Current therapies focusing on cardiovascular disease (CVD) event prevention largely target low-density lipoprotein cholesterol (LDL-c) reduction or inhibition of platelet function. Despite the widespread use of these medication classes, CVD has remained the number one cause of death since 1911, and still accounts for approximately 30% of deaths globally [1].

A new frontier in therapeutics is the targeting of inflammation as a modifiable CVD risk factor. It is widely accepted that inflammation contributes to atherothrombosis [2] and that markers of inflammation including C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and IL-1 are associated with CVD events [3,4]. Statin therapy reduces inflammatory markers [5,6] and the JUPITER (Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin) Study demonstrated a significant reduction in CVD events in patients with elevated CRP (>2.0 mg/l) but normal LDL-c levels (<130 mg/dl) treated with rosuvastatin.

The Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) was the first randomized, double-blind trial to directly study the ‘inflammatory hypothesis’ [7-9]. Canakinumab is a therapeutic monoclonal antibody targeting IL-1β (part of the IL-1 and IL-6 signaling pathways), thereby reducing inflammation. CANTOS examined the impact of canakinumab on cardiovascular events in patients with elevated CRP (>2.0). Over a median of 3.7 years follow-up, the absolute risk reduction of canakinumab compared to placebo was small (0.64%) and unfortunately patients with lower CRP levels were not studied.

In 2019, more data testing the inflammatory hypothesis are anticipated, including the results of the Cardiovascular Inflammation Reduction Trial (CIRT) [8]. CIRT has enrolled 7000 patients who are post-myocardial infarction or have documented multivessel coronary disease and either diabetes or the metabolic syndrome. Patients have been randomized to methotrexate 20 mg weekly (which has been shown to reduce TNF-α, IL-6 and CRP) or placebo. Together with CANTOS, these trials will have enrolled approximately 25,000 patients testing the inflammatory hypothesis.

The results from these trials may spark a new anti-inflammatory approach to secondary prevention for CVD and possibly pave the way for a new wave of drugs targeting inflammation. The effects of tocilizumab (a monoclonal humanized antibody that blocks the IL-6 receptor) on endothelial function were recently examined in a randomized controlled trial in patients with rheumatoid arthritis. Although tocilizumab worsened the lipid profile, it improved flow-mediated arterial dilation (from 3.43 to 5.96%, P = 0.03) [9]. This suggests that reducing inflammation may provide CVD benefits, even when adversely affecting a traditional risk factor.

It remains to be seen whether the Food and Drug Administration will provide approval for these agents and how insurance companies will react to their cost, given their modest clinical benefits in comparison to current pharmaceuticals like statins, which reduce CVD risk by approximately 30% [10,11]. Administration of canakinumab may prove prohibitively expensive. For comparison, a recent cost-effectiveness analysis of evolocumab, a PCSK9 inhibitor, required a 71% price reduction ($14,542–$4217) to demonstrate cost-effectiveness at the level of $100,000 per quality adjusted life year [12]. It will also be interesting to see how CRP is incorporated into future risk prediction algorithms and if universal screening with CRP will eventually be recommended.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING
Papers of particular interest, published within the annual period of review, have been highlighted as:
★ of special interest
★★ of outstanding interest

8. Landmark randomized clinical trial showing the efficacy of using a fully human monoclonal antibody targeting inflammation in reducing the risk of cardiovascular events.
11. A trial demonstrating the positive effect of IL-6 inhibition with tocilizumab, a monoclonal humanized antibody, on endothelial function response. Despite worsening the lipid profile, endothelial function was improved with therapy.

FURTHER RECOMMENDED READING

This article provides a discussion of key therapeutic targets of vascular inflammation and the data from basic science that support the causal role of these targets in the development of atherothrombosis. This review also points to recent clinical data that led to the ongoing trials that are testing the inflammatory hypothesis of CVD.


A review of the evolution of treatment options for atherosclerosis and atherothrombosis. The authors also discuss future pathways to target and combinations of drugs that reduce cardiovascular risk and are likely to be investigated further.


A holy grail of cardiovascular intervention has been identification of vascular plaques that are most likely to rupture. Instability of plaques appears to be driven by localized inflammation. The authors describe a new imaging metric which they label as the ‘perivascular fat attenuation index’ that may assist in the early detection of coronary inflammation and identify high-risk plaques and patients.