Thirtv years ago, a diagnosis of rheumatoid arthritis (RA) resigned the majority of patients to a lifetime of chronic inflammation and progressive joint destruction. With the potent disease-modifying antirheumatic drugs (DMARDs) available today, severe disability from RA is the exception rather than the rule. Now, the leading cause of mortality in RA is cardiovascular disease. In fact, the risk of cardiovascular disease in RA is 1.5 times that of age- and sex-matched individuals from the general population. This excess risk in RA has been attributed to chronic inflammation rather than a higher prevalence of traditional cardiovascular risk factors. Large observational studies show that treatment with DMARDs, such as methotrexate and tumor necrosis factor inhibitors, is associated with reduced cardiovascular risk. The exact mechanisms linking inflammation with cardiovascular risk remain unclear. Studying pathways shared by both RA and atherosclerosis may provide insight into potential mechanisms of risk.

Patients with RA differ from the general population in both the magnitude and variability of inflammation they experience. As an example, a C-reactive protein (CRP) level of ≥3 mg/L is considered a marker for elevated cardiovascular risk and is high for an individual from the general population. In comparison, the mean CRP in a cohort of treated patients was 9.7 mg/L. Fluctuations in CRP >50% routinely occur as part of RA flares and treatment. This amplification of fluctuations in the levels of inflammation provides a unique opportunity to study the association of changes in inflammation with physiological parameters of cardiovascular risk such as flow-mediated dilatation and coronary flow reserve.

Treatment of RA with DMARDs targets preventing joint damage by controlling inflammation. Anti-cytokine DMARDs are directed at specific inflammatory mediators that are also involved in the pathogenesis of atherosclerosis: tumor necrosis factor-α, interleukin-6 (IL-6), and interleukin-1 (IL-1). Treatment of RA with these DMARDs provides a natural experimental system to study the effect of inhibition of specific inflammatory pathways on different aspects of cardiac and vascular function.

In this issue of Circulation: Cardiovascular Imaging, Ikonomidou et al.12 study the association between short-term IL-1 inhibition on cardiac and vascular function, as well as markers of oxidative stress and apoptosis. They conducted a randomized, double-blind crossover trial of 80 patients with RA: 60 with pre-existing coronary artery disease (CAD) and 20 without known CAD. Each subject was randomized to either receive an IL-1 receptor antagonist (anakinra) or placebo at baseline, with crossover at 48 hours; the half-life of anakinra is only 4 to 6 hours. They studied a wide range of cardiac and vascular physiological measurements including vasomotor function as measured by flow-mediated dilatation and coronary flow reserve, arterial compliance and resistance, and left ventricular (LV) myocardial function assessed by echocardiograms including ejection fraction, myocardial velocity, and LV rotation and twisting. In addition, they measured markers of oxidative stress and apoptosis: malondialdehyde, nitrotyrosine, protein carbonyls, and Fas and Fas ligand levels before and after the intervention. The investigators included a third comparison group consisting of 30 controls without RA recruited from an outpatient cardiology clinic with similar age, sex, and cardiovascular risk factors to the 80 patients with RA. These controls had the same physiological and biomarker measurements as the patients with RA at baseline but did not receive an intervention.

The investigators highlight that baseline IL-1β was significantly higher in RA patients with CAD compared with those without CAD. After anakinra therapy, all patients with RA experienced significant improvements in vasomotor function as measured by flow-mediated dilatation and coronary flow reserve, as well as systemic arterial compliance and vascular resistance. Similarly, significant improvements were observed in myocardial velocity measured by tissue Doppler and LV twisting by speckle tracing in both groups. For all measurements, the magnitude and significance of improvements were higher in RA patients with CAD compared with RA patients without. Levels of nitrotyrosine, malondialdehyde, protein carbonyls, and Fas and Fas ligand were also reduced in all subjects who received anakinra. No significant differences were observed in either the physiological or biomarker measurements after placebo. Ikonomidou et al.13 published similar findings in a 2008 study of 23 RA patients without CAD.
using anakinra and the same randomized, placebo-controlled crossover design. They observed improvements in both vascular and LV function after anakinra administration compared with placebo. The inclusion of RA patients with CAD in this study provides additional information potentially more relevant to patients with CAD.

This study raises several questions. First, the authors highlight a difference in CRP and IL-1β levels at baseline between the CAD and non-CAD groups. The RA patients with CAD had similar levels of CRP and RA disease activity to those without, but the difference between IL-1β between the 2 groups was significant (3.8 versus 0.35 pg/mL). The RA disease activity score (which includes CRP) is highly correlated with IL-1β levels in RA. Because the disease activity scores were similar in both groups, we would not expect a significant difference in the IL-1β levels, regardless of the CAD status. Second, the investigators conducted several physiological and biomarker measurements. Although the authors report correction for the level of significance to account for multiple comparisons, in most instances they maintained a P<0.05 cutoff. Precise P values were also not reported, leaving the readers to wonder whether any of the significant associations were because of chance. Finally, the outcome measures were conducted after 3 hours, and it would be interesting to know the durability of these responses in a long-term study.

In the Clinical Perspective segment of this article, the authors state that anakinra may become the treatment of choice for patients with RA and CAD. Because anakinra is seldom used clinically for RA, this is a bold statement. Anakinra has less efficacy in controlling joint pain and damage in RA than other anti-cytokine DMARDs. As a result, anakinra was not discussed in the 2012 American College of Rheumatology RA treatment guidelines. Furthermore, the patients in this study may not be representative of a typical RA population, limiting the generalizability of these findings. The mean baseline disease activity score of both the CAD and non-CAD groups was moderate to high, suggesting that the patients had an inadequate response to their current RA treatment regimen. For these patients, the 2012 American College of Rheumatology and the 2013 European League Against Rheumatism treatment guidelines would recommend escalation of therapy such as initiating an anti-cytokine DMARD in the near future. In current practice, the majority of patients would start a tumor necrosis factor inhibitor as the next step, which data suggest may confer similar cardiovascular benefits as IL-1 inhibition. This leads us to our final point which is whether the improvements in cardiac and vascular function observed in this study were a result of specific IL-1 inhibition or a general response to reduction in inflammation. This question cannot be answered based on data from this study because inflammatory markers were not measured at follow-up. In their previous study, the inflammatory markers IL-6 and CRP were measured before and after anakinra administration. The authors reported a significant reduction in IL-6 but not CRP at 3 hours. In the nonrandomized arm of patients with RA who received anakinra for 30 days, the authors reported a significant reduction in both IL-6 and CRP. These data suggest that IL-1 inhibition is associated with a reduction in other markers of inflammation, as would be expected based on previous RA clinical trial data of anakinra. The correlations between reduction in IL-6 and CRP with improvements in cardiac and vascular function suggest that other anti-cytokine DMARDs may provide similar benefits. The authors should be encouraged to consider similar trials with tumor necrosis factor inhibitor agents.

Despite the limitations of this study, we think that Ikonomidis et al provide additional mechanistic insight into the relationship between inflammation and cardiovascular risk. Similar to their previous work, they demonstrated that reducing inflammation with an IL-1 inhibitor results in significant short-term improvements in vasomotor and LV function. The novelty of this study is that RA patients with concurrent CAD experienced greater improvements in cardiac and vascular physiological function compared with RA patients without CAD, with the caveat that patients with CAD began with poorer function at baseline. If we assume that the patients with CAD were optimally managed with cardiovascular disease treatments, this study implies that we can be doing more for patients with RA by reducing inflammation. These findings also suggest that reducing inflammation in patients with CAD from the general population can improve cardiovascular risk. This question is being addressed in an ongoing clinical trial, Cardiovascular Inflammation Reduction Trial (CIRT), a randomized controlled trial investigating whether methotrexate therapy in patients with known CAD (without RA) reduces risk for a future cardiovascular disease event; a similar trial is also investigating canakinumab, an IL-1β inhibitor. Additional studies are needed to understand whether other DMARDs are associated with similar improvements in cardiac and vascular function followed by a careful weighing of the risks and benefits of these therapies.

Disclosures
None.

References


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Mechanistic Insights Into the Link Between Inflammation and Cardiovascular Disease: Rheumatoid Arthritis as a Human Model of Inflammation
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