CLINICAL RESEARCH STUDY

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Effect of Allopurinol on Cardiovascular Outcomes in Hyperuricemic Patients: A Cohort Study

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ABSTRACT

BACKGROUND: Hyperuricemia and gout have been associated with increased cardiovascular risk. Allopurinol is an effective urate-lowering drug. Whether lowering of urate by allopurinol improves the cardiovascular risk in hyperuricemic patients remains to be established.

OBJECTIVE: Our objective was to investigate the effect of allopurinol on cardiovascular outcomes in hyperuricemic patients in an observational setting.

METHODS: We had access to a study population consisting of all patients from Funen County, Denmark with high urate levels (≥6 mg/dL) from 1992 to 2010. We linked 4 registries; all blood samples, all in- and outpatient contacts in hospitals, all reimbursed prescriptions and causes of death. We identified all incident allopurinol users and matched them 1:1 to nonusers of urate-lowering therapy, with similar urate levels, by using propensity scores. Hazard ratios were calculated using competing risk regression model, with respect to Antiplatelet Trialists' Collaboration composite outcome (myocardial infarction, stroke, or cardiovascular death) and all-cause mortality.

RESULTS: Among 65,971 patients with hyperuricemia, we found 7127 patients on allopurinol treatment. In the propensity score-matched cohort we found a hazard ratio of 0.89 (95% confidence interval, 0.81-0.97) for the main outcome among allopurinol treated compared with nonusers of allopurinol. The corresponding hazard ratio for all-cause mortality was 0.68 (95% confidence interval, 0.62-0.74).

CONCLUSION: Allopurinol treatment is associated with a decreased cardiovascular risk among hyperuricemic patients.

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KEYWORDS: Allopurinol; Cardiovascular outcomes; Gout; Hyperuricemia

Gout is the most frequent inflammatory arthritis among adults in developed countries, with a prevalence of 1%-4%.[1,2] Gout is associated with multiple comorbidities, including the metabolic syndrome.[3] Both hyperuricemia and gout prevalences are increasing.[2]

Hyperuricemia and gout are widely accepted as risk factors for cardiovascular diseases.[4-7] However, whether urate-lowering therapy prevents cardiovascular events in hyperuricemic patients is controversial.[8,9]

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Authorship: All authors had access to the data used in this study and have contributed equally to the conception and design of this study, revised the manuscript for important intellectual content, and approved the final version.

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Recent trials have shown positive effects of allopurinol on mild hypertension among hyperuricemic adolescents,[10] as well as on exercise capacity among patients with stable angina pectoris and no history of gout or hyperuricemia,[11] and by decreasing cardiovascular event rates among patients with chronic kidney disease.[12] Allopurinol has also shown beneficial effects on vascular oxidative stress and endothelial dysfunction.[13,14]

Despite accumulating evidence of the association among hyperuricemia, gout, and cardiovascular diseases, and suggested positive effects of allopurinol on cardiovascular risk factors, it is not established whether allopurinol per se has a beneficial effect on cardiovascular risk in hyperuricemic patients in general. The aim of this study was to investigate the effect of allopurinol on cardiovascular outcomes and all-cause mortality in a large cohort of hyperuricemic patients.

CLINICAL SIGNIFICANCE

- We find that allopurinol is associated with decreased cardiovascular outcomes.
- Our findings favor a more aggressive approach to prescribing allopurinol.

METHODS

The study was conducted as a cohort study using Danish health care databases in Funen County (approximately 480,000 inhabitants). Among hyperuricemic patients, we identified all incident allopurinol users, and matched this cohort, using propensity scores, with a comparable cohort of nonusers of allopurinol. We then compared the cardiovascular event rate between the 2 cohorts.

Data Sources

Data were extracted from 4 different databases: biochemical values were retrieved from the laboratory database of Odense University Hospital; information on redeemed prescription was identified in the Odense University Pharmacoepidemiological Database[15]; the Funen County Patient Administrative System holds information on all in- and outpatient contacts at hospitals; and causes of death were retrieved from the Danish Register of Causes of Death.[16] Further details on the databases can be found in the Appendix (available online).

The record linkage was made possible by a unique personal identifier, the Danish Central Person Registry Code,[17] assigned to all Danish citizens since 1968. In Denmark, public health authorities provide virtually all health services, which allows true population-based epidemiological studies.[18]

Urate Measurements

We had access to all analyses of urate concentration of residents from Funen County. Urate levels are derived from all individuals who had their electrolytes measured during the study period. Urate is included in a standard panel of analyses, but is reported only if it is also requested. The vast majority of the retrieved urate values were thus never reported to physicians or patients. On average, included individuals had 5 urate measurements. We choose a urate level $\geq$6.0 mg/dL (0.36 mmol/L) to define hyperuricemia, as this level is widely recognized as the treatment target of urate-lowering treatment[19,20] and is below the saturation point of urate at physiological condition.

Cohorts

We identified all adults ($\geq$18 years) with urate $\geq$6.0 mg/dL during the period of December 1992 through December 2010. Furthermore, we required individuals to be cancer free for a period of 5 years before cohort entry, defined as no diagnosis of malignancies (International Classification of Diseases, 8th Revision [ICD8] 140-207, ICD10 C00-C96), not considering nonmelanoma skin cancer (ICD8 173, IDC10 C44). Lastly, all individuals who redeemed any urate-lowering drugs (ATC M04AA, M04AB) at any time point before their first elevated urate were excluded.

Individuals were included in the study 30 days after the first elevated urate for nonusers of allopurinol or 30 days after the first redeemed allopurinol prescription for allopurinol users. We applied this 30-day quarantine period because urate measurements often were undertaken during an acute admission, and some of these admissions were related to an outcome.

Individuals were censored from both cohorts upon occurrence of any of the following events: main outcome (see below), death, migration, redeeming of any urate-lowering drug other than allopurinol, or study end.

Follow-up was divided into 2 cohorts: allopurinol treated and nontreated, see below.

To avoid immortal-time bias,[21] individuals could contribute follow-up to both the treated and nontreated cohort. Consider an individual with a record of elevated urate in 2000 who later, in 2005, redeems the first prescription for allopurinol. This individual would always contribute follow-up to the treated cohort (from 2005 and onwards), but would also contribute person-time to the nontreated cohort if sampled as a nonuser in 2000.

Allopurinol Treatment

An individual was considered treated with allopurinol on a given day if his most recent allopurinol prescription would cover that day, assuming an average daily intake of one tablet. We added a grace period of 25% to the period covered by each prescription, to allow for varying adherence and irregular prescription renewal.

Propensity Scores

A propensity score models the probability that a given individual will be treated. Matching on the propensity score offers an advantage in settings with many covariates in providing an optimal balancing of known covariates between the treated and nontreated cohorts.[22] Matching on the propensity score will largely exclude from analysis individuals with contraindications and individuals with absolute indication, as they have no available comparator.[22]

The propensity scores were calculated using logistic regression, estimating the likelihood that the individual was treated with allopurinol at the time of entry into the cohort. We included all available covariates at baseline with expected influence on outcome (risk factors), as well as covariates with suspected influence on both treatment and outcome (true confounders). For dichotomous variables, missing values were set as "not present," and for continuous variables we used median value imputation. For individuals contributing follow-up time in both cohorts, we calculated separate propensity scores, with baseline covariates referring to the time of inclusion. Details of the propensity score model are presented in the **Supplementary Table** (Appendix, available online).

Outcomes

The primary outcome was the Antiplatelet Trialists' Collaboration composite cardiovascular endpoint, in brief described as nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death.[23]

Secondarily, we looked at the diagnosis of acute myocardial infarction, stroke, cardiovascular death, and all-cause mortality independently.

All outcomes diagnoses were based on either discharge diagnoses from patients' records or death diagnoses from the Danish Register of Causes of Death, which builds on information from death certificates. For further details of the outcome definitions, see the Appendix (available online).

Analysis

We used pairwise nearest neighbor matching by the propensity score to match each allopurinol-treated individual to a nontreated one, applying a caliper of 0.05 on the propensity score scale.[24]

We then calculated hazard ratios with 95% confidence intervals (CIs) using competing risk regression. This method was chosen to account for the presumably large amount of informative censoring introduced by other than cardiovascular deaths (for the primary endpoint) during the long follow-up of this study.

For the main analysis, we introduced allopurinol as a time-varying exposure, comparing allopurinol-treated follow-up in the treated cohort with follow-up in the nontreated cohort. As this comparison may involve a skewed sampling of follow-up after allopurinol initiation that might affect the comparability achieved by propensity score matching, we chose to include in the model the covariates that were used to build the propensity score. Colchicine is not included, as it was not commercially available in Denmark during the entire study period and the use has therefore been extremely limited.

Cumulative incidence function curves were generated to illustrate users vs nonusers of allopurinol.

Prespecified Sensitivity and Subgroup Analyses

A number of sensitivity and subgroup analyses were performed. We stratified by age, sex, previous history of cardiovascular events, and renal function (according to chronic kidney disease stages).[25] Second, we performed the analysis on different Charlson Comorbidity Index groups.[26] Third, we analyzed the data considering only the first 5 years of follow-up. Fourth, we analyzed the data introducing a lag time of 90 days instead of 30. Fifth, we analyzed the data in an intention-to-treat manner, by introducing allopurinol as a dichotomous variable, where an individual was allocated to the allopurinol-exposed group once they redeemed a prescription for allopurinol. This was performed to investigate if noncausal effects of allopurinol would contribute, especially to all-cause mortality.

Finally, we included an analysis of how large a potential confounder should be to explain our results using the rule-out approach.[27]

This project was approved by the Danish Data Protection Agency. Registry-based studies do not require ethical approval in Denmark.[28]

RESULTS

A total of 65,971 patients fulfilled the inclusion criteria. After applying the 1:1 matching, a total of 14,254 patients were included in the analyses (**Figure 1**).

The baseline characteristics of allopurinol-treated and nontreated individuals were generally very well balanced (**Table 1**). The median age for both cohorts was 64 years (interquartile range 51-75 years), with more than 70% men, and the mean follow-up was 5.08 years. Their urate levels were 8.57 mg/dL and 8.24 mg/dL among the allopurinol users and nonusers, respectively.

Cardiovascular Events

The overall major cardiovascular event rate was 44.0 per 1000 person-years. For allopurinol users and nonusers, the event rate was 43.3 per 1000 treated person-years and 44.2 per 1000 person-years, respectively. Adjusted propensity score matched competing risk regression for hyperuricemic patients receiving allopurinol, demonstrated an adjusted hazard ratio for the primary outcome of 0.89 (95% CI, 0.81-0.97) compared with those not treated with allopurinol. Similar effect sizes were seen for myocardial infarctions, strokes, and cardiovascular deaths, although they did not reach statistical significance (**Table 2**).

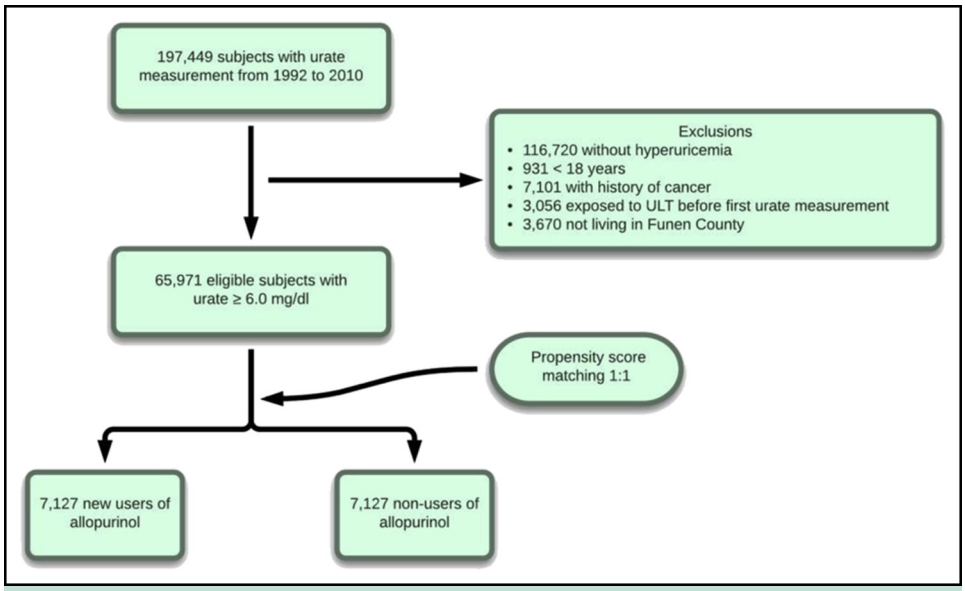

Figure 1 Study flow diagram. ULT = urate-lowering therapy.

A cumulative incidence function curve illustrating the occurrence of the main outcome for users vs nonusers of allopurinol is shown in Figure 2.

All-cause Mortality

The cohorts had a crude mortality of 39.6 per 1000 treated person-years in the allopurinol group and 47.1 per 1000 person-years among the nonusers, respectively. There was a significantly lower mortality among allopurinol users compared with nonusers (adjusted hazard ratio 0.68; 95% CI, 0.62-0.74) (Table 2).

All-cause mortality was consistently lower among allopurinol users compared with nonusers through all sensitivity analyses.

Subgroup Analyses

Different subgroup analyses on age strata, sex, urate level, or diabetes did not differ from main analysis, although in some subgroups the differences did not reach statistical significance. However, some tendencies were seen; among individuals with younger age and lower urate concentrations along with exclusion of individuals with former myocardial infarction or stroke, allopurinol seemed to have a more pronounced inverse association with cardiovascular events (Table 3).

Sensitivity Analyses

We performed an analysis including all follow-up time after inclusion without accounting for allopurinol pauses or discontinuations (intention-to-treat). In this analysis, no differences were identified between the allopurinol users and nonusers (hazard ratio 0.96, 95% CI, 0.89-1.03) with respect to the cardiovascular outcomes. Other sensitivity analyses did not differ from the main results (data not shown). The estimated size of how large an unmeasured confounder should be to account for our results is presented in the Supplementary Figure (Appendix, available online).

DISCUSSION

Main Findings

In this study, allopurinol use was associated with a decreased risk of major cardiovascular events, measured as the composite of myocardial infarction, stroke, and cardiovascular death.

Comparison with Other Studies

Allopurinol has, in small randomized controlled trials, shown its potential for lowering cardiovascular risk factors.[10-13] Allopurinol increases working capacity in angina patients,[11] and ameliorates hypertension[10] and vascular oxidative stress,[13] and lowers cardiovascular event rate among non-gout kidney patients.[12] It also seems that allopurinol can slow renal impairment in patients with chronic kidney disease.[12] Although none of these studies were made on a gout population, they support the finding in this study. One epidemiologic study has shown decreased cardiovascular risk among high-dose allopurinol users, compared with low-dose users.[29] Altogether, this indicates a protective effect of allopurinol use on major cardiovascular outcomes. In contrast to our findings, a newly published cohort study from Taiwan did not identify any associations between allopurinol use and no use in a population of gout patients.[30] The inverse association seen with all-cause mortality has been seen in other observational studies.[31,32]

Table 1 Baseline Characteristics of Allopurinol-treated and Nontreated Propensity Score-matched Hyperuricemic Patients

	Allopurinol Users	Nonusers of Allopurinol
Male	5197 (72.9%)	5141 (72.1%)
Age, median (IQR)	63 (51-74)	64 (51-76)
Charlson score		
Charlson 0	4140 (58.1%)	4090 (57.4%)
Charlson 1	1365 (19.2%)	1465 (20.6%)
Charlson 2	807 (11.3%)	812 (11.4%)
Charlson 3+	815 (11.4%)	760 (10.7%)
History of		
COPD	463 (6.5%)	472 (6.6%)
Heart failure	878 (12.3%)	834 (11.7%)
Ischemic heart disease	1499 (21.0%)	1509 (21.2%)
Transitory ischemic attack	197 (2.8%)	205 (2.9%)
Atrial fibrillation	759 (10.6%)	747 (10.5%)
Alcohol-related diagnoses	352 (4.9%)	357 (5.0%)
Diabetes mellitus	625 (8.8%)	603 (8.5%)
Hypertension	1400 (19.6%)	1331 (18.7%)
Stroke	382 (5.4%)	371 (5.2%)
Current drug use (baseline)		
Diabetes drugs	543 (7.6%)	522 (7.3%)
Diabetes drugs (ever use)	639 (9.0%)	627 (8.8%)
Vitamin K antagonists	443 (6.2%)	436 (6.1%)
Clopidogrel	73 (1.0%)	78 (1.1%)
Low-dose ASA	856 (12.0%)	850 (11.9%)
Dipyridamole	141 (2.0%)	144 (2.0%)
Comp of ASA and dipyridamole	49 (0.7%)	48 (0.7%)
Heart glycosides	701 (9.8%)	683 (9.6%)
Nitrates	431 (6.0%)	417 (5.9%)
Thiazide diuretics	777 (10.9%)	738 (10.4%)
Loop diuretics	1884 (26.4%)	1839 (25.8%)
Aldosterone antagonists	392 (5.5%)	370 (5.2%)
Beta-blockers	1308 (18.4%)	1302 (18.3%)
Calcium antagonists	1026 (14.4%)	1033 (14.5%)
RAAS blockers	2073 (29.1%)	2033 (28.5%)
Statins	969 (13.6%)	925 (13.0%)
COPD drugs	411 (5.8%)	434 (6.1%)
Systemic corticosteroids	555 (7.8%)	552 (7.7%)
NSAIDs	4028 (56.5%)	4188 (58.8%)
Alcohol related drugs	13 (0.2%)	15 (0.2%)
Blood measurements (baseline)		
Urate (mg/dL), median (IQR)	8.57 (7.73-9.58)	8.24 (7.23-9.75)
eGFR (ml/min), median(IQR)	64 (49-73)	65 (48-73)
High HbA1c	589 (8.3%)	569 (8.0%)
High cholesterol	2262 (31.7%)	2161 (30.3%)
Proteinuria	744 (10.4%)	689 (9.7%)

ASA = acetylsalicylic acid; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; IQR = interquartile range; NSAID = nonsteroidal anti-inflammatory drugs; RAAS = renin-angiotensin-aldosterone-system.

It is well known that gout patients have poor compliance[33,34] and are often undertreated.[35,36] In this light, the findings of this study become even more important, as the effect of allopurinol might be underestimated.

Strengths

This was a large cohort study including the entire population of Funen County in Denmark, with up to 18 years of follow-up. This region has a stable population and we were able to account for migration during the study period on the individual level. We had full coverage of admissions, outpatient visits, prescription data, causes of death, and all blood samples including urate measurements. The outcome diagnoses in the Danish registries have previously been validated.[37,38] Allopurinol users were comparable with the nonusers of allopurinol on all available important covariates through matching, including baseline levels of urate and Charlson Comorbidity Index (**Table 1**); thereby limiting the confounding by indication that would otherwise be introduced by increased likelihood of allopurinol treatment among patients with higher urate levels.[39] This also will diminish the confounding potentially introduced by increased health care utilization from having a gout diagnosis.

We undertook several sensitivity analyses, all with no changes to the main conclusion.

Limitations

The potential confounders were limited by the input from the various databases. Most importantly, we did not have access to smoking status, body mass index, and blood pressure, which are known risk factors for ischemic heart disease.[40,41] Heavy smoking was partly accounted for by controlling for chronic obstructive pulmonary diseases and related drug use.

The indication for prescribing allopurinol is restricted to patients who already have experienced urate precipitations (more than one gout attack, tophi, or urate nephrolithiasis).[19,42] Patients in the allopurinol-treated cohort are therefore more likely to have experienced a gout attack even though they are comparable on urate levels at baseline. The occurrence of gout was therefore unequally distributed. Gout itself is associated with increased acute and chronic inflammation,[43] and inflammatory activity can be prothrombotic and lead to ischemic cardiovascular events.[44,45] All together, this suggests a conservative bias in our estimates, that is, we are likely to underestimate the beneficial effect of allopurinol because the nontreated were less likely to be burdened by chronic inflammation.

Dietary compounds rich in purines, for example, shellfish, red meat, peas, spinach, and beer, are known to trigger gout,[46,47] and body mass index[41] was recently associated with urate levels. We do not have evidence to support that these factors were equally or unequally distributed. But even if these potential confounders were unevenly distributed, it would presumably not have affected our estimates, as the contribution from these factors is mediated through urate levels, which were comparable between the groups.

The apparently protective effect of allopurinol on all-cause mortality is more pronounced than the effect on our other outcomes, as allopurinol was associated with 32% lower all-cause mortality. Restriction of drugs due to frailty,

Table 2 Cardiovascular Outcomes and All-cause Mortality Among Allopurinol-treated and Nontreated Patients

	Allopurinol-treated Events/Person-years	Nontreated Events/Person-years	HR (95% CI)	Adjusted* HR (95% CI)
APTC events	792/18,272	1364/30,878	0.99 (0.91-1.08)	0.89 (0.81-0.97)
Nonfatal MI	168/18,272	288/30,878	1.00 (0.82-1.21)	0.89 (0.73-1.08)
Nonfatal stroke	259/18,272	484/30,878	0.92 (0.79-1.08)	0.88 (0.75-1.03)
CV death	365/18,272	592/30,878	1.03 (0.90-1.18)	0.90 (0.78-1.03)
All-cause deaths	723/18,272	1455/30,878	0.81 (0.74-0.89)	0.68 (0.62-0.74)

Nonusers of urate-lowering drugs was set as reference.
APTC = Antiplatelet Trialists' Collaboration (composite of MI, stroke, CV death); CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction.
*Adjusted for variables included in the propensity score model (**Supplementary Table**).

that is, drug discontinuation or selective nonprescribing in patients with short life expectancy[48] and immeasurable time bias[49] are probably the main cause of the inverse association with all-cause mortality. We do not expect this potential bias to affect the main outcome to the same extent. Preventive drugs are often withheld in patients whose prognosis is considered dismal, for example, in terminal cancer patients. However, the timing of strokes and myocardial infarctions are not as predictable as death in a terminal cancer patient, and thus preventive drugs cannot be withheld in anticipation of an acute vascular event.

In this study we do not have data to support whether urate was treat to target (<6.0 mg/dL) or not. Therefore, we cannot speculate as to whether the proposed effect found by allopurinol in this study is derived by the urate-lowering effect or by another mechanism, for example, by inhibition of xanthine oxidase.

Clinical Implication and Interpretation

In conclusion, allopurinol seems to be associated with a favorable cardiovascular outcome. This favors a more aggressive approach toward lowering uric acid in hyperuricemic gouty arthritis patients or possibly even in asymptomatic hyperuricemia. This will have to be elucidated in a randomized controlled trial.

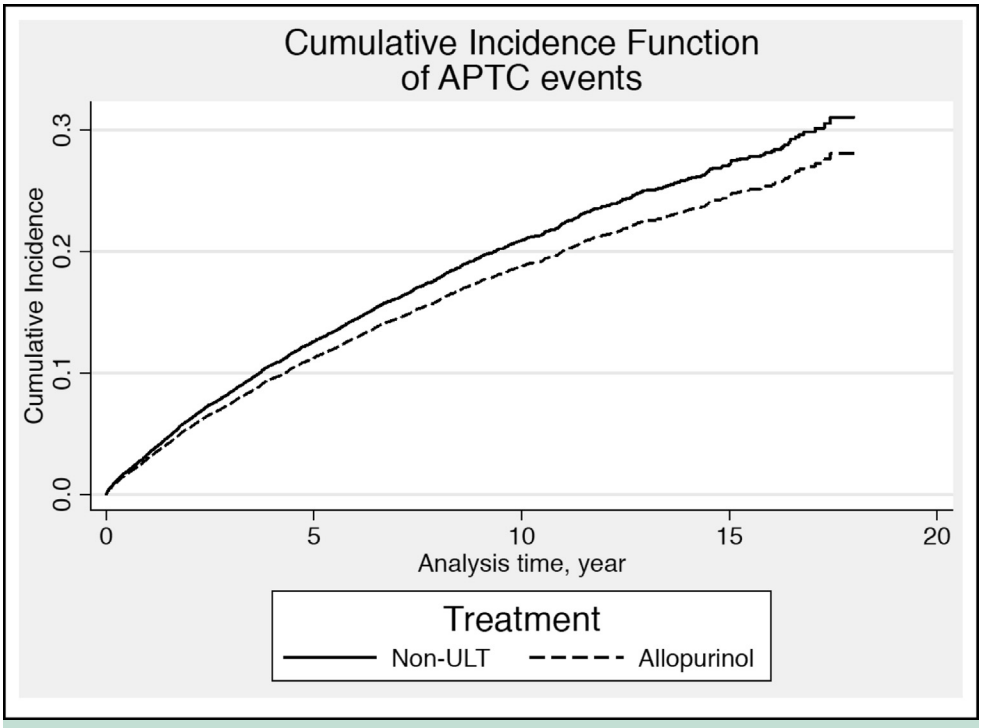

Figure 2 Cumulative incidence function of main composite cardiovascular outcomes in users and nonusers of allopurinol. APTC = Antiplatelet Trialists' Collaboration; ULT = urate-lowering therapy.

Table 3 Main Outcome in Different Subgroups Among Allopurinol-treated and Nontreated Patients

	Allopurinol-treated Events/Person-years	Nontreated Events/Person-years	Adjusted HR* (95% CI)
All	792/18,272	1364/30,878	0.89 (0.81-0.97)
Age <60 y	105/8,750	211/15,833	0.71 (0.55-0.91)
Age 60-79 y	393/7714	662/11,919	0.81 (0.71-0.92)
Age 80+ y	294/1808	491/3126	1.01 (0.87-1.17)
Male	553/13,807	902/22,822	0.88 (0.79-0.99)
Female	239/4465	462/8055	0.89 (0.76-1.05)
Urate <6.72 mg/dL	31/973	162/5604	0.72 (0.46-1.12)
Urate ≥6.72 mg/dL	761/17,299	1202/25,274	0.89 (0.81-0.98)
Urate <8.41 mg/dL	232/7393	614/18,707	0.86 (0.73-1.00)
Urate ≥8.41 mg/dL	560/10,879	750/12,171	0.93 (0.83-1.04)
No previous MI or stroke	519/16,339	988/28,042	0.85 (0.76-0.95)
Only previous MI or stroke	273/1933	376/2835	1.00 (0.85-1.18)
eGFR <30 mL/min	104/754	161/1338	1.05 (0.80-1.39)
eGFR 30-59 30 mL/min	453/6431	681/8456	0.88 (0.78-1.00)
eGFR 60-89 mL/min	224/10,413	499/18,996	0.76 (0.64-0.90)
eGFR ≥90 mL/min	11/674	23/2088	1.50 (0.62-3.60)
Diabetes	128/1578	192/2238	0.89 (0.70-1.13)
No diabetes	664/16,694	1172/28,640	0.88 (0.80-0.97)

Nonusers of urate-lowering drugs was set as reference.

CI = confidence interval; CV = cardiovascular; eGFR = estimated glomerular filtration rate; HR = hazard ratio; Main outcome = MI, stroke, CV death; MI = myocardial infarction.

*Adjusted for variables included in the propensity score model (**Supplementary Table**).

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SUPPLEMENTARY DATA

Supplementary table, figure and references associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.amjmed.2015.11.003

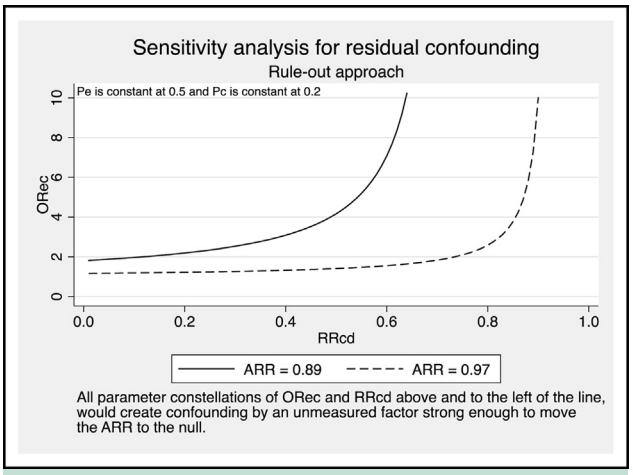
APPENDIX

Data Sources and Outcome Definition

The laboratory database of Odense University Hospital is a clinical laboratorial system, which contains information on all blood samples analyzed on various hospital laboratories in Funen County since November 1992. The coverage includes both primary and secondary health providers as well as both inpatients and outpatients. Blood samples not covered are some C-reactive protein, sedimentation rate, hemoglobin, and blood glucoses measured at general practitioners' offices, as well as some arterial blood analysis and blood glucoses measured at wards (primarily intensive care units and emergency departments) with independent equipment. All urate concentration measurements in primary or secondary care are covered.

Odense University Pharmaco-epidemiological Database (OPED) is a prescription database that holds information on redeemed, reimbursed prescriptions for the citizens of Funen County since 1990. Data included are identifiers of the prescription holder, a full account of the dispensed product, and the date of dispensing. The product is described in terms of the defined daily dose (DDD) and the anatomical-therapeutic-chemical (ATC) code.[1] Over-the-counter drugs are not included. OPED includes a demographic module with information on residency, migration, births, and death, which allowed us to account for censoring. Colchicine is not covered, as it was not commercially available in Denmark during the entire study period.

The Funen County Patient Administrative System holds data on all hospital contacts and discharge diagnosis for the population of Funen County since 1977 for inpatients and since 1989 for outpatients. The diagnoses are encoded according to the International Classification of Diseases, 8th Revision (ICD8) until January 1994 and ICD10 thereafter. ICD9 has never been used in Denmark.



Supplementary Figure Graphical illustration of how large a potential unmeasured confounder should be to account for our results. ARR = Apparent relative risk; ORec = Association between drug use and confounder; Pc = Prevalence of (potential unmeasured) confounder; Pe = prevalence af drug (in this case allopurinol) exposure; RRcd = Association between confounder and outcome.

The Danish Register of Causes of Death holds information on all causes of death in Danish citizens, encoded according to the ICD classification system mentioned above. It is mandatory by law to complete a death certificate in any case of death in Denmark, and the National Board of Health established the current register in 1875.

The Antiplatelet Trialists' Collaboration composite cardiovascular endpoint[2] was defined as any of the following diagnoses: acute myocardial infarction (ICD8 410; ICD10 I21-22), stroke (ICD8 430-434; ICD10 I60-I64), cardiovascular death (ICD8 390-458; ICD10 I00-99), or unknown causes of death (ICD8 780-796; ICD10 R96-99).

Supplementary Table ECovariates Included in the Propensity Score Model

	ICD 8	ICD 10	ATC Code
Sex			
Age*			
Inclusion year (clustered 5 y)			
Current use of:			
Antidiabetics			A10
Statins			C10AA
Heart glycosides			C01A
Low-dose ASA			B01AC06, B01AC30
Vitamin K antagonists			B01AA
RAAS blockers			C09
β-blockers			C07
Calcium channel blockers			C08
Loop diuretics			C03C
Thiazide diuretics			C03A
Spironolactone			C03DA
Systemic corticosteroids			H02AB
Nitrates			C01DA
ADP receptor inhibitors			B01AC04, B01AC22, B01AC24
Dipyridamole			B01AC07, B01AC30
NSAID			M01A
COPD-related medicine			R03BA, R03AC, R03BB
Previous history of:			
Diabetes	249-250	E10-14	
COPD	490-491	J44	
Alcohol-related diagnosis	303, 571	F10, K70	
Ischemic Stroke	432-434	I63, I64	
Transitory ischemic attack	435	G45	
Hypertension	40	I10	
Atrial fibrillation	4274	I48	
Ischemic heart disease	410-414	I20-25	
Heart failure	4270-4271	I110, I130, I132, I50	
Charlson Comorbidity Index			
Baseline blood measurements:			
eGFR*			
HbA1c >6.5%			
Total cholesterol >200 mg/dL			
Proteinuria			
Urate level*			

Current drug use was defined as redeeming a prescription within 90 days of inclusion, besides inhaled drugs, which was defined as ≥ 2 redeemed prescriptions within 180 days of inclusion. Previous diseases were defined by International Classification of Diseases, 8th Revision-(ICD8-) or ICD10-coded outpatient visits or admissions before inclusion.

ADP = adenosine diphosphate; ASA = acetylsalicylic acid; ATC = anatomical therapeutic chemical; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; ICD = International Classification of Diseases; NSAID = nonsteroidal antiinflammatory drugs; RAAS = renin-angiotensin-aldosterone system.

*Urate levels, eGFR, and age were included as continuous variables.

Supplementary References

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