

# Hyperuricemia, Gout, and Cardiovascular Disease

## An Important “Muddle”

Robert T. Keenan, M.D., M.P.H., and Michael H. Pillinger, M.D.

### Abstract

*Multiple epidemiologic studies confirm an association between hyperuricemia and cardiovascular disease (CVD), but it remains uncertain whether hyperuricemia is an independent or dependent risk factor for CVD. The question is particularly complex since patients with gout frequently have multiple comorbid conditions and adjusting for these conditions tends to reduce the strength of hyperuricemia as a risk factor. In this article, we review the data supporting a possible independent role for hyperuricemia in CVD. A close reading of the literature suggests that hyperuricemia may be both an independent and dependent risk factor, and is more likely to act as an independent risk factor in blacks, women, and patients with high risk for CVD. We also review the literature that suggests that hyperuricemia may directly contribute to the development of a number of comorbid conditions that in turn contribute to CVD risk (e.g., hypertension, glucose intolerance, renal insufficiency, and adiposity), suggesting that adjusting studies for these risk factors may be biologically inappropriate. Finally, we review the limited literature addressing the question of whether gout per se, above and beyond the presence of hyperuricemia, may convey an additional independent CVD risk. Given the ready ability of physicians to pharmacologically manage serum urate levels, a better understanding of*

*the interaction between hyperuricemia, gout and vascular disease may be critical for the reduction of morbidity and mortality in high-risk CVD patients.*

Cardiovascular disease remains a major public health problem. More than 80 million individuals in the United States alone have some form of cardiovascular disease; more than 73 million Americans have hypertension, 16 million have documented coronary artery disease, and 5.8 million have suffered a stroke.<sup>1</sup> Recent advances in the field of rheumatology indicate that the problem may be particularly acute among patients with rheumatic diseases. For example, cardiovascular disease is the leading cause of death among patients with rheumatoid arthritis, and patients with lupus may be even more susceptible: approximately 15% of all deaths among lupus patients are due to cardiovascular disease.<sup>2-5</sup> Additionally, patients with ankylosing spondylitis and psoriatic arthritis have a relative risk for atherosclerosis that is 1.6-times that of the general population.<sup>5</sup>

An underlying commonality between cardiovascular and rheumatologic diseases is the presence of inflammation. The atherosclerotic lesion is highly inflammatory, involving as it does an influx of macrophages, as well as mast cells and T cells.<sup>6</sup> The process of thrombus formation, intrinsic to the ischemic lesion, is also part of the inflammatory process of atherosclerosis. Less well understood is the distinction between intrinsic inflammation in the atherosclerotic lesion and the impact of extrinsic inflammation on the vessel wall. Nonetheless, elevations of inflammatory markers, such as C-reactive protein (CRP) levels, are associated with cardiovascular risk.<sup>7</sup>

Gout is a rheumatic disease whose underlying cause is the presence of systemic hyperuricemia. The transition from hyperuricemia to gout occurs when elevated uric acid levels result in the precipitation of uric acid, which drives

Robert T. Keenan, M.D., M.P.H., is from the Division of Rheumatology, Department of Medicine, NYU Hospital for Joint Diseases. Michael H. Pillinger, M.D., is Associate Professor of Medicine and Pharmacology, New York University School of Medicine, and, from the Division of Rheumatology, Department of Medicine, NYU Hospital for Joint Diseases, NYU Langone Medical Center, New York, New York, and the Department of Medicine, New York Harbor VA Healthcare System New York Campus, New York, New York. Correspondence: Michael H. Pillinger, M.D., Division of Rheumatology, NYU Hospital for Joint Diseases, 301 East 17th Street, New York, New York 10003; michael.pillinger@med.nyu.edu.

**Table 1** Population Studies That Include Hyperuricemia and CVD Data

Study	Follow-Up (Years)	Independent Predictor?	Reference
Framingham (1999)	17.3	No	20
Honolulu Heart	21	Yes	39
KIHD	11.9	Yes	11
NHANES I	16.4	Yes	19
ARIC	8	No	41
MRFIT	6.5	Yes	38
Chinese Cohort Study	7-9	Yes	23
Women of Gothenburg Study	12	Yes*	42
MONICA	8	Yes*	43
CASTEL	7	Yes*	44
British Regional Heart Study	16.8	No	45
Health Professional Follow-up Study	12	Yes (Gout only)	40
Chicago Heart Association Detection Program	11.5	Yes (Females only)	46
PreCIS	(retrospective)	Yes	22
Social Institute of Finland	5	No	47

\*All-cause mortality. Abbreviations: KIHD, Kuopio Ischemic Heart Disease Risk Factor Study; NHANES, National Health and Nutrition Examination Survey; ARIC, Atherosclerosis Risk in Community Study; MRFIT, Multiple Risk Factor Intervention Trial; MONICA, Monitoring of Trends and Determinants in Cardiovascular Disease (World Health Organization), Augsburg Cohort; CASTEL, Cardiovascular Study in the Elderly; PreCIS, Preventive Cardiology Information System.

both acute inflammatory attacks and the deposition of uric acid in large aggregates (tophi) in tissues. Gout is a highly inflammatory disease,<sup>8-10</sup> but the medical community has not yet achieved consensus as to the question of whether hyperuricemia or gout, per se, represent independent risk factors for cardiovascular disease. In this article, we review the current state of the art as to the association and potential role of hyperuricemia and gout in the progression of cardiovascular disease.

### Hyperuricemia and Cardiovascular Disease: Population-Based Studies

Virtually every large population study performed in the past 40 years has detected an association between elevated uric acid levels and cardiovascular disease (Table 1). For example, Niskanen and colleagues observed a dose-dependent increase in cardiovascular mortality with rising uric acid levels in a Finnish population.<sup>11</sup> Controversy arises, however, with the question of whether the association between uric acid and cardiovascular disease is an independent one, or instead results from the co-associations of elevated uric acid levels and known cardiovascular risk factors. Indeed, in contrast to other rheumatic diseases, it is perhaps more common to see gout patients with multiple comorbid conditions, than to see gout alone.<sup>12,13</sup> In a recent study in the New York Harbor Health Care System of the Department of Veterans Affairs, we observed that the average gout patient had three comorbidities, and that some patients carried as many as seven.<sup>14</sup> Typical comorbidities seen in conjunction with gout include: hypertension, obesity, hyperlipidemia, renal insufficiency, and insulin resistance or diabetes, or both.<sup>12,15,16</sup> Each of these comorbid conditions is independently associated with cardiovascular disease, and col-

lectively, they may aggregate as the metabolic syndrome. Any attempt to examine the independent role of uric acid in cardiovascular disease must, therefore, account for these factors in some way.

To some extent, independence may be in the eye of the beholder. For example, Johnson and coworkers reviewed a collection of 14 population-based studies, observing that 10 of these studies supported hyperuricemia as an independent predictor of cardiovascular disease.<sup>17</sup> In contrast, Wheeler and associates reviewed a different but overlapping group of 15 studies, in which 14 had demonstrated an increased relative risk for cardiovascular disease (albeit not all significant), yet concluded that the independent risk for cardiovascular disease in the setting of hyperuricemia was either small or nonexistent.<sup>18</sup> In this context, it may be useful to examine the study that showed the strongest independent effect of uric acid level on cardiovascular disease and compare it with the study that showed the weakest association. In so doing, we may gain insight into which population data may or may not be misleading.

The first National Health and Nutrition Examination Survey (NHANES I) was conducted from 1971 to 1975 on a probability sample of the U.S. civilian population. More than 20,000 persons aged 25 to 74 years were included, and 70% of these underwent medical examination. A subsample of 6913 were examined in greater depth, including measurements of serum uric acid levels. In 2000, Fang and colleagues published a study using this data, as well as data from the NHANES I Epidemiologic Follow-up Study (NHEFS).<sup>19</sup> Of the 6913, a small number were excluded for preexisting myocardial infarction, gout, or stroke; pregnancy at the time of enrollment; or self-reporting regarding race as neither black nor white. The remainder became the subjects

of analysis. Adjusting for age, Fang and coworkers observed a dose-dependent increase in cardiovascular mortality across quartiles of serum uric acid levels. This effect was most pronounced among black members of the study group. Consistent with previous reports, females with elevated uric acid had a higher risk of cardiovascular disease than males with similar serum uric acid levels.

The Framingham study enrolled 5209 males and females between the ages of 30 and 60, all of whom resided in Framingham, Massachusetts, and followed them meticulously for many years. An offspring study enrolled an additional 5124 individuals, all of whom were included in subsequent follow-up. From amongst these populations, Culleton and associates enrolled 7940 in an examination of the relationship between uric acid and cardiovascular risk.<sup>20</sup> In contrast to the NHANES I and NHEFS, the Framingham population revealed no relationship between uric acid level and cardiovascular disease in males. A strong association was observed between uric acid and cardiovascular risk in females; however, this association evaporated when the data was adjusted for confounding variables.

How can two such large, thorough and well-conducted studies yield such different results? A comparison of the patient populations in the two studies may shed some light on the nature of the discrepancy. Enrollees in the Framingham study were mostly white, economically middle- to upper-middle class and with a high education level. As a whole, the patients in the Framingham study had ready physician access and a low incidence of both general and cardiovascular events, compared with the general population. In contrast, the NHANES study included a larger representation of minority groups and enrolled patients with a broad range of economic and educational levels. As a group, these patients had less physician access and experienced a higher incidence of adverse events during the study period. Is it possible, then, that the Framingham population—and others like it—may simply be too healthy to “register” the adverse cardiovascular effects of hyperuricemia? Or, put another way, do the cardiovascular risk factors that co-associate with hyperuricemia, as well as others, such as black race, provide a permissive background against which the cardiovascular effects of hyperuricemia may be manifest?

Baker and colleagues took an interesting approach to this question.<sup>21</sup> They selected a time frame of 6 years prior to the date of their analysis, which excluded all studies that had previously been evaluated for associations between hyperuricemia and cardiovascular disease. Within that time frame, they identified all large population-based studies that had been published. They then segregated the patient populations studied as either healthy and at low risk, or at high cardiovascular risk upon enrollment (i.e., with hypertension, diabetes, etc.), and compared the adjusted association between hyperuricemia and cardiovascular risk in the low-risk versus high-risk cohorts. Among low-risk populations, only

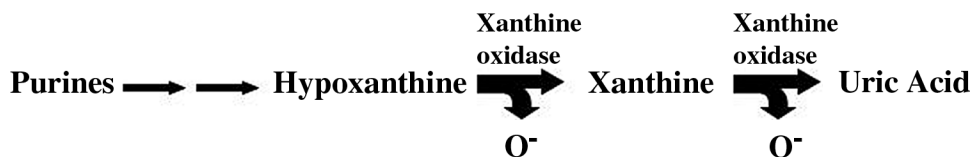
six out of 10 studies revealed an independent association between uric acid and cardiovascular disease. In contrast, in the high-risk groups, eight of nine groups showed an independent association. The authors concluded that patients with a high background cardiovascular risk are more likely to have an independent association between their uric acid levels and cardiovascular disease.

Several recent, large population-based studies have confirmed uric acid as an independent risk factor for cardiovascular disease, including the Preventative Cardiology Information System (PreCIS) study.<sup>22</sup> The most recent large study, a Chinese cohort study, is the largest investigation, to date, looking at the relationship between uric acid and cardiovascular risk, and sheds some additional light on the issue of preexisting risk. The Chinese cohort study screened 146,900 individuals participating in a private health system in Taiwan between 1994 and 1996.<sup>23</sup> After excluding individuals younger than 35 years of age, 93,393 participants were enrolled, approximately 50% male and 50% female. Patients enrolled were of all economic classes, with 25% of low socioeconomic status. All enrollees completed a detailed questionnaire and were measured for blood pressure and serum urate, lipid, and glucose levels upon enrollment. Mortality was determined using the Taiwanese National Death Registry; since deaths are legally-mandated to be entered into this registry, virtually all deaths during the study period (10 years) were captured.

The results were, in many ways, confirmatory of prior studies that supported an independent role for serum urate in cardiovascular mortality. For both males and females, cardiovascular mortality increased with increasing serum urate level in a dose-dependent manner. As in other studies, this effect was more pronounced for females than males, and persisted after adjustment for other risk factors. For example, the hazard ratio for overall cardiovascular death among females with hyperuricemia (urate > 7.0 mg/dL) was 1.69 ( $p < 0.001$ ), whereas the hazard ratio among males was only 1.10 ( $p = 0.02$ ). Nonetheless, given the large number of patients evaluated, even this slight increased risk may be clinically meaningful when extrapolated to an entire population. Strikingly, when the investigators divided the population into those individuals at low risk for cardiovascular disease and those at high risk (hypertension or diabetes), the increased hazard ratio was statistically significant only among the high risk patients. These data again support that studies looking for associations between uric acid and cardiovascular disease may be most pertinent to patients with other underlying cardiovascular risk.

### Uric Acid as an Agent of Cardiovascular Disease: Biological Plausibility?

If uric acid is an independent risk factor for cardiovascular disease, by what mechanisms might it have its effects? Studies in both in vitro and in animal models have raised some possibilities. For example, Kang and coworkers have



**Figure 1** Purine metabolism. For every one molecule of uric acid produced, two oxygen radicals are produced.

demonstrated that soluble concentrations of uric acid, when applied to vascular endothelial cells, inhibit the synthesis of nitric oxide in a dose-dependent manner.<sup>24</sup> Indeed, rats treated with oxonic acid (a uricase inhibitor) simultaneously experience a rise in serum urate and a fall in serum nitric oxide, an effect that can be reversed with the lowering of uric acid by allopurinol (a xanthine oxidase inhibitor). Uric acid also induces vascular smooth muscle proliferation in a dose-dependent manner. The combination of loss of the vasodilatory actions of nitric oxide, together with the proliferation of vascular smooth muscle, would appear to be a potent combination for constriction of the vascular bed. Interestingly, Kang and associates have also shown that uric acid induces CRP production by human vascular endothelial and smooth muscle cells.<sup>24,25</sup> Given the growing understanding of CRP as a risk factor for cardiovascular disease, the latter observation at least raises the possibility that urate-induced CRP production in the vasculature might participate in cardiovascular risk.

However, not all investigators are convinced that uric acid is a “bad actor” in vascular disease. As far back as 1981, Ames and colleagues demonstrated that urate is a scavenger of singlet oxygen species, and proposed that high urate levels evolved to protect against vascular disease.<sup>26</sup> The antioxidant capacities of uric acid can be observed in both in vitro and in animal models; Ames and coworkers suggested that from an evolutionary point of view, rises in serum urate in humans and great apes may have occurred to compensate for a loss of intrinsic production of ascorbate, another potent antioxidant. Uric acid also can function to prevent the inactivation of superoxide dismutase, an enzyme that degrades toxic oxygen molecules.<sup>27</sup> Thus, urate may have multiple beneficial effects on the oxidant state of the organism. The situation is more complex than it would appear at first, however, since the generation of a single molecule of urate is accompanied by the generation of two molecules of superoxide anion (Fig. 1). Moreover, some data suggest that intracellular urate can actually have pro-oxidant, rather than antioxidant effects.<sup>24,28</sup>

### Adjustment of Clinical Studies for Other Risk Factors: A Good Idea Gone Wrong?

Given the many comorbidities that may accompany hyperuricemia, it makes good statistical sense to adjust risk calculations to account for those factors that also produce cardiovascular risk. But is good sense—statistical or otherwise—always correct? In this case, the answer would seem to be a guarded “no.” Up to this point, we have

considered models in which any effect of uric acid on cardiovascular disease is obscured by the effects of other potentially more potent or important risk factors. We have also considered the possibility that uric acid is increased, at least in part, as a consequence of these other risk factors, making serum uric acid the dependent variable. Finally, we have considered the possibility that the other risk factors might raise the potential for elevated serum urate levels to produce a measurable increase in cardiovascular risk. But there remains one more possibility—that some of the other risk factors noted (hypertension, diabetes, hyperlipidemia, obesity, renal insufficiency, etc.) might actually not be a cause, but a consequence of hyperuricemia. If that were the case, then they would become the dependent variables, and adjusting for them would be tantamount to wiping out some of the effect of uric acid. Is this possible? Actually, it is.

Studies from the Johnson group have made a strong case for a role of hyperuricemia in the onset of hypertension.<sup>24,29</sup> We have already noted the ability of uric acid to stimulate vascular smooth muscle hypertrophy and to inhibit nitric oxide synthase. Hypertension also has been shown to develop in those rats treated with oxonic acid, which can be reversed with allopurinol.<sup>29</sup> In addition, Johnson and associates have demonstrated that elevated levels of uric acid can stimulate the renin-angiotensin axis, and induce renal interstitial and tubular injury.<sup>29,30</sup> That the net effect of these actions may be hypertension has been shown in rats. In humans, Feig and colleagues have demonstrated the ability of allopurinol to normalize blood pressure in adolescents with premature hyperuricemia and essential hypertension.<sup>31</sup> Thus, uric acid may play a role in blood pressure and renal injury.

Less well established, but perhaps even more intriguing, is the possibility that uric acid may play a role in the onset of insulin resistance and possibly even diabetes. Nakagawa and coworkers have employed an animal model in which feeding rats a diet chronically high in fructose resulted in insulin resistance.<sup>32</sup> Insulin resistance could be abrogated, however, and serum insulin levels reduced, by treatment with allopurinol to lower serum urate. In this same model, hypertriglyceridemia was also produced by the high-fructose diet, and reversed with allopurinol. Perhaps most surprising, similar effects could be seen on overall body mass, which was increased with fructose feeding but returned towards normal with administration of allopurinol. The investigators suggest that all of these mechanisms may be secondary to the underlying ability

of serum urate to lower nitric oxide and to induce vascular disease.

### But What About Gout?

Up until now we have been discussing the possibility that hyperuricemia acts as an independent risk factor for cardiovascular disease. But what about gout per se? Gout differs from hypericemia in that it marks the presence of formed crystals, in both the fluid phase and as deposits in aggregates in tissues. These crystals, in turn, induce inflammatory responses that can be local or systemic, intermittent or—especially late in the course of the disease—persistent and ongoing.<sup>33-36</sup> Is there any evidence that a diagnosis of gout conveys additional cardiovascular risk over and above that conferred by hyperuricemia?

To date, relatively few studies have addressed this question specifically and in a manner that adequately distinguishes between gout and hyperuricemia. Intriguingly, evidence in favor of a role for gout in cardiovascular disease may come from the Framingham study. Although Cullerton and associates used the Framingham data to conclude that hyperuricemia was not an independent risk factor for cardiovascular disease, another group, headed by Abbott, later used the same database to show that gout is a risk factor.<sup>37</sup> While these Framingham-derived studies are not directly comparable, they suggest the possibility that gout may confer an incremental increase in cardiovascular risk, compared with hyperuricemia. Further evidence in favor of gout as an independent cardiovascular risk factor may be found in an analysis of the Multiple Risk factor Intervention Trial (MRFIT), an interventional randomized control trial that included 12,866 patients, ages 35 to 57. Krishnan and coworkers evaluated 2385 subjects from the MRFIT study, observing not only that mean blood pressure was significantly increased in gout patients, but also that gout, per se, was a significant independent risk factor for cardiovascular disease.<sup>38</sup>

### Summary and Conclusions

A review of the literature reveals that virtually all population-based studies to date demonstrate an association between gout and cardiovascular disease, and that in a majority of studies this association is an independent one. Studies that have failed to find an independent association may be marred by the selection of low-risk populations or by overzealous attempts to adjust for comorbidities whose presence may be both a cause and a consequence of hyperuricemia. At a biological level, investigations support that uric acid at inappropriately high levels may promote vascular, renal, and other responses that may directly or indirectly promote cardiovascular risk. Although these data are compelling, it is probably still premature to attempt urate lowering in otherwise healthy individuals with hyperuricemia. On the other hand, these data hold out promise that urate lowering—a strategy already readily available to rheumatologists manag-

ing patients with gout—may eventually provide a way of lowering cardiovascular risk in a safe and effective manner.

### Disclosure Statement

The authors have no financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

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