

EDITORIAL COMMENT

Cooling Off Hot Hearts: A Specific Therapy for Vulnerable Plaque?*

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A few decades ago, cardiac pathologists taught us that coronary atheroma can be either stable or vulnerable. The vulnerable plaque has the key histological features of local inflammation: a higher temperature, roughly 4 times more macrophages than stable plaques, and a thin fibrous cap only one-third as thick as stable atheroma (1–4). Because acute coronary syndromes (ACS) are caused by vulnerable plaques, therapy targeting the inflammatory process has seemed compellingly rational.

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The early logical choice among anti-inflammatory therapies was corticosteroids. A 2002 meta-analysis of 11 trials (2,646 patients) revealed a 26% decrease in mortality with corticosteroids in acute myocardial infarction (AMI) (odds ratio: 0.74; 95% confidence interval [CI]: 0.59 to 0.94), but sensitivity analysis limited to randomized, controlled trials showed lack of efficacy (odds ratio: 0.95; 95% CI: 0.72 to 1.26) (5). Steroids were abandoned amidst concern for impaired wall healing resulting in cardiac rupture, although this risk may be lessened with concomitant reperfusion (6).

In subsequent years, attention focused on selective and nonselective nonsteroidal anti-inflammatory drugs (NSAIDs). All of these agents, with the exception of aspirin, increase the risk for AMI, especially in those patients known to have coronary heart disease. A recent Danish study of 99,187 patients experiencing a first-time AMI reported that subsequent NSAID use was persistently associated with increased mortality (hazard ratio: 1.63; 95% CI: 1.52 to 1.74) over a 5-year period (7).

Still, provocative hints remained. The well-documented anti-inflammatory effects of statins may play a role in

reducing cardiac events, and some anti-inflammatory drugs used in noncardiac conditions, such as methotrexate in arthritis and psoriasis, seem to reduce cardiac events. One such intriguing anti-inflammatory candidate is colchicine. With its array of anti-inflammatory actions on macrophages, neutrophils, and endothelial cells, it is highly effective in management in gout, recurrent pericarditis, and familiar Mediterranean fever (8). In a retrospective, cross-sectional study of 1,288 patients with gout, colchicine use was associated with a lower incidence of MI (1.2% vs. 2.6%; $p = 0.03$) than nonuse (9). There were also fewer deaths and lower C-reactive protein (CRP) levels in colchicine users than nonusers in this study, although CRP levels did not decrease in another study of patients with ACS or acute ischemic stroke (10). Colchicine has not been found to reduce post-angioplasty restenosis (11).

In this issue of the *Journal*, Nidorf et al. (12) presented the first trial of colchicine as an anti-inflammatory therapy in coronary disease. In a prospective, randomized, observer-blinded endpoint (PROBE) design study of 532 patients with stable coronary artery disease receiving aspirin and/or clopidogrel (93%) and statins (95%), patients were assigned to colchicine 0.5 mg/day or no colchicine and followed for a median of 3 years (12). The primary outcome was a composite of ACS, out-of-hospital cardiac arrest, or non-cardioembolic ischemic stroke. By intent-to-treat analysis, this outcome occurred in 5% of the colchicine cohort compared with 16% of patients assigned to no colchicine, with a highly significant hazard ratio of 0.33. The well-known narrow toxic/therapeutic ratio of colchicine was responsible for 11% withdrawal of colchicine within 30 days, and another 11% withdrew from therapy later. Nevertheless, on-treatment analysis produced analogous outcomes, with a reduction in ACS (4.6% vs. 13.6%) as the predominant reason for the difference.

The colchicine study carries the potential to be a breakthrough for anti-inflammatory therapy in coronary artery disease. The magnitude of the reported treatment effect is striking, both in magnitude and in contrast to prior studies of anti-inflammatory therapy. The 67% coronary event reduction with colchicine is about twice that obtained with aggressive statin therapy.

On the other hand, the study is best viewed as hypothesis generating rather than a mandate for therapy for several reasons. The reported efficacy may be too good to be true, a familiar scenario for initial reports of therapies studied in relatively small cohorts. But if even only partly true, larger studies should have no difficulty demonstrating significance. The 5.3% annual incidence of cardiovascular events in the no colchicine group, especially considering the very frequent use of statins and antiplatelet agents, is somewhat higher than expected. By contrast, the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial reported an 11.8% incidence of ACS in the optimal medical treatment cohort over 4.6 years, whereas

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the current study reported a 13.6% incidence of ACS in the no colchicine group over 3 years (13). As the authors acknowledged, the PROBE design is less rigorous than that of a randomized clinical trial. Finally, the current study did not provide information on the mechanism of colchicine's efficacy, leaving us ignorant of whether anti-inflammatory effects should be predominantly local, systemic, or both and which inflammatory processes to target. In this context, Nidorf et al. (12) previously reported a 60% reduction in CRP levels with colchicine in patients with stable coronary artery disease and CRP levels >2.0 mg/l, but they did not find a decrease in CRP levels when colchicine was used in the setting of ACS or acute ischemic stroke (11).

The colchicine trial now stands as a harbinger of several new anti-inflammatory trials. Among these are the CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) and the CIRT (Cardiovascular Inflammation Reduction Trial) trials. The CANTOS trial will evaluate the effectiveness of a human monoclonal antibody to the inflammatory cytokine interleukin 1-beta in 17,200 stable patients post-MI, randomized to subcutaneous drug or placebo and followed over 4 years (14). The CIRT study will determine the effect of low-dose methotrexate (10 to 20 mg/week) on cardiovascular events in 7,000 patients with prior AMI, elevated CRP levels, and type 2 diabetes (15).

While we await new trials, the striking additional reduction in events in statin-treated patients on anti-inflammatory therapy already suggests a new concept: the lipid effects of statins may predominantly inhibit atherogenesis, whereas specific anti-inflammatory agents, such as colchicine, may work synergistically with statins to inhibit plaque rupture. If the results can be confirmed, this study may one day stand as the seminal trial in the use of anti-inflammatory therapy to cool off hot hearts.

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