

## Correspondence

### Response: Re: To Treat or Not to Treat? Effect of Urate-Lowering Therapy on Renal Function, Blood Pressure and Safety in Patients with Asymptomatic Hyperuricemia

*To the Editor:* We would like to thank Dr. Kawada for his interest in our article. He mentioned the meta-analysis by Gao et al, in which a better safety outcome for febuxostat compared with allopurinol was observed in gout patients in terms of urgent coronary revascularization and stroke.<sup>1</sup> In our network meta-analysis (NMA),<sup>2</sup> trials reporting cardiovascular events all used febuxostat as the treatment, so we could not compare its cardiovascular effect to allopurinol in patients with asymptomatic hyperuricemia. Besides, the cardiovascular events in our analysis included several types of cardiovascular diseases, such as heart failure and non-fatal myocardial infarction. Our study, nevertheless, found that patients using febuxostat had significantly lower diastolic blood pressure than those using placebo, indicating that febuxostat has a cardiovascular protective effect. Similar effects on diastolic blood pressure were not observed in the allopurinol group. We need more randomized controlled trials to clarify this issue.

The safety comparison between allopurinol and febuxostat continues to attract attention. The Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) trial and The Febuxostat versus Allopurinol Streamlined Trial (FAST) are 2 important trials on this issue. However, the CARES trial found increased all-cause mortality and risk of death from cardiovascular causes in gout patients using febuxostat than those using allopurinol. In contrast, the FAST trial demonstrated no increased risk of composite cardiovascular events, cardiovascular disease mortality, or all-cause mortality in gout patients with febuxostat compared with those with allopurinol.<sup>3,4</sup> There are notable differences between these 2 studies: CARES trial recruited patients with a history of major cardiovascular disease; they were likely to have a higher risk of cardiovascular disease during the follow-up than patients in the FAST trial, in which only about one-third had previous major cardiovascular comorbidity. FAST only recruited patients who were already under urate-lowering therapy and might have a lower urate crystal burden, which may relate to a lower

cardiovascular risk. As our NMA focused on patients with asymptomatic hyperuricemia, we consider that they may have a lower risk of cardiovascular diseases than symptomatic patients. Consequently, our results may be supplemented by the FAST trial, which reported no association between the long-term use of febuxostat and an increased risk of death or serious cardiovascular events compared with those with allopurinol in asymptomatic patients. However, more randomized controlled trials focusing on asymptomatic hyperuricemia patients are required to provide more evidence on this safety issue.

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#### References

1. 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.
2. Tien YY, Shih MC, Tien CP, Huang HK, Tu YK. To treat or not to treat? Effect of urate-lowering therapy on renal function, blood pressure and safety in patients with asymptomatic hyperuricemia: a systematic review and network meta-analysis. *J Am Board Fam Med* 2022;35:140–51.
3. White WB, Saag KG, Becker MA, CARES Investigators, et al. Cardiovascular safety of febuxostat or allopurinol in patients with gout. *N Engl J Med* 2018;378:1200–10.
4. Mackenzie IS, Ford I, Nuki G, et al. 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.

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