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Evaluation of the Relationship Between Serum Urate Levels, Clinical Manifestations of Gout, and Death From Cardiovascular Causes in Patients Receiving Febuxostat or Allopurinol in an Outcomes Trial

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Objective. To investigate whether serum urate levels, number of gout flares, and tophi burden are related to death from cardiovascular (CV) causes after treatment with febuxostat or allopurinol in patients with gout from the Cardiovascular Safety of Febuxostat or Allopurinol in Patients With Gout and Cardiovascular Comorbidities (CARES) trial.

Methods. Patients were randomly assigned to receive febuxostat (40 mg or 80 mg once daily, according to serum urate levels at week 2) or allopurinol titrated in 100-mg increments from 200–400 mg or 300–600 mg (with dose determined according to kidney function). Changes from baseline in serum urate level, gout flares, and tophus resolution were key exploratory efficacy parameters in the overall population and in subgroups of patients who died and those who did not die from a CV-related cause. The latter subgroup included patients who died due to non-CV causes and those who did not die due to any cause.

Results. Patients received treatment with febuxostat (n = 3,098) or allopurinol (n = 3,092) for a median follow-up period of 32 months (for a maximum of 85 months). In the overall population, mean serum urate levels were lower in those receiving febuxostat compared with those receiving allopurinol at most study visits. There were no associations between serum urate levels and death from CV causes with febuxostat. The number of gout flares requiring treatment was higher within 1 year of treatment with febuxostat compared with allopurinol (mean incidence of gout flares per patient-years of exposure 1.33 versus 1.20), but was comparable thereafter and decreased overall throughout the study period (mean incidence of gout flares per patient-years of exposure 0.35 versus 0.34 after 1 year of treatment; overall mean incidence 0.68 versus 0.63) irrespective of whether the patient died from a CV-related cause. Overall, 20.8% of patients had ≥1 tophus at baseline; tophus resolution rates were similar between treatment groups, with cumulative resolution rates of >50%.

Conclusion. In the CARES trial, febuxostat and allopurinol (≤600 mg doses) had comparable efficacy in patients with gout and CV disease, and there was no evidence of a relationship between death from CV causes and serum urate levels, number of gout flares, or tophus resolution among the patients receiving febuxostat.

INTRODUCTION

Gout is the most common form of inflammatory arthritis, affecting an estimated 9.2 million adults in the US (1). Development of hyperuricemia, defined as elevated serum urate levels above the limit of urate solubility (~6.8 mg/dl), is an important prerequisite for the development of gout (2,3).

There is a high incidence of comorbidities, especially cardiovascular disease (CVD) and chronic kidney disease, associated with both hyperuricemia and gout (4,5). Several recent studies demonstrated an increased risk of CV events (including those leading to death) in patients with gout compared with those without (6–8). There is some evidence to suggest that high serum urate levels may be an independent predictive factor for CVD (8,9). Indeed, after

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adjusting for other risk factors (including age, sex, smoking status, alcohol consumption, body weight, blood pressure, history of CVD, kidney function, and plasma glucose levels), serum urate levels were still strongly associated with death from all causes, including CVD (9). However, contrary to findings from these epidemiologic studies, data from Mendelian randomization studies do not support a consistent causal role of serum urate in CVD (10,11). Therefore, the relationship between serum urate levels and death from CV causes remains to be determined (12,13).

The mainstay of chronic gout management is reduction of serum urate levels and maintenance of these levels at <6.0 mg/dl (14–16). The urate-lowering xanthine oxidase inhibitors are considered first-line pharmacologic therapy for hyperuricemia in patients with gout (13–16). Currently, allopurinol and febuxostat are the only available xanthine oxidase inhibitors.

The Cardiovascular Safety of Febuxostat or Allopurinol in Patients With Gout and Cardiovascular Comorbidities (CARES) trial (ClinicalTrial.gov identifier: NCT01101035) examined rates of major CV events in patients with gout and CVD who received treatment with febuxostat or allopurinol (17). The CARES trial has the longest study duration (median follow-up period of 32 months), and largest data set (n = 6,190) of any randomized controlled trial comparing febuxostat with allopurinol. In this study, the proportion of patients with the primary end point (a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and unstable angina with urgent revascularization) was noninferior between febuxostat and allopurinol. However, in the secondary end point analysis, the rate of death from CV causes was greater in patients who received treatment with febuxostat compared with patients who received treatment with allopurinol (4.3% and 3.2%, respectively; hazard ratio [HR] 1.34) (17). In addition, prespecified subgroup analyses were performed in order to investigate the potential effects of nonsteroidal antiinflammatory drug (NSAID) use, since NSAIDs are known to be associated with CVD (18). These analyses found that both the use of NSAIDs and absence of low-dose aspirin at baseline were associated with death from CV causes (unadjusted $P < 0.05$ for both comparisons) (17). With the exception of NSAID use for gout flair prophylaxis and/or treatment, use of NSAIDs and low-dose aspirin were not systematically monitored during the study. In an additional analysis, all-cause mortality was higher with febuxostat treatment compared with allopurinol treatment (HR 1.22) as a result of an imbalance in the rates of death from CV causes (17).

The objective of this exploratory analysis was to evaluate data from the CARES trial to investigate if serum urate levels, gout flares, and tophi burden were associated with death from CV causes after febuxostat or allopurinol treatment.

PATIENTS AND METHODS

The CARES trial has been described previously (17,19). In brief, the CARES trial was a multicenter, randomized, double-blind trial designed to evaluate the CV safety and efficacy of febuxostat compared with allopurinol in patients with gout and significant CV comorbidities.

Patients. Patients were men aged ≥50 years and women aged ≥55 years who had been postmenopausal for ≥2 years. Eligibility criteria included a history or presence of gout according to the American College of Rheumatology criteria (20), as well as a history of major CVD or cerebrovascular disease, including ≥1 of the following: myocardial infarction, cardiac or cerebrovascular revascularization, stroke, hospitalization for unstable angina or transient ischemic attack, peripheral vascular disease, or history of diabetes mellitus with evidence of microvascular disease or macrovascular disease. Patients had serum urate levels ≥7.0 mg/dl at screening, or ≥6.0 mg/dl at screening and inadequately controlled gout (i.e., the presence of flares and/or the presence of tophi in the 12 months prior to screening). Written informed consent was obtained from each patient in accordance with the Declaration of Helsinki and the International Council for Harmonisation Guidelines for Good Clinical Practice, and the study was conducted in accordance with all applicable laws and regulations. The appropriate national and institutional regulatory authorities and ethics committees approved the trial design.

Key exclusion criteria included myocardial infarction within 60 days prior to screening, secondary hyperuricemia, history of xanthinuria, known hypersensitivity to febuxostat or allopurinol, or an estimated creatinine clearance (CrCl) of <30 ml/minute using the Cockcroft-Gault formula.

Treatments and procedures. Eligible patients were randomly assigned in a 1:1 ratio to receive once-daily febuxostat or allopurinol. Patients randomized to receive febuxostat initially received 40 mg every day; patients with serum urate levels <6.0 mg/dl at the week 2 visit continued to receive the 40-mg dose for the remainder of the study. Patients with serum urate levels ≥6.0 mg/dl at week 2 received once-daily febuxostat (80 mg) at week 4 and continued to receive this dose for the remainder of the study. Patients who were randomized to receive allopurinol and who had normal renal function or mild renal impairment (estimated CrCl ≥60 ml/minute) initially received 300 mg of allopurinol daily, with the dose increased in 100-mg increments monthly until either the serum urate level was <6.0 mg/dl or a daily allopurinol dosage of 600 mg was achieved. Patients who had moderate renal impairment (estimated CrCl ≥30 but <60 ml/minute) initially received once-daily allopurinol (200 mg), with the dose increased in 100-mg increments monthly until either the serum urate level was <6.0 mg/dl or a daily allopurinol dosage of 400 mg was achieved.

For the first 6 months of the study, all patients received once-daily colchicine (0.6 mg) as gout flare prophylaxis. Alternatively, if once-daily 0.6 mg of colchicine was not tolerated by the patient, 0.6 mg every other day was permitted. If colchicine was not tolerated and the estimated CrCl was ≥50 ml/minute, naproxen was

Table 1. Baseline demographic and clinical characteristics of patients with gout in the modified intent-to-treat population*

	Overall		Patients who died from a CV-related cause		Patients who did not die from a CV-related cause†	
	Febuxostat (n = 3,098)	Allopurinol (n = 3,092)	Febuxostat (n = 134)	Allopurinol (n = 100)	Febuxostat (n = 2,964)	Allopurinol (n = 2,992)
Years since gout diagnosis, mean ± SD‡	11.8 ± 11.4	11.9 ± 11.2	11.5 ± 12.2	10.3 ± 11.5	11.8 ± 11.4	11.9 ± 11.2
Baseline serum urate level, mean ± SD mg/dl	8.7 ± 1.7	8.7 ± 1.7	9.3 ± 1.8	9.8 ± 1.9	8.7 ± 1.7	8.7 ± 1.7
Baseline serum urate category						
<7 mg/dl	412 (13.3)	436 (14.1)	8 (6.0)	5 (5.0)	404 (13.6)	431 (14.4)
7–<8 mg/dl	631 (20.4)	620 (20.1)	26 (19.4)	11 (11.0)	605 (20.4)	609 (20.4)
8–<9 mg/dl	735 (23.7)	759 (24.5)	26 (19.4)	19 (19.0)	709 (23.9)	740 (24.7)
9–<10 mg/dl	666 (21.5)	646 (20.9)	28 (20.9)	26 (26.0)	638 (21.5)	620 (20.7)
≥10 mg/dl	654 (21.1)	631 (20.4)	46 (34.3)	39 (39.0)	608 (20.5)	592 (19.8)
Months since last gout flare						
<1	1,017 (32.8)	978 (31.6)	47 (35.1)	42 (42.0)	970 (32.7)	936 (31.3)
1–<4	981 (31.7)	1,009 (32.6)	39 (29.1)	29 (29.0)	942 (31.8)	980 (32.8)
4–<6	311 (10.0)	353 (11.4)	14 (10.4)	9 (9.0)	297 (10.0)	344 (11.5)
6–<12	471 (15.2)	455 (14.7)	20 (14.9)	10 (10.0)	451 (15.2)	445 (14.9)
≥12	317 (10.2)	296 (9.6)	14 (10.4)	10 (10.0)	303 (10.2)	286 (9.6)
No. of gout flares in the past year						
1–3	1,880 (60.7)	1,842 (59.6)	77 (57.5)	56 (56.0)	1,803 (60.8)	1,786 (59.7)
4–6	544 (17.6)	544 (17.6)	25 (18.7)	17 (17.0)	519 (17.5)	527 (17.6)
>6	356 (11.5)	409 (13.2)	18 (13.4)	17 (17.0)	338 (11.4)	392 (13.1)
Presence of tophi	668 (21.6)	650 (21.0)	28 (20.9)	30 (30.0)	640 (21.6)	620 (20.7)
No. of tophi, mean ± SD	4.1 ± 10.2	4.2 ± 7.0	12.3 ± 39.6	5.3 ± 6.2	3.8 ± 6.3	4.1 ± 7.0
Renal function at baseline§						
Moderately impaired	1,636 (52.8)	1,631 (52.7)	93 (69.4)	78 (78.0)	1,543 (52.1)	1,553 (51.9)
Mildly impaired	1,217 (39.3)	1,231 (39.8)	34 (25.4)	19 (19.0)	1,183 (39.9)	1,212 (40.5)
Normal	239 (7.7)	228 (7.4)	6 (4.5)	3 (3.0)	233 (7.9)	225 (7.5)
Patients who received prior urate-lowering therapy	1,914 (61.8)	1,914 (61.9)	88 (65.7)	68 (68.0)	1,826 (61.6)	1,846 (61.7)

* Except where indicated otherwise, values are the number (%) of patients. CV = cardiovascular.
† Included patients who died due to non-CV causes and those who did not die due to any cause.
‡ Years are calculated according to the first double-blind dose of study drug.
§ Moderately impaired indicates an estimated creatinine clearance (CrCl) 30–59 ml/minute, mildly impaired indicates an estimated CrCl 60–89 ml/minute, and normal indicates an estimated CrCl ≥90 ml/minute. Seven patients had baseline estimated CrCl <30 ml/minute. One patient was missing baseline estimated CrCl measurements.

administered at a dose of 250 mg twice daily with 15 mg of once-daily lansoprazole. In instances when patients could not receive colchicine or naproxen, other NSAIDs or prednisone were provided at the investigator's discretion. In the event that colchicine, naproxen, other NSAIDs, proton-pump inhibitors, or prednisone were not tolerated or were contraindicated, the investigator could choose not to use prophylaxis but rather to manage gout flares as they occurred.

End points and assessments. In this analysis, key exploratory efficacy end points included changes from baseline in serum urate levels, gout flares, and tophus assessment. Effects on the efficacy end points were explored in post hoc analyses in patients who died from a CV-related cause and patients who did not die from a CV-related cause (i.e., the remainder of the study population, which included those who died due to non-CV causes and those who did not die due to any cause).

Clinic visits occurred on weeks 2, 4, 6, 8, and 10; months 3 and 6; and every 6 months thereafter. If a patient's serum urate level was <6.0 mg/ml at week 4 or 8, then that patient would not be required to return to the study clinic until month 3. Clinical assessments, including those regarding gout flare assessment, serum urate measurements, tophus physical examination, vital signs, treatment compliance, and concomitant medication usage were performed at each visit.

Statistical analysis. Efficacy end points were assessed in the modified intent-to-treat (ITT) population, which included all randomized patients who received ≥1 dose of study medication. Demographic and baseline clinical characteristics and changes in efficacy parameters in the subgroup of patients who died from a CV-related cause and those who did not die from a CV-related cause are summarized.

Gout flare rate was stratified by post-baseline serum urate levels and was calculated as the number of flares from the end of the first year of treatment to the end of the study divided by the length of time on treatment during the period after the first year of treatment until the end of the study.

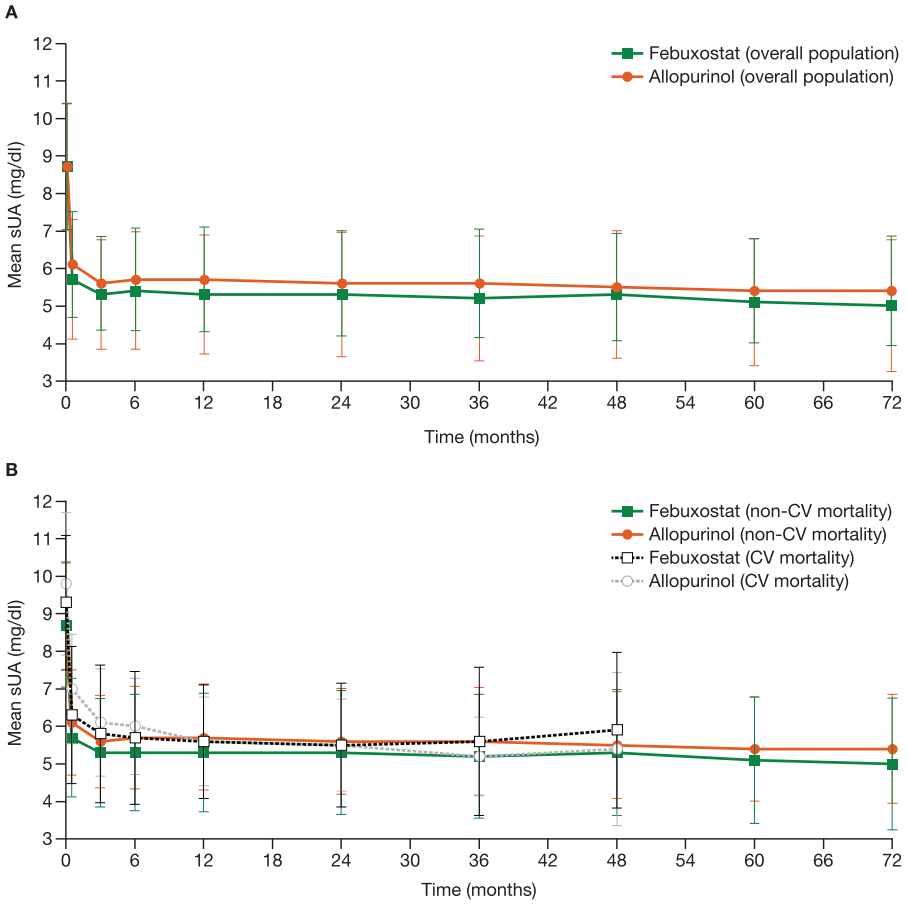

Figure 1. Change in mean serum urate (sUA) levels in patients receiving febuxostat and those receiving allopurinol in the overall modified intent-to-treat (ITT) population (**A**) and in the subgroup of patients who died from a cardiovascular (CV)–related cause compared with patients who did not die from a CV-related cause (**B**). The modified ITT population comprised patients randomized to a treatment group who received ≥1 dose of study drug. Bars show the mean ± SD. Patient numbers are summarized in Supplementary Table 2 (available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.42160). The number of patients in each subgroup who had serum urate (sUA) data at months 60 and 72 was too low (n ≤ 5) to allow for meaningful interpretation of serum urate levels at these time points.

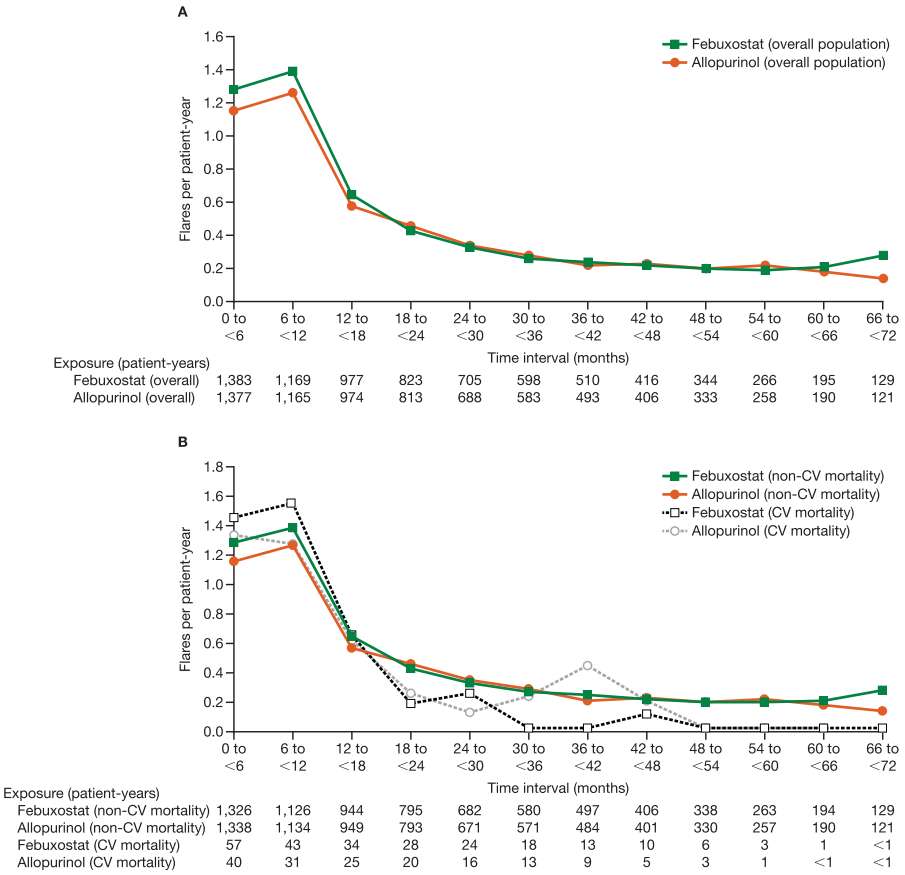

Figure 2. Gout flares requiring treatment among patients receiving febuxostat or allopurinol in the overall modified ITT population (**A**) and in the subgroup of patients who died from a CV-related cause compared with patients who did not die from a CV-related cause (**B**). The modified ITT population comprised patients who were randomized to a treatment group and received ≥1 dose of study drug. Symbols represent the mean number of gout flares per patient-years of exposure, with numbers of patient-years shown in the tables below the graphs. See Figure 1 for definitions.

Post hoc analyses for the relationship between treatment, death from CV causes, and on-treatment serum urate levels were performed using Cochran-Armitage test for trend. Reported *P* values are nominal and are not provided as indicators of statistical significance.

RESULTS

A total of 6,198 patients were enrolled and were randomized to receive either febuxostat or allopurinol in the CARES trial; of these, 8 patients did not receive treatment; therefore, 6,190 patients were included in the modified ITT population. Patients were randomized to receive treatment with febuxostat (n = 3,098) or allopurinol (n = 3,092). The median follow-up period was 32 months (maximum 85 months).

Baseline demographic and clinical characteristics have been described previously and were comparable between treatment arms (17). The study population was predominantly male (83.9%) and White (69.5%), the median (range) age was 65.0 (44–93) years, and the mean ± SD body mass index was 33.5 ± 6.92 kg/m^2. The overall mean ± SD serum urate level at baseline was 8.7 ± 1.7 mg/dl; 20.8% of patients had a baseline serum urate level ≥10.0 mg/dl. Approximately 90% of patients in the CARES trial had experienced a gout flare within the year prior to study entry, and most patients (61.8%) previously received a urate-lowering therapy. In total, 21.3% of patients had a tophus or tophi at baseline (Table 1). Data regarding the disposition of patients have been previously reported (Supplementary Table 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.42160) (17).

Death from CV causes subgroups were composed of patients in the CARES trial who died from a CV-related cause (febuxostat n = 134; allopurinol n = 100) and those who did not die from a CV-related cause (febuxostat n = 2,964; allopurinol n = 2,992) (see Table 1 for baseline demographic and clinical characteristics).

Relationship between serum urate levels and death from a CV-related cause. In the overall modified ITT population, baseline serum urate levels were comparable between the febuxostat treatment group (8.7 mg/dl, n = 3,098) and

Table 2. Incidence of gout flares among patients receiving febuxostat or allopurinol, by treatment duration and severity of flare*

	Febuxostat (n = 3,098)†			Allopurinol (n = 3,092)‡		
	Overall	≤1 year of treatment	>1 year of treatment	Overall	≤1 year of treatment	>1 year of treatment
All flares	0.68	1.33	0.35	0.63	1.20	0.34
Severe	0.20	0.40	0.09	0.17	0.32	0.09
Moderate	0.33	0.63	0.17	0.30	0.56	0.16
Mild	0.14	0.27	0.08	0.15	0.29	0.08

* The highest level of severity reported for the 4 symptoms collected for each flare (swelling, redness, tenderness, and joint warmth) was used to categorize the flare as mild, moderate, or severe. Values are the mean incidence of flares per patient-years of exposure. The total number of patients for each treatment group refers to the number at baseline.
† Per 7,574 patient-years of exposure.
‡ Per 7,455 patient-years of exposure.

allopurinol treatment group (8.7 mg/dl, n = 3,092) (Figure 1 and Supplementary Table 2, http://onlinelibrary.wiley.com/doi/10.1002/art.42160). However, after the first dose of study medication, serum urate levels in patients receiving febuxostat were nominally lower than in those receiving allopurinol at most study visits (week 2 and months 3, 6, 12, 24, 36, 48, 60, and 72). Baseline serum urate levels were higher in patients who died from a CV-related cause (febuxostat 9.3 mg/dl, n = 134; allopurinol 9.8 mg/dl, n = 100) than in those who did not die from a CV-related cause (8.7 mg/dl in both the febuxostat treatment group [n = 2,964] and allopurinol treatment group [n = 2,992]). In patients who did not die from a CV-related cause, serum urate levels with febuxostat treatment were nominally lower than with treatment with allopurinol at week 2 and months 3, 6, 12, 24, 36, 48, 60, and 72. By contrast, in the subgroup of patients who died from a CV-related cause, serum urate levels varied throughout the study period and were comparable between the febuxostat and allopurinol treatment group (Figure 1 and Supplementary Table 2, http://onlinelibrary.wiley.com/doi/10.1002/art.42160).

Gout flares. *Relationship between gout flares requiring treatment and death from CV causes.* The incidence rates of gout flares requiring treatment (per patient-year) were similar between the febuxostat and allopurinol treatment groups over the entire study period (overall modified ITT population, febuxostat 0.68 versus allopurinol 0.63) (Figure 2 and Supplementary Table 3, http://onlinelibrary.wiley.com/doi/10.1002/art.42160). In the overall modified ITT population, gout flare rates (per patient-year) had a trend of being higher with febuxostat than with allopurinol during the first year of treatment (overall modified ITT population, 1.33 versus 1.20, respectively) but were comparable thereafter (overall modified ITT population >1 year, febuxostat 0.35 versus allopurinol 0.34) and decreased over the study period in both treatment groups (Figure 2 and Supplementary Table 3, http://onlinelibrary.wiley.com/doi/10.1002/art.42160). The incidence rates of gout flares within the first year of study treatment were slightly higher in the subgroup of patients who died from a CV-related cause compared with the subgroup of patients who did not die from a CV-related cause, but was generally lower for the remainder of the study period (Figure 2 and Supplementary Table 3). Throughout the duration of the study, gout flare severity was similar between the febuxostat and allopurinol treatment groups, with most flares classified as moderate in intensity (febuxostat 0.33 versus allopurinol 0.30) (Table 2), although the number and severity of gout flares were slightly higher within the first year of treatment in the febuxostat group (overall 1.33 flares versus moderate-to-severe flares 1.03) compared with the allopurinol group (overall flares 1.20 versus moderate-to-severe flares 0.88) (Table 2).

In the overall modified ITT population, gout flare rates within the 3-month period over which data were available closest to death from a CV-related cause were low. The number of gout flares was higher with febuxostat treatment (6% [8 of 134])

Table 3. Gout flare rates among patients receiving febuxostat or allopurinol according to post-baseline mean serum urate levels, overall and by treatment group*

	Mean flare rates per patient-years of exposure (95% CI)		
Post-baseline mean serum urate level	Febuxostat	Allopurinol	Total
<4.0 mg/dl	0.27 (0.24–0.31)	0.25 (0.19–0.33)	0.27 (0.24–0.30)
4.0–5.0 mg/dl	0.27 (0.25–0.30)	0.20 (0.18–0.23)	0.24 (0.23–0.26)
5.0–6.0 mg/dl	0.35 (0.32–0.39)	0.31 (0.29–0.34)	0.33 (0.31–0.35)
≥6.0 mg/dl	0.49 (0.45–0.53)	0.52 (0.48–0.55)	0.50 (0.48–0.53)

* Post-baseline serum urate level measurements were collected from the end of the first year of treatment until the end of the study. The mean flare rates per patient-years of exposure (with 95% confidence intervals [95% CIs]) include occurrence of gout flares from the end of the first year of treatment until the end of the study.

Table 4. Numbers of patients who died from a CV-related cause by average post-baseline mean serum urate level and treatment group*

	Post-baseline mean serum urate level				*P* for trend, death from CV-related cause and mean serum urate level†
	<4.0 mg/dl	4.0–<5.0 mg/dl	5.0–<6.0 mg/dl	≥6.0 mg/dl	
Overall					0.034
Total no. of patients	383	1,353	2,345	2,109	
Patients who died from a CV-related cause	6 (1.6)	16 (1.2)	34 (1.4)	47 (2.2)	
Patients who did not die from a CV-related cause	377 (98.4)	1,337 (98.8)	2,311 (98.6)	2,062 (97.8)	
Febuxostat					0.199
Total no. of patients	298	838	1,012	950	
Patients who died from a CV-related cause	6 (2.0)	13 (1.6)	18 (1.8)	25 (2.6)	
Patients who did not die from a CV-related cause	292 (98.0)	825 (98.4)	994 (98.2)	925 (97.4)	
Allopurinol					0.012
Total no. of patients	85	515	1,333	1,159	
Patients who died from a CV-related cause	0 (0)	3 (0.6)	16 (1.2)	22 (1.9)	
Patients who did not die from a CV-related cause	85 (100.0)	512 (99.4)	1,317 (98.8)	1,137 (98.1)	

* The mean serum urate level was calculated using all post-baseline serum urate values collected after the first dose of study drug and >1 day after a patient's final dose of study drug. Death from a cardiovascular (CV)–related cause includes deaths up to 30 days after a patient's final dose of study drug. Except where indicated otherwise, values are the number (%) of patients.
† Other associations evaluated included the overall relationship between treatment and death from a CV-related cause ($P = 0.038$) and between treatment and mean serum urate level ($P \leq 0.001$). *P* values were determined by Cochran–Armitage test for trend.

compared with allopurinol (2% [2 of 100]) (Supplementary Table 4, http://onlinelibrary.wiley.com/doi/10.1002/art.42160).

Relationship between post-baseline serum urate levels, gout flares, and death from CV causes. In a post hoc analysis, we identified a trend toward a reduction in gout flare rates with lower serum urate levels in both the febuxostat and allopurinol treatment groups (Table 3). There was a positive association between serum urate levels and death from CV causes in the overall population ($P = 0.034$) and in the allopurinol treatment group ($P = 0.012$), but not in the febuxostat treatment group ($P = 0.199$). The total number of deaths from CV causes that occurred during treatment and up to 30 days after the final dose of study medication was lower ($P = 0.038$) in those who received allopurinol (1.3% [41 of 3,092]) compared with those who received febuxostat (2.0% [62 of 3,098]) (17), but the number of deaths was lower in patients with serum urate levels <5 mg/dl compared with those who had levels ≥5 mg/dl in both treatment groups (febuxostat n = 19 [1.7%] versus n = 43 [2.2%]; allopurinol n = 3 [0.5%] versus n = 38 [1.5%]) (Table 4).

Relationship between tophus resolution and death from CV causes. The overall proportion of patients with ≥1 tophus at baseline was 20.8% (1,287 of 6,190), with similar proportions in the febuxostat group (21.0% [650 of 3,098]) and allopurinol group (20.6% [637 of 3,092]). Tophus resolution rates were similar between treatment groups in year 1 and remained similar throughout the study period. By the end of the treatment period, cumulative tophus resolution rates in both treatment groups were >50% (Supplementary Figure 1A, http://onlinelibrary.wiley.com/doi/10.1002/art.42160). Tophus resolution rates within the first 2 years of treatment in the study were also comparable between treatment groups irrespective of whether the patient died from a CV-related cause or not (Supplementary Figure 1B, http://onlinelibrary.wiley.com/doi/10.1002/art.42160).

DISCUSSION

The CARES trial has the longest study duration of any trial investigating patients with gout and CVD. In this analysis, we evaluated the relationships between serum urate levels, gout flares, tophus resolution, and deaths from CV causes. In the CARES trial, the incidence rates of the nonfatal components of the composite primary end point were similar between febuxostat and allopurinol treatment groups (17). However, in the secondary end point analysis, the rate of death from CV causes was higher in patients who received treatment febuxostat compared with those who received allopurinol. All-cause mortality was higher in patients who received febuxostat compared with allopurinol as a result of the imbalance in the rates of deaths from CV causes (17). Further analyses of data from the CARES trial demonstrated that both febuxostat and allopurinol were associated with comparable, clinically relevant improvements in efficacy. We did not observe a relationship between gout flares and deaths from CV causes; however, there was a positive association between greater serum urate levels and deaths from CV causes in the overall population and in the allopurinol treatment group, while the rates of death from CV causes in the febuxostat treatment group were similar across serum urate levels. Additionally, data from the Febuxostat versus Allopurinol Streamlined Trial demonstrated that febuxostat was noninferior to allopurinol with regard to the occurrence of major CV outcomes with no indication of increased all-cause mortality or deaths from CV causes with febuxostat treatment (21). Therefore, the underlying mechanisms of the increase in deaths from CV causes observed in patients who received febuxostat compared with those who received allopurinol in the CARES trial remain unclear.

The primary goal of urate-lowering therapy in gout is to lower and maintain serum urate levels at subsaturating levels in

order to prevent progressive joint damage resulting from flare recurrence and reduce deformity caused by tophus formation. Achievement of long-term serum urate levels at a minimum of <6.0 mg/dl or even lower at <5.0 mg/dl to durably improve the signs and symptoms of gout, including palpable and visible tophi detected on physical examination (16,22), is essential to preventing these pathologic processes. In the overall modified ITT population in the CARES trial, febuxostat was associated with lower serum urate levels than allopurinol at most study visits. To further investigate a potential association between febuxostat and increased deaths from CV causes, we analyzed participants from the CARES trial organized into subgroups of either patients who died from a CV-related cause or those who did not die from a CV-related cause. Baseline serum urate levels in the CARES trial patient population were higher in those who died from a CV-related cause than in those who did not. In the subgroup of patients who did not die from a CV-related cause, at most study visits those who received treatment with febuxostat had lower serum urate levels than those who received allopurinol. In the subgroup of patients who died from a CV-related cause there were no clear relationships between serum urate levels and treatment groups; however, interpretation of these findings is limited by the small number of patients (febuxostat n = 134 versus allopurinol n = 100).

In the overall modified ITT population, gout flare rates were similar in patients who received febuxostat and those who received allopurinol and decreased during the study period regardless of whether the patient died from a CV-related cause or not. Moreover, in patients who died of a CV-related cause, 94% and 98% of those who received febuxostat and those who received allopurinol, respectively, did not have a reported gout flare within 3 months of death. Across different post-baseline serum urate categories, regardless of treatment group, there was a trend toward a reduction in the rate of gout flare at lower serum urate levels.

The overall proportion of patients with ≥1 tophus at baseline was 20.8%, with similar proportions of patients in the febuxostat and allopurinol treatment groups. Tophus resolution rates were similar between treatment groups throughout the study period. Within the first 2 years, tophus resolution rates remained comparable between treatment groups, regardless of whether the patient died from a CV-related cause or not.

The links between serum urate levels, hyperuricemia, gout flares, and CVD are unclear. Some studies suggest that there is no link between increased serum urate levels and coronary heart disease (10). However, other studies indicate that increased serum urate levels may be associated with worse outcomes in patients with CVD and renal disease (6,7,9). One potential mechanism by which serum urate levels could lead to increased CV events is by impairing nitric oxide synthesis, resulting in vascular endothelial dysfunction that may lead to inflammation and prothrombosis (23). It is important to note the relatively high CV risk in patients from the CARES trial, which included patients with CV event rates of >10%, which is higher compared with other gout studies (17,24,25). The CARES trial previously demonstrated that the rates of predefined major adverse CV events with febuxostat treatment were noninferior to allopurinol (17). Findings from the present analyses show that very few patients experienced a gout flare within the 3-month period over which data were available closest to a cardiac event. Furthermore, there were no imbalances in nonfatal CV events, including acute coronary syndrome, ischemic stroke, or revascularization rates in the CARES trial (17). These findings suggest a lack of an association between an off-target effect of febuxostat on mechanisms such as inflammation and prothrombosis.

Our study had several strengths. First, it is the largest and longest clinical trial in the gout population. Second, it is the only trial enriched for CVD. Finally, there were frequent measurements of serum urate levels and clinical assessments for gout flares and tophi status during the trial. This allowed for examination of the relationships between serum urate levels and gout flares with CV outcomes in the entire cohort as well as each treatment assignment.

Limitations of this study have been discussed previously (17). First, there was no placebo arm in the trial, which could have characterized the incidence rates of CV events in the high-risk gout population; use of a placebo group was not feasible considering the planned length of the trial. Second, a large proportion of participants either discontinued participation in the study, did not complete follow-up, or discontinued treatment, making the complete analysis of all patients difficult. However, baseline demographic and clinical characteristics were comparable between treatment groups and between patients who either continued or discontinued treatment (17). Third, we cannot draw any conclusions between levels of inflammation markers in serum and death from CV causes in this study, as the former was not collected as part of the CARES study design. Additionally, it is important to note that the positive association between serum urate levels and death from CV causes seen in the overall population and in allopurinol treatment group, but not in the febuxostat treatment group, was based on post hoc analyses and should be considered exploratory. Further studies with large sample sizes are necessary to confirm these trends. Finally, rates of gout flares in clinical trials are difficult to capture accurately, despite the best efforts by site personnel (study coordinator, study nurse, or the investigator). Misclassification of gout flares may complicate the interpretation of data and potentially bias findings toward the null hypothesis.

In conclusion, in this new analysis of patients from the CARES trial, we found no relationships between death from CV causes and gout flares or tophus resolution in patients who received treatment with febuxostat or allopurinol. There were also no clear associations between serum urate levels and death from CV causes in patients who received treatment with febuxostat.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Saag had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Becker, White, Whelton, Hunt, Gunawardhana.

Acquisition of data. Saag, Becker, White, Whelton, Borer, Gorelick, Hunt, Castillo, Gunawardhana.

Analysis and interpretation of data. Saag, Becker, White, Whelton, Borer, Gorelick, Hunt, Castillo, Gunawardhana.

ROLE OF THE STUDY SPONSOR

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