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Dr. Deng et al reply

To the Editor:

We sincerely appreciate Dr. Kawada's comments in response to our metaanalysis.[1] We agree with most of these opinions and would like to clarify our views here.

The CARES trial conducted by White et al indicated that febuxostat increased heart-related death as compared with allopurinol,[2] whereas the FAST trial demonstrated that febuxostat was not associated with the increased cardiovascular (CV) mortality.[3] There are various reasons for the inconsistency of the 2 large studies and include the following possibilities. First, the CARES trial included patients with gout in combination with ≥ 1 CV disease (CVD), and only excluded the patients who had myocardial infarction (MI) or stroke within 60 days prior to screening. In contrast to the CARES trial, the FAST trial included only approximately one-third of patients with CVDs at baseline.[2,3] At the same time, patients who had severe renal disease or who experienced MI or stroke in the previous 6 months were excluded.[2,3] Differences in baselines may explain the different outcomes in the 2 trials. Second, the CARES trial had high rates of medication discontinuation (> 50% of participants), with large amounts of loss to follow-up (approximately 45% of participants did not complete all trial visits).[2] Therefore, we are concerned that the majority of CV deaths might have occurred in the absence of regular medication in the CARES trial, possibly resulting in attrition bias as well as reporting bias of these study results. Third, most of the participants underwent long-term allopurinol treatment before the FAST trial. The serum uric acid (SUA) concentrations of patients at baseline in the FAST trial were significantly lower than those in the CARES trial. In previous studies, SUA has been sufficiently confirmed as an independent risk factor for adverse CV events.[4] Further, the doses of febuxostat intake were higher in the FAST trial. In our metaanalysis,[1] the pooled results indicated that the CV side effects of febuxostat were not significantly dose-dependent. Combined with a series of early clinical trial studies from Becker et al (ie, the CONFIRM trial[5] and FACT trial[6]) as well as our metaanalysis,[1] febuxostat use was not associated with increased CV events and heart-related mortality. Accordingly, at least for now, we believe that febuxostat is a drug with pharmacotherapy safety in patients without CVD or prior CVDs. As for patients with severe CVD, whether febuxostat increases CV mortality is uncertain because more complete data are still needed.

The metaanalysis conducted by Gao et al[7] demonstrated that febuxostat has a higher safety profile in coronary revascularization and nonfatal stroke compared with allopurinol. However, the certainty of the evidence is moderate because this study included a cohort study in older patients by Zhang et al.[8] Further, the weights in this cohort were too great in the metaanalysis by Gao et al,[7] with > 60% in the pooled results of nonfatal stroke and 80% in coronary revascularization. More clinical trials should verify the pharmacological safety of febuxostat in patients with gout with or without a history of CVD.

Hao Deng[1], Master Degree
Xiu Hong Yang[1], MD, PhD
Hui Min Jin[1], MD, PhD
[1]Division of Nephrology, Shanghai Pudong Hospital, Fudan University, Pudong Medical Center, Shanghai, China.

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The authors declare no conflicts of interest relevant to this article.

Address correspondence to Dr. H.M. Jin, Division of Nephrology, Shanghai Pudong Hospital, Fudan University, Pudong Medical Center, 2800 Gong Wei Road, Shanghai, China. Email: hmjgli@163.com.

REFERENCES

1. Deng H, Zhang BL, Tong JD, Yang XH, Jin HM. Febuxostat use and risks of cardiovascular disease events, cardiac death, and all-cause mortality: metaanalysis of randomized controlled trials. J Rheumatol 2021;48:1082-9.
2. White WB, Saag KG, Becker MA, et al; CARES Investigators. Cardiovascular safety of febuxostat or allopurinol in patients with gout. N Engl J Med 2018;378:1200-10.
3. Mackenzie IS, Ford I, Nuki G, et al; FAST Study Group. Long-term cardiovascular safety of febuxostat compared with allopurinol in patients with gout (FAST): a multicentre, prospective, randomised, open-label, non-inferiority trial. Lancet 2020;396:1745-57.
4. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. N Engl J Med 2008;359:1811-21.
5. Becker MA, Schumacher HR Jr, Espinoza LR, et al. The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial. Arthritis Res Ther 2010;12:R63.
6. Becker MA, Schumacher HR Jr, Wortmann RL, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. N Engl J Med. 2005;353:2450-61.
7. Gao L, Wang B, Pan Y, Lu Y, Cheng R. Cardiovascular safety of febuxostat compared to allopurinol for the treatment of gout: a systematic and meta-analysis. Clin Cardiol 2021;44:907-16.
8. Zhang M, Solomon DH, Desai RJ, et al. Assessment of cardiovascular risk in older patients with gout initiating febuxostat versus allopurinol: population-based cohort study. Circulation 2018;138:1116-26.