

## ORIGINAL ARTICLE

# Failure to reach uric acid target of <0.36 mmol/L in hyperuricaemia of gout is associated with elevated total and cardiovascular mortality

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**ABSTRACT**

**Objective** To determine the impact of achieving serum uric acid (sUA) of <0.36 mmol/L on overall and cardiovascular (CV) mortality in patients with gout.

**Methods** Prospective cohort of patients with gout recruited from 1992 to 2017. Exposure was defined as the average sUA recorded during the first year of follow-up, dichotomised as  $\leq$  or  $>$ 0.36 mmol/L. Bivariate and multivariate Cox proportional hazards models were used to determine mortality risks, expressed HRs and 95% CIs.

**Results** Of 1193 patients, 92% were men with a mean age of 60 years, 6.8 years' disease duration, an average of three to four flares in the previous year, a mean sUA of 9.1 mg/dL at baseline and a mean follow-up 48 months; and 158 died. Crude mortality rates were significantly higher for an sUA of  $\geq$ 0.36 mmol/L, 80.9 per 1000 patient-years (95% CI 59.4 to 110.3), than for an sUA of <0.36 mmol/L, 25.7 per 1000 patient-years (95% CI 21.3 to 30.9). After adjustment for age, sex, CV risk factors, previous CV events, observation period and baseline sUA concentration, an sUA of  $\geq$ 0.36 mmol/L was associated with elevated overall mortality (HR=2.33, 95% CI 1.60 to 3.41) and CV mortality (HR=2.05, 95% CI 1.21 to 3.45).

**Conclusions** Failure to reach a target sUA level of 0.36 mmol/L in patients with hyperuricaemia of gout is an independent predictor of overall and CV-related mortality. Targeting sUA levels of <0.36 mmol/L should be a principal goal in these high-risk patients in order to reduce CV events and to extend patient survival.

**INTRODUCTION**

Gout has emerged as the most common inflammatory arthritis in men, as well as one of the most common causes of arthritis in elderly women in high-income countries<sup>1</sup> A large body of evidence incriminates gout as a major determinant of mortality, both total and cardiovascular (CV).<sup>2,3</sup> This risk increases with the severity of the gout.<sup>4,5</sup> Treatment of gout has not been consistently associated with reductions in mortality<sup>6,7</sup> due to the fact that serum uric acid (sUA)–mortality associations

**Key messages**

- ▶ Severe gout is associated with cardiovascular mortality.
- ▶ Achieving and maintaining a serum uric acid target below normal levels (<0.36 mmol/L or 6 mg/dL) in the first year reduces the risk of dying substantially.
- ▶ Lower uric acid level targets should be recommended for hyperuricaemic patients with gout. This information may help increase adherence to treatment if well explained to patients.

have not been sufficiently explored while on therapy.

International guidelines recommend target sUA levels of below 0.36 mmol/L (6 mg/dL) to reduce the frequency of gout flares and morbidity,<sup>8,9</sup> although many treating physicians accept higher threshold values.<sup>10</sup> High baseline sUA levels plus tophi are associated with elevated mortality,<sup>4</sup> suggesting a plausible pathophysiological link between greater total body urate load and CV disease. It is speculated that patients with sUA levels beyond 0.36 mmol/L experience increased mortality despite urate-lowering therapy (ULT) and, therefore, a target threshold of at least <0.36 mmol/L should be set as the desired threshold based on this premise.

We recently reported a strong independent association between the severity of gout and increased mortality,<sup>4</sup> but this was during a period when the concept of *treat-to-target* was not yet established and the optimal target levels were not clearly defined. During this period, most patients were on active ULTs and patients not on target had short periods of follow-up. In this current study, we have expanded the primary cohort of patients with gout and the period of follow-up in order to explore the association of achieved sUA levels

with mortality. Our objective was to determine whether elevated sUA levels and their pharmacological control are associated with increased total and CV mortality.

## METHODS

We conducted a longitudinal prospective study nested in a clinical database for which all participants had provided consent for data collection.

### Patients

All patients with a confirmed diagnosis of gout who attended a designated gout clinic at Cruces Hospital from 1 January 1992 to 31 December 2017 were eligible for inclusion. The clinic serves an industrial and suburban area from the Basque Country with over 400 000 inhabitants and as a regional referral centre for patients with difficult to treat gout.

Gout was defined as recurrent acute episodes of joint inflammation associated with sustained (>1 year) hyperuricaemia (>0.41 mmol/L) and a remission of gout flares during follow-up after adequate control of sUA levels. For the majority of patients, monosodium urate crystals were demonstrated in synovial fluid samples or in material aspirated from nodules suspicious to be tophi in patients. When such samples for crystal observation were unavailable (previous long-term treatment, or rejection of consent for aspirating joints or tophi), or ultrasound examination did not find neat double contour or tophaceous deposits, gout was defined based on the above clinical definition.

All patients with at least one follow-up visit were included in the analysis. Patients in whom gout was associated with a haematological malignancy or other malignant disease known not to be in remission were excluded for this analysis.

### Procedures, variables and data collection

Patients included in the study were evaluated at first clinic visit (baseline) and at subsequent follow-up visits, managed by a single rheumatologist (FPR). At least three visits were scheduled for the first year of follow-up. Afterwards, follow-up visits were established every 3–12 months, according to the patient's clinical status, treatment response and comorbidities. Patients who did not attend follow-up visits were assessed periodically for vital status. Patients who refused further follow-up at the hospital or who were discharged for primary care or to other physicians were censored at the last visit for this study. The primary endpoint was mortality. The time and cause of death were confirmed through medical records, patients' families or local mortality registry if needed.

The principal exposure was sUA level defined as the mean sUA concentration recorded in the year following the first clinic visit. For all patients, levels were monitored during follow-up, and the average sUA level dichotomised as  $\leq 0.36$  mmol/L vs  $> 0.36$  mmol/L was used as explanatory variable.

Baseline data were captured on patient characteristics recorded at first clinic visit. These included data on age, sex, body mass index (BMI), previous treatment with ULT, number of joints affected at entry, presence of subcutaneous tophi, radiographical evidence of gout-related articular damage, number of gout flares in the preceding year, previous diagnosis of CV disease, namely, coronary heart disease, heart failure, stroke, peripheral vascular disease or current treatment with acenocumarol as anticoagulant; loop diuretic use; alcohol intake, defined as an average ethanol consumption of  $\geq 20$  g/day; diabetes mellitus, fasting glucose level of  $> 7.8$  mmol/L or prescribed insulin or oral antidiabetic drugs; hypertension (HT), systolic blood pressure of  $> 140$  mmHg or diastolic blood pressure of  $> 90$  mmHg or on antihypertensive treatment; hyperlipidaemia, total cholesterol of  $> 62.4$  mmol/L or triglycerides  $> 1.71$  mmol/L; or on lipid-lowering agents. Kidney function was evaluated at baseline by calculating creatinine and urea clearances from 24 hours of urinary collections in the first years of the cohort, and based on modification of diet in renal disease (MDRD) and chronic kidney disease (CKD)-Epi equations thereafter. Clinically relevant renal function impairment was defined as a creatinine clearance of  $< 60$  mL/min. In addition, patients were automatically classified in the informatics system according to the extended Kaiser pyramid into four levels, from low death to high death risk, as suggested by the Basque country chronic care model.<sup>11</sup>

Medications for gout were also recorded during follow-up. All participants were treated in a similar manner that included prophylaxis with low-dose colchicine (0.5–1.0 mg orally once daily) prescribed for 6–12 months, depending on the presence or absence of subcutaneous tophi, respectively, or prednisone (2.5 mg PO, two times per day) if colchicine was not tolerated or contraindicated in non-diabetic patients. ULTs were prescribed to patients with sUA levels over 0.36 mmol/L on a shared decision process and doses adjusted during follow-up to target sUA levels of 0.36 mmol/L.

### Statistical analysis

A descriptive analysis was conducted using summary statistics, mean or median and SD or IQR, for continuous variables, and frequency tables and percentages, for categorical ones. Baseline characteristics were compared between patients alive or deceased at the end of follow-up. Normally distributed continuous variables were compared using Student's t-test with unequal variances, and continuous non-parametric variables by Kruskal-Wallis and Mann-Whitney U tests. The differences in frequency of categorical variables were determined by chi-square and Fisher's exact tests.

Survival analysis was performed using the Kaplan-Meier method. Survival time started at the date of the first clinic visit. Differences between patients achieving or not the therapeutic goal—sUA of  $< 0.36$  mmol/L—during the first year, were evaluated by the Mantel-Haenszel statistic

(log-rank test). Total mortality and CV-related mortality (stroke, acute myocardial infarction, heart failure, ischaemic heart disease, pulmonary thromboembolism and unknown cause) were compared between groups. The overall mortality rate was calculated as the ratio between the number of deaths observed and the cumulative survival time, expressed as patient-years.

Bivariate and multivariate Cox proportional hazards models were used to determine the variables associated with survival. Potential predictive factors in the bivariate Cox model were age at disease onset, number of gout flares per year, sex, disease duration, BMI, serum creatinine and sUA at cohort entry, diuretic use, high blood pressure, hyperlipidaemia, diabetes mellitus, presence of tophi, prior CV event, ULT, achieving target sUA of <6mg/dL, radiographical involvement, prophylaxis with colchicine, anakinra or prednisone, first-line treatment and presentation form. In the multivariate models, the role of the Kaiser strata was evaluated as a possible confounder or effect modification factor. All the variables with a *p* value of <0.10 in the bivariate analysis were incorporated into the multivariate models.

Multivariate models were constructed by successive inclusion/elimination of variables according to their contribution to the dependent variable (mortality). The final model is the most parsimonious, that is, the model that explains more with fewer variables. In order to take into account possible changes in patient management during the long observation period of the cohort (1991–2017), a time period stratification variable was introduced in the models.

We also performed a stepwise regression model to compare the results using Akaike's Information Criteria (AIC) and Bayesian Information Criteria (BIC) criteria. However, these criteria were not finally used, since the more parsimonious model with successive manual elimination of variables was chosen to support this selection based on clinical reasoning rather than on statistical methods. Missing values were not imputed in the models and all analyses were performed with STATA V.12. The significance limit was set at 0.001.

## RESULTS

The cohort included 1193 patients, mostly men (92%), with a mean age of 60 years and a disease duration of 6.8 years, who presented an average of three to four flares during the previous year (range 0–66). At cohort entry, the mean sUA was 9.1 mg/mL (range 4.8–17.1), and the mean creatinine clearance was 73.3 mL/min. Severe gout was frequent, as well as polyarticular gout, present at entry in 36%, and with tophi observed in 33% of cases. The diagnosis was based primarily on microscopy (79%), then on clinical data (15%) and less frequently on specific ultrasound findings (6%). Regarding comorbidity and risk factors, HT was present in 52%, diabetes in 20%, lithiasis in 8%, and 32% consumed alcohol. Almost a third of cases (31%) had history of previous CV

**Table 1** Description of the sample from the gout clinic at Hospital de Cruces

Variable	N	Value
Sex (male), n (%)	1192	1095 (91.9)
Age (years), m±SD	1192	60.8±13.6
Diagnosis, n (%)	1192	
Clinical		178 (14.9)
Microscopy		942 (79.0)
Ultrasound		72 (6.0)
Disease duration (years), median (P <sub>25</sub> –P <sub>75</sub> )	1187	4 (2–10)
Clinical evolution, n (%)	1184	
Tophi without arthritis		3 (0.2)
Monoarticular		176 (14.9)
Oligoarticular		573 (48.4)
Polyarticular		432 (36.5)
Number of flares in the previous year, median (P <sub>25</sub> –P <sub>75</sub> )	1179	2 (2–4)
Tophi, n (%)	1191	398 (33.4)
sUA (baseline) (mg/dL), m±SD	1181	9.1±1.5
sUA levels during follow-up after optimisation, n (%)	1095	
<0.36 mmol/L		916 (83.6)
≥0.36 mmol/L		179 (16.3)
Comorbidity and risk factors		
BMI (kg/m <sup>2</sup> ), m±SD	1173	28.1±4.0
Creatinine (baseline) (mg/dL), m±SD	1176	1.27±0.89
Creatinine clearance (mL/min), m±SD	1044	73.3±33.0
Ethanol consumption >20g/day, n (%)	1171	378 (32.3)
Arterial hypertension, n (%)	1172	606 (51.7)
Diabetes, n (%)	1171	235 (20.1)
Hyperlipidaemia, n (%)	1170	565 (48.3)
Previous CV event, n (%)	1171	363 (31.0)
Urate lithiasis, n (%)	1170	97 (8.3)
Treatment	1192	
Urate-lowering drugs, n (%)	1190	483 (40.5)
First-line treatment, n (%)		
Without treatment		133 (11.2)
Allopurinol		740 (62.2)
Benzbromarone		213 (17.9)
Febuxostat		104 (8.7)

BMI, body mass index; CV, cardiovascular; m, mean; sUA, serum uric acid.

events, and only 40% had received ULT before entering the study (see [table 1](#)).

## Mortality

The mean follow-up was 48.6±49.5 months (median 30, range 0–272), with loss to follow-up in 286 cases (24%). Only 16.3% of patients could not maintain the sUA target of <0.36 mmol/L, despite treatment.

A total of 158 (13%) patients died, of whom 82 did so in relation to a CV event. Compared with survivors,

patients who died during follow-up were older (median 75 vs 58), experienced a greater number of flares during the previous year (median 3 vs 2), had higher sUA levels (median 9.3 vs 8.7), lower creatinine clearance (57 vs 75) and had lower alcohol consumption. In addition, polyarticular presentation was more common among decedents (51.9% vs 34.1%), as well as the use of benzbromarone as first-line treatment (29.1% vs 16.2%), tophi (52.5% vs 30.6%), HT (77.7% vs 47.7%), diabetes mellitus (37.6% vs 17.4%) and previous CV events (66.2% vs 25.5%). Deceased cases also had greater baseline comorbidity,

and 47% of them were in a situation of frailty ( $\geq 5$  chronic diseases) vs 15% of alive. Finally, the proportion of patients who did not reach the therapeutic goal (sUA  $< 0.36$  mmol/L) was significantly higher among those who died (26.7% vs 14.7%) (table 2).

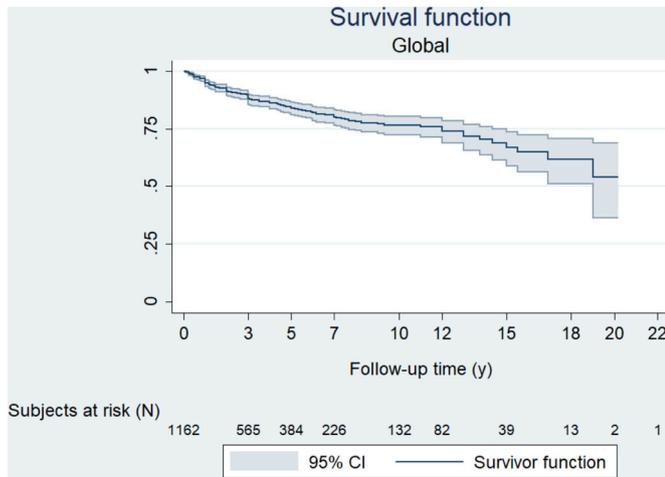
All patients were included in the survival analysis (n=1192), although 30 were excluded due to lack of follow-up (follow-up time=0). Follow-up time was 4830.2 patient-years (maximum of 22.7 years). Median survival was not reached; therefore, we calculated the 25th percentile (12 and 19 years for overall and CV mortality,

**Table 2** Baseline characteristics by vital status at the end of follow-up

Variable	Alive	Dead	P value
Age (years)	58 (49–69)	75 (64–80)	<0.001
Disease duration (years)	4 (2–10)	4 (2–10)	0.936
Number of flares/previous year	2 (2–4)	3 (2–6)	<0.001
Tophi	75 (47.5%)	83 (52.5%)	<0.001
sUA (baseline) (mg/dL)	8.7 (8.1–9.7)	9.3 (8.5–10.7)	<0.001
Creatinine clearance (mL/min)	75.0 (48.0–98.0)	57.2 (39.7–86.4)	<0.001
Clinical evolution			<0.001
Tophi without arthritis	3 (0.3%)	–	
Monoarticular	162 (15.8%)	14 (8.9%)	
Oligoarticular	511 (49.8%)	62 (39.2%)	
Polyarticular	350 (34.10%)	82 (51.9%)	
First-line treatment			<0.001
Without treatment	120 (11.6%)	13 (8.2%)	
Allopurinol	658 (63.8%)	82 (51.9%)	
Benzbromarone	167 (16.2%)	46 (29.1%)	
Febuxostat	87 (8.4%)	17 (10.8%)	
Tophi	315 (30.5%)	83 (52.5%)	<0.001
Comorbidity and risk factors			
BMI (kg/m <sup>2</sup> )	27.8 (25.6–30.4)	27.2 (24.6–30.5)	0.163
Ethanol consumption >20g/d	350 (34.5%)	28 (17.8%)	<0.001
Hypertension	484 (47.7%)	122 (77.7%)	<0.001
Diabetes	176 (17.4%)	59 (37.6%)	<0.001
Hyperlipidaemia	505 (49.9%)	60 (38.2%)	0.007
Previous CV event	259 (25.5%)	104 (66.2%)	<0.001
Kaiser strata			<0.001
No risk factors	67 (22.9%)	2 (6.2%)	
1–2 chronic diseases	92 (31.5%)	6 (18.7%)	
Comorbidity (3–4 diseases)	89 (30.5%)	9 (28.1%)	
Frailty (5+ diseases)	44 (15.1%)	15 (46.9%)	
Treatment and target			
Urate-lowering drugs	417 (40.3%)	66 (41.8%)	
sUA target achieved			<0.001
Yes	806 (85.3%)	110 (73.3%)	
No	139 (14.7%)	40 (26.7%)	

Continuous variables are presented as median (IQR).

BMI, body mass index; CV, cardiovascular; sUA, serum uric acid.



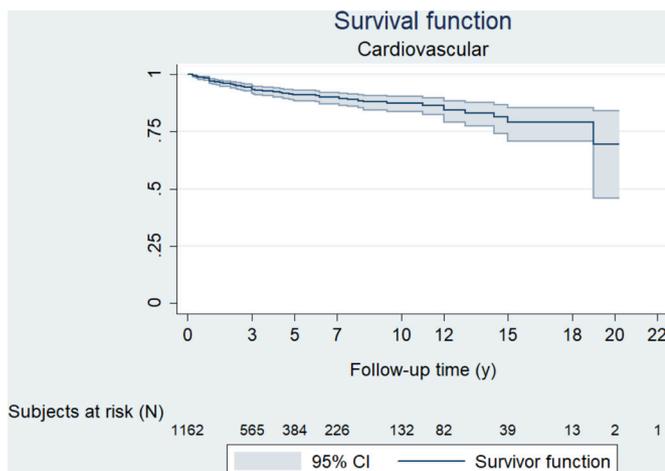
**Figure 1** Survival function: overall mortality in persons with gout.

respectively). The corresponding mortality rate was overall 32.7 (95% CI (shaded areas) 28.0 to 38.2) and CV-related 17.0 (95% CI (shaded areas) 13.7 to 21.1) per 1000 patient-years (figures 1 and 2).

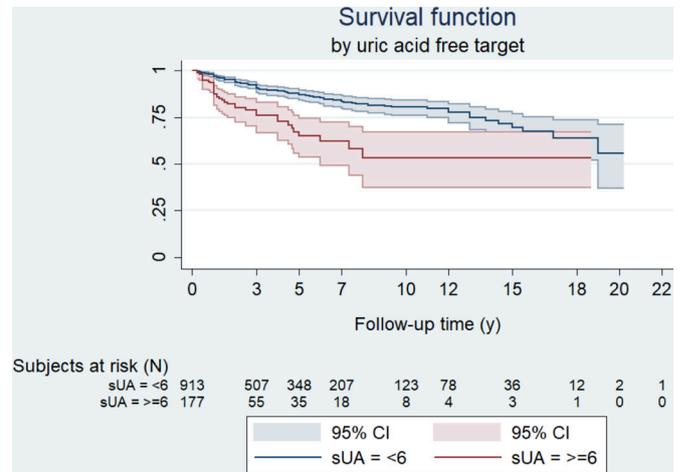
The survival function was significantly different by whether target sUA was achieved or not (log-rank  $p < 0.001$ ), with higher mortality among patients with an sUA of  $\geq 0.36$  mmol/L both, overall and CV-related (figures 3 and 4; shaded areas represent 95% CI).

In the group with an sUA of  $< 0.36$  mmol/L, 110 deaths occurred during a follow-up time of 4285.6 person-years (mortality rate of 25.7 per 1000 person-years; 95% CI 21.3 to 30.9), whereas in the group with an sUA of  $\geq 0.36$  mmol/L, 40 deaths occurred during 494.2 person-years (mortality rate 80.9 per 1000 person-years, 95% CI 59.4 to 110.3).

In univariate analysis, the variables associated with higher overall mortality were increasing age, number of flares in the previous year, baseline sUA and creatinine, HT, diabetes mellitus, previous CV events, diuretic use, presence of tophi, radiological involvement and failure to achieve the therapeutic goal of 0.36 mmol/L. In the



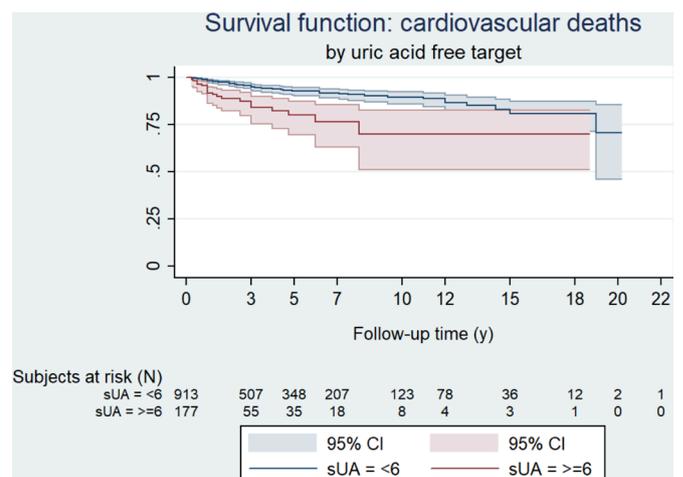
**Figure 2** Survival function: cardiovascular mortality in persons with gout.



**Figure 3** Survival function in persons with gout by whether the sUA target was achieved or not: overall mortality. sUA, serum uric acid.

multivariate model ( $n = 1068$ ), failure to achieve an sUA of  $< 0.36$  mmol/L was associated with elevated mortality, with an HR of 2.33, and this effect was independent of age, the initial sUA levels, previous CV events and year of inclusion in the cohort (table 3). The introduction of sex and/or disease duration in the final model did not modify the overall likelihood of the model or the coefficients.

For CV-related mortality, the main determinants in the bivariate analysis were age, sex, baseline sUA and creatinine, ethanol consumption, HT, hyperlipidaemia, previous CV events, diuretic use and tophi. In the multivariate analysis, failure to reach an sUA of  $< 0.36$  mmol/L was associated with increased mortality risk (HR=2.05,  $p = 0.007$ ), regardless of age, baseline sUA, previous CV events, CV risk factors and strata of observation's period. As in global mortality, the introduction of demographic variables, like sex and disease duration, in the final model did not modify the obtained results (table 4).



**Figure 4** Survival function in persons with gout according to sUA target ( $< 6$  vs  $\geq 6$ ): cardiovascular mortality. sUA, serum uric acid.

**Table 3** Determinants of overall mortality

Variable	Univariate HR (95% CI)	P value	Multivariate HR (95% CI)	P value
Age*	1.10 (1.08 to 1.12)	<0.001	1.08 (1.06 to 1.10)	<0.001
Sex (male)	0.44 (0.28 to 0.68)	<0.001		
Clinical evolution				
Tophi only or mono	1			
Oligo	1.18 (0.66 to 2.10)	0.584		
Polyarticular	2.04 (1.15 to 3.59)	0.014		
Disease duration*	0.99 (0.97 to 1.01)	0.491		
Number of flares in the previous year	1.03 (1.01 to 1.06)	0.002		
sUA (baseline)*	1.33 (1.22 to 1.46)	<0.001	1.21 (1.10 to 1.33)	<0.001
Tophi	2.21 (1.61 to 3.02)	<0.001		
Radiological assessment				
Normal	1			
Joint damage	1.79 (1.13 to 2.84)	0.013		
Comorbidity and risk factors				
BMI	0.98 (0.94 to 1.03)	0.486		
Creatinine (baseline)*	1.21 (1.10 to 1.32)	<0.001		
Ethanol consumption	0.44 (0.29 to 0.67)	<0.001		
Hypertension	4.23 (2.89 to 6.17)	<0.001		
Diabetes mellitus	2.64 (1.91 to 3.64)	<0.001		
Hyperlipidaemia	0.68 (0.49 to 0.94)	0.020		
Previous CV event	6.22 (4.44 to 8.71)	<0.001	2.70 (1.82 to 3.98)	<0.001
Diuretic treatment	5.55 (3.99 to 7.71)	<0.001		
Kaiser strata				
Without risk factors	1			
1–2 chronic diseases	2.16 (0.44 to 10.7)	0.345		
3–4 chronic diseases	3.20 (0.69 to 14.8)	0.137		
≥5 chronic diseases	9.97 (2.28 to 43.6)	0.002		
Follow-up and treatment				
Prophylaxis				
None	1			
Anakinra	0.51 (0.10 to 2.66)	0.429		
Colchicine	0.76 (0.30 to 1.97)	0.578		
Prednisone	2.10 (0.50 to 8.83)	0.310		
Cochicine				
No	1			
Yes	1.29 (0.86 to 1.94)	0.213		
First-line treatment				
Without treatment	1			
Allopurinol	0.34 (0.19 to 0.62]	<0.001		
Benzbromarone	0.46 (0.24 to 0.87]	0.017		
Febuxostat	0.79 (0.38 to 1.64]	0.536		
Urate-lowering drugs	0.92 (0.67 to 1.26)	0.606		
sUA levels achieved				
Yes	1			

Continued



Table 3 Continued

Variable	Univariate HR (95% CI)	P value	Multivariate HR (95% CI)	P value
No	2.95 (2.05 to 4.26)	<0.001	2.33 (1.60 to 3.41)	<0.001
Cohort entry (year period)				
1991–2000	1			
2001–2010	1.78 (1.17 to 2.71)	0.007	1.14 (0.74 to 1.78) <sup>1</sup>	0.546
2011–2017	2.68 (1.67 to 4.31)	<0.001	1.17 (0.70 to 1.95)	0.543

\*Per unit (year, mg/dL).

BMI, body mass index; CV, cardiovascular; sUA, serum uric acid.

## DISCUSSION

In this large prospective cohort study of patients with gout, we found that the risks of overall and CV mortality were significantly elevated for patients who failed to achieve target sUA concentrations of 0.36 mmol/L. These risks were substantial with over twofold higher mortality compared with similar patients with gout who met target UA levels and were not accounted for by demographic or clinical factors, including several acute illness indicators. The findings from this study add credence to the hypothesis that elevated UA concentrations above 6 mg/dL contribute substantially to mortality and to shortened life spans.

A possible mechanism through which high concentrations of uric acid influence inflammatory responses by facilitating interleukin (IL)-1 $\beta$  production in peripheral blood mononuclear cells (PBMCs) has been described by Crisan *et al.*<sup>12</sup> Hyperuricaemia causes a shift in the IL-1 $\beta$ /IL-1Ra balance produced by PBMCs after exposure to monosodium urate (MSU) crystals and toll-like receptors (TLR)-mediated stimuli, and this phenomenon is likely to reinforce the enhanced state of chronic inflammation.

In a previous study, we observed an excess mortality among patients with gout compared with the general population, which was in part related to an excess of CV risk factors but also due to the severity of gout as indicated by subcutaneous tophi.<sup>4</sup> In the current Cruces cohort, we highlight several important new findings. First, gouty erosions as detected on X-ray were independently predictive of mortality in this new multivariable model, whereas gouty tophi detected from clinical examination were not. These would suggest that erosive radiological changes indicate greater severity of inflammation and urate burden than tophi alone. Interestingly, erosive gout is a reflection of tophaceous deposits,<sup>13</sup> and articular deposits are much more frequent than subcutaneous ones.<sup>14,15</sup> Second, serum UA levels in the follow-up period, beyond baseline levels, continue to exert a significant predictive impact on future mortality, representing the continued risk of long-standing hyperuricaemia.<sup>13,16</sup> Baseline serum UA level relevance may be interpreted either as an independent effect or mediated by unapparent burden of deposits, as subcutaneous deposition

may not reflect necessarily what ultrasound or dual-energy CT studies may disclose.<sup>17</sup>

Variability in the number of sUA determinations during the first year, as well as their timing before or after 12 months after up-titrating treatment could have some effect on mortality. In order to avoid this limitation, all patients in the cohort had a minimum of three urate (UA) levels during the first year (3, 6 and 12 months). Besides, in the majority of patients, follow-up sUA levels were obtained after ULT had worked (84% had a follow-up time longer than 12 months).

The impact of ULT on CV events is controversial, with studies showing allopurinol treatment is associated with a reduction in the risk of myocardial infarction<sup>18</sup> and outweighing the impact of rare serious adverse effects,<sup>19</sup> and other studies showing no impact on CV mortality.<sup>20</sup> In our study, we confirm the beneficial impact of allopurinol and benzbromarone in reducing overall mortality, as each of these was associated with improved survival. This positive benefit also extended to lower rates of CV death, although the level of significance was less likely related to the smaller event rate. No safety signal was observed for first-line treatment with either allopurinol, febuxostat or benzbromarone, as multivariate analysis included confounding variables for CV risk factors, comorbidity and severity of gout. No benefit was observed for colchicine prophylaxis, but the number of patients was small and clinically heterogeneous (patients not willing to take any more colchicine, with formal contraindication, and some exposed to anakinra as off-label prophylaxis). Therefore, we are cautious with this negative result.

To put things in context, the prevalence of gout in adults in the USA has been estimated in 3.7% and the prevalence of gout with an indication of ULT in 2.2% (4.5 million people).<sup>21</sup> Of the latter, target sUA may only be achieved in half of the patients.<sup>21</sup> Very high sUA levels have been reported in association with atherogenesis, independently from HT and other CV risk factors.<sup>22</sup> Some concerns have also been raised on the impact of excessive lowering of sUA, as studies have shown that hypouricaemia is correlated with endothelial dysfunction.<sup>23</sup> The evidence to support this, however, is limited.<sup>24</sup> Taken together, there is increasing evidence to support

**Table 4** Determinants of CV-related mortality

Variable	Bivariate HR (95% CI)	P value	Multivariate HR (95% CI)	P value
Age*	1.12 (1.09 to 1.14)	<0.001	1.08 (1.06 to 1.11)	<0.001
Sex (male)	0.30 (0.17 to 0.53)	<0.001		
<b>Clinical evolution</b>				
Tophi only or mono	1			
Oligo	0.98 (0.43 to 2.27)	0.968		
Polyarticular	2.43 (0.10 to 5.37)	0.028		
Disease duration*	0.99 (0.96 to 1.02)	0.527		
Number of flares in the previous year	1.03 (1.00 to 1.06)	0.080		
sUA (baseline)*	1.39 (1.24 to 1.57)	<0.001	1.22 (1.08 to 1.38)	0.001
Tophi	2.83 (1.82 to 4.40)	<0.001	1.65 (1.02 to 2.66)	0.040
<b>Radiological assessment</b>				
Normal	1			
Joint damage	2.97 (1.32 to 6.69)	0.009		
<b>Comorbidity and risk factors</b>				
BMI	1.01 (0.95 to 1.07)	0.727		
Creatinine (baseline)*	1.21 (1.07 to 1.38)	0.003		
Ethanol consumption	0.35 (0.19 to 0.65)	0.001		
Hypertension	5.83 (3.27 to 10.40)	<0.001		
Diabetes mellitus	3.90 (2.52 to 6.04)	<0.001	1.69 (1.05 to 2.72)	0.029
Hyperlipidaemia	0.58 (0.37 to 0.92)	0.022	0.58 (0.35 to 0.95)	0.032
Previous CV event	10.14 (6.02 to 17.05)	<0.001	3.82 (2.08 to 6.99)	<0.001
Diuretic treatment	7.05 (4.40 to 11.32)	<0.001		
<b>Kaiser strata</b>				
Without risk factors	1			
1–2 chronic diseases	1.45 (0.13 to 16.00)	0.761		
3–4 chronic diseases	3.55 (0.41 to 30.37)	0.248		
≥5 chronic diseases	9.19 (1.13 to 74.83)	0.038		
<b>Follow-up and treatment</b>				
<b>Prophylaxis</b>				
None	1			
Anakinra	0.64 (0.06 to 7.14)	0.720		
Colchicine	1.05 (0.24 to 4.54)	0.952		
Prednisone	1.73 (0.16 to 19.11)	0.654		
<b>Cochicine</b>				
No	1			
Yes	1.40 (0.81 to 2.44)	0.230		
<b>First-line treatment</b>				
Without treatment	1			
Allopurinol	0.40 (0.17 to 0.97)	0.043		
Benzbromarone	0.49 (0.19 to 1.26)	0.140		
Febuxostat	0.81 (0.28 to 2.34)	0.694		
Urate-lowering drugs	1.00 (0.64 to 1.54)	0.992		
<b>sUA levels achieved</b>				
Yes	1		1	

Continued



Table 4 Continued

Variable	Bivariate HR (95% CI)	P value	Multivariate HR (95% CI)	P value
No	3.27 (2.00 to 5.34)	<0.001	2.05 (1.21 to 3.45)	0.007
Cohort entry (year period)				
1991–2000	1		1	
2001–2010	1.57 (0.90 to 2.74)	0.111	0.80 (0.44 to 1.48)	0.486
2011–2017	2.10 (1.09 to 4.03)	0.026	0.73 (0.36 to 1.50)	0.398

No stratified analysis was performed because the Kaiser strata did not modify the risk associated with sUA.

\*Per unit (year, mg/dL).

BMI, body mass index; CV, cardiovascular; sUA, serum uric acid.

lower sUA thresholds of at least 6 mg/dL in patients with gout to improve survival.

We and others have advocated for earlier intervention in gout primarily to avoid exposure to long-standing hyperuricaemia and reduce the risk of chronic tophaceous gout.<sup>25</sup> The *treat-to-target strategy* represents a global effort to improve gout control by reducing acute gout flares, preventing chronic tophaceous gout and its attendant morbidity. The findings from this study also support a treat-to target strategy for improving the outcomes of patients with gout by preventing low grade inflammation and reducing the risks of CV and total mortality.<sup>26 27</sup>

Our study has some inherent limitations. Patients not reaching the target also were the ones with shortest follow-up; something hard for us to interpret, and to foresee potential biases. Also our models did not adjust for smoking or non-steroidal anti-inflammatory drug use due to missing data. In addition, the Kaiser Permanente risk stratification was used as a measure of comorbidity instead of other indices, such as the Charlson index, being the former more prone to subjectivity; on the other hand, the stratification we used is readily available in all patients, as the algorithm used to stratify is embedded in the electronic system. Our cohort was derived from patients attending a specialist clinic, and may represent a sicker cohort of patients than commonly seen in primary care. Nevertheless, our objective was not descriptive, but analytical, and we cannot think of reasons why this relationship between not reaching a sUA target and death may not be replicated in other settings. Finally, the design was not that of a clinical trial, and treatment may be driven by extraneous factors, and even by the availability of medications (benzbromarone was not available for some periods of time, then was second line after allopurinol, finally febuxostat became available in 2010). Others have used propensity-score matching to reduce bias attributed to physician prescribing and practices.<sup>20 28 29</sup> However, given that most patients were on ULT in our cohort, monitored and treated by same physician, and that the associations of UA and death were far stronger than with any individual treatment, we believe that the association between UA and mortality is robust. Our cohort was established over a long period of time (26 years), during which there have possibly been major changes in the

spectrum of patients with gout and in treatment; that is to say, the different time strata may have some effect, such as on the CV risk of rheumatoid arthritis. However, in a subsequent paper the same group showed that, contrary to RA, it did not happen in gout. Nevertheless, our rate of proper control is one of the highest ever published and is similar throughout the cohort.

On the other hand, the way how patients were treated may have changed and may indeed be a predictor of mortality. However, there was no signal for mortality for any prophylaxis schedule. Therapy was within approved label, and therefore, not aggressive.

Finally, the number of flares during therapy is not included in the analysis, while the number of flares in the precedent year were. This has been considered a surrogate, among others, for severity of gout, as an accepted outcome by agencies and outcome measures rheumatic diseases clinical trials (OMERACT) for trials, and even an indication for ULT in the ACR2012 recommendations.<sup>30 31</sup>

This study also has several strengths that deserve mention. First, most studies that have explored the mortality risks of gout have lacked crucial information on sUA levels, radiographical evaluation and disease severity indicators—tophi and clinical joint involvement.<sup>2</sup> The Cruces cohort, in contrast, permits a closer exploration of these factors on the gout–mortality relationship. Second, all patients underwent serial clinical evaluations by a single specialist, reducing the risk of variation in disease assessment and facilitating a more homogeneous approach to management. Third, the study cohort benefited from a comprehensive assessment of demographic, clinical and disease severity indicators, allowing us to explore the independence of these factors on mortality in adjusted models.

In conclusion, patients with hyperuricaemia of gout who fail to achieve guideline-recommended lowering of UA to <0.36 mmol/L experience higher rates of total and CV mortality that are not explained by prevailing disease indicators. The adoption and implementation of ULT lowering strategies that lower sUA levels to <0.36 mmol/L are likely to confer a survival advantage beyond gout control and to improve patient outcomes.

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## REFERENCES

- Smith EUR, Díaz-Torné C, Perez-Ruiz F, *et al*. Epidemiology of gout: an update. *Best Pract Res Clin Rheumatol* 2010;24:811–27.
- Clarson LE, Chandratne P, Hider SL, *et al*. Increased cardiovascular mortality associated with gout: a systematic review and meta-analysis. *Eur J Prev Cardiol* 2015;22:335–43.
- Lottmann K, Chen X, Schädlich PK. Association between gout and all-cause as well as cardiovascular mortality: a systematic review. *Curr Rheumatol Rep* 2012;14:195–203.
- Perez-Ruiz F, Martínez-Indart L, Carmona L, *et al*. Tophaceous gout and high level of hyperuricaemia are both associated with increased risk of mortality in patients with gout. *Ann Rheum Dis* 2014;73:177–82.
- Serlachius A, Gamble G, House M, *et al*. Illness perceptions and mortality in patients with gout: a prospective observational study. *Arthritis Care Res* 2017;69:1444–8.
- Chen J-H, Lan J-L, Cheng C-F, *et al*. Effect of urate-lowering therapy on all-cause and cardiovascular mortality in hyperuricemic patients without gout: a case-matched cohort study. *PLoS One* 2015;10:e0145193.
- Solomon DH, Liu C-C, Kuo I-H, *et al*. Effects of colchicine on risk of cardiovascular events and mortality among patients with gout: a cohort study using electronic medical records linked with Medicare claims. *Ann Rheum Dis* 2016;75:1674–9.
- Neogi T, Mikuls TR. To treat or not to treat (to target) in gout. *Ann Intern Med* 2017;166:71–2.
- Kiltz U, Smolen J, Bardin T, *et al*. Treat-to-target (T2T) recommendations for gout. *Ann Rheum Dis* 2017;76:632–8.
- Perez Ruiz F, Sanchez-Piedra CA, Sanchez-Costa JT, *et al*. Improvement in diagnosis and Treat-to-Target management of hyperuricemia in gout: results from the GEMA-2 transversal study on practice. *Rheumatol Ther* 2018;5:243–53.
- Osakidetza. Chronicity in Basque country, 2010. Available: [http://www.osakidetza.euskadi.eus/r85-gkgnr100/es/contenidos/informacion/documentos\\_cronicos/es\\_cronic/adjuntos/ChronicityBasqueCountry.pdf](http://www.osakidetza.euskadi.eus/r85-gkgnr100/es/contenidos/informacion/documentos_cronicos/es_cronic/adjuntos/ChronicityBasqueCountry.pdf) [Accessed 4 Oct 2019].
- Crişan TO, Cleophas MCP, Oosting M, *et al*. Soluble uric acid primes TLR-induced proinflammatory cytokine production by human primary cells via inhibition of IL-1ra. *Ann Rheum Dis* 2016;75:755–62.
- McQueen FM, Chhana A, Dalbeth N. Mechanisms of joint damage in gout: evidence from cellular and imaging studies. *Nat Rev Rheumatol* 2012;8:173–81.
- Dalbeth N, Nicolaou S, Baumgartner S, *et al*. Presence of monosodium urate crystal deposition by dual-energy CT in patients with gout treated with allopurinol. *Ann Rheum Dis* 2018;77:364–70.
- Naredo E, Uson J, Jiménez-Palop M, *et al*. Ultrasound-detected musculoskeletal urate crystal deposition: which joints and what findings should be assessed for diagnosing gout? *Ann Rheum Dis* 2014;73:1522–8.
- Stack AG, Hanley A, Casserly LF, *et al*. Independent and conjoint associations of gout and hyperuricaemia with total and cardiovascular mortality. *QJM* 2013;106:647–58.
- Dalbeth N, House ME, Aati O, *et al*. Urate crystal deposition in asymptomatic hyperuricaemia and symptomatic gout: a dual energy CT study. *Ann Rheum Dis* 2015;74:908–11.
- Grimaldi-Bensouda L, Alperovitch A, Aubrun E, *et al*. Impact of allopurinol on risk of myocardial infarction. *Ann Rheum Dis* 2015;74:836–42.
- Dubreuil M, Zhu Y, Zhang Y, *et al*. Allopurinol initiation and all-cause mortality in the general population. *Ann Rheum Dis* 2015;74:1368–72.
- Kuo C-F, Grainger MJ, Mallen C, *et al*. Effect of allopurinol on all-cause mortality in adults with incident gout: propensity score-matched landmark analysis. *Rheumatology* 2015;54:kev246–150.
- Juraschek SP, Kovell LC, Miller ER, *et al*. Gout, urate-lowering therapy, and uric acid levels among adults in the United States. *Arthritis Care Res* 2015;67:588–92.
- Tavil Y, Kaya MG, Oktar SO, *et al*. Uric acid level and its association with carotid intima-media thickness in patients with hypertension. *Atherosclerosis* 2008;197:159–63.
- Sugihara S, Hisatome I, Kuwabara M, *et al*. Depletion of uric acid due to SLC22a12 (Urat1) loss-of-function mutation causes endothelial dysfunction in hypouricemia. *Circ J* 2015;79:1125–32.
- Gwag HB, Yang JH, Park TK, *et al*. Uric acid level has a U-shaped association with clinical outcomes in patients with vasospastic angina. *J Korean Med Sci* 2017;32:1275–80.
- Perez-Ruiz F, Moreno-Lledó A, Urionaguena I, *et al*. Treat to target in gout. *Rheumatology* 2018;57:i20–6.
- Vincent ZL, Gamble G, House M, *et al*. Predictors of mortality in people with recent-onset gout: a prospective observational study. *J Rheumatol* 2017;44:368–73.
- Aday AW, Ridker PM. Targeting residual inflammatory risk: a shifting paradigm for atherosclerotic disease. *Front Cardiovasc Med* 2019;6.
- Chen J-H, Lan J-L, Cheng C-F, *et al*. Effect of urate-lowering therapy on the risk of cardiovascular disease and all-cause mortality in patients with gout: a case-matched cohort study. *J Rheumatol* 2015;42:1694–701.
- Coburn BW, Michaud K, Bergman DA, *et al*. Allopurinol dose escalation and mortality among patients with gout: a national Propensity-Matched cohort study. *Arthritis Rheumatol* 2018;70:1298–307.
- Khanna D, Fitzgerald JD, Khanna PP, *et al*. 2012 American College of rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res* 2012;64:1431–46.
- Khanna D, Khanna PP, Fitzgerald JD, *et al*. 2012 American College of rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis of acute gouty arthritis. *Arthritis Care Res* 2012;64:1447–61.