Letter to the Editor

Is febuxostat associated with higher risk of cardiovascular death than allopurinol in treating gout or asymptomatic hyperuricemia?

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An article published by Wang *et al.* (1) in the October issue of *Annals of Palliative Medicine* caught our attention with great interest. In that meta-analysis the authors concluded that febuxostat had a higher risk of cardiovascular (CV) death than allopurinol. There are, however, four important limitations we believe should be discussed in more depth.

Firstly, 11 relevant randomized control trials (RCTs) and 7 cohort studies were pooled for this study (1). It was not known why the authors included RCTs and observational studies together in a meta-analysis. For evaluation of efficacy of interventions, RCTs are preferred (2). It is usually more likely that observational studies will contain selection bias compared to RCTs, which can weaken the validity of their conclusions. Furthermore, the combination of RCTs and cohort studies in this meta-analysis is inappropriate due to the differences in study designs and comparison groups, which can cause a high degree of methodological heterogeneity (2). Secondly, in a systematic review and meta-analysis, a thorough literature search is a crucial step that can affect the outcome. It was unfortunate that one eligible published RCT (3) was missed by the search in this meta-analysis. The RCT (3) have a relatively large study sample (n=3,063 participants) and its conclusion is completely opposite to authors. Thirdly, it is likely that Wang and colleagues have made mistakes in data extraction. Some data for CV safety originate from review (4) instead of the primary research article, which results in the inclusion of duplicate studies. The numbers of major CV events in a study (5) was incorrectly calculated. There were 134 CV deaths, 111 nonfatal myocardial infarction, 71 nonfatal stroke, 49 urgent revascularization for unstable angina in this study. Three hundred and thirty-five reached primary end point (including CV death, nonfatal myocardial infarction, nonfatal stroke, or urgent revascularization for unstable angina) and 296 met secondary end point (including CV death, nonfatal myocardial infarction, or nonfatal stroke). Totals may not add up due to repeated data. At the same time, Wang and colleagues made a mistake in extracting the numbers of major CV events in a study (6) and it was 670 but not 70. Fourthly, inappropriate quality assessment was utilized in the present systematic review (1). In general, the quality of a meta-analysis depends directly on the quality of the studies included. For different types of studies, there are various quality assessment scales, the Cochrane Risk of Bias tool was used for the RCT, and the Newcastle-Ottawa rating scale was used for the observational clinical studies (OCSs). Wang and colleagues used the Cochrane risk of bias tool to assess two types of studies. Thus, we conducted a further meta-analysis to evaluate the CV safety of febuxostat compared to allopurinol in the treatment of gout or asymptomatic hyperuricemia.

In our meta-analysis, there were no statistically significant difference in major CV events (RR: 1.15, 95% CI: 0.83–1.58, P=0.40; *Figure 1A*), CV death (RR: 0.93, 95% CI: 0.51–1.72, P=0.82; *Figure 1B*) and all-cause

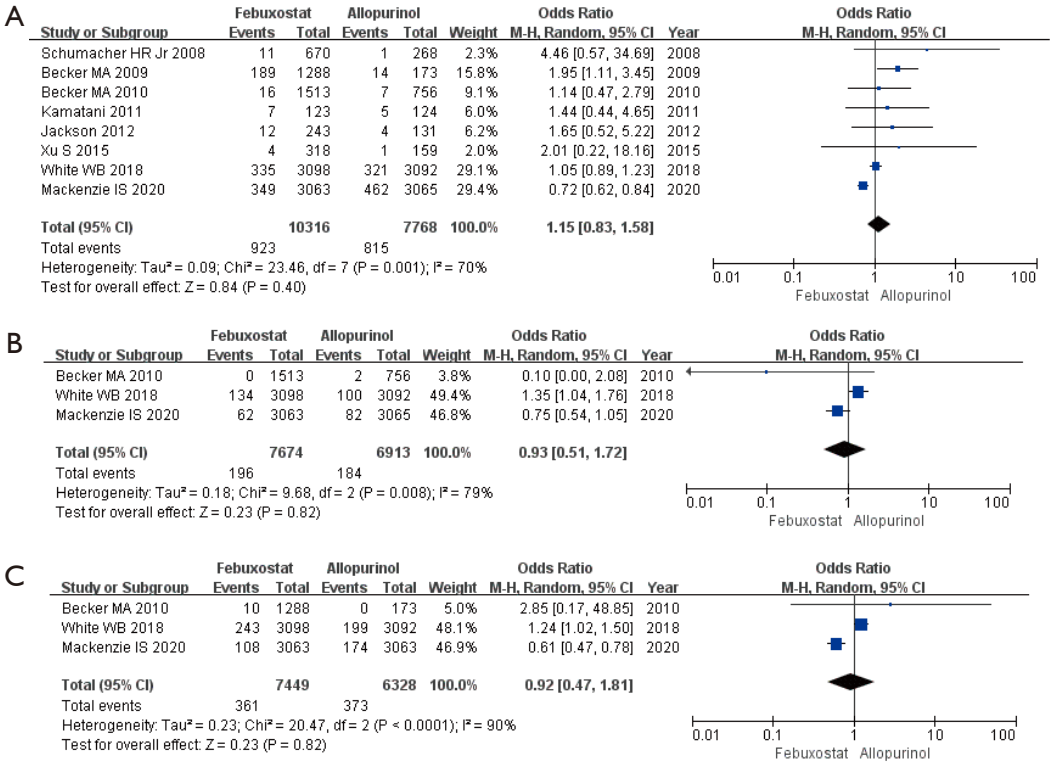

Figure 1 Forest plots showing the safety of febuxostat versus allopurinol in gout or hyperuricemia (1). (A) Odds ratios of major cardiovascular events of febuxostat and allopurinol in gout or hyperuricemia. (B) Odds ratios of cardiovascular death of febuxostat and allopurinol in gout or hyperuricemia. (C) Odds ratios of all-cause mortality of febuxostat and allopurinol in gout or hyperuricemia.

mortality (RR: 0.92, 95% CI: 0.47–1.81, P=0.82; *Figure 1C*) between febuxostat and allopurinol.

Overall, the CV safety profile of febuxostat was comparable to allopurinol in treating gout or asymptomatic hyperuricemia. This conclusion was inconsistent with Wang and colleagues (1). The authors have done a good job on this study, and we hope that the points we mentioned above will help frame future discussions.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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