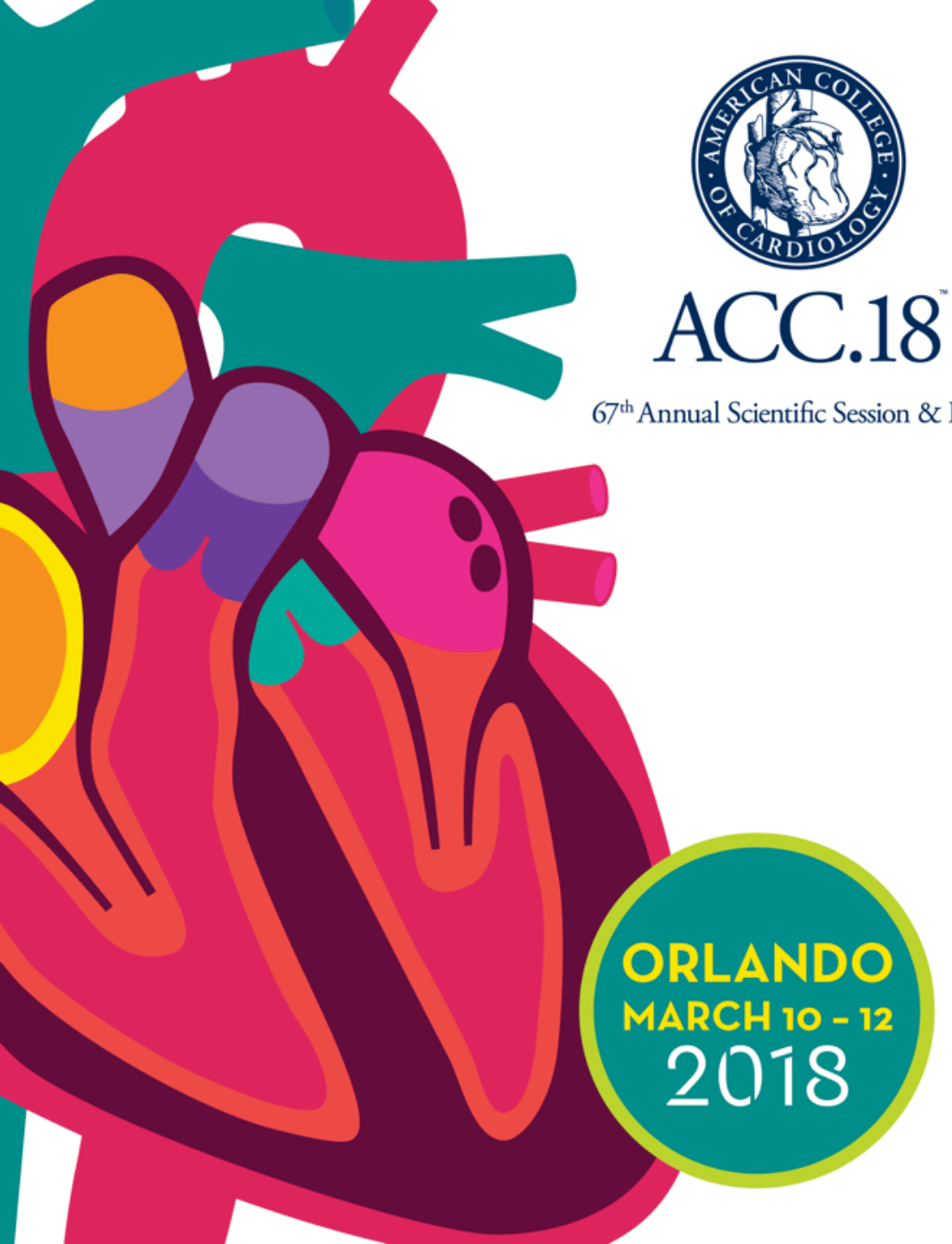

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CARDIOVASCULAR SAFETY OF FEBUXOSTAT OR ALLOPURINOL IN PATIENTS WITH GOUT AND CARDIOVASCULAR DISEASE (The CARES Trial)

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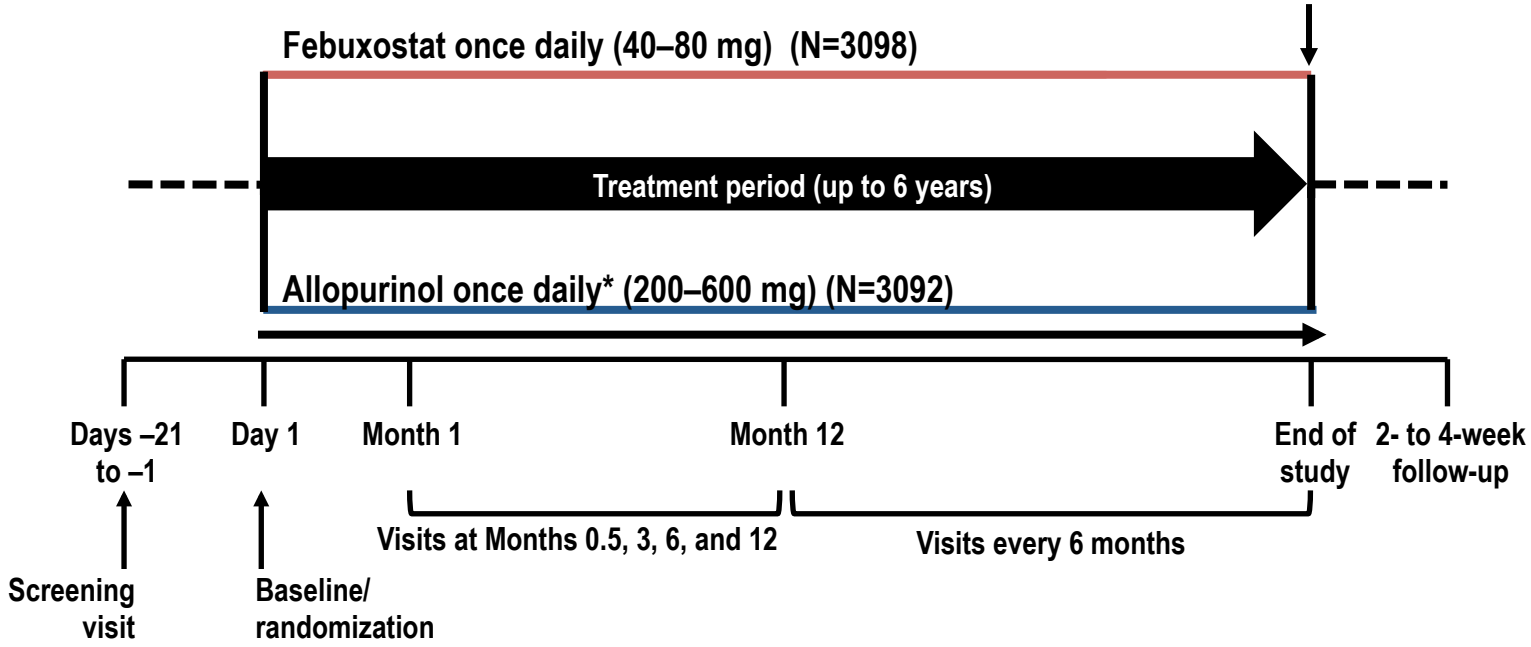
Objectives and Endpoints of CARES

- **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

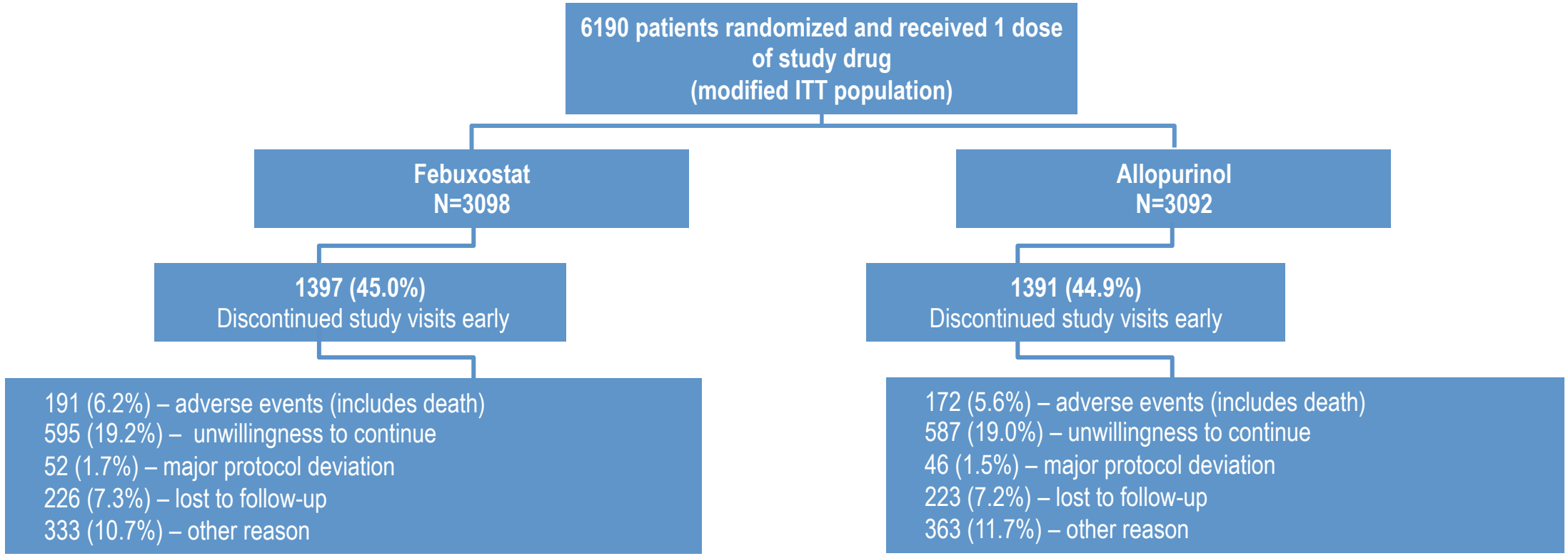
- Randomized, double-blind, multicenter controlled study of febuxostat versus allopurinol in patients with gout and cardiovascular disease in the USA, Canada, and Mexico



*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.

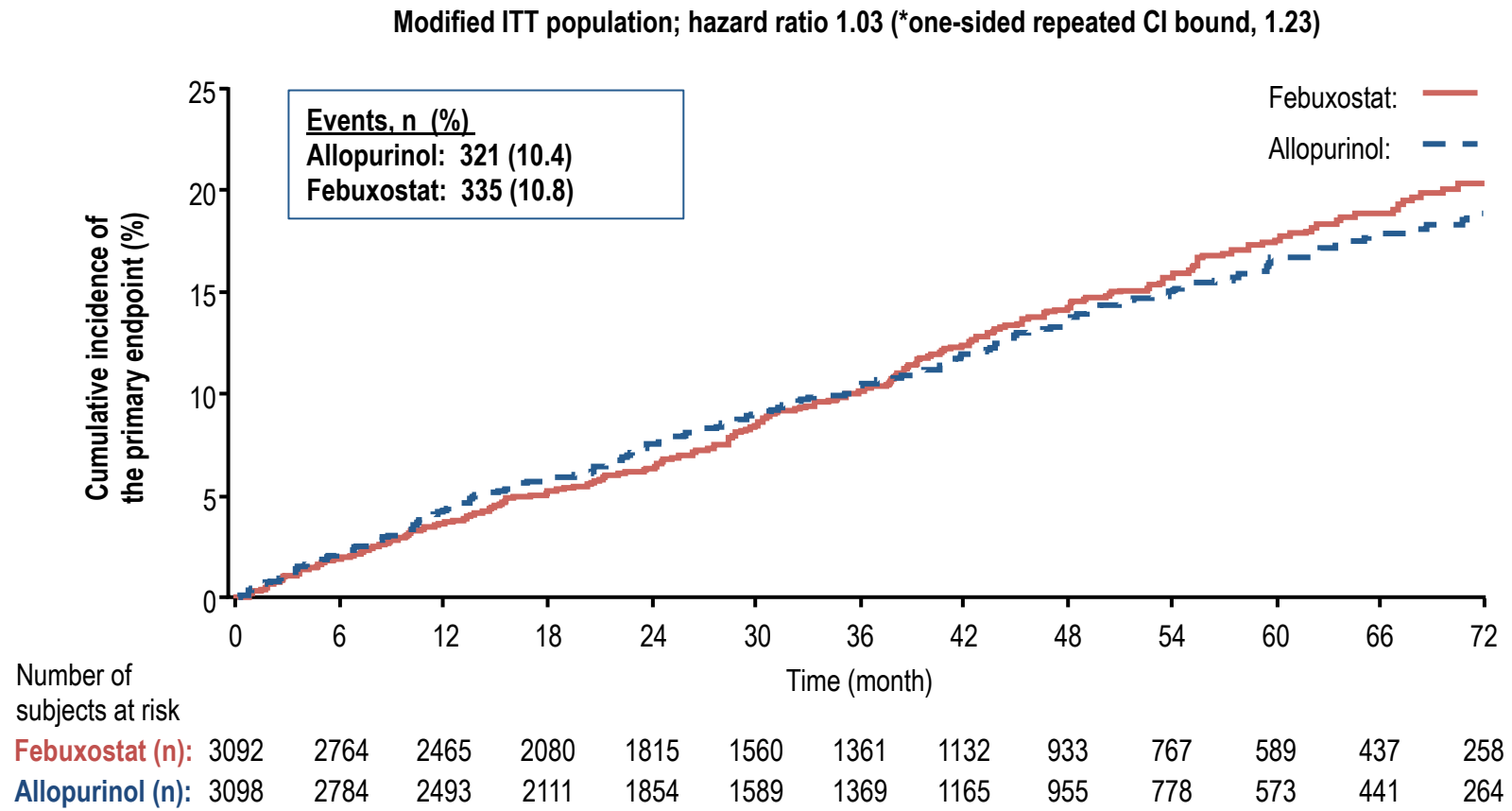
White WB, et al. *Am Heart J* 2012;164:14–20.

Disposition of Patients



ITT, intention-to-treat.

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



*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)

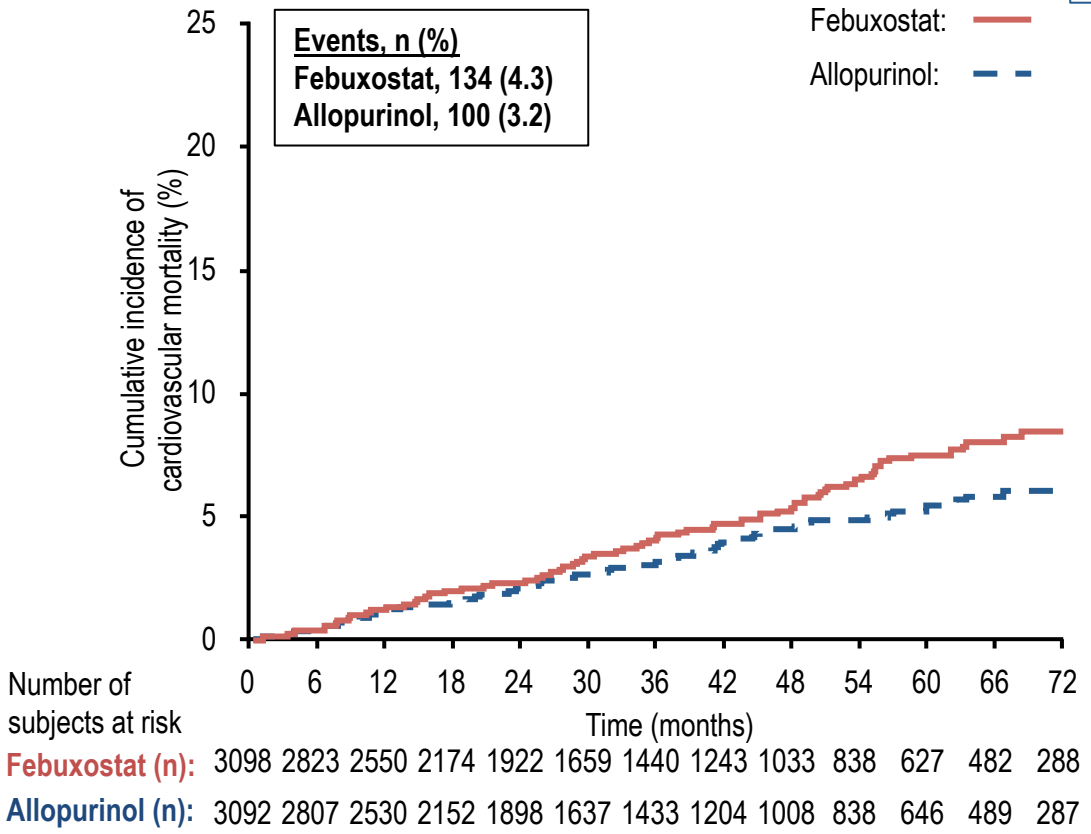
*P=0.034.
CI, confidence interval; CV, cardiovascular; MI, myocardial infarction.

Mortality Endpoints

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

Cardiovascular Mortality

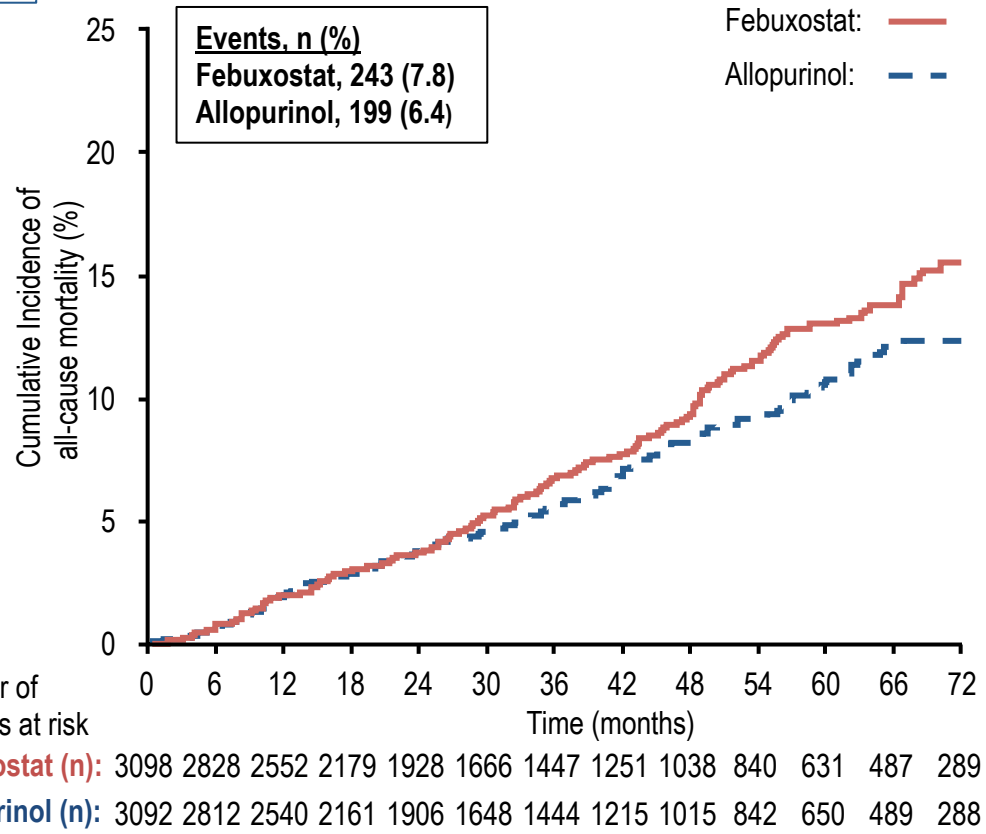
Modified ITT; hazard ratio 1.34 (95% CI 1.03, 1.73)



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.

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.