Anti-inflammatory Strategies in Atherosclerosis

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Abstract

Atherosclerotic vascular disease and its related complications are the major cause of mortality in Western societies. Atherosclerosis is a chronic inflammatory disease of the arterial wall triggered by traditional and nontraditional risk factors and mediated by inflammatory and immune responses. Recent clinical trials provided compelling evidence corroborating that atherosclerosis is an inflammatory disease and demonstrated efficacy of anti-inflammatory interventions in reducing cardiovascular events and mortality. Traditional risk factors drive vascular inflammation, further justifying the instrumental role of intensified risk factor management in attenuating and preventing atherosclerotic disease and complications. Promising therapeutic approaches specifically related to inhibition of inflammation span traditional anti-inflammatory drugs, specific immunomodulation, and development of vaccination against atherosclerotic disease. Here, we review the inflammatory component in atherogenesis, the available evidence from clinical trials evaluating efficacy of therapeutic anti-inflammatory interventions in patients with high cardiovascular risk, and discuss potential future targets for anti-inflammatory or immune modulatory treatment in atherosclerotic cardiovascular disease.

Keywords

- inflammation
- atherosclerosis
- strategies

Introduction

A plethora of preclinical data and more recently also a growing body of clinical data implicate chronic inflammation and immunity in the nascence, propagation, and complication of atherosclerosis. First indicators supporting the inflammatory theory of atherogenesis were discovered early on by the histologic examinations of Rudolf Virchow. However, it was not until Russell Ross's response-to-injury theory in the 1990s that the concept of atherosclerosis as a chronic inflammatory disease gained trust among cardiovascular (CV) experts.[1] In the last two decades, key propagators such as Peter Libby, Göran Hansson, and Paul Ridker finally consolidated this evidence and successfully achieved the translation of much of the basic knowledge into meaningful clinical studies identifying residual inflammation as potent risk factor and major contributor to clinical morbidity and mortality en par with low-density lipoprotein (LDL) cholesterol.[2–4]

Inflammation Drives Every Step of Atherogenesis

The mechanisms underlying atherogenesis have been extensively reviewed elsewhere.[5,6] In brief, our current concept of these inflammatory processes can be divided into several stages.

Endothelial Activation

The initial trigger of plaque formation is represented by the activation of the endothelial layer resulting in the expression of adhesion molecules and the production of inflammatory cytokines propagating endothelial activation in an autocrine manner. Several factors have been proposed over time. Among them are inflammatory cytokines of different sources such as from visceral adipose tissue in patients with metabolic disease,[7] from other systemic inflammatory conditions (e.g., in rheumatoid arthritis), from activated alveolar macrophages (e.g., in smokers or by particles associated with air

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pollution),[8] or from the vessel wall itself disturbed by disrupted flow conditions or by conditions of shear stress (e.g., in high blood pressure). Similarly, activated leukocytes (e.g., by atherogenic lipids or by genetic predisposition as in clonal hematopoiesis) and other cellular blood components such as platelets as well as the interaction between both participate in and facilitate endothelial activation.[9] Furthermore, other factors such as hypoxia, modified LDL particles (e.g., in hypercholesterolemia), or other modified proteins such as advanced glycation end-products (e.g., in diabetes mellitus) have been shown to play a role in induction of vascular inflammation.

Recruitment of Inflammatory Cells

Following endothelial activation, inflammatory cells such as monocytes and T cells are recruited from the blood stream, roll along and adhere to the vessel wall, and finally transmigrate into the nascent atherosclerotic plaque carrying inflammation into the subendothelial layers of the vessel wall. While recent new technologies such as single-cell immune mapping demonstrated a high diversity of inflammatory pools within plaques, not macrophages but rather T cells may represent the predominant immune cell type in the plaque.[10,11] Upon the destabilization of the barrier function of the endothelium lipids, LDL particles accumulate in the vessel wall where they become oxidized. Monocytes and macrophages, the troops of the innate immune system, detect these "alien" particles and phagocytize them. Macrophages then turn into the so-called foam cells—a process heavily altering their gene expression—and finally die from apoptosis, thereby contributing to the growth of the so-called necrotic core of atherosclerotic plaques. In addition to inflammatory cells, smooth muscle cells originating from the media are attracted to the plaque, also take up lipids, and produce collagen forming the so-called fibrous cap. Fibrous cap and a covering endothelial cell barrier then separate the thrombogenic necrotic core from the blood stream.

Plaque Destabilization

Interestingly, plaque growth occurs not at a steady rate but rather in a burst of growth. Intraplaque ischemia and hemorrhage have been implicated among others as triggers of such bursts.[12] The fate of a plaque (stable vs. unstable) and particularly the associated clinical sequelae depend on its inflammatory burden and the balance between factors associated with a stable phenotype (e.g., smooth muscle cells and collagen content) and that associated with an unstable phenotype (e.g., monocytes/macrophages and lipid content).[13] While the initial stages of plaque formation are dominated by the activation of the innate immune system, the propagation of plaque growth and destabilization are processes heavily controlled by the adaptive immune system.[14] Antigens from several origins but predominantly from the major protein in LDL particles, ApoB, are displayed in an MHC (major histocompatibility complex) class-dependent manner to T cells by antigen-presenting cells such as dendritic cells. The latter recognize those antigens and while initially maintaining tolerance begin to proliferate and to induce a strong inflammatory response fueling the inflammatory downward spiral within the plaque.[15]

Plaque Rupture and Plaque Erosion

The more inflammation present in the plaque, the more digestive enzymes such as matrix metalloproteinases are produced, thinning out the fibrous cap which keeps the plaque and its atherogenic debris together, and ultimately opening the door for plaque rupture and intraluminal coronary thrombosis. More recently, a second pathology called plaque erosion has been described. In that case, shear stress destabilizes the endothelial layer and through activation of signaling cascades such as toll-like receptor signaling results in formation of neutrophil extracellular traps with subsequent thrombus formation.[16] Interestingly, most recently the authors of the OPTICO-ACS trial also provided evidence of enrichment of CD4+ and CD8+ T cells in blood from patients with vulnerable lesions, implying a principal role of adaptive immunity in the pathogenesis of plaque erosion and rupture during acute coronary syndrome.[17]

Inflammasome and TNF Superfamily

Recent work highlights the central role of the inflammasome and its protein product, interleukin-1β (IL-1β), as a key factor in the proatherogenic processes described above. Several recent review articles summarize the available data in an excellent manner.[18] In brief, the NLR (nucleotide-binding domain leucine-rich repeat containing) family pyrin domain containing 3 (NLRP3) inflammasome is activated by numerous factors such as disturbed flow conditions, other cytokines, cholesterol crystals, and others and results in the production of pro-IL-1β that once activated by capase-1 represents a central proinflammatory stimulus. Downstream of IL-1β, other cytokines such as IL-6 are produced and hepatic production of C-reactive protein (CRP) is upregulated. Genetic deletion of IL-1β or overexpression of its natural antagonist, IL-1 receptor antagonist, attenuates murine atherosclerosis.[19] Of note, this concept has recently been extended by work from the Libby group, establishing also a pivotal role for IL-1α in vascular remodeling during early atherogenesis, whereas IL-1β may drive inflammation during atherogenesis and the development of advanced atheroma.[20] Similar to blocking IL-1 signaling, other mechanisms limiting inflammasome activation can attenuate atherosclerosis. For example, the danger molecule, P_2X_7, contributes to maturation and release of IL-1β from the inflammasome, and deletion or inhibition of P_2X_7 promotes resolution of plaque inflammation and mitigated atherosclerosis.[21]

Others and we previously demonstrated that also members of the tumor necrosis factor (TNF) superfamily play important roles in the formation and destabilization of atherosclerotic plaques. Among them, the CD40 ligand mediates atherogenesis as an important recruitment factor via interaction with the leukocyte integrin Mac-1, a process we were able to target with an interfering small peptide matching the binding site sequence within the I-domain of Mac-1.[22,23] This interaction also proved instrumental in more acute settings of inflammation such as peritonitis.[24]

Similarly, the classic CD40 receptor contributes to atherogenesis.[25–27] Alike, key downstream signaling intermediates such as TNF-receptor-associated factors showed the potential to modulate experimental atherosclerotic as well as metabolic disease.[28–30]

Traditional and Nontraditional Risk Factors Drive Vascular Inflammation

While the inflammatory hypothesis was initially perceived to challenge the role of traditional risk factors, it has become clear that this is not true. In fact, traditional risk factors such as hypercholesterolemia, hypertension, smoking, and diabetes, but also selected comorbidities such as chronic kidney disease (CKD) that increase atherosclerotic risk, may be viewed as direct propagators of intravascular inflammation, the degree of which finally determines clinical outcome (►Fig. 1). Apart from traditional risk factors, a new nontraditional risk factor, i.e., systemic inflammation, originating from other inflammatory sources within the body such as visceral adipose tissue in obesity, other chronic proinflammatory conditions (e.g., rheumatoid arthritis, lupus, goat, etc.), infections, or even subclinical conditions such as chronic sinusitis or gingivitis, may drive vascular inflammation and risk. Any type of persisting inflammation ultimately appears to trigger an increase in CV events.[31] Since those traditional and nontraditional risk factors are not distributed equally in our patients, this very individual risk pattern lays the foundation for the prospect of a personalized individualized therapy.

High-Sensitivity CRP Measures Residual Inflammatory Risk

Residual CV risk can be defined as the remaining risk of CV events or progression of CV disease that persists despite treatment according to current evidence-based recommendations. Ridker and others showed in various collectives that high-sensitivity CRP (hsCRP) measures residual inflammatory risk (i.e., remaining CV risk due to persistent inflammation) and predicts CV events independently from LDL cholesterol.[32] In fact, the contribution from LDL and hsCRP on CV risk are additive. Subjects displaying low levels in both are of lowest risk, whereas subjects with high levels of both mark the highest risk groups. In the JUPITER trial, approximately 17,000 subjects without known CV disease and average LDL cholesterol levels of 130 mg/dL were randomized to placebo versus rosuvastatin. While the expected risk for CV events was low in the placebo group, rosuvastatin nevertheless almost halved the residual risk. Interestingly,

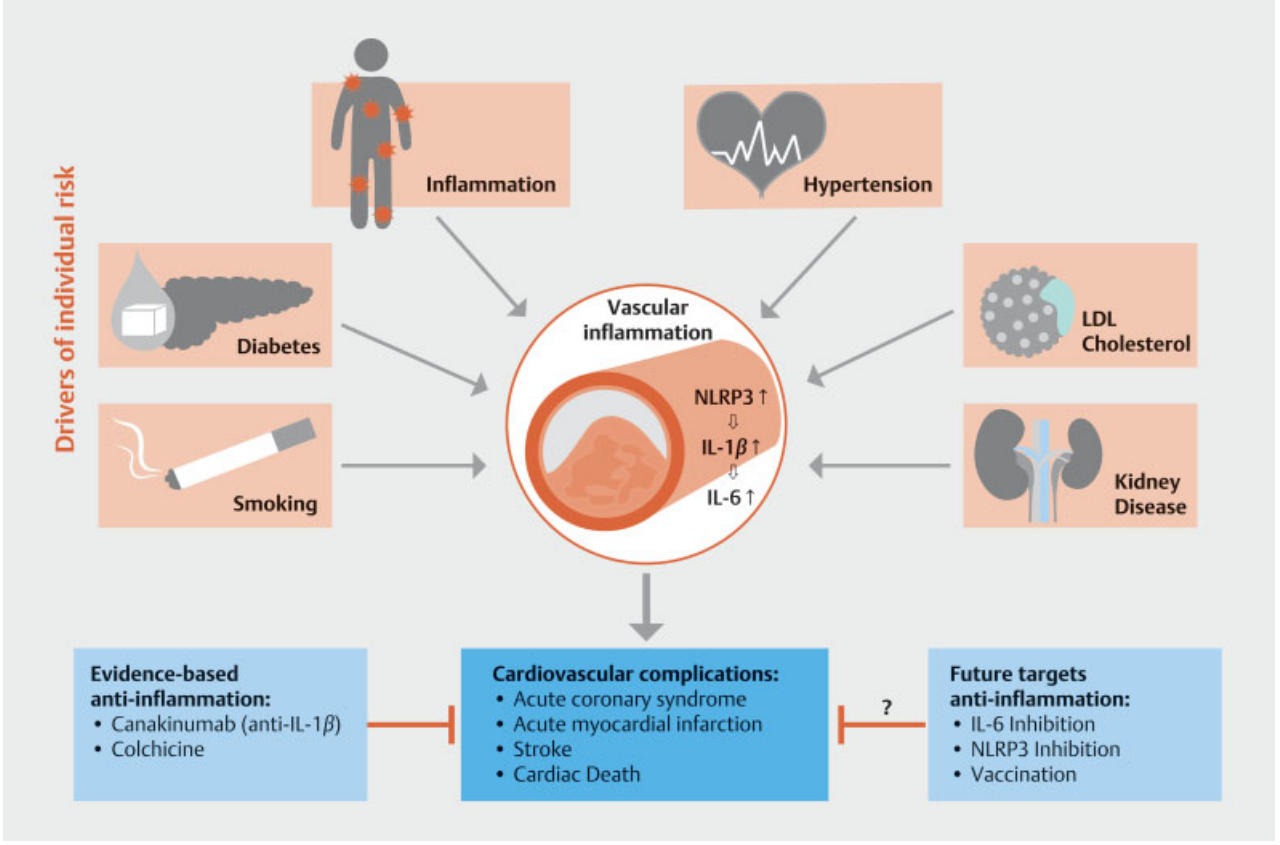

Fig. 1 Triggers and complications of vascular inflammation in atherosclerosis, and evidence-based and future anti-inflammatory therapies. Traditional risk factors such as smoking, diabetes mellitus, hypertension, hypercholesterolemia, and chronic kidney disease, but also conditions of systemic inflammation drive individual cardiovascular risk and onset and progression of vascular inflammation. Vascular inflammation increases the risk for cardiovascular complications, which can be reduced by treatment with canakinumab or colchicine. Future targets for anti-inflammatory therapy include IL-6 inhibition, NLRP3 inhibition, or vaccination against atherosclerosis. IL-6, interleukin-6.

patients in which LDL cholesterol was not reduced under the threshold of 70 mg/dL but CRP was reduced below 2 mg/L profited just as much as those where LDL cholesterol was reduced below 70 mg/dL while CRP levels stayed above 2 mg/L.[33] Alike, in collectives in which statins were used for secondary prevention, subjects with a measurable residual inflammatory risk (as defined by hsCRP levels above 2 mg/L) proved to be at much higher risk.[34] Most recently, subanalyses of the FOURIER trial, a trial investigating the use of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors in a high-risk collective of CV patients, showed that risk prediction of hsCRP remains valid even in patients with very low LDL cholesterol levels.[35] In a real-world collective of patients with chronic coronary syndrome, we recently reported a proportion of approximately one-third that qualify for residual inflammatory risk after adequate control of LDL cholesterol.[36]

Anti-inflammatory Therapies that Reduce Cardiovascular Endpoints

Canakinumab

The first major study interrogating inflammation and its impact on hard CV endpoints in a large clinical collective was the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS). In the CANTOS trial, more than 10,000 patients in the stable phase following an acute coronary syndrome—representing a very high risk population—were screened for residual inflammation after initializing a standard medical care including moderate-to-high intensity lipid lowering therapy. Patients exceeding the threshold of 2 mg/L hsCRP were randomized to placebo or received various doses of the antibody, canakinumab. This antibody neutralizes the protein product of the NLRP3 inflammasome, IL-1β. The intervention with canakinumab led to a significant decrease in the primary endpoint composed of nonfatal myocardial infarction, nonfatal stroke, and CV death by approximately 15%.[37] Interestingly, a posthoc analysis showed that among the collective of approximately 4,000 patients that normalized their hsCRP levels after the first dose, canakinumab resulted in a much larger reduction of events, including a 30% reduction in overall mortality.[32] Unfortunately, the company decided to pursue this drug in other indications, foremost in cancer since the trial also revealed a significant reduction of up to 60% of the incidence of fatal lung cancer.[37]

Colchicine

Early on, another agent, colchicine, has been suggested to exhibit atheroprotective properties. In an initial study, the Low-Dose Colchicine (LoDoCo) trial, Nidorf et al showed in a small collective of 532 patients with preexisting coronary artery disease that colchicine treatment resulted in a reduction of the primary endpoint of acute coronary syndrome, out-of-hospital cardiac arrest, or noncardioembolic ischemic stroke over a median follow-up of 3 years.[38] Colchicine has experienced a renaissance in CV medicine given its great success in treatment of inflammatory conditions such as pericarditis. Interestingly, colchicine does not only inhibit microtubule assembly but also acts as an anti-inflammatory agent by inhibiting the NLRP3 inflammasome resulting in a decrease of IL-1β protein levels and other inflammatory mediators.[39]

Recently, two major clinical trials investigating colchicine in high-risk CV collectives turned out positive warranting its clinical application. In the LoDoCo2 trial, the investigators aimed to confirm the beneficial effects of the LoDoCo trial in a larger cohort with higher risk. A total of 5,522 patients with chronic coronary syndrome were randomized to receive either 0.5 mg colchicine daily or placebo. After a median follow-up of 28.6 months, the colchicine group indeed showed a significant 31% reduction of the primary composite endpoint of myocardial infarction, stroke, coronary revascularization, and CV death.[40] Unfortunately, this trail did not measure blood pressure values, lipid levels, CRP, and other parameters limiting exploration of the underlying mechanism of this beneficial effect. In the light of previous trials testing anti-inflammatory therapies, we can, however, conclude with sufficient confidence that colchicine's salutary effects were mediated by interference with proinflammatory signaling.

In the Colchicine Cardiovascular Outcomes Trial (COLCOT), 4,745 patients who experienced a myocardial infarction no longer than 30 days ago were also randomized to colchicine at a dose of 0.5 mg a day or to placebo. After a median follow-up of 22.6 months, colchicine significantly reduced the primary end point composed of death from CV causes, resuscitated cardiac arrest, myocardial infarction, stroke, or urgent hospitalization for angina leading to coronary revascularization by 22%. This was particularly driven by a 50% decrease in hospital admissions requiring urgent revascularization and afforded hardly any adverse events.[41] CRP levels did not drop more rapidly in the colchicine group versus the placebo group. However, baseline CRP levels were elevated due to recovery from myocardial infarction, and the resolution of acute CRP elevation can obscure an anti-inflammatory action of colchicine. Taken together, three major clinical trials demonstrated beneficial effects on CV outcomes, both in patients suffering recent myocardial infarction or with chronic coronary syndrome. Given that not only efficacy but also safety and tolerability of colchicine treatment were confirmed in these recent large-scale trials, it is now the time to discuss adoption of low-dose colchicine treatment in clinical practice for secondary prevention.

Anti-inflammatory Therapies without Beneficial Cardiovascular Effects

Methotrexate

Methotrexate is an antifolate metabolite used as chemotherapeutic, and low-dose therapy is effectively used for immunomodulation, e.g., in patients with rheumatoid arthritis. In that very collective, retrospective analyses showed reduced CV events.[42] In 2018, the Cardiovascular Inflammation Reduction Trial (CIRT) sought to determine whether low-dose methotrexate therapy may achieve similar CV benefit to that observed in CANTOS. A similar collective of high-risk

subjects was investigated, with additional type 2 diabetes or metabolic syndrome; however, the subjects were not preselected for residual elevated hsCRP. Unlike CANTOS, no effect on the primary composite endpoint of nonfatal myocardial infarction, nonfatal stroke, and CV death was observed.[43] Given that hsCRP in CIRT was on average only 1.6 mg/L (vs. 4.2 mg/L in CANTOS) and that treatment did not reduce levels of IL-1β, IL-6, or CRP (as opposed to CANTOS), the lack of a beneficial effect may be related to low baseline inflammation in the investigated cohort and/or insufficient targeting of inflammatory pathways responsible for lowering of CV risk.

Corticosteroids

Corticosteroids have been investigated since the 1960s since their general immunosuppressive function was hypothesized to suppress inflammation in patients with acute myocardial infarction. However, a meta-analysis of randomized and controlled trials reported in 2003 that mortality was not improved by steroid treatment,[44] and a major concern with corticosteroid therapy in patients with acute myocardial infarction was an inhibited healing of the infarcted myocardium and increased risk of cardiac rupture. In another small study, patients with active rheumatoid arthritis were randomized to either prednisolone or no prednisolone, and carotid intima-media thickness, prevalence of atherosclerotic plaques, and endothelial function were not different among the groups.[45] In contrast, a randomized controlled trial interrogating 375 subjects who received coronary stent implantation with or without accompanying corticosteroid treatment demonstrated an improvement of event-free survival of CV death, myocardial infarction, and target vessel revascularization at 1 year.[46] Despite some potential benefit, the significant side effects such as induction of hyperlipidemia and hyperglycemia, which may aggravate atherosclerotic lesions, have lessened the enthusiasm for corticosteroid therapy as a therapeutic option to mitigate inflammatory processes in atherosclerosis.

Nonsteroidal Anti-inflammatory Drugs

Interest in effects of nonsteroidal anti-inflammatory drugs (NSAIDs) on atherosclerotic heart disease evolved around 2000. However, except for aspirin, all tested NSAIDs did not decrease but even increased the risk of myocardial infarction. For example, an analysis of a nationwide registry in Denmark involving almost 100,000 subjects with first myocardial infarction identified a persistently increased risk for myocardial infarction or coronary death during 5 years of follow-up in individuals taking NSAIDs versus nonusers of NSAIDs.[47] This phenomenon may be related to the fact that aspirin nonselectively inhibits cyclooxygenase (COX) I and II, thus including inhibition of COX I in platelets, resulting in less thromboxane A2 production and thus inhibition of platelet aggregation. In contrast, selective COX II inhibitors only inhibit COX II, which reduces endothelial production of prostacyclin and does not affect platelet aggregation. Thus, except for aspirin, NSAIDs are not recommended for long-term pain treatment in patients with atherosclerotic CV disease.

TNF-α Antagonists

TNF-α signaling is crucially involved in initiation and progression of atherosclerosis. Agents antagonizing TNF-α are commonly used as highly effective therapies in chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease. A systematic review evaluated the effect of TNF-α blockers on the progression of subclinical atherosclerosis in patients with inflammatory arthritis. The analysis suggests that antagonizing TNF-α was effective in preventing or even reversing intima-media thickness in this patient cohort. In mouse models of atherosclerosis, treatment with the recombinant soluble TNF receptor I or the monoclonal antibody infliximab reduced plaque lesion size and/or improved endothelial function.[48,49] In contrast, despite successful inhibition of systemic inflammation, treatment with a monoclonal anti-TNF-α antibody increased plaque burden and vascular inflammation and decreased markers of plaque stability.[50] Data from randomized clinical trials investigating CV outcomes in response to TNF-α blockade are unfortunately not available yet, leaving potential use of this therapeutic approach open for debate. A loss of enthusiasm of testing this anti-inflammatory strategy may be related to the observation of increased rates of mortality and heart failure hospitalization in the ATTACH trial, particularly in the group who were receiving the highest dose of infliximab.[51]

New Future Targets

Inhibition of IL-6 Signaling

Preclinical and clinical data suggest that drugs targeting IL-1β/IL-6 signaling achieve positive results. Recent pilot studies suggest that specific intervention of IL-6 signaling and thus downstream of IL-1β may also convey beneficial CV effects. In the RESCUE trial, 264 subjects with elevated hsCRP and CKD, a collective with high CV risk, have been randomized to receive the fully humanized monoclonal IL-6-blocking antibody, ziltivekimab, or placebo. After 12 and 24 weeks, the ziltivekimab group showed markedly reduced biomarkers of inflammation and thrombosis relevant to atherosclerosis.[52] Based on these promising data, conduction of a large-scale CV outcomes trial evaluating the effect of ziltivekimab in patients with CKD, increased hsCRP, and established CV disease has already been announced.

In the ASSessing the effect of Anti-IL-6 treatment in MI (ASSAIL-MI) trial, 199 patients with acute myocardial infarction were randomly assigned either to tocilizumab (IL-6 receptor antagonist; prompt single infusion of 280 mg) treatment or placebo treatment. The myocardial salvage index, measured by magnetic resonance imaging and defined as the proportion of the myocardium at risk salvaged by treatment following percutaneous coronary intervention, was significantly improved by tocilizumab treatment.[53] In a prespecified subgroup analysis, it was found that patients with ischemic episodes lasting longer than 3 hours before percutaneous coronary intervention had a more significant effect with tocilizumab. Even though the reduction of the myocardial salvage index (5.6% absolute difference) was rather small

and the cohort was limited in size, the results of these two trials that evaluated effects of IL-6 interference may predict a promising expansion of anti-inflammatory intervention as a treatment strategy from stable coronary patients into acute myocardial ischemia, an area of considerable clinical relevance. Although the mechanisms of action may be different between acute and chronic coronary syndrome, these encouraging results should further large-scale clinical trials investigating the effect of IL-6 interference on hard CV endpoints.

NLRP3 Inhibition

Preclinical studies in large animal models are available on specific inhibition of the NLRP3 inflammasome. MCC950 is a novel, selective small-molecule NLRP3 inflammasome inhibitor.[54] Compared with placebo, treatment with MCC950 reduced infarct size and preserved cardiac function in a randomized, blinded translational study performed in landrace pigs subjected to 75 minutes of transient balloon occlusion followed by 7 days of reperfusion.[55] These data are in line with the concept that anti-inflammatory intervention successfully attenuates myocardial damage in response to ischemia-reperfusion and suggest that NLRP3 inhibition may be another promising anti-inflammatory approach to attenuate CV disease burden. A wide array of additional direct and indirect NLRP3 inflammasome inhibitors is available as well (reviewed in van Hout et al[56]). Unfortunately, robust clinical data on CV outcomes are not available yet.

Vaccination against Atherosclerosis

The inflammatory response in atherosclerosis attracts cells of innate but also adaptive immunity into plaques, including T cells and B cells, indicating the existence of an autoimmunity component in the pathogenesis of atherosclerosis.[57] Since atherosclerosis is accompanied by immunoglobulin G antibodies against LDL, oxidized LDL, and ApoB, and since a T cell population with even distinct phenotypes recognizes ApoB-100 in oxidized LDL particles, ApoB as a core protein of LDL cholesterol seems to be the most prominent known antigen in atherosclerosis.[15,58,59] In addition, other antigens such as heat shock proteins, distinct viruses, and as yet unidentified antigens have been proposed to play a role in atherogenesis.[60,61] Furthermore, increased interactions between T cells and antigen-presenting cells within the plaque, increased maturation of T cells into antigen-experienced T cells, and clonal expansion of lesional T cells indicate the presence of several antigens within plaque.[62,63] Based on the discovery of an autoimmune component in atherosclerosis, the concept evolved that immunization with LDL or with peptides from ApoB may prevent atherosclerosis by inducing or maintaining the traits of protective immunity against ApoB.[64] Indeed, part of the autoimmune response conveys atheroprotective effects, including regulatory T cells (Tregs) which secrete anti-inflammatory IL-10, plaque-stabilizing TGF-β, and which suppress proliferation of proinflammatory T-effector cells.[65–67] A protective effect of vaccination with LDL has been reported to exert atheroprotective effects in a variety of species, as well as when using several distinct LDL preparations, routes, and adjuvants.[61,68] Immune responses held responsible for these protective effects include Tregs and secretion of anti-inflammatory IL-10. Recent data suggest that our immune system recognizes ApoB100 fragments already in the absence of manifest atherosclerosis as evidenced by an immune response that includes protective Tregs. While these Tregs are similarly maintained even after onset of atherosclerosis, rather a proliferation of pathogenic TH1 T cells may fuel the development of atherosclerotic plaques. Therefore, a valid strategy may reside in attempting to keep the immune system tolerogenic toward these atherogenic epitopes.[15] Currently, translation of vaccination into humans is complicated by defining an appropriate way and dose of vaccine application, lack of data on safety and desirable immune responses in humans, and identification of subjects which may benefit the most from antiatherosclerotic vaccination.[64] Nevertheless, this approach may represent an elegant future therapeutic strategy with potential long-term effects to lower the burden of atherosclerosis.

Cardiovascular Risk Factor Management

Increased inflammation and altered immunity are fundamental mechanisms contributing to atherogenesis, and anti-inflammatory or immune modulatory interventions represent clinically applicable and efficacious therapeutic strategies to reduce progression and complications of atherosclerosis. Given that traditional risk factors drive inflammation (among other pathogenic mechanisms), intensive risk factor management is instrumental in attenuating inflammation and risk of atherosclerotic complications. An approach for risk factor management integrating current guideline recommendations, personal suggestions, and future options is depicted in ►Fig. 2. Given that individual risk factors are unevenly distributed among people, individual risk stratification is an integral initial step for therapeutic decisions, followed by personalized therapy of individual risk factors. General guideline-recommended strategies include lifestyle modification, antithrombotic therapy, and high-intensity lipid-lowering therapy, preferably using statins. In case of type 2 diabetes mellitus, which is a low-grade inflammatory disease and may thus represent an own class of CV risk, novel antidiabetic drugs such as sodium–glucose linked transporter 2 inhibitors (SGLT2i) or glucagon-like peptide-1 receptor agonists (GLP-1RA) for which beneficial CV outcomes have been demonstrated should be administered.[69–71] In fact, particularly GLP-1RA but also SGLT2i has been shown to directly mitigate vascular inflammation and atherosclerosis, including mechanisms such as interference with the NLRP3 inflammasome, decreasing TNF signaling, increasing NO bioavailability, decreasing vascular leukocyte infiltration, promoting polarization of macrophage toward an anti-inflammatory phenotype, attenuating vascular oxidative stress, and decreasing expression of vascular adhesion molecules, among other mechanisms.[72,73] In case of CKD, administration of SGLT2i is capable of reducing hard renal endpoints both in individuals with or without diabetes,[74] and treatment of subjects with hypertension should be initiated using a renin–angiotensin system blocker in combination with a calcium channel blocker or diuretic.[75]

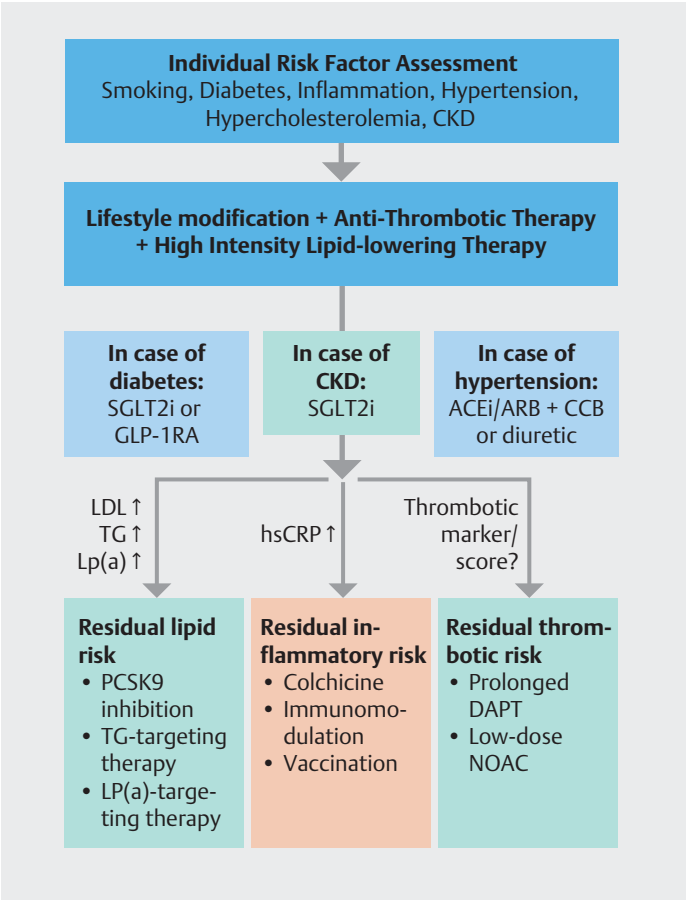

Fig. 2 Model of cardiovascular risk factor management. Following assessment of individual risk factors, lifestyle modifications and antithrombotic therapy and high-intensity lipid-lowering therapies should be initiated. In case of coexisting type 2 diabetes, early addition of novel antidiabetic drugs with beneficial cardiovascular effects is recommended. In case of coexisting CKD, addition of SGLT2i improves renal outcomes. In case of coexisting arterial hypertension, treatment using an ACEi/ARB in combination with a CCB or diuretic is recommended. Residual lipid risk indicated by increased LDL, TG, or Lp(a) levels can be addressed using PCSK9 inhibition, TG-lowering therapies, and Lp(a)-specific therapy once available. Residual thrombotic risk may call for prolonged dual antiplatelet therapy or low-dose NOAC treatment; unfortunately, markers or scores to evaluate thrombotic risk are not yet available. Residual inflammatory risk is reflected by increased hsCRP levels and requires anti-inflammatory intervention using colchicine treatment, immune modulatory therapy, and in the future potentially vaccination against atherosclerosis. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; GLP1-RA, glucagon-like peptide-1 receptor agonist; NOAC, non-vitamin K antagonist oral anticoagulant; PCSK9, proprotein convertase subtilisin/kexin type 9; SGLT2i, sodium-glucose linked transporter 2 inhibitor; TG, triglyceride.

Initiation of these standard therapies should be followed by evaluation of individual residual risk using biomarker or metabolite measurements to allow a personalized and optimal risk reduction therapy. If target LDL levels have not been achieved, i.e., residual lipid risk remains, addition of PCSK9 inhibitors will further reduce LDL levels and has been shown to reduce CV events when administered on top of statin therapy.[76,77] In addition, remaining increased levels of triglycerides should be lowered below 150 mg/dL. Specific therapy of increased Lp(a) levels represents another reasonable goal once these interventions have been proven efficacious in phase III clinical trials. Prolonged dual antiplatelet therapy using aspirin and ticagrelor, and low-dose therapy using novel oral anticoagulants (e.g., rivaroxaban 2.5 mg twice daily) can be considered to manage residual thrombotic risk, although no simple biomarker or score is currently available to indicate such residual risk. A residual inflammatory risk is present if levels of hsCRP remain higher than 2 mg/L despite treatment of other risk factors. Based on the available evidence presented above, we propose this justifies specific anti-inflammatory intervention using colchicine or immunomodulation with IL-inhibiting agents such as canakinumab.[32,78] Vaccination against atherosclerosis is an attractive approach for future CV risk management. We like to remind that the higher the CV risk, the more is the benefit, and the earlier the start of risk factor management, the better are effects in controlling or preventing atherosclerotic disease. Many examples may serve as proof of that.[35,79]

Conclusions

It is now clear that increased inflammation and altered immunity are fundamental mechanisms contributing to atherogenesis, driven by traditional CV risk factors, but

also by the presence of increased systemic inflammation of other etiologies. Studies that proved efficacy and safety of anti-inflammatory interventions such as inhibiting IL-1β signaling or administration of colchicine in large-scale clinical trials accentuate the need to introduce anti-inflammatory therapies to further improve CV outcomes in patients at risk. Novel future targets have been identified and should be interrogated in clinical studies. Now, novel high-power technologies such as single-cell RNA sequencing are available to unravel mechanisms of inflammation and immunity in CV disease. Besides determining residual inflammatory risk using hsCRP, such high-parametric technologies could also be exploited toward advanced individual assessment of inflammatory risk to potentially guide anti-inflammatory interventions. Such integration of novel diagnostic tools and therapies addressing the pathophysiologic contribution of inflammatory mechanisms will facilitate to achieve the ultimate goal of personalized therapy to mitigate onset, progression, and complications of atherosclerotic heart disease.

Author Contributions

All authors contributed equally to this manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

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