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EDITORIAL COMMENT

Moving Beyond Beta-Blockers and Amiodarone

The Use of Anti-Inflammatories to Treat Post-Cardiac Surgery Atrial Fibrillation*

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Post-operative atrial fibrillation (POAF) still occurs commonly after cardiac surgery and is associated with stroke, congestive heart failure, acute kidney injury, and death (1). A comprehensive framework for management of POAF should include: 1) modification of potential triggers and exacerbating factors; 2) control of ventricular rate and/or maintenance of sinus rhythm to mitigate symptoms and prevent end-organ dysfunction related to tachycardia; 3) categorization of patients' stroke risk and initiating oral anticoagulation for stroke prevention when indicated; and 4) planning appropriate follow-up to address rate/rhythm control and need for ongoing oral anticoagulation.

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Historically, colchicine has been used mainly to treat gout and other specific inflammatory diseases, such as familial Mediterranean fever and Behçet syndrome. In recent years randomized trials have evaluated the use of colchicine in a variety of cardiac diseases where it was postulated that its unique anti-inflammatory action may prove to be beneficial for reduction of pericarditis, post-pericardiotomy syndrome, and POAF (2–6). In this issue of *JACC: Clinical Electrophysiology*, Lee et al. (7) publish the results of a meta-analysis pooling data from randomized controlled trials (RCTs) examining the effect of colchicine for preventing post-cardiac surgery atrial fibrillation.

The authors identified and pooled results from 3 blinded placebo-controlled RCTs enrolling a total of 912 patients undergoing cardiac surgery (8–10). There was considerable variability including procedure type (isolated coronary artery bypass graft [10] vs. coronary artery bypass graft, valvular or aortic surgery, or a combination thereof [8,9]), duration of treatment (5 days [10] vs. 1 month [8,9]), dosage (0.5 mg twice daily in all trials; however, in 2 of the 3 RCTs [8,9] it was cut in half for intolerance or patient weighing <70 kg), and initiation date (the night before surgery [10], post-operative Day 3 [8], or 2 to 3 days pre-operatively [9]). Despite these procedural differences, each of the three trials showed reduced rates of atrial fibrillation in the intervention group, which was statistically significant in 2 of 3 RCTs (8,10). The pooled result showed a one-third decrease in POAF from an average baseline rate of just over 30% in the placebo to just over 20% in the colchicine group, which was statically significant ($p = 0.01$). There was moderate heterogeneity in the results; however, differences in outcomes between trials did not clearly correlate with the different treatment regimens or methods of monitoring for POAF. Also, of the 2 included RCTs that reported the use of beta-blockers and amiodarone (8,9), beta-blocker use was statistically significantly lower in 1 of the 2 RCTs (8).

The biggest limitation of the meta-analysis is the small number of trials and patients included. Although the authors used high-quality meta-analytic methods, they chose a fairly narrow search strategy that yielded only 196 citations despite the use of multiple databases. Nevertheless, they did not

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seem to miss RCTs compared with other published meta-analyses (3). An additional related RCT comparing the use of colchicine to prevent atrial fibrillation recurrence after radiofrequency pulmonary vein isolation in patients with paroxysmal atrial fibrillation (11) was not included in the current meta-analysis, which was restricted to post-cardiac surgery RCTs. This additional RCT demonstrated a similar one-third reduction in atrial fibrillation so that adding it to the pooled results would not change the effect size but would reduce the confidence interval (3). Despite the small numbers, the results of this meta-analysis are consistent with those in other inflammatory-mediated cardiac conditions including post-pericardiotomy syndrome and pericarditis where the presumed anti-inflammatory effects of colchicine resulted in even larger pooled reductions in the occurrence or recurrence of these conditions by about one-half.

Adding results from these related RCTs may help to more clearly define the side effect profile of colchicine in this patient population because only 2 of the RCTs in the current meta-analysis reported data on adverse events including a more than doubling of gastrointestinal side effects (nausea, vomiting, diarrhea, abdominal pain), which was statistically significant, whereas the rate of early treatment discontinuation was one-third higher but did not achieve statistical significance. Pooling adverse event data from RCTs evaluating the use of colchicine in all cardiac conditions (13 RCTs, n = 3,022) (3), also demonstrates a statistically significant doubling of gastrointestinal side effects, and a higher rate of colchicine discontinuation, in particular when this was caused by adverse events, that was also statistically significant when including data from all RCTs. Interestingly, RCTs evaluating the effect of colchicine on pericarditis recurrence, which reduced the dose for intolerance or low body weight and enrolled generally younger patients, showed a <20% increase in gastrointestinal adverse events that was not statistically significant; this increase was significantly lower than in the RCTs evaluating the use of colchicine in patients with cardiovascular disease or post-cardiac procedures (interaction p = 0.01) (3). The short duration of treatment and follow-up means that primarily early drug intolerance side effects are being recorded in these RCTs. For short interventions, such as POAF prevention, it suggests a need to develop prophylaxis measures to address mostly gastrointestinal intolerance. Although colchicine seems relatively safe under these conditions, for longer term use, or if used in larger numbers of patients with multiple comorbidities or on multiple medications, one would need to more closely monitor for other potential adverse effects of colchicine including neuromuscular, dermatologic, myelotoxic, renal, and hepatic adverse events.

Currently, the use of colchicine to prevent POAF is a class IIb recommendation in the 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society atrial fibrillation guidelines (12). Based on the mounting evidence, clinicians may consider including colchicine in their framework for rhythm control for POAF. The relatively manageable side effect profile adds to its appeal compared with other anti-inflammatory medications, such as corticosteroids, which have shown efficacy for POAF management (13). Finally, the apparent effectiveness of an anti-inflammatory medication such as colchicine for reduction of POAF suggests that conceptualization of POAF as a primarily inflammatory rather than an electrophysiological condition may open other novel focused treatment strategies.

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