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META-ANALYSIS

Changes in serum uric acid levels and cardiovascular events: A meta-analysis

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Summary *Background and Aims:* The association between serum uric acid (SUA) levels and cardiovascular (CV) risk or all-cause death has been repeatedly reported. However, it has not been assessed whether reduction of SUA levels is associated with reduced CV risk. The aim of the current study was to evaluate the relationship between changes of SUA levels and CV events as well as all-cause death.
Methods and Results: Randomised trials reporting SUA at baseline and at the end of follow-up and clinical end-points (all-cause death, myocardial infarction (MI), stroke, heart failure (HF) and CV death) were included in the study. Meta-regression analysis was performed to test the relationship between SUA changes and clinical end-points. Eleven trials enrolling 21,373 participants followed up for 2.02 ± 1.76 years and reporting 4533 events were included. In meta-regression analysis, no relationship between SUA changes from baseline to end of follow-up and the composite outcome including CV death, stroke, MI and HF was found (change in Tau^2 (t) = −0.64; p *Tau* (p) = 0.541). Similarly, no relationship was found between SUA changes and single components of the composite outcome (MI: $t = -0.83$; $p = 0.493$; stroke: $t = 0.46$; $p = 0.667$; HF: $t = 2.44$; $p = 0.162$; CV death: $t = -0.54$; $p = 0.614$) and all-cause death ($t = -0.72$; $p = 0.496$). Results were confirmed by sensitivity analysis. No heterogeneity among studies or publication bias was detected.

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Conclusions: Changes in SUA levels observed during pharmacologic treatments do not predict the risk of all-cause death or CV events. As SUA levels are associated with increased CV risk, additional studies with direct xanthine-oxidase inhibitors are requested.

Introduction

Several experimental and epidemiological studies have reported an association between elevated levels of serum uric acid (SUA) and risk of cardiovascular (CV) disease or all-cause death [1]. In fact, SUA levels are associated with increased prevalence of CV risk factors including obesity [2], hypertension [3], dyslipidaemia [4] and diabetes [5]. In addition, a direct pathogenetic role of SUA in the progression of atherosclerotic lesions has also been hypothesised [5,6]. An association between SUA levels and sub-clinical or clinical atherosclerosis has also been reported in several patient populations, spanning from patients without CV risk factors in whom SUA predicted the presence of carotid plaques [7] to patients with heart failure (HF) [8]. A recent meta-analysis demonstrated an independent association between SUA and coronary artery disease and CV mortality, although the strength of this relationship substantially weakened when corrected for concomitant CV risk factors [9]. Subsequently, Levantesi et al. [10] reported that in patients with recent myocardial infarction (MI), enrolled in the GISSI Prevenzione (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico) trial, addition of SUA to CV risk factors significantly improved the identification of patients at higher risk of CV events.

Noteworthy, although the risk of developing metabolic syndrome [11], CV events [12] or peripheral artery disease [13] is mostly increased in patients with abnormal SUA levels and gout, the association between SUA and CV events is also observed within the normal SUA level range and in patients without gout [6].

Yet, despite evidence of association with CV events, SUA is currently not listed among CV risk factors in CV guidelines [14,15] and there is no evidence that a reduction of SUA is associated with reduced CV risk. Therefore, we conducted a meta-analysis and a meta-regression analysis of published data from randomised clinical trials to verify whether a decrease of SUA is associated with reduced clinical events.

Methods

Data sources and searches

The study was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [16] statement. MEDLINE, Cochrane, ISI Web of Science and SCOPUS databases were searched for articles published until June 2012.

Study selection

Study inclusion criteria were: report of SUA at baseline and at the end of follow-up and of major CV end-points (CV death, MI, stroke and HF) or all-cause death; comparison of active drug treatment versus placebo or of different doses of active drugs; randomised protocol design. Studies were identified combining the following major medical subject headings: 'uric acid', 'clinical trial' and 'randomized'. Only 3 studies reporting changes in SUA levels and CV events were conducted with xanthine-oxidase inhibitors ($n = 2$ with allopurinol and $n = 1$ with allopurinol and febuxostat). By contrast, the same relationship was mainly reported in studies with anti-hypertensive agents known to alter SUA levels ($n = 5$, mainly with angiotensin II receptor antagonists), or with other anti-hypertensive drugs suggested to have the same ability ($n = 2$) or with vitamin D + calcium supplementation ($n = 1$).

Data extraction and quality assessment

Two independent reviewers screened articles for fulfilment of inclusion criteria. Corresponding authors were asked to provide full-text articles, when not available. Reviewers compared selected trials and discrepancies were resolved by consensus. Baseline characteristics, SUA at baseline and at the end of follow-up, outcomes including all-cause death, CV death, MI, HF and stroke were abstracted. Changes of SUA from baseline to the end of studies were first regressed against all-cause death and the composite outcome including CV death, MI, HF and stroke. Additionally, they were regressed against each single component of the composite outcome. The quality of trials was evaluated by the Detsky method [17]. Publication bias was assessed using Macaskill's modified test [18].

Of 5401 articles identified by the initial search, 35 were retrieved for a more detailed evaluation and 11 trials were included in the study (Fig. 1).

Outcome meta-analysis

Odds ratios (ORs) and 95% confidence intervals (CIs) for each outcome were separately calculated for each trial, with grouped data, in intention-to-treat analyses, using the metan command (STATA version 12.0, Stata Corp, College Station, TX, USA) [19]. The choice to use ORs was driven by the retrospective design of the meta-analysis based on published studies. Overall estimates of effect were calculated by a fixed-effects, random-effects model or the Peto method, as appropriate. Statistical homogeneity was assessed using the Q statistic and further quantified with the I^2 statistic. The significance level for the overall estimates of effect and for meta-regression analyses was set at $p \leq 0.05$.

Meta-regression analysis

Weighted random-effects meta-regression analysis was performed by the metareg command (STATA version 12.0, Stata Corp, College Station, TX, USA) [20] to test the relationship between SUA changes and incidence of clinical events. For this analysis, the achieved differences (expressed as percent of baseline values) between SUA changes in active treatment and control groups were considered. Tau^2 and the restricted