EDITORIAL

# Pretenders and Contenders: Inflammation, C-Reactive Protein, and Interleukin-6

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The initiation of atherosclerosis and its progression to an acute coronary syndrome (ACS) are intricate processes with many factors, but one central factor is inflammation. Interleukin-6 is a proinflammatory cytokine that may have a role in the initiation, progression, and vulnerability of atherosclerotic lesions. Interleukin-6 works upstream of CRP (C-reactive protein) and downstream of interleukin-1β and triggers its proinflammatory response via activation of membrane-bound interleukin-6 receptors on the cell surface. Epidemiologic studies and large meta-analyses have found an association between both interleukin-6 and CRP levels and risk of coronary heart disease (CHD) among apparently healthy men[1] and women.[2–4] An association between both markers and increased mortality has also been described in patients with unstable coronary disease.[5–7]

Although the association between CHD and both CRP and, to a lesser extent, interleukin-6 is well documented, establishing a direct causative role for these inflammatory cytokines is more challenging. Two large Mendelian randomization analyses implicated the interleukin-6 pathway as potentially causative in CHD.[8,9] In these studies, genetic polymorphisms leading to increased levels of the soluble interleukin-6 receptor were associated with a decreased risk of CHD. Together, these studies suggested interleukin-6 and interleukin-6 receptor may be reasonable targets for therapeutic intervention aimed at preventing CHD. On the other hand, Mendelian randomization studies have to date not found evidence of a link between genes related to CRP and CHD outcomes.[10,11]

In this issue of *JAHA*, 2 new studies provide additional evidence of an association between interleukin-6 and cardiovascular disease (CVD).[12,13] Both are large, prospective substudies of previously reported randomized clinical trials of darapladib, an anti-inflammatory lipoprotein-associated phospholipase $A_2$ (Lp-$PLA_2$) inhibitor. Lp-$PLA_2$ is a proinflammatory enzyme secreted by macrophages. Like interleukin-6 and CRP, levels of Lp-$PLA_2$ have been linked to risk of CVD. In both parent trials (one in patients with stable, chronic coronary artery disease and the other in patients within 30 days of an ACS), darapladib did not result in any significant reduction in the primary outcome (the composite of cardiovascular death, myocardial infarction [MI], or stroke in the STABILITY [Stabilization of the Atherosclerotic Plaque by Initiation of Darapladib Therapy ] trial, and major coronary events in the SOLID-TIMI 52 [Stabilization of Plaque Using Darapladib-Thrombolysis in Myocardial Infarction 52] trial). The substudies now reported were performed to assess the independent association between interleukin-6, high-sensitivity (hs)-CRP, and other markers of inflammation, with incident CVD.

Held and colleagues[12] report on the results derived from >14 000 stable patients with CHD from the STABILITY trial. During a median 3.7-year follow-up, higher baseline interleukin-6 levels were significantly and independently associated with incident cardiovascular events, including cardiovascular death, MI, and heart failure, but not stroke; they were also associated with noncardiovascular death and cancer. These associations remained significant even after adjusting for clinical variables and other prognostic biomarkers, including hs cardiac troponin T, NT-proBNP (N-terminal pro-B-type natriuretic peptide), cystatin-C, hs-CRP, and others. In contrast, hs-CRP was not independently associated with any of these outcomes on adjusted analyses.

In the second study, Fanola and colleagues[13] present results from >4000 subjects enrolled in the biomarker cohort of the SOLID-TIMI 52 trial. This study included patients within 30 days of an ACS who were followed up for a median of 2.5 years. Baseline interleukin-6 concentrations were measured a median of 14 days from the ACS event. Similar to the STABILITY trial, these authors found that higher interleukin-6 concentrations were independently associated with an



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increased risk of cardiovascular events, including cardiovascular death or heart failure, but not stroke, after adjusting for clinical variables and other biomarkers. The association appeared to be stronger after ST-segment elevation MI compared with non–ST-segment elevation MI, but was independent of left ventricular ejection fraction and management strategy. The magnitude of the association between interleukin-6 and CHD (24% increased risk per SD increase in log interleukin-6 concentrations) was also similar to that seen in a recent large meta-analysis of individuals without clinical CVD.[3]

Interleukin-6 concentrations were not independently associated with stroke in either study, and although the reason for this is not immediately clear, it could be because of the heterogeneous nature of this diagnosis. In both studies, ischemic stroke included thrombotic and embolic entities, and the role of inflammation in embolic stroke may be negligible.

Median interleukin-6 concentrations in both cohorts were higher, as expected, than those seen in cohorts free of overt CVD, where baseline interleukin-6 concentrations tend to average in the 1.3 to 1.6 pg/mL range.[1–3] More surprising is that the median interleukin-6 concentration in the SOLID-TIMI 52 population of patients with recent ACS was similar to, and not higher than, that in the SOLID-TIMI 52 population of patients with stable CHD (2.1 versus 2.0 pg/mL, respectively). This might reflect the fact that the STABILITY population was, itself, a high-risk population.

In both studies, there was a significant association between interleukin-6 and heart failure. The SOLID-TIMI 52 authors suggest that this may reflect induction of matrix metalloproteinase expression by interleukin-6 and subsequent progression of fibrosis and cardiac remodeling. This is an intriguing hypothesis that could be explored further by examining how interleukin-6 relates to various blood and imaging markers of fibrosis.

Key takeaways from these informative and thorough analyses include the fact that not all inflammatory markers are created equal. For years, there has been debate about hs-CRP as mediator versus bystander, and although these studies do not provide the definitive answer, they provide yet another piece of evidence that we can probably do better than hs-CRP for risk stratification. Despite its role in certain risk prediction algorithms, hs-CRP seems to provide little to no added benefit once clinical variables and other markers are accounted for. Moving upstream from hs-CRP to interleukin-6, in contrast, appears to provide a risk marker that is not only more robust, but that also may well be on the causal pathway for atherosclerosis and plaque instability.

Moving yet further upstream, canakinumab is a human monoclonal antibody against interleukin-1β, a cytokine that drives the interleukin-6 signaling pathway. As demonstrated in the recent CANTOS (Canakinumab Antiinflammatory Thrombosis Outcome Study) of patients with a previous MI and elevated hs-CRP level, canakinumab at the 150-mg dose level lowered interleukin-6 levels without a reduction in low-density lipoprotein cholesterol and also lowered the incidence of the primary end point (nonfatal MI, nonfatal stroke, and cardiovascular death) compared with placebo.[14] Although this came at the cost of more deaths from infection, canakinumab also lowered the risk of cancer mortality and, thus, had a neutral effect on mortality overall. The effect on cancer in CANTOS is noteworthy in the setting of the positive association between interleukin-6 and cancer death, described by Held and colleagues,[12] in the current STABILITY substudy.

A few other anti-inflammatory agents that also work on the interleukin-1/interleukin-6 axis are undergoing clinical trials and are relevant to the present studies. One is methotrexate, a drug with many mechanisms of action, including suppression of interleukin-1β production by mononuclear cells. The effect of low-dose methotrexate on major vascular events is being studied in the CIRT (Cardiovascular Inflammation Reduction Trial) of patients with prior MI and either type 2 diabetes mellitus or the metabolic syndrome.[15] Another agent, tocilizumab, works via inhibition of the interleukin-6 receptor. Tocilizumab reduced peak troponin T levels in patients with non– ST-segment elevation MI in a phase 2 study[16]; however, it appears to increase low-density lipoprotein cholesterol levels, which could be a safety concern. Cardiovascular outcome trials are ongoing.

Now that CANTOS has shown that targeting the interleukin-1/interleukin-6 inflammatory axis can provide clinical benefit for improving cardiovascular outcomes, an important question to address is how to optimize the benefit from these new agents, while minimizing risk of infection and other adverse outcomes. Future study should focus on whether biomarkers of inflammation can be used to help this optimization process. Perhaps interleukin-6 (or other markers) can be used to identify patients in whom inflammation plays a particularly important role for CHD and in whom canakinumab and/or other anti-inflammatory treatments may be more beneficial. This was not true with darapladib in SOLID-TIMI 52, where elevated interleukin-6 concentrations did not identify patients who benefited from the study drug, but it might be true with other drugs that have positive overall effects and that target the interleukin-1/interleukin-6 axis. Enthusiasm for this approach could accrue if a significant interaction in CANTOS (and in future studies) between interleukin-6 levels and therapeutic benefit can be demonstrated.

Clinicians and scientists continue to search for the best way to identify unstable plaque and risk stratify individuals at risk for future CHD, and the present studies further this mission. Association cannot prove causation. However, the robust associations between interleukin-6 and CHD, evaluated in conjunction with genetic polymorphism studies and

outcome studies of drugs targeting the interleukin-1/interleukin-6 axis, lend support to the notion that interleukin-6 may be a true "contender" and not just an innocent bystander on the pathway to atherosclerosis and ACS. However, we must keep our focus on the real goal, which remains not only identifying risk, but also modulating it.

## Disclosures

Daniels has received speaking fees from Critical Diagnostics and Roche Diagnostics, has served as an independent contractor for Siemens, and has served as a consultant for Roche Diagnostics.

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