European Heart Journal Advance Access published February 2, 2016

European Heart Journal
doi:10.1093/eurheartj/ehv759

REVIEW

Novel therapeutic concepts

Inflammatory cytokines in atherosclerosis: current therapeutic approaches

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Received 21 September 2015; revised 25 November 2015; accepted 24 December 2015

The notion of atherosclerosis as a chronic inflammatory disease has intensified research on the role of cytokines and the way these molecules act and interact to initiate and sustain inflammation in the microenvironment of an atherosclerotic plaque. Cytokines are expressed by all types of cells involved in the pathogenesis of atherosclerosis, act on a variety of targets exerting multiple effects, and are largely responsible for the crosstalk among endothelial, smooth muscle cells, leucocytes, and other vascular residing cells. It is now understood that widely used drugs such as statins, aspirin, methotrexate, and colchicine act in an immunomodulatory way that may beneficially affect atherogenesis and/or cardiovascular disease progression. Moreover, advancement in pharmaceutical design has enabled the production of highly specific antibodies against key molecules involved in the perpetuation of the inflammatory cascade, raising hope for advances in the treatment of atherosclerosis. This review describes the actions and effects of these agents, their potential clinical significance, and future prospects.

Keywords Atherosclerosis • Cytokines • Inflammation • Interleukins • Treatment • Antibodies

Introduction

Atherosclerosis is considered to be a chronic inflammatory disease[1] and scientific interest has focussed on the role of cytokines as possible therapeutic agents for atherosclerosis, as cytokines are known to orchestrate the complex inflammatory response within the atherosclerotic plaque. Indeed, cytokines are produced by and act (often synergistically) on almost all cells involved in the pathogenesis of atherosclerosis, participating in all steps of the process, from the early endothelial dysfunction to the late formation and disruption of a vulnerable plaque.[2]

Throughout the years multiple therapeutic approaches in the cardiovascular field, i.e. statins and anti-hypertensive agents, have shown their ability to modify immunological and inflammatory responses in parallel to their principal effects as cholesterol-lowering agents or blood pressure reduction.[3] Moreover, novel agents directed against specific targets in the inflammatory cascade are now also being applied in clinical settings.[4] Interest in this novel therapeutic field is expanding rapidly, as demonstrated by the large number of ongoing clinical trials involving this kind of agents. As our knowledge regarding the role of cytokines in atherogenesis expands, newer approaches come to light and many show promising results in the fight against atherosclerosis. The goal of this review is to describe the actions and effects of anti-inflammatory agents, highlight available data on their clinical significance, and provide further insight regarding their future prospects.

Cytokines and atherosclerosis

In the context of atherosclerosis, cytokines can be classified broadly as pro- or anti-atherogenic, depending on their effects on the formation and progression of the atherosclerotic plaque (*Figure 1*).

Pro-atherogenic cytokines

Pro-atherogenic cytokines such as tumour necrosis factor-α (TNF-α), interleukin (IL)-1, and IL-6 are secreted by macrophages, lymphocytes, natural killer cells, and vascular smooth muscle cells.[2] Tumour necrosis factor-α and IL-1 signalling is mainly mediated by the p38 mitogen-activated protein kinase (p38MAPK)/nuclear factor kappa-light-chain-enhancer of the activated B-cell (NF-κB) pathway,[5] and this affects almost all cells involved in atherogenesis by

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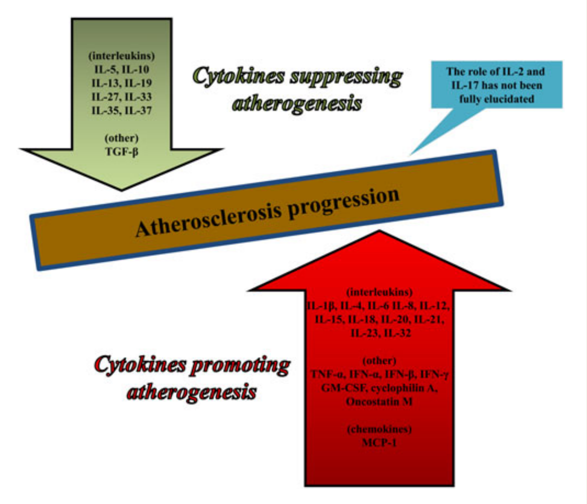

Figure 1 Pro- and anti-atherogenic cytokines. Cytokines can be divided into two groups depending on whether they promote or suppress atherogenesis. Notably, there are also cytokines such as interleukin-2 and interleukin-17 whose exact role in atherogenesis has not been fully elucidated. GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN-α,β,γ, interferon-α, -β, and -γ; IL, interleukin (e.g. IL-1β, interleukin-1β); MCP-1, monocyte chemoattractant protein-1; TGF-β, transforming growth factor-β; TNF-α, tumour necrosis factor-α.

promoting the expression of cytokines, adhesion molecules, and the migration and mitogenesis of vascular smooth muscle and endothelial cells.[2]

The actions of pro-atherogenic cytokines can be better appreciated based on experimental studies with hyperlipidaemic mouse models. For example, TNF-α$^{-/-}$, apolipoprotein E (ApoE)$^{-/-}$ double knockout mice showed decreased atherogenesis, endothelial adhesiveness, and inflammatory markers when compared with controls.[6] Similar conclusions were drawn when ApoE$^{-/-}$ mice were treated with a recombinant soluble TNF-αp55 receptor that acted as decoy to inhibit TNF-α activity.[7] In humans, TNF-α promotes the interaction between circulating leucocytes and the endothelium through up-regulation of adhesion molecules such as vascular cell adhesion molecule 1 (VCAM-1).[8]

Interleukin-6 actions on the other hand are mediated by the IL-6 receptor and a signal transducing protein called gp130, which result in activation of Janus kinase 1 (JAK1) and signal transducer and activator of transcription 1 and 3.[9] In studies with ApoE-deficient mice, recombinant IL-6 injections exacerbated the progression of atherosclerosis.[10] Clinical studies have further revealed that IL-6 serum levels are increased in unstable angina patients and are considered an independent risk factor for coronary artery disease (CAD).[2,11]

Anti-atherogenic cytokines

Contrary to TNF-α, IL-1, and IL-6, several other cytokines appear to act in a protective manner against the formation of atherosclerotic plaques. For example, transforming growth factor-β (TGF-β) is closely associated with T-regulatory (Treg) cells, a distinct subset of T lymphocytes with known immunomodulatory activity. It is known that part of the immunomodulatory activity of Treg cells is mediated by the secretion of anti-inflammatory and atheroprotective cytokines including TGF-β, IL-10, and IL-35.[12] As far as IL-10 is concerned, it appears to possess multiple anti-atherogenic activities including but not limited to down-regulation of TNF-α production[13] and intercellular adhesion molecule 1 (ICAM-1) expression on endothelial cells.[14]

Even though a detailed presentation of the role of all cytokines goes beyond the scope of this review, it is crucial to keep in mind that cytokine actions are extremely complex. This issue represents an enormous challenge when developing and testing novel cytokine-related treatments, a problem that will become more evident as we discuss the potential risks and benefits of newer therapeutic approaches.

The emerging role of cytokine-related treatment

Established clinical approaches in humans

The first steps towards the development of anti-inflammatory treatments in atherosclerosis were accomplished while studying patients with chronic inflammatory and autoimmune diseases, such as psoriasis or rheumatoid arthritis. It has long been known that these conditions are associated with an increased risk of atherosclerosis similar to that of diabetes mellitus[15] and a more severe presentation of adverse cardiovascular events.[16,17] In addition, treatment with methotrexate or biological agents in rheumatoid arthritis protects against atherosclerosis,[18] whereas anti-TNF-α therapy is also associated with a reduced risk for all cardiovascular events.[19]

In general, anti-inflammatory approaches in atherosclerosis can be divided into two major categories. The first includes conventional drugs with broad-based anti-inflammatory properties such as statins, aspirin, methotrexate, and colchicine, which can additionally affect the inflammatory cascade. The second group includes anti-inflammatory drugs designed to inhibit specific mediators and cytokines in the inflammatory pathway (*Table 1* and *Figure 2*). Several ongoing and completed clinical trials testing the effects of these interventions in humans are summarized in *Tables 2* and *3*.

Statins

Statins are traditionally known for their hypolipidaemic effects but have also been shown to act in an immunomodulatory manner. This is believed to be due to decreased production of isoprenoid intermediates that are responsible for the post-translational modification of small GTPases. In other words, statins are able to modify intracellular inflammatory pathways.[3]

Indeed, several statins have been shown to antagonize the effects of inflammatory cytokines (*Figure 3*). For example, simvastatin appears to neutralize the pro-inflammatory and pro-atherogenic actions of TNF-α through inhibition of the TNF-α-induced expression of VCAM-1 and suppression of thrombomodulin and endothelial nitric oxide synthase.[20] Atorvastatin improves vascular nitric oxide bioavailability and decreases the post-glucose loading levels of TNF-α.[21] In addition, statins have been shown to affect the production of cytokines by leucocytes[43] down-regulating the production of pro-inflammatory IL-1 and up-regulating the anti-inflammatory

Table 1 Examples of cytokine-related therapeutic approaches in atherosclerosis

Intervention type	Author	Subjects	Specific type of intervention	Anti-atherogenic effects
I. Clinical studies in humans				
Ia. Broad-based anti-inflammatory agents	Bergh *et al.*[20]	Humans	Simvastatin, rosuvastatin	Suppression of VCAM-1, thrombomodulin, and eNOS expression in endothelial cells
	Tousoulis *et al.*[21]	Humans	Atorvastatin	↓ The post-glucose loading levels of TNF-α
	Dahlman-Ghozlan *et al.*[22]	Human	Methotrexate	↓ E-selectin, VCAM-1, and ICAM-1
	Elango *et al.*[23]	Human	Methotrexate	↓ IL-6 levels
	Nidorf *et al.*[24]	Human	Colchicine	↓CRP in patients with clinically stable CAD
Ib. Blockade of inflammatory cytokines	Tam *et al.*[25]	Humans	Anti-TNF-α antagonists	↓ Progression of subclinical atherosclerosis
	Spinelli *et al.*[26]	Human	Anti-TNF-α antagonists (etanercept or adalimumab)	↓ ADMA levels
	Avgerinou *et al.*[27]	Human	Anti-TNF-α antagonists (adalimumab)	↓ ICAM and improves endothelial function
	Ridker *et al.*[28]	Human	Inhibition of IL-1β (canakinumab)	↓ Glycated haemoglobin, glucose, CRP, IL-6, and fibrinogen levels
	Morton *et al.*[29]	Human	Inhibition of IL-1 by IL-1 receptor antagonist (anakinra)	↓ CRP and IL-6 in patients after myocardial infraction
	Protogerou *et al.*[30]	Human	Inhibition of IL-6 (tocilizumab)	Improved endothelial function and decreased aortic stiffness
II. Animal studies				
IIa. Delivery of anti-inflammatory cytokines	Tian *et al.*[31]	Rats	Adenovirus-mediated IL-19 delivery	↓ Neointimal proliferation in balloon angioplasty-injured rat carotid arteries
	Almer *et al.*[32]	Mice	Liposomes coupled with IL-10	↓ Atherosclerosis
IIb. Targeting intracellular signalling	Yoshimura *et al.*[33]	Rats	*In vivo* transfection with an oligonucleotide that acts as decoy binding site for NF-κB	↓ Intimal hyperplasia after balloon angioplasty
IIc. Inducing T-regulatory cells	Steffens *et al.*[34]	Mice	Anti-CD3 antibodies	↓ Atherogenesis ↑ TGF-β and Treg induction
	Dietrich *et al.*[35]	Mice	Local IL-2 delivery	↓ Atherogenesis ↑ Treg expansion

↑, increased; ↓, decreased; ADMA, asymmetric dimethyl arginine; CAD, coronary artery disease; CD3, cluster of differentiation 3; CRP, C-reactive protein; eNOS, endothelial nitric oxide synthase; ICAM-1, intercellular adhesion molecule 1; IL, interleukin; LDL, low-density lipoprotein; NF-κB, nuclear factor κB; NO, nitric oxide; TGF-β, transformation growth factor-β; TIMP, tissue inhibitor of matrix metalloproteinases; TNF-α, tumour necrosis factor-α; VCAM-1, vascular cell adhesion molecule 1.

cytokine IL-10.[44,45] Interestingly, recent studies have shown that the reduction of C-reactive protein (CRP) levels with statin treatment is independent from the reduction in LDL cholesterol levels.[46]

It is therefore generally accepted that statins exert pleiotropic actions and affect a variety of parameters associated with atherosclerosis. Early administration of low-dose atorvastatin in patients with ST-elevation myocardial infarction (SEMI) can even improve the clinical outcome by down-regulating endothelial activation and inflammation.[47] Recently, the PRATO-ACS (Protective Effect of Rosuvastatin and Antiplatelet Therapy on Contrast-Induced Acute Kidney Injury and Myocardial Damage in ACS Patients) has reported the beneficial effects of rosuvastatin in contrast-induced nephropathy caused in subjects with ST elevation myocardial infarction.[48] Since inflammation promotes endothelial dysfunction and vulnerability of kidney vessels, this action may be mediated by anti-inflammatory effects of statins, as it was recently proposed.[49]

In regard to clinical applicability, several studies have revealed that an inflammatory-based treatment approach may be useful. In the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), a 5-year randomized trial that included 5742 subjects without CAD, it was shown that lovastatin prevented ACS especially in the high CRP group despite a favourable lipid profile. Indeed, lovastatin reduced CRP levels by 15%, and it was effective to reduce cardiovascular events even in patients with favourable lipid profile at baseline but with increased CRP levels. Importantly, it was found that the number needed to treat to prevent one event in this category of patients with CRP levels >0.16 mg/dL was 48.[50] In line with this evidence, the JUPITER trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin)—one of the most important large-scale randomized control studies, which included 17 802 apparently healthy individuals randomized to either rosuvastatin 20 mg/day or placebo with follow-up for a

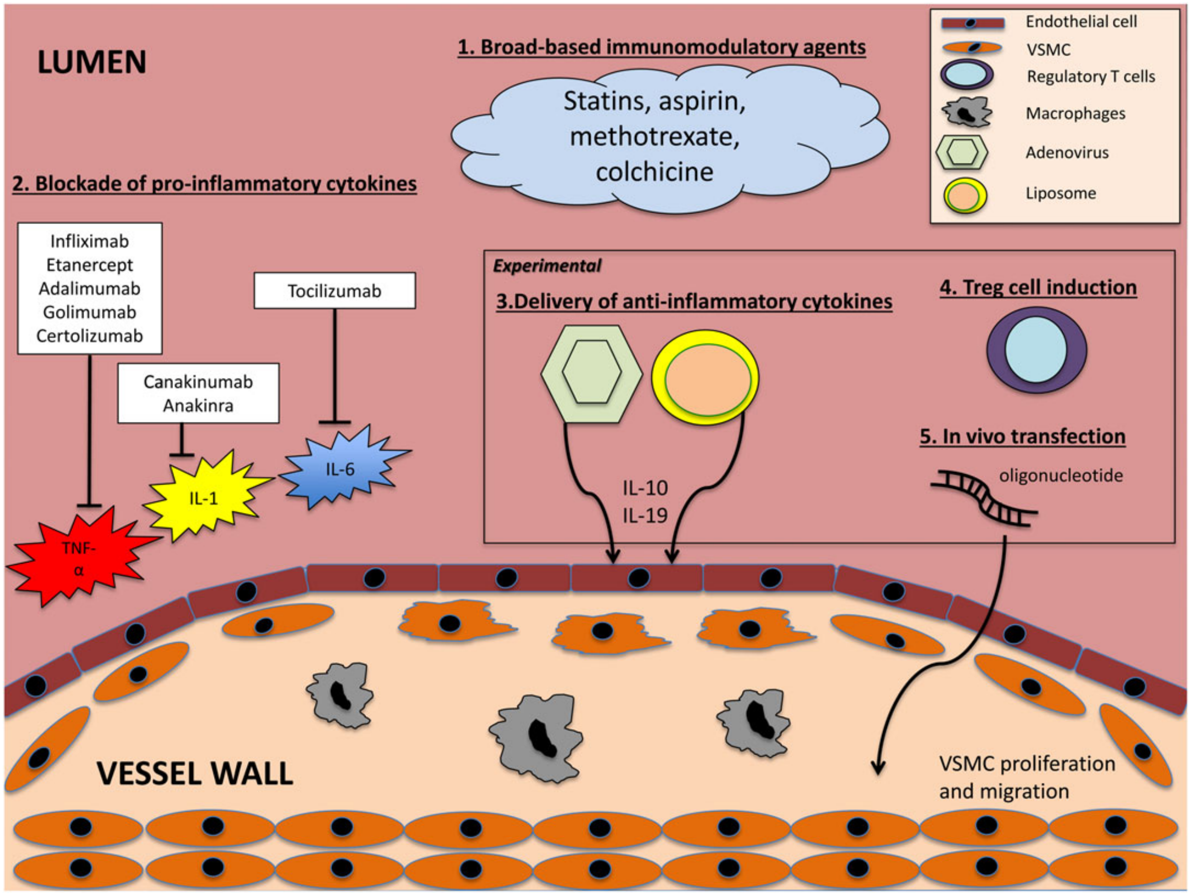

Figure 2 Cytokine-related therapeutic approaches in atherosclerosis. In the context of atherosclerosis, several methods have been studied to modify the inflammatory cascade. 1. Broad-based immunomodulatory agents. 2. Blockade of pro-inflammatory cytokines. 3. Delivery of anti-inflammatory cytokines with adenovirus vectors or liposomes. 4. Induction of regulatory T cells. 5. *In vivo* transfection with oligonucleotides. IL, interleukin; TNF-α, tumour necrosis factor-α; VSMC, vascular smooth muscle cell.

median of 1.9 years—demonstrated that in subjects with CRP levels >2 mg/L, even with low LDL cholesterol levels, rosuvastatin treatment can decrease adverse cardiovascular events.[51] Notably, the greatest benefit is observed in patients in whom rosuvastatin treatment decreases not only LDL levels <70 mg/dL but also CRP levels <1 mg/L (79% reduction in the event rate compared with subjects in the placebo arm or 0.24 events per 100 persons compared with 1.11 events per 100 persons, respectively).[52] This is in accordance with several studies which show that the beneficial effects of statins cannot and should not be solely attributed to their lipid-lowering effects but are also related to their ability to dampen inflammation or improve endothelial[53] and arterial wall function[54] through lipid-independent mechanisms.[3]

Aspirin

Aspirin inhibits cyclooxygenase irreversibly and suppresses the production of prostaglandins and thromboxanes.[55] Therefore, it acts not only as an antiplatelet agent but also as an anti-inflammatory one. In murine models of atherosclerosis, low-dose aspirin improves vascular inflammation and plaque stability.[56] Recent data in ApoE-deficient mice support the hypothesis that aspirin can also reduce fractalkine levels (fractalkine acts both as a chemokine and as an adhesion molecule) and improve the severity of atherosclerotic lesions.[57] Recently, it was also documented in humans that low-dose aspirin treatment reduces chemerin (a peptide chemoattractant for macrophages and an adipokine-regulating adipocyte differentiation and metabolism) secretion by adipocytes through reduction of pro-inflammatory cytokine secretion by macrophages.[58] Aspirin further protects human endothelial function in the presence of inflammation[59] and decreases the plasma levels of several inflammatory cytokines and markers such as IL-6, CRP, and monocyte colony-stimulating factor (M-CSF) in patients with stable angina.[60] Interestingly, the use of aspirin as a primary prevention therapy is associated with a reduction in the development of myocardial infarction, which appears to be directly related to CRP levels, raising the possibility that the anti-inflammatory properties of aspirin may be as important as its anti-thrombotic effects.[61] Moreover, in primary prevention, aspirin can improve arterial stiffness even after 2 weeks of low dose (160 mg/day).[62] However, we have to notice that the exact anti-atherosclerotic effect of aspirin cannot be determined

Table 2 **Ongoing anti-inflammatory clinical trials in atherosclerosis**

Drug	Target	NCT trial number and name	Size	Status	Estimated completion date	Study population	Primary endpoint
Canakinumab	IL-1	NCT01327846 (CANTOS)	10 000	Not recruiting	April 2017	Patients with MI and elevated hsCRP	Time to first occurrence of MACE
Anakinra	IL-1Ra	NCT01950299 (VCU-ART3)	99	Recruiting	September 2017	STEMI patients	CRP levels during the first 14 days period after STEMI (secondary: new heart failure after 12 months)
Adalimumab	TNF-α	NCT01722214	106	Not recruiting	February 2016	Psoriasis patients	Change in ascending aorta inflammation as assessed with FDG-PET after 16 weeks of treatment
		NCT01954381	60	Completed, results not published	July 2015	RA patients	CF-PWV, central aortic pulse pressure and FMD after 24 weeks of treatment
Etanercept		NCT01522742	50	Recruiting	January 2016	Psoriasis patients starting etanercept and matched controls	Change in aortic-coronary inflammation status as assessed with FDG-PET after 3 months of treatment
Tocilizumab	IL-6	NCT01491074	120	Completed, results not published	April 2014	Post-NSTEMI patients	hsCRP levels during 56 h follow-up (secondary: infarct size, hsTrT, left ventricle size and function, endothelial function and coronary flow reserve)
		NCT02419937	125	Recruiting	May 2017	NSTEMI, STEMI patients with drug or placebo given within 24 h	MACE within 30 days
		NCT01331837 (Entracte)	3080	Not recruiting	October 2016	Rheumatoid arthritis patients treated with tocilizumab vs. etanercept	Time to occurrence of primary MACE
Methotrexate	Multiple	NCT01594333 (CIRT)	7000	Recruiting	December 2018	Stable CAD patients with T2DM or MetS	MACE rate
		NCT02576067 (CIRT)	216	Not open yet	May 2019	Patients with prior MI or angiographically demonstrated multi-vessel CAD	Change in arterial inflammation as assessed with FDG-PET at 8 months
		NCT01741558 (TETHYS)	80	Unknown	August 2014	STEMI patients	Reduction of infarct size
Methotrexate and colchicine	Multiple	NCT02366091	120	Recruiting	November 2018	Stable CAD patients with hsCRP > 2 mg/L	Coronary segment endothelial function at 8 weeks
Colchicine	Multiple	NCT02551094	4500	Not open yet	March 2019	Patients with recent (<30 days) acute MI	MACE events
		NCT01709981	400	Recruiting	April 2017	Patients referred for PCI	Post-PCI IL-6 levels (secondary: 30 days MACE)
		NCT02162303	106	Not recruiting	December 2015	Patients with atherosclerotic vascular disease	Change in inflammation of the ascending aorta as assessed with FDG-PET at 6 months

CANTOS, Canakinumab Anti-inflammatory Thrombosis Outcomes Study; CAD, coronary artery disease; CF-PWV, carotid-femoral pulse wave velocity; CIRT, Cardiovascular Inflammation Reduction Trial; CK, creatinine kinase; FDG-PET, 18-fluorodeoxyglucose positron emission tomography; FMD, flow-mediated dilatation; hsCRP, high-sensitivity C-reactive protein; hsTrP, high-sensitivity troponin T; IL-1Ra, interleukin-1 receptor antagonist; MACE, major adverse cardiovascular event; MetS, metabolic syndrome; (N)STEMI, (non)-ST-segment elevation myocardial infarction; NCT, national clinical trial; PCI, percutaneous coronary intervention; T2DM, type 2 diabetes mellitus; TETHYS, The Effects of mETHotrexate Therapy on ST Segment Elevation Myocardial InfarctionS; TNF-α, tumour necrosis factor-α; VCU-ART3, Virginia Commonwealth University Anakinra Remodeling Trial.

as reports support the notion that aspirin can reduce hypertriglyceridaemia, cholesterol, and free fatty acid production[63] but also increases lipid peroxidation.[64] Indeed, the exact benefit of aspirin in chronic CAD has recently been questioned by the results of the CONFIRM study (Coronary CT Angiography EvaluatioN for Clinical Outcomes study). In this multicentre international registry, 5712

Table 3 **Completed anti-inflammatory clinical trials in atherosclerosis**

Drug	Target	Author	Size (treated/ controls)	Study population	Results
Golimumab	TNF-α	Tam *et al.*[25]	41 (20/21)	Ankylosing spondylitis patients	Placebo group showed an increase in arterial stiffness (PWV) over 6 months when compared with the group treated with golimumab
Anakinra	IL-1Ra	Morton *et al.*[36] MRC-ILA-HEART study	182 (91/91)	NSTEMI patients	IL-1Ra treatment reduces inflammatory markers at 14 days post-NSTEMI. However, MACE at 30 days and 3 months were similar and at 1 year greater in the IL-1Ra than the control group
Anakinra	IL-1Ra	Ikonomidis *et al.*[37]	80 (cross-over)	Rheumatoid arthritis patients with and without CAD	Anakinra leads to a greater improvement in endothelial, coronary, and aortic function in RA patients with CAD than non-CAD
Anakinra	IL-1Ra	Abbate *et al.*[38] VCU-ART2 (Virginia Commonwealth University Anakinra Remodeling Trial)	40 (20/20)	STEMI patients	Anakinra for 2 weeks post-STEMI has neutral effect on recurrent ischaemic events but may prevent new-onset heart failure or death in the long term after STEMI period
Colchicine	Multiple	Nidorf *et al.*[39] LoDoCo trial (low-dose colchicine trial)	532 (282/250)	Patients with stable CAD	Colchicine 0.5 mg/day in addition to standard therapy prevents CV events
Methotrexate	Multiple	Choi *et al.*[40]	1240 (588/652)	Rheumatoid arthritis patients	Methotrexate use is associated with lower all-cause and CV mortality risk
Corticosteroids	Multiple	Giugliano *et al.*[41]	2646 (meta-analysis)	Acute MI patients	Corticosteroid therapy in the acute setting after MI shows no significant mortality benefit in randomized control trials
Ustekinumab/ briakinumab	IL-12/23	Tzellos *et al.*[42]	4653 (3179/1474)	Psoriasis patients	Patients on anti-IL-12/23 treatment had a significantly higher risk of MACEs compared with placebo

CAD, coronary artery disease; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; IL-1Ra, interleukin-1 receptor antagonist; MACE, major adverse cardiovascular event; MI, myocardial infarction; NNT, number needed to treat; OR, odds ratio; PWV, pulse wave velocity; RA, rheumatoid arthritis; (N)STEMI, (non-)ST-segment elevation myocardial infarction; TNF-α, tumour necrosis factor-α.

individuals with normal coronary arteries and 4706 individuals with non-obstructive CAD were followed up for a median of 27.2 months, and aspirin use, contrary to statins, was not associated with mortality benefit in patients with non-obstructive CAD irrespective of the status of the plaque.[65] Similarly, data from the prevention of progression of arterial disease and diabetes (POPADAD) trial have shown that even in patients with diabetes mellitus and asymptomatic peripheral arterial disease aspirin did not reduce the rate of cardiovascular events.[66] Moreover, in 1884 recipients of low-dose aspirin with chronic kidney disease paired with 1884 non-recipients, the incidence of atherosclerotic events was significantly higher in the aspirin users.[67] It would be interesting to study the effects of aspirin in groups with elevated vs. low levels of circulating inflammatory markers.

Methotrexate

Methotrexate is an antimetabolite drug that acts by inhibiting the metabolism of folic acid. Its anti-inflammatory actions, however, may also be attributed to an increase in adenosine levels.[68] In fact, methotrexate treatment reduces the size of experimentally induced myocardial infarction probably via adenosine release which not only reduces inflammation but also improves coronary flow in the culprit lesion.[69] In addition, previous studies have shown that methotrexate can further modulate the expression of ICAM-1, E-selectin, VCAM-1,[22] and IL-6.[23]

Interestingly, studies have proved that low-dose methotrexate can decrease the cardiovascular risk of patients with chronic inflammatory disease. In patients with rheumatoid arthritis, methotrexate may provide a substantial survival benefit, largely by reducing cardiovascular mortality.[40] Similar results were also described by van Halm *et al.* in a case–control study.[70] However, some studies did not

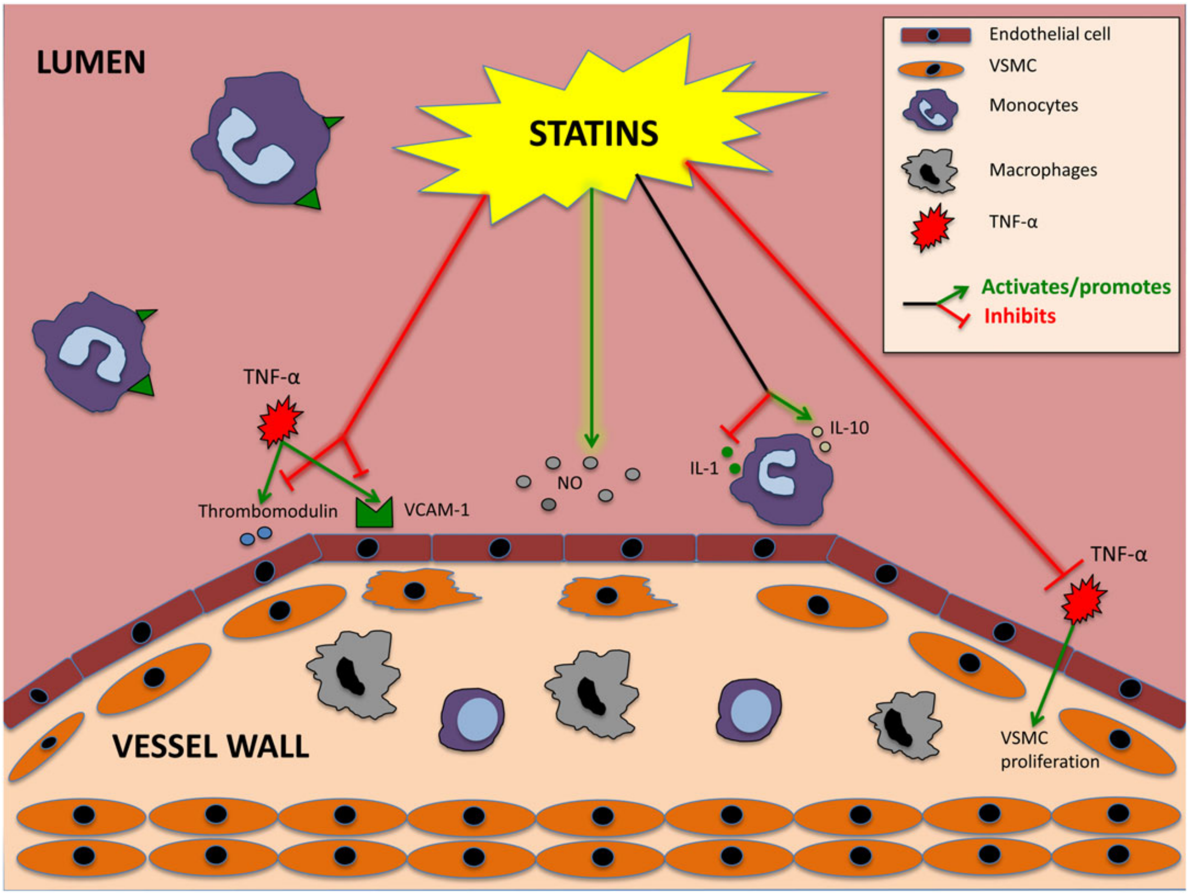

Figure 3 Examples of cytokine-related statin effects in the microenvironment of an atherosclerotic plaque. Statins have been shown to antagonize the effects of inflammatory cytokines. For example, simvastatin neutralizes the pro-atherogenic actions of tumour necrosis factor-α through inhibition of the tumour necrosis factor-α-induced expression of vascular cell adhesion molecule 1 and suppression of thrombomodulin, whereas atorvastatin improves vascular nitric oxide bioavailability. Simvastatin can potently down-regulate the production of known pro-inflammatory cytokines such as interleukin-1 while also up-regulating the expression of anti-inflammatory cytokines such as interleukin-10. Finally, simvastatin is also able to counteract the combined pro-proliferative effects of tumour necrosis factor-α and interleukin-18 on aortic smooth muscle cells. IL, interleukin; TNF-α, tumour necrosis factor-α; VCAM-1, vascular cell adhesion molecule 1; VSMC, vascular smooth muscle cell.

confirm the protective role of methotrexate in the incidence of cardiovascular events in rheumatoid arthritis patients.[71] Therefore, further studies have now been designed to test this hypothesis. For example, the Cardiovascular Inflammation Reduction Trial (CIRT) aims to enrol 7000 individual to test the role of methotrexate in the medical management of stable CAD patients with persistent elevation of high-sensitivity CRP,[72] while the TETHYS trial aims to evaluate its value in reducing infarct size when administered within the first 6 h of admission for ST-elevation myocardial infarction.[73] Furthermore, a recently announced CIRT sub-study aims to evaluate the effects of methotrexate in arterial inflammation (as seen on PET-CT scanning) in patients with prior MI or multi-vessel CAD (NCT02576067). It is difficult, however, to definitely conclude that the beneficial effect of methotrexate in cardiovascular incidence is solely due to its anti-inflammatory properties. Studies have recently documented that methotrexate modifies lipid levels increasing both HDL and LDL cholesterol and affects macrophage cholesterol handling opposing foam cell formation.[74]

Colchicine

Evidence for the ability of colchicine to modify cytokine levels is based on patients with familiar Mediterranean fever. In this condition, modification of the inflammatory cascade with colchicine not only reduces symptoms of the disease but also decreases the risk for ischaemic heart disease.[75] In addition, a retrospective cross-sectional study concluded that long-term treatment of gout with low-dose colchicine decreased not only CRP levels but also the incidence of myocardial infarction.[76] Furthermore, Nidorf and Thompson showed that colchicine, in addition to aspirin and high-dose atorvastatin treatment, can significantly lower high-sensitivity CRP in patients with stable CAD.[24] Finally, in the Low-Dose Colchicine (LoDoCo) trial—a prospective, randomized, observer blinded endpoint design study of 532 subject—addition of colchicine 0.5 mg/day to aspirin and/or clopidogrel and statins in CAD patients resulted in lower incidence (5.3%) of acute coronary syndrome, out-of-hospital cardiac arrest, or non-cardioembolic ischaemic stroke vs. the placebo group (16%).[39] Currently, several ongoing trials aim to evaluate the potential benefit of colchicine in improving cardiovascular indices and prognosis in patients with CAD as summarized in *Tables 2* and *3*.

Corticosteroids

A few reports that examined intermediate atherosclerotic markers such as arterial stiffness as assessed by pulse wave velocity have shown that the use of corticosteroids can act beneficially in some chronic inflammatory disorders such as polymyalgia rheumatic.[77] However, corticosteroids in the setting of acute myocardial infarction have failed to demonstrate significant mortality benefit, as shown in one meta-analysis of randomized control trials.[41] In addition, long-term use of corticosteroids in rheumatoid arthritis patients is associated with a significantly higher incidence of acute myocardial infarction.[78]

Specific target-based anti-inflammatory treatment

Blockade of pro-inflammatory and delivery of anti-inflammatory cytokines

As described in the previous section, the prophylactic effect of broad-based anti-inflammatory treatments is currently limited to statins and aspirin. Nevertheless, especially for aspirin, its value in primary prevention is equivocal while for methotrexate, colchicine, and corticosteroids results are not definitive. Therefore, several novel strategies have been developed to more specifically antagonize the actions of pro-inflammatory cytokines, the most important being the administration of soluble decoy receptors, direct receptor antagonists (e.g. endogenous IL-1Ra), and monoclonal antibodies (*Table 4*).

Anti-tumour necrosis factor-α treatment

Several anti-TNF agents (infliximab, etanercept, adalimumab, golimumab, and certolizumab) have been introduced recently against inflammatory and autoimmune diseases.[85]

Interestingly, spare pre-clinical data have shown that anti-TNF treatment can favourably affect atherosclerosis. Recently, in a model that reproduced *in vivo* interactions between leucocytes and endothelial cells, anti-TNF treatment diminished leucocyte-endothelial interactions induced by inflammatory stimuli.[86] It is currently known that treatment with anti-TNF agents can improve endothelial function and arterial wall properties in patients with autoimmune diseases, such as psoriasis.[27] Moreover, it has been reported that inhibition of TNF-α in rheumatoid arthritis can increase circulating

Table 4 **Targeting pro-inflammatory cytokines for atherosclerosis treatment**

Pro-inflammatory cytokines	Role in atherosclerosis	Possible treatments
TNF-α	Promotes atherosclerosis, adhesion of leucocytes to endothelium and impairs glucose tolerance	*Anti-TNF agents (etanercept, adalimumab, golimumab, and infliximab)*: • Improve endothelial function and arterial wall properties[27] • Restore asymmetric dimethyl arginine serum levels in patients with rheumatoid arthritis[26] • Increase circulating endothelial progenitor cells[79] • Improve insulin resistance[80] • Improve lipid profile[81] • Enhance plaquestability[82]
IL-1β	Promotes atherosclerosis and is associated with the extent of atherosclerotic lesions	*Canakinumab* (monoclonal human IL-1β antibody) • Reduces glycated haemoglobin, glucose, CRP, IL-6, and fibrinogen levels in stable diabetes mellitus patients[28] • CANTOS is in progress studying whether canakinumab can reduce heart attacks, strokes, and cardiovascular deaths in high-risk patients[83] *Anakinra* (a non-glycosylated version of human IL-1Ra) • Reduces IL-6 and endothelin-1 levels with a parallel increase in flow-mediated dilation, coronary flow reserve, and aortic distensibility[84] • But: MRC-ILA-HEART study in myocardial infraction patients: at the end of the 1-year follow-up rate of adverse events turns out to be higher in the treatment group[29]
IL-6	Exacerbates the progression of atherosclerosis, promotes inflammation	*Tocilizumab* (a monoclonal antibody that blocks IL-6 receptor) • Improves endothelial function and decreases aortic stiffness[30] • The effect of tocilizumab in patients with non-ST elevation myocardial infraction is tested in phase II trials (e.g. NCT01491074)
Anti-inflammatory cytokines	Role in atherosclerosis	Possible treatments
IL-19	Promotes T helper 2 cell response and dampens inflammation	Adenovirus-mediated IL-19 delivery in rat models decreases neointimal proliferation after balloon angioplasty[31]
IL-10	Suppresses immune and inflammatory responses	Liposomes coupled with IL-10 in mice attenuate atherosclerosis[32]

TNF-α, tumour necrosis factor-α; IL-1β, interleukin-1β; CRP, C-reactive protein; IL-6, interleukin-6; MCP-1, monocyte chemoattractant protein; eNOS, endothelial nitric oxide synthase; IL-19, interleukin-19; IL-10, interleukin-10.

endothelial progenitor cells concurrently with a proportional decrease of disease activity[79] and decrease serum asymmetric dimethyl arginine levels.[26]

Clinical studies have revealed that anti-TNF-α therapies in patients with ankylosing spondylitis improve subclinical atherosclerosis and aortic stiffness when compared with placebo controls.[87] A meta-analysis published in 2011 showed that anti-TNF-α treatment in rheumatoid arthritis is associated with a lower risk for all cardiovascular events.[19] Nevertheless, we have to take into consideration that studies with these agents in patients with chronic heart failure have failed to improve patient outcome.[88] Unfortunately, there are currently no ongoing trials evaluating the exact health or mortality benefit of anti-TNF-α agents in a large cohort of healthy or CAD patients and studies so far have been limited to rheumatological patients.

Interleukin-1β inhibition

Canakinumab is a monoclonal human antibody that binds to human IL-1β, blocking its interaction with its receptor. Interleukin-1β has so far been used in the treatment of rare hereditary IL-1β-driven disorders, such as Muckle–Wells syndrome. Treatment of such cryopyrin-associated periodic syndromes and rheumatoid arthritis with canakinumab produces a rapid and sustained inhibition of the acute phase response resulting in a substantial reduction in CRP levels.[89,90]

Previously, studies have shown that IL-1-deficient mice show decreased atherosclerosis.[91] Moreover, in an atherosclerotic mouse model, inhibition of IL-1 orients tissue macrophages to an anti-inflammatory phenotype and atherosclerotic lesions are therefore reduced.[92]

Furthermore, canakinumab has been shown to effectively reduce glycated haemoglobin, glucose, CRP, IL-6, and fibrinogen levels in male patients with well-controlled diabetes mellitus and high cardiovascular risk.[28] However, a definite cardiovascular event or survival benefit has not been demonstrated yet but is currently investigated by the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS), which focusses on post-myocardial patients with persistent elevation of high-sensitivity CRP.[83]

Another approach used to modify IL-1 activity is by enhancing the activity of IL-1Ra, which in turn negatively regulates IL-1 signalling. For example, anakinra, a human IL-1Ra, can block the biological activity of IL-1 in rheumatoid arthritis patients by competitively inhibiting the binding of IL-1 to the IL-1-type receptor and also reduces IL-6 and endothelin-1 levels with a parallel increase in flow-mediated dilation, coronary flow reserve, and aortic dispensability.[84] In the MRC-ILA-HEART study, subcutaneous IL-1Ra administration for 14 days in non-SEMI (NSTEMI) patients resulted in lower CRP and IL-6 levels at the end of the treatment; however, a higher rate of MACE was observed after the treatment (HR 3.39, 95% CI 1.10–10.4, $P = 0.023$).[29] The VCU-ART 2 (Virginia Commonwealth University Anakinra Remodeling Trial) study showed that anakinra given for 2 weeks post-STEMI has a neutral effect on recurrent ischaemic events but may lower new heart failure incidence or mortality at 1 year (HR 0.16, 95% CI 0.03–0.76, $P = 0.008$),[38] a finding that will be further evaluated by the more recent VCU-ART-3 trial (NCT01950299).

Intereleukin-6 inhibition

Potential strategies using anti-IL-6 therapies have not been as widely tested as in the case of TNF-α or IL-1. Tocilizumab is a monoclonal antibody that blocks both membrane-bound and circulating IL-6 receptor. Randomized trials in patients with rheumatoid arthritis have shown that tocilizumab increases total, HDL, and LDL cholesterol and triglyceride levels.[93] Moreover, it results in improved endothelial function and decreased aortic stiffness.[30] Currently, several ongoing studies investigate the role of tocilizumabin in NSEMI (NCT01491074, Phase 2 trial) and in comparison to etanercept in patients with rheumatoid arthritis and cardiovascular risk factors (NCT01331837, Phase 4 trial).

Anti-interleukin-12/23p40 and anti-interleukin-17 agents

Monoclonal antibodies that are targeted against the shared p40 subunit of IL-12 and IL-23 have recently been introduced in the treatment of psoriasis. These cytokines mediate the function of Th17 cells, a distinct subset of T cells that have been identified as a pro-atherogenic group of leucocytes within the atherosclerotic plaque.[94] Despite these pro-atherogenic effects, a recent meta-analysis concluded that treatment with such agents (ustekinumab and briakinumab) may even increase the risk for major adverse cardiovascular events when compared with placebo.[42] Brodalumab (an IL-17 receptor A antagonist), ixekizumab, and secukinumab (IL-17A antagonists), also used in psoriasis, are potential antagonists of atherosclerosis, given the pro-inflammatory nature of IL-17.[95] Interleukin-17 inhibition attenuates atherosclerosis in animals,[96] but clinical studies in humans are not available to date.

Anti-P-selectin agents

P-selectin, a cell adhesion molecule that organizes endothelial cell and platelet interactions, plays a role in leucocyte activation, formation of thrombi, and neointimal formation. The SELECT ACS study in 544 patients with NSTEMI showed that inclacumab—a recombinant monoclonal antibody against P-selectin—decreases the myocardial damage.[97] However, the SELECT CABG study, a Phase 2 trial, which is planning to test the efficacy of inclacumab in saphenous vein graft disease, has not yet been published.

Targeting post-ischaemic reperfusion injury

Re-establishment of coronary perfusion after an acute ischaemic event causes the so-called reperfusion injury, which is attributed to oxidative stress, accumulation of reactive oxygen species, and ultimately diminished mitochondrial ability to produce energy in the form of ATP.[98] Bendavia is an intravenously administered mitochondrial targeting peptide that has been shown to reduce myocardial infarct size and attenuate coronary no-reflow in experimental models when given before reperfusion.[99] Therefore, the EMBRACE STEMI study enrolled 300 patients with first anterior STEMI to test whether Bendavia is superior to placebo for the reduction of myocardial infarction size.[100] The first preliminary reports of this study have recently been announced and have shown that Bendavia infusion is safe although it did not achieve a significant reduction in the infarct size. However, future trials are planning to test if higher doses can be beneficial in patients with systolic heart failure (NCT02388464 and NCT02388529).

Experimental approaches in animal models

Future directions concerning the targeted modification of the inflammatory cascade can be derived from experimental models.

However, the extrapolation of animal outcomes to human patients is not straightforward as significant differences exist in the pathophysiology of atherosclerosis between different species.[101]

Delivery of anti-inflammatory cytokines

Delivery of anti-inflammatory cytokines for therapeutic purposes has been attempted in experimental animal models with promising results. It is now possible to locally deliver anti-inflammatory cytokines to specific atherosclerosis sites via adenoviruses. Such is the case of IL-19 which is an anti-inflammatory cytokine that promotes the Th2 anti-inflammatory cell phenotype.[31] Furthermore, a recently developed method exploits stealth liposomes that are coupled with IL-10 and act to specifically and reliably transfer the atheroprotective cytokine to the desired site in atherosclerotic plaques.[32] It is obvious that these methods may have unknown risks, and studies on safety and efficacy are warranted before they can be applied in humans.

Targeting intracellular signalling

Certain studies have succeeded in limiting atherosclerosis by manipulating intracellular signalling in animal models. For example, an oligonucleotide that acted as a decoy binding site for NF-κB succeeded in preventing intimal hyperplasia following balloon angioplasty.[33] An adenovirus-expressed suppressor of cytokine signalling 3 has also been successful in limiting inflammation though not in a model of atherosclerosis,[102] and similar efforts have been done trying to block JAK3 signalling.[103] However, given the ubiquitous nature of these molecules (especially NF-κB), it is important to guarantee that treatment does not interfere with normal processes in order to minimize adverse effects.

Promoting the actions of T-regulatory cells

Administration of anti-CD3 antibodies in mice with progressed atherosclerosis managed to suppress atherogenesis and was linked to up-regulated TGF-β and Foxp3 expression in lymphoid organs.[34,104] In addition, oral calcitriol administration to hyperlipidaemic mice blocked atherosclerosis possibly by inducing the expansion of T-regulatory cells,[105] whereas local delivery of IL-2 suppressed atherogenesis in already existing lesions through the same mechanism.[35]

Unanswered questions and future directions

The immune and inflammatory networks are complex and not fully understood at present, and even though our knowledge regarding the basic mechanisms of action of cytokines in humans is constantly expanding, there are still no absolute data on the benefit of targeted anti-inflammatory therapy in atherosclerosis. Notably, as demonstrated by the MRC-ILA-HEART study[36] and other direct and indirect anti-inflammatory strategies such as with anti-IL-12/23 antibodies,[42] corticosteroids,[41] aspirin[65] and COX-2 inhibitors,[106] targeted and broad-based anti-inflammatory treatments may even lead to an increased rate of adverse cardiovascular events in some cases. Indeed, our experience shows that several drugs with promising results in animals fail to demonstrate similar efficacy in humans, such as Bendavia in the recent EMBRACE STEMI trial.[100]

Nevertheless, other studies have shown significant benefit for such anti-inflammatory strategies. Overall, there seems to be a significant gap between our detailed understanding of cytokine actions and the benefit of such targeted interventions. This could be explained by the complex actions of a huge number of cytokines that are involved in atherogenesis as well as by the lack of large-scale clinical trials that can provide reliable data on the efficacy of these strategies.

Therefore, modulation of cytokines poses a therapeutic dilemma and the risks and benefits of inflammation suppression must be weighed before treatment. Particularly in regard to the newer biological agents, observations are limited mostly to rheumatological patients, and small-scale clinical trials and evidence regarding health and survival benefit are lacking in some cases (e.g. TNF inhibitors). Interestingly, there are currently several such clinical trials that are taking place (most notably the CANTOS, CIRT, and Entracte trials) whose results are eagerly awaited and may shape the future of atherosclerosis management and treatment.

Conclusion

Atherosclerosis is considered an inflammatory disease, and the significant role of cytokines in the initiation and maintenance of a pro-inflammatory state is well established. In recent years, novel therapeutic approaches capable of modulating cytokine production or their actions have been tested or are under investigation. Indeed, broad-based immunomodulatory therapies or specific molecules against inflammatory cytokines are now under investigation for the treatment of high-risk atherosclerotic subjects generating new hopes for the future. However, so far, there are no definitive data on the benefit of targeted anti-inflammatory therapy in atherosclerosis and therefore further studies are needed. Hopefully, in the next few years, we are going to have new data that will provide answers and guidance for our next steps in the fight against atherosclerosis and coronary heart disease.

Authors' contributions

E.O. and E.K.E. contributed to the conception and design of the manuscript, drafted the manuscript, and approved the submitted manuscript. D.T., F.C., and J.C.K. contributed to the conception and design of the manuscript, revised the manuscript critically for important intellectual content, and approved the submitted manuscript.

Conflict of interest: none declared.

References

1. Ross R. Atherosclerosis – an inflammatory disease. *N Engl J Med* 1999;**340**:115–126.
2. Tedgui A, Mallat Z. Cytokines in atherosclerosis: pathogenic and regulatory pathways. *Physiol Rev* 2006;**86**:515–581.
3. Ray KK, Cannon CP. The potential relevance of the multiple lipid-independent (pleiotropic) effects of statins in the management of acute coronary syndromes. *J Am Coll Cardiol* 2005;**46**:1425–1433.
4. Ridker PM, Luscher TF. Anti-inflammatory therapies for cardiovascular disease. *Eur Heart J* 2014;**35**:1782–1791.
5. Chan KF, Siegel MR, Lenardo JM. Signaling by the TNF receptor superfamily and T cell homeostasis. *Immunity* 2000;**13**:419–422.

6. Ohta H, Wada H, Niwa T, Kirii H, Iwamoto N, Fujii H, Saito K, Sekikawa K, Seishima M. Disruption of tumor necrosis factor-alpha gene diminishes the development of atherosclerosis in ApoE-deficient mice. *Atherosclerosis* 2005;**180**: 11–17.
7. Canault M, Peiretti F, Mueller C, Kopp F, Morange P, Rihs S, Portugal H, Juhan-Vague I, Nalbone G. Exclusive expression of transmembrane TNF-alpha in mice reduces the inflammatory response in early lipid lesions of aortic sinus. *Atherosclerosis* 2004;**172**:211–218.
8. Mackesy DZ, Goalstone ML. ERK5: novel mediator of insulin and TNF-stimulated VCAM-1 expression in vascular cells. *J Diabetes* 2014;**6**:595–602.
9. Ait-Oufella H, Taleb S, Mallat Z, Tedgui A. Recent advances on the role of cytokines in atherosclerosis. *Arterioscler Thromb Vasc Biol* 2011;**31**:969–979.
10. Huber SA, Sakkinen P, Conze D, Hardin N, Tracy R. Interleukin-6 exacerbates early atherosclerosis in mice. *Arterioscler Thromb Vasc Biol* 1999;**19**:2364–2367.
11. Biasucci LM, Liuzzo G, Fantuzzi G, Caligiuri G, Rebuzzi AG, Ginnetti F, Dinarello CA, Maseri A. Increasing levels of interleukin (IL)-1Ra and IL-6 during the first 2 days of hospitalization in unstable angina are associated with increased risk of in-hospital coronary events. *Circulation* 1999;**99**:2079–2084.
12. Pastrana JL, Sha X, Virtue A, Mai J, Cueto R, Lee IA, Wang H, Yang XF. Regulatory T cells and atherosclerosis. *J Clin Exp Cardiol* 2012;**2012**:2.
13. Rajasingh J, Bord E, Luedemann C, Asai J, Hamada H, Thorne T, Qin G, Goukassian D, Zhu Y, Losordo DW, Kishore R. IL-10-induced TNF-alpha mRNA destabilization is mediated via IL-10 suppression of p38 MAP kinase activation and inhibition of HuR expression. *FASEB J* 2006;**20**:2112–2114.
14. Lisinski TJ, Furie MB. Interleukin-10 inhibits proinflammatory activation of endothelium in response to *Borrelia burgdorferi* or lipopolysaccharide but not interleukin-1beta or tumor necrosis factor alpha. *J Leukoc Biol* 2002;**72**:503–511.
15. Peters MJ, van Halm VP, Voskuyl AE, Smulders YM, Boers M, Lems WF, Visser M, Stehouwer CD, Dekker JM, Nijpels G, Heine R, Dijkmans BA, Nurmohamed MT. Does rheumatoid arthritis equal diabetes mellitus as an independent risk factor for cardiovascular disease? A prospective study. *Arthritis Rheum* 2009;**61**: 1571–1579.
16. Mantel A, Holmqvist M, Jernberg T, Wallberg-Jonsson S, Askling J. Rheumatoid arthritis is associated with a more severe presentation of acute coronary syndrome and worse short-term outcome. *Eur Heart J* 2015;**36**:3413–3422.
17. Klingenberg R, Luscher TF. Rheumatoid arthritis and coronary atherosclerosis: two cousins engaging in a dangerous liaison. *Eur Heart J* 2015;**36**:3423–3425.
18. Kisiel B, Kruszewski R, Juszkiewicz A, Raczkiewicz A, Bachta A, Tlustochowicz M, Staniszewska-Varga J, Klos K, Duda K, Boguslawska-Walecka R, Ploski R, Tlustochowicz W. Methotrexate, cyclosporine A, and biologics protect against atherosclerosis in rheumatoid arthritis. *J Immunol Res* 2015;**2015**:759610.
19. Barnabe C, Martin BJ, Ghali WA. Systematic review and meta-analysis: anti-tumor necrosis factor alpha therapy and cardiovascular events in rheumatoid arthritis. *Arthritis Care Res* 2011;**63**:522–529.
20. Bergh N, Larsson P, Ulfhammer E, Jern S. Effect of shear stress, statins and TNF-alpha on hemostatic genes in human endothelial cells. *Biochem Biophys Res Commun* 2012;**420**:166–171.
21. Tousoulis D, Koniari K, Antoniades C, Papageorgiou N, Miliou A, Noutsou M, Nikolopoulou A, Marinou K, Stefanadi E, Siasos G, Charakida M, Kamboli AM, Stefanadis C. Combined effects of atorvastatin and metformin on glucose-induced variations of inflammatory process in patients with diabetes mellitus. *Int J Cardiol* 2011;**149**:46–49.
22. Dahlman-Ghozlan K, Ortonne JP, Heilborn JD, Stephansson E. Altered tissue expression pattern of cell adhesion molecules, ICAM-1, E-selectin and VCAM-1, in bullous pemphigoid during methotrexate therapy. *Exp Dermatol* 2004;**13**:65–69.
23. Elango T, Dayalan H, Subramanian S, Gnanaraj P, Malligarjunan H. Serum interleukin-6 levels in response to methotrexate treatment in psoriatic patients. *Clin Chim Acta* 2012;**413**:1652–1656.
24. Nidorf M, Thompson PL. Effect of colchicine (0.5 mg twice daily) on high-sensitivity C-reactive protein independent of aspirin and atorvastatin in patients with stable coronary artery disease. *Am J Cardiol* 2007;**99**:805–807.
25. Tam LS, Kitas GD, Gonzalez-Gay MA. Can suppression of inflammation by anti-TNF prevent progression of subclinical atherosclerosis in inflammatory arthritis? *Rheumatology (Oxford)* 2014;**53**:1108–1119.
26. Spinelli FR, Di Franco M, Metere A, Conti F, Iannuccelli C, Agati L, Valesini G. Decrease of asymmetric dimethyl arginine after anti-TNF therapy in patients with rheumatoid arthritis. *Drug Dev Res* 2014;**75**(Suppl. 1):S67–S69.
27. Avgerinou G, Tousoulis D, Siasos G, Oikonomou E, Maniatis K, Papageorgiou N, Paraskevopoulos T, Miliou A, Koumaki D, Latsios G, Therianiou A, Trikas A, Kampoli AM, Stefanadis C. Anti-tumor necrosis factor alpha treatment with adalimumab improves significantly endothelial function and decreases inflammatory process in patients with chronic psoriasis. *Int J Cardiol* 2011;**151**:382–383.
28. Ridker PM, Howard CP, Walter V, Everett B, Libby P, Hensen J, Thuren T, Group CPI. Effects of interleukin-1beta inhibition with canakinumab on hemoglobin A1c, lipids, C-reactive protein, interleukin-6, and fibrinogen: a phase IIb randomized, placebo-controlled trial. *Circulation* 2012;**126**:2739–2748.
29. Morton AC, Rothman AM, Greenwood JP, Gunn J, Chase A, Clarke B, Hall AS, Fox K, Foley C, Banya W, Wang D, Flather MD, Crossman DC. The effect of interleukin-1 receptor antagonist therapy on markers of inflammation in non-ST elevation acute coronary syndromes: the MRC-ILA Heart Study. *Eur Heart J* 2014; **36**:377–384.
30. Protogerou AD, Zampeli E, Fragiadaki K, Stamatelopoulos K, Papamichael C, Sfikakis PP. A pilot study of endothelial dysfunction and aortic stiffness after interleukin-6 receptor inhibition in rheumatoid arthritis. *Atherosclerosis* 2011; **219**:734–736.
31. Tian Y, Sommerville LJ, Cuneo A, Kelemen SE, Autieri MV. Expression and suppressive effects of interleukin-19 on vascular smooth muscle cell pathophysiology and development of intimal hyperplasia. *Am J Pathol* 2008;**173**:901–909.
32. Almer G, Frascione D, Pali-Scholl I, Vonach C, Lukschal A, Stremnitzer C, Diesner SC, Jensen-Jarolim E, Prassl R, Mangge H. Interleukin-10: an anti-inflammatory marker to target atherosclerotic lesions via PEGylated liposomes. *Mol Pharm* 2013;**10**:175–186.
33. Yoshimura S, Morishita R, Hayashi K, Yamamoto K, Nakagami H, Kaneda Y, Sakai N, Ogihara T. Inhibition of intimal hyperplasia after balloon injury in rat carotid artery model using cis-element 'decoy' of nuclear factor-kappaB binding site as a novel molecular strategy. *Gene Ther* 2001;**8**:1635–1642.
34. Steffens S, Burger F, Pelli G, Dean Y, Elson G, Kosco-Vilbois M, Chatenoud L, Mach F. Short-term treatment with anti-CD3 antibody reduces the development and progression of atherosclerosis in mice. *Circulation* 2006;**114**:1977–1984.
35. Dietrich T, Hucko T, Schneemann C, Neumann M, Menrad A, Willuda J, Atrott K, Stibenz D, Fleck E, Graf K, Menssen HD. Local delivery of IL-2 reduces atherosclerosis via expansion of regulatory T cells. *Atherosclerosis* 2012;**220**:329–336.
36. Morton AC, Rothman AM, Greenwood JP, Gunn J, Chase A, Clarke B, Hall AS, Fox K, Foley C, Banya W, Wang D, Flather MD, Crossman DC. The effect of interleukin-1 receptor antagonist therapy on markers of inflammation in non-ST elevation acute coronary syndromes: the MRC-ILA Heart Study. *Eur Heart J* 2015; **36**:377–384.
37. Ikonomidis I, Tzortzis S, Andreadou I, Paraskevaidis I, Katseli C, Katsimbri P, Pavlidis G, Parissis J, Kremastinos D, Anastasiou-Nana M, Lekakis J. Increased benefit of interleukin-1 inhibition on vascular function, myocardial deformation, and twisting in patients with coronary artery disease and coexisting rheumatoid arthritis. *Circ Cardiovasc Imaging* 2014;**7**:619–628.
38. Abbate A, Kontos MC, Abouzaki NA, Melchior RD, Thomas C, Van Tassell BW, Oddi C, Carbone S, Trankle CR, Roberts CS, Mueller GH, Gambill ML, Christopher S, Markley R, Vetrovec GW, Dinarello CA, Biondi-Zoccai G. Comparative safety of interleukin-1 blockade with anakinra in patients with ST-segment elevation acute myocardial infarction (from the VCU-ART and VCU-ART2 pilot studies). *Am J Cardiol* 2015;**115**:288–292.
39. Nidorf SM, Eikelboom JW, Budgeon CA, Thompson PL. Low-dose colchicine for secondary prevention of cardiovascular disease. *J Am Coll Cardiol* 2013;**61**: 404–410.
40. Choi HK, Hernan MA, Seeger JD, Robins JM, Wolfe F. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. *Lancet* 2002;**359**: 1173–1177.
41. Giugliano GR, Giugliano RP, Gibson CM, Kuntz RE. Meta-analysis of corticosteroid treatment in acute myocardial infarction. *Am J Cardiol* 2003;**91**:1055–1059.
42. Tzellos T, Kyrgidis A, Zouboulis CC. Re-evaluation of the risk for major adverse cardiovascular events in patients treated with anti-IL-12/23 biological agents for chronic plaque psoriasis: a meta-analysis of randomized controlled trials. *J Eur Acad Dermatol Venereol* 2013;**27**:622–627.
43. Okopien B, Huzarska M, Kulach A, Stachura-Kulach A, Madej A, Belowski D, Zielinski M, Herman ZS. Hypolipidemic drugs affect monocyte IL-1beta gene expression and release in patients with IIa and IIb dyslipidemia. *J Cardiovasc Pharmacol* 2005;**45**:160–164.
44. Waehre T, Yndestad A, Smith C, Haug T, Tunheim SH, Gullestad L, Froland SS, Semb AG, Aukrust P, Damas JK. Increased expression of interleukin-1 in coronary artery disease with downregulatory effects of HMG-CoA reductase inhibitors. *Circulation* 2004;**109**:1966–1972.
45. Liu Y, Jiang H, Liu W, Shang H, Tang Y, Zhu R, Li B. Effects of fluvastatin therapy on serum interleukin-18 and interleukin-10 levels in patients with acute coronary syndrome. *Acta Cardiol* 2010;**65**:285–289.
46. Chu AY, Guilianini F, Barratt BJ, Nyberg F, Chasman DI, Ridker PM. Pharmacogenetic determinants of statin-induced reductions in C-reactive protein. *Circ Cardiovasc Genet* 2012;**5**:58–65.
47. Stefanadi E, Tousoulis D, Antoniades C, Katsi V, Bosinakou E, Vavuranakis E, Triantafyllou G, Marinou K, Tsioufis C, Papageorgiou N, Latsios G, Stefanadis C. Early initiation of low-dose atorvastatin treatment after an acute ST-elevated myocardial infarction, decreases inflammatory process and prevents endothelial injury and activation. *Int J Cardiol* 2009;**133**:266–268.

48. Leoncini M, Toso A, Maioli M, Tropeano F, Villani S, Bellandi F. Early high-dose rosuvastatin for contrast-induced nephropathy prevention in acute coronary syndrome: results from the PRATO-ACS Study (Protective Effect of Rosuvastatin and Antiplatelet Therapy On Contrast-Induced Acute Kidney Injury and Myocardial Damage in Patients with Acute Coronary Syndrome). *J Am Coll Cardiol* 2014;**63**: 71–79.
49. Toso A, Leoncini M, Maioli M, Tropeano F, Di Vincenzo E, Villani S, Bellandi F. Relationship between inflammation and benefits of early high-dose rosuvastatin on contrast-induced nephropathy in patients with acute coronary syndrome: the pathophysiological link in the PRATO-ACS study (Protective Effect of Rosuvastatin and Antiplatelet Therapy on Contrast-Induced Nephropathy and Myocardial Damage in Patients With Acute Coronary Syndrome Undergoing Coronary Intervention). *JACC Cardiovasc Interv* 2014;**7**:1421–1429.
50. Ridker PM, Rifai N, Clearfield M, Downs JR, Weis SE, Miles JS, Gotto AM Jr, Air Force/Texas Coronary Atherosclerosis Prevention Study Investigators. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. *N Engl J Med* 2001;**344**:1959–1965.
51. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ, Group JS. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008;**359**:2195–2207.
52. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, Macfadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ. Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. *Lancet* 2009;**373**:1175–1182.
53. Oikonomou E, Siasos G, Zaromitidou M, Hatzis G, Mourouzis K, Chrysohoou C, Zisimos K, Mazaris S, Tourikis P, Athanasiou D, Stefanadis C, Papavassiliou AG, Tousoulis D. Atorvastatin treatment improves endothelial function through endothelial progenitor cells mobilization in ischemic heart failure patients. *Atherosclerosis* 2015;**238**:159–164.
54. Tousoulis D, Oikonomou E, Siasos G, Chrysohoou C, Zaromitidou M, Kioufis S, Maniatis K, Dilaveris P, Miliou A, Michalea S, Papavassiliou AG, Stefanadis C. Dose-dependent effects of short term atorvastatin treatment on arterial wall properties and on indices of left ventricular remodeling in ischemic heart failure. *Atherosclerosis* 2013;**227**:367–372.
55. Toth L, Muszbek L, Komaromi I. Mechanism of the irreversible inhibition of human cyclooxygenase-1 by aspirin as predicted by QM/MM calculations. *J Mol Graph Model* 2013;**40**:99–109.
56. Cyrus T, Sung S, Zhao L, Funk CD, Tang S, Pratico D. Effect of low-dose aspirin on vascular inflammation, plaque stability, and atherogenesis in low-density lipoprotein receptor-deficient mice. *Circulation* 2002;**106**:1282–1287.
57. Liu H, Jiang D, Zhang S, Ou B. Aspirin inhibits fractalkine expression in atherosclerotic plaques and reduces atherosclerosis in ApoE gene knockout mice. *Cardiovasc Drugs Ther* 2010;**24**:17–24.
58. Herova M, Schmid M, Gemperle C, Loretz C, Hersberger M. Low dose aspirin is associated with plasma chemerin levels and may reduce adipose tissue inflammation. *Atherosclerosis* 2014;**235**:256–262.
59. Kharbanda RK, Walton B, Allen M, Klein N, Hingorani AD, MacAllister RJ, Vallance P. Prevention of inflammation-induced endothelial dysfunction: a novel vasculo-protective action of aspirin. *Circulation* 2002;**105**:2600–2604.
60. Ikonomidis I, Andreotti F, Economou E, Stefanadis C, Toutouzas P, Nihoyannopoulos P. Increased proinflammatory cytokines in patients with chronic stable angina and their reduction by aspirin. *Circulation* 1999;**100**:793–798.
61. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997;**336**:973–979.
62. Pietri P, Vlachopoulos C, Terentes-Printzios D, Xaplanteris P, Aznaouridis K, Petrocheilou K, Stefanadis C. Beneficial effects of low-dose aspirin on aortic stiffness in hypertensive patients. *Vasc Med* 2014;**19**:452–457.
63. van Diepen JA, Vroegrijk IO, Berbee JF, Shoelson SE, Romijn JA, Havekes LM, Rensen PC, Voshol PJ. Aspirin reduces hypertriglyceridemia by lowering VLDL-triglyceride production in mice fed a high-fat diet. *Am J Physiol Endocrinol Metab* 2011;**301**:E1099–E1107.
64. He Z, Peng Y, Duan W, Tian Y, Zhang J, Hu T, Cai Y, Feng Y, Li G. Aspirin regulates hepatocellular lipid metabolism by activating AMPK signaling pathway. *J Toxicol Sci* 2015;**40**:127–136.
65. Chow BJ, Small G, Yam Y, Chen L, McPherson R, Achenbach S, Al-Mallah M, Berman DS, Budoff MJ, Cademartiri F, Callister TQ, Chang HJ, Cheng VY, Chinnaiyan K, Cury R, Delago A, Dunning A, Feuchtner G, Hadamitzky M, Hausleiter J, Karlsberg RP, Kaufmann PA, Kim YJ, Leipsic J, LaBounty T, Lin F, Maffei E, Raff GL, Shaw LJ, Villines TC, Min JK. Prognostic and therapeutic implications of statin and aspirin therapy in individuals with nonobstructive coronary artery disease: results from the CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes: an InteRnational Multicenter registry) registry. *Arterioscler Thromb Vasc Biol* 2015;**35**:981–989.
66. Belch J, MacCuish A, Campbell I, Cobbe S, Taylor R, Prescott R, Lee R, Bancroft J, MacEwan S, Shepherd J, Macfarlane P, Morris A, Jung R, Kelly C, Connacher A, Peden N, Jamieson A, Matthews D, Leese G, McKnight J, O'Brien I, Semple C, Petrie J, Gordon D, Pringle S, MacWalter R, Prevention of Progression of Arterial Disease and Diabetes Study Group, Diabetes Registry Group, and Royal College of Physicians Edinburgh. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *BMJ* 2008;**337**:a1840.
67. Kim AJ, Lim HJ, Ro H, Ko KP, Han SY, Chang JH, Lee HH, Chung W, Jung JY. Low-dose aspirin for prevention of cardiovascular disease in patients with chronic kidney disease. *PLoS ONE* 2014;**9**:e104179.
68. Cronstein BN, Naime D, Ostad E. The antiinflammatory mechanism of methotrexate. Increased adenosine release at inflamed sites diminishes leukocyte accumulation in an in vivo model of inflammation. *J Clin Invest* 1993;**92**:2675–2682.
69. Asanuma H, Sanada S, Ogai A, Minamino T, Takashima S, Asakura M, Ogita H, Shinozaki Y, Mori H, Node K, Tomoike H, Hori M, Kitakaze M. Methotrexate and MX-68, a new derivative of methotrexate, limit infarct size via adenosine-dependent mechanisms in canine hearts. *J Cardiovasc Pharmacol* 2004;**43**:574–579.
70. van Halm VP, Nurmohamed MT, Twisk JW, Dijkmans BA, Voskuyl AE. Disease-modifying antirheumatic drugs are associated with a reduced risk for cardiovascular disease in patients with rheumatoid arthritis: a case control study. *Arthritis Res Ther* 2006;**8**:R151.
71. Greenberg JD, Kremer JM, Curtis JR, Hochberg MC, Reed G, Tsao P, Farkouh ME, Nasir A, Setoguchi S, Solomon DH, Investigators C. Tumour necrosis factor antagonist use and associated risk reduction of cardiovascular events among patients with rheumatoid arthritis. *Ann Rheum Dis* 2011;**70**:576–582.
72. Ridker PM. Testing the inflammatory hypothesis of atherothrombosis: scientific rationale for the Cardiovascular Inflammation Reduction Trial (CIRT). *J Thromb Haemost* 2009;**7**(Suppl. 1):332–339.
73. Moreira DM, Lueneberg ME, da Silva RL, Fattah T, Mascia Gottschall CA. Rationale and design of the TETHYS trial: the effects of methotrexate therapy on myocardial infarction with ST-segment elevation. *Cardiology* 2013;**126**:167–170.
74. Ronda N, Greco D, Adorni MP, Zimetti F, Favari E, Hjeltnes G, Mikkelsen K, Borghi MO, Favalli EG, Gatti R, Hollan I, Meroni PL, Bernini F. Newly identified antiatherosclerotic activity of methotrexate and adalimumab: complementary effects on lipoprotein function and macrophage cholesterol metabolism. *Arthritis Rheum* 2015;**67**:1155–1164.
75. Langevitz P, Livneh A, Neumann L, Buskila D, Shemer J, Amolsky D, Pras M. Prevalence of ischemic heart disease in patients with familial Mediterranean fever. *Isr Med Assoc J* 2001;**3**:9–12.
76. Crittenden DB, Lehmann RA, Schneck L, Keenan RT, Shah B, Greenberg JD, Cronstein BN, Sedlis SP, Pillinger MH. Colchicine use is associated with decreased prevalence of myocardial infarction in patients with gout. *J Rheumatol* 2012;**39**: 1458–1464.
77. Schillaci G, Bartoloni E, Pucci G, Pirro M, Settimi L, Alunno A, Gerli R, Mannarino E. Aortic stiffness is increased in polymyalgia rheumatica and improves after steroid treatment. *Ann Rheum Dis* 2012;**71**:1151–1156.
78. Avina-Zubieta JA, Abrahamowicz M, De Vera MA, Choi HK, Sayre EC, Rahman MM, Sylvestre MP, Wynant W, Esdaile JM, Lacaille D. Immediate and past cumulative effects of oral glucocorticoids on the risk of acute myocardial infarction in rheumatoid arthritis: a population-based study. *Rheumatology* 2013;**52**: 68–75.
79. Spinelli FR, Metere A, Barbati C, Pierdominici M, Iannuccelli C, Lucchino B, Ciciarello F, Agati L, Valesini G, Di Franco M. Effect of therapeutic inhibition of TNF on circulating endothelial progenitor cells in patients with rheumatoid arthritis. *Mediators Inflamm* 2013;**2013**:537539.
80. Pina T, Armesto S, Lopez-Mejias R, Genre F, Ubilla B, Gonzalez-Lopez MA, Gonzalez-Vela MC, Corrales A, Blanco R, Garcia-Unzueta MT, Hernandez JL, Llorca J, Gonzalez-Gay MA. Anti-TNF-alpha therapy improves insulin sensitivity in non-diabetic patients with psoriasis: a 6-month prospective study. *J Eur Acad Dermatol Venereol* 2014;**29**:1325–1330.
81. van Eijk IC, de Vries MK, Levels JH, Peters MJ, Huizer EE, Dijkmans BA, van der Horst-Bruinsma IE, Hazenberg BP, van de Stadt RJ, Wolbink GJ, Nurmohamed MT. Improvement of lipid profile is accompanied by atheroprotective alterations in high-density lipoprotein composition upon tumor necrosis factor blockade: a prospective cohort study in ankylosing spondylitis. *Arthritis Rheum* 2009;**60**:1324–1330.
82. Catrina AI, Lampa J, Ernestam S, af Klint E, Bratt J, Klareskog L, Ulfgren AK. Anti-tumour necrosis factor (TNF)-alpha therapy (etanercept) down-regulates serum matrix metalloproteinase (MMP)-3 and MMP-1 in rheumatoid arthritis. *Rheumatology* 2002;**41**:484–489.
83. Ridker PM, Thuren T, Zalewski A, Libby P. Interleukin-1beta inhibition and the prevention of recurrent cardiovascular events: rationale and design of the

Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS). *Am Heart J* 2011;**162**:597–605.

84. Ikonomidis I, Lekakis JP, Nikolaou M, Paraskevaidis I, Andreadou I, Kaplanoglou T, Katsimbri P, Skarantavos G, Soucacos PN, Kremastinos DT. Inhibition of interleukin-1 by anakinra improves vascular and left ventricular function in patients with rheumatoid arthritis. *Circulation* 2008;**117**:2662–2669.
85. Geiler J, Buch M, McDermott MF. Anti-TNF treatment in rheumatoid arthritis. *Curr Pharm Des* 2011;**17**:3141–3154.
86. Rios-Navarro C, de Pablo C, Collado-Diaz V, Orden S, Blas-Garcia A, Martinez-Cuesta MA, Esplugues JV, Alvarez A. Differential effects of anti-TNF-alpha and anti-IL-12/23 agents on human leukocyte-endothelial cell interactions. *Eur J Pharmacol* 2015;**765**:355–365.
87. Tam LS, Shang Q, Kun EW, Lee KL, Yip ML, Li M, Li TK, Zhu TY, Pui MO, Li EK, Yu CM. The effects of golimumab on subclinical atherosclerosis and arterial stiffness in ankylosing spondylitis-a randomized, placebo-controlled pilot trial. *Rheumatology* 2014;**53**:1065–1074.
88. Mann DL, McMurray JJ, Packer M, Swedberg K, Borer JS, Colucci WS, Djian J, Drexler H, Feldman A, Kober L, Krum H, Liu P, Nieminen M, Tavazzi L, van Veldhuisen DJ, Waldenstrom A, Warren M, Westheim A, Zannad F, Fleming T. Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). *Circulation* 2004;**109**:1594–1602.
89. Kuemmerle-Deschner JB, Ramos E, Blank N, Roesler J, Felix SD, Jung T, Stricker K, Chakraborty A, Tannenbaum S, Wright AM, Rordorf C. Canakinumab (ACZ885, a fully human IgG1 anti-IL-1beta mAb) induces sustained remission in pediatric patients with cryopyrin-associated periodic syndrome (CAPS). *Arthritis Res Ther* 2011;**13**:R34.
90. Ait-Oudhia S, Lowe PJ, Mager DE. Bridging clinical outcomes of canakinumab treatment in patients with rheumatoid arthritis with a population model of IL-1 beta kinetics. *CPT Pharmacometrics Syst Pharmacol* 2012;**1**:e5.
91. Kirii H, Niwa T, Yamada Y, Wada H, Saito K, Iwakura Y, Asano M, Moriwaki H, Seishima M. Lack of interleukin-1beta decreases the severity of atherosclerosis in ApoE-deficient mice. *Arterioscler Thromb Vasc Biol* 2003;**23**:656–660.
92. Abderrazak A, Couchie D, Mahmood DF, Elhage R, Vindis C, Laffargue M, Mateo V, Buchele B, Ayala MR, El Gaafary M, Syrovets T, Slimane MN, Friguet B, Fulop T, Simmet T, El Hadri K, Rouis M. Anti-inflammatory and anti-atherogenic effects of the NLRP3 inflammasome inhibitor arglabin in ApoE2.Ki mice fed a high-fat diet. *Circulation* 2015;**131**:1061–1070.
93. Kawashiri SY, Kawakami A, Yamasaki S, Imazato T, Iwamoto N, Fujikawa K, Aramaki T, Tamai M, Nakamura H, Ida H, Origuchi T, Ueki Y, Eguchi K. Effects of the anti-interleukin-6 receptor antibody, tocilizumab, on serum lipid levels in patients with rheumatoid arthritis. *Rheumatol Int* 2011;**31**:451–456.
94. Gao Q, Jiang Y, Ma T, Zhu F, Gao F, Zhang P, Guo C, Wang Q, Wang X, Ma C, Zhang Y, Chen W, Zhang L. A critical function of Th17 proinflammatory cells in the development of atherosclerotic plaque in mice. *J Immunol* 2010;**185**:5820–5827.
95. Coimbra S, Figueiredo A, Santos-Silva A. Brodalumab: an evidence-based review of its potential in the treatment of moderate-to-severe psoriasis. *Core Evidence* 2014;**9**:89–97.
96. Erbel C, Chen L, Bea F, Wangler S, Celik S, Lasitschka F, Wang Y, Bockler D, Katus HA, Dengler TJ. Inhibition of IL-17A attenuates atherosclerotic lesion development in apoE-deficient mice. *J Immunol* 2009;**183**:8167–8175.
97. Tardif JC, Tanguay JF, Wright SS, Duchatelle V, Petroni T, Gregoire JC, Ibrahim R, Heinonen TM, Robb S, Bertrand OF, Cournoyer D, Johnson D, Mann J, Guertin MC, L'Allier PL. Effects of the P-selectin antagonist inclacumab on myocardial damage after percutaneous coronary intervention for non-ST-segment elevation myocardial infarction: results of the SELECT-ACS trial. *J Am Coll Cardiol* 2013;**61**:2048–2055.
98. Brown DA, Sabbah HN, Shaikh SR. Mitochondrial inner membrane lipids and proteins as targets for decreasing cardiac ischemia/reperfusion injury. *Pharmacol Ther* 2013;**140**:258–266.
99. Cho J, Won K, Wu D, Soong Y, Liu S, Szeto HH, Hong MK. Potent mitochondria-targeted peptides reduce myocardial infarction in rats. *Coron Artery Dis* 2007;**18**:215–220.
100. Chakrabarti AK, Feeney K, Abueg C, Brown DA, Czyz E, Tendera M, Janosi A, Giugliano RP, Kloner RA, Weaver WD, Bode C, Godlewski J, Merkely B, Gibson CM. Rationale and design of the EMBRACE STEMI study: a phase 2a, randomized, double-blind, placebo-controlled trial to evaluate the safety, tolerability and efficacy of intravenous Bendavia on reperfusion injury in patients treated with standard therapy including primary percutaneous coronary intervention and stenting for ST-segment elevation myocardial infarction. *Am Heart J* 2013;**165**:509–514.e7.
101. Ramji DP, Davies TS. Cytokines in atherosclerosis: key players in all stages of disease and promising therapeutic targets. *Cytokine Growth Factor Rev* 2015;**26**:673–685.
102. Shouda T, Yoshida T, Hanada T, Wakioka T, Oishi M, Miyoshi K, Komiya S, Kosai K, Hanakawa Y, Hashimoto K, Nagata K, Yoshimura A. Induction of the cytokine signal regulator SOCS3/CIS3 as a therapeutic strategy for treating inflammatory arthritis. *J Clin Invest* 2001;**108**:1781–1788.
103. Changelian PS, Flanagan ME, Ball DJ, Kent CR, Magnuson KS, Martin WH, Rizzuti BJ, Sawyer PS, Perry BD, Brissette WH, McCurdy SP, Kudlacz EM, Conklyn MJ, Elliott EA, Koslov ER, Fisher MB, Strelevitz TJ, Yoon K, Whipple DA, Sun J, Munchhof MJ, Doty JL, Casavant JM, Blumenkopf TA, Hines M, Brown MF, Lillie BM, Subramanyam C, Shang-Poa C, Milici AJ, Beckius GE, Moyer JD, Su C, Woodworth TG, Gaweco AS, Beals CR, Littman BH, Fisher DA, Smith JF, Zagouras P, Magna HA, Saltarelli MJ, Johnson KS, Nelms LF, Des Etages SG, Hayes LS, Kawabata TT, Finco-Kent D, Baker DL, Larson M, Si MS, Paniagua R, Higgins J, Holm B, Reitz B, Zhou YJ, Morris RE, O'Shea JJ, Borie DC. Prevention of organ allograft rejection by a specific Janus kinase 3 inhibitor. *Science* 2003;**302**:875–878.
104. Sasaki N, Yamashita T, Takeda M, Shinohara M, Nakajima K, Tawa H, Usui T, Hirata K. Oral anti-CD3 antibody treatment induces regulatory T cells and inhibits the development of atherosclerosis in mice. *Circulation* 2009;**120**:1996–2005.
105. Takeda M, Yamashita T, Sasaki N, Nakajima K, Kita T, Shinohara M, Ishida T, Hirata K. Oral administration of an active form of vitamin D3 (calcitriol) decreases atherosclerosis in mice by inducing regulatory T cells and immature dendritic cells with tolerogenic functions. *Arterioscler Thromb Vasc Biol* 2010;**30**:2495–2503.
106. Nissen SE. Cox-2 inhibitors and cardiovascular disease: considerable heat, but not much light. *Eur Heart J* 2012;**33**:2631–2633.