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EDITORIAL COMMENT

Treating Gout in Patients With Cardiovascular Disease

Mutual Benefit or Unintended Consequences?*

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I confidently affirm that the greater part of those who are supposed to have died of gout, have died of the medicine rather than the disease— a statement in which I am supported by observation.

—Thomas Sydenham, British physician (1624 to 1669) (1)

More than 50 years ago, McCarty and Hollander used polarizing light microscopy to identify negatively birefringent urate crystals in the synovial fluid of patients with gout (2). Since then, both the incidence and prevalence of gout have grown significantly in developed countries; it is currently estimated that >8 million Americans suffer from this common inflammatory arthritis (3). Hyperuricemia, resulting from the increased production and/or decreased excretion of uric acid, underlies the development of gout. Additionally, hyperuricemia has been associated with excess risk of cardiovascular disease (CVD), including hypertension, myocardial infarction (MI), stroke and heart failure (HF) (4). This association is not coincidental as systemic inflammation and oxidative stress underlie both gout and CVD. Indeed, plasma levels of interleukin (IL)-1β, IL-6, and tumor necrosis factor-α are elevated in both disease states and predict worse outcomes.

Vascular-derived xanthine oxidase is a potential source of oxidant stress in inflammatory conditions (5). During purine metabolism, increased xanthine oxidase activity leads to production of superoxide and uric acid. Allopurinol, the most widely used urate-lowering therapy for gout, acts by inhibiting xanthine oxidase and thereby decreasing the production of uric acid. By contrast, the uricosuric agent probenecid is a weak organic acid that promotes uric acid excretion by inhibiting urate reabsorption in the proximal tubule. Both agents have been shown to exert anti-inflammatory effects in animal models and humans that may explain "off-target" effects on CVD outcomes. Recently, there has been increasing interest by both clinical investigators and the Food and Drug Administration in defining the benefit versus risk of pharmacotherapy in chronic disease states associated with CVD, such as diabetes and chronic kidney disease (CKD).

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In this issue of the *Journal*, Kim et al. (6) sought to examine the effect of uric acid-lowering therapy with either probenecid or allopurinol on cardiovascular risk in older patients with gout. Using Medicare claims data over a 6-year period, the authors identified >38,000 individuals ≥65 years of age that were naive of urate-lowering therapy for ≥1 year before drug initiation, and estimated incidence rate and hazard ratio (HR) for the composite endpoint of hospitalization for MI or stroke. Secondary analyses focused on MI, stroke, HF, and mortality. Propensity score matching on >65 variables associated with severity of gout and cardiovascular risk was used to control for baseline confounders, although inverse probability of treatment weighted method was not employed. As expected, this older, predominantly white cohort had high rates of cardiovascular and other comorbidities at baseline, including

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TABLE 1 Cardiovascular Effects of Drug Therapy for Gout

Drug	Mechanisms	Possible Cardiovascular Indications	Contraindications and Toxicity
Probenecid	URAT1 inhibition TRPV2 stimulation Pannexin-1 inhibition	Hypertension Ischemic heart disease Cerebrovascular disease	Chronic kidney disease Nephrolithiasis
Allopurinol	Xanthine oxidase inhibition Purine synthesis inhibition	Refractory angina Hypertension Heart failure	Creatinine clearance <30 ml/min Hypersensitivity syndrome
Febuxostat	Selective xanthine oxidase inhibition	Hypertension	Heart failure Chronic liver disease
Colchicine	Microtubule spindle formation blockade Cytokine inhibition Neutrophil chemotaxis impairment	Recurrent pericarditis Post-cardiotomy atrial fibrillation	Myopathy Neuropathy
Canakinumab*	IL-1β inhibition	Coronary artery disease	Immunosuppression Active Infection

*Not FDA approved for treatment of gout.

IL = interleukin; TRPV = transient receptor potential vanilloid; URAT = uric acid transporter.

hypertension (91%), diabetes (46%), CKD (28%), coronary artery disease (21%), atrial fibrillation (22%), and HF (27%). In the primary "as-treated" analysis, the incident rate of the composite endpoint was 2.36 events per 100 person-years among probenecid initiators compared with 2.83 among allopurinol initiators (HR: 0.80; 95% confidence interval [CI]: 0.69 to 0.93). Incident rates of selected secondary outcomes, including worsening HF and mortality, were also lower in the probenecid versus allopurinol group (HR: 0.91 [95% CI: 0.83 to 0.98] and 0.87 [95% CI: 0.76 to 1.00], respectively). Finally, in subgroups of healthier patients (i.e., those without CVD or CKD at baseline), the primary outcomes analyses were similar. All of these medication-related associations were observed on top of background cardioprotective therapy with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (61%), beta-blockers (43%), and statins (54%).

Large sample size, propensity score matching, and intention-to-treat and sensitivity analyses were used effectively by Kim et al. (6) to support their findings. An additional strength of this analysis is the "new user" design where the initiation of treatment defines the beginning of follow-up. However, as with any observational study, especially one using provider drug prescription and International Classification of Diseases-Ninth Revision codes, the likelihood of misclassification bias and confounding by indication cannot be excluded. In the overall Medicare cohort, <3% of patients with gout were initiated on probenecid compared with 89% on allopurinol. At baseline, probenecid-treated patients had less CKD and HF, were less likely to be receiving diuretics, and were more likely to be treated with colchicine or allopurinol. Furthermore, during follow-up, probenecid-treated patients were less likely to have their drug dose increased (9% vs. 22%) and were much less adherent to prescribed therapy (26% vs. 82% of days covered), raising questions about biological plausibility of the primary results. No data on heart rate, blood pressure, or renal function are provided.

POTENTIAL MECHANISMS OF BENEFIT

Prior studies in patients with hyperuricemia (with or without gout) show that probenecid and allopurinol are equally effective at lowering serum uric acid levels in a dose-dependent manner (7). Therefore, any difference in subsequent cardiac risk would be expected to be independent of uric acid-lowering effects. Probenecid in particular may exert additional effects on cellular and molecular mechanisms that could explain CVD benefit (**Table 1**). First, probenecid is a partial agonist of the transient receptor potential vanilloid (TRPV) type 2 channel (8). Stimulation of TRPV2 under physiological conditions leads to improved cardiac inotropy and lusitropy in vitro and in vivo. Importantly, these direct myocardial effects are load independent and do not occur through the traditional inotropic pathway of β-adrenergic stimulation, but are secondary to transient increases in cytosolic calcium through sarcoplasmic reticulum release. Notably, mice that are deficient in TRPV2 have decreased basal contractility and impaired relaxation due to impaired calcium handling, whereas cardiac-specific overexpression of TRPV2 results in cardiomyopathy due to calcium overload (9).

Beyond the heart, TRPV2 may function as an important stretch receptor in vascular smooth muscle cells raising the possibility that probenecid exerts vasodilator effects in large and smaller conduit arteries. In adolescents with pre-hypertension, probenecid caused significant reductions in systolic