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REVIEW

Insights into the Role of Inflammation in the Management of Atherosclerosis

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Abstract: Atherosclerosis is the biological basis of ischemic heart disease and ischemic stroke, the leading causes of death in the world. After decades of studies, the understanding of atherosclerosis has evolved dramatically, and inflammation has been recognized as one of the most relevant pillars in all phases of atherosclerotic disease. Nevertheless, only recently, the trial CANTOS, and subsequent outcome studies with colchicine, finally provided proof-of-concept evidence that anti-inflammatory therapies were able to reduce cardiovascular events with no influence on lipid levels. These landmark studies inaugurated an era of clinical and pre-clinical studies of immunomodulatory strategies focused on reduction of cardiovascular risk. Although there are promising results in the field, selection of the most appropriate immunomodulatory therapy and identification of patients who could benefit the most, are still enormous challenges. Further research is imperative before we can finally advance towards regular use of anti-inflammatory agents to reduce atherosclerotic events in our clinical practice.

Keywords: inflammation, atherosclerosis, anti-inflammatory therapies, cardiovascular risk

Introduction

Atherosclerosis is the biologic substrate of ischemic heart disease and ischemic stroke, the two leading causes of death in the world. According to data from the World Health Organization (WHO), cardiovascular diseases were responsible for approximately 32% of all global deaths in 2019, with an estimation of 17.9 million deaths. Coronary heart disease and stroke accounted for 85% of those deaths.[1]

Atherosclerotic disease refers to formation of plaques within the arterial intima derived from the accumulation of lipidic and/or fibrous material.[2] Upon entry and accumulation of circulating low-density lipoprotein (LDL) particles in the arterial intima, followed by biochemical modification that can turn them into more pro-inflammatory particles, a sequence of various events culminates in the formation of an atheroma. Despite the clear importance of lipids in the genesis of this phenomenon, there is undeniable evidence that inflammation participates in the entire atherosclerotic process, from the development of incipient fatty streaks to the occurrence of ischemic outcomes. In the early phase of atherogenesis, inflammatory responses represent an important interface between the presence of risk factors and initiation of plaque formation.[2] Once an atheroma is formed, inflammation may continue playing a role in its progression, with participation of elements of both innate and adaptive immunity, including factors with pro- and anti-inflammatory properties. Finally, inflammatory mediators can also operate critically in plaque rupture and plaque erosion, the most important triggers of thrombotic complications of atherosclerosis.

In addition to the evidence linking inflammation to the biology of atherosclerosis, population studies also demonstrate an association between concentrations of inflammatory biomarkers, such as high sensitivity C-reactive protein (CRP), and risk of ischemic events.[3] Post hoc analyses of outcome studies testing statins and other lipid-lowering therapies have also suggested that lowering inflammation, in addition to LDL-C control, may also contribute to reduce the risk of atherosclerotic events.[4,5] Despite all the previous suggestive evidence, the *Canakinumab Antiinflammatory Thrombosis*

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Outcomes Study (CANTOS) was the first trial that successfully demonstrated a causal relationship between inflammation and atherothrombotic events.[6] By showing that use of Canakinumab, an anti-inflammatory therapy targeting the interleukin-1β (IL-1β) immunity pathway, resulted in a significantly lower incidence of cardiovascular events compared to placebo, CANTOS provided solid proof on the role of inflammation in the management of atherosclerotic disease[6] and paved the way for subsequent clinical studies with other anti-inflammatory agents, such as colchicine.[7,8] This review intends to recapitulate the evidence suggesting an important role of inflammation in the management of atherosclerosis, and the most promising anti-inflammatory therapies in the field of cardiovascular prevention.

The Role of Inflammation in the Pathophysiology of Atherothrombosis

Atherosclerosis refers to the presence of atheroma within the arterial wall. Inflammation consists in a fundamental pillar of the entire process of atherosclerosis, through numerous inflammatory cells and mediators, participating in its inception, progression and in thrombotic complications.

Initiation of Atherosclerosis

In the early stage of atherosclerosis, traditional and non-traditional risk factors can activate inflammatory pathways that can alter the behavior of cells of the artery wall towards a proatherogenic milieu.[2] LDL particles can accumulate in the subendothelial space, particularly in the presence of a dysfunctional endothelium, and can be retained by extracellular matrix macromolecules. While trapped in the intima, the LDL particles can undergo biochemical modification, such as oxidation. The retained and now modified lipoproteins can elicit an innate inflammatory response. Endothelial cells express adhesion molecules that in conjunction with locally secreted chemokines, lead to leukocyte recruitment.[9] Circulating monocytes that infiltrated the intima can differentiate into macrophages in response to macrophage-colony stimulating factor (M-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF), derived from endothelial cells and other cell types.[9] In addition to persistent recruitment and differentiation, monocyte-derived macrophages can also proliferate locally, representing a major cell subset in the atheroma.[10,11] Accumulated macrophages in the sub-endothelial space can engulf the retained lipoproteins through the so-called scavenger receptors. Distinctly from the LDL receptors, the scavenger receptors are not downregulated by the intracellular cholesterol content, allowing macrophage lipid overloading, and thus formation of foam cells.[12] According to recent data, smooth muscle cells may also generate macrophage-like foam cells and contribute to lesion progression.[13]

Progression of Atherosclerosis

Activated macrophages in atherosclerotic plaques are critical determinants of the local inflammatory milieu, by secreting proinflammatory cytokines and chemokines, and producing reactive oxygen and nitrogen species.[14] Macrophages can also amplify inflammation through crosstalks with smooth muscle cells and T cells. Due to a deficient capacity to migrate, macrophages in the atheroma undergo apoptosis, with consequent accumulation of cell debris, and formation of a necrotic core in the plaque.[15] Despite the known role of macrophages in the maintenance of plaque inflammation, these cells are notorious for their plasticity, and can assume distinct functions and phenotypes depending on several factors.[16,17] Experimental studies suggested the concept of a subclassification of macrophages into a more inflammatory M1 subset, activated by interferon-γ (IFNγ) and lipopolysaccharide, and a less inflammatory M2 subset, activated by IL-4 or IL-13.[16] Although both M1 and M2 macrophages have been found in humans and mice plaques,[18,19] recent data suggest that the M1/M2 classification may be an oversimplification of macrophage heterogeneity.[20,21]

The activation of the *NACHT, LRR and PYD domains containing protein 3* (NLRP3) inflammasome in macrophages has received particular visibility in the context of atherosclerosis. Cholesterol crystals formed in foam cells can activate the NLRP3 inflammasome, which unleashes caspase-1 to cleave the pro-form IL-1β to its active form.[22,23] The functional IL-1β stimulates smooth muscle cells to secrete IL-6, a messenger cytokine that induces an acute phase response through CRP production.[24] After CANTOS demonstrated the clinical relevance of IL-1β inhibition in the reduction of atherosclerotic events, the inflammatory pathway from NLRP3 to IL-1 to IL-6 to CRP turned into a central target for atheroprotection.[25]

Smooth muscle cells also have critical functions in atherosclerosis. These cells migrate from the media to the intima, where they can proliferate and secrete extracellular matrix macromolecules, contributing to the elaboration of an atheroma fibrous cap. In addition to the known beneficial role in fibrous cap strength and stabilization, smooth muscle cells can actually have a broad participation in atherosclerosis, by secreting chemokines that induce leukocyte recruitment, by transitioning to macrophage-like cells, and by contributing to necrotic core formation upon death.[25]

Adaptive immunity has also a pivotal role in atherothrombosis. MHC class II-expressing cells and T cells are the most representative elements of adaptive immunity in the atherosclerotic plaque.[9] $CD4^+$ T cells are often identified in atherosclerotic plaques. Whereas T helper 1 (Th1) cells have a pro-atherogenic role, producing IFNγ, a cytokine that can promote macrophage activation, and counteract cap formation, regulatory T cells (T_{reg}) present anti-atherogenic functions, by controlling the proinflammatory effects of other cells. Considerable evidence supports the idea that atherosclerosis-specific antigens, such as LDL and its apolipoprotein B (ApoB) drive an immune response, probably started in the lymph nodes.[26] The roles of other Th cell subsets in atherosclerosis, such as Th2 and Th17 among others, are still less understood.[26]

Complications of Atherosclerosis

During a great course of atheroma expansion, the vessel lumen is preserved, and so the blood flow through the affected artery. Flow-limiting lesions leading to tissue ischemia, particularly in the context of higher oxygen demands, result from the incapacity of these lesions to further centrifugal expansion.

Acute vascular events, such as myocardial infarctions and ischemic strokes are, in general, complications of atherosclerosis that result from acute thrombosis. The rupture of a plaque´s fibrous cap allows the interaction between components of the blood and thrombogenic material inside the atheroma, leading to a thrombus formation. Much of the strength of a fibrous cap derives from interstitial collagen, and its thinning, strongly implicated in plaque fracture, likely results from inflammation-related processes.[27] Indeed, inflammatory elements in the atheroma can interfere in both production and degradation of interstitial collagen contributing to the weakening of fibrous cap: cytokines can attenuate smooth muscle cells' collagen production, and inflammatory cells-derived enzymes can break important matrix components.

While plaque rupture accounts for most of the fatal acute coronary syndrome cases, another mechanism, plaque erosion, has been on the rise.[27,28] Widespread use of lipid-lowering therapy may have attenuated the classical vulnerable plaque phenotype, more commonly associated with plaque fissure. Instead, the superficial plaque erosion involves endothelial cell injury and desquamation on the plaque surface, due to activation of toll-like receptor 2, likely linked to local flow disturbance. Circulating granulocytes get trapped, resulting in neutrophils extracellular traps (NETs), which can contribute to thrombus formation.[29]

The critical involvement of inflammatory elements and processes in all phases of atherosclerosis immediately raised the question on the benefit of anti-inflammatory strategies to prevent cardiovascular risk.

Anti-Inflammatory Strategies

Lifestyle Interventions and Clinical Trials

The control and treatment of atherosclerotic cardiovascular disease risk factors result in risk reduction and prevention of future cardiovascular events. Statins have been recognized as a major weapon in the battle against atherosclerosis after the demonstration of a significant reduction of cardiovascular events in several clinical trials.[30] Interestingly, besides reducing LDL-C levels, statins can also reduce inflammation, an effect represented by the fall of CRP levels. In *Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin* (JUPITER), a clinical study that tested whether primary prevention individuals with LDL-C <130 mg/dL and high hs-CRP levels would benefit from a statin, the most favorable clinical outcomes were observed in participants who achieved a reduction in both LDL-C and hs-CRP.[31] Subjects allocated to rosuvastatin group who achieved LDL-C < 70 mg/dL but with hs-CRP > 2 mg/L had 45% reduction in cardiovascular events, while those that achieved both LDL-C < 70 mg/dL and hs-CRP < 2 mg/L had 65% reduction in cardiovascular events.[31] Similar findings were demonstrated in *Pravastatin or Atorvastatin Evaluation and Infection Therapy Trial* (PROVE-IT/TIMI-22) and *The Improved Reduction of Outcomes: Vytorin Efficacy International Trial* (IMPROVE-IT),

which included patients with acute coronary syndrome: individuals that achieved both targets of LDL-C and hs-CRP after statin therapy had better clinical outcomes.[4,5] These data clearly show that a residual inflammatory risk can persist after statin therapy and may represent an important therapeutic target. Both lifestyle intervention and pharmacologic therapies that reduce inflammation could translate in reduction of cardiovascular events as discussed in the following topics.

Lifestyle Interventions

A healthy lifestyle is the primordial intervention to reduce cardiovascular risk, but its practical application is not easy for patients to adhere. Several of lifestyle modifications are known to improve inflammatory processes.[32]

Regular practice of physical exercise of moderate intensity promotes an anti-inflammatory status, and therefore, in long term, prevents the development of chronic diseases.[33] Cumulative evidence suggests that a pro-inflammatory phenotype is favored by physical inactivity, while the regular practice of moderate intensity physical exercise directs the immune response towards a less proinflammatory state.[33,34]

Obesity is also characterized by a low-grade chronic inflammatory status and inflammation likely plays a causative role in the development of insulin resistance.[35] In fact, pro-inflammatory cytokines seem to interfere with insulin signaling in peripheral tissues or induce β-cell dysfunction and subsequent insulin deficiency, increasing the risk of type 2 diabetes.[36] For example, IL-6 inhibits the expression of insulin receptors and reduces adiponectin expression.[37] Increased production of TNF-α in adipose tissue is positively correlated with the degree of obesity, insulin level and insulin resistance.[37] Lifestyle interventions focused on weight reduction are associated with improvement in inflammatory status mainly in obese subjects. A previous randomized study in patients with normal or overweight body mass index (BMI) submitted to 25% caloric restriction for 2 years showed a mean weight reduction of 7.5 kg and a significant reduction in CRP compared to the control group.[38] Another randomized study in obese women compared weight loss intervention with a Mediterranean-style diet versus control, showing a significant reduction in BMI (−4.2 Kg/m2, $p<0.001$) and CRP (−1.6 mg/L, $p=0.008$) in the intervention group.[39]

Smoking increases inflammation and oxidative stress. Previous studies showed that in middle age (about 30 to 69 years of age), mortality among cigarette smokers was two to three times the mortality among otherwise similar persons who had never smoked, leading to a reduction in life span by an average of about 10 years.[40] Moreover, smoking cessation prolongs life expectancy: those who have smoked cigarettes since early adulthood but stop at 30, 40, or 50 years of age gain about 10, 9, and 6 years of life expectancy, respectively, as compared with those who continue smoking.[40] Smoking cessation reduces systemic inflammation. A previous study has showed that only 14 days of smoking cessation returned inflammatory markers like IL-4, IL-6, IL-10 and IL-12p70 towards levels seen in non-smokers ($p<0.05$).[41]

A healthy diet is part of all guidelines for prevention of cardiovascular disease. There are many aspects related to the benefits of a healthy diet, of which we can highlight the improvement in the inflammatory profile. A previous study included 180 patients meeting criteria for metabolic syndrome, who were randomized to a Mediterranean or a control prudent diet.[42] After 2 years, patients on the Mediterranean diet had significantly reduced serum concentrations of hs-CRP, IL-6, IL-7, and IL-18 compared to patients on the control diet.[42] Nonetheless, this finding is not an unanimity in the literature. A small study with 90 subjects with abdominal obesity were placed on a Mediterranean diet for 2 months and compared to a control group.[43] CRP concentrations did not differ between the 2 groups, but there was an improvement on endothelial function in the Mediterranean group.[43] Additionally, consumption of specific elements or nutrients, such as Mg, fiber, ω-3 PUFAs, MUFAs, flavonoids and carotenoids, also seems associated with decreased levels of inflammatory markers in serum.[44]

Taking all the evidence together, one can conclude that a healthy lifestyle including exercise, a healthy diet (Mediterranean pattern, for example), weight reduction in overweight or obese subjects and smoking cessation consist in non-pharmacological anti-inflammatory interventions that can translate in better cardiovascular outcomes and should be strongly emphasized for all patients.

Clinical Trials

In the last decade, several clinical trials testing therapies that modulate inflammation, focusing on the reduction of atherosclerotic cardiovascular disease, were published. We will discuss the main findings of the principal studies (Table 1).

Canakinumab

As previously stated, CANTOS was a landmark trial that showed unequivocally that targeting inflammation should be the next step in treating atherosclerosis.[6] CANTOS assessed whether canakinumab could reduce atherosclerotic risk through reduction of inflammation. Canakinumab is a fully human monoclonal antibody targeting IL-1β, a cytokine that drives the IL-6 signaling pathway.[45] A previous study has showed that IL-1β inhibition with canakinumab markedly reduced plasma levels of IL-6 and hs-CRP.[46] Canakinumab is approved for rare autoinflammatory syndromes and as a second-line biologic agent for rheumatoid disease.[47]

CANTOS enrolled 10,061 individuals with an acute myocardial infarction at least thirty days before enrollment and evidence of persistent inflammation defined as hs-CRP ≥ 2 mg/L despite medical therapy including high-intensity statin.[6] The trial compared three doses of canakinumab (50 mg, 150 mg, and 300 mg, administered subcutaneously every 3 months) with placebo.[6] The median follow-up was 3.7 years. In the 50 mg group there was no significant effect regarding the primary end point.[6] However, a significant effect was observed in the 150 mg group [hazard ratio (HR) vs placebo, 0.85; p = 0.02075].[6] In the 300 mg group, the HR was similar to that in the 150 mg group, but the P value did not meet the prespecified threshold for significance.[6] The 150 mg dose of canakinumab also reduced the secondary cardiovascular end point (HR: 0.83, p= 0.00525).[6] Those individuals who achieved hs-CRP concentrations < 2 mg/L derived the most substantial benefit. Concerning adverse events, more deaths attributed to infection or sepsis occurred in the pooled canakinumab groups.[6] Interestingly, cancer mortality was significantly lower with canakinumab than with placebo. In fact, canakinumab was associated with lower incidence and mortality due to lung cancer.[48] CANTOS trial showed strong evidence that an anti-inflammatory intervention with no change in lipids could result in significant reduction in cardiovascular outcomes. Maybe the most important contribution of CANTOS trial was bringing the concept that treatment of inflammatory residual risk could be the next step in the fight against atherosclerotic cardiovascular disease, since generalized use of canakinumab seems unlikely due to its high cost and increase in fatal infections.

Colchicine

Colchicine acts by impairing leukocyte locomotion and interfering with the assembly of multiple components that comprise inflammasomes.[49] There are studies also suggesting that colchicine may prevent NLRP3 inflammasome activation.[50]

The effect of colchicine on cardiovascular events was first investigated in a randomized, open-label study, the *Low-Dose Colchicine for Secondary Prevention of Cardiovascular Disease* (LoDoCo) trial, that tested whether colchicine 0.5 mg/day prevented recurrent cardiovascular events.[51] This trial included 532 patients with angiographically proven coronary disease, age 35 to 85 years and clinically stable for at least 6 months. In a median follow-up of 36 months, colchicine reduced the composite endpoint (acute coronary syndrome, fatal or nonfatal out-of-hospital cardiac arrest or non-cardioembolic ischemic stroke): 5.3% (colchicine) vs 16% (no colchicine); HR: 0.33; 95% CI 0.18 to 0.59; p= 0.001.[51] More recently, the LoDoCo 2 trial confirmed the benefit of colchicine in chronic coronary heart disease, in a larger placebo-controlled study, showing a reduction of 31% in the composite cardiovascular endpoint.[7]

Colchicine was also studied in patients with acute coronary syndrome. The *Colchicine Cardiovascular Outcomes Trial* (COLCOT) tested whether colchicine 0.5 mg/day could prevent the composite of myocardial infarction (MI), stroke, urgent hospitalization for angina leading to unplanned coronary revascularization, or death from cardiovascular causes in 4745 participants recruited within 30 days of MI.[8] Colchicine led to a 23% reduction in the primary endpoint (HR 0.77, 95% CI 0.67–0.96) during a median of follow-up of 23 months.[8]

The *Colchicine in Patients with Acute Coronary Syndromes* (COPS) trial evaluated the clinical usefulness of colchicine among acute coronary syndrome patients, including ST elevation MI, non-ST elevation MI and unstable angina.[52] A total of 795 patients were included. This trial did not show a benefit from colchicine: during 12-month follow-up, there were 24

Table 1 Summary of Clinical Trials of Anti-Inflammatory Drugs for the Prevention of Atherosclerotic Cardiovascular Events

Acute Coronary Syndrome Population								
Trial	**Population**	**N**	**Intervention**	**Follow-Up**	**Primary End Point**	**Secondary End Point**	**Adverse Events**	**Drug Targeting**
COLCOT[8]	MI within 30 days before enrollment	4745	0.5 mg of colchicine vs placebo	Median: 22.6 months	Death from cardiovascular causes, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina leading to coronary revascularization: 5.5% of the patients in the colchicine group, as compared with 7.1% of those in the placebo group (HR, 0.77; 95% confidence interval [CI], 0.61 to 0.96; P=0.02)	Death from cardiovascular causes, resuscitated cardiac arrest, MI, or stroke; and total mortality occurred in 4.7% of the patients in the colchicine group and in 5.5% of those in the placebo group (HR, 0.85; 95% CI, 0.66 to 1.10)	Nausea was more common in the colchicine group than in the placebo group (1.8% vs 1.0%, P=0.02). Pneumonia event in 0.9% of the patients in the colchicine group, as compared with 0.4% of those in the placebo group (P=0.03)	Various anti-inflammatory properties:[107] inhibits components of NLRP3 inflammasome; binds tubulin and subsequent disruption of cell mitosis, transport activities; inhibits neutrophil migration and adhesion
COPS[52]	18–85 years who presented with ACS (included STEMI, non-STEMI, and unstable angina) and had evidence of coronary artery disease on coronary angiography	795	Colchicine (0.5 mg twice daily for the first month, then 0.5 mg daily for 11 months) or placebo	12 months treatment	Composite of death from any cause, ACS (STEMI/non-STEMI/unstable angina), ischemia driven urgent revascularization, and noncardioembolic ischemic stroke: colchicine group compared with the placebo group: 24 [6.1%] versus 38 [9.5%]; HR 0.65 (0.38–1.09), *p*=0.10	Components of the primary end point as well as hospitalization for chest pain (colchicine vs placebo): • Deaths from any cause: HR 8.20 (1.03–65.61), p=0.047 • Cardiovascular death: HR 3.09 (0.32–29.71), p=0.33 • ACS: HR 0.56 (0.27–1.18), p= 0.13 • Stroke: HR 0.41 (0.008–2.10), p=0.28 • Urgent revascularization: HR 0.26 (0.007–0.092), p= 0.037 • Hospitalization for chest pain: HR 0.34 (0.04–3.31), p= 0.36	Any adverse effect: colchicine 91 (23%) vs placebo 99 (24.8%) Gastrointestinal symptoms: colchicine 91 (23%) vs placebo 83 (20.8%)	See above
Chronic coronary disease population								
Trial	Population	N	Intervention	Follow-up	Primary end point	Secondary end point	Adverse events	Drug targeting
LoDoCo[51]	Angiographically proven coronary disease; age 35 to 85 years; clinically stable for at least 6 months	532	Colchicine 0.5 mg/day or no colchicine	Median: 36 months	Composite of ACS, fatal or nonfatal out-of-hospital cardiac arrest, or noncardioembolic ischemic stroke: 5.3% (colchicines) vs 16% (no colchicines); HR: 0.33; 95% CI 0.18 to 0.59; p= 0.001; number needed to treat: 11	Individual components of the primary outcome and the components of ACS unrelated to stent disease: • ACS: 13.6 vs 4.6; HR: 0.33 (0.18–0.63), p<0.001 • Cardiac arrest: 0.8 vs 0.35; HR: 0.47 (0.04–5.15), p=0.534 • Noncardioembolic stroke: 1.6 vs 0.35; HR: 0.23 (0.03–2.03), p= 0.184	Reported causes of withdrawals from therapy: 7 (2.5%) intestinal upset; 2 (0.9%) myalgia	See above

CIRT[54]	Stable condition with history of myocardial infarction or multivessel coronary disease and either type 2 diabetes or the metabolic syndrome	4786	Low-dose methotrexate (at a target dose of 15 to 20 mg weekly) vs placebo	Median: 2.3 years	Nonfatal MI, nonfatal stroke, or cardiovascular death: incidence rate, 4.13 (methotrexate) vs 4.31 (placebo) per 100 person-years; hazard ratio, 0.96; 95% confidence interval [CI], 0.79 to 1.16	Methotrexate vs placebo: • Death from any cause: 1.80 vs 1.55; HR: 1.16 (0.87–1.56); • Composite of major adverse cardiovascular events plus any coronary revascularization: 5.86 vs 6.15; HR: 0.95 (0.81–1.12) • Hospitalization for congestive heart failure: 0.95 vs 1.0; HR: 0.89 (0.60–1.31) • Composite of major adverse cardiovascular events plus coronary revascularization, hospitalization for congestive heart failure, or death from any cause: 7.30 vs 7.42; HR: 0.98 (0.84–1.14)	Methotrexate was associated with elevations in liver-enzyme levels, reductions in leukocyte counts and hematocrit levels, and a higher incidence of non–basal-cell skin cancers than placebo.	Modulates inflammation via inhibition of aminoimidazole-4-carboxamide ribonucleotide, which leads to elevated adenosine levels[53]
CANTOS[6]	History of MI (at least 30 days before randomization) and had a blood level of high-sensitivity CRP of 2 mg or more per liter	10.061	Three doses of canakinumab (50 mg, 150 mg, and 300 mg, administered subcutaneously every 3 months) vs placebo	Median: 3.7 years	Nonfatal MI, any nonfatal stroke, or cardiovascular death: Placebo: 4.50 events per 100 persons-years 50 mg: 4.11 events per 100 persons-years (HR, 0.93; P=0.30) 150 mg: 3.86 events per 100 persons-years (HR vs placebo, 0.85; P=0.02075) 300 mg: 3.90 events per 100 persons-years (HR vs placebo, 0.86; P=0.0314)	Secondary end point included the components of the primary end point as well as hospitalization for unstable angina that led to urgent revascularization. 150 mg: HR versus placebo 0.83 (P = 0.00525, with a threshold P value of 0.00529). OBS: formal significance testing for the prespecified secondary end point was not performed for the 50 mg group and the 300 mg group	Neutropenia, thrombocytopenia and more deaths attributed to infection or sepsis in canakinumab than placebo	Fully human monoclonal antibody targeting interleukin-1β[45]
LoDoCo2[7]	Patients 35 to 82 years with chronic coronary disease on invasive coronary angiography or computed tomography angiography or a coronary-artery calcium score of at least 400 Agatston units	5522	0.5 mg of colchicine vs placebo	Median: 28.6 months	Cardiovascular death, spontaneous MI, ischemic stroke, or ischemia-driven coronary revascularization occurred in 187 patients (6.8%) in the colchicine group and in 264 patients (9.6%) in the placebo group, with incidence rates of 2.5 and 3.6 events, respectively, per 100 person-years (HR, 0.69; 95% confidence interval [CI], 0.57 to 0.83; P<0.001)	Cardiovascular death, spontaneous MI, or ischemic stroke occurred in 115 patients (4.2%) in the colchicine group and in 157 patients (5.7%) in the placebo group, with incidence rates of 1.5 and 2.1 events, respectively, per 100 person-years (HR, 0.72; 95% CI, 0.57 to 0.92; P=0.007)	Non cardiovascular deaths occurred more frequently among the patients who received colchicine than among those who received placebo, with incidence rates of 0.7 and 0.5 events, respectively, per 100 person-years (HR, 1.51; 95% CI, 0.99 to 2.31)	See above

Abbreviations: MI, Myocardial infarction; ACS, Acute coronary syndrome; HR, Hazard ratio; STEMI, ST elevation myocardial infarction; CRP, C-reactive protein.

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events in the colchicine group compared with 38 events in the placebo group (p=0.09, log-rank).[52] One of the main limitations of this trial was failure to include the target sample size (1009 patients), which may have resulted in lack of power to demonstrate the true benefit of colchicine.[52]

Methotrexate

Methotrexate is commonly used as first-line treatment in auto-immune, inflammatory disease such as rheumatoid arthritis and psoriatic arthritis. Methotrexate modulates inflammation via inhibition of aminoimidazole-4-carboxamide ribonucleotide, which leads to elevated adenosine levels. This effect diminishes inflammation by suppressing pro-inflammatory cytokines (IL-12, IL-6, TNF-α) and upregulating anti-inflammatory cytokines (IL-10 and IL-1 receptor antagonists).[53]

The *Cardiovascular Inflammation Reduction Trial* (CIRT) tested whether use of the anti-inflammatory methotrexate would result in lower cardiovascular event rates among patients with a history of MI or multivessel coronary artery disease who additionally had either type 2 diabetes or the metabolic syndrome.[54] The primary end point was a composite of nonfatal MI, nonfatal stroke, or cardiovascular death. Near the conclusion of the trial, hospitalization for unstable angina that led to urgent revascularization was added to the primary end point.[54] The trial was stopped after a median follow-up of 2.3 years. Methotrexate did not result in lower IL-1β, IL-6, or CRP levels than placebo, and also failed to show reduction in cardiovascular events.[54] There was no difference in the primary end point comparing methotrexate versus placebo, occurring in 201 patients in the methotrexate group and in 207 in the placebo group (incidence rate, 4.13 vs 4.31 per 100 person-years; hazard ratio, 0.96; 95% confidence interval [CI], 0.79 to 1.16).[54] Concerning adverse events, modest leukopenia and elevations of ALT and AST levels were more common in the methotrexate group.[54] There was a larger number of patients with non-basal-cell skin cancer in the methotrexate group (31 vs 10; rate ratio, 3.08; P = 0.002).[54]

At this point comes the question: why is CIRT neutral, while CANTOS showed a positive result? Both trials enrolled patients in stable secondary prevention, however CANTOS included patients with residual inflammatory risk (hs-CRP of 2 mg/L or more), while CIRT did not include a high inflammatory marker as one of the inclusion criteria. As a result, CANTOS patients had higher median baseline hs-CRP: 4.2 mg/L versus 1.6 mg/L in CIRT. In addition, in CANTOS there was a significant reduction in inflammatory biomarkers in the canakinumab group, which was not observed in the methotrexate group of CIRT.

Preclinical Studies and Perspectives

Despite the enormous relevance of CANTOS and the recent colchicine trials in the process of clinical translation of immunomodulatory therapeutics in CVD reduction, these studies have not changed yet the cardiovascular risk management in clinical practice. Besides, as previously mentioned, not all tested anti-inflammatory therapies have demonstrated a cardiovascular benefit in clinical trials. The use of methotrexate in CIRT and several other anti-inflammatory therapies, such as the p38 inhibitor, have failed to reduce cardiovascular events or mortality in patients with CVD.[54] Therefore, a lot of work remains to be done, finding the "right" patients and the "right" inflammatory target to address.

In this section, we will summarize the promising Phase II studies, the ongoing trials targeting the immune system in atherosclerosis and identify important challenges that need to be addressed to advance the translation of novel immunotherapeutics into the clinic. We will also highlight the new therapeutic targets emerging from preclinical studies with the biggest potential for translational results in the medium and long term.

Promising Phase II Clinical Trials and Ongoing Clinical Trials of Anti-Inflammatory Therapies for Atherosclerosis

Cytokine blockers are the first line of biologics for the treatment of chronic inflammatory diseases, including rheumatoid arthritis, inflammatory bowel disease and psoriasis.[55–57] Several cytokine blockers have shown promising results in phase II trials for cardiovascular disease.

IL-1 Blockade (Figure 1)

IL-1 is a well-recognized pro-inflammatory cytokine that drives inflammation in atherosclerosis.[58] It is a family of cytokines, including 11 members, among them IL-1α, IL-1β and IL-18. Studies in mice have shown that IL-1α has a role in the remodeling of arteries during early stages of atherogenesis and also connects the immune system and coagulation through its activation by thrombin, highlighting the importance of this isoform in the pathogenesis of adverse cardiovascular events.[59] The IL-1β isoform stimulates vascular inflammation in later stages of atherosclerosis[60] and had a protective role in advanced atherosclerosis in mice through the promotion and maintenance of a fibrous cap rich in VSMCs and collagen.[60] The levels of IL-1β in human coronary arteries are higher in patients with CAD than in patients with non-ischemic cardiomyopathy.[61] Several options are available for IL-1 blockade, including canakinumab (selective IL-1β targeting) as described above, anakinra (a recombinant human IL-1 receptor antagonist (IL-Ra) that blocks signaling by both IL-1β and −1α) and xilonix (a monoclonal antibody specifically targeting IL-1α).

Anakinra

In two separate studies, therapy with anakinra significantly reduced hs-CRP levels in the acute setting in patients with ACS compared with placebo.[62,63] Anakinra has also been evaluated in a Phase 2 trial involving 182 patients with NSTEMI.[63] Results have showed that during the 14-day treatment period, CRP and IL-6 levels were significantly lower in the anakinra group. However, by day 30, the hs-CRP levels in patients treated with anakinra were significantly higher than in the placebo group, and an unexpected increase of late recurrent ischemic events was observed. Interestingly, a recent study carried out by the Interleukin-1 Genetics Consortium supports the hypothesis that long-term IL-1 inhibition may be associated with an increase in cardiovascular events. In this study, individuals who carried four IL-1Ra raising alleles were found to have an increased odds ratio for coronary heart disease (1.15) compared to those carrying no IL-1Ra raising alleles.[64] Whether anakinra will be taken into a Phase 3 study to assess for clinical outcome is still unclear. In summary, the relationship between IL-1 targeting and clinical outcomes seems more complex than originally thought. Further understanding of the distinct roles of the different IL-1 isoforms would enhance our understanding of clinical trial data and improve future trial design.

Xilonix

Xilonix is an immunoglobulin G1 monoclonal antibody specific for human IL-1α. Therapy with xilonix plus standard of care showed a non-significant trend towards a reduction in restenosis and the incidence of major adverse cardiovascular events compared with standard of care only in patients undergoing percutaneous femoral artery revascularization.[65] Xilonix did not have a significant impact on hs-CRP levels; however, the cohort of patients had unusually high CRP levels at baseline with important intragroup and intergroup differences. Given the substantial body of evidence implicating IL-1α in the pathogenesis of atherosclerosis, xilonix may be worthy of further consideration in phase 2 trials in patients with CAD.

IL-6 Blockade (Figure 1)

Interleukin-6 is a pleiotropic cytokine involved in different pathways of the immune system. It can result in both pro- and anti-inflammatory responses that can be explained by the different signaling arms engaged. Although IL-6 has traditionally been viewed as an inflammatory cytokine, in fact, it has become clear that most of IL-6–dependent inflammation may be related to IL-6 binding to its soluble IL-6 receptor (sIL-6R). This is termed IL-6 trans-signaling and activates a pro-inflammatory pathway. On the other hand, IL-6 binding of transmembrane IL-6 receptor (mIL-6R) does not always lead to inflammatory cell activation. Prolonged activation of STAT3 downstream of mIL6R signaling is involved in several physiological processes and is indeed anti-inflammatory.[66] Thus, although IL-6 injection into mice exacerbates atherosclerosis,[67] lifetime total IL-6 deficiency is not protective; it accelerates atherosclerosis, and may lead to increased serum cholesterol levels.[68] In contrast, selective targeted modulation of IL-6 trans-signaling reduces atherosclerosis.[69] Data from humans show that elevated IL-6 levels in the plasma are associated with an increased risk of MI, and genetic studies have provided evidence of a causal role for IL-6 receptor signaling in CVD.[70,71] Targeting the IL-6 axis may be crucial to reduce the residual inflammation responsible for the increased risk of cardiovascular events.

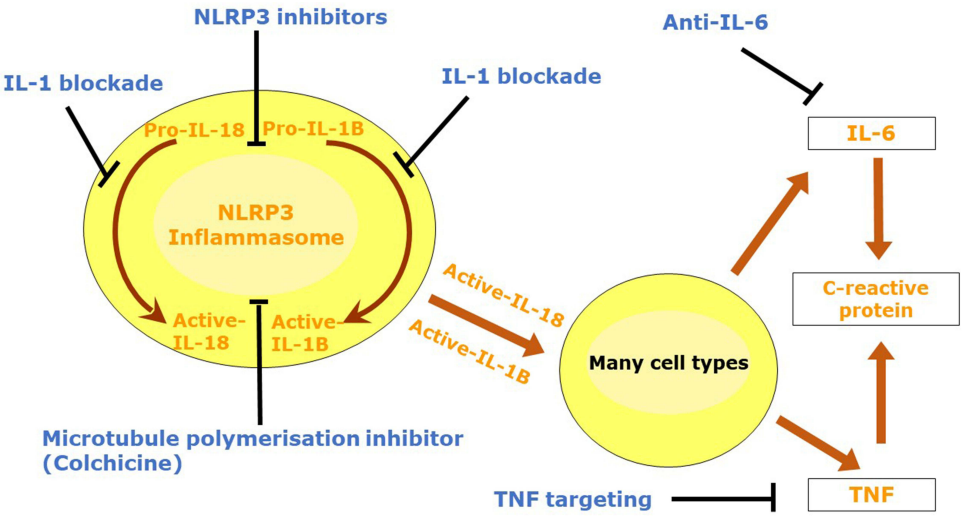

Figure 1 Therapies targeting inflammation and atherosclerotic cardiovascular disease (ASCVD) prevention. This figure summarizes some of the main inflammatory targets for CVD prevention and their directed therapies: NLRP3 and microtubule polymerisation inhibitors, IL-1 and IL-6 blockade and TNF targeting.

Several clinical trials have tested the therapeutic benefit of targeting the IL-6 axis using Tocilizumab. Tocilizumab is a humanized anti-IL-6R antibody that blocks IL-6R signaling through both the membrane and trans-signaling routes. Tocilizumab was tested in a phase 2 trial in 117 patients with NSTEMI and led to a decrease in hs-CRP levels in patients with NSTEMI[72] compared with placebo. In the ASSAIL-MI Trial, tocilizumab therapy also significantly increased the myocardial salvage index in patients with STEMI;[73] however, the absolute difference between the tocilizumab and placebo groups was only 5.6%, meaning that this increase might be of limited clinical relevance.

It is important to keep in mind that although tocilizumab treatment mirrors the impact of the *IL6R* genetic variant on downstream inflammatory biomarkers, it is also associated with increased circulating levels of cholesterol and triglycerides, unlike the *IL6R* genetic variant, which does not alter lipid parameters.[71] Therefore, there is a risk that the potential anti-inflammatory and atheroprotective effects of tocilizumab may become compromised in the long-term.

In a phase II trial published in 2021 (RESCUE), IL-6 blocking with the monoclonal antibody ziltivekimab dramatically reduced hs-CRP levels in patients with chronic kidney disease, individuals who are at high atherosclerotic risk,[74] with no relevant toxicity or adverse changes in lipid markers. Follow-up studies, including the ZEUS trial,[75] a large-scale study with ziltivekimab versus placebo in individuals with established atherosclerotic cardiovascular disease, chronic kidney disease and systemic inflammation, will provide a more complete picture of the clinical relevance of IL-6-targeted therapies in CVD.

Despite the promising results, higher-powered studies are required to better evaluate the safety and efficacy of current IL-6 targeting agents in atherosclerosis prevention. Besides, detailed understanding of the distinct roles of membrane and trans-signaling pathways of IL-6 should lead to development of more specific and safer therapies in the future.

TNF Targeting (Figure 1)

Alternatives to IL-1 and IL-6 blockade include TNF blockers since preclinical and clinical research has demonstrated a pro-atherogenic role for this cytokine.[76]

TNF is a pro-inflammatory cytokine mainly produced by macrophages, T cells, endothelial cells and smooth muscle cells (SMCs).[77] In humans, TNF is highly expressed in human atherosclerotic plaques and its levels in peripheral blood predict future coronary events in patients with MI.[78]

In observational studies in patients with arthritis, inflammation was a strong risk factor for cardiovascular events, and TNF blockade resulted in reduced atherogenesis and lower incidence of cardiovascular events compared with patients not receiving TNF-blocking therapy.[79] Two meta-analyses also confirmed that RA patients treated with anti-TNF therapy had a lower risk of cardiovascular events in comparison with patients treated with antirheumatic drugs.[80,81]

Currently, five different anti-TNF drugs are approved for clinical use, including the soluble TNF-receptor (etanercept) and TNF monoclonal antibodies (adalimumab, infliximab, golimumab, and certolizumab pegol). Among them, adalimumab and golimumab have shown promising results.

Three small studies (two in RA patients and one in psoriatic patients) showed that treatment with adalimumab improves endothelial-dependent vasodilatation.[82,83] However, a larger study[84] including 107 psoriatic patients randomized to receive either adalimumab for 52 weeks or placebo for 16 weeks followed by adalimumab for 36 weeks (per-protocol setting), showed no difference in vascular inflammation at 16 weeks. At the 52-week time point, there was no difference observed in the ascending aorta with adalimumab, but a modest increase in vascular inflammation in carotids was described.[84] Thus, the effect of adalimumab in ASCVD remains unclear.

Golimumab is a fully humanized monoclonal anti-TNF antibody approved for the treatment of RA, ankylosing spondylitis (AS), psoriatic arthritis, and ulcerative colitis. It has been studied in patients with ASCVD with encouraging results[85] in a randomized, double-blind, placebo-controlled trial aimed to assess the efficacy of golimumab in preventing atherosclerosis progression and arterial stiffness in AS patients. A total of 20 patients received 50 mg of golimumab monthly, with 21 receiving placebo treatment, for 1 year. After one year, no significant change in vascular parameters (ie aortic stiffness, carotid intima/media thickness) was observed between the two groups. However, a significant progression of the mean intima-media thickness (IMT) was only seen in the placebo group and not in the golimumab group. Further large-scale studies are needed to fully validate the potential effects seen in this study.

Interestingly, a recent meta-analysis including 7697 coronary artery disease (CAD) patients and 9655 controls has investigated the association of TNF gene polymorphisms and CAD susceptibility.[86] The authors concluded that the TNF-α 238G/A genotype showed a significant association with higher CAD susceptibility in the subgroup of Europeans and North Asians, suggesting a direct role of TNF in CAD. On the other hand, several studies described an adverse effect of TNF inhibitors on lipid profiles with increase of total cholesterol and triglycerides levels.[87] In summary, further large-scale studies are required to evaluate the potential benefits of anti-TNF agents.

Hydroxychloroquine

Other alternative therapeutic target currently being tested in trials is hydroxychloroquine. Hydroxychloroquine is an antimalarial and a disease-modifying antirheumatic drug largely used for the treatment of inflammatory rheumatic diseases, especially systemic lupus erythematosus (SLE) and RA. The most important mechanisms to explain the immunomodulatory actions are its ability to reduce inflammatory pathways and Toll-like receptors activation, reducing the production of pro-inflammatory cytokines, including type I interferons.[88] In observational studies, hydroxychloroquine therapy was associated with a 72% decrease in the risk of cardiovascular events in patients with RA and a 68% reduction in thromboembolic events in patients with SLE.[89] Hydroxychloroquine is currently being tested in clinical trials in patients with coronary artery disease.[90]

NLRP3 Inhibitors (Figure 1)

Despite the importance of the NLRP3 inflammasome in several inflammatory diseases, there is currently no approved inflammasome inhibitor for the treatment or prevention of atherosclerosis. Nevertheless, many small molecule compounds targeting the NLRP3 inflammasome have been developed, with promising results. Importantly, both canonical and non-canonical NLRP3 activation pathways can be targeted.

MCC950

MCC950 is a small molecule inhibitor of the NLRP3 pathway, with a mechanism which is yet to be fully understood.[91] Nevertheless, it was found to reduce atherosclerotic lesion formation in ApoE -/- mice, which was associated with decreased expression of the adhesion molecules ICAM-1 and VCAM-1, as well as reduced macrophage infiltration within plaques and no change in necrotic core size.[92] This early data suggests that MCC950 represents an interesting candidate to target NLRP3-induced inflammation in atherosclerosis.

Tranilast

Tranilast, which was originally used to treat allergy, was shown to inhibit NLRP3 by facilitating its ubiquitination and impairing ASC oligomerization.[93] Tranilast decreased the initiation and progression of atherosclerosis in mice.[94] Thus, pharmacologic manipulation of NLRP3 ubiquitination offers a potential strategy of atheroprotection. Despite encouraging results in animal models, many questions remain to be answered concerning the safety of NLRP3 inhibitors. It will be critical to further examine how these compounds affect the activity of other inflammasomes and how the host immune response is affected in the long run. The initiation of new clinical trials evaluating the benefit of NLRP3 inhibitors in the context of cardiovascular diseases will also depend on these factors.

Low Doses of IL-2 Therapy

Interleukin-2 is a cytokine that plays a key role in the regulation of T cell activity and survival. Although IL-2 has the ability to regulate all T cells, it appears to be particularly important in the development and survival of Tregs,[95] which have a role in the control of inflammation.

Low-dose IL-2 therapy has been studied in patients with SLE, RA and psoriasis. The principle of using low doses of IL-2 for the treatment of inflammatory diseases is based on the differential sensitivity of distinct immune cell subsets to IL-2. The activation threshold for Tregs is lower than for other effector T cells,[96] owing to elevated surface expression of the IL-2 receptor subunit-α (also known as CD25) and the high-affinity of IL-2 receptor complex in this cell subset, which may explain the somewhat paradoxical effect of IL-2 therapy. While high-dose IL-2 therapy is thought to promote effector immunity, low-dose IL-2 stimulates immunosuppressive Tregs[97] and the expression of functional markers, such as CD25, in patients with other inflammatory diseases. Preclinical studies have shown that administration of recombinant IL-2 complexed with monoclonal antibodies against IL-2 increases the levels of Tregs and reduces atherosclerotic plaque burden in mice.[98] The ongoing phase II LILACS clinical trial is testing low-dose IL-2 therapy in patients with stable ischemic heart disease and acute coronary syndromes and aims to assess the safety and tolerability of escalating doses of recombinant IL-2, as well as its ability to alter Treg, effector T cell and other immune cell populations. Preliminary results indicate the treatment is well tolerated and induces robust increases in Tregs without affecting effector T cells. Interestingly, a dose-dependent reduction in B cells was also seen, which may have further beneficial effects on atherosclerosis.[99] The subsequent phase II IVORY trial will assess changes in vascular inflammation in patients with acute coronary syndromes with low-dose IL-2 (NCT04241601- Low-dose Interleukin-2 for the Reduction of Vascular Inflammation in Acute Coronary Syndromes (IVORY)). One limitation of low-dose IL-2 therapy is potential off-target effects, which include mild increases in NK cells and eosinophils.[99] Furthermore, initially protective Tregs may undergo a phenotypic switch toward a proinflammatory TH1-like phenotype with progressing disease in mice.[100] It remains to be addressed whether this switch can occur in humans.

Potential Future Therapies in Preclinical Development

There are currently several promising cellular and molecular therapeutic targets that have not yet made to the clinical trial phase but are in active development. These include strategies that interfere with immunometabolic processes and trained immunity, focusing on transcriptomic, epigenetic and metabolic rewiring of innate immune cells;[101] strategies that interfere with the pro-inflammatory signaling pathways CD40-induced tumor necrosis factor receptor-associated factor (TRAF) signaling in macrophages,[102] strategies that inhibit CD47 signaling to reduce atherosclerosis by enhancing efferocytosis[103] and strategies as anti-CD20 mediated B cell depletion that could ameliorate the development of several cardiovascular pathologies including atherosclerosis.

One of the potential and hopeful approaches is the favorable modulation of atherosclerosis by vaccination by using antigens relevant to atherosclerosis. This would involve the development of antigen-specific antibodies or induction of antigen-specific Treg cells or other athero-protective immune responses. However, some obstacles that we must overcome are the identification of relevant antigenic epitopes in human atherosclerotic disease and some difficulties in vaccine design (for example, choice of the adjuvant, safety, and stability).

Finally, multiple experimental studies have also demonstrated that smooth muscle cell and endothelial cell phenotypic modulation can modify atherosclerosis, opening a new avenue for therapeutic possibilities.[104,105] For instance, whereas

transforming growth factor-β (TGF-β) can transform endothelial cells into pro-inflammatory cells, inhibition of TGF-β-receptor signalling in endothelial cells can reverse atherosclerosis in mice.[105]

Use of Anti-Inflammatory Therapy in Clinical Practice

Despite the strong evidence that targeted immunomodulation can reduce atherothrombotic events, further studies, particularly on safety, are still lacking for a consensual recommendation of anti-inflammatory therapies. Nevertheless, the 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice suggest low-dose colchicine (0.5 mg o.d.) as a class IIb recommendation in selected high-risk individuals, such as those in secondary prevention of CVD with other insufficiently controlled risk factors of if recurrent CVD events occur under optimal therapy.[106]

Conclusion

Our understanding of the relevance of inflammation in atherosclerosis has dramatically improved over the past decades and the immune system plays a major role in the onset, progression, and complications of atherosclerosis. Recent clinical trials finally answered an important question, demonstrating that modulation of inflammation can reduce cardiovascular events. Still, the inflammatory network operating in atherosclerosis includes several branches, and selecting the best target is very challenging. As previously mentioned, not all the anti-inflammatory agents tested provided a cardiovascular benefit and/or have led to unwanted side effects, such as increased infections. Indeed, anti-inflammatory therapies can depress host defense mechanisms, and thus identifying the most appropriate agent, and the patients who could benefit the most, will be mandatory to increase the net clinical benefit. Therefore, further research remains to be done until the proper balance between favorable and harmful effects on selected patients is found. More targeted approaches using biologics, vaccination and cell-targeted delivery approaches might allow specific destination of atherosclerotic anti-inflammatory agents and thus minimizing off-target effects. It is important to emphasize that not all patients should receive anti-inflammatory therapy, pointing toward the era of personalized and precision medicine.

Disclosure

Dr Viviane Zorzanelli Rocha reports personal fees from Amgen, personal fees from Novartis, personal fees from NovoNordisk, personal fees from Astra Zeneca, personal fees from Aché, personal fees from GSK, personal fees from BIOLAB outside the submitted work. Dr Marcio Hiroshi Miname reports personal fees from NovoNordisk, personal fees from Aché, personal fees from Amgen, outside the submitted work. The authors report no other conflicts of interest in this work.

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