# Association between serum uric acid and atrial fibrillation: A systematic review and meta-analysis

Leonardo Tamariz, MD, MPH,[*†] Fernando Hernandez, MD,[*†] Aaron Bush, MD,[*] Ana Palacio, MD, MPH,[*†] Joshua M. Hare, MD[*‡]

*From the [*]Department of Medicine, Miller School of Medicine, University of Miami, Miami, Florida, [†]Veterans Affairs Medical Center, Miami, Florida, and [‡]Division of Cardiology, University of Miami, Miami, Florida.*

**BACKGROUND** Atrial fibrillation (AF) is mediated by oxidative stress, neurohormonal activation, and inflammatory activation. Serum uric acid (SUA) is a surrogate marker of oxidative stress. Xanthine oxidase produces SUA and is upregulated by inflammation and neurohormones.

**OBJECTIVE** To perform a meta-analysis to evaluate the evidence supporting an association between AF and SUA.

**METHODS** We searched the MEDLINE database (1966 to 2013) supplemented by manual searches of bibliographies of key relevant articles. We selected all cross-sectional and cohort studies in which SUA was measured and AF was reported. In cross-sectional studies, we calculated the pooled standardized mean difference of SUA between those with AF and those without AF. In cohort studies, we calculated the pooled relative risk with the corresponding 95% confidence interval (CI) for incident AF by using the random effects method.

**RESULTS** The search strategy yielded 40 studies, of which only 9 met our eligibility criteria. The 6 cross-sectional studies comprised 7930 evaluable patients with a median prevalence of heart failure of 4% (IQR 0%–100%). The standardized mean difference of SUA for those with AF was 0.42 (95% CI 0.27–0.58) compared with those without AF. The 3 cohort studies evaluated 138,306 individuals without AF. The relative risk of having AF for those with high SUA was 1.67 (95% CI 1.23–2.27) compared with those with normal SUA.

**CONCLUSION** High SUA is associated with AF in both cross-sectional and cohort studies. It is unclear whether SUA represents a disease marker or a treatment target.

**KEYWORDS** Atrial fibrillation; Uric acid; Epidemiology; Oxidative stress; Meta-analysis

**ABBREVIATIONS** **AF** = atrial fibrillation; **CI** = confidence interval; **HR** = hazard ratio; **IQR** = interquartile range; **SMD** = standardized mean difference; **SUA** = serum uric acid

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## Introduction

Atrial fibrillation (AF) is an important cause of morbidity and mortality. Along with the increased risk of death, AF can lead to stroke and decreased quality of life.[1] The pathogenesis of AF remains incompletely understood.

Uric acid is produced by xanthine oxidase (XO), is the terminal breakdown product of purine nucleotides, and is a surrogate marker of oxidative stress. Recent studies have demonstrated that there is a strong association between serum uric acid (SUA) levels with an important AF mediator (such as heart failure mortality)[2] and incident coronary artery disease.[3]

The key pathways implicated in the development of AF are neurohormonal activation,[4] oxidative stress/nitroso–redox imbalance,[5] and immune activation.[6] There seems to be a common mechanism linking all 3 pathways since mechanical stretch mediated by neurohormones leads to oxidative stress and inflammation upregulates XO[7–9]; therefore, SUA may play a role in the etiology and persistence of AF. Identifying new associations and mechanisms of AF could lead to therapeutic targets in the future. Therefore, the purpose of this meta-analysis was to help define the relationship between SUA and AF in an effort to better understand the pathophysiology of the disease.

**Address reprint requests and correspondence:** Dr Leonardo Tamariz, Department of Medicine, Miller School of Medicine, University of Miami, 1120 NW 14th St, Suite 967, Miami, FL 33136. E-mail address: ltamariz@med.miami.edu.

## Methods

### Search strategy

A search was conducted through the MEDLINE database by using PubMed, which contained articles from 1966 to July 2013. This search was conducted by filtering all articles except those containing key terms such as uric acid and AF. More specifically, the search was performed by entering the following: (“uric acid”[MeSH Terms] OR (“uric”[All Fields] AND “acid”[All Fields]) OR “uric acid”[All Fields]) AND (“atrial fibrillation”[MeSH Terms] OR (“atrial”[All Fields] AND “fibrillation”[All Fields]) OR “atrial fibrillation”[All

Fields]). All searches were conducted in July 2013 and were supplemented by manual searches of bibliographies of key relevant articles. We also conducted a search of EMBASE, Scopus, and CINAHL and did not identify any new studies. We did not include meeting abstracts or studies in other languages.

### Selection criteria

The abstract of each citation identified was reviewed by 2 investigators. When either investigator selected an article for full-text review, the full text was reviewed by 2 investigators. Agreement on whether to review the full text or include the article in the evidence table was calculated by using interrater agreement. Articles were considered for inclusion if they were cross-sectional, cohort, or case-control and reported the necessary data for mathematical pooling.

### Data abstraction

One investigator (A.B.) was responsible for completing the evidence table, and the second investigator (F.H.) confirmed the accuracy of the data abstracted. Differences between the 2 reviewers were resolved by consensus with L.T. Relevant baseline characteristics were reported in evidence tables. The recorded information for cross-sectional studies included demographic characteristics, relevant comorbidities, and medications that can affect uric acid, such as angiotensin receptor blockers, diuretics, and uric acid–lowering medications. For cohort studies, we also collected the SUA cutoff used, the variables used in the multivariate analysis, and the follow-up period.

For mathematical pooling of cross-sectional studies, we abstracted the number of patients with their mean SUA and the corresponding SD in patients with and without AF. For cohort studies, we abstracted the number of patients who developed incident AF by the SUA cutoff level.

### Definition of uric acid

The key exposure variable was the SUA measurement at baseline in mg/dL. If the studies reported SUA in μmol/L, we converted those values by using the following conversion equivalence: 1 mg/dL = 59.48 μmol/L. All studies measured SUA by using the uricase-peroxidase enzymatic method.

For cohort studies, we dichotomized the SUA variable. For the primary analysis, we defined hyperuricemia or high SUA as an SUA $>7$ mg/dL; if SUA was reported in quartiles or tertiles, we selected $>7$ mg/dL or the highest level quartile reported or the highest cutoff and compared it with the lowest cutoff.

### Definition of AF

The outcome variable of interest was the incidence of AF. AF was reported in all articles defined as either electrocardiographic recording of AF or *International Classification of Diseases, Ninth Revision*–based diagnosis during the follow-up period. At the same time, we abstracted event data in each of the reported SUA cutoffs.

### Quality evaluation

We used the 22-item STROBE checklist.[10] These items relate to the article's title and abstract (item 1), the introduction (items 2 and 3), methods (items 4–12), results (items 13–17), and discussion (items 18–21) sections and other information (item 22 on funding). We used the 22-item appraisal for our evaluation since we included both cohort and cross-sectional studies. Eighteen items are common to the 2 designs, while 4 (items 6, 12, 14, and 15) are design-specific, with different versions for all or part of the item. Two investigators were responsible for completing the quality evaluation (A.B. and F.H.). Differences between the 2 reviewers were resolved by consensus with L.T., and we calculated interrater agreement. We assigned a score of 1 to each item if the item had been met appropriately or 0 if not and then added it to a total score. For those items that had subitems, we also assigned a score for each subitem. Therefore, the maximum score for cross-sectional studies was 32 and for cohort studies it was 33.

### Statistical analysis

We reported relevant baseline characteristics as median values of the reported means or percentages with the interquartile range (IQR). Because we have no patient level data, the medians reflect only the distribution of the reported data. To assess for heterogeneity across studies, we used the Cochran Q $\chi^2$ statistic (significance level of $P < .010$) and the $I^2$ statistic.

For the quantitative analysis, we used Stata 12 (StataCorp LP, College Station, TX) and conducted 2 different analyses depending on the study design. For cross-sectional studies, we calculated the standardized mean difference (SMD) in SUA between those with AF and those without AF. The SMD represents the difference between the weighted mean and SD of the SUA of individuals with AF and that of the controls.

For cohort studies, we calculated the relative risk (RR) of AF with the respective 95% confidence intervals (CIs) and *P* values. For our main analysis, we categorized the data by the incidence of AF and hyperuricemia rates. We used both fixed effects and DerSimonian and Laird random effects models to calculate the pooled RR across levels of SUA. Because of heterogeneity, we elected to use the random effects model.

To assess the robustness of our findings, we conducted a series of subanalyses. First, we evaluated the effects of certain variables explaining the results and heterogeneity using weighted meta-regression. To assess the effect of variables adjusted for in the statistical models, we used the number of variables and the appropriateness of the variables and we also evaluated the effect of the level of SUA used in the analysis. Second, we conducted an analysis in cross-sectional studies that included only individuals who had not used uric acid–lowering medications.

## Results

### Literature search

Our search yielded 40 abstracts (Figure 1). We excluded 21 at the abstract level because they did not met our inclusion