Effect of Urate-lowering Therapy on the Risk of Cardiovascular Disease and All-cause Mortality in Patients with Gout: A Case-matched Cohort Study

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ABSTRACT. ***Objective.*** To examine (1) the risk of death from cardiovascular disease (CVD) and from all causes in patients with gout who do not undergo urate-lowering therapy (ULT), and (2) the effect of ULT on mortality risk in patients with gout.

Methods. In this prospective case-matched cohort study, 40,623 Taiwanese individuals aged ≥ 17 years were followed for 6.5 years. Mortality rate was compared between 1189 patients with gout who did not receive ULT and reference subjects (no gout, no ULT) matched for age, sex, and the index date of gout diagnosis (1:3 patients with gout/reference subjects), and between 764 patients with gout who received ULT and 764 patients with gout who did not receive ULT matched 1-to-1 based on their propensity score and the index date of ULT prescription. Cox proportional hazard modeling was used to estimate the respective risk of CVD (International Classification of Diseases, 9th ed. code 390–459) and all-cause mortality.

Results. After adjustment, patients with gout not treated with ULT had an increased risk of CVD mortality (HR 2.43, 95% CI 1.33–4.45) and all-cause mortality (1.45, 1.05–2.00) relative to the matched reference subjects (no gout, no ULT). Patients with gout treated with ULT had a lower risk of CVD (0.29, 0.11–0.80) and all-cause mortality (0.47, 0.29–0.79) relative to patients with gout not treated with ULT. This survival benefit persisted for users of either allopurinol or benzbromarone.

Conclusion. Patients with gout who received ULT had significantly better survival rates than those who did not. Thus, undertreatment of gout has serious negative consequences. (First Release June 15 2015; J Rheumatol 2015;42:1694–701; doi:10.3899/jrheum.141542)

Key Indexing Terms:
ALLOPURINOL BENZBROMARONE GOUT
MORTALITY URATE-LOWERING THERAPY

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Gouty arthritis is a common crystal-induced inflammation that presents with recurrent acute attacks and chronic joint deformity. Asymptomatic hyperuricemia with subsequent deposition of monosodium urate (MSU) crystals in the articular and periarticular soft tissues[1] increases the risk of an acute gout attack[2,3,4]. During the intercritical stage of chronic gouty arthritis, the deposited MSU crystals may potentiate chronic inflammation and aggravate systemic involvement[5,6].

The European League Against Rheumatism and the American College of Rheumatology recommend treating gout by administering urate-lowering therapy (ULT), including allopurinol and other uricosuric agents, to reduce the serum uric acid (SUA) level to 6 mg/dl[7,8]. Although the benefits of lowering SUA to reduce recurrent gouty attacks[9] and tophi size[10] are well understood, the management of gout is still suboptimal[11,12].

The associations between gouty arthritis and cardiovascular disease (CVD) and all-cause mortality have been examined[13,14,15]. Studies from around the world[16,17,18,19],

including 1 from Taiwan[20], have consistently reported that men with gout have a 50–60% greater risk of death from coronary heart disease and a 20–30% greater risk of premature death from all causes than do men without gout. It has been suggested that the modest but persistent inflammation that is present in patients with gout may promote atherosclerosis and thrombogenesis[6]. It was also suggested that hyperactivity of xanthine oxidase may result in target organ damage that could be prevented by the reduction of SUA levels, especially when xanthine oxidase is inhibited[21].

The burden of gout[12] is rising, with worldwide incidence and prevalence increasing since the 1980s[22,23]. The growing prevalence of obesity and metabolic syndrome may be related to this trend[24]. The estimated prevalence of gout is similar in the United States (3.9%)[25] and Taiwan (3.8%)[15], but the reported effect of gout on the risk of myocardial infarction (HR 1.23) is lower in Taiwan[15] than elsewhere (HR 1.6 in the Framingham Study and HR 1.55 in the Health Professionals Follow-Up Study)[16,17,18,19]. The discrepancy between Taiwan and other countries may be because of the popularity of prescribing ULT for hyperuricemia in Taiwan[26]. Thus, we hypothesized that ULT modifies the mortality risk of gout and examined the potential effect of ULT on the risk of premature mortality in patients with gout.

MATERIALS AND METHODS

Data source. This prospective case-matched cohort study used clinical data collected from the nationwide MJ Health Screening Centers that enrolled participants from all regions of Taiwan. All members of the cohort were self-paying participants. The database contained 49,460 individuals who were ≥ 17 years old and who had a physical checkup in 1996. Individuals were excluded if they had invalid or missing drug exposure time (n = 2351) or clinical measurements (n = 927), self-reported treatment with ULT at baseline (n = 1683), or died before 1997 (n = 52). The remaining 44,447 individuals were considered for inclusion in the present study. Information on demographics, lifestyle factors, comorbidities, medical history, and surgical history was collected with a structured questionnaire. Anthropometric measurements and biochemical assays of fasting blood samples were carried out. All participants had provided consent for the release of data. The MJ cohort data have been used in several publications[27,28,29].

The MJ dataset is linked to the National Health Insurance Research Database (NHIRD) that records all medical claims for drugs dispensed to Taiwanese patients covered by the National Health Insurance, with minimal underreporting and misclassification[30]. The MJ database is also linked to the National Mortality Registry, which provides the date and cause of all deaths[31]. The Department of Health performed all record linkages anonymously using encrypted data. All traceable personal identifiers were removed from the dataset before the statistical analysis to protect patient confidentiality. The Institutional Review Board of the China Medical University Hospital in Taichung (DMR96-IRB-241, DMR99-IRB-074, CMUH103-REC1-020) approved this study.

Definition of patients with gout with ULT drug exposure. Subjects with gout were defined as patients in the NHIRD with the diagnosis code of gout [274.X of the International Classification of Diseases, 9th ed (ICD-9)] and with concomitant use of a nonsteroidal antiinflammatory drug (NSAID) or colchicine between January 1, 1997, and December 31, 2002. Our definition did not include the use of corticosteroids because corticosteroids were not prescribed alone for treating gout, but were usually used concomitantly with NSAID or colchicine. Additionally, we did not include coxibs when we considered NSAID use. Although coxibs could be used to treat acute inflammation of gouty arthritis, Taiwanese NHIRD did not include the indication of coxib in gout treatment. There were 2646 patients with incident gout among the 44,447 individuals in the study database. Of these, 1457 (55%) were treated with ULT. The most common ULT were benzbromarone (73.0%), allopurinol (52.6%), probenecid (2.5%), and sulphinpyrazone (0.8%). Of the remaining 41,801 individuals with no gout diagnosis, 3824 were prescribed a ULT for other reasons and were excluded from the study. The remaining 37,977 patients formed the reference cohort (Supplementary Figure 1, available online at jrheum.org).

The cohort of patients with gout (n = 2646) and the subcohort of untreated patients with gout (n = 1189) were matched with reference subjects (no gout and no ULT) at a 1-to-3 ratio (i.e., 1 patient with gout was matched with 3 corresponding reference subjects) according to age (within a 5-yr age span), sex, and index date of gout diagnosis (Supplementary Figure 1, available online at jrheum.org). The index date for each reference subject was randomly assigned to match the index date of a patient with gout. The observation time was calculated from the index date of gout diagnosis to the censored date, which was either the time of death or the end of followup (December 31, 2002).

Outcomes. The primary outcome was CVD (ICD-9 390–459) mortality, and the secondary outcome was all-cause mortality. Kaplan-Meier survival curves were used to plot the survival probability of CVD mortality for patients with gout treated with ULT, patients with gout who were not treated with ULT, and the matched reference subjects (no gout, no ULT), and were tested by log-rank test.

Propensity score as the indication probability of ULT use. A propensity score (0 to 1) was used to determine the likelihood of a patient with gout being prescribed a ULT by a physician given his or her individual characteristics[32]. This analysis was performed separately for all patients treated with ULT and for those treated with allopurinol only or benzbromarone only. Stepwise logistic regression analysis was conducted to determine significant predictors for ULT use from 104 baseline variables defined at the physical checkup in 1996 (C-statistic = 0.79). Patients with gout treated with ULT and patients with gout not treated with ULT were then matched at a 1-to-1 ratio based on the propensity score and the index date of ULT prescription by a greedy algorithm[33]. The index dates for reference subjects not treated with ULT were randomly assigned and then used to match each reference subject with a patient with gout based on his/her date of ULT prescription. There was 1 reference subject for each identified patient with gout treated with ULT. Matching for propensity score was performed to remove the bias associated with the drug indication, and matching for the index date of ULT prescription was performed to remove the immortal time bias between treatment and no treatment. Of the 1457 patients with gout treated with ULT, 764 were successfully matched to a patient with gout not treated with ULT, with the nearest propensity score by applying a caliper of 0.05 on the propensity score scale and the same index date of ULT prescription[34]. The observation time was calculated from the index date of ULT prescription until the time of death or the censored date. Using a similar matching technique, we separately derived 286 matched pairs of allopurinol-only users and 504 matched pairs of benzbromarone-only users among patients with gout. Each identified patient with gout treated with allopurinol only or benzbromarone only was matched with 1 patient with gout who did not receive ULT.

Statistical analysis. Baseline demographic data were compared between patients with gout and their respective reference groups using the Student t test for continuous data and the chi-square test for categorical data. The mortality events resulting from CVD and all-causes were compared (1) between all patients with gout and the matched reference subjects (no gout, no ULT), (2) between patients with gout who did not receive ULT and the matched reference subjects (no gout, no ULT), and (3) between the 1-to-1 matched pairs of patients with gout with and without ULT. The Cox proportional hazard model was used to estimate the adjusted HR of CVD mortality and all-cause mortality.

Subgroup analysis for ULT use in patients with gout. The concomitant use of antihypertensive, antidiabetic, and lipid-lowering drugs may lower SUA

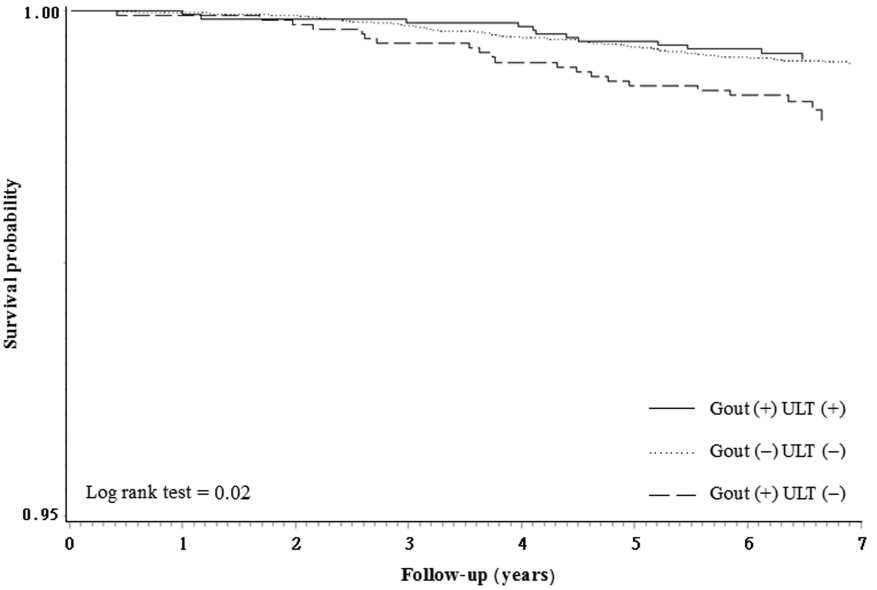

Figure 1. Survival probability of CVD mortality in patients with gout with and without ULT and in matched reference subjects (no gout, no ULT). The curves are not adjusted for confounding factors. Gout–, ULT–: 7872 matched reference subjects (no gout, no ULT). Gout+, ULT–: 1189 patients with gout with no ULT. Gout+, ULT+: 1443 patients with gout with ULT (14 patients were not qualified for matching criteria). CVD: cardiovascular disease; ULT: urate-lowering therapy.

levels[35,36,37]. The effect of ULT with concomitant medication on mortality in patients with gout was analyzed by stratifying with respect to the presence or absence of each concomitant medication. The patients with gout treated with ULT were compared with their 1-to-1 matched counterparts within each stratified subgroup. The duration of ULT use may also bias the estimates. A similar matching method with a 1-to-1 ratio was applied by stratifying patients with gout treated with ULT with respect to the cumulative ULT use duration. This approach maintained comparability between the case and reference cohorts in terms of the baseline characteristics, and could be considered close to the scheme of clinical trials with an intent-to-treat approach. All analyses were performed using SAS statistical software version 9.3 (SAS Institute).

RESULTS

Demographic data. In total, 40,623 subjects [37,977 non-gout, non-ULT users (reference subjects); 1189 patients with gout who were not treated with ULT, and 1457 patients with gout who were treated with ULT) satisfied the inclusion criteria and were followed up for a mean of 6.5 years (Supplementary Table 1, available online at jrheum.org). Some of the baseline characteristics differed across the 3 groups. The SUA level was 8.1 mg/dl in patients with gout who received ULT, 6.5 mg/dl in patients with gout who did not receive ULT, and 5.7 mg/dl in reference subjects. Patients with gout, especially those who received ULT, had a worse metabolic profile and a higher prevalence of comorbidities than the reference subjects.

Table 1 shows the demographic, lifestyle, and clinical characteristics of the 3 subgroups of patients after matching with their paired controls: (1) all patients with gout (n = 2632, 14 patients were not qualified for matching criteria) and their matched reference subjects (n = 7872, 24 patients were not qualified for matching criteria), (2) patients with gout who did not receive ULT (n = 1189) and their matched reference subjects (n = 3556, 11 patients were not qualified for matching criteria), and (3) patients with gout who received ULT (n = 764) and the reference group of patients with gout who did not receive ULT (n = 764) who were matched for propensity score and index date. The patients with gout with and without ULT had a similar SUA level (p = 0.47).

Kaplan-Meier survival curves. The Kaplan-Meier survival curves showed that CVD mortality in patients with gout who received ULT was similar to that of reference subjects (non-gout, non-ULT; log rank test, $p > 0.05$) and was lower than that in patients with gout who did not receive ULT (log rank test, p = 0.02; Figure 1).

Mortality risks associated with gout. Matching was performed to improve the similarity of confounding variables across comparison groups. The comparison of all patients with gout (n = 2632) to a matched reference group (non-gout, non-ULT users, n = 7872) indicated no significant effect of gout on CVD mortality (HR 0.96, 95% CI 0.63–1.46) or all-cause mortality (HR 0.84, 95% CI 0.68–1.04) after adjusting for age; sex; lifestyle factors of smoking, drinking, and exercise; and comorbidities of obesity, hypertension, diabetes, renal failure, and hepatitis (data not shown). However, the comparison of patients with gout who did not receive ULT (n = 1189) to a matched reference group (non-gout, non-ULT users, n = 3556) indicated a significant effect of gout on CVD mortality (adjusted HR 2.43, 95% CI 1.33–4.45) and all-cause mortality (adjusted HR 1.45, 95%

Table 1. Baseline demographic data of patients with gout and their respective matched references. Values are mean ± SD or n (%) unless otherwise specified.

Characteristics	Gout+, n = 2632	Gout–, ULT–, n = 7872	p	Gout+, ULT–, n = 1189	Gout–, ULT–, n = 3556	p	Gout+, ULT+, n = 764	Gout+, ULT– , n = 764	p
Age, yrs	50.3 ± 15.3	50.3 ± 15.3	0.99	47.6 ± 15.2	47.6 ± 15.2	0.98	50.6 ± 14.8	50.5 ± 15.1	0.91
Male	1639 (62.3)	4902 (62.3)	0.99	542 (45.6)	1622 (45.6)	0.99	482 (63.1)	507 (66.4)	0.18
Followup time, yrs	6.4 ± 0.7	6.4 ± 0.7	0.96	6.4 ± 0.8	6.4 ± 0.7	0.24	6.5 ± 0.6	6.4 ± 0.8	< 0.01
Uric acid, mg/dl	7.4 ± 2.0	6.0 ± 1.4	< 0.01	6.5 ± 1.8	5.9 ± 1.4	< 0.01	7.4 ± 1.7	7.3 ± 1.7	0.47
Systolic BP, mmHg	129.8 ± 22.8	126.6 ± 22.0	< 0.01	124.3 ± 21.5	124.5 ± 22.0	0.82	129.3 ± 21.8	129.6 ± 22.2	0.80
Diastolic BP, mmHg	77.0 ± 12.1	74.0 ± 11.9	< 0.01	71.8 ± 12.0	71.3 ± 11.6	0.20	76.2 ± 11.5	75.6 ± 11.9	0.45
Cholesterol, mg/ dl	208.2 ± 41.9	200.1 ± 37.8	< 0.01	204.0 ± 44.0	199.3 ± 38.2	< 0.01	209.2 ± 39.4	207.2 ± 42.9	0.34
HDL-C, mg/ dl	44.3 ± 14.3	44.0 ± 13.5	0.50	46.6 ± 14.0	46.8 ± 13.8	0.59	44.4 ± 14.2	45.3 ± 13.7	0.30
Triglyceride, mg/ dl	147.7 ± 90.0	120.8 ± 69.7	< 0.01	166.1 ± 87.2	117.0 ± 77.6	< 0.01	149.0 ± 80.2	151.3 ± 106.6	0.64
Glucose, mg/ dl	104.4 ± 30.2	102.8 ± 28.5	0.02	133.1 ± 94.3	100.8 ± 25.3	< 0.01	105.0 ± 30.0	106.2 ± 33.5	0.45
eGFR, 1.73 m^2, ml/min	73.3 ± 17.2	77.4 ± 15.1	< 0.01	77.6 ± 16.7	78.9 ± 15.2	0.01	72.3 ± 16.3	74.2 ± 16.7	0.03
BMI, kg/m^2	24.9 ± 3.5	23.6 ± 3.3	< 0.01	24.2 ± 3.6	23.4 ± 3.4	< 0.01	25.1 ± 3.5	25.1 ± 3.4	0.97
Comorbidity									
Hypertension	107 (4.1)	154 (2)	< 0.01	33 (2.8)	53 (1.5)	< 0.01	25 (3.3)	27 (3.5)	0.78
Heart disease	448 (17)	811 (10.3)	< 0.01	146 (12.3)	330 (9.3)	< 0.01	144 (18.8)	127 (16.6)	0.25
Diabetes mellitus	32 (1.2)	55 (0.7)	0.01	14 (1.2)	30 (0.8)	0.30	10 (1.3)	11 (1.4)	0.83
Alcohol drinking			0.03			0.12			0.63
Never	346 (13.1)	947 (12)		180 (15.1)	442 (12.4)		81 (10.6)	103 (13.5)	
Abstained	1126 (42.8)	3586 (45.6)		571 (48)	1782 (50.1)		328 (42.9)	322 (42.1)	
1–2 drinks/week	124 (4.7)	305 (3.9)		42 (3.5)	97 (2.7)		34 (4.5)	35 (4.6)	
3–4 drinks/week	661 (25.1)	2026 (25.7)		261 (22)	828 (23.3)		207 (27.1)	202 (26.4)	
Daily	272 (10.3)	730 (9.3)		102 (8.6)	316 (8.9)		81 (10.6)	74 (9.7)	
Missing data	103 (3.9)	278 (3.5)		33 (2.8)	91 (2.6)		33 (4.3)	28 (3.7)	
Cigarette smoking			< 0.01			0.48			0.97
Never	416 (15.8)	1149 (14.6)		208 (17.5)	563 (15.8)		108 (14.1)	118 (15.4)	
Abstained	1154 (43.8)	3417 (43.4)		594 (50)	1754 (49.3)		345 (45.2)	336 (44)	
Occasionally	239 (9.1)	685 (8.7)		73 (6.1)	228 (6.4)		64 (8.4)	64 (8.4)	
Often	111 (4.2)	304 (3.9)		45 (3.8)	135 (3.8)		35 (4.6)	38 (5)	
Daily	259 (9.8)	712 (9)		111 (9.3)	327 (9.2)		76 (9.9)	77 (10.1)	
Missing data	453 (17.2)	1605 (20.4)		158 (13.3)	549 (15.4)		136 (17.8)	131 (17.1)	
Smoking amount			< 0.01			0.15			0.76
None or missing	1728 (65.7)	4865 (61.8)		871 (73.3)	2502 (70.4)		493 (64.5)	503 (65.8)	
< 5 per day	123 (4.7)	392 (5)		49 (4.1)	165 (4.6)		37 (4.8)	28 (3.7)	
5–10 per day	172 (6.5)	551 (7)		59 (5)	221 (6.2)		53 (6.9)	47 (6.2)	
11–19 per day	391 (14.9)	1457 (18.5)		133 (11.2)	456 (12.8)		118 (15.4)	114 (14.9)	
1–2 pack per day	213 (8.1)	602 (7.6)		74 (6.2)	209 (5.9)		62 (8.1)	70 (9.2)	
> 2 packs per day	5 (0.2)	5 (0.1)		3 (0.3)	3 (0.1)		1 (0.1)	2 (0.3)	

For alcohol consumption and cigarette smoking, "Never" indicates the subjects have never been exposed and "Abstained" indicates that although the subjects have been exposed before, they have stopped the usage. Gout +: total patients with gout (n = 2632). Gout+, ULT–: patients with gout without ULT (n = 1189). Gout–, ULT–: non-gout and non-ULT individuals who were matched 1-to-3 to subgroups of Gout+ and Gout+, ULT– by age, sex, and index date of the gout diagnosis (n = 7872 and 3556, respectively). Gout+, ULT+ versus Gout+, ULT–: 764 pairs of patients with gout treated with and without ULT matched by propensity score and the index date of ULT prescription. UTL: urate-lowering therapy; BP: blood pressure; HDL-C: high-density lipoprotein cholesterol; eGFR: estimated glomerular filtration rate; BMI: body mass index.

CI 1.05–2.00; Table 2). This difference may indicate a survival effect of ULT in patients with gout.

ULT in patients with gout. In the 1-to-1 matched groups of patients with gout with and without ULT, the CVD and all-cause mortality rates of ULT users were lower than the rates in non-ULT users (Table 2). Patients with gout who received ULT had significantly lower mortality from CVD (HR 0.29, 95% CI 0.11–0.80) and all causes (HR 0.47, 95% CI 0.29–0.79) relative to the matched patients with gout who did not receive ULT.

Allopurinol or benzbromarone use in patients with gout. A potential effect of the type of ULT on mortality outcomes was considered. We compared CVD and all-cause mortalities in patients with gout who received either allopurinol, a xanthine oxidase inhibitor, or benzbromarone, a uricosuric agent, with those who did not receive any ULT (Supplementary Table 2, available online at jrheum.org). A significantly lower risk of death was found in patients who received allopurinol only and in patients who received benzbromarone only, relative to the corresponding matched non-ULT users (Table 3). Nevertheless, the small number of mortality events made these risk estimates less reliable.

Effect of ULT with concomitant medication. In each subgroup stratified according to concomitant medication, which

Table 2. Mortality risk based on the presence of gout and ULT.

Gout	ULT	n	PY	CVD Mortality					All-cause Mortality				
				E	M	MRR	HR (95% CI)	p	E	M	MRR	HR (95% CI)	p
–*	–	3556	22,916	25	1.09		Reference		117	5.11		Reference	
+*	–	1189	7630	21	2.75	2.52	2.43 (1.33–4.45)	< 0.01	60	7.86	1.54	1.45 (1.05–2.00)	0.01
+	–	764	4886	16	3.27		Reference		44	9.01		Reference	
+	+	764	4966	5	1.01	0.31	0.29 (0.11–0.80)	0.02	23	4.63	0.51	0.47 (0.29–0.79)	0.01

* HR were adjusted for age, sex, lifestyle (smoking, drinking, and exercise), and comorbidity (obesity, hypertension, diabetes, renal failure, and hepatitis). ULT: urate-lowering therapy; PY: person-years; CVD: cardiovascular disease; E: number of events; M: mortality rate per 1000 person-years; MRR: mortality rate ratio.

Table 3. Mortality risk based on the presence of gout and ULT of either allopurinol (A) or benzbromarone (B).

Gout	ULT	n	PY	CVD Mortality					All-cause Mortality				
				E	M	MRR	HR (95% CI)	p	E	M	MRR	HR (95% CI)	p
+	–	286	1784	12	6.73		Reference		36	20.18		Reference	
+	A*	286	1825	1	0.55	0.08	0.37 (0.01–0.48)	< 0.01	17	9.32	0.46	0.39 (0.22–0.70)	< 0.01
+	–	504	3204	11	3.43		Reference		32	9.99		Reference	
+	B**	504	3291	1	0.30	0.09	0.07 (0.01–0.52)	0.01	14	4.25	0.43	0.24 (0.12–0.49)	< 0.01

* HR were further adjusted for glucose level. ** HR were further adjusted for comorbidities of hypertension and heart disease. ULT: urate-lowering therapy; PY: person-years; CVD: cardiovascular disease; E: number of events; M: mortality rate per 1000 person-years; MRR: mortality rate ratio; A: allopurinol; B: benzbromarone.

consisted of antihypertensive, antidiabetic, and lipid-lowering agents, there were generally fewer mortality events in patients with gout who received ULT than in the 1-to-1 matched nonusers. However, only subgroups examining concomitant use of antihypertensive medication (243 pairs), without antidiabetic medication (496 pairs), and without lipid-lowering medication (563 pairs), had sufficient power for a risk estimate of all-cause mortality (Figure 2; Supplementary Table 3, available online at jrheum.org). There was an independent effect of ULT on all-cause mortality in patients with gout who did not receive antidiabetic drugs and in patients with gout who did not receive lipid-lowering agents. In the presence of concomitant antihypertensive drugs, ULT reduced the risk of all-cause mortality by 59%.

Duration of ULT use. Among the patients with gout who were treated with ULT, fewer than half (38.9%) received ULT

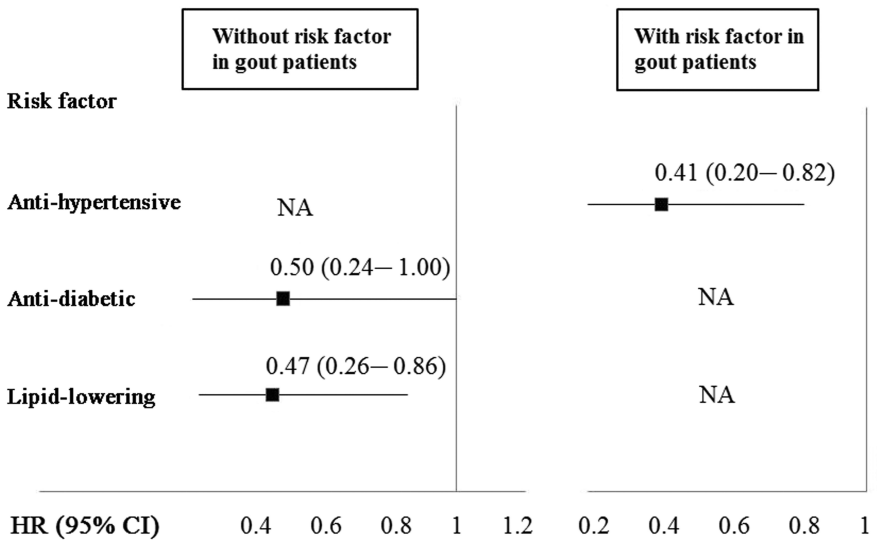

Figure 2. Mortality risk according to the presence of ULT in subgroups stratified by presence or absence of concomitant medications, including antihypertensive, antidiabetic, and lipid-lowering drugs. ULT: urate-lowering therapy; NA: result not available because there were 0 events in the subgroup of ULT users.

cumulatively for > 2 years (Supplementary Table 3, available online at jrheum.org). There was no significant difference in mortality rates between patients with gout who received ULT for < 2 years and the 1-to-1 matched non-ULT users. The all-cause mortality rate of patients with gout who received ULT for > 2 years was significantly lower than that of the 1-to-1 matched non-ULT users (Figure 3). There were too few CVD events to show the effect of ULT on CVD mortality.

DISCUSSION

Previous studies have clearly indicated increased mortality in patients with gout[16,17,19]. Our findings confirm this in untreated patients with gout, with a 143% increased risk of CVD mortality and a 45% increased risk of all-cause mortality compared with reference subjects who did not have gout and did not receive ULT. However, the increased risk in patients with gout was modified by ULT, with an apparent risk reduction of 71% for CVD mortality and 53% for all causes of death. The positive survival benefit of ULT in patients with gout persisted in subgroup analysis with respect to concomitant drugs. Patients with gout with chronic ULT use (> 2 yrs) had significantly reduced mortality risk.

Although gouty arthritis has a high prevalence and is associated with comorbidity, treatment of gout is considered suboptimal[11]. Only 37.6% of patients with gout in the United Kingdom received ULT, and the adherence to treatment was as low as 39.7%[12]. In the current study, we demonstrated that more than half (55.5%) of the patients with gout in Taiwan received ULT and that ULT modified the mortality outcomes. This raises the serious concern that suboptimal treatment of gout relates not only to arthritis recurrence, but also to mortality.

The inflammation present in gouty arthritis initiates from the phagocytosis of MSU crystals by white blood cells[38]. Although each acute episode of gout resolves spontaneously, the persistence of tophi causes subsequent recurrence[5]. MSU crystals in chronic gouty arthritis are 1 of the damage-associated molecular patterns that contribute to atherosclerosis and are recognized as an NLRP3 inflammasome- and interleukin 1–mediated sterile inflammatory response[6]. Drugs that lower the SUA level may suppress the inflammatory response by dissolving MSU crystals[9,10] and reducing activation of the NLRP3 inflammasome[6,38]. A previous study on rats showed that the SUA level and blood pressure were lowered by either allopurinol or benziodarone, another uricosuric agent[39]. Allopurinol may improve endothelial function[40] and lower systolic and diastolic blood pressure[41] in addition to lowering the SUA level. Although the initial period of allopurinol use after acute heart failure increases mortality, continuous allopurinol use for > 30 days by patients with a history of gout leads to a reduction in mortality risk[42]. These studies support and are comparable with our observation that patients with gout who received ULT had favorable outcomes relative to patients with gout who did not receive ULT, especially those with longterm ULT use.

Although a recent Taiwanese report with a median followup duration of 5.25 years indicated no beneficial effect of allopurinol on CVD mortality[43], this result may be biased by the residual confounders, including the allopurinol indication and its contraindication. We used a 1-to-1 propensity score–matching scheme, and our findings demonstrated a positive survival benefit for allopurinol. This is compatible with a recent cohort study that showed that allopurinol initiation reduced the risk of all-cause mortality by 19% in patients with gout[44]. The positive survival effect of benzbromarone on CVD mortality in the present study is compatible and superior to that estimated by the previous Taiwanese report[43].

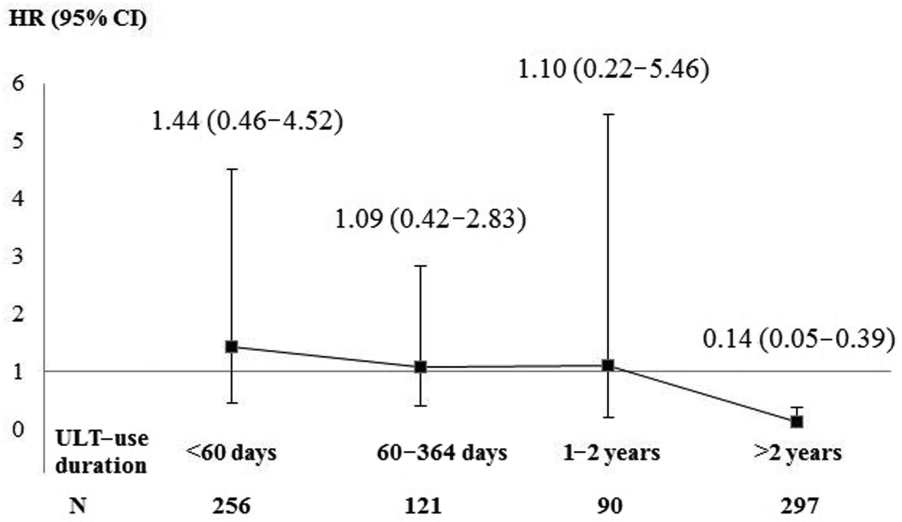

Figure 3. Mortality risk according to the presence of urate-lowering therapy (ULT) in subgroups stratified by duration of ULT use.

We found far fewer allopurinol users than benzbromarone users in this Taiwanese cohort study. This may be related to the potential risk of HLA-B*5801–associated hypersensitivity syndrome in Asian patients[45]. Although benzbromarone has been examined for gout treatment[46], this drug was once withdrawn from the market because of serious hepatotoxicity[47]. It may, however, be better tolerated than allopurinol by Taiwanese patients, as indicated by its higher frequency of use in the present cohort. Although a possible adverse effect on CVD events was reported for febuxostat, a new selective xanthine oxidase inhibitor, it will be of interest to reevaluate its potential effect on heart disease in the future[48].

A few strengths of our study should be mentioned. We relied upon the large amount of recorded information available in the national database to examine the potential benefit of ULT on mortality in patients with gout. Although patients with gout had a greater risk of premature mortality and higher prevalence of concomitant medication, including colchicine and NSAID, than the reference subjects, the potential confounders were balanced between patients with gout who did and did not receive ULT through a 1-to-1 matching of propensity scores and the index date of ULT prescription. The use of a large number of measured covariates (104 in total) may overcome the limitation of using propensity scores in a 1-to-1 case-matched cohort analysis[32]. The national census and accuracy of national death files in Taiwan are known to be complete[31], and there is no reason to suspect the presence of a nondifferential bias.

There were several limitations to our study. First, this was not a randomized clinical trial, so we cannot attribute all the observed mortality benefits to ULT. Bias could have resulted from confounding by indication; however, this was prevented by a greedy matching technique of the propensity score in which patients with gout who did and did not receive ULT had a balanced pattern of known comorbidities such as hypertension, diabetes, and obesity. The immortal time bias was also avoided because if a non-ULT user died before the first date of ULT prescribed to their matched ULT user, we reselected subjects by matching the index date of ULT prescription. Second, some patients who were prescribed ULT may have had poor compliance. However, by using a rigorous 1-to-1 greedy matching process to maximize statistical power, the characteristics of ULT users and nonusers were comparable in each of the stratified subgroups, including the duration of cumulative ULT use. The major analysis and the subgroup analysis stratified by concomitant drug use and the cumulative interval of ULT use all indicated that ULT had a direct and independent positive effect on survival in patients with gout. Third, our information regarding gout diagnosis and ULT prescription came from the NHIRD, a record of dispensed drug claims. Although the potential for misclassification does exist, gout diagnosis has previously been validated in a sensitivity analysis[3]. In addition, only the initial baseline data were used, yet the metabolic profile could vary over time. Only a few of the examinees had repeated measurement of their SUA level. We were thus unable to relate the benefit of ULT to the degree of SUA lowering. However, by relying on a single measurement, our study was able to more simply assess the relationship between gout and mortality risk[29]. Finally, it is equivocal whether a residual or unknown confounding effect, such as better physical fitness in patients with better drug compliance, may exist, and members of the cohort came from self-paying participants who were above average in socioeconomic class. However, the HR were internally compared, so these should not be subject to the influence of these factors.

The current study demonstrates a markedly increased mortality risk in untreated patients with gout relative to reference subjects without gout who did not receive ULT. Use of either allopurinol or benzbromarone significantly modified the survival outcome of patients with gout relative to that of patients with gout who did not receive ULT. Undertreatment of gout has serious negative consequences, and the important role of ULT in gout treatment warrants further evaluation and recognition.

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ONLINE SUPPLEMENT

Supplementary data for this article are available at jrheum.org.

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