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Inflammation and Cardiovascular Disease – a narrative review

Vnetje in kardiovaskularne bolezni – pregledni članek

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Abstract

Chronic inflammation is a key mechanism in atherosclerosis and is associated with different stages of the atherosclerotic process and its complications. Cytokines, including interleukins, amplify the inflammatory cascade within the vessel wall and play a critical role throughout the pathogenetic process of atherosclerosis. Most risk factors for atherosclerosis exert harmful effects on the vessel wall by inducing an inflammatory process. Several inflammatory biomarkers are available to identify low-grade inflammation. Incorporating determination of inflammatory biomarkers, especially highly sensitive CRP (hsCRP), into CV risk prediction in primary prevention may help reclassify CV risk, particularly in low-risk patients and in subjects in whom traditional risk scores do not provide an exact estimation of risk. However, the existing guidelines do not include any inflammatory biomarkers in their scoring systems.

A healthy lifestyle, including exercise, weight loss, and smoking cessation, has been shown to reduce CV events by reducingng systemic inflammatory response. Also, drug treatment of risk factors, including antihypertensive agents and lipid-lowering drugs, reduces levels of circulating inflammatory biomarkers. With statins, it has been shown that the greatest reduction in ischemic events was achieved in patients with reduced low-density lipoprotein cholesterol and hsCRP. Despite the effects on levels of inflammatory biomarkers, only a limited number of anti-inflammatory agents have shown convincing results in lowering CV risk. Targeting interleukins, particularly interleukin-6, represents the most compelling evidence for reducing CV events. Canakinumab, colchicines, and some other new anti-inflammatory drugs are promising. However, further studies will be needed to determine the specific inflammatory mechanisms that contribute to CV events and to identify novel therapeutic strategies.

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Izvleček

Kronično vnetje je ključni mehanizem ateroskleroze. Povezan je z različnimi stopnjami aterosklerotičnega procesa in njegovih zapletov. Citokini, vključno z interlevkini, pospešujejo vnetno kaskado v žilni steni in igrajo odločilno vlogo v patogenezi ateroskleroze. Večina dejavnikov tveganja ateroskleroze izraža škodljive učinke na žilno steno s spodbujanjem vnetnega procesa. Na voljo so številni vnetni kazalci za odkrivanje vnetja nizke stopnje. Vključevanje vrednosti vnetnih kazalcev, še posebej visoko občutljivega CRP (hsCRP), v napovedovanje tveganja za srčno-žilne dogodke v primarni preventivi bi lahko omogočila novo klasifikacijo srčno-žilnega tveganja, še posebej pri bolnikih z nizkim tveganjem in posameznikih, pri katerih tradicionalni točkovniki ne omogočajo natančno oceniti tveganja. Obstoječe smernice pa v svojih točkovnikih žal nimajo nobenega od kazalcev za vnetje.

Zdrav življenjski slog, ki vključuje telesno dejavnost, izgubo telesne mase in opustitev kajenja, dokazano zmanjšuje srčno-žilne (CV) dogodke z zmanjšanjem sistemskega vnetnega odziva. Tudi zdravljenje dejavnikov tveganja z zdravili, vključno z antihipertenzivi in zdravili za zniževanje maščob, zmanjšuje ravni krožečih vnetnih bioloških označevalcev. Za statine se je pokazalo, da se je doseglo največje zmanjšanje ishemičnih dogodkov prav pri bolnikih, pri katerih sta bili znižani tako raven holesterola lipoproteinov nizke gostote (LDL) kot tudi hsCRP. Kljub dokazanemu vplivu na ravni vnetnih bioloških označevalcev pa je samo omejeno število protivnetnih učinkovin pokazalo prepričljive rezultate pri zmanjševanju srčno-žilnega tveganja. Najbolj prepričljive rezultate za zmanjšanje srčno-žilnih dogodkov je doseglo usmerjanje na interlevkine, zlasti na interlevkin-6. Canakinumab, kolhicin in nekatera druga nova protivnetna zdravila so obetavna. Toda za opredelitev specifičnih vnetnih mehanizmov, ki prispevajo k srčno-žilnim dogodkom, zato da bi lahko razvili nove terapevtske strategije, bodo še potrebne nove raziskave.

1 Introduction

Inflammation is a host defence mechanism that promotes tissue repair. However, chronically activated inflammation may lead to tissue injury and damage to target organs. Inflammation plays a critical role in the genesis, progression, and manifestation of cardiovascular disease (CVD) (1). The evidence from clinical trials shows that inflammation plays a key role in the pathogenesis of atherosclerotic and non-atherosclerotic CVD (2) and venous thromboembolic disease (3). The mechanisms linking inflammation to CVD are multiple and multifactorial. Inflammation is most probably the common denominator of the harmful effects of risk factors of atherosclerosis and venous thromboembolic disease (VTE). Management of risk factors, particularly dyslipidaemias, decreases a systemic inflammatory response. However, several studies showed that, despite statin therapy and other preventive measures, systemic inflammatory response is increased in subjects at high risk (4,5). Therefore, targeting inflammation with a new anti-inflammatory drug may offer a novel and more effective approach to reducing the risk of cardiovascular events.

Herein, this narrative review provides an overview of the role of inflammation in CVD and discusses the predictive value of various inflammatory biomarkers. Also, the results of clinical trials evaluating the efficacy of various pharmacologic and non-pharmacologic interventions to attenuate the inflammation and its impact on cardiovascular events are discussed.

2 Inflammation and pathogenesis of atherosclerotic cardiovascular disease

Until recently, atherosclerotic CVD was understood as a disease of the arterial wall caused by cholesterol imbibition and its passive accumulation in the subintimal layer. Recently, atherosclerosis has been recognised as a chronic inflammatory disease that promotes atherosclerotic plaque formation, triggers their progression and rupture, and leads to cardiovascular (CV) events (6). The studies showed that inflammation is involved at all stages of atherothrombosis (7). The formation of atherosclerotic lesions begins with subintimal cholesterol accumulation, which provokes an inflammatory response in the vessel wall. It starts with upregulation of adhesion molecules such as intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), which promote the binding and transmigration of inflammatory cells into the subintimal layer of the arterial wall. Infiltrating monocytes transform into macrophages in the subendothelial space (8). Activated macrophages form an inflammasome, which stimulates the production of different interleukins, including interleukin-6 (IL-6). IL-6 stimulates the synthesis of C-reactive protein in the liver and amplifies the inflammatory cascade in the vessel wall (9). The production of cytokines, interleukins, and reactive oxygen species and peroxide anions promotes the development and progression of atherosclerotic plaques. Moreover, other inflammatory cells, such as T cells, mast cells, and dendritic cells, modulate

plaque formation (10). Macrophages accumulate lipids and transform into foam cells, which can lead to the formation of a necrotic lipid core.

Inflammation also plays a key role in the vulnerability of atherosclerotic plaques by influencing the synthesis and degradation of fibrous tissues, especially collagen in the fibrous cap. Thinning of the fibrous cap and lipid core causes plaque instability, increasing the risk of rupture and thrombus formation, which can lead to acute events, such as acute coronary syndrome, ischemic cerebrovascular events or ischemia of the lower leg (11).

Further, inflammation is also involved in atherosclerotic plaque calcification. Activated macrophages in atherosclerotic plaques release proinflammatory cytokines, which promote vascular smooth muscle cell apoptosis and release of matrix vesicles with high content of calcium and phosphate (12). Calcium foci propagate the inflammatory response, and additional cell apoptosis, fibrous cap thinning, and favour plaque rupture (13).

3 Risk factors and systemic inflammatory response

3.1 Smoking

Tobacco smoke compounds initiate a substantial inflammatory response and lead to dysfunction of cells that regulate immunity (14). Smoking also induces genetic mutations and expression of proinflammatory cytokines (15). Further, smoking induces an acute rise in neutrophil and circulating T- cell counts and activity (16). Constituents of smoke induce local lung inflammation, leading to the release of proinflammatory cytokines and causes a systemic inflammatory response (17).

3.2 Dyslipidaemia

Dyslipidaemia promotes inflammation through several mechanisms. Through insulin resistance it inhibits hormone-sensitive lipase, which hydrolyses triglycerides within adipocytes and releases free fatty acids (18). Circulating free fatty acids promote inflammation by activating toll-like receptor-2 on cell surfaces (19). Circulating free fatty acids taken by hepatocytes are converted into triglycerides, which are associated with increased expression of ApoC III and, consequently, upregulate NF-kB and cytokine production (20).

Further, HDL is also involved in systemic inflammatory response. It inhibits the expression of adhesion molecules and inhibits the oxidation of LDL cholesterol (21).

3.3 Hypertension

Accumulating evidence indicates that inflammation is involved in the genesis and evolution of hypertension. Elevated blood pressure is a consequence of vascular inflammation and microvascular remodelling (22). Hypertension is accompanied by a chronic inflammatory response characterised by the accumulation and activation of inflammatory cells, the release of proinflammatory cytokines, and the generation of free radicals (23). High blood pressure is associated with elevated circulating inflammatory markers that reflect vascular inflammatory process. Therefore, inflammation of the vessel wall and associated hypertension could be the link between elevated blood pressure levels and the atherosclerotic process (24). Further, mechanical stress caused by elevated blood pressure and activation of humoral factors, such as the renin-angiotensin-aldosterone system, increases oxidative stress and promotes inflammatory process, which stimulates the development of atherosclerotic lesions.

3.4 Obesity

Adipose tissue promotes low-grade inflammation by releasing a variety of inflammatory mediators, such as interleukin-1 (IL-1), IL-6, and tumour necrosis factor-α (TNF-α) (25). A high level of inflammation was found in visceral fat, particularly in omental and hepatic fat. Increased visceral adiposity is associated with elevated circulating biomarkers of inflammation, which are related to leptin resistance (26). The production of inflammatory mediators by adipose tissue has been considered an important mechanism for the promotion and development of atherosclerosis (22).

3.5 Diabetes mellitus

It promotes atherosclerosis through inflammation, insulin resistance, hyperglycaemia, dyslipidemia and oxidative stress (27). The studies showed that patients with type 2 diabetes mellitus have higher systemic inflammatory markers, such as high-sensitivity C-reactive protein (hsCRP) and IL-1ß. Hyperglycaemia promotes the production of reactive oxygen species which stimulate the expression and release of inflammatory and adhesion molecules. Therefore, diabetes mellitus

increases oxidative stress and inflammation and promotes the development of diabetic atherosclerosis (28).

3.6 Sedentary lifestyle

It is a known risk factor of atherosclerosis, and a significant association between a sedentary lifestyle and the levels of circulating markers of inflammation was shown (29). One study showed that longer sedentary time was associated with higher IL-6 levels, and that increased physical exercise was associated with reduced hs-CRP levels (30). Physical inactivity leads to visceral fat accumulation and induces systemic inflammatory response (31).

4 Biomarkers of inflammation

Numerous biomarkers associated with inflammation have been identified, providing targets for monitoring atherosclerosis and cardiovascular risk. In addition, the potential usefulness of inflammatory biomarkers lies in monitoring the effects of anti-atherosclerotic therapeutic approaches.

4.1 C-reactive protein (CRP)

It is one of the most actively studied and established inflammatory biomarkers for cardiovascular events. The majority of CRP is produced in the liver as an acute protein in response to circulating cytokines, especially IL-6. However, CRP response is triggered by many disorders unrelated to cardiovascular disease, which interferes with the clinical application (32). Although observational studies have shown a strong association between CRP levels and cardiovascular risk (33), CRP itself is not causally linked to atherosclerosis. The Reynolds risk score, which incorporates hs-CRP measurement into CV risk prediction, shows high agreement with the Pooled Cohort equation in low-risk patients (34). However, this association is diminished in patients at high risk. In subjects with known risk factors, the predictive value of elevated CRP levels for estimating CV risk is only modest. Adding hsCRP measurement to risk prediction is more prominent in males than in females, in smokers, and in patients with higher estimated CV risk (>10%) (35).

4.2 Interleukins

It was shown that biomarkers upstream of CRP, like interleukins, are linked to CV risk. In the Women's Health Study and the Physician Health Study, healthy individuals with the highest quartile of IL-6 levels at baseline had around two times higher risk of CV events compared to those in the lowest quartile (33,36). In patients with acute coronary syndromes, levels of IL-6 were an independent predictor of increased mortality (37). Increased levels of IL-6 were also observed in the young post-myocardial patient, and IL-6 levels correlated with endothelial dysfunction, as measured by flow-mediated dilation of the brachial artery (38). Further, the data indicate the causal link between IL-1 and atherosclerosis. However, IL-1 measurement in epidemiological studies and its predictive value for CV events have been limited (9).

4.3 Other inflammatory markers

Neutrophil gelatinase-associated lipocalin (NGAL) is an acute-phase protein that regulates inflammation and is elevated in patients with CV disease (39). It has been shown that NGAL levels were higher in patients with high total atherosclerotic plaque volume than in those with low plaque volume. Therefore, NGAL could be used as a prediction tool for CV events in patients with asymptomatic atherosclerosis.

Myeloperoxidase (MPO) is typically released by inflammatory cells in response to bacterial infection. However, in healthy individuals with low CV risk, elevated MPO predicted the risk of coronary events (40), and in symptomatic coronary patients, levels of MPO predicted the risk of major adverse CV events in the future. The clinical utility of measuring MPO for predicting CV events is questionable.

Lipoprotein-associated phospholipase A2 (Lp-PLA2) is another inflammatory marker that can predict CV events. It is synthesized by macrophages and foam cells in atherosclerotic plaques (41). These enzymes release pro-atherogenic oxidized fatty acids and induce oxidative stress, which promotes progression of atherosclerotic plaques (42). Lp-PLA2 was shown to be positively correlated to the seriousness of coronary artery disease (43). Further, plasma Lp-PLA2 activity was associated with plaque rupture in patients with coronary artery disease independently of traditional risk factors (44). However, until now, the utility of measuring Lp-PLA2 and its clinical relevance remain uncertain.

5 Genetic polymorphisms and inflammation

Genetic polymorphisms modulate the risk of CV events through multiple pathways related to risk factors

such as cholesterol and inflammation (45). Several genetic polymorphisms determine the systemic inflammatory response, as evidenced by circulating and inflammatory marker levels. Differences in gene expression of inflammatory mediators may explain why inflammatory responses vary between individuals with similar risk factors. The collaborative meta-analysis of 82 studies investigating IL-6 receptor polymorphism showed that some polymorphisms were associated with a lower incidence of coronary artery disease, independent of lipid levels, blood pressure, or adiposity (46).

Polymorphisms in genes involved in cytokine synthesis may also explain some differences in CV risk among different races (47). Therefore, population-based genetic studies showed significant variation between individuals in levels of circulating biomarkers, and that genetic polymorphisms may, independent of traditional risk factors, determine the prognostic value. The studies also demonstrated that single gene polymorphism has a limited effect on overall heritable traits and cytokine levels (48). Genetic polymorphism may explain why some individuals have variable responses to targeted anti-inflammatory therapies. In the CANTOS trial, some individuals randomized to canakinumab did not experience hsCRP lowering (49). Identification of genome loci associated with inflammatory mediators of atherosclerosis could be a suitable target for anti-inflammatory treatment and for blocking atherosclerosis development (50).

6 Impact of rheumatic and other inflammatory diseases on atherosclerosis

Besides classical risk factors, which promote atherosclerosis through an inflammatory process, some inflammatory diseases, particularly rheumatic diseases, are related to cardiovascular disease, which is the most common cause of death in these patients. Classical risk factors for atherosclerosis are more common in patients with rheumatoid arthritis (51). Patients with rheumatoid arthritis often present comorbidities such as hypertension, dyslipidaemia, diabetes and obesity. However, the high incidence of cardiovascular events occurring in patients with rheumatoid arthritis is not related only to the presence of classical risk factors, but inflammation, as a basic pathogenetic mechanism of rheumatoid arthritis by itself promotes atherosclerosis. Inflammation, as evidenced by elevated levels of proinflammatory cytokines and acute-phase reactants, may contribute to the development of premature atherosclerosis in these patients. Therefore, systemic inflammation, as evidenced by the presence of proinflammatory cytokines and increased levels of C-reactive protein, seems to play an important role in atherosclerosis development in patients with rheumatic diseases.

Also, patients with psoriasis have elevated atherosclerotic risk. Patients with psoriasis tend to have significantly higher presence of risk factors of atherosclerosis, but inflammation is thought to be an independent risk factor of cardiovascular events in psoriatic patients (52).

7 Imaging biomarkers of inflammation

The novel imaging techniques enable visualization of arterial wall inflammation. The most frequently used technique is positron emission tomography (PET). Measurement of inflammation is based on fluorodeoxyglucose (FDG) radiotracer uptake in metabolically active cells, such as macrophages, in inflamed atherosclerotic plaques. Consequently, inflamed atherosclerotic plaques with a high macrophage density exhibit higher FDG uptake on PET imaging. In the subgroup analysis of the Progression of Early Subclinical Atherosclerosis (PESA) study individuals with a higher number of risk factors had higher FDG uptake in different arterial territories (53). One study showed that FDG uptake is associated with the accumulation of inflammatory cells in specimens of atherosclerotic lesions obtained by endarterectomy of the femoral and carotid arteries (54). Inflammation of atherosclerotic plaques may influence circulating biomarker levels and an interrelationship between the intensity of atherosclerotic plaque inflammation, as shown by FDG uptake, and circulating inflammatory markers was observed (55). Therefore, the determination of inflammatory markers can help to identify individuals with inflamed and unstable plaques, which are a risk for CV events. Using PET-FDG is also useful to demonstrate response to treatment with drugs that have anti- inflammatory effects. The meta-analysis of 7 studies, which included patients treated with statins, PET-FDG showed a reduction of arterial wall inflammation (56).

8 Management of systemic inflammatory response

Several therapeutic options have been shown to attenuate low-grade inflammation associated with CV events. However, guidelines addressing the treatment of low-grade inflammation to prevent CV disease are lacking. It is becoming increasingly clear that

inflammation within the arterial wall and atherosclerotic plaques represents an important contributor to atherosclerosis-related MACE and is a driver of cardiovascular morbidity and mortality. Therefore, anti-inflammatory treatment becomes a basic option for the prevention and treatment of atherosclerosis (57). As most risk factors of atherosclerosis promote inflammation, their elimination attenuates the inflammatory response. Besides nonpharmacological options, several anti-inflammatory therapeutics are now being developed, including cytokines, phospholipase A2 inhibitors, and anti-leukotrienes (58,59).

8.1 Nonpharmacological options

A healthy lifestyle, which includes physical activity, diet and elimination of risk factors of atherosclerosis, has been shown to be associated with a significant reduction of systemic inflammation and related CV risk (60). Multiple intervention studies have demonstrated that lifestyle changes can reduce inflammation and improve health. Inflammation biomarkers improve in patients who consume a certain amount of fibre per day (60). Fasting in combination with calorie restriction modulates molecular mechanisms and significantly reduces inflammatory marker levels, as well as improves metabolic markers (61). Further, omega-3 fatty acids lower blood triglyceride concentration, modulate T-cell differentiation, give rise to various prostaglandins, and promote resolution of tissue injury and inflammation (62).

8.2 Physical activity

Regular exercise attenuates low-grade inflammation and related risk for CV events. The anti-inflammatory effects, as measured by levels of inflammatory cytokines, depend on the type and intensity of physical activity (63). Observational studies also showed that regular exercise, in a dose-dependent manner, reduces the levels of inflammatory biomarkers (64). The ATTICA study showed that a physically active lifestyle reduces levels of inflammatory mediators: TNF-α by 20%, IL-6 by 32%, and CRP by 29% compared with a sedentary lifestyle (65).

Exercise induces a multiple-phase systemic inflammatory response. Acute exercise induces a significant increase in IL-6, which is proportional to exercise intensity and duration (66). The acute release of IL-6 during exercise reduces lipolysis and stimulates fatty acid oxidation. At the same time, anti-inflammatory mediators are released as a counterweight to an inflammatory response: the production of IL-1Ra, IL-10, and the release of macrophage inflammatory proteins1-alpha and1-β (67).

Repeated exercise modulates the pro-inflammatory response and has anti-inflammatory and insulin-sensitizing effects. It is associated with a decrease in hsCRP levels, particularly in subjects with reducedbody mass index (68). Exercise also reduces systemic inflammation by improving lipid profile and blood pressure.

8.3 Weight loss

Weight loss has been shown to reduce inflammatory markers. Adipocytes and adipose tissue infiltration with inflammatory cells are important sources of adipokines, and reducing body fat has favourable effects on reducing of proinflammatory cytokines (69).

8.4 Smoking cessation

Smoking provokes chronic inflammation of the arterial wall and induces atherosclerosis (70). Further, exposure to cigarette smoke exerts profound effects on endothelial function and, together with inflammation, stimulates the development and progression of atherosclerosis (71). The net effect of smoking on inflammation depends on many variables, including the dose and type of tobacco and chronicity of exposure (72). Therefore, smoking cessation significantly reduces CV risk through different mechanisms, including substantially reducing inflammation. There is an inverse-dose-dependent relationship between years of smoking cessation and levels of hsCRP. The studies showed that inflammatory markers return to normal values after an average of 5 years of smoking cessation (73).

8.5 Treatment of hypertension

As probably low-grade systemic inflammation is involved in the pathogenesis of hypertension, anti-inflammatory approaches to the management of hypertension are investigated. Limited data show that anti-inflammatory agents might have blood-pressure lowering effects in subjects with uncontrolled hypertension, and these effects appear to be limited to patients with active prohypertensive inflammatory mechanisms (74). The data also indicated that standardized therapy of hypertension may reduce blood pressure, but not treat the underlying pathophysiology, which may contribute to the development of cardiovascular disease, such

as atherosclerosis. Therefore, another approach would be a treatment for hypertension focused more on epigenetic modifications that facilitate vascular dysfunction, insulin resistance, and inflammation (75). The studies demonstrated that the blood-pressure-lowering effects of treating hypertension with angiotensin receptor blockers or calcium channel blockers are further exerted through improved endothelial function and decreased inflammation of the vascular wall (76). Angiotensin-converting enzyme inhibitors have been shown to improve endothelial function in patients with hypertension. However, few studies have evaluated the effects of treatment with these drugs on the reduction of C-reactive protein and other inflammatory markers (77). First- or second-generation beta blockers do not appear to improve expression of inflammatory cytokines or other inflammatory markers in patients with hypertension (78).

8.6 Lipid-lowering therapies

It has been demonstrated that statins, besides their cholesterol-lowering effects, have also anti-inflammatory action through lipid-dependent and independent pathways (79). Their anti-inflammatory effect is mediated through the mevalonate precursor in the formation of isoprenoid intermediates such as farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP). Consequently, pro-inflammatory cytokines such as IL-1-β, IL-6, and TNF-alpha are downregulated (79). Furthermore, statins downregulate the expression of adhesion molecules (ICAM-1 and VCAM-1) through the reduction of intracellular redox status, which leads to a reduction in vascular wall inflammation. Additionally, there is downregulation of transcription of proinflammatory genes (80). The Pravastatin Inflammation CRP Evaluation (PRINCE) study first showed a reduction in hsCRP independent of LDL-C levels achieved in patients with and without CV disease (81). As the primary outcome of the Justification for the Use of Statins in Prevention and Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, a low-dose rosuvastatin (20 mg) caused a 50% reduction in LDL-C and 37% reduction in hsCRP. The greatest benefit (reduction in ischemic events) was seen in patients with reduced LDL-C (<70 mg/dl) and hsCRP (<1 mg/L) (82). The Beyond Endorsed Lipid Lowering With Electron Beam Tomography Scanning (BELLES) trial showed that atorvastatin and pravastatin, independent of achieved LDL-C level, both reduce inflammation of epicardial adipose tissue (83). The ability of different lipid-lowering drugs to reduce inflammation varies. In a study by Qin et al., it was shown that ezetimibe significantly reduced CRP value in apolipoprotein E-deficient mice fed with a high-fat diet (84). However, when ezetimibe was used as a monotherapy in patients with hypercholesterolemia, the reduction in CRP levels compared to placebo was not significant (85).

8.7 PCSK9 inhibitors

In the Cardiovascular Outcome Research PCSK9 Inhibition Subjects with Elevated Risk (FOURIER) study, patients were treated with the PCSK9 inhibitor evolocumab and an antiinflammatory effect associated with improved CV outcomes was observed. Evolocumab caused the greatest absolute reduction of CV events in patients with higher CRP (>3 mg/L) (86). PCSK9 inhibitors inhibit macrophage stimulation and the production of inflammatory cytokines such as IL-1β and TNF- α (Figure 1) (87).

9 Target anti-inflammatory drugs for preventing CV events

A key role in inflammation is played by cytokines; therefore, targeting interleukins, particularly IL-6, represents most compelling evidence for reducing CV events.

9.1 Canakinumab inhibition of IL-1β

The Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS), a randomized, double-blind, placebo-controlled trial that included stable patients with previous myocardial infarction, evaluated the effect of preventing recurrent vascular events in patients with elevated hsCRP, which led to a significant reduction in recurrent CV events compared to placebo (49). Canakinumab, a fully human monoclonal antibody targeting IL-1β has an anti-inflammatory effect and reduces plasma levels of IL-6 and hsCRP. The effect of canakinumab was primarily reflected in a lower incidence of myocardial infarction, with a significant reduction in hsCRP levels, rather than in changes in LDL-C levels. Prespecified analysis also showed that a significant risk reduction in major CV events occurred only when canakinumab was associated with a drop of hsCRP levels < 2 mg/L. The results of the CANTOS trial and canakinumab opened a new era of therapeutic targeting of inflammation for CV secondary prevention and the development of targeted anti-cytokine

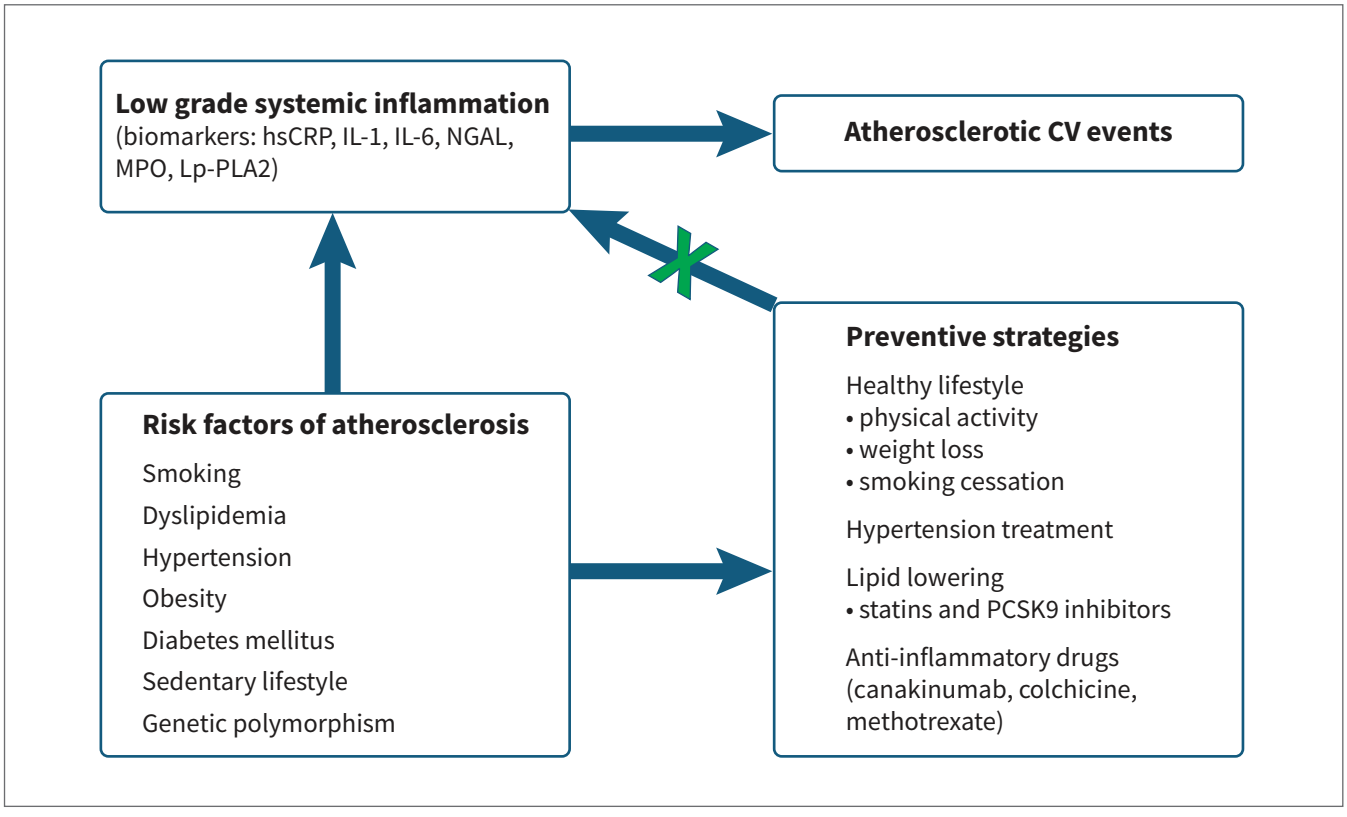

Figure 1: Risk factors of atherosclerosis and management of systemic inflammatory response.
Legend: hsCRP – high-sensitive CRP; Lp-PLA2 - Lipoprotein- associated phospholipase-A2; MPO - myeloperoxidase; NGAL – neutrophil gelatinase-associated lipocalin; PCSK9 - proprotein convertase subtilisin/kexin type 9.

therapies for the management of atherothrombosis (88).

The potential benefits of the reduction in inflammatory markers induced by canakinumab should be carefully balanced against the unknown long-term safety profile.

9.2 Colchicine

Colchicine is a medication primarily used to prevent and treat gout, familial Mediterranean fever, and Bechet's disease. It is an alkaloid derived from dried seeds of the autumn crocus (89). However, colchicine therapy has also shown to reduce CV events in patients with established atherosclerotic CV disease (89). Colchicine exerts its anti-inflammatory effects by inhibiting microtubule polymerization, thereby impairing inflammatory cell adhesion and activation. Besides this, inhibition of the inflammasome pathway was observed (90,91). Further, colchicine modulates inflammasome gene expression and consequently reduces the production of IL-1β and IL-18. The Low-Dose-Colchicine for CVD prevention (LoDoCo) trial, which included 532 patients with stable coronary artery disease (follow-up 3 years), showed a significantly reduced relative risk (67%) of the composite primary endpoint in patients on low-dose colchicine for secondary prevention. The reduction in CV events was almost entirely due to a reduction in non-fatal CV events (92).The Colchicine Cardiovascular Outcomes Trial (COLCOT) investigated the effects of colchicine on cardiovascular outcomes in patients with myocardial infarction within 30 days. Colchicine showed a significant (23%) reduction in the risk of the composite primary CV events (93). However, in the CLEAR SYNERGY trial, low-dose colchicine in post-myocardial infarction patients with percutaneous coronary intervention did not reduce major cardiovascular events (94).

Gastrointestinal intolerance, including diarrhea, nausea, vomiting, and abdominal pain, is the most common adverse effect occurring in approximately 10-20% of patients, followed by myalgias. In the COLCOT (Colchicine Cardiovascular Outcomes Trials) study, which used a low-dose colchicine regimen of 0.5 mg daily, gastrointestinal side effects were not significantly higher than in the placebo group (95).

9.3 Methotrexate

Methotrexate inhibits the production of inflammatory cytokines and has been investigated as a potential anti-inflammatory drug in patients with atherosclerotic disease. The Cardiovascular Inflammation Reduction Trial (CIRT), a double-blind trial, included 4786 patients with myocardial infarction or multi-vessel coronary disease. Methotrexate had no impact on the primary endpoint of major CV events. Mortality was higher in the low-dose methotrexate group, and the trial was prematurely stopped (96). Methotrexate was associated with elevated liver enzyme levels, reducted leucocyte counts, and a higher incidence of non-basal cell skin cancers.

Currently, selective inhibitors and antithrombotic medications are also being investigated.

10 Conclusions and future perspectives

Atherosclerosis is a chronic inflammatory vascular disease driven by traditional and non-traditional risk factors. The concept of inflammation as a driver of atherosclerosis provides a mechanism by which traditional risk factors induce atherosclerotic disease and its complications. Further, some inflammatory diseases, such as rheumatic disease, directly provoke inflammation of the vessel wall and initiate the atherosclerotic process. Inflammation of the vessel wall includes upregulation of adhesion molecules, migration of monocytes into the endothelial space, and formation of an inflammasome which stimulates the production of different interleukins. Inflammation also plays a key role in the vulnerability of atherosclerotic plaques by influencing the synthesis and degradation of fibrous tissue, especially in the fibrous cap.

Targeting inflammation offers the potential for an orthogonal approach that may address the residual risk associated with well controlled lipid profiles and other risk factors. Inflammation has opened the door to a new therapeutic target for atherosclerosis treatment. However, the potential benefits of anti-inflammatory drugs should be carefully balanced against their long-term safety profile.

Conflict of interest

None declared.

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