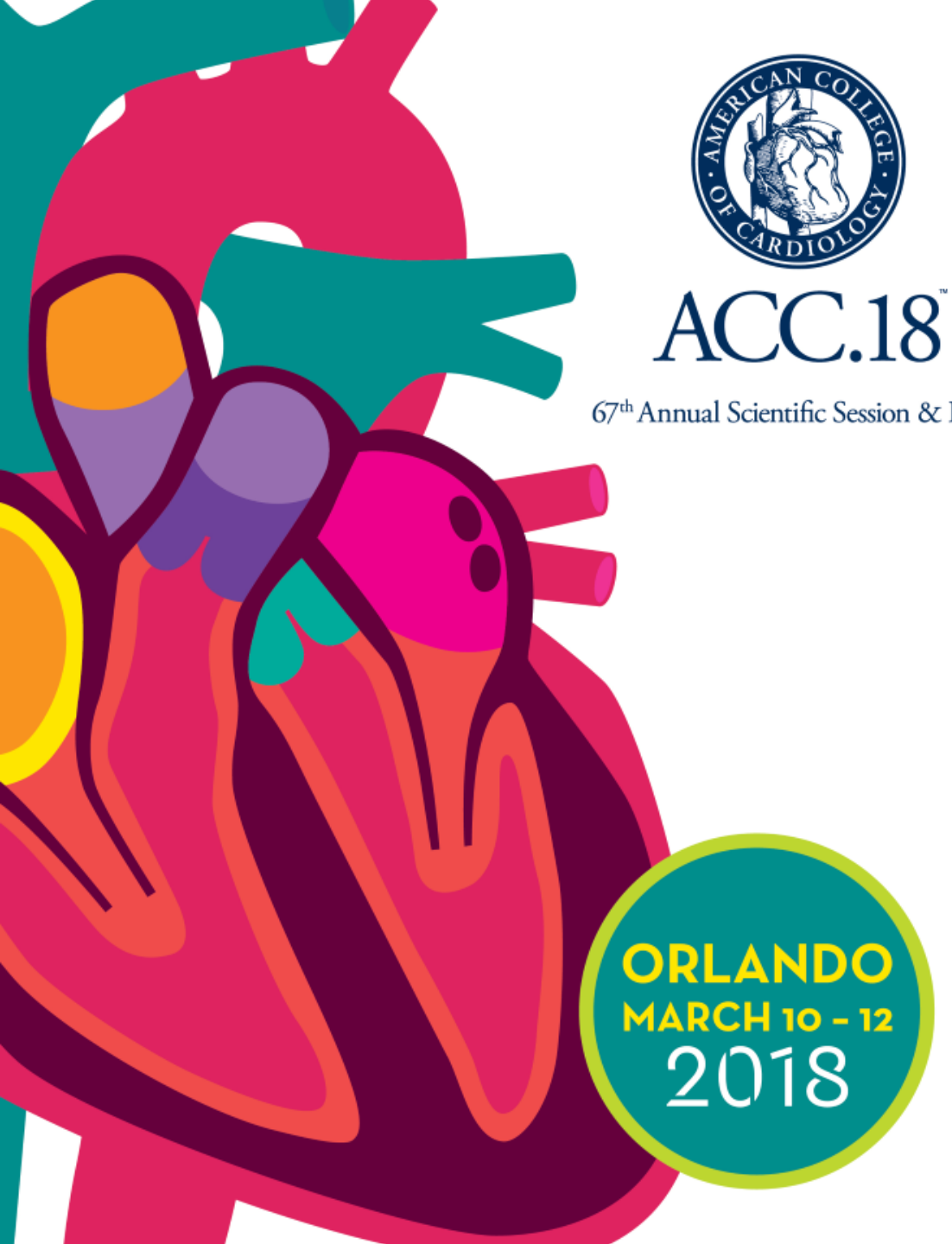

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CARDIOVASCULAR SAFETY OF FEBUXOSTAT OR ALLOPURINOL IN PATIENTS WITH GOUT AND CARDIOVASCULAR DISEASE (The CARES Trial)

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Background

- The risk of CV disease is elevated in people with gout. The mainstay of urate-lowering therapy in gout is the xanthine oxidase inhibitors
- **Allopurinol** is a purine analog xanthine oxidase inhibitor that has been approved for the treatment of gout since 1966
- **Febuxostat** is a non-purine xanthine oxidase inhibitor that was approved for the treatment of gout in 2009
- An imbalance in CV events without a known mechanism was observed during clinical development (0.74 vs 0.60 events per 100 patient-years for febuxostat vs allopurinol)
- This led to a post-marketing requirement by the FDA to conduct the **CARES** trial to evaluate the CV safety of febuxostat

CV, cardiovascular.

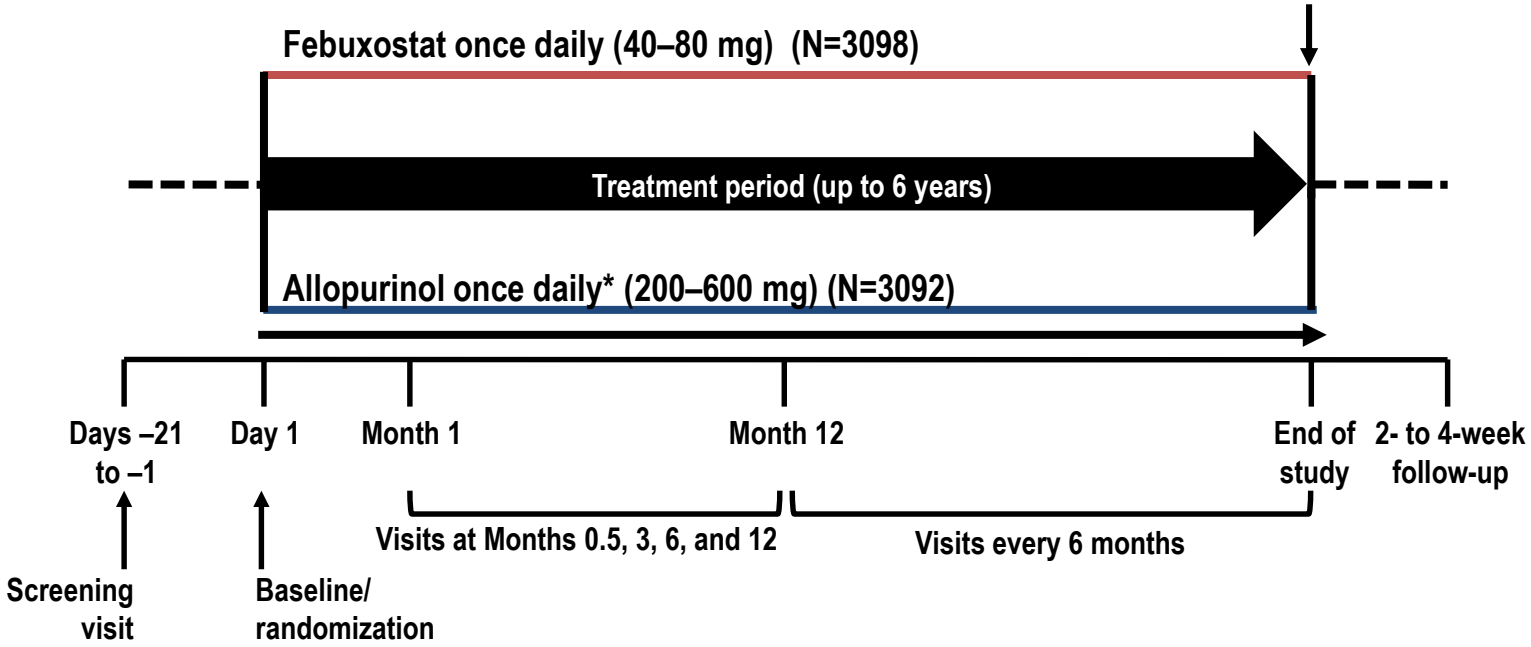
Objectives and Endpoints of CARES

- **Primary objective**: To demonstrate that major CV event rates with febuxostat are noninferior to allopurinol in patients with gout with CV disease
  - **Primary endpoint**: Composite of first occurrence of CV death, nonfatal MI, nonfatal stroke, and urgent revascularization for unstable angina
  - **Secondary endpoints**: Evaluation of time from randomization to the first occurrence of MACE:
    - Composite of CV death, nonfatal MI, nonfatal stroke
    - Other secondary endpoints: individual rates of CV death, nonfatal MI, or nonfatal stroke
    - Other endpoint: All-cause mortality

CV, cardiovascular; MACE, major adverse cardiovascular event; MI, myocardial infarction.

Study Design

- Randomized, double-blind, multicenter controlled study of febuxostat versus allopurinol in patients with gout and cardiovascular disease in the USA, Canada, and Mexico



*At randomization, patients were stratified according to renal function. After randomization, dose titration of allopurinol was made on the basis of renal function. Febuxostat did not require dose adjustment by renal function.

White WB, et al. *Am Heart J* 2012;164:14–20.

Study Patients

- Age ≥50 years old for males, ≥55 years old for females
- Diagnosis of gout based on American Rheumatism Association criteria
- Serum urate levels ≥7.0 mg/dL, or ≥6.0 mg/dL if flares or tophi present
- CV disease: Historical documentation of coronary, cerebrovascular, or peripheral arterial disease, or diabetes with small vessel disease
- Patients with unstable CV conditions, those with secondary hyperuricemia, or those with estimated creatinine clearance <30 mL/minute were excluded

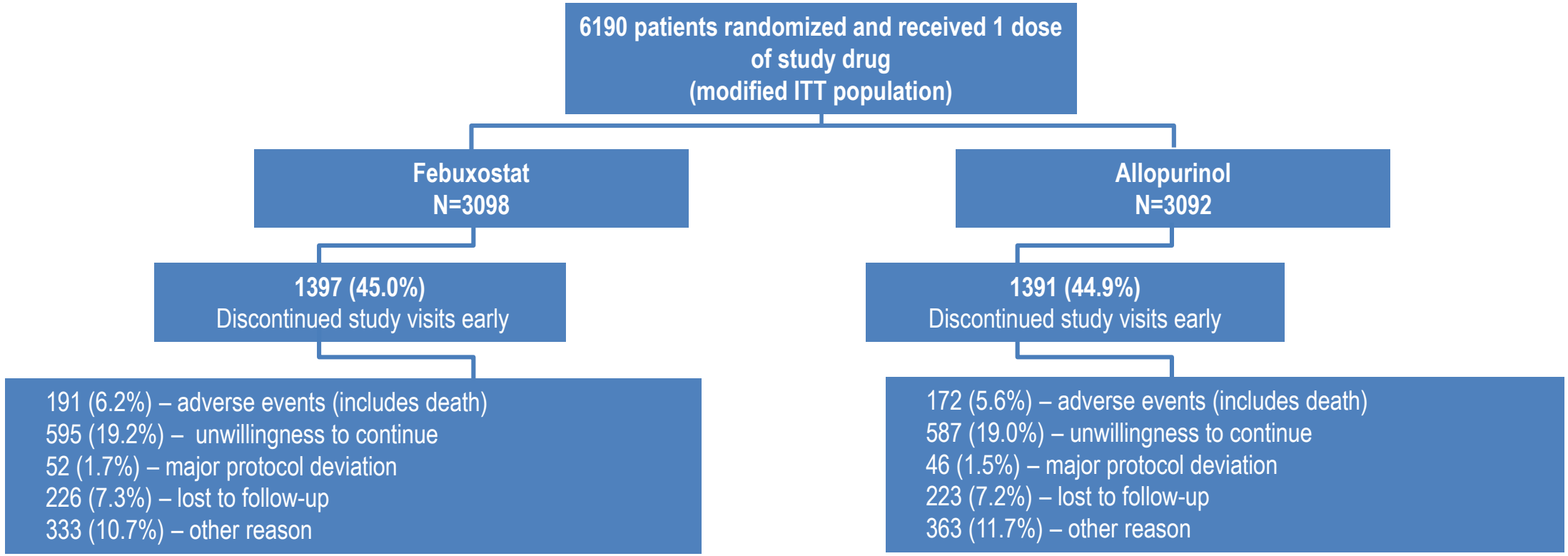
CV, cardiovascular.

Statistical Analyses

- **Primary endpoint**
  - Cox PH model of time to primary endpoint stratified by baseline renal function, based on the modified ITT population
  - One-sided 98.5% CI calculated for HR at final analysis
- **Interim analyses for primary endpoint** when 25%, 50%, and 75% of events were accrued
  - Lan-DeMets-O'Brien-Fleming-alpha spending function used to control overall one-sided significance level of 0.025
- **Noninferiority** concluded if upper bound of repeated CI for HR (febuxostat to allopurinol) <1.3
- **Secondary and major exploratory endpoints**
  - Cox PH model of time to endpoint stratified by baseline renal function with two-sided 95% CI for HR

CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; PH, proportional hazards.

Disposition of Patients



ITT, intention-to-treat.

Baseline Patient Characteristics

	Febuxostat (N=3098)	Allopurinol (N=3092)
Age		
Median, years	64.0	65.0
Patients ≥65 years, n (%)	1514 (48.9)	1586 (51.3)
Sex		
Male, n (%)	2604 (84.1)	2592 (83.8)
Race, n (%)		
White	2160 (69.7)	2140 (69.2)
Black	552 (17.8)	593 (19.2)
Asian	92 (3.0)	96 (3.1)
Native American	262 (8.5)	234 (7.6)
Kidney function (estimated creatinine clearance), n (%)		
Stages 1 and 2	1456 (47.0)	1459 (47.2)
Stage 3	1636 (52.8)	1631 (52.7)

Baseline Patient Characteristics (2)

	Febuxostat (N=3098)	Allopurinol (N=3092)
Duration of gout		
Mean, years	11.8	11.9
BMI		
Mean, kg/m^2	33.6	33.4
Serum urate		
Mean ± SD, mg/dL	8.7 ± 1.7	8.7 ± 1.7
Cardiovascular disease, n (%)		
Myocardial infarction	1197 (38.6)	1231 (39.8)
Stroke	460 (14.8)	410 (13.3)
Peripheral vascular disease	412 (13.3)	375 (12.1)
Diabetes with small vessel disease	1193 (38.5)	1213 (39.2)
Coronary revascularization	1129 (36.4)	1182 (38.2)

BMI, body mass index; SD, standard deviation.

Baseline Cardiovascular Therapies

	Febuxostat (N=3098)	Allopurinol (N=3092)
Concomitant medications at baseline, n (%)		
Antiplatelet agents Aspirin Thienopyridine	2397 (77.4) 1839 (59.4) 558 (18.0)	2473 (80.0) 1877 (60.7) 596 (19.3)
Lipid-lowering agents	2293 (74.0)	2281 (73.8)
β-blockers	1796 (58.0)	1834 (59.3)
Renin–angiotensin system blockers	2144 (69.2)	2187 (70.7)

Prior Urate-Lowering Therapies

	Febuxostat (N=3098)	Allopurinol (N=3092)
Prior urate-lowering therapies, n (%)		
All agents	1914 (61.8)	1914 (61.9)
Allopurinol	1738 (56.1)	1742 (56.3)
Febuxostat	134 (4.3)	130 (4.2)
Probenecid	37 (1.2)	36 (1.2)
Other	5 (0.2)	6 (0.2)

Final Titrated Doses of Study Drug to Achieve a Serum Urate <6 mg/dL

- Doses of febuxostat (not adjusted for renal function)
  - 40 mg – 61%
  - 80 mg – 39%
- Doses of allopurinol (adjusted for renal function)*
  - 200 mg – 22%
  - 300 mg – 45%
  - 400 mg – 25%
  - 500 mg – 4%
  - 600 mg – 4%

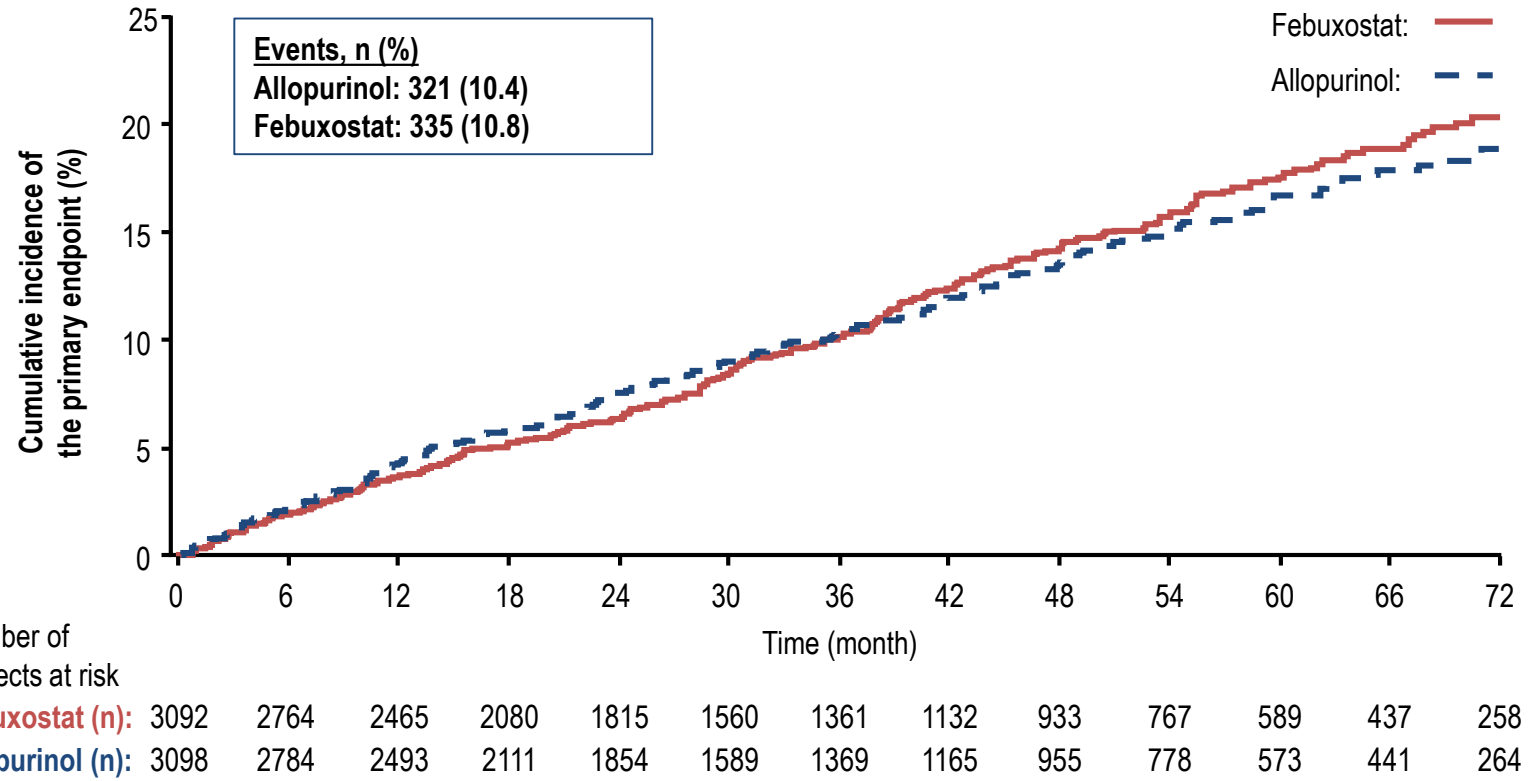
*Maximal doses of allopurinol were 600 mg for those with stage 1-2 chronic kidney disease and 400 mg for stage 3 chronic kidney disease. Median exposure for febuxostat was 728 days and for allopurinol was 719 days.

Changes in Biochemical Tests and Flare Rates

- The proportion of patients achieving serum urate levels of <6 mg/dL and <5 mg/dL was greater on febuxostat than on allopurinol
- Flare rates:
  - 0.68 per patient-year on febuxostat
  - 0.63 per patient-year on allopurinol
- No differences were observed between treatment groups throughout the trial for renal function, blood pressure, electrolytes, or lipids

Time to Primary Endpoint (CV Death, Nonfatal MI, Nonfatal Stroke, Urgent Revascularization for UA)

Modified ITT population; hazard ratio 1.03 (*one-sided repeated CI bound, 1.23)



*Using alpha=0.015.

CI, confidence interval; CV, cardiovascular; ITT, intention-to-treat; MI, myocardial infarction; UA, unstable angina.

Secondary Endpoints

Number (%)	Febuxostat (N=3098)	Allopurinol (N=3092)	Hazard ratio for febuxostat group (95% CI)
Composite of CV death, nonfatal MI, or nonfatal stroke	296 (9.6)	271 (8.8)	1.09 (0.92, 1.28)
CV death	134 (4.3)	100 (3.2)	1.34 (1.03, 1.73)*
Nonfatal MI	111 (3.6)	118 (3.8)	0.93 (0.72, 1.21)
Nonfatal stroke	71 (2.3)	70 (2.3)	1.01 (0.73, 1.41)
Urgent revascularization due to unstable angina	49 (1.6)	56 (1.8)	0.86 (0.59, 1.26)

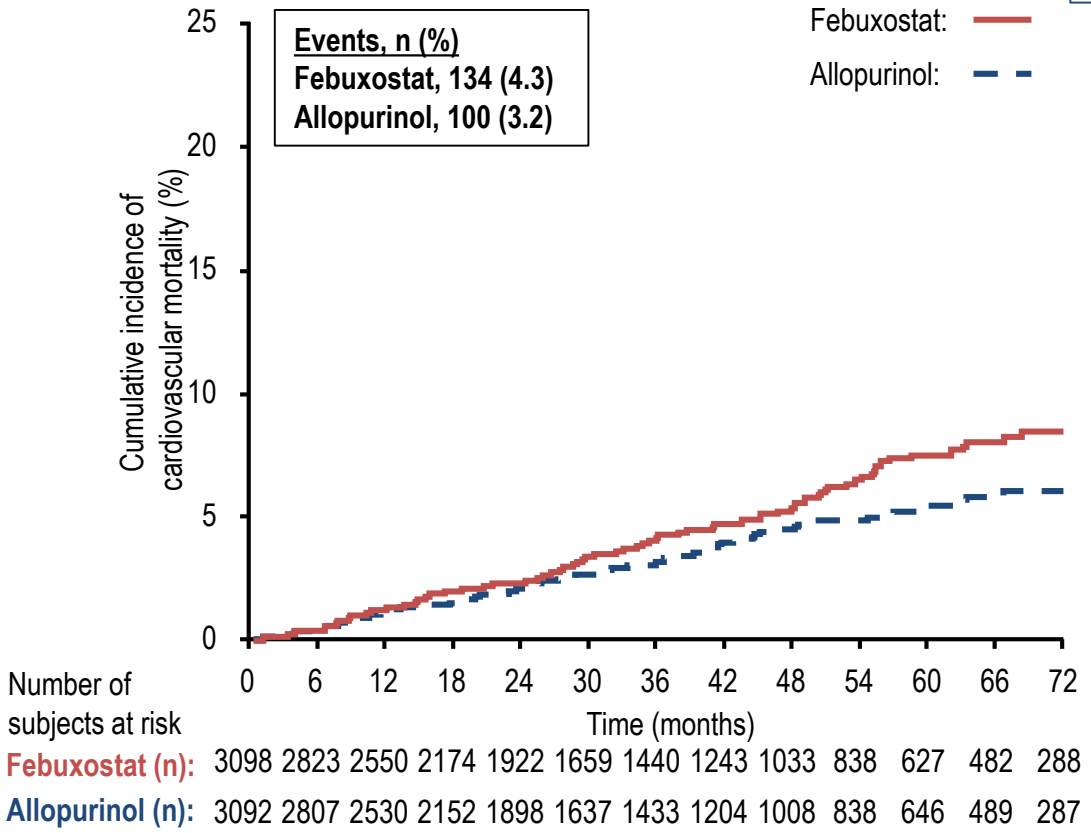
*P=0.034.
CI, confidence interval; CV, cardiovascular; MI, myocardial infarction.

Mortality Endpoints

Events of adjudicated sudden cardiac death
Febuxostat, 83 (2.7%)
Allopurinol, 56 (1.8%)

Cardiovascular Mortality

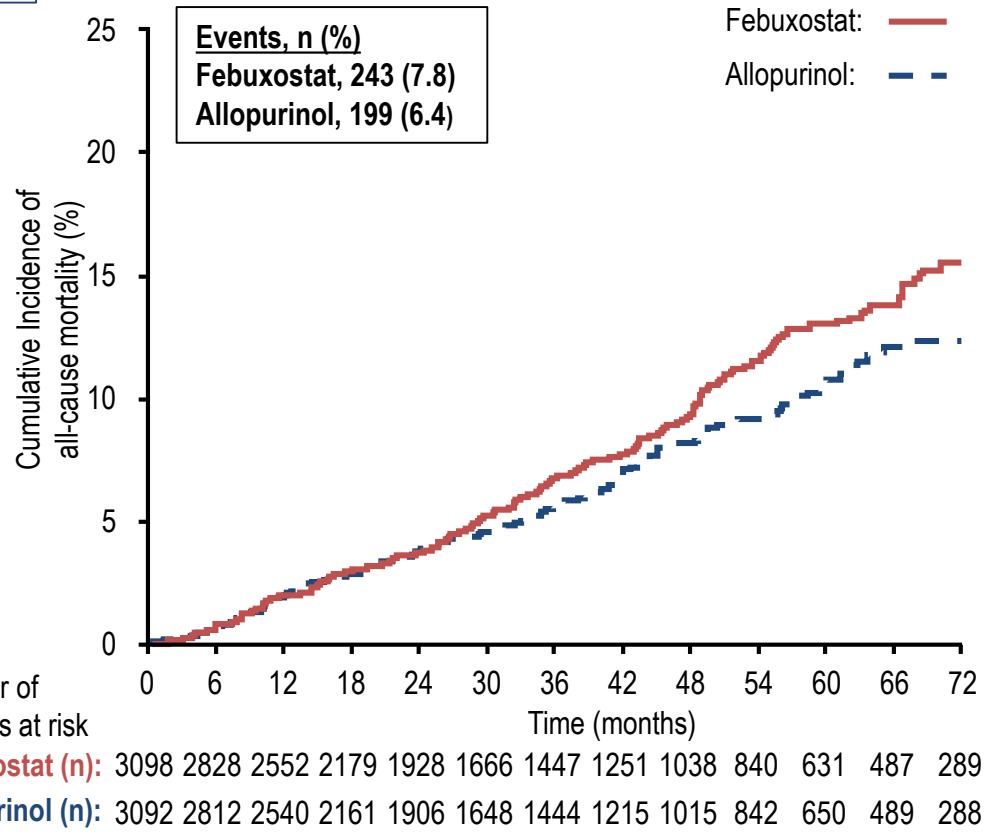
Modified ITT; hazard ratio 1.34 (95% CI 1.03, 1.73)



Number of subjects at risk													
Febuxostat (n):	3098	2823	2550	2174	1922	1659	1440	1243	1033	838	627	482	288
Allopurinol (n):	3092	2807	2530	2152	1898	1637	1433	1204	1008	838	646	489	287

All-Cause Mortality

Modified ITT; hazard ratio 1.22 (95% CI 1.01, 1.47)



Number of subjects at risk													
Febuxostat (n):	3098	2828	2552	2179	1928	1666	1447	1251	1038	840	631	487	289
Allopurinol (n):	3092	2812	2540	2161	1906	1648	1444	1215	1015	842	650	489	288

CI, confidence interval; ITT, intent-to-treat.

On-Treatment Analysis*

Number (%)	Febuxostat (N=3098)	Allopurinol (N=3092)	Hazard ratio for febuxostat group (95% CI)
Primary endpoint	242 (7.8)	238 (7.7)	1.00 (0.82, 1.22)**
CV death	62 (2.0)	41 (1.3)	1.49 (1.01, 2.22)†
Nonfatal MI	93 (3.0)	106 (3.4)	0.87 (0.66, 1.34)
Nonfatal stroke	59 (1.9)	62 (2.0)	0.94 (0.66, 1.34)
Urgent revascularization due to unstable angina	45 (1.5)	44 (1.4)	1.00 (0.66, 1.52)
Death from any cause	92 (3.0)	72 (2.3)	1.26 (0.93, 1.72)

*Prespecified: On drug and up to 30 days off drug; **97.0% CI; †P=0.047.
CI, confidence interval; CV, cardiovascular; MI, myocardial infarction.

All-Cause Mortality Incorporating Known Vital Status

Number (%)	Febuxostat (N=3098)	Allopurinol (N=3092)	Hazard ratio for febuxostat group (95% CI)
Intention-to-treat analysis	332 (10.7)	309 (10.0)	1.09 (0.94, 1.28)
On drug	36 (1.2)	28 (0.9)	1.27 (0.77, 2.08)
On drug and within 30 days of drug discontinuation	94 (3.0)	74 (2.4)	1.25 (0.92, 1.70)

CI, confidence interval.

Subgroup Analyses for Cardiovascular Mortality

Baseline characteristic	Febuxostat (N=3098)	Allopurinol (N=3092)	RR (95% CI) febuxostat vs allopurinol	P value for heterogeneity
NSAID use, % (n/N)				
Yes	5.7 (33/579)	2.5 (16/650)	2.32 (1.29, 4.16)	**0.036**
No	4.0 (101/2519)	3.4 (84/2442)	1.17 (0.88, 1.55)	
Low-dose aspirin use (<325 mg)				
Yes	3.6 (45/1239)	3.9 (48/1222)	0.92 (0.62, 1.38)	**0.019**
No	4.0 (101/2519)	3.4 (84/2442)	1.17 (0.88, 1.55)	
Colchicine use during study				
Yes	5.0 (35/699)	2.3 (16/694)	2.17 (1.21, 3.89)	0.062
No	4.1 (99/2399)	3.5 (84/2398)	1.18 (0.89, 1.57)	

CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drug; RR, relative risk.

Summary

- Rates of major adverse CV events on febuxostat were noninferior to allopurinol in patients with gout and CV disease
- All-cause mortality was greater on febuxostat versus allopurinol due to an imbalance in CV deaths, particularly sudden cardiac death
- These observations occurred in the following context:
  - Urate lowering on febuxostat was greater than allopurinol
  - Similar gout flare rates between groups during the trial
  - No differences between groups for serum potassium, lipids, glucose, creatinine, or blood pressure
  - No preclinical signals for cardiac toxicity observed with febuxostat
  - No differences in the rates of major nonfatal cardiovascular events

CV, cardiovascular.

Summary (2)

- There was a high rate of study discontinuation (45%)
- Rates of withdrawal were similar in the febuxostat and allopurinol groups
- Sensitivity analysis (on treatment plus 30 days within discontinuation of study drug) showed:
  - Similar rates of the primary endpoint on febuxostat and allopurinol, comparable with the modified ITT analysis
  - Higher rates of all-cause and CV death on febuxostat versus allopurinol were also comparable with the modified ITT analysis
  - The majority of deaths occurred off drug
- Further safety analyses from the trial are ongoing to evaluate the unexpected mortality findings in CARES

CV, cardiovascular; ITT, intent-to-treat.

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ORIGINAL ARTICLE

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