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Effects of Febuxostat on Mortality and Cardiovascular Outcomes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

Objective: To investigate the association between using febuxostat and cardiovascular events.

Methods: Systematic search of randomized controlled trials was performed using PubMed/MEDLINE, Cochrane review, and EMBASE databases through April 17, 2019. Meta-analysis was performed using random effect model and estimates were reported as risk difference (RD) with 95% CIs. The certainty of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation approach. The main outcomes of interest were cardiovascular mortality and all-cause mortality.

Results: A total of 15 randomized controlled trials (16,070 participants) were included. The mean ± SD age was 58.1±11.7 years. At the median follow-up of 6.4 months, use of febuxostat was not associated with statistically significant risk of cardiovascular mortality (RD, 0.12%; 95% CI, -0.25% to 0.49%; I^2=48%; low certainty evidence), all-cause mortality (RD, 0.20%; 95% CI, -0.28% to 0.68%; I^2 =60%; very low certainty evidence), major adverse cardiovascular events (RD, 0.40%; 95% CI, -0.34% to 1.13%; I^2=26%; low certainty evidence), myocardial infarction (RD, -0.06%; 95% CI, -0.29% to 0.17%; I^2 =0%; moderate certainty evidence), stroke (RD, 0.10%; 95% CI, -0.15% to 0.35%; I^2=0%; moderate certainty evidence), or new-onset hypertension (RD, 1.58%; 95% CI, -0.63% to 3.78%; I^2=58%; very low certainty evidence). These findings were consistent in patients with existing cardiovascular disease.

Conclusion: This meta-analysis suggested that use of febuxostat was not associated with higher risk of mortality or adverse cardiovascular outcomes in patients with gout and hyperuricemia. The results were limited by low to moderate certainty of evidence.

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Gout is a chronic inflammatory condition characterized by the deposition of monosodium urate crystals within the organs.[1,2] Hyperuricemia is known to increase the risk of gout attacks[3] and incidence of uric acid kidney stones.[4] Consequently, therapeutic lowering of the serum uric acid level is the focus of the management of gout.[5] Traditionally, this has been achieved either by reducing the production of uric acid with the use of xanthine oxidase inhibitors and/or enhancement of uric acid excretion with a uricosuric agent.[6] Febuxostat is a selective non−purine based xanthine oxidase inhibitor that limits the production of uric acid.[7,8]

Recent studies have raised safety concerns regarding the use of febuxostat in the management of hyperuricemia. The Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) trial reported a higher risk of cardiovascular mortality with the use febuxostat vs control[9] that led to a boxed warning by the US Food and Drug Administration in 2019.[10] However, since the mortality hazard was shown in a single randomized controlled trial (RCT), assessment of the drug's

safety profile in larger population settings is warranted. A recent meta-analysis[11] has found that febuxostat did not increase the risk of major adverse cardiovascular events (MACE) but may increase the risk of cardiovascular death. Herein, we conducted a systematic review and meta-analysis by including a higher number of RCTs than the previously published meta-analysis to examine the effects of febuxostat on mortality and MACE in patients with gout.

METHODS

This trial level meta-analysis was conducted in accordance with Cochrane collaboration guidelines[12] and reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis protocols.[13] The protocol of the present study was registered at PROSPERO register (CRD42019133121).

Study Search and Selection Criteria

The literature search was performed using electronic databases of PubMed/MEDLINE, Cochrane review, and EMBASE without language limitations through April 17, 2019, by two independent reviewers (H.E. and S.U.). The following keywords were used: febuxostat, hyperuricemia, gout, and clinical trial (Supplementary Material, available online at http://www.mcpiqojournal.org). References of retrieved studies were screened for further relevant studies suitable for this meta-analysis.

The pre-determined inclusion criteria were: (1) RCTs comparing febuxostat vs control (placebo or allopurinol) among adult patients with hyperuricemia; and (2) studies reporting mortality and cardiovascular endpoints of interest. There were no restrictions on language, sample size, and follow-up durations. We excluded reviews, editorials, letters, and non-human studies. We also excluded observational studies as they carry risk of selection and attrition bias to minimize the risk of confounding.

Data Extraction and Quality Assessment

The data abstraction was performed on a prespecified data collection form by two independent reviewers (A.B. and A.J.), and any discrepancy was resolved by a third reviewer (A.A.). The following information was abstracted: baseline characteristics of trials and participants, crude point estimates, raw events, sample sizes, and follow-up duration. Two reviewers (A.J. and A.B.) assessed the quality and certainty of the evidence under the supervision of third reviewer (A.A.) using the Jadad scale[14] (Supplemental Table 1, available online at http://www.mcpiqojournal.org), and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (GRADEpro GDT),[15] which was classified as high, moderate, low, or very low (Supplemental Tables 2 and 3, available online at http://www.mcpiqojournal.org).[16] The risk of bias assessment was determined using the Cochrane risk of bias scale (Supplemental Figure 1, available online at http://www.mcpiqojournal.org). Publication bias was assessed using funnel plot (Supplemental Figure 2, available online at http://www.mcpiqojournal.org), and Egger's regression test.

Outcomes of Interest

The main outcomes of interest were cardiovascular mortality and all-cause mortality. The additional endpoints were MACE, myocardial infarction (MI), stroke, and new-onset hypertension. The definition of MACE in each of the involved trials is shown in Supplemental Table 3.

Statistical Analysis

Outcomes were pooled using a random effects Mantel-Haenszel model. The DerSimonian and Laird method was used for estimation of τ^2. We reported effect sizes as risk difference (RD) with 95% CI. The 95% CIs that did not cross zero were considered statistically significant. We reported the number needed to treat or harm (NNT/H) for all outcomes. We used the I^2 statistic to measure statistical heterogeneity; I^2>50% was considered to have significant heterogeneity. Sensitivity analyses were performed by limiting the results to patients with pre-existing cardiovascular disease (CVD), and by excluding one trial at a time. To assess whether the current meta-analysis was powered to assess 30% difference between groups with moderate heterogeneity, power analysis was performed as suggested by Borenstein et al.[17] (Supplemental Figure 3, available online at http://www.

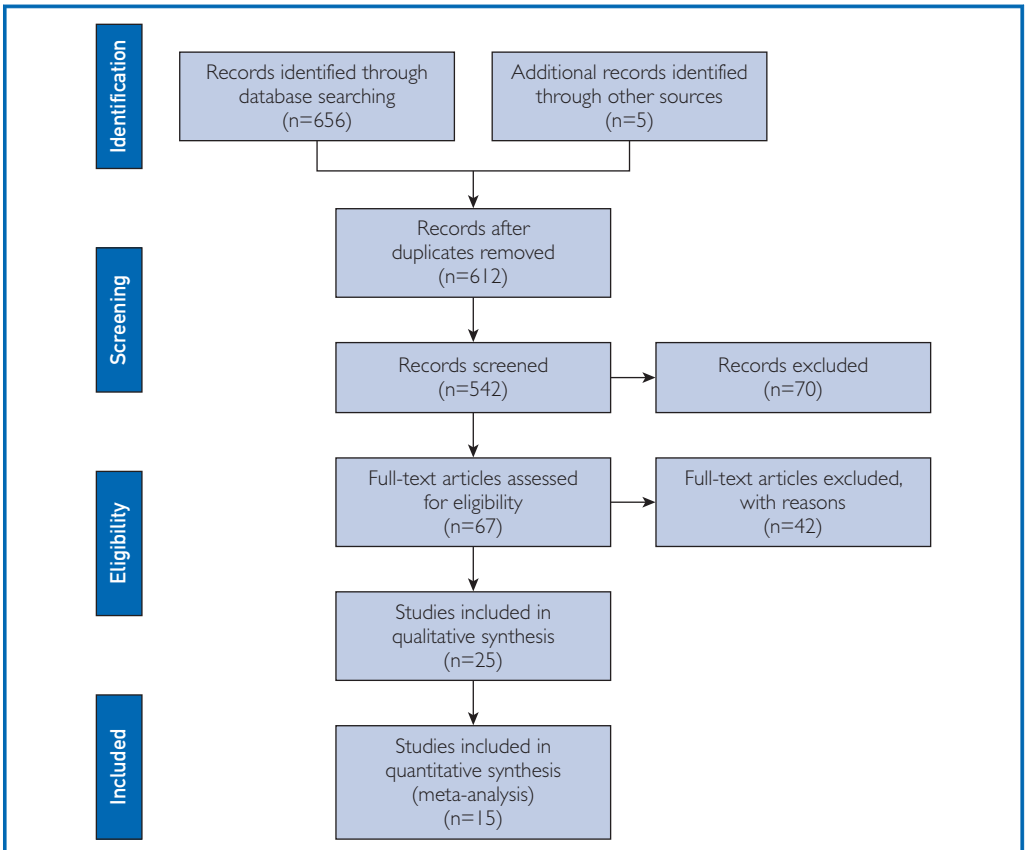

FIGURE 1. Details of the search results.

mcpiqojournal.org). This meta-analysis was 100% powered for primary endpoints.

Analyses were performed using Review Manager (RevMan) Version 5.3 (Copenhagen, Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

RESULTS

Of 661 articles, 67 full-text articles were reviewed after removal of duplicates. Finally, 15 RCTs encompassing 16,070 participants met the inclusion criteria (Figure 1).[9,18-31] Egger's regression test did not detect significant publication bias (P (two-tailed) = .51).

Characteristics of Trials and Participants

Tables 1 and 2 report baseline characteristics of trials and participants. The mean ± SD age was 58.1±11.7 years. The proportion of patients with hypertension varied from 27.7% to 100.0% and diabetes 6.9% to 100.0%. The median follow-up across the trials was 6.4 months (range: 4 to 24 months).

Cardiovascular Mortality and All-Cause Mortality

The use of febuxostat was not associated with a significant risk of cardiovascular mortality (RD, 0.12%; 95% CI, -0.25% to 0.49%; P=.53; I^2=48%; NNH=454.5; low certainty evidence) (Figure 2*A*) or all-cause mortality (RD, 0.20%; 95% CI, -0.28% to 0.68; P=.42; I^2 =60%; NNH=149.3; very low certainty of evidence) (Figure 2*B*).

Cardiovascular Outcomes

The use of febuxostat was not associated with a significant risk of MI (RD, -0.06%; 95% CI, -0.29% to 0.17%; P=.61; I^2 =0%; NNH=128.2; moderate certainty evidence), MACE (RD, 0.40%; 95% CI, -0.34% to 1.13%; P=.29 I^2 =26%; NNH=155.3; low

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TABLE 1. Details of the Randomized Clinical Trials

Study, year	N	Comparative treatment	Study period	Country	Follow-up (mo)	Population
Becker et al, 2005[25]	760	Febuxostat 80 mg vs febuxostat 120 mg vs allopurinol	July 2002–February 2004	United States and Canada	12	Gout and hyperuricemia
Schumacher et al, 2008[23]	1072	Febuxostat 80 mg vs febuxostat 120 mg vs febuxostat 240 mg vs allopurinol vs placebo	February 2003–April 2004	United States	6.4	Gout
Becker et al, 2009[18]	1086	Febuxostat 80 mg vs febuxostat 120 mg vs allopurinol	—	United States and Canada	40	Gout
Becker et al, 2010[24]	2269	Febuxostat 40 mg vs febuxostat 80 mg vs allopurinol	—	United States	6	Gout
Huang et al, 2014[20]	516	Febuxostat 40 mg vs febuxostat 80 mg vs allopurinol	February 2010–December 2010	China	6.4	Gout
Nagakomi et al, 2015[20]	61	Febuxostat 40 mg vs allopurinol	September 2011–April 2013	Japan	12	Heart failure and hyperuricemia
Saag et al, 2016[22]	96	Febuxostat 30 mg twice daily vs Febuxostat 40–80 mg once daily vs placebo	–	United States	12	Gout and chronic kidney disease
Dalbeth et al, 2017[26]	314	Febuxostat 40–80 mg vs placebo	–	United States	24	Gout
Gunawardhana et al, 2017[28]	121	Febuxostat 80 mg vs placebo	–	United States	1.5	Hypertension and hyperuricemia
Gunawardhana et al, 2018[27]	189	Febuxostat IR 40 mg vs febuxostat XR 40 mg vs febuxostat IR 80 mg vs febuxostat XR 80 mg vs placebo	May 2014–October 2015	United States	3	Gout
Kimura et al, 2018[30]	443	Febuxostat 10–40 mg vs placebo	November 2012–January 2014	Japan	25	Asymptomatic hyperuricemia and stage 3 chronic kidney disease
Mukri et al, 2018[19]	93	Febuxostat 40 mg vs placebo	—	Malaysia	6	Diabetic nephropathy (chronic kidney disease stage 3 and 4) and hyperuricemia
White et al, 2018[9]	6190	Febuxostat 40–80 mg vs allopurinol	April 2010–May 2017	United States	32	Gout and previous cardiovascular events

Continued on next page

TABLE 1. Continued

Study, year	N	Comparative treatment	Study period	Country	Follow-up (mo)	Population
Kojima et al, 2019[31]	1070	Febuxostat 10–40 mg vs non-febuxostat group (allopurinol 100 mg given if serum uric acid was elevated)	November 2013–October 2014	Japan	36	Elderly patients aged ≥65 y with hyperuricemia (serum uric acid >7.0 to ≤9.0 mg/dL) who had one or more risks for cerebral, cardiovascular, or renal disease
Saag et al, 2019[21]	1790	Febuxostat IR 40 mg vs febuxostat XR 40 mg vs febuxostat IR 80 mg vs febuxostat XR 80 mg vs placebo	April 2015–November 2016	United States	3	Gout

certainty evidence), stroke (RD, 0.10%; 95% CI, -0.15% to 0.35%; P=.43; I^2 =0%; NNH=476.2; moderate certainty evidence), or new onset hypertension (RD, 1.58%; 95% CI, -0.63% to 3.78%; P=.16; I^2 =58%; NNH=44.8; very low certainty evidence) compared with control (Supplemental Figures 4 *A* to *4D*, available online at http://www.mcpiqojournal.org).

Sensitivity Analyses

In sensitivity analyses restricted to trials including only patients with pre-existing CVD (4 RCTs, 7442 participants), use of febuxostat was not associated with significant risk of cardiovascular mortality (RD, 0.48%; 95% CI, -0.58% to 1.54%; P=.37; I^2 =30%; NNH=117.8; low certainty evidence), all-cause mortality (RD, 0.32%; 95% CI, -1.30% to 1.94%; P=.70; I^2 =46%; NNH=94.8; low certainty evidence), MACE (RD 0.24% [-1.01% to 1.49%]; P=.71; I^2 =0%; NNH=377.4; moderate certainty evidence), and MI (RD, -0.30%; 95% CI, -1.03% to 0.43%; P=.42; I^2 =0%; NNH=396.8; moderate certainty evidence) (Supplemental Figures 5*A* to *D*, available online at http://www.mcpiqojournal.org). Sensitivity analysis by excluding one trial at a time was not associated with significant changes in the results (Supplemental Table 4, available online at http://www.mcpiqojournal.org).

DISCUSSION

In this systematic review and meta-analysis of 15 RCTs including more than 16,000 patients, we found that febuxostat was not associated with a significant risk of cardiovascular or all-cause mortality among patients with gout and hyperuricemia compared with control. In conformity, there was no significant risk of MACE, nonfatal MI, stroke, or new-onset hypertension with use of febuxostat vs control.

Observational studies have suggested a beneficial cardiovascular outcome with febuxostat in patients with gout.[32,33] This cardioprotective effect could be attributed to the lower frequent of gout flares which has a detrimental effect on the cardiovascular system.[34] On the other hand, using data from an observational cohort study from Taiwan, Su et al[35] found a significant increased risk of adverse cardiovascular events and mortality with

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TABLE 2. Baseline Characteristics of the Included Trials[a]

Study, year	Trial arm, dosage (mg)	N	Males	Age ± SD, y	Patient population, n			
					DM	HTN	CAD	BMI
Becker et al, 2005[25]	FBX, 80	256	243	51.8±11.7	17	106	23	32.7±6.1
	FBX, 120	251	243	52.0±12.1	17	113	28	32.3±5.7
	ALP, 300	253	243	51.6 ± 12.6	19	112	23	32.6±6.1
Schumacher et al, 2008[23]	FBX, 80	267	251	51±12	—	124	38	33±6
	FBX, 120	269	255	51±12	—	124	37	33±7
	FBX, 240	134	126	54±13	—	70	24	33±7
	ALP, 100-300	268	249	52±12	—	123	27	33±6
	Placebo	134	123	52±12	—	61	18	32±6
Becker et al, 2009[18]	FBX, 80	649	—	51.4±11.95	46	295	71	32.3±5.78
	FBX, 120	292	—	50.9±11.57	15	115	33	33.2±6.17
	ALP, 300	145	—	51.0±11.30	12	73	14	33.8±6.79
Becker et al, 2010[24]	FBX, 40	757	722	52.5±11.68	89	—	421	32.9±6.37
	FBX, 80	756	710	53.0±11.79	113	—	440	32.9±6.39
	ALP, 200–300	756	709	52.9±11.73	110	—	436	32.7±6.23
Huang et al, 2014[29]	FBX, 40	172	167	46.12±10.90	—	54	57	25.63±2.80
	FBX, 80	172	169	47.40±11.18	—	45	47	25.25±2.64
	ALP, 300	172	168	46.17±11.56	—	44	45	25.44±2.53
Nakagomi et al, 2015[20]	FBX, 40	31	22	69.3±10	9	27	20	23.6±2.4
	ALP, 100-300	30	18	71.8±8	12	30	24	23.1±3.1
Saag et al, 2016[22]	FBX, 30 (twice daily)	32	25	67.3±11.11	12	30	—	32.8±6.45
	FBX, 40–80 (once daily)	32	26	63.6±8.15	15	31	—	34.2±7.30
	Placebo	32	26	66.3±12.05	16	31	—	33.3±6.36
Dalbeth et al, 2017[26]	FBX, 40–80	157	145	50.1±11.7	—	—	—	32.3±6.23
	Placebo	157	143	51.4±12.4	—	—	—	33.1±6.40
Gunawardhana et al, 2017[28]	FBX, 80	61	50	52.2±10.5	—	43	—	31.99±5.13

[a]ALP = allopurinol; BMI = body mass index; CAD = coronary artery disease; DM = diabetes mellitus; ER = extended release; FBX = febuxostat; HTN = hypertension; IR = immediate release.

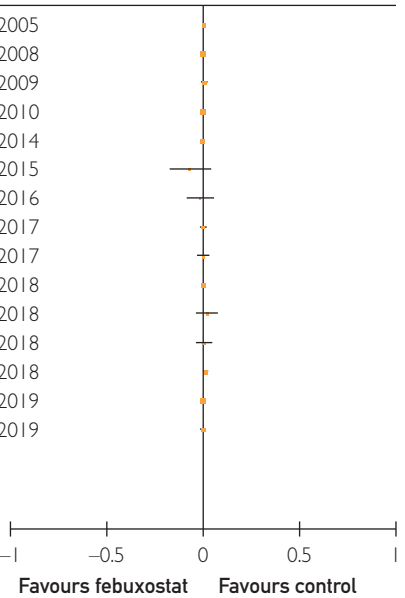
febuxostat and the association was dose dependent. In 2018, White et al[9] published the CARES trial, which was the largest reported RCT that evaluated the cardiovascular safety of febuxostat in patients with gout compared with allopurinol. This trial, which included 6190 patients, found no overall difference in MACE between the two groups, but there were more cardiovascular and all-cause mortality events in the febuxostat group. However, we did not find an association of febuxostat with cardiovascular or all-cause mortality in our analysis of pooled RCT data that included more than 16,000 patients. The CARES trial included patients with higher cardiovascular risk who had events rate more than 10% higher than the other trials, which could have contributed to this higher mortality rates seen in this trial.[9] The mechanism behind any potential risks is unknown. Experimental trials have reported no cardiac toxic effect on both heart function and rhythm.[36-38] Furthermore, the rates of MI, arrhythmias, and MACE were similar in both groups of the CARES trial and this was consistent with our analysis.

A recent meta-analysis[11] had included 10 trials and found that febuxostat did not increase the risk of MACE but may increase the risk of cardiovascular death. We found that MACE was defined differently across different RCTs (Supplemental Table 5, available online at http://www.mcpiqojournal.org) and using it as a primary outcome is

Study or subgroup	Febuxostat Events	Febuxostat Total	Control Events	Control Total	Weight	Risk difference M-H, random, 95% CI	Year
Becker 2005	2	507	0	253	9.9%	0.0039 [−0.0042, 0.0121]	2005
Schumacher 2008	0	670	0	402	15.6%	0.0000 [−0.0040, 0.0040]	2008
Becker 2009	6	941	0	145	7.2%	0.0064 [−0.0045, 0.0172]	2009
Becker 2010	0	1513	2	756	15.4%	−0.0026 [−0.0068, 0.0015]	2010
Huang 2014	0	344	0	172	9.0%	0.0000 [−0.0090, 0.0090]	2014
Nakagomi 2015	0	31	2	30	0.1%	−0.0667 [−0.1717, 0.0384]	2015
Saag 2016	1	64	1	32	0.3%	−0.0156 [−0.0831, 0.0519]	2016
Dalbeth 2017	1	157	1	157	3.6%	0.0000 [−0.0176, 0.0176]	2017
Gunawardhana 2017	0	61	0	60	1.3%	0.0000 [−0.0317, 0.0317]	2017
Kimura 2018	0	219	0	222	9.1%	0.0000 [−0.0088, 0.0088]	2018
Mukri 2018	1	47	0	46	0.4%	0.0213 [−0.0360, 0.0786]	2018
Gunawardhana 2018	1	151	0	38	0.9%	0.0066 [−0.0320, 0.0453]	2018
White 2018	134	3098	100	3092	8.4%	0.0109 [0.0014, 0.0204]	2018
Saag 2019	2	1427	1	356	13.0%	−0.0014 [−0.0072, 0.0044]	2019
Kojima 2019	6	537	6	533	5.9%	−0.0001 [−0.0127, 0.0125]	2019
Total (95% CI)		**9767**		**6294**	**100.0%**	**0.0012 [−0.0025, 0.0049]**	
Total events	154		113				

Heterogeneity: Tau^2=0.00; Chi^2=26.81, df=14 (*P*=.02); I^2=48%

Test for overall effect: Z=0.63 (*P*=.53)

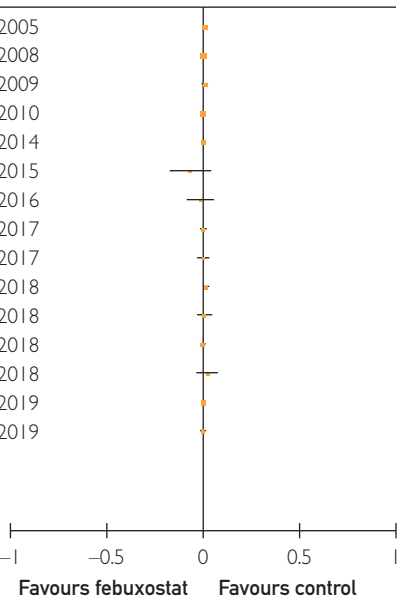


A

Study or subgroup	Febuxostat Events	Febuxostat Total	Control Events	Control Total	Weight	Risk difference M-H, random, 95% CI	Year
Becker 2005	4	507	0	253	9.6%	0.0079 [−0.0019, 0.0177]	2005
Schumacher 2008	0	670	0	402	14.5%	0.0000 [−0.0040, 0.0040]	2008
Becker 2009	10	941	0	145	8.3%	0.0106 [−0.0010, 0.0222]	2009
Becker 2010	2	1513	3	756	13.8%	−0.0026 [−0.0075, 0.0022]	2010
Huang 2014	0	344	0	172	10.3%	0.0000 [−0.0090, 0.0090]	2014
Nakagomi 2015	0	31	2	30	0.2%	−0.0667 [−0.1717, 0.0384]	2015
Saag 2016	1	64	1	32	0.5%	−0.0156 [−0.0831, 0.0519]	2016
Dalbeth 2017	1	157	1	157	5.1%	0.0000 [−0.0176, 0.0176]	2017
Gunawardhana 2017	0	61	0	60	2.0%	0.0000 [−0.0317, 0.0317]	2017
White 2018	243	3098	199	3092	7.5%	0.0141 [0.0013, 0.0269]	2018
Gunawardhana 2018	1	151	0	38	1.4%	0.0066 [−0.0320, 0.0453]	2018
Kimura 2018	1	219	1	222	7.7%	0.0001 [−0.0125, 0.0126]	2018
Mukri 2018	1	47	0	46	0.7%	0.0213 [−0.0360, 0.0786]	2018
Saag 2019	2	1427	1	356	13.0%	−0.0014 [−0.0072, 0.0044]	2019
Kojima 2019	10	537	12	533	5.3%	−0.0039 [−0.0209, 0.0131]	2019
Total (95% CI)		**9767**		**6294**	**100.0%**	**0.0020 [−0.0028, 0.0068]**	
Total events	276		220				

Heterogeneity: Tau^2=0.00; Chi^2=35.40, df=14 (*P*=.001); I^2=60%

Test for overall effect: Z=0.80 (*P*=.42)



B

FIGURE 2. (A) Forest plot of cardiovascular mortality. (B) Forest plot of all-cause mortality. M = Mantel; H = Haenszel.

unreliable. Therefore, we focused on cardiovascular mortality as the primary outcome. Our study has many other important strengths, including extensive search focusing on cardiovascular events, examining multiple individual MACE endpoints, a larger number

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of included trials, performance of a key sensitivity analysis, and analyzing the data using the RD instead of risk ratio because we are handling a dataset in which many of the event frequencies were zero; thus, using the risk ratio may exaggerate the effect of treatment.[39]

Study Limitations

On the other hand, our study also has some limitations worth mentioning. First, although we included a higher number of trials than the prior meta-analysis,[11] there was high heterogeneity of study populations across the various trials. We tried to overcome that by pooling results using the random effects model and doing sensitivity analysis. Second, among these trials, the number of cardiovascular events were low in both febuxostat and control arms of the trials and this is likely because the primary endpoints of most of these studies were not cardiovascular events. Third, there were only limited number of studies which included only patients with history of CVD.[9,20,28,31] If future studies are planned, we recommend further trials that measure cardiovascular events and mortality as an outcome, defining MACE, and comparing the outcomes among different doses of febuxostat over a longer follow-up duration. Finally, there are many ongoing trials that are measuring cardiovascular events and mortality as an outcome such as the Febuxostat versus Allopurinol Streamlined Trial (FAST)[40] trial (ISRCTN72443728) and other trials with specific types of patients; for example, the Lowering-hyperuricemia Treatment on Cardiovascular Outcomes in Peritoneal Dialysis Patients (LUMINA) trial (NCT03200210) includes only patients on peritoneal dialysis, and the The Impact of Urate-lowering Therapy on Kidney Function (IMPULsKF) trial (NCT03336203) includes patients with chronic kidney disease. All of these trials will help in estimating the associated risk of cardiovascular events and mortality with using febuxostat.

CONCLUSION

This meta-analysis including 16,070 participants showed that there was no significant difference in cardiovascular mortality, all-cause mortality, MACE, MI, stroke, and new-onset hypertension between febuxostat and the control group.

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The protocol was registered at the PROSPERO register (CRD42019133121). The authors Dr Kabir A. Yousuf for his assistance with administrative support.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **CARES trial** = The Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities; **CVD** = cardiovascular disease; **MACE** = major adverse cardiovascular events; **MI** = myocardial infarction; **RCT** = randomized controlled trials; **RD** = risk difference

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