Impact of allopurinol use on urate concentration and cardiovascular outcome

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Guidelines recommend that the therapeutic goal of urate-lowering therapy (ULT) is to achieve a urate concentration of ≤ 6 mg dl^{-1}.
- High-dose allopurinol is associated with reduced cardiovascular events and mortality in heart failure patients.

WHAT THIS STUDY ADDS

- Less than 50% of patients taking allopurinol reached target urate concentration.
- Higher doses of allopurinol were associated with better control of urate and lower risks of both cardiovascular events and mortality in all patients on allopurinol treatment.

AIMS

To characterize patients with urate measurements by urate-lowering therapy (ULT) use and to study the impact of allopurinol treatment on cardiovascular and mortality outcomes.

METHODS

A cohort study using a record-linkage database. The study included 7135 patients aged ≥ 60 years with urate measurements between 2000 and 2002 followed up until 2007. A Cox regression model was used. The association between urate levels, dispensed allopurinol and cardiovascular hospitalization and mortality was determined.

RESULTS

Six thousand and forty-two patients were not taking ULT and 45.9% of those (2774 of 6042) had urate concentrations ≤ 6 mg dl^{-1}. Among 1035 allopurinol users, 44.7% (45.6% for men and 43.3% for women) reached target urate concentration. There was no significant increased risk of cardiovascular events for allopurinol users when compared with non-ULT users [adjusted hazard ratio (HR) 1.10, 95% confidence interval (CI) 0.95–1.26] and the non-ULT group with urate >6 mg dl^{-1} (adjusted HR 1.07, 95% CI 0.89–1.28). Within the allopurinol use cohort, cardiovascular event rates were 74.0 (95% CI 61.9–86.1) per 1000 person years for the 100 mg group, 69.7 (49.6–89.8) for the 200 mg group and 47.6 (38.4–56.9) for the ≥ 300 mg group. Compared with low-dose (100 mg) users, high-dose (≥ 300 mg) users had significant reductions in the risk of cardiovascular events (adjusted HR 0.69, 95% CI 0.50–0.94) and mortality (adjusted HR 0.75, 95% CI 0.59–0.94).

CONCLUSIONS

Less than 50% of patients taking allopurinol reached target urate concentration. Higher doses of allopurinol were associated with better control of urate and lower risks of both cardiovascular events and mortality.

Introduction

Allopurinol is a widely used urate-lowering therapy (ULT) in patients with gout and hyperuricaemia. The therapeutic aim is to lower serum urate levels and prevent the precipitation of urate crystals. Clinical studies have shown that maintaining serum uric acid levels ≤ 6.0 mg dl^{-1} (or ≤ 0.36 µmol l^{-1}) results in a reduction in the incidence of gout flares, decreased numbers of urate crystals in aspirated fluid from joints and reductions in size and number of tophi [1–3].

However, a significant limitation of this therapy is that the target urate level of ≤ 6.0 mg dl^{-1} is achieved in less than 50% of patients with gout receiving a standard dose of 300 mg of allopurinol [4]. Recently it has been shown that dose escalation may help to increase the success rate of lowering urate to target levels [5].

Uric acid is an independent predictor of mortality and cardiovascular events in both high-risk patients, such as those with heart failure [6] and diabetes [7], and the general population [8–10]. Allopurinol improves endothelial function, defects in which are known to be associated with progression of cardiovascular disease [11]. We have previously found that high-dose allopurinol is associated with reduced cardiovascular events and mortality in heart failure patients [12]. However, it is not clear whether this finding extends to all patients on allopurinol treatment. The present study is a cohort study in all patients having urate concentration measurements to determine the effect of allopurinol on cardiovascular hospitalization and mortality outcome.

Patients and methods

This study was carried out in the Tayside population of Scotland, using the MEMO (MEdicines MOnitoring Unit) record-linkage database [13]. The MEMO database covers a population that is geographically compact and serves about 400 000 National Health Service in Scotland (NHSiS) patients, 97% of whom are of white ethnic origin. The NHSiS is tax funded, free at the point of consumption and covers the entire population. In Tayside, there is almost no healthcare delivered outwith the NHS and there is a low rate of patient migration (less than 3% of patients aged 60 years or over left the Tayside region over a 5 year period of 2004–2008). In brief, the database contains several data sets including all dispensed community prescriptions, hospital discharge data, mortality data, biochemistry data and other data that are linked by a unique patient identifier, the community health index number. The data have been validated and made anonymous for the purposes of research as approved by the government-appointed guardians of patient confidentiality (the Tayside Caldecott Guardians).

The project was also approved by the Tayside Research Ethics Committee.

Study design

This was a cohort study using a UK record-linkage database.

Study subjects

The study subjects included all patients from the hospitals and communities who had urate concentration measurements between January 2000 and December 2002 and were aged 60 years old or over (i.e. the entire cohort of those who had urate measured within the region). They were either resident in Tayside throughout the study period of January 2000 to December 2007 (i.e. a fixed cohort with complete follow-up for each patient) or died during the study period.

If patients had more than one urate measurement, the last measurement was used for the study. They were divided into three groups according to whether they were on ULT during the same period: (i) allopurinol use group; (ii) other ULT use group; and (iii) non-ULT use group. Within the allopurinol use group, subjects were further divided into three groups according to allopurinol daily dose (i.e. 100, 200 and ≥ 300 mg). There were only two patients who had a daily dose of 150 mg and they were categorized into the 200 mg group.

Patients with a diagnosis of cancer or hospitalization malignancy (International Classification of Disease (ICD) codes of C00-C97 and D00-D09) before the time of entry into the study were excluded from the analysis.

Definition of APTC end-point

The Antiplatelet Trialists' Collaboration (APTC) combined end-point of nonfatal myocardial infarction, nonfatal stroke and cardiovascular mortality was used in this study [14]. Outcomes were ascertained from the hospital discharge diagnosis data, Scottish Mortality Record-1 (SMR1) coded by primary International Classification of Diseases (ICD)-9 codes and ICD-10 code and from death certification from the General Register Office in Scotland.

Outcome variables

The outcomes of the study were the APTC combined end-point and all-cause mortality during the follow-up period until December 2007. The minimal follow-up for each subject was 5 years.

Covariates

Covariates included age, sex and Carstair's deprivation code (derived from patients' postcode and 2001 census data comprising social class, overcrowding, male unemployment and car ownership), prior hospitalization for cardiovascular disease, gout or hyperuricaemia, hypertension, renal disease and diabetes mellitus, cardiovascular drugs including aspirin, anticoagulants, angiotensin-converting

enzyme (ACE) inhibitors, angiotensin receptor blockers, β-blockers, cardiac glycosides, thiazide diuretics, other diuretics, nitrates and calcium-channel blockers, diabetes drugs, nonsteroidal anti-inflammatory drugs (NSAIDs), steroids or colchicine at baseline or any time during the follow-up.

Statistical analysis

Data were summarized as means (standard deviations) for continuous variables and numbers of subjects (percentages) for categorical variables. Data distributions and Cox model assumption were checked before any statistical tests were carried out. Chi-square and *t*-tests were performed to determine significant differences. The Cox proportional hazard model was used to compare risks of cardiovascular event or mortality between the allopurinol daily dosage groups. To minimize confounding by indication, where patients with more severe illness are more likely to be treated with allopurinol, we calculated a propensity index for each subject, i.e. the likelihood that a patient would be treated by allopurinol based on known baseline characteristics. A propensity score matched cohort analysis was carried out for the high-dose allopurinol group *vs.* the low-dose allopurinol group. All statistical analyses were carried out using SAS (Statistical Analysis System) software version 9.1 (SAS Institute, Cary, NC, USA).

Prespecified sensitivity analysis

A number of sensitivity analyses were performed subsequent to the primary analysis of the data. Firstly, we matched for baseline urate level for the incident high-dose allopurinol users and non-ULT users to see whether high-dose allopurinol reduced events/mortality over non-ULT takers (sensitivity 1). Secondly, we used the first urate measurement instead of the last measurement for the analysis (sensitivity 2). Thirdly, we re-ran the analysis by excluding patients with renal disease (sensitivity 3). Fourthly, we repeated the analysis by removing patients with previous cardiovascular disease (sensitivity 4).

Results

There were 7135 study subjects. Of these, 1093 (15.3%) were taking ULT treatment. Among the ULT users, 94.7% (*n* = 1035) were taking allopurinol treatment and only 5.3% (*n* = 58) were on other ULT treatments (colchicine, sulfinpyrazone and probenecid). Table 1 shows the characteristics of patients who were on allopurinol and those who were not on any ULT treatment. There were no significant differences in age, urate concentration, social deprivation and previous hospitalizations for diabetes mellitus or hypertension between the allopurinol and non-ULT groups. However, patients in the allopurinol group were more likely to be male, had more co-morbidities and more concurrent drug use than patients in the non-ULT group (*P* <

0.05; Table 1). Table 2 shows the patient characteristics of the different allopurinol dose groups. Patients in the high daily dose group (432 patients were prescribed 300 mg or more but of these, only 12 patients were prescribed more than 300 mg allopurinol per day) were significantly younger, more likely to be male, had less renal disease and diabetes, less use of anticoagulants and diuretics and more use of NSAIDs than the lower dose groups.

Urate concentration target and allopurinol treatment

The proportion of patients reaching target urate concentrations (defined as ≤ 6 mg dl^{-1}) in the allopurinol use group was 44.7% overall [45.6% of men (295 of 647) and 43.3% of women (168 of 388); *P* < 0.01]. Looking at the effects of daily dose of allopurinol, the proportions of patients with urate concentrations attaining target levels for men and women were 24.2 and 24.4% for 100 mg, 40.6 and 56.9% for 200 mg and 64.7 and 66.7% for 300 mg or over, respectively (Table 3). Women tended to be on lower doses of allopurinol compared with men [51.8 (201 on 100 mg) *vs.* 38.3% (248 on 100 mg), *P* < 0.01; Table 3]. The median age was 73 years old (interquartile range 67–79) for the 100 mg group, 73 years old (interquartile range 66–79) for the 200 mg group and 71 years old (interquartile range 65–77) for the 300 mg or over group.

Cardiovascular event rates and all-cause mortality

Comparison between the allopurinol cohort and non-ULT cohort There were 1145 cardiovascular events and 1943 deaths in the non-ULT use group (with 732 cardiovascular events and 1218 deaths in those with a urate level >6 mg dl^{-1}) and 273 cardiovascular events and 475 deaths in the allopurinol group during a median follow-up time of 5.6 years. The cardiovascular event rates were 38.5 per 1000 person years [95% confidence interval (CI) 36.3–40.7] for the non-ULT use group, 48.5 per 1000 person years (95% CI 45.1–51.9) for the non-ULT group with urate >6 mg dl^{-1} and 61.4 per 1000 person years (95% CI 54.3–68.4) for the allopurinol use group. There was no significant increased risk of cardiovascular events for allopurinol users when compared with the non-ULT users [adjusted hazard ratio (HR) 1.10, 95% CI 0.95–1.26] and the non-ULT group with urate >6 mg dl^{-1} (adjusted HR 1.07, 95% CI 0.89–1.28). A further propensity score matched analysis of allopurinol users *vs.* non-ULT users showed that the adjusted HR was 0.88, 95% CI 0.73–1.05. Within the non-ULT use group, there was a strong relationship between urate concentration and cardiovascular outcome (Figure 1). However, in the allopurinol use group, the risk of adverse outcome decreased with increased ULT dose (Figure 2), and the effect of allopurinol did not depend on the urate concentration. There was no clear relationship between urate concentration and cardiovascular outcome in Figure 2 except with the high-dose group, and this is probably due to small

Table 1

Characteristics of patients by allopurinol use status

	Allopurinol group n (%)	Non-ULT group n (%)	P-value
Number	1035	6042	–
Gender			
Men	647 (62.5)	2843 (47.1)	<0.01
Women	388 (37.5)	3199 (52.9)	–
Age (mean, SD)	72.6 (7.8)	72.4 (7.1)	0.43
Social deprivation			
1	64 (6.2)	393 (6.6)	0.60
2	192 (18.6)	1175 (19.7)	–
3	268 (26.0)	1658 (27.8)	–
4	102 (9.9)	563 (9.4)	–
5	116 (11.2)	580 (9.7)	–
6 and 7	290 (28.1)	1101 (26.8)	–
Urate concentration (mg dl^{-1})			
≤6	463 (44.7)	2774 (45.9)	0.65
6.01–7	200 (19.3)	1162 (19.2)	–
7.01–8	140 (13.5)	871 (14.4)	–
8.01–9	104 (10.1)	544 (9.0)	–
>9	128 (12.4)	691 (11.4)	–
Previous hospitalization			
Diabetes mellitus	6 (0.6)	17 (0.3)	0.12
Gout or hyperuricaemia	19 (1.8)	26 (0.4)	<0.01
Renal disease	77 (7.4)	209 (3.5)	<0.01
Cardiovascular disease	100 (9.7)	437 (7.2)	<0.01
Hypertension	8 (0.8)	38 (0.6)	0.59
Drugs in concurrent use			
Aspirin	506 (48.9)	2312 (38.3)	<0.01
Anticoagulants	127 (12.3)	360 (6.0)	<0.01
Angiotensin-converting enzyme inhibitors	373 (36.0)	1556 (25.8)	<0.01
β-Blockers	274 (26.5)	1188 (19.7)	<0.01
Cardiac glycosides	131 (12.7)	329 (5.5)	<0.01
Calcium-channel blockers	314 (30.3)	1553 (25.7)	<0.01
Thiazides	106 (10.2)	1068 (17.7)	<0.01
Other diuretics	513 (49.6)	1503 (24.9)	<0.01
Nitrates	273 (26.4)	936 (15.5)	<0.01
Statins	371 (35.9)	1602 (26.5)	<0.01
Nonsteroidal anti-inflammatory drugs	328 (31.7)	1490 (24.7)	<0.01
Colchicine	66 (6.0)	1 (0.2)	<0.01

sample size and different cut-off limits used in the stratification of urate concentration.

Comparison within the allopurinol cohort In the allopurinol use group, cardiovascular event rates were 61.3 per 1000 person years (95% CI 54.3–68.4), 74.0 per 1000 person years (95% CI 61.9–86.1) for the 100 mg daily group, 69.7 per 1000 person years (95% CI 49.6–89.8) for the 200 mg group and 47.6 per 1000 person years (95% CI 38.4–56.9) for the 300 mg and over group. Only one cardiovascular event occurred in the 12 patients who took more than 300 mg allopurinol per day. Table 4 shows the hazard ratios of cardiovascular disease and all-cause mortality in the different dose groups. The 300 mg and over group had significantly lower risk for both cardiovascular events and all-cause mortality than the 100 mg group (adjusted HR 0.69, 95% CI 0.50–0.94 and adjusted HR 0.75, 95% CI 0.59–0.94, respectively). The adjusted HR of cardiovascular events was 0.63, 95% CI 0.44–0.91, for a propensity score matched

analysis of high-dose vs. low-dose allopurinol therapy. The death rates per 1000 person years in the allopurinol use group were 100.7 (95% CI 92.2–109.3) overall, 120.3 (95% CI 105.8–134.9) for the 100 mg group, 108.6 (95% CI 84.9–132.3) for the 200 mg group and 73.2 (95% CI 62.2–84.2) for the 300 mg and over group.

Results of sensitivity analyses The risks of cardiovascular and mortality outcomes in the allopurinol group changed little when compared with the non-ULT group. The results of sensitivity analysis 1 (i.e. incident high-dose group vs. non-ULT group) showed that the adjusted HRs for cardiovascular events and all-cause mortality were 0.54 (95% CI 0.32–0.92) and 0.96 (95% CI 0.55–1.68), respectively. Compared with the 100 mg group, the HRs were 0.73 (95% CI 0.54–0.99) and 0.76 (95% CI 0.61–0.96) for sensitivity analysis 2, 0.68 (95% CI 0.49–0.95) and 0.76 (95% CI 0.59–0.96) for sensitivity analysis 3 and 0.62 (95% CI 0.44–0.86) and 0.75 (95% CI 0.58–0.97) for sensitivity analysis 4, respectively.

Table 2

Characteristics of patients by daily dose in the allopurinol users

|	100 mg n (%)	200 mg n (%)	≥300 mg n (%)	P-value
Number	449	154	432	–
Gender				
Men	248 (55.2)	96 (62.3)	303 (70.1)	<0.01
Women	201 (44.8)	58 (37.7)	129 (29.9)	–
Age (mean, SD)	73.2 (7.8)	72.9 (7.8)	71.8 (7.8)	0.02
Social deprivation				
1	31 (6.9)	8 (5.2)	25 (5.8)	0.56
2	88 (19.6)	35 (22.7)	69 (16.1)	–
3	105 (23.4)	39 (25.3)	124 (28.4)	–
4	49 (10.9)	15 (9.7)	38 (8.8)	–
5	54 (12.1)	18 (11.7)	44 (10.2)	–
6 and 7	121 (27.0)	39 (25.3)	130 (30.2)	–
Urate concentration (mg dl^{-1})				
≤6	109 (24.3)	72 (46.7)	282 (65.3)	<0.01
6.01–7	104 (23.2)	42 (27.3)	54 (12.5)	–
7.01–8	91 (20.3)	13 (8.4)	36 (8.3)	–
8.01–9	66 (14.7)	18 (11.7)	20 (4.6)	–
>9	79 (17.6)	9 (5.8)	40 (9.3)	–
Previous hospitalization				
Diabetes mellitus	2 (0.5)	3 (2.0)	1 (0.2)	0.05
Gout or hyperuricaemia	10 (2.2)	2 (1.3)	7 (1.6)	0.69
Renal disease	54 (12.0)	15 (9.7)	8 (1.9)	<0.01
Cardiovascular disease	46 (10.2)	13 (8.4)	41 (9.5)	0.80
Hypertension	5 (1.1)	1 (0.7)	2 (0.5)	0.53
Drugs in concurrent use				
Aspirin	208 (46.3)	83 (53.9)	215 (49.8)	0.24
Anticoagulants	69 (15.4)	18 (11.7)	40 (9.3)	0.02
Angiotensin-converting enzyme inhibitors	160 (35.6)	55 (35.7)	158 (36.6)	0.95
β-Blockers	124 (27.6)	42 (27.3)	108 (25.0)	0.66
Cardiac glycosides	63 (14.0)	15 (9.7)	53 (12.3)	0.37
Calcium-channel blockers	147 (32.7)	50 (32.5)	117 (27.1)	0.16
Thiazides	48 (10.7)	15 (9.7)	43 (10.0)	0.91
Other diuretics	257 (57.2)	76 (49.4)	180 (41.7)	<0.01
Nitrates	125 (27.8)	37 (24.0)	111 (25.7)	0.60
Statins	153 (34.1)	65 (42.2)	153 (35.4)	0.19
Nonsteroidal anti-inflammatory drugs	144 (32.1)	26 (16.9)	158 (36.6)	<0.01
Colchicine	17 (3.8)	6 (3.9)	8 (1.9)	0.19

Table 3

Distribution of urate concentration (mg dl^{-1}) in patients aged 60 years and over by allopurinol daily dose

Daily dose (mg)	Urate concentration (mg dl^{-1}) n (%)					Percentage of patients reaching target (≤6 mg dl^{-1})
	≤6	6.01–7	7.01–8	8.01–9	>9	
Men (n = 647)						
100	60 (20.34)	60 (43.48)	50 (60.24)	41 (63.08)	37 (56.06)	24.19
200	39 (13.22)	33 (23.91)	9 (10.84)	13 (20.00)	2 (3.03)	40.63
≥300	196 (66.44)	45 (32.60)	24 (28.91)	11 (16.92)	27 (40.91)	64.69
Total	295 (100.00)	138 (100.00)	83 (100.00)	65 (100.00)	66 (100.00)	45.60
Average dose	253 mg	191 mg	172 mg	153 mg	184 mg	
Women (n = 388)						
100	49 (29.17)	44 (70.97)	41 (71.93)	25 (64.10)	42 (67.74)	24.38
200	33 (19.64)	9 (14.52)	4 (7.02)	5 (12.82)	7 (11.29)	56.90
≥300	860 (51.19)	9 (14.52)	12 (21.05)	9 (23.08)	13 (20.97)	66.67
Total	168 (100.00)	62 (100.00)	57 (100.00)	39 (100.00)	62 (100.00)	43.30
Average dose	226 mg	144 mg	149 mg	158 mg	152 mg	
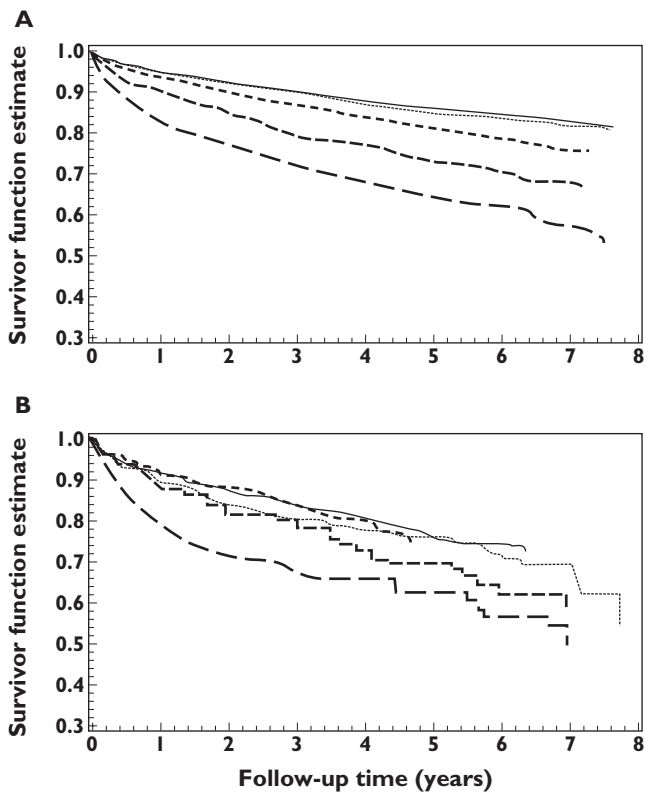
Figure 1

Kaplan–Meier plot of the Antiplatelet Trialists' Collaboration (APTC) event rate by urate concentration in non-users of urate-lowering therapy (non-ULT users; A) and in allopurinol users (B). ≤6 mg dl^{-1} (——); 6.01–7 mg dl^{-1} (········); 7.01–8 mg dl^{-1} (- - -); 8.01–9 mg dl^{-1} (——); >9 mg dl^{-1} (— ·)
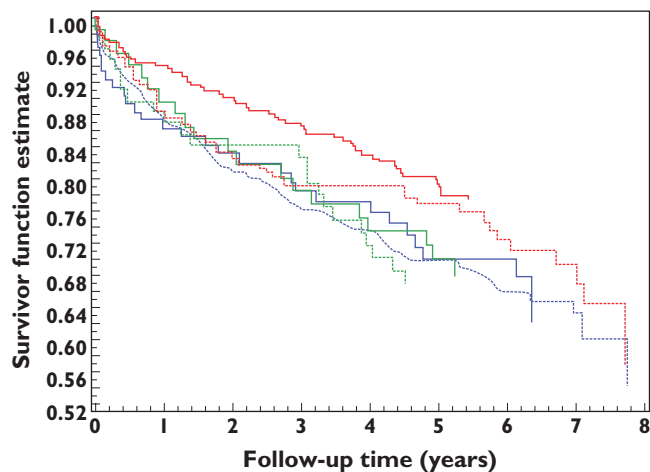
Figure 2

Kaplan–Meier plot of the APTC event rate by urate concentration and allopurinol daily dose. Dose = 100 mg: ≤6 mg dl^{-1} (——); >6 mg dl^{-1} (········); Dose = 200 mg: ≤6 mg dl^{-1} (——); >6 mg dl^{-1} (········); Dose >= 300 mg: ≤6 mg dl^{-1} (——); >6 mg dl^{-1} (········)

Discussion

In this study, we found that less than half of patients reached target urate concentration, and high-dose allopurinol was associated with reduced cardiovascular events and all-cause mortality. The results suggest that the benefit of high-dose allopurinol observed in the high-risk patients, such as those with diabetes or heart failure [6, 12, 15], could be extended to all patients who taking allopurinol. We have done a number of *post hoc* sensitivity analyses for the study to make sure our results were consistent. All the results were similar to the primary results except that the risk reduction of mortality for the incident high-dose group became statistically nonsignificant when compared with the non-ULT group in sensitivity 1.

Previous evidence has suggested that high-dose allopurinol may be associated with reduced risk of mortality and cardiovascular events through its patho-physiological pathway [16] by the following two mechanisms: higher doses of allopurinol may have an increased ability to improve endothelial function; and higher doses may also improve cardiac structure [17]. These two mechanisms are noteworthy because both endothelial function and cardiac function are independent predictors of mortality [7, 18, 19]. Other mechanisms could contribute, such as allopurinol reducing myocardial oxygen consumption for a particular stroke volume, and this has been confirmed in a randomized clinical trial in patients with chronic stable angina [20]. Notably, a recent crossover trial in 30 adolescents with newly diagnosed, never-treated stage 1 essential hypertension and serum uric acid levels ≥6 mg dl^{-1} showed that allopurinol reduced mean 24 h ambulatory systolic and diastolic blood pressures [21]. This implies that treatment with allopurinol may reduce blood pressure, which could potentially reduce the risk of cardiovascular disease. More recently, Luk *et al.* reported a significant survival benefit of allopurinol treatment in hyperuricaemic patients (adjusted HR 0.78, 95% CI 0.67–0.91) [22]. We also observed this benefit in our high-dose group when compared with non-ULT patients (sensitivity 1).

The EULAR (European League Against Rheumatism) guideline has recommended that the therapeutic goal of ULT is to achieve a urate concentration ≤6 mg dl^{-1} [23]. The allopurinol dose should be increased progressively until a target urate concentration or maximal tolerated doses are achieved [24]. Our study showed that less than half of the patients achieved this goal. However, there was a strong dose–response relationship between allopurinol dose and urate concentration, with about two-thirds of patients who were on 300 mg daily dose achieving this goal. This highlights that dose adjustment should be considered in order to achieve the maximal benefit of the therapy in routine clinical practice. Our study result was consistent with the finding that the proportion of gout patients achieving their target urate concentration level (≤6 mg dl^{-1}) was

Table 4

Univariate and multivariate hazard ratios (HR) for cardiovascular disease and all-cause mortality in patients who had urate concentration measurement

Allopurinol daily dose	Univariate		Multivariate†	
	HR	95% Confidence interval	HR	95% Confidence interval
Cardiovascular outcome				
100 mg	1.00	–	1.00	–
200 mg	0.94	0.67–1.33	1.01	0.70–1.45
≥300 mg	0.66	0.51–0.86**	0.69	0.50–0.94**
All-cause mortality				
100 mg	1.00	–	1.00	–
200 mg	0.92	0.71–1.20	0.92	0.70–1.21
≥300 mg	0.63	0.52–0.77**	0.75	0.59–0.94*

*$P < 0.05$; **$P < 0.01$. †Adjusted for age, gender, social deprivation, urate concentration, gout/hyperuricaemia, renal disease, cardiovascular disease, diabetes mellitus, concurrent use of colchicine, nonsteroidal anti-inflammatory drugs, diabetic medication and cardiovascular drugs during the follow-up and number of cardiovascular prescriptions.

higher in those taking recommended doses (based on creatinine clearance) compared with those taking lower than recommended doses (38 *vs*. 19%; $P < 0.01$) [25]. A recent clinical trial in stroke patients also showed that there was a dose–response relationship for reduction of uric acid level by allopurinol at 6 weeks (reductions in uric acid were 0.14 mmol l^{-1} for the 300 mg group and 0.02 mmol l^{-1} for the 100 mg group) [26].

The strengths of the present study are as follows. (i) The study was a population-based cohort design with complete follow-up over the study period. Unlike clinical trials, which focus on highly selected patients, our study method allows for a 'real-world' population to be studied, representing all socio-economic groups and within a universal healthcare coverage scheme [27]. (ii) A complete biochemistry database was available for this population. (iii) MEMO only collects dispensed prescribing data and so primary noncompliance was eliminated as a source of error [28]. (iv) Our study also had details of concomitant drug treatment.

The limitations of this study are as follows. (i) MEMO does not have information on certain risk factors, such as lifestyle, i.e. body mass index, smoking, alcohol and exercise. These limitations are not unique to MEMO's record-linkage database; other databases also do not have routinely collected information on lifestyle or drug indication. However, we used a socio-economic deprivation score as a surrogate marker for this, as data from Scotland have shown that there is a significant correlation between body mass index, smoking and social deprivation [29]. (ii) We assumed that if a prescription was filled then patients would adhere to treatment, but we had no way of knowing whether or not subjects took the medication. (iii) Our study also did not account for whether subsequent to the urate measurement used in the analysis, patients might have had a change in their allopurinol dosage. (iv) Although we have used multivariate analyses, observational studies cannot exclude residual confounding factors. (v) We did not obtain information on adverse secondary effects of high-dose allopurinol use in this study. Further investigation is needed to clarify this issue.

In conclusion, more than half of the patients taking allopurinol did not reach the recommended target urate levels. High-dose allopurinol use was associated with a lower risk of cardiovascular events and all-cause mortality than low-dose allopurinol use, suggesting that higher doses of allopurinol may be of benefit by reducing cardiovascular disease or death.

Competing Interests

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