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Gout and the Risk of Acute Myocardial Infarction

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Objective. **To determine if hyperuricemia and gouty arthritis are independent risk factors for acute myocardial infarction (MI) and, if so, whether they are independent of renal function, diuretic use, metabolic syndrome, and other established risk factors.**

Methods. **We performed multivariable logistic and instrumental variable probit regressions on data from the Multiple Risk Factor Intervention Trial (MRFIT).**

Results. **Overall, there were 12,866 men in the MRFIT who were followed up for a mean of 6.5 years. There were 118 events of acute MI in the group with gout (10.5%) and 990 events in the group without gout (8.43%; $P = 0.018$). Hyperuricemia was an independent risk factor for acute MI in the multivariable regression models, with an odds ratio (OR) of 1.11 (95% confidence interval [95% CI] 1.08–1.15, $P < 0.001$). In multivariable regressions in which the above risk factors were used as covariates, gout was found to be associated with a higher risk of acute MI (OR 1.26 [95% CI 1.14–1.40], $P < 0.001$). Subgroup analyses showed that a relationship between gout and the risk of acute MI was present among nonusers of alcohol, diuretics, or aspirin and among those who did not have metabolic syndrome, diabetes mellitus, or obesity. In separate analyses, a relationship between gout and the risk of acute MI was evident among those with and without those hyperuricemia.**

Conclusion. **The independent risk relationship between hyperuricemia and acute MI is confirmed. Gouty arthritis is associated with an excess risk of acute MI, and this is not explained by its well-known links with renal function, metabolic syndrome, diuretic use, and traditional cardiovascular risk factors.**

The caricature of the typical patient with hyperuricemia is an obese middle-aged man with hypertension, diabetes mellitus, and hyperlipidemia who is given to excessive drinking. Among such individuals, it is not surprising to observe a surfeit of coronary artery disease as compared with the general population (1–5). While skeptics point toward residual confounding (6), evidence from prospective observational and interventional studies suggests that hyperuricemia is indeed a risk factor for cardiovascular disease independently of other risk factors, such as obesity, hyperlipidemia, diabetes mellitus, and hypertension (7).

When chronic and/or severe hyperuricemia leads to the precipitation of urate crystals within joints, it results in an inflammatory response that manifests as gouty arthritis (gout) (8). The inflammatory activity associated with gout can itself be proatherogenic and promote a prothrombotic environment that leads to acute coronary events (9). Thus, in theory, gout can be expected to increase the risk of acute myocardial infarction (MI). Yet, this important hypothesis has been examined in relatively few epidemiologic studies, and the results have been inconclusive (10–12). For a conclusive study, one would need to have a large cohort of high-risk individuals who had been followed up for long enough to accrue a sufficient number of outcome events. The Multiple Risk Factor Intervention Trial (MRFIT), a randomized primary cardiovascular prevention trial conducted and supported by the National Heart, Lung, and Blood Institute in collaboration with the MRFIT investigators, is one such study with the information on

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traditional and other confounding risk factors that has been unaccounted for in previous studies.

We used data from the MRFIT to test the following hypotheses: that hyperuricemia is an independent risk factor for acute MI, that gouty arthritis is an independent risk factor for acute MI, and that gouty arthritis increases the risk of acute MI independently of hyperuricemia.

SUBJECTS AND METHODS

Role of the funding source. This study was supported by an unrestricted grant from TAP Pharmaceutical Products, Inc., Lake Forest, IL. This was an investigator-initiated project, and TAP Pharmaceutical Products, Inc. was not involved in the design, data collection, or analysis and interpretation of the data.

Study subjects. The MRFIT was a randomized controlled trial designed to examine the efficacy of a program of coronary risk reduction among men at high risk of adverse coronary events. Subjects were eligible to join the study if scores for the combination of 3 risk factors (smoking, hyperlipidemia, and hypertension) were sufficiently high to place them in the upper 15% of a risk score distribution based on data from the Framingham Heart Study (13). Screening for the study started in 1973. Overall, 361,662 men were screened for recruitment into the MRFIT. Blood pressure measurements, smoking history, and cholesterol measurements were obtained at the first screening visit. Subjects were excluded from the trial if they had diabetes mellitus requiring medication, a history of acute MI, an elevated serum cholesterol level (≥350 mg/dl), or a diastolic blood pressure ≥115 mm Hg. Subjects were also excluded at this time if their risk of coronary heart disease was considered low.

At the second visit, a medical history, 4 blood pressure measurements, a resting electrocardiogram (EKG), a fasting blood draw, and a glucose tolerance test were performed. Subjects were also excluded at this stage based on an EKG-determined previous MI, body weight >150% of desirable weight, angina (by the Rose Questionnaire), untreated symptomatic diabetes mellitus, a diet incompatible with the diet prescribed as a part of the intervention, lipid-lowering treatment, or treatment with hydralazine, insulin, guanethidine, or oral hypoglycemic agents.

At the third screening visit, resting and exercise EKGs, a detailed smoking questionnaire, and a 24-hour dietary recall were obtained. If no major changes in cardiovascular status had occurred since the second screening visit, subjects were enrolled in the trial into either the usual care group or the special intervention group. Detailed risk factor assessments, including serum uric acid concentrations, were performed at baseline and on subsequent visits.

A total of 12,866 men were randomized into the study and were followed up prospectively for ~6.5 years. All subjects were eligible to participate for 6 annual visits. The response rates and completeness of followup were high (>90%). Ascertainment of hospitalization and availability of hospitalization records overall was 97% for both arms of the trial. Dropouts from the study (i.e., those who continued through the fourth year of the study but did not attend any of the last 4 annual visits [n = 434]) did not differ from those who remained in the study in terms of baseline characteristics, except that they were more likely to smoke and to drink more alcohol and were less likely to have an ischemic response to exercise (14).

Ethical approval for the present study was obtained from the University of Pennsylvania Medical Center.

Intervention program. The study design of the MRFIT has been described in detail elsewhere (13). In the original study design, one-half of the men enrolled were randomized to participate in a special intervention program aimed at smoking cessation and reduction of serum cholesterol and blood pressure levels. The remaining men were randomized to receive usual care and were referred to their personal physicians in the community for such treatment of their risk factors as was considered individually appropriate.

In the special intervention program, a 3-pronged approach to the treatment of risk factors for acute MI was used. Men in this program received smoking cessation counseling, nutrition counseling, and treatment of hypertension in a stepped-care program similar to that used in the Hypertension Detection and Follow-up Program (15). Hypertension was considered to be present if the man reported that antihypertensive medication had been prescribed for him by his personal physician or if an untreated man was found to have a diastolic blood pressure of at least 90 mm Hg on 2 consecutive monthly visits during the trial. Blood pressure goals were diastolic measurements of no more than 89 mm Hg or a reduction of 10 mm Hg, whichever was lower. Subjects already receiving antihypertensive agents were assigned a goal diastolic blood pressure of 80 mm Hg or lower. Dietary recommendations were made to reduce saturated fat intake to 10% of calories (to 8% starting in 1976), to increase polyunsaturated fat to 10% of calories, and to reduce dietary cholesterol to 300 mg/day (to 250 mg/day starting in 1976). Weight reduction, by reducing calorie intake and increasing moderate physical activity, was sought for subjects whose weight was ≥115% of desirable body weight. Behavior modification techniques, including hypnosis in some cases, were used to promote smoking cessation in those subjects who smoked cigarettes.

Baseline measurements. At baseline, subjects underwent a detailed medical history, including medication and social histories, and a full physical examination. Standard and random-zero blood pressure measurements were recorded as the average of 2 measurements. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Laboratory tests, including lipid profiles, blood glucose levels obtained after fasting and 1-hour after glucose loading, peripheral blood cell count, urinalysis, and blood chemistry tests, including serum uric acid and serum creatinine levels, were performed on the same day. Blood samples were sent to a central laboratory for analysis, and the results were determined as previously described (14).

Definition of hyperuricemia. There is no universally accepted definition for hyperuricemia. While, statistically speaking, information is lost when continuous variables are dichotomized, this process helps to better model any underlying nonlinear relationship between serum uric acid levels and

acute MI. Therefore, we studied hyperuricemia at baseline both as a continuous variable and as a dichotomous variable. Hyperuricemia was defined as a serum uric acid concentration ≥7.0 mg/dl. This cutoff is commonly used in clinical laboratories, and it has been used in published literature to define hyperuricemia (16). Furthermore, this cutoff point approximates a serum urate concentration that exceeds the limit of solubility (17). In our study population, this serum concentration was approximately the 60th percentile of uric acid measurements.

Definition of gout. In this study, we used the term gout synonymously with gouty arthritis. Epidemiologic criteria for gout can seldom be as rigorous as clinical criteria. In the Meharry-Hopkins Study, gout was defined as a self-report of gout (11). This case definition did not include hyperuricemia but was successfully validated against the American College of Rheumatology preliminary criteria for gout (18).

In the Framingham Heart Study, the diagnosis of gout was attributed if the subject had experienced acute joint pain, accompanied by swelling and heat, lasting from a few days to 2 weeks and followed by complete remission of symptoms. Evidence of gout was further confirmed when an attack of arthritis exhibited a prompt response to therapeutic doses of colchicine, often resulting in nausea, vomiting, and diarrhea. Any pill taken every hour and producing such an effect was presumed to be colchicine (10).

We used a case definition of gout that was very similar to the definition used in the Meharry-Hopkins Study (i.e., an affirmative answer to the question, "Have you been told by your physician that you have gout?") but added the requirement for documentation of sustained hyperuricemia (serum uric acid level ≥7.0 mg/dl on at least 4 visits).

Definition of outcomes. The primary outcome of interest was the total number of acute MIs (fatal and nonfatal combined). When there was >1 event per person, such as a nonfatal hospitalization followed by death from another acute MI, only the first event was taken into account for defining primary outcome. The closing date for the mortality end point was December 31, 1985. Nonfatal acute MI was ascertained until the subject's last followup visit. Cause of death was adjudicated according to a prespecified protocol by a physician committee using information from the death certificates and medical records. Nonfatal acute MI was ascertained by annual physician evaluations, review of hospital records, annual EKGs, and coronary artery bypass graft (CABG) surgery. The validity of these approaches within the MRFIT has been studied and confirmed (14). Further details of outcome assessment have been published elsewhere (14).

Statistical analysis. *General.* Bivariate analyses were performed using chi-square and Student's *t*-tests. Bonferroni-corrected Pearson's correlation coefficient was used to quantify correlations between covariates.

Logistic regression models. In these regressions, the dependent variable of interest was the dichotomous variable denoting occurrence or nonoccurrence of acute MI. Risk of acute MI associated with gout and hyperuricemia was modeled after adjusting for baseline values for age, diastolic blood pressure, total serum cholesterol, BMI, fasting blood glucose (a surrogate for insulin resistance), smoking, serum creatinine, diuretic use, aspirin use, alcohol use, incident diabetes mellitus, and family history of acute MI.

Instrumental variable probit regression models with endogenous regressors. The interrelationship between gout, serum uric acid concentration, blood pressure, serum creatinine level, insulin resistance, obesity, and diuretic use is complex and is indeed the basis for the controversy about the relationship between gout and coronary artery disease. In fitting these covariates to logistic regression models in previous studies, an implicit assumption was that these are independent covariates. This assumption may not be true, and there is a risk of estimating erroneous size and variance of the risk estimate if one were to use these variables as simple covariates. We therefore fitted a separate set of multivariable instrument–variable probit models (19) with acute MI as the dependent variable. In these regressions, the variable indicating the presence/absence of gout was modeled as the endogenous regressor, and age, serum cholesterol level, smoking, alcohol use, BMI, blood pressure, family history of acute MI, (newly incident) diabetes mellitus, serum creatinine level, aspirin use, and diuretic use were the exogenous regressors. This model affords us the ability to specify the interrelationships between the covariates (Figure 1).

Estimation of variance. An assumption of clustering within the 2 arms of the trial was made, since the medical and nonmedical interventions differed systematically across these groups but was homogeneous within the groups. Accordingly, a cluster option was specified in the logistic regression models and probit models that were performed using Stata software (version 8 SE, 2004; StataCorp, College Station, TX). Robust standard errors were calculated instead of conventional ones, since the former make fewer statistical assumptions, such as those regarding autocorrelation and heteroscedasticity.

RESULTS

Baseline characteristics. *Overall characteristics.* Overall, 12,866 men were in the MRFIT. The mean ± SD age of the cohort was 46 ± 6 years. The subjects were randomized into either the special intervention group (6,428 subjects [49.96%]) or the usual care group (6,438 subjects [50.04%]).

Characteristics of subjects with hyperuricemia. There were 5,337 men (41.5%) with hyperuricemia at baseline. Table 1 contrasts the baseline cardiovascular risk characteristics between the group with hyperuricemia and the group without hyperuricemia. The intercorrelation between known coronary heart disease risk factors and serum uric acid levels was examined using Pearson's product-moment correlation coefficients. These were only modestly correlated with each other (correlation coefficients ≤0.20, $P < 0.05$).

Characteristics of subjects with gout. Over the study period, 1,123 individuals (8.7%; 12 per 1,000 person-years) reported gouty arthritis. The mean ± SD

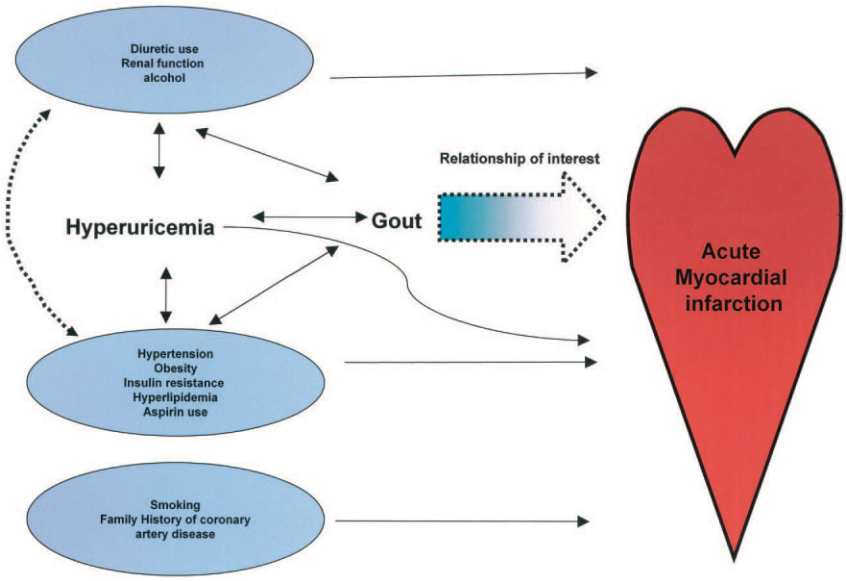

Figure 1. A risk model for hyperuricemia, gouty arthritis (gout), and acute myocardial infarction.

baseline serum uric acid concentration in subjects with gout (8.0 ± 0.9 mg/dl) was higher than that in those without gout (6.7 ± 1.21 mg/dl; $P < 0.001$). Table 1 shows the characteristics of the subjects with gout and those without gout. There was no statistically significant difference between the 2 groups with regard to serum cholesterol level, aspirin use, randomization arm, family history of acute MI, and cumulative incidence of diabetes mellitus. However, the group with gout was significantly more likely to have used diuretics and alcohol. Modest, but statistically significant, elevations of blood pressure, age, fasting blood glucose, and BMI were observed in the gout group. Subjects in the group with gout were less likely to be current smokers than were those in the group without gout.

Acute MI outcomes. During the followup period for this study, there were 1,108 recorded incidents of acute MI in the cohort; 246 of these were fatal. Among

Table 1. Characteristics of men with and those without hyperuricemia and gout in the Multiple Risk Factor Intervention Trial*

	Presence or absence of hyperuricemia			Presence or absence of gout		
	No hyperuricemia	Hyperuricemia	*P*	No gout	Gout	*P*
No. of subjects	7,529	5,337	–	11,743	1,123	–
Age, mean ± SD years	46.2 ± 6	46.0 ± 6	0.02	46 ± 6	47 ± 5	<0.001
BMI, mean ± SD kg/m^2	27 ± 3	28 ± 3	<0.001	28 ± 3	29 ± 3	<0.001
Systolic blood pressure, mean ± SD mm Hg	137 ± 15	139 ± 15	<0.001	137 ± 15	140 ± 15	<0.001
Diastolic blood pressure, mean ± SD mm Hg	92 ± 10	94 ± 10	<0.001	93 ± 10	95 ± 10	<0.001
Fasting glucose, mean ± SD mg/dl	98 ± 17	101 ± 14	<0.001	99 ± 16	101 ± 13	<0.001
No. of drinks per week, mean ± SD	11 ± 11	14 ± 13	<0.001	12 ± 12	14 ± 14	<0.001
Prevalence of smoking, %	67	54	<0.001	63	52	<0.001
Proportion receiving diuretics, %	82	86	<0.001	83	90	<0.001
Serum cholesterol, mean ± SD mg/dl	252 ± 37	255 ± 36	<0.001	254 ± 37	255 ± 36	0.25
Aspirin use at baseline, %	34	37	0.009	35	38	0.13
Family history of acute MI, %	39	40	0.51	39	42	0.09
Cumulative incidence of diabetes mellitus	3.5	4.1	0.86	3.8	3.7	0.98
Years of formal education, mean ± SD	14 ± 3	14 ± 3	0.06	14 ± 3	14 ± 3	0.93
Proportion in special intervention group, %	50	50	0.51	50	49	0.66

* Hyperuricemia was defined as a serum uric acid level ≥7.0 mg/dl. *P* values were determined by chi-square test for differences in proportions and by Student's *t*-test for differences in means. BMI = body mass index; MI = myocardial infarction.

Table 2. Cumulative incidence and risk of acute MI among men with and those without hyperuricemia and gout in the Multiple Risk Factor Intervention Trial*

Outcome	Presence or absence of hyperuricemia			Presence or absence of gout		
	No hyperuricemia	Hyperuricemia	*P*	No gout	Gout	*P*
Acute MI based on hospitalization records	254 (3.37)	206 (3.86)	0.14	408 (3.47)	52 (4.6)	0.046
Acute MI based on annual EKGs	191 (2.54)	145 (2.70)	0.53	302 (2.6)	34 (3.0)	0.360
Coronary artery bypass graft surgery	228 (3.03)	171 (3.20)	0.57	354 (3.0)	45 (14)	0.067
All nonfatal acute MIs	515 (6.8)	390 (7.3)	0.31	806 (6.8)	99 (8.8)	0.015
Fatal acute MIs	152 (2.02)	94 (1.76)	0.55	224 (1.9)	22 (1.96)	0.904
Overall (fatal plus nonfatal acute MIs)	639 (8.49)	469 (8.79)	0.30	990 (8.43)	118 (10.5)	0.018

* Values are the number (%) of events. Hyperuricemia was defined as a serum uric acid level ≥7.0 mg/dl. *P* values were determined by chi-square test. MI = myocardial infarction; EKGs = electrocardiograms.

the nonfatal acute MIs, 460 were identified from hospital records, and 336 were identified by serial electrocardiograms. CABG surgery was performed in 399 subjects.

Table 2 lists the cumulative incidence of acute MI among subjects with hyperuricemia. Table 3 shows the multivariable logistic regression model for predictors of any acute MI. When serum uric acid was entered into this model as a continuous variable, it was associated with a 4% increase in the risk of acute MI for each mg/dl increase in the serum uric acid value ($P < 0.001$).

The cumulative incidence of acute MI was higher among subjects with gout as compared with those without gout (Table 2). After adjustment for potential confounders, the risk of acute MI was increased among those with gout as compared with those without gout (Table 3).

Findings of subgroup analyses. A relationship between gout and the risk of acute MI was observed across the various strata of potential sources of confounding and interaction, such as alcohol use, aspirin use, and diabetes mellitus (Table 4).

Incident cases of gout. Further analyses were performed using only incident cases of gout by excluding individuals who reported gout at the baseline visit but retaining the criterion of sustained hyperuricemia. In these multivariable analyses, gout (n = 940) remained an independent risk factor for acute MI, with an odds ratio (OR) of 1.17 and a 95% confidence interval (95% CI) of 1.07–1.27.

Subjects with obesity and metabolic syndrome. Overall, 1,108 individuals could be classified as having metabolic syndrome according to the World Health Organization criteria (20). Multivariable analysis that adjusted for the effect of traditional risk factors, serum creatinine level, aspirin use, and alcohol use on the risk of acute MI was performed after excluding all subjects with metabolic syndrome. This showed an OR of 1.30 (95% CI 1.04–1.64) ($P = 0.02$) for gout. When this analysis was repeated with serum uric acid as the independent variable of interest, an OR of 1.02 (95% CI 1.01–1.05) ($P = 0.02$) for each mg/dl increase in uric acid was noted. When multivariable analyses were performed

Table 3. Risk-adjusted ORs for primary and secondary end points, by multivariable logistic regression*

Outcome	Presence versus absence of hyperuricemia		Presence versus absence of gout	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Acute MI based on hospitalization records	1.20 (1.08–1.32)	<0.001	1.32 (1.2–1.5)	<0.001
Acute MI based on annual EKGs	1.16 (1.04–1.28)	0.006	1.17 (0.64–2.2)	0.68
Coronary artery bypass graft surgery	1.17 (1.16–1.19)	<0.001	1.38 (0.91–2.11)	0.13
All nonfatal acute MIs	1.15 (1.12–1.19)	<0.001	1.31 (1.24–1.38)	<0.001
Fatal acute MIs	0.91 (0.65–1.27)	0.57	0.96 (0.66–1.44)	0.83
All acute MIs	1.11 (1.08–1.15)	<0.001	1.26 (1.14–1.40)	<0.001

* Odds ratios (ORs) were adjusted for the effect of "clustering" within the randomization arms of the study, as well as for age, blood pressure, serum cholesterol level, serum creatinine level, (newly incident) diabetes mellitus, smoking, family history of acute myocardial infarction (MI), aspirin use, diuretic use, alcohol use, and body mass index. Hyperuricemia was defined as a serum uric acid level ≥7.0 mg/dl. 95% CI = 95% confidence interval; EKGs = electrocardiograms.

Table 4. Results of multivariable logistic regression for the relationship between gout and acute MI in selected subpopulations*

	No. of subjects without gout		No. of subjects with gout		*P* for difference in cumulative incidence†	Stratified multivariable analysis	
	No acute MI	Acute MI	No acute MI	Acute MI		OR (95% CI)	*P*
Diuretic nonusers	1,837	155	99	12	0.251	1.49 (1.20–1.80)	<0.001
Diuretic users	8,916	835	906	1,042	0.039	1.22 (1.07–1.41)	0.004
Aspirin nonusers	6,983	626	624	78	0.009	1.37 (1.15–1.64)	<0.001
Aspirin users	3,770	364	381	40	0.632	1.08 (1.02–1.16)	0.016
Alcohol nonusers	797	101	59	18	0.002	2.33 (1.99–2.72)	<0.001
Alcohol users	9,956	889	946	100	0.127	1.16 (1.03–1.30)	0.014
No hypertension in men	3,885	345	249	33	0.032	1.52 (1.47–1.57)	<0.001
Hypertension in men	6,868	654	756	85	2.135	1.2 (1.08–1.30)	0.001
No diabetes mellitus	10,353	948	971	110	0.045	1.22 (1.06–1.40)	0.005
Incident diabetes mellitus	400	42	34	8	0.052	2.49 (1.97–3.13)	<0.001

* Except in the stratified multivariable analyses, the odds ratios (ORs) were adjusted for the effect of "clustering" within the randomization arms of the study, as well as for age, blood pressure, serum cholesterol level, (newly incident) diabetes mellitus, smoking, family history of acute myocardial infarction (MI), aspirin use, diuretic use, alcohol use, and body mass index. 95% CI = 95% confidence interval.
† Determined by chi-square test.

after excluding only those with a BMI >30 units, the OR for gout was 1.42 (95% CI 1.19–1.68).

Findings of sensitivity analyses. *Potential misclassification of cases of gout.* In this study, we used 1 self-reported physician diagnosis and 4 occasions of documented hyperuricemia as the diagnostic criteria for gout. A self-report of gout was closely associated with the serum uric acid concentration. In univariable logistic regression, each unit increase in the serum uric acid level was associated with a 1.8-fold greater likelihood (95% CI 1.80–1.96) of a self-report of gout.

To examine the sensitivity of our results to the case definition, we performed multiple sensitivity analyses with varying case definitions for gout. Thus, different numbers of self-reports and different numbers of occasions of documented hyperuricemia were used to define gout, and the data were reanalyzed. The direction of the risk relationship between gout and acute MI remained robust, although the 95% CIs were wide because of the small number of acute MIs in these subgroups.

Sensitivity to statistical modeling assumptions. Even though the correlation coefficients between various cardiac risk factors examined in this study were modest (≤0.20), it is possible that collectively, they could potentially violate the assumptions of independence of covariates. This can potentially skew the risk estimates. We therefore fitted separate instrumental variable probit models for examining the relationship between gout and the risk of acute MI, as described in Subjects and Methods. Gout remained an independent correlate of acute MI (probit coefficient 0.41, $P < 0.001$).

DISCUSSION

This study is the first to show that among men with no previous history of coronary artery disease, gouty arthritis is a significant independent correlate of subsequent acute MI. Confounders such as obesity, diuretic use, aspirin use, renal function, alcohol use, insulin resistance, metabolic syndrome, serum uric acid level, and other traditional risk factors did not account for this association. The absolute magnitude of the relative risk for the presence of gout was not high. Yet, the odds ratio associated with gout was the third largest among categorical variables, after smoking and family history of acute MI. Furthermore, the association was consistent across all analyses.

For acute MI to occur, an environment that promotes atherogenesis and thrombogenesis is needed. Hyperuricemia is well known to be an independent risk factor for atherosclerotic diseases in general (7), and since chronic hyperuricemia is strongly associated with gout, it is not very surprising that an independent coronary risk for the presence of both hyperuricemia and gout was observed. The available pathophysiologic evidence points toward inflammation, the characteristic difference between gout and hyperuricemia, as the likely pathway. Even when there is no active arthritis, the synovial fluid of patients with gout shows low-grade inflammatory activity (21). Inflammation as a pathogenic process has been considered to be the key to coronary artery disease, in both atherogenesis and thrombogenesis (9,22–24). According to this model,

persistent inflammation anywhere in the body can initiate and drive atherosclerosis and promote a prothrombotic environment that can lead to an acute coronary syndrome or stroke, depending on the site involved (9,22,25). Such a persistent inflammatory state is known to be present in rheumatic diseases such as lupus and rheumatoid arthritis, and the association of such diseases with premature atherovascular disease has been well established (26–28).

The link between gout and atherosclerosis has been observed for more than 100 years (1–5,15,29). While the link between acute MI and hyperuricemia has been well known, the link between acute MI and gout has been much less studied. One of the large-scale epidemiologic studies of this link was reported by Abbott et al (10), who used data from the Framingham Heart Study. They observed 37 events among 94 men (39%) with gout unrelated to diuretic use, compared with 509 events in 1,764 men without gout (29%). After risk adjustment, they found an excess risk of ~60% for coronary artery disease among subjects with gout as compared with those without gout (10). In their analyses, the investigators excluded cases of diuretic-induced gout and adjusted for potential confounding by age, systolic blood pressure, total cholesterol level, alcohol intake, BMI, and diabetes mellitus, but no adjustment for the effect of smoking was made. The association was observed only in men and was primarily due to excess cases of angina pectoris.

Another prospective observational study that addressed this question was based on the Meharry and Johns Hopkins Precursors cohorts of male physicians (11). The former group was composed entirely of African American subjects, and the latter group was composed entirely of white subjects. The confounders adjusted for in that analysis were cholesterol level, smoking, BMI, alcohol use, hypertension, and diabetes mellitus. However, the effect of other powerful confounders, such as family history and aspirin use, was not addressed. More importantly, information on uric acid levels, diuretic use, and renal function was not available. The results were contradictory to those of the Framingham Heart Study, with a pooled, risk-adjusted relative risk of 0.59 and a 95% CI ranging from 0.24 to 1.46. That study, however, was underpowered, with just 3 coronary artery disease events among the 31 subjects in the gout group of the Meharry cohort and 4 events in the corresponding group of 62 subjects of the Johns Hopkins Precursors cohort. Furthermore, the study subjects were relatively prosperous physicians, and serum uric acid measurements were not available.

Recently, analysis of 170 cases of gout in a general practice database in The Netherlands (12) showed that the cumulative incidence of cardiovascular disease (a pooled outcome combining angina pectoris, MI, heart failure, cerebrovascular accident, transient ischemic attack, or peripheral vascular disease) was higher in individuals with gout (26%) than in controls matched for age, sex, and physician practice (20%). In a Cox proportional hazards regression model in which hypertension, diabetes mellitus, and hyperlipidemia were adjusted for, the risk associated with gout was 0.98 (95% CI 0.65–1.47). Other confounding factors, such as diuretic use, smoking, family history, aspirin use, etc., were not accounted for in that analysis. Information on serum uric acid levels was also unavailable. Interestingly, the risk estimate for hyperlipidemia (0.56 [95% CI 0.20–1.56]) was lower than that for gout.

There are important correlates of hyperuricemia that merit special consideration as potential confounders. The first, hypertension, is related to hyperuricemia through changes in renal vascular mechanisms (30,31). The second is the use of diuretics, since diuretics are known to be associated with clinically significant elevations in serum uric acid levels. The third is alcohol use; this can raise uric acid levels and can also independently influence the risk of coronary heart disease. As expected, in the MRFIT data, these factors had statistically significant intercorrelations; however, the magnitude of all of these correlations was very small ($\leq$0.20).

The MRFIT examined a very highly selected group of men at high risk of developing coronary artery disease (~3% of those screened). Men at lower risk and those at very high risk were excluded. Therefore, extrapolation of these results to routine clinical practice should be done cautiously. We did not perform time-to-event regression analyses (such as Cox proportional hazards regressions) because the data on gout and hyperuricemia were essentially left censored and because we could not date the occurrence of acute MIs that were detected from EKGs.

Our case definition for gout is less perfect than that used in the clinical practice setting. In the Meharry-Hopkins study, 75% of self-reported cases of gout were verifiable as meeting the American College of Rheumatology preliminary criteria for gout (11,32). Our definition that mandates the presence of persistent hyperuricemia has better face validity and is more conservative than the definition used in both the Framingham Heart

Study and the Hopkins Study. Furthermore, our sensitivity analyses showed that the observed relationship between gout and acute MI is unlikely to be due to misclassification bias.

The traditional cardiac enzymes assayed for the detection of acute MI were the triad of lactate dehydrogenase, aspartate transaminase, and creatine kinase (CK) (33). The new diagnostic criteria include a characteristic rise and fall in blood concentrations of cardiac troponin and/or CK-MB in the context of spontaneous ischemic symptoms or coronary intervention (34). If it is accepted that any myocardial necrosis caused by ischemia constitutes acute MI, many patients who were formerly diagnosed as having unstable angina pectoris will now be diagnosed as having had a small acute MI. The limitations of the new definition of acute MI include the lack of a definition of cardiac arrest, as well as the lack of an acute MI classification in patients who present with characteristic symptoms of acute MI but die within 4–6 hours of symptom onset, a period during which cardiac markers, the EKG, and histologic findings (which take some hours to develop) may be nondiagnostic. The new definition will increase by ~40% the number of patients with non–ST-segment elevation acute coronary syndromes who will be diagnosed as having had an acute MI (35).

Gout is the most common inflammatory arthritis in the US population, accounting for an estimated 3.9 million physician visits in 2002 (36). Even a small magnitude of risk elevation among these individuals can mean substantially higher absolute numbers of acute MI in the general population. We hope that our results will stimulate further research into this area.

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