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Review article

PCSK9 inhibition and inflammation: A narrative review

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HIGHLIGHTS

- PCSK9 monoclonal antibodies dramatically reduce LDL-C, but not hs-CRP.
- The two-dose regimen of inclisiran (300 mg), a siRNA direct against PCSK9, reduced hs-CRP by 16.7%.
- hs-CRP levels identify ASCVD patients who better respond to PCSK9 monoclonal antibodies.
- In the Anitschkow study, evolocumab modestly reduced Lp(a) with no changes of hs-CRP or arterial inflammation.

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ABSTRACT

Atherosclerotic cardiovascular disease (ASCVD) remains a leading cause of morbidity and mortality despite excellent pharmacological and revascularization approaches. Low-density lipoproteins (LDL) are undoubtedly the most significant biochemical variables associated with atheroma, however, compelling data identify inflammation as critical for the maintenance of the atherosclerotic process, underlying some of the most feared vascular complications. Although its causal role is questionable, high-sensitivity C-reactive protein (hs-CRP) represents a major biomarker of inflammation and associated risk in CVD. While statin-associated reduced risk may be related to the lowering of both LDL-C and hs-CRP, PCSK9 inhibitors leading to dramatic LDL-C reductions do no alter hs-CRP levels. On the other hand, hs-CRP levels identify groups of patients with a high risk of CV disease achieving better ASCVD prevention in response to PCSK9 inhibition. In the FOURIER study, even in patients with extremely low levels of LDL-C, there was a stepwise risk increment according to the values of hs-CRP: +9% (< 1 mg/L), +10.8% (1–3 mg/L) and +13.1% (> 3 mg/L). Likewise, in the SPIRE-1 and -2 studies, bococizumab patients with hs-CRP > 3 mg/L had a 60% greater risk of future CV events. Most of the patients enrolled in the PCSK9 trials were on maximally tolerated statin therapy at baseline, and an elevated hs-CRP may reflect residual inflammatory risk after standard LDL-C lowering therapy. Moreover, data on changes in inflammation markers in carriers of *PCSK9* loss-of-function mutations are scanty and not conclusive, thus, evidence from the effects of anti-inflammatory molecules on PCSK9 levels might help unravel this hitherto complex tangle.

1. Introduction

Studies on patients with myocardial infarction (MI) have clearly established that all post-MI patients are at increased risk for recurrence of events, despite early revascularization and well established pharmacological therapies [1]. Among patients with clinically manifest vascular disease, more than 20% showed a risk of recurrent events in the excess of 30% over 10 years, including MI, stroke, or vascular death, thus indicating an area of unmet medical need [2]. The persistence of high risk has been increasingly associated with elevated levels of proinflammatory molecules, such as cytokines and acute-phase reactants [3]. Indeed, beyond the well-known role of LDL in atherosclerosis, data from the proof-of-concept CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcome Study) trial [4] have clearly identified inflammation as one of the key biological processes of atherosclerosis.

Low-density lipoproteins (LDL) represent the most significant biochemical variable associated with atheroma. The extent of lowering of

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LDL-C and cardiovascular (CV) risk reduction has been evaluated across different statin and non-statin therapies. The relative risk reduction of major vascular events was similar for all drug classes (statins, bile acid sequestrants, ezetimibe, and fibrates), and the achieved lowering of LDL-C was associated with a reduced incidence of major CV events [5].

The CV risk linked to increased inflammatory markers was well established following the detection of elevated high sensitivity C-reactive protein (hs-CRP) in post MI patients with a residual inflammatory risk [6]. This initial observation in patients with relatively normal lipoprotein profile and positive response to statins gave the first rationale for the validity of the approach [7]. CRP is a liver-derived acute phase protein associated with inflammation. Being readily assayable in the circulation, it has reached an established role in the evaluation of bacterial infections, but also of the clinical status of generalized inflammatory diseases. Among these, foremost is rheumatoid arthritis, followed by chronic diseases such as spondylitis, lupus and others [8].

High sensitivity (hs)-CRP > 2 mg/L associates with major CV risk markers, such as elevated LDL-C, as well as with the progression of CV lesions [9], although the existence of a well defined threshold is disputed [10,11]. Use of this marker for an early detection of lesions and, more importantly, for the monitoring of agents reducing CV risk, has gained wide acceptance. Clinical studies on statins, in particular, have shown that also patients with coronary disease not associated with marked hypercholesterolemia, benefit from the reduction of hs-CRP [12].

Overall, although the earlier meta-analysis of Kinlay et al. [13] supported a strong correlation between LDL-C reduction and lowering of hs-CRP, the case is certainly different for the newly developed PCSK9 antagonists with which a dramatic reduction of LDL-C, in the range of 50–60%, is not associated with any changes in hs-CRP. Thus, the present review will discuss the evidence linking PCSK9 and inflammation with a particular emphasis on hs-CRP a marker of residual inflammatory CV risk, especially in secondary prevention.

2. Lipid mediated-inflammation

A number of studies have described pathways leading to vascular inflammation in atherosclerosis. Flow perturbations on endothelial cells (EC), particularly at areas of complex geometry, predispose to lesion development [14]. These areas express adhesion molecules and inflammatory genes to a higher extent [15]. In vessels with compromised glycocalyx, LDL penetrate the arterial intima via endothelial vesicles (transcytosis) or open endothelial junctions [16]. Lipoproteins < 70 nm in diameter, *i.e.* all HDL, LDL and intermediate-density lipoprotein (IDL) particles, in addition to very-low density lipoprotein (VLDL) and small chylomicron remnants, can pass the endothelial barrier and enter intima directly from the circulation [17]. Once in the arterial subendothelium, lipoproteins are trapped by subendothelial proteoglycans through a charge-based interaction [18,19]. LDL then undergo oxidation by the combined action of lipoxygenases, reactive oxygen species, peroxynitrite, and/or myeloperoxidase [20]. OxLDL and LDL-derived oxidized phospholipids further stimulate the inflammatory activation of macrophages and vascular smooth muscle cells; they provide also oxidation-specific epitopes (OSEs) recognized by the C-reactive protein, complement system proteins and innate “natural” IgM antibodies [21]. OxLDL stimulate endothelial cells by inducing the expression of cell surface adhesion molecules that mediate the rolling and adhesion of blood leukocytes (monocytes and T cells) [22]. OxLDL are rapidly recognized by macrophage scavenger receptors, leading to the formation of lipid-laden foam cells; scavenger receptor uptake is not subject to feedback inhibition by intracellular sterols, and phagocytosis and/or receptor uptake can continue unabated [23]. OxLDL are immunogenic by presenting different lipid peroxidation-derived structures, such as oxidized phospholipids and malondialdehyde that are recognized as antigens by the immune system [24]. These oxidized products thus act as targets of innate immunity and as critical modulators of inflammatory responses [25].

Although foam cell populations in atherosclerotic lesions have been considered as primarily of leukocyte origin, smooth muscle cells (SMC) contribute significantly to foam cell populations in human atheroma, 50% of foam cells being SMC-derived [26]. Among scavenger receptors, the LDL receptor-related protein 1 (LRP1) is a key mediator of aggregated LDL-induced cholesteryl ester accumulation in SMCs [27], expressed in both SMCs and macrophages of human atherosclerotic lesions [28].

The activated endothelium allows the entry to the intima of bone-marrow-derived monocytes, *e.g.* the Ly6C^{hi} subpopulation, which differentiate into macrophages. As a result of the activation of inflammatory macrophages and dendritic cell (DC), an inflammatory adaptive immune response involving T helper cells (Th1), but also Th17, Th2 as well as B cells develops [29].

After entering macrophages through scavenger receptor CD36, ox-LDL can prime and activate the innate immune signaling complex NOD-like receptor pyrine domain-containing protein 3 (NLRP3) inflammasome in macrophages, induced by cholesterol crystallization [30]. Cholesterol crystal formation is consequent to an imbalance between esterified and free cholesterol and by changes in HDL function [31]. Upon activation by different endogenous triggers abundantly present in atherosclerotic lesions, *e.g.* cholesterol crystals [32], NLRP3 leads to an increased secretion of IL-1β [33]. IL-1 stimulates adhesion molecules that recruit leukocytes as well as chemokines, *e.g.* monocyte chemoattractant protein (MCP)-1 (also known C–C motif chemokine ligand [CCL]-2). Reduction of cholesterolemia reduces cholesterol crystal formation and, as a consequence, atheromas. Whether reduction of the inflammatory potential of macrophages may occur in the absence of NLRP3 activation remains an open question [34].

In addition to the well established role of LDL-C [35], the contribution of triglycerides (TG) to a raised CV risk has become clear both after long-term prospective studies [36] and a recent mendelian randomization analysis [37]. TG-rich lipoproteins may penetrate the arterial wall and are retained within the sub-endothelial space; after oxidative modification they may lead to the development of atherosclerotic plaques. Lipolysis of TG-rich lipoproteins may release oxidized free-fatty acids (FFA) and lysolecithin, further stimulating endothelial cell inflammation and coagulation [38]. A *post-hoc* evaluation of the REDUCE-IT study [39] reports a significant reduction of CV events in patients with hypertriglyceridemia treated with high dose EPA, and indicates that even low levels of plasma TG, *e.g.* between 81 and 131 mg/dL can carry a CV risk [39].

3. PCSK9 contribution to the development of atherosclerosis

Besides the role of PCSK9 in the regulation of LDL-C, its expression in endothelial cells, VSMC and, at a low level, in macrophages [40], implies the potential role of PCSK9 in atherosclerosis plaque development (Fig. 1). VSMC produce more PCSK9 than endothelial cells, especially in response to shear stress [41]. In particular, VSMC of human atherosclerotic plaques secrete PCSK9, that acts in a paracrine manner on vessel macrophages by reducing LDLR expression and LDL uptake [42]. Thus, PCSK9 may be a possible determinant of LDL retention in the intima of arterial walls [43]. In line with these findings, a positive association between PCSK9 and arterial stiffness - a parameter associated with the presence of carotid plaques - has been described [44], a conclusion further supported by a study in patients of Italian ancestry in whom short-term therapy with monoclonal antibodies improved endothelial function [45] and arterial stiffness [46].

The hypothesis that PCSK9 may affect atherosclerosis in a manner not exclusively related to lipid changes was assessed in models of *LDLR*$^{-/-}$ or *apoE*$^{-/-}$ mice overexpressing human PCSK9 (hPCSK9). This latter accumulates in the arterial walls and can directly affect atherosclerotic lesion size and composition independent of lipid and

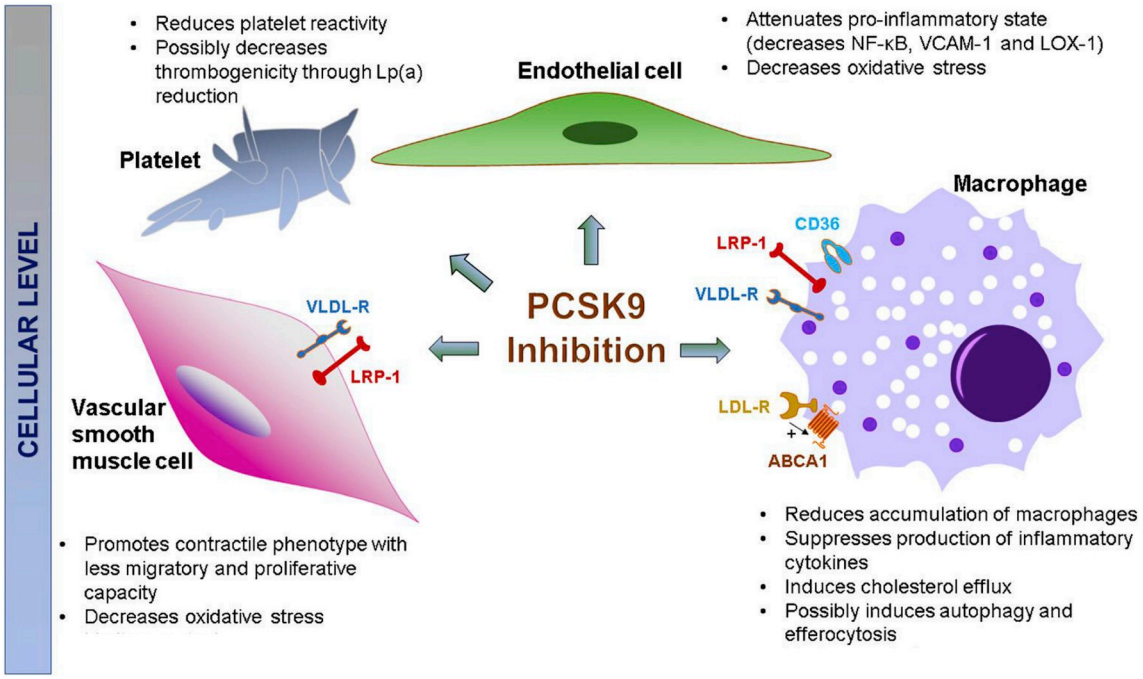

Fig. 1. Possible pleiotropic effects of PCSK9 inhibition in atherosclerosis.
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lipoprotein changes [47]. These findings go together with those reporting that bone marrow macrophages derived from hPCSK9 mice progressively accumulate in lesions of *apoE*$^{-/-}$ recipient mice with a markedly raised infiltration of Ly6C (hi) inflammatory monocytes (+32%) [48]. In line with these findings, *PCSK9*$^{-/-}$ mice are partially protected from neointimal plaque formation, further supporting an effect of PCSK9 on intimal thickening [49]. A direct clinical translation of these findings comes from the ATHEROREMO-IVUS (The European Collaborative Project on Inflammation and Vascular Wall Remodeling in Atherosclerosis – Intravascular Ultrasound) study, showing that higher PCSK9 levels are linearly associated with a higher necrotic core fraction in coronary atheromas [50].

A distinct conclusion on this topic came from a recent study reporting that in an atherosclerosis-prone mouse model, the deletion of *Pcsk9* gene reduced atherogenesis via mechanisms independent of LDLR. Indeed, endothelial cells exposed to lipoproteins from these animals expressed fewer adhesion molecules, such as *Icam-1*, and chemotactic factors, *e.g. Ccl2* (*Mcp-1*) and *Ccl-7* (*Mcp-3*), all promoting monocyte adhesion and infiltration into the vessel wall [51].

The pro-atherogenic role of PCSK9 was further supported by findings which demonstrated that PCSK9 directly alters cholesterol homeostasis in macrophages by inhibiting ATP-binding cassette transporter ABCA1 mediated cholesterol efflux [52]. Indeed, lipid accumulation in the artery wall depends on a balance between entry and egress. Another facet of the association among inflammation, PCSK9, and atherosclerosis relates to ox-LDL. Dendritic cells (DC) from vulnerable carotid plaques induce PCSK9 when exposed to OxLDL; in a feed-forward loop PCSK9 stimulates DC maturation, pro-inflammatory cytokine production and T-cell proliferation [53]. Inhibition of PCSK9, in turn, reverts the effects of OxLDL by decreasing production of inflammatory cytokines, *e.g.* TNF-α, IL-1 β and IL-6 [53]. In a previous study evaluating the contribution of the TLR4/NF-kB pathway, PCSK9 overexpression in macrophages upregulated TLR4 expression with a higher NF-kB nuclear translocation, followed by a raised secretion of proinflammatory cytokines mediated by OxLDL [54]. In human primary macrophages, exposure to human recombinant PCSK9 upregulated pro-inflammatory cytokines and chemokine genes, *e.g. IL-1β, IL-6, TNF-α, CXCL2, and MCP1*, once again showing a pro-inflammatory behavior linked to PCSK9 [55]. In this scenario, the positive feedback between PCSK9 and LOX-1 - a scavenger receptor responsible for binding, internalization and degradation of OxLDL - should not be underestimated. In arterial tissues and cultured ECs and SMCs, mitochondrial ROS generation exacerbates a positive cross-talk between PCSK9 and LOX-1, in which PCSK9 stimulates LOX-1 and LOX-1 stimulates PCSK9 [56]. This process may contribute to atherogenesis, considering that PCSK9 stimulates the expression of other scavenger receptors, *e.g.* scavenger receptors class A (SRA) and CD36 [57]. The relationship between PCSK9 and vascular inflammation was further investigated in the APOE*3-Leiden.CETP mice: vascular inflammation (by reducing T cell accumulation in aortic plaques) and necrotic core formation were attenuated upon treatment with the PCSK9 monoclonal antibody alirocumab [58] or an anti-PCSK9 vaccine [59].

When considering immune cells and atherosclerosis, there is now evidence that LDL-lowering by PCSK9 inhibition can reduce accumulation of lipid droplets in monocytes, counteracting both lipid-induced monocyte activation and reactivity [60]. Monocytes from FH patients intolerant to statins show a pro-inflammatory and migratory signature with an increased intracellular lipid droplet accumulation. Given the role of monocytes, and the interaction between chemokines (e.g. CCL2) and chemokine receptors (*e.g.*, CCR2) in atherosclerosis development, these findings highlight how PCSK9 inhibition might alter the inflammatory response aside from hs-CRP changes [60]. These conclusions support the notion that severe hyperlipidemia leads to increased intracellular lipid accumulation and foamy monocyte formation. Foamy monocytes can enhance monocyte migration from the circulation into the arterial walls, accelerating differentiation into foamy macrophages, thus contributing to the development of atheromas [61].

Whether reduction in immune cell activity following LDL-C and Lp (a) lowering by PCSK9 inhibition will translate into decreased inflammation in atherosclerotic lesions has been addressed in the Anitschkow Study. This trial enrolled coronary patients with elevated Lp(a) > 50 mg/dL, LDL-C ≥ 100 mg/dL and arterial wall inflammation as assessed by the most diseased target-to-background ratio (MDS-TBR) ≥1.6 on 18F-fluoro-deoxyglucose positron-emission tomography/computed tomography (FDG-PET/CT). A 16-week treatment with evolocumab (420 mg/every 4 weeks) reduced LDL-C by 61% with a 14% Lp

(a) lowering and no evidence of reduction of hs-CRP or of arterial inflammation (MDS-TBR -8.3% for evolocumab *vs* −5.3% for placebo) [62]. Considering that hs-CRP seems not to correlate with arterial wall inflammation [63], Lp(a) may be a better marker linked to pro-inflammatory changes. Lp(a) likely contributes to CVD risk being more atherogenic than LDL since it contains both the proatherogenic components of LDL and the oxidized phospholipids (OxPL), abundant in the apo(a) tail [64]. OxPL are crucial mediators of the arterial wall inflammation process among patients with elevated Lp(a) [65]. However, the role of raised plasma Lp(a) levels in thrombosis remains controversial (reviewed in Ref. [66]). Genetic, epidemiological and clinical studies have, however, firmly established that elevated concentrations of Lp(a) are an independent and probably causal CV risk factor. In the FOURIER study, evolocumab significantly reduced Lp(a) levels (median changes −26.9%), and patients with higher baseline Lp(a) levels benefited more in terms of absolute Lp(a) reduction [67]. In the ODYSSEY OUTCOMES trial, absolute changes in Lp(a) increased progressively with increasing quartile: −5.12%, −9.8% and −20.2%, being the overall Lp(a) reductions associated with CV risk reduction (commented in Ref. [68]).

4. Correlations between hs-CRP and CV risk

Questions on the validity of hs-CRP as a causal determinant of CV risk have been raised because of the absence, in particular, of genetic loci associated with hs-CRP levels and with the occurrence of CV events, in contrast to neighboring loci such as *IL-6R* or *APOE-CI-CII* cluster [69]. Mendelian randomization analysis of single polymorphisms showed elevation in hs-CRP concentrations without an increased risk of CHD, a finding discordant with the risk ratio [1.33 (1.23–1.43)] observed for CHD per 1 SD higher hs-CRP found in prospective studies [70]. Null associations betwenn hs-CRP-related and actual risk of CHD were found also in a genome-wide association study demonstrating no association between genetically elevated hs-CRP levels and risk of CHD [71]. Although hs-CRP may be considered unquestionably a good marker of CV risk [72], the evidence for causality is uncertain. In humans, C-reactive protein is a relatively moderate predictor of coronary heart disease [73] and when infused into healthy adults no meaningful increment in proinflammatory cytokine levels has been found [74]. These conclusions were in line with those of different experimental models in which transgenic expression of human or rabbit CRP [75–77] or CRP deletion [78] did not support any proatherogenic role of this pentraxin. On the other hand, the biological basis recognizing hs-CRP as a biomarker of CV risk has been, very recently, further reinforced in acute coronary syndrome patients with LDL-C of 64.9 mg/dL and hs-CRP > 2.4 mg/L; the initial and serial measurements of hs-CRP provided a very effective tool for the identification of patients at higher risk for mortality and morbidity, independent of optimal evidence-based pharmacological therapies [79].

Elevated hs-CRP levels are definitively associated to an increased CV risk and their reduction by statins is beneficial. However, there is no agreement so far as to whether the two variables, *i.e.* reduction of LDL-C and hs-CRP, are correlated or not. Indeed, a recent re-evaluation of 25 primary and secondary prevention statin trials suggested that the CV benefit from statins are not mediated through pleiotropic effects but rather only through their LDL-C lowering effect [80]. The earliest positive evidence stems from the CARE (Cholesterol and Recurrent Events) trial involving patients with post-MI in which pravastatin reduced CRP levels independent of the magnitude of LDL-C reduction [81]. Conversely, from the 2-year JUPITER study, in which LDL-C and hs-CRP reductions were only weakly correlated, it appeared that reduction in both LDL-C and hs-CRP are indicators of successful treatment with statins [82]. However, for the same reduction of LDL-C (< 70 mg/dL) the magnitude of benefit was superior in those achieving hs-CRP < 1 mg/dL compared to hs-CRP < 2 mg/dL, *i.e.* 65% and 79% reductions in vascular events, respectively [83].

In a review article assessing the correlation between LDL-C lowering and inflammatory changes [84], the most prominent hs-CRP reduction occurred in a study with extreme baseline hs-CRP elevation [85]. High intensity statins provided the highest CRP lowering: in the REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering) Study, an IVUS comparative evaluation of plaque progression, atorvastatin treatment reduced CRP (not hs-CRP) by 35.6% *vs* 5.2% for pravastatin [86]. In the very large Heart Protection Study, investigating the preventive activity of simvastatin [87], the reduction in vascular deaths appeared instead to be independent of baseline hs-CRP levels.

Concerning plaque development, in a virtual histology (VH) intravascular ultrasound study, there was clear evidence that changes of hs-CRP had a significant positive correlation with reductions in the percent necrotic core, percent dense calcium volume and absence of thin cap fibroatheroma, and a negative linear relationship with changes in percent fibrous and percent fibro-fatty volumes [88]. In contrast, LDL-C changes were not associated with any of these. This evidence should be considered when evaluating the conclusions of the GLAGOV (GLobal Assessment of Plaque reGression With a PCSK9 antibOdy as Measured by intraVascular Ultrasound) study, reporting that addition of evolocumab to statins did not result in any VH change [89]. At another arterial site, *i.e.* the carotid artery, in neurologically asymptomatic patients, narrowing of > 50% associated with elevated hs-CRP gave the best prognostic information [90]. Evaluation of the coronary wall thickness by a similar ultrasound method, together with hs-CRP, may offer a useful non invasive approach to the determination of CV risk [91].

5. PCSK9 antagonists and hs-CRP

Although it is undoubted that the use of PCSK9 inhibitors is associated with a significant reduction of major adverse cardiovascular events (MACEs) [relative risk: 0.83; 95%CI 0.78–0.88] [92] with myocardial infarction [odds ratio (OR): 0.72 (95%CI: 0.64–0.81)], stroke [OR: 0.80 (95%Cl: 0.67–0.96)] and coronary revascularization [OR: 0.78 (95%Cl: 0.67–0.96)] [93, 94], at the same time, it is evident that these new agents do not have an impact on hs-CRP levels [95]. A recent meta-analysis on 10 RTCs, not comprising the cardiovascular outcome trials (CVOT), found that short-term PCSK9 inhibitory treatment did not reduce hs-CRP concentrations, irrespective of the type of antibody (evolocumab, alirocumab or bococizumab) and patient characteristics (FH, non-FH, ACSVD). Similar results were found when data were corrected for age, sex and LDL-C lowering [96]. These findings do not confirm previous conclusions, showing that non-statin lipid lowering treatments result in significant hs-CRP reductions only in patients with baseline levels above 2 mg/L [84]. However, being most of the patients in the PCSK9 trials on maximally tolerated statin therapy or on standard care lipid lowering therapies, baseline hs-CRP may not reflect the true residual inflammatory risk. Unfortunately, when PCSK9 inhibitors were given as monotherapy in statin intolerant patients (ODYSSEY ALTERNATIVE [97], in the GAUSS-1, -2 and -3 [98−100] RCTs) or in hypercholesterolemic patients (MENDEL and MENDEL-2 RCTs), data on hs-CRP were missing at follow-up. The only exception was the GAUSS-2 study reporting that, against an LDL-C reduction of about 50%, hs-CRP was lowered from 1.8 (0.9–3.3) to 1.5 (0.8–3.2) mg/L [99]. In the GAUSS-3 and ODYSSEY ALTERNATIVE baseline levels were 1.7 mg/L.

Since a significant number of patients still has recurrent events or show progression in IVUS studies, secondary analyses of the FOURIER and SPIRE studies clearly demonstrated that, in spite of the dramatic lowering of LDL-C to below 30 mg/dL, hs-CRP remained a risk marker across all categories of achieved LDL-C: the higher the baseline levels, the larger the risk reduction [9]. These data suggest that drivers of inflammation other than LDL-C contribute to residual events in secondary prevention [101]. This general observation has made the relationship between PCSK9 and the arterial inflammatory process a

Table 1
Percentage changes of hs-CRP and LDL-C upon drug treatments.

	Clinical study	hs-CRP (mg/L)			LDL-C (mg/dL)		
		Pre	post	Δ	pre	post	Δ
Canakinumab (IL-1β mAb)	CANTOS [4]	4.3	2.0	-37% *vs* placebo	82.4	84.7	+3.1% *vs* placebo
Evolocumab (PCSK9 fully human mAb)	FOURIER [104]	1.7	1.4	0% *vs* placebo	92.0	30.0	-59% vs placebo
Bococizumab (PCSK9 humanized mAb)	SPIRE-1 and -2 [101]	1.88	1.84	at week 14: mean change was +6.6% *vs* placebo (median change 0%); at week 52: +6.7%	96.5	34.7	-60.5% *vs* placebo (week 14)
Alirocumab (PCSK9 fully human mAb)	ODYSSEY COMBOII [149]	3.58	3.51	-2% *vs* baseline	108.0	53.3	-49.5% *vs* baseline
Alirocumab (PCSK9 fully human mAb)	ODYSSEY OUTCOMES [107]	1.6 (0.8-3.9)	NA	NA	87.0	53.0	-54.7% vs placebo

mAb, monoclonal antibody; NA, not available.

matter of intensive debate. While inflammation raises PCSK9 liver expression [102] and PCSK9 is positively linked to TNF-α levels [55], there is no clear relationship between PCSK9 levels and hs-CRP [55].

In the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) study, recruiting stable CAD patients (LDL-C > 70 mg/dL), hs-CRP > 2.0 mg/dL was listed as a minor risk factor among inclusion criteria [103]. Basal hs-CRP levels were 1.7 mg/L and 1.8 mg/L in the evolocumab and placebo groups, respectively; 29% had hs-CRP values < 1 mg/L, 41% between 1 and 3 mg/dL and 30% > 3 mg/dL (Table 1). CV benefit was present across the different baseline hs-CRP strata and patients with the highest absolute risk reduction were those in the highest hs-CRP stratum: 1.6% (< 1 mg/L), 1.8% (1–3 mg/L) and 2.6% (> 3 mg/L). The corresponding NNTs to prevent a primary endpoint event at 3 years were 56 and 38, respectively, in patients with baseline hs-CRP levels of 1–3 mg/L and > 3 mg/dL (Table 2). Considering hs-CRP mean changes were −0.2 mg/L in both treatment arms, the largest absolute CV risk decrement was found in patients with baseline hs-CRP > 3 mg/L. This *post hoc* analysis allows to identify individuals getting the largest benefit from PCSK9 antagonists; even in those achieving an on-treatment LDL-C of < 20 mg/dL there was a 3-year stepwise risk increment according to the baseline values of hs-CRP: +9% (hs-CRP < 1 mg/L), +10.8% (hs-CRP 1–3 mg/L) and +13.1% (hs-CRP > 3 mg/L) [104]. Moreover, event rates were lowest in patients achieving the lowest levels of both LDL-C and hs-CRP. To sum-up, baseline hs-CRP levels do not modify the lipid effects of evolocumab but do identify a group with a higher risk for CV disease, associated with a lower NNT. A higher baseline hs-CRP associates to a higher prevalence of other CV risk factors, *e.g.* hypertension, diabetes mellitus, smoking, and renal dysfunction, and a higher rate of comorbid conditions, *e.g.* prior stroke and peripheral artery disease [104]. Briefly, in the FOURIER study, according to hs-CRP strata (< 1 mg/L, 1–3 mg/L and > 3 mg/L) hypertension was present in 76%, 81% and 84%, respectively; diabetes mellitus was found in 31%, 36% and 43%, respectively, and finally smoking was reported in 23%, 29% and 32%, respectively [104]. Thus, the use of a similar risk-stratification strategy with an even broader range of factors can ensure that PCSK9 inhibitors are made available to those who may benefit the most.

Evidence of residual inflammatory risk was particularly evident in a *post hoc* analysis of SPIRE- 1 and -2 (Studies of PCSK9 Inhibition and the Reduction of Vascular Events) trials with bococizumab, enrolling either patients with a previous CV or a history of familial hypercholesterolemia (high-risk primary prevention cohort). When data from the two studies were pooled, baseline levels of hs-CRP were 2.0 mg/L in both bococizumab and placebo arms with some differences upon separate evaluations: SPIRE-1: 1.8 *vs* 1.7 mg/dL and SPIRE-2: 2.3 *vs* 2.3 (Table 1). Overall, patients with higher hs-CRP were those with concomitant CV risk factors, *e.g.* diabetes mellitus, diagnosed hypertension or current smokers. When examining findings in more detail, against a mean −60.5% fall in LDL-C, a +6.6% rise in hs-CRP was found in the bococizumab arm. Despite the magnitude of LDL-C lowering, when the analysis was stratified according to on-treatment levels of hs-CRP a continuous gradient in risk for future CV events was found. Adjusted hazard ratios (HRs) for future CV events were 1.0 (hs-CRP < 1 mg/L), 1.16 (hs-CRP 1–3 mg/L) and 1.62 (hs-CRP > 3 mg/L) (Table 3). The percentage of patients allocated to each group were 30.4%, 34.8% and 34.9%, respectively. Interestingly, if only LDL-C changes are considered HRs are 1.0 (LDL-C < 30 mg/dL), 0.87 (LDL-C 30–50 mg/dL) and 1.21 (LDL-C > 50 mg/dL) (Table 3) [101].

The most recently published ODYSSEY OUTCOMES with alirocumab, recruiting ACS patients, 89.5% on high intensity statins, reported instead that the primary CV end points were reduced by 19% in the group with hs-CRP < 2 mg/L (HR: 0.81; 95%CI 0.71–0.92) and by a non-significant 11% in the group with hs-CRP > 2 mg/L (HR: 0.89; 95%CI 0.79–1.01) [105]. No absolute changes for hs-CRP have been reported in this study and, so far, there are no further *sub-analyses* aimed at exploring the impact of inflammation even after the achievement of very low LDL-C (Table 1). Nevertheless, it has now become clear that also in the ODYSSEY OUTCOMES trial baseline hs-CRP levels identify subjects at higher risk. Among 18,924 patients with a recent ACS, alirocumab was superior to placebo in reducing first post-randomization MI by 15%: −13% relative to type 1 MI and −23%

Table 2
Analysis of the FOURIER study according to hs-CRP strata.

hs-CRP strata (mg/L)	FOURIER [104]					
	Primary Endpoints			Secondary Endpoints		
	ARR	RRR (HR)	NNT	ARR	RRR (HR)	NNT
< 1 (0.6; 0.4-0.8)	1.6% (-0.5 – 3.7)	0.82(0.70 – 0.95)	-	0.8% (-1.1 – 2.7)	0.81 (0.66 – 0.99)	-
1-3 (1.7; 1.3-2.3)	1.8% (0 – 3.5)	0.93 (0.83 – 1.05)	56	2.0% (0.4 – 3.4)	0.87 (0.75 – 1.02)	50
> 3 (5.4; 3.9-8.8)	2.6% (0.4 – 4.9)	0.80 (0.71 – 0.90)	38	3.0% (1.0 – 5.0)	0.73 (0.63 – 0.85)	33

ARR, absolute risk reduction; hs-CRP, high-sensitivity C-reactive protein; HR, hazard ratio; NNT, number need to treat; RRR, relative risk reduction.

Table 3
Analyses of the SPIRE-1 and -2 studies according to hs-CRP and LDL-C strata.

SPIRE-1 and -2 [101]			
hs-CRP strata (mg/L)	HR for future CV events	LDL strata (mg/dL)	HR for future CV events
< 1 (0.7; 0.4-1.2)	1 (REF)	< 30	1 (REF)
1-3 (1.8; 1.1-2.9)	1.16 (0.81 – 1.66)	30-50	0.87 (0.62 – 1.22)
> 3 (4.7; 2.7-7.6)	1.62 (1.14 – 2.30)	> 50	1.21 (0.87 – 1.68)

REF, reference value.

relative to type 2 MI. Compared to the subgroup with no MI event (17,719), patients who experienced a post-randomization MI had higher baseline levels of LDL, Lp(a) and hs-CRP. Across the three subgroups "no event", "first event = type 1" and "first event = type 2", LDL-C (mg/dL) were 86, 91 and 91, respectively; Lp(a) (mg/dL) 20.8, 25.4 and 34.9, respectively and hs-CRP (mg/L) 1.6, 2.3 and 2.6, respectively. These parameters did not differ statistically between type 1 and type 2 MI [106].

A further benefit of alirocumab over placebo has been the reduction in the all-cause deaths, 3.5% vs 4.1%, respectively, with an HR of 0.85 (95%CI: 0.73–0,98). Among survivors, median baseline hs-CRP levels were 1.6 mg/L (similar to the whole cohort) compared to 2.8 mg/L in those who died. Conversely, when the analysis was restricted to the 8,242 patients eligible to maintain the treatment for ≥3 years, against a more pronounced benefit of alirocumab on all-cause death [HR 0.78 (95%CI: 0.65–0.94)] no between-group differences were found in basal hs-CRP levels (1.6 *vs* 1.7 mg/L) [107].

Finally, in the *post-hoc* analysis evaluating whether the efficacy of alirocumab was influenced by the presence of polyvascular diseases, higher levels of LDL-C, Lp(a) and hs-CRP were more pronounced in the presence of two or three affected vascular beds. According to this, LDL-C (mg/dL) was 86 (monovascular disease), 91 (coronary + peripheral artery disease), 90 (coronary + cerebrovascular diseases) and 95 (coronary + peripheral artery and cerebrovascular diseases); Lp(a) (mg/dL) was 20.8, 25.5, 23.0 and 29.4, respectively and hs-CRP was 1.6, 2.6, 2.2, and 2.1, respectively [108].

Concerning alternative therapeutic strategies which modulate PCSK9 levels, inclisiran is a siRNA that acts by reducing both the intracellular and extracellular PCSK9 levels. Upon its s.c. administration, inclisiran leads to plasma lipoprotein changes that are quite similar to those mediated by the anti-PCSK9 monoclonal antibodies [109]. Patients receiving a single dose of inclisiran 300 or 500 mg had non-significant reductions of 16.2% and 19.8%, respectively of hs-CRP, with a wide distribution'. Conversely, patients at a two-dose regimen of inclisiran (300 mg) showed a 16.7% significant decrement in hs-CRP [110]. In the context of atheroma formation, theoretically, inclisiran should result in a lower amount of PCSK9 able to penetrate plaques, with no impact on local PCSK9 production by macrophages and smooth muscle cells in the atheroma (Fig. 2) [111].

More recently, in order to better assess mechanisms and consequences of PCSK9 inhibition, a comparison between a genetic lowering of PCSK9 and that occurring after statin treatment was carried out [112]. Individuals with a loss of function allele of PCSK9 had a reduced lowering of VLDL-cholesterol compared to statin therapy (−54 *vs* −77% reduction) for an equivalent lowering of LDL-C. This study also evaluated a novel biomarker for future CV events. GlycA is part of the mammalian genome: glycans are attachments known to functionally modify cytokines and other inflammatory proteins. Among these, GlycA quantifies the NMR signal that originates from a number of plasma glycoproteins and was hypothesized to be a clinical marker of systemic inflammation [113]. By standardized NMR a 17-year follow up of 27,490 in the Women's Health Study showed a clear association between increased GlycA levels and risk of all cause, CV and cancer mortality [114]. The JUPITER study also showed that levels of GlycA associate with CV risk, independent of hs-CRP and reduced by rosuvastatin [115]. In contrast, genetic lowering of PCSK9 was not associated with any change of GlycA [112]; no data were given on CRP.

6. PCSK9 antagonism benefit in high-risk populations

A number of reports have evaluated the potential benefit of PCSK9 antagonists in conditions not strictly related to LDL-C. An important case is that of human immunodeficiency virus (HIV) infection, a global epidemic affecting 37 million people worldwide. While modern drug therapy has improved HIV patient survival, the rate of MI among affected individuals has risen by 50% [116]. In these subjects, chronic inflammation, together with immune activation, have been reported as a possible trigger of the accelerated HIV-related atherosclerosis process [117]. However, since no clear mechanisms have been described identifying non-traditional CV risk factors, elevated PCSK9 levels may provide another cue to an improved understanding [118]. Indeed, in HIV^+ patients not on antiretroviral therapy (ART), PCSK9 levels were significantly elevated compared to matched HIV^- subjects, an effect not related to the ART. Interestingly, PCSK9 associates with infection severity only when patients are not on ART, whereas it is lost after ART initiation. In spite of this dichotomy, no statistical correlations between PCSK9 and hs-CRP or IL-6 were found in HIV^+ patients either before or after ART initiation [119]. Quite similar conclusions were reached in HIV/HCV-coinfected patients [120] and in a Swiss cohort of HIV patients not on statin treatment [121]. In this last case, marijuana consumption and low CD4 values were associated with higher PCSK9 levels, although PCSK9 did not correlate with hs-CRP or other inflammatory markers, *e.g.* IL-8 or IL-10. Altogether this evidence highlights that the expression of PCSK9 may be altered by the inflammatory milieu, as in the case of patients with sepsis [122] or in those with severe trauma injury [123]. Currently, two trials with PCSK9 inhibitors are being carried out: (i) the EPIC-HIV (effect of PCSK9 inhibition on CV Risk in treated HIV Infection) study evaluating the effect of alirocumab on vascular inflammation, endothelial function, and non-calcified plaques and (ii) the BEIJERINCK (Evolocumab Effect on LDL-C Lowering on Back-ground Statin Therapy) study testing the efficacy of evolocumab in HIV^+ subjects with hyperlipidemia and/or mixed dyslipidemia.

A further case is that of diabetic patients, not only at an increased risk of developing ASCVD but encountering worse outcomes when ASCVD is already present. Specifically, type 2 diabetic patients show a rise in levels of markers and mediators of inflammation and acute-phase reactants including CRP, IL-6 and fibrinogen [124]. Considering that in insulin-resistant patients PCSK9 associates with the secretion rate of intestinal lipoproteins and that *PCSK9* loss-of-function carriers have reduced levels of fasting and postprandial TG [125], this may be the mechanism through which PCSK9 may mediate the atheroma inflammatory burden in diabetics. Indeed, TRL remnants induce endothelial dysfunction, inhibit fibrinolysis, and enhance coagulation and vascular inflammation [38]. Aside from the *post-hoc* analysis of the FOURIER study showing that evolocumab in patients with diabetes resulted in higher absolute risk reduction in the primary endpoint/coronary revascularization, *i.e.* −2.7% in patients with diabetes vs −1.6% reduction in non-diabetic patients [126], results of the recent BANTING (The evolocumaB efficAcy aNd safeTy IN type 2 diabetes mellitus on backGround statin therapy) study supports the efficacy and safety of evolocumab in patients with type 2 diabetes mellitus, hyperlipidemia or mixed dyslipidemia. Among 280 out of 421 individuals given evolocumab for 12 weeks, LDL-C was decreased by 54–65% and non-HDL-C by 47–57%, more patients reaching an LDL-C < 70 mg/dL or an LDL-C reduction ≥50%. A benefit was also found for Lp(a) (−32.6%), triacylglycerol (−13.7%) and VLDL-C (−13.3%), findings confirmed in the post-prandial state [127]. The consistency of these findings also relies on the recent knowledge highlighting how in high-risk patients with diabetes and already at statins, an incremental

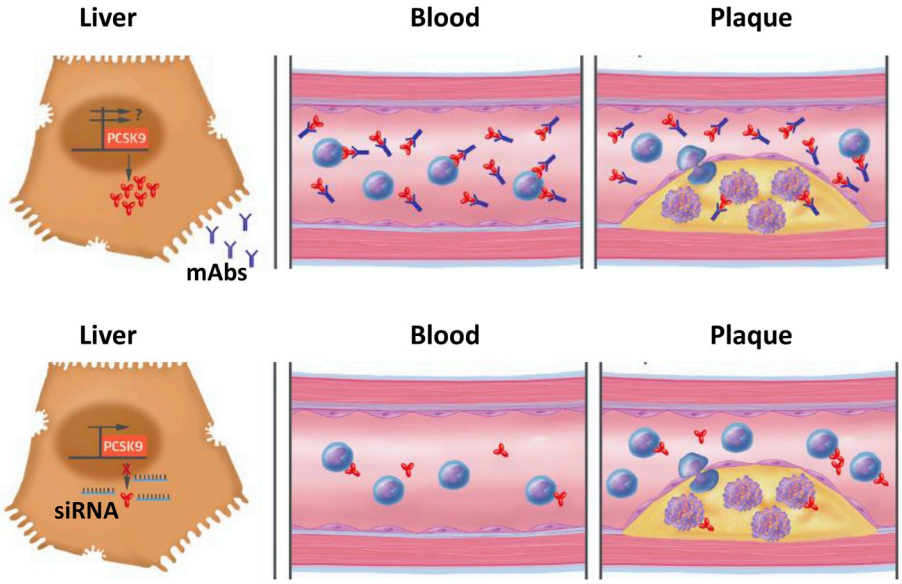

Fig. 2. Presence of PCSK9 in the atheroma upon inhibition by monoclonal antibodies or siRNA (inclisiran).
(Upper panel) Monoclonal antibodies bind PCSK9 leading to its circulation in immune complexes either free or bound to LDL. These complexes may enter atheromas. (Lower panel) siRNA does not affect the local production of PCSK9 by macrophages and smooth muscle cells in the atheroma, but it reduces the amount of circulating PCSK9 penetrating plaques. mAbs, monoclonal antibodies; siRNA, silencing RNA. Modified with permission from Elsevier [111].

attainment of ASCVD risk, independent of LDL-C changes, is observed in patients experiencing the higher reductions of VLDL and their associated cholesterol [128].

In the case of alirocumab, in ODYSSEY OUTCOMES study patients with diabetes (28.8%) randomized to alirocumab had the largest absolute risk reduction, *i.e.* 2.3% *vs* 1.2% in those with prediabetes or with normal glycemia [129].

7. Discussion

Persistence of a high risk of CV events following ACS in optimally drug and revascularization treated patients has indicated that other variables may account for the increased risk [130]. Availability of novel powerful lipid lowering agents, *i.e.* PCSK9 inhibitors in addition to statins, allowed to evaluate their activity on both lipids and inflammatory markers, that are mainly characterized by elevated levels of hs-CRP, a biomarker of CV risk although not playing a clear causal role in atherosclerosis. Another still debated issue is the clinical relevance of measuring circulating PCSK9 levels. Indeed, this protein is closely regulated at the transcriptional and translational levels, leading to concentrations varying over an approximately 100-fold range (reviewed in Ref. [109]). In a large Swiss multicenter cohort of patients hospitalized for ACS, higher PCSK9 levels were associated with a higher degree of inflammation, as assessed by hs-CRP, but they did not predict mortality at 1 year. Conversely, data from an observational study did not find any association between PCSK9 and hs-CRP in spite of a positive association with the severity of coronary artery lesions [131,132]. In a most recent study PCSK9 levels were found to predict the occurrence of ACS in patients with severe carotid artery stenosis, the best predictive values being above 431.3 mg/dL [133].

Again on a pharmacological clinical approach, in spite of the general suggestion that PCSK9 inhibitors should be recommended only after an initial 2–3 month run-up treatment adaptation with maximally tolerated statin doses, an earlier initiation of PSCK9 mAb treatment may be justified by the evidence that in the acute phase of ACS PCSK9 may raise coronary plaque vulnerability, inflammation and platelet aggregation [130]. Findings from the EVOPACS [EVOlocumab for Early Reduction of LDL-cholesterol Levels in Patients With Acute Coronary Syndromes (NCT03287609)] trial will certainly shed light on this matter [134].

The two major variables resulting from lipid lowering medications, *i.e.* reduction of LDL-C and hs-CRP in ASCVD patients appear to be additive as independent predictors [135,136]. In major statin trials, *e.g.* the JUPITER study with rosuvastatin, maximal benefit was observed in patients achieving reduced levels of both variables, *i.e.* LDL-C < 70 mg/dL and hs-CRP < 2 mg/L. The validity of this conclusion has been confirmed by statin and non-statin ttherapies aimed at lowering LDL-C, *e.g.* the PROVE-IT trial showing that patients who attained LDL-C below 70 mg/dL and hs-CRP < 2 mg/dL derived the largest clinical benefit [137]. The successful achievement of the dual goal was highlighted again in the IMPROVE-IT study in which patients achieving both targets had lower recurrence of CV events than those meeting neither, *i.e.* −38.9% *vs* −28.0%, respectively [138]. Since concomitant reductions of hs-CRP and LDL-C appear to lead to maximal benefit [139], appropriate clinical studies, *e.g.* with a 2X2 factorial design, with aggressive LDL-C-lowering and anti-inflammatory therapies are eagerly awaited [140]. This hypothesis has become of critical interest after the divergent conclusion of the REGARDS (Reasons for Geographical and Racial Differences in Stroke) study in which in high-risk patients the variable mainly associated with a CV risk reduction was hs-CRP < 2 mg/dL with no further protective effect when LDL-C was < 70 mg/dL [141]. Indeed, the two variables appear to be linked to different morphological vascular outcomes. Whereas reduced hs-CRP is linked to anatomical changes in the atheroma [88,142], *i.e.* reduced percent necrotic core and absence of thin cap macroatheroma, this is not found with just LDL-C changes [89]. In the virtual histology evaluation of the GLAGOV study with evolocumab, this did not lead to meaningful reductions in hs-CRP levels [89]. Interpretation of findings from the GLAGOV study, however, should consider that coronary patients were on statin background, and that HMGCo-A reductase inhibitors are associated *per se* with a slower progression of coronary atheromas, with increased plaque calcification and reduction of high-risk plaque features [143]. In the near future, findings from other ongoing RCTs will certainly shed light on the correlation between PCSK9 inhibition and plaque regression.

8. Conclusions

In the context of an optimal treatment strategy aimed at reducing CV risk, it is useful to identify effects that are specific or shared by either lipid lowering drugs, or anti-inflammatory drugs or a combination of both [139,144]. Moreover, since association studies do not necessarily imply a causal role of PCSK9 in the inflammatory response [145] and data from carriers of loss-of-function mutations in *PCSK9*, aimed to establish a correlation between plasma inflammation markers and PCSK9 levels are scanty and not conclusive [146,147], evidence

from the effects of anti-inflammatory molecules on PCSK9 levels might help to unravel this hitherto complex tangle.

Conflicts of interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

L.T. received honoraria or consulting for the following companies:Abbott, Aegerion, Actelion, Amgen, Astra Zeneca, Boehringer-Ingelheim, Daiichi Sankyo, Servier, Pfizer, Bayer, Sanofi Aventis, Merck Sharp & Dohme, Menarini, Mylan, Novartis, Recordati.

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M.R. and C.R.S. have nothing to declare.

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