

Urate-Lowering Drugs and Prevention of Cardiovascular Disease The Emerging Role of Xanthine Oxidase Inhibition

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The relevance of elevated plasma levels of serum uric acid (SUA) in patients with cardiovascular disease was historically described 2 centuries ago when Alexander Heig published a paper dealing with the causative role of hyperuricemia in patients with hypertension and several other diseases.¹ More recently, a remarkable number of epidemiological and experimental studies have demonstrated that hyperuricemia and gout are strongly related with hypertension, metabolic syndrome, chronic kidney disease, and cardiovascular disease.² The relationship between hyperuricemia and hypertension and metabolic syndrome has been confirmed in both pediatric and adolescent populations² and is maintained after an extensive adjustment for almost all of the possible confounding conditions (eg, hypertension, diabetes mellitus, lipid disorders, renal function, etc), thereby supporting the role of elevated SUA as an emerging independent cardiovascular risk factor in patients with and without gout. The mechanisms that link elevated SUA levels and gout with cardiovascular comorbidities seem to be multifactorial, implicating low-grade systemic inflammation and xanthine oxidase (XO) activity, as well as the deleterious effects of hyperuricemia itself. As expected, a decrease in SUA levels has been associated with an improvement in blood pressure control,^{3–5} as well as with some additional benefits in selected populations of patients with cardiovascular diseases (eg, coronary artery disease, heart failure, etc).² Most of these favorable effects have been achieved by treating the patients with allopurinol or its derivative oxipurinol^{3,4} that have been used in the great majority of studies aimed at evaluating the cardiovascular preventive/therapeutic role of urate-lowering treatment in patients with hyperuricemia. The same treatment has been reported to reduce all-cause and cardiovascular mortality,⁵ clearly supporting a possible preventive

role of SUA modulation through XO inhibition. In the present issue of *Hypertension*, MacIsaac et al⁶ have reported the results of an important study where the treatment with different doses of allopurinol over a 10-year period significantly improved the cardiovascular outcome in 2032 elderly hypertensive patients (over 65 years) included in the United Kingdom Clinical research Practice Datalink and compared with a propensity-matched, nonexposed population. In particular, the active treatment with allopurinol reduced the risk of stroke (–50%) and cardiac event (–39%), and the reduction was significantly larger in patients treated with the higher allopurinol dose. This article of MacIsaac et al expanded the bulk of observation supporting the possible role of xanthine oxidase inhibitors in the prevention of cardiovascular disease and could open a new frontier in clinical research aimed at developing a solution for the challenging problem of residual cardiovascular risk in patients with hypertension. Indeed, the results of the EURIKA (European Study on Cardiovascular Risk Prevention and Management in Usual Daily Practice) study⁷ and many others in the same field have provided a clear demonstration that well-controlled hypertension is associated with a considerable amount of residual cardiovascular risk that could be partially reduced by decreasing SUA through XO inhibition. The mechanism involved in the favorable effects of allopurinol in the MacIsaac study would be the prevention of the oxidative stress linearly associated with the biochemical process, leading to uric acid formation that may clearly explain the evidence provided by a recent review of Higgins et al⁸ focused on the possible beneficial effects of XO inhibitors in patients with cardiovascular diseases. The plausibility of this interpretation is well supported by the characteristics of this new study that does not include patients with gout or evidence of uric acid deposition and is focused on hypertensive subjects with high cardiovascular risk profile (age >70 years, 23% diabetes mellitus, 28% ischemic heart disease, current treatment with cardiovascular drugs) where the preventive effect of XO inhibition can be magnified. In addition, the dose-dependency of the cardiovascular effects of allopurinol observed in the study further supports the importance of the mechanism of action of allopurinol beyond its propensity of reducing the plasma levels of uric acid that are expected to be probably within the normal range in a large percentage of the studied population. The possible prevailing role of the antioxidant effect of allopurinol over the serum urate decrease is in agreement with the results of 2 recent studies in patients with congestive heart failure where the negative impact of hyperuricemia was restricted to overproducer patients with normal renal function.⁹ In the same congestive heart failure population,

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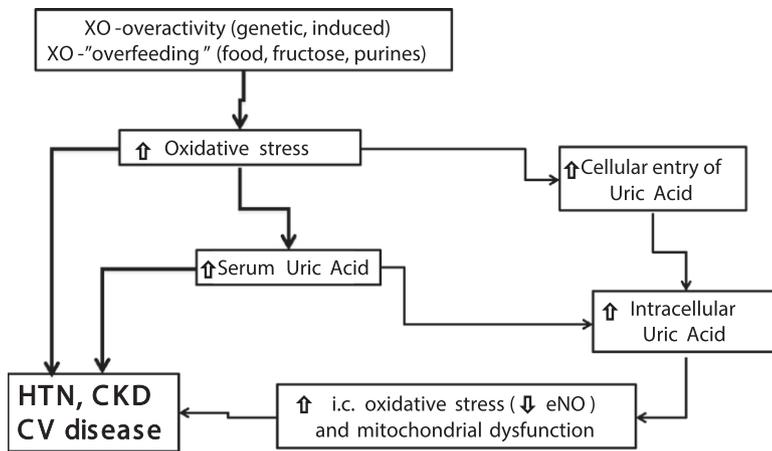


Figure. Serum uric acid, oxidative stress, and cardiovascular (CV) disease: a reassessment of an hypothesis. CKD indicates chronic kidney disease; HTN, hypertension; NO, nitric oxide; and XO, xanthine oxidase.

the increase in the endothelium-dependent forearm vasodilatation was enhanced by allopurinol in a dose-dependent manner, whereas no effect was observed after the administration of probenecid, despite a comparable reduction in SUA.¹⁰ All this observation suggest the importance of the extent and selectivity of XO inhibition and reasonably support the hypothesis that more selective inhibitors of the enzyme (eg, Febuxostat) could have a greater impact on cardiovascular prevention, and more research in this field is warranted.

Interestingly, the major strength of the study (benefit of allopurinol apparently beyond hyperuricemia) is at the same time its possible main limitation. Baseline levels of SUA are available only for a limited proportion of the enrolled patients (n=703), whereas changes in uricemia were tested in only about one third of them (n=299). However, in this subset of patients, the average level of SUA was within the normal range (≈ 3 mg/dL) and comparable across the subgroups of patients treated with different doses of allopurinol. Because the cardiovascular preventive impact of allopurinol has been reported to be dose-dependent, this formally excludes the primary protective role of lower SUA levels and reinforces the importance of oxidative stress and XO inhibition. So in agreement with all this consistent evidence, we support the plausible idea that beyond the generic term hyperuricemia, we might identify several typologies of patients probably not bearing the same disease. In particular, although the gouty-hyperuricemia is probably responsible for SUA deposition and its consequences, the cardiovascular-hyperuricemia is just the mirroring image of the level of XO-induced free-radical production during uric acid formation. The negative impact of XO-generated pro-oxidation may be further complicated by the effects of circulating uric acid (even at normal serum concentration) according with the mechanistic hypothesis of a remarkable contribution from raised intracellular uric acid. An article of Lanaspá et al¹¹ has demonstrated that the ability of allopurinol to reduce oxidative stress in fructose-treated cells can be reversed by adding uric acid. An increase in the concentration of uric acid inside the vascular cells might negatively affect nitric oxide availability and mitochondrial cellular function and contribute to the development of cardiovascular disease, as well as to the worsening of clinical prognosis of patients with overt heart diseases¹² (Figure).

In conclusion, after ≈ 120 years from its first formal scientific report, the importance of SUA as a risk factor for

cardiovascular disease is still surfing the tip of the wave. Findings from many epidemiological studies have been corroborated by the results of interventional studies like that of MacIsaac et al,⁶ where long-term pharmacological inhibition of XO decreases the risk of coronary and cerebrovascular disease, probably through modulation of residual cardiovascular risk. A couple of questions are still unanswered: (1) Does XO inhibition represents a new therapeutic strategy for future management of cardiovascular diseases? (2) Which one is the role of the interaction between drugs, degree of XO inhibition, and cardiovascular prevention? All these open problems are still matter of active investigation, and several randomized clinical trials are actually recruiting patients to confirm that we are surfing the wave in the right direction.

Disclosures

None.

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