## CORRESPONDENCE



# Reply to comment on "Cardiovascular safety of febuxostat compared to allopurinol for the treatment of gout: A systematic and meta-analysis"

We thank profs. Deng and Zhang for their comment on our manuscript.<sup>1</sup>

First, profs. Deng and Zhang mentioned that it was unknown why we selected randomized controlled trials (RCTs) and observational studies simultaneously in the same meta-analysis. A high quality meta-analysis based on RCTs is regarded as the highest level of evidence-based medical evidence, and the formulation of many clinical guidelines also follows this standard, but this does not mean that we should unconditionally believe in RCT-based meta-analysis, especially when the results of RCTs are different from those of observational efficacy comparison trials. The implementation of RCTs is limited by the scale of funds and usually can only ensure the statistical efficiency of the primary outcome indicators. Considering the operability and other factors, the included population is often different from that in clinical practice, the external applicability of evidence is limited, and the direct application to clinical practice sometimes cannot achieve the expected effect. The population included in the observational efficacy comparison study is closer to clinical practice, but since there is no randomization, there are many factors that may interfere with the final results. When answering a clinical question, do not just believe in RCTs. Observational efficacy comparative studies also need to be included in the evaluation. Moreover, if the results of RCTs are inconsistent with those of observational studies, it is more necessary to carefully evaluate the reasons for the differences. Sometimes the conclusions of observational studies are more credible.<sup>2</sup> In fact, the current meta-analysis can integrate the results of observational studies and RCTs at the same time, so as to make full use of the data and get a more comprehensive result.

Second, both profs. Deng and Zhang have noted that two eligible published studies were missed in our meta-analysis. One of the missed studies compares major cardiovascular events in patients with gout and concurrent cardiovascular disease and chronic kidney disease who receive febuxostat or allopurinol.<sup>3</sup> One of the exclusion criteria in our meta-analysis was patients with severe kidney dysfunction. Therefore, one of the studie suggested by profs. Deng and Zhang did not meet the inclusion criteria. The study recommended by the authors was included and the meta-analysis was updated<sup>4</sup> (Figure 1). Compared with allopurinol treatment group, the febuxostat group had a better safety outcome, which was the composite of urgent coronary revascularization<sup>1</sup> (odds ratio [OR]: 0.84, 95% confidence interval [CI]: 0.77–0.90, p < .0001 and stroke (Figure 1(A)) (OR: 0.87, 95% CI: 0.79–0.96, p = .006). However, that difference was not found in nonfatal myocardial infarction (Figure 1B) (OR: 0.95 95% CI: 0.79–1.15, p = .63), cardiovascular-related mortality (Figure 1C) (OR: 1.01, 95% CI: 0.72–1.43, p = .94), and all-cause mortality (Figure 1D) (OR: 0.97, 95% CI: 0.78–1.22, p = .82).

Third, we agree with profs. Deng and Zhang that another probably missing critical point is the quality assessment of the included studies. Study quality was independently assessed (by Gao L. G. and Cheng R.) according to a tool that was specifically developed for the randomized studies based on the Delphi Consensus.<sup>5</sup> The following criteria were used for scoring the quality of each study: (a) Was a method of randomization performed? (b) Was the treatment allocation concealed? (c) Were the groups similar at baseline regarding the most important prognostic indicators? (d) Were the eligibility criteria specified? (e) Was the outcome assessor blinded? (f) Was the care provider blinded? (g) Was the patient blinded? (h) Were point estimates and measures of variability presented for the primary outcome measures? (i) Did the analysis include an intention-to-treat analysis? A combined guality score was obtained by adding the scores for each criterion. Thus, the quality score could range from 0 to 9 points. Study quality was rated as poor (scores  $\leq$  3), fair (4–5), or high (>5). All of the included randomized studies were of high quality on the Delphi consensus criteria.

The Newcastle Ottawa Scale (NOS) was used to assess the quality of the included nonrandomised studies.<sup>6</sup> Using this scale, each study is judged on eight items, categorized into three groups: the selection of the study groups; the comparability of the groups; and how diet pattern was ascertained (objectively or subjectively). Stars are awarded for each quality item and the highest quality studies are awarded up to nine stars. A study is considered of good quality if there are three or four stars in the selection domain and one or two stars in the comparability domain and two or three stars in the outcome/exposure domain. For NOS, a score of at least six out of nine indicated high quality.<sup>7</sup> All of the included nonrandomized studies were of high quality according to NOS.

We have benefited a lot from this discussion. This meta-analysis was updated and supplemented according to valuable opinions,

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(A)							
Febuxostat		Allopurinol		Odds Ratio		Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
Chen et al. 2019	91	5262	105	5257	11.6%	0.86 [0.65, 1.15]	
Kang EH et al. 2019	78	9910	382	39640	17.0%	0.82 [0.64, 1.04]	
Kojima et al. 2019	9	537	7	533	0.8%	1.28 [0.47, 3.46]	
Mackenzie et al 2020	58	3063	80	3065	8.8%	0.72 [0.51, 1.01]	
White WB et al 2018	71	3098	70	3092	7.7%	1.01 [0.73, 1.41]	
Zhang et al 2020	291	24936	977	74808	54.2%	0.89 [0.78, 1.02]	-=+
Total (95% CI)		46806		126395	100.0%	0.87 [0.79, 0.96]	•
Total events	598		1621				
Heterogeneity: Chi <sup>2</sup> = 2.9	96, df = 5						
Test for overall effect: Z =	= 2.74 (P		0.5 0.7 1 1.5 Z				
		,					Favours Febuxostat Favours Allopurinol

(B)								
(=)	Febuxostat		Allopurinol		Odds Ratio		Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	
Becker et al. 2010	0	757	1	756	0.3%	0.33 [0.01, 8.17]	<	
Becker et al. 2010	1	756	1	756	0.5%	1.00 [0.06, 16.02]	• • • •	
Chen et al. 2019	50	5262	65	5257	12.6%	0.77 [0.53, 1.11]		
Kang EH et al. 2019	20	9910	88	39640	9.4%	0.91 [0.56, 1.48]		
Kojima et al. 2019	4	537	7	533	2.2%	0.56 [0.16, 1.94]	•	
Mackenzie et al 2020	102	3063	110	3065	16.1%	0.93 [0.70, 1.22]		
Su CY et al. 2019	272	44111	193	44111	19.7%	1.41 [1.17, 1.70]	_ <b>_</b>	
White WB et al 2018	111	3098	118	3092	16.5%	0.94 [0.72, 1.22]		
Zhang et al 2020	457	24936	1579	74808	22.5%	0.87 [0.78, 0.96]		
Total (95% CI)		92430		172018	100.0%	0.95 [0.79, 1.15]	-	
Total events	1017		2162					
Heterogeneity: Tau <sup>2</sup> = 0.1	04; Chi <sup>2</sup> =							
Test for overall effect: Z =	= 0.48 (P	U.S. U.7 1 1.S. 2						
							Favours Febuxostat Favours Allopurinol	

**FIGURE 1** Meta-analysis of studies that compared the safety of febuxostat therapy and allopurinol-treated patients with gout during followup. (A) Nonfatal stroke; (B) nonfatal myocardial infarction; (C) cardiovascular death; and (D) death from any cause.

(C)						0.11 B.C.		
	Febuxo	ostat	Allopu	rinol		Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	
Becker et al 2005	1	251	0	253	1.1%	3.04 [0.12, 74.88]	•	+
Becker et al 2005	1	256	0	253	1.1%	2.98 [0.12, 73.41]	•	+
Becker et al. 2009	6	801	0	178	1.4%	2.92 [0.16, 52.02]		+
Becker et al. 2010	0	757	2	756	1.3%	0.20 [0.01, 4.16]	•	
Becker et al. 2010	0	756	2	756	1.3%	0.20 [0.01, 4.16]	•	
Chen et al. 2019	5	5278	1	5278	2.4%	5.00 [0.58, 42.84]		+
Cicero et al. 2019	8	120	20	135	10.6%	0.41 [0.17, 0.97]	<b>-</b>	
Mackenzie et al 2020	62	3063	82	3065	23.4%	0.75 [0.54, 1.05]		
Nakagomi et al 2015	2	31	5	30	3.6%	0.34 [0.06, 1.94]	<	
Su CY et al. 2019	468	44111	334	44111	28.4%	1.41 [1.22, 1.62]		
White WB et al 2018	134	3098	100	3092	25.5%	1.35 [1.04, 1.76]		
Total (95% CI)		58522		57907	100.0%	1.01 [0.72, 1.43]	+	
Total events	687		546					
Heterogeneity: Tau <sup>2</sup> = 0.1	11; Chi <sup>2</sup> =	: 25.79, (	df = 10 (F	= 0.004	); I <sup>2</sup> = 619	6		_
Test for overall effect: Z =	= 0.07 (P	= 0.94)					U.Z U.S 1 Z 5	

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(D)	Fahuw	atat	Allen	rinel		Odda Datia	Odda Datio			
	Febuxo	ostat	Апори			Odds Rauo	Odds Rauo			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl			
Becker et al 2005	2	256	0	253	0.5%	4.98 [0.24, 104.26]	· · · · · · · · · · · · · · · · · · ·			
Becker et al 2005	2	251	0	253	0.5%	5.08 [0.24, 106.35]	· · · · · · · · · · · · · · · · · · ·			
Becker et al. 2009	7	649	0	145	0.6%	3.40 [0.19, 59.81]	• • • • • • • • • • • • • • • • • • • •			
Becker et al. 2009	3	292	0	145	0.5%	3.52 [0.18, 68.57]	· · · · · · · · · · · · · · · · · · ·			
Becker et al. 2010	1	757	3	756	0.9%	0.33 [0.03, 3.20]	<b>←</b>			
Becker et al. 2010	1	756	3	756	0.9%	0.33 [0.03, 3.20]	•			
Chen et al. 2019	5	5262	4	5257	2.5%	1.25 [0.34, 4.65]				
Kang EH et al. 2019	135	9910	545	39640	17.1%	0.99 [0.82, 1.20]				
Kojima et al. 2019	10	537	12	533	5.1%	0.82 [0.35, 1.92]				
Mackenzie et al 2020	108	3063	174	3065	15.8%	0.61 [0.48, 0.78]				
Su CY et al. 2019	1630	44111	1301	44111	19.2%	1.26 [1.17, 1.36]	-			
White WB et al 2018	243	3098	199	3092	17.0%	1.24 [1.02, 1.50]				
Zhang et al 2020	1144	24936	4022	74808	19.3%	0.85 [0.79, 0.91]	-			
Total (95% CI)		93878		172814	100.0%	0.97 [0.78, 1.22]	+			
Total events	3291		6263							
Heterogeneity: Tau <sup>2</sup> = 0.07: Chi <sup>2</sup> = 87.79. df = 12 (P < 0.00001); i <sup>2</sup> = 86%										
Test for overall effect: 7 =	= 0.22 (P	= 0.82)					0.5 0.7 1 1.5 2			
restion overall enect. Z -	- 0.22 (1	= 0.02)					Favours Febuxostat Favours Allopurinol			

FIGURE 1 (Continued)

which further makes up for the shortcomings of this analysis. We appreciate the authors' comments on our study. Your valuable suggestions will be of great help to our future scientific research work.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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