EVIDENCED-BASED CARDIOLOGY

What is the effect on cardiovascular events of reducing hyperuricemia with allopurinol? An evidence-based review[☆]

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Abstract
Introduction: High levels of uric acid (UA) have been associated with cardiovascular (CV) disease, but its role as an independent risk factor is the subject of debate. Treating hyperuricemia may be useful in reducing CV risk.
Objective: To review the evidence on the effect of treatment with allopurinol in patients with hyperuricemia on reducing CV events.
Methods: We searched medical databases for randomized controlled trials (RCT), cohort studies (CS) and case-control studies (CCS), meta-analyses, systematic reviews and guidelines, published between January 2002 and December 2013 in Portuguese and English. Level of evidence (LE) and strength of recommendation were graded according to the definitions used by the European Society of Cardiology.
Results: Out of 46 articles, one RCT, three CS and one CCS were included. In the RCT, treatment with allopurinol decreased CV events in patients with moderate chronic renal failure by 71% compared to controls (LE B). In one CS, patients treated with high doses had a greater reduction in CV events compared to low doses (LE B). The other two CS, in patients with heart failure (HF), found similar benefits in patients treated with high doses of allopurinol (LE B). In the CCS, in patients with HF and a history of gout, treatment with allopurinol reduced HF admission and all-cause mortality (LE B).
Discussion and Conclusions: Prolonged treatment with high doses of allopurinol may be associated with a reduction in morbidity and mortality in high CV risk populations (class of recommendation IIa). More studies evaluating the effect of therapy with allopurinol in reducing CV events in patients with and without risk are needed.
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PALAVRAS-CHAVE
Ácido úrico;
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Qual o efeito da redução da hiperuricemia nos eventos cardiovasculares? Revisão baseada na evidência

Resumo
Introdução: Níveis elevados de ácido úrico (AU) têm sido associados a doença cardiovascular (cv), mas o papel deste como fator de risco independente é controverso. O tratamento da hiperuricemia pode ser relevante na abordagem do risco CV.
Objetivo: Rever a evidência do tratamento com alopurinol, em doentes com hiperuricemia, na redução de eventos cardiovasculares.
Metodologia: Pesquisa de ensaios clínicos controlados aleatorizados (ECA), estudos coorte (EC) e caso-controlo (CC), meta-análises, revisões sistemáticas e normas de orientação, publicados entre janeiro/2002 e dezembro/2013, em bases de dados científicas. O nível de evidência e a força de recomendação foram atribuídos de acordo com escalas pré-definidas pela Sociedade Europeia de Cardiologia.
Resultados: De 46 artigos foram incluídos um ECA, três EC e um CC. No ECA o tratamento com alopurinol *versus* grupo controlo diminuiu em 71% os eventos cardiovasculares em doentes com insuficiência renal crónica moderada (LE B). Num dos EC, doentes tratados com doses altas tiveram uma redução mais significativa do risco de eventos CV (LE B). Os outros dois EC realizados em doentes com insuficiência cardíaca (IC) verificaram benefícios idênticos em doentes tratados com doses elevadas de alopurinol (LE B). No estudo CC, em doentes com IC e história de gota o tratamento com alopurinol reduziu internamentos/mortalidade por IC (LE B).
Discussão: O tratamento prolongado com doses elevadas de alopurinol pode estar associado a uma redução da morbimortalidade CV em populações de risco (Classe de Recomendação IIa). São necessários mais estudos que avaliem os efeitos da terapêutica com alopurinol na diminuição de eventos CV em doentes sem risco.

Introduction

Based upon the solubility limit of urate in body fluids, hyperuricemia is defined as uric acid (UA) concentrations exceeding 7 mg/dl (416 μmol/l), as measured by automated enzymatic methods.[1]

UA is produced in the liver and is the final product of purine metabolism. Since most UA is the result of this process, diet is a significant source of UA precursors. The catabolic steps that generate UA from free nucleic acids and purine nucleotides include degradation of the intermediates hypoxanthine and xanthine, the latter being oxidized to UA in successive reactions catalyzed by xanthine oxidase. Humans have a very limited ability to metabolize UA, which must be eliminated via the intestines and kidneys to maintain homeostasis. Intestinal bacteria degrade a third and the kidneys excrete the remainder.[2,3]

Around 10% of the population will have documented hyperuricemia at least once in their lives. Most such episodes do not require further investigation or treatment.[2] However, hyperuricemia is associated with gout, hypertension, diabetes, chronic renal failure (CRF) (uric acid nephropathy) and urolithiasis, as well as with increased risk for cardiovascular disease.[4] The role of hyperuricemia as a risk factor is the subject of debate, as to whether it contributes independently to the pathophysiology of cardiovascular disease or is an epiphenomenon resulting from concomitant conditions such as hypertension, renal disease or metabolic syndrome.

The treatment of choice for hyperuricemia is allopurinol, which reduces the formation of UA by inhibiting xanthine oxidase and improves endothelial function. The latter is an early manifestation of vascular injury and contributes to the development of atherosclerosis. Cardiovascular disease remains the leading cause of death in Portugal,[5] and so treating hyperuricemia could play an important role in reducing cardiovascular risk.

The aim of this study is to review the evidence on the effect of treatment with allopurinol in patients with hyperuricemia on reducing cardiovascular events.

Methods

MEDLINE, the Cochrane Library, Bandolier, DARE, CMA Infobase, National Guideline Clearinghouse, and NHS Evidence were searched using the MeSH terms ''uric acid'', ''cardiovascular diseases'' and ''allopurinol''. The search was limited to guidelines, meta-analyses, systematic reviews, randomized controlled trials (RCT), cohort studies (CS) and case-control studies (CCS) published between January 2002 and December 2013 in Portuguese and English. Related articles were also considered.

We included studies on adults with hyperuricemia treated with allopurinol at different doses compared with placebo, analyzing reduction of fatal and non-fatal cardiovascular outcomes and all-cause mortality. Repeated articles and

Table 1 Randomized controlled trial.

	Aims and methods	Results	LE
Goicoechea et al.[6]	To study the effect of allopurinol treatment on renal disease progression, CV events and hospitalization for any cause 113 patients with GFR <60 ml/min Allopurinol 100 mg/day (n=57) vs. control (n=56) Outcomes: hospitalizations, CV events, end-stage renal disease requiring dialysis therapy, mortality Duration: 24 months	86.7% completed the trial (51 vs. 47) Allopurinol treatment reduced CV events by 71% and hospitalizations by 62%	B

CV: cardiovascular; GFR: glomerular filtration rate; LE: level of evidence.

those that did not meet the inclusion criteria (studies of transplanted patients, cancer patients under chemotherapy and/or radiotherapy, and those with congenital heart disease) were excluded.

Level of evidence and strength of recommendation were graded according to the definitions used by the European Society of Cardiology.

Results

Of the 46 articles found, 41 were excluded on the grounds of repetition or failure to fulfill the inclusion criteria. Five publications were thus selected: one RCT, three CS and one CCS.

Randomized controlled trial

In the RCT by Goicoechea et al.[6] (Table 1), after 24 months of treatment with 100 mg allopurinol serum UA levels fell from 7.8±2.1 mg/dl to 6.0±1.2 mg/dl (p=0.001) but remained stable in the control group (7.3±1.6 mg/dl at baseline and 7.5±1.7 mg/dl at 24 months) (p=0.016 between groups and time period).

After a mean follow-up of 23.4±7.8 months, 22 patients had suffered a cardiovascular event: 15 in the control group and seven in the allopurinol group. These were eight cases of congestive heart failure, seven ischemic coronary events, five strokes, one peripheral arterial disease, and one arrhythmia. Kaplan–Meier survival analysis showed that patients in the allopurinol group had lower cardiovascular risk than those in the control group (log rank: 4.24; p=0.039). Diabetes (p=0.004), elevated C-reactive protein (p=0.031) and previous coronary disease (p=0.005) increased the risk. Allopurinol treatment decreased the risk of cardiovascular events by 71% (p=0.026). Twenty-two patients from the control group and 12 from the allopurinol group were hospitalized (p=0.032). Allopurinol treatment reduced the risk of hospitalization by 62% in a Cox regression model that included age, glomerular filtration rate, presence of diabetes, and coronary disease (hazard ratio 0.378 [0.154–0.927]; p=0.033).

Level of evidence B was attributed since this was a clinical trial with a sizable sample (113 patients), not double-blinded, with an adequate follow-up period and a dropout rate of 13% (six in the treatment group and nine in the control group).

Cohort studies (Table 2)

Struthers et al.[7] performed a cohort study of 1760 patients with chronic heart failure (HF) divided into four groups: (1) those who had never received allopurinol; (2) recent (<4 years) low dose allopurinol group (<299 mg); (3) longstanding (≥4 years) low dose allopurinol group; (4) longstanding high dose allopurinol group (≥300 mg). The study endpoints were all-cause mortality, cardiovascular mortality, and emergency cardiovascular hospitalization. Longstanding high dose allopurinol group mortality (relative risk [RR] 0.59, 95% confidence interval [CI] 0.37–0.95) and hospitalizations for cardiovascular disease were reduced, while mortality was higher in the longstanding low dose allopurinol group (RR 2.04, 95% CI 1.48–2.81). This study was attributed level of evidence B.

The 2011 cohort study by Wei et al.[8] assessed the impact of allopurinol treatment on cardiovascular events and all-cause mortality outcomes in patients aged ≥60 years who were followed for at least five years up to December 2007. The study endpoints were nonfatal myocardial infarction (MI), nonfatal stroke and cardiovascular and all-cause mortality. There were 7135 study subjects, of whom 14.5% (n=1035) were taking allopurinol and 6042 (84.7%) were not under urate-lowering therapy. Patients taking allopurinol were divided into three groups: low-dose (100 mg/day), 200 mg/day and high-dose (≥300 mg/day).

No significant difference was observed in the rate of cardiovascular events between patients treated with allopurinol and those not receiving urate-lowering therapy and with UA ≥6 mg/dl (adjusted hazard ratio [HR] 1.07, 95% CI 0.89–1.28), while in the high-dose allopurinol group, cardiovascular events and all-cause mortality were reduced with higher doses (≥300 mg/day) compared to the low-dose group (100 mg/day) (adjusted HR 0.75; 95% CI 0.59–0.94). This effect was not influenced by UA levels.

The results of the study show that high-dose allopurinol reduces cardiovascular events and all-cause mortality irrespective of the level of CV risk.

Table 2 Cohort studies.

	Aims and methods	Results	LE
Struthers et al.[7]	To examine whether different doses of allopurinol are associated with any alteration in CV and all-cause mortality and CV hospitalizations 1760 patients with chronic HF Four groups: (1) those who had never received allopurinol; (2) recent (<4 years) low dose allopurinol group (<299 mg); (3) longstanding (≥4 years) low dose allopurinol group; (4) longstanding high dose allopurinol group (≥300 mg). Outcomes: all-cause and CV mortality and CV hospitalization Duration: 4 years	Possible reduction in CV mortality only with high-dose allopurinol Low-dose allopurinol may be insufficient to treat hyperuricemia and was associated with increased mortality	B
Wei et al.[8]	To study the impact of allopurinol treatment on cardiovascular events and all-cause mortality 7135 patients aged ≥60 years Allopurinol (n=1035) vs. no treatment (n=6042) Allopurinol 100 mg (low dose) vs. 200 mg vs. ≥300 mg (high dose) Follow-up: 5–8 years Outcomes: non-fatal stroke and MI, CV and all-cause mortality	No difference in CV events between allopurinol and no treatment No difference in CV events between allopurinol and no treatment with UA ≥6 mg/dl Increased CV risk in the non-treatment group with increased UA level Reduced CV risk in the allopurinol group independent of UA level and dependent on allopurinol dose Significant reduction in CV events and all-cause mortality in the high-dose vs. low-dose allopurinol groups	B
Wei et al.[9]	To assess whether allopurinol affects mortality and CV hospitalizations in patients with HF 4785 HF patients Allopurinol group: Prevalent users (prescribed in 1st 180 days after discharge, n=258): cumulative low dose <18 400 mg, medium dose (18 400–44 800 mg) and high-dose (>44 800 mg) Incident users (prescribed ≥180 days after discharge, n=267): <299 mg/day (low dose) vs. ≥300 mg/day (high dose) Non-treatment group (n=4260) Median follow-up: non-treatment 4.9 y; incident 5 y, prevalent 3.1 y Outcomes: all-cause mortality, CV mortality, CV recurrence	Alopurinol vs. treatment Low dose: – incident group: increased all-cause and CV mortality and CV recurrence – prevalent group: increased CV mortality High dose: no effect on CV risk High dose: no effect on CV risk High vs. low dose: – prevalent group: reduced all-cause mortality – prevalent vs. incident groups: no difference in effect on CV risk	B

CV: cardiovascular; HF: heart failure; LE: level of evidence; MI: myocardial infarction; UA: uric acid; y: years.

The main strengths of the study are that it was a population-based cohort study with a large sample size and the fact that possible confounding factors such as comorbidities and concomitant drug treatment were taken into account. Compliance with medication was monitored through dispensed prescribing data, the follow-up was long with a low estimated loss to follow-up, and the outcomes were patient-oriented. The main limitations were that the investigators did not confirm whether participants actually took the medication prescribed, and that there may have been changes in allopurinol dosage after UA measurement, which was only performed once. The study was therefore attributed level of evidence B.

The aim of the 2009 cohort study by Wei et al.[9] was to explore the long-term effect of allopurinol on mortality and cardiovascular hospitalizations in HF patients. The study outcomes were all-cause mortality, cardiovascular mortality and cardiovascular disease recurrence (hospitalization with a primary diagnosis of angina, MI, HF, stroke or transient ischemic attack). Patients were divided into three groups according to allopurinol exposure during the study period: non-users, prevalent users (who had at least one prescription of allopurinol during the screening period), and incident users (who did not receive any allopurinol prescriptions during the screening period but received at least one prescription of allopurinol after the screening period.

Table 3 Case-control study.

	Aims and methods	Results	LE
Thanassoulis et al.[10]	To determine whether gout and allopurinol use are associated with HF outcomes Cases (n=14 327): HF readmission (52.9%) All-cause mortality (47.1%) Controls (n=143 225) Exposure: Allopurinol: Duration of use ≤30 days, >30 days Dose ≤100 mg/day, >100 mg/day Gout: remote <5 years, acute <60 days Outcomes: HF readmission and all-cause mortality Duration: median 2.1 years	No association between allopurinol use and outcomes Allopurinol treatment in patients with a history of gout reduced HF readmissions and mortality	B

HF: heart failure; LE: level of evidence.

Allopurinol users were further divided: prevalent users according to cumulative dosage during the screening period: low-dose group (<18 400 mg), medium-dose group (18 400–44 800 mg) and high-dose group (>44 800 mg), and incident users as high and low-dose exposure based on the dose of the first prescription (<299 mg/day or ≥300 mg/day).

A total of 4785 HF patients (4260 non-users, 267 incident users and 258 prevalent users) were studied between 1993 and 2002. Median follow-up was 4.8 years. Multivariate analysis adjusted for social deprivation, medication and comorbidities was performed.

In patients receiving low-dose allopurinol in the incident group, there was an increase in risk of all-cause mortality (adjusted HR 1.6; 95% CI, 1.26–2.03); cardiovascular mortality (adjusted HR 1.70; 95% CI, 1.29–2.23) and cardiovascular recurrence (adjusted HR 1.44, 95% CI, 1.01–2.07) compared with non-users. These results may be explained by the fact that subjects who are prescribed allopurinol have high UA, which is a risk factor for cardiovascular disease. High-dose allopurinol use was associated with a lower risk of all-cause mortality compared with low-dose allopurinol use (adjusted HR 0.65, 95% CI 0.42–0.99). This may be due to the effect of allopurinol on endothelial function, the benefits showing a steep dose-response curve. However, high dose did not significantly reduce risk for cardiovascular recurrence and cardiovascular mortality compared to low dose in the prevalent users group (adjusted HR 0.93, 95% CI 0.56–1.53 and adjusted HR 0.64, 95% CI 0.39–1.04, respectively).

This study was classified as level of evidence B. It was a population-based cohort study with a large sample size and some possible confounding factors such as comorbidities were taken into account. Compliance with medication was monitored through dispensed prescribing, the follow-up period was long with complete follow-up, and the outcomes were patient-oriented. However, there was no information on other prescribed medication, particularly losartan, or on UA levels. Furthermore, the diagnosis of renal disease was made on the basis of creatinine level only, the investigators did not confirm whether participants actually took the allopurinol prescribed, and the two groups of allopurinol users were only similar in terms of comorbidities. There was

inconsistency in the methods used to estimate the level of exposure to allopurinol, and when calculating risks, high and low doses were considered, with no data being presented on medium-dose users in the prevalent use group.

Case-control study (Table 3)

Thanassoulis et al.[10] carried out a case-control study in 25 090 patients with HF aged ≥66 years. The primary outcome of a composite measure of HF readmission (52.9%) and all-cause mortality (47.1%) was experienced by 14 327 cases. The control group was selected randomly to up to 10 controls for each case. Allopurinol use was divided into two durations of current use: new users (≤30 continuous days) and continuous users (>30 continuous days) and exposure was also dichotomized by daily dose (≤100 mg/d and >100 mg/d). Previous allopurinol users were considered unexposed, since the physiologic effect of allopurinol is relatively short after drug cessation. A remote history of gout was defined as a diagnosis of gout in the last five years, and acute gout as a primary diagnosis of gout within 60 days of the event date.

There was no statistically significant association between allopurinol use and HF readmissions or death (adjusted rate ratio 1.02; 95% CI, 0.95–1.10, p=0.55), but allopurinol was associated with reduced HF readmissions or death (adjusted rate ratio 0.69; 95% CI, 0.60–0.79, p<0.001) among patients with a history of gout. No significant differences in effect were detected among men and women treated with allopurinol.

As this was a case-control study, it was attributed level of evidence B.

Discussion

According to the best and most recent evidence available, prolonged treatment with high doses of allopurinol may be associated with reduced cardiovascular morbidity and mortality in at-risk populations (class of recommendation IIa).

This conclusion is supported by the fact that in all the selected studies performed in at-risk patients (Goicoechea et al.[6] on patients with chronic renal disease, Wei et al.[9] and Struthers et al.[7] in patients with HF, and Thanassoulis et al.[10] in patients with HF and gout), cardiovascular outcomes were reduced by high-dose rather than low-dose allopurinol.

It should be borne in mind that these studies differ in their methodology, with bias arising from UA measurements, lack of data on patients' lifestyles (particularly alcohol consumption) and body mass index, selection bias (with heterogeneity in terms of age and comorbidities), and differing dosages.

According to the European Society of Cardiology (ESC) 2012 guidelines on diagnosis and treatment of heart failure, hyperuricemia and gout are common in HF and may be caused or aggravated by diuretic treatment. Hyperuricemia is associated with a worse prognosis in HF with reduced ejection fraction.[11]

Previous evidence has suggested that high-dose allopurinol may be associated with reduced risk of mortality and cardiovascular events through its pathophysiological pathway, since higher doses of allopurinol are associated with improvement in endothelial function and may also improve cardiac structure. These two mechanisms are noteworthy because both endothelial function and cardiac function are independent predictors of mortality.[10] According to the 2013 ESC guidelines on the management of stable coronary artery disease, allopurinol has anti-anginal properties; in a randomized crossover study of 65 patients with stable angina, allopurinol 600 mg/day increased times to ST-segment depression and to chest pain.[12]

Although side effects of allopurinol treatment are beyond the scope of this article, none were reported in the selected studies. However, serious side-effects do occur, particularly Stevens-Johnson syndrome.

Patients with CRF develop hyperuricemia as glomerular filtration rate falls. In Goicoechea et al.,[6] progression of CRF was slower in patients under allopurinol treatment.

Treatment of asymptomatic hyperuricemia is still the subject of debate; the risks and benefits should be carefully assessed before beginning urate-lowering therapy. Methodologically rigorous research is required, with greater statistical power and adjustment for confounding factors, to assess the effect of therapy with allopurinol in reducing fatal and non-fatal cardiovascular events in patients with and without risk.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Becker MA. Asymptomatic hyperuricemia. Literature review current through; 2012. Available at: www.uptodate.com
2. Dincer HE, Dincer PD, Levinson DJ. Asymptomatic hyperuricemia: to treat or not to treat. Cleve Clin J Med. 2002;69:594, 7, 600–2.
3. Becker MA. Uric acid balance. Literature review current through; 2012. Available at: www.uptodate.com
4. Baker JF, Krishnan E, Chen L, et al. Serum acid and cardiovascular disease: recent developments, and where do they leave us? Am J Med. 2005;118:816–26.
5. Programa Nacional para as Doenças Cerebro-Cardiovasculares Orientações Programáticas. Available at: www.dgs.pt [accessed 05.09.12].
6. Goicoechea M, de Vinuesa SG, Verdalles U, et al. Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. Clin J Am Soc Nephrol. 2010;5:1388–93.
7. Struthers AD, Donnan PT, Lindsay P, et al. Effect of allopurinol on mortality and hospitalisations in chronic heart failure: a retrospective cohort study. Heart. 2002;87:229–34.
8. Wei L, Mackenzie IS, Chen Y, et al. Impact of allopurinol use on urate concentration and cardiovascular outcome. Br J Clin Pharmacol. 2011;71:600–7.
9. Wei L, Fahey T, Struthers AD, et al. Association between allopurinol and mortality in heart failure patients: a long-term follow-up study. Int J Clin Pract. 2009;63:1327–33.
10. Thanassoulis G, Brophy JM, Richard H, et al. Gout, allopurinol use, and heart failure outcomes. Arch Intern Med. 2010;170:1358–64.
11. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012;33: 1787–847.
12. Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J. 2013;34:2949–3003.