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Gout (A Gibofsky, Section Editor)

Gout and Hyperuricemia—Serious Risk Factors for Morbidity and Mortality or Just Indicators of "The Good Life"—The Evidence to Date

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Opinion statement

Gout and hyperuricemia are associated with cardiovascular disease and its major risk factors and even more closely with chronic kidney disease. The preponderance of results from observational cohorts demonstrate that gout and hyperuricemia are associated with an increased risk of cardiovascular disease and chronic kidney disease that is independent of other factors, though that increase is of a smaller magnitude than that seen with traditional risk factors. In some studies, the relative increase in risk associated with elevated uric acid is more pronounced in women than in men. We have interpreted these results as a prompt to be more aggressive in screening our gout patients for modifiable cardiovascular risk factors and chronic kidney disease and reducing those risks as much as possible through lifestyle changes, modifications to diet, and medications. Many gout patients have indications for urate-lowering therapy related to their disease, so the dilemma of whether to initiate treatment is not present. There has not yet been sufficient demonstration in randomized controlled trials of benefit from urate-lowering therapies in patients with asymptomatic hyperuricemia with regard to cardiovascular or renal outcomes. However, there are intriguing preliminary results in several studies that may demonstrate a specific benefit of allopurinol or febuxostat in certain populations.

Introduction

Gout has been associated with a multitude of cardiovascular risk factors, including the metabolic syndrome, hypertension, diabetes mellitus, and hyperlipidemia in a variety of populations [1–8, 9••]. It has also been shown that gout is associated with cardiovascular disease itself, including coronary artery disease (CAD) and myocardial infarction (MI), congestive heart failure (CHF), stroke, and peripheral arterial disease [9••, 10, 11•]. There has been increasing evidence from very large cross-sectional studies that asymptomatic hyperuricemia may be associated with cardiovascular disease and mortality, as well canonical cardiovascular risk factors [1, 9••, 12]. In addition, some studies have shown that risk of developing conditions as disparate as chronic kidney disease (CKD) or end-stage renal disease (ESRD), dementia, Parkinson disease, and cancer may be affected by the presence of hyperuricemia or gout [2, 13–16]. However, there has been some considerable debate about whether gout and hyperuricemia are independent risk factors for disease or are merely markers of other comorbid conditions. A recent systematic review concluded that the attributable cardiovascular risk associated with hyperuricemia is small, if present at all, and while the risk appears to be elevated in gout patients, this has been less well studied in prospective cohorts. They did find a convincing association between hyperuricemia and risk of incident chronic kidney disease [17].

This review will evaluate recent developments in epidemiological studies in gout and hyperuricemia as it relates to cardiovascular disease and other comorbid conditions. Additionally, there have been several randomized controlled trials that may provide some insight into whether therapy for gout or hyperuricemia leads to better outcomes.

Myocardial infarction and angina

There have been several prospective observational studies of the relationship between gout and hyperuricemia and subsequent mortality or development of coronary artery disease. Prospective cohorts with prolonged follow-up, including the Multiple Risk Factor Intervention Trial (MRFIT) and Health Professionals Follow-up, found an increased risk of mortality attributable to coronary artery disease in male and female patients with gout [11•, 18•] (Table 1). The Framingham prospective cohort was similarly evaluated and found that over a 32-year follow-up period, 39.4/100 male gout patients suffered a coronary heart disease (CHD) event, compared with 28.9/100 male patients without gout, and this difference was statistically significant. They saw no difference in female patients; however, there were only 19 women with gout in the entire cohort [19] (Table 2).

More recently, a large number of sizable cross-sectional and retrospective analyses have leveraged the power of national health care systems and electronic medical records to examine the link between gout and risk of cardiovascular events. One such study using the Taiwanese National Health Insurance system examined records from 3,858,840 controls, 164,436 of whom had gout, and found an increased adjusted hazard ratio (HR) of cardiovascular mortality of 1.10 in patients with gout [20•]. Overall prevalence of gout in this population is 4.26 %, much higher than the 1.4 % cited in Germany and Britain [10] but close to the extrapolated prevalence of 3.9 % in the USA [9••]. A different study using the same dataset looking at MI incidence alone found an adjusted HR for MI of 1.23 in the gout group over an 8-year period, with even more pronounced risk in patients without traditional cardiovascular risk factors [21].

Table 1. Key cohort studies of gout and cardiovascular disease

Author	Cohort	Size (patients)	Effect of gout	Follow-up time (years)
Prospective				
Krishnan et al.[18•]	MRFIT	9105	HR 1.35 (cardiovascular mortality)	17
Choi et al.[11•]	Health Professionals Follow-up	51,297	RR 1.31 (cardiovascular mortality)	12
Abbott et al.[19]	Framingham	5209	RR 1.6 (coronary heart disease—men)	32
Retrospective				
Kok et al.[20•]	Taiwan National Health Insurance Research Database	3,858,840	HR 1.10 (cardiovascular mortality)	4
De Vera et al.[23]	British Columbia Linked Health Database	57,852	RR 1.67 (acute MI—women) RR 1.11 (acute MI—men[a])	7
Clarson et al.[24]	UK Clinical Practice Research Datalink	48,152	HR 1.25 (any vascular event—women) HR 1.06 (any vascular event—men)	10

[a]Not significant

Table 2. Key cohort studies of hyperuricemia and cardiovascular disease

Author	Cohort	Size (patients)	Effect of hyperuricemia	Follow-up time (years)
Strasak et al.[26]	Vorarlberg Health Maintenance and Prevention Program	83,683 men	HR 1.05 (men—cardiovascular mortality[a,b])	13.6
Strasak et al.[25]	Vorarlberg Health Maintenance and Prevention Program	28,613 women	HR 1.35 (women—cardiovascular mortality[b])	13.6
Fang and Alderman [27]	NHANES I Epidemiologic Follow-up	5926	HR 1.09 (cardiovascular mortality—men[c]) HR 1.26 (cardiovascular mortality—women[c])	16.4
Koton et al.[29]	UK-TIA/Oxford-TIA	2435/290	HR 1.17 (stroke or coronary heart disease event[c])	7.25/10
Navaneethan et al.[28]	Atherosclerosis Risk In Communities	15,366	HR 1.09 (cardiovascular events[c])	11
Culleton et al.[30]	Framingham and Framingham Offspring	6763	HR 0.92 (cardiovascular mortality—men[a]) HR 1.46 (cardiovascular mortality—women[a])	23

[a]Not significant
[b]Comparing highest to lowest quintile of sUA
[c]For each 1 mg/dL increase in sUA

An analysis of retrospective analysis of hospital records from the entire UK found that patients who had been admitted to the hospital for gout flares were much more likely to be admitted to the hospital or die from an MI or stroke, with a relative risk (RR) of 1.82 for MI, 1.71 for stroke, with stronger associations seen in younger age groups and in women [22]. However, while this last study has a very impressive scope, it has the significant limitation of being unable to control for a number of potential confounders due to the inability to examine clinical records.

Two other studies found a specifically increased risk of cardiovascular disease in women with gout. One study in British Columbia observed an increased risk of MI in women with gout, with an odds ratio (OR) of 1.39, while the trend toward increased risk of MI in men with gout did not reach statistical significance [23]. Clarson compared 8386 patients with newly incident gout to 39,766 matched controls with regard to incident cardiovascular disease over a 10-year period. They found that the combination of all vascular events was associated with gout in both men and women, while stroke and TIA were only significantly associated in female patients. Further, the magnitude of gout as a risk factor for cardiovascular disease was much greater for women than for men [24].

The related question of whether elevated uric acid alone or in the absence of gout has been examined extensively as well in prospective cohorts as well as cross-sectional analyses. Strasak et al. examined large prospective cohorts of Austrian men and women with regard to uric acid and cardiovascular mortality over a 20-year period. They found that there was a significantly increased adjusted HR in women in the highest quintile of serum uric acid (sUA) when compared to the lowest quintile for CAD (1.37), CHF (1.5), and strokes (1.37) [25]. In a separate analysis of men, in the multivariate analysis, only CHF and strokes were found to be significantly more common in subjects in the highest quintile of sUA [26]. A similar gender discrepancy was noted in 16-year follow-up in the NHANES I Epidemiologic Follow-up study, with an increased risk of CHD and cardiovascular mortality in men (adjusted HR 1.17/1.09) and in women (adjusted HR 1.30/1.26) for each 1 mg/dL increase in uric acid, with more pronounced differences noted in patients with fewer canonical cardiovascular risk factors and in those who were not taking diuretics [27]. A study of the Atherosclerosis Risk in Communities (ARIC) cohort showed increased cardiovascular events with an adjusted HR of 1.09 for each 1 mg/dL increase in uric acid [28]. Koton et al. found an increased HR of stroke or CHD event of 1.17 (adjusted only for age and sex) with each increase in uric acid by 1 mg/dL in a cohort of patients in the UK with history of TIAs, but this difference was driven entirely by events in female patients [29]. In contrast to the above studies, Culleton et al. found a non-significant decline in CHD in men in the highest quintile of sUA in 6763 subjects in the Framingham cohort. They did find an association between elevated sUA and CHD or cardiovascular-attributable mortality in women, but these findings did not remain significant after multivariate adjustment [30].

Hypertension

A number of prospective studies support an association between uric acid and hypertension. Sundstrom et al. analyzed data from 3329 subjects over the age of

50 in the Framingham study without pre-existing hypertension or gout and found a 4-year adjusted OR of developing hypertension of 1.17 per each standard deviation (SD) increase in uric acid [31]. A study using follow-up information from the Bogalusa Heart study found that uric acid levels measured during childhood were associated with the development of diastolic hypertension in young adulthood [32]. Mellen et al. examined 9104 subjects in the ARIC study for incident hypertension and found that the adjusted HR of developing hypertension was 1.08 for each increase in baseline uric acid by a standard deviation. Interestingly, this overall significant difference was driven entirely by increased risk in the African-American subjects [33].

More recent retrospective studies continue to confirm this association, particularly in patients without high numbers of comorbid conditions. An analysis of National Health and Nutrition Examination Survey (NHANES) 2009–2010, limiting analysis to subjects without the metabolic syndrome, found an increased risk of hypertension in patients with a sUA >7 mg/dL, with an adjusted OR of 2.2 [34]. A single-center cross-sectional study of 90,143 adults with no history of hypertension found every 1 mg/dL increase in uric acid above the lowest quartile was associated with an OR of 1.2 for finding an elevated blood pressure at the intake visit [35].

CKD

Gout and hyperuricemia are much more prevalent in patients with impaired renal function. Thirty percent of patients with stage 4 CKD in one study reported having been diagnosed with gout [36]. Several prospective cohort studies have identified hyperuricemia as a risk factor for incident CKD and progression to ESRD. In a Japanese cohort of 6403 patients, men with a sUA >8 mg/dL had an OR for incident CKD at 2 years of 2.91 when compared to pts with a sUA <5 mg/dL, while in women, the OR for CKD was 10.4, though the latter OR was based on only eight events [37]. A subsequent study evaluating for risk of progression to ESRD in the same cohort found an increased HR of ESRD in patients in the highest quartile of sUA levels, but after multivariate correction, that difference was only significant in female patients, with a HR of 5.8 [38]. Another study, using data from the prospective Viennese Health Screening Project, analyzed 21,475 patients with a mean of 7.4 years of follow-up for incident CKD. In that group, baseline uric acid predicted incident renal disease, with an adjusted OR of CKD of 1.26 for patients with a uric acid of 7–9 mg/dL and of 1.63 if the uric acid was >9 mg/dL [39].

Diabetes

As detailed above, retrospective and cross-sectional analyses have frequently shown an association between gout and diabetes [6, 13]. However, the association of gout and hyperuricemia with incident DM has also been confirmed in several large prospective cohorts.

Choi et al. evaluated 11,351 patients in the prospective MRFIT cohort for incident diabetes, 644 of whom had a diagnosis of gout. They saw increased rates of new diabetes in the gout group (30.8 vs 17.9/1000 patient-years), with an adjusted relative risk of incident diabetes of 1.34 [40].

With regard to hyperuricemia, a strong link between uric acid levels and incident diabetes was seen in the prospective Rotterdam cohort of 4536 patients in the Netherlands. The risk of development of diabetes increased in a stepwise fashion with an elevation of uric acid, with a HR of 1.68 for incident diabetes seen in patients in the highest quartile of uric acid [41]. An association between uric acid levels and increased diabetes risk was also seen in an analysis of the Framingham cohort and the Framingham offspring cohort in the USA, with an adjusted relative risk of incident diabetes of 1.2 in the original group and 1.15 in the offspring group for every 1 mg/dL rise in uric acid above 5 mg/dL [42].

While these studies support an association of hyperuricemia and gout with incidence of diabetes, there is evidence that the converse may not be true; rather, that pre-existing severe diabetes is actually associated with decreased incidence of gout. One study compared 24,768 patients in the UK with incident gout to 50,000 randomly sampled controls and found that incident gout was much less prevalent in the patients with pre-existing diabetes, with the difference becoming more pronounced with increased duration of diabetes [43]. A study using data from NHANES examined the relationship between uric acid, hemoglobin A1C, fasting blood glucose, insulin, and C-peptide levels. They noted a bell-shaped distribution of uric acid in patients with relation to varying A1C or fasting glucose levels, where uric acid concentration rose to a peak in patients with an A1C of 6–6.9 % and declined in groups of patients with higher A1C [44]. However, there was a linear increase in uric acid with rising levels of insulin or C-peptide, confirming an association between hyperinsulinemia and hyperuricemia seen in several other studies.

Neurologic disease

In contrast to cardiovascular disease, there is some evidence that hyperuricemia can be protective in certain neurologic conditions. One large cross-sectional study in the UK found that the prevalence of dementia was lower in gout patients than in controls [2], and elevated uric acid has also been shown to be associated with slower progression in amyotrophic lateral sclerosis [45].

Parkinson disease has been shown to be less common in gout patients in a large case-control study in the UK, but the association was only significant in male patients [46]. In subsequent analyses of patients enrolled in the DATATOP study of selegiline and vitamin E in Parkinson disease showed slowed disease progression in patients with uric acid >6.3 mg/dL, corresponding to the highest quintile in that study [15]. Based on those results, a safety and efficacy study of inosine supplementation, titrated to a goal level of uric acid >6 or >7 mg/dL, was undertaken. There were some few instances of gout symptoms and nephrolithiasis in the treatment arms, but no change in cardiovascular endpoints, and overall, there was no significant difference in adverse events compared to placebo. While the study was a safety study, they did observe some early evidence that progression of Parkinson disease symptoms was slowed in the treatment arms of the study relative to the placebo arm [47•]. It will be instructive if there is any change in cardiovascular endpoints with longer-term studies of an intentional elevation of uric acid.

The literature pertaining to cerebrovascular disease has been more varied, with some studies emphasizing the potentially beneficial antioxidant properties

of uric acid in stroke, while others focused on the association between elevated uric acid and increased risk of stroke along with other cardiovascular outcomes. As such, there have been studies of uric acid treatment as well as uric acid lowering. One-time treatment with bolus uric acid infusion following tPA administration in acute stroke was studied in the URICO-ICTUS trial, which showed a trend toward improved likelihood of excellent neurologic outcome (39 vs 33 % in the placebo arm), but this did not reach statistical significance [48]. In more long-term studies, randomized trials of allopurinol use for secondary prevention of stroke have shown a reduction in laboratory indices of inflammation and endothelial dysfunction [49], as well as central blood pressure and progression of carotid intima-to-media thickness [50]. However, no benefit on actual recurrent stroke incidence has been reported yet.

Cancer

There is a limited amount of information regarding risk of developing cancer in patients with gout and hyperuricemia. A large population-based cohort study of men in Austria found a higher incidence of various cancers, including lymphatic, urinary, and digestive tract cancer, in patients with serum uric acid >8 mg/dL [51]. Another study of gout patients in a random sample of one million patients in Taiwan found an adjusted HR of 1.15 for cancers of all kinds in the gout group, as well as a specific increase in risk for prostate cancer [16]. Boffetta et al. identified an elevated standardized incidence ratio for cancer of 1.25 in Swedish patients with gout as assessed by hospital admission records between 1965 and 1995 but were unable to control for many confounders given the study design [52]. While there may be some degree of increased risk of cancer in patients with gout, the evidence to date is not definitive, and there is no evidence that treatment of gout results in a lower risk of cancer.

The impact of urate-lowering therapy on clinical outcomes

If gout and hyperuricemia are in fact independent contributors to the development of cardiovascular disease or its primary risk factors, it is possible that intervention with urate-lowering therapies has the potential to affect cardiovascular outcomes. The lack of uniform consistency among observational studies, along with the cost and potential for rare but serious hypersensitivity reactions to allopurinol, has led to reluctance to test this in randomized controlled trials with clinically significant cardiovascular endpoints. However, there is some evidence that allopurinol or other urate-lowering therapy can have significant effects in both recent observational studies as well as interventional trials.

There have been several retrospective cohort studies comparing mortality rates between hyperuricemic patients taking allopurinol and other patients who were not prescribed allopurinol, but the results have not been uniform, with one study in Taiwanese gout patients indicating an increased HR of 1.25 of cardiovascular events in patients on allopurinol [53], while a study of mostly male hyperuricemic patients in the VA found an adjusted HR of death of 0.77 in those on allopurinol [54]. Dubreuil et al. identified patients in the UK who were initiated on

allopurinol and generated propensity scores to match those patients to controls who would have a similar likelihood of starting allopurinol. They found a decreased adjusted HR of death in the allopurinol group of 0.86 [55]. While these trials controlled for it in different ways, they all are subject to significant confounding by indication, limiting the conclusions that can be drawn.

Given the close association between uric acid levels and hypertension, particularly in adolescents and young adults, there have been a number of studies looking at allopurinol with regard to its effects on blood pressure. Kanbay et al. performed an open-label, non-randomized trial of allopurinol 300 mg/day for 12 weeks in 48 patients with hyperuricemia, compared to 21 non-hyperuricemic controls who received no treatment. The 36 patients who had hypertension at baseline who received allopurinol had a significant decrease in blood pressure (BP) over the course of the study; however, there was no significant difference between this group and the control group at the end of 12 weeks [56]. A follow-up open-label study by the same group, done with a randomized design and with the addition of a hyperuricemic control group, also found an improvement in the allopurinol group relative to the other hyperuricemic patients and normouricemic controls [57]. Interestingly, both studies also showed subtle improvement in estimated GFR in the allopurinol-treated subjects.

Feig et al. performed a randomized, double-blind, placebo-controlled crossover study evaluating the effect of allopurinol 400 mg/day on BP in 30 adolescent patients with sUA >6 mg/dL and newly diagnosed hypertension. They found a decrease in BP when the patients were receiving allopurinol, measured in the office as well as by 24-h ambulatory monitoring, with two thirds of the subjects achieving a normal BP [58••]. A second randomized, double-blind trial was done comparing allopurinol, probenecid, and placebo with regard to their respective impact on BP in 60 pre-hypertensive obese adolescents. Patients in the two treatment arms saw a decrease in BP along with uric acid relative to the placebo group, indicating that it was the degree of uric acid lowering, rather than inhibition of xanthine oxidase, that led to reduction of BP in these subjects [59]. A systematic review and meta-analysis of allopurinol use for the treatment of hypertension concluded that in some settings allopurinol may be efficacious as an adjunctive antihypertensive agent [60].

There is some evidence that allopurinol treatment can improve angina symptoms and exercise tolerance in patients with CAD and stable angina. Noman et al. enrolled 60 patients with known CAD and stable angina in a randomized, placebo-controlled crossover study of examining the effects of allopurinol on performance on an exercise tolerance test using the Bruce protocol. In the treatment phase, allopurinol was quickly uptitrated to 300 mg twice daily and continued for 6 weeks prior to crossover. While patients in the placebo phase had an improvement in median time to ST-depression, median total exercise time, and median time to chest pain, there was an additional statistically significant improvement in those parameters during the allopurinol treatment phase [61••]. The role of allopurinol in patients with existing ischemic heart disease is currently being evaluated in a randomized, controlled fashion in the EU (http://allheartstudy.org).

Results of trials with urate-lowering therapies in CHF have been less encouraging, despite uric acid levels being useful in multiple CHF prognostic indices [62, 63], and a number of trials indicating positive responses in biomarkers pertaining to CHF with allopurinol treatment [64–66]. A trial of allopurinol 300 mg/day in patients with NYHA stage II or III CHF did not result in improved exercise tolerance in a 6-min walk test [67]. Further, the randomized, placebo-controlled trial of oxypurinol (a metabolite of allopurinol that inhibits xanthine oxidase) in 400 patients with NYHA stages III–IV CHF with EF <40 % (OPT-CHF) did not meet its primary endpoint and, if anything, showed a trend toward worse outcomes in the treatment arm. Subgroup analysis demonstrated a possible benefit of oxypurinol in patients with a uric acid >9.5, but there were only 60 patients at that level in the oxypurinol-treated group [68]. Of note, in the study by Anker et al., a uric acid cutoff of 9.5 defined a substantial difference in 1-year mortality in their prognostic model, 52 versus 92 % in the patients below and above 9.5 mg/dL, respectively [62].

Some of the most interesting studies using urate-lowering therapy have focused on CKD, where the evidence of close association with gout and hyperuricemia has been most consistent. Two trials have focused on urate-lowering therapy in the perioperative setting in patients undergoing vascular and cardiothoracic surgery, with some potential benefit in late postsurgical outcomes and in GFR [69, 70]. Another randomized trial of allopurinol in addition to hydration found a significant reduction in contrast-induced nephropathy in patients undergoing heart catheterization [71]. One open-label randomized trial of allopurinol in 54 patients with CKD stage III or proteinuria >0.5 g/day found a significant slowing of progression of CKD in patients on allopurinol at the end of 12 months, with 16 % in the allopurinol arm versus 46 % of control patients experiencing a >40 % decrease in baseline GFR [72]. However, the degree of uric acid elevation, with a baseline of >9.7 mg/dL in both groups, may limit the generalizability of this trial to studies with milder hyperuricemia, even among pts with CKD.

Goicoechea et al. performed a randomized open-label trial of allopurinol 100 mg/day in 113 patients with an estimated GFR of <60. They did not find a significant change in BP between the groups at 24 months, but there was a subtle increase in estimated GFR in the patients receiving allopurinol versus a decline in the control group, and this difference between the groups was statistically significant. There was a very significant difference in risk of cardiovascular events between groups, with 15 occurring in the control group versus 7 in the allopurinol group [73]. A long-term follow-up study of the patients in this group demonstrated ongoing benefit in the patients originally assigned to the allopurinol arm, despite ten patients in the control arm eventually receiving allopurinol. The allopurinol group had a HR of 0.32 for initiation of dialysis or eGFR decline of ≥50 %, and of 0.43 for cardiovascular events over a median follow-up time of 7 years. All-cause mortality did not differ between the groups [74•]. This is a very striking result, but awaits confirmation in additional placebo-controlled trials. A larger, prospective, randomized placebo-controlled trial of febuxostat in hyperuricemic patients with stage III CKD (FEATHER) is planned [75], and the PERL study of allopurinol in patients with type I diabetes and renal impairment is ongoing (http://perl-study.org/index.html), which will hopefully shed additional insight on whether correcting hyperuricemia with delay CKD progression.

Conclusion

The preponderance of evidence shows a significant, albeit small, incremental increase in cardiovascular disease and mortality in patients with gout and hyperuricemia. However, this has been a matter of some debate due to variation seen in studies evaluating this question. Lastly, the role of urate-lowering therapy in modifying these risks in either group is less clear.

There are several potential reasons for the variable results seen with regard to hyperuricemia and risk of cardiovascular disease and mortality. The impact of thiazides may be important in biasing results to the null, as they increase uric acid levels but are proven to reduce mortality, and studies vary in controlling for diuretic exposure. Variable inclusion of women may affect the results, as some studies note a more dramatic risk associated with elevated uric acid in female patients [22–25, 27, 29, 37, 38]. There is evidence that uric acid may be of greater importance in younger people with regard to initiation of comorbid conditions like hypertension, but less important once these conditions have become established [76].

The last few years have seen a tremendous improvement in understanding of genetic factors that predispose to gout, which are likely differentially distributed, and different populations of patients may vary with regard to the impact of hyperuricemia and gout. Richette et al. performed a cluster analysis of French gout patients based on comorbidities and were able to establish five distinct clusters with very different patterns of comorbidities, only one of whom manifested cardiovascular disease [77•]. As this was a cross-sectional study, it is unclear if patients in one group would evolve into other groups, or if these phenotypes are durable, but it is tempting to think that some of the variations seen is due to their different genetic backgrounds. There is a striking difference in DM prevalence among gout patients in the UK (8 %) and Germany (25 %) [10], while the population-wide prevalence of DM in the two countries (6 % in UK versus 7.5 % in Germany) is much more similar. While the impact of social and environmental factors cannot be ignored, the impact of hyperuricemia on mortality and cardiovascular disease may be more evident in some populations.

A more definitive understanding of the risks associated with hyperuricemia, and the possible benefits of treatment, will only come with randomized, placebo-controlled trials; hopefully, trials like the ALL-HEART, PERL, and FEAT HER will be able to answer whether urate-lowering therapy is helpful in subgroups of hyperuricemic patients and trials of inosine in Parkinson's disease will be instructive to see if the converse is true.

Compliance with Ethics Guidelines

Conflict of Interest
David R. Fernandez and Joseph A. Markenson declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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