

Gout, Allopurinol Use, and Heart Failure Outcomes

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Background: Hyperuricemia is associated with reduced survival among patients with heart failure (HF), but the effect of gout on HF outcomes is unknown. A recent randomized trial suggested that allopurinol may reduce adverse outcomes among patients with hyperuricemia and HF. Our objective was to determine whether gout and allopurinol use are associated with HF outcomes.

Methods: Time-matched, nested case-control analysis of a retrospective cohort of patients with HF who were 66 years or older using health care databases in Quebec, Canada. The primary outcome measure was a composite measure of HF readmission and all-cause mortality. The secondary outcome measure was all-cause mortality. Rate ratios were calculated using conditional logistic regression and adjusted for known prognostic factors.

Results: Of the 25 090 patients in this cohort, 14 327 experienced the primary outcome. Both a remote his-

tory of gout and an acute episode of gout (within 60 days of the event date) were associated with an increased risk of HF readmission or death (adjusted rate ratio, 1.63; 95% confidence interval, 1.48-1.80; $P < .001$ and 2.06; 1.39-3.06; $P < .001$, respectively). Continuous allopurinol use (>30 days of continuous use) was not associated with the primary outcome among the overall population with HF (adjusted rate ratio, 1.02; 95% confidence interval, 0.95-1.10; $P = .55$) but was associated with reduced HF readmissions or death (0.69; 0.60-0.79; $P < .001$) and all-cause mortality (0.74; 0.61-0.90; $P < .001$) among patients with a history of gout.

Conclusions: Patients with HF and a history of gout represent a high-risk population. Among such patients, the use of allopurinol is associated with improved outcomes.

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AMONG PATIENTS WITH heart failure (HF), elevated serum uric acid levels¹⁻³ and increased oxidative stress⁴⁻⁶ have been associated with increased mortality, implicating xanthine oxidase as a possible therapeutic target.⁷⁻⁹ Elevated serum uric acid levels predispose patients to gout, which has been shown to be an independent risk factor for ischemic heart disease and mortality.^{10,11} Whether a similar association exists between gout and HF mortality is unknown.

Allopurinol, an inhibitor of xanthine oxidase, may be a novel therapeutic agent for HF. Allopurinol reduces uric acid levels, prevents acute gout, and acts as an antioxidant, which could be beneficial among HF patients.⁸ In animal models of HF, allopurinol has been shown to improve cardiac function,¹²⁻¹⁵ reduce left ventricular dimensions,¹⁶⁻¹⁸ and reduce mortality.¹⁹ Small clinical studies with allopurinol have demonstrated improvements in cardiac function,^{20,21} reductions in endothelial dysfunction,^{22,23} reductions in oxidative stress,²⁴ and improvements in surrogate outcomes among HF patients.²⁵ Al-

though a recent clinical trial failed to demonstrate any improvement among the overall HF population, it suggested possible benefits among the subgroup with elevated uric acid levels.²⁶

Given the potential of xanthine oxidase inhibition in HF and the conflicting reports regarding the benefits of this strategy, we conducted a large, population-based observational cohort study using a nested case-control analysis to evaluate the effect of a remote history of gout, episodes of acute gout, and allopurinol use on HF readmission and mortality among HF patients. Because of the recently suggested benefits among patients with hyperuricemia, we specifically evaluated the effect of allopurinol in patients with a history of gout.

METHODS

OVERVIEW

We conducted a population-based, retrospective cohort study using a nested case-control approach.²⁷ The use of a nested case-control approach provided a computationally efficient method to analyze the effect of medications and to investigate multiple exposures simultaneously.²⁸

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In a cohort of symptomatic HF patients, we evaluated the association between a remote history of gout, episodes of acute gout, or allopurinol use and 2 distinct outcome measures: (1) a primary composite outcome measure of HF readmission and all-cause mortality and (2) a secondary outcome measure of all-cause mortality alone. This project was approved by the institutional review board of McGill University Health Center, Montreal, Quebec, Canada.

DATA SOURCE

We used administrative databases from the Quebec universal health insurance program that covers all residents of Quebec. All physician visits, hospital admissions, patient comorbidities, and outpatient prescriptions are recorded in these databases, which have been validated and previously used for cardiovascular outcomes research.^{29,30} Medical claims data (including physician visits, hospital admissions, comorbidities, and procedures) are complete and available for all Quebec residents; prescription data are available only for residents 65 years and older.

Using an encrypted individual identifier for each subject, we linked patient data from the hospitalization database (which includes primary and 15 secondary diagnoses using *International Classification of Diseases, Ninth Revision*³¹ [ICD-9] codes), outpatient drug claims, the physician services database, and the vital statistics database.

COHORT DEFINITION

The source population consisted of all patients 66 years or older who had been discharged from the hospital with a primary diagnosis of HF (ICD-9 code 428.x) between April 1, 1998, and March 31, 2004. The cohort was limited to patients 66 years or older because complete prescription data are available only for this age group. The use of the ICD-9 428.x code has been previously shown to be accurate for HF diagnosis, in agreement with the Framingham HF score and clinical diagnosis.^{32,33}

We excluded patients with the following criteria from the cohort: (1) admission to the hospital with a primary diagnosis of HF within the previous 3 years, to minimize the effect of disease severity; (2) less than 7 days of follow-up, to allow adequate time to define the exposure of interest; (3) patients older than 105 years; (4) patients discharged to a long-term care institution, rehabilitation center, psychiatric institution, or another province or other reasons leading to incomplete coverage with the provincial health plan, because complete medication data were not available for these patients; and (5) an invalid health insurance number.

Cohort entry for each subject was defined as the date of discharge with a primary diagnosis of HF and the start date of follow-up. Follow-up ended on the event date, which was the date of the outcome (HF readmission or death) or March 31, 2005 (end of study).

SELECTION OF CASES AND CONTROLS

Cases were defined as subjects from the cohort with HF readmission or death during follow-up. We considered the subject to have HF readmission when he or she was admitted to the hospital with a primary diagnosis of HF. The day of HF readmission or death was defined as the event date for each case. Two separate case-control analyses were performed using (1) HF readmission or death as a composite outcome measure and (2) all-cause mortality.

For each case, up to 10 controls were randomly sampled from a risk set defined by the event date of the case (incidence

density sampling).³⁴ We sampled controls from each risk set without considering future case status or use of the same control for another case.³⁵⁻³⁷ Therefore, subjects could serve as controls for several cases while they remained at risk for the event.³⁷ This is analogous to standard survival methods, in which virtually all controls are used more than once.³⁴ Controls were matched to cases by the calendar day (within 5 days) of admission to the cohort. By matching on entry into the cohort, follow-up time was equal for all sets of cases and controls.

EXPOSURE ASSESSMENT OF ALLOPURINOL USE

We defined current allopurinol use as having a prescription for allopurinol that overlapped the event date. To allow for varying adherence, we considered a subject to have current exposure if a prescription ended within 7 days of the event date. We also examined duration of exposure by calculating the total number of days of continuous allopurinol use. Current allopurinol use was divided into 2 mutually exclusive durations of continuous use: new users (≤ 30 continuous days) and continuous users (> 30 continuous days). We also dichotomized current exposure by daily dose (≤ 100 mg/d and > 100 mg/d). Previous allopurinol users were considered unexposed, since the physiologic effect of allopurinol is relatively short after drug cessation.⁸

EXPOSURE ASSESSMENT OF GOUT

We used a history of gout as a surrogate for elevated serum uric acid levels because biochemical measures are not available in administrative databases. Elevated serum uric acid levels represent the sine qua non of gouty arthritis and are necessary for the development of gout. Therefore, patients with a diagnosis of gout have an increased likelihood of elevated serum uric acid levels. A remote history of gout was defined as a diagnosis of gout (ICD-9 codes 274.0, 274.1, 274.8, and 274.9) coded as a comorbidity during a hospital admission in the last 5 years before enrollment in the cohort or a primary diagnosis of gout during a physician visit, emergency department (ED) visit, or hospital admission within the last year before enrollment in the cohort. Because of reported difficulties in accurately ascertaining a history of gout using administrative data,³⁸ we also performed a sensitivity analysis in which we evaluated the following alternate definitions of gout: (1) gout coded solely as a comorbidity during a hospital admission in the last 5 years before cohort enrollment; (2) gout coded solely as a primary diagnosis during a physician visit, ED visit, or hospital admission in the last year before cohort enrollment; (3) gout defined by a diagnosis as a comorbidity in the last 5 years and a primary diagnosis during a physician visit, ED visit, or hospital admission within the last year before cohort enrollment, to enhance specificity; and (4) gout defined by fulfilling the definitions of both comorbidity and primary diagnosis and by having a prescription for nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or colchicine in the month before the event date. To evaluate the specific effect of acute gout, we defined an acute gout episode as a hospital admission or ED visit with a primary diagnosis of gout within 60 days of the event date.

STATISTICAL ANALYSIS

We assessed the association between a remote history of gout, acute gout, or allopurinol exposure and HF outcomes using conditional logistic regression.^{28,39} This method has been shown to provide precise and unbiased estimates similar to those obtained from cohort analyses^{28,40} and has been used frequently in the literature.^{41,42}

We compared the risk of HF outcomes in patients with and without a remote history of gout, acute gout, or allopurinol use.

Table 1. Baseline Characteristics of Cases and Controls^a

Characteristic	HF Readmission or Death		All-Cause Mortality	
	Cases (n=14 327)	Controls (n=143 255)	Cases (n=11 674)	Controls (n=116 734)
Male sex	50.4	48.8	51.3	48.9
Age, mean (SD), y	78.7 (7.4)	77.0 (7.0)	79.3 (7.5)	76.8 (7.0)
Charlson score				
0	20.0	28.2	18.5	28.1
1	28.8	31.9	28.0	31.7
≥2	51.5	39.9	0.53	40.1
History of hypertension	58.2	57.7	58.2	56.0
History of renal failure	30.7	19.8	42.6	19.7
History of myocardial infarction				
Remote	39.4	34.0	39.3	35.0
Recent	3.1	0.0	5.1	0.04
Admission to teaching hospital	18.3	14.7	18.6	14.8
Medication use				
ACE-Is/ARBs	54.6	70.6	44.8	70.8
β-Blockers	33.1	40.3	26.5	41.3
Statins	22.3	30.2	16.3	32.2
Digoxin	32.9	32.9	30.8	34.2
Calcium channel blockers	28.8	31.8	24.1	32.7
Antiplatelets	41.4	47.7	36.4	48.6
Warfarin	25.7	29.5	20.6	29.7
Spironolactone	10.6	13.0	12.9	14.6
Amiodarone	11.3	10.1	10.0	10.8
Hydralazine	3.4	1.6	3.9	2.04
Metolazone	1.6	0.7	2.6	0.9
Thiazides and other diuretics	3.2	4.7	3.0	5.0
NSAIDs	5.4	5.1	4.1	5.0
Prednisone	4.1	3.1	4.2	3.1
Furosemide dose, mean (SD), mg/d	60.4 (80.2)	51.1 (58.8)	66.0 (95.6)	55.8 (66.0)
Procedures				
Angiography	10.8	16.3	9.2	16.4
CABG	2.6	4.9	1.9	5.4
ICD	0.3	0.4	0.3	0.5

Abbreviations: ACE-Is/ARBs, angiotension-converting enzyme inhibitors and angiotensin receptor blockers; CABG, coronary artery bypass grafting; HF, heart failure; ICD, implantable cardiac defibrillator; NSAIDs, nonsteroidal anti-inflammatory drugs.

^aData are presented as percentage unless otherwise indicated.

Multivariate models were adjusted for sex, age, and comorbidities using the Deyo modification of the Charlson index.⁴³ Models were adjusted for the following additional conditions because they represented important confounders: any diagnosis of hypertension, myocardial infarction, or renal failure within the last 5 years before cohort enrollment. Models were also adjusted for recent hospital discharge for acute myocardial infarction within the 7 days before the event date, cardiac procedures performed in the year before cohort entry (ie, coronary angiography, coronary artery bypass grafting, and defibrillator insertion), HF medications (including angiotensin-converting enzyme inhibitors, β-blockers, antiplatelet agents, anticoagulants, aldosterone antagonists, and daily dose of diuretics), and medications used to treat acute gout that are known to exacerbate HF (such as NSAIDs and corticosteroids). All medications were ascertained based on current prescriptions at the time of the event date (ie, if a filled prescription overlapped the event date).

For analyses evaluating the effects of acute gout exposure, we adjusted for 2 additional covariates to limit the possibility of reverse causality. First, to limit the possible effect of recent changes in diuretic dose, we created a variable that indicated a recent change (in the month preceding the event date) in diuretic dose of more than 10 mg/d. Second, to evaluate whether worsening HF preceded the onset of acute gout and could explain the effect of acute gout on the HF outcome, we created a variable of physician visits or ED visits with a primary diagnosis of HF within 7 days before the acute gout episode as a marker of a recent worsening in HF status. We evaluated for modification of the allopurinol effect by sex and history of gout using a multiplicative model. For all multivariate models, collinearity between covariates was assessed using variance inflation factors. All results are presented as crude and adjusted rate ratios (RRs) and 95% confidence intervals (CIs).

RESULTS

The study population consisted of 25 090 patients (mean age, 77 years) discharged from the hospital with a recent diagnosis of HF. Median follow-up was 2.1 years. During cohort follow-up, there were 14 327 events for the composite outcome measure of HF readmission or death and 11 674 events for all-cause mortality. Of the 14 327 events for the composite outcome measure, 7581 (52.9%) were for an HF readmission and 6746 (47.1%) were for mortality.

Table 2. Association Between History of Gout and HF Readmission or Death

Gout Definition	HF Readmission or Death			
	Patients, No. (%)		Rate Ratio (95% CI)	
	Cases	Controls	Unadjusted	Adjusted ^a
Any gout	1053 (7.3)	6631 (4.6)	1.64 (1.53-1.75)	1.63 (1.48-1.80)
Gout defined by				
Comorbidity	713 (5.0)	4645 (3.2)	1.56 (1.44-1.69)	1.56 (1.38-1.76)
Primary diagnosis	222 (1.5)	1340 (0.9)	1.67 (1.44-1.92)	1.67 (1.37-2.03)
Comorbidity and primary diagnosis	118 (0.8)	646 (0.5)	1.83 (1.50-2.23)	1.77 (1.32-2.37)
Comorbidity, primary diagnosis, and gout medications	11 (0.1)	54 (0.0)	2.04 (1.07-3.90)	11.07 (3.14-39.0)

Abbreviations: CI, confidence interval; HF heart failure.

^aCovariates included age; sex; Charlson score; history of hypertension, renal failure, and myocardial infarction (recent and past 5 years); cardiac procedures in prior year (including coronary angiography, coronary artery bypass grafting, and defibrillator insertion); and drug use at time of index event (including dose of loop diuretics, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, β-blockers, spironolactone, metolazone, other diuretics [hydrochlorothiazide and amiloride], statins, amiodarone, digoxin, calcium channel blockers, antiplatelets [acetylsalicylic acid and clopidogrel], warfarin, hydralazine, nonsteroidal anti-inflammatory drugs, and corticosteroids).

Table 3. Acute Gout Within 60 Days of Event Date and HF Outcomes

Gout Status Within 60 d of Event Date	HF Readmission or Death			All-Cause Mortality		
	Unadjusted RR (95% CI)	Adjusted RR ^a (95% CI)	P Value	Unadjusted RR (95% CI)	Adjusted RR ^a (95% CI)	P Value
No acute gout	1 [Reference]	1 [Reference]	...	1 [Reference]	1 [Reference]	...
Any acute gout	2.43 (1.68-3.52)	2.06 (1.39-3.06)	<.001	2.33 (1.61-3.38)	1.76 (1.08-2.86)	.02
All hospital admissions for gout	4.83 (2.55-9.14)	2.77 (1.38-5.58)	.004	2.86 (1.58-5.17)	1.14 (0.49-2.61)	.76
All ED visits for gout	1.90 (1.22-2.97)	1.63 (1.02-2.63)	.04	2.13 (1.38-3.28)	2.10 (1.19-3.70)	.01

Abbreviations: CI, confidence interval; ED, emergency department; HF, heart failure; RR, rate ratio.

^aCovariates included age; sex; Charlson score; history of hypertension, renal failure, gout, and myocardial infarction (recent and past 5 years); recent ambulatory HF visit to ED or outpatient clinic; cardiac procedures in prior year (including coronary angiography, coronary artery bypass grafting, and defibrillator insertion); and drug use at time of index event (including dose of loop diuretics, recent increase in loop diuretic dose in past 30 days, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, β -blockers, spironolactone, metolazone, other diuretics [hydrochlorothiazide and amiloride], statins, amiodarone, digoxin, calcium channel blockers, antiplatelets [acetylsalicylic acid and clopidogrel], warfarin, hydralazine, nonsteroidal inflammatory drugs, and corticosteroids).

Table 4. Effect of Allopurinol in All Patients With HF

Allopurinol Exposure	HF Readmission or Death				
	Patients, No. (%)		Rate Ratio (95% CI)		P Value
	Cases	Controls	Unadjusted	Adjusted ^a	
No current use	13 064 (91.2)	133 051 (92.9)	1 [Reference]	1 [Reference]	...
Current use	1263 (8.8)	10204 (7.1)	1.26 (1.19-1.34)	1.02 (0.95-1.10)	.55
Duration of use ^b					
<30 d	187 (1.6)	954 (0.8)	2.00 (1.71-2.35)	1.65 (1.39-1.95)	<.001
>30 d	881 (7.7)	7603 (6.7)	1.18 (1.10-1.27)	0.97 (0.89-1.06)	.52
Dose					
≤100 mg/d	997 (7.0)	8216 (5.7)	1.24 (1.16-1.32)	0.97 (0.90-1.05)	.52
>100 mg/d	266 (1.8)	1988 (1.4)	1.36 (1.20-1.55)	1.25 (1.09-1.43)	.002

Abbreviations: CI, confidence interval; HF, heart failure.

^aCovariates included age; sex; Charlson score; history of hypertension, renal failure, and myocardial infarction (recent and past 5 years); cardiac procedures in prior year (including coronary angiography, coronary artery bypass grafting, and defibrillator insertion); and drug use at time of index event (including dose of loop diuretics, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, β -blockers, spironolactone, metolazone, other diuretics [hydrochlorothiazide and amiloride], statins, amiodarone, digoxin, calcium channel blockers, antiplatelets [acetylsalicylic acid and clopidogrel], warfarin, hydralazine, nonsteroidal inflammatory drugs, and corticosteroids).

^bAnalysis was limited to patients with more than 30 days of follow-up.

The baseline characteristics of cases and controls are presented in **Table 1**. Case patients were older (mean age, 78.7 years) and had a higher burden of comorbidities based on the modified Charlson index, particularly a higher prevalence of renal failure and prior myocardial infarction.

ASSOCIATION BETWEEN HISTORY OF GOUT AND HF READMISSION OR DEATH

For the combined outcome measure of HF readmission or death, a remote history of gout was recorded in 4.6% of controls and 7.3% of cases. Compared with patients without gout, patients with a remote history of gout were at increased risk for the composite outcome of HF readmission or death (adjusted RR, 1.63; 95% CI, 1.48-1.80; $P < .001$). Because of limitations in the ascertainment of gout in administrative databases, we also evaluated 4 other definitions of gout in varying degrees of stringency to determine the robustness of the association. Irrespective of the definition used to determine a history of gout, there was a marked and statistically significant association between gout and HF outcomes (**Table 2**).

ASSOCIATION BETWEEN ACUTE GOUT AND HF READMISSION OR DEATH

For the combined outcome measure of HF readmission or death, there were 38 cases (0.4%) and 155 controls (0.1%) with a recent acute episode of gout in the 60 days before the event date. An acute episode of gout was associated with an increased risk of adverse HF outcomes (adjusted RR, 2.06; 95% CI, 1.39-3.06; $P < .001$ for HF readmission or death; and 1.76; 1.08-2.86; $P = .02$ for all-cause mortality) (**Table 3**).

ASSOCIATION BETWEEN ALLOPURINOL USE AND HF READMISSION OR DEATH

In the overall HF patient population, we found no statistically significant association between allopurinol use and the combined outcome of HF readmission or death (adjusted RR, 1.02; 95% CI, 0.95-1.10; $P = .55$). Results for HF readmission or death are summarized in **Table 4**. When we limited the outcome measure to all-cause mortality, results were similar (data not shown).

Table 5. Effect of Allopurinol in Patients With HF and a Remote History of Gout

Allopurinol Exposure	HF Readmission or Death				
	Patients, No. (%)		Rate Ratio (95% CI)		P Value
	Cases	Controls	Unadjusted	Adjusted ^a	
No current use	565 (53.7)	2712 (40.9)	1 [Reference]	1 [Reference]	...
Current use	488 (46.3)	3919 (59.1)	0.60 (0.52-0.68)	0.69 (0.60-0.79)	<.001
Duration of use ^b					
≤30 d	58 (7.1)	243 (4.9)	1.50 (1.11-2.02)	1.12 (0.81-1.56)	.49
>30 d	341 (41.9)	2900 (57.9)	0.52 (0.45-0.61)	0.66 (0.56-0.77)	<.001
Dose					
≤100 mg/d	382 (36.3)	3087 (46.6)	0.65 (0.57-0.75)	0.65 (0.69-0.76)	<.001
>100 mg/d	106 (10.1)	832 (12.5)	0.78 (0.63-0.97)	0.87 (0.69-1.09)	.23

Abbreviations: CI, confidence interval; HF, heart failure.

^aCovariates included age; sex; Charlson score; history of hypertension, renal failure, and myocardial infarction (recent and past 5 years); cardiac procedures in prior year (including dose of loop diuretics, coronary angiography, coronary artery bypass grafting, and defibrillator insertion); and drug use at time of index event (including angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, β-blockers, spironolactone, metolazone, other diuretics [hydrochlorothiazide and amiloride], statins, amiodarone, digoxin, calcium channel blockers, antiplatelets [acetylsalicylic acid and clopidogrel], warfarin, hydralazine, nonsteroidal inflammatory drugs, and corticosteroids).

^bAnalysis was limited to patients with more than 30 days of follow-up.

However, among patients with a remote history of gout, allopurinol use was associated with reduced HF readmission or death (adjusted RR, 0.69; 95% CI, 0.60-0.79) and reduced all-cause mortality (0.74; 0.61-0.90) (**Table 5**). We also found that among allopurinol users, the association between gout and adverse HF outcomes that we observed in the overall HF population was no longer statistically significant (adjusted RR, 0.95; 95% CI, 0.84-1.08 for HF readmission or death). We did not detect any differences in effect among men and women treated with allopurinol (adjusted RR for sex interaction, 0.92; 95% CI, 0.80-1.04).

COMMENT

In this population-based study of 25 090 symptomatic HF patients, we have shown that a remote history of gout and an acute episode of gout are risk factors for HF readmission and/or death. The association with gout and adverse HF outcomes persisted despite adjustments for many important confounders such as prior myocardial infarction, renal failure, daily diuretic dose, and gout treatments known to precipitate HF such as NSAIDs and corticosteroids. In addition, among patients with HF and a history of gout, allopurinol use was strongly associated with improved outcomes.

Our results are consistent with those of a multicenter, masked, placebo-controlled randomized trial addressing the use of oxypurinol, the active metabolite of allopurinol, in HF.²⁶ This trial, conducted in 405 patients, showed that the addition of oxypurinol to standard HF therapy did not produce clinical improvements in HF status after 24 weeks in the overall cohort, but did demonstrate a trend toward improved outcomes among patients with elevated serum uric acid levels. However, because of the small number of patients, these subgroup analyses did not reach the threshold for statistical significance. In our study, using remote history of gout as a surrogate for symptomatic elevations in uric acid levels, we found that allopurinol use was associated with

clinically and statistically significant reductions in HF readmission or death. Our population-based study adds important evidence that allopurinol may be beneficial in a subset of patients with HF, symptomatic hyperuricemia, and gout.

Inhibition of xanthine oxidase has been hailed as a promising therapeutic strategy for HF. Several animal models and subclinical studies have shown clinical benefits using various xanthine oxidase inhibitors including allopurinol. However, results among human subjects have been quite variable with respect to important outcomes such as HF readmission and death. In the Seattle Heart Failure Model,⁴⁴ allopurinol was associated with an increased risk of death or urgent transplantation. Similarly, a retrospective analysis of a UK cohort with HF demonstrated that high-dose but not low-dose allopurinol was associated with a reduction in HF hospitalization and death.⁴⁵ Previous analyses of allopurinol use in HF have had several methodologic limitations. Specifically, these studies did not evaluate patients with a documented history of gout and may also have been biased by residual confounding and measurement errors. In our study we carefully defined a history of gout according to comorbidity, physician visits, and anti-inflammatory medications and evaluated drug exposure using a nested case-control approach.

The observed association between allopurinol use and HF outcomes among patients with gout could be mediated by reductions in uric acid levels or by decreases in superoxide anions since these biochemical markers have been associated with adverse outcomes in HF patients.^{1-3,24} Our observation of a protective association with allopurinol use only among patients with HF and gout indicates that the effects of allopurinol may be evident only in patients with markedly elevated xanthine oxidase activity. In animal models of HF, experimentally induced ventricular dysfunction led to upregulation of xanthine oxidase by 50% to 400% with resulting elevations in superoxide ions.⁴⁶⁻⁴⁸ Increased oxidative stress causes inactivation of nitric oxide, which can worsen endothe-

lial dysfunction and reduce myocardial contractility.^{14,17,18} Allopurinol has been reported to reverse many of these adverse effects.^{12-18,47,48} Allopurinol improves myocardial contractility by restoring myocardial calcium sensitivity and β -adrenergic responsiveness in HF.⁴⁹ It may also improve endothelial dysfunction, leading to vasodilatation and reductions in afterload.^{23,24,45} George et al²⁴ showed that the administration of allopurinol to HF patients led to marked improvements in endothelial function by decreasing oxidative stress. Decreases in uric acid levels may further reduce afterload since uric acid has been shown to stimulate renin release.⁵⁰ A recent randomized trial in adolescents with hypertension demonstrated lowered plasma renin activity, peripheral resistance, and blood pressure after 4 weeks of treatment with allopurinol.⁵¹

On the basis of our results, patients with HF and a history of gout appear to represent a high-risk subgroup owing to elevated xanthine oxidase activity. Therefore, a history of gout among HF patients may be an indication for low-dose allopurinol therapy unless an important contraindication arises (ie, renal failure). Whether asymptomatic patients with hyperuricemia and HF should also be treated with allopurinol to reduce xanthine oxidase activity is unclear. Because of the observational nature of our study, our results should be interpreted with caution and should not be used as evidence supporting the clinical use of allopurinol in HF. Given the possible serious adverse events associated with allopurinol, only a large randomized trial among patients with hyperuricemia and HF, both with and without a history of gout, can evaluate the risks and benefits of such a strategy and provide the required evidence for the use of allopurinol in clinical practice.

Some limitations of our study merit discussion. First, this was an analysis of administrative data, so misclassification of some exposures, covariates, and outcomes is always possible. We used validated end points of HF readmission and death to minimize misclassification of outcomes. The diagnosis of gout using administrative databases may also be prone to misclassification. We chose an inclusive definition of gout that accounted for any primary or secondary diagnosis in an effort to include all patients with a possible remote history of gout. In addition, we performed a sensitivity analysis using variable definitions of gout to ensure that our results were robust to our definition of gout. Nonetheless, despite our efforts, some patients may have been misclassified according to gout status, which could have biased our effect estimates for remote gout and may have led to some residual confounding. Second, despite adjustments in our models for many important confounders such as renal failure, myocardial infarction, history of gout, daily diuretic dose, and comorbidities (using the Charlson index), some degree of confounding may still modify our estimates. We could not adjust for obesity, alcohol use, or socioeconomic status since these variables were not available. We also could not adjust our models for ejection fraction because this covariate was not available. However, on the basis of the pathophysiological mechanisms of allopurinol, which is known to

improve endothelial function, allopurinol should have similar benefits in systolic and diastolic HF. Third, because we used prescriptions to assess drug use, we could not account for use of over-the-counter drugs (such as NSAIDs) and could not measure compliance with prescribed drugs. Fourth, because we compared allopurinol users with nonusers, our results may be biased by confounding by indication. Because we were studying the unintended effects of allopurinol use on HF outcomes, our estimates are less likely influenced by such confounding. However, it is possible that in certain patients with HF and gout, lack of allopurinol use (or stopping allopurinol use) may itself represent a risk factor for adverse HF outcomes. Fifth, our analysis of acute gout may be inflated owing to reverse causality. We attempted to limit this problem by adjusting for covariates that suggested a recent worsening in HF (eg, a recent visit to a physician or ED for HF or a recent increase in diuretic dose).

In conclusion, our results indicate that patients with HF and a recent or remote history of gout represent a high-risk subgroup, and in these high-risk patients allopurinol use appears to be associated with important reductions in adverse outcomes. Given the limited novel treatment options available for HF patients, allopurinol may be an important therapeutic consideration in certain subgroups of patients with HF. A randomized trial evaluating allopurinol use among patients with increased xanthine oxidase activity based on elevated serum uric acid levels or increased markers of oxidative stress may help to clarify the role of allopurinol in HF.

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