

Editorial

Is Febuxostat Use Associated With Increased Risk of Cardiovascular Disease Events? The Answer Is Crystal Clear



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Gout is the most common inflammatory arthritis¹, historically poorly managed, and is arguably the only one of the inflammatory arthritides that is curable with appropriate urate-lowering therapy (ULT)². Whereas febuxostat has been shown to be a more effective ULT³, allopurinol has been the cornerstone of treatment for decades; however, allopurinol is problematic in the elderly, those with renal impairment, and those who carry the HLA-B*5801 antigen who are primarily of Asian origin. Severe cutaneous allergic reactions (SCAR) are more common in the latter group as they carry up to a 30% mortality rate for the most severe form. Based on this, the Clinical Pharmacogenetics Implementation Consortium and other organizations have declared that allopurinol should be considered contraindicated in HLA-B*5801–positive individuals⁴. Even in those who do not carry the antigen, adverse skin reactions to allopurinol are also frequently seen; on the other hand, febuxostat carries a lower risk for these⁵. Including HLA-B*5801-positive patients, the elderly, those with renal impairment, and others who do not tolerate allopurinol at maximal doses, there is a significant proportion of patients for whom febuxostat is the best alternative. However, the use of febuxostat has faced significant challenges, including the “black box” warning from the FDA and the subsequent Health Canada statement^{6,7} regarding cardiovascular (CV) risk and death, both of which have created a great deal of confusion for prescribers.

Febuxostat, even prior to any perceived adverse CV disease (CVD) risk profile, has been somewhat restricted in coverage by insurers across Canada, primarily due to the initial cost difference when compared to allopurinol. Several provincial plans

require “demonstrated hypersensitivity to allopurinol” prior to coverage of febuxostat, which seems unnecessary due to the inability to predict those who may have severe reactions. The province of Alberta also requires failure or contraindication to sulfinpyrazone, a second-line uricosuric agent that has very little evidence to support its use in gout⁸ and is associated with a high risk of bleeding due to interactions with antiinflammatories and anticoagulants⁹. Another widely used uricosuric, probenecid (which is not commercially available in Canada), has a better safety profile, but these agents are not as effective⁸ as those agents that interfere with urate production. In fact, uricosurics are not effective in patients with even mild chronic kidney disease and may result in further renal complications with development of nephrolithiasis¹⁰. Other uricosurics—lesinurad, benzbromarone, and the novel pegloticase—are not available in Canada and all can have significant side effects or have warnings and concerns associated with them¹¹. Given the lack of efficacy and safety of these other drugs, it is unfortunate that recent publications have recommended against febuxostat based on the results of a single study¹². Canadians with gout who also have preexisting CVD would then be deprived of a more effective first-line option where allopurinol is contraindicated.

It is within this context that the recent article by Deng, *et al*, published in this issue of *The Journal*¹³ is of the utmost clinical importance for the various reasons. First, the background and aim of the study have been clearly defined. Second, notwithstanding the inherent problems associated with metaanalyses, the methodology and statistics are sound, the heterogeneity of the various studies is clearly evaluated, and any issues leading to potential bias are comprehensively addressed. Third, the quality of the evidence evaluated is appropriately graded in accordance with international best practice¹⁴. Finally, the finding that patients with gout—already at an inherently disproportionate risk of CVD^{15,16}—who receive febuxostat are not put at any further risk, is an important contribution to the literature.

The CARES randomized controlled trial (RCT)¹⁷ showed

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See Febuxostat and mortality, page 1082

an increase in both CV death and all-cause mortality with a number needed to harm (NNH) of 91 and 72, respectively¹², for febuxostat over allopurinol. This was the study that prompted the federal warnings in North America, but several recent meta-analyses^{18,19,20,21}, including this one by Deng, *et al*¹³, have questioned the safety outcomes seen in this single RCT. Deng, *et al*¹³ provides valuable perspective and real-world insight by including an analysis of patients with gout who received a placebo, and also by including further studies reflecting a more diverse population than CARES. As the authors correctly detail, restricting the use of an effective drug, especially in patients who cannot or should not take allopurinol, may also lead to negative outcomes that were not accounted for in the CARES study. Further, only 3% of patients in the CARES study were of Asian descent and thus, those at greater risk of SCAR with allopurinol were not adequately represented. In those at high risk of allopurinol hypersensitivity, a slight cardiac benefit may not be enough to overcome the morbidity and mortality risks associated with SCAR. This is consistent with a previous subanalysis of the Asian subjects in the trial that found febuxostat to be safer and more effective than allopurinol²¹.

What this study by Deng, *et al* best conveys is that most gout patients are at risk for CV death and all-cause mortality¹³. We know that gout and hyperuricemia are strongly associated with CVD and increased CV mortality^{15,16}. Additionally, those with gout frequently have other comorbidities associated with CVD and increased mortality such as obesity, diabetes/metabolic syndrome, hypertension, and hypercholesterolemia. By including a more diverse population for analysis and through evaluation of those subjects receiving a placebo, we see that there is no increased CV risk associated with febuxostat over patients who receive no treatment or over those who receive less effective second-line treatments. The morbidity associated with inadequately treating gout, which is essentially a curable disease, should also not be discounted in this discussion and the optimal treatment of this most common inflammatory arthritis should be a primary goal. The metaanalysis by Deng, *et al*¹³ provides much-needed clarity for prescribers regarding the use of febuxostat in their gout patients with comorbid CVD and with an intolerance or contraindication to allopurinol.

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