



Clinical Insights

Xanthine oxidase inhibition and cardiovascular protection: Don't shoot in the dark

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Substantial evidence suggests that chronic hyperuricemia is an independent risk factor for hypertension, metabolic syndrome, chronic kidney disease and cardiovascular disease [1,2]. However, whether lowering serum UA can improve cardiovascular and renal outcomes, and what therapeutic mechanism of action could provide more clinical benefits to patients, is still a matter of discussion. Evidence from observational studies suggests possible cardiovascular benefits associated with ULT, in particular for the XO-inhibitors, while the evidence from randomized controlled trials is scarce and somewhat conflicting [2]. These discrepancies could be explained by the existence of different phenotypes across hyperuricemic patients with a non-homogeneous distribution of clinical benefits from ULT.

1. In the beginning there were monosodium urate crystals

The relationship between gout and cardiovascular disease has been supported by epidemiological observations demonstrating a significant increase of the risk of death from cardiovascular disease and coronary artery disease in patients with gout [2,3]. From a pathophysiological point of view this association could be explained by the precipitation of MSU crystals within the vessel wall leading to a chronic vascular [4] and systemic inflammation that characterizes both acute and chronic gout [5]. The observed increase in coronary calcium score described in patients with hyperuricaemia and the asymptomatic joint urate deposition could explain the increased cardiovascular risk in patients with

“symptomless gout” [2].

Thus, a first phenotype of interest might include patients with increased cardiovascular risk related to either overt or subclinical MSU crystal deposition (Fig. 1). In patients with this phenotype, a guideline-based ULT aimed at promoting the dissolution of MSU deposits and at preventing the formation of new accumulations has also the biological possibility to exert a cardiovascular protection by reducing both vascular and systemic inflammation.

2. Then, was the time for uric acid

The inflammation promoted by the deposition of MSU crystals cannot entirely explain the relationship between UA and cardiovascular disease which is already evident when UA levels are in the normal to high range (5.0–5.5 mg/dL), largely below the precipitation threshold of MSU that occurs at 6.4 mg/dL (aqueous solution, 37 °C, pH 7.4) [6]. From a pathophysiological point of view, UA can modify its biological properties based on the concentrations reached in the biological fluids and the presence of concomitant environmental conditions. In particular, the antioxidant properties described for low serum UA levels can turn into pro-oxidant properties for high-normal serum UA levels [1,2]. Some evidence describes a direct vascular damage caused by UA because of oxidative stress leading to endothelial activation and dysfunction [1, 2].

Thus, at this point we should consider a second phenotype of patients

Abbreviations: FAD, flavin adenine dinucleotide cofactor; Mo, molybdopterin cofactor; MSU, monosodium urate; NAD⁺, oxidized nicotinamide adenine; NADH, reduced nicotinamide adenine dinucleotide; NO, nitric oxide; UA, uric acid; ULT, urate lowering treatment; XDH, xanthine dehydrogenase; XO, xanthine oxidase.

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with an increased cardiovascular risk directly related to the pro-oxidative properties of UA per se, independently on the presence of MSU crystals deposition (Fig. 1). For patients with this phenotype an indication for a ULT does not exist yet, although some epidemiological evidence suggests a possible cardiovascular benefit, mainly with XO-inhibitors.

3. Finally, xanthine oxidase came to complete the picture

Evidence from some mendelian randomization studies indicates that genetically raised serum uric acid levels are associated with gout but not with an increased risk of cardiovascular disease or metabolic disorders [1]. However, most of these studies were focused on polymorphisms involved in renal urate handling without considering alternative pathways. On the other hand, genetic polymorphisms of XO, the main enzymatic activity responsible for the generation of UA, have been linked with changes in blood pressure and incident hypertension. From a pathophysiological point of view, XO has all the biological capability to deeply influence the development of cardiovascular and metabolic diseases [7]. Indeed, XO activity is associated with the production of both reactive oxygen species and UA with pathophysiological consequences, including a pro-inflammatory and pro-thrombotic response involving endothelial cells. In addition, the increased activity of circulating XO is associated with hypertension, dyslipidaemia, diabetes, and it may contribute to the pathogenesis of atherosclerosis. Interestingly, the stronger predictive effect of serum UA on cardiovascular events in female patients could further support a role for XO in atherosclerotic disease suggesting a predominance of the UA generating pathway in women beyond the relevant uricosuric effects of estrogens [8]. In addition, a higher activity of plasma XO is associated with an increased risk of all cardiac events and cardiac mortality in patients with chronic heart failure [9] where also low plasma XO activity is associated with severity and clinical outcome [9]. This suggests the possibility of a

J-shaped curve for the relationship between plasma XO activity and clinical outcome, with both high and low plasma XO activity being associated with an increased risk of cardiovascular events [9]. These findings are not surprising considering the multiple physiological effects resulting from XO activation including modulation of innate immunity, redox signaling, endothelial activation, vascular tone, blood pressure, fat accumulation and release of NO with potential cardioprotective effects [7]. This dual effect could represent a critical point in the decision-making process on the possible use of XO-inhibitors in cardiovascular prevention. Theoretically, patients with an high XO activity should be the ideal target for cardiovascular prevention through XO inhibition, while this treatment could be unsuccessful and potentially harmful in patients with a low XO activity. According to this speculative hypothesis, some epidemiological evidence suggests that allopurinol use is associated with a reduced risk of cardiovascular events, but this association is not universally confirmed in patients taking high doses of allopurinol (> 300 mg/day) [10]. The same dual mechanism of action could explain the lack of evidence of a protective effect of high doses of allopurinol in patients with heart failure and reduced ejection fraction enrolled in the Xanthine Oxidase Inhibition for Hyperuricemic Heart Failure Patients - EXACT-HF [11]. In this study the disappointing results could be the consequence of a balanced effect between the protective effect associated with XO inhibition in some patients and the potentially negative result in some others [11]. The slight discrepancy in cardiovascular deaths observed in patients with gout and established cardiovascular disease and treated with febuxostat vs. allopurinol in the North American Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout - CARES trial could be somewhat related to the stronger XO inhibitory activity of febuxostat [12]. Indeed, no difference between the same treatments has been reported in patients with less advanced cardiovascular disease enrolled in the Febuxostat versus Allopurinol Streamlined Trial - FAST [13]. In addition, a moderate XO inhibition, such as that assumed in the Febuxostat for Cerebral and

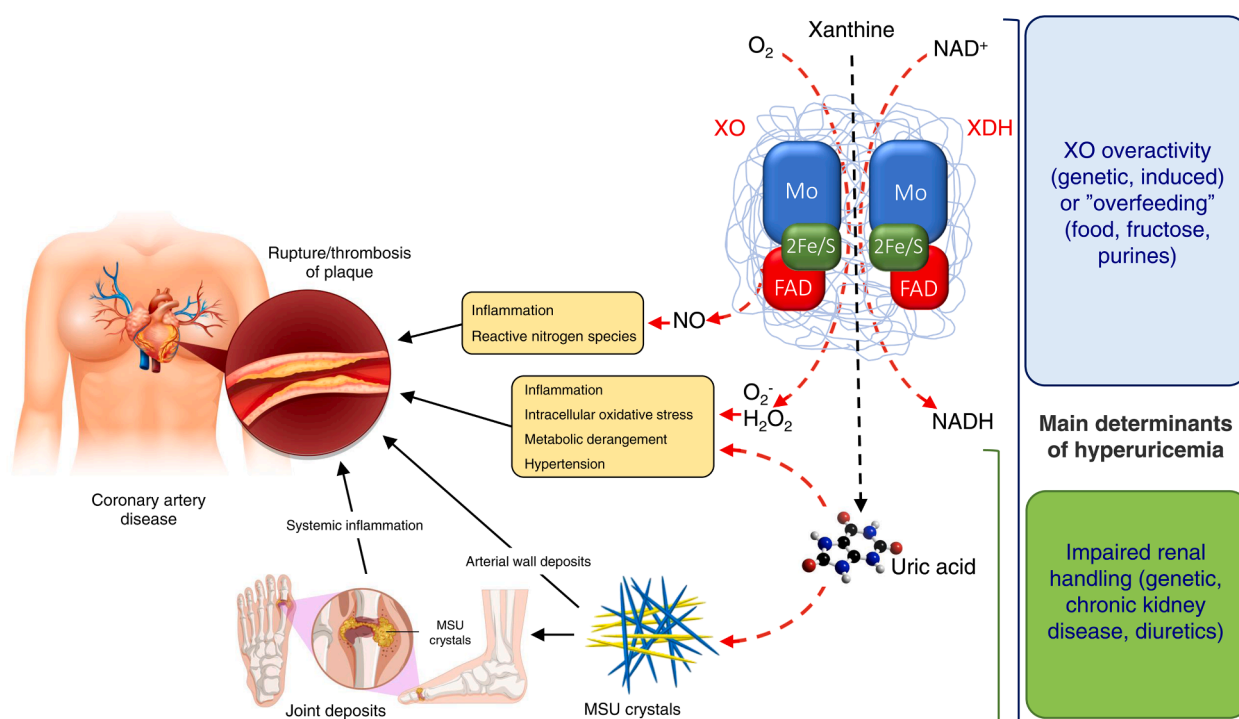


Fig. 1. Pathophysiological mechanisms linking uric acid metabolism with cardiovascular disease. Xanthine oxidoreductase exerts four main enzymatic activities: XDH performs the last two steps of the purine catabolism, from hypoxanthine to uric acid; XO, besides the purine catabolism, produces reactive oxygen species; nitrite reductase generates NO; NADH oxidase produces reactive oxygen species. All these activities could exert either physiological or pathological effects mainly in relationship to their degree of activation. Unlike in hyperuricemia related to an impaired renal handling of uric acid, xanthine oxidoreductase overactivity entirely activates this complex pathophysiological pathway thus being potentially more dangerous for the cardiovascular system.

CaRdiorenovascular Events PrEvEntion Study - FREED, with a mean febuxostat dose per day close to 30 mg/day, was associated with a significant reduction of the primary study outcome of cerebral, cardiovascular, and renal events and all deaths in patients with increased cardiovascular risk [14]. This suggests the possibility of risk-related cardiovascular benefits of the administration of XO-inhibitors whose doses should be reasonably adjusted with the increase in the baseline risk of cardiovascular disease. The same speculative approach cannot be applied to the lack of effect of allopurinol in improving cardiovascular outcomes among patients with ischemic heart disease enrolled in the recently published ALL-HEART trial [15]. In this study, a large proportion of the studied population might lack an increased activity of XO, as suggested by a mean serum UA level within the normal range. Taken together, these data suggest that the inhibition of XO activity appears more promising than just the control of serum UA levels in preventing cardiovascular events, possibly because it contributes to reduce the intracellular accumulation of urate but also blunts the production of reactive oxygen species [1,2].

Thus, a third, and likely more relevant, pathophysiological phenotype could be represented by patients with XO overactivity due to genetic or acquired factors or to its overfeeding, for instance because of an increased dietary intake of fructose or purine-rich foods (Fig. 1).

4. So, what about xanthine oxidase inhibition for cardiovascular prevention?

Although the above pathophysiological journey might seem too speculative, each step is supported by robust scientific evidence. Behind the same UA levels, we must imagine different phenotypes, identifiable according to prevalent pathophysiological mechanisms individually involved in the relation between UA metabolism and cardiovascular disease. In particular, first we should consider the systemic inflammation related to MSU deposits, whether clinically overt or not. This pathophysiological pathway is likely responsible only for a small amount of the burden of cardiovascular disease related to the UA metabolism. The whale of the underground sea is likely represented by the cardiovascular disease related to both UA as molecule and XO activity. The latter could represent the most important determinant of the cardiovascular risk related to UA metabolism and the ideal target for a hypothetical preventive strategy based on XO-inhibitors. The three different pathophysiological mechanisms could be partially imbricated but with a different impact in various subsets of patients. Obviously, this phenotyping is less relevant in patients with MSU deposits bearing a definite indication for ULT even when a pre-treatment evaluation of the degree of activity of XO may allow for the identification of subjects potentially at higher risk of cardiovascular side effects. This implies that if we want to move forward in cardiovascular prevention with XO-inhibitors, we must consider a necessary characterization of patients. Otherwise, we will probably continue to shoot good bullets in the dark.

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