Meta-analysis assessing cardiovascular outcomes with febuxostat versus allopurinol for patients with gout

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Background: Gout, the most common inflammatory arthritis in the USA, represents an established risk factor for cardiovascular disease and coronary artery disease mortality. In addition, patients with gout experience an increased risk for non-fatal myocardial infarction, while they might also feature increased risk for stroke. Recent real-world data also highlight the association between gout and atrial fibrillation, which inevitably augments cardiovascular burden. Allopurinol, a xanthine oxidase inhibitor, remains the uric acid-lowering treatment option of first choice, while febuxostat is prescribed, when allopurinol is contraindicated or not tolerated. Unfortunately, medication adherence among gout patients is poor, associated with age and related co-morbidities.

Purpose: We sought to determine the comparative efficacy of febuxostat versus allopurinol across surrogate cardiovascular outcomes of interest, by pooling data from the 2 dedicated cardiovascular outcome trials available so far. The motive for this analysis was the U.S. Food and Drug Administration (FDA) warning raised after the publication of the CARES trial, regarding the increased risk for cardiovascular and all-cause death with febuxostat compared to allopurinol.

Methods: We pooled data from the 2 dedicated cardiovascular outcome trials (CARES and FAST) and we assessed the following cardiovascular outcomes of interest: cardiovascular death, all-cause death, non-fatal myocardial infarction (MI), non-fatal stroke, fatal MI, fatal stroke, transient ischemic attack, hospitalization for heart failure, coronary revascularization, cerebrovascular revascularization and atrial fibrillation. Risk of bias was low across the included studies.

Results: Our analysis in a total of 12,318 patients with gout showed that febuxostat compared to allopurinol treatment does not confer significant risk reduction for any of the assessed, prespecified surrogate outcomes in a study population with significant cardiovascular co-morbidities (Figure 1). One third of patients enrolled in the FAST trial and 40% of the patients enrolled in the CARES trial had pre-existing cardiovascular disease, as depicted in Figure 2. Heterogeneity was low for the vast majority of the assessed outcomes, except for cardiovascular and all-cause death and fatal MI.

Conclusions: There is no significant difference across surrogate cardiovascular outcomes of interest between febuxostat and allopurinol in patients with gout and cardiovascular co-morbidities. Febuxostat seems to be a safe treatment alternative to allopurinol, despite initial concerns in terms of its cardiovascular safety.

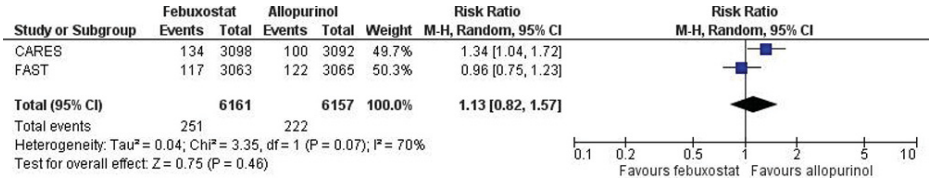

Figure 1

Outcome (febuxostat vs. allopurinol)	Risk ratio (95% CI)	Heterogeneity	p-value
Cardiovascular death	1.13 (0.82 – 1.57)	70%	0.46
All-cause death	1.01 (0.71 – 1.45)	88%	0.94
Fatal myocardial infarction	1.00 (0.30 – 3.27)	65%	1.00
Fatal stroke	1.00 (0.54 – 1.84)	0%	1.00
Non-fatal myocardial infarction	0.93 (0.78 – 1.12)	0%	0.46
Non-fatal stroke	0.96 (0.77 – 1.20)	0%	0.73
Hospitalization for heart failure	1.01 (0.83 – 1.23)	15%	0.91
Transient ischemic attack	1.00 (0.60 – 1.50)	4%	1.00
Coronary revascularization	0.98 (0.77 – 1.24)	0%	0.86
Cerebrovascular revascularization	0.37 (0.11 – 1.26)	0%	0.11
Atrial fibrillation	1.00 (0.83 – 1.21)	0%	0.99

*CI; confidence interval

Figure 2