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 history 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.

Arch Intern Med. 2010;170(15):1358-1364

Among patients with heart failure (HF), elevated serum uric acid levels have been associated with increased mortality, implicating xanthine oxidase as a possible therapeutic target. 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. 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. In animal models of HF, allopurinol has been shown to improve cardiac function, reduce left ventricular dimensions, and reduce mortality. Small clinical studies with allopurinol have demonstrated improvements in cardiac function, reductions in endothelial dysfunction, reductions in oxidative stress, and improvements in surrogate outcomes among HF patients. Although 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.

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. 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.
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 Internatio

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,39,40 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 analyses28,41 and has been used frequently in the literature.31,42 We compared the risk of HF outcomes in patients with and without a remote history of gout, acute gout, or allopurinol use.
### 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, 7,581 (52.9%) were for an HF readmission and 6,746 (47.1%) were for mortality.

#### Table 1. Baseline Characteristics of Cases and Controlsa

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HF Readmission or Death</th>
<th>All-Cause Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases (n=14,327)</td>
<td>Controls (n=11,674)</td>
</tr>
<tr>
<td>Male sex</td>
<td>59.4 (48.8)</td>
<td>51.3 (48.9)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>78.7 (7.4)</td>
<td>77.0 (7.0)</td>
</tr>
<tr>
<td>Charlson score</td>
<td>0.20 (0.28)</td>
<td>0.18 (0.28)</td>
</tr>
<tr>
<td>1</td>
<td>28.8 (31.9)</td>
<td>28.0 (31.7)</td>
</tr>
<tr>
<td>≥2</td>
<td>51.5 (39.9)</td>
<td>0.53 (40.1)</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>58.2 (57.7)</td>
<td>58.2 (56.0)</td>
</tr>
<tr>
<td>History of renal failure</td>
<td>30.7 (19.8)</td>
<td>42.6 (19.7)</td>
</tr>
<tr>
<td>Procedures</td>
<td>18.3 (14.7)</td>
<td>18.6 (14.8)</td>
</tr>
<tr>
<td>Medication use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE-Is/ARBs</td>
<td>54.6 (70.6)</td>
<td>44.8 (70.8)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>33.1 (40.3)</td>
<td>26.5 (41.3)</td>
</tr>
<tr>
<td>Statins</td>
<td>22.3 (30.2)</td>
<td>16.3 (32.2)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>32.9 (32.9)</td>
<td>30.8 (34.2)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>28.8 (31.8)</td>
<td>24.1 (32.7)</td>
</tr>
<tr>
<td>Antiplatelets</td>
<td>41.4 (47.7)</td>
<td>36.4 (48.6)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>25.7 (29.5)</td>
<td>20.6 (29.7)</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>10.6 (13.0)</td>
<td>12.9 (14.6)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>11.3 (10.1)</td>
<td>10.0 (10.8)</td>
</tr>
<tr>
<td>Hydrozaine</td>
<td>3.4 (1.6)</td>
<td>3.9 (2.04)</td>
</tr>
<tr>
<td>Metolazone</td>
<td>1.6 (0.7)</td>
<td>2.6 (0.9)</td>
</tr>
<tr>
<td>Thiadiazides and other diuretics</td>
<td>3.2 (4.7)</td>
<td>3.0 (5.0)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>5.4 (5.1)</td>
<td>4.1 (5.0)</td>
</tr>
<tr>
<td>Prednisone</td>
<td>4.1 (3.1)</td>
<td>4.2 (3.1)</td>
</tr>
<tr>
<td>Furosemide dose, mean (SD), mg/d</td>
<td>60.4 (51.1)</td>
<td>55.8 (66.0)</td>
</tr>
<tr>
<td>Angiography procedures</td>
<td>10.8 (16.3)</td>
<td>9.2 (16.4)</td>
</tr>
<tr>
<td>CABG</td>
<td>2.6 (4.9)</td>
<td>1.9 (5.4)</td>
</tr>
<tr>
<td>ICD</td>
<td>0.3 (0.4)</td>
<td>0.3 (0.5)</td>
</tr>
</tbody>
</table>

Abbreviations: ACE-Is/ARBs, angiotension-converting enzyme inhibitors and angiotension 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.

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

<table>
<thead>
<tr>
<th>Gout Definition</th>
<th>HF Readmission or Death</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any gout</td>
<td>1053 (7.3)</td>
<td>6631 (4.6)</td>
</tr>
<tr>
<td>Gout defined by</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbidity</td>
<td>713 (5.0)</td>
<td>4645 (3.2)</td>
</tr>
<tr>
<td>Primary diagnosis</td>
<td>222 (1.5)</td>
<td>1340 (0.9)</td>
</tr>
<tr>
<td>Comorbidity and primary diagnosis</td>
<td>118 (0.8)</td>
<td>646 (0.5)</td>
</tr>
<tr>
<td>Comorbidity, primary diagnosis, and gout medications</td>
<td>11 (0.1)</td>
<td>54 (0.0)</td>
</tr>
</tbody>
</table>

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

4Covariates 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, angiotension-converting enzyme inhibitors and angiotension 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).

©2010 American Medical Association. All rights reserved.
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 = .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 3. Acute Gout Within 60 Days of Event Date and HF Outcomes

<table>
<thead>
<tr>
<th>Gout Status Within 60 d of Event Date</th>
<th>HF Readmission or Death</th>
<th>All-Cause Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted RR (95% CI)</td>
<td>Adjusted RR (95% CI)</td>
</tr>
<tr>
<td>Any acute gout</td>
<td>2.43 (1.68-3.52)</td>
<td>2.06 (1.39-3.06)</td>
</tr>
<tr>
<td>All hospital admissions for gout</td>
<td>4.83 (2.55-9.14)</td>
<td>2.77 (1.38-5.58)</td>
</tr>
<tr>
<td>All ED visits for gout</td>
<td>1.90 (1.22-2.97)</td>
<td>1.63 (1.02-2.63)</td>
</tr>
</tbody>
</table>

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

### Table 4. Effect of Allopurinol in All Patients With HF

<table>
<thead>
<tr>
<th>Allopurinol Exposure</th>
<th>Patients, No. (%)</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
</tr>
<tr>
<td>No current use</td>
<td>13 064 (91.2)</td>
<td>133 051 (92.9)</td>
</tr>
<tr>
<td>Current use</td>
<td>1263 (8.8)</td>
<td>10204 (7.1)</td>
</tr>
<tr>
<td>Duration of use b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30 d</td>
<td>187 (1.6)</td>
<td>954 (0.8)</td>
</tr>
<tr>
<td>&gt;30 d</td>
<td>881 (7.7)</td>
<td>7603 (6.7)</td>
</tr>
<tr>
<td>Dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤100 mg/d</td>
<td>997 (7.0)</td>
<td>8216 (5.7)</td>
</tr>
<tr>
<td>&gt;100 mg/d</td>
<td>266 (1.8)</td>
<td>1988 (1.4)</td>
</tr>
</tbody>
</table>

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

©2010 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/pdfaccess.ashx?url=/data/journals/intemed/20257/ on 05/28/2017
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).

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

| Allopurinol Exposure | Patients, No. (%) | HF Readmission or Death | | | | |
|----------------------|------------------|------------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
|                      | Cases            | Controls               | Unadjusted     | Adjusted<sup>a</sup> | P Value          |                   |
| 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<sup>b</sup> |                   |                       |                 |                 |                 |                   |
| ≤ 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.

<sup>a</sup>Covariates 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, antplatelets [acetylsalicylic acid and clopidogrel], warfarin, hydralazine, nonsteroidal inflammatory drugs, and corticosteroids).

<sup>b</sup>Analysis was limited to patients with more than 30 days of follow-up.

**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.<sup>26</sup> 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,<sup>44</sup> 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.<sup>5</sup> 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.<sup>1,3,24</sup> 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.<sup>46-48</sup> Increased oxidative stress causes inactivation of nitric oxide, which can worsen endothe-
dilatation and reductions in afterload.23,24,45 George et al24 also improve endothelial dysfunction, leading to vaso-
sensitivity and cardiac contractility by restoring myocardial calcium sen-
tance, and blood pressure after 4 weeks of treatment with
stratified lowered plasma renin activity, peripheral resist-
ance.12-18,47,48 Allopurinol improves myo-
mechanisms of allopurinol, which is known to
able. However, on the basis of the observational nature
of our study, our results should be interpreted with cau-
tion and should not be used as evidence supporting the
clinical use of allopurinol in HF. Given the possible se-
rious adverse events associated with allopurinol, only a
large randomized trial among patients with hyperuric-
emia and HF, both with and without a history of gout, can
evaluate the risks and benefits of such a strategy and pro-
vide 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 mis-
classification of outcomes. The diagnosis of gout using
administrative databases may also be prone to misclas-
sification. 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 sensi-
tivity 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 con-
founding. 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 esti-
mates. 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 avail-
ble. However, on the basis of the pathophysiolog-
ical 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 analy-
sis of acute gout may be inflated owing to reverse cau-
sality. We attempted to limit this problem by adjusting
for covariates that suggested a recent worsening in HF
(e.g., 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 repre-
sent 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 activ-
ity based on elevated serum uric acid levels or
increased markers of oxidative stress may help to
clarify the role of allopurinol in HF.

Accepted for Publication: January 25, 2010.
Correspondence: Louise Pilote, MD, MPH, PhD, De-
partment of Medicine, McGill University Health Cen-
ter, 687 Pine Ave W, Room A4.23, Montreal, QC H3A
1A1, Canada (louise.pilote@mcgill.ca).

Author Contributions: Drs Thanassoulis, Brophy, and
Pilote had full access to all of the data in the study and
take responsibility for the integrity of the data and the
accuracy of the data analysis. Study concept and design:
Thanassoulis, Brophy, Richard, and Pilote. Acquisition of
data: Thanassoulis, Brophy, Richard, and Pilote. Analysis
and interpretation of data: Thanassoulis, Brophy, and
Pilote. Drafting of the manuscript: Thanassoulis, Brophy,
and Pilote. Critical revision of the manuscript for impor-
tant intellectual content: Thanassoulis, Brophy, Richard,
and Pilote. Statistical analysis: Thanassoulis and Richard.
Obtained funding: Thanassoulis and Pilote. Administra-
tive, technical, and material support: Pilote. Study sup-
ervision: Brophy and Pilote.

Financial Disclosure: None reported.

Funding/Support: Dr Thanassoulis is a recipient of the
Fonds de Recherche en Sante du Quebec (FRSQ) MSc
Award for Medical Professionals. Drs Brophy and Pilote
are recipients of the FRSQ Chercheur-Boursier Award.

Role of the Sponsor: The sponsor had no role in the de-
sign and conduct of the study; collection, management,
analysis, and interpretation of the data; or preparation,
review, or approval of the manuscript.


