RHEUMATOLOGY

Original article

doi:10.1093/rheumatology/kex232

Allopurinol and the risk of incident peripheral arterial disease in the elderly: a US Medicare claims data study

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Abstract

Objective. The aim was to examine whether allopurinol use is independently associated with a reduction in the risk of incident peripheral arterial disease (PAD) in the US elderly.

Methods. We used the 5% random Medicare sample from 2006 to 2012 to examine the association of allopurinol use and duration of use with the risk or hazard of incident PAD in a retrospective cohort study using a new user design. Multivariable Cox regression models adjusted for demographics, co-morbidity, cardiac medications and cardiac conditions. Hazard ratios (HRs) and 95% CIs were calculated.

Results. We identified 26 985 episodes of incident allopurinol use in 25 282 beneficiaries; 3167 allopurinol use episodes (12%) ended in incident PAD. In multivariable-adjusted analyses, allopurinol use was associated with an HR of 0.88 (95% CI: 0.81, 0.95) for incident PAD, as was female gender, HR 0.84 (95% CI: 0.78, 0.90). In a separate multivariable-adjusted model, compared with no allopurinol use, longer durations of allopurinol use were associated with lower HR of PAD: 181 days to 2 years, 0.88 (95% CI: 0.79, 0.97); and >2 years, 0.75 (95% CI: 0.63, 0.89). Other factors significantly associated with a higher HR of PAD were age 75 to <85 and $\geqslant 85$ years, higher Charlson index score and black race. Sensitivity analyses that adjusted for cardiac conditions and medications confirmed these findings, with minimal to no attenuation of HRs.

Conclusion. New allopurinol use was independently associated with a lower risk of PAD in the elderly. Longer allopurinol use durations seemed more protective. Mechanisms of the protective effect need to be investigated in future studies.

Key words: allopurinol, peripheral arterial disease, risk factor, elderly, Medicare claims, urate-lowering therapy, peripheral vascular disease.

CLINICAL SCIENCE

Rheumatology key messages

- Allopurinol use was independently associated with a lower risk of peripheral arterial disease in the elderly.
- Longer durations of allopurinol use seemed more protective against peripheral arterial disease than shorter durations.
- Compared with those with gout, people without gout had lower hazard of peripheral arterial disease.

Introduction

Peripheral arterial disease (PAD) is a common manifestation of atherosclerosis, with >200 million patients suffering with the disease worldwide [1]. PAD affects 8.5 million Americans, and its prevalence increases with age; 20–25% of adults 80 years and older have PAD [2]. The annual hospitalization costs for PAD ranged from $3775 for patients with asymptomatic PAD to $5800 for

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Submitted 9 March 2017; revised version accepted 22 May 2017

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revascularization in the USA [3]. Patients with PAD are also at higher risk of myocardial infarction (MI) and stroke [4]. Thus, PAD is a major public health problem, especially in the elderly.

Rheumatic conditions, including autoimmune arthritides, with a hallmark of systemic inflammation are associated with an increased risk of coronary artery disease (CAD) [5, 6]. Gout, characterized by hyperuricaemia with associated crystal-induced inflammation and joint disease, is the most common inflammatory arthritis in adults [7]. In a nested case-cohort study of 431 patients, hyperuricaemia was independently associated with higher risk of vascular events [8]. Hyperuricaemia was a significant independent risk factor for PAD in patients with type 2 diabetes [9]. In an analysis of a randomized controlled trial [10] and a UK clinical practice research database [11], gout was independently associated with a higher risk of PAD.

Recently, we found that use of allopurinol, the most commonly used urate-lowering therapy (ULT), was associated with a reduction of the risk of MI and stroke, acute manifestations of CAD [12, 13]. There are no data on whether ULT reduces the risk of incident CAD. With a recently described link between gout/hyperuricaemia and PAD and a similarity of disease pathophysiology between PAD and CAD (both manifestations of atherosclerosis), an important question is whether allopurinol use reduces the risk of PAD. If data support this link/hypothesis, it might constitute some of the first evidence of cardiovascular disease modification by the use of ULT. To our knowledge, no previous study has examined this question. We hypothesized that in the elderly, who have a high known burden of PAD [2], allopurinol use (hypothesis 1) and the duration of allopurinol use (hypothesis 2) will be associated with a reduction of incident PAD.

Methods

Study setting, data source and patient population

Data were obtained from the Centers for Medicare and Medicaid Services Chronic Condition Data Warehouse. A retrospective cohort study was conducted using a 5% random sample of persons who were Medicare beneficiaries during the period 2006–12. These data contain all insurance claims for each beneficiary and have been widely used for health services and outcomes research [14, 15]. We used several files to obtain data of interest, as follows: a beneficiary summary file that contained demographic information, birth date, death date, sex, race and monthly entitlement indicators (A/B/C/D); a Part D file that provided information on prescription claims, dose, supply and drug name; and inpatient and outpatient claim files that listed the diagnosis codes, procedure codes and claim dates. Beneficiaries were eligible for the study if they resided in the USA from 2006 to 2012, were enrolled in Medicare fee-for-service and pharmacy coverage (Parts A, B and D) and not enrolled in a Medicare Advantage Plan, and received new treatment with allopurinol (see next section for definition). The study was approved by the institutional review board at the University of Alabama at Birmingham, who waived the need for informed consent because this was a retrospective analysis of a database.

Study outcome

The outcome of interest was incident PAD, defined as the first occurrence of the diagnosis of PAD during the study period after initiation of new allopurinol use and the absence of PAD diagnosis during a baseline period of at least 365 days before the allopurinol initiation date. PAD was identified with the following list of International Classification of Diseases, ninth revision, common modification (ICD-9-CM) codes: 440.x, 441.x, 443.1–443.9, 447.1, 557.1, 557.9 and V43.4. This approach was found to be valid in 21 712 patients evaluated in the vascular laboratory, and outperformed a model-based algorithm with a higher specificity, 89 *vs* 83%, when compared with the gold-standard vascular laboratory-based definition of PAD [16]. The same codes have been used in the Elixhauser index [17], the second commonest medical co-morbidity index based on Charlson co-morbidities [18], used in claims-based studies [19]. The follow-up for each treatment episode began on the earliest allopurinol treatment initiation date during the study period and ended on the earliest of first date of PAD diagnosis, first date of losing full Medicare coverage, the date of death or the end of the study (31 December 2012). Patients could contribute multiple allopurinol treatment episodes during different time periods.

Allopurinol treatment definition and covariates

We used a new (incident) user design for this study. Days of exposure to treatment with allopurinol were calculated using the day's supply variable provided in the Medicare Part D records. New allopurinol treatment (or use) was defined as a filled allopurinol prescription, preceded by a 365-day baseline period during which no allopurinol prescriptions were filled. The exposure period extended 30 days past the end of supply of the filled allopurinol prescription; that is, a 90-day supply equated 120 days of exposure, 90 days of supply plus 30 days residual. We used the 30-day residual period to account for any residual protective effects of allopurinol and to capture less than perfect medication adherence, because most patients have left-over supply. If another allopurinol prescription was filled within 30 days of the end of supply, then we regarded this as a continuation of the treatment episode. If >30 days elapsed between filled allopurinol prescriptions, then they were considered separate allopurinol treatment episodes. Allopurinol use duration was categorized as none, 1–180 days, 181 days to 2 years and $\geqslant 2$ years. This arbitrary categorization was performed *a priori* for clinical relevance indicating short-term, intermediate-term and long-term allopurinol use.

The Medicare denominator file served as the source of covariates and included age at the index date of each allopurinol episode, gender, race, use of other common medications for cardiac disease and PAD [statins, diuretics,

angiotensin-converting enzyme (ACE) inhibitors, β-blockers, aspirin, clopidogrel, cilostazol and pentoxifylline], common cardiac conditions and risk factors (CAD, diabetes, hypertension, hyperlipidaemia and tobacco use disorder), identified using the respective ICD-9-CM codes (CAD, 410.xx, 411.xx, 412, 413.x, 414.xx; diabetes, 250.0x, 250.1x, 250.2x, 250.3x, 250.4x, 250.5x, 250.6x, 250.7x, 250.8x, 250.9x; hypertension, 401.xx, 402.xx, 403.xx, 404.xx, 405.xx; hyperlipidaemia, 272.0, 272.1, 272.2, 272.3, 272.4; tobacco use disorder, 305.1) and co-morbidity scores in the baseline period for each allopurinol treatment episode. We used the Charlson–Romano co-morbidity index score, which is a valid measure of medical co-morbidity [20]. We calculated the Charlson–Romano co-morbidity index using the ICD-9-CM codes for each co-morbidity [20] both with and without PAD contributing to the total score (see sensitivity analyses).

Statistical analyses

We compared episodes with and without occurrence of incident PAD and by allopurinol exposure *vs* not, by examining the summary statistics. We used Cox proportional hazard regression analyses to assess the association between incident allopurinol use and incident PAD as well as between the duration of allopurinol use and incident PAD. We performed univariate and multivariable-adjusted analysis adjusted for age, gender, race, Charlson–Romano co-morbidity index score and cardiac medications (models 1 and 2). Analyses were episode level rather than person level; therefore, patients could contribute more than one episode of new allopurinol use. We accounted for this correlation attributable to multiple episodes per person with the Huber–White 'sandwich' variance estimator [21] and used it to calculate robust standard errors for all estimates.

We performed sensitivity analyses using multivariable-adjusted Cox regression models to assess the associations after adding additional drugs commonly used for the treatment of PAD and related disorders (aspirin, clopidogrel, cilostazol and pentoxifylline; models 3 and 5) or additionally replacing the Charlson–Romano index by CAD and CAD risk factors (diabetes, hypertension, hyperlipidaemia and tobacco use disorder; models 4 and 6). Additional sensitivity models were run to account for a different calculation of the Charlson–Romano co-morbidity index score that excluded PAD. We also conducted sensitivity analyses, adjusting the main multivariable-adjusted Cox regression models for the duration of gout, including all patients or limited to patients with gout. We calculated hazard ratios (HRs) with 95% CIs. The level of statistical significance was set at $P < 0.05$.

Results

Cohort characteristics

We identified 26 985 episodes of incident allopurinol use (Fig. 1) from 25 282 eligible patients, who represented the 5% random sample of Medicare enrolees aged ⩾65 years receiving a new prescription of allopurinol and without PAD at baseline. Of these, 22 673 (84%) had gout. Of all incident allopurinol use episodes, 3167 (12%) episodes ended in a new diagnosis of PAD, whereas most allopurinol use episodes, 23 818 (88%), did not. We observed that an older age, higher Charlson–Romano index score and residence in the Northeast region were associated with incident PAD episodes; slight differences were also noted by race, but not by gender (Table 1).

Unadjusted and adjusted association of allopurinol use with incident PAD

The crude incidence rate of PAD per 1 000 000 person-days was lower with longer allopurinol use duration: 1–180 days, 212; 181 days to 2 years, 154; and >2 years, 115/1 000 000 person-days. In multivariable-adjusted analyses, allopurinol use was associated with a HR of 0.88 for incident PAD, that is, a 12% reduction in the expected hazard (Table 2). Other factors associated with significantly higher hazard of incident PAD were older age, male gender, higher Charlson–Romano index score, black race and the use of β-blockers.

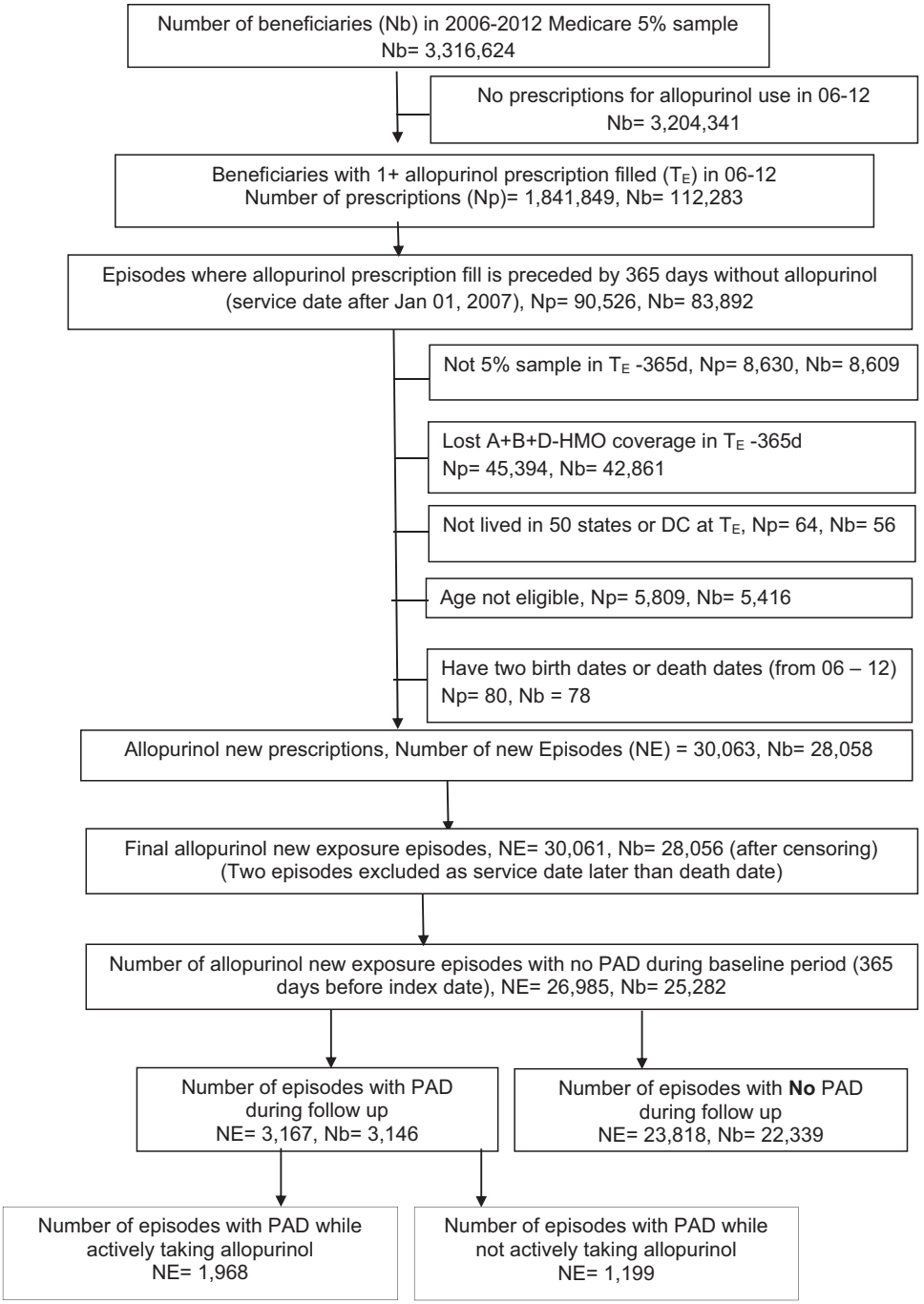
In a similar separate multivariable model, longer allopurinol use durations were associated with lower hazards of incident PAD compared with periods of non-use: 1–180 days was not significant, but 181 days to 2 years, and >2 years were significantly associated (Table 2).

Sensitivity analyses

The sensitivity analyses for allopurinol use (Table 3) or allopurinol use duration (Table 4), conducted by adding the drugs commonly used for the treatment of PAD and related disorders (aspirin, clopidogrel, cilostazol and pentoxifylline; models 3 and 5) or replacing the Charlson–Romano index by CAD, diabetes, hypertension, hyperlipidaemia and tobacco use disorder (models 4 and 6), confirmed the main results with minimal or no attenuation of HRs. CAD, hypertension and tobacco use disorder were also associated with a higher hazard of PAD, as were medications for PAD (Table 3). There were minimal or no changes in the estimates for allopurinol use or use duration in any model when the Charlson–Romano score was calculated without PAD (supplementary Table S1, available at *Rheumatology* Online).

We additionally adjusted models 1 and 2 (main analyses) for gout duration, both by including all patients and limiting the analyses to those with a diagnosis of gout (supplementary Table S2, available at *Rheumatology* Online). We found that this led to minimal attenuation of association of allopurinol use or allopurinol use duration with the risk of incident PAD and no change in significance (supplementary Table S2, available at *Rheumatology* Online). Duration of gout was not associated with the risk of PAD. Compared with those who had gout, people without gout had lower hazards of PAD (supplementary Table S2, available at *Rheumatology* Online).

Fig. 1 Patient selection flow chart



The flow chart shows the selection of new allopurinol exposure episodes after applying all the eligibility criteria, including an absence of PAD and the absence of any allopurinol filled prescription in the baseline period of 365 days (new user design). We found 26 985 new allopurinol exposure episodes in 25 282 patients. Of these, 3167 ended in incident PAD and 23 818 ended without incident PAD. We followed each eligible patient with a new filled allopurinol prescription until the patient lost full Medicare coverage, had PAD (the outcome of interest), died or reached the end of the study period on 31 December 2012, whichever came first. Given that some beneficiaries have multiple reasons for exclusions, numbers do not add up exactly. Also, beneficiaries could contribute multiple episodes, some resulting and some not resulting in incident PAD, and therefore the total exceeds the box right above (third from the bottom of the figure). Nb: number of beneficiaries; NE: number of qualified episodes of new allopurinol prescriptions; Np: number of allopurinol prescriptions; PAD: peripheral arterial disease; T_E: treatment episodes.

Table 1 Demographic and clinical characteristics of episodes of new allopurinol use[a]

	Allopurinol episodes	Incident PAD[b] during the follow-up		P-value[c]
		Yes	No	
Total episodes, n	26 985	3167	23 818	
Age, mean (S.D.), years	76.4 (7.4)	**77.7 (7.4)**	**76.3 (7.4)**	**<0.0001**
Gender, n (%)				0.070
Male	13 217 (49.0)	1599 (50.5)	11 618 (48.8)	
Female	13 768 (51.0)	1568 (49.5)	12 200 (51.2)	
Race/ethnicity, n (%)				**0.028**
White	21 279 (78.9)	**2486 (78.5)**	**18 793 (78.9)**	
Black	3305 (12.2)	**420 (13.3)**	**2885 (12.1)**	
Hispanic	558 (2.1)	**75 (2.4)**	**483 (2.0)**	
Asian	1203 (4.5)	**129 (4.1)**	**1074 (4.5)**	
Native American	93 (0.3)	**5 (0.2)**	**88 (0.4)**	
Other/unknown	547 (2.0)	**52 (1.6)**	**495 (2.1)**	
Region, n (%)				**<0.0001**
Northeast	4176 (15.5)	**676 (21.4)**	**3500 (14.7)**	
Midwest	6959 (25.8)	**740 (23.4)**	**6219 (26.1)**	
South	10 905 (40.4)	**1241 (39.2)**	**9664 (40.6)**	
West	4945 (18.3)	**510 (16.1)**	**4435 (18.6)**	
Charlson–Romano co-morbidity score, mean (S.D.)	3.48 (3.17)	**4.20 (3.19)**	**3.39 (3.15)**	**<0.0001**

Numbers listed are at episode level and do not reflect the number of individual patients. Bold represents statistically significant values with $P < 0.05$. [a]A new allopurinol prescription was defined as a filled allopurinol prescription, preceded by a 365-day baseline period during which no allopurinol prescriptions were filled. [b]Incident PAD was defined as a new diagnosis of PAD after a qualifying allopurinol prescription, with no PAD diagnosis in the baseline period of 365 days before the index date of allopurinol episode. [c]*t*-tests for difference between means for age and Charlson score and χ^2 tests for categorical variables. PAD: peripheral arterial disease.

Discussion

PAD is associated with a significant public health burden [1] and cost burden [2, 3]. Studies have shown that hyperuricaemia is associated with PAD [8, 9]. In the present study, we investigated whether treatment of hyperuricaemia with ULT, in our case allopurinol (the most commonly used ULT), reduced this risk. We found that allopurinol use was associated with a reduction of risk of PAD in the US elderly. Several study findings provide new insights and merit further discussion.

Our study showed that the incident allopurinol use was independently associated with a lower hazard of incident PAD in a large, representative sample of the US elderly, with a 12% reduction in multivariable-adjusted analyses. The magnitude of hazard reduction is clinically meaningful. Given that allopurinol is generally safe to use, including patients with renal impairment [22], and the annual patient out-of-pocket expense may be as low as <$50 at discount pharmacies ($12 for 90-day supply), regardless of health insurance status in the USA, this is also practical. The expense of allopurinol in other countries is likely to be similar or lower.

The exact mechanism by which allopurinol is potentially protective against the risk of PAD is unknown. Xanthine oxidase has long been suspected to play a role in cardiovascular disease. Xanthine oxidase inhibitors, such as allopurinol, have been of great interest owing to a dual mechanism of reduction of oxidative stress and urate lowering, which can potentially reduce the risk of cardiovascular disease. In addition, recent studies showed that hyperuricaemia was a significant independent risk factor for PAD in patients with type 2 diabetes [9] and vascular events (including PAD) [8]. Likewise, gout, a condition characterized by hyperuricaemia and symptomatic arthritis, was independently associated with a higher risk of PAD [10, 11]. We speculate that the positive association of allopurinol use and prevention of PAD noted in our study may be mediated via the urate-lowering action. The antioxidant action of allopurinol [23–30] and associated improvement in endothelial function noted in renal failure, diabetes, sleep apnoea and heart failure [31–41] may also contribute to this beneficial effect of preventing PAD. These mechanisms may delay the progression of atherosclerosis [42] and thus may explain the risk reduction of incident PAD with allopurinol. We believe that additional evidence is needed from animal models of PAD and well-planned prospective studies in humans to gain a better understanding of this potential benefit of PAD risk reduction with allopurinol.

Our study also found that, when compared with periods of allopurinol non-use, longer durations of allopurinol use (>6 months) were independently associated with significant hazard reduction for incident PAD (durations of >6–24 months, 12% and >2 years, 25% hazard reductions), whereas a duration of ⩽6 months was not. These associations did not attenuate after adjusting for use of common treatments for PAD and related disorders or after

Table 2 Allopurinol use and the hazard of incident peripheral arterial disease[a] in new allopurinol users[b]

	Univariate		Multivariable adjusted (model 1)		Multivariable adjusted (model 2)	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age, years						
65 to < 75	Ref.		Ref.		Ref.	
75 to < 85	**1.37 (1.27, 1.48)**	**<0.0001**	**1.31 (1.21, 1.42)**	**<0.0001**	**1.32 (1.22, 1.43)**	**<0.0001**
⩾85	**1.83 (1.66, 2.01)**	**<0.0001**	**1.74 (1.58, 1.92)**	**<0.0001**	**1.78 (1.61, 1.96)**	**<0.0001**
Gender						
Male	Ref.		Ref.		Ref.	
Female	0.93 (0.87, 1.00)	0.052	**0.84 (0.78, 0.90)**	**<0.0001**	**0.84 (0.78, 0.90)**	**<0.0001**
Race						
White	Ref.		Ref.		Ref.	
Black	**1.16 (1.05, 1.29)**	**0.005**	**1.15 (1.03, 1.27)**	**0.009**	**1.15 (1.04, 1.28)**	**0.007**
Other	0.92 (0.81, 1.05)	0.21	0.92 (0.81, 1.04)	0.19	0.91 (0.80, 1.03)	0.15
Charlson–Romano score, per unit change	**1.12 (1.11, 1.13)**	**<0.0001**	**1.11 (1.10, 1.12)**	**<0.0001**	**1.11 (1.09, 1.12)**	**<0.0001**
Diuretics	**1.19 (1.03, 1.38)**	**0.02**	1.10 (0.94, 1.29)	0.23	1.04 (0.88, 1.23)	0.66
Statins	1.03 (0.88, 1.22)	0.69	0.99 (0.83, 1.17)	0.89	0.92 (0.76, 1.10)	0.36
ACE inhibitor	1.05 (0.87, 1.26)	0.62	1.04 (0.86, 1.26)	0.68	1.01 (0.82, 1.24)	0.91
β-Blockers	**1.34 (1.15, 1.56)**	**0.0001**	**1.28 (1.09, 1.50)**	**0.002**	**1.29 (1.09, 1.54)**	**0.003**
Allopurinol (Ref., no)	**0.91 (0.84, 0.98)**	**0.01**	**0.88 (0.81, 0.95)**	**0.001**	–	–
Allopurinol use duration[c]						
0 days	Ref.		–	–	Ref.	
1–180 days	0.97 (0.88, 1.08)	0.64	–	–	0.96 (0.86, 1.07)	0.43
181 days to 2 years	0.91 (0.82, 1.00)	0.06	–	–	**0.88 (0.79, 0.97)**	**0.008**
>2 years	**0.77 (0.65, 0.91)**	**0.002**	–	–	**0.75 (0.63, 0.89)**	**0.001**

Model 1: allopurinol use + age + race + gender + Charlson–Romano score + β-blockers + diuretics + ACE inhibitors + statins. Model 2: allopurinol duration + age + race + gender + Charlson–Romano score + β-blockers + diuretics + ACE inhibitors + statin. Bold represents statistically significant values with p-value <0.05. [a]Incident PAD was defined as a new diagnosis of PAD after a qualifying allopurinol prescription, with no PAD diagnosis in the baseline period of 365 days before the index date of allopurinol episode. [b]A new allopurinol prescription was defined as a filled allopurinol prescription, preceded by a 365-day baseline period during which no allopurinol prescriptions were filled. [c]Based on person day count. ACE: angiotensin-converting enzyme; HR: hazard ratio; PAD: peripheral arterial disease; Ref.: reference category; –: variable not included in the model.

adjusting for CAD and associated risk factors. This dose–response relationship with the longer allopurinol use durations is interesting, fulfils an additional Bradford–Hill criterion for causation and further supports the notion that allopurinol use is associated with a reduction of hazard of incident PAD.

We are unaware of previous studies that have investigated allopurinol and the risk of PAD; therefore, to our knowledge, there are no data with which to compare our study results. However, studies have examined whether allopurinol increases the risk of CAD, a condition similar to PAD. Allopurinol use was associated with a 48% reduction in the HR for incident non-fatal MI in an incident user design study of a Spanish database [43] *vs* a 25% increase in the HR of a cardiovascular event requiring hospitalization (including MI, hypertension, stroke, etc.) in a prevalent user design study of Taiwanese patients with gout [44]. A randomized, placebo-controlled, crossover trial of 65 adults with angiographically documented CAD, a positive exercise tolerance test and stable chronic angina pectoris to allopurinol (600 mg/day) *vs* placebo for 6 weeks showed that allopurinol led to a statistically significant increase in the median time to ST depression (P = 0.0002; difference 43 s) and median total exercise time (P = 0.0003) [45]. In a recent study of Medicare data, we found that allopurinol use was associated with a reduction of the risk of incident MI in the elderly [12]. Thus, evidence from observational studies (except one study) and a randomized trial suggests a cardioprotective effect of allopurinol.

We conducted several sensitivity analyses that confirmed the findings of the main model. Sensitivity models substituted Charlson–Romano index score with specific conditions, including CAD as well as diabetes, hyperlipidaemia and tobacco use disorder (risk factors for CAD and PAD) [46] or added medications used for PAD or CAD (aspirin, clopidogrel, pentoxifylline or cilostazol) or used a modified Charlson–Romano score without PAD. Findings from the main analyses were replicated in these analyses, indicating that our findings of associations of allopurinol use and allopurinol use duration with PAD were robust.

Allopurinol is the most commonly used ULT [47, 48]. Our findings have implications for patient care. Most patients with gout are treated with allopurinol, and cardiovascular co-morbidity is very common in these patients [49]. If our finding can be replicated independently, it would be reasonable to discuss an added potential

TABLE 3 Sensitivity analyses: allopurinol use and the risk of incident peripheral arterial disease, adjusted for specific medications or cardiovascular disease and risk factors

	Univariate		Multivariable adjusted[a] (model 3)		Multivariable adjusted[a] (model 4)	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age, years						
65 to < 75	Ref.		Ref.		Ref.	
75 to < 85	**1.37 (1.27, 1.48)**	**<0.0001**	**1.32 (1.22, 1.43)**	**<0.0001**	**1.27 (1.18, 1.38)**	**<0.0001**
⩾85	**1.83 (1.66, 2.01)**	**<0.0001**	**1.77 (1.60, 1.95)**	**<0.0001**	**1.67 (1.51, 1.85)**	**<0.0001**
Gender	–	–	–	–	–	–
Male	Ref.		Ref.		Ref.	
Female	0.93 (0.87, 1.00)	0.052	**0.84 (0.78, 0.90)**	**<0.0001**	**0.88 (0.82, 0.95)**	**0.0004**
Race	–	–	–	–	–	–
White	Ref.		Ref.		Ref.	
Black	**1.16 (1.05, 1.29)**	**0.005**	**1.15 (1.04, 1.28)**	**0.007**	**1.17 (1.05, 1.30)**	**0.0037**
Other	0.92 (0.81, 1.05)	0.21	0.91 (0.80, 1.03)	0.14	0.93 (0.81, 1.05)	0.24
Charlson–Romano score	**1.12 (1.11, 1.13)**	**<0.0001**	**1.10 (1.09, 1.12)**	**<0.0001**	-	-
Specific conditions[b]						
CAD	**2.15 (2.00, 2.31)**	**<0.0001**	–	–	**1.79 (1.65, 1.93)**	**<0.0001**
Diabetes	**1.32 (1.23, 1.42)**	**<0.0001**	–	–	1.05 (0.97, 1.14)	0.23
Hypertension	**1.41 (1.27, 1.57)**	**<0.0001**	–	–	**1.15 (1.03, 1.29)**	**0.014**
Hyperlipidaemia	**1.11 (1.03,1.19)**	**0.0057**	–	–	0.97 (0.89, 1.04)	0.35
Tobacco use disorder	**1.55 (1.20, 2.00)**	**0.0009**	–	–	**1.51 (1.16, 1.95)**	**0.002**
Diuretics	**1.19 (1.03, 1.38)**	**0.02**	1.09 (0.93, 1.27)	0.31	1.08 (0.92, 1.26)	0.34
Statins	1.03 (0.88, 1.22)	0.69	0.92 (0.78, 1.10)	0.36	0.90 (0.75, 1.07)	0.21
ACE inhibitor	1.05 (0.87, 1.26)	0.62	1.02 (0.84, 1.23)	0.88	1.01 (0.84, 1.22)	0.90
β-Blockers	**1.34 (1.15, 1.56)**	**0.0001**	**1.21 (1.03, 1.43)**	**0.019**	1.16 (0.99, 1.37)	0.070
Allopurinol (Ref., no)	**0.91 (0.84, 0.98)**	**0.015**	**0.89 (0.82, 0.96)**	**0.001**	**0.87 (0.81, 0.94)**	**0.0005**

Sensitivity analyses for the association of allopurinol use duration with the risk of incident PAD, including specific drugs commonly used for the treatment of PAD and related disorders (model 3; clopidogrel, cilostazol, pentoxifylline and aspirin with or without dipyridamole) or additionally replacing Charlson–Romano index by coronary artery disease (CAD) and CAD risk factors (model 4; diabetes, hypertension, hyperlipidaemia, tobacco use disorder). Model 3 = model 1 + drugs commonly used for the treatment of PAD. Model 4 = model 1 + drugs commonly used for the treatment of PAD + CAD and CAD risk factors (instead of Charlson–Romano index). Bold represents statistically significant values with $P < 0.05$. [a]Additionally adjusted for clopidogrel, cilostazol, pentoxifylline and aspirin (with or without dipyridamole); all except aspirin were significantly associated. [b]Specific conditions were identified by the presence of the respective ICD-9-CM codes: CAD, 410.xx, 411.xx, 412, 413.x, 414.xx; diabetes, 250.0x, 250.1x, 250.2x, 250.3x, 250.4x, 250.5x, 250.6x, 250.7x, 250.8x, 250.9x; hypertension, 401.xx, 402.xx, 403.xx, 404.xx, 405.xx; hyperlipidaemia, 272.0, 272.1, 272.2, 272.3, 272.4; tobacco use disorder, 305.1. ACE: angiotensin-converting enzyme; CAD: coronary artery disease; HR: hazard ratio; PAD: peripheral arterial disease; Ref.: reference category; –: variable not included in the model.

benefit of allopurinol of lowering of the risk of PAD during the risk–benefit assessment with a patient starting allopurinol. We are confident that more investigations in this area will better define the magnitude of this effect.

Our study findings must be interpreted and applied considering study limitations and strengths. Confounding bias is a limitation of the study design and a potential limitation. We adjusted our observational study for PAD and CAD risk factors, medical co-morbidity, demographics and the use of cardiac medications, to account for several potential confounders to decrease the risk of residual confounding. Medicare data permit us only to account for conditions that are accurately labelled with an ICD-9 code for the diagnosis. PAD evolves slowly, disease often exists before symptoms manifest, and symptoms often exist years before diagnosis is made. Medicare data do not allow access to the patients' charts to verify the validity of the diagnosis code listed in the claim file. Therefore, underdiagnosis and/or misclassification bias are both possible, which would be likely to have biased findings towards null. This indicates that these estimates are, at best, conservative estimates of the real effect, and we may have missed some associations. However, this list of ICD-9 codes has been validated against vascular laboratory diagnosis of PAD with specificity of 89% and positive predictive value of 94% [16]. This ICD-9 code is also used in the Elixhauser index [17], the second commonest co-morbidity index used in claims studies after the Deyo index [19]. The association of PAD medications with the risk of PAD indicated that PAD medication use was a surrogate for some people with undiagnosed PAD (data available on request). We considered, but decided *a*

Table 4 Sensitivity analyses: allopurinol use duration and the risk of incident peripheral arterial disease, adjusted for specific medications or cardiovascular disease

	Univariate		Multivariable adjusted[a] (model 5)		Multivariable adjusted[a] (model 6)	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age, years						
65 to < 75	Ref.		Ref.		Ref.	
75 to < 85	**1.37 (1.27, 1.48)**	**<0.0001**	**1.32 (1.22, 1.43)**	**<0.0001**	**1.28 (1.18, 1.38)**	**<0.0001**
⩾85	**1.83 (1.66, 2.01)**	**<0.0001**	**1.77 (1.60, 1.95)**	**<0.0001**	**1.68 (1.51, 1.85)**	**<0.0001**
Gender	–	–	–	–	–	–
Male	Ref.		Ref.		Ref.	
Female	0.93 (0.87, 1.00)	0.052	**0.84 (0.78, 0.90)**	**<0.0001**	**0.88 (0.82, 0.94)**	**0.0004**
Race	–	–	–	–	–	–
White	Ref.		Ref.		Ref.	
Black	**1.16 (1.05, 1.29)**	**0.005**	**1.15 (1.04, 1.28)**	**0.009**	**1.16 (1.05, 1.29)**	**0.005**
Other	0.92 (0.81, 1.05)	0.21	0.90 (0.80, 1.03)	0.12	0.92 (0.81, 1.05)	0.21
Charlson–Romano score	**1.12 (1.11, 1.13)**	**<0.0001**	**1.10 (1.09, 1.12)**	**<0.0001**	–	–
Specific conditions[b]						
CAD	**2.15 (2.00, 2.31)**	**<0.0001**	–	–	**1.79 (1.65, 1.93)**	**<0.0001**
Diabetes	**1.32 (1.23, 1.42)**	**<0.0001**	–	–	1.05 (0.97, 1.14)	0.23
Hypertension	**1.41 (1.27, 1.57)**	**<0.0001**	–	–	**1.15 (1.03, 1.29)**	**0.013**
Hyperlipidaemia	**1.11 (1.03, 1.19)**	**0.006**	–	–	0.96 (0.89, 1.04)	0.35
Tobacco use disorder	**1.55 (1.20, 2.00)**	**0.001**	–	–	**1.51 (1.17, 1.95)**	**0.002**
Diuretics	**1.19 (1.03, 1.38)**	**0.02**	1.08 (0.93, 1.27)	0.32	1.08 (0.92, 1.26)	0.35
Statins	1.03 (0.88, 1.22)	0.69	0.92 (0.78, 1.09)	0.35	0.89 (0.75, 1.06)	0.20
ACE inhibitor	1.05 (0.87, 1.26)	0.62	1.01 (0.84, 1.23)	0.89	1.01 (0.84, 1.22)	0.91
β-Blockers	**1.34 (1.15, 1.56)**	**0.0001**	1.21 (1.03, 1.43)	0.020	1.16 (0.99, 1.37)	0.07
Allopurinol use duration[c]						
0 days	Ref.		Ref.		Ref.	
1–180 days	0.97 (0.88, 1.08)	0.64	0.96 (0.86, 1.06)	0.40	0.94 (0.85, 1.05)	0.28
181 days to 2 years	0.91 (0.82, 1.00)	0.056	**0.88 (0.79, 0.97)**	**0.008**	**0.86 (0.78, 0.95)**	**0.003**
>2 years	**0.77 (0.65, 0.91)**	**0.002**	**0.75 (0.63, 0.89)**	**0.001**	**0.75 (0.63, 0.89)**	**0.001**

Sensitivity analyses for the association of allopurinol use duration with the risk of incident PAD, including specific drugs commonly used for the treatment of PAD and related disorders (model 5; clopidogrel, cilostazol, pentoxifylline and aspirin with or without dipyridamole) or additionally replacing Charlson–Romano index by CAD and CAD risk factors (model 6; diabetes, hypertension, hyperlipidaemia, tobacco use disorder). Model 5 = model 2 + drugs commonly used for the treatment of PAD. Model 6 = model 2 + drugs commonly used for the treatment of PAD + CAD and CAD risk factors. Bold represents statistically significant values with $P < 0.05$. [a]Additionally adjusted for clopidogrel, cilostazol, pentoxifylline and aspirin (with or without dipyridamole); all except aspirin were significantly associated. [b]Specific conditions were identified by the presence of the respective ICD-9-CM codes: CAD, 410.xx, 411.xx, 412, 413.x, 414.xx; diabetes, 250.0x, 250.1x, 250.2x, 250.3x, 250.4x, 250.5x, 250.6x, 250.7x, 250.8x, 250.9x; hypertension, 401.xx, 402.xx, 403.xx, 404.xx, 405.xx; hyperlipidaemia, 272.0, 272.1, 272.2, 272.3, 272.4; tobacco use disorder, 305.1. [c]Based on person-day count. ACE: angiotensin-converting enzyme; CAD: coronary artery disease; HR: hazard ratio; PAD: peripheral arterial disease; Ref.: reference category; –: variable not included in the model.

priori, not to use PAD medications in the definition for PAD, because a small proportion of PAD is treated, and the validity of such an approach has not been established.

The main strength of this study is the use of a sample representative of all US elderly. Therefore, the findings are generalizable to the elderly population of the USA; generalizability to other populations is not known. We adjusted for multiple confounders and covariates and performed multiple sensitivity analyses, which confirmed the robustness of these findings. We used the incident (or new) user design, which has many advantages over a prevalent user design in that it reduces bias by allowing capture of both early and late events and avoiding adjustment for factors potentially in the causal pathway [50].

Conclusion

In conclusion, using a new user design, robust analyses and a 5% random Medicare beneficiary sample representative of all US elderly, we found that allopurinol use was independently associated with a lower risk of incident PAD. This study also showed that compared with non-use, allopurinol use durations of > 6 months were associated with increasing risk reduction of PAD. Our results based on retrospective observational data have

generated hypotheses that need to be proved by larger prospective interventional controlled trials. Mechanisms of this potential protective effect, that is, urate lowering *vs* anti-oxidative stress action, need to be examined in future prospective observational and randomized studies as well as using animal models.

Acknowledgements

We thank our patients at the University of Alabama Health Sciences Foundation Gout clinic and at the rheumatology clinic at the University of Alabama at Birmingham, who turned our attention to this important clinical problem and guided our study question. Author contributions: J.A.S.: study conception and design, development of study protocol, review of statistical analyses, writing the first draft of the manuscript, critical revisions and submission of the manuscript, approval of the final manuscript version. D.C.: data programming and quality monitoring, performance of statistical analyses, critical revisions and approval of the final manuscript version. The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government.

Funding: This material is the result of work supported by research funds from UAB Division of Rheumatology and the resources and use of facilities at the Birmingham VA Medical Center. The funding agency had no role in designing, interpreting or making the decision to submit the study. These decisions were made solely by the study authors.

Disclosure statement: J.A.S. has received research grants from Takeda and Savient and consultant fees from Savient, Takeda, Regeneron, Merz, Iroko, Bioiberica, Crealta/Horizon and Allergan pharmaceuticals, WebMD, UBM LLC and the American College of Rheumatology (ACR), serves as the principal investigator for an investigator-initiated study funded by Horizon pharmaceuticals through a grant to DINORA, Inc., a 501 (c)(3) entity, is a member of the executive of OMERACT, an organization that develops outcome measures in rheumatology and receives arms-length funding from 36 companies; a member of the ACR Annual Meeting Planning Committee; Chair of the ACR Meet-the-Professor, Workshop and Study Group Subcommittee; and a member of the Veterans Affairs Rheumatology Field Advisory Committee and is the editor and Director of the UAB Cochrane Musculoskeletal Group Satellite Center on Network Meta-analysis. The other author has declared no conflicts of interest.

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