Global collaborative research through OHDSI network:

Febuxostat vs Allopurinol

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Background: Pharmacologic treatment in gout

- Febuxostat is widely used urate-lowering agent because it is more effective than allopurinol to lower serum urate in patients with gout.
- Furthermore, febuxostat can be used without dosage adjustment in chronic kidney disease.

Background: Recent study about cardiovascular safety of febuxostat vs allopurinol in gout

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

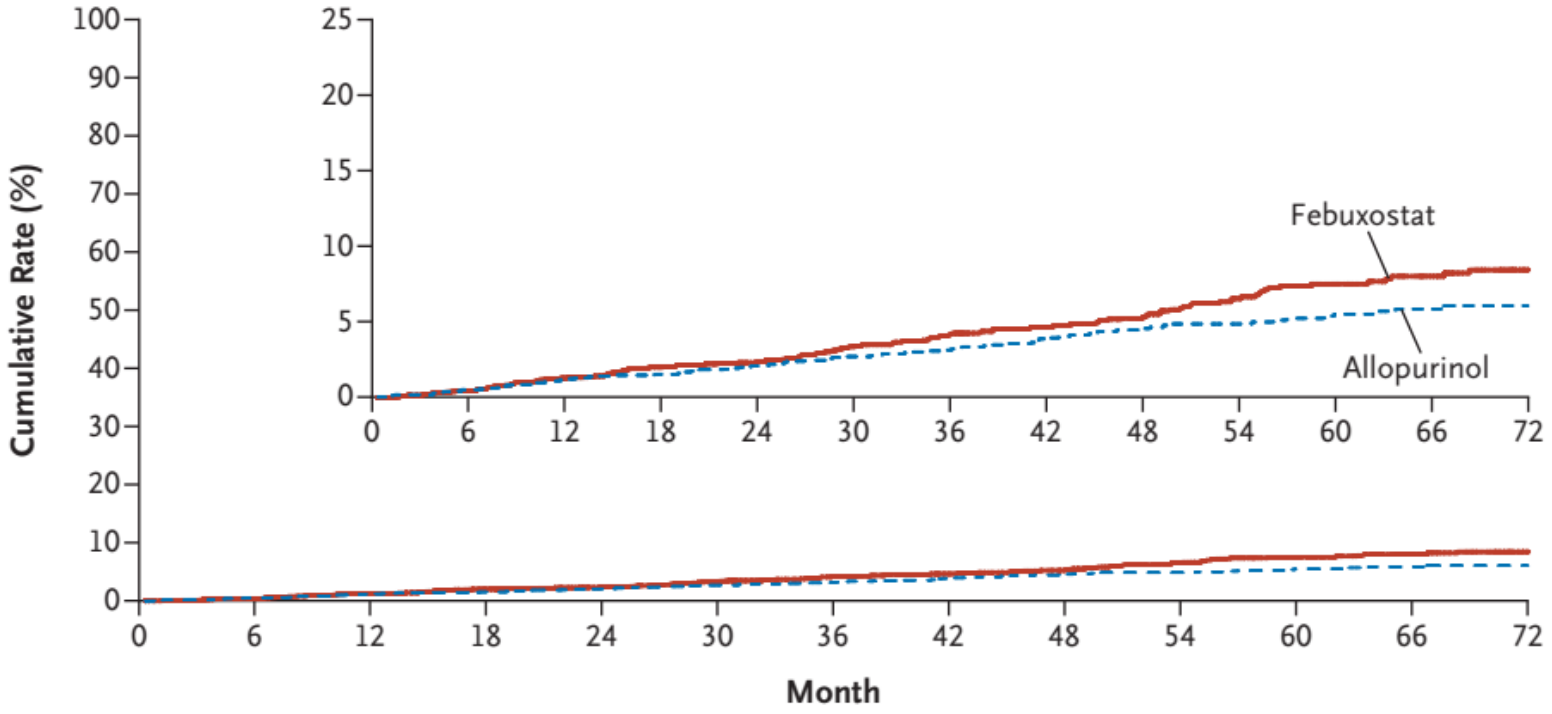
Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout

William B. White, M.D., Kenneth G. Saag, M.D., Michael A. Becker, M.D., Jeffrey S. Borer, M.D., Philip B. Gorelick, M.D., Andrew Whelton, M.D., Barbara Hunt, M.S., Majin Castillo, M.D., and Lhanoo Gunawardhana, M.D., Ph.D., for the CARES Investigators*

White et al., *NEJM*, Mar 2018

Background: Recent study about cardiovascular safety of febuxostat vs allopurinol in gout

B Cardiovascular Mortality



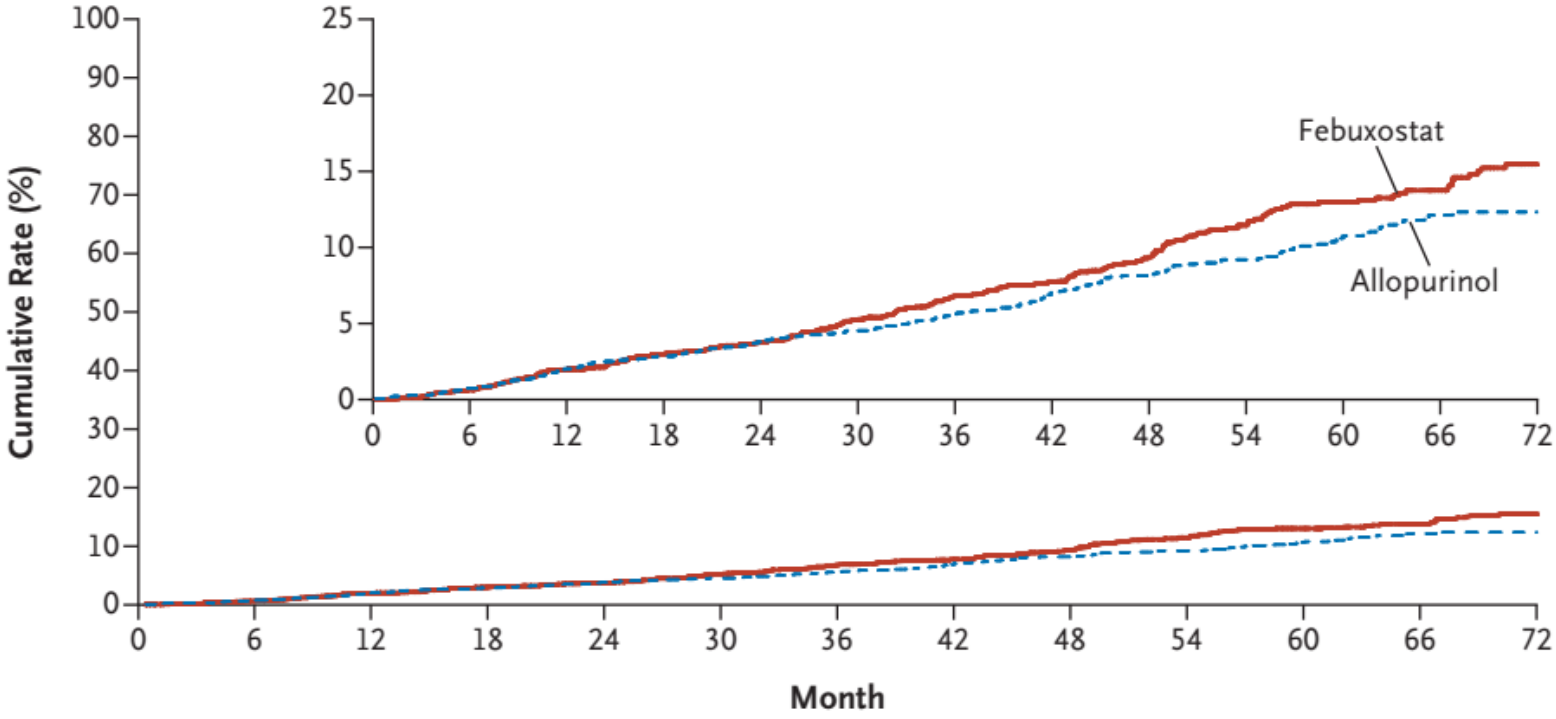
No. at Risk

Febuxostat	3098	2823	2550	2174	1922	1659	1440	1243	1033	838	627	482	288
Allopurinol	3092	2807	2530	2152	1898	1637	1433	1204	1008	838	646	489	287

White et al., *NEJM*, Mar 2018

Background: Recent study about cardiovascular safety of febuxostat vs allopurinol in gout

C All-Cause Mortality



No. at Risk

Febuxostat	3098	2828	2552	2179	1928	1666	1447	1251	1038	840	631	487	289
Allopurinol	3092	2812	2540	2161	1906	1648	1444	1215	1015	842	650	489	288

White et al., *NEJM*, Mar 2018

Event between febuxostat and allopurinol

Table 3. Events That Occurred during Treatment or within 30 Days after Discontinuation of Treatment.*

End Point	Febuxostat (N = 3098)	Allopurinol (N = 3092)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)			
Primary end point: composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or urgent revascularization due to unstable angina	242 (7.8)	238 (7.7)	1.00 (0.82–1.22)†	0.99
Secondary end points				
Cardiovascular death	62 (2.0)	41 (1.3)	1.49 (1.01–2.22)	0.047
Nonfatal myocardial infarction	93 (3.0)	106 (3.4)	0.87 (0.66–1.15)	0.32
Nonfatal stroke	59 (1.9)	62 (2.0)	0.94 (0.66–1.34)	0.72
Urgent revascularization for unstable angina	45 (1.5)	44 (1.4)	1.00 (0.66–1.52)	0.98
Composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke	205 (6.6)	200 (6.5)	1.01 (0.83–1.22)	0.93
Death from any cause	92 (3.0)	72 (2.3)	1.26 (0.93–1.72)	0.14

* This analysis was prespecified in the statistical analysis plan.
† The 97% confidence interval is provided here.

White et al., *NEJM*, Mar 2018

The cause of CV death in CARES

Table S7. Adjudicated Causes of Cardiovascular Death

	Febuxostat (N=3098) n (%)	Allopurinol (N=3092) n (%)
Cardiovascular Deaths (total)	**134 (4.3)**	**100 (3.2)**
Sudden cardiac death	83 (2.7)	56 (1.8)
Death due to heart failure	20 (0.6)	13 (0.4)
Death due to stroke	8 (0.3)	11 (0.4)
Death due to MI	11 (0.4)	6 (0.2)
Death due to arrhythmia	7 (0.2)	9 (0.3)
Death due to valvular heart disease	3 (<0.1)	2 (<0.1)
Death due to heart and respiratory failure	1 (<0.1)	1 (<0.1)
Death due to CV hemorrhage (anticoagulation related)	0	1 (<0.1)
Death due to peripheral arterial disease	0	1 (<0.1)
Other CV death (aortic aneurysm rupture)	1 (<0.1)	0

White et al., *NEJM*, Mar 2018

AIM

- Head-to-head comparison of the sudden cardiac death risk between febuxostat and allopurinol across OHDSI network

Method: Study Population

All subjects will be included who meet the following criteria (note: the index date is the start of the first exposure to febuxostat or allopurinol) :

- Exposure to febuxostat (treatment) or allopurinol (comparator) more than 30 days
- A diagnose of gout disorder on within 30 months prior to the index date
- No diagnosis of the myeloproliferative disorder or primary malignant neoplasm of bone marrow preceding the index date
- No diagnosis of the xanthinuria preceding the index date
- Without other uricosuric drug within preceding 1 year

https://github.com/OHDSI/StudyProtocolSandbox/tree/master/FebuxostatVsAllopurinolCVD

Method: Study Population

Primary endpoint: Sudden Cardiac Death

- Defined by diagnosis code for sudden cardiac death or ventricular fibrillation and flutter

Secondary endpoint

- All-cause mortality
- Hospitalized acute myocardial infarction
- Hospitalized heart failure
- Hospitalized stroke
- Drug hypersensitivity: occurrence of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), or drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome
- Gout flare: Emergency room visit with drug for gout flare or procedure for gout flare

https://github.com/OHDSI/StudyProtocolSandbox/tree/master/FebuxostatVsAllopurinolCVD

Method: Statistical Analysis

- Time-at-risk: **From 1 day after index date to 30 days after termination of the drug of interest**. Maximum of 30-day gap was allowed between drug exposures.
- Large-scale Propensity score matching:
- Sensitivity analyses include:
  - No PS model
  - Using stratification based on PS with ten equally-sized strata.
  - Variable ratio matching on the PS.
- All analyses will be repeated using an intent-to-treat risk window definition, which starts on treatment initiation, and ends when observation ends.
- Because PS between groups have not been matched because of small sample size, only results without PS matching are shown

https://github.com/OHDSI/StudyProtocolSandbox/tree/master/FebuxostatVsAllopurinolCVD

Method: Data sources

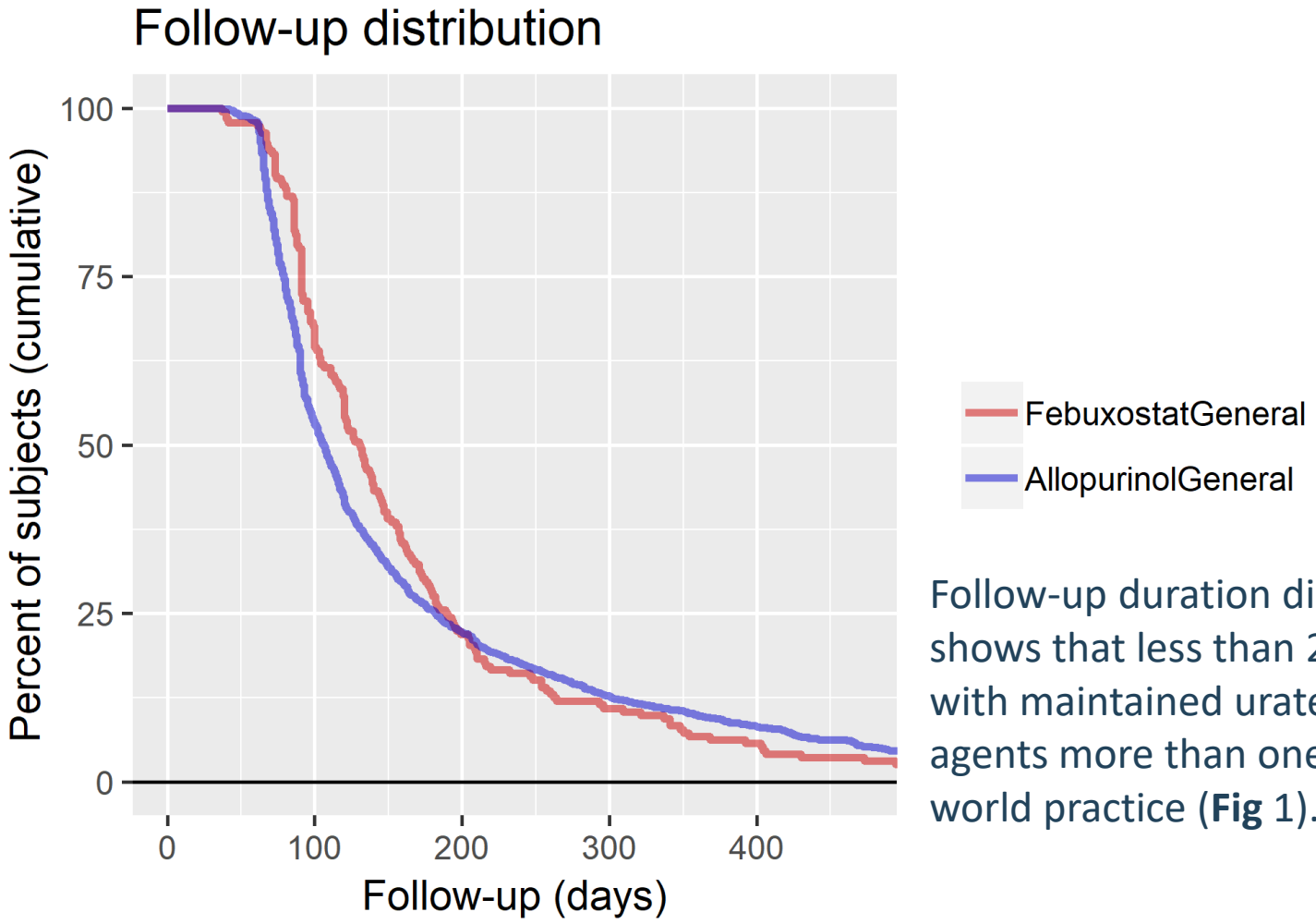
- Korea
  - NHIS-national sample cohort (**NHIS-NSC**) DB
    - 1M patients, 2002-2013
    - Febuxostat was adopted in Korea since 2013

Lee et al., *Int J Epidemiol.* 2016

Results: Baseline characteristics

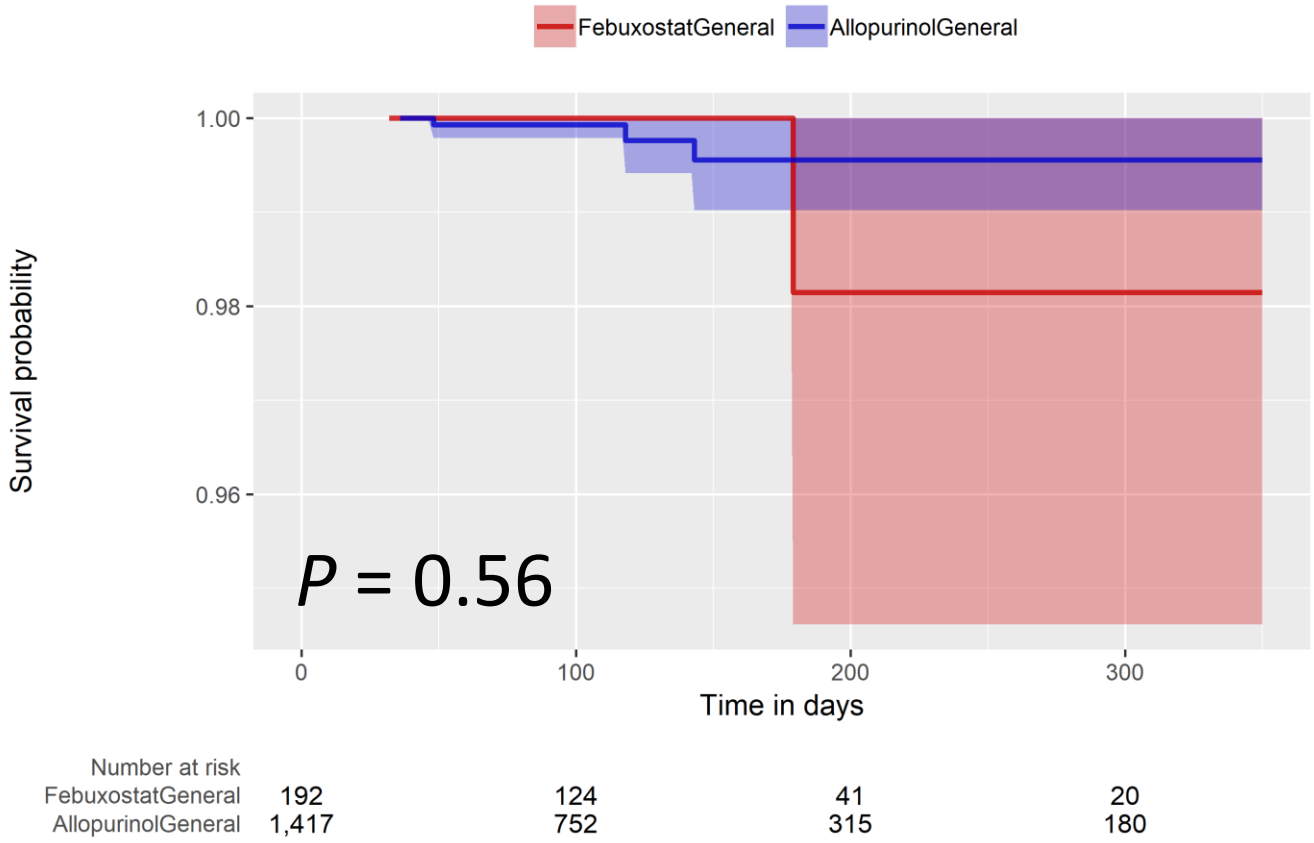
Covariates	Febuxostat, % (n=192)	Allopurinol, % (n=1423)	Standardized difference
Age group			
35-39	8.3	8.1	0.01
40-44	10.4	9.0	0.05
45-49	12.5	9.9	0.08
50-54	12.5	12.7	-0.01
55-59	7.8	11.7	-0.13
60-64	8.3	9.0	-0.02
65-69	8.9	8.5	0.01
70-74	9.4	8.7	0.02
75-79	7.3	6.0	0.05
Female	9.4	12.8	-0.11
Myocardial infarction	1.6	1.7	-0.01
Cerebrovascular accident	0.5	1.5	-0.10
Heart failure	0.6	0.7	-0.05
Hypertension	56.3	51.2	0.10
Peripheral vascular disease	27.1	22.9	-0.03
Chronic renal failure	11.5	6.1	0.19

Drug continuation period



Follow-up duration distribution shows that less than 20% of patients with maintained urate-lowering agents more than one year in real-world practice (**Fig** 1).

Risk of sudden cardiac death without PS matching



Sudden cardiac death occurred more in febuxostat compared to allopurinol group. The hazard ratio was not significantly different between groups (HR = 2.1, 95% CI = 0.10-16.5)

Result: Risk of secondary endpoints without PS matching

Outcome	Febuxostat		Allopurinol		Hazard ratio
	Patient	Event	Patient	Events	
Overall mortality	192	<5	1423	15	0.52
Acute myocardial infarction	188	<5	1378	<5	0.32
Heart failure	155	<5	1197	24	0.32
Stroke	183	<5	1324	12	0.32
Gout flare	182	<5	1383	11	1.35
Drug hypersensitivity	192	<5	1422	<5	NA

Summary

- This is inconclusive study because of small sample size
- Please join this study!
  - applegna@gmail.com
  - https://github.com/OHDSI/OhdsiStudies
  - https://github.com/chandryou/FebuxostatVsAllopurinolCVD


Thank You
for your time