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ARTICLE

Cardiovascular risk of urate-lowering drugs: A study using the National Database of Health Insurance Claims and Specific Health Checkups of Japan

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Abstract

In the present study, we aimed to investigate the association between urate-lowering drugs and cardiovascular events, primarily focusing on the risk of febuxostat and topiroxostat when compared with allopurinol in Japan. We conducted an observational study with a cohort design using the National Database of Health Insurance Claims and Specific Health Checkups of Japan, including new urate-lowering drugs users between August 1, 2010, and March 31, 2018. Exposure and control groups were defined based on the first prescription of urate-lowering drugs as follows: febuxostat or topiroxostat for exposure groups, allopurinol for the control group, and benzbromarone for the secondary control group. The primary outcome was cardiovascular events, defined as a composite of acute coronary syndrome, cerebral infarction, and cerebral hemorrhage. Hazard ratios were estimated using a Cox proportional hazards model. The number of patients in each exposure and control group was 1,357,671 in the febuxostat group, 83,683 in the topiroxostat group, 1,273,211 in the allopurinol group, and 258,786 in the benzbromarone group. The adjusted hazard ratios for the cardiovascular risk were 0.97 (95% confidence interval [CI]: 0.95–0.98) for febuxostat and 0.84 (95% CI: 0.78–0.90) for topiroxostat groups. The benzbromarone group exhibited similar results. No increased cardiovascular risk was observed with febuxostat or topiroxostat when compared with allopurinol in patients with hyperuricemia in Japan. These results provide real-world evidence regarding the cardiovascular risk associated with urate-lowering drugs, indicating that no additional safety-related regulatory actions are warranted in Japan.

Past presentation on this research: A part of this article was included in an official Pharmaceuticals and Medical Devices Agency (PMDA) report available on the PMDA website (https://www.pmda.go.jp/files/000239435.pdf).

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

The risk of cardiovascular death in patients with gout was higher in the febuxostat group than in the allopurinol group in the CARES trial; however, the extrapolation of these results to Japan remains unclear.

WHAT QUESTION DID THIS STUDY ADDRESS?

The specific aim of this study was to compare the risk of cardiovascular events associated with febuxostat and topiroxostat with that associated with allopurinol in Japan.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The present study revealed that there was no observed risk of cardiovascular events with febuxostat and topiroxostat when compared with allopurinol in Japan.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

These results indicate that no additional safety measures are required to mitigate potential cardiovascular events associated with febuxostat and topiroxostat use in Japan.

INTRODUCTION

Febuxostat reduces serum uric acid through an inhibitory action of xanthine oxidase[1] and was first approved in the European Union in April 2008,[2] followed by the United States in February 2009[3] and Japan in January 2011.[4] In 2017, the US Food and Drug Administration (FDA) concluded that febuxostat could increase the risk of cardiovascular death and all-cause mortality when compared with allopurinol, based on an analysis of post-market clinical trial data (CARES trial).[5,6] This conclusion led to an update of the US febuxostat prescribing information in February 2019, with the addition of a boxed warning regarding cardiovascular death.[6] Furthermore, the use of febuxostat was limited to patients who were not effectively treated or experienced severe side effects with allopurinol.[6] Likewise, the European Medicine Agency recommended avoiding the use of febuxostat in patients with a history of major cardiovascular disease based on the findings of the CARES trial.[7]

In July 2019, the febuxostat package insert was also revised in Japan to indicate the increased risk of cardiovascular deaths for providing an important precaution,[8] based on the results of the CARES trial and a postmarketing study in Japan,[9] as well as other related information, such as published literature[9–15] and Japanese clinical guidelines published by academic societies.[16–19] However, the extrapolability of the risk of cardiovascular events in the CARES trial to Japan remains unclear for the following three reasons: (1) lower cardiovascular risks have been reported in the Japanese population than in the European and American populations[20]; (2) fewer Asian subjects were enrolled in the CARES trial (~70% White vs. ~3% Asians)[5]; and (3) no increased cardiovascular death induced by febuxostat was detected in clinical trials conducted in Japan.[10,21] Therefore, to attain a deeper understanding of the cardiovascular risk of febuxostat in Japan, the Pharmaceuticals and Medical Devices Agency (PMDA) designed and conducted an observational study using real-world data in Japan to compare the risk of cardiovascular events associated with febuxostat, topiroxostat, and allopurinol.

METHODS

Study design and setting

We conducted an observational study with a cohort design using the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB).[22] We deemed that the NDB would be the most appropriate database considering the objective of the present study to examine the low frequency of cardiovascular events, including late-onset cases, based on the following reasons: (1) NDB is the largest database managed by the Ministry of Health, Labour, and Welfare (MHLW), collecting information on nation-based medical claims from hospitals, clinics, pharmacies, and dental clinics in Japan; and (2) the long follow-up period from hospitals where patients underwent treatment can be ensured.[23,24]

Target population

As shown in Figure 1, among patients who were prescribed febuxostat, topiroxostat, allopurinol, benzbromarone, or probenecid between August 1, 2010, and March 31, 2018, we included those whose initial medical claims were recorded more than 8 months prior to the month of the first

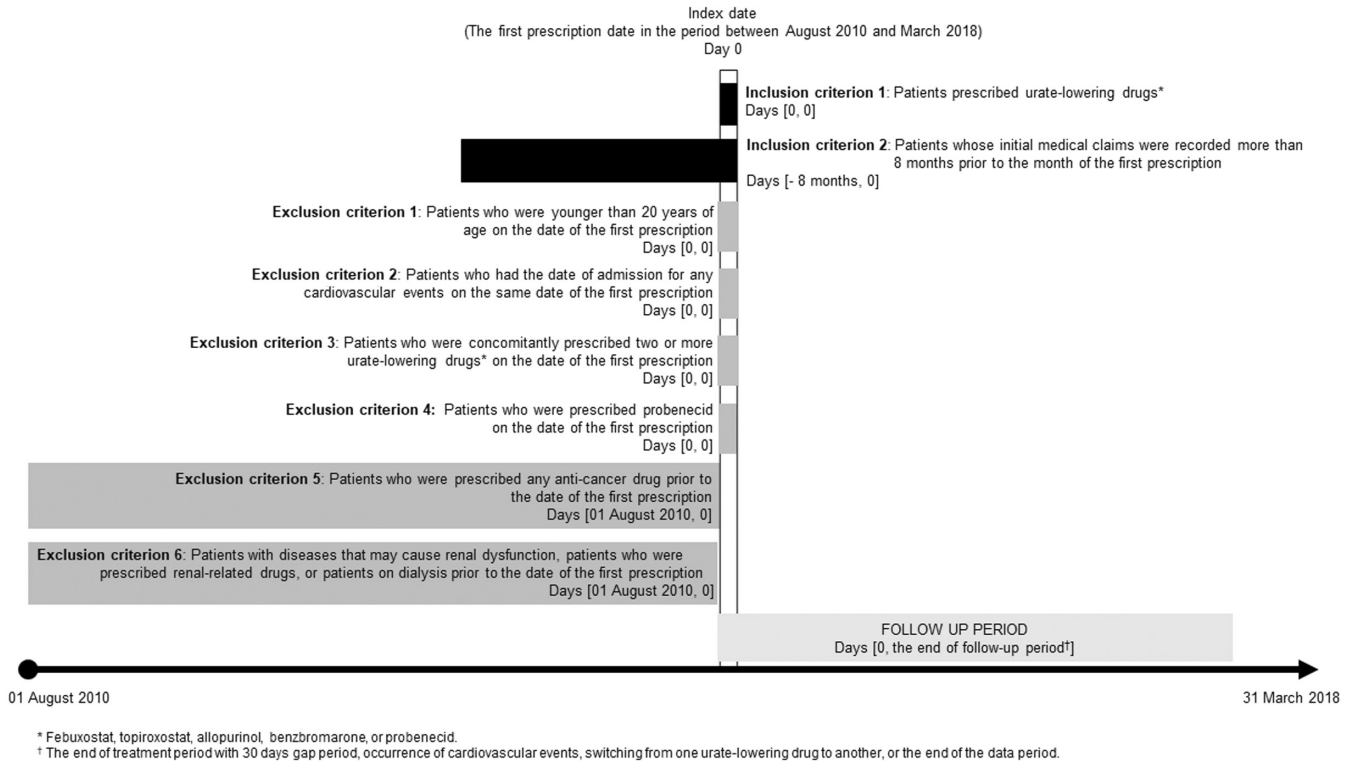

FIGURE 1 Study design

prescription to allow a look-back period for assessing past prescriptions or a history of urate-lowering drug usage. We also included topiroxostat in this study because its pharmacological action is similar to that of febuxostat (i.e., xanthine oxidase inhibitor) and its use in Japan in clinical settings. Furthermore, to select a more appropriate target population and minimize bias, patients who met the following criteria were excluded: (1) patients who were younger than 20 years of age on the date of the first prescription; (2) patients who had the date of admission for any cardiovascular events on the same date of the first prescription; (3) patients who were concomitantly prescribed two or more urate-lowering drugs on the date of the first prescription; (4) patients who were prescribed probenecid on the date of the first prescription; (5) patients who were prescribed any anticancer drug prior to the date of the first prescription; and (6) patients with diseases that may cause renal dysfunction, patients who were prescribed renal-related drugs, or patients on dialysis prior to the date of the first prescription (see Table S1 for more detailed reasons and Table S2 for the medicine codes of urate-lowering drugs).

Exposure and control groups

Patients were categorized into exposure or control groups based on the type of urate-lowering drug first prescribed: febuxostat or topiroxostat for exposure groups, allopurinol for the control group, and benzbromarone for the secondary control group. Allopurinol was selected as the primary control because it was also used as the control in the CARES trial. In addition to allopurinol, benzbromarone was established as the secondary control, given that allopurinol might reduce the risk of cardiovascular events and overall mortality.[25,26] However, such effects have not been widely reported with benzbromarone administration, and no cardiovascular-related warnings are included on the package insert of benzbromarone in Japan, indicating that benzbromarone could be considered as a negative control.

The follow-up period continued with the same urate-lowering drug prescribed from the date of the first prescription. If the gap between the end date of the previous prescription and the start date of the next prescription was within 30 days, we considered it a continuous prescription period for the patient. The follow-up period was also censored on observing the following events: occurrence of cardiovascular events (acute coronary syndrome, cerebral infarction, or cerebral hemorrhage; see below for more details), switching from one urate-lowering drug to another (febuxostat, topiroxostat, allopurinol, benzbromarone, and probenecid), or the end of the data period (March 31, 2018).

Outcome definitions

The primary outcome of this study was the occurrence of cardiovascular events, including acute coronary syndrome, cerebral infarction, and cerebral hemorrhage, during the follow-up period. Each event was defined by using algorithms (A, B, or C) using the medicine, diagnosis, and procedure codes (see Tables S2, S3, and S4, respectively). Algorithm A for acute coronary syndrome was defined based on observations from at least one of the following therapeutic interventions, that is, percutaneous coronary intervention, coronary artery bypass graft, intra-aortic balloon pumping, percutaneous cardiopulmonary support, or thrombolysis within 30 days from and on the date of admission for acute coronary syndrome. Algorithm B for cerebral infarction was defined based on observations from at least one of the following examinations, that is, computed tomography, magnetic resonance imaging, or magnetic resonance angiography, as well as at least one of the following therapeutic interventions, namely, cerebro-protective agents, injectable anti-platelet agents, injectable anti-coagulant agents, thrombolytic agents, anti-edema agents, craniotomy, or mechanical thrombectomy within 30 days after and on the date of admission for cerebral infarction. Algorithm C for cerebral hemorrhage was defined based on observations from at least one of the following examinations, that is, computed tomography, magnetic resonance imaging, or magnetic resonance angiography, as well as at least one of the following therapeutic interventions, namely, anti-edema drugs, injectable antihypertensive drugs, or hematoma evacuation within 30 days of the date of admission for cerebral hemorrhage. These definitions were based on results of the outcome validation study for cardiovascular events by utilizing data from MID-NET, another medical information database in Japan (data not shown),[27,28] with few minor modifications applied to the original definitions to ensure that data categories fitted to the NDB but not MID-NET.

Furthermore, as a higher risk of cardiovascular death in the febuxostat group was observed in the CARES trial, cardiovascular death was set as the secondary outcomes in addition to an individual component of the primary outcome (acute coronary syndrome, cerebral infarction, and cerebral hemorrhage). "Cardiovascular death" was defined as a patient who met one of the algorithms (A, B, or C) described above and had the disease records for "death." However, the investigation of cardiovascular death was for the exploratory purpose, as identifiability of "death" was expected to be low and has been less established in the analysis of NDB data.

Ethical considerations

As this study was conducted as an official activity of the PMDA under the Pharmaceuticals and Medical Devices Agency Law Article 15–5–(c) and (f),[29] it was not subject to review by institutional review boards.[30]

Statistical analysis

Main analysis and secondary analysis

For the main analysis comparing the febuxostat group with the allopurinol group, or the topiroxostat group with the allopurinol group, the incidence rates (IRs) of outcomes (primary and secondary outcomes) in each group were calculated, followed by calculating the incidence rate ratio of the exposure groups to the control group (allopurinol). Crude and adjusted hazard ratios (aHRs) were also estimated using the Cox proportional hazards model with the following adjusted factors: age group, sex, the presence of diseases (acute coronary syndrome, stroke, heart failure, peripheral vascular disease, liver disease, dyslipidemia, diabetes mellitus, hypertension, arrhythmia, and gout <diagnosis with drug treatment for gout>), and drug prescription (anti-platelet agents, anti-coagulants, and colchicine; see Table S5 for more details of the covariates). For the secondary analysis comparing the febuxostat group with the benzbromarone group, or the topiroxostat group with the benzbromarone group, the analysis was the same as the main analysis for the primary outcome.

Sensitivity analysis

In the sensitivity analysis, we conducted two analyses of primary outcomes. The first focused on patients who were followed, regardless of the end of the prescription period or switching from one urate-lowering drug to another, until the occurrence of cardiovascular events or censored at the end of the data period, whichever occurred first (sensitivity analysis 1). In the second analysis, we changed the exclusion criterion 6 in the main analysis to the criterion (patients with diseases that may cause *severe* renal dysfunction) for allowing to include patients with mild renal dysfunction for analysis (sensitivity analysis 2).

Subgroup analysis

We also conducted a subgroup analysis, in which the target population was limited to patients with a history of

cardiovascular diseases, to consider the influence of the history of cardiovascular diseases on the primary outcome.

All analyses were conducted using the SAS statistical software (version 9.4; SAS Institute).

RESULTS

Study flow and patient characteristics

Figure 2 presents a flow diagram to establish the target population. The number of patients prescribed urate-lowering drugs between August 1, 2010, and March 31, 2018, was 8,190,879. After applying inclusion and exclusion criteria as described in "Section 2," the number of eligible patients decreased to 2,973,351, which was largely affected by the inclusion criteria 2, "patients whose initial medical claims were recorded more than 8 months prior to the month of the first prescription" and by the exclusion criteria 6, "patients with diseases that may cause renal dysfunction, patients who were prescribed renal-related drugs, or patients on dialysis prior to the date of the first prescription." The number of eligible patients in the exposure and control groups was 1,357,671 in the febuxostat group, 83,683 in the topiroxostat group, 1,273,211 in the allopurinol group, and 258,786 in the benzbromarone group. The median and quartile ranges (QRs) of a follow-up period for each group were 245 days (QR: 85–714) for the febuxostat group, 167 days (QR: 64–404) for the topiroxostat group, 213 days (QR: 70–790) for the allopurinol group, and 145 days (QR: 61–545) for the benzbromarone group. No major differences in patient characteristics were observed between the exposure and control groups, except for the higher prevalence of heart failure in the febuxostat group and the shorter follow-up periods in the topiroxostat and benzbromarone groups (Table 1).

Risk assessment

The results of the cardiovascular risk analysis are shown in Table 2. The IRs were similar among the three groups, and the aHRs were 0.97 (95% confidence interval [CI]: 0.95–0.98) in the febuxostat group and 0.84 (95% CI: 0.78–0.90) in the topiroxostat group.

Considering the secondary outcome, the results of individual components of the primary outcome were consistent

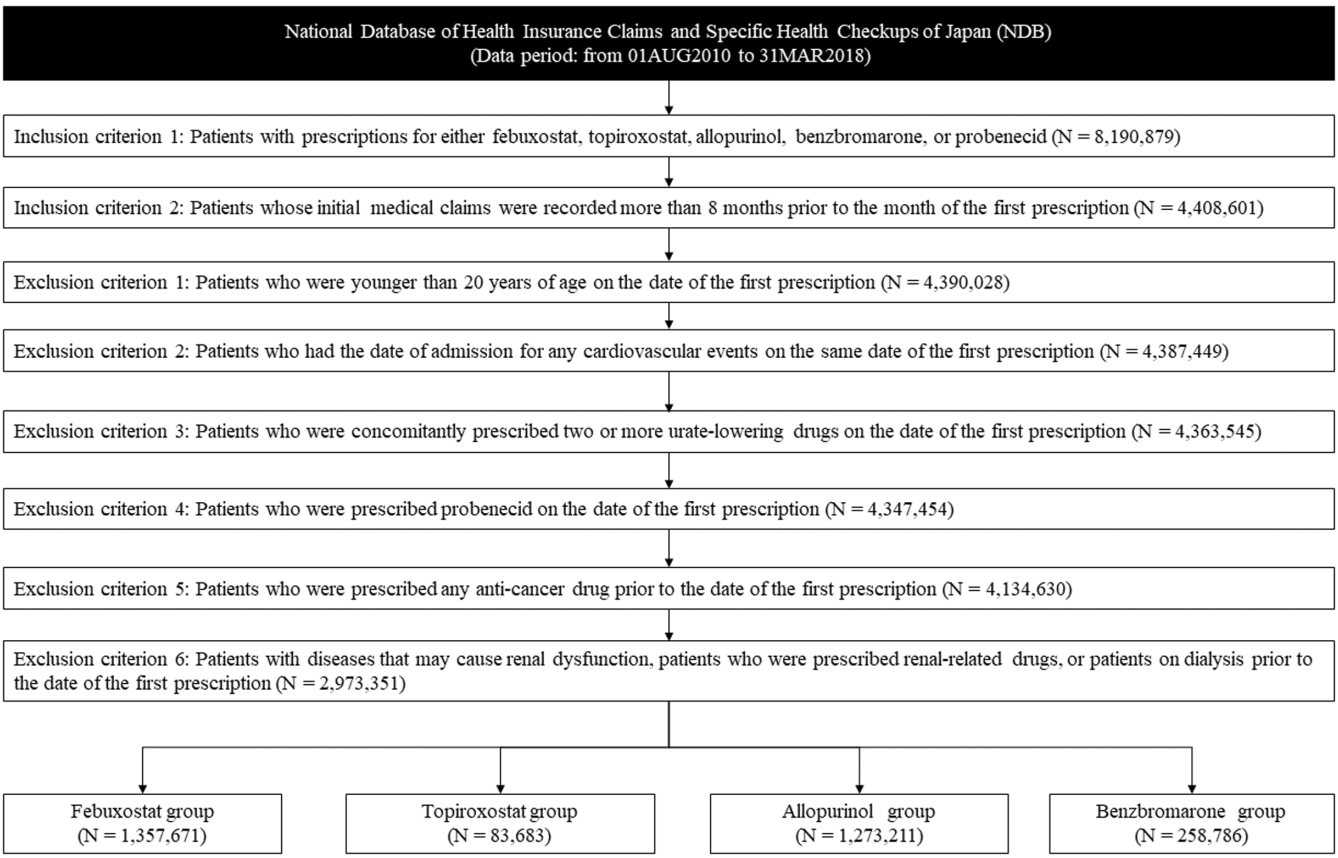

FIGURE 2 Study flow chart for the cohort identification

TABLE 1 Patient characteristics

	Febuxostat (*N* = 1,357,671)		Standardized difference with allopurinol	Topiroxostat (*N* = 83,683)		Standardized difference with allopurinol	Allopurinol (*N* = 1,273,211)		Benzbromarone (*N* = 258,786)	
Age group, *n* (%)										
20–24	11,330	0.80%	0.000	816	1.00%	0.021	9788	0.80%	2546	1.00%
25–29	22,997	1.70%	0.016	1782	2.10%	0.045	19,189	1.50%	5339	2.10%
30–34	38,593	2.80%	0.012	2926	3.50%	0.052	32,798	2.60%	8817	3.40%
35–39	64,287	4.70%	0.005	4507	5.40%	0.037	59,019	4.60%	15,426	6.00%
40–44	96,209	7.10%	0.020	6610	7.90%	0.050	84,354	6.60%	20,755	8.00%
45–49	108,195	8.00%	0.023	7583	9.10%	0.062	93,930	7.40%	22,599	8.70%
50–54	110,968	8.20%	0.011	7228	8.60%	0.025	100,771	7.90%	23,133	8.90%
55–59	112,781	8.30%	0.011	6936	8.30%	0.011	108,861	8.60%	24,370	9.40%
60–64	126,679	9.30%	0.040	7247	8.70%	0.061	133,936	10.50%	28,888	11.20%
65–69	151,568	11.20%	0.006	9011	10.80%	0.019	144,823	11.40%	28,467	11.00%
70–74	133,929	9.90%	0.020	7803	9.30%	0.040	133,709	10.50%	24,480	9.50%
75–79	126,674	9.30%	0.014	7421	8.90%	0.028	123,554	9.70%	21,041	8.10%
80–84	111,998	8.20%	0.004	6425	7.70%	0.015	103,286	8.10%	16,115	6.20%
85–89	83,720	6.20%	0.017	4531	5.40%	0.017	73,864	5.80%	10,163	3.90%
90–94	43,162	3.20%	0.012	2193	2.60%	0.024	37,626	3.00%	5006	1.90%
95–99	12,708	0.90%	0.000	584	0.70%	0.022	11,724	0.90%	1435	0.60%
100–	1873	0.10%	0.026	80	0.10%	0.026	1979	0.20%	206	0.10%
Sex, *n* (%)										
Male	1,093,792	80.60%	0.020	68,016	81.30%	0.003	1,036,863	81.40%	224,558	86.80%
Female	263,879	19.40%	0.020	15,667	18.70%	0.003	236,348	18.60%	34,228	13.20%
Presence of disease at baseline, *n* (%)										
Acute coronary syndrome[a]	89,762	6.60%	0.092	4072	4.90%	0.019	57,919	4.50%	8001	3.10%
Stroke[a]	230,674	17.00%	0.049	13,616	16.30%	0.030	193,017	15.20%	30,520	11.80%
Heart failure[a]	314,052	23.10%	0.124	15,579	18.60%	0.013	229,860	18.10%	32,226	12.50%
Peripheral vascular disease[a]	142,382	10.50%	0.075	9192	11.00%	0.092	106,256	8.30%	17,678	6.80%
Liver disease	262,308	19.30%	0.025	16,474	19.70%	0.015	258,129	20.30%	42,810	16.50%
Dyslipidemia	301,938	22.20%	0.039	19,179	22.90%	0.056	262,489	20.60%	43,921	17.00%

(Continues)

TABLE 1 (Continued)

	Febuxostat (*N* = 1,357,671)		Standardized difference with allopurinol	Topiroxostat (*N* = 83,683)		Standardized difference with allopurinol	Allopurinol (*N* = 1,273,211)		Benzbromarone (*N* = 258,786)	
Diabetes	127,994	9.40%	0.024	7490	9.00%	0.011	110,695	8.70%	16,564	6.40%
Hypertension	672,252	49.50%	0.036	38,936	46.50%	0.024	607,512	47.70%	102,900	39.80%
Arrhythmia	92,640	6.80%	0.086	3910	4.70%	0.005	61,109	4.80%	8587	3.30%
Gout										
Disease code + NSAIDs	16,942	1.20%	0.040	1272	1.50%	0.066	10,617	0.80%	4320	1.70%
Disease code + Steroid	14,697	1.10%	0.042	1028	1.20%	0.052	9110	0.70%	3496	1.40%
Drug prescription at baseline, *n* (%)										
Anti-platelet agents	195,871	14.40%	0.011	9653	11.50%	0.075	178,001	14.00%	26,933	10.40%
Anti-coagulants	160,032	11.80%	0.092	5315	6.40%	0.098	114,821	9.00%	14,672	5.70%
Colchicine	32,089	2.40%	0.027	2504	3.00%	0.064	25,902	2.00%	8345	3.20%
Follow-up period, days										
Mean (SD)	479.4	(±524.9)	0.098	293.2	(±310.4)	0.479	537.3	(±650.0)	434.5	(±591.8)
Median (Q1–Q3)	245	(85–714)		167	(64–404)		213	(70–790)	145	(61–545)

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation.

[a]Baseline indicates the period before the first prescription. As for other diseases or drug prescriptions without this mark, baseline indicates the 90 days prior to the first prescription.

TABLE 2 Risk of cardiovascular events in the febuxostat group vs. the allopurinol group or the topiroxostat group vs. the allopurinol group

	N	Total follow-up period in person-years	Number of events	IR	IRR	cHR (95% CI)	aHR[a] (95% CI)
Febuxostat	1,357,671	1781,989.8	23,043	0.013	1.05	1.04 (1.02–1.06)	0.97 (0.95–0.98)
Topiroxostat	83,683	67,178.6	708	0.011	0.86	0.80 (0.74–0.86)	0.84 (0.78–0.90)
Allopurinol	1,273,211	1873,101.0	23,062	0.012	Reference	Reference	Reference

Abbreviations: aHR, adjusted hazard ratio; cHR, crude hazard ratio; CI, confidence interval; IR, incidence rate; IRR, incidence rate ratio.

[a]Adjusted for age group, sex, presence of diseases (acute coronary syndrome, stroke, heart failure, peripheral vascular disease, liver disease, dyslipidemia, diabetes mellitus, hypertension, arrhythmia, and gout), and drug prescription (anti-platelet agents, anti-coagulants, and colchicine).

TABLE 3 Sensitivity analysis 1: Risk of cardiovascular events in the febuxostat group vs. the allopurinol group or the topiroxostat group vs. the allopurinol group on changing the censuring events

	N	Total follow-up period in person-years	Number of events	IR	IRR	cHR (95% CI)	aHR[a] (95% CI)
Febuxostat	1,357,671	3,768,059.6	40,156	0.011	1.06	1.02 (1.01–1.03)	0.97 (0.96–0.98)
Topiroxostat	83,683	139,498.3	1274	0.009	0.91	0.83 (0.78–0.87)	0.87 (0.83–0.92)
Allopurinol	1,273,211	5,646,585.6	56,757	0.010	Reference	Reference	Reference

Abbreviations: aHR, adjusted hazard ratio; cHR, crude hazard ratio; CI, confidence interval; IR, incidence rate; IRR, incidence rate ratio.

[a]Adjusted for age group, sex, presence of diseases (acute coronary syndrome, stroke, heart failure, peripheral vascular disease, liver disease, dyslipidemia, diabetes mellitus, hypertension, arrhythmia, and gout), and drug prescription (anti-platelet agents, anti-coagulants, and colchicine).

TABLE 4 Sensitivity analysis 2: Risk of cardiovascular events in the febuxostat vs. the allopurinol group or the topiroxostat group vs. the allopurinol group in the cohort, excluding patients with diseases that may cause severe renal dysfunction

	N	Total follow-up period in person-years	Number of events	IR	IRR	cHR (95% CI)	aHR[a] (95% CI)
Febuxostat	1,736,801	2,326,712.3	32,411	0.014	1.08	1.06 (1.05–1.08)	0.97 (0.95–0.98)
Topiroxostat	108,865	90,863.8	1099	0.012	0.94	0.87 (0.82–0.93)	0.88 (0.82–0.93)
Allopurinol	1,488,664	2,206,022.4	28,433	0.013	Reference	Reference	Reference

Abbreviations: aHR, adjusted hazard ratio; cHR, crude hazard ratio; CI, confidence interval; IR, incidence rate; IRR, incidence rate ratio.

[a]Adjusted for age group, sex, presence of diseases (acute coronary syndrome, stroke, heart failure, peripheral vascular disease, liver disease, dyslipidemia, diabetes mellitus, hypertension, arrhythmia, and gout), drug prescription (anti-platelet agents, anti-coagulants, and colchicine), and presence of disease codes related to "mild to moderate renal dysfunction."

with the results of the primary outcome. Furthermore, the aHRs for cardiovascular death were 0.90 (95% CI: 0.84–0.96) in the febuxostat group and 0.61 (95% CI: 0.44–0.84) in the topiroxostat group (Table S6). Considering results for the secondary analysis (compared with the benzbromarone group), the aHR for the primary outcome was 0.96 (95% CI: 0.93–1.00) in the febuxostat group and 0.84 (95% CI: 0.77–0.91) in the topiroxostat group (Table S7). Furthermore, the results of sensitivity analyses 1 and 2 revealed similar tendencies to those of the main analysis (Tables 3 and 4). The subgroup analysis results limited to patients with a history of cardiovascular diseases were also consistent with the main analysis results (aHR in the febuxostat group: 0.91, 95% CI: 0.87–0.96, aHR in the topiroxostat group: 0.61, 95% CI: 0.50–0.75; Table S8).

DISCUSSION

In the present study, the aHR for cardiovascular events, composed of acute coronary syndrome, cerebral infarction, and cerebral hemorrhage, in the febuxostat group compared to the allopurinol group was ~1 (aHR: 0.97, 95% CI: 0.95–0.98), indicating that the cardiovascular risk of febuxostat is similar to that of allopurinol. This finding was supported by sensitivity and subgroup analyses (see Tables 3 and 4; Table S8). In addition, we detected no increase in the cardiovascular risk associated with febuxostat when compared with that of benzbromarone. To further examine the risk of febuxostat, we compared cardiovascular death between febuxostat and allopurinol and detected no increased risk of cardiovascular death

associated with febuxostat (aHR: 0.90, 95% CI: 0.84–0.96). These results are consistent with the findings of the Febuxostat versus Allopurinol Streamlined Trial (FAST) and CARES trial in terms of cardiovascular events but not cardiovascular death,[5,31] and might be, in part, influenced by the different conditions of the target study populations (CARES trial: patients with gout and history of cardiovascular disease and FAST trial: patients with gout and at least one additional cardiovascular risk factor; vs. the present study: patients with hyperuricemia) and study design (CARES trial and FAST trial: randomized clinical trial; vs. the present study: observational study with secondary use of real-world data). The study results may also be affected by pharmacogenetic factors because differences on the risks of gout and urate-lowering drug responses among ethnic populations including Japanese have been reported.[32] Moreover, the results of death based on NDB used in the present study should be carefully interpreted, as such events in the secondary utilization of claim-based databases in Japan may be less comprehensive and accurate than those in clinical trials (e.g., not-covered for costs of postmortem procedures), including some errors as reported.[33]

Considering topiroxostat, the aHR of cardiovascular events was 0.84 (95% CI: 0.78–0.90), suggesting that the risk of topiroxostat is lower than that of allopurinol. This observation was supported by secondary, sensitive, and subgroup analyses (even in evaluating cardiovascular death). In addition, the aHR for topiroxostat was lower than that for febuxostat; however, further investigation is warranted to conclude the clinical impact of these results, as the number of outcomes and total follow-up period in person-years for topiroxostat were smaller than those observed with febuxostat. The shorter follow-up period of topiroxostat could be due to the later approval and launch of topiroxostat than allopurinol and febuxostat in Japan and may be not enough to capture events occurred in longer term.

Given that the NDB used in the present study is a nation-based database in Japan, the results would reflect the general situation in Japan. However, it is difficult to exclude the possibility that other unexpected factors, which were not adjusted in the present study, could have impacted the study results.

The PMDA conducted a safety assessment of the risk of febuxostat and topiroxostat based on the present study results and other available data, including spontaneous adverse drug reaction reports, literature, and the results of the FAST trial, and concluded that no additional regulatory actions are currently warranted. The study results were valuable for the PMDA to consider appropriate regulatory actions, taking into account the safety profiles of these drugs in the real-world clinical scenario in Japan.

In conclusion, no increased cardiovascular risk associated with febuxostat or topiroxostat when compared with allopurinol was confirmed in Japan. The potential differences of the cardiovascular risk among populations should be recognized in clinical practice for the proper use of urate-lowering drugs.

AUTHOR CONTRIBUTIONS

S.S., H.S., C.I., R.K., Y.N., T.I., Y.O., and Y.U. wrote the manuscript. S.S., H.S., C.I., R.K., T.I., Y.O., and Y.U. designed the research. S.S. and H.S. performed the research. S.S. and K.K. analyzed the data.

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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