Clinical Rheumatology
https://doi.org/10.1007/s10067-024-06866-y

CORRECTION

Correction to: Association between urate-lowering therapy and cardiovascular events in patients with asymptomatic hyperuricemia

Hiroyuki Hashimoto[1] · **Masato Takeuchi**[1] · **Koji Kawakami**[1]

Correction to: Clinical Rheumatology (2023) 42:3075-3082
https://doi.org/10.1007/s10067-023-06710-9

In the original published version of this article, the Tables 1, 2, 3, 4 should be corrected. In Table 1, the total number of subjects after weighting was incorrect. Although the data from all subjects (5270 in the ULT group and 146896 in the Control group) was used, the mathematically correct number of subjects after weighting was 4472 for both groups.

In Tables 2, 3, 4, the units of incidence rate were not stated and we have added the units "Weighted incidence rate per 1000 person-years".

The corrected tables are shown as follows:

The original article can be found online at https://doi.org/10.1007/s10067-023-06710-9.

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Published online: 26 January 2024

Table 1 Baseline characteristics of each group before and after overlap weighting

	Crude			After overlap weighting		
	ULT Group (n = 5,270)	Control Group (n = 146,896)	SDif	ULT Group (n = 4,472)	Control Group (n = 4,472)	SDif
Sex (%)	80 (1.5)	5755 (3.9)	0.15	76 (1.7)	76 (1.7)	0.00
Age, mean (SD), y	47.7 (9.3)	41.9 (9.9)	0.61	47.2 (9.3)	47.2 (9.5)	0.00
BMI, mean (SD)	26.0 (4.1)	24.8 (3.8)	0.32	25.9 (4.0)	25.9 (4.2)	0.00
Systolic BP, mean (SD), mmHg	128.7 (15.9)	123.5 (15.0)	0.33	128.3 (15.8)	128.3 (16.2)	0.00
Diastolic BP, mean (SD), mmHg	82.1 (11.7)	77.2 (11.5)	0.42	81.7 (11.7)	81.7 (12.0)	0.00
Laboratory Data, mean (SD)						
Baseline uric acid, mg/dL	8.1 (1.0)	7.5 (0.8)	0.62	8.0 (0.9)	8.0 (3.3)	0.00
LDL, mg/dL	129.6 (33.3)	129.8 (33.0)	0.00	130.1 (33.5)	130.1 (32.9)	0.00
HDL, mg/dL	55.6 (15.2)	56.5 (14.7)	0.06	55.7 (15.3)	55.7 (15.1)	0.00
TG, mg/dL	176.8 (144.2)	142.3 (112.5)	0.27	172.2 (132.7)	172.2 (158.3)	0.00
HbA1c, %	5.6 (0.7)	5.5 (0.5)	0.28	5.6 (0.7)	5.6 (0.6)	0.00
eGFR, mL/min/1.73 m2	71.0 (15.1)	78.4 (13.7)	0.51	71.9 (14.9)	71.9 (12.9)	0.00
Comorbidity (%)						
Liver disease	1229 (23.3)	15919 (10.8)	0.34	964 (21.5)	964 (21.5)	0.00
Hepatitis	276 (5.2)	3143 (2.1)	0.16	216 (4.8)	216 (4.8)	0.00
Dementia	1 (0.0)	25 (0.0)	0.00	1 (0.0)	1 (0.0)	0.00
Arthritis	1277 (24.2)	5504 (3.7)	0.62	858 (19.2)	858 (19.2)	0.00
Fatigue	24 (0.5)	917 (0.6)	0.02	22 (0.5)	22 (0.5)	0.00
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Schizophrenia	43 (0.8)	933 (0.6)	0.02	37 (0.8)	37 (0.8)	0.00
Substance abuse	37 (0.7)	1785 (1.2)	0.05	34 (0.8)	34 (0.8)	0.00
Medication (%)						
Polypharmacy	527 (10.0)	9227 (6.3)	0.14	393 (8.8)	393 (8.8)	0.00
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Other antidiabetes drug	8 (0.2)	19 (0.0)	0.05	4 (0.1)	4 (0.1)	0.00

BMI body mass index, *BP* blood pressure, *COPD* chronic obstructive pulmonary disease, *DPP4* dipeptidyl peptide-4, *GLP1* glucagon-like peptide-1, *HbA1c* hemoglobin A1c, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *RAS* renin-angiotensin system, *SD* standard deviation, *SDif* standardized difference, *SGLT2* sodium glucose transporter, *TG* triglyceride

Table 2 Association between ULT and cardiovascular events after overlap weighting in intention-to-treat analysis with complete cases

	Weighted incidence rate per 1000 person-years		HR (95% CI)	*P* value
	ULT Group	Control Group		
CVD composite	24.2	24.1	1.01 (0.89 to 1.13)	0.93
Coronary artery disease	8.4	9.1	0.92 (0.76 to 1.12)	0.42
Stroke	15.0	14.6	1.03 (0.89 to 1.20)	0.67
Atrial fibrillation	2.7	2.9	0.95 (0.68 to 1.33)	0.75
All-cause mortality	0.6	0.6	0.96 (0.47 to 1.96)	0.92

CVD cardiovascular disease, *HR* hazard ratio, *ULT* urate-lowering therapy

Table 3 Sensitivity analysis with various sUA cutoff points on index date and on follow-up date

	Weighted incidence rate per 1000 person-years		HR (95% CI)	*P* value
	ULT Group	Control Group		
Serum UA before ULT (on index date)				
< 8.0	25.0	25.5	0.98 (0.84 to 1.15)	0.80
8.0 ≤, < 9.0	22.5	24.1	0.94 (0.75 to 1.18)	0.58
9.0 ≤	24.7	20.3	1.22 (0.90 to 1.64)	0.20
Serum UA after ULT (on follow-up date)				
Cutoff 6.0				
≤ 6.0	28.1	25.2	1.11 (0.88 to 1.39)	0.38
> 6.0	23.6	24.2	0.98 (0.86 to 1.12)	0.77
Cutoff 7.0				
≤ 7.0	24.8	25.2	0.98 (0.83 to 1.14)	0.77
> 7.0	24.1	23.8	1.01 (0.86 to 1.19)	0.90
Cutoff 8.0				
≤ 8.0	23.8	24.8	0.96 (0.84 to 1.09)	0.53
> 8.0	26.1	22.4	1.17 (0.92 to 1.49)	0.20

HR, hazard ratio; *UA*, uric acid; *ULT*, urate-lowering therapy

Table 4 Subgroup analysis investigating the interaction between ULT and other variables on the primary outcome

	Weighted incidence rate per 1000 person-years		HR (95% CI)	*P* value
	ULT Group	Control Group		
Sex				
Male	24.2	24.0	1.01 (0.89 to 1.13)	0.92
Female	27.9	25.6	1.09 (0.44 to 2.70)	0.86
Age				
< 40	13.6	15.5	0.89 (0.63 to 1.26)	0.51
≥ 40, < 60	26.4	24.7	1.07 (0.94 to 1.22)	0.33
≥ 60	32.0	46.5	0.69 (0.45 to 1.06)	0.09
DM				
DM (+)	38.6	32.0	1.21 (0.83 to 1.75)	0.32
DM (-)	23.2	23.5	0.99 (0.87 to 1.12)	0.83
CKD				
CKD (+)	32.7	30.6	1.06 (0.82 to 1.38)	0.65
CKD (-)	22.6	22.7	1.00 (0.87 to 1.14)	0.96
HT				
HT (+)	29.3	29.2	0.99 (0.84 to 1.18)	0.94
HT (-)	23.2	23.5	0.99 (0.87 to 1.12)	0.83
Type of ULT				
Allopurinol	24.7	26.0	0.94 (0.78 to 1.14)	0.54
Febuxostat	24.0	23.9	1.01 (0.83 to 1.22)	0.95
Topiroxostat	45.3	23.2	1.89 (1.18 to 3.03)	0.01
Benzbromarone	28.5	24.9	1.12 (0.82 to 1.53)	0.49

CI, confidence interval; *CKD*, chronic kidney disease; *DM*, diabetes mellitus; *HR*, hazard ratio; *HT*, hypertension; *ULT,* urate-lowering therapy

The original article has been corrected.

Clinical Rheumatology (2024) 42:3075–3082
https://doi.org/10.1007/s10067-023-06710-9

ORIGINAL ARTICLE

Association between urate-lowering therapy and cardiovascular events in patients with asymptomatic hyperuricemia

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Received: 22 May 2023 / Revised: 12 July 2023 / Accepted: 16 July 2023 / Published online: 24 July 2023

Abstract

Introduction/objectives To investigate the role of urate-lowering therapy (ULT) in the prevention of cardiovascular disease (CVD) in patients with asymptomatic hyperuricemia using the Japanese healthcare record database.

Methods This retrospective cohort study used data from the JMDC Claims Database, which includes records of medical check-ups and Japanese health insurance claims. Subjects aged at least 18 years with a serum uric acid (sUA) level ≥ 7.0 mg/dL and at least one medical check-up from January 2007 to August 2021 were included in this study. The exposure was any ULT prescription, and the primary outcome included composite CVD outcomes, including coronary artery disease, stroke, and atrial fibrillation. Analysis was performed with a new-user design and overlap weighting to balance the baseline characteristics of the subjects. Cox proportional hazards models were used to investigate the association between ULT and the development of CVD.

Results In total, 152,166 patients were included in the main analysis before overlap weighting in this retrospective cohort study. The number of subjects in the ULT group was 5,270, and there were 146,896 subjects in the control group. Composite CVD outcomes were observed in a total of 7,703 patients. The risk of developing composite CVD outcomes was not different between the ULT group and the control group (HR: 1.01, 95% CI: 0.89 to 1.13).

Conclusions ULT for patients with asymptomatic hyperuricemia did not prevent the development of CVD based on the Japanese claims database.

Key points

- *Among subjects with asymptomatic hyperuricemia, ULT was not associated with a lower risk of CVD*
- *There was no appropriate cutoff for initiating ULT in patients with asymptomatic hyperuricemia*
- *There was no appropriate cutoff as the therapeutic goal of ULT in patients with asymptomatic hyperuricemia*

Keywords Allopurinol · Cardiovascular risk · Epidemiology · Febuxostat · Gout · Hyperuricemia · Xanthine oxidase inhibitor

Introduction

Cardiovascular diseases (CVDs) remain a main cause of death worldwide [1]. An association between hyperuricemia and CVD has been reported in some studies, and this association is observed even in younger generations [2–4].

Urate-lowering therapy (ULT) for patients with gout has been implemented in many countries, and some studies have reported efficacy in reducing the development of CVD in patients with gout [5, 6]. However, it remains unknown whether ULT can prevent CVD in patients with asymptomatic hyperuricemia. In the European League Against Rheumatism recommendations and the American College of Rheumatism guidelines, there are no recommendations regarding ULT for patients with asymptomatic hyperuricemia, and there is little evidence to support the use of ULT for asymptomatic hyperuricemia [7, 8]. In contrast, ULT for asymptomatic hyperuricemia is conditionally recommended

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in the Japanese Guideline on Management of Hyperuricemia and Gout (JGMHG), 3rd edition, for the prevention of lifestyle-related diseases [9]. In this study, a Japanese healthcare record database was used to assess the association between ULT and CVD prevention in patients with asymptomatic hyperuricemia. The objective of this study was to use a Japanese healthcare record database to investigate whether ULT in patients with asymptomatic hyperuricemia could reduce the development of CVD.

Methods

Study population

This retrospective cohort study used data from the JMDC Claims Database, which includes records of medical check-ups and Japanese health insurance claims. The JMDC collects data from various Japanese organizations that provide health insurance coverage to employees and their dependents. Health check-ups, which are not required for insured persons, are conducted annually by insurers so that health insurance societies can ascertain the health statuses of insured persons. The database can also track each person's medical information, including when the patient visited or was hospitalized at various types of medical institutions. The database provides information on drug prescriptions, diagnostic codes and medical check-up data, including sex, blood pressure, body mass index (BMI), smoking status and laboratory data, although the test items may vary depending on the health insurer.

The study period was divided into three phases: the lookback period, the index period and the follow-up period. The index date was defined as the first medical check-up detecting a serum uric acid (sUA) level ≥ 7.0 mg/dL. The lookback period was defined as 6 months prior to the index date. The index period was approximately 1 year from the index date to the date of the next check-up (follow-up date). The follow-up period was defined as the period after the follow-up date (Fig. 1).

Subjects aged at least 18 years with sUA ≥ 7.0 mg/dL and at least one medical check-up from January 2007 to August 2021 were included in this study. Subjects who met at least one of the following exclusion criteria before the follow-up date were excluded: subjects who could not be followed for the six-month lookback period or one-year follow-up period, subjects without serum creatinine values on the index date, subjects who were diagnosed with composite CVD outcomes defined in the "outcome" section, subjects diagnosed with gout (M10) or a malignancy (C00-97, D00-09) before the index date, subjects who were undergoing renal replacement therapy or who were prescribed ULT (M04 except for colchicine) before the index date (online supplementary Table S1) or subjects with missing covariate values in their medical check-ups.

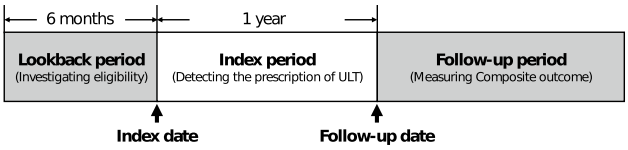

Fig. 1 Definitions of the lookback period, index period and follow-up period. ULT, urate-lowering therapy

Exposure

The exposure of interest was whether ULT was prescribed at least once; this was investigated using a new-user design during the index period for each individual subject.

Outcome

The primary outcome was the composite of CVD outcomes, which included coronary artery disease, stroke and atrial fibrillation [4]. Secondary outcomes were all-cause mortality; this was extracted from the ledger of insured persons in claims, coronary artery disease (I210-4, I219), stroke (I600-11, I613-6, I619, I629-36, I638-9), and atrial fibrillation (I480-4, I489).

Covariates

Information on age, sex, blood pressure, BMI, smoking status, estimated glomerular filtration rate, hemoglobin, LDL-cholesterol, HDL-cholesterol, triglyceride and HbA1c were collected from medical check-up data on the index date. Information on comorbidities (hypertension, arthritis, depression, diabetes, atrial fibrillation, dementia, fatigue, gait abnormality, posttraumatic stress disorder, sleep apnea, liver disease, schizophrenia, substance abuse) (Online supplementary Table S1) and prescriptions (angiotensin converting enzymes, statins, nonstatin lipid-lowering drugs, α-blockers, β-blockers, Ca-channel blockers, antidiabetic drugs, diuretics and polypharmacy defined as 5 or more drug classes) [10] were obtained during the lookback period (online supplementary Table S1).

Statistical analysis

First, the patient characteristics of each group were described. Continuous variables are reported as the mean and standard deviation, and categorical variables are reported as numbers and percentages. We created a propensity score using the covariates for adjusting confounders and applied overlap weighting

to minimize the impact of extreme propensity scores on the results [10–14]. Person-years of follow-up for each individual were calculated from the index date to outcome occurrence, the first disenrollment in the database or the end of the study period. We fit Cox proportional hazards models with a robust estimator to assess the association between ULT and outcomes. The results are presented as hazard ratios (HRs) and 95% confidence intervals (CIs). Intention-to-treat (ITT) analysis was performed as the main analysis. In the ITT analysis, even if crossover occurred, cases were not censored; rather, the patients were followed until the end of follow-up based on the group to which the patient originally belonged.

Four planned sensitivity analyses and one post hoc sensitivity analysis were performed in this retrospective cohort study. The first was an analysis changing the cutoff of sUA on the index date. This analysis was carried out to explore the appropriate cutoff of sUA on the index date as an index of treatment initiation. The second analysis was an analysis changing the cutoff of sUA on the follow-up date. We performed this analysis to investigate the best cutoff of sUA as an index of treatment goal because little rationale has been published regarding the cutoff value, and the research question was taken from the JGMHG, 3rd edition [9]. The third sensitivity analysis was an on-treatment analysis. During the follow-up period, crossover was treated as a censored case in the on-treatment analysis. Crossover from the ULT group was defined as the 60-day absence of ULT prescription, and crossover from the control group was defined as the starting prescription of ULT. Fourth, a sensitivity analysis was performed using the multiple imputation method for all explanatory variables that had missing data. Moreover, one post hoc analysis with the model including alcohol consumption status and exercise status was performed.

We also performed a subgroup analysis to investigate the interaction between ULT and other variables on the primary outcome. The subgroups were divided by type of ULT (febuxostat, allopurinol, benzbromarone and topiroxostat) as well as the presence of hypertension, diabetes (HbA1c $< 6.5\%, \geq 6.5\%$ or prescription of antidiabetic drugs) and chronic kidney disease (CKD) ($< 60, \geq 60$) among all subjects and whether the sUA level dropped to 6.0 mg/dL at the next medical check-up among the ULT group. P values with a two-sided test were reported, and $P < 0.05$ was considered to indicate statistical significance. R ver. 4.1.6 was used to perform all statistical analyses.

Results

Participant characteristics

We identified 573,411 subjects whose sUA level was over 7.0 mg/dL on annual medical check-ups from January 2007 to August 2021. A total of 421,245 subjects were excluded

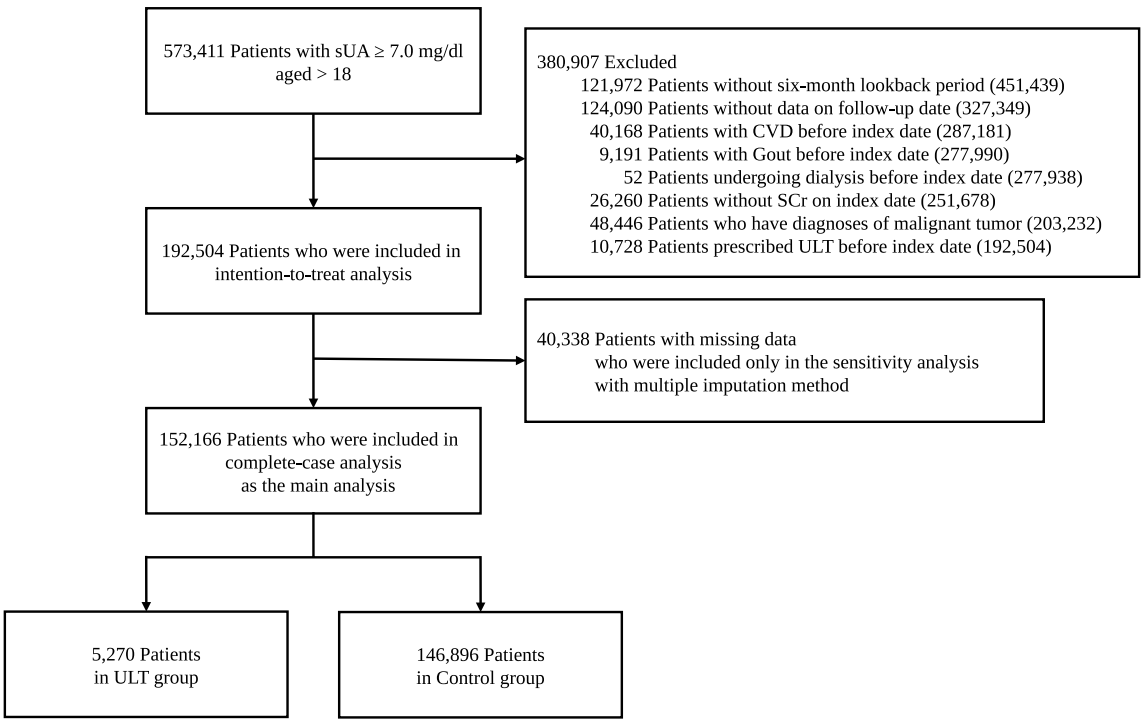

Fig. 2 Flow diagram of case selection**.** CVD, cardiovascular disease; sUA, serum uric acid; sCr, serum creatinine; ULT, urate-lowering therapy

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SGLT2 inhibitor	43 (0.8)	308 (0.2)	0.09	33 (0.7)	33 (0.7)	0.00
Other antidiabetes drug	8 (0.2)	19 (0.0)	0.05	4 (0.1)	4 (0.1)	0.00

BMI, body mass index; BP, blood pressure; COPD, chronic obstructive pulmonary disease; DPP4, dipeptidyl peptide-4; GLP1, glucagon-like peptide-1; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RAS, renin-angiotensin system; SD, standard deviation; SDif, standardized difference; SGLT2, sodium glucose transporter; TG, triglyceride

Table 2 Association between ULT and cardiovascular events after overlap weighting in intention-to-treat analysis with complete cases

	Weighted incidence rate per 1000 person-years		HR (95% CI)	*P* value
	ULT Group	Control Group		
CVD composite	24.2	24.1	1.01 (0.89 to 1.13)	0.93
Coronary artery disease	8.4	9.1	0.92 (0.76 to 1.12)	0.42
Stroke	15.0	14.6	1.03 (0.89 to 1.20)	0.67
Atrial fibrillation	2.7	2.9	0.95 (0.68 to 1.33)	0.75
All-cause mortality	0.6	0.6	0.96 (0.47 to 1.96)	0.92

CVD, cardiovascular disease; HR, hazard ratio; ULT, urate-lowering therapy

because they met one or more of the exclusion criteria mentioned in the "Study Population" section. In total, 152,166 patients were included in this retrospective cohort study (Fig. 2) for complete-case analysis as the main analysis, while 192,504 patients were included for multiple imputation sensitivity analysis. The number of subjects in the ULT group was 5,270, and there were 146,896 subjects in the control group. The baseline characteristics of each group before and after overlap weighting are described in Table 1. Standardized differences after overlap weighting were balanced for all measured covariates. The mean follow-up period was 38.7 (interquartile range: 12.1 to 58.0) months.

Table 3 Sensitivity analysis with various sUA cutoff points on index date and on follow-up date

	Weighted incidence rate per 1000 person-years		HR (95% CI)	*P* value
	ULT Group	Control Group		
Serum UA before ULT (on index date)				
< 8.0	25.0	25.5	0.98 (0.84 to 1.15)	0.80
8.0 ≤, < 9.0	22.5	24.1	0.94 (0.75 to 1.18)	0.58
9.0 ≤	24.7	20.3	1.22 (0.90 to 1.64)	0.20
Serum UA after ULT (on follow-up date)				
Cutoff 6.0				
≤ 6.0	28.1	25.2	1.11 (0.88 to 1.39)	0.38
> 6.0	23.6	24.2	0.98 (0.86 to 1.12)	0.77
Cutoff 7.0				
≤ 7.0	24.8	25.2	0.98 (0.83 to 1.14)	0.77
> 7.0	24.1	23.8	1.01 (0.86 to 1.19)	0.90
Cutoff 8.0				
≤ 8.0	23.8	24.8	0.96 (0.84 to 1.09)	0.53
> 8.0	26.1	22.4	1.17 (0.92 to 1.49)	0.20

HR, hazard ratio; UA, uric acid; ULT, urate-lowering therapy

Primary outcome

Composite CVD outcomes were observed in a total of 7,703 subjects. The risk of developing composite CVD outcomes was not different between the ULT group and the control group (HR: 1.01, 95% CI: 0.89 to 1.13) (Table 2). The risk of mortality for each CVD outcome, including coronary artery disease, stroke and atrial fibrillation, was not different between the two groups.

Sensitivity analysis

We performed sensitivity analyses that changed the cutoff of sUA on the index date as the index of treatment initiation and used the follow-up date as the therapeutic goal of ULT. No associations between ULT and the development of CVD were observed across all groups in either analysis using various cutoff points (Table 3). In the on-treatment analysis, there was no significant difference in the risk of developing CVD between the ULT group and the control group (HR: 0.98, 95% CI: 0.83 to 1.15) (online supplementary Table S2). Moreover, no association was observed between the two groups for developing CVD based on the multiple imputation sensitivity analysis (HR: 1.06, 95% CI: 0.77 to 1.35) (online supplementary Table S3). In the post hoc analysis with the model including alcohol consumption status and physical activity status, the results were consistent with the results of the main analysis (HR: 0.96, 95% CI: 0.84 to 1.09) (online supplementary Table S4-5).

Subgroup analysis

In the subgroup analysis, no associations were observed between ULT and developing the CVD composite across all groups except for the type of ULT. Subjects prescribed topiroxostats had a higher risk of developing CVD (Table 4).

Table 4 Subgroup analysis investigating the interaction between ULT and other variables on the primary outcome

	Weighted incidence rate per 1000 person-years		HR (95% CI)	*P* value
	ULT Group	Control Group		
Sex				
Male	24.2	24.0	1.01 (0.89 to 1.13)	0.92
Female	27.9	25.6	1.09 (0.44 to 2.70)	0.86
Age				
< 40	13.6	15.5	0.89 (0.63 to 1.26)	0.51
≥ 40, < 60	26.4	24.7	1.07 (0.94 to 1.22)	0.33
≥ 60	32.0	46.5	0.69 (0.45 to 1.06)	0.09
DM				
DM (+)	38.6	32.0	1.21 (0.83 to 1.75)	0.32
DM (-)	23.2	23.5	0.99 (0.87 to 1.12)	0.83
CKD				
CKD (+)	32.7	30.6	1.06 (0.82 to 1.38)	0.65
CKD (-)	22.6	22.7	1.00 (0.87 to 1.14)	0.96
HT				
HT (+)	29.3	29.2	0.99 (0.84 to 1.18)	0.94
HT (-)	23.2	23.5	0.99 (0.87 to 1.12)	0.83
Type of ULT				
Allopurinol	24.7	26.0	0.94 (0.78 to 1.14)	0.54
Febuxostat	24.0	23.9	1.01 (0.83 to 1.22)	0.95
Topiroxostat	45.3	23.2	1.89 (1.18 to 3.03)	0.01
Benzbromarone	28.5	24.9	1.12 (0.82 to 1.53)	0.49

CI, confidence interval; CKD, chronic kidney disease; DM, diabetes mellitus; HR, hazard ratio; HT, hypertension; ULT, urate-lowering therapy

Discussion

In the analysis of the overlap weighted cohort of 152,166 subjects with an sUA of 7.0 mg/dL or more, we did not find any association between ULT and the development of CVD. The results were consistent with those of the sensitivity analyses, such as analysis of various sUA cutoff points, on-treatment analysis, and multiple imputation analysis. In the subgroup analysis, subjects prescribed topiroxostat had a higher risk of developing CVD.

Our findings were inconsistent with the results of previous studies investigating the impact of ULT on subjects with gout [5, 6, 15]. Although a previous study reported that compared to uricosuric drugs, allopurinol reduced oxidative stress [16], in the present study, compared to uricosuric drugs, allopurinol did not reduce the incidence of CVD based on the subgroup analysis. Our results may indicate that the suppression of CVD development in gout patients may not be due to a reduction in oxidative stress but may be due to the reduction in urate deposits in vessels [17]. Therefore, the impact of ULT on reducing the development of CVD was small in patients with asymptomatic hyperuricemia, who may have fewer urate deposits in their vessels.

In the subgroup analysis, there was a significantly higher risk of CVD development in the topiroxostat group; however, because that was a subgroup analysis, this result should be considered exploratory.

There were three strengths in the present study. First, the sample size was large. It is generally difficult to collect data for over one hundred thousand subjects with regular sUA measurements. Moreover, we were able to utilize the data of subjects who were prescribed ULT with asymptomatic hyperuricemia because it is recommended in the Japanese guidelines, unlike in other countries. The large sample size allowed us to obtain highly accurate results with a narrow 95% CI. Second, we were able to use various types of covariates in the present study. The confounders for developing CVD, such as blood pressure, smoking status and comorbidities, were almost covered [18], and they were adjusted by the overlap weighting method to investigate the association between ULT and CVD development. Finally, we performed various types of sensitivity analyses to confirm the validity of our results. We assumed that the missing mechanism in the present study was missing completely at random [19, 20] and chose complete case analysis as the main analysis because the missing data from the annual medical check-up system, including test items that could not be chosen by insured

persons, were supposed to be independent of the background characteristics of the subjects. However, we also performed the analysis with a multiple imputation method in the case that the missing mechanism in the present study was missing at random [19–21], and the result was consistent with that of complete-case analysis. We also performed on-treatment analysis as a sensitivity analysis, and the results did not differ from those of the main analysis, which was assumed to be an intention-to-treat analysis [22, 23]. Another type of sensitivity analysis we conducted was an analysis with varying sUA cutoff points. These were very important analyses in the present study because there was not enough evidence to determine the cutoff point of sUA for initiating treatment of hyperuricemia or the cutoff point for targeting sUA treatment [9]. From this analysis, we showed that there were no appropriate sUA cutoff points for preventing CVD development in patients with asymptomatic hyperuricemia.

There were four limitations in this study. First, the population was limited. Almost all subjects were male. The sample size of females in the present study was 1.7% after overlap weighting, which was much smaller than that of males, and the confidence interval of the HR of females in the subgroup analysis was much wider than that of males. Moreover, almost all subjects in the JMDC claims database were Japanese, and the generalizability of these results to other races is unclear. Second, this was a retrospective cohort study. Although we were able to utilize various types of confounders in our analysis, there should be unmeasured confounding factors, such as ejection fraction or other unknown confounders, between the ULT group and the control group, which may influence the association between ULT and CVD development [24, 25]. Third, we could not adjust for changes in confounding factors during the follow-up period, such as changes in statin use. Such changes may have some impact on the development of CVD. Finally, although we applied a new user design by providing a lookback period [26, 27], there may be some subjects who were prescribed ULT prior to the lookback period who could not be screened. Previous ULT prescriptions in the control group may have reduced the difference in CVD risk between the two groups.

Conclusion

In conclusion, for patients with asymptomatic hyperuricemia, ULT did not prevent the development of CVD based on data from a Japanese claims database. The secondary outcomes, including coronary artery disease, stroke, atrial fibrillation and mortality, were also not associated with ULT.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10067-023-06710-9.

Acknowledgements We thank the editing service "American Journal Experts" for proofreading our manuscript.

Author contributions All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this article. They also reviewed the manuscript critically for important intellectual content and have given their approval for the final version to be published.

H.H. contributed to the conception and design of the work; the acquisition, analysis, and interpretation of data; and the drafting of the manuscript. M.T. contributed to the analysis and interpretation of the work. K.K. contributed to the conception of the work and the acquisition of data for the work. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding This work was supported by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (grant number: 20H03941). The funder and the data provider had no role in the present study, including collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data availability Data sharing is not permitted under the JMDC policy. If readers are interested in our dataset, please contact JMDC for data availability (https://www.jmdc.co.jp).

Declarations

Ethics approval This study was approved by the Institutional Review Board at Kyoto University. We performed this study in accordance with the ethical standards laid out in the 1964 Declaration of Helsinki and its later amendments. The data were obtained by contract from JMDC Inc. and permission was obtained to use them in the study and to publish the results in a scientific paper. Individual consent was not needed because the data were anonymized.

Competing interests Koji Kawakami has received research funds from Eisai Co., Ltd., Kyowa Kirin Co., Ltd., Sumitomo Pharma Co., Ltd., Mitsubishi Corporation, and Real World Data Co. Ltd.; consulting fees from LEBER Inc., JMDC Inc., Shin Nippon Biomedical Laboratories Ltd., and Advanced Medical Care Inc.; executive compensation from Cancer Intelligence Care Systems, Inc.; and honoraria from Mitsubishi Corporation, Pharma Business Academy, and Toppan Inc. Other authors have no conflicts of interest to declare.

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