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NARRATIVE REVIEW

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Hypercholesterolemia and inflammation—Cooperative cardiovascular risk factors

Antonio Gallo[1] | **Wilfried Le Goff**[1] | **Raul D. Santos**[2] | **Isabella Fichtner**[3] | **Stefano Carugo**[4,5] | **Alberto Corsini**[3] | **Cesare Sirtori**[3] | **Massimiliano Ruscica**[3,4]

[1]Lipidology and Cardiovascular Prevention Unit, Department of Nutrition, APHP, Hôpital Pitié-Salpètrière, Sorbonne Université, INSERM UMR1166, Paris, France

[2]Academic Research Organization Hospital Israelita Albert Einstein and Lipid Clinic Heart Institute (InCor), University of Sao Paulo Medical School Hospital, Sao Paulo, Brazil

[3]Department of Pharmacological and Biomolecular Sciences "Rodolfo Paoletti", Università degli Studi di Milano, Milan, Italy

[4]Department of Cardio-Thoracic-Vascular Diseases, Foundation IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy

[5]Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milan, Italy

Correspondence
Massimiliano Ruscica, Department of Pharmacological and Biomolecular Sciences "Rodolfo Paoletti", Università degli Studi di Milano, Via Balzaretti 9, Milan, Italy.
Email: massimiliano.ruscica@unimi.it

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Abstract

Background: Maintaining low concentrations of plasma low-density lipoprotein cholesterol (LDLc) over time decreases the number of LDL particles trapped within the artery wall, slows the progression of atherosclerosis and delays the age at which mature atherosclerotic plaques develop. This substantially reduces the lifetime risk of atherosclerotic cardiovascular disease (ASCVD) events. In this context, plaque development and vulnerability result not only from lipid accumulation but also from inflammation.

Results: Changes in the composition of immune cells, including macrophages, dendritic cells, T cells, B cells, mast cells and neutrophils, along with altered cytokine and chemokine release, disrupt the equilibrium between inflammation and anti-inflammatory mechanisms at plaque sites. Considering that it is not a competition between LDLc and inflammation, but instead that they are partners in crime, the present narrative review aims to give an overview of the main inflammatory molecular pathways linked to raised LDLc concentrations and to describe the impact of lipid-lowering approaches on the inflammatory and lipid burden. Although remarkable changes in LDLc are driven by the most recent lipid lowering combinations, the relative reduction in plasma C-reactive protein appears to be independent of the magnitude of LDLc lowering.

Conclusion: Identifying clinical biomarkers of inflammation (e.g. interleukin-6) and possible targets for therapy holds promise for monitoring and reducing the ASCVD burden in suitable patients.

KEYWORDS
atherosclerosis, atherosclerosis, inflammasome, inflammation

1 | INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) remains a leading cause of morbidity and mortality despite excellent pharmacological and revascularization approaches. Following the seminal 4S (Scandinavian Simvastatin Survival Study) trial, demonstrating that statin therapy reduced rates of recurrent myocardial infarction (MI), stroke and cardiovascular death among secondary prevention patients with overt hyperlipidaemia,[1] statin trials have shown that an extensive range of patients benefited from statins, including those without evidence of overt vascular disease or hyperlipidaemia.[2] Among patients with clinically evident vascular disease who receive optimal treatment, a significant proportion (>20% and even >30%) remain at risk of recurrent events (e.g. MI, stroke or vascular death) over a 10-year period.[3] While one aspect of the residual risk is undoubtedly related to the further reduction in low-density lipoprotein cholesterol (LDLc), it is worth recalling that Rudolf Virchow, more than a century ago, proposed that atherosclerosis was a chronic inflammatory condition induced by cholesterol.[4] In addition to data from the interventional studies reducing LDLc concentrations, the PESA (Progression of Early Subclinical Atherosclerosis) study found an independent and a direct link between LDLc and atherosclerotic burden (as assessed by subclinical atherosclerosis) in apparently healthy individuals without conventional ASCVD risk factors (e.g. smoking and hypertension).[5] Indeed, maintaining low blood LDLc over time decreases the number of LDL particles trapped within the artery wall, slows the progression of atherosclerosis, delays the age at which mature atherosclerotic plaques develop, and substantially reduces the lifetime risk of ASCVD events.[6]

Moving to the inflammatory hypothesis,[7] inflammation in both its chronic and acute forms may represent one of the yet underappreciated cardiovascular risk factors considering that many patients presenting with an acute MI do not exhibit elevated LDLc but show features of increased inflammation.[8] Data from the proof-of-concept CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcome Study) trial have clearly identified inflammation as one of the critical biological processes leading to coronary events.[9] Similarly, in the COLCOT (Colchicine Cardiovascular Outcomes Trial) study, low-dose colchicine effectively prevented major adverse cardiovascular events (MACE) in patients who experienced a recent MI compared to placebo.[10] As a result, the US Food and Drug Administration approved using low-dose colchicine for patients with established ASCVD. Additionally, the European Society of Cardiology guidelines recommended considering colchicine as an option to the standard of care to prevent recurrent cardiovascular events in patients with acute coronary syndromes.[11] However, the impact of colchicine on atherosclerotic plaque needs to be directly clarified. The COLCOT study (Colchicine for the Stability of Coronary Plaque in Acute Coronary Syndrome) demonstrated that in patients with acute coronary syndrome, colchicine resulted in plaque stabilization, evidenced by a greater increase in minimum fibrous cap thickness, a reduction in the lipid arc and decreased macrophage infiltration.[12] Conversely, the results of the COCOMO-ACS trial (COlchicine for COronary Plaque MOdification in Acute Coronary Syndrome) found that optical coherence tomography did not detect a significant effect of colchicine on minimum fibrous cap thickness, maximum lipid arc in non-culprit imaged segments or lipid-rich plaques.[13]

Thus, identifying biomarkers of inflammation that could be used in clinical practice (e.g. interleukin-6 (IL-6) or IL-1β) holds promise for targeting the right patients with the aim of reducing ASCVD.[14] Besides that, in patients receiving more intensive lipid-lowering therapy, high-sensitivity C-reactive protein (hs-CRP) was a stronger predictor of future cardiovascular events than LDLc alone.[15,16] Elevated hs-CRP levels were associated with an increased risk of recurrent cardiovascular events and mortality, regardless of the vessel territory involved (i.e. coronary artery disease, cerebrovascular disease, peripheral artery disease and abdominal aortic aneurysm).[17] Prospective studies also indicated that elevated preoperative hs-CRP levels were linked to an increased risk of early restenosis following carotid endarterectomy.[18] Notably, among 1069 individuals who underwent endarterectomy, those with hs-CRP levels ≥2 mg/L exhibited a pro-inflammatory and adverse plaque phenotype characterized by elevated plaque cytokine levels of IL-6 and IL-8.[19]

Since chronic inflammation hallmarks lipid-mediated atherogenesis, the presence of an inflammatory state cannot be overlooked in individuals with familial hypercholesterolemia (FH).[20] FH is a metabolic disorder due to impaired hepatic uptake of blood LDL particles, triggering an increased compensatory cholesterol synthesis and ultimately resulting in high plasma LDLc levels. The uptake of LDL by the LDL-receptor (LDLR) dependent pathway is impaired as a consequence of genetic variants on the *LDLR*, apolipoprotein B (*APOB*), and pro-protein convertase subtilisin kexin type 9 (*PCSK9*) genes, accounting respectively for >90%, >5% and >1% of cases.[21] FH is inherited as an autosomal dominant disease and can be distinguished as mono-allelic or bi-allelic. The first condition, known as heterozygous FH (HeFH), is the most frequent monogenic disease, with an estimated prevalence of one in 200–350 subjects.[22–24] The second condition, commonly known as homozygous FH (HoFH), is infrequent with an estimated prevalence

of one in 160–300,000 subjects.[21,25,26] HoFH can also be caused by variants in the LDLR-associated protein 1 (*LDLRAP1*), which is transmitted as an autosomal recessive disease. This form of FH accounts for <1% of cases and is caused by bi-allelic loss-of-function variants in *LDLRAP1*.[27,28]

The lifelong exposure to increased LDLc concentrations since childhood associates this condition with an increased risk of premature coronary artery disease.[29] However, considerable variability in the latter's expression has been reported. On one side, up to 45% of HeFH subjects do not exhibit any ASCVD, and some HoFH patients have also been reported as resilient to atherosclerosis.[30,31] Conversely, despite sharing the same genetic and environmental background, some patients encounter a much more accelerated disease that evolves into premature cardiovascular artery disease despite statin treatment.[32] However, early diagnosis and treatment are essential in attenuating the excessive cardiovascular risk in both sexes.[33]

Finally, although not within the remit of the present article, it is worth reporting that autoimmune diseases, including systemic lupus erythematosus and rheumatoid arthritis, are associated with an increased risk of ASCVD and cardiovascular death. As reviewed by Porsch & Binder, inflammation is a dominant contributor to cardiovascular risk in patients with autoimmune conditions.[34]

Based on this background, the aim of the present narrative review was to give an overview of the main inflammatory molecular pathways linked to raised levels of LDLc, including those linked to FH, and to describe the differences among lipid-lowering approaches in ameliorating the double sword of inflammation and lipid burden (Figure 1).

2 | ATHEROSCLEROSIS AND INFLAMMATION: A MOLECULAR OVERVIEW

Plaque development and vulnerability result not only from lipid accumulation but also from inflammation.[35] The critical players in plaque rupture include the extent of the inflamed area, lipid core dimension, fibrous cap thickness, apoptosis of smooth muscle cells, and the balance between proteolytic enzymes and plaque calcification.[36] Changes in the composition of immune cells,[37] including macrophages, dendritic cells, T cells, B cells, mast cells, and neutrophils, along with altered cytokine and chemokine release, disrupt the equilibrium between inflammation and anti-inflammatory mechanisms at plaque sites.[38] The initial step in atherogenesis involves the subendothelial retention of apolipoprotein B—containing lipoproteins. Local biological responses to these retained lipoproteins, including chronic and maladaptive inflammatory reactions dominated by macrophage and T cells, contribute to subsequent lesion formation.[39]

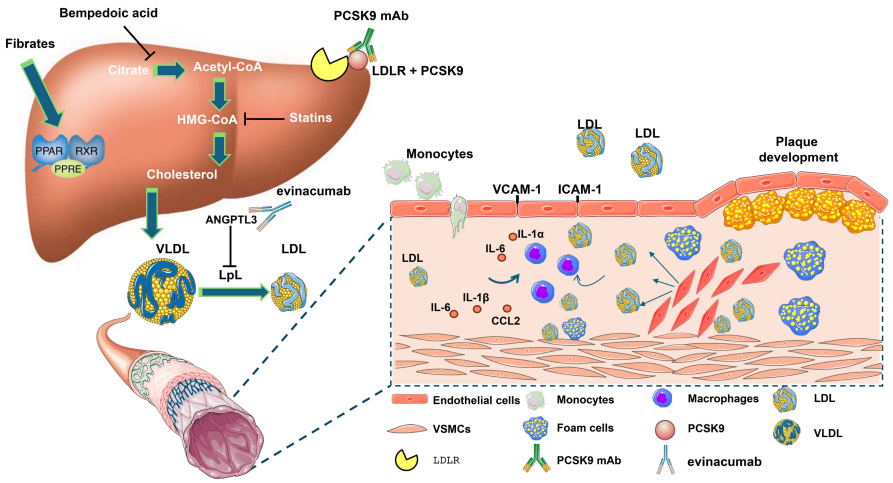

FIGURE 1 Schematic representation of the mechanisms by which lipid-lowering processes lead to a decreased production of atherogenic lipoproteins. Low-density lipoprotein (LDL) is the main factor in the development of atherogenesis. Important aspects include the entry and retention of LDL in the arterial intima, followed by modification processes that result in the accumulation of extracellular cholesterol and the creation of macrophage foam cells filled with cholesteryl ester droplets. Once in circulation, triglycerides are removed from very low-density lipoproteins (VLDL) by lipoprotein lipase (LpL) to become VLDL remnant particles and then LDL. Angiopoietin-like protein 3 (ANGPTL3) is a regulator of lipid metabolism by virtue of its inhibitory effect on LpL and endothelial lipase. Proprotein convertase subtilisin/kexin type 9 (PCSK9) fosters the degradation of LDL receptor (LDLR). Vascular smooth muscle cells (VSMCs) are capable of adopting various phenotypes such as those similar to foam cells or macrophages, thus influencing the disease progression. Foam cells trigger the production of cytokines and chemokines, leading to the further recruitment of circulating immune cells and initiating the cascade of the inflammatory response.

The inflammatory nature of atherosclerosis is confirmed by the consequent endothelial dysfunction leading to a pro-adhesive and prothrombotic phenotype of endothelial cells associated with disease progression.[40] The role of shear stress in early atherogenesis is mediated mainly through the stimulation of intramural synthesis of molecules (e.g. proteoglycans), which promotes the retention of lipoproteins.[39] The particular sensitivity of endothelial cells is crucial, given their exposure to noxious stimuli. It is thus part of an extensive process involving several immunity and inflammation mediators with more severe consequences in the presence of elevated cholesterol. Within the context of atheroma formation, dysfunctional maintenance of lipid rafts plays a significant role. Lipid rafts are formed because of molecular interactions between cholesterol and sphingolipids.[41] At the membrane level, these lipid rafts create a sensitive area by clustering receptors, which affects how leukocytes roll and adhere to the endothelium. Upon activation, resident and recruited proteins within lipid rafts initiate signalling cascades that lead to inflammation.[42]

Additionally, lipid rafts have been suggested to play a role in the production and composition of extracellular vesicles (EVs).[43] These are a heterogeneous population of small phospholipid bilayer-delimited particles, devoid of a nucleus, released from all cell types in most biological fluids. While once thought to be a means of eliminating cellular waste, EVs are now known to play a pivotal role in various physiological and pathological processes. They are considered key players in intercellular communication owing to their ability to transport proteins, lipids and nucleic acids, all reflecting the state of their specific cell of origin.[44] It is well-established that EVs are involved in multiple cardiovascular diseases,[45] including atherosclerosis,[46,47] heart failure, cardiomyopathies,[48] and atrial fibrillation.[49] An improved understanding of the role of lipid rafts has become of particular significance in the processes regulating vascular inflammation and holds promise in the prevention and treatment of ASCVD.[50]

A further connection between lipoproteins and inflammation arises from prolonged or excessive exposure to oxidized phospholipids, a subset of oxidation-specific epitopes. Oxidized phospholipids are usually carried by pro-atherogenic lipoprotein(a) particles. The innate and adaptive immune systems recognize these epitopes as damage-associated molecular patterns. Oxidized phospholipids engage specific receptors on a variety of vascular cells, including a cluster of differentiation (CD)36 and other scavenger receptors, CD14, toll-like receptors, and oxidized LDL (oxLDL) receptor 1 (also known as LOX1), triggering a pro-inflammatory cascade.[51]

Along with toll-like receptors, scavenger receptors share a fundamental role in internalizing modified LDL particles, generally oxLDL. Within the nascent plaque, plaque macrophages internalize oxidized lipids through scavenger receptors and differentiate into foam cells.[52] Macrophages are usually subdivided into two subgroups: M1 macrophages (pro-inflammatory) and M2 (anti-inflammatory). While the formation of M1 is induced by proinflammatory cytokines or by pathogens producing inflammatory cytokines (IL-1β, IL-6, IL-12, IL-23 and tumour necrosis factor (TNF)-α), M2 arise from exposure to cytokines IL-4 and IL-13 and produce IL-10, this latter with anti-inflammatory properties. In early atherosclerotic lesions, M1 are present, and their proportion increases as plaques progress to more complex inflammatory lesions.

Conversely, during atherosclerosis regression, there is a shift in the balance between M1 and M2, with M2 becoming more prominent.[53] Activation of M1 primarily relies on anaerobic glycolysis, leading to significant metabolic rewiring, which is characterized by increased glucose uptake and enhanced aerobic glycolysis. This metabolic shift coincides with impaired oxidative phosphorylation via the tricarboxylic acid cycle. In contrast, M2 exhibit a sharp increase in fatty acid oxidation and oxidative phosphorylation, which is believed to contribute to anti-inflammatory responses.[54]

When oxLDL are taken up without regulation, it forms intracellular cholesterol crystals that can activate the nucleotide-binding oligomerization domain, leucine-rich repeat–containing receptor (NLR) family pyrin domain-containing 3 (NLRP3).[55] NLRP3 assembles a cytosolic innate immune complex that activates the cysteine protease caspase-1, which in turn cleaves gasdermin D to induce pyroptosis, a regulated mode of lytic cell death.[56] These steps favour plaque macrophages to produce a higher amount of IL-1β, thus amplifying the transductional pathways involved in inflammation.[57] Pro-inflammatory signals from saturated fatty acids undergoing intracellular crystallization can also go through the toll-like receptors, particularly the isoform 4, activating an inflammatory cascade.[58] Within this context, Yalcinkaya et al. suggested that transport of cholesterol between the plasma membrane cholesterol and endoplasmic reticulum triggers inflammasome activation.[59]

Lymphocyte T helper 1 (T_{h1}) cells have pro-atherogenic roles, and T regulatory (Treg) cells have anti-atherogenic roles, although the function of these latter may change in specific conditions.[60] Immune adaptive cells can hold pro-inflammatory (T_{h1} or T_{h17} lymphocytes) and anti-inflammatory (T_{reg} lymphocytes) properties. T_{h1} are present in high numbers in atherosclerotic plaques and by favouring the release of pro-inflammatory cytokines may activate macrophages, lymphocytes, and other cells in the plaque, thus raising the inflammatory response.[61] Another lineage to be considered is the T_{h17} cells, a subset of $CD4^+$

T helper cells characterized by the production of IL-17. This cytokine has mixed effects on atheroma, perhaps promoting inflammation and increasing fibrosis.[62] T_{reg} cells, which have anti-inflammatory properties, may lose these characteristics during atherosclerosis. Cholesterol accumulation in T_{regs} of ASCVD patients may enhance differentiation into pro-atherogenic T-cell subsets.[63] Reduced numbers of T_{regs} are detected in vulnerable plaques compared to stable plaques.[64] Additionally, tissue-resident memory T cells (T_{RM}), which are a T-cell subset, reside at the site of prior antigen recognition, providing protection against reoccurring encounters.[65] Despite being a minor population in atherosclerotic lesions, T_{RM} is associated with increased lesion stability.[66]

The role of B cells in atherosclerosis is complex and multifaceted. While some evidence suggests that B cells play a significant role in influencing the progression of atherosclerotic plaques, other studies have shown competing effects of B cell populations on plaque formation.[67] In the context of humoral response, N-glycosylation of IgG, which reflects galactosylation and sialylation patterns, is consistently associated with the recurrence of ASCVD events. Alterations in the pattern of IgG glycosylation can modulate IgG receptor binding, directly impacting the inflammatory cascade.[68]

During the atheroma development, activated neutrophils degranulate to promote monocyte recruitment and secrete reactive oxygen species and proteases. This process dysregulates the endothelial cell layer, allowing LDLc to extravasate. As atherosclerosis progresses, neutrophils also secrete myeloperoxidase, which oxidize LDL particles, further forming foam cells. In advanced atherosclerotic lesions, neutrophils can destabilize the plaque by secreting neutrophil extracellular traps (NETs), which perforate and lyse vascular smooth muscle cells, leading to thinning of the fibrous cap and the formation of vulnerable rupture-prone plaques.[69] Both observational and genetic data support the hypothesis that elevated blood neutrophil counts are a causal risk factor for ASCVD.[70]

In advanced age myeloid associated changes are generally characterized by two aspects: (a) NETosis, which is a major mechanism responsible for bacterial killing, but also for sterile inflammation such as in arterial disease,[71] and (b) epigenetic changes in neutrophils, potentially leading to dysfunction associated with low grade inflammation, altering immune response and facilitating inflammatory responses.[72] NETs and NETosis add an anatomical marker of neutrophil infiltration in atherosclerotic lesions. NLRP3 activation indirectly stimulates neutrophil recruitment and entry into plaques leading to NETosis.[73]

The bone marrow was originally not thought to be responsible for an enhanced inflammatory cell recruitment (particularly monocytes) in the arterial intima,[74] but more recently a definite reduction of circulating haematopoietic progenitor cells was encountered in patients with peripheral arterial disease.[75] Clonal expansion of mutated haematopoietic cells, termed clonal haematopoiesis, is common in aging humans and leads to a raised ASCVD risk.[76]

Clonal haematopoiesis reduces the epigenetic modifier enzyme ten-eleven translocation 2 (TET2) linked to a raised atherosclerosis risk.[77] This epigenetic modifier is an effective intermediary in the inflammatory pattern of atherosclerosis and was identified in the epigenetic remodelling of macrophages. Through DNA methylation or histone modifications (e.g. methylation, acetylation, and lactylation), TET2 determines or switches the macrophage polarization via transcriptional reprogramming of gene expression and intracellular metabolic rewiring, thus representing a promising target for anti-inflammatory therapy in arterial disease.[78] Direct clinical evaluation of clonal haematopoiesis of indeterminate potential may provide a practical approach to improve the feasibility of specific anti-inflammatory treatments in large number of cardiological patients.[79]

Clonal haematopoiesis, particularly in TET2 deficient cells, markedly increases plaque size and NLRP3 inflammasome-mediated IL-1β secretion.[80] An exploratory analysis of CANTOS study showed that patients with haematopoiesis of indeterminate potential due to somatic variants in *TET2* had reduced risk for MACE while taking canakinumab.[81] Genetic mutations of DNA methyltransferase 3 alpha (DNMT3A) are of particular interest. DNMT3A catalyses the de novo DNA methylation of cytosine, which is associated with gene silencing, whereas TET2 encodes a methylcytosine dioxygenase initiating a sequence of reactions leading to cytosine demethylation. Loss of Dnmt3a enhanced inflammation in macrophages in vitro and generated a distinct adventitial macrophage population in vivo which merges a resident macrophage profile with an inflammatory cytokine signature.[82]

Another interesting mechanism linking cholesterol and inflammation involves galectin-9 (gal9), a member of β-galactoside binding proteins family expressed by the endothelium in inflammatory environments. Following high fat diet, $apoE^{-/-}$, $Gal9^{-/-}$ mice had significantly reduced aortic plaque burden compared to their $ApoE^{-/-}$ littermates.[83]

Reverse cholesterol transport (RCT), a highly antiatherogenic process responsible for the efflux of excess cholesterol to apolipoprotein A-I,[84] is impaired by inflammation which can impede several steps of the RCT pathways, particularly cholesterol flux through the liver to bile and faeces.[85] Defective cholesterol efflux promotes monocyte and neutrophil production in the bone marrow and the spleen, involving the proliferation of

haematopoietic stem cells and myeloid progenitor cells, mobilization of haematopoietic stem cells and extramedullary haematopoiesis.[86]

The high interest in high-density lipoproteins (HDL) functionality is witnessed, among others, by the pre-β1 HDL paradox, where an elevated pre-β1 HDL fraction, generally indicative of improved RCT, associates instead with decreased functionality and lower cholesterol CEC in patients with acute coronary syndrome and elevated levels of hs-CRP.[87]

3 | INFLAMMATION, IMMUNITY AND FAMILIAL HYPERCHOLESTEROLEMIA

Low-grade inflammation and alteration of the immune response are key features of ASCVD, and some clinical trials have provided evidence of the benefits associated with therapeutic targeting of the immune system in atherosclerosis.[88]

Classical inflammatory markers such as hs-CRP are strongly associated with atherogenic dyslipidaemia and atherosclerosis in patients with FH and their family members.[89] FH is associated with an increased risk of ASCVD, which may reflect the significant impact of cholesterol on inflammation and the immune response. Such effects result from the impact of LDLc at the atherosclerotic plaque level but also in the bone marrow compartment. Indeed, hypercholesterolemia drives inflammation through a direct action in cells from the vascular arterial wall but also in the proliferation, differentiation, and mobilization of haematopoietic stem/progenitor cells, leading to an expansion of immune cells and inflammatory response.[90] A recent study proposed that upregulation of the Srebp2-regulated Notch1 signalling might orchestrate haematopoietic stem/progenitor cell homeostasis in hypercholesterolemic individuals.[91]

Thus, LDLc concentrations in patients with FH led to a marked modulation of leucocyte counts characterized by an increased number of monocytes and lymphocytes, whereas that of granulocytes was reduced.[92] Elevated count of neutrophils contributes to the development of atherosclerosis. However, the impact of hypercholesterolemia on the circulating levels of neutrophils is not strongly supported in humans and no data are available on FH patients.[93]

Under high-intensity cholesterol-lowering therapy, circulating $CD4^+$ T lymphocytes isolated from FH patients were independently associated with coronary artery calcium presence.[94] Beyond an elevation of the lymphocyte count, an increased activation of $CD4^+$ T cells and an impaired Treg immunosuppressive response were detected in patients with FH.[95] In addition, *LDLR* variants in patients with FH contributed to a defective $CD8^+$ T cell activation by altering lysosomal cholesterol availability and activating the protein kinase mechanistic target of rapamycin complex 1 (mTORC1).[96] Notably, these effects were not observed in $CD4^+$ T cells, highlighting a distinct role of cholesterol metabolism according to T cell subpopulations. A recent study further emphasized the dysregulation of lymphocyte function upon hypercholesterolemia by demonstrating that the increased extracellular vesicle release originating from T cells was associated with immunity and endothelial dysfunction in patients with FH and could contribute to accelerated atherosclerosis.[97]

In FH patients, LDLc levels drive the production of proinflammatory monocytes enriched in lipid droplets by impacting haematopoiesis.[92] Interestingly, treatment with cholesterol-lowering therapy reverted the myelomonocytic skewing but not the pro-inflammatory and pro-migratory pathways of monocytes in the bone marrow.

In humans, blood monocytes are usually classified in subsets based on the expression of CD14 and CD16 markers (classical: $CD14^{++}CD16^{-}$, intermediate: $CD14^{++}CD16^{+}$, non-classical: $CD14^{+}CD16^{++}$) with specific inflammatory signatures associated with aortic infiltration.[98] Previous studies indicated that these monocyte subsets' amount and functions were modified in patients with FH[99,100] although this alteration was not consistently observed.[101] However, monocytes from hypercholesterolemic patients exhibited an increased expression of activation markers, including CCR2, as compared to monocytes from control individuals.[101–103] Exacerbated pro-inflammatory phenotype, migratory capacity, and lipid accumulation of circulating classical monocytes from patients with FH were dampened by LDLc lowering by PCSK9 monoclonal antibodies and statins.[103] The anti-inflammatory effect of PCSK9 monoclonal antibodies in FH also involved the attenuated adhesion of leucocytes to dysfunctional arterial endothelium.[104] Monocytes from patients with FH displayed a marked regulation of genes involved in cholesterol metabolism and an increased oxidized or native LDL uptake and lipid accumulation compared to those from healthy individuals.[105]

Analysis of the circulating monocyte profile from FH patients by RNA sequencing revealed an enrichment of the immune and metabolic (oxidative phosphorylation, glycolysis, and amino acid synthesis) pathways as compared to normocholesterolemic individuals underlying the trained immune phenotype of FH monocytes.[101] This trained immunity is characterized by enhanced cytokine

production, a pro-inflammatory transcriptional reprogramming associated with persistent epigenetic changes of histone modifications that statin treatment did not revert.[101] Thus, trained immunity of monocytes might contribute to the residual cardiovascular risk of patients with familial hypercholesterolemia treated with cholesterol-lowering therapies.

Monocyte-derived macrophages exert a major role in the development of ASCVD by modulating inflammation and cholesterol homeostasis in response to elevated LDLc within atherosclerotic plaques. In FH, macrophages were characterized by an increased pro-inflammatory phenotype which may also be independent of LDLc and involved epigenetic control such as miR-505-3p.[106] However, numerous studies reported alterations between both lipid metabolism and the inflammatory phenotype of macrophages in FH. Cholesterol efflux to exogenous acceptors and lipoprotein lipase activity, which play an essential role in lipid accumulation in macrophages, were respectively unaltered[107] or increased[108] in macrophages from FH patients compared to those from control individuals. Interestingly, Artieda et al. described that macrophage from FH patients with tendon xanthomas exhibited a higher inflammatory phenotype and cholesterol uptake in the presence of oxidized LDL than those from FH patients without tendon xanthomas.[109] Beyond variants in the *LDLR* gene, macrophages from patients with FH preserved their capacity to uptake lipids after aggregated LDL exposure through the LRP5 receptor, for which the expression was more elevated than in macrophages from healthy individuals. Such a mechanism alters the CD163 expression, an anti-inflammatory marker, in macrophages from patients with FH.[110]

4 | IMPACT OF LIPID-LOWERING APPROACHES TO REDUCE INFLAMMATION

Management of the inflammatory condition by lipid-lowering drugs is a therapeutic strategy based on the knowledge that pathogenic lipids, such as lipopolysaccharides (LPS), are incorporated into LDL, subsequently being cleared from the circulation by hepatocytes through the LDLR.[111] The demonstration of a pharmacological therapeutic benefit of LDLc reduction in hypercholesterolemic patients started almost 40 years ago with the non-absorbable bile acid binding resins, cholestyramine, and colestipol, afterward partly replaced by colesevelam. This drug reduced LDLc by 20%–30%, but with better tolerability. The LRC-CPPT (The Lipid Research Clinics Coronary Primary Prevention Trial) study testing the efficacy of cholestyramine in 3806 patients with hypercholesterolemia was the first to show evidence for a causal role of LDLc in the pathogenesis of cardiovascular events.[112] It opened the way to a large series of clinical investigations on this major therapeutic strategy. A beneficial coronary atheroma regression was reported later in the CLAS (Cholesterol Lowering Atherosclerosis Study) trial with colestipol plus niacin.[113]

Studies on resins did not go far into the potential protective mechanisms other than the lipid reduction linked to the binding of bile acids to the resins. Bile acids exerted inflammatory changes by activating pro-inflammatory cytokine release from Kupffer cells.[114] Cytokines go from capillaries to hepatocytes, activating the toll-like receptor signalling and the Ras/MEK4/7/JNK1/2 signal cascade.[115] The colesevelam HCl, which was hydrophilic, not hydrolysed by digestive enzymes, and not undergoing intestinal absorption, was effective in lowering LDLc concentrations in monotherapy and in combination with statins and fenofibrate. In patients with mild hypercholesterolemia, colesevelam reduced hs-CRP, however without affecting IL-6 and TNF-α.[116]

Statins are definitely associated with dramatic plasma LDLc lowering with concurrent ASCVD risk reduction.[2,117,118] However, several cholesterol-independent cardioprotective mechanisms, prominent among others, an anti-inflammatory effect associated with significant reductions of hs-CRP,[119] were reported (Figure 2). Statins inhibit the expression of adhesion molecules in endothelial cells and monocytes. By regulating different oxidation pathways that control NADPH oxidase, myeloperoxidase, and endothelial nitric oxide (eNOS) activity,[120] statins promote antioxidation and restore redox homeostasis.[121] Statins reduce NF-κB activation and chemokine and metalloproteinase (MMP) expression and promote the expression of anti-inflammatory and cytoprotective molecules in endothelium.[122]

The anti-inflammatory effects of statins translating into a reduction of plasma hs-CRP have been repeatedly reported. In the large JUPITER (Justification for Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) cardiovascular prevention study with rosuvastatin, there was clear evidence of an association between LDLc reduction and lower hs-CRP levels.[123] Further analysis of this trial showed that the lower hs-CRP levels were the best marker of ASCVD risk reduction in patients receiving rosuvastatin.[124] A direct comparison of the cardiovascular risk among patients with ASCVD on statin therapy participating in the PROMINENT (Pemafibrate to Reduce Cardiovascular OutcoMes by Reducing Triglycerides IN patiENts With diabeTes), the REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl—Intervention Trial), or the STRENGTH (Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High

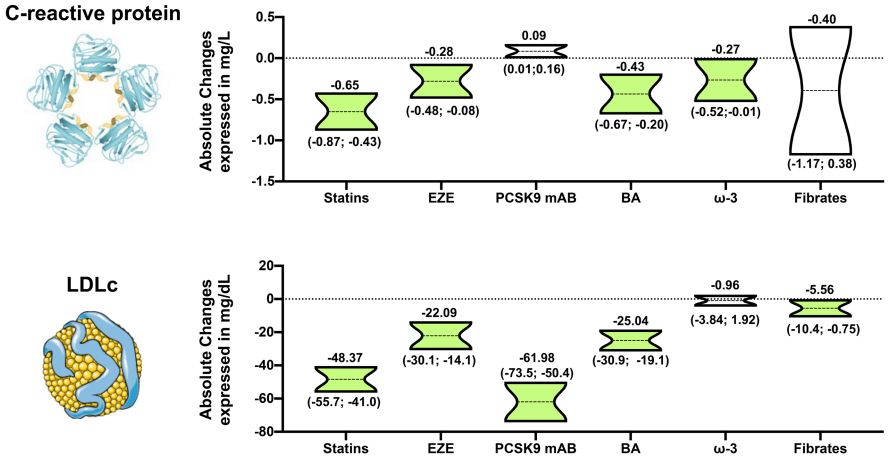

FIGURE 2 Schematic representation of changes in hs-CRP and LDLc driven by lipid-lowering therapies. Violin plots coloured in light green identify significant statistical changes. hs-CRP, high sensitivity C-Reactive protein; LDLc, low-density lipoprotein cholesterol. EZE, ezetimibe; PCSK9, proprotein convertase subtilisin/kexin type 9; mAB, monoclonal antibodies; ω, omega. Numbers above violin graphs indicate absolute changes. Numbers within parentheses represent 95% Confidence Interval (CI). Data were extrapolated from Xie S et al.[125]

Cardiovascular Risk Patients with Hypertriglyceridemia) trials, concluded for a stronger predictivity of inflammation (as assessed by hs-CRP) compared to LDLc for the incident of MACE. However, cardiovascular death and all-cause death were significantly higher in participants with both residual cholesterol and inflammatory risk (hs-CRP ≥2 mg/L and LDLc ≥70 mg/dL) than in participants with hs-CRP <2 mg/L and LDLc <70 mg/dL.[15]

However, a meta-regression analysis of all major trials with statins showed no significant correlation between changes in hs-CRP and LDLc levels, even after adjustment by age, sex and intervention duration.[125] These data were in agreement with those previously described by Asher et al. who reported that the statin-driven decrement in the levels of hs-CRP (which is roughly 60%) appears to be independent of the magnitude of LDLc lowering.[126]

As different types of statins are concerned, while the REAL-CAD (Randomized Evaluation of Aggressive or Moderate Lipid-Lowering Therapy With Pitavastatin in Coronary Artery Disease) trial showed a decrement in the levels of hs-CRP after 6 months of pitavastatin therapy,[127] no significant changes were observed with the latter in the RETRIEVE (Evaluating the Use of Pitavastatin to Reduce the Risk of Cardiovascular Disease in HIV-Infected Adults) trial patients.[128]

Additionally, even though some lipid-lowering therapies lower IL-6, this inflammatory pathway and the LDLc are two separate causes of ASCVD. Indeed, fewer individuals in the general population are exposed to high IL-6 levels than high LDLc.[129] An analysis of 397,060 White British UK Biobank participants without known ASCVD showed that any benefit of inhibiting IL-6 signalling for ASCVD risk reduction was proportional to the absolute reductions in the levels of hs-CRP.[130]

Ezetimibe is a cholesterol transport protein NPC1-like 1 (NPC1L1) antagonist that inhibits intestinal cholesterol absorption, and it is frequently used in association with statins.[131,132] Ezetimibe leads to incremental lowering of LDLc levels and improved cardiovascular outcomes (2% reduction of absolute risk) without signs of drug–drug interaction.[133] Limited information is available on its potential anti-inflammatory effects. Clinical studies have not provided homogeneous findings, mostly conducted in combination with statins and only a tiny number as monotherapy. In the SHARP (Study on the Heart and Renal Protection) trial in patients with chronic kidney disease,[134] the combination of simvastatin and ezetimibe led to a 35% reduction of LDLc and a 21% reduction of hs-CRP compared to placebo. However, no evidence of a contribution of hs-CRP lowering to the cardiovascular benefit was reported.[135]

A pooled analysis of randomized, placebo-controlled ezetimibe trials in patients with hypercholesterolemia, showed no differences in hs-CRP.[136] However, when ezetimibe was added to baseline statin therapy, a 10% reduction of hs-CRP was observed[137] (Figure 2). A similar effect was observed in the IMPROVE-IT trial, where simvastatin plus ezetimibe resulted in a further 20% reduction of LDLc and 0.3 mg/L (14%) hs-CRP reduction.[138] This led to significantly more patients meeting the targets of LDLc <70 mg/dL and hsCRP <2 mg/L.

Gomez-Garre et al. conducted a mechanistic analysis of the ENHANCE (Ezetimibe and Simvastatin in Hypercholesterolemia Enhance Atherosclerosis Regression) study, which investigated the effects of

combining ezetimibe and simvastatin in rabbits fed a combination of hyperlipidaemic diet and undergoing vascular injury. The combination treatment resulted in a notable decrease in plaque monocyte/macrophage content and specific proinflammatory markers.[139]

Some studies have also investigated statin therapy versus statins in combination with ezetimibe on endothelial function as a measure of vascular inflammation, with inconstant findings.[140] Two cross-over studies evaluating molecular mechanisms reached discordant conclusions. One showed an unchanged endothelial function with the addition of ezetimibe to statin alone,[141] and the other reported a protective activity on ischemia/reperfusion injury based on an anti-oxidant mechanism.[142] Ezetimibe can thus provide an additive effect to statins on LDLc and arterial inflammation.

No changes in systemic inflammatory markers were reported in the cardiovascular outcome trials with monoclonal PCSK9 inhibitors (Figure 2). The decrease in hs-CRP does not parallel the robust LDLc reduction obtained by inhibiting PCSK9.[125] On the contrary, numerous preclinical and in vivo reports have described a feed-forward loop between PCSK9 and inflammation.[143] Prominent in this field was the study by Bernelot Moens et al. demonstrating that monocytes of FH patients had a pro-inflammatory phenotype, which was dampened by LDLc lowering after the therapy with PCSK9 monoclonal antibodies.[103] More recently, in a small study on 41 subjects with ASCVD and type 2 diabetes and LDLc >70 mg/dL, evolocumab modulated circulating immune cell transcriptional responses to stress. Indeed, to unmask functional differences in circulating immune cells, RNA-seq analysis was performed on immune cells stimulated with LPS and compared to naïve immune cells of patients treated or not with evolocumab.[144]

Additionally, in 645 patients undergoing carotid endarterectomy, PCSK9 inhibitors led to a beneficial remodelling of the inflammatory burden within the human atheroma, an effect possibly or partly independent of their ability to lower LDLc.[145] Overall, it seems that PCSK9 inhibition hold promises in atherosclerotic plaque remodelling, acute coronary syndrome, inflammation, and immune response.[146]

A new addition to the therapeutic resources for the treatment of elevated cholesterol, mainly addressed to statin-intolerant patients, was provided by bempedoic acid, an inhibitor of ATP-citrate lyase (ACLY), an enzyme responsible for producing extra-mitochondrial acetyl-CoA. Cholesterol-lowering with bempedoic acid requires the conversion of the pro-drug to the active compound. A specific isozyme mediates this, the very long-chain acyl-CoA synthetase-1, which resides exclusively in the liver, thus sparing the disturbing side effects of statins.[147]

Regarding the relationship between LDLc and inflammation, the fixed-dose combination of bempedoic acid/ezetimibe led to a 35.1% reduction in hs-CRP levels. In comparison, the placebo group (receiving simvastatin alone) experienced a decrease of 21.6%, while the group receiving ezetimibe alone showed an 8.2% reduction.[148] This anti-inflammatory action is supposedly associated with AMP-activated protein kinase (AMPK) activation, which translates into the suppression of the anabolic events in immune cells and restriction of energy availability for protein biosynthesis leading to the switch of macrophages toward an anti-inflammatory profile.[149] Additionally, targeting ACLY in macrophages can attenuate inflammatory responses and decrease atherosclerotic plaque vulnerability.[150]

Pooled data from four phase 3 trials concluded that bempedoic acid significantly reduced hs-CRP irrespective of background statin therapy (Figure 2). This effect was largely independent of changes in LDLc.[151] The CLEAR Outcome (Evaluation of Major Cardiovascular Events in Participants With, or at High Risk for, Cardiovascular Disease Who Are Statin Intolerant Treated With Bempedoic Acid (ETC-1002) or Placebo) study further showed the superiority of bempedoic acid to reduce hs-CRP (−21.6%) and LDLc (−21.1%) compared to placebo at 6 months. As baseline hs-CRP levels were significantly associated with the primary composite endpoint of MACE, cardiovascular mortality, and all-cause mortality irrespective of LDLc, these findings reinforce the hypothesis that inflammation mediates potentially catastrophic events.[16]

A drug with a highly restricted indication is lomitapide. This molecule is a potent inhibitor of the microsomal transfer protein (MTP) and has entered clinical use in treating HoFH. Long-term, extensive studies, albeit in small patient series, showed remarkable and sustained LDLc reductions of roughly −50%.[152] However, limited attention was given to inflammatory markers. A long-term study evaluating LDLc reductions noted a dramatic progressive reduction of hs-CRP (i.e. 60% from baseline to week 246).[153] A similar decrease was observed in an Italian study after 6 months of lomitapide treatment, describing additional lowering of TNF-α (48%), IL-13 (70%) and IL-7 (31%). An increase of IFN-γ (71%) and of the anti-inflammatory cytokines IL-18 (41%), IL-17 (44%), and IFN-γ (71%) was also described.[154]

Among lipid-lowering drugs specifically effective in FH, evinacumab, a potent inhibitor of the angiopoietin-like-3 (ANGPTL3) system, was associated with robust LDLc reductions in FH patients. The ELIPSE HoFH (Efficacy and Safety of Evinacumab in Patients With Homozygous Familial Hypercholesterolemia) trial showed that evinacumab, a monoclonal antibody

antagonist of ANGPTL3, when given to HoFH patients, resulted in a between-group LDLc difference of −49% compared to placebo.[155] In an open-label extension study, the efficacy of evinacumab was confirmed. Patients with HoFH who received evinacumab every 4 weeks had a 46.3% reduction in LDLc, an effect which was maintained throughout the 48-week of the open-label treatment period.[156] Among the key-secondary endpoints, long-term evinacumab, when used alongside other lipid-lowering therapies, including lipoprotein apheresis, improved cardiovascular event-free survival of patients with HoFH.[157]

The mechanism of LDLc reduction with evinacumab is still unclear, most unlikely related to LDLR residual activity but driven by an increased apoB-containing lipoprotein clearance.[158] However, the activity of evinacumab on the inflammatory pathway was found to be of potential benefit. ANGPTL3 showed a pro-inflammatory and pro-angiogenic profile with a negative effect on cholesterol efflux,[159] a finding attributed to endothelial lipase's and lipoprotein lipase's local rise. In vitro studies on THP-1 monocytes showed that ANGPTL3 increased the production of IL-1β and TNF-α as well as the expression of toll-like receptor 4.[160] A variable reduction of hs-CRP (with a mean of 9%) was reported in a small series of Italian HoFH patients, associated to a mean 46.8% LDLc reduction.[161] If confirmed in larger studies, these anti-inflammatory mechanisms may positively affect cardiovascular risk beyond those associated with lipid-lowering.

Probucol is a bisphenol compound synthesized as an antioxidant in a manufacturing plant and unexpectedly found to exert a cholesterol-lowering activity. Probucol is associated with a stimulated cholesterol ester transfer protein (CETP) activity and reduced HDLc.[162] In many clinical studies, probucol was positively associated with ASCVD prevention.[163] The significant HDLc-lowering activity was attributed to CETP stimulation, leading to an improved cholesterol efflux capacity, resulting in regression of tendon xanthomas in humans.[164] These studies led to a reduction in restenosis incidence after angioplasty after long-term administration.[165]

The activity of probucol on atherosclerosis progression and vascular inflammation was described in preclinical studies. An early study on the WHHL rabbit (an animal model of FH) established reduced atherosclerosis progression. In this model, probucol lowered coronary atherosclerosis and MI and delayed death from heart failure, also increasing lifespan.[166] In a model of apoE$^{-/-}$ mice, probucol reduced plaque area with fewer inflammatory macrophages within the lesion and a reduced expression of the vascular cell adhesion molecule 1.[167] In vitro studies on vascular cells showed that probucol reduced the inflammatory process by decreasing the production and activity of matrix MMP-2 and-9 and raising the expression of miR-47.[168]

In the context of CETP modulation,[169] data from the BROADWAY (NCT05142722) and BROOKLYN (NCT05425745) studies with obicetrapib (a selective inhibitor of CEPT) are awaited. These are placebo-controlled, double-blind, randomized Phase III trials designed to examine the efficacy, safety, and tolerability of obicetrapib as an adjunct to dietary intervention and maximally tolerated lipid-modifying therapies in participants with a history of ASCVD and/or underlying HeFH whose LDLc is not adequately controlled. Changes in hs-CRP will be also evaluated.[170] Furthermore, the PREVAIL trial is a further study designed to assess the potential of obicetrapib to reduce occurrences of MACE in patients with a history of ASCVD who do not have adequate LDLc control despite being on maximally tolerated statin therapies.[171]

Somewhat less evaluated pathways leading to vascular disease, particularly vascular calcification, are those mediated by the bromo-and extraterminal (BET) proteins. Bromodomains are protein interaction modules specifically recognizing ε-N-lysine acetylation motifs, key events in the reading process of epigenetic marks.[172] Apobetalone is a bromodomain and extra terminal protein inhibitor targeting BRD2 and is hypothesized to have favourable effects on pathways related to atherothrombosis. Although a large phase 3 study[173] did not show the superiority of apobelatalone compared to control to reduce MACE, the latter reduced vascular inflammation, in particular, lowering adhesion molecules, cytokines, and MMPs.[174] Later studies also indicated potentially significant adverse effects of this drug (e.g. raised liver enzymes).[175]

5 | LDL-APHERESIS IN FH AND ITS ROLE IN INFLAMMATION

Lipoprotein apheresis is currently recommended for treating the most severe and resistant forms of HeFH and HoFH.[176] In HoFH, lipoprotein apheresis is generally associated with drug treatment and has represented the standard of care.[177,178] Lipoprotein apheresis initiated during childhood and adolescence is associated with reduced risk of ASCVD and death.[179] However, data from the largest worldwide database on HoFH show that barely 30% of HoFH subjects are treated with lipoprotein apheresis.[21] Lipoprotein apheresis results in a significant reduction of LDLc, ranging from 50% to 80% in one session.[180] However, as a result of both enhanced synthesis and reduced hepatic clearance of LDL particles, the LDLc returns to baseline within 1 to 2 weeks, so time-averaged LDLc reduction is around 40%, in line with a modestly potent statin.[177] Lipoprotein apheresis has some pleiotropic

effects, such as an anti-inflammatory activity and acting favourably on oxidative stress and rheology, thus slowing the atherosclerotic process.

Circulating inflammatory biomarkers have been evaluated in FH patients treated with lipoprotein apheresis, and studies showed a slight but significant reduction in hs-CRP.[181] Reduced concentrations of adhesion molecules, such as the monocyte chemoattractant protein (MCP-1) and P-selectin[182,183] were also found after lipoprotein apheresis sessions. More recently, the soluble activated leukocyte cell adhesion molecule, considered a homologue of the HDL receptor, was shown to be positively affected by lipoprotein apheresis.[184] Finally, a reduction of circulating inflammatory cytokines such as TNF-α, IL-1β and CD-14 and in the relative expression of miRNA for IL-1α, IL-6, and TNF-α was reported after two sessions of lipoprotein apheresis in FH subjects.[185] Another study that focused on MMP-9 and the tissue inhibitor (TIMP-1) did not confirm this beneficial activity of lipoprotein apheresis. These two cytokines increased and decreased in HoFH patients compared to HeFH and non-FH controls, resulting in a high MMP9/TIMP-1 ratio. Lipoprotein apheresis did not influence the short-term expression of these markers.[186]

The anti-inflammatory effect of lipoprotein apheresis improved coronary microcirculation and inflammation of the arterial wall.[187] This latter was evaluated before and after lipoprotein apheresis by an (18)F-fluorodeoxyglucose positron emission tomography ((18)FDG-PET) imaging technique. The target-to-background of FDG uptake in the arterial wall, a measure of arterial wall inflammation, was higher in FH subjects and correlated to LDLc levels, despite statin treatment. Together with the expected reduction of LDLc, lipoprotein apheresis significantly reduced target-to-background on follow-up FDG-PET imaging.[188]

6 | LIPOPROTEIN(a) AND INFLAMMATION

Lipoprotein(a) is the most diverse of the lipoproteins, consisting of a LDL-like particle with one molecule of apolipoprotein (apo)B-100 covalently bound to apo(a), a glycoprotein with repeated "kringle" structures reminiscent of Scandinavian pastries. This lipoprotein is highly genetically controlled, with about 90% of its concentration being heritable. This lipoprotein consists of not only the mass of apoB and apo(a) but also the mass of carbohydrates on apo(a), as well as cholesterol, cholesterol esters, and phospholipids.[189] While we await the results of trials on the cardiovascular benefits of lowering lipoprotein(a) levels,[190] in the last decade epidemiological and genetic studies have highlighted a link between ASCVD risk and elevated lipoprotein(a) levels. Inflammation and lipoprotein(a) are closely connected; the phosphocholine containing oxidized phospholipids associated with the apo(a) moiety of lipoprotein(a) increases arterial wall inflammation by activating monocytes and endothelial cells, contributing to its atherogenicity. Additionally, lipoprotein(a) has an IL-6 response element and is elevated in acute and chronic inflammatory diseases like sepsis and rheumatoid arthritis, further increasing inflammation-driven ASCVD risk.[191]

In patients with FH, lipoprotein(a) concentrations above 30 mg/dL contribute to an increased risk of ASCVD. Epidemiological studies have reported that about one-third of FH patients have elevated levels of lipoprotein(a), defined as >50 mg/dL, and around 5% have levels above 100 mg/dL, compared to 2.6% in non-FH hypercholesterolemic patients.[192] Overall, elevated lipoprotein(a) in FH creates a unique situation where two genetically determined proatherogenic factors contribute to lifelong atherosclerotic cardiovascular risk burden.

Taking advantage of this knowledge, testing for elevated lipoprotein(a) during FH cascade screening helps identify relatives with high lipoprotein(a) and heightened risk of ASCVD, especially when the proband has both FH and elevated lipoprotein(a). However, it is important to note that FH does not cause elevated lipoprotein(a), rather, elevated lipoprotein(a) increases the likelihood of clinical recognition of genetic FH.[193]

7 | TRIGLYCERIDE-RICH LIPOPROTEINS AND INFLAMMATION

Beyond just LDLc and FH, the atherogenicity nature of remnant cholesterol, also known as triglyceride-rich lipoproteins (TRL), cannot be overlooked. Strong and increasing evidence from epidemiologic and genetic studies indicates that TRL and their remnants are causally related to the risk of ASCVD.[194–196] Remnant cholesterol refers to the cholesterol content in apolipoprotein (apo) B-containing lipoproteins that are not part of LDLc (i.e. it equals total cholesterol minus LDLc minus high-density lipoprotein (HDL) cholesterol or can be directly measured). The intestine and liver release chylomicrons and very-low density lipoproteins into the bloodstream, which then undergo lipolysis and rapid remnant removal to ensure a steady supply of triglycerides, especially during periods of food scarcity.[197] Lipoprotein lipase is the crucial enzyme in the intravascular hydrolysis of triglycerides in circulating TRLs, facilitating the release of fatty acids to be stored in adipose tissue or used as an energy source by muscles. Although there is no evidence that triglycerides

directly cause atherogenic effects, free fatty acids released during the lipolysis of TRLs (in the subendothelial space or at the endothelial surface) can have proinflammatory effects on endothelial cells and monocyte-derived macrophages.[198] This is particularly true for saturated fatty acids, but not for polyunsaturated forms (e.g. ω-3 free fatty acids). Fatty acids metabolism is highly complex because these molecules are precursors to metabolites that are both proinflammatory (prostaglandins and leukotrienes) and anti-inflammatory (resolvins, protectins and maresins), while others are involved in intracellular signalling pathways and various other functions (e.g. regulating membrane fluidity and serving as ligands for nuclear receptors).[199] Free fatty acids activate NF-κB and cytokine expression in macrophages via toll-like receptor 4 signalling.[200] Additionally, saturated fatty acids, similar to cholesterol, can cause intracellular crystallization and subsequent lysosomal dysfunction, activating the NLRP3 inflammasome.[58]

Foam cells loaded with lipids and smooth muscle cells in lesions, which are rich sources of lipoprotein lipase, enhance endothelial activation and permeability. Lipoprotein lipase in arterial macrophages may also directly promote atherogenesis. Unlike LDL particles, remnants (<70 nm in diameter, which excludes most newly secreted, non-lipolysed chylomicrons and very large very-low density lipoproteins) can penetrate the arterial wall by transcytosis and be retained in the arterial intima without modifications.[201] Apolipoprotein B in remnants further aids in binding these remnants to the extracellular arterial proteoglycans. Once remnants are trapped in the arterial intima, cholesterol accumulation in the extracellular space triggers inflammation. The hydrolysis of triglycerides in remnants produces free fatty acids and monoacylglycerol, both of which can cause inflammation at the endothelial surface and within the intima. These inflammatory responses accelerate the progression of atherosclerosis.[202]

Epidemiological studies have shown that TRL and inflammation can be partner in crime, increasing the risk of ASCDV. Data from Copenhagen General Population Study[203] and Multi-Ethnic Study of Atherosclerosis[204] highlight the harmful effects of having both high levels of TRL and low-grade inflammation. Additionally, data from the Brazilian Longitudinal Study of Adult Health support the hypothesis that TRLs, particularly medium and larger sub-particles, may induce a low-grade inflammatory environment involving leukocyte activation, which is detected by GlycA, but not hs-CRP.[205]

The PESA study results indicated that among individuals with low to moderate cardiovascular risk but with triglycerides >150 mg/dL experienced a significant increase in risk of developing subclinical atherosclerosis and in the number of affected noncoronary vascular territories. Both arterial inflammation and the number of inflamed plaques (measured by fluorine-18 fluorodeoxyglucose uptake on positron emission tomography) rose with increasing triglycerides levels.[206]

Nevertheless, our comprehension of the links between TRL and ASCVD risk remains limited due to scarcity of conclusive evidence from randomized, blinded, placebo-controlled trials demonstrating that lowering triglycerides specifically reduces ASCVD events, especially when statins are given as background. The main triglyceride-lowering medications available are fibrates and fish oil products containing eicosapentaenoic acid (EPA) or a combination of EPA and docosahexaenoic acid (DHA).

The interest in the dietary management of hypercholesterolemia and the possible associated anti-inflammatory benefits has led to extensive studies with unsaturated fatty acids, particularly of the n-3 series.[207] Higher intakes of ω-3 polyunsaturated fatty acids (n3 PUFAs), principally eicosapentaenoic acid (EPA, C20:5) and docosahexaenoic acid (DHA, C22:6), have been linked with better health outcomes across many systems.[208]

In this context, two cardiovascular outcome trials, the STRENGTH with EPA + DHA, and the REDUCE-IT with a purified form of EPA (Icosapent Ethyl) showed contrasting findings. While the former had neutral cardiovascular benefit, the latter proved a cardiovascular beneficial activity of EPA with a relative risk reduction of 25% (for the primary endpoint), 26% for the key secondary endpoint, and 32% for total ischemic events. The benefit began early in the study and persisted across prespecified interim analyses through the final analysis.[209] Relative to the inflammatory parameters, at 24 months, the Icosapent Ethyl reduced hs-CRP by 13.9% (from baseline) with minimal or no changes in IL-6 and IL-1 β.[210] However, when compared with other trials centred around the major inflammatory IL-1β/IL-6/hs-CRP pathway, these findings indicate the REDUCE-IT population was overall less inflamed to begin with.[211]

Trying to explain the above-described results, Sherret et al. showed how EPA was superior to DHA in counteracting the oxidation of small dense LDL and very low-density lipoprotein particles.[212] After 72 hours, EPA significantly inhibited membrane oxidation by 89% compared with vehicle, whereas DHA had a less effective inhibitory effect on oxidation.

The ω-3 FAs may lower ASCVD risk through several pleiotropic mechanisms (e.g. by lowering blood pressure, mediating antithrombotic effects, providing precursors for the synthesis of specialized pro-resolving mediators that can inhibit inflammation or modulating the lipid rafts enriched in cholesterol and sphingolipids). High levels of EPA and DHA had the potential of reducing or antagonizing platelet reactivity, alleviating oxidative stress

and reducing biomarkers of chronic inflammation such as CRP and TNF-α.[213] The conversion of membrane FAs to active molecules regulating inflammatory processes is of particular significance in the case of ω-3 FAs. These may enter the cell membranes at the expense of arachidonic acid, resulting in inhibited arachidonic acid metabolism and consequent decreased expression of the cyclooxygenase gene and, as a final consequence, reduction of arachidonic acid-derived inflammatory eicosanoids. EPA and DHA affect the membrane structure differently due to differences in hydrocarbon length and number of double bonds. The longer hydrocarbon length and higher number of double bonds for DHA lead to increased membrane fluidity and promotion of cholesterol domains. EPA has a more stable and extended structure that contributes to membrane stability and reduces lipid oxidation and cholesterol domain formation.[214] In endothelial cells, EPA increases the expression of proteins involved in NO production, including hemeoxygenase-1 and dimethylarginine dimethylaminohydrolase-1, and proteins associated with neutrophil degranulation. Additionally, EPA reverts the endothelial NO synthase uncoupling induced by IL-6 as evidenced by an increased[215] peroxynitrite release ratio.[216]

Another possible anti-inflammatory activity driven by ω-3 FAs involves the so-called pro-resolving lipid mediators, resolvins (short for resolution phase interaction products), produced from EPA (E-series) and DHA (D-series) and protectins and maresins (short for macrophage mediators in resolving inflammation) from DHA.[217]

Interestingly, supplementation with ω-3 fatty acid ethyl ester improves postprandial lipemia in FH patients receiving standard care.[218] Indeed, postprandial dyslipoproteinemia can be present in FH, as a consequence of the overproduction and decreased catabolism of TRLs, which may be a consequence of LDL receptor deficiency.[219] Postprandial hypertriglyceridemia reflects prolonged accumulation of TRLs, including VLDL-apolipoprotein B (apoB)-100 and apoB-48-containing chylomicrons and their remnants in the circulation.

Regarding fibrates (PPARα agonist), the current guidelines from European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS), which were published before PROMINENT (The Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes) study, suggest with a class of recommendation IIb and level C evidence that fenofibrate or bezafibrate may be considered in combination with statins for high-risk patients who have reached their LDLc goal but have triglycerides levels >2.3 mmol/L (>200 mg/dL).[220] These recommendations will probably be reviewed to class III for ASCVD prevention after the negative results of PROMINENT.[221] In terms of the effect of fibrates on the circulating CRP levels, they exert only a marginal and non-significant reduction.[125] Despite this, fenofibrate improves vascular endothelial function by reducing oxidative stress and increasing in eNOS.[222] Additionally, fenofibrate slows the progression of microvascular complications of patients with diabetes, including reducing nonfatal coronary events, decreasing need for laser treatment of diabetic retinopathy, and delaying the progression of diabetic nephropathy.[223]

8 | CONCLUSIONS

The role played by local and systemic inflammation in atherosclerosis development is well established. Indeed, atherosclerosis is a chronic inflammatory disease wherein dysregulation and activation of the innate and adaptive immune systems in the context of endothelial dysfunction promote aberrant LDLc uptake, oxidation, and accumulation, in turn inciting plaque development. However, since this is not a competition between LDLc and inflammation,[224] once a patient reaches the LDLc target, a biomarker to assess the presence of residual inflammatory risk should be used instead.[225]

Weight loss, smoking cessation, and physical activity have been shown to reduce hs-CRP and ASCVD events. Colchicine is an alternative recommended in guidelines and approved for ASCVD reduction.[226]

Possibly the beneficial effects of GLP-1 receptor agonists are in part mediated by anti-inflammatory mechanisms in people with type 2 diabetes and excess body weight. Indeed, these agonists can suppress endothelial dysfunction and inflammation, reduce monocyte recruitment and foam cell formation, as well as decrease plaque development and thrombosis.[227]

In the meantime, one can wait for the results of further trials targeting the inflammatory burden, for examples, the ZEUS (A Research Study to Look at How Ziltivekimab Works Compared to Placebo in People With Cardiovascular Disease, Chronic Kidney Disease and Inflammation) trial aimed at evaluating the impact of IL-6 inhibition in patients with ASCVD and elevated inflammatory burden or the CLEAR SYNERGY (Colchicine and Spironolactone in Patients With Myocardial Infarction/Synergy Stent Registry) aimed at assessing the effects of low-dose colchicine and spironolactone in largely unselected post-MI patients who undergo percutaneous coronary intervention.

IL, interleukin.

AUTHOR CONTRIBUTIONS

AG, CS and MR conceived the hypothesis, wrote the original text, and revised the final version. IS created the two

illustrations and assisted in addressing the reviewers' comments. WLG wrote the section relative to inflammation and FH and critically revised the entire text. RDS, AC and SC revised the text.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

ORCID

Massimiliano Ruscica https://orcid.org/0000-0002-0195-7061

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