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EVIDENCED-BASED CARDIOLOGY

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

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KEYWORDS
Uric acid;
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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;
Doenças cardiovasculares;
Alopurinol

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.
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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

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