Gout Flare and Cardiovascular Events

To the Editor A recent study[1] reported that experiencing a recent gout flare was associated with subsequent cardiovascular events among individuals with gout. While these results are interesting, I am concerned that the authors did not control for use of low-dose aspirin, which is commonly prescribed for people who are at higher risk of myocardial infarction or stroke. In this study, more individuals with gout and cardiovascular events had a history of cardiovascular disease and high to very high cardiovascular risk than matched controls with gout who did not have cardiovascular events.

Low-dose aspirin, which is frequently used for primary or secondary prevention of cardiovascular and cerebrovascular events, may increase urate levels.[2] Indeed, aspirin had been shown to have a biphasic effect on serum urate levels.[3] Low doses of aspirin (≤2 g/d), which are commonly used for prevention of cardiovascular events, elevate serum urate levels, while high doses (>3 g/d) decrease serum urate.[3] These effects are explained by 2 modes of salicylate interaction with urate monocarboxylate exchanger 1. At low doses, salicylate acts as an exchange substrate to facilitate urate reabsorption, but at high doses it can inhibit urea tubular reabsorption.[4] Moreover, other frequently used drugs, such as diuretics, β-blockers and insulin,[2] may also increase serum uric acid levels and potentiate the effect of aspirin.

A study[4] that evaluated use of low-dose aspirin and risk of recurrent gout attacks among patients with gout reported an adjusted odds ratio (OR) for gout attack of 1.81 (95% CI, 1.30-2.51) in patients using 325 mg per day or less of aspirin on 2 consecutive days, compared with no aspirin use. This study[4] found an even higher OR of 1.91 (95% CI, 1.32-2.85) with use of lower doses of aspirin (≤100 mg). Therefore, it would be informative if the authors of this study[1] could report their results controlling for the use of low-dose aspirin.

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1. Cipolletta E, Tata LJ, Nakafero G, Avery AJ, Mamas MA, Abhishek A. Association between gout flare and subsequent cardiovascular events among patients with gout. *JAMA*. 2022;328(5):440-450. doi:10.1001/jama.2022.11390

2. Leung N, Yip K, Pillinger MH, Toprover M. Lowering and raising serum urate levels: off-label effects of commonly used medications. *Mayo Clin Proc*. 2022;97(7):1345-1362. doi:10.1016/j.mayocp.2022.02.027

3. Yu TF, Gutman AB. Study of the paradoxical effects of salicylate in low, intermediate and high dosage on the renal mechanisms for excretion of urate in man. *J Clin Invest*. 1959;38(8):1298-1315. doi:10.1172/JCI103905

4. Khanra D, Soni S, Ola R, Duggal B. Acute attack of gout precipitated by concomitant use of aspirin and diuretic in a rheumatic mitral stenosis patient. *BMJ Case Rep*. 2019;12(9):e232085. doi:10.1136/bcr-2019-232085

In Reply Dr Fonseca raises the issue of potential confounding by low-dose aspirin in our study[1] of the association between gout flare and cardiovascular events. While we did not adjust for low-dose aspirin specifically, our multivariable model included adjustment for current (≤60 days) or past (>60 days) prescription of any antiplatelet drug (ie, aspirin [tablet strength of ≤325 mg], dipyridamole, clopidogrel, prasugrel, ticlopidine, and ticagrelor) prior to the cardiovascular event or matched index date for controls. In our study population of 62 574 patients with gout, 64.6% were ever prescribed antiplatelet drugs. Among them, 90.4% were ever prescribed low-dose aspirin (34 429/36 542 [94.2%] at a tablet strength of ≤100 mg and 2113/36 542 [5.8%] at a tablet strength of 101-325 mg).

If a recent prescription of low-dose aspirin were to elevate serum urate modestly,[2,3] and thereby be associated with gout flares,[4] such prescription should also, by a more direct mechanism, reduce the risk of cardiovascular events.[5,6] Thus, a recent prescription of low-dose aspirin would be more likely to reduce than increase the association between recent prior gout flares and cardiovascular events.

Nevertheless, we performed an additional multivariable conditional logistic regression analysis using the fully adjusted model[1] with separate adjustment for current and past low-dose aspirin (tablet strength of ≤325 mg) and current and past nonaspirin antiplatelet drug prescriptions. Our results did not change substantially. Patients with cardiovascular events, compared with control patients without cardiovascular events, had significantly higher odds of a gout flare within the prior 0 to 60 days (adjusted OR, 1.89 [95% CI, 1.53-2.33]) and 61 to 120 days (adjusted OR, 1.53 [95% CI, 1.23-1.91]), but there was no significant difference in the odds of a gout flare within the prior 121 to 180 days (adjusted OR, 1.05 [95% CI, 0.81-1.32]). When

low-dose aspirin was defined as a dose of 100 mg or lower, the adjusted OR of a gout flare within the prior 0 to 60 days was 1.96 (95% CI, 1.59-2.41); for 61 to 120 days, 1.52 (95% CI, 1.22-1.89); and for 121 to 180 days, 1.09 (95% CI, 0.86-1.36).

We also performed new sensitivity analyses for the nested case-control study and the self-controlled case series by restricting to patients with current prescription of low-dose aspirin within 60 days of the cardiovascular event date or matched index date. In the nested case-control study (n = 10 815), a statistically significant association between acute cardiovascular events and recent prior gout flares was observed in days 0 to 60 (adjusted OR, 2.73 [95% CI, 1.32-5.69]) but not in days 61 to 120 (adjusted OR, 1.72 [95% CI, 0.74-4.04]) or in days 121 to 180 (adjusted OR, 0.80 [95% CI, 0.31-2.07]). In the self-controlled case series study (n = 353), gout flares were associated with a significant increase in the incidence rate ratio (IRR) of cardiovascular events in days 0 to 60 (adjusted IRR, 1.72 [95% CI, 1.26-2.34]) but not in days 61 to 120 (adjusted IRR, 1.30 [95% CI, 0.97-1.75]) or in days 121 to 180 (adjusted IRR, 0.90 [95% CI, 0.52-1.58]) compared with the baseline period.

In summary, these results provide reassurance that prescription of low-dose aspirin was not a confounder in the association between gout flare and cardiovascular events in our study.[1]

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1. Cipolletta E, Tata LJ, Nakafero G, Avery AJ, Mamas MA, Abhishek A. Association between gout flare and subsequent cardiovascular events among patients with gout. *JAMA*. 2022;328(5):440-450. doi:10.1001/jama.2022.11390

2. Caspi D, Lubart E, Graff E, Habot B, Yaron M, Segal R. The effect of mini-dose aspirin on renal function and uric acid handling in elderly patients. *Arthritis Rheum*. 2000;43(1):103-108. doi:10.1002/1529-0131(200001)43:1<103::AID-ANR13>3.0.CO;2-C

3. Zhang P, Wang H, Chen XH, Liang WY, Liu WW, Liu ML. Effect of low-dose aspirin on serum uric acid levels in Chinese individuals over 60: subanalysis of a multicentre randomized clinical trial. *Eur Rev Med Pharmacol Sci*. 2020;24(5):2719-2724. doi:10.26355/EURREV_202003_20544

4. Zhang Y, Neogi T, Chen C, Chaisson C, Hunter DJ, Choi H. Low-dose aspirin use and recurrent gout attacks. *Ann Rheum Dis*. 2014;73(2):385-390. doi:10.1136/annrheumdis-2012-202589

5. Baigent C, Sudlow C, Collins R, Peto R; Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ*. 2002;324(7329):71-86. doi:10.1136/bmj.324.7329.71

6. Baigent C, Blackwell L, Collins R, et al; Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet*. 2009;373(9678):1849-1860. doi:10.1016/S0140-6736(09)60503-1