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Editorial Commentary: Prevention and treatment of atrial fibrillation: Is hyperuricemia the next target? ☆

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Atrial fibrillation (AF) is the most common heart rhythm disorder and worldwide health epidemic, with an estimated prevalence of 4% and incidence that is expected to double by 2030 [1]. Established risk factors for AF include hypertension, obesity, obstructive sleep apnea and diabetes mellitus in addition to primary cardiovascular pathology such as heart failure (HF), valvular heart disease, and myocardial infarction [2]. Although anti-arrhythmic drugs and catheter ablation represent effective treatment options for AF, increasing emphasis is being placed on risk factor identification and modification for prevention and treatment of AF as the estimated direct costs of AF-related care have continued to soar to an estimated $6 billion annually [3]. Patients with AF randomized to continuous positive airway pressure (CPAP) for obstructive sleep apnea, structured weight management for obesity, or blood pressure reduction for hypertension have been shown to have fewer AF episodes and lower rates of AF recurrence after radiofrequency catheter ablation, making identification of additional modifiable risk factors an attractive approach [4–6].

In this issue of *Trends in Cardiovascular Medicine,* Giannopoulos and colleagues [7] describe a growing body of literature examining the connection between hyperuricemia and gout and atrial fibrillation. Gout is characterized by deposition of monosodium urate (MSU) crystals in joints due to under-secretion or overproduction of uric acid, and represents the most common form of inflammatory arthritis with a prevalence of 4%. Hyperuricemia is present in nearly a quarter of the US population, and defined as a serum uric acid (SUA) level exceeding 6.8 mg/dL. The association between hyperuricemia and atrial fibrillation was consistent, including the 15,382 patient Atherosclerosis Risk in Communities (ARIC) study and 122,524 patient Taiwanese study by Chao et al, which found adjusted hazard ratios (HR) of 1.16 and 1.19 for development of AF, respectively [8,9]. The authors should be commended for describing the limitations of the analyzed studies including the possibility that residual confounders including obesity, hypertension, renal disease and heart failure (HF) may not be fully accounted for by multivariable adjustment. The HRs associated with hyperuricemia are seem relatively modest when contrasted with established AF risk factors from the Framingham Heart Study, such as hypertension (HR 1.5), obesity (HR 1.5), age (HR 2.1 per decade).

The mechanism by which elevated uric acid levels could promote development and maintenance of atrial fibrillation are unknown. Hyperuricemia has been independently associated with increased left atrial diameter, a known marker of atrial fibrosis and re-entrant substrate [9]. Uric acid could also promote development of arrythmogenic substrate by activation of the renin-angiotensin-aldosterone (RAAS) system and increased xanthine-oxidase mediated free radical generation. Importantly, the authors suggest that systemic inflammation may promote development of atrial fibrosis in patients with gout via increased TGF-β activity secondary to activation of the nucleotide-binding domain leucine-rich repeat-containing protein 3 (NLRP3)-inflammasome. In support of this inflammatory hypothesis, a large cohort study from the Swedish National Patient Register (NPR) recently demonstrated elevated risk for AF in patients with both ankylosing spondylitis (HR 1.35) and psoriatic arthritis (HR 1.46) [10]. Rheumatoid arthritis (RA), another systemic inflammatory effecting the synovium, was also found to be statistically associated with increased risk for AF (HR 1.29) in a separate large meta-analysis of cohort studies involving 39,912 patients with RA [11].

Hyperuricemia represents a particularly attractive target for prevention and treatment of AF. Considering the growing burden of AF and significant number of patients with concomitant hyperuricemia and gout, we believe that prospective clinical investigation should not await delineation of a precise molecular mech-

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anism. Low cost therapies that predictably lower uric acid levels such as the xanthine oxidase inhibitors (XOI) allopurinol and febuxostat are inexpensive and widely available. Allopurinol use has been associated with reduced risk for AF in the Medicare population, Singh and Yu [12] reduced atrial fibrosis in mouse models of oxidative stress, [13] and prevented atrial pacing induced AF in dogs [14]. Although little clinical equipoise exists for the use of XOIs in the vast majority of individuals who suffer from gout flares, those with AF and asymptomatic hyperuricemia represent a large potential treatment population not currently receiving XOI therapy. Importantly, while XOIs do not interact with common antiarrhythmic drugs, allopurinol can inhibit oxidative metabolism of warfarin and increase the internal normalized ratio (INR) [15].

Although high-quality prospective trials of XOIs for prevention and treatment of AF have not yet been conducted, optimism could be tempered by disappointing results in the HF population. After smaller observational studies suggested an association between hyperuricemia and worsened survival and functional status in HF, Anker et al. [16] analysis of a large US insurance database found that XOI therapy had no effect on rates of cardiovascular death, myocardial infarction or death in 24,108 patients with hyperuricemia compared to propensity matched untreated controls [17]. Prospective clinical trials have since failed to demonstrate any benefit to uric acid lowering therapy in HF. In the Xanthine Oxidase Inhibition for Hyperuricemic Heart Failure Patients (EXACT-HF) study, 253 patients with symptomatic HF, LVEF $< 40\%$ and uric acid levels > 9.5 mg/dL were randomized to allopurinol or placebo [18,19]. The EXACT-HF investigators found no significant impact of XOI therapy on quality of life or 6 minute walk distance at 24 weeks [18].

The studies described by Giannopoulos and colleagues [7] provide a rationale for further investigation of a strategy that employs routine screening and treatment of hyperuricemia in AF risk modification clinics. The impact of uric-acid lowering therapy could be assessed by AF-specific quality of life questionnaires such as the Mayo AF-Specific Symptom Inventory (MAFSI) [20], and quantification of AF burden by ambulatory monitoring and/or interrogation of cardiac implantable electronic devices. Several studies have also described an association between hyperuricemia and increased risk of AF recurrence after catheter ablation [21]. Importantly, enthusiasm for catheter ablation of AF in patients with concomitant HF is growing after several prospective randomized trials have demonstrated reductions in cardiovascular hospitalization and mortality. Considering that patients with HF and AF are likely to have more severe hyperuricemia than the general AF population, prospective trials assessing the impact of uric acid lowering therapy on outcomes after AF catheter ablation in patients with and without HF are clearly needed.

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