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RESEARCH LETTER

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

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Allopurinol was the only available treatment for gout until the approval of febuxostat in 2009. Premarketing trials of febuxostat raised a potential signal for major adverse cardiovascular events (MACE) when compared with placebo and allopurinol.[1,2] The US Food and Drug Administration mandated a postmarketing cardiovascular safety trial of febuxostat (CARES [Cardiovascular Safety of Febuxostat and Allopurinol in Patients With Gout and Cardiovascular Morbidities]) that suggested noninferiority with respect to the rates of MACE for febuxostat compared with allopurinol (hazard ratio [HR], 1.03; 95% CI, 0.87–1.23), but higher all-cause mortality (HR, 1.22; 95% CI, 1.01–1.47) and cardiovascular mortality (HR, 1.34; 95% CI, 1.03–1.73).[3] Recently, the FAST trial (Febuxostat Versus Allopurinol Streamlined Trial), recommended by the European Medicines Agency, showed that febuxostat was noninferior to allopurinol for the risk of a composite cardiovascular outcome (ie, hospitalization for nonfatal myocardial infarction, biomarker-positive acute coronary syndrome, nonfatal stroke, or cardiovascular death [HR, 0·85; 95% CI, 0·70–1·03]). FAST also found no differences in rates of all-cause mortality between the groups (7.1% versus 8.6%).[4]

To evaluate these cardiovascular safety concerns in a real-world setting, we previously conducted a cohort study using Medicare fee-for-service claims data from 2008 to 2013.[5] As more data on febuxostat use accumulated in recent years, and the information on cardiovascular mortality became available, we aimed to re-evaluate the cardiovascular safety of febuxostat using data up to December 31, 2016, with additional end points of 3-point MACE and cardiovascular mortality. We identified Medicare enrollees with gout aged ≥65 years who initiated allopurinol or febuxostat. In our previous analyses, febuxostat users could use allopurinol before in a prevalent new-user design to maximize statistical power. To further minimize confounding, this study used an incident new-user design by selecting only patients with no use of either medication for ≥1 year before the first dispensing of febuxostat or allopurinol (ie, index date).

The primary outcome was 3-point MACE, defined as the first occurrence of myocardial infarction, nonfatal stroke, or cardiovascular mortality. Secondary outcomes were the individual components of the primary outcome, all-cause mortality, coronary revascularization, and heart failure hospitalizations. Outcomes were defined using previously validated algorithms. The information on cause of death was obtained through the linked National Death Index. We calculated propensity scores (PS) for all patients as the probability of starting febuxostat versus allopurinol using a logistic regression model adjusting for 81 prespecified variables. For confounding control, we utilized 1:3 PS matching. In the primary as-treated analyses, the follow-up began 1 day after the index date and continued until the first occurrence of an outcome, treatment discontinuation/switch, nursing home admission, plan disenrollment, or December 31, 2016. Subgroup analyses were conducted in patients with and without baseline cardiovascular

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Table. Selected Patient Characteristics and Outcomes in Patients With Gout Initiating Febuxostat or Allopurinol (1:3 PS Matched)

Baseline Covariates		Febuxostat (n=27 881)	Allopurinol (n=83 643)	Standardized Mean Differences, %
Demographic characteristics	Age, median (IQR), y	71 (76–83)	71, 76–82	0.00
	Race, White, n (%)	21 605 (77.49)	65 057 (77.78)	−0.70
	Sex, male, n (%)	14 233 (51.05)	42 533 (50.85)	0.40
Comorbidities	Claims-based frailty index, median (IQR)	0.16 (0.19–0.24)	0.16 (0.19–0.24)	0.00
	Combined comorbidity index, mean (SD)	3.87 (3.30)	3.87 (3.34)	0.00
	Atrial fibrillation, n (%)	7988 (28.65)	23 851 (28.52)	0.29
	CVD, n (%)	8808 (31.59)	26 467 (31.64)	−0.11
	Myocardial infarction, n (%)	1124 (4.03)	3422 (4.09)	−0.30
	Peripheral vascular disease, n (%)	6965 (24.98)	20 884 (24.97)	0.02
	Stroke, n (%)	1935 (6.94)	5711 (6.83)	0.43
	Transient ischemic attack, n (%)	1303 (4.67)	3907 (4.67)	0.00
	HF, n (%)	10 228 (36.68)	30 780 (36.80)	−0.25

Population	Outcome	Febuxostat (n=27 881)	Allopurinol (n=83 643)	Febuxostat vs Allopurinol, HR (95% CI)
		Incidence Rate/1000 Patient-y (95% CI)		
Overall	MACE	49.96 (47.85–52.16)	49.22 (48.12–50.35)	0.99 (0.93–1.04)
	Myocardial infarction	20.58 (19.25–22.00)	20.99 (20.28–21.73)	0.95 (0.86–1.03)
	Stroke	11.22 (10.25–12.28)	10.63 (10.13–11.16)	1.06 (0.93–1.20)
	Coronary revascularization	19.16 (17.87–20.54)	19.43 (18.74–20.15)	0.99 (0.89–1.08)
	Cardiovascular death	23.40 (21.99–24.90)	22.49 (21.76–23.25)	1.01 (0.92–1.10)
	All-cause death	49.16 (47.09–51.32)	50.66 (49.55–51.79)	0.92 (0.87–0.97)
No history of HF	HF hospitalization	58.74 (55.95–61.66)	54.81 (53.41–56.25)	1.03 (0.96–1.10)
Prior history of HF		406.37 (394.03–419.10)	404.53 (397.82–411.36)	0.94 (0.90–0.98)
Patients with no baseline CVD	MACE	36.93 (34.81–39.17)	37.09 (35.97–38.25)	0.97 (0.89–1.05)
	Myocardial infarction	15.11 (13.78–16.56)	15.36 (14.65–16.11)	0.93 (0.81–1.05)
	Stroke	8.83 (7.83–9.96)	9.07 (8.53–9.65)	0.94 (0.79–1.10)
	Coronary revascularization	13.85 (12.58–15.25)	14.59 (13.89–15.32)	0.92 (0.80–1.04)
	Cardiovascular death	16.84 (15.44–18.36)	16.23 (15.50–16.99)	1.04 (0.92–1.17)
	All-cause death	38.92 (36.77–41.20)	40.31 (39.15–41.50)	0.94 (0.87–1.02)
Patients with baseline CVD	MACE	84.00 (78.86–89.48)	83.54 (80.79–86.38)	0.94 (0.85–1.02)
	Myocardial infarction	34.77 (31.54–38.34)	35.31 (33.55–37.16)	0.91 (0.79–1.04)
	Stroke	17.27 (15.05–19.82)	17.15 (15.95–18.44)	0.94 (0.78–1.14)
	Coronary revascularization	32.97 (29.80–36.48)	34.21 (32.46–36.05)	0.91 (0.78–1.04)
	Cardiovascular death	40.30 (36.85–44.07)	38.67 (36.85–40.58)	0.98 (0.86–1.11)
	All-cause death	75.14 (70.37–80.23)	78.78 (76.17–81.48)	0.90 (0.82–0.98)

CVD indicates cardiovascular disease; HF, heart failure; HR, hazard ratio; IQR, interquartile range; MACE, major adverse cardiovascular events; and PS, propensity score.

disease (CVD). The institutional review board of the Brigham and Women's Hospital approved the study protocol and patient privacy precautions. Data may be obtained from a third party and are not publicly available.

After applying inclusion/exclusion criteria, we identified 467 461 patients with gout aged ≥65 years who were enrolled in Medicare for ≥365 days before the index date (allopurinol=439 563; febuxostat=27 898). Before PS matching, the median age of febuxostat and allopurinol initiators was similar (71 versus 70 years), and 32% of febuxostat and 29% of allopurinol users had baseline CVD. After PS matching, 27 881 febuxostat initiators were matched to 83 643 allopurinol initiators. All baseline characteristics between the PS-matched groups were well-balanced. The mean follow-up for febuxostat and allopurinol was 284 (SD, 370) and 339 (SD, 419) days, respectively. The HR for 3-point MACE in PS-matched initiators of febuxostat versus allopurinol was 0.99 (95% CI, 0.93–1.05). The result was consistent among patients with CVD (HR, 0.94; 95% CI, 0.86–1.02). Secondary analyses were also similar (Table):

myocardial infarction (HR, 0.95; 95% CI, 0.86–1.04), stroke (HR, 1.06; 95% CI, 0.94–1.20), cardiovascular mortality (HR, 1.01; 95% CI, 0.93–1.10), and all-cause mortality (HR, 0.92; 95% CI, 0.87–0.98).

Prompted by the added boxed warnings for febuxostat based on cardiovascular and all-cause mortality risk noted in the CARES trial, we conducted an updated analysis from the observational study evaluating the comparative safety of febuxostat. Compared with allopurinol, febuxostat was not associated with higher risk of MACE or all-cause mortality in patients with gout who did or did not have baseline CVD. These findings are also concordant with FAST results.[4] Our results are largely consistent with the results from the CARES trial; however, the CARES trial found higher cardiovascular and all-cause mortality risk associated with febuxostat. Although, questions have been raised regarding the biologic plausibility of these results given a high dropout rate (≈50%) and occurrence of deaths (≈85%) after treatment continuation.[3] Our findings are reassuring to patients with intolerability to allopurinol who require treatment with febuxostat, as we did not observe elevated cardiovascular or all-cause mortality even in patients with a history of CVD. Our study has several strengths including its incident new-user and active-comparator design with the use of PS matching, which minimizes confounding. Our findings are also generalizable to the large population of older patients with gout. The primary as-treated approach helps reduce bias caused by nonadherence to medications, a major limitation of the CARES trial. However, residual confounding cannot be ruled out, and misclassification bias is possible because participant eligibility, covariates, and outcome identification were largely dependent on diagnosis codes.

In conclusion, this large real-world data cohort trial showed that febuxostat initiation was not associated with higher cardiovascular risk, including cardiovascular or all-cause mortality, compared with allopurinol among older patients with gout who did or did not have baseline CVD.

ARTICLE INFORMATION

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