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EDITORIAL

The difficult relationship between uric acid and cardiovascular disease

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This editorial refers to 'Comparative effectiveness of allopurinol and febuxostat for the risk of atrial fibrillation in the elderly: a propensity-matched analysis of Medicare claims data', by J.A. Singh and J.D. Cleveland, doi:10.1093/eurheartj/ehz154.

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide.[1] Despite the development of risk prediction scores that enable identification of subjects at greater risk of future events, CVD risk assessment based on common cardiovascular risk factors still lacks precision. Novel risk factors or markers that enable more accurate CVD risk profiling are necessary in order to enhance patient care. Among the different molecules tested with this scope, levels of serum uric acid (SUA) have shown robust and strong associations with the future risk of CVD.[2,3] This resulted in a series of observational studies assessing the capacity of urate-lowering therapies and, specifically, of xanthine oxidase inhibitors (XOIs), to reduce the risk of CVD related to high SUA.[4–6] While this treatment was expected to have a positive impact on the cardiovascular outcome of patients with hyperuricaemia, the recent results of the CARES trial have created considerable debate around the cardiovascular safety of febuxostat compared with allopurinol.[7] Febuxostat is an XOI with a greater urate-lowering effect compared with allopurinol. However, the CARES trial documented an increased CVD mortality leading to increased total mortality in patients allocated to febuxostat compared with allopurinol. Importantly, the excess mortality recorded in the febuxostat group was primarily due to an increased risk of sudden cardiac death, although the causes of this increase remained largely unexplained.[7]

In this issue of the *European Heart Journal*, Singh and Cleveland have assessed the risk of incident atrial fibrillation (AF) related to initiation of febuxostat vs. allopurinol treatment in a 5% random sample (age >65 years) derived from a US Medicare cohort.[8] The study originates from the growing number of publications documenting a high risk of AF in patients with hyperuricaemia,[9,10] as well as from the evidence that, despite good progresses in the management of patients with AF, this arrhythmia remains one of the major causes of stroke, heart failure, and sudden death in the world.[11] The investigators used extensive propensity score matching to minimize the impact of potential confounders. The final population consisted of >23 000 patients with a follow-up of 6 years (2006–2012). The outcome of interest was the first occurrence of incident AF during the follow-up, identified by the presence of an International Classification of Diseases, ninth revision, common modification (ICD-9-CM) code of 427.31, with an absence of this diagnosis in the previous 365 days. Febuxostat was associated with a higher risk of AF compared with allopurinol, and this risk was greater in patients taking a higher dose of the drug (80 mg/day), in the first 6 months of treatment, and in people with a previous history of myocardial infarction.[8]

These results are in keeping with the findings reported in previous studies that documented a potential increase of the risk of adverse cardiovascular events, including AF, in patients taking febuxostat. In a 28-week, Phase III trial, Schumacher *et al.* documented a non-significant excess of adverse cardiovascular events, including chest pain, coronary artery disease, myocardial infarction, and AF, in subjects treated with febuxostat 80 mg or 120 mg daily when compared with those receiving placebo or allopurinol.[12] In the FOCUS study, of the 116 patients treated with febuxostat, 6 had occurrence of AF or atrioventricular block over a follow-up of 5 years, but these events were considered unrelated to the drug.[13] Similarly, the EXCEL trial documented an excess of serious adverse cardiovascular events in patients taking 80 mg or 120 mg of febuxostat compared with allopurinol, although these events were again not considered related to the drug treatment.[14]

Based on these findings and those obtained from other studies, the Food and Drug Administration (FDA) required a post-marketing randomized clinical trial (RCT) of adequate size and duration to compare febuxostat and allopurinol for risk of serious adverse cardiovascular events. This led to the design and conduction of the CARES study, that can be considered the first multicentre, double-blind, non-inferiority RCT with adequate power to clarify the febuxostat cardiovascular safety issue. Although one could suggest that the results of

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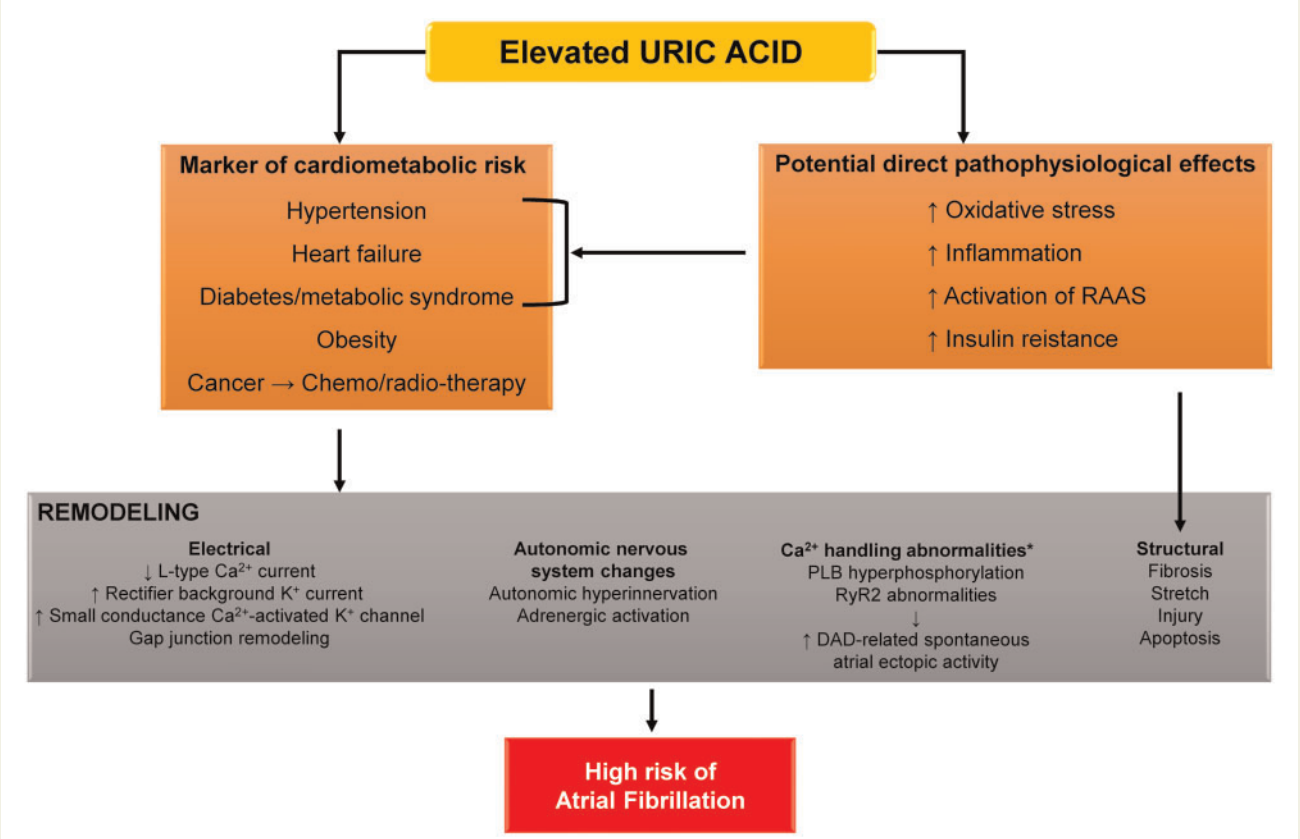

Take home figure Multiple potential mechanisms might underpin the remodelling process of the myocardial tissue and increase the risk of AF in patients with hyperuricaemia. Structural alterations might be directly promoted by the elevated SUA levels that can increase local oxidative stress, inflammation, insulin resistance, and renin–angiotenisin–aldosterone system (RAAS) activation. These pathways might promote the development of hypertension, heart failure, and diabetes/metabolic syndrome that, in turn, might contribute to the process of atrial structural remodelling and increase vulnerability to AF also inducing electrical remodelling, autonomic nervous system changes, and Ca^{2+} handling abnormalities. The same mechanisms could account for an increased risk of AF in conditions where elevated SUA levels reflect the presence of an underlying predisposing disease. *The key mechanism underlying Ca handling abnormalities in AF is considered the induction of delayed afterdepolarization (DAD)-related spontaneous atrial ectopic activity with increased sarcoplasmic reticulum Ca^{2+} load due to phospholamban (PLB) hyperphosphorylation and ryanodine receptor 2 (RyR2) abnormalities.

the study by Singh and Cleveland might explain, at least in part, the excess in cardiovascular and total mortality reported in the CARES trial, there are important differences in the results of the two studies that should be highlighted. First, the risk of AF associated with febuxostat was higher in the first 180 days from the initiation of treatment,[8] while a careful analysis of the Kaplan–Meier curves of the CARES trial documents that the increased cardiovascular and total mortality in the febuxostat group became evident >24 months from the initiation of the treatment.[7] Thus, if any adverse electrical effects could be attributed to febuxostat in the CARES trial, this should be considered a late rather than an early complication of the treatment. Furthermore, adjudicated hospitalization for atrial and ventricular arrhythmias in the CARES trial were comparable on febuxostat and allopurinol.[7] Therefore, the results presented in the current study do not seem to confirm or explain those obtained in the CARES trial. When considering the differences between the data from the two reports, it is important to highlight the two very different types of studies. The CARES trial was a randomized clinical trial with cardiovascular endpoints that were prospectively adjudicated by an expert committee blinded to the patient treatment allocation.[7] The study by Singh and Cleveland, in contrast, is a retrospective observational study in which episodes of AF were identified through claims data.[8] This difference is important as AF is difficult to document when paroxysmal, and might remain silent in clinically stable patients. The risk of symptomatic AF, in turn, increases in heart failure and coronary artery disease,[15] two conditions that are included in the Charlson–Romano index of comorbidity that, after propensity score matching, was higher in the febuxostat than in the allopurinol group. This might lead to the hypothesis that identification of the episodes of AF was easier and thus more accurate in the febuxostat group than in the allopurinol group, potentially accounting for the different incidence of the disease observed between the two drugs. Another important difference lies in the population included in the two studies. The CARES trial was limited to subjects with a history of gout and previous cardiovascular disease,[7] while the sample examined by Singh and Cleveland consisted of a mixed population, including also individuals with asymptomatic hyperuricaemia and without previous history of cardiovascular events.[10]

The study by Singh and Cleveland has several strengths. It included a large number of patients and the follow-up was very long. The use of data derived from a US Medicare cohort has the advantage of making researchers' findings more representative of the general population. Conversely, immediate translation to the general population of the results obtained from clinical trials may be more difficult because of the high risk of the population commonly included in these studies.

Beyond its merits, the study also has some limitations. First, it lacks information on several parameters that could potentially help to understand the mechanisms underlying the presented findings. For example, the authors emphasized the potential anti-inflammatory activity of XOIs in mediating their positive effect on the risk of AF (see also *Take home figure*). However, no information on inflammatory markers was provided to confirm this hypothesis. Similarly, the study does not report the levels of SUA achieved by patients under treatment. This is important information as it could provide evidence of the effectiveness of the treatment. Indeed, despite extensive propensity score matching to lessen confounding, there was a higher prescription of diuretics in the febuxostat compared with the allopurinol group. Several diuretics tend to increase SUA levels by mechanisms that are related to a reduced excretion rather than an increased production.[16] This might attenuate the efficacy of XOIs (including febuxostat) in lowering SUA, thus leaving subjects at a greater risk of AF despite treatment. Even the evidence that only the high dose of febuxostat was associated with an increased risk of developing AF might lie in this potential explanation. Indeed, subjects receiving a higher dose of febuxostat might represent the group with more difficult control of SUA. Following the authors' hypothesis, these patients might have been exposed for longer periods to inflammation and oxidative stress that promote atrial remodelling and thus be at increased risk of AF because of the difficulties in controlling SUA, rather than a direct pro-arrhythmic effect of the drug (*Take home figure*). With the available information, it was also impossible to exclude an underlying valvular pathology as a cause of AF. Finally, it was impossible to establish the chronic burden of several diseases that are likely to influence the association between hyperuricaemia and increased risk of AF, as strongly associated with both conditions (*Take home figure*).

In conclusion, the data presented by Singh and Cleveland add another important argument to the debate about the cardiovascular safety of febuxostat compared with allopurinol, using data from a real-world setting that are likely to be representative of the characteristics of the general population. However, they also leave several uncertainties regarding the influence of potential confounders on the described association between febuxostat treatment and AF. Such uncertainties should be addressed with studies reporting a more detailed phenotypic characterization of the patients, in order to confirm the presented results, identify potential mechanisms accounting for them, and clarify the population with hyperuricaemia that is likely to obtain the greatest benefits from the treatment with allopurinol or febuxostat.

Conflict of interest: none declared.

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