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Anti-inflammatory agents in peripheral arterial disease

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Inflammation is pivotally involved in coronary and peripheral atherosclerotic disease. This established concept is based on both experimental animal models of vascular inflammation and Mendelian randomization studies demonstrating a causal relationship between pro-inflammatory cytokines (e.g. interleukin-6) and cardiovascular disease risk. More recently, the reduction of cardiovascular events by use of an interleukin-1β inhibitor (canakinumab) has revived interest in the use of anti-inflammatory agents for the treatment of atherosclerotic disease, including peripheral arterial disease. In this mini review article we provide an update on the pleiotropic anti-inflammatory properties of approved drugs for use in cardiovascular disease (e.g. antiplatelets, statins, PCSK9 inhibitors) and discuss the role of targeted or untargeted anti-inflammatory atheroprotection in peripheral arterial disease by agents such as colchicine, methotrexate, anti-TNF-α agents and monoclonal antibodies against interleukin-signaling.

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Introduction

Coronary and peripheral atherosclerosis are inflammatory diseases [1••], characterized by the initiation and progression of the lesion and plaque-rupture related complications, and involve mononuclear and macrophage cells [1••]. Downstream inflammatory signaling by C-reactive protein (CRP) as well as upstream signaling by interleukin (IL)-1β and IL-6 is involved in atherosclerosis-related systemic low grade inflammation [2]. The signaling mediators involved in atherosclerotic plaque and vascular wall inflammation have also been well-characterized. Nuclear factor κ-B activation orchestrates and amplifies vascular inflammation via the local expression of pro-inflammatory cytokines and matrix metalloproteinases. Toll-like receptors (TLRs) [3], the NLRP3 inflammasome [4], proprotein convertase subtilisin/kexin type 9 (PCSK9), and neutrophil extracellular traps (NETs) [5] also have a critical role in plaque-related inflammation.

The role of inflammation in atherosclerosis is now well-established not only by studies measuring of pro-inflammatory biomarkers in human plasma [6], but also by Mendelian randomization studies demonstrating a causal relationship between genetic variation in cytokine signaling, such as IL-6 receptor [7•] and the risk of development of atherosclerotic disease phenotypes.

Beside the established knowledge on the molecular mediators of inflammation and its role in the pathophysiology of atherosclerosis, imaging (e.g. ^{18F}FDG positron emission tomography) has also contributed in our understanding of atherosclerosis as an inflammatory disease, by enabling the visualization of vascular wall inflammation and demonstrating its independent association with clinical outcomes [8]. Clinical data now also support the rationale of reducing inflammation as a means to improve cardiovascular outcomes. First strong indirect evidence was provided by the Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial [9•] and the reduction of cardiovascular events by rosuvastatin in patients with low cholesterol levels but high systemic inflammation as assessed by circulating CRP levels. Even more important for the notion of anti-inflammatory atheroprotection were the results of the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) [10••], in which inhibition of IL-1β by a monoclonal antibody substantially reduced cardiovascular disease risk.

Currently, several agents are available for the therapeutic targeting of inflammation in atherosclerosis and include antiplatelet σ, renin–aldosterone–angiotensin system blockers, statins and PCKS9 inhibitors that may exert beneficial effects by lowering plaque inflammation. Also broad based anti-inflammatory agents/immunosuppressants e.q, colchicine and methotrexate or targeted anti-inflammatory treatment by inhibition of P-selectin, tumor necrosis factor-α (TNF-α) or pro-inflammatory cytokine (e.g. IL-6, IL-1β, IL12/23, etc.) signaling appear promising for use against both coronary and peripheral artery atherosclerosis. In the present mini review we summarize the existing evidence on the use of anti-inflammatory

agents in atherosclerosis and peripheral arterial disease (PAD).

Established agents against atherosclerotic disease with anti-inflammatory properties

***Antiplatelet agents — P2Y$_{12}$ inhibition*:** Clopidogrel is an irreversible ADP receptor ($P2Y_{12}$) antagonist that effectively inhibits the platelet reactivity. Inhibition of platelet reactivity blocks the expression of P-selectin (CD62P), CD63 and thrombospondin, CD40L and RANTES on the surface of activated platelets, which regulate platelet-vessel interactions. Clopidogrel reduces the expression of CD62p and CD63 on the surface of activated platelets, attenuating platelet accumulation, and reduces soluble CD40L (sCD40L) release, which regulates atherothrombosis and the release of pro-inflammatory cytokines from vascular cells [11,12]. At the clinical level, these effects of clopidogrel may be partly responsible for their superior efficacy compared to aspirin in reducing vascular events, especially ιν patients with peripheral artery disease (PAD) [13]. In patients with PAD, when clopidogel is combined with aspirin significant reductions are observed in platelet reactivity and systemic inflammatory response as compared to aspirin alone (Table 1) [14].

***Direct oral anticoagulants*:** Rivaroxaban, an oral anticoagulant, is a direct inhibitor of factor Xa. Histological analyses demonstrate that in experimental studies rivaroxaban significantly decreases lipid deposition, collagen loss, macrophage accumulation and matrix metallopeptidase-9 (MMP-9) expression in aortic atherosclerotic plaques [15]. In the recent Cardiovascular OutcoMes for People Using Anticoagulation StrategieS (COMPASS) trial, in the subgroup of 7470 patients with PAD (atherosclerotic disease of lower extremities or carotid artery disease) the combination of low-dose rivaroxaban and aspirin reduced major adverse cardiovascular and limb events, including severe limb ischemia and amputation [16]. These effects were independent of any change in plasma lipid or blood pressure levels and are important since they pave the road to the testing of other low-dose anticoagulation regimens in vascular disease.

***Renin–angiotensin–aldosterone synthesis blockers*:** Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptors blockers (ARBs) are anti-hypertensive agents which counteract angiotensin-II deleterious effects on the vasculature. In animal models ACEi/ARBs attenuate atherosclerosis progression, the main cause of PAD [17], properties which are related to their effects on angiotensin-II and bradykinin formation. Angiotensin II induces the migration and proliferation of vascular smooth muscle cells, and vascular oxidative stress via NADPH oxidases activation, resulting in increased generation of superoxide anions and endothelial dysfunction. At the clinical level, ramipril treatment benefits patients with intermittent claudication by significantly increasing pain-free and maximum treadmill walking time compared with placebo [17]. This is independent of any direct hemodynamic effects, for example improvement in ankle-brachial pressure index (ABPI), but may rather be mediated via improvement in vascular mechanics and reduction of arterial stiffness [18]. Telmisartan has similar beneficial effects, improving walking distance and endothelial function in patients with PAD [19].

***Statins*:** Statins (or HMG-Co-A reductase inhibitors) constitute the mainstay of primary and secondary prevention therapy against cardiovascular disease. This is attributed not only to the role of low-density-lipoprotein as a major risk factor for atherosclerosis development, and the potency of statins as lipid lowering agents, but also to their pleiotropic, anti-inflammatory effects. Our previous studies on human arterial and vein grafts were among the first providing direct evidence on statin pleiotropic effects on human vessels [20,21,22•]. Atorvastatin exerts rapid effects (before any lipid lowering takes place) and improves nitric oxide vascular bioavailability by increasing tetrahydrobiopterin synthesis and lowering the activity of NADPH oxidases in the vascular wall [20,21,22•]. Further to their anti-oxidant properties, statins lower vascular wall inflammation and stabilize atheromatous plaques [23,24]. Ample experimental as well as clinical evidence has now established the notion of statin pleiotropy, such as the landmark JUPITER trial [9•], which demonstrated benefits in cardiovascular outcomes with rosuvastatin treatment in patients with low LDL cholesterol levels and high plasma CRP levels. In PAD, there is limited evidence from randomized clinical trials on the benefit of statin treatment. In 5480 patients with asymptomatic PAD (defined as ABPI $\leq$0.95) the use of statins therapy was associated with a reduction in major adverse cardiac events (MACE) and all-cause mortality [25]. In the IDEAL trial (Incremental Decrease in End Points Through Aggressive Lipid Lowering Study Group) comparing high dose atorvastatin to moderate-dose simvastatin in 8888 post-myocardial infarction patients, the use of high dose atorvastastin significantly reduced the incidence of PAD compared with usual-dose statin therapy with simvastatin [26].

***PCSK9 inhibitors*:** Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a member of the proprotein convertase family of proteins which regulates LDL receptor internalization and catabolism in hepatic cells [32]. Recent trials have demonstrated the potent lipid lowering effects of PCSK9 inhibition by alirocumab and evolocumab. In the Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound (GLAGOV) trial evolocumab yielded significantly attenuated atherosclerosis progression, yielding greater reductions in percent atheroma volume compared to placebo in patients with angiographic evidence of coronary disease treated with statins [27]. In patients with