Uric acid and xanthine oxidase: future therapeutic targets in the prevention of cardiovascular disease?

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Serum uric acid may be an independent risk factor for cardiovascular disease. This review examines this association, potential mechanisms, and explores whether strategies to reduce uric acid will improve outcomes. The recent studies of xanthine oxidase inhibition are given particular focus. Epidemiological evidence supports the theory that uric acid is an independent risk factor for cardiovascular disease. Recent studies of losartan, atorvastatin and fenofibrate suggest that uric acid reduction contributes to the risk reduction offered by these therapies. Several small studies of xanthine oxidase inhibition have shown improvements in measures of cardiovascular function of a similar magnitude to that of other proven preventative treatments. These trial data and the convincing epidemiological evidence mandate that large clinical trials of uric acid-lowering strategies are performed in patients with or at high risk of cardiovascular disease. If such approaches are shown to be effective in reducing cardiovascular events, they would represent a novel and cost-effective preventative approach.

Introduction

The role of serum uric acid in the development of cardiovascular disease has been the subject of controversy for many years. Epidemiological evidence clearly suggests an association between increasing uric acid concentrations and event rates and mortality in a variety of cardiovascular disease states. However, the presence of a causal relationship is less clear. Elevated concentrations of uric acid may reflect a separate underlying disease process, atherosclerosis itself or increased xanthine oxidase activity, all of which may influence vascular risk. Conversely, a causal role has been suggested

by posthoc analyses of the losartan intervention for endpoint reduction (LIFE) study [1], clinical trials of fenofibrate [2] and atorvastatin [3] and preclinical data suggestive of direct deleterious effects on platelet and endothelial function. Interventional studies of xanthine oxidase inhibition, which will reduce both uric acid and oxidative stress, have been conducted in patients with or at high risk of vascular disease [4–13]. Although these are small and few in number, their results suggest a potential benefit of intervention to modify uric acid metabolism in the prevention of cardiovascular disease.
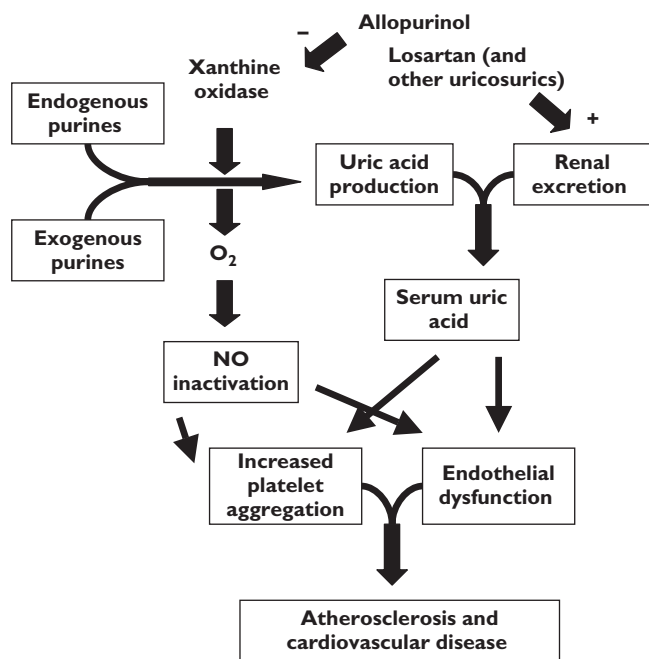
Figure 1
Potential mechanisms by which elevated serum uric acid is related to cardiovascular disease and potential methods of risk reduction

Table 1
Summary of studies examining the relationship between serum uric acid and outcome

Ref.	Population	Change in outcome measure
[18]	DM	HR 1.91 (1.24, 2.94) (serum uric acid >295 μmol l^{-1}) for risk of stroke
[19]	DM	OR 1.004 (1.001, 1.008)* for presence of PVD
[20]	DM	OR 1.03 (1, 1.06)* for presence of PVD
[27]	DM/stroke	HR 1.49 (1.21, 1.84)* for recurrent CV event
[26]	Acute stroke	RR 1.27 (1.18, 1.36)* for recurrent CV events
[28]	Acute stroke	Serum uric acid? in those with early clinical deterioration ($P = 0.001$)
[21]	↑ BP	HR 1.73 (1.01, 3)† for CV event rates
[22]	↑ BP	HR 1.32 (1.03, 1.69)† for CV events
[23]	↑ BP	HR 1.22 (1.11, 1.35)¶ for development of CV disease
[24]	↑ BP	HR 1.14 (1.02, 1.27)‡ for CV mortality / HR 1.34 (1.14, 1.57)‡ for fatal stroke
[25]	↑ BP	HR 1.03 (0.93, 1.14)‡ for CV mortality / HR 1.06 (0.99, 1.13)‡ for all CV events
[29]	CAD	HR 1.5 (1.02, 2.1)† for all-cause mortality
[30]	CAD	HR 1.23 (1.11, 1.36)§ for all-cause mortality

Results expressed as ratio and 95% CI. DM, Diabetes mellitus; PVD, peripheral vascular disease; CV, cardiovascular; CAD, angiographic coronary disease. *Per additional 0.1 mmol l^{-1} in serum uric acid. †For highest vs. lowest quintile/quartile. ‡For each 50 μmol l^{-1} increment in serum urate; §¶Per additional 0.6 and 0.86 mmol l^{-1} in serum uric acid, respectively.

This article will briefly review evidence concerning the relationship between uric acid and cardiovascular disease and discuss possible pathophysiological mechanisms before focusing on the interventional studies to date and discussing the significance of their findings.

Biochemistry of uric acid in man

Uric acid is a breakdown product of ingested and endogenously synthesized purines (Figure 1). DNA and RNA are degraded into purine nucleotides and bases, which are then metabolized, via the action of xanthine oxidase, to xanthine and uric acid. These later steps are irreversible and generate superoxide anions. Uric acid undergoes no further metabolism in humans and is excreted by the kidneys and intestinal tract. In the kidney, it is filtered and can be subsequently reabsorbed or further excreted in the proximal tubule, predominantly under the action of a urate transporter (URAT1) [14].

Serum concentrations are governed by the balance of production and excretion. Production can be increased by several mechanisms including rare enzymatic defects, states of high cell turnover and alcohol ingestion (partly because of purines contained in alcoholic drinks [15, 16]). However, the majority of cases of elevated serum uric acid result from impaired renal excretion, possibly because of interindividual differences in function of the URAT transporter.

Uric acid as a cardiovascular risk factor

Most large, well-conducted epidemiological studies support the hypothesis that elevated serum uric acid is a powerful predictor of increased vascular event rate and mortality in patients with hypertension, diabetes, and in those with known cardiovascular disease (Table 1). The results in healthy populations are less consistent. Studies have typically utilized data from randomized control trials or epidemiological databases and expressed results as change in relative risk per increment of uric acid or as relative risk across uric acid quintiles. A more detailed discussion of these studies can be found elsewhere [17].

Cardiovascular risk states

In patients with diabetes, serum uric acid concentrations above the median (295 µmol l^{-1}) have been associated with near double an increased risk of stroke [hazard ratio (HR) 1.91, 95% confidence interval (CI) 1.24, 2.94] [18], while increasing uric acid concentrations were associated with increased prevalence of peripheral arterial disease in both a Taiwanese [19] and Australian cohort [20] [odds ratio (OR) 1.004, 95% CI 1.001, 1.008 and 1.03, 95% CI 1, 1.06, per additional 0.1 mmol l^{-1} in serum uric acid, respectively].

In patients with essential hypertension, serum urate in the highest quartile was associated with an increased cardiovascular event rate (HR 1.73, 95% CI 1.01, 3), cardiovascular mortality and all-cause mortality (HR 1.63, 95% CI 1.02, 2.57) [21]. A similar positive association was seen in the SHEP trial, where serum uric acid in the highest quartile conveyed an increased risk of cardiovascular events (HR 1.32, 95% CI 1.03, 1.69) but not of all-cause mortality or stroke [22]. Other large studies have shown that small increments in serum uric acid are associated with increasing incidence of cardiovascular disease and with cardiovascular death [23, 24]. These associations persist despite adequate adjustment for confounding factors and other risk factors. However, in the Syst-Eur study of hypertensive patients, a trend but no association was seen with cardiovascular events or mortality (HR 1.06, 95% CI 0.99, 1.13 and HR 1.03, 95% CI 0.93, 1.14 per 50 µmol l^{-1} increment in serum urate, respectively) [25]. While the event rate was similar to that in other studies, the proportion of females was far greater, meaning it is possible that a gender effect has attenuated the association.

Cardiovascular disease

In patients with stroke, increasing serum uric acid concentrations have been associated with a reduced likelihood of a favourable outcome and an increased risk of recurrent vascular events [OR 0.78, 95% CI 0.67, 0.91 and relative risk (RR) 1.27, 95% CI 1.18, 1.36 per additional 0.1 mmol l^{-1} in serum uric acid, respectively] [26]. This association was more prominent in diabetic patients [27]. Elevated concentrations of serum uric acid in the early stages after acute stroke have also been associated with early clinical deterioration [28]. In patients with angiographically defined coronary artery disease, serum uric acid in the highest quintile [29] and quartile [30] has been shown to be predictive of all-cause mortality (HR 1.5, 95% CI 1.02, 2.1 and HR 1.23, 95% CI 1.11, 1.36, respectively). Increasing concentrations of serum uric acid have also been shown to strongly predict mortality, need for cardiac transplant and in-hospital mortality in those with cardiac failure [31, 32]. Conversely, it has been shown that increased serum uric acid in the acute phase following stroke is associated with a good outcome [33], a finding that is addressed later.

Healthy populations

The NHANES study [34] showed an association with each 59.48 µmol l^{-1} increment in serum uric acid leading to increased risk of cardiovascular events (HR 1.09, 95% CI 1.02, 1.18 in men) and cardiac mortality (HR 1.17, 95% CI 1.06, 1.28 in men). A yet more significant association was seen in women. However, a large analysis from the Framingham Heart study cohort found no association with cardiovascular mortality after adjustment for diuretic therapy [35] and a similar lack of association has been reported in other large studies of healthy individuals [36–38]. Lower event rates in such healthy populations may explain this inconsistency; larger sample sizes are required and some may have lacked power to detect an independent association.

Against a direct causal association

It is argued that elevated serum uric acid in those with cardiovascular disease simply reflects the presence of other risk factors such as hypertension or diabetes, diuretic treatment, impaired renal function, atherosclerosis itself or increased oxidative stress.

Worsening renal function is associated with increased serum uric acid concentrations and increased burden of cardiovascular disease. Markers of oxidative stress are increased in patients with chronic renal disease and are predictive of increased cardiovascular mortality [39, 40]. Successful renal transplantation [41–43] improves such markers. Therefore, the association may simply reflect impaired renal function and the associated oxidative stress and cardiovascular risk. While most studies have adequately adjusted for renal impairment, it cannot be excluded that raised uric acid concentrations reflect or contribute to subclinical levels of renal impairment which contribute to the association in as yet undefined ways.

Even in those with normal renal function, higher concentrations of uric acid may reflect higher levels of xanthine oxidase activity and oxidative stress. This would also explain why serum uric acid concentrations rise after an ischaemic insult, as discussed below. The action of xanthine oxidase leads to generation of superoxide anions and is one of the principle sources of reactive oxygen species (ROS) in the human vasculature [44, 45]. The molecular effects and importance of ROS in cardiovascular disease has already been extensively reviewed [46–49]. In summary, once formed, superoxide

anions can inactivate nitric oxide (NO), leading to formation of peroxynitrite, which is also a strong oxidant. This inhibits endothelium-dependent vasorelaxation, limits the favourable effects of NO on platelet aggregation and vascular smooth muscle proliferation and causes oxidation of DNA and lipids; all factors integral to development of atherosclerosis [50]. Under normal circumstances, ROS production is usually countered by antioxidant defence mechanisms, including the action of superoxide dismutase (SOD) [51].

As well as this putative role in atherosclerosis development, ROS production increases acutely following cerebral or cardiac ischaemia and may contribute to the degree and extent of tissue damage [52–54]. This hypothesis is supported by animal models of ischaemic stroke where SOD knockout mice exhibit greater lesion volumes after temporary middle cerebral artery occlusion [55–57], whereas SOD-overexpressing mice exhibit reduced lesion volume [58]. Infusion of SOD and catalase have led to a reduction in stroke lesion volume in a murine stroke model [59]. Human studies have also shown that locally increased oxidative stress and reduced peripheral antioxidant activity are associated with increased stroke lesion volume and a greater neurological deficit [60, 61]. Similar work in animal models of myocardial infarction has suggested oxidative stress is associated with increased development of heart failure [62, 63]. It is also likely that oxidative stress predisposes to development of heart failure after acute myocardial infarction in humans [64, 65]. Thus, increased uric acid concentrations may simply reflect increased xanthine oxidase activity, which may directly contribute to the development of atherosclerotic disorders and predispose to more severe vascular events.

There is evidence that uric acid has antioxidant activity and that concentrations may rise after an ischaemic insult. This has led to an alternate hypothesis that elevated serum uric acid represents a physiological, and perhaps protective, response to the oxidative stress that characterizes many vascular disease states [66, 67]. In a rat model of cerebral ischaemia, brain uric acid concentrations increased [68, 69] and in a transient ischaemia model, infusion of uric acid led to a reduction of infarct volume and improved behavioural outcome [69]. This is further supported by data from a rat model of traumatic brain injury and a mouse model of multiple sclerosis, where uric acid was found to reduce formation of peroxynitrite radicals [70, 71]. In healthy human volunteers, uric acid administration has been shown to increase serum antioxidant capacity [72]. In a study of 800 patients with ischaemic stroke, admission serum uric acid was higher in those with a good outcome and increasing levels associated with a good outcome (OR 1.12, 95% CI 1, 1.25 per additional mg dl^{-1} uric acid) [33]. This finding is in direct contrast to those of other studies [26–28].

While these findings warrant consideration, the potential antioxidant properties of uric acid *in vitro* or *in vivo* should not be overinterpreted. Increased local tissue concentrations in animal models of ischaemia and brain injury may simply reflect the levels of oxidative stress and xanthine oxidase activity, and not an innate protective response. The substance itself may well have antioxidant properties but its generation and associated superoxide anion production may be of much greater significance and detriment. Even the intriguing findings that uric acid infusion may be protective in animal models of brain ischaemia do not imply that uric acid-lowering strategies, and particularly those involving xanthine oxidase inhibition, could not have favourable effects *in vivo*.

For a causal association

Data from animal and *in vitro* studies raise the possibility of a direct causal mechanism for uric acid in cardiovascular disease, which provides further support for the convincing epidemiological associations. Monosodium urate crystals have been shown to stimulate release of the platelet constituents serotonin, adenosine triphosphate and adenosine diphosphate [73], while uric acid has been shown to stimulate rat vascular smooth muscle production *in vitro* [74]. Uric acid may also increase oxygenation of low-density lipoprotein (LDL) [75] and may have a causative role in the development of hypertension [76–78].

Pharmacological intervention to lower uric acid

Several drugs are known to lower uric acid. These either increase uric acid excretion (urosuric drugs), block the final step in uric acid production via xanthine oxidase inhibition or lead to uric acid breakdown (rasburicase). The most effective urosuric drugs are probenecid and sulfinpyrazone, while fenofibrate (a fibrate) [79] and losartan (an angiotensin II antagonist) [80, 81] also have urosuric activity. Rasburicase is a recombinant urate-oxidase enzyme which converts uric acid to allantoin. It is used in association with some anticancer treatments and is unsuitable for repeated dosing. There are two commercially available xanthine oxidase inhibitors, allopurinol and oxypurinol. Allopurinol is rapidly metabolized to oxypurinol, which is an analogue of xanthine and preferentially binds to xanthine oxidase, thereby inhibiting its activity [82]. Because of its action on both uric acid concentrations and xanthine oxidase

activity, allopurinol is a logical drug to study in trials of cardiovascular risk reduction.

Allopurinol is generally well tolerated with few side-effects. Its major indication is in the prophylaxis of gout [83]. Side-effects typically comprise gastrointestinal upset and rashes. A rash develops in approximately 2% of patients and typically subsides after treatment is discontinued. More serious side-effects, such as generalized hypersensitivity, occur in less than 1 in 1000 cases and include exfoliative dermatitis, often with vasculitis, fever, liver dysfunction, eosinophilia and acute interstitial nephritis [84]. The rate of adverse reaction is highest in patients with renal dysfunction and rashes are more common with concurrent amoxicillin therapy [85, 86]. There is a known interaction with azathioprine and 6-mercaptopurine therapy and some rare reports of cytopenia. This side-effect profile is comparable to that of commonly used secondary preventative agents such as HMG-CoA reductase inhibitors [87] and angiotensin converting enzyme inhibitors [88, 89].

Urate-lowering drugs and cardiovascular risk

Three drugs known to reduce cardiovascular mortality have been shown to reduce serum uric acid. This may explain some of their beneficial effect, but changes in other risk factors such as renal function and blood pressure may explain both the beneficial effects and changes in uric acid concentrations.

Fenofibrate is a fibric acid derivative known to reduce total and LDL-cholesterol by approximately 15%, with a similar increase in high-density lipoprotein-cholesterol and with larger reductions in triglyceride concentrations [90]. Fibrates reduce the incidence of cardiac events in dyslipidaemic patients [91] and in those with coronary disease [92]. These benefits may be greatest in Type 2 diabetes [93], where they have been shown to reduce atherosclerosis progression [2] and total vascular events [94]. Fenofibrate reduces serum uric acid concentrations (via increased renal excretion) by as much as 46% in healthy volunteers, hypertensive and diabetic patients and those with gout on specific urate-lowering therapy [95–97]. This may provide adjunctive efficacy in the treatment of gout when combined with allopurinol [98, 99] and may contribute to the reduced vascular risk associated with fibrate therapy. This effect is not seen with other fibrates [100] and its mechanism is elusive, although unlikely to be mediated by improvements in renal function [101].

Losartan is an angiotensin II receptor antagonist which is superior to atenolol in the prevention of cardiovascular events when given to hypertensive patients with left ventricular hypertrophy [102]. Losartan is known to increase renal uric acid excretion [103] (by as much as 30%), thereby causing significant reductions in serum uric acid [104]. This is mediated via effects on the urate/anion transport mechanism in the renal proximal tubule [105]. This is not a class effect; other angiotensin II antagonists have little or no effect on serum uric acid excretion [106]. Up to 29% of the 13% relative risk reduction seen with losartan use in the LIFE study has been attributed to its effect on serum uric acid [1]. Serum uric acid increased with both atenolol and losartan use in the LIFE study, but the increase was significantly less with losartan. Whether this underpins much of the benefit of losartan and whether it can attenuate the possibly detrimental effects of diuretics on uric acid requires further clarification. Although the effect was independent of measures of renal function, treatment with ACE blockade or angiotensin II antagonists reduce levels of oxidative stress [107], which could itself account for this added benefit.

Statin therapy has also been shown to lower serum uric acid. In the GREACE study, atorvastatin was associated with a fall in serum uric acid (by 8.2%), whereas serum uric acid increased in those patients allocated to the placebo group (by 3.3%). After extensive adjustment of several risk factors, including change in renal function, each 60 μmol l^{-1} reduction in serum uric acid was associated with a reduction in vascular event rates (HR 0.76, 95% CI 0.62, 0.89) [3]. A fall in serum uric acid has been mirrored in other studies of statin therapy [108, 109] but typically in association with improvements in serum creatinine. Atorvastatin, however, has repeatedly been shown to lower uric acid (by 6.4%) in other studies [110, 111] even after adjustment for renal function, possibly because of decreased uric acid production [112]. As yet, this has not been adequately studied and cannot be assumed to explain some of atorvastatin's effects, although it may represent a further beneficial effect.

Specific intervention to lower serum uric acid and xanthine oxidase inhibition

The effect of xanthine oxidase inhibition on measures of endothelial and cardiovascular function has also been tested in a number of small studies, performed in the context of diabetes, hypercholesterolaemia, hypertension, elevated 10 years' cardiovascular risk, angiographically confirmed cardiovascular disease and heart failure [4–13]. Study design has varied, using either oral or intravenous xanthine oxidase inhibition whilst typically employing a crossover design with changes in forearm blood flow, and therefore endothelial function, as the outcome measure (Table 2). Some studies have

Ref.	Population	Intervention	Change following treatment
[12]	CHF,↑ uric acid	I.a. infusion of allopurinol	Increase in radial artery LD*
[12]	CHF,↑ uric acid	1 week allopurinol†	23% increase in lower limb post-ischaemic blood flow
[11]	CHF	3 months allopurinol†	Fall in BNP concentrations from baseline. No change in exercise tolerance
[13]	CHF	1 month allopurinol†	Increase in FBF responses*‡
[10]	Idiopathic DCM	I.c. allopurinol infusion	$16 \pm 5\%$ reduction in MVO_2 $22 \pm 9\%$ increase in myocardial efficiency
[5]	Smokers	Single p.o. dose allopurinol†§	Increase in FBF responses*‡ towards control values. No change in controls
[9]	CAD	Single i.v. oxypurinol infusion	Attenuation of coronary vasoconstrictor response* and increase in CBF
[7]	↑ chol	4 weeks' allopurinol†	No change in FBF responses*‡
[6]	↑ chol,↑ BP	Single infusion of oxypurinol§	Improvement in FBF responses* in ↑ chol patients. No change in ↑ BP or controls
[8]	↑ uric acid, ↑ CV risk	3 months allopurinol§	Increase in FBF responsese. No change in controls
[4]	DM	1 month's allopurinol†§	Approximate 30% increase in FBF responses*‡. No change in controls

*I.a., Intra-arterial, brachial; LD, luminal diameter. *In response to intra-arterial acetylcholine infusion. †Crossover design. FBF, Forearm blood flow; BNP, B-type natriuretic peptide. ‡Expressed as percentage Δ in ratio of infused FBF compared with non-infused arm FBF. I.c., Intracoronary; MVO_2, myocardial O_2 consumption. §Control arm. ¶Ischaemia-induced percentage change in BA diameter.*

involved a single dose of allopurinol or oxypurinol, suggesting that xanthine oxidase inhibition rather than change in serum uric acid was the mechanism of benefit.

Improvements in endothelial function following allopurinol have been shown in patients with Type 2 diabetes and mild hypertension [4]. Endothelial function, expressed as percentage change in ratio of infused forearm blood flow (FBF) compared with non-infused arm FBF in response to intra-arterial acetylcholine infusion, was found to return to near normal following 1 month of 300 mg allopurinol treatment. No effect was seen on control patients. Using similar methods, a single oral dose of allopurinol was found to improve peripheral endothelial function towards normal in smokers but had

no effect in the nonsmoking control group [5]. The rapidity of the improvement strongly suggests that xanthine oxidase is a key contributor to the endothelial dysfunction seen in smokers. These techniques have also shown an improvement in forearm endothelial function in patients with hypercholesterolaemia following intra-arterial administration of oxypurinol [6], a finding not replicated in a similar but smaller study of 4 weeks' oral allopurinol treatment [7]. It is possible this later study was underpowered; the power calculation was based upon the effect size seen following 3 months of simvastatin treatment [113]. The anticipated treatment effect was larger than that seen in other studies of allopurinol use, while the effect seen at 1 month was more similar and approximately half this.

FBF responses, expressed as ischaemia-induced change in brachial artery diameter, were also improved by a 3-month course of allopurinol in a group of patients with elevated 10-year cardiovascular risk [8] and hyperuricaemia. A recent study in patients with stable coronary artery disease [9] has shown that intravenous administration of oxypurinol improved both peripheral endothelial function and coronary endothelial function (expressed as the coronary vasoconstrictor response to acetylcholine and changes in coronary blood flow) in those with impaired baseline function.

There are four small studies of xanthine oxidase inhibition in the context of heart failure. Intracoronary infusion of oxypurinol has been shown to reduce myocardial oxygen consumption, probably via preserved NO bioactivity, and to increase myocardial efficiency measurements significantly. Both an intravenous infusion [12] and a 1-month oral course [13] of allopurinol have been shown to improve a variety of measures of peripheral endothelial function in patients with heart failure. Recent work has shown that B-type natriuretic peptide (BNP) concentrations are reduced by a 3-month course of oral allopurinol [11], but no improvements in exercise tolerance were demonstrated.

Abnormalities in peripheral and coronary arterial responses are accepted to signify endothelial dysfunction and are associated with other markers of cardiovascular disease [114]. Improvements in these parameters have been shown to follow treatment with thiazolidinediones [115, 116] and agents such as ACE inhibitors [117–119], HMG-COA reductase inhibitors [116, 119–123] and amlodipine [124]. Most of these agents have been shown to be effective in reducing cardiovascular event rates and mortality. While direct comparisons are flawed and difficult, the magnitude of the changes effected by xanthine oxidase inhibition seems comparable to that caused by these agents (bar the exception outlined above) [107, 119, 120, 125]. Further, the reductions in BNP concentrations seen were comparable to those induced by ACE inhibition, angiotensin II antagonists [126], β-blockade [127] and spironolactone [128]. It is therefore possible, but entirely speculative, that allopurinol could have an impact on clinical outcomes similar that of these agents. The side-effect profile of allopurinol is also comparable to other treatments, but the cost is not; allopurinol is cheap, making it an attractive preventative treatment.

We have shown that following stroke, each additional 0.1 mmol l^{-1} increase in serum uric acid is associated with a 27% increased relative risk of a recurrent cardiovascular event [28]. We have also shown that following stroke, 300 mg allopurinol causes a sustained reduction in serum uric acid from a mean of 0.35 mmol l^{-1} (SD 0.09) to 0.22 mmol l^{-1} (SD 0.05) (unpublished data). Using a secondary prevention stroke trial as an example, it would therefore be reasonable to expect a 27% relative risk reduction in cardiovascular event rate with this treatment. With a predicted cardiovascular event rate of 6/100 patient years, or 16% over 3.5 years (as used to design and seen in the recent ESPRIT trial [129]), approximately 3000 patients would be required to be followed for a mean of 3 years to confirm this benefit. It is important to remember that this figure may actually be less because the beneficial effects of allopurinol on endothelial function would be expected to contribute to the treatment effect regardless of changes in uric acid.

Summary

The epidemiological evidence to support a role of elevated serum uric acid in cardiovascular disease is cogent. These associations are seen across healthy populations (albeit less consistently), those with cardiovascular risk factors and in those with established cardiovascular disease. While a clear pathophysiological role for uric acid in the development of cardiovascular disease has yet to be established, there are data to support detrimental and prothrombotic effects on platelet and endothelial function. Post-hoc analyses suggest that some of the beneficial effects of proven treatments for cardiovascular disease may be due to changes in serum uric acid concentrations. Furthermore, xanthine oxidase-mediated oxidative stress is likely to have a significant role in the development of atherosclerosis and several small studies have shown that xanthine oxidase inhibition improves endothelial function and markers of oxidative stress in a variety of disease states. Thus, even if serum uric acid is simply a marker of oxidative stress, there is a wealth of epidemiological, animal and now clinical data to suggest the benefits of strategies to lower uric acid and inhibit xanthine oxidase. Large-scale trials with clinical end-points are justified to address this important question in the context of heart failure (such as the OPT-CHF trial), coronary disease and in broader categories of cardiovascular risk. Despite being an old drug, allopurinol may prove to be a cheap, effective and novel preventative therapy for the 21st century.

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