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Anti-inflammatory therapy in atherosclerosis

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TABLE OF CONTENTS

1. ABSTRACT

Cardiovascular disease (CVD) is the leading cause of death. Although once considered merely as a lipid storage disease, studies indicate the role of inflammation in initiation and progression of atherosclerotic CVD, as well as the development of thrombotic complications. Despite significant advances in treatment of atherosclerosis, there still exists a residual risk for CVD-related morbidity and mortality. Even with optimal treatment, the rate of a new event after an index acute coronary syndrome event, such as myocardial ischemia or infarction, in the first three years has been reported to be as high as 20%. In the last decades, inflammation due to apoB-lipoproteins and other traditional risk factors, such as hypertension, diabetes and smoking, is accepted as a new target for CVD prevention. Up to now, several anti-inflammatory drugs have been tested for use in atherosclerosis. This review focuses on the current status of anti-inflammatory drug therapy for atherosclerotic CVD in humans.

2. INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death (1). According to 2015 World

Health Organization data, CVD mortality accounts for 31% of all deaths worldwide (1). The most common form of CVD is atherosclerosis. Although once considered merely as a lipid storage disease, studies indicate the role of inflammation in the initiation and progression of the atherosclerotic CVD, as well as the development of thrombotic complications.

It has been believed that the main initiators of inflammation in atherosclerotic CVD are apolipoprotein B-containing lipoproteins (apoB-LPs). Besides causing inflammation in plaques, they also cause progression of the disease via interacting with other traditional CVD risk factors, such as hypertension, diabetes and smoking (2). Despite significant advances in treatment of atherosclerosis, there still exists a residual risk for CVD-related morbidity and mortality. Even with optimal treatment, the rate of a new event after an index acute coronary syndrome (ACS) event, such as myocardial ischemia or infarction, in the first three years has been reported to be as high as 20% (3). In the last decades, inflammation due to apoB-LPs and other traditional risk factors, such as hypertension, diabetes and smoking, is accepted as a new target for CVD prevention. Up to now, several anti-inflammatory drugs have been tested for use in atherosclerotic CVD.

Randomized clinical trials (RCTs) have demonstrated that in addition to their lipid lowering effects, statins are useful in the primary (4) and secondary (5) prevention from CVD due to their anti-inflammatory potential. The landmark *Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (*JUPITER) trial has suggested that in normolipidemic subjects (low-density lipoprotein [LDL]-cholesterol< 130 mg/dL) without evident coronary heart disease but with elevated C-reactive protein (CRP) levels (> 2.0 mg/L), suppression of low-grade inflammation by rosuvastatin 20 mg/day resulted in a risk reduction of 0.56 (95% CI: 0.46-0.69, p<0.00001) for the combined primary endpoint when compared to placebo at a median follow-up of 1.9 years(6). A recent plaque imaging study in 218 patients using intravascular ultrasound has shown that after 12-month rosuvastatin treatment a greater high sensitivity-CRP (hs-CRP) reduction, but not LDL-cholesterol, was associated with a greater decrease in percent necrotic core volume and absence of intravascular ultrasound defined thin-cap fibroatheroma, suggesting a link between the anti-inflammatory action of statins and plaque stabilization (7). This review focuses on the current status of anti-inflammatory drug therapy other than statins in atherosclerotic CVD in humans.

3. ANTI-INFLAMMATORY DRUGS

3.1. Anti-inflammatory drugs with low probability to improve cardiovascular outcomes

3.1.1. Corticosteroids

Corticosteroids are among the most prescribed anti-inflammatory drugs. They have a wide spectrum of anti-inflammatory actions, including increasing transcription of genes coding anti-inflammatory proteins (such as lipocortin-1, interleukin-10, interleukin-l receptor antagonist), inhibiting expression of various inflammatory genes (such as cytokines, enzymes, receptors and adhesion molecules)- possibly via activated transcription of nuclear factor-κB, activator protein-1- and directly inhibiting inflammatory cells (such as macrophages, dendritic cells, mast cells) (8). Glucocorticoids (GCs) were already established therapeutic agents in various inflammatory diseases prior to introduction of RCTs. Therefore, their effects on cardiovascular (CV) outcomes have been evaluated in epidemiological studies only.

Increased risk of death from myocardial infarction (MI) or stroke at early ages before surgical treatment of Cushing's syndrome has supported a link between accelerated atherosclerosis and long-term excessive GC exposure (9). Observational studies suggested that rheumatoid arthritis (RA) and systemic lupus erythematosus patients under corticosteroids have significantly more atherosclerosis than those not treated with steroids and the risk of atherosclerosis is related to the cumulative exposure to corticosteroids (10-12). However, extent of inflammation is an important confounder in atherosclerosis associated with rheumatologic disease. This limitation could also

apply to population-based observational studies, which were designed to assess the relationship between GC therapy and CV events (13, 14), owing to the fact that increased odds ratio (OR) of any CV or cerebrovascular outcome may be attributable to the underlying disease being treated rather than to the use of GCs. However, in both studies (13, 14), effects wereconsistent across different disease indications.

Nevertheless, in other studies involving cohorts of RA patients, there was evidence of interactions between effects of GCs and the underlying inflammatory disease on CV risk. In an US cohort (n= 603), a dose-dependent risk of CVD with GC exposure was confirmed, but that risk was only detectable among rheumatoid factor-positive patients (15). Other studies, which had relatively smaller study populations, revealed contradictory findings (12, 13). Adjustment for the presence of components of the metabolic syndrome did not eliminate the effect of GCs (13, 14, 16), raising the possibility that the influence of GCs on CV outcomes is not mediated exclusively by traditional CV risk factors.

Various clinical trials have been undertaken to test the effects of GCs administered in the first days after MI. A meta-analysis of 11 controlled trials (n= 2.646) (18) has revealed a 26% decrease in mortality with corticosteroids (OR: 0.74, 95% CI: 0.59-0.94). Sensitivity analyses limited to large studies and RCTs revealed ORs of 0.76 (95% CI: 0.53-1.09) and 0.95 (95% CI: 0.72-1.26), respectively, suggesting that corticosteroids at least did not cause any harm in acute MI. However, the increased incidence of heart failure amongst GC users in the epidemiological studies described above (13, 14) raises the possibility that longer-term GC therapy has an adverse effect on cardiac remodelling.

Corticosteroids have also been used to prevent restenosis after angioplasty. Systemic GCs have been beneficial in some (19-22), but not all (23-27) clinical studies. Discrepancy in the results may be explained by the fact that the benefits of local anti-inflammatory effects may be offset by adverse systemic effects. Second, the anti-inflammatory effects of GR activation may be offset by pro-inflammatory MR activation (28). To overcome these limitations, GC-eluting stents have been proposed to deliver local anti-inflammatory therapy (29-31) using GCs devoid of affinity for MR, such as dexamethasone and prednisolone. However, there still exists the risk that GR activation may induce changes within the vessel which may offset any benefit of conventional anti-inflammatory effects, such as increasing local angiotensin-II (32, 33) or endothelin-1 (34) generation or decreasing endothelial nitric oxide generation (35).

3.1.2. Pexelizumab

The classical complement pathway, which is one of three pathways that activate the complement system, may directly damage the myocardium (36). Complement 5 inhibitor, pexelizumab, is a humanized monoclonal antibody inhibiting C5 complement, thereby blocking its cleavage into active forms: C5a and C5b-9. C5a is a powerful peptide mediator of inflammation, whereas C5b triggers the late events in which the terminal components of complement assemble into a membrane-attack complex that can damage the membrane of certain pathogens (37).

In a systemic review and meta-analysis of seven trials (n= 15.196, 7.019 patients with ST segment elevation MI (STEMI) and 8.177 undergoing coronary artery bypass grafting (CABG), the impact of pexelizumab versus placebo on CV outcomes was investigated. Endpoints were–the composite risk of all-cause death, MI and thromboembolic stroke; the risk of single end points and heart failure. There was not any benefit of pexelizumab on the endpoints in STEMI, however it was associated with a 26% reduction of death risk in the setting of CABG (OR: 0.74, 95% CI: 0.58-0.94, p= 0.01) (38).

3.1.3. Tranilast

Mast cells stabilizers block mast cell degranulation, thereby preventing the release of histamine and related mediators. Tranilast is an anti-fibrotic drug which prevents collagen synthesis by inhibiting the release of mast cell factors, including histamine, prostaglandins, platelet derived growth factor, transforming growth factor-beta and interleukin (IL)-1beta (39). Three RCTs evaluating the impact of tranilast on CV outcomes are

Table 1. Summary of three randomized controlled trials that evaluate the impact of tranilast on cardiovascular outcomes

Trial	Study protocol	Outcomes	Results
The Tranilast REstenosis following Angioplasty Trial (TREAT) (137)	- Double-blind, placebo-controlled trial - n= 255 patients -Randomization: 600 mg/day tranilast po, 300 mg/day tranilast po or placebo po for 3 months after successful PTCA	Restenosis rates after successful PTCA - loss of ≥50% of the initial gain - % stenosis of ≥50% at follow-up	- 14.7% in the 600 mg/day tranilast group, 35.2% in the 300 mg/day tranilast group and 46.5% in the placebo group (p< 0.0001 for 600 mg/day tranilast vs placebo) - 17.6% in the 600 mg/day tranilast group, 38.6% in the 300 mg/day tranilast group, and 39.4% in the placebo group (p= 0.005 for 600 mg/day tranilast vs placebo)
TREAT-2 (138)	- Double-blind, placebo-controlled trial - n= 297 patients - Randomization: 600 mg/day tranilast po or placebo po for 3 months after successful PTCA	Restenosis rates after successful PTCA - loss of ≥50% of the initial gain - % stenosis of ≥50% at follow-up	- 18.8% in the tranilast group vs. 44.1% in the placebo group, p<0.001 -- in *de novo* lesions: 18.9% in the tranilast group vs. 41.2% in the placebo group, p= 0.003 -- in restenotic lesions: 18.4% in the tranilast group vs. 53.3% in the placebo group, p= 0.004 - 25.9% in the tranilast group vs. 41.9% in the placebo group, p= 0.012
Prevention of REStenosis with Tranilast and its Outcomes (PRESTO) trial (40)	- Double-blind, placebo-controlled trial - n= 11.484 patients - Randomization: 300 and 450 mg twice daily tranilast or placebo for 1 or 3 months within 4 hours after successful percutaneous coronary intervention of at least 1 vessel	- Primary endpoint: the first occurrence of death, MI or ischemia-driven target vessel revascularization within 9 months - In the angiographic substudy (n= 2.018 patients): MLD measured by quantitative coronary angiography -- a subset of patients (n= 1.107) underwent intravascular ultrasound at follow-up	- 15.8% in the placebo group, 15.5% to 16.1% in the tranilast groups (p= 0.77 and p= 0.81) - MLD was 1.76±0.77 mm in the placebo group; 1.72±0.76, p= 0.49 and 1.78±0.80 mm, p= 0.89 in the tranilast groups -- plaque volume was 39.3 mm^3 in the placebo and 37.5 and 46.1 mm^3 in the tranilast groups (p= 0.16 and p= 0.72, respectively)
CI confidence interval, MI myocardial infarction, MLD minimal lumen diameter, PTCA percutaneous transluminal coronary angioplasty.			

summarized in Table 1. The largest trial, *Prevention of REStenosis with Tranilast and its Outcomes* (PRESTO), failed to demonstrate beneficial effects of tranilast on CV outcomes (40).

3.1.4. Anti-tumor necrosis factor (anti-TNF) therapy

Anti-tumor necrosis factor (anti-TNF) therapy is a widely used biological therapy of several immune-mediated inflammatory diseases such as RA, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis and severe chronic plaque psoriasis. Infliximab, etanercept and adalimumab are the most commonly used anti-TNF treatments. Infliximab is a recombinant humanized monoclonal anti-TNF-alpha antibody, whereas etanercept binds and inactivates TNF. Adalimumab is also a recombinant human monoclonal anti-TNF-alpha antibody; in addition, it lyses surface TNF-expressing cells *in vitro* and modulates biologic responses responsible for leukocyte migration.

Data from *the South Swedish Arthritis Treatment Group* (SSATG) has shown that RA patients treated with etanercept or infliximab had a reduced incidence of first CV event compared to

patients not exposed to anti-TNF (14.0/1000 person-years at risk, 95% CI: 5.7-22.4 vs. 35.4/1000 person-years, 95% CI: 16.5-54.4), but not overall events (41). The analysis of patients from a different register, *the British Society for Rheumatology Biologics Register* (BSRBR) has shown no reduction in the incidence of MI in 8.670 patients treated with anti-TNF when compared to 2.170 patients treated with standard disease modifying anti-rheumatic drugs (DMARDs) (incidence rate ratio: 1.44, 95% CI: 0.56-3.67) (42). However, responders to anti-TNF therapy in the first 6 months had a decrease in MI compared to non-responders (adjusted incidence rate ratio: 0.36, 95% CI: 0.19-0.69), which suggests that inflammation control may be associated with lowering the CV burden in these patients. Data from 10.156 RA patients enrolled in *the Consortium of Rheumatology Researchers of North America RA registry* has shown that patients under anti-TNF therapy had a reduced risk of the primary composite CV endpoint compared with users of non-biological DMARDs (hazards ratio [HR]: 0.39, 95% CI 0.19-0.82). The risk reduction associated with TNF antagonists was also observed for non-fatal CV events (HR: 0.35, 95% CI 0.16-0.74) (43). Another study has compared the composite CV endpoint of MI, stroke or coronary revascularization at 6 months between 11.587 new users of anti-TNF therapy and 8.656 new users of a non-biological DMARDs. Incidence rates per 100 person-years for the composite CV end point were 2.52 (95% CI: 2.12-2.98) for TNF-α blocking agents and 3.05 (95% CI: 2.54-3.65) for DMARDs (44).

The Pilot Study on the Effect of Adalimumab on Vascular Inflammation in Patients with Moderate to Severe Plaque Psoriasis has sought to determine the effect of adalimumab on inflammation of blood vessels. This RCT included 30 patients with moderate-severe psoriasis and a history or multiple risk factors of coronary atherosclerosis. Patients were randomized to receive either adalimumab subcutaneously for 4 months or control non-systemic treatment (topical therapies or phototherapy). Vascular inflammation was measured in the carotid artery and ascending aorta at baseline and week 15 by 18F-fluorodeoxyglucose uptake on positron emission tomography. However, the change in the FDG measurement (target:background ratio) in patients randomized to adalimumab was similar to that in controls (45).

3.1.5. Phospholipase A2 (PLA2) inhibitors

Phospholipase A2 (PLA2) inhibitors are inhibitors of phospholipases, the enzymes that promote inflammation by producing precursors of arachidonic acid from membrane glycerophospholipids (46). There is a soluble (sPLA2) and a lipoprotein-associated form (Lp-PLA2). Circulating levels and enzymatic activity of these two families of PLA2 enzymes have been evaluated as biomarkers of CV risk in population-based studies including subjects with and without established coronary heart disease (47, 48). Darapladib inhibits Lp-PLA2 activity, whereas varespladib is an inhibitor of sPLA2. Three RCTs evaluating the impact of PLA2 inhibitors on CV outcomes are summarized in Table 2. However, these agents failed to demonstrate beneficial effects on the primary composite endpoint of CV death, MI and stroke. Indeed, sPLA2 inhibition with varespladib has been shown to be harmful after ACS (49).

3.1.6. Losmapimod

p38 mitogen-activated protein kinase (MAPK) inhibitors inhibit the p38 MAPK, which is activated in the CV system by a variety of stressors, including oxidized LDL-cholesterol, hypertension, ischemia and volume overload (50). Selective inhibitors of p38 MAPK have been shown to inhibit lipopolysaccharide-stimulated IL-1 and TNF-alpha production in human monocytes and the production of several other cytokines, including IL-6, IL-8, and granulocyte-macrophage colony-stimulating factor (51, 52). Losmapimod is a selective, reversible, competitive inhibitor of p38 MAPK with onset as early as 30 minutes after oral dosing. RCTs evaluating the impact of p38 MAPK inhibitors on CV outcomes are summarized in Table 3.

3.1.7. Salsalate

Salsalate is a prodrug dimer of salicylates marketed for relief of arthritic pain. Anti-inflammatory actions of salicylates mainly focus on their ability to inhibit the proinflammatory kinase I kappa B kinase (IKK) (53), which activates the pro-

Table 2. Summary of three randomized controlled trials that evaluate the impact of phospholipase A2 inhibitors on cardiovascular outcomes

Trial	Study protocol	Median follow-up	Outcomes	Results
The Stabilization Of pLaques usIng Darapladib-Thrombolysis In Myocardial Infarction 52 (SOLID-TIMI-52) trial (139)	- Double-blind, placebo-controlled trial - n= 13.026 patients - Randomization: 160 mg/day darapladib po or placebo po within 30 days of hospitalization with MI	2.5 years	- Primary endpoint: the composite of CV death, MI or urgent coronary revascularization for myocardial ischemia - The composite of CV death, MI or stroke	- in 903 patients in the darapladib group (16.3%) and 910 in the placebo group (15.6%), HR: 1.00 (95% CI, 0.91-1.09), p= 0.93 - in 824 patients in the darapladib group (15.0%) and 838 in the placebo group (15.0%), HR: 0.99 (95% CI, 0.90-1.09), p= 0.78
The Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy (STABILITY) trial (140)	- Double-blind, placebo-controlled trial - n= 15.828 patients (with at least one of the following: previous MI, previous PCI or CABG, or multivessel coronary artery disease - Randomization: 160 mg/day darapladib po (median drug exposure: 3.5 years) or placebo po (median drug exposure: 3.6 years)	3.7 years	- Primary endpoint: the composite of CV death, MI or stroke - Secondary endpoints: the components of the primary endpoint as well as major coronary events (death from coronary heart disease, MI or urgent coronary revascularization for myocardial ischemia) and total coronary events (death from coronary heart disease, MI, hospitalization for unstable angina, or any coronary revascularization)	- in 769 of 7.924 patients (9.7%) in the darapladib group and 819 of 7.904 patients (10.4%) in the placebo group, HR: 0.94, (95% CI, 0.85-1.03), p= 0.20 - no significant between-group differences in the rates of the individual components of the primary endpoint or in all-cause mortality - reduction in the rate of major coronary events: 9.3% in the darapladib group vs. 10.3% in the placebo group, HR: 0.90, (95% CI, 0.82-1.00), p= 0.045 - reduction in the rate of total coronary events: 14.6% in the darapladib group vs. 16.1% in the placebo group, HR: 0.91, (95% CI: 0.84-0.98), p= 0.02
The Evaluation of Safety and Efficacy of Short-term A-002 Treatment in Subjects with Acute Coronary Syndrome (VISTA-16) trial (47)	- Double-blind, placebo-controlled trial - Halted prematurely. Aimed to randomize 5.145 patients within 96 hours of presentation of an acute coronary syndrome. - Randomization: 500 mg/day varespladib po or placebo po for 16 weeks	- Halted prematurely at a pre-specified interim analysis, including 212 primary endpoint events.	- Primary endpoint: the composite of CV mortality, non-fatal MI, nonfatal stroke or unstable angina with evidence of ischemia requiring hospitalization at 16 weeks - Secondary endpoint: the composite of CV mortality, MI and stroke	- in 136 patients (6.1%) in the varespladib group and in 109 patients (5.1%) in the placebo group, HR: 1.25, (95% CI, 0.97-1.61), p= 0.08 - in 107 patients (4.6%) in the varespladib group and in 79 patients (3.8%) in the placebo group, HR: 1.36, (95% CI, 1.02-1.82), p= 0.04

CABG coronary-artery bypass grafting, CI confidence interval, CV cardiovascular, MI myocardial infarction, PCI percutaneous coronary intervention.

inflammatory and pro-atherosclerotic transcription mediator NF-κB (54-55). However, its anti-inflammatory effects independent of NF-κB have also been shown (56-59).

The Targeting Inflammation Using Salsalate in Cardiovascular Disease (TINSAL-CVD) trial is a double-blind, placebo-controlled trial that randomized 257 overweight and obese statin-using patients with established, stable coronary heart disease to salsalate (3.5 g/day) (n= 129) or placebo (n= 128) orally over 30 months. The primary endpoint was progression of noncalcified coronary artery plaque assessed by multidetector computed tomographic angiography. 190 participants (n= 89 in the salsalate group, n=101 in the placebo group) completed the study.

Table 3. Summary of randomized controlled trials that evaluate the impact of p38 mitogen-activated protein kinase inhibitors on cardiovascular outcomes

Trial	Study protocol	Outcomes	Results
A Study to Evaluate the Safety of 12 Weeks of Dosing with GW856553 and Its Effects on Inflammatory Markers, Infarct Size, and Cardiac Function in Subjects with Myocardial Infarction without ST-segment Elevation (SOLSTICE) trial (141)	- Double-blind, placebo-controlled trial - n= 526 NSTEMI patients - Randomization: losmapimod po (7.5 mg or 15 mg loading dose followed by 7.5 mg twice daily) or matching placebo	- Primary endpoints: hsCRP and BNP concentrations at 72 h and 12 weeks and troponin I AUC over 72 h - Secondary inflammation measures: hsCRP concentrations at 14 weeks and IL-6 concentrations at 24 h and 12 weeks. - Secondary infarct size measures: CK-MB AUC and peak troponin I concentration over 72 h or discharge - The primary substudy endpoints: infarct size (% of the left ventricle) on delayed-enhancement MRI and LV ejection fraction at days 3-5 and week 12 - Secondary MRI endpoints: LV end-diastolic and end-systolic volumes at days 3-5 and week 12	- geometric mean hsCRP concentrations at 72 h: lower in the losmapimod group than in the placebo group (64.1 nmol/L, 95% CI 53.0–77.6 vs 110.8 nmol/L, 95% CI: 83.1–147.7, p=0.0009) - hsCRP concentrations at 12 weeks: similar - geometric mean BNP concentrations at 72 h: similar - geometric mean BNP concentrations at 12 weeks: lower in the losmapimod group (37.2 ng/L, 95% CI 32.3–42.9 vs 49.4 ng/L, 38.7–63.0, p=0.04) - reduced geometric mean IL-6 at 72 hours in the losmapimod group (6.6 ng/L, 95% CI: 5.8-7.4 vs. 10.6 ng/L, 95% CI: 8.6-13.1, p< 0.001), but similar in the losmapimod and placebo groups at 12 weeks - CK-MB AUC over 72 h and peak troponin I at 72 h or discharge similar in the losmapimod and placebo groups - similar infarct size in the losmapimod and placebo groups - higher mean LVEF both at days 3-5 (56.86% vs. 52.13%, p= 0.05) and week 12 (60.28% vs. 55.14%, p= 0.039) in the losmapimod group - lower mean LV end-diastolic and end-systolic volumes both at days 3-5 (127.18 mL vs. 147.06 mL, p= 0.039 and 56.13 mL vs. 71.65 mL, p= 0.023) and week 12 (127.74 mL vs. 147.83 mL, p= 0.020 and 51.47 mL vs. 67.99 mL, p= 0.010) in the losmapimod group
LosmApimod To Inhibit p38 MAP Kinase as a TherapeUtic Target and moDify Outcomes After an Acute Coronary syndromE (LATITUDE)-TIMI 60 trial (142)	- Double-blind, placebo-controlled, parallel-group trial - Part A: a leading cohort (n= 3.503) to provide an initial assessment of safety and exploratory efficacy before considering progression to part B Part B: approximately 22.000 patients - Subjects hospitalized with an acute MI and had at least 1 additional predictor of CV risk - Randomization: twice-daily losmapimod (7.5 mg) or matching placebo for 12 weeks	Primary endpoint: the composite of CV death, MI or severe recurrent ischemia requiring urgent coronary revascularization at week 12.	- In part A, the primary endpoint occurred by 12 weeks in 123 patients treated with placebo (7.0%) and 139 patients treated with losmapimod (8.1%) (HR: 1.16; (95% CI, 0.91-1.47), p=<0.24). The on-treatment rates of serious adverse events were 16.0% with losmapimod and 14.2% with placebo. - The results of part A did not justify proceeding to part B
AUC area under the curve, BNP B-type natriuretic peptide, CI confidence interval, CK-MB creatine kinase-myocardial band, CV cardiovascular, hsCRP high-sensitivity C-reactive protein, IL interleukin, LV left ventricular, MI myocardial infarction, MRI magnetic resonance imaging, NSTEMI non-ST segment elevation myocardial infarction.			

Compared with baseline, there was no increase in non-calcified plaque volume in the placebo-treated patients and no difference in change between the salsalate and placebo groups (mean difference: −1 mm^3, 95% CI: −11 to 9 mm^3, p=<0.87). The absence of progression of noncalcified plaque

volume in the placebo group has been suggested to limit interpretation of the trial results (60).

3.1.8. Interleukin-1 receptor antagonists (IL-1Ra)

Interleukin-1 receptor antagonists (IL-1Ra) block the signaling receptor that binds either IL-1 alpha (IL-1α) or beta (IL-1β). There is a wide spectrum for the role of IL-1 in CVD, such as activation of endothelial cells (61) and smooth muscle cell proliferation (62), and IL-6 secretion that in turn promotes thrombosis and limits fibrinolysis (63). Taking the human genetic studies revealing a causal link between IL-6 and coronary heart disease into account (64, 65), IL-1, as an inducer of IL-6, has considerable importance in atherothrombosis pathogenesis.

Anakinra is a short-acting recombinant IL-1Ra that blocks both IL-1α and IL-1β signalling via binding to the IL-1 type I receptor. It is currently approved for use in RA, cryopyrin-associated periodic syndromes and Still disease. *MRC-ILA Heart Study* has been undertaken to examine the effect of anakinra on hsCRP levels in patients with NSTE-ACS (66). In this phase II, double-blinded, placebo-controlled study, 182 patients were randomized within <48 h from onset of chest pain to either daily subcutaneous anakinra or placebo for 14 days. Treatment compliance was 85% at 7 days. The primary endpoint (area under curve [AUC] for CRP over the first 7 days) was lower in the anakinra group (geometric mean ratio= 0.51 mg/L, 95% CI 0.32–0.79, p= 0.003). In the anakinra group, 14-day achieved hsCRP (p< 0.001) and IL-6 levels (p= 0.02) were lower than day 1, however on day 30 (16 days after discontinuation of the treatment) hsCRP levels rose again (IL-1ra group:; 3.50 mg/L [2.65–4.62], placebo group: 2.21 mg/L [1.67–2.92], p= 0.022). Major adverse CV events at day 30 and 3 months were similar but at 1 year there was a significant excess of events in the anakinra group (66). This finding may be supported by a genome-wide association study on genetic variants upstream of IL1RN, which is the gene encoding the IL-1Ra, showing that dual IL-1α/β inhibition provided by IL-1Ra could increase CV risk, probably due to an increase in pro-atherogenic lipid concentrations (67).

Following two pilot studies undertaken in patients with STEMI (68, 69), the extended follow-up data of these 40 patients with STEMI randomized to anakinra 100 mg/day for 14 days or placebo has been published. Endpoints included death, cardiac death, recurrent acute MI, stroke, unstable angina and symptomatic heart failure. At a median follow-up of 28 months, treatment with anakinra was associated with a HR of 1.08 (95% CI 0.31-3.74, p= 0.90) for the combined endpoint of death, recurrent acute MI, unstable angina pectoris or stroke and a HR of 0.16 (95% CI 0.03-0.76, p= 0.008) for death or heart failure. These data have suggested that IL-1 blockade with anakinra for 2 weeks in STEMI patients may prevent new-onset heart failure in long term after STEMI despite neutral effects on recurrent ischemic events (70).

3.1.9. Methotrexate

Methotrexate (MTX) is a dihydrofolate reductase inhibitor, and when given at high doses, it prevents the synthesis of both purine and pyrimidine nucleotides. Low-dose MTX (LDM) has been suggested to exert atheroprotective effects via various mechanisms. These include inhibition of cytokine production (71), induction of inflammatory cell apoptosis (72), increased adenosine release and subsequent agonism of the adenosine A2A receptor, which in turn induces the expression of key proteins in reverse cholesterol transport (73) and reduces expression of adhesion molecules commonly associated with the development of atheroma, such as vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 (74). Direct anti-inflammatory effects of LDM at the level of the vascular endothelium have also been suggested (75).

Low dose methotrexate (which partially acts on the IL-6 pathway as demonstrated by reduction of IL-6 plasma levels) has been shown to reduce CV events in patients with RA in several studies, where HRs ranged between 0.30 and 0.85 (76-78). *The Cardiovascular Inflammation Reduction Trial* (CIRT), which is a double-blind, placebo-controlled study, aimed to randomize a total of 7.000 stable coronary artery disease patients with either type 2 diabetes or metabolic

syndrome to LDM (15-20 mg/week) or placebo (79). The primary trial endpoint was determined initially as the rate of non-fatal MI, non-fatal stroke or CV death. Near the conclusion of the trial, but before unblinding, hospitalization for unstable angina that led to urgent revascularization was added to the primary end point. The trial was ended prematurely in May 2018 after 4.786 patients of the 7.000 patients were enrolled, not due to any apparent safety concerns but to acquisition of enough data to answer the main question of the study. Results of the trial came out recently in the American Heart Association Scientific Sessions 2018. At a median follow-up of 2.3 years, LDM did not lower IL-1β, IL-6 or CRP levels compared to placebo. The final primary end point occurred in 201 patients in the LDM group and in 207 in the placebo group (incidence rate: 4.13 vs. 4.31 per 100 person-years; HR: 0.96; 95% CI: 0.79-1.16). The original primary end point occurred in 170 patients in the methotrexate group and in 167 in the placebo group (incidence rate: 3.46 vs. 3.43 per 100 person-years; HR: 1.01; 95% CI: 0.82-1.25). Despite the low dose, MTX was associated with a higher incidence of non–basal-cell skin cancers than placebo (31 vs. 10, rate ratio: 3.08, p=0.002) (81), as well as elevations in liver-enzyme levels, reductions in leukocyte counts and hematocrit levels.

3.2. Anti-inflammatory drugs with probability to improve cardiovascular outcomes

3.2.1. Colchicine

Colchicine has been used for gout for at least several hundred years. It downregulates inflammation through blocking microtubule spindle formation, disrupting inflammasome function (particularly NLRP3 inflammasome, a cytosolic complex responsible for the production of IL-1β and IL-18) (82), inhibiting cytokine production (82, 83) and impeding neutrophil chemotaxis (84).

Colchicine has been demonstrated to have no effect on angiographic restenosis in patients undergoing balloon angioplasty (85) but reduce the risk of neo-intimal hyperplasia in diabetic patients undergoing coronary stenting (86). Regarding its effects on ischemia/ reperfusion injury, perioperative oral colchicine has been reported to reduce the levels of troponin and creatine kinase- myocardial band in patients undergoing CABG (87).

The potential benefit of long-term colchicine in patients with stable coronary disease was suggested in retrospective studies in patients with familial Mediterranean fever (88) and gout (89), and was demonstrated prospectively in the LoDoCo trial, which tested the same low dose of colchicine used for secondary prevention in gout (90). In LoDoCo trial, which had a prospective, randomized, observer-blinded endpoint design, 532 patients with stable coronary disease were randomized to either colchicine 0.5 mg/day or no colchicine and followed for a median of 3 years. The primary outcome was the composite incidence of ACS, out-of-hospital cardiac arrest, or non-cardioembolic ischemic stroke. The primary analysis was by intention-to-treat. The primary outcome occurred in 15 of 282 patients (5.3%) who received colchicine and 40 of 250 patients (16.0%) assigned to no colchicine (HR: 0.33; 95% CI 0.18-0.59, $p < 0.001$). In a pre-specified secondary on-treatment analysis that excluded 32 patients (11%) assigned to colchicine, who withdrew within 30 days due to intestinal intolerance and a further 7 patients (2%) who did not start treatment, the primary outcome occurred in 4.5% vs. 16.0% (HR: 0.29; 95% CI: 0.15- 0.56, $p< 0.001$) (90).

A meta-analysis of 15 colchicine RCTs (n= 3.431 patients, median treatment 3 months, median follow-up 15 months, 1 mg/day colchicine except for 2 patients) has pointed towards an overall benefit on CV risk reduction, in addition to its ability to reduce pericarditis (85). In 5 trials that included patients with CVD (n= 1.301), colchicine reduced composite CV outcomes (risk ratio: 0.44, 95% CI 0.28-0.69, $p< 0.001$) and showed a trend towards lower all-cause mortality though not reaching statistical significance (risk ratio: 0.50, 95% CI 0.23-1.08, p=0.08) (91). The potential association between colchicine and CV risk and all-cause mortality has also been evaluated in a population-based case-control study that included subjects diagnosed with gout using data from an electronic medical record database linked with Medicare claims (2006–2011) (92). 501 colchicine users were matched with an equal number of non-

users and followed-up at a median of 16.5 months for the primary outcome, a composite of MI, stroke or transient ischemic attack. Incidence rates per 1.000 person-years were 35.6 for users and 81.8 for non-users. After full adjustment, colchicine use was associated with a lower risk (HR 0.51, 95% CI: 0.30–0.88) in the primary CV outcome, as well as a reduction in all-cause mortality (HR 0.27, 95% CI: 0.17–0.43) (92).

Recently, in a prospective, non-randomized study of 80 patients with recent ACS (<1 month), colchicine 0.5 mg/day has been reported to result in a significant reduction of low attenuation plaque volume (LAPV) as assessed by coronary computed tomography angiography (mean 15.9 mm^3 (-40.9%) vs. 6.6 mm^3 (-17.0%); p= 0.008) at a mean follow-up of 12.6 months. This change in LAPV was positively associated to a reduction in hsCRP levels in those patients receiving colchicine (mean 1.10 mg/L (-37.3%) vs. 0.38 mg/L (-14.6%); p < 0.001). There was also a significant linear association (p< 0.001) and strong positive correlation (r= 0.578) between change in LAPV and hsCRP (93).

The promise of low dose colchicine in patients with coronary artery disease is being explored in two trials. The LoDoCo2 study is designed to determine its effects in ~5.000 patients with stable coronary disease (94) and the COLCOT study of similar size, is examining its effects in patients with recent ACS (95).

3.2.2. Tocilizumab

IL-6 signalling serves as a potential target in coronary atherosclerotic disease. A clear association between IL-6 and atherogenesis has been suggested by a meta-analysis of 82 studies published in 2012 (64). Indeed, it has also been proposed to have a causal role in coronary artery disease (65). Furthermore, IL-6 is involved in ischaemia–reperfusion injury (96), and is associated with increased myocardial injury and mortality in ACS patients (97). Tocilizumab (TCZ) is a monoclonal antibody that competitively inhibits the binding of IL-6 to its receptor. It is currently used in patients with RA, giant cell arteritis and cytokine release syndrome. RCTs evaluating the impact of IL-6 signalling inhibitors on CV outcomes are summarized in Table 4.

Evidence suggest that IL-6 has a positive impact on the lipid handling system through upregulation of ATP binding cassette transporter (ABC)A1, a protein involved in macrophage lipid efflux (98) and that IL-6 may inhibit several pro-inflammatory cytokines (99-102). Changes in lipid profile have been reported with TCZ use. TCZ has been shown to increase body weight and elevate triglycerides and cholesterol (LDL-cholesterol, high density lipoprotein [HDL]-cholesterol, total cholesterol, triglycerides, total cholesterol to HDL ratio) (103). A recent proteomic study in 20 female subjects with moderate-severe RA has shown that TCZ changed HDL composition, reducing atherogenic proteins such as serum amyloid A (104). TCZ has also been shown to reduce circulating levels of lipoprotein (Lp) (a), a predictor of vascular events and an independent risk factor for atherosclerotic CVD containing a highly glycosylated apolipoprotein (a), covalently attached to apolipoprotein B-100 (105, 106). After 12 weeks of TCZ treatment, patients with RA had reduced apolipoprotein (a) within LDL particles (104).

Currently, an ongoing phase IV trial named "*Effect of Subcutaneous Actemra on Inflamed Atherosclerotic Plaques in Patients With Rheumatoid Arthritis*" aims to test the hypothesis that subcutaneous TCZ 62 mg/week (in addition to MTX or monotherapy) is effective for reducing plaque inflammation measured by FDG-PET in patients with RA who are inadequate responders to DMARDs and are naive to biologic therapy. Effect of TCZ on arterial plaque inflammation will be examined by measuring the change in FDG uptake in the carotid arteries, coronary arteries and aorta between the baseline and 12-week FDG-PET/MRI (107).

3.3. Anti-inflammatory drugs currently being tested in cardiovascular outcome studies

3.3.1. Canakinumab

Anti-IL-1β inhibitor canakinumab, is approved for use in systemic juvenile idiopathic arthritis and cryopyrin-associated periodic

Table 4. Summary of randomized controlled trials that evaluate the impact of p38 mitogen-activated protein kinase inhibitors on cardiovascular outcomes

Trial	Study protocol	Outcomes	Results
Effect of a single dose of the interleukin-6 receptor antagonist tocilizumab on inflammation and troponin T release in patients with non-ST-elevation myocardial infarction (143)	- Double-blind, placebo-controlled trial - n= 117 patients with NSTEMI (at a median of 2 days after symptom onset) - Randomization: Single dose intravenous 280 mg TCZ (n = 58) or placebo (n = 59), administered prior to coronary angiography	- Primary endpoint: AUC for hsCRP at days 1-3 - Secondary endpoint: AUC for hsTnT at days 1-3	- median AUC for hsCRP was lower in the TCZ group (2.0 mg/L/h vs. 4.2 mg/L/h, p< 0.001) - TCZ-induced reduction in hsCRP was more pronounced in patients treated with percutaneous coronary intervention - median AUC for hsTnT was lower in the TCZ group (159 ng/L/h vs. 234 ng/L/h, p= 0.007)
A Clinical Outcomes Study to Evaluate the Effects of IL-6 Receptor Blockade with Tocilizumab in Comparison with Etanercept on the Rate of Cardiovascular Events in Patients with Moderate to Severe Rheumatoid Arthritis (ENTRACTE) (144)	- An open-label study - RA patients who newly started TCZ or TNF inhibitor; all patients were required to have previously used a different TNF inhibitor: abatacept or tofacitinib. - Randomization: intravenous 8 mg/kg TCZ every 4 weeks (n= 9.218) or subcutaneous 50 mg TNF inhibitor etanercept weekly (n= 18.810), with or without non-biologic DMARD	Primary endpoint: a composite CV endpoint of hospitalization for MI or stroke at a mean study period of 0.9 years	0.52 (95% CI: 0.37-0.71) per 100 person years in the TCZ group and 0.59 (95% CI: 0.47–0.72) per 100 person years for etanercept
The Short-Term Application of Tocilizumab during Myocardial Infarction (STAT-MI) study (145)	- Double-blind, placebo-controlled trial - n= 28 patients admitted with MI - Randomization: a single TCZ dose of 162 mg subcutaneously (n= 12) or placebo (n= 16).	- Primary endpoint: 30-day MACE defined as recurrent MI, development of a new arrhythmia, new septal/valve rupture, evidence of dissection, pericarditis, or tamponade. - Secondary efficacy outcomes: readmission rates within 30 days of receiving the study medication, differences in CRP levels at 30 days as compared to levels before receiving the study medication and changes in QT/corrected QT	- was similar in both groups (9/12 in TCZ group vs. 3/16 in placebo group) - was similar in both groups

AUC area under curve, CRP C-reactive protein, CV cardiovascular, DMARD disease modifying anti-rheumatic drug, hsCRP high-sensitivity C- reactive protein, hsTnT high-sensitivity TrT, MACE major adverse cardiovascular event, MI myocardial infarction, TCZ tocilizumab, TNF tumor necrosis factor.

syndromes. It is a fully human monoclonal antibody that directly and specifically inhibits soluble IL-1β, sparing IL-1α signalling. IL-1β is believed to be a key pro-atherogenic cytokine that stimulates cytokine secretion, activation of endothelial cells (108) and leukocytes (109) and fibroblast proliferation (110, 111). IL-1β levels have been shown to correlate with coronary artery disease severity (112).

Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) was a double-blind, placebo-controlled, event-driven trial of quarterly subcutaneous canakinumab in the prevention of recurrent CV events among stable post-MI patients with elevated hsCRP. It has tested the hypothesis that canakinumab treatment of patients with MI at least one month prior to study entry and elevated hsCRP (≥ 2 mg/L) would prevent recurrent CV events. A total of 10.061 subjects were randomized to either 50 mg, 150 mg, 300 mg canakinumab or placebo. The primary endpoint of the study was time to first occurrence of major

adverse CV event, a composite of CV death, non-fatal MI and non-fatal stroke. At a median follow-up of 3.7 years, the primary outcome occurred in 4.11/100 person-years of the 50 mg group vs. 3.86/100 person-years of the 150 mg group vs. 3.90/100 person-years of the 300 mg group vs. 4.50/100 person-years of the placebo group (p = 0.02 for 150 mg group vs. placebo; other comparisons non-significant). Secondary endpoints included time to first occurrence of the composite CV endpoint consisting of CV death, non-fatal MI, non-fatal stroke and hospitalization for unstable angina requiring unplanned revascularization; time to new onset type 2 diabetes among people with pre-diabetes at randomization; time to occurrence of non-fatal MI, non-fatal stroke or all-cause mortality; and time to all-cause mortality. hsCRP reduction from baseline vs. placebo was 26% greater in the 50 mg group, 37% greater in the 150 mg group and 41% greater in the 300 mg group (p< 0.001 for all comparisons with placebo). Fatal infection or sepsis rate was higher in the canakinumab group (0.31/100 person-year in the combined canakinumab vs. 0.18/100 person-year in the placebo group, p = 0.02). The overall rates of adverse events (AEs), serious AEs and discontinuations due to AEs were similar to placebo across all doses (113). Results of secondary analysis addressing relationship of hsCRP reduction to event reduction showed that among patients who were randomized to canakinumab and achieved on-treatment hsCRP< 2 mg/L, there was a reduction in major adverse CV events (HR 0.75, 95% CI 0.66-0.85, p < 0.0001), compared with no benefit among those with on-treatment hsCRP≥ 2 mg/L (HR 0.90, 95% CI 0.79-1.02, p = 0.11) (114). In a similar way, secondary analysis to investigate CV outcomes in correspondence to the amount of reduction in IL-6 demonstrated that among those who experienced an on-treatment reduction in IL-6 below the median value, there was a 32% reduction in major adverse CV events for canakinumab vs. placebo (p< 0.0001) (115). CANTOS trial is of particular importance to suggest that in patients with a history of MI and elevated hsCRP, 150 mg dose of canakinumab is effective at preventing major adverse CV events over a median of 3.7 years, supporting the inflammation hypothesis of atherosclerosis. This trial validates for the first time that anti-inflammatory therapies may address the residual risk in CVD that exists despite intense lipid-lowering therapy. FDA has recently declared that the modest absolute clinical benefit of canakinumab cannot currently justify its routine use in patients with previous MI unless more data about its efficacy and safety is obtained and cost-effectiveness evaluation supports it (116).

In an ongoing substudy of CANTOS, it is aimed to evaluate the effect of quarterly subcutaneous canakinumab treatment for 24 months compared with placebo on the carotid plaque burden measured by vascular MRI in patients enrolled in CANTOS (117).

3.3.2. Rituximab

Rituximab is an anti-CD20 antibody that is used clinically to treat inflammatory autoimmune diseases and B-lymphocyte cancers. *Rituximab in Patients with Acute ST-elevation Myocardial Infarction* (RITA-MI) study is currently recruiting participants to test its clinical efficacy and safety in acute MI (118).

3.4. Possible future anti-inflammatory drug targets for treatment of atheroclerosis

Possible anti-inflammatory drugs may target NLRP3 inflammasome (119, 120); IL-1; IL-2; IL-18; IL-33; MCP-1 (CCL-2)/ CCR-2 (121-123); CCL5/CXCR4 (124, 125); CD40/ CD40L, tumor necrosis factor receptor- associated factor-6 (TRAF-6) (126-130); MPO (131) and glucagon-like peptide-1 (GLP-1) (132) for treatment of atherosclerosis.

Currently only IL-2 is under assessment in a clinical trial for investigating its safety and efficacy in the setting of coronary artery disease. Recent *in vivo* studies have suggested that low-dose IL-2 can increase the number of regulatory T cells, which are known to induce immune tolerance and preserve immune homeostasis (graft-versus-host disease (133, 134) and in hepatitis C virus-induced vasculitis (135)). Aldesleukin is a human recombinant form of IL-2 that has been used therapeutically in several autoimmune diseases. *Low Dose Interleukin-2 in Patients with Stable Ischemic Heart Disease and*

Acute Coronary Syndromes (LILACS) is a double-blind, placebo-controlled trial will allow assessment of the safety and efficacy of low-dose IL-2 in patients with stable ischaemic heart disease and in ACS patients, both conditions where it is currently contraindicated (136).

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