GOUTY ARTHRITIS, SYSTOLIC DYSFUNCTION AND HEART FAILURE: RESULTS FROM A 30-YEAR PROSPECTIVE COHORT STUDY

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2011-000282
Article Type:	Research
Date Submitted by the Author:	29-Jul-2011
Complete List of Authors:	KRISHNAN, ESWAR; Stanford University, Medicine/Rheumatology
Primary Subject Heading:	Rheumatology
Keywords:	Heart failure < CARDIOLOGY, gout, risk factor

STROBE checklist for "Gouty arthritis, systolic dysfunction and heart failure: results from a 30-year prospective study", Krishnan E

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-6*
Bias	9	Describe any efforts to address potential sources of bias	5-6
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	6-7

		(*d*) If applicable, explain how loss to follow-up was addressed	6-7
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7-9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	**Table** 1 and page 8
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	7-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7-9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	3,10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

GOUTY ARTHRITIS, SYSTOLIC DYSFUNCTION AND HEART FAILURE: RESULTS FROM A 30-YEAR PROSPECTIVE COHORT STUDY

Brief title: Gout and heart failure

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Abstract: 225

Total word count: 2,501

Tables: 5

Figure: 1

References: 50

Journal Subject Codes:

[11] Other heart failure, [8] epidemiology

Abstract

Objective: Gout, one of the most common types of inflammatory arthritis, is associated with premature development of coronary artery disease. It is not known if gout is an antecedent to subclinical or incident heart failure-a question addressed in this study.

Design: Prospective observational study**.** Using Cox, Poisson and generalized linear models, we prospectively analyzed the independent relationship between gout, incident heart failure and mortality in participants in the Framingham Offspring Cohort (n= 4,989, mean age 36 years, 52% female). In a subset of 2,337 participants, we cross sectionally studied the relationship between gout and echocardiographic assessment of systolic dysfunction.

Results: Participants with gout (n=229) 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 hazard ratio of 1.74 (1.03-2.93) for incident heart failure and relative risks of 3.70 (1.68-8.16) for abnormally low left ventricular ejection fraction and of 3.60 (1.80-7.72) 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 hazard ratio 1.58; 1.40-1.78). Mortality was elevated in subgroup of patients with gout and heart failure (1.50; 1.301.73).

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

Clinical trial registration: NCT00005121

Key Words: heart failure, hyperuricemia, left ventricular systolic dysfunction, uric acid, risk, gout

Article Summary

Article focus

- Gout is a common inflammatory arthritis that is a risk factor for cardiovascular disease in general
- We hypothesized that gout is a specific risk factor for heart failure

Key messages

- Gout is an independent risk factor for incident heart failure
- Among those with heart failure gout increases the case fatality

Limitations

- This study does not address the pathophysiological pathways that link gout to heart failure.
- The impact of gout treatment on heart failure risk cannot be assessed.

Funding Statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing Interests

Dr. Krishnan has consultant/advisor/grant-recipient relationships with Takeda Pharmaceuticals International Inc. (Deerfield, IL). In the past Dr. Krishnan has been a shareholder of Savient Pharmaceuticals and currently holds common stock of Savient Pharmaceuticals. Dr. Krishnan is an investigator for a clinical trial performed by ARDEA, Inc. Dr. Krishnan serves on advisory boards for Takeda, URL Pharma, and UCB LLC. This manuscript does not discuss any proprietary products manufactured by these companies.

INTRODUCTION

Heart failure is a major public health problem in the United States; 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 utilization.(2) The major risk factors amenable to intervention are obesity, hyperlipidemia, hypertension, diabetes, alcohol abuse and smoking.(3) A common antecedent for heart failure, atherosclerosis, is also an independent risk factor for gouty arthritis (gout).(4-7) 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.(8-12) We hypothesized 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.(8) Hyperuricemia is necessary but not sufficient for development of gout.(13, 14) Gouty arthritis is characterized by periods of intense inflammatory response with lower grade systemic inflammation in the period between acute attacks.(15) We prospectively analyzed the independent relationship between gout, left ventricular systolic function and incident heart failure in participants in the Framingham Offspring Study (FOS) Cohort. In addition we 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.

METHODS

Study cohort and data source and design

The FOS is a longitudinal observational cohort assembled in 1971 and includes 5,124 men and women who are the offspring of the Framingham Heart Study Cohort and their spouses. (16)

All participants provided informed consent. This study used deidentifed 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=4,989). 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 in the present analysis.

Outcome assessment

Mortality data were available through the follow up cut-off date. These included death certificates and the final hospitalization record where applicable. Information on clinical heart failure was validated by medical chart review. Clinical heart failure and cause of death data was determined by a study physician panel based on predetermined criteria .(17) (18) Both incident and subsequent exacerbations of heart failure were assessed. There were no participants with heart failure at baseline.

Echocardiographic evaluation was performed on all the available participants at visit 6 (~ year 24; n=2,337). Routine transthoracic cardiac echocardiograms with Doppler color-flow imaging were performed using a Sonos 1000 Hewlett-Packard machine (Andover, MA). (19) 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.(20, 21) Details of echocardiographic measurements including LV mass, LV end-diastolic internal dimensions, LV wall thickness and fractional shortening have been published.(22) 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.(20),[22,25] LV wall thickness was calculated by

adding together the diastolic thicknesses of the septum and the posterior wall.(22) LV systolic dysfunction was defined as a fractional shortening of less than 0.29.(23) 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.(23)

Measurement of covariates

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(24). This case definition is known to have high degree of reliability, (25) validated using medical records in two large epidemiological studies.(26, 27) Information on renal dysfunction, obesity measures, blood pressure, serum lipids, serum glucose, smoking and use of alcohol, aspirin, anti-hypertensive medication and anti-diabetic medication were collected. Serum creatinine or other laboratory measures of renal function was not available for the present analysis. For our analyses, details of individuals' anti-hypertensive and diabetes medications, such as the specific drug, dosage, and duration of treatment were not available. Participants were evaluated for coronary artery disease at baseline and at subsequent visits by medical history, clinician assessment and electrocardiogram. The determination of renal function at baseline was made by the study physician. Hypertension and diabetes mellitus was defined per standard criteria and by the utilization of relevant medication. (28, 29) 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.

Statistical analysis

We performed a cohort analysis for incident heart failure outcomes and cross sectional analyses for echocardiographic outcomes among those who did not develop clinical heart failure

during the study observation period. Longitudinal data analyses addressed the question of whether gouty arthritis was a risk factor for heart failure. In these analyses we 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 a) the date of incidence of clinical heart failure, b) date of death or c) last day of follow up. The Cox model was chosen since preliminary examination of the data confirmed the proportionality assumption.

For analyses of echocardiographic data we used cross sectional analysis methods as these data were obtained only on visit 6. Generalized linear regression models (GLM) were used to estimate unadjusted and adjusted coefficients for continuous echocardiographic measures. A modified Poisson approach was used to calculate relative risks of dichotomous echocardiographic measures.(30) These relative risk estimates are more conservative (smaller magnitude) than would be expected from odds ratio estimates using logistic regression models.(30) These models were also utilized for mortality analyses as the Cox model fit , was unsatisfactory.

This study was unsponsored. Dr Krishnan 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, College Station TX).

RESULTS

Heart failure incidence

Data were available for 4,989 Framingham Offspring Study participants. **Table 1** summarizes characteristics of the cohort. 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.

The total observation time was 135,991 person years. The median follow up time was 15.9 years (interquartile range 8.1-24.0). Overall there were 201 incident cases of heart failure. The overall incidence rate was 1.5 (1.29-1.70) per 1000 person-years. The rates among men and women were 2.2 (1.89-2.62) and 0.81 (0.62-1.04), respectively. Among those with gout the incidence of heart failure was 3.5 (2.30-5.32) per 1000 person-years. Among men there were 19 incident cases and among women there were 3. There were no statistically significant differences in incidence rates between men (3.6, 2.3-5.6) and women (3.0, 1.0-9.2). Since the number of women with gout and heart failure were so few, meaningful statistical adjustment in multivariable regressions was not possible. As the direction of risk was similar in both groups, the data were combined. Figure 1 shows the risk of heart failure over time by gout status.

Gout and the risk for incident heart failure

The mean age of the cohort was 36 years at the baseline. There were relatively few cases of heart failure in the first 10 years of follow up. **Figure 1** shows the Aalen-Nelson cumulative risk curves for heart failure. The curves for subjects with and without gout began to diverge at follow-up year 12 when the mean age of the cohort was 47 years. By Year 30 (mean age 66 years) the risk of heart failure was more than 2-fold higher in the gout group than in the non-gout group.

In unadjusted Cox regression models, gout was associated with an increased risk of heart failure with a hazard ratio of 2.8 (1.8-4.4). In the multivariable regression models, adjusting for effects of age, hypertension, total-cholesterol/HDL ratio, renal dysfunction, diabetes, alcohol use, smoking and body mass index, gout was associated with an increased risk for incident heart failure with a hazard ratio 1.75 (1.04-2.95). Valvular heart disease (i.e presence of heart murmur on clinical examination) was not significantly associated with heart failure incidence and this variable was not used for multivariable analyses. Gout was a significant predictor of heart failure in the

subgroups of patients without hypertension or diabetes and in those with renal impairment (**Table 2**).

Gout and left ventricular dysfunction

At visit 6, 2,237 participants had not developed heart failure and had echocardiograms of acceptable quality available for our analysis. Those with gout had thicker, wider and heavier left ventricles and had worse indices of LV function (**Table 2**). In the multivariable GLM regressions, participants with gout had greater LV thickness, lower fractional shortening and greater LV mass and dimensions (**Table 3**). The Poisson regression models showed greater LV mass, LV dimensions and smaller fractional shortening and ejection fraction in those with gout. This was consistent with the global assessment of systolic dysfunction **Table 4**.

Mortality analyses of the heart failure group

Mortality rates by gout and heart failure status are shown in **Table 5**. 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 to 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 Framingham Offspring Study 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 meaning 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 generalizability of our results and conclusions. Our risk estimates may be an underestimate of the true underlying risk for gout since we 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 i.e 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 we observed could be attributed to this class of drugs and not to gout *per se*. In studies that span three decades competing risks for morbidity and mortality and consequent survivor effects are inevitable. Lastly, information on the duration and severity of gout was not available.

The gout-mortality association we 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 hospitalization and death.(31) Tissue hypoxia—a hallmark of heart failure—is a stimulus for the production of urate;(32) among those with heart failure, serum urate concentrations are inversely correlated with maximal oxygen uptake and functional status.(33) Serum urate levels correlate well with circulating markers of inflammation and with oxidative stress in patients with chronic heart failure. (33)·(34) Indeed, there is an inverse relationship between serum urate concentrations and peripheral blood flow in patients with chronic heart failure.(35) Serum urate levels can predict mortality in patients with chronic heart failure.(36, 37)

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.(38) Hyperuricemia has been linked to incident heart failure. (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, tumor necrosis factor, soluble tumor necrosis factor receptors and interleukin 6.(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.(40) Uric acid can inhibit nitric oxide production by vascular endothelial cells and their proliferation and migration.(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.(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.(43) Data on these biological factors are not available for the present study but they merit a separate follow up study.

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 favorable effect of the gout medication allopurinol (and its metabolite oxypurinol) on endothelial and myocardial function among those with hyperuricemia.

(10) These molecules have been associated with improved endothelial function in patients with hypercholesterolemia,(44) type 2 diabetes with mild hypertension(45) or chronic heart failure.(11, 46) Some studies have shown an improvement in both LV hypertrophy and endothelial function due to treatment with allopurinol.(47, 48). Other studies have reported improvements in clinical outcomes of heart failure among patients with hyperuricemia upon allopurinol treatment.(10, 49, 50) Interventional studies might be able to assess whether allopurinol use can reduce the incidence of heart failure and subsequent poor outcomes.

ACKNOWLEDGEMENTS

The Framingham Offspring Study is conducted and supported by the National Heart Lung and Blood Institute (NHLBI) in collaboration with the Framingham Study investigators. This manuscript was prepared using a limited access dataset obtained from the NHLBI and does not necessarily reflect the opinions or views of the Framingham Study investigators or the NHLBI. This study was not supported by any industrial funding. Dr. Krishnan Obtained the datasets, analyzed the data and wrote the manuscript. Due to the terms and conditions of data user agreement, we are not able to share data.

FIGURE LEGEND

Figure 1. Nelson-Aalen cumulative risk estimates for heart failure among those with and without gout (n= 228 and 4,761, respectively) in the Framingham Offspring Study. The number of participants at risk for heart failure in each group are provided in two rows. The number of incident cases of heart failure in each time interval is provided within parenthesis.

Table 1. Baseline characteristics of participants of Framingham Offspring Study

Characteristic	Mean ± standard deviation/percent		
	No gout N=4,291	Gout N=228	p value
Age in years	36±10	40±9	<0.001
Proportion of men	46	83	<0.001
Body mass index (kg/m^2)	25±4.3	28±4.1	<0.001
Alcohol use	85	95	<0.001
Ever smokers	62	72	0.03
Proportion of current smokers	63	72	0.003
Diuretic users	3.2	7	<0.001
Systolic blood pressure (mm Hg)	120±15	133±17	<0.001
Diastolic blood pressure (mm Hg)	78±10	86±10	<0.001
Fasting glucose (mg/dl)	94±22	104±32	<0.001
Total cholesterol (mg/dl)	195±39	213±38	<0.001
LDL cholesterol (mg//dl)	124±35	138±34	<0.001
HDL cholesterol (mg/dl)	51±15	45±14	<0.001
Total cholesterol/HDL cholesterol ratio	4.2±1.6	5.1±1.7	<0.001
Triglycerides (mg/dl)	91±80	140±98	<0.001
Serum uric acid (mg/dl)	5.3±1.3	7.3±1.4	<0.001
Renal dysfunction	3.8	5.8	0.14
Diabetes	1.5	3.2	0.06
Valvular heart disease*	7.3	4.4	0.1
Blood pressure medications	2	8.8	<0.001

*Valvular heart disease was defined for this study as presence of cardiac murmur at baseline. Gout was determined based on physician diagnosis. Hypertension was defined 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. LDL indicates low-density lipoprotein; HDL, high-density lipoprotein.

Table 2. Multivariable Cox regression model for gout as an antecedent of heart failure.

	Hazard ratio for gout	95% confidence interval
Overall	1.76	1.04-2.95
Subgroups		
Hypertension	1.82	1.06-6.71
No hypertension	0.87	0.11-6.71
Diabetes	1.58	0.70-3.57
No diabetes	1.94	1.0-3.83
Renal impairment	1.15	0.24-5.60
No renal impairment	1.9	1.10-3.30
Non-smokers*	1.97	1.16-3.34

The hazard ratios were adjusted for the effect of age, hypertension, renal impairment, diabetes, LDL/HDL cholesterol ratio alcohol use, body mass index and smoking status in the overall model. In the subgroup analyses, the relevant variable was excluded as a covariate. Hypertension was defined 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.

* The statistical model did not converge among smoker category and was deemed unreliable.

Table 3: Echocardiographic characteristics at the Framingham Offspring Study visit 6 (n=2,337)

Echocardiographic measure	Gout	No gout	p value
	n=96	n=2,241	
LV thickness (**cm**)	2.07±0.26	1.88±0.24	<0.001
LV fractional shortening (range 0-1)	0.35±0.07	0.37±0.06	0.006
LV diastolic internal dimension (**cm**)	5.04± 0.48	4.79± 0.52	<0.001
LV mass (**g**)	196± 43	158±45	<0.001
Systolic dysfunction, n(%) §	89 (4%)	16 (17%)	<0.001
Low e**jection** f**raction, n(%)** §	11 (11.5%)	63 (2.8%)	<0.001

Hypertension was defined 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. LV left ventricle

¶ Defined as a measured fractional shortening of left ventricle <0.29. No units

§ 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.

Table 4: Gout and echocardiographic measures of participants of the Framingham Offspring Study visit 6 (n=2,337)- results of adjusted regression models§

Model/Dependent variable	Number of observations in the model		95% confidence interval
Generalized linear model		**Beta coefficient**	
LV thickness (cm)	2,100	0.11**	0.07 - 0.16
LV fractional shortening (range 0-1)	2,054	-0.01*	-0.03 - -0.00
LV diastolic internal dimension (cm)	2,071	0.15**	0.04 - 0.26
LV mass (g)	2,066	23.05**	14.38 - 31.72
Logistic regression model		**Odds ratio**	
LV systolic dysfunction §	2,283	3.60**	1.80 - 7.18
Low ejection fraction §	2,283	3.70**	1.68 - 8.16

* <0.05; ** p<0.001. LV left ventricle § Adjusted for the effects of age hypertension, body mass index, renal dysfunction, diabetes, alcohol use, smoking and total cholesterol/HDL cholesterol ratio.

§ 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.

Table 5. Mortality analyses by gout and heart failure status in the Framingham Offspring Study (n=4,989)

Unadjusted mortality rates			
	Rate per 1000 person-years (number of deaths)		
	Non-gout group (n=4,760)	**Gout group (n=229)**	**Overall (n=4989)**
Non-CHF group	6.5(727)	8.2(40)	6.5(767)
CHF group	53.7(109)	95.2(16)	56.9(125)
Overall	7.3 (836)	11.1(56)	7.4 (892)
Poisson analyses			
Unadjusted estimates	**Number of observations in the model**	**Relative risk for death**	**95% confidence interval**
Heart failure vs. no heart failure	32,267	5.28	4.89-5.69
Gout vs. no gout	32,267	1.74	1.57-1.93
Gout vs. no gout among those without heart failure	30,774	1.55	1.34-1.76
Gout vs. no gout among those with heart failure	1,493	1.24	1.02-1.51
Adjusted estimates*			
Heart failure vs. no heart failure	27209	3.73	3.39-4.10
Gout vs. no gout	27209	1.58	1.40-1.78
Gout vs. no gout among those without heart failure	26073	1.50	1.30-1.73
Gout vs. no gout among those with heart failure	1136	1.37	1.10-1.74

*Adjusted for the effects of age hypertension, body mass index, renal dysfunction, diabetes, alcohol use, smoking and total cholesterol/HDL ratio.

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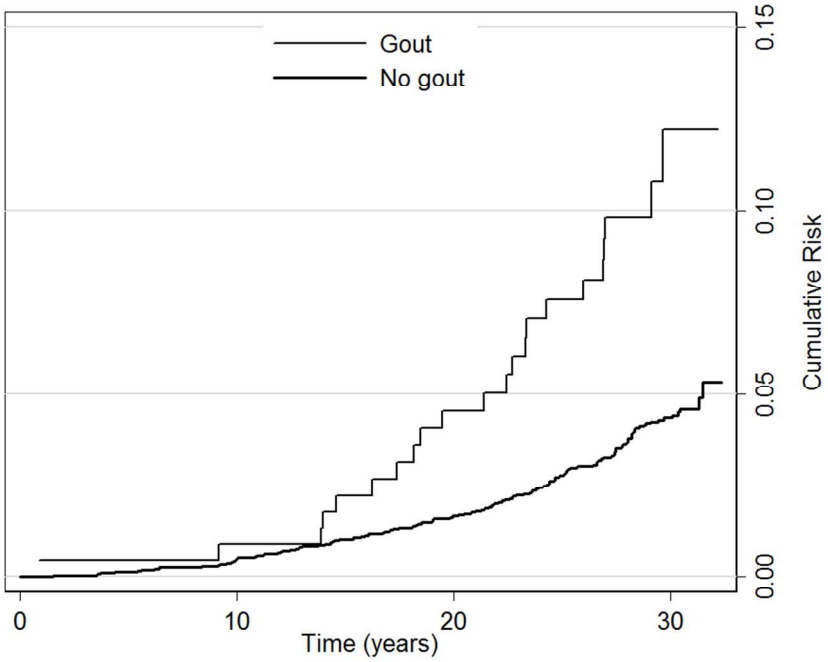

Figure 1 (uploaded as PNG)
373x261mm (72 x 72 DPI)

GOUT AND THE RISK FOR INCIDENT HEART FAILURE AND SYSTOLIC DYSFUNCTION

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2011-000282.R1
Article Type:	Research
Date Submitted by the Author:	30-Nov-2011
Complete List of Authors:	KRISHNAN, ESWAR; Stanford University, Medicine/Rheumatology
Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Rheumatology
Keywords:	Heart failure < CARDIOLOGY, gout, risk factor

STROBE checklist for "Gouty arthritis, systolic dysfunction and heart failure: results from a 30-year prospective study", Krishnan E

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-6*
Bias	9	Describe any efforts to address potential sources of bias	5-6
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	6-7

		(*d*) If applicable, explain how loss to follow-up was addressed	6-7
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7-9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	**Table** 1 and page 8
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	7-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7-9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	3,10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

GOUT AND THE RISK FOR INCIDENT HEART FAILURE AND SYSTOLIC DYSFUNCTION

Brief title: Gout and heart failure

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Abstract: 225

Total word count: 2,501

Tables: 5

Figure: 1

References: 50

Journal Subject Codes:

[11] Other heart failure, [8] epidemiology

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: 4,989 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 hazard ratio of 1.74 (1.03-2.93) for incident heart failure and relative risks of 3.70 (1.68-8.16) for abnormally low left ventricular ejection fraction and of 3.60 (1.80-7.72) 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 hazard ratio 1.58; 1.40-1.78). Mortality was elevated in subgroup of patients with gout and heart failure (1.50; 1.30-1.73).

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

Key Words: heart failure, hyperuricemia, left ventricular systolic dysfunction, uric acid, risk, gout

Article Summary

Article focus

- Gout is a common inflammatory arthritis that is a risk factor for cardiovascular disease in general
- We hypothesized that gout is a specific risk factor for heart failure

Key messages

- Gout is an independent risk factor for incident heart failure
- Among those with heart failure gout increases the case fatality

Limitations

- This study does not address the pathophysiological pathways that link gout to heart failure.
- The impact of gout treatment on heart failure risk cannot be assessed.

Funding Statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing Interests

Dr Krishnan 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.

Data Sharing Statement

We are unable to share data due to data sharing agreements in place with the NHLBI.

Contributorship

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

Introduction

Heart failure is a major public health problem in the United States; 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 utilization.[2] The major risk factors amenable to intervention are obesity, hyperlipidemia, hypertension, diabetes, alcohol abuse and smoking.[3] A common antecedent for heart failure, atherosclerosis, is also an independent risk factor for gouty arthritis (gout).[4-7] 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.[8-12] We hypothesized 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.[8] Hyperuricemia is necessary but not sufficient for development of gout.[13 14] Gouty arthritis is characterized by periods of intense inflammatory response with lower grade systemic inflammation in the period between acute attacks.[15] We prospectively analyzed the independent relationship between gout, left ventricular systolic function and incident heart failure in participants in the Framingham Offspring Study (FOS) Cohort. In addition we 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.

Methods

Study cohort and data source and design

The FOS is a longitudinal observational cohort assembled in 1971 and includes 5,124 men and women who are the offspring of the Framingham Heart Study Cohort and their spouses. [16] All

participants provided informed consent. This study used deidentifed 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=4,989). 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 utilized for the present analysis. This study is registered at clinicaltrials.gov (NCT00005121).

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 was determined predetermined criteria, included in **Table** 1.[1718] 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: paroxysmal nocturnal dyspnea, orthopnea, jugular venous distension, hepatojugular reflux, pulmonary rales, radiographic evidence of cardiomegaly, acute pulmonary edema, third heart sound, central venous pressure above 16 cm of water and weight loss greater than 4.5 kg during the first five days of treatment for suspected heart failure. Minor criteria included: bilateral ankle edema, nocturnal cough, dyspnea on ordinary exertion, hepatomegaly, pleural effusion and heart rate greater than 120 beats per minute. 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 hospitalization record where applicable. Information on clinical heart

failure was validated by medical chart review. We used all-cause mortality data for our analyses as there was not sufficient power to analyze 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=2,337). Routine transthoracic cardiac echocardiograms with Doppler color-flow imaging were performed using a Sonos 1000 Hewlett-Packard machine (Andover, MA). [19] 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.[20 21] Details of echocardiographic measurements including LV mass, LV end-diastolic internal dimensions, LV wall thickness and fractional shortening have been published.[22] 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.[20,22,25] LV wall thickness was calculated by adding together the diastolic thicknesses of the septum and the posterior wall.[22] LV systolic dysfunction was defined as a fractional shortening of less than 0.29.[23] 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.[23]

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[24]. This case definition is known to have high degree of reliability, [25] validated using medical records in two large epidemiological studies.[26 25]

Other risk factors of heart failure

Information on obesity measures, blood pressure, serum lipids, serum glucose, smoking and use of alcohol, aspirin, anti-hypertensive medication and anti-diabetic medication were collected. Hypertension and diabetes mellitus was defined per standard criteria and by the utilization of relevant medication. [27 28] 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' anti-hypertensive 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 gut. Wherever applicable, all covariates were used as time varying covariates whereby the values of these measures were updated by visits in the statistical models.

1. 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 we 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/HDL ratio as continuous variables and hypertension, body mass index, renal dysfunction, diabetes, alcohol use, and smoking as categorical variables.

2. 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.

3. Cross sectional analyses for echocardiographic data

For analyses of echocardiographic data we 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 relative risks of dichotomous echocardiographic measures.[29] These relative risk estimates are more conservative (smaller magnitude) than would be expected from odds ratio estimates using logistic regression models.[29] This study was unsponsored. Dr. Krishnan 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, College Station TX).

RESULTS

Heart failure incidence

Data were available for 4,989 Framingham Offspring Study participants (**Figure** 1). **Table** 2 summarizes 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 analyzed. Table 3 compares the baseline characteritiscs 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 15.9 years (interquartile range 8.1-24.0). Overall there were 202 incident cases of heart failure. Of these 187 were associated with hospitalization and 15 were diagnosed and treated in the inpatient settings. The overall incidence rate (95% confidence interval) was 1.5 (1.29-1.70) per 1000 person-years. The rates among men and women were 2.2 (1.89-2.62) and 0.81 (0.62-1.04), respectively.

Incidence among participants with gout

Among those with gout the incidence of heart failure was 3.5 (2.30-5.32) per 1000 person-years. Among men there were 19 incident cases and among women there were 3. There were no statistically significant differences in incidence rates between men (3.6, 2.3-5.6) and women (3.0, 1.0-9.2). 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.

Gout and the risk for incident heart failure

Overall there were 228 participants with gout. There were relatively few cases of heart failure in the first 10 years of follow up. **Figure** 2 shows the Aalen-Nelson cumulative risk curves for heart failure. The curves for subjects with and without gout began to diverge at follow-up year 12 when the mean age of the cohort was 47 years. By Year 30 (mean age 66 years) the risk of heart failure was more than 2-fold higher in the gout group than in the non-gout group.

In unadjusted Cox regression models, gout was associated with an increased risk of heart failure with a hazard ratio of 2.8 (1.8-4.4). In the multivariable regression models, adjusting for effects of age, hypertension, total-cholesterol/HDL ratio, renal dysfunction, diabetes, alcohol use, smoking and body mass index, gout was associated with an increased risk for incident heart failure with a hazard ratio 1.75 (1.04-2.95). Valvular heart disease (i.e presence of heart murmur on clinical examination) was not significantly associated with heart failure incidence and this variable was not used for multivariable analyses. Gout was a significant predictor of heart failure in the subgroups of patients without hypertension or diabetes and in those with renal impairment.

Gout and left ventricular dysfunction

At visit 6, 2,237 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 to those who entered the cohort at baseline but did not obtain echocardiogram due to attrition or death. (**Table** 2) Those with gout had thicker, wider and heavier left ventricles and had worse indices of LV function after adjustment of covariates (**Table** 4). 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** 3 were the independent

variables, patients with gout had a relative risk of 3.60 (1.80-7.18) for systolic dysfunction and a relative risk of 3.70 (1.68-8.16) for low ejection fraction.

Mortality analyses of the heart failure group

Mortality rates by gout and heart failure status are shown in **Table 5**. 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 to 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 Framingham Offspring Study 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 generalizability of our results and conclusions. Our risk estimates may be an underestimate of the true underlying risk for gout since we 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 i.e 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 we observed could be attributed to this class of drugs and not to gout *per se*. In studies that span three 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 we 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 hospitalization and death.[30] Tissue hypoxia—a hallmark of heart failure—is a stimulus for the production of urate;[31] among those with heart failure, serum urate concentrations are inversely correlated with maximal oxygen uptake and functional status.[32] Serum urate levels correlate well with circulating markers of inflammation and with oxidative stress in patients with chronic heart failure. [3233] Indeed, there is an inverse relationship between serum urate concentrations and peripheral blood flow in patients with chronic heart failure.[34] Serum urate levels can predict mortality in patients with chronic heart failure.[35 36] 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.[37] Hyperuricemia has been linked to incident heart failure. [38] 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, tumor necrosis factor, soluble tumor necrosis factor receptors and interleukin 6.[33] The National Health and Nutrition Survey conducted in former West Germany also showed an association between serum uric acid concentration and C-reactive protein.[39] Uric acid can inhibit nitric oxide production by vascular endothelial cells and their proliferation and migration.[40] 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.[41] 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.[42] 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 a anti-inflammatories and renal dysfunction. We were 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 favorable effect of the gout medication allopurinol (and its metabolite oxypurinol) on endothelial and myocardial function among those with hyperuricemia. [10] These molecules have been associated with improved endothelial function in patients with hypercholesterolemia,[43] type 2 diabetes with mild hypertension[44] or chronic heart failure.[11 45] Some studies have shown an improvement in both LV hypertrophy and endothelial function due to

treatment with allopurinol.[46 47]. Other studies have reported improvements in clinical outcomes of heart failure among patients with hyperuricemia upon allopurinol treatment.[10 48 49] Interventional studies might be able to assess whether allopurinol use can reduce the incidence of heart failure and subsequent poor outcomes.

ACKNOWLEDGEMENTS

The Framingham Offspring Study is conducted and supported by the National Heart Lung and Blood Institute (NHLBI) in collaboration with the Framingham Study investigators. This manuscript was prepared using a limited access dataset obtained from the NHLBI and does not necessarily reflect the opinions or views of the Framingham Study investigators or the NHLBI. This study was not supported by any industrial funding. Dr. Krishnan Obtained the datasets, analyzed the data and wrote the manuscript. Due to the terms and conditions of data user agreement, we are not able to share data.

FIGURE LEGEND

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 jeopardize de-identification process used in the Limited Access Program or they preferred the data not to be shared with non- Framingham Offspring Study Investigators.

Figure 2. Nelson-Aalen cumulative risk estimates for heart failure among those with and without gout (n= 228 and 4,761, respectively) in the Framingham Offspring Study. The number of participants at risk for heart failure in each group are provided in two rows. The number of incident cases of heart failure in each time interval is provided within parenthesis.

Table 1. Framingham Criteria for Congestive Heart Failure[21]

Major criteria:
Paroxysomal nocturnal dyspnea
Jugular venous distention
Pulmonary rales
Increasing heart size on chest X-ray film
Acute pulmonary edema
Third heart sound
Central venous pressure of at least 16 cm H20
Hepatojugular reflux
Weight loss of ≥4.5 kg in response to diuretics
Autopsy evidence of pulmonary edema
Minor criteria:
Bilateral ankle edema
Nocturnal dyspnea
Dyspnea on ordinary exertion
Hepatomegaly
Pleural effusion
Decrease in vital capacity by one third from prior maximum recorded value
Heart rate ≥120 beats per minute

At least 2 major or 1 major plus 2 minor criteria; minor criteria were included only if they were not attributed to another disease process.

Table 2. Characteristics of participants included in the analysis

	Mean ± standard deviation/percent	
	For longitudinal analyses of incident heart failure; assessed at the first visit	For cross sectional analyses of echocardiographic measures of systolic dysfunction; assessed at visit 6 unless otherwise specified.
Number of participants	4,989	2,336
Characteristic		
Age in years	36±10	57±10
Proportion of men (%)	46	45
Body mass index (kg/m²)	25±4.3	27.0±4.3
Any current alcohol use (%)	85	62
Proportion of current smokers	63	14.3
Current Diuretic users (%)	3.2	7.3
Systolic blood pressure (mm Hg)	120±15	126±18
Diastolic blood pressure (mm Hg)	78±10	74±9
Fasting glucose (mg/dl)	94±22	101±25
Total cholesterol (mg/dl)	195±39	206±39
LDL cholesterol (mg//dl)	124±35	130±36

HDL cholesterol (mg/dl)	51±15	52±16
Total cholesterol/HDL cholesterol ratio	4.2±1.6	1.7±0.4
Triglycerides (mg/dl)	91±80	134±100
Serum urate at visit 1 (mg/dl)	5.3±1.3	5.2±1.3
Renal disease/dysfunction(%)*	3.8	3.08
Diabetes(%)*	1.5	7.5
Valvular heart disease(%)*	7.3	8.1
Current antihypertensive therapy(%)	2.4	24.3
Gout anytime during study(%)	4.6	4.1

***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 per JNC 7 guidelines and/or use of antihypertensive medications. Diabetes was defined per the American Diabetes Association criteria or use of anti-diabetes medications. LDL indicates low-density lipoprotein; HDL, high-density lipoprotein. Renal disease was assessed by study physician based on history and study laboratory examination.**

Table 3. Comparison of participants with and without gout

Characteristic	Mean ± standard deviation/percent		
	No gout	Gout	p value
	N=4,291	N=228	
Age in years	36±10	40±9	<0.001
Proportion of men (%)	46	83	<0.001
Body mass index (kg/m²)	25±4.3	28±4.1	<0.001
Current alcohol use (%)	85	95	<0.001
Proportion of current smokers	63	72	0.003
Current diuretic use (%)	3.2	7	<0.001
Systolic blood pressure (mm Hg)	120±15	133±17	<0.001
Diastolic blood pressure (mm Hg)	78±10	86±10	<0.001
Fasting glucose (mg/dl)	94±22	104±32	<0.001
Total cholesterol (mg/dl)	195±39	213±38	<0.001
LDL cholesterol (mg//dl)	124±35	138±34	<0.001
HDL cholesterol (mg/dl)	51±15	45±14	<0.001

Total cholesterol/HDL cholesterol ratio	4.2±1.6	5.1±1.7	<0.001
Triglycerides (mg/dl)	91±80	140±98	<0.001
Serum urate (mg/dl)	5.3±1.3	7.3±1.4	<0.001
Renal disease/dysfunction (%)*	3.8	5.8	0.14
Diabetes(%)*	1.5	3.2	0.06
Valvular heart disease (%)*	7.3	4.4	0.1
Current anti-hypertensive therapy (%)*	2	8.8	<0.001

***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 per JNC 7 guidelines and/or use of antihypertensive medications. Diabetes was defined per the American Diabetes Association criteria or use of anti-diabetes medications. LDL indicates low-density lipoprotein; HDL, high-density lipoprotein. Renal disease was assessed by study physician based on history and study laboratory examination.**

Table 4: Echocardiographic characteristics at the Framingham Offspring Study visit 6 (N=2,337)

	Adjusted for age and body mass index			Adjusted for age hypertension, body mass index, renal dysfunction, diabetes, alcohol use, smoking and total cholesterol/HDL cholesterol ratio.		
Echocardiographic measure	**Gout**	**No gout**	**p value**	**Gout**	**No gout**	**P value**
Mean LV thickness (cm)	2.02	1.89	<0.0001	1.99	1.89	<0.0001
Mean LV fractional shortening (range 0-1)	0.35	0.37	0.006	0.35	0.37	0.005
Mean LV diastolic internal dimension (cm)	5.00	4.79	<0.0001	4.96	4.79	0.003
Mean LV mass (g)	188.51	159.29	<0.0001	182.47	159.58	<0.001
Proportion of participants with systolic dysfunction (%), §	12.7	3.5	<0.0001	10.0	2.3	0.002
Proportion of participants with low ejection fraction, (%) §	7.7	2.3	0.001	5.3	1.6	0.003

Hypertension was defined 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.

LV left ventricle

§ 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.

Table 5. Mortality analyses by gout and heart failure status in the Framingham Offspring Study using Poisson regressions (n=4,989)

Unadjusted estimates	Number of observations in the model	Relative risk for death	95% confidence interval
Heart failure vs. no heart failure	32,267	5.28	4.89-5.69
Gout vs. no gout	32,267	1.74	1.57-1.93
Gout vs. no gout among those without heart failure	30,774	1.55	1.34-1.76
Gout vs. no gout among those with heart failure	1,493	1.24	1.02-1.51
Adjusted estimates*			
Heart failure vs. no heart failure	27209	3.73	3.39-4.10
Gout vs. no gout	27209	1.58	1.40-1.78
Gout vs. no gout among those without heart failure	26073	1.50	1.30-1.73
Gout vs. no gout among those with heart failure	1136	1.37	1.10-1.74

*Adjusted for age, body mass index, and total cholesterol/HDL ratio as continuous variables and hypertension, body mass index, renal dysfunction, diabetes, alcohol use, and smoking as categorical variables.

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