LONG-TERM CARDIOVASCULAR MORTALITY AMONG MIDDLE-AGED MEN WITH GOUT

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Background: There are limited data available on the association of gouty arthritis (gout) in middle age with long-term cardiovascular disease (CVD) mortality.

Methods: We performed a 17-year follow-up study of 9105 men, aged 41 to 63 years and at above-average risk for coronary heart disease, who were randomized to the Multiple Risk Factor Intervention Trial and who did not die or have clinical or electrocardiographic evidence of coronary artery disease during the 6-year trial. Risk of CVD death and other causes subsequent to the sixth annual examination associated with gout was assessed by means of Cox proportional hazards regressions.

Results: The unadjusted mortality rates from CVD among those with and without gout were 10.3 per 1000 person-years and 8.0 per 1000 person-years, respectively, representing an approximately 30% greater risk. After adjustment for traditional risk factors, use of diuretics and aspirin, and serum creatinine level, the hazard ratio (gout vs no gout) for coronary heart disease mortality was 1.35 (95% confidence interval [CI], 1.06-1.72). The hazard ratio for death from myocardial infarction was 1.35 (95% CI, 0.94-1.93); for death from CVD overall, 1.21 (95% CI, 0.99-1.49); and for death from any cause, 1.09 (95% CI, 1.00-1.19) (P=.04). The association between hyperuricemia and CVD was weak and did not persist when analysis was limited to men with hyperuricemia without a diagnosis of gout.

Conclusion: Among middle-aged men, a diagnosis of gout accompanied by an elevated uric acid level imparts significant independent CVD mortality risk.

Trial Registration: clinicaltrials.gov Identifier: NCT00000487

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GOUTY ARTHRITIS (GOUT) is a common arthritic condition characterized by chronic hyperuricemia with periods of intense inflammatory flares and deposition of monosodium urate crystals in joints and extraarticular tissues. Hyperuricemia is a condition associated with adverse cardiovascular disease (CVD) outcomes1,2 in its own right. People with gout have chronic and sometimes severe hyperuricemia and additionally experience intense inflammatory episodes. The Framingham Heart Study Group found an association between gout, unrelated to diuretic use, and coronary heart disease, primarily angina pectoris. During the intervention phase of the Multiple Risk Factor Intervention Trial (MRFIT), gout was associated with an increased risk of nonfatal acute myocardial infarction (MI) but not with an increased risk of fatal acute MI.3,4 Some of the other studies that attempted to evaluate the association between gout and CVD were too small,5,6 lacked uric acid information,6 selected inappropriate controls,7 or used administrative data with limited data on other CVD risk factors.8 Among larger studies with some form of diagnostic validation, a large study from Taiwan reported a relationship between gout and electrocardiographic evidence of MI.9 The Health Professionals Study reported significant cardiovascular mortality risk for patients with gout; however, information on serum uric acid levels was not studied in that report.10 The present study was undertaken to address the gout-CVD link and to assess the role of hyperuricemia in this link.

STUDY PARTICIPANTS

The present study participated in participants in the MRFIT,1 a randomized controlled trial where the effectiveness of a special intervention program (smoking cessation, cholesterol management through dietary control, and blood pressure control) was tested against the contemporary usual...
peruricemia: a mean serum uric acid concentration over all the visit change in serum uric acid level in the MRFIT cohort, we fully validated against the American College of Rheumatology case definition did not include hyperuricemia but was success-
cations did not ensure a diagnosis of gout, and therefore we or uric acid level (we recognized that prescription of these medi-
preceding the sixth annual visit irrespective of gout diagnosis 
use of 2 alternate case definitions: (1) use of any gout-specific 
tion. While the accuracy of self-reported gout is unlikely to be 
tation of hyperuricemia as defined in the preceding subsec-
that you have gout?”) by adding the requirement for documen-
class criteria. In the Meharry-Hopkins Study of physicians, gout 
death certificate data as follows: from March 1, 1982, through December 31, 1999, vital status was determined by means of the National Death Index. For deaths that occurred through 1990, death certificates were obtained and centrally coded by a trained nosologist using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). From 1991 onward, the National Death Index Plus Service was used to obtain the primary cause of death, according to either ICD-9 or ICD-10. Strategies for determining renal cause of death from mortality data have been detailed elsewhere.6,17 The ICD-9 codes used for all-cardiovascular cause were 390 to 459; for CHD, 410 to 414 and 429.2; and for acute MI, 410. For deaths in 1999, the corresponding ICD-10 codes were 100 to 109 (all cardiovascular), 120 to 125 (CHD), and 121 to 122 (acute MI).

OUTCOMES OF INTEREST

The primary outcome was death from CVD. Secondary outcomes included death from MI, death from coronary heart dis-
disease (CHD), and death from any cause.

MORTALITY OUTCOMES

Standardized protocols13 were used to ascertain cause of death from the death certificate data as follows: from March 1, 1982, through December 31, 1999, vital status was determined by means of the National Death Index. For deaths that occurred through 1990, death certificates were obtained and centrally coded by a trained nosologist using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). From 1991 onward, the National Death Index Plus Service was used to obtain the primary cause of death, according to either ICD-9 or ICD-10. Strategies for determining renal cause of death from mortality data have been detailed elsewhere.6,17 The ICD-9 codes used for all-cardiovascular cause were 390 to 459; for CHD, 410 to 414 and 429.2; and for acute MI, 410. For deaths in 1999, the corresponding ICD-10 codes were 100 to 109 (all cardiovascular), 120 to 125 (CHD), and 121 to 122 (acute MI).

STATISTICAL ANALYSIS

Differences in means and proportions were summarized with unpaired, 2-tailed t tests and Pearson χ² tests. We used Cox proportional hazards regression models, stratified by the 22 clinical centers, for computing unadjusted and adjusted hazard ratios (HRs). Data from men in the usual-care and special-intervention groups were analyzed separately and together.

For multivariate analyses, the following variables were considered: age, systolic and diastolic blood pressure, low-density lipoprotein cholesterol levels, high-density lipoprotein cholesterol levels, plasma triglyceride levels, serum creatinine levels, fasting glucose levels, cigarettes per day, family history of MI assessed at baseline, daily aspirin and diuretic use, alcoholic drinks per day, and body mass index. For risk adjustment in our primary analyses, we used values of the continuous variables (such as blood pressure and body mass index) averaged over all study visits during the trial at which the data were collected.

RESULTS

BASELINE CHARACTERISTICS

Of the 12 866 men originally randomized into the MRFIT, 9105 men aged 41 to 63 years were alive and free of cardio-
vascular and other major conditions and attended the sixth annual examination. The gout-related characteristics of the participants in the 2 treatment groups are shown in Table 1. Consistent with the special-intervention strategy that included diuretics, hyperuricemia was more common among the special-intervention group. Gout medications were also prescribed more often in the special-intervention group than in the usual-care group; however, the percentage of men with gout, as defined in this
Hyperuricemia was defined as a mean serum uric acid level over all visits of 7.0 mg/dL or greater. Gout was defined as at least 1 visit with a self-reported physician diagnosis of gout and a serum uric acid level of 7.0 mg/dL or greater averaged over all visits. Unless specified, values were averaged over trial visits through year 6. The year 6 visit was the designated baseline visit for this study. Gout medications included allopurinol, probenecid, and colchicine.

Table 1. Uric Acid, Hyperuricemia, and Gout in MRFIT Participants by Randomization Groupa

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Participants</th>
<th>Special Intervention</th>
<th>Usual Care</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants</td>
<td>9105</td>
<td>4699</td>
<td>4406</td>
<td></td>
</tr>
<tr>
<td>Uric acid, mg/dL, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>6.8 (1.3)</td>
<td>6.8 (1.3)</td>
<td>6.8 (1.3)</td>
<td>.39</td>
</tr>
<tr>
<td>Average at follow-up</td>
<td>6.8 (1.2)</td>
<td>6.9 (1.2)</td>
<td>6.8 (1.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hyperuricemia, %b</td>
<td>43.9</td>
<td>46.1</td>
<td>41.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hyperuricemia, %c</td>
<td>10.6</td>
<td>10.9</td>
<td>10.3</td>
<td>.41</td>
</tr>
<tr>
<td>Self-reported physician diagnosis of gout, %</td>
<td>9.5</td>
<td>12.4</td>
<td>6.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Gout medications at 1 or more visits, %c</td>
<td>7.2</td>
<td>7.1</td>
<td>7.3</td>
<td>.59</td>
</tr>
<tr>
<td>Gout by this study case definition, %d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: MRFIT, Multiple Risk Factor Intervention Trial. SI conversion factors: To convert uric acid to micromoles per liter, multiply by 0.0113.

SI conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.0259; glucose to millimoles per liter, multiply by 0.0555; triglycerides to millimoles per liter, multiply by 0.1104.

HYPERURICEMIA AND MORTALITY

There were 2752 deaths from all causes during this study period, of which 1241 were attributed to CVD. Table 3 shows the relationship between hyperuricemia and death from MI, CHD, and CVD. For men in the special-intervention and usual-care groups combined, the adjusted HRs for these 3 end points were 1.06 (P = .59), 1.12 (P = .13), and 1.13 (P = .06), respectively. Findings were similar for the usual-care and special-intervention groups.
considered separately. Analyses by quintile of uric acid level were also performed, and these analyses indicated no evidence of a linear trend for any of the outcomes (data not shown).

We also considered the association between hyperuricemia and all-cause mortality, and the adjusted HR was 1.09 (95% confidence interval, 1.00-1.19) ($P = .04$). However, like the other outcomes, there was no evidence of a linear trend with uric acid level ($P = .49$).

**GOUT AND RISK OF MORTALITY**

Table 4 gives mortality rates and HRs for subjects with and without gout. In general, the associations with mortality and our definition of gout were stronger than for hyperuricemia alone.

**SENSITIVITY ANALYSES**

We reanalyzed data by using a second case definition of gout: current or during-trial use of any of the common gout-related medicines such as allopurinol, probenecid, and colchicine regardless of the self-report or serum uric acid concentration. With this definition, there were 974 men with gout. Adjusted HRs for MI, CHD, CVD, and all-cause mortality were 1.31 ($P = .10$), 1.26 ($P = .03$), 1.18 ($P = .08$), and 1.23 ($P < .001$), respectively. Another set of sensitivity analyses examined associations with each component of our gout definition (Table 5). The strongest association was for participants with both hyperuricemia and self-reported gout. Approximately two-thirds of patients with a history of gout also had hyperuricemia. Of those with hyperuricemia, only 16% reported gout. Compared with the group with neither hyperuricemia nor gout, the adjusted HR for CVD mortality was 1.30 ($P = .02$). Corresponding HRs for MI, CHD, and all-cause mortality were 1.40 ($P = .08$), 1.43 ($P = .006$), and 1.22 ($P = .009$).

**COMMENT**

Previous studies have indicated higher rates of angina pectoris and nonfatal acute MI among men with gout.
In this study, we have observed that a diagnosis of gout accompanied by an elevated uric acid level is associated with increased long-term (approximately 17 years) risk of all-cause mortality that arises largely from an increased risk of CVD mortality. Such increased mortality risk was not observed in our earlier study that looked at a much shorter follow-up term (6 years) within the intervention phase of the MRFIT but was observed in the Health Professionals follow-up study. A previous study from Taiwan showed that, among patients with established gout, the risk of acute MI is proportional to disease duration and disease severity as indicated by the presence of tophi.

Uric acid can generate aminocarbonyl radicals that amplify the oxidization of liposomes and low-density lipoprotein cholesterol. Hyperuricemia induces redox-dependent signaling and oxidative stress in adipocytes. Oxidized low-density lipoprotein plays a major role in the development and progression of atherosclerosis. In a study by Tsutsumi et al., serum concentrations of oxidized low-density lipoprotein autoantibodies were significantly higher in patients with gout than in control subjects and were significantly decreased after allopurinol treatment, but not by treatments resulting in increased urinary clearance of uric acid. This observation was independent of the baseline serum concentration of uric acid and total serum antioxidant status, suggesting an independent role for xanthine oxidase, the enzyme inhibited by allopurinol. In epidemiologic studies, hyperuricemia has been observed to be independently associated with coronary artery calcification, a precursor of clinical CVD. The hyperuricemia–CVD events link is attenuated by the effect of diuretics. In our study as well, consistent with high utilization of diuretics, the hyperuricemia-CVD link was weaker than the gout-CVD link.

It is, however, not certain whether hyperuricemia is the mediator in the gout-CVD association. Gout is caused by hyperuricemia, but not everyone with hyperuricemia develops gout. For example, in the 5-year follow-up period of the Normative Aging Study, about 22% of those with a serum uric acid level of 9.0 mg/dL or greater and only 3% of those with a serum uric acid level between 7.0 and 8.9 mg/dL developed gout. This suggests that the presence of hyperuricemia alone is not su-

Table 4. Mortality Risk of Gout: the MRFIT Study

<table>
<thead>
<tr>
<th>Mortality Rate per 1000 Person-years</th>
<th>Cox Regression Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted HR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Death from acute MI</td>
<td></td>
</tr>
<tr>
<td>Special intervention</td>
<td></td>
</tr>
<tr>
<td>No gout</td>
<td>4367</td>
</tr>
<tr>
<td>Gout</td>
<td>332</td>
</tr>
<tr>
<td>Usual care</td>
<td></td>
</tr>
<tr>
<td>No gout</td>
<td>4083</td>
</tr>
<tr>
<td>Gout</td>
<td>323</td>
</tr>
<tr>
<td>All participants</td>
<td></td>
</tr>
<tr>
<td>No gout</td>
<td>8450</td>
</tr>
<tr>
<td>Gout</td>
<td>655</td>
</tr>
<tr>
<td>Death from CHD</td>
<td></td>
</tr>
<tr>
<td>Special intervention</td>
<td></td>
</tr>
<tr>
<td>No gout</td>
<td>4367</td>
</tr>
<tr>
<td>Gout</td>
<td>332</td>
</tr>
<tr>
<td>Usual care</td>
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<td>323</td>
</tr>
<tr>
<td>All participants</td>
<td></td>
</tr>
<tr>
<td>No gout</td>
<td>8450</td>
</tr>
<tr>
<td>Gout</td>
<td>655</td>
</tr>
<tr>
<td>Death from any cardiovascular end point</td>
<td></td>
</tr>
<tr>
<td>Special intervention</td>
<td></td>
</tr>
<tr>
<td>No gout</td>
<td>4367</td>
</tr>
<tr>
<td>Gout</td>
<td>332</td>
</tr>
<tr>
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<td>Gout</td>
<td>323</td>
</tr>
<tr>
<td>All participants</td>
<td></td>
</tr>
<tr>
<td>No gout</td>
<td>8450</td>
</tr>
<tr>
<td>Gout</td>
<td>655</td>
</tr>
</tbody>
</table>

Abbreviations: CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; MRFIT, Multiple Risk Factor Intervention Trial.

*Restricted to those who did not have a nonfatal cardiovascular disease event through year 6. Gout was defined as at least 1 visit with a self-reported physician diagnosis of gout and a serum uric acid level of 7.0 mg/dL or greater (to convert to micromoles per liter, multiply by 59.48) averaged over all 6 annual study visits.

*Adjusted for clinical center, age, systolic blood pressure, diastolic blood pressure, low- and high-density lipoprotein cholesterol levels, plasma triglyceride level, serum creatinine level, fasting glucose level, cigarettes per day, family history of acute myocardial infarction, daily aspirin use at year 6, diuretic use at year 6, alcoholic drinks per day, and body mass index. Unless specified, covariates were averaged over trial visits through year 6.
flammation in these individuals.33
is also evidence of ongoing, subclinical intra-articular in-
flammation in acute gout flare has received scrutiny,34
leagues29 examined this hypothesis in a cohort of 957 people
gout, and atherosclerosis. When Ruggerio and col-
nistic pathway for the link between serum uric acid level,
raises the possibility that inflammation might be a mecha-

in other population-based studies30 and hospital-based stud-
neutrophil count, increased with increasing levels of se-
flammation, such as C-reactive protein, interleukin 6, and
in the general population, they found that markers of in-
flammatory activity.33 Although the mechanism of joint
inflammation, such as C-reactive protein, interleukin 6, and
neutrophil count, increased with increasing levels of se-
rum uric acid. Observations such as this have been made
in other population-based studies30 and hospital-based stud-
ies.31,32 Locally, even when there is no active arthritis, the
synovial fluid of patients with gout shows low-grade in-
flammatory activity.33 Although the mechanism of joint
inflammation in acute gout flare has received scrutiny,34
few data are available on the presence or absence of sys-
temic inflammation, especially in the period between gout
attacks. During periods of gout flares, monosodium urate
crystals induce secretion of tumor necrosis factor-α, in-
terleukin 1β, and interleukin 6 from monocytes.34 There
is also evidence of ongoing, subclinical intra-articular in-
flammation in these individuals.33

The results presented in this report should be inter-
preted with a few caveats. First, we did not have infor-
mation on the risk factor status of individuals after the
end of the intervention phase of the study, and individu-
als could have changed their lifestyle behaviors. This could
potentially influence associations between gout and long-
term mortality, but the nature of the effect is not likely
to be great unless there was a systematic adoption of
healthier lifestyles by either those with gout or those with-
out gout. The study was performed in men who are at
high risk for CHD, and so extrapolation of these results
to the general population should be done cautiously. It
is unknown whether these results are applicable to
women. Data on uric acid levels, gout medications, as-
pirin use, and other potential correlates of cardiovascu-
mortality were not available after the baseline visit for
this study. Finally, despite our sensitivity analyses, po-
tential misclassification errors remain.

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edu).

Author Contributions: Dr Neaton (principal investi-
gator), and Messrs Svendsen and Grandits had full access
to all of the data in the study and take responsibility for
the integrity of the data and the accuracy of the data analy-
sis. Study concept and design: Krishnan. Acquisition of data:
Neaton and Kuller. Analysis and interpretation of data:
Krishnan, Svendsen, Neaton, Grandits, and Kuller. Draft-
ing of the manuscript: Krishnan and Neaton. Critical re-
vision of the manuscript for important intellectual content:
Svendsen, Grandits, and Kuller. Statistical analysis:
Krishnan, Svendsen, Neaton, and Grandits. Obtained fund-
ing: Neaton and Kuller. Administrative, technical, and ma-
terial support: Svendsen, Neaton, Grandits, and Kuller.
Study supervision: Neaton and Kuller.

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ucts Inc and serves on its scientific advisory board. He also
holds stock in Savient Pharmaceutical Products Inc. None
of these companies’ products are discussed in this article.

Table 5. MRFIT Mortality Rates by Hyperuricemia Alone, Self-reported Gout Alone, and Study-Defined Gout

<table>
<thead>
<tr>
<th>Mortality Rate/1000 Person-years</th>
<th>Cox-Regression Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted HR (95% CI)</td>
</tr>
<tr>
<td>Death from acute myocardial infarction</td>
<td></td>
</tr>
<tr>
<td>No hyperuricemia or self-reported gout</td>
<td>4798 179 2.2</td>
</tr>
<tr>
<td>Hyperuricemia alone</td>
<td>3343 129 2.3</td>
</tr>
<tr>
<td>Self-reported gout alone</td>
<td>309 16 3.3</td>
</tr>
<tr>
<td>Both hyperuricemia and self-reported gout</td>
<td>655 36 3.4</td>
</tr>
<tr>
<td>Death from coronary heart disease</td>
<td></td>
</tr>
<tr>
<td>No hyperuricemia or self-reported gout</td>
<td>4798 418 5.2</td>
</tr>
<tr>
<td>Hyperuricemia alone</td>
<td>3343 302 5.4</td>
</tr>
<tr>
<td>Self-reported gout alone</td>
<td>309 35 7.2</td>
</tr>
<tr>
<td>Both hyperuricemia and self-reported gout</td>
<td>655 78 7.3</td>
</tr>
<tr>
<td>Death from any cardiovascular disease</td>
<td></td>
</tr>
<tr>
<td>No hyperuricemia or self-reported gout</td>
<td>4798 612 7.7</td>
</tr>
<tr>
<td>Hyperuricemia alone</td>
<td>3343 470 8.4</td>
</tr>
<tr>
<td>Self-reported gout alone</td>
<td>309 49 10</td>
</tr>
<tr>
<td>Both hyperuricemia and self-reported gout</td>
<td>655 110 10.3</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio; MRFIT, Multiple Risk Factor Intervention Trial.

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