

Peer Review File

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Reviewer A

Major comment

Comment 1: 'Regarding to CV death and musculoskeletal and connective tissue signs and symptoms, febuxostat were more than allopurinol (OR 1.38, 95% CI:1.23 to 1.54, $P < 0.00001$ for CV death, Figure 3B; OR 1.27, 95% CI:1.01 to 1.61, $P = 0.04$ for musculoskeletal and connective tissue signs and symptoms Figure 3C).' This is incomplete sentence and mismatch to figures. On Fig 3B and 3C, the risks of cv death and musculoskeletal/connective tissue signs and symptoms seems to be larger in allopurinol than febuxostat. This is so confusing.

Reply 1: Yes, this is an incomplete sentence, on the Fig 3B and 3C, we can see that the rhombus was located on the right and OR values were greater than one. This showed that the risks of CV death and musculoskeletal and connective tissue signs and symptoms were larger in febuxostat than allopurinol.

Changes in the text: We have completed the sentence (line 203-205).

Comment 2: The risk of all-cause mortality was neutral between drugs, whereas the risk of cv death was imbalanced. Please explain or speculate this discordance more in detail. Furthermore, authors should discuss the potential increased risk of cv death of allopurinol (or febuxostat?) and its clinical perspectives. This increased risk is clinically very critical issue of concern, though authors simply concluded that there was no difference in the incidence of major cv events.

Reply 2: The risk of CV death of febuxostat group was occurred more than allopurinol, and the risk of all-cause mortality was neutral between drugs. It could be the cause by allopurinol hypersensitivity syndrome. In the study, the occurrence of skin reactions of allopurinol was significantly more than febuxostat. The allopurinol hypersensitivity syndrome is potentially life-threatening, and is associated with significant mortality (line 65-67).

In clinical, allopurinol and febuxostat should be commenced at an initial dose, and the dose increased gradually. Pay close attention to the major cardiovascular events, the febuxostat CV death, allopurinol hypersensitivity syndrome.

Changes in the text: line 252-254 and line 292-296.

Comment 3: How about other individual components of major cv events? Authors should enhance more assessments for such cv events than those for non-cv AEs.

Reply 3: The components of major CV events have been mentioned in line 117-118.

Due to inconsistent observations of the components of major CV events in the literatures, there was no way to analyze individual components.

Changes in the text: no change.

Reviewer B

Interesting paper on CV risk in Febuxostat versus Allopurinol

Major issues:

Comment 1: Discussion should be enriched with CARES (White WB et al NEJM) and FAST (MacKenzie IS et al Lancet) data.

Reply 1: We already enriched with CARES (White WB et al NEJM) and FAST (MacKenzie IS et al Lancet) data.

Changes in the text: line 251-255, line 269-272 and line 293-297.

Comment 2: Dose used in literature are non-equipotent; please elaborate on bias due to more potent Febuxostat versus lower efficacy Allopurinol: 300mg allopurinol is equipotent to 40mg febuxostat.

Reply 2: There was no data to show that 300mg allopurinol is equipotent to 40mg febuxostat. American College of Rheumatology recommends that allopurinol should be commenced at an initial dose of 100 mg/day, febuxostat an initial dose of 40 mg/day, and the dose increased gradually. In clinical, 200/300mg/d up to 600mg/d allopurinol, and 40mg/80mg of febuxostat were often observed.

Changes in the text: no change.

Comment 3: Urgent question still to be answered: is XO1 beneficial in preventing CV disease? Please discuss this.

Reply 3: Allopurinol has been the main xanthine oxidase inhibitor used to reduce uric acid in clinic. We have discussed allopurinol and CV disease in the article in line 238-245.

Minor points

Comment 4: Rule 39 40 may be improved into a correct sentence

Changes in the text: We have completed the sentence. (see line 39).

Comment 5: Rule 71 Views instead of Insights

Changes in the text: see line 70.

Comment 6: "It was very necessessary", please skip these words

Changes in the text: we deleted the words, see line 71.

Comment: Table 1: Did Anne-Kathrin use 90mg febuxostat? Please check/correct

Reply: 90mg febuxostat was a mean dosage.

Changes in the text: No change.