ORIGINAL RESEARCH ARTICLE

Xanthine oxidase inhibition for the treatment of cardiovascular disease: an updated systematic review and meta-analysis

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Abstract

Background   Previous studies have shown that xanthine oxidase inhibitors (XOI) might improve outcome for patients with cardiovascular disease. However, more evidence is required.

Methods and results   We published a meta-analysis of trials conducted before 2014 examining the effects of XOI on mortality in patients with cardiovascular disease. At least two further trials ($N = 323$ patients) have since been published. Accordingly, we repeated our analysis after a further search for randomized controlled trials of XOI in PubMed/MEDLINE, EMBASE, and Cochrane Databases. We identified eight relevant trials with 1031 patients. The average age of the patients was 61 years and 68% were men (one study did not report gender). There were 57 deaths in these eight trials, 26 in those assigned to XOI, and 31 in those assigned to the control. The updated meta-analysis could not confirm a reduction in mortality for patients assigned to XOI compared with placebo (odds ratio 0.84) but 95% confidence intervals were wide (0.48–1.47).

Conclusions   This updated meta-analysis does not suggest that XOI exert a large reduction in mortality but also cannot exclude the possibility of substantial harm or benefit.

Introduction

Xanthine oxidase inhibitors (XOIs) reduce the production of uric acid (UA), its serum concentration, and UA crystal deposition in joints, thereby reducing the risk of recurrent gout. The production of UA by xanthine oxidase also generates free radicals that might adversely affect mitochondrial function and ATP production. XOIs might reduce free radical production, leading to improved left ventricular (LV) function and reverse LV remodeling and renal function.[1–12] There is a substantial literature suggesting that serum UA concentrations are associated with worse cardiovascular outcomes.[13–15] However, UA is excreted by the kidney and therefore a marker of renal function which is also strongly associated with cardiovascular outcome. UA is also an anti-oxidant.[16] Accordingly, there are theoretical reasons why XOI could improve, worsen, or have no effect on cardiovascular outcomes.[17]

We previously reported a systematic review of the effects of XOI on mortality in randomized controlled trials (RCTs) conducted in patients with cardiovascular disease.[18] The overall odds ratio (OR) and 95% confidence intervals (CI) were: 0.52 (0.19–1.40) suggesting that there might be a large benefit for XOIs, but with insufficient evidence to be certain. The recent EXACT-HF Study adds a substantial new dataset using XOI for patients with heart failure (HF),[19] and we were also aware of a further recent study.[20] We therefore updated our systematic review.

Methods

The study was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement.[21] Inclusion criteria were as follows: RCTs combined with XOI use. Participants were patients with known cardiovascular disease. Observational studies and studies that did not report mortality were excluded. There were no language restrictions.

The PubMed/Medline, Embase, and Cochrane Central Register of Controlled Trials database were searched until September 2015. Studies were identified with the following headings: allopurinol, oxypurinol, xanthine oxidase, cardio-vascular disease, clinical trial, and randomized controlled trial. We also searched reference lists of the retrieved articles to identify other eligible studies.

Two investigators independently reviewed all titles, or titles and abstracts from the search results to identify articles that met the inclusion criteria. Selected trials were compared, and disagreement was resolved by review team discussion and consensus. If any of the eligibility criteria were not met, the article was excluded. If results were incomplete or unclear, attempts were made to contact the study authors. Articles finally selected for the review were checked to avoid inclusion of data published in duplicate. Relevant information was collected on baseline characteristics, New York Heart Association (NYHA) functional classification, background cardiovascular disease, study interventions, clinical outcomes at baseline, and end follow-up. One study[22] combined death and nonfatal myocardial infarction/stroke as a major adverse cardiac event and did not report them separately. We included these events in the meta-analysis. Of 183 articles identified by the initial search, 42 were retrieved for more detailed evaluation. Only eight studies were included in the review largely because of absence of mortality data.

Statistical analysis was carried out using the Review Manager software (RevMan version 5.5). OR with 95% CI were used to assess all-cause mortality between the two treatment groups. Heterogeneity was assessed using chi-squared tests as well as I-squared test. Forest plots are used to represent the results generated from the random-effects meta-analysis graphically. The pooled OR and the degree of heterogeneity are presented. Publication bias was minimized by comprehensive literature searching. In addition, a graphical display (funnel plot) of the size of the treatment effect against the precision of the trial (one/standard error) was used to investigate publication bias. However, the funnel plot approach was not used where the number of included studies was small.

Results

Eight studies were identified including 1031 patients (*Table 1*). The average age of the patients was 61 ± 8 years, and 68% were men excluding 113 patients in one study that did not report gender. Where NYHA class was reported, most patients were in class III or IV. Common adverse effects in the trials are shown in *Table 2*.

Compared with placebo, initiation of XOI prior to coronary artery bypass graft (CABG) surgery improved recovery of cardiac function,[23] maintained normal sinus rhythm after open-heart surgery,[24] and might have reduced heart muscle injury and clinical outcomes after percutaneous coronary intervention (PCI)[25] in a series of small studies. One new study[20] showed that patients with high serum urate assigned to allopurinol for three months after an acute ischemic stroke had improved functional outcome evaluated by a modified Rankin scale (OR = 4.65, $p = 0.014$). However, there was no effect on mortality compared with placebo ($p = 0.28$).

For patients with chronic HF, Gavin and Struthers[26] showed that the plasma B-type natriuretic peptide (BNP) concentrations fell after 2–3 months treatment with allopurinol compared with placebo. However, Hare *et al.*[27] reported that there was no effect of XOI on NYHA class over 24 weeks ($p = 0.42$). The recent EXACT-HF study[19] enrolled 253 patients with left ventricular ejection fraction (LVEF) $\leq 40\%$ and randomly allocated them to allopurinol or placebo. There was no effect of allopurinol on the primary composite end point of survival, worsening HF, and patient global assessment at 24 weeks or LVEF despite a reduction in serum acid.

The two new studies[19,20] almost double the number of deaths reported in trials of XOI in cardiovascular disease. In the meta-analysis, there are now 1031 patients with 57 events. The mean duration of follow-up in the studies was about 5.4 months. Although the OR for mortality is 0.84 in favour of XOI, the 95% CI was wide (0.48–1.47) (*Figure 1*). A funnel plot for publication bias (*Figure 2*) suggests that it is unlikely that XOI have a striking effect on mortality but that substantial benefit or harm cannot be ruled out. Further analyses, confined to studies or subgroups with hyperuricaemia, provide a similar result.

Discussion

We found that use of XOI was associated with a reduction of serum UA but there was no convincing evidence that this translated into a reduction in mortality in patients with cardiovascular disease.

Many studies have shown that elevated serum concentrations of UA are a risk factor for cardiovascular events[28,29] with the notable exception of Framingham Heart Study that concluded that UA did not have a causal role in the development of coronary heart disease and

Table 1 Patient characteristics

Study	Treatment (N)	Control (N)	Age (years)	Men (%)	Follow-up	NYHA class III/IV (%)	LVEF	AF or flutter (%)	Systolic PB	HR (%)	CV disease
Coghlan 1994[23]	Allopurinol (300 mg) N = 25	Placebo N = 25	58 ± 2	84%	24 h	80%	4% of patients <40%	—	—	—	Angina undergoing first CABG operation
Gavin 2005[26]	Allopurinol (300 mg/day) N = 25	Placebo N = 25	67 ± 9	77%	3 months (controlled crossover trial with one month washout in between)	27%	—	28%	—	—	CHF (NYHA class II and III) and LV systolic dysfunction
Hare 2008[27]	Oxypurinol (600 mg/day) N = 203	Placebo N = 202	65 ± 13	73%	24 weeks	96%	<40%	—	—	—	Symptomatic HF (NYHA class III to IV) and LVEF ≤40%
Talwar 2010[24]	Allopurinol (300 mg the night before the surgery) N = 25	Placebo N = 25	31 ± 13	54%	24 h	—	—	24%	—	—	Valvular heart disease undergoing open-heart surgery
Rentoukas 2010[22]	Allopurinol (loading dose 400 mg followed by 100 mg for 1 month) N = 21	Placebo N = 19	64 ± 10	73%	1 month	—	42 ± 7%	—	—	—	Admitted with ST segment elevation myocardial infarction
Goicoechea 2010[42]	Allopurinol (100 mg/day) N = 57	Usual therapy N = 56	72 ± 9	—	24 months	—	—	—	146 ± 18	—	Presence of renal disease (eGFR < 60 mL/min)
Taheraghdam 2014[20]	Allopurinol (200 mg/day) N = 35	Placebo N = 35	68.9 ± 11.33	36%	3 months	—	—	—	—	—	Acute ischemic stroke diagnosed during admission
Givertz 2015[19]	Allopurinol (600 mg daily) N = 128	Placebo N = 125	63 (53–73)	82%	24 weeks	134 (53%)	<40%	49%	110 ± 16	74 ± 13	Symptomatic HF, LVEF ≤40% and uric acid levels ≥9.5 mg/dL

was not associated with either cardiovascular or all-cause mortality.[30] UA can have both pro- and anti-oxidant effects.[31,32] Under normal conditions, reactive oxygen species are generated by xanthine oxidase that may impair nitric oxide production, and consequently induce endothelial dysfunction, and impair mitochondrial ATP production.[33] UA may also stimulate production of C-reactive protein, inhibit endothelial cell proliferation, which can also cause endothelial dysfunction,[34] induce smooth muscle cell proliferation, and increase the production of angiotensin II.[35] However, UA is excreted by the kidney. Renal impairment will lead to both an increase in serum UA and is associated with an increase in cardiovascular risk. Whether, serum UA mediates some of the relationship between renal impairment and cardiovascular risk is uncertain; serum UA may just be an alternative to serum creatinine as a measure of renal dysfunction.

Filipatos *et al.*[36] showed an association between hyperuricaemia and all-cause mortality (HR with 95%CI: 1.4 (1.1–1.8), *p* = 0.005) and hospitalization for HF (HR with 95% CI: 1.5 (1.2–1.9), *p* = 0.001) in patients with HF who did not have chronic kidney disease (CKD), but this association did not persist in those with CKD. They hypothesized that it was over-production of UA with attendant oxidative stress rather than simply an elevated plasma concentration of UA that accounted for these observations. Ekundayo *et al.*[37] showed similar associations amongst community dwelling older adults.

Several observational studies suggest that allopurinol use is associated with lower mortality but association does not prove causality.[38,39] Other treatments for gout have also been purported to have effects on cardiovascular outcome.[40] A recent study[41] suggested that colchicine use was associated with a 73% reduction in all-cause mortality over 16.5 months in patients with gout. However, colchicine users were more likely to take allopurinol (42% vs. 16%, *p* < 0.0001). Allopurinol may just be a surrogate marker for a different pattern or quality of care rather than an effective treatment to reduce cardiovascular risk. Differences amongst studies might also reflect the dose of allopurinol used.

There are several limitations to this analysis. Most RCTs were single-centre which are more prone to investigator biases, include few patients, and have a relatively short follow-up time and very few events. Robust conclusions should not be drawn from such data. The trials also studied heterogeneous groups of patients who were at different risks of mortality both in terms of rate and cause. The heterogeneity among the patients can explain the inconclusive results and the wide confidence limits of the analysis. The dose of XOI might also be important. Doses of allopurinol ranged from 100 mg/day to 600 mg/day. There might be a steep dose–response relationship between allopurinol and its cardiovascular effects.

Table 2 Adverse effects reported with the use of allopurinol in chronic heart failure
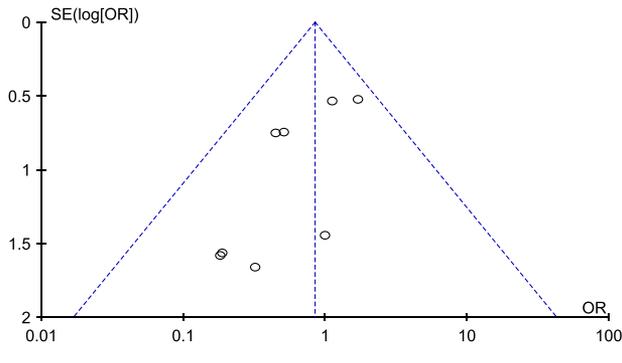
Study	Treatment	Control	Treatment adverse effects (% of patients)	Control adverse effects (% of patients)
Coghlan 1994[23]	Allopurinol (300 mg) Each patient received one tablet at 8 pm on the evening before the operation and one tablet with their premedication (1 h before the operation).	Placebo	Two required sodium nitroprusside infusion to maintain systolic blood pressure below 120 mm Hg	One required sodium nitroprusside infusion to maintain systolic blood pressure below 120 mm Hg
Gavin 2005[26]	Allopurinol (300 mg/day)	Placebo	Two patients developed a skin rash	One patient developed alopecia, one developed severe back pain, one developed diabetes
Hare 2008[27]	Oxypurinol (600 mg/day)	Placebo	—	—
Talwar 2010[24]	Allopurinol (300 mg the night before the surgery)	Placebo	The highest value of troponin $T = 3.5$ ng/mL; After 24 h the highest value of troponin $T = 4.0$ ng/mL	The highest value of troponin $T = 3.2$ ng/mL; After 24 h the highest value of troponin $T = 4.0$ ng/mL
Rentoukas 2009[22]	Allopurinol (loading dose 400 mg followed by 100 mg for 1 month)	Placebo	—	—
Goicoechea 2010[42]	Allopurinol (100 mg/day)	Usual therapy	No hematologic alterations or serious adverse events in relation to allopurinol treatment appeared in the follow-up study	—
Taheraghdam 2014[20]	Allopurinol (200 mg/day)	Placebo	Skin rashes or dermatitis 4 (11.4%) Nausea 6 (17.1%) Abdominal pain 4 (11.4%) Diarrhea 4 (11.4%) Hepatic enzyme disorders 2 (5.7%) Drowsiness 4 (11.4%) Paresthesia 1 (2.8%) Headache 7 (20%)	Skin rashes or dermatitis 0 Nausea 5 (14.2%) Abdominal pain 2 (5.7%) Diarrhea 3 (8.5%) Hepatic enzyme disorders 1 (2.8%) Drowsiness 5 (14.2%) Paresthesia 1 (2.8%) Headache 9 (25.7%)

Figure 1 Forest plots of odds ratios for risk of mortality with the exception of the trial by Rentoukas (2009) that only reported a composite of death, stroke, and myocardial infarction. Removing this trial did not materially alter the overall result [odds ratio and 95% confidence interval: 0.92 (0.50–1.68)].
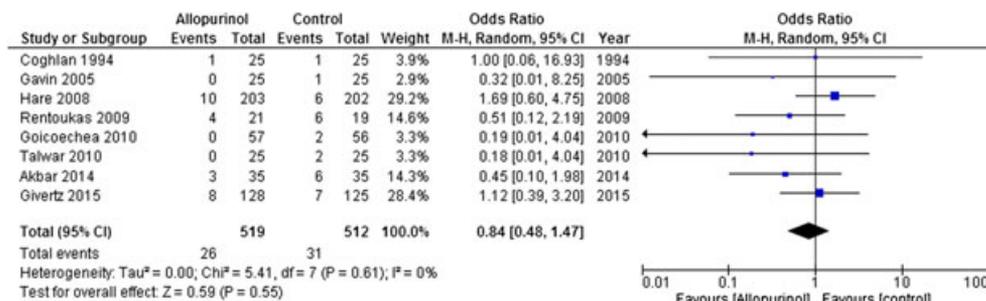
In conclusion, studies of XOI conducted in patients with cardiovascular disease do not suggest a large benefit but also do not exclude either substantial harm or benefit. The optimal dose of XOI is uncertain. Further large, multi-centre randomized controlled clinical trials are required to ensure the safety of using long-term XOI in patients with cardiovascular disease and hyperuricaemia and to confirm that this leads to a reduction in potential UA-related disease, such as gout

Figure 2 Funnel plot of estimates of the intervention effect from individual studies. Effect estimates from small studies are nearer the bottom of the graph with larger studies nearer the top. There is evidence of publication bias with several small studies suggesting a large benefit but no small studies suggesting substantial harm. Larger studies (although they are still small) in this meta-analysis are closer to neutrality. This may lead to an overestimate of benefit in this meta-analysis.[43,44]

and renal dysfunction. This will demonstrate whether or not XOI reduce cardiovascular morbidity and mortality. Future studies might stratify patients not only on serum UA concentration but also renal function to tease out the respective roles of high serum UA concentration and high UA production.

Conflict of interest

None declared.

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