn RJ, MacFadyen JG, Nissen SE; PROMINENT, REDUCE-IT, and STRENGTH Investigators. Inflammation and cholesterol as predictors of cardiovascular events among patients receiving statin therapy: a collaborative analysis of three randomised trials. *Lancet.* 2023;401:1293-301.

28. Kobo O, Roguin A, Zukermann R, Kerner A, Marcusohn E. Gout Is Associated With Worse Post-PCI Long-Term Outcomes. *Cardiovasc Revasc Med.* 2022;41:166-9.

29. Di Fusco SA, Arca M, Scicchitano P, Alonzo A, Perone F, Gulizia MM, Gabrielli D, Oliva F, Imperoli G, Colivicchi F. Lipoprotein(a): a risk factor for atherosclerosis and an emerging therapeutic target. *Heart.* 2022;109:18-25.

30. Pirinccioglu AG, Gökalp D, Pirinccioglu M, Kizil G, Kizil M. Malondialdehyde (MDA) and protein carbonyl (PCO) levels as biomarkers of oxidative stress in subjects with familial hypercholesterolemia. *Clin Biochem.* 2010;43:1220-4.

31. Adam CA, Şalaru DL, Prisacariu C, Marcu DTM, Sascău RA, Stătescu C. Novel Biomarkers of Atherosclerotic Vascular Disease-Latest Insights in the Research Field. *Int J Mol Sci.* 2022;23:4998.

32. Ghafouri-Fard S, Gholipour M, Taheri M. Role of MicroRNAs in the Pathogenesis of Coronary Artery Disease. *Front Cardiovasc Med.* 2021;8:632392.

33. Gottsäter M, Ford LB, Ostling G, Persson M, Nilsson PM, Melander O. Adrenomedullin is a marker of carotid plaques and intima-media thickness as well as brachial pulse pressure. *J Hypertens.* 2013;31:1959-65.

34. West M, Kirby A, Stewart RA, Blankenberg S, Sullivan D, White HD, Hunt D, Marschner I, Janus E, Kritharides L, Watts GF, Simes J, Tonkin AM; LIPID Study Group *. Circulating Cystatin C Is an Independent Risk Marker for Cardiovascular Outcomes, Development of Renal Impairment, and Long-Term Mortality in Patients With Stable Coronary Heart Disease: The LIPID Study. *J Am Heart Assoc.* 2022;11:e020745.

35. Gonçalves I, Edsfeldt A, Ko NY, Grufman H, Berg K, Björkbacka H, Nitulescu M, Persson A, Nilsson M, Prehn C, Adamski J, Nilsson J. Evidence supporting a key role of Lp-PLA2-generated lysophosphatidylcholine in human atherosclerotic plaque inflammation. *Arterioscler Thromb Vasc Biol.* 2012;32:1505-12.

36. Olejarz W, Łacheta D, Kubiak-Tomaszewska G. Matrix Metalloproteinases as Biomarkers of Atherosclerotic Plaque Instability. *Int J Mol Sci.* 2020;21:3946.

37. Poznyak A, Grechko AV, Poggio P, Myasoedova VA, Alfieri V, Orekhov AN. The Diabetes Mellitus-Atherosclerosis Connection: The Role of Lipid and Glucose Metabolism and Chronic Inflammation. *Int J Mol Sci.* 2020;21:1835.

38. Solak Y, Afsar B, Vaziri ND, Aslan G, Yalcin CE, Covic A, Kanbay M. Hypertension as an autoimmune and inflammatory disease. *Hypertens Res.* 2016;39:567-73.

39. Frostegård J. Atherosclerosis in patients with autoimmune disorders. *Arterioscler Thromb Vasc Biol.* 2005;25:1776-85.

40. Blaha MJ, DeFilippis AP. Multi-Ethnic Study of Atherosclerosis (MESA): JACC Focus Seminar 5/8. *J Am Coll Cardiol.* 2021;77:3195-216.

41. Nowak AJ, Relja B. The Impact of Acute or Chronic Alcohol Intake on the NF-κB Signaling Pathway in Alcohol-Related Liver Disease. *Int J Mol Sci.* 2020;21:9407.

42. Nimmo MA, Leggate M, Viana JL, King JA. The effect of physical activity on mediators of inflammation. *Diabetes Obes Metab.* 2013;15 Suppl 3:51-60.

43. Bevan GH, Al-Kindi SG, Brook RD, Münzel T, Rajagopalan S. Ambient Air Pollution and Atherosclerosis: Insights Into Dose, Time, and Mechanisms. *Arterioscler Thromb Vasc Biol.* 2021;41:628-37.

44. McClelland RL, Chung H, Detrano R, Post W, Kronmal RA. Distribution of coronary artery calcium by race, gender, and age: results from the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation.* 2006;113:30-7.

45. Ridker PM. Residual inflammatory risk: addressing the obverse side of the atherosclerosis prevention coin. *Eur Heart J.* 2016;37:1720-2.

46. Ridker PM. How Common Is Residual Inflammatory Risk? *Circ Res.* 2017;120:617-9.

47. Guedeney P, Claessen BE, Kalkman DN, Aquino M, Sorrentino S, Giustino G, Farhan S, Vogel B, Sartori S, Montalescot G, Sweeny J, Kovacic JC, Krishnan P, Barman N, Dangas G, Kini A, Baber U, Sharma S, Mehran R. Residual Inflammatory Risk in Patients With Low LDL Cholesterol Levels Undergoing Percutaneous Coronary Intervention. *J Am Coll Cardiol.* 2019;73:2401-9.

48. Tsigalou C, Konstantinidis T, Paraschaki A, Stavropoulou E, Voidarou C, Bezirtzoglou E. Mediterranean Diet as a Tool to Combat Inflammation and Chronic Diseases. An Overview. *Biomedicines.* 2020;8:201.

49. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, Benetos A, Biffi A, Boavida JM, Capodanno D, Cosyns B, Crawford C, Davos CH, Desormais I, Di Angelantonio E, Franco OH, Halvorsen S, Hobbs FDR, Hollander M, Jankowska EA, Michal M, Sacco S, Sattar N, Tokgozoglu L, Tonstad S, Tsioufis KP, van Dis I, van Gelder IC, Wanner C, Williams B; ESC National Cardiac Societies; ESC Scientific Document Group. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J.* 2021;42:3227-337.

50. Zhou Y, Khan H, Xiao J, Cheang WS. Effects of Arachidonic Acid Metabolites on Cardiovascular Health and Disease. *Int J Mol Sci.* 2021;22:12029.

51. Tułowiecka N, Kotlęga D, Prowans P, Szczuko M. The Role of Resolvins: EPA and DHA Derivatives Can Be Useful in the Prevention and Treatment of Ischemic Stroke. *Int J Mol Sci.* 2020;21:7628.

52. Dessì M, Noce A, Bertucci P, Manca di Villahermosa S, Zenobi R, Castagnola V, Addessi E, Di Daniele N. Atherosclerosis, dyslipidemia, and inflammation: the significant role of polyunsaturated Fatty acids. *ISRN Inflamm.* 2013;2013:191823.

53. Chacon D, Fiani B. A Review of Mechanisms on the Beneficial Effect of Exercise on Atherosclerosis. *Cureus.* 2020;12:e11641.

54. Gambardella J, Sardu C, Sacra C, Del Giudice C, Santulli G. Quit smoking to outsmart atherogenesis: Molecular mechanisms underlying clinical evidence. *Atherosclerosis.* 2017;257:242-5.

55. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet.* 1994;344:1383-9.

56. Proute MC, Kothur N, Georgiou P, Serhiyenia T, Shi W, Kerolos ME, Pradeep R, Akram A, Khan S. The Effect of Statin Therapy on Inflammatory Biomarkers: A Systematic Review. *Cureus.* 2021;13:e18273.

57. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM; Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med.* 2004;350:1495-504.

58. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM; IMPROVE-IT Investigators. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med. 2015;372:2387-97.

59. Chou R, Cantor A, Dana T, Wagner J, Ahmed A, Fu R, Ferencik M. Statin Use for the Primary Prevention of Cardiovascular Disease in Adults: A Systematic Review for the U.S. Preventive Services Task Force [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2022. (Evidence Synthesis, No. 219.) Available from: https://www.ncbi.nlm.nih.gov/books/NBK583661/. (Last accessed 9 December 2023).

60. Zhang J, Wang X, Tian W, Wang T, Jia J, Lai R, Wang T, Zhang Z, Song L, Ju J, Xu H. The effect of various types and doses of statins on C-reactive protein levels in patients with dyslipidemia or coronary heart disease: A systematic review and network meta-analysis. Front Cardiovasc Med. 2022;9:936817.

61. Yusuf S, Bosch J, Dagenais G, Zhu J, Xavier D, Liu L, Pais P, López-Jaramillo P, Leiter LA, Dans A, Avezum A, Piegas LS, Parkhomenko A, Keltai K, Keltai M, Sliwa K, Peters RJ, Held C, Chazova I, Yusoff K, Lewis BS, Jansky P, Khunti K, Toff WD, Reid CM, Varigos J, Sanchez-Vallejo G, McKelvie R, Pogue J, Jung H, Gao P, Diaz R, Lonn E; HOPE-3 Investigators. Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease. N Engl J Med. 2016;374:2021-31.

62. Gómez-Garre D, Muñoz-Pacheco P, González-Rubio ML, Aragoncillo P, Granados R, Fernández-Cruz A. Ezetimibe reduces plaque inflammation in a rabbit model of atherosclerosis and inhibits monocyte migration in addition to its lipid-lowering effect. Br J Pharmacol. 2009;156:1218-27.

63. Morrone D, Weintraub WS, Toth PP, Hanson ME, Lowe RS, Lin J, Shah AK, Tershakovec AM. Lipid-altering efficacy of ezetimibe plus statin and statin monotherapy and identification of factors associated with treatment response: a pooled analysis of over 21,000 subjects from 27 clinical trials. Atherosclerosis. 2012;223:251-61.

64. Pokhrel B, Yuet WC, Levine SN. PCSK9 Inhibitors. [Updated 2022 May 13]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK448100/. (Last accessed 21 Nov 2023).

65. Bohula EA, Giugliano RP, Leiter LA, Verma S, Park JG, Sever PS, Lira Pineda A, Honarpour N, Wang H, Murphy SA, Keech A, Pedersen TR, Sabatine MS. Inflammatory and Cholesterol Risk in the FOURIER Trial. Circulation. 2018;138:131-40.

66. Pradhan AD, Aday AW, Rose LM, Ridker PM. Residual Inflammatory Risk on Treatment With PCSK9 Inhibition and Statin Therapy. Circulation. 2018;138:141-9.

67. Punch E, Klein J, Diaba-Nuhoho P, Morawietz H, Garelnabi M. Effects of PCSK9 Targeting: Alleviating Oxidation, Inflammation, and Atherosclerosis. J Am Heart Assoc. 2022;11:e023328.

68. Rosenson RS, Goonewardena S. Inhibition of PCSK9 With Evolocumab Modulates Immune-Cell Activation in High-Risk ASCVD Patients – the METCHNIKOFF Clinical Trial. J Am Coll Cardiol. 2023;81:1632.

69. Wu H, Ballantyne CM. Dyslipidaemia: PCSK9 inhibitors and foamy monocytes in familial hypercholesterolaemia. Nat Rev Cardiol. 2017;14:385-6.

70. Räber L, Ueki Y, Otsuka T, Losdat S, Häner JD, Lonborg J, Fahrni G, Iglesias JF, van Geuns RJ, Ondracek AS, Radu Juul Jensen MD, Zanchin C, Stortecky S, Spirk D, Siontis GCM, Saleh L, Matter CM, Daemen J, Mach F, Heg D, Windecker S, Engstrøm T, Lang IM, Koskinas KC; PACMAN-AMI collaborators. Effect of Alirocumab Added to High-Intensity Statin Therapy on Coronary Atherosclerosis in Patients With Acute Myocardial Infarction: The PACMAN-AMI Randomized Clinical Trial. JAMA. 2022;327:1771-81.

71. Nissen SE, Lincoff AM, Brennan D, Ray KK, Mason D, Kastelein JJP, Thompson PD, Libby P, Cho L, Plutzky J, Bays HE, Moriarty PM, Menon V, Grobbee DE, Louie MJ, Chen CF, Li N, Bloedon L, Robinson P, Horner M, Sasiela WJ, McCluskey J, Davey D, Fajardo-Campos P, Petrovic P, Fedacko J, Zmuda W, Lukyanov Y, Nicholls SJ; CLEAR Outcomes Investigators. Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients. N Engl J Med. 2023;388:1353-64.

72. Rayan RA, Sharma S. Lomitapide. [Updated 2022 Jul 18]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available

from: https://www.ncbi.nlm.nih.gov/books/NBK560849/. (Last accessed 21 Nov 2023).

73. Waldmann E, Vogt A, Crispin A, Altenhofer J, Riks I, Parhofer KG. Effect of mipomersen on LDL-cholesterol in patients with severe LDL-hypercholesterolaemia and atherosclerosis treated by lipoprotein apheresis (The MICA-Study). Atherosclerosis. 2017;259:20-5.

74. Bhatt DL, Hull MA, Song M, Van Hulle C, Carlsson C, Chapman MJ, Toth PP. Beyond cardiovascular medicine: potential future uses of icosapent ethyl. Eur Heart J Suppl. 2020;22:J54-64.

75. Tang X, Mao L, Chen J, Zhang T, Weng S, Guo X, Kuang J, Yu B, Peng D. High-sensitivity CRP may be a marker of HDL dysfunction and remodeling in patients with acute coronary syndrome. Sci Rep. 2021;11:11444.

76. Ullah W, Gowda SN, Fischman D. Safety and Efficacy of Colchicine in Patients With Coronary Artery Disease: A Systematic Review and Meta-Analysis. Cardiovasc Revasc Med. 2021;23:1-6.

77. Rakocevic J, Dobric M, Borovic ML, Milutinovic K, Milenkovic S, Tomasevic M. Anti-Inflammatory Therapy in Coronary Artery Disease: Where Do We Stand? Rev Cardiovasc Med. 2023;24:10.

78. Nidorf SM, Eikelboom JW, Budgeon CA, Thompson PL. Low-dose colchicine for secondary prevention of cardiovascular disease. J Am Coll Cardiol. 2013;61:404-10.

79. Nidorf SM, Fiolet ATL, Mosterd A, Eikelboom JW, Schut A, Opstal TSJ, The SHK, Xu XF, Ireland MA, Lenderink T, Latchem D, Hoogslag P, Jerzewski A, Nierop P, Whelan A, Hendriks R, Swart H, Schaap J, Kuijper AFM, van Hessen MWJ, Saklani P, Tan I, Thompson AG, Morton A, Judkins C, Bax WA, Dirksen M, Alings M, Hankey GJ, Budgeon CA, Tijssen JGP, Cornel JH, Thompson PL; LoDoCo2 Trial Investigators. Colchicine in Patients with Chronic Coronary Disease. N Engl J Med. 2020;383:1838-47.

80. Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, Pinto FJ, Ibrahim R, Gamra H, Kiwan GS, Berry C, López-Sendón J, Ostadal P, Koenig W, Angoulvant D, Grégoire JC, Lavoie MA, Dubé MP, Rhainds D, Provencher M, Blondeau L, Orfanos A, L'Allier PL, Guertin MC, Roubille F. Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. N Engl J Med. 2019;381:2497-505.

81. Lee SY, Jeong YH, Yun KH, Cho JY, Gorog DA, Angiolillo DJ, Kim JW, Jang Y. $P2Y_{12}$ Inhibitor Monotherapy Combined With Colchicine Following PCI in ACS Patients: The MACT Pilot Study. JACC Cardiovasc Interv. 2023;16:1845-55.

82. Ridker PM, MacFadyen JG, Everett BM, Libby P, Thuren T, Glynn RJ; CANTOS Trial Group. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial. Lancet. 2018;391:319-28.

83. Abbate A, Trankle CR, Buckley LF, Lipinski MJ, Appleton D, Kadariya D, Canada JM, Carbone S, Roberts CS, Abouzaki N, Melchior R, Christopher S, Turlington J, Mueller G, Garnett J, Thomas C, Markley R, Wohlford GF, Puckett L, Medina de Chazal H, Chiabrando JG, Bressi E, Del Buono MG, Schatz A, Vo C, Dixon DL, Biondi-Zoccai GG, Kontos MC, Van Tassell BW. Interleukin-1 Blockade Inhibits the Acute Inflammatory Response in Patients With ST-Segment-Elevation Myocardial Infarction. J Am Heart Assoc. 2020;9:e014941.

84. Ridker PM, Devalaraja M, Baeres FMM, Engelmann MDM, Hovingh GK, Ivkovic M, Lo L, Kling D, Pergola P, Raj D, Libby P, Davidson M; RESCUE Investigators. IL-6 inhibition with ziltivekimab in patients at high atherosclerotic risk (RESCUE): a double-blind, randomised, placebo-controlled, phase 2 trial. Lancet. 2021;397:2060-9.

85. Anstensrud AK, Woxholt S, Sharma K, Broch K, Bendz B, Aakhus S, Ueland T, Amundsen BH, Damås JK, Hopp E, Kleveland O, Stensæth KH, Opdahl A, Kløw NE, Seljeflot I, Andersen GØ, Wiseth R, Aukrust P, Gullestad L. Rationale for the ASSAIL-MI-trial: a randomised controlled trial designed to assess the effect of tocilizumab on myocardial salvage in patients with acute ST-elevation myocardial infarction (STEMI). Open Heart. 2019;6:e001108.

86. Huse C, Anstensrud AK, Michelsen AE, Ueland T, Broch K, Woxholt S, Yang K, Sharma K, Tøllefsen IM, Bendz B, Amundsen BH, Damås JK, Berg ES, Bjørkelund E, Quiles-Jiménez A, Bjerkeli V, Bendz C, Kleveland O,

Stensaeth KH, Opdahl A, Kløw NE, Andersen GØ, Wiseth R, Halvorsen B, Gullestad L, Seljeflot I, Aukrust P, Osnes L, Dahl TB. Interleukin-6 inhibition in ST-elevation myocardial infarction: Immune cell profile in the randomised ASSAIL-MI trial. *EBioMedicine*. 2022;80:104013.

87. Gilbert J, Lekstrom-Himes J, Donaldson D, Lee Y, Hu M, Xu J, Wyant T, Davidson M; MLN1202 Study Group. Effect of CC chemokine receptor 2 CCR2 blockade on serum C-reactive protein in individuals at atherosclerotic risk and with a single nucleotide polymorphism of the monocyte chemoattractant protein-1 promoter region. *Am J Cardiol*. 2011;107:906-11.

88. Ridker PM, Everett BM, Pradhan A, MacFadyen JG, Solomon DH, Zaharris E, Mam V, Hasan A, Rosenberg Y, Iturriaga E, Gupta M, Tsigoulis M, Verma S, Clearfield M, Libby P, Goldhaber SZ, Seagle R, Ofori C, Saklayen M, Butman S, Singh N, Le May M, Bertrand O, Johnston J, Paynter NP, Glynn RJ; CIRT Investigators. Low-Dose Methotrexate for the Prevention of Atherosclerotic Events. *N Engl J Med*. 2019;380:752-62.

89. Floris A, Piga M, Mangoni AA, Bortoluzzi A, Erre GL, Cauli A. Protective Effects of Hydroxychloroquine against Accelerated Atherosclerosis in Systemic Lupus Erythematosus. *Mediators Inflamm*. 2018;2018:3424136.

90. Okafor ON, Farrington K, Gorog DA. Allopurinol as a therapeutic option in cardiovascular disease. *Pharmacol Ther*. 2017;172:139-50.

91. Goldfine AB, Buck JS, Desouza C, Fonseca V, Chen YD, Shoelson SE, Jablonski KA, Creager MA; TINSAL-FMD (Targeting Inflammation Using Salsalate in Type 2 Diabetes–Flow-Mediated Dilation) Ancillary Study Team. Targeting inflammation using salsalate in patients with type 2 diabetes: effects on flow-mediated dilation (TINSAL-FMD). *Diabetes Care*. 2013;36:4132-9.

92. Klück V, Jansen TLTA, Janssen M, Comarniceanu A, Efdé M, Tengesdal IW, Schraa K, Cleophas MCP, Scribner CL, Skouras DB, Marchetti C, Dinarello CA, Joosten LAB. Dapansutrile, an oral selective NLRP3 inflammasome inhibitor, for treatment of gout flares: an open-label, dose-adaptive, proof-of-concept, phase 2a trial. *Lancet Rheumatol*. 2020;2:e270-80.

93. Ridker PM, Lüscher TF. Anti-inflammatory therapies for cardiovascular disease. *Eur Heart J*. 2014;35:1782-91.

94. STABILITY Investigators; White HD, Held C, Stewart R, Tarka E, Brown R, Davies RY, Budaj A, Harrington RA, Steg PG, Ardissino D, Armstrong PW, Avezum A, Aylward PE, Bryce A, Chen H, Chen MF, Corbalan R, Dalby AJ, Danchin N, De Winter RJ, Denchev S, Diaz R, Elisaf M, Flather MD, Goudev AR, Granger CB, Grinfeld L, Hochman JS, Husted S, Kim HS, Koenig W, Linhart A, Lonn E, López-Sendón J, Manolis AJ, Mohler ER 3rd, Nicolau JC, Pais P, Parkhomenko A, Pedersen TR, Pella D, Ramos-Corrales MA, Ruda M, Sereg M, Siddique S, Sinnaeve P, Smith P, Sritara P, Swart HP, Sy RG, Teramoto T, Tse HF, Watson D, Weaver WD, Weiss R, Viigimaa M, Vinereanu D, Zhu J, Cannon CP, Wallentin L. Darapladib for preventing ischemic events in stable coronary heart disease. *N Engl J Med*. 2014;370:1702-11.

95. Stark K, Massberg S. Interplay between inflammation and thrombosis in cardiovascular pathology. *Nat Rev Cardiol*. 2021;18:666-82.

96. Fornell D. FDA approves colchicine, the first anti-inflammatory drug for treating cardiovascular disease. Cardiovascular Business. June 20, 2023. Available at: https://cardiovascularbusiness.com/topics/clinical/pharmaceutics/fda-colchicine-anti-inflammatory-cardiovascular-disease. (Last accessed 21 Nov 2023).

97. AGEPHA Pharma USA, LLC. U.S. FDA Approves First Anti-Inflammatory Drug for Cardiovascular Disease. 2023 June 20. https://us.agephapharma.com/blog/2023/06/20/us-fda-approves-first-anti-inflammatory-drug-for-cardiovascular-disease/. (Last accessed 21 Nov 2023).

98. Nelson K, Fuster V, Ridker PM. Low-Dose Colchicine for Secondary Prevention of Coronary Artery Disease: JACC Review Topic of the Week. *J Am Coll Cardiol*. 2023;82:648-60.

99. Soehnlein O, Libby P. Targeting inflammation in atherosclerosis - from experimental insights to the clinic. *Nat Rev Drug Discov*. 2021;20:589-610.

100. Huet F, Delbaere Q, Aguilhon S, Dupasquier V, Delseny D, Gervasoni R, Macia JC, Leclercq F, Jammoul N, Kahlouche S, Soltani S, Cardon F, Dupuy AM, Cristol JP, Mariano-Goulart D, Akodad M, Nagot N, Roubille F. Colchicine to Prevent Sympathetic Denervation after an Acute Myocardial Infarction: The COLD-MI Trial Protocol. *Medicina (Kaunas)*. 2021;57:1047.

101. National Health and Medical Research Council (NHMRC). COLCARDIO-ACS. https://ctc.usyd.edu.au/our-research/research-areas/cardiovascular/active-trials/colcardio/ (Last accessed 18 Sept 2023).

102. Ridker PM. From RESCUE to ZEUS: will interleukin-6 inhibition with ziltivekimab prove effective for cardiovascular event reduction? *Cardiovasc Res*. 2021;117:e138-40.

103. Kelly P, Weimar C, Lemmens R, Murphy S, Purroy F, Arsovska A, Bornstein NM, Czlonkowska A, Fischer U, Fonseca AC, Forbes J, Hill MD, Jatuzis D, Kõrv J, Kruuse C, Mikulik R, J Nederkoorn P, O'Donnell M, Sandercock P, Tanne D, Tsivgoulis G, Walsh C, Williams D, Zedde M, Price CI. Colchicine for prevention of vascular inflammation in Non-CardioEmbolic stroke (CONVINCE) - study protocol for a randomised controlled trial. *Eur Stroke J*. 2021;6:222-8.

104. Population Health Research Institute. Colchicine and Spironolactone in Patients With MI / SYNERGY Stent Registry (CLEAR SYNERGY). https://classic.clinicaltrials.gov/ct2/show/NCT03048825. (Last accessed 27 July 2023).

105. AstraZeneca. Efficacy and Safety of MEDI6570 in Patients With a History of Myocardial Infarction (GOLDILOX). https://classic.clinicaltrials.gov/ct2/show/NCT04610892 (Last accessed 27 Jul 2023).

106. Broch K, Anstensrud AK, Woxholt S, Sharma K, Tøllefsen IM, Bendz B, Aakhus S, Ueland T, Amundsen BH, Damås JK, Berg ES, Bjørkelund E, Bendz C, Hopp E, Kleveland O, Stensæth KH, Opdahl A, Kløw NE, Seljeflot I, Andersen GØ, Wiseth R, Aukrust P, Gullestad L. Randomized Trial of Interleukin-6 Receptor Inhibition in Patients With Acute ST-Segment Elevation Myocardial Infarction. *J Am Coll Cardiol*. 2021;77:1845-55.