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ORIGINAL RESEARCH ARTICLE

Assessment of Cardiovascular Risk in Older Patients With Gout Initiating Febuxostat Versus Allopurinol

Population-Based Cohort Study

Editorial, see p 1127

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BACKGROUND: Hyperuricemia and gout are associated with an increased risk of cardiovascular disease. Xanthine oxidase inhibitors, allopurinol and febuxostat, are the mainstay of urate-lowering treatment for gout and may have different effects on cardiovascular risk in patients with gout.

METHODS: Using US Medicare claims data (2008–2013), we conducted a cohort study for comparative cardiovascular safety of initiating febuxostat versus allopurinol among patients with gout ≥65 years of age. The primary outcome was a composite end point of hospitalization for myocardial infarction or stroke. Secondary outcomes were individual end points of hospitalization for myocardial infarction, stroke, coronary revascularization, new and recurrent heart failure, and all-cause mortality. We used propensity score matching with a ratio of 1:3 to control for confounding. We estimated incidence rates and hazard ratios for primary and secondary outcomes in the propensity score–matched cohorts of febuxostat and allopurinol initiators.

RESULTS: We included 24 936 febuxostat initiators propensity score–matched to 74 808 allopurinol initiators. The median age was 76 years, 52% were male, and 12% had cardiovascular disease at baseline. The incidence rate per 100 person-years for the primary outcome was 3.43 in febuxostat and 3.36 in allopurinol initiators. The hazard ratio for the primary outcome was 1.01 (95% CI, 0.94–1.08) in the febuxostat group compared with the allopurinol group. Risk of secondary outcomes including all-cause mortality was similar in both groups, except for a modestly decreased risk of heart failure exacerbation (hazard ratio, 0.94; 95% CI, 0.91–0.99) in febuxostat initiators. The hazard ratio for all-cause mortality associated with long-term use of febuxostat (>3 years) was 1.25 (95% CI, 0.56–2.80) versus allopurinol. Subgroup and sensitivity analyses consistently showed similar cardiovascular risk in both groups.

CONCLUSIONS: Among a cohort of 99 744 older Medicare patients with gout, overall there was no difference in the risk of myocardial infarction, stroke, new-onset heart failure, coronary revascularization, or all-cause mortality between patients initiating febuxostat compared with allopurinol. However, there seemed to be a trend toward an increased, albeit not statistically significant, risk for all-cause mortality in patients who used febuxostat for >3 years versus allopurinol for >3 years. The risk of heart failure exacerbation was slightly lower in febuxostat initiators.

Key Words: adverse events ■ complication ■ cardiovascular outcomes ■ gout ■ treatment

Sources of Funding, see page 1125

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Clinical Perspective

What Is New?

- In the CARES trial, febuxostat was noninferior to allopurinol with respect to rates of adverse cardiovascular events, but febuxostat users had a greater risk of cardiovascular mortality and all-cause mortality.
- In this cohort study of 99 744 older patients with gout enrolled in Medicare, overall we found no difference in cardiovascular risk, including myocardial infarction, stroke, coronary revascularization, new heart failure, or all-cause mortality between febuxostat and allopurinol initiators.

What Are the Clinical Implications?

- Among older patients with gout with and without cardiovascular comorbidities, the risk of cardiovascular events and all-cause mortality was similar between febuxostat and allopurinol initiators.
- However, there is a suggestion for an increased risk of all-cause mortality associated with long-term use of febuxostat versus allopurinol.

Gout, a disorder characterized by monosodium urate crystal deposition in the joints, is 1 of the most common inflammatory arthropathies, affecting ≈8.3 million individuals in the United States.[1,2] Although the association between gout and cardiovascular disease (CVD) has been well documented, the evidence for a causal relationship between xanthine oxidase inhibitors (XOI) and CVD remains equivocal.[3–6] Although some studies have demonstrated a protective effect of allopurinol against myocardial infarction (MI), cardiovascular outcomes, and all-cause mortality, other studies have shown no benefit on heart failure (HF).[7–11] A recent cohort study comparing patients with gout on XOI with nonusers who have hyperuricemia showed that XOI initiation had no effect on cardiovascular risk.[12] The current literature for XOI-mediated CVD risk reduction remains inconsistent.[13–16]

Indeed, the concern for an XOI-related increased CVD risk has even been raised. In the original 2 phase III randomized controlled trials of febuxostat, APEX and FACT, febuxostat (at 80 and 120 mg/d) was more effective at lowering serum uric acid levels compared with allopurinol (at 300 mg/d) over 1 year.[17,18] Despite the more potent urate-lowering effect of febuxostat, the incidence of major adverse cardiovascular events, including nonfatal MI, nonfatal stroke, and cardiovascular death in both trials, was numerically, although not statistically significantly, higher with febuxostat than allopurinol, and rates of cardiovascular events did not correlate with febuxostat dose.[17–19] These initial findings prompted the US Food and Drug Administration to mandate additional safety evaluations. Subsequently, the phase IIIB randomized controlled CARES trial was conducted to further investigate the cardiovascular safety of febuxostat compared with allopurinol in patients with gout with known cardiovascular comorbidities.[20] The CARES trial ultimately showed no difference in the combined risk of cardiovascular death, nonfatal MI, nonfatal stroke, and unstable angina with urgent coronary revascularization for febuxostat compared with allopurinol. However, the individual risks of cardiovascular mortality and all-cause mortality were 1.2 to 1.3 times higher in febuxostat initiators. A similar randomized controlled trial titled FAST is also underway in Europe.[21] Given the relatively limited evidence and overall high prevalence of CVD in patients with gout, we sought to examine the risk of cardiovascular events in patients with gout with and without baseline CVD who started febuxostat or allopurinol (both at typical and equipotent dosing) using longitudinal comprehensive medical and pharmacy dispensing claims data from US Medicare.

METHODS

The data and study materials cannot be made available to other researchers because of the data use agreement with the Centers for Medicare and Medicaid Services.

Data Source

We conducted a cohort study among patients with gout initiating febuxostat versus allopurinol using longitudinal claims data from Medicare Parts A/B/D from January 1, 2008, to December 31, 2013. Medicare, a federal health insurance program in the United States, provides coverage for legal residents ≥65 years of age, patients <65 years of age with certain disabilities, and those with end-stage renal disease requiring dialysis or transplant. Medicare Part A covers inpatient care. Part B coverage encompasses physician services, including outpatient visits, laboratory testing, and imaging. Finally, Part D provides outpatient prescription drug coverage.[22] As a result, the study database includes patient information on demographics, diagnosis, and procedure codes from outpatient visits; emergency room visits and acute care hospitalizations; and dispensing records of prescription drugs. The study protocol and waiver for patient-informed consent were approved by the Institutional Review Board of the Brigham and Women's Hospital.

Study Cohort

Patients ≥65 years of age with a diagnosis of gout based on the *International Classification of Diseases, 9th Revision, Clinical Modification* codes 274.00, 274.01, 274.02, 274.03, 274.81, 274.82, 274.89, or 274.9 were eligible for the study. Patients with uric acid nephrolithiasis were not included. We identified initiators of febuxostat or allopurinol using the national drug codes in Part D claims. The index date was the drug initiation date. Drug initiation was defined as having ≥365 days free of a given drug. In other words, allopurinol initiators were allowed to use febuxostat in the 365 days before the first prescription of allopurinol and vice versa. This restriction was to

reflect typical prescription practices for febuxostat initiation. Naivety to both drugs before the index date was examined in subsequent sensitivity analyses (see Statistical Analysis).

Exclusion criteria included <65 years of age on the index date, <365 days of insurance eligibility in Parts A/B/D before the index date, no active claim in the 365 days before the index date, use of pegloticase or rasburicase in the 365 days before the index date, and end-stage renal disease/dialysis in the 365 days before the index date.

Outcome Definition

The primary outcome was defined as a composite end point of hospitalization for MI or stroke (excluding transient ischemic attacks). Secondary outcomes included hospitalization for MI, stroke, coronary revascularization, HF subdivided into new-onset HF or HF exacerbation, and all-cause mortality. Cause-specific mortality was not available in the Medicare database. New-onset HF was defined as hospitalization for HF among patients with no baseline history of HF based on the primary inpatient diagnosis. HF exacerbation was defined as hospitalization for HF in patients with a baseline history of HF based on the primary inpatient diagnosis. These outcomes were identified with previously validated claims-based algorithms with the positive predictive value >80%.[23–25]

Covariates Assessment

To adjust for potential confounders between the 2 XOI groups, we assessed 81 prespecified baseline variables in the 365 days before the index date or on the index date (see Table 1 for partial list of covariates). Covariates included demographic data (age, sex, place of residence), index year, cardiovascular comorbidities (ie, MI, stroke, coronary revascularization), other medical comorbidities (ie, any stage of chronic kidney disease, diabetes mellitus, mellitus, hyperlipidemia), gout-related medications (ie, probenecid, colchicine, nonsteroidal antiinflammatory drugs, steroids), other medications (ie, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics), and healthcare utilization patterns (ie, number of emergency room visits, outpatient visits, various tests ordered). To better account for potential confounding by various comorbidities, we also used a comorbidity score that incorporated 20 different medical conditions, including HF, renal failure, respiratory disease, cirrhosis, and malignancy.[26]

Statistical Analysis

Main Analysis (Propensity Score Matching, Primary and Secondary Outcomes)

For confounding adjustment, we used propensity score (PS) matching, in which all the baseline covariates were simultaneously adjusted for. The PS was defined as the probability of receiving febuxostat versus allopurinol given patients' baseline characteristics and calculated based on multivariable logistic regression models that incorporated baseline variables such as demographic information, medical comorbidities, medications, and healthcare utilization patterns listed in Table 1. Using nearest-neighbor matching within a caliper of 0.05 on the PS scale, febuxostat initiators were matched to allopurinol initiators with a fixed ratio of 1:3 to optimize the size of the febuxostat group and overall study cohort. The fixed ratio of 1:3 was maintained throughout all subsequent main, subgroup, and sensitivity analyses. We compared baseline characteristics of febuxostat and allopurinol initiators before and after PS matching. Variables with standardized differences <10% between the 2 groups were considered well balanced after PS matching.[27,28]

For the primary as-treated analysis, follow-up started on the day after the index date and ended on the earliest date of the following censoring events: drug discontinuation, last day of study database, insurance disenrollment (Part A/B/D), and occurrence of outcome, death, or nursing home admission. The last drug available date was defined as the last dispensing date plus days of supply with a 30-day grace period. Treatment adherence was calculated using a proportion of days covered, where proportion of days covered (%) was equal to the number of days covered by prescriptions multiplied by 100, divided by the total number of days of follow-up.

For the secondary intention-to-treat 365-day analysis, follow-up time was truncated on the 366th day after the index date unless patients were censored based on the previously mentioned criteria except drug discontinuation. This analysis was conducted to address the potential for lower adherence over long term follow-up.

Incidence rates (IRs) and 95% CIs were calculated for the previously mentioned primary and secondary outcomes among the PS-matched groups separately. Cox proportional hazards regression compared the risk of primary and secondary outcomes in the PS-matched cohorts of febuxostat and allopurinol initiators. Cumulative incidence plots between treatment groups were compared. We assessed the proportional hazards assumption by testing the significance of the interaction term between exposure and follow-up time and found that the assumption was violated for the all-cause mortality analysis (P=0.02 for the interaction term). Therefore, we conducted Cox regression stratified by follow-up time for all-cause mortality. In addition, we ran follow-up time-stratified Cox regression for the primary outcome.

Subgroup Analyses

We conducted two subgroup analyses. The first analysis was an a priori defined PS-matched subgroup analysis by the presence or absence of baseline CVD (defined as history of MI, hospitalized unstable angina, coronary or cerebral revascularization, stroke, or hospitalized transient ischemic attack). IR and hazard ratio (HR) were calculated for both primary and secondary outcomes. In the second subgroup analysis, we identified patients with high cardiovascular risk, similar to the CARES inclusion criteria (ie, peripheral vascular disease or diabetes mellitus in addition to the previously defined CVD).

Sensitivity Analyses

We also performed two sensitivity analyses. The first analysis was limited to patients who initiated equipotent dosing of febuxostat (≥40 mg daily) versus allopurinol (≥300 mg daily) on the index date. The second analysis was limited to patients who initiated equipotent dosing of febuxostat (≥40 mg daily) versus allopurinol (≥300 mg daily) on the index date and were naïve to both drugs prior to index date.

All analyses were done using SAS 9.4 statistical software (SAS Institute, Cary, NC).

Table 1. Baseline Characteristics of the 1:3 PS-Matched Cohort

	Febuxostat	Allopurinol	Standardized Difference, %
N	24936	74808	—
Demographics			
Age, y median (IQR)	76 (70–82)	76 (71–82)	0
Male, %	52.3	52.3	0.1
White race, %	76.4	76.2	0.4
US region			
Midwest, %	19.3	19.1	0.6
Northeast, %	18.7	19.0	–0.6
South, %	42.5	42.4	0.3
West, %	19.4	19.5	–0.4
Cardiovascular comorbidities			
Myocardial infarction	3.5	3.6	–0.2
Stroke	7.2	7.3	–0.2
Coronary revascularization	2.3	2.3	0.1
Heart failure, %	35.7	35.8	–0.2
Recent heart failure, 60 d, %	5.1	5.1	–0.1
Venous thromboembolism, %	7.7	7.6	0.4
Hypertension, %	95.4	95.4	–0.1
Peripheral vascular disease, %	19.7	19.7	–0.1
Cardiovascular disease, %	12.2	12.2	–0.2
Other comorbidities			
Hyperlipidemia, %	82.8	82.9	–0.2
Chronic kidney disease, %	57.1	58.0	–1.7
Chronic obstructive pulmonary disease, %	32.5	32.5	–0.1
Diabetes mellitus, %	55.0	55.2	–0.6
Malignancy, %	21.7	21.5	0.4
Renal stone, %	5.6	5.7	–0.3
Liver disease, %	7.1	7.1	0.2
Obesity, %	17.5	17.3	0.6
Sleep apnea, %	9.5	9.3	0.5
Smoking, %	6.0	5.9	0.3
Comorbidity score, median (IQR)	3 (1–6)	3 (1–6)	0
Gout-related medications			
Colchicine, %	42.8	43.1	–0.7
NSAIDs/COXIB, %	41.0	41.0	0.1
Opioids, %	49.4	49.0	0.6
365-d Cumulative prednisone equivalent dose, mg, median (IQR)	0 (0–240)	0 (0–210)	0
Any steroid use, 365 d, %	41.4	41.2	0.3
Recent steroid use, 90 d, %	29.4	29.2	0.4
Other medications			
ACE inhibitors/angiotensin receptor blockers, %	68.2	68.3	–0.2
ß-Blockers, %	47.1	47.1	–0.1
Calcium channel blockers, %	42.8	43.1	–0.5
Diuretics, %	76.5	76.6	–0.4
Nitrates, %	17.3	17.4	–0.2
Noninsulin antidiabetic drugs, %	30.1	30.3	–0.4
Insulin, %	14.9	15.1	–0.5
Anticoagulants, %	21.2	21.1	0.4
Antiplatelets, %	17.8	18.0	–0.5
Statins, %	61.4	61.5	–0.1
Other lipid-lowering drugs, %	17.2	17.3	–0.2
Healthcare utilization pattern			
No. of emergency room visits, median (IQR)	0 (0–1)	0 (0–1)	0
No. of all outpatient visits, median (IQR)	14 (8–21)	13 (8–21)	0
No. of prescription drugs, median (IQR)	15 (11–20)	15 (11–20)	0
Hospitalization, %	33.7	33.7	0
No. of cardiology visits, median (IQR)	0 (0–2)	0 (0–2)	0
No. of rheumatology visits, median (IQR)	0 (0–0)	0 (0–0)	0.1
CRP test ordered, %	22.1	22.0	0.2
ECG ordered, %	63.7	64.0	–0.5
Echocardiogram ordered, %	2.1	2.2	–0.3
Cardiac stress test ordered, %	16.3	16.6	–0.8
Hemoglobin A1c ordered, %	54.4	54.7	–0.6
Lipid/cholesterol test ordered, %	80.8	80.9	–0.3
Uric acid test ordered, %	86.5	87.1	–1.7
Serum creatinine test ordered, %	97.9	98.1	–1.3

Recent history of MI (60 d), stroke (60 d), alcoholism, and phosphate binders was present in <1% of patients. For all covariates, standardized differences were less than 10%.

ACE indicates angiotensin converting enzyme; COXIB, Cox-2 inhibitor; CRP, C-reactive protein; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; and PS, propensity score.

RESULTS

Cohort Selection

Application of inclusion and exclusion criteria resulted in a total of 331 134 patients with gout aged 65 years or older continuously enrolled in Medicare Parts A, B and D for at least 365 days prior to initiation of febuxostat (n=26 233) and allopurinol (n=304 901) (Figure in the online-only Data Supplement). Following 1:3 PS matching, 95% of febuxostat initiators (n=24 936) and 25% of allopurinol initiators (n=74 808) were included in the study.

Patient Characteristics

Baseline demographics and clinical characteristics of each group after 1:3 PS matching are summarized in Table 1 (see Table in the online-only Data Supplement for baseline characteristics before PS matching). Among febuxostat users, the median (interquartile range) age was 76 (70–82) years and 52% were male. Among allopurinol users, the median (interquartile range) age was 76 (71–82) years and 52% were male. In both groups, 12% had CVD at baseline. Hypertension (95%), chronic kidney disease (58%), diabetes (55%), and heart failure (36%) were common comorbidities in both groups. Use of gout-related medications including colchicine (43%), nonsteroidal anti-inflammatory drugs (41%), and steroids (41%) was also common among all users. All the baseline covariates were well balanced between the PS-matched groups with a standardized difference <10%.[27]

The mean (SD) follow-up time was 1.1 (1.1) years among febuxostat initiators and 1.2 (1.2) years among allopurinol initiators. There were 5013 (20.1%) febuxostat and 18235 (24.4%) allopurinol initiators, who had over 730 days of follow-up time. Of the febuxostat initiators, 30.4% had been on allopurinol at some point during the 365 days prior to febuxostat initiation. Among allopurinol initiators, 0.4% had been on febuxostat during the 365 days prior to allopurinol initiation.

Patterns of Febuxostat and Allopurinol Treatment

In the febuxostat group, the median (interquartile range) proportion of days covered was 93.85% (51.96–100) up to 180 days and 89.34% (48.15–100) up to 365 days. In the allopurinol group, the median (interquartile range) proportion of days covered was 85.08% (50.28–100) up to 180 days and 79.78% (33.33–98.92) up to 365 days. Among febuxostat initiators, 98.89% were on a dosage of 40 mg or higher per day. For allopurinol initiators, 30.67% were on a daily dosage of 300 mg of higher. Of febuxostat initiators, 13.2% had a dose increase during follow-up compared to 22.8% of allopurinol initiators.

Risk of Cardiovascular Events

In the primary as-treated analysis, the IR per 100 person-years for the primary outcome (ie, hospitalization for MI or stroke) was 3.43 (95% CI, 3.22–3.66) in febuxostat and 3.36 (95% CI, 3.25–3.49) in allopurinol initiators (Table 2). In the intention-to-treat 365-day analysis, the IR for the primary outcome was also similar in the two groups: IR per 100 person-years of 3.72 (95% CI, 3.45–4.00) for febuxostat and 3.83 (95% CI, 3.67–4.00) for allopurinol initiators. The HR for the primary outcome was 1.01 (95% CI, 0.94–1.08) in the febuxostat compared with allopurinol initiators (Table 2). Cumulative incidence plots also showed null results for the primary outcome with the log-rank test *P* value of 0.83 (Figure [A]). In the Cox regression analysis stratified by follow-up time (ie, treatment duration) for the primary outcome, the HR (95% CI) associated with febuxostat versus allopurinol was 0.84 (0.73–0.98) for 0 to 1 year of follow-up, 0.88 (0.61–1.25) for 1 to 2 years, 0.76 (0.42–1.39) for 2 to 3 years, and 1.17 (0.45–3.05) for >3 years.

The risk of developing secondary outcomes was also similar between the 2 groups. In the as-treated analysis, the HR in febuxostat initiators was 1.03 (95% CI, 0.94–1.13) for MI, 0.98 (95% CI, 0.87–1.10) for stroke, 0.95 (95% CI, 0.87–1.03) for coronary revascularization, and 0.95 (95% CI, 0.89–1.02) for all-cause mortality (Table 2). Cumulative incidence plots for all-cause mortality was also consistent with the log-rank test *P* value of 0.15 (Figure [B]). In the Cox regression analysis stratified by follow-up time for all-cause mortality, the HR (95% CI) associated with febuxostat was 0.75 (0.66–0.86) for 0 to 1 year of follow-up, 0.85 (0.63–1.15) for 1 to 2 years, 0.72 (0.53–1.54) for 2 to 3 years, and 1.25 (0.56–2.80) for >3 years.

The intention-to-treat 365-day analyses showed consistent results as well for the secondary outcomes.

Risk of Heart Failure

For new-onset HF hospitalizations, the IR per 100 person-years was 5.71 (95% CI, 5.37–6.06) for febuxostat initiators compared to 5.41 (95% CI, 5.23–5.60) for allopurinol initiators in the as-treated analysis (Table 3). The HR for new-onset HF in the as-treated analysis was 1.05 (95% CI, 0.98–1.12). For HF exacerbations, the IR per 100 person-years was 42.70 (95% CI, 41.16–44.29) for febuxostat initiators compared to 44.06 (95% CI, 43.18–44.96) for allopurinol initiators in the as-treated analysis. The HR for HF exacerbation in the as-treated analysis was 0.94 (95% CI, 0.91–0.99). Although this last HR was statistically significantly lower than 1.0, the degree of risk reduction appeared modest. Intention-to-treat 365-day analysis yielded similar results, with no difference between the 2 groups for new-onset HF and borderline risk reduction for HF exacerbation.

Subgroup Analyses

In the first subgroup analysis by baseline CVD, we noted no significant difference in the primary outcome between febuxostat and allopurinol initiators (Table 4). For the secondary outcome of all-cause mortality, the HR for febuxostat versus allopurinol was 0.97 (95% CI, 0.90–1.04) in those without baseline CVD and 0.85 (95% CI, 0.72–0.99) among those with baseline CVD.

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Table 2. Risk of Cardiovascular Events in Febuxostat vs Allopurinol Initiators: 1:3 PS-Matched Analysis

Outcome	Febuxostat (n=24 936)				Allopurinol (n=74 808)			
	Event (n)	Person-Years	IR* (95% CI)	HR (95% CI)	Event (n)	Person-Years	IR* (95% CI)	HR (95% CI)
As-treated analysis								
Primary outcome								
MI or stroke	935	27 251	3.43 (3.22–3.66)	1.01 (0.94–1.08)	3105	92 264	3.36 (3.25–3.49)	Ref
Secondary outcomes								
MI	596	27 440	2.17 (2.00–2.35)	1.03 (0.94–1.13)	1935	92 962	2.08 (1.99–2.18)	Ref
Stroke	372	27 609	1.35 (1.22–1.49)	0.98 (0.87–1.10)	1272	93 487	1.36 (1.29–1.44)	Ref
Coronary revascularization	719	27 209	2.64 (2.46–2.84)	0.95 (0.87–1.03)	2525	91 815	2.75 (2.65–2.86)	Ref
All-cause mortality	1144	27 809	4.11 (3.88–4.36)	0.95 (0.89–1.02)	4022	94 219	4.27 (4.14–4.40)	Ref
$ITT_{365\text{-}d}$ analysis								
Primary outcome								
MI or stroke	711	19 132	3.72 (3.45–4.00)	0.97 (0.89–1.06)	2146	55 986	3.83 (3.67–4.00)	Ref
Secondary outcomes								
MI	442	19 192	2.30 (2.10–2.53)	0.97 (0.87–1.08)	1334	56 190	2.37 (2.25–2.51)	Ref
Stroke	285	19 254	1.48 (1.32–1.66)	0.95 (0.83–1.09)	876	56 357	1.55 (1.45–1.66)	Ref
Coronary revascularization	570	19 133	2.98 (2.74–3.23)	0.93 (0.84–1.02)	1804	55 946	3.23 (3.08–3.38)	Ref
All-cause mortality	995	19 317	5.15 (4.84–5.48)	0.94 (0.88–1.01)	3092	56 571	5.47 (5.28–5.66)	Ref

HR indicates hazard ratio; IR, incidence rate; $ITT_{365\text{-}d}$, intention-to-treat analysis up to the 365th day of follow-up; MI, myocardial infarction; PS, propensity score; and Ref, reference.

*IR is per 100 person-years.

In the second subgroup analysis for high cardiovascular risk defined similar to the CARES's inclusion criteria, we also found no difference in both primary and secondary outcomes, including all-cause mortality (Table 5).

Sensitivity Analyses

For the sensitivity analysis limited to patients who initiated febuxostat ≥40 mg daily versus allopurinol ≥300 mg daily on the index date, the risk for the primary outcome

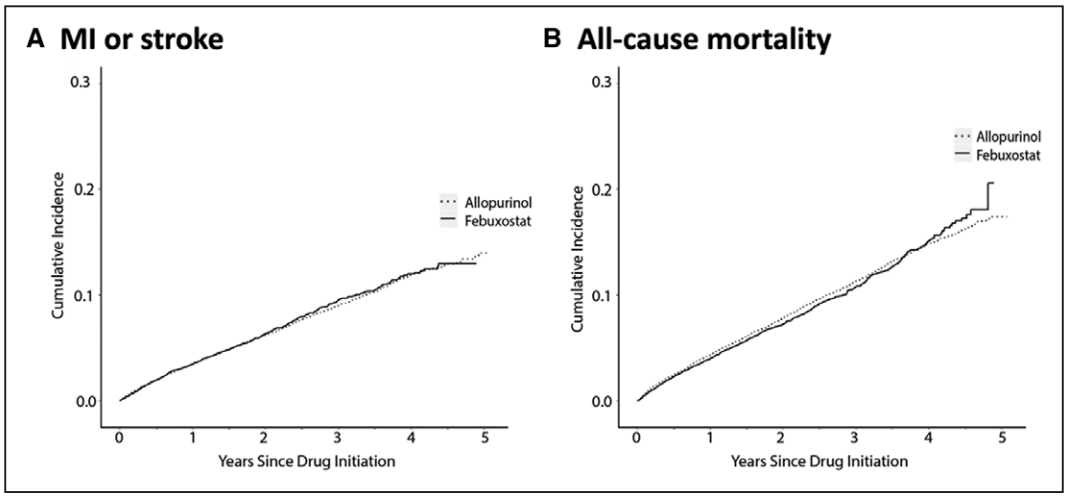

Figure. Cumulative incidences of the composite end point of MI or stroke and all-cause mortality.
Among the 1:3 propensity score-matched cohort of febuxostat and allopurinol initiators, the cumulative incidences of the composite end point of MI or stroke (**A**) and all-cause mortality (**B**) were compared with the log-rank test (P=0.8 for MI or stroke and P=0.15 for all-cause mortality). MI indicates myocardial infarction.

Table 3. Risk of Heart Failure (HF) in Febuxostat Initiators vs Allopurinol Initiators: 1:3 PS-Matched Analysis

Outcome	Febuxostat					Allopurinol				
	N	Event (n)	Person-Years	IR* (95% CI)	HR (95% CI)	N	Event (n)	Person-Years	IR* (95% CI)	HR (95% CI)
As-treated analysis										
New-onset HF†	15929	1056	18500	5.71 (5.37–6.06)	1.05 (0.98–1.12)	47787	3437	63507	5.41 (5.23–5.60)	Ref
HF exacerbation‡	8977	2855	6687	42.70 (41.16–44.29)	0.94 (0.91–0.99)	26931	9426	21394	44.06 (43.18–44.96)	Ref
$ITT_{365\text{-}d}$ analysis										
New-onset HF†	15929	760	12892	5.90 (5.49–6.33)	0.99 (0.91–1.07)	47787	2250	37723	5.97 (5.72–6.22)	Ref
HF exacerbation‡	8977	2646	5300	49.92 (48.06–51.86)	0.93 (0.89–0.98)	26931	8127	15137	53.69 (52.53–54.87)	Ref

HF indicates heart failure; HR, hazard ratio; IR, incidence rate; $ITT_{365\text{-}d}$, intention-to-treat analysis up to the 365th day of follow-up; PS, propensity score; and Ref, reference.
*IR is per 100 person-years.
†Among the subgroup of patients with no baseline history of HF.
‡Among the subgroup of patients with baseline history of HF, only counting the first exacerbation after the index date.

(hospitalization for MI or stroke) was similar between the PS-matched febuxostat and allopurinol groups with an HR of 1.05 (95% CI, 0.94–1.18) (Table 6). Results for the secondary outcomes, including MI, stroke, coronary revascularization, new-onset HF, HF recurrence, and all-cause mortality, were all consistent with the main analyses.

When we further restricted the cohort to those who initiated equipotent dosing (ie, ≥40 mg/d febuxostat or 300 mg/d allopurinol) and had no prior use of either febuxostat or allopurinol before the index date, there was no difference in risk between the 2 groups for the primary outcome (HR, 0.96; 95% CI, 0.85–1.08) (Table 7) as well as all secondary outcomes.

DISCUSSION

In our study of US Medicare patients with gout, initiation of febuxostat compared with allopurinol was not

Table 4. Subgroup Analysis by Baseline CVD: 1:3 PS-Matched As-Treated Analysis

Outcome	Febuxostat					Allopurinol				
	N	Event (n)	Person-Years	IR* (95% CI)	HR (95% CI)	N	Event (n)	Person-Years	IR* (95% CI)	HR (95% CI)
Without baseline CVD										
MI or stroke	21821	726	24526	2.96 (2.75–3.18)	0.99 (0.91–1.08)	65463	2471	83379	2.96 (2.85–3.08)	Ref
MI	21821	457	24683	1.85 (1.69–2.03)	0.98 (0.88–1.08)	65463	1579	83911	1.88 (1.79–1.98)	Ref
Stroke	21821	291	24813	1.17 (1.05–1.32)	1.00 (0.88–1.15)	65463	977	84420	1.16 (1.09–1.23)	Ref
Coronary revascularization	21821	577	24501	2.36 (2.17–2.56)	0.92 (0.84–1.01)	65463	2098	82859	2.53 (2.43–2.64)	Ref
All-cause mortality	21821	946	24972	3.79 (3.55–4.04)	0.97 (0.90–1.04)	65463	3309	84984	3.89 (3.76–4.03)	Ref
With baseline CVD										
MI or stroke	3067	207	2655	7.80 (6.80–8.93)	0.97 (0.83–1.13)	9201	693	8803	7.87 (7.31–8.48)	Ref
MI	3067	139	2686	5.18 (4.38–6.11)	0.98 (0.81–1.19)	9201	461	8938	5.16 (4.71–5.65)	Ref
Stroke	3067	79	2726	2.90 (2.32–3.61)	1.03 (0.80–1.32)	9201	252	9093	2.77 (2.45–3.14)	Ref
Coronary revascularization	3067	146	2634	5.55 (4.72–6.52)	1.10 (0.91–1.33)	9201	435	8820	4.93 (4.49–5.42)	Ref
All-cause mortality	3067	195	2765	7.05 (6.13–8.12)	0.85 (0.72–0.99)	9201	756	9235	8.19 (7.62–8.79)	Ref

CVD indicates cardiovascular disease; HR, hazard ratio; IR, incidence rate; MI, myocardial infarction; PS, propensity score; and Ref, reference.
*IR is per 100 person-years.

Table 5. Subgroup Analysis by High CV Risk: 1:3 PS-Matched As-Treated Analysis

Outcome	Febuxostat					Allopurinol				
	N	Event (n)	Person-Years	IR* (95% CI)	HR (95% CI)	N	Event (n)	Person-Years	IR* (95% CI)	HR (95% CI)
Without high CV risk										
MI or stroke	16 174	674	16 943	3.98 (3.69–4.29)	0.97 (0.89–1.06)	48 522	2280	56 347	4.05 (3.88–4.22)	Ref
MI	16 174	448	17 062	2.63 (2.39–2.88)	1.00 (0.90–1.11)	48 522	1479	56 814	2.60 (2.47–2.74)	Ref
Stroke	16 174	252	17 208	1.46 (1.29–1.66)	0.96 (0.84–1.11)	48 522	866	57 335	1.51 (1.41–1.61)	Ref
Coronary revascularization	16 174	509	16 920	3.01 (2.76–3.28)	0.91 (0.82–1.00)	48 522	1840	56 089	3.28 (3.13–3.43)	Ref
All-cause mortality	16 174	801	17 337	4.62 (4.31–4.95)	0.93 (0.86–1.00)	48 522	2,847	57 821	4.92 (4.75–5.11)	Ref
With high CV risk										
MI or stroke	8645	253	10 212	2.48 (2.19–2.80)	1.03 (0.90–1.19)	25 935	832	34 790	2.39 (2.23–2.56)	Ref
MI	8645	143	10 279	1.39 (1.18–1.64)	1.01 (0.84–1.22)	25 935	479	35 029	1.37 (1.25–1.50)	Ref
Stroke	8645	116	10 303	1.13 (0.94–1.35)	1.04 (0.85–1.28)	25 935	378	35 123	1.08 (0.97–1.19)	Ref
Coronary revascularization	8645	202	10 198	1.98 (1.73–2.27)	1.02 (0.87–1.19)	25 935	668	34 725	1.92 (1.78–2.08)	Ref
All-cause mortality	8645	332	10 371	3.20 (2.88–3.57)	0.97 (0.86–1.10)	25 935	1162	35 366	3.29 (3.10–3.48)	Ref

CV indicates cardiovascular; HR, hazard ratio; IR, incidence rate; MI, myocardial infarction; PS, propensity score; and Ref, reference.
*IR is per 100 person-years.

associated with a change in risk of cardiovascular events for MI, stroke, new-onset HF, coronary revascularization, or all-cause mortality. This finding was observed in the main as-treated as well as intention-to-treat analyses truncated at 1 year of follow-up. However, in a follow-up time-stratified analysis, we observed a trend toward a greater risk of all-cause mortality in the febuxostat group with >3 years of follow-up versus the allopurinol

Table 6. Sensitivity Analysis: Risk of Cardiovascular Events in Febuxostat (≥40 mg/d) vs Allopurinol (≥300 mg/d) Initiators: 1:3 PS-Matched As-Treated Analysis

Outcome	Febuxostat					Allopurinol				
	N	Event (n)	Person-Years	IR* (95% CI)	HR (95% CI)	N	Event (n)	Person-Years	IR* (95% CI)	HR (95% CI)
Primary outcome										
MI or stroke	12 252	404	13 848	2.92 (2.65–3.22)	1.05 (0.94–1.18)	36 756	1359	49 755	2.73 (2.59–2.88)	Ref
Secondary outcomes										
MI	12 252	242	13 938	1.74 (1.53–1.97)	1.08 (0.93–1.24)	36 756	796	50 144	1.59 (1.48–1.70)	Ref
Stroke	12 252	178	13 993	1.27 (1.10–1.47)	1.05 (0.89–1.24)	36 756	605	50 314	1.20 (1.11–1.30)	Ref
Coronary revascularization	12 252	358	13 779	2.60 (2.34–2.88)	1.01 (0.90–1.14)	36 756	1247	49 379	2.53 (2.39–2.67)	Ref
New-onset HF	9021	471	10 461	4.50 (4.11–4.93)	1.00 (0.91–1.11)	27 063	1687	37 948	4.45 (4.24–4.66)	Ref
HF exacerbation	3261	948	2556	37.09 (34.80–39.53)	0.97 (0.90–1.04)	9783	3274	8866	36.93 (35.68–38.22)	Ref
All-cause mortality	12 252	426	14 091	3.02 (2.75–3.32)	0.93 (0.84–1.04)	36 756	1620	50 720	3.19 (3.04–3.35)	Ref

HF indicates heart failure; HR, hazard ratio; IR, incidence rate; MI, myocardial infarction; PS, propensity score; and Ref, reference.
*IR is per 100 person-years.

Table 7. Sensitivity Analysis: Risk of Cardiovascular Events in Febuxostat (≥40 mg/d) vs Allopurinol (≥300 mg/d) Initiators Naïve to Both Drugs: 1:3 PS-Matched As-Treated Analysis

	Febuxostat					Allopurinol				
Outcome	N	Event (n)	Person-Years	IR* (95% CI)	HR (95% CI)	N	Event (n)	Person-Years	IR* (95% CI)	HR (95% CI)
Primary outcome										
MI or stroke	11220	368	12080	3.05 (2.75–3.37)	0.96 (0.85–1.08)	33660	1346	42943	3.13 (2.97–3.31)	Ref
Secondary outcomes										
MI	11220	224	12151	1.84 (1.62–2.10)	0.97 (0.84–1.13)	33660	811	43284	1.87 (1.75–2.01)	Ref
Stroke	11220	158	12219	1.29 (1.11–1.51)	0.97 (0.81–1.15)	33660	575	43489	1.32 (1.22–1.44)	Ref
Coronary revascularization	11220	308	12047	2.56 (2.29–2.86)	0.97 (0.86–1.10)	33660	1100	42691	2.58 (2.43–2.73)	Ref
New-onset HF	7785	454	8667	5.24 (4.78–5.74)	1.05 (0.95–1.17)	23355	1541	31460	4.90 (4.66–5.15)	Ref
HF exacerbation	3412	1,022	2561	39.91 (37.54–42.44)	1.00 (0.93–1.07)	10236	3393	8891	38.16 (36.90–39.47)	Ref
All-cause mortality	11220	420	12295	3.42 (3.10–3.76)	0.93 (0.83–1.03)	33660	1597	43848	3.64 (3.47–3.83)	Ref

HF indicates heart failure; HR, hazard ratio; IR, incidence rate; MI, myocardial infarction; PS, propensity score; and Ref, reference.
*IR is per 100 person-years.

group with >3 years of follow-up. We also found a modestly decreased risk for HF exacerbation associated with febuxostat versus allopurinol in the primary as-treated (HR, 0.94; 95% CI, 0.91–0.99) and intention-to treat analyses (HR, 0.93; 95% CI, 0.89–0.98).

In the subgroup analysis, there was no difference in the risk of cardiovascular events between the 2 groups with and without baseline CVD, except for a modestly decreased risk of all-cause mortality in febuxostat users with baseline CVD (HR, 0.85; 95% CI, 0.72–0.99). Among patients with high cardiovascular risk at baseline, we noted no difference in the risk of cardiovascular events or all-cause mortality between the 2 drugs. Finally, in the 2 sensitivity analyses where we compared (1) equipotent index dosages (febuxostat ≥40 mg versus allopurinol ≥300 mg daily) without naivety to both drugs before the index date and (2) equipotent index dosages (febuxostat ≥40 mg versus allopurinol ≥300 mg daily) with naivety to both drugs before the index date, we found no difference in cardiovascular risk between febuxostat and allopurinol users.

Although the original phase III randomized controlled trials for febuxostat (APEX and FACT) revealed a numerically higher but statistically nonsignificant risk for adverse cardiovascular events in febuxostat initiators compared with allopurinol initiators, the rates of cardiovascular events did not correlate with febuxostat dosage, and the number of cardiovascular events did not increase over the duration of the study.[17,18] In APEX, the number of adverse cardiovascular events ranged from 1 to 5 (<1% to 2%) in each of the febuxostat groups (80, 120, and 240 mg) versus 1 (<1%) in the allopurinol group.[17] In FACT, the number of adverse cardiovascular events was 1 (<1%) in each of the febuxostat groups (80 mg and 120 mg) versus 0 (0%) in the allopurinol group.[18] In both trials, the adverse cardiovascular events were considered to be unlikely related to the study drug. Nonetheless, the US Food and Drug Administration required the sponsor to collect additional safety data.

The recent CARES trial on cardiovascular risk of febuxostat versus allopurinol showed that the individual risk of cardiovascular mortality and all-cause mortality was higher in both febuxostat initiators.[20] There was no difference in risk of the composite end point of cardiovascular death, nonfatal MI, nonfatal stroke, and unstable angina with urgent coronary revascularization between the 2 drug groups. Similar to CARES, we found no difference in individual risk for MI, stroke, or coronary revascularization between the 2 groups. However, we also found no difference in the risk of all-cause mortality in the primary analysis, as well as subgroup analyses limited to those with baseline CVD or baseline high cardiovascular risk (ie, CVD, including peripheral vascular disease or diabetes mellitus as seen in CARES).

The discrepancy in results for mortality between CARES and our study may be related to differences in the underlying populations. CARES was restricted to patients with high cardiovascular risk defined as those with a history of major cardiovascular or cerebrovascular disease, including MI, hospitalized unstable angina, coronary or cerebral vascularization procedure, stroke, hospitalized transient ischemic attack, peripheral vascular disease, or diabetes mellitus with micro- and macrovascular complications. Our main analysis included

patients with and without CVD. Our Medicare study population was also older, with a more equal sex distribution compared with CARES (52% male with a median age of 76 years in our trial versus 84% male with a median age of 64 years in CARES). However, in our follow-up time-stratified analysis, the risk for all-cause mortality appeared to be increased, albeit not statistically significantly, among patients who used febuxostat over 3 years compared with those who used allopurinol over 3 years. We were unable to assess cause-specific deaths, including cardiovascular mortality, because of limitations with the Medicare database.

There are several strengths to our study. By using an active comparator design (febuxostat versus allopurinol rather than febuxostat versus placebo), we increased the overlapping characteristics of the 2 groups and minimized unmeasured confounding.[29] We increased generalizability with a large sample size, performed a comprehensive covariate adjustment via PS matching, and used validated algorithms for outcome measurement. In addition, unlike the CARES study, we included patients who are representative of Medicare enrollees regardless of baseline cardiovascular comorbidities.

Limitations included misclassification bias because participant eligibility was largely dependent on diagnosis code, although this was likely minimized by the additional inclusion criteria of being prescribed ≥1 urate-lowering drug. Second, Medicare claims data did not provide information on cause-specific mortality, family history of CVD, severity of gout, and use of over-the-counter medications such as nonsteroidal antiinflammatory drugs or aspirin, which could have led to residual confounding. Third, with regard to generalizability, our gout cohort was roughly 52% male, which may appear low; however, this prevalence is comparable to other US Medicare gout studies and may reflect the older age of the cohort.[11,30] Fourth, mean follow-up time was ≈1.2 years, which led to less precise estimates for the long-term effects of febuxostat on cardiovascular as well as all-cause mortality, although our study still included many patients (n=23 317) with >2 years of follow-up. Fifth, because the aim of our study was to determine comparative cardiovascular safety of febuxostat and allopurinol, we did not examine the risk of cardiovascular events associated with XOIs compared with untreated patients with gout. Finally, our study did not include participant serum urate levels, so it is possible that participants were underdosed and inadequately treated. Any instances of suboptimal gout treatment, however, likely reflect real-life patterns of urate-lowering treatment allocation in the United States because prior studies on medication use and serum uric acid monitoring in patients with gout on urate-lowering therapy demonstrate widespread suboptimal dosing.[3]

CONCLUSIONS

In this retrospective cohort study of 99 744 patients with gout >65 years of age enrolled in Medicare, we noted no overall difference in the risk for MI, stroke, coronary revascularization, new HF, or all-cause mortality between febuxostat and allopurinol initiators. However, we noted a trend toward an increased risk, not statistically significant, for all-cause mortality in long-term users of febuxostat (>3 years) versus long-term users of allopurinol. The risk of HF exacerbation was slightly lower among febuxostat initiators versus allopurinol. Subgroup and sensitivity analyses showed consistent results.

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