Gout and the risk for incident heart failure and systolic dysfunction

Eswar Krishnan

ABSTRACT

Objective: To test the hypothesis that gouty arthritis (gout) is a risk factor for incidence of heart failure and for echocardiographic measures signifying subclinical heart failure.

Design: Post-hoc, longitudinal and cross-sectional analyses of a prospective cohort study where data were collected in 4-year intervals since 1971.

Settings: The population-based Framingham Offspring Study.

Participants: 4989 adults (mean age 36 years, 52% women) free of clinical heart failure at baseline.

Outcome measures: Incident heart failure, echocardiographic measures of left ventricular systolic dysfunction, dilatation and hypertrophy.

Results: Participants with gout (n = 228) had two to three times higher incidence of clinical heart failure and echocardiographic measures of systolic dysfunction compared with those without. In Cox regression analyses, gout was associated with an adjusted HR of 1.74 (95% CI 1.03 to 2.93) for incident heart failure and RR of 3.70 (95% CI 1.68 to 8.16) for abnormal left ventricular ejection fraction and of 3.60 (95% CI 1.80 to 7.72) for global left ventricle systolic dysfunction. These risk relationships were consistently observed in all clinical subgroups. Overall, participants with gout had greater mortality than those without (adjusted HR 1.58, 95% CI 1.40 to 1.78). Mortality was elevated in subgroup of patients with gout and heart failure (adjusted HR 1.50, 95% CI 1.30 to 1.73) compared to those with heart failure but without gout.

Conclusion: Gout is associated with increased risk for clinical heart failure, subclinical measures of systolic dysfunction and mortality.

INTRODUCTION

Heart failure is a major public health problem in the USA; about 5 million US adults suffer from heart failure with an annual incidence of approximately 550,000.1 Heart failure is associated with a high risk of morbidity, mortality and hospital utilisation.2 The major risk factors amenable to intervention are obesity, hyperlipidaemia, hypertension, diabetes, alcohol abuse and smoking.3 A common antecedent for heart failure, atherosclerosis, is also an independent risk factor for gouty arthritis (gout).4–8 Patients with gout often use medications such as xanthine oxidase inhibitors and non-steroidal anti-inflammatory drug that can decrease or increase the risk for heart failure, respectively.9–13 I hypothesised that patients with gout will have a greater risk for clinical heart failure than would be expected from their risk profile. Gout affects over 3.5 million Americans annually.9 Hyperuricaemia is necessary but not sufficient for development of gout.14 15 Gouty arthritis is characterised by periods of intense inflammatory response with lower grade systemic inflammation in the period between acute attacks.16 I prospectively analysed the independent relationship between gout, left ventricular systolic function and incident heart failure in participants in the Framingham Offspring Study (FOS) Cohort. In addition, I sought to study the link between gout and all-cause mortality in the entire cohort and among those who developed heart failure. Being of observational design and consequent inability to account for treatment allocation bias, the analysis of relationship between gout medications such as allopurinol and the risk of heart failure was not included within the scope of the present study.
Clinical heart failure and mortality

Outcomes

Clinical Heart failure and mortality

Incidence of heart failure was assessed by questionnaires and by physician interview at the time of follow-up visits. Clinical heart failure and cause of death data were determined predetermined criteria, included in box 1.19 20 Specifically, the simultaneous presence of either two major or one major plus two minor criteria, in the absence of an alternative explanation for the symptoms and signs, was required to make the diagnosis of heart failure. Major criteria included the following: paroxysmal nocturnal dyspnoea, orthopnoea, jugular venous distension, hepatojugular reflux, pulmonary rales, radiographic evidence of cardiomegaly, acute pulmonary oedema, third heart sound, central venous pressure above 16 cm of water and weight loss >4.5 kg during the first 5 days of treatment for suspected heart failure. Minor criteria included the following: bilateral ankle oedema, nocturnal cough, dyspnoea on ordinary exertion, hepatomegaly, pleural effusion and heart rate >120 bpm. Hospital and outpatient records were reviewed by a panel of three physicians for adjudication of the heart failure outcomes. There were no participants with heart failure at baseline.

Mortality data were available through the follow-up cut-off date. These included death certificates and the final hospitalisation record where applicable. Information on clinical heart failure was validated by medical chart review. I used all-cause mortality data for our analyses as there was not sufficient power to analyse by individual causes of death.

Echocardiographic measures of left ventricle

Echocardiographic evaluation was performed on all the available participants at visit 6 (~ year 24; n=2337). Routine transthoracic cardiac echocardiograms with Doppler colour-flow imaging were performed using a Sonos 1000 Hewlett-Packard machine (Andover, Massachusetts, USA).21 M-mode measurements of left ventricle (LV) dimensions were performed by a leading edge to leading edge technique according to the American Society of Echocardiography guidelines.18 22 Details of echocardiographic measurements including LV mass, LV end-diastolic internal dimensions, LV wall thickness and fractional shortening have been published.23 Only those echocardiograms deemed to be of fair or good quality were included in the present analysis. Echocardiographic metrics were treated as continuous and as dichotomous (no abnormality/any abnormality) measures. A validated formula was used to determine LV mass.22–24 LV wall thickness was calculated by adding together the diastolic thicknesses of the septum and the posterior wall.23 LV systolic dysfunction was defined as a fractional shortening of <0.29.25 In addition, two-dimensional echocardiography was globally assessed by the FOS physician for abnormal ejection fraction and evidence of mild or greater systolic dysfunction as assessed by visual assessment in multiple views.25

Assessment of gout

Gout was defined as a study physician diagnosis and/or use of allopurinol and other gout medications such as probenecid and colchicine definite gouty arthritis.26 This case definition is known to have high degree of reliability,24 validated using medical records in two large epidemiological studies.24 27

Other risk factors of heart failure

Information on obesity measures, blood pressure, serum lipids, serum glucose, smoking and use of alcohol, 

METHODS

Study cohort and data source and design

The FOS is a longitudinal observational cohort assembled in 1971 and includes 5124 men and women who are the offspring of the Framingham Heart Study Cohort and their spouses.17 All participants provided informed consent. This study used de-identified data from the FOS obtained through the National Heart, Lung and Blood Institute Limited Access Program that excluded those who did not provide consent for such data sharing and those with unique characteristics that were deemed to be identifiable (n=4989). These individuals were observed over time by periodic examinations approximately 4 years apart; the latest cycle of data collection being in 2008. Data from the medical review, physical examinations and laboratory testing were used for the present analysis. This study is registered at http://clinicaltrials.gov (NCT00005121).

Outcomes

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aspirin, antihypertensive medication and anti-diabetic medication were collected. Hypertension and diabetes mellitus were defined as per standard criteria and by the utilisation of relevant medication. For the purpose of this study, participants with a cardiac murmur at the time of the first study visit were assessed to have valvular heart disease. These data were validated by medical record review.

Participants were evaluated for coronary artery disease at baseline and at subsequent visits by medical history, clinician assessment and electrocardiogram.

Medications
For all medications, current use and past (without specification of time interval) were assessed at the time of the study visits. Information on current use was used for the present study. For our analyses, details of individuals’ antihypertensive and diabetes therapy, such as the specific drug, dosage and duration of treatment, were not available.

Renal function
Based on history and laboratory examination, study physician and staff determined the presence or absence of renal dysfunction. Serum creatinine or other laboratory measures of renal function was not available for the present analysis.

Statistical analysis
There were three main components for the statistical analysis plan: these included a cohort analysis of gout as a risk factor for heart failure, a longitudinal mortality analysis that assessed the links between gout, heart failure and mortality and finally a cross-sectional analysis of visit 6 data that compared the echocardiographic metrics of those with and without gout. Wherever applicable, all covariates were used as time varying covariates whereby the values of these measures were updated by visits in the statistical models.

Longitudinal analyses for incident heart failure
Longitudinal data analyses addressed the question of whether gouty arthritis was a risk factor for heart failure. In these analyses, I used Cox proportional hazards regression models where observation time started at baseline or at the time of incident gout and ended on the earliest of the date of incidence of clinical heart failure. Observations were censored at the last available time point in the case of death or loss to follow-up. The Cox model was chosen for heart failure incidence analyses since preliminary examination of the data confirmed the proportionality assumption. The covariates used were selected based on whether they were known risk factors of heart failure: age, body mass index and total cholesterol/high-density lipoprotein ratio as continuous variables and hypertension, body mass index, renal dysfunction, diabetes, alcohol use and smoking as categorical variables.

Longitudinal analyses for mortality risk
These analyses used Poisson regression models where covariates of interest were presence or absence of gouty arthritis; variables adjusted were as above. Cox models were not fitted as the proportionality assumptions were not consistently met.

Cross-sectional analyses for echocardiographic data
For analyses of echocardiographic data, I used cross-sectional analysis methods as these data were obtained only on visit 6. Ordinary least squared regression models were used to compute adjusted mean echocardiographic measures such as left ventricular thickness. Logistic regression models were used to adjusted estimate proportion of participants with gout and without gout with evidence of left ventricular systolic dysfunction and low ejection fraction. A Poisson approach was used to calculate RRs of dichotomous echocardiographic measures. These RR estimates are more conservative (smaller magnitude) than would be expected from OR estimates using logistic regression models. This study was unsponsored. EK possesses raw data, analysis code and will be the guarantor of the scientific integrity of this work. All analyses were performed using STATA (Release 11).

RESULTS
Heart failure incidence
Data were available for 4989 FOS participants (figure 1). Table 1 summarises baseline characteristics of the analysis groups used for longitudinal and cross-sectional analyses. None of the participants had heart failure, renal dysfunction or coronary artery disease at the baseline visit. There were 157 individuals who used allopurinol during the course of follow-up; none of these patients developed heart failure and hence effects of allopurinol on heart failure could not be analysed. Table 2 compares the baseline characteristics of participants with gout and without gout within the cohort.

Overall heart failure incidence
The total observation time was 135 991 person-years. The median follow-up time was 13.9 years (IQR 8.1–24.0). Overall, there were 292 incident cases of heart failure. Of these, 187 were associated with hospitalisation and 15 were diagnosed and treated in the inpatient settings. The overall incidence rate (95% CI) was 1.5 (95% CI 1.29 to 1.70) per 1000 person-years. The rates among men and women were 2.2 (95% CI 1.89 to 2.62) and 0.81 (95% CI 0.62 to 1.04), respectively.

Incidence among participants with gout
Among those with gout, the incidence of heart failure was 3.5 (95% CI 2.30 to 5.32) per 1000 person-years. Among men, there were 19 incident cases and among women, there were three. There were no statistically significant differences in incidence rates between men (3.6, 95% CI 2.3 to 5.6) and women (3.0, 95% CI 1.0 to 9.2). Since the number of women with gout and heart
failure were so few, meaningful statistical adjustment in multivariable regressions was not possible and the data were combined for both the genders.

**Figure 1** Flow diagram of participants and measurements in the present study. Data from 135 participants were not available either because the characteristics are so unique as to jeopardise de-identification process used in the Limited Access Program or they preferred the data not to be shared with non-Framingham Offspring Study Investigators.

### Table 1 Characteristics of participants included in the analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>For longitudinal analyses of incident heart failure; assessed at the first visit</th>
<th>For cross-sectional analyses of echocardiographic measures of systolic dysfunction; assessed at visit 6 unless otherwise specified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>4989</td>
<td>2336</td>
</tr>
<tr>
<td>Age in years</td>
<td>36 ± 10</td>
<td>57 ± 10</td>
</tr>
<tr>
<td>Proportion of men (%)</td>
<td>46</td>
<td>45</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25 ± 4.3</td>
<td>27.0 ± 4.3</td>
</tr>
<tr>
<td>Any current alcohol use (%)</td>
<td>85</td>
<td>62</td>
</tr>
<tr>
<td>Proportion of current smokers</td>
<td>63</td>
<td>14.3</td>
</tr>
<tr>
<td>Current diuretic users (%)</td>
<td>3.2</td>
<td>7.3</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>120 ± 15</td>
<td>126 ± 18</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>78 ± 10</td>
<td>74 ± 9</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>94 ± 22</td>
<td>101 ± 25</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>195 ± 39</td>
<td>206 ± 39</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>124 ± 35</td>
<td>130 ± 36</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>51 ± 15</td>
<td>52 ± 16</td>
</tr>
<tr>
<td>Total cholesterol/HDL cholesterol ratio</td>
<td>4.2 ± 1.6</td>
<td>1.7 ± 0.4</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>91 ± 80</td>
<td>134 ± 100</td>
</tr>
<tr>
<td>Serum urate at visit 1 (mg/dl)</td>
<td>5.3 ± 1.3</td>
<td>5.2 ± 1.3</td>
</tr>
<tr>
<td>Renal disease/dysfunction (%)</td>
<td>3.8</td>
<td>3.08</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>1.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Valvular heart disease (%)</td>
<td>7.3</td>
<td>8.1</td>
</tr>
<tr>
<td>Current antihypertensive therapy (%)</td>
<td>2.4</td>
<td>24.3</td>
</tr>
<tr>
<td>Gout anytime during study (%)</td>
<td>4.6</td>
<td>4.1</td>
</tr>
</tbody>
</table>

*Valvular heart disease was defined for this study as presence of cardiac murmur at baseline. Gout was determined based on physician diagnosis and/or gout medication use. Hypertension was defined as per JNC 7 guidelines and/or use of antihypertensive medications. Diabetes was defined as per the American Diabetes Association criteria or use of anti-diabetes medications. Renal disease was assessed by study physician based on history and study laboratory examination. HDL, high-density lipoprotein; LDL, low-density lipoprotein.*
Gout and left ventricular dysfunction

At visit 6, 2237 participants had not developed heart failure and had echocardiograms of acceptable quality available for our analysis. The baseline characteristics of these individuals indicated better health status compared with those who entered the cohort at baseline but did not obtain echocardiogram due to attrition or death (table 1). Those with gout had thicker, wider and heavier LVs and had worse indices of LV function after adjustment of covariates (table 3). For the Poisson regression models where the global assessment of LV function was the dependent variable and gout along with the covariates described in table 4 were the independent variables, patients with gout had a RR of 3.60 (95% CI 1.80 to 7.18) for systolic dysfunction and a RR of 3.70 (95% CI 1.68 to 8.16) for low ejection fraction.

Mortality analyses of the heart failure group

Out of the 22 participants in the gout group who developed heart failure, 16 (73%) died, whereas among the 178 participants with heart failure but no gout, 109 (61%) died. Within the gout group, incidence heart failure was associated with substantially higher mortality rate at 95/1000 person-years compared with those without heart failure 8/1000 person-years. Gout was associated with higher mortality rates in unadjusted and adjusted analyses, and this was statistically significant. The magnitude of excess mortality risk associated with gout was not modified by the presence or absence of heart failure.

DISCUSSION

Our analysis of data collected on FOS participants indicates that gout is an independent risk factor for subclinical myocardial dysfunction, incident heart failure and mortality after incidence of heart failure.
This study adds to the growing body of evidence suggesting that gout has major consequences on the cardiovascular system. The cohort studied was large, events were numerous enough for meaningful analyses and the subclinical, clinical and mortality outcomes were well defined. Nevertheless, it is important to keep in mind that data characteristics of FOS could have affected generalisability of our results and conclusions. Our risk estimates may be an underestimate of the true underlying risk for gout since I included allopurinol (a drug with beneficial effect on myocardial systolic function) use as a case definition and since there were no heart failure events among those who took allopurinol. Misclassification of gout diagnosis would have introduced measurement error and reduced the power of this study, that is, type 2 error. There is a concern for residual confounding by factors that were not measured such as the impact of non-steroidal anti-inflammatory drugs often used by patients with gout. Some of the excess risk I observed could be attributed to this class of drugs and not to gout per se. In studies that span 3 decades, competing risks for morbidity and mortality and consequent survivor effects are inevitable. Another important data limitation was that urate levels were measured only in the first two visits and the relative importance of urate and gout could not be assessed. Lastly, information on the duration and severity of gout was not available.

The gout—mortality association I have documented is consistent with prior observations. Studies using data from administrative databases have suggested that among patients with pre-existing heart failure, active gout is associated with 50%—100% excess risk for poor outcomes such as hospitalisation and death. Tissue hypoxia—a hallmark of heart failure—is a stimulus for

<table>
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<tr>
<th>Table 3</th>
<th>Echocardiographic characteristics at the Framingham Offspring Study visit 6 (N=2337)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Echocardiographic measure</strong></td>
<td><strong>Adjusted for age and body mass index</strong></td>
</tr>
<tr>
<td></td>
<td>Gout</td>
</tr>
<tr>
<td>Mean LV thickness (cm)</td>
<td>2.02</td>
</tr>
<tr>
<td>Mean LV fractional shortening (range 0–1)</td>
<td>0.35</td>
</tr>
<tr>
<td>Mean LV diastolic internal dimension (cm)</td>
<td>5.00</td>
</tr>
<tr>
<td>Mean LV mass (g)</td>
<td>188.51</td>
</tr>
<tr>
<td>Proportion of participants with systolic dysfunction (%)*</td>
<td>12.7</td>
</tr>
<tr>
<td>Proportion of participants with low ejection fraction (%)*</td>
<td>7.7</td>
</tr>
</tbody>
</table>

Hypertension was defined as per JNC 7 guidelines and/or use of antihypertensive medications. Diabetes was defined using the American Diabetes Association criteria or use of anti-diabetes medications.

*Two-dimensional echocardiography was globally assessed by study physician for abnormal ejection fraction and evidence of mild or greater systolic dysfunction as assessed by visual assessment in multiple views.

HDL, high-density lipoprotein; LV, left ventricle.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Mortality analyses by gout and heart failure status in the Framingham Offspring Study using Poisson regressions (n=4989)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of observations in the model</strong></td>
<td><strong>RR for death (95% CI)</strong></td>
</tr>
<tr>
<td><strong>Unadjusted estimates</strong></td>
<td></td>
</tr>
<tr>
<td>Heart failure vs no heart failure</td>
<td>32267</td>
</tr>
<tr>
<td>Gout vs no gout</td>
<td>32267</td>
</tr>
<tr>
<td>Gout vs no gout among those without heart failure</td>
<td>30774</td>
</tr>
<tr>
<td>Gout vs no gout among those with heart failure</td>
<td>1493</td>
</tr>
<tr>
<td><strong>Adjusted estimates</strong>*</td>
<td></td>
</tr>
<tr>
<td>Heart failure vs no heart failure</td>
<td>27209</td>
</tr>
<tr>
<td>Gout vs no gout</td>
<td>27209</td>
</tr>
<tr>
<td>Gout vs no gout among those without heart failure</td>
<td>26073</td>
</tr>
<tr>
<td>Gout vs no gout among those with heart failure</td>
<td>1136</td>
</tr>
</tbody>
</table>

*Adjusted for age, body mass index and total cholesterol/high-density lipoprotein ratio as continuous variables and hypertension, body mass index, renal dysfunction, diabetes, alcohol use and smoking as categorical variables.
the production of urate\textsuperscript{32}; among those with heart failure, serum urate concentrations are inversely correlated with maximal oxygen uptake and functional status.\textsuperscript{33} Serum urate levels correlate well with circulating markers of inflammation and with oxidative stress in patients with chronic heart failure.\textsuperscript{33} Indeed, there is an inverse relationship between serum urate concentrations and peripheral blood flow in patients with chronic heart failure.\textsuperscript{35} Serum urate levels can predict mortality in patients with chronic heart failure.\textsuperscript{36} 37 In our study, urate was measured only in first two visits.

The pathophysiological pathways that link gout and myocardial dysfunction are unclear. The two major categories of heart failure are those caused by hypertension and those caused by atherosclerotic coronary artery disease. This study cannot assess the relative contributions of such pathways as the risk factors that cause atherosclerotic heart disease are collinear with those for heart failure. Furthermore, gout is known to be associated with both of these intermediate steps to heart failure.\textsuperscript{38} Hyperuricaemia has been linked to incident heart failure.\textsuperscript{39} Increased serum acid levels may contribute to the echocardiographic abnormalities associated with heart failure through effects on endothelial function and inflammation. In a small study in patients with chronic heart failure (n = 55), the concentration of serum uric acid was an independent predictor of the inflammation markers intracellular adhesion molecule 1, tumour necrosis factor, soluble tumour necrosis factor receptors and interleukin 6.\textsuperscript{34} The National Health and Nutrition Survey conducted in former West Germany also showed an association between serum uric acid concentration and C reactive protein.\textsuperscript{40} Uric acid can inhibit nitric oxide production by vascular endothelial cells and their proliferation and migration.\textsuperscript{41} Another possibility is that the link might be mediated through hypertension. In an analysis of Framingham Study participants who did not have hypertension, myocardial infarction, heart failure, renal failure or gout at baseline, serum uric acid levels were an independent predictor of hypertension and progression to a higher blood pressure stage.\textsuperscript{42} Finally, the renin–angiotensin system has been proposed to cause left ventricular hypertrophy and cardiac fibrosis through mechanisms including blood pressure increase, direct action of angiotensin II on cardiac myocytes and effects of aldosterone.\textsuperscript{43} Data on these biological factors are not available for the present study but they merit a separate follow-up study. Furthermore, our study cannot assess the specific pathways that link gout and heart failure, such as hypertension, atherosclerotic cardiovascular diseases, drugs, such as anti-inflammatory drugs, and renal dysfunction. I was also unable to tease out the role of serum urate in gout–heart failure link as it was measured only in the first two cycles.

Heart failure is a major health problem in terms of morbidity, mortality and costs. This study provides yet another potentially modifiable risk factor for heart failure. Future studies will need to examine the relationship between gout severity and heart failure. There have been numerous studies that have reported a favourable effect of the gout medication allopurinol (and its metabolite oxypurinol) on endothelial and myocardial function among those with hyperuricaemia.\textsuperscript{11} These molecules have been associated with improved endothelial function in patients with hypercholesterolaemia,\textsuperscript{44} type 2 diabetes with mild hypertension,\textsuperscript{45} or chronic heart failure.\textsuperscript{12} Some studies have shown an improvement in both LV hypertrophy and endothelial function due to treatment with allopurinol.\textsuperscript{47} 48 Other studies have reported improvements in clinical outcomes of heart failure among patients with hyperuricaemia upon allopurinol treatment.\textsuperscript{11} 49 50 Interventional studies might be able to assess whether allopurinol use can reduce the incidence of heart failure and subsequent poor outcomes.

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Competing interests EK has received honoraria, research grants, ad-board fees or consulting fees from the following entities: Ardea Biosciences, UCB, Inc., Centocor OrthoBiotech, URL Pharma, Metabolex, Takeda Pharmaceuticals and Savient Pharmaceuticals. In the past 5 years, he has held common stocks of Savient Pharmaceuticals. This manuscript does not discuss any proprietary products manufactured by these companies.

Contributors This study was unsponsored. EK possesses raw data, analysis code and will be the guarantor of the scientific integrity of this work.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement I am unable to share data due to data sharing agreements in place with the National Heart, Lung and Blood Institute.

REFERENCES


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