MEDICAL SCIENCE MONITOR

META-ANALYSIS

e-ISSN 1643-3750
© Med Sci Monit, 2016; 22: 1389-1397
DOI: 10.12659/MSM.898370

Received: 2016.03.06
Accepted: 2016.03.14
Published: 2016.04.25

Effects of Allopurinol on Arterial Stiffness: A Meta-Analysis of Randomized Controlled Trials

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Source of support: This work was supported by the Fund of National Natural Science Foundation of China (NSFC 81271407)

Background: Several studies have tested the effects of allopurinol on arterial stiffness, but the results have been inconclusive. We aimed to conduct a meta-analysis to investigate the impacts of allopurinol treatment on arterial stiffness, as measured by pulse wave velocity (PWV) and augmentation index (AIx).

Material/Methods: Randomized controlled trials (RCTs) assessing the effects of allopurinol on arterial stiffness were identified through searching PubMed, Web of Science, EMBASE, the Cochrane Library for Central Register of Clinical Trials, and China National Knowledge Infrastructure up to December 2015. The primary endpoints were the change of PWV and AIx after allopurinol treatment. The weighted mean difference (WMD) or standardized mean difference (SMD) and the 95% confidence interval (CI) of each study were pooled for meta-analysis.

Results: A total of 11 RCTs met the inclusion criteria and were included in the final meta-analysis. Eight RCTs with 1,111 patients were pooled for PWV; eight RCTs with 397 patients were pooled for PWV. Allopurinol administration did not significantly change PWV (WMD=–0.19 m/s, 95% CI: –0.49 to 0.12, Z=1.21, p=0.23), but significantly reduced AIx (SMD=–0.34, 95% CI: –0.54 to –0.14, Z=3.35, p=0.0008).

Conclusions: Although our meta-analysis showed some favorable effects of allopurinol treatment on improving AIx, its impact on arterial stiffness must be tested in more large-scale RCTs.

MeSH Keywords: Allopurinol • Meta-Analysis • Vascular Stiffness

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/898370

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Background

Arterial stiffness has emerged as an independent predictor of cardiovascular events and all-cause mortality [1,2]. It also has been associated with brain and kidney end-organ damage [3]. Thus, improving arterial stiffness may reduce the risk of cardiovascular events, all-cause mortality and end-organ damage. Methods of assessing arterial stiffness include the measurement of arterial compliance and distensibility by ultrasound, augmentation index (AIx) and pulse wave velocity (PWV). PWV, which is based on calculating the velocity of the pressure wave travelling between two different sites along a vascular segment, is a validated estimate of arterial stiffness [4]. AIx, a ratio calculated from the blood pressure waveform, is mainly a measure of arterial wave reflections and may be affected by heart rate, height, and age [5–7]. AIx normalized for a heart rate of 75 beats per minute (AIx@75) was commonly used to take into account the effect of heart rate on AIx. Because of its correlation with PWV, AIx has also been considered as a measure of arterial stiffness [5].

Uric acid (UA) is produced by the metabolism of purines through catalyzation by the enzyme xanthine oxidase. Increased serum UA or hyperuricemia has been demonstrated to be associated with increased arterial stiffness [8–11]. Allopurinol, a xanthine oxidase inhibitor, is commonly used as a uric acid lowering agent. Recently allopurinol has been shown to influence arterial stiffness. While some self-controlled and cross-sectional studies showed beneficial effects of allopurinol [12,13], randomized controlled trials (RCTs) showed conflicting results, with some studies revealing favorable outcomes [14–20], and some finding no significant change post-treatment [21–23]. These RCTs generally featured a small sample size; therefore, we aimed to perform a meta-analysis to quantitatively evaluate the effect of allopurinol treatment on arterial stiffness.

Material and Methods

Search strategy

This meta-analysis conformed to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement. We systematically searched the electronic databases, PubMed, Web of Science, EMBASE, the Cochrane Library for Central Register of Clinical Trials, and China National Knowledge Infrastructure up to December 2015. The MeSH terms used for search purposes were "allopurinol" [MeSH] AND ("pulse wave analysis" [MeSH] OR "vascular stiffness" [MeSH]). Free text words were also used as follows: (allopurinol OR oxypurinol OR "xanthine oxidase inhibitor") AND (stiffness OR "pulse wave" OR PWV OR PWA OR "augmentation index" OR AIx OR "wave reflection"). No language restriction was used. Articles of relevant studies in the references were also manually searched.

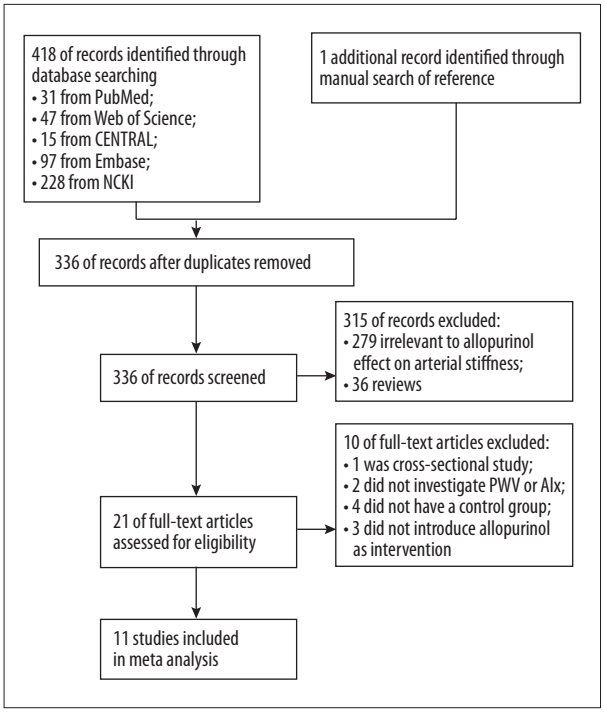

Figure 1. Flow chart of the study. PWV – pulse wave velocity; AIx – augmentation index.

Study selection

The studies were included if they met the following criteria: (1) studies were RCTs about allopurinol treatment versus placebo or no treatment control; (2) subjects were age ≥18 years old; and (3) outcomes included arterial stiffness as measured by PWV or AIx. Studies were excluded if there were insufficient information for data extraction. Non-RCTs, case reports, and reviews were also excluded.

Data extraction

Four authors (Deng, Qiu, Li, and Fang) independently extracted the data. Arbitration (Zhang) resolved disagreements, and a consensus was reached after discussion. The following information was extracted: first author, publication year, study design, inclusion/exclusion criteria, sample size and gender composition, age of the participants, total duration of follow-up, daily allopurinol dose, baseline AIx and PWV, mean change after treatment, measuring methods for arterial stiffness, and baseline serum uric acid. The AIx@75 of each study was extracted and used for analysis, unless only AIx was available. Authors of the articles were contacted by e-mail if the data were unclear.

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Table 1. Characteristics of the included randomized controlled trials.

Study	Design	Duration	Allopurinol dose (mg/d)	Inclusion criteria	Exclusion criteria	Jadad score
Szwejkowski 2013 [21]	Parallel	9 m	600	T2DM, LVH and office BP <150/90 mm Hg	Gout, GFR <60 ml/min, EF <45%	4
Dawson 2009a [23]	Parallel	3 m	300	aged over 18 years with subcortical stroke	>70% ECAS, known CAD, Scr >250 mmol/L	4
Dawson 2009b [36]	Cross-over	2 w	300	male, age >40 years, T2DM < 5 year and A1C <9.0%	CAD, severe ECAS, receiving insulin	3
Higgins 2014 [22]	Parallel	12 m	300	aged over 18 years with ischaemic stroke or TIA	>70% ECAS, GFR <50 mL/min	4
Kao 2011 [17]	Parallel	9 m	300	LVH and CKD stage 3	Active gout; EF <45%; severe hepatic disease	3
Rekhraj 2013 [14]	Parallel	9 m	600	CAD, LVH and office BP <150/90 mm Hg	Active gout, GFR<60 ml/min, HF	4
Khan 2008 [16]	Parallel	8 w	300	stroke survivors with high serum urate	No	3
Rajendra 2011 [15]	Cross-over	8 w	300/600	CAD and preserved left ventricular systolic function	Unstable angina, HF, CKD stage 4 or worse, SBP >160 mm Hg and DBP >100 mm Hg	4
Wang 2012 [19]	Parallel	3 m	300	Hyperuricemia, or gout	Active gout, CAD, carcinoma, acute infection, liver or renal dysfunction	2
Mao 2015 [20]	Parallel	3 m	300	Hyperuricemia	No	3
Wang 2015 [18]	Parallel	3 m	300	Atherosclerosis and hyperuricemia	Active gout, blood disease, carcinoma, acute infection, liver or renal dysfunction	3

ECAS – extracranial carotid artery stenosis; CAD – coronary artery disease; Scr – serum creatinine; T2DM – type 2 diabetes mellitus; TIA – transient ischemic attack; GFR – glomerular filtration rate; LVH – left ventricular hypertrophy; CKD – chronic kidney disease; EF – ejection fraction; HF – heart failure; SBP – systolic blood pressure; DBP – diastolic blood pressure.

Risk of bias assessment

Two investigators (Qiu and Li) independently assessed the included studies' risk of bias by using the Cochrane Collaboration's tool [24]. Seven domains were assessed: randomization sequence generation, allocation concealment, blinding of participants and study personnel, blinding of outcome assessors, incomplete outcome data, selective reporting, and other biases. The risk of each domain was rated as "low risk," "unclear risk," or "high risk," accordingly. The Jadad score for evaluating RCTs was also used [25], with a score ≥3 suggestive of high quality.

Statistical analysis

Meta-analysis was performed using STATA 12 (STATA Corporation, College Station, TX, USA) and Review Manager (RevMan) 5.2 (Nordic Cochrane Centre, Copenhagen, Denmark). With respect to AIx, the pooled estimate of the standardized mean difference (SMD) and 95% CI were calculated, as the outcome measurements were not the same (AIx or AIx@75). However, weighted mean difference (WMD) was used for PWV. The change of PWV or AIx was used for both of the two meta-analyses. When necessary, mean and standard deviations (SDs) were estimated from median, interquartile range and sample size using the method proposed by Wan et al. [26], or from the baseline and follow-up values via the method described by Follmann et al. [27] Heterogeneity among the included studies was evaluated using Cochrane's Q test ($P_{heterogeneity}$ <0.10 indicating significant heterogeneity) and I^2 statistic (I^2 >50%=significant heterogeneity; I^2 ≤25%=insignificant heterogeneity). The fixed-effect model was used for heterogeneous data; otherwise, the random-effect model was used. Furthermore, sensitivity analysis was conducted to investigate the influence of a single study on the overall efficacy of allopurinol. Publication bias was assessed by the Begg's and Egger's tests. A *p* value <0.05 was considered as statistically significant.

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Table 2. Baseline characteristics of the patients of the included studies.

Study	No. of patients (men,%)		Age (years)		Baseline UA (mmol/L)		Baseline PWV (m/s)		Baseline AIx (%)	
	Allo	Placebo	Allo	Placebo	Allo	Placebo	Allo	Placebo	Allo	Placebo
Szwejkowski 2013 [21]	29 (89.7)	30 (70)	63.17 (8.64)	66.03 (8.86)	0.55 (0.15)	0.54 (0.10)	7.2 (1.2)	6.9 (1.0)	11.76 (9.40)	10.47 (10.78)
Dawson 2009a [23]	20 (NR)	25 (NR)	59.4 (9.3)	57.3 (11.5)	0.35 (0.1)	0.33 (0.09)	7.6 (1.6)	8.1 (1.6)	24.4 (12.3)	22.4 (11.5)
Dawson 2009b [36]	10 (100)		53.1 (10.8)		NR		9 (7.6–9.6)*		23.5 (18.5–29.5)*	
Higgins 2014 [22]	40 (60)	40 (55)	66.9 (8.72)	68.8 (10.25)	0.32 (0.09)	0.30 (0.08)	NR		28.4 (8.1)	29.3 (7.9)
Kao 2011 [17]	27 (59)	26 (46)	70.6 (6.9)	73.7 (5.3)	0.44 (0.09)	0.42 (0.08)	7.7 (1.3)	8.2 (1.2)	18.5 (10.2)	17.2 (6.3)
Rekhraj 2013 [14]	31 (83.9)	29 (96.6)	65 (6.7)	64 (7.2)	0.59 (0.09)	0.56 (0.14)	7.6 (6.9–8.7)*	8.5 (7.4–9)*	20 (7)	19.5 (9)
Khan 2008 [16]	14 (78.6)	14 (78.6)	68.2 (5.4)	68.7 (10.3)	NR		NR		21.47 (9.69)	19.65 (8.42)
Rajendra 2011 [15]	80 (80)	80 (80)	65.5 (7.73)	65.5 (7.73)	NR		NR		27.3 (5.0)	27.8 (5.9)
Wang 2012 [19]	29 (79.3)	30 (66.7)	47.52 (9.31)	45.00 (9.70)	0.49 (0.08)	0.46 (0.08)	15.2 (1.4)	14.8 (1.6)	NR	
Mao 2015 [20]	366 (NR)	366 (NR)	NR		0.49 (0.09)	0.49 (0.11)	15.1 (NR)	15.2 (NR)	NR	
Wang 2015 [18]	43 (28)	42 (26)	47.6 (9.3)	48.8 (8.4)	0.38 (0.08)	0.38 (0.08)	15.3 (1.4)	15.3 (1.4)	NR	

Values are presented as mean (SD) unless indicated. * Median (interquartile range). UA – uric acid; PWV – pulse wave velocity; AIx – augmentation index; Allo – allopurinol; NR – not reported.

Results

Search results

Figure 1 shows the study's flow diagram. A total of 419 records were initially identified by manual and electronic database searches. After removing duplicates, 336 records were obtained. All the abstracts were reviewed, and 315 records were excluded. The remaining 21 full-text studies were assessed, and 10 studies were further excluded due to the following reasons: one was a cross-sectional study [12]; two did not measure PWV or AIx [28,29]; four did not have a control group [13,30–32]; three did not introduce allopurinol as intervention [33–35]. Finally, 11 RCTs were considered eligible for meta-analysis [14–23,36].

Characteristics of the included studies

The 11 eligible studies included 594 patients who were treated with allopurinol, and 594 patients who received placebo. Of the 11 studies, nine were parallel RCTs [14,16–23], and the remaining two were cross-over RCTs [15,36]. Eight studies evaluated allopurinol's effect on PWV [14,17–21,23,36], while eight studies evaluated the effect on AIx [14–17,21–23,36]. AIx@75 was reported in six studies [14–17,21,22]. Eight studies were performed in the UK [14–17,21–23,36] and the other three in China [18–20]. In all trials, the major characteristics of patients at baseline were similar between the study groups. The mean age of patients ranged from 45 years to 73.7 years. Baseline uric acid ranged from 0.30 to 0.59 mmol/L. Baseline PWV ranged

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from 6.9 to 15.3 m/s, and baseline AIx ranged from 10.47% to 29.3%. The daily dose of allopurinol ranged from 300 mg to 600 mg, all by oral administration. Duration of follow-up ranged from two weeks to 12 months. The detailed characteristics of these studies are summarized in Tables 1 and 2.

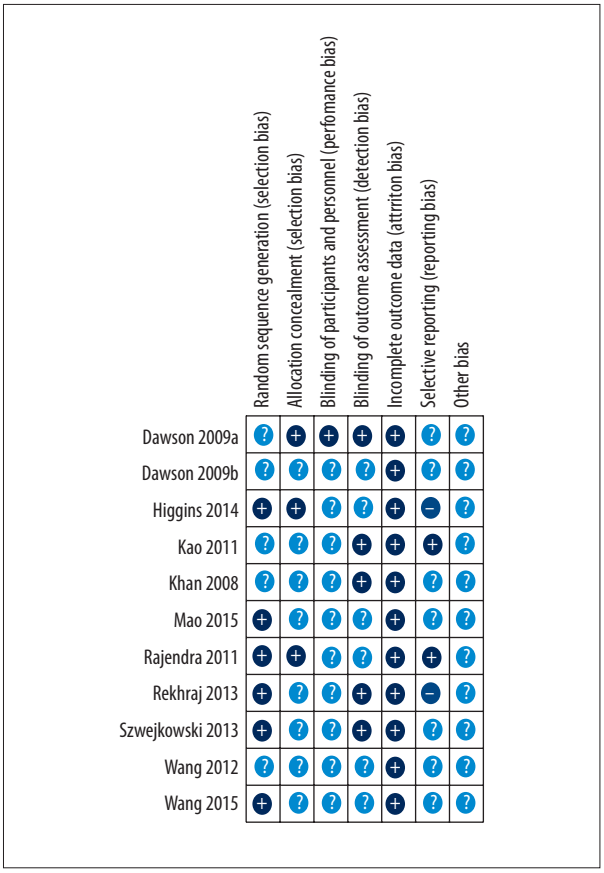

Figure 2. Risk of bias assessment. "+" indicates "low risk", "?" indicates "unclear risk", "–" indicates "high risk".

Risk of bias

Study quality is summarized in Figure 2. All 11 studies were reported as randomized, double-blind, placebo-controlled trials. Although only one study described the double-blinding method [23], five studies described the methods of random sequence generation [14,15,18,21,22], three reported methods of allocation concealment [15,22,23], and five reported outcome assessment blinding [14,16,17,21,23]. Four studies were registered on a trial register [14,15,17,22], and two of them did not report part of the pre-specified outcomes [14,22]; thus, they were rated as "high risk" in the domain of "selective reporting." All 11 studies had a Jadad score ≥3 except one [19], indicating high quality.

Pooled analysis and Publication bias

No significant change of PWV was observed after allopurinol treatment (WMD=–0.19 m/s, 95% CI: –0.49 to 0.12, Z=1.21, p=0.23; Figure 3). There was significant heterogeneity among the included seven studies ($p_{heterogeneity}$<0.00001, I^2=97%); therefore, a random-effect model was used. Egger's test showed that significant publication bias existed though Begg's test indicated no significant publication bias (p=0.536 for Begg's test; p=0.006 for Egger's test).

Allopurinol significantly decreased AIx (SMD=–0.34, 95% CI: –0.54 to –0.14, Z=3.35, p=0.0008; Figure 4). There was no evidence of heterogeneity among the eight included studies ($p_{heterogeneity}$=0.26, I^2=22%); therefore, a fixed-effect model was used. Begg's and Egger's tests showed that there was no significant publication bias (p=1.000 for Begg's test; p=0.732 for Egger's test).

Study or subgroup	Allopurinol Mean	SD	Total	Control Mean	SD	Total	Weight	Mean difference IV, random, 95% CI
Dawson 2009a	0.09	1.63	17	–0.41	1.5	22	6.8%	0.50 [–0.50, 1.50]
Dawson 2009b	0.74	2.255	10	2.58	6.29	10	0.5%	–1.84 [–5.98, 2.30]
Kao 2011	–0.39	1.13	27	0.2	1.28	26	11.6%	–0.59 [–1.24, 0.06]
Mao 2015	0.14	0.1	29	0.039	0.086	30	24.4%	0.10 [0.05, 0.15]
Rekhraj 2013	–0.14	0.82	31	–0.2	1.22	29	14.1%	0.06 [–0.47, 0.59]
Szwejkowski 2013	–0.71	2.65	29	–0.7	2.22	30	4.8%	–0.01 [–1.26, 1.24]
Wang 2012	–0.053	0.231	366	0.297	0.31	366	24.4%	–0.35 [–0.39, –031]
Wang 2015	–1.59	1.33	43	–0.9	1.34	42	13.3%	–0.69 [–1.26, –0.12]
Total (95% CI)			**552**			**555**	**100.0%**	**–0.19 [–0.49, 0.12]**

Heterogeneity: Tau²=0.10; Chi²=211.46, df=7 (P<0.00001); I²=97%
Test for overall effect: Z=1.21 (P=0.23)

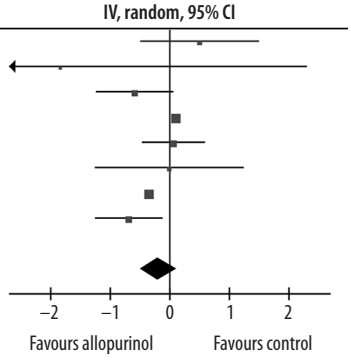

Figure 3. Forest plot illustrating allopurinol effect on pulse wave velocity. SD – standard deviation; IV – inverse variance; CI – confidence interval.

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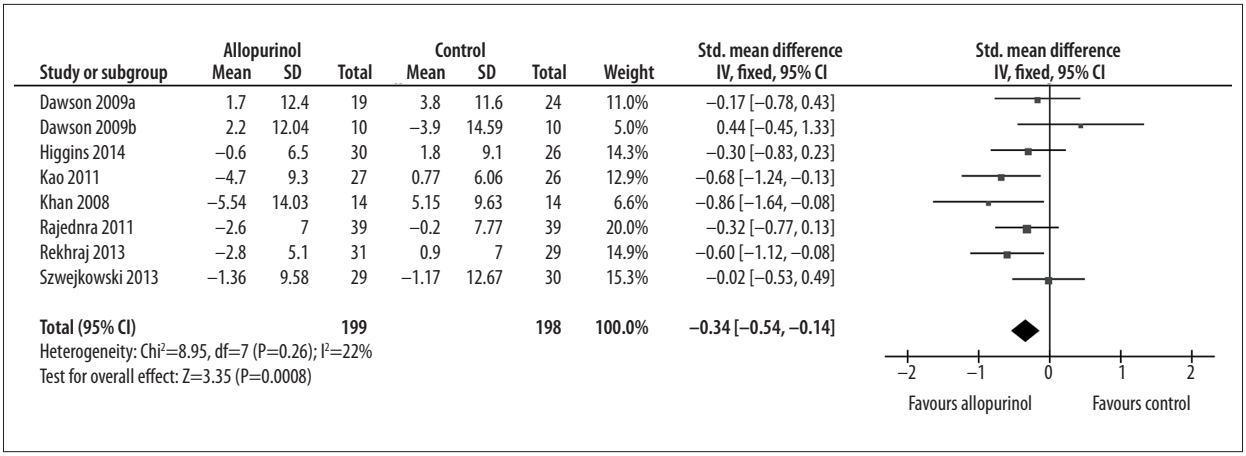

Figure 4. Forest plot illustrating allopurinol effect on augmentation index. SD – standard deviation; IV – inverse variance; CI – confidence interval.

Table 3. The results of subgroup analyses for pulse wave velocity.

Subgroup	No. of patients (allopurinol/placebo)	No. of studies	WMD	95% CI	I^2 (%)	*P*	P_{sub}
Doses							
≤300 mg	492/496	6	−0.24	−0.59 to 0.10	98	0.16	0.34
>300 mg	60/59	2	0.05	−0.44 to 0.54	0	0.84	
Duration of follow-up							
≤3 m	465/470	5	−0.19	−0.56 to 0.19	98	0.33	0.99
>3 m	87/85	3	−0.19	−0.63 to 0.25	16	0.40	

WMD – weighed mean difference; CI – confidence interval; psub – p value for subgroup differences.

Table 4. The results of subgroup analyses for augmentation index.

Subgroup	No. of patients (allopurinol/placebo)	No. of studies	WMD	95% CI	I^2 (%)	*P*	P_{sub}
Doses							
≤300 mg	100/100	5	−0.37	−0.66 to −0.09	37	0.01	0.76
>300 mg	99/98	3	−0.31	−0.59 to −0.03	19	0.03	
Duration of follow-up							
≤3 m	82/87	4	−0.28	−0.58 to 0.03	37	0.08	0.58
>3 m	117/111	4	−0.39	−0.65 to −0.13	22	0.004	

SMD – standard mean difference; CI – confidence interval; psub – p value for subgroup differences.

Subgroup analyses showed that neither the dose of allopurinol nor duration of intervention affected the above results (Tables 3, 4).

Sensitivity analysis

Sensitivity analysis showed that omitting any of the studies did not overthrow the pooled analysis result (Figure 5).

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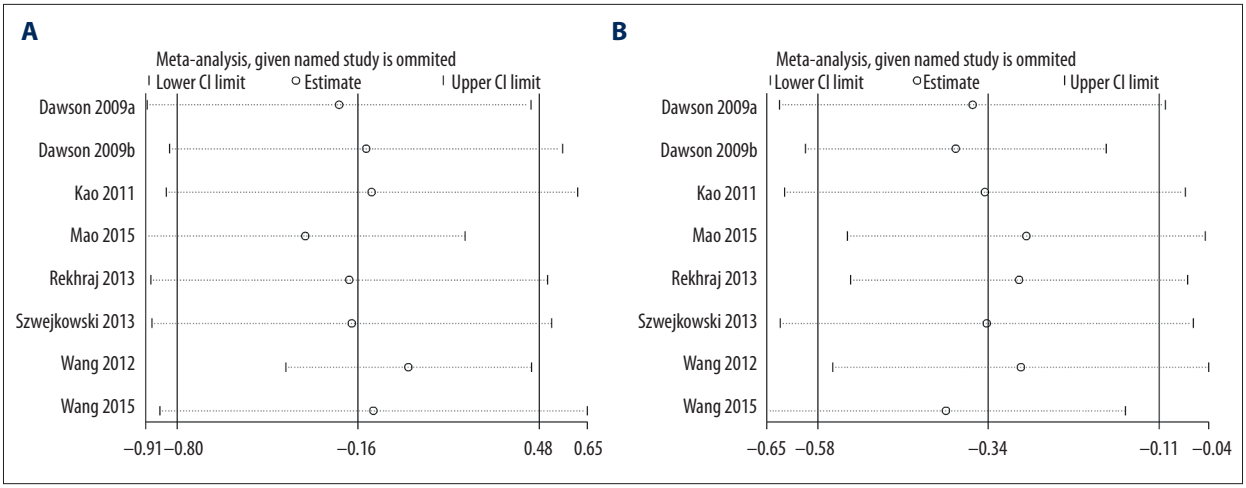

Figure 5. Sensitivity analysis results of the studies assessing allopurinol effect on pulse wave velocity (**A**) and augmentation index (**B**) by omitting each study in turn. CI – confidence interval.

Discussion

This is the first meta-analysis of RCTs to determine the impact of allopurinol on arterial stiffness. Our meta-analysis has quantitatively assessed the change in two markers of arterial stiffness, PWV and AIx, after allopurinol treatment. The findings of the present meta-analysis suggest that allopurinol might be an effective intervention for improving AIx, but not for improving PWV, which is the gold-standard measurement for arterial stiffness.

Numerous methods have been adopted to measure the arterial stiffness in various conditions, among them ultrasound and applanation tonometry (as applied in our included studies) remain the most commonly used, due to low cost, noninvasiveness, and lack of ionizing radiation [37]. However, it is limited by the inaccurate measurement of distance between two measuring sites along the vascular segment [37]. Recently magnetic resonance imaging has emerged as a validated approach in evaluating PWV, having the advantage of not depending on the knowledge of central arterial pressure or geometrical assumptions that may limit other noninvasive measurement tools [38]. Also, CT scan has been used to measure the arterial stiffness [39], providing more noninvasive methods.

UA is derived from the metabolism of the purine nucleotides, a process mediated by the enzyme xanthine oxidase. Hyperuricemia, or even high-normal serum uric acid, has been repeatedly demonstrated to be a risk factor for arterial stiffness [8–11]. Inhibition of xanthine oxidase with allopurinol not only lowers uric acid levels, but also reduces the formation of reactive oxidative species [40], improves endothelial function [41], and suppress inflammation [42], potentially providing benefit for arterial stiffness considering oxidative stress, endothelial dysfunction and inflammation all contribute to arterial stiffness [43].

Interestingly, allopurinol treatment only improved AIx, but not PWV. The pathophysiology has been rarely investigated. One possible explanation is that the treatment duration of the included studies was not long enough or that the sample size was too small to draw a positive conclusion. Another possible explanation is that allopurinol may have a greater influence on microvascular functions than central macrovascular functions, since factors affecting mainly the small arteries but not the large elastic arteries might influence AIx independently of PWV [44].

In fact, although PWV and AIx have both been shown to be independent predictors of cardiovascular events and mortality, they represent different aspects of arterial stiffness and are not interchangeable. The response of these two indices to treatment has been shown to be different sometimes [44,45]. In the included studies in our meta-analysis, only five studies measured PWV and AIx simultaneously [14,17,21,23,36]. In the future, studies focusing on influence of therapies on both PWV and AIx should be planned.

In the included 11 RCTs, one study reported three cases of adverse effects (including rash and arthralgia) in the allopurinol treatment group [17], another one reported two cases but did not describe the detail [21]; Rekhraj et al. [14] and Dawson et al. [23] reported adverse effects deemed unrelated to allopurinol use. The remaining studies did not report any adverse effects, suggesting the safety of allopurinol administration.

The strengths of this meta-analysis lie mainly in the inclusion of only RCTs, and these RCTs were generally of high quality, according to the risk of bias assessment and the Jadad scores. Second, no heterogeneity or publication bias was observed in the meta-analysis evaluating allopurinol effects on AIx. In

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addition, the sensitivity analysis showed no change in the statistical significance of the pooled estimate. Therefore, the outcome of the present study was convincing.

Some limitations of this meta-analysis have to be acknowledged. First, the capacity of the methods to detect publication bias was limited because of a limited number of studies. Second, most of the studies had a small sample size. Third, significant heterogeneity existed among the eight studies evaluating allopurinol effect on PWV; also, the Egger's test indicated that publication bias may existed.

Conclusions

This meta-analysis may provide support for a favorable effect of allopurinol treatment on improving AIx. But allopurinol did not show a beneficial effect for PWV. Because this meta-analysis is based on a limited number of studies with relatively small sample sizes, the benefit of allopurinol on arterial stiffness has still not been established. We suggest that larger multicenter RCTs assessing allopurinol's effect on arterial stiffness, both of PWV and AIx, are needed.

Conflict of interest statement

The authors have no financial conflicts of interest.

Acknowledgments

We thank Dr. Jesse Dawson and Dr. Faisel Khan for providing some essential unpublished data.

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