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SYSTEMATIC REVIEWS AND META-ANALYSES

The net clinical benefits of febuxostat versus allopurinol in patients with gout or asymptomatic hyperuricemia – A systematic review and meta-analysis

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Abstract *Background and aims:* Systemic reviews and meta-analyses suggest hyperuricemia is a cardiovascular risk factor. The effects of xanthine oxidase inhibitors on cardiac outcomes remain unclear. We assessed the effects of febuxostat and allopurinol on mortality and adverse reactions in adult patients with hyperuricemia.
Methods and results: PubMed and EMBASE were searched to retrieve randomized controlled trials of febuxostat and allopurinol from January 2005 to July 2018. The meta-analysis consisted of 13 randomized controlled trials with a combined sample size of 13,539 patients. Febuxostat vs. allopurinol was not associated with an increased risk of cardiac-related mortality in the overall population (OR: 0.72, 95% CI: 0.24–2.13, P = 0.55). Regarding adverse skin reactions, the patients receiving febuxostat had significantly fewer adverse skin reactions than those receiving allopurinol treatment (OR: 0.50, 95% CI: 0.30–085, P = 0.01). Compared with allopurinol, febuxostat was associated with an improved safety outcome of cardiac-related mortality and adverse skin reactions (OR: 0.72, 95% CI: 0.55–0.96, P = 0.02). The net clinical outcome, composite of incident gout and the safety outcome, was not different significantly in the patients receiving febuxostat or allopurinol (OR: 1.04, 95% CI: 0.76–0.1.42, P = 0.79). In sensitivity analyses, a borderline significance was found in the patients randomized to febuxostat vs. allopurinol regarding cardiac-related mortality (OR: 1.29, 95% CI: 1.00–1.67, P = 0.05) after the CARES study was included.
Conclusion: Febuxostat vs. allopurinol was associated with the improved safety outcome and have comparable mortality and net clinical outcome in patients with hyperuricemia.
Registration number: PROSPERO(CRD42018091657).

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Introduction

Elevated levels of serum uric acid (SUA) induce nitric oxide deficiency in endothelial cells, the inflammatory response in pancreatic islet cells, and interstitial fibrosis in kidneys [1–4]. An elevated level of SUA, which is generally considered hyperuricemia in humans, is reportedly associated with various clinical diseases, such as metabolic syndrome, hypertension, left ventricular hypertrophy, diabetes, and coronary artery disease [3,5–8]; hyperuricemia has been reported to be associated with an increased risk of mortality in patients with coronary heart disease or acute myocardial infarction [9–11]. The contemporary guidelines therefore suggest that SUA is a nontraditional risk factor for major adverse atherosclerotic cardiovascular disease [12], and the measurement of SUA is recommended as part of the screening process for hypertensive patients and SUA is classified as a factor influencing cardiovascular risk in patients with hypertension [13].

A growing body of evidence suggests that hyperuricemia is a risk factor for cardiovascular disease, but few studies have investigated the association between urate-lowering therapy (ULT) and cardiovascular outcomes. Although some meta-analyses have suggested that ULT lowers blood pressure and attenuates the progression of chronic kidney disease [14,15], other meta-analyses reported conflicting results that showed insufficient support for an association between ULT and decreased blood pressure and the amelioration of chronic kidney disease [16,17]. ULT was not associated with a decreased risk of cardiovascular events in patients with gout [18]. One possible explanation for the discrepancies among these studies might be that hyperuricemia is only a surrogate biomarker and not a direct factor attributable to the harmful effects of cardiovascular diseases in patients with hyperuricemia.

SUA is a terminal product of purine metabolism; a critical enzyme essential for metabolizing xanthine and hypoxanthine into SUA is xanthine oxidase (XO), which generates reactive oxygen species and inflammatory responses [19]. Because a specific XO receptor is present in cardiomyocytes, XO-induced oxidative stress can inhibit the release of nitric oxide and induce myocardial contractile dysfunction [20]. XO inhibitors might reduce oxidative damage to cardiomyocytes and theoretically improve cardiac dysfunction and even cardiovascular outcomes in patients with hyperuricemia. Low-to-moderate levels of evidence from a meta-analysis also showed that XO inhibitors were associated with reduced cardiovascular events [21].

Two XO inhibitors, febuxostat and allopurinol, have comparable abilities to prevent gout flare-ups in patients with gout, although febuxostat has a greater ability to lower SUA levels [22]. Allopurinol, a xanthine analog, competes with xanthine to bind to XO, and its active metabolite similarly competes with hypoxanthine, thereby inhibiting SUA formation; in contrast, febuxostat specifically inhibits XO activity without subsequent metabolite involvement. We therefore postulated that the differences in chemical structures and mechanisms between febuxostat and allopurinol might result in different effects on cardiovascular outcomes. Additionally, it is well known that allopurinol is associated with severe skin reactions and mortality, especially in Asian patients carrying the HLAB*5801 gene [23].

Allopurinol hypersensitivity has been reported more frequently in Asian studies than in studies from Western countries due to genetic differences [24,25]. Almost one-fifth of Taiwanese individuals carry the HLAB *5801 gene and are genetically susceptible to severe skin reactions [26]. Although allopurinol hypersensitivity is rarely reported in Western countries [25], the mortality rate remains high in non-Asian patients carrying the HLAB*-5801 gene [27,28]. Regarding allopurinol treatment, patients with cardiovascular diseases at the baseline had mortality rates that were three times higher than those of patients without cardiovascular disease at the baseline in a nationwide population-based study [29]. In contrast to allopurinol, severe skin reactions have rarely been reported in patients with febuxostat treatment [26]. A network analysis showed that higher doses of febuxostat have greater efficacy in lowering urate but inferior safety compared with allopurinol [30]. Hence, we assumed that a net clinical benefit that was a composite of mortality and skin reactions might be different between patients receiving febuxostat or allopurinol treatment. The aims of the present study were to evaluate the effects of febuxostat and allopurinol in patients with hyperuricemia on (1) all-cause mortality, (2) cardiac-related mortality, (3) any serious adverse reaction or adverse skin reaction, and (4) a composite clinical net benefit incorporating mortality and adverse skin reactions in prespecified subgroups.

Methods

Data sources and searches

We systematically searched randomized controlled clinical trials in adult humans in PubMed and EMBASE from January 2005 to March 2018 during the first stage of the study, and the final search was updated on 2018/7/31. The review protocol was previously registered in PROSPERO (CRD42018091657), and the study was conducted according to the PRISMA guidelines [31].

Study selection

The prespecified eligibility criteria were as follows: randomized clinical trials or cohort studies investigating the use of febuxostat and allopurinol in patients with hyperuricemia. We excluded studies that enrolled patients with acute hyperuricemia, such as patients with tumor lysis syndrome or secondary hyperuricemia (e.g., end-stage renal disease). We did not restrict the study period or the doses of febuxostat or allopurinol. The prespecified outcomes were all-cause mortality, cardiac-related mortality, any adverse reactions, serious adverse reactions, adverse skin reactions, a composite outcome of cardiac-related mortality and adverse skin reactions as a safety outcome, and a composite outcome of the safety outcome and the incident gout flare as a net clinical outcome in prespecified subgroups.

Data extraction and quality assessment

The first three authors independently searched the databases with the keywords “febuxostat” or “allopurinol” to identify relevant randomized controlled trials or cohort studies according to their titles and abstracts, without a language limitation. Any disagreements between the three reviewers regarding the eligibility of particular studies were resolved following discussion with the rest of the team members. The second and third authors used the Cochrane Collaboration’s risk of bias tool to assess the risk of bias in the eligible studies [32].

Data synthesis and statistical analyses

We recorded the numbers of deaths in the studies and then transformed those values into odds ratios (ORs) and 95% confidence intervals (CIs) because hazard or odds ratios are more appropriate for representing the risk of mortality than a binary variable. If no deaths occurred in a study, we added 0.5 to each column for the number of deaths and the total number of patients in the febuxostat and allopurinol groups to calculate the ORs [33]. Other dichotomous outcomes were expressed as the number, including any serious adverse reactions or adverse skin reactions. Regarding the net clinical benefits, we first combined the number of deaths and the number of adverse skin reactions and then transformed them into ORs. The pooled data were estimated with the Mantel-Haenszel method. We used fixed-effect models in the studies with low heterogeneity, and random effect models were used to assess the impact of heterogeneity on the study interests if substantial heterogeneity, defined as an I^2 value more than 50 percent, was present. All P-values were two-tailed; $P < 0.05$ was considered significant. We performed the statistical analyses with Review Manager (RevMan) [computer program], Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Subgroup and sensitivity analyses

We evaluated our outcomes of interest in subgroups according to study period, race, and dose of febuxostat. The study period subgroups were divided ≤12 weeks, >12 and <24 weeks, ≥24 and < 52 weeks, and ≥52 weeks. The racial subgroups were Asian and non-Asian to evaluate the effect of the genetic susceptibility to skin reactions induced by allopurinol in Asians. The febuxostat dose subgroups were 120 mg, 80 mg, and 40 mg. The detail of sensitivity described in supplementary material.

Results

Study selection and characteristics

We finally identified 13 relevant RCTs with a combined sample size of 13,539 patients [22,34–45]. The details of the study flow chart and the study outcomes are shown in eFig. 1 and supplementary material. Table 1 shows the details of the study characteristics. The assessment of the risk of bias of the included studies is shown in eFigures 2 and 3. Regarding inconsistence of the mortality and adverse reactions among our systematic review and the included studies, we described the detail of the discrepancies in supplementary material. We performed meta-analyses of each outcome with or without including the CARES study, whose trial design is severely bias and involves a very small proportion of the patients with gout bearing a combination of severe obesity and previous cardiovascular diseases. Although three cohort studies were included [46–48], our outcomes of interest were reported in only one cohort study [47]. Therefore, we did not perform a meta-analysis of the cohort studies.

Association of febuxostat and allopurinol with all-cause or cardiac-related mortality

Compared with the allopurinol group, the febuxostat group was not associated with increases risks of all-cause and cardiac-related mortality in the overall study population (OR: 0.78, 95% CI: 0.31–2.0, P = 0.60 for all-cause mortality; OR: 0.72, 95% CI: 0.24–2.13, P = 0.55 for cardiac-related mortality, Fig. 1a). The insignificant association changed after the CARES study were included in the meta-analysis of mortality (OR: 1.29, 95% CI: 1.00–1.66, P = 0.05 for all-cause mortality; OR: 1.29, 95% CI: 1.00–1.67, P = 0.05 for cardiac-related mortality, Fig. 1b). In a subgroup analysis of the study period, compared with the allopurinol group, the febuxostat group was not associated with an increased risk of cardiac-related mortality in the studies with various study periods (eFig. 4a). After the CARES study were included in a subgroup analysis of the study period, the febuxostat group was associated with an increased risk of mortality in the studies with study periods of one year or more as compared with the allopurinol group (OR: 1.36, 95% CI: 1.05–1.76, P = 0.02 for all-cause mortality, and OR: 1.35, 95% CI: 1.04–1.75, P = 0.03 for cardiac-related mortality, eFig. 4b).

Table 1a Study characteristics of the included randomized-controlled trials.

Year	Study	Sample size	Study periods	Mean age	Male	BMI (kg/m2)	SUA (mg/dl)	Allopurinol	Febuxostat	HTN	Hyperlipidemia	DM	CVD	Renal disease
2005	FACT study by Becker et al. [22]	760	52 weeks	51.8	96%	32.5 ± 6 kg/m^2	9.8 mg/dl	300 mg (253)	80 mg (256) 120 mg (251)	44%	34%	7%	10%	35% CCr $<$ 80 ml/min
2008	APEX study by Schumacher et al. [34]	1072	28 weeks	52	94%	33 kg/m^2	9.9 mg/dl	300 mg (268)	80 mg (267) 120 mg (269) 240 mg (134)	47%	33%	NA	13%	4% Cr between 1.5 and 2.0 mg/dl
2009	EXCEL study by Becker et al. [35]	1280	172 weeks	51	NA	33 kg/m^2	9.8 mg/dl	300 mg (178)	80 mg (801) 120 mg (487)	44%	34%	7%	11%	2% Cr $>$ 1.5 mg/dl
2010	CONFIRMS study by Becker et al. [36]	2269	28 weeks	53	94%	33 kg/m^2	9.6 mg/dl	200 mg or 300 mg (756)	40 mg (757) 80 mg (756)	53%	42%	14%	57%	48% CCr 60–89 ml/min 18% CCr 30–59 ml/min
2011	Naoyuki et al. [37] (phase 2 study)	40	16 weeks	53	95%	NA	8.5 mg/dl	300 mg (20)	40 mg (10) 60 mg (10)	40%	43%	5%	NA	0 Cr $>$ 1.5 mg/dl excluded
2011	Naoyuki et al. [38] (phase 3 study)	244	8 weeks	52	97%	NA	8.9 mg/dl	200 mg (122)	40 mg (122)	33%	39%	10%	NA	7% (renal diseases)
2013	Kumar and Agarwal [39]	414	12 weeks	NA	NA	NA	10.7 mg/dl	300 mg (176)	40 mg (238)	NA	NA	NA	NA	NA
2014	Huang et al. [40]	516	28 weeks	47	98%	25 kg/m^2	9.9 mg/dl	300 mg (172)	40 mg (172) 80 mg (172)	28%	3%	6%	29%	3% (renal diseases)
2015	Xu et al. [41]	504	24 weeks	48	95%	25 kg/m^2	9.5 mg/dl	300 mg (168)	40 mg (168) 80 mg (168)	15%	8%	5%	2%	0
2015	Nakagomi et al. [42]	61	52 weeks	71.5	60%	23 kg/m^2	9.4 mg/dl	300 mg (30)	40 mg (31)	93%	97%	34%	72%	NA
2015	Tanaka et al. [43]	40	12 weeks	68	86%	25 kg/m^2	8.0 mg/dl	300 mg (19)	40 mg (21)	NA	NA	NA	13%	100% CKD stage III
2016	Yu et al. [44]	109	12 weeks	46	97%	27 kg/m^2	NA	300 mg (55)	80 mg (54)	NA	NA	NA	NA	NA
2018	CARES study by White et al. [45]	6190	32 months	64	84%	33.5 kg/m^2	8.7 mg/dl	200 mg (674) 300 mg (1379) 400 mg (779) 500 mg (133) 600 mg (127)	40 mg (1890) 80 mg (1208)	92%	87%	39%	39% MI 37% R 28% angina	47% CKD stage I-II 53% CKD stage III

Abbreviations: BMI, body mass index; SUA, serum uric acid; HTN, hypertension; DM, diabetes; CVD, cardiovascular disease; CKD, chronic kidney disease; CCr, creatinine clearance; NA, not available; Cr, creatinine; MI, myocardial infarction; R, revascularization.

Table 1b Study outcomes of the included randomized-controlled trials.

Year	Study	Sample size	Study periods	Study outcomes	the allopurinol group (n)	the febuxostat group (n)		
2005	FACT study by Becker et al. [22]	760	52 weeks		300 mg (253)	80 mg (256)	120 mg (251)	
				All-cause mortality	0	2	2	
				Cardiac mortality	0	1	1	
				Any adverse events	57	63	60	
				Serious adverse events	19	11	21	
				Skin adverse events	4	1	1	
				Gout flare	202	202	240	
2008	APEX study by Schumacher et al. [34]	1072	28 weeks		300 mg (268)	80 mg (267)	120 mg (269)	240 mg (134)
				All-cause mortality	0	0	0	0
				Cardiac mortality	0	0	0	0
				Any adverse events	200	181	183	98
				Serious adverse events	7	11	9	5
				Skin adverse events	14	14	17	6
				Gout flare	61	73	97	69
2009	EXCEL study by Becker et al. [35]	1086	172 weeks		300 mg (178)	80 mg (801)	120 mg (487)	
				All-cause mortality	0	7	3	
				Cardiac mortality	0	6[a]		
				Any adverse events	423	3362	1736	
				Serious adverse events	21	165	73	
				Skin adverse events	NA	NA		
2010	CONFIRMS study by Becker et al. [36]	2269	28 weeks		300 mg (756)	40 mg (757)	80 mg (756)	
				All-cause mortality	3	1	1	
				Cardiac mortality	2	0	0	
				Any adverse events	433	429	410	
				Serious adverse events	31	19	28	
				Skin adverse events	55	44	42	
2011	Naoyuki et al. [37] (phase 2 study)	40	16 weeks		300 mg (20)	40 mg (10)	60 mg (10)	
				All-cause mortality	0*	0*	0*	
				Cardiac mortality	0*	0*	0*	
				Any adverse events	39	34[b]		
				Serious adverse events	0*	0*	0*	
				Skin adverse events	NA	NA	NA	
2011	Naoyuki et al. [38] (phase 3 study)	244	8 weeks		200 mg (121)	40 mg (122)		
				All-cause mortality	0*	0*		
				Cardiac mortality	0*	0*		
				Any adverse events	220	213		
				Serious adverse events	0*	0*		
				Skin adverse events	5	0		
				Gout flare	7	14		
2013	Kumar and Agarwal [39]	414	12 weeks		300 mg (176)	40 mg (238)		
				All-cause mortality	NA	0		
				Cardiac mortality	NA	0		
				Any adverse events	NA	0		
				Serious adverse events	NA	0		
				Skin adverse events	6	0		
2014	Huang et al. [40]	516	28 weeks		300 mg (172)	40 mg (172)	80 mg (172)	
				All-cause mortality	0	0	0	
				Cardiac mortality	0	0	0	
				Any adverse events	103	96	89	
				Serious adverse events	2	2	1	
				Skin adverse events	1	0	0	
				Gout flare	16	9	7	
2015	Xu et al. [41]	504	24 weeks		300 mg (168)	40 mg (168)	80 mg (168)	
				All-cause mortality	0*	0*	0*	
				Cardiac mortality	0*	0*	0*	
				Any adverse events	54	63	61	
				Serious adverse events	0	0	1	
				Skin adverse events	5	3	1	
2015	Nakagomi et al. [42]	61	52 weeks		300 mg (30)	40 mg (31)		
				All-cause mortality	0*	0*	0*	
				Cardiac mortality	0*	0*	0*	
				Any adverse events	NA	NA	NA	
				Serious adverse events	0*	0*	0*	
				Skin adverse events	NA	NA	NA	

(*continued on next page*)

Table 1b (*continued*)

Year	Study	Sample size	Study periods	Study outcomes	the allopurinol group (n)	the febuxostat group (n)	
2015	Tanaka et al. [43]	40	12 weeks		300 mg (19)	40 mg (21)	
				All-cause mortality	0*	0*	0*
				Cardiac mortality	0*	0*	0*
				Any adverse events	NA	NA	NA
				Serious adverse events	0*	0*	0*
				Skin adverse events	NA	at least 2	NA
2016	Yu et al. [44]	109	12 weeks		300 mg (55)	80 mg (54)	
				All-cause mortality	0	0	
				Cardiac mortality	0	0	
				Any adverse events	35	38	
				Serious adverse events	1	2	
				Skin adverse events	9	3	
				Gout flare	19	22	
2018	CARES study by White et al. [45]	6190	32 months		200–600 mg (3092)	40/80 mg (3098)	
				All-cause mortality	199	243	
				Cardiac mortality	100	134	
				Any adverse events	644	618	
				Serious adverse events	NA	NA	
				Skin adverse events	NA	NA	

* The number of the mortality was not reported directly in these studies but none of the serious adverse events was reported.
[a] The detail of cardiac mortality was not reported in the febuxostat group.
[b] The detail of any adverse events were not reported in the febuxostat group.

Regarding the association between the different doses of febuxostat and allopurinol and all-cause mortality, no significant differences were found among the groups, although the direction of the association changed between the febuxostat 120 mg and febuxostat 40 mg groups (OR: 1.94, 95% CI: 0.16–23.2; P = 0.60 for febuxostat 120 mg; OR: 1.00, 95% CI: 0.23–4.26, P = 1.00 for febuxostat 80 mg; OR: 0.75, 95% CI: 0.18–3.12, P = 0.69 for febuxostat 40 mg or 60 mg) (eFig. 5 for cardiac-related mortality).

Association of febuxostat vs. allopurinol with any or serious or skin adverse reaction

Regarding any adverse reactions, no significant association was found in the febuxostat and allopurinol groups after the studies with a very high number of adverse reactions were excluded (eFig. 6) [35,37,38]. There were no significant associations of serious adverse reactions with febuxostat or allopurinol in all studies and in the subgroup analyses when the EXCEL trial was excluded (eFig. 7).

In the analysis of all studies, patients who received febuxostat had a lower risk of adverse skin reactions than patients who received allopurinol (OR: 0.65, 95% CI: 0.49–0.85, P < 0.01); the same result was found in the subgroup of studies with study periods <12 weeks or ≥52 weeks (eFig. 8), and in the Asian subgroup (OR: 0.25, 95% CI: 0.11–058, P < 0.01) (Fig. 2).

Associations of febuxostat and allopurinol with net clinical benefits

Compared with the allopurinol group, the febuxostat group had a better safety outcome, which was the composite of all-cause mortality and adverse skin reactions (OR: 0.75, 95% CI: 0.57–0.98, P = 0.03), and a significant association was consistently found between the administration of febuxostat and the composite of cardiac-related mortality and adverse skin reactions (OR: 0.72, 95% CI: 0.55–0.96, P = 0.02). No significant difference in safety outcome was noted in the subgroup analyses of the different study periods. The Asian group receiving febuxostat had an improved safety outcome compared with the group receiving allopurinol (OR: 0.31, 95% CI: 0.13–0.73, P < 0.01 for both), whereas no such significant difference was found in the non-Asian group (Fig. 3a). Regarding the net clinical outcome composite of the incident gout flare, cardiac mortality and adverse skin reactions, no significant differences was found in the overall study population and in subgroups of the Asian vs. non-Asian, but the direction of the association were opposite in theses subgroups (Fig. 3b).

Sensitivity analysis and publication bias

The main results did not change in the sensitivity analyses of high-quality studies vs. low-to-moderate quality studies. A lower dose of febuxostat was not associated with increased all-cause and cardiac-related mortality in the sensitivity analysis of higher vs. lower doses of febuxostat compared with a single dose of allopurinol; this result changed after was the CARES study was included (data not shown). No publication bias existed in the main results except for the association between adverse skin reactions and net clinical benefits (eFig. 9).

Discussion

The present study suggests compared with allopurinol, the use of febuxostat results in moderately increased risks of all-cause and cardiac-related mortality in the overall

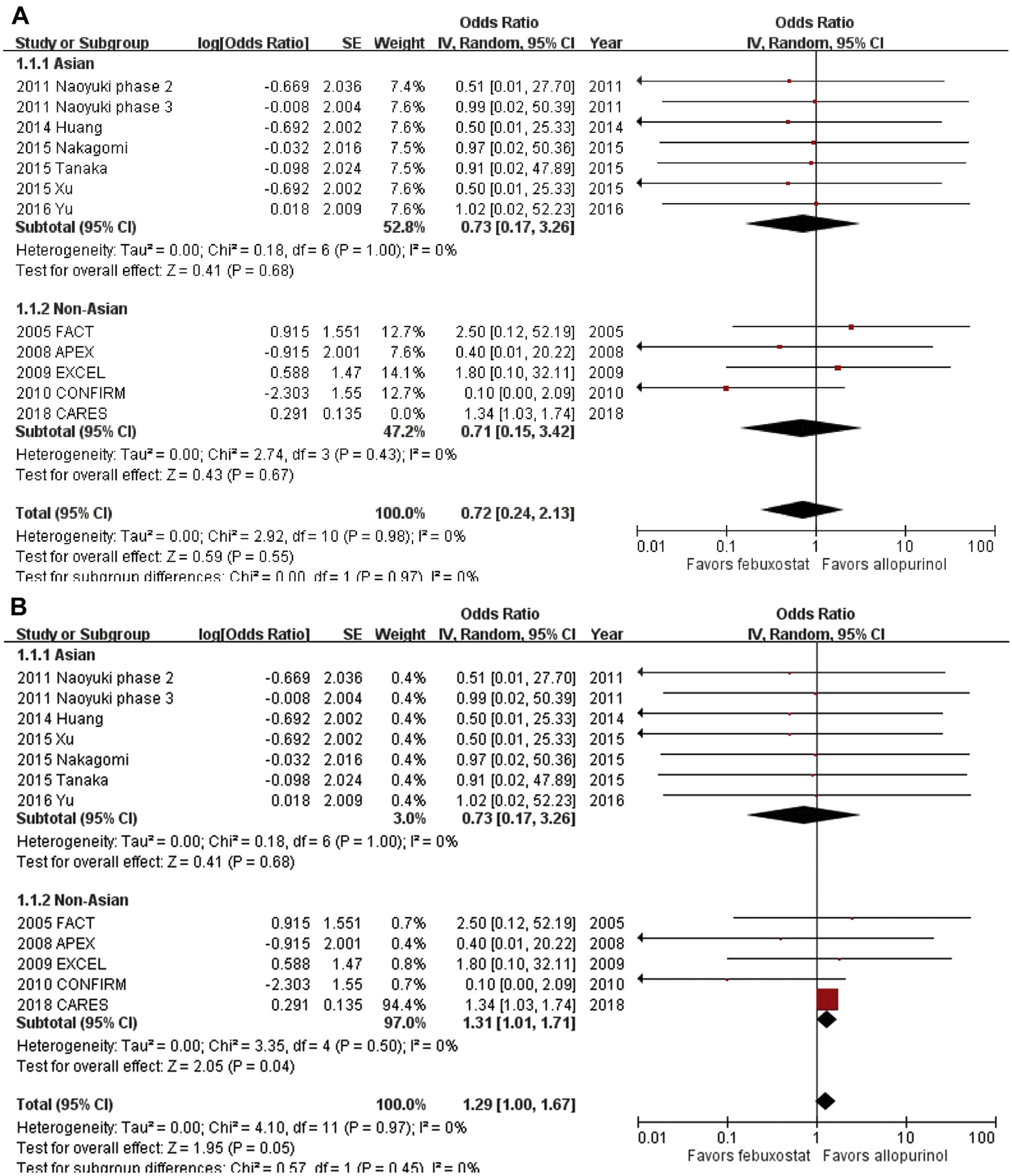

Figure 1 Randomization to febuxostat vs. allopurinol had comparable risks of cardiac-related mortality (A), but febuxostat was associated with an increased risk of cardiac-related mortality in the overall study population other than in the Asian subgroup after the CARES study was included in the meta-analysis (B).

population; however, that difference was not found in the Asian subgroup. The Asian subgroup receiving febuxostat had a decreased risk of adverse skin reactions compared with the group receiving allopurinol; the same result was found in the non-Asian group, although it did not reach statistical significance. Regarding the net clinical benefits, the Asian subgroup receiving febuxostat had a significantly better prognosis than the Asian subgroup receiving

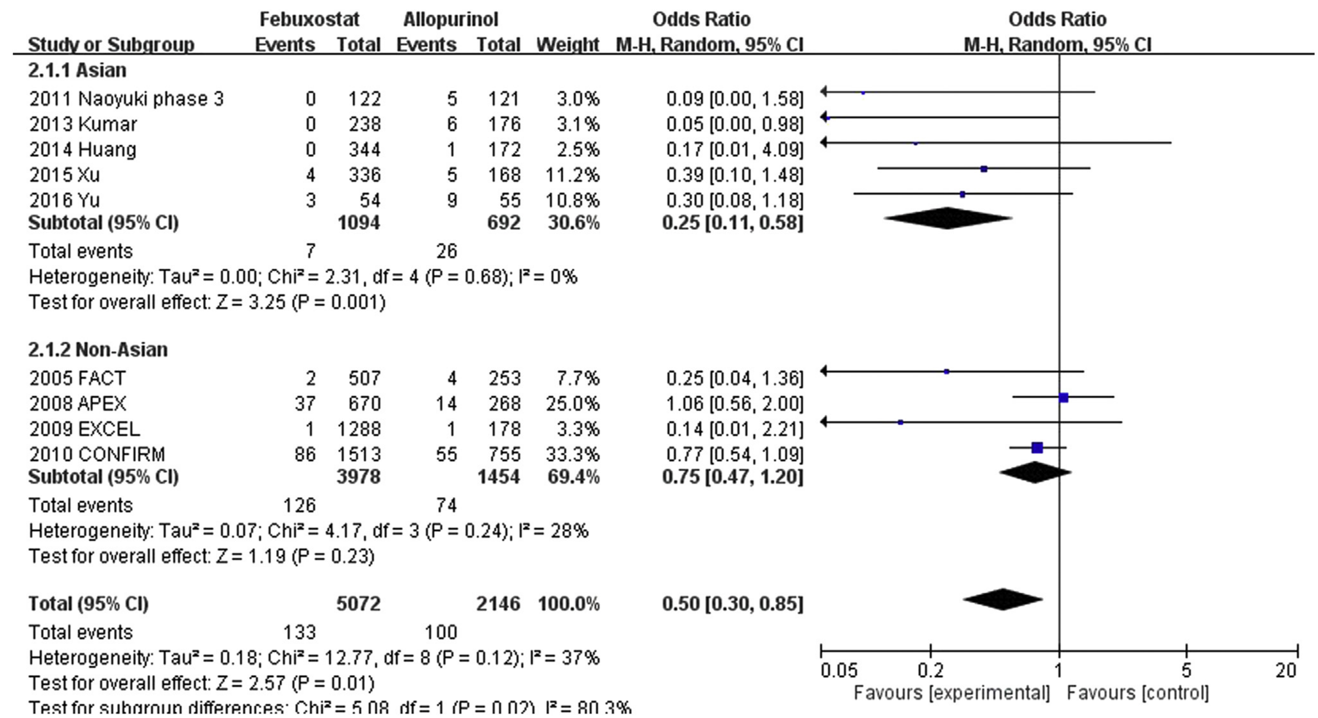

Figure 2 The Asians receiving febuxostat vs. allopurinol treatment had a significantly lower risk of skin adverse reactions.

allopurinol, and the net clinical benefits were similar in the non-Asian patients receiving febuxostat and those receiving allopurinol. Although our meta-analysis suggests that febuxostat and allopurinol had comparable safety in terms of the net clinical benefits in patients with hyperuricemia, the actual effects of XO inhibitors on the composite endpoints of cardiovascular outcomes and adverse skin reactions remain controversial. Several discrepancies existed between our meta-analysis and the results of the largest RCT, the CARES study, which had the longest follow-up period among the included RCTs but was a low-quality study. The ratio of discontinuing intervention was 56.7% in the CARES study much greater than the other studies (33.2% in the FACT, 28.5% in the APEX and less than 20% in the other studies).

The aim of the CARES study was to evaluate the cardiovascular safety of febuxostat and allopurinol in patients at high risk of cardiovascular problems, whereas as the patients in the other RCTs had at relatively low cardiovascular risks. In the CARES study, 38% of the patients had medical histories of myocardial infarction, 53% of the patients had chronic kidney diseases stages III, and 39% of the patients had diabetes; the prevalence of hypertension and hyperlipidemia were as high as 92% and 87%. However, most of the other RCTs enrolled patients with histories of cardiovascular diseases defined as hypertension or coronary heart diseases and the proportions of patients with diabetes and chronic kidney disease were also lower than those in the CARES study. All these risk factors were highly associated with mortality in the CARES study. We supposed that the results of the CARES study might not be validated externally in the general population, which has an overall low risk of cardiovascular issues. We cannot estimate the real effects of combining the CARES study with the other studies in our meta-analysis for the analysis of the net clinical benefits because adverse events due to study medication were not reported in the CARES study. Although the CARES study has a large sample size, we confidently believe the result in the Asian subgroup that showed a decreased risk of adverse skin reactions in those receiving febuxostat compared to those receiving allopurinol.

The study by Yu et al. [44] demonstrated that compared with allopurinol, febuxostat resulted in a lower incidence of adverse skin reactions in patients not carrying the HLAB*5801 gene [44]; another retrospective cohort study also showed that in patients with allopurinol hypersensitivity, the incidence of adverse skin reactions due to febuxostat was less than one tenth of that due to allopurinol [46]. The significant association of decreased skin adverse events with febuxostat group may not change given that the non-Asian studies conducted in America had only approximately 3% of the study population who were Asian Americans (329 patients) [22,35,36,45]; more than half of the patients would need to experience adverse skin reactions to change the significant association to an insignificant one, with an assumption that the incidence of the skin reactions would have a balanced distribution in the febuxostat and allopurinol groups. Similarly, we estimated that the association of cardiac-related mortality and net clinical outcomes might be unchanged in the Asian subgroup. The result of the CARES trial should be carefully interpreted in Asian patients, given that allopurinol hypersensitivity might attenuate the mortality benefit, with

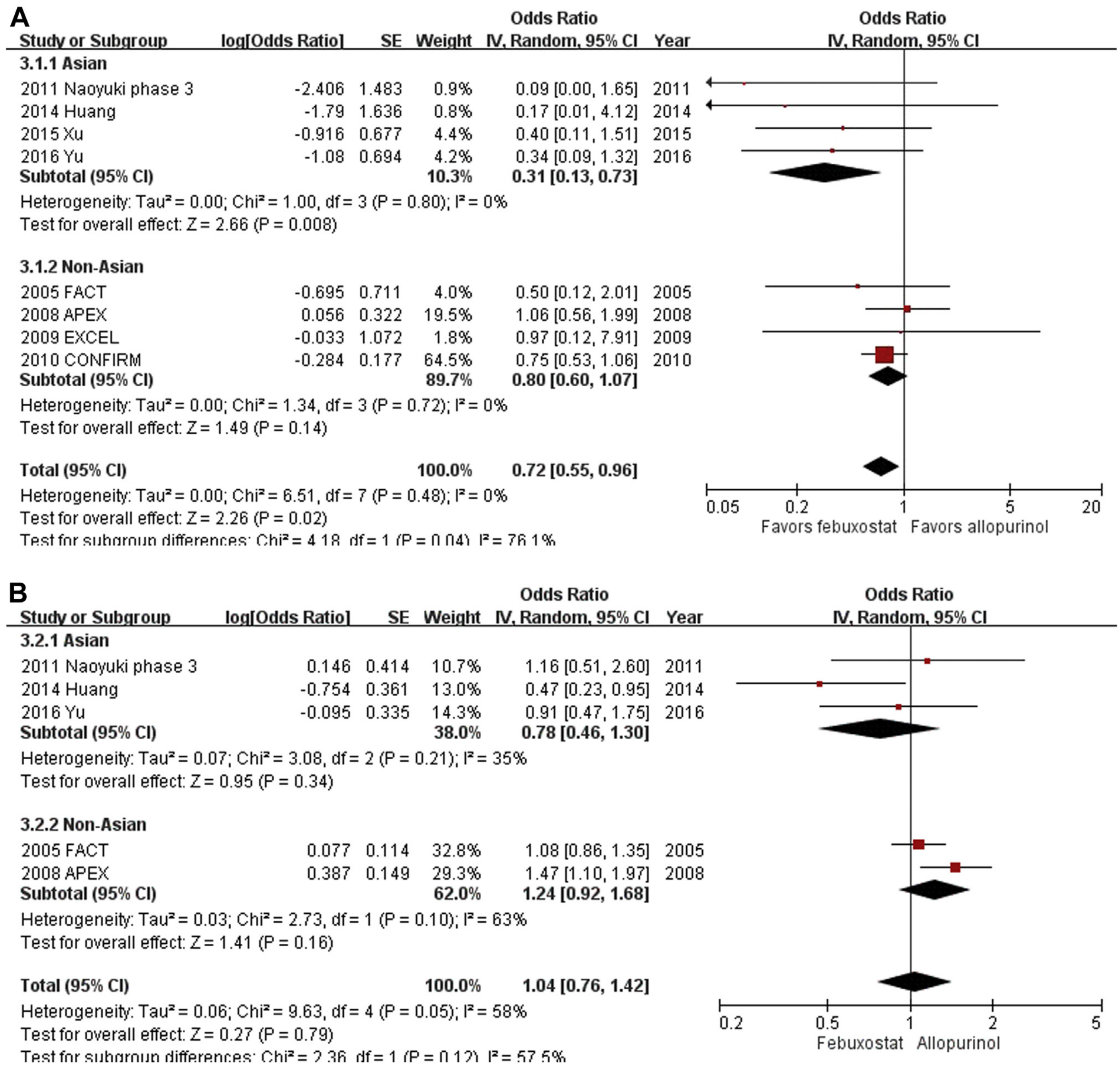

Figure 3 The Asians had the improved safety outcome that were composite of cardiac-related mortality and adverse skin reactions (A). The net clinical outcome, composite of the safety outcome and the incident gout flare, were comparable in the two groups (B).

allopurinol hypersensitivity proceeding mortality in Asians. We are uncertain whether the net clinical benefits would be changed if the CARES study had reported the actual numbers of patients experiencing adverse skin reactions. We advocate for future studies reporting the complete data on cardiac outcomes and adverse skin reactions in both Asian and non-Asian patients; this would allow an accurate estimation of the true effects febuxostat and allopurinol on the net clinical benefits.

Limitations

Several limitations should be addressed in our meta-analysis. The major issue is whether adverse skin reactions are equivalent to cardiac mortality in the field of XO inhibitors. Allopurinol hypersensitivity causes patients to discontinue allopurinol, thereby preventing hypersensitivity-related death; however, this phenomenon was not observed for febuxostat. This implies that the genetic difference of carrying the HLAB*5801 gene plays an important role in explaining the conflicting results between Asian and non-Asian studies and why adverse skin reactions are meaningful in Asians. Second, the differences in the mortality based on the length of treatment are due to the huge rate of withdrawal from treatment in the long-term studies and we do not have any information about the open-label treatment after withdrawn. More probably, it was based on allopurinol that has a lower price and we have to rely only on the results of the shorter period of observation. Third, we counted the subgroups of the studies with different doses as independent studies and could not calculate the overall effect of the pooled studies. The higher doses of febuxostat seemed to be associated with greater risks of cardiac-related mortality, and a tendency toward significantly decreased mortality could exist in the group receiving a lower dose of febuxostat compared with the group receiving allopurinol. Fourth, the Asian subgroup was not reported in four studies [22,35,36,45], and we did not receive patient-level data from the corresponding authors. Reporting the comprehensive data for the Asian subgroup is critical for accurately determining the effects of febuxostat and allopurinol on the net clinical benefits, given the high incidence of HLAB*5801 in Asia. In the future, we expect that principal investigators will report detailed data in the ongoing RCTs. Ongoing studies aiming to determine the efficacy and safety of febuxostat and conventional urate-lowering therapies might provide additional information for our meta-analysis [49,50].

Conclusions

Febuxostat is associated with a moderately increased risk of cardiac-related mortality in the overall study population, whereas a significant association with increased cardiac-related mortality was not found in the Asian subgroup. The results of the meta-analysis disagree with those of the CARES study but provide an explanation for the discrepancies. The Asian patients receiving febuxostat treatment had significantly fewer skin adverse reactions and better net clinical outcomes compared with the patients receiving allopurinol treatment, although the associations were not significantly different in the non-Asian studies. This meta-analysis suggests distinguishing Asian patients from non-Asian patients when discussing the use of XO inhibitors and net clinical outcomes in patients with hyperuricemia. The reporting of comprehensive data in ongoing trials might further contribute to closing the gaps in this meta-analysis. Future RCTs might assess whether lower doses of febuxostat improve cardiac-related mortality or net clinical outcomes.

Conflicts of interest

The authors report no relationships that could be construed as a conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2019.06.016.

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