Febuxostat for Cerebral and CaRdiorenovascular Events PrEvEntion StuDy (FREED)

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Declaration of interest

- Others (This study was funded by a grant from Teijin Pharma Limited, but the sponsor had no involvement in the planning, implementation, analysis, or interpretation of study results.)

Background -1-

- Urate-lowering therapy with anti-hyperuricemic drugs can prevent the recurrence of urate deposition–related diseases.

(Perez-Ruiz F et al. *Arthritis Rheum* 2002)

- Hyperuricemia may contribute to the development and progression of cerebrocardiovascular diseases and mortality.

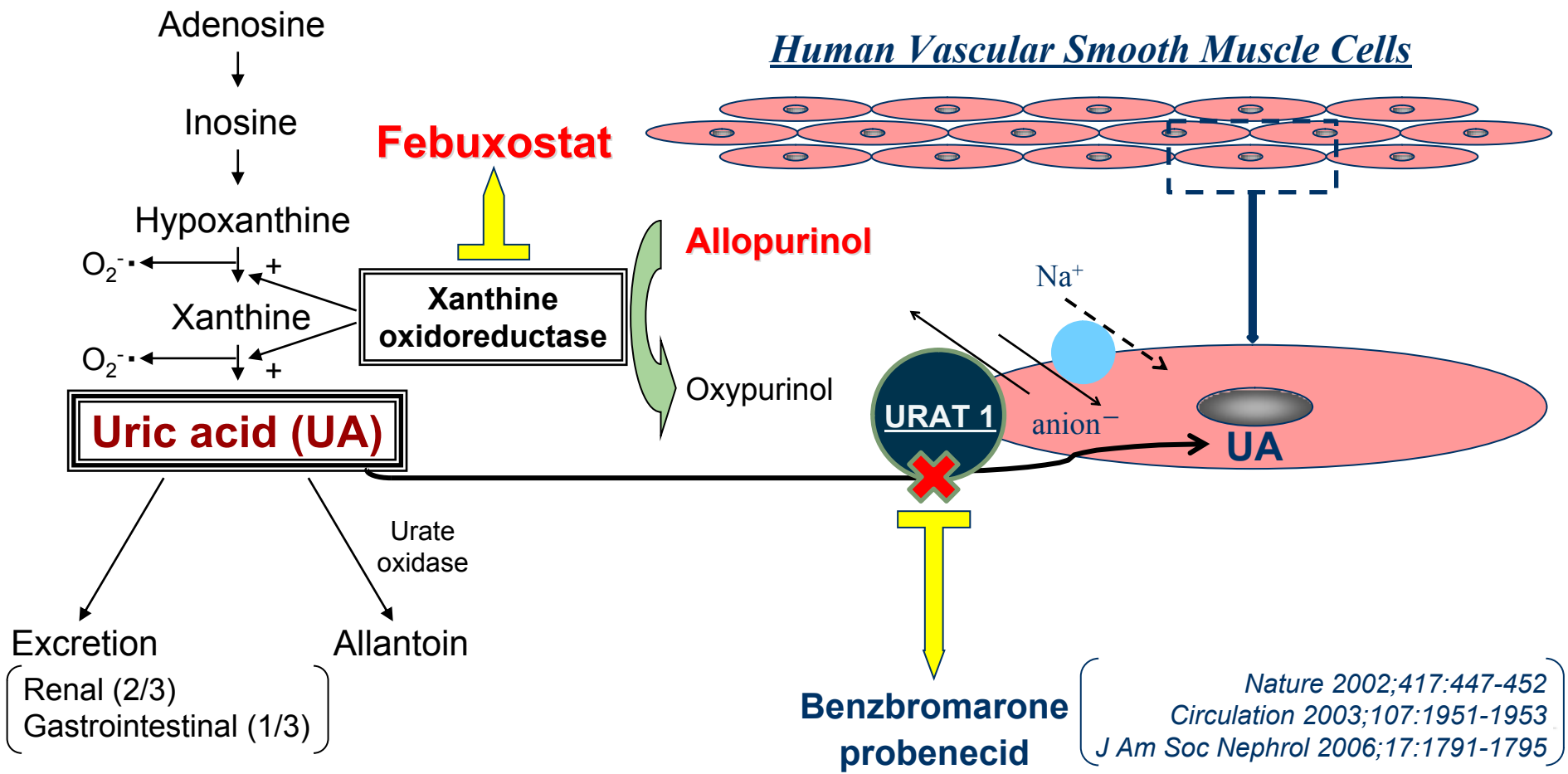
(Kojima S, et al. *Am J Cardiol* 2005)

(Li M, et al. *Sci Rep* 2016)

- Febuxostat approved in 2011 in Japan has a more potent serum uric acid–lowering effect compared with that of allopurinol.

(Kamatani N, et al. *J Clin Rheumatol* 2011)

Production and Metabolism of Uric Acid



Nature 2002;417:447-452
Circulation 2003;107:1951-1953
J Am Soc Nephrol 2006;17:1791-1795

Background -2-

- The Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) trial revealed that all-cause mortality and cardiovascular mortality were higher with febuxostat treatment than with allopurinol treatment in gout patients with cardiovascular disease.

(White WB, et al. *N Engl J Med* 2018)

- It remains to be elucidated whether the mortality results of the CARES trial are due to beneficial effects of allopurinol or deleterious effects of febuxostat.

(Choi H, et al. *Arthritis Rheumatol* 2018)

Aim

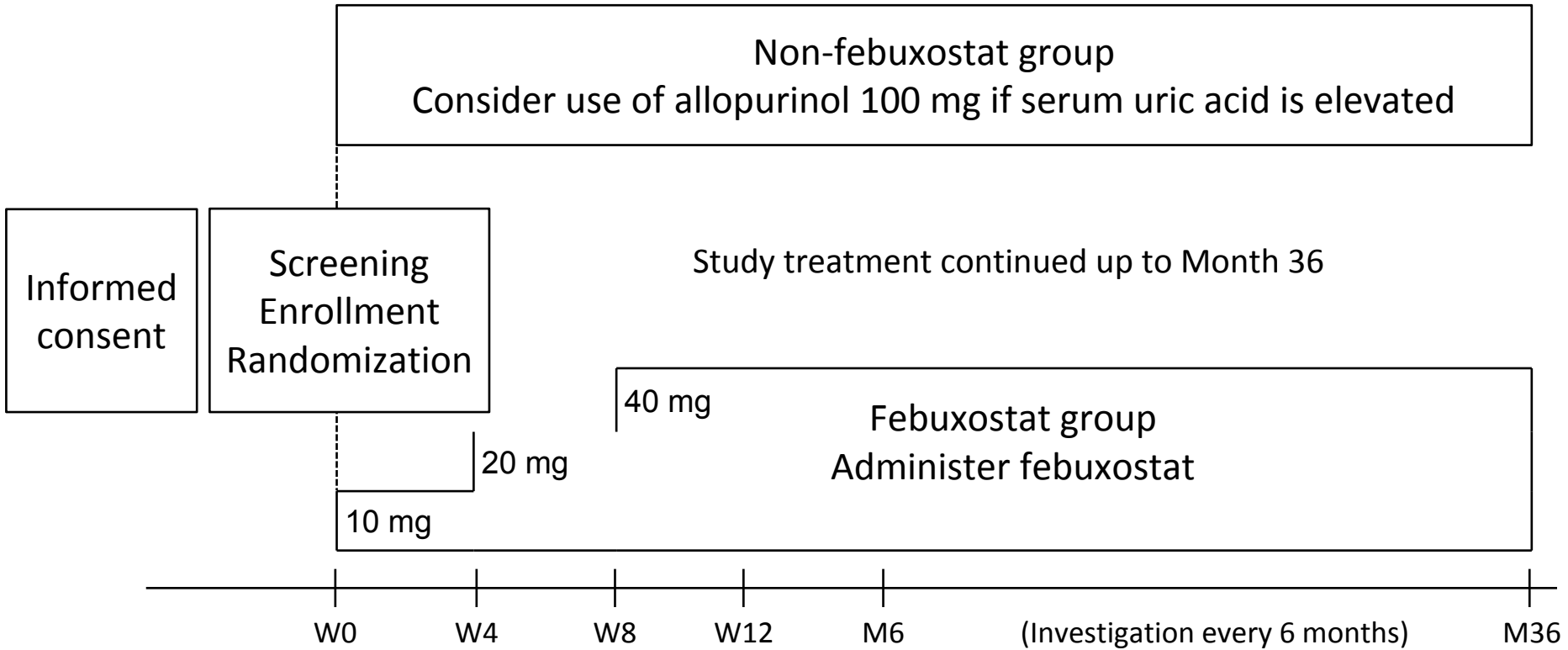
- The Febuxostat for Cerebral and CaRdiorenovascular Events PrEvEntion StuDy (FREED) was conducted to compare the occurrence of cerebral, cardiovascular, and renal events in elderly patients with hyperuricemia at risk for cerebral or cardiorenovascular disease treated with febuxostat and those treated with conventional therapy.

Study Design -1-

- Design
  - Multicenter, prospective, randomized open-label, blinded end point (PROBE), two-arm parallel treatment groups study
- Subjects
  - Elderly patients aged 65 years or older with hyperuricemia (serum uric acid level >7.0 to ≤9.0 mg/dL) who had one or more risks for cerebral, cardiovascular, or renal disease
    a. History of active hypertension
    b. History of active type 2 diabetes mellitus
    c. Renal disorder (eGFR ≥30 to <60 mL/min/1.73 m^2) within 3 months prior to enrollment
    d. History of cerebrocardiovascular disease occurring >3 months prior to enrollment

(Kojima S, et al. *J Cardiol* 2017;69:169−75)

Study Design -2-



Lifestyle modification for management of hyperuricemia in all patients

(Kojima S, et al. *J Cardiol* 2017;69:169–75)

End Point -1-

- Primary composite end point
  - (1) Death due to cerebral or cardiorenal vascular disease
  - (2) New or recurring cerebrovascular disease (stroke [cerebral hemorrhage, cerebral infarction, subarachnoid hemorrhage, stroke of unknown type], transient ischemic attack)
  - (3) New or recurring non-fatal coronary artery disease (myocardial infarction, unstable angina)
  - (4) Cardiac failure requiring hospitalization
  - (5) Arteriosclerotic disease requiring treatment (aortic aneurysm, aortic dissection, and arteriosclerosis obliterans)

(Kojima S, et al. *J Cardiol* 2017;69:169–75)

End Point -2-

- Primary composite end point (*continued*)
  - (6) Renal impairment (development of microalbuminuria[*]/mild proteinuria[#], progression to overt albuminuria[$]/severe proteinuria[&] or worsening of overt albuminuria, doubling of serum creatinine (Cr) level, progression to end-stage renal disease)
  - (7) New atrial fibrillation (including paroxysmal atrial fibrillation)
  - (8) Death due to other cause

[*]microalbuminuria (≤30 to <300 mg/gCr)

[#]mild proteinuria (≤0.15 to <0.50 g/gCr)

[$]overt albuminuria (≤300 mg/gCr)

[&]severe proteinuria (<0.50 g/gCr)

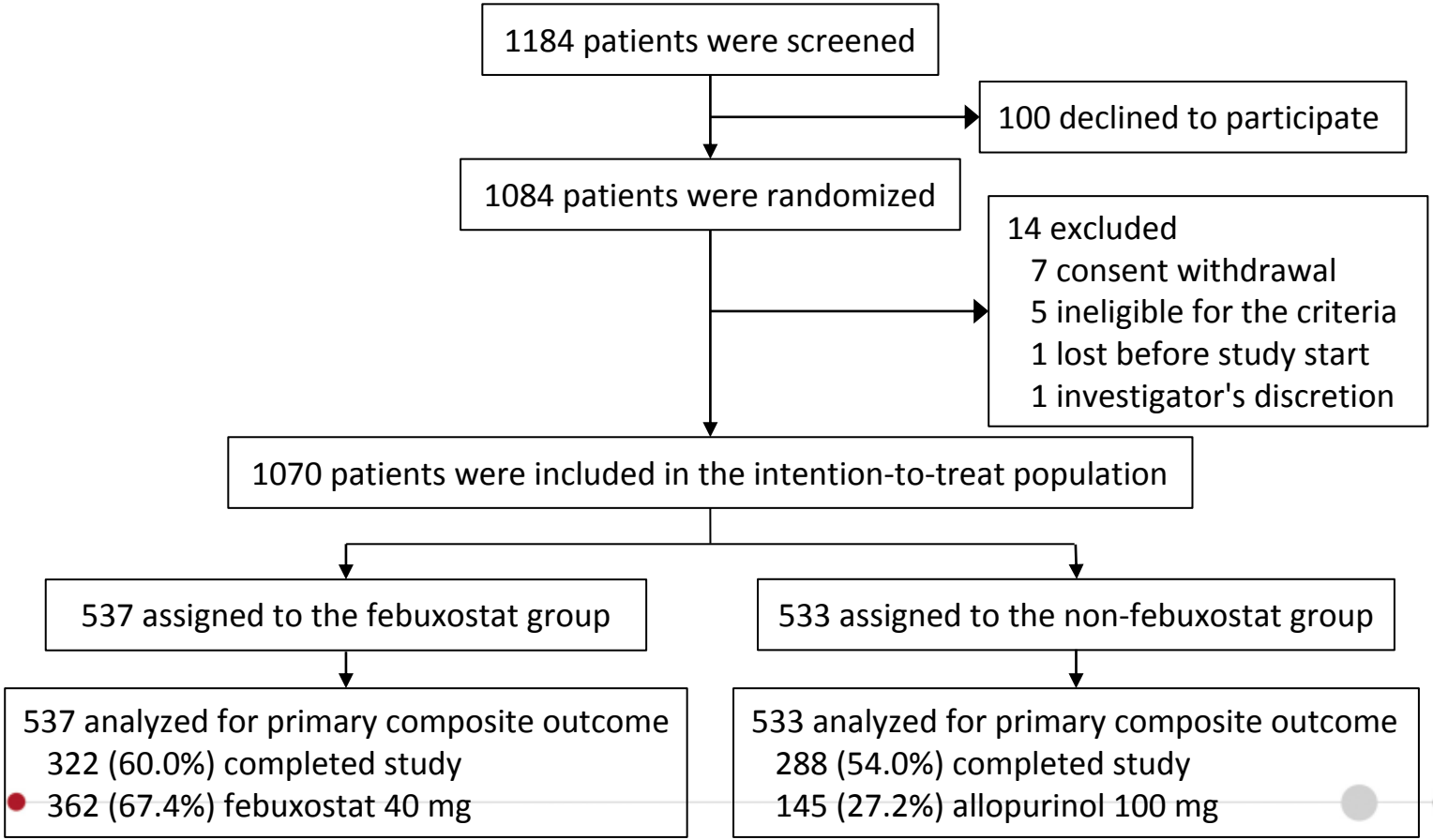
(Kojima S, et al. *J Cardiol* 2017;69:169–75)

End Point -3-

- Secondary end point
  - (1) Each component of cerebral, cardiovascular, and renal vascular events
  - (2) Hard end point (composite of death due to any cause, cerebrovascular disease, or non-fatal coronary artery disease)
  - (3) Primary composite events according to achieved serum uric acid level

(Kojima S, et al. *J Cardiol* 2017;69:169–75)

Patient Distribution



Baseline Characteristics -1-

	Febuxostat group (n=537)	Non-febuxostat group (n=533)	P value (febuxostat vs. non-febuxostat)
Male	371 (69.1)	368 (69.0)	1.000
Age (year)	75.4±6.7	76.0±6.5	0.137
Body mass index (kg/m^2)	24.74±3.71	24.61±3.65	0.325
Hemoglobin (g/dL)	13.55±1.60	13.46±1.65	0.424
Total protein (g/dL)	7.20±0.45	7.19±0.46	0.928
Total bilirubin (mg/dL)	0.62±0.30	0.59±0.28	0.299
Hypertension	506 (94.2)	501 (94.0)	0.897
Systolic blood pressure (mmHg)	132.9±14.8	132.3±14.0	0.426
Diastolic blood pressure (mmHg)	73.5±10.2	73.6±10.2	0.716
Type 2 diabetes	197 (36.7)	199 (37.3)	0.849
Hemoglobin A1c (%)	5.87±0.63	5.87±0.60	0.815
Hyperlipidemia	317 (59.0)	305 (57.2)	0.577
LDL cholesterol (mg/dL)	108.3±31.2	106.3±28.1	0.421
HDL cholesterol (mg/dL)	54.2±14.9	54.4±15.0	0.812
Triglyceride (mg/dL)	135.0 [96.0-193.5]	138.0 [94.0-189.0]	0.757

Values are presented as n (%), mean±standard deviation, or median (25th-75th percentile ranges)

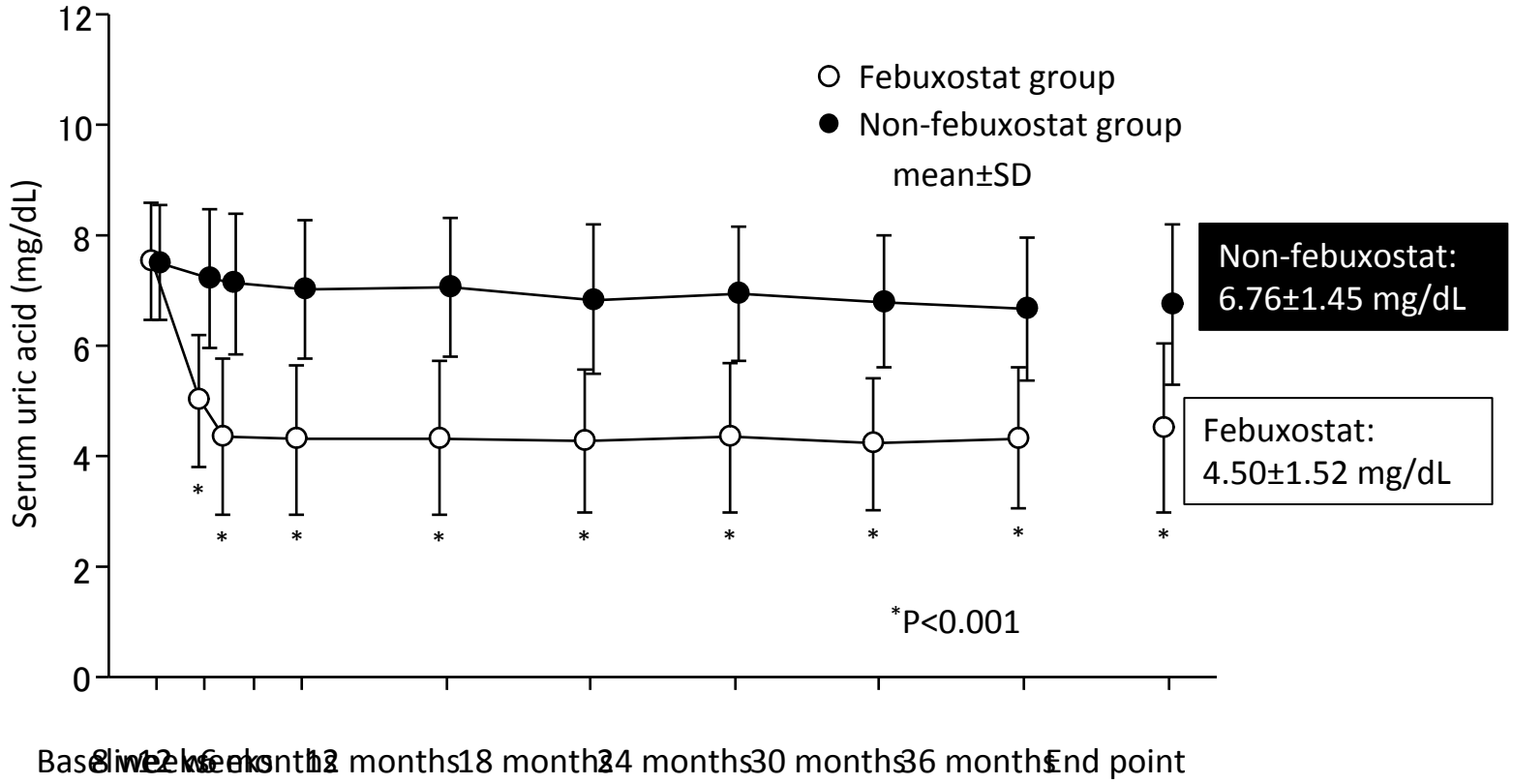
Baseline Characteristics -2-

	Febuxostat group (n=537)		Non-febuxostat group (n=533)		P value (febuxostat vs. non-febuxostat)
Renal disease*	357	(66.5)	350	(65.7)	0.796
eGFR (mL/min/1.73 m²)	54.62±14.11		55.35±15.16		0.608
Alcohol habitat	239	(44.5)	238	(44.7)	1.000
Active smoking	222	(41.3)	239	(44.8)	0.267
Coronary artery disease	45	(8.4)	45	(8.4)	1.000
Chronic heart failure	41	(7.6)	33	(6.2)	0.393
Stroke	39	(7.3)	47	(8.8)	0.370
Vascular disease	9	(1.7)	16	(3.0)	0.162
Malignant tumor	15	(2.8)	17	(3.2)	0.724
hs-CRP (mg/dL)	0.082 [0.040-0.172]		0.078 [0.039-0.167]		0.520
NT-proBNP (pg/mL)	114.0 [58.0-268.0]		124.0 [62.0-263.0]		0.328
Serum uric acid (mg/dL)	7.54±1.06		7.50±1.03		0.324
Urinary albumin (mg/g·Cr)	17.4 [7.5-54.8]		19.5 [8.3-67.45]		0.278
Urinary protein (g/g·Cr)	0.082 [0.043-0.163]		0.086 [0.044-0.170]		0.558

Values are presented as n (%), mean±standard deviation, or median (25th-75th percentile ranges)

*Renal disease defined as eGFR <60 mL/min/1.73 m²

Changes in serum uric acid level



Proportion of patients with serum uric acid level <6.0 mg/dL

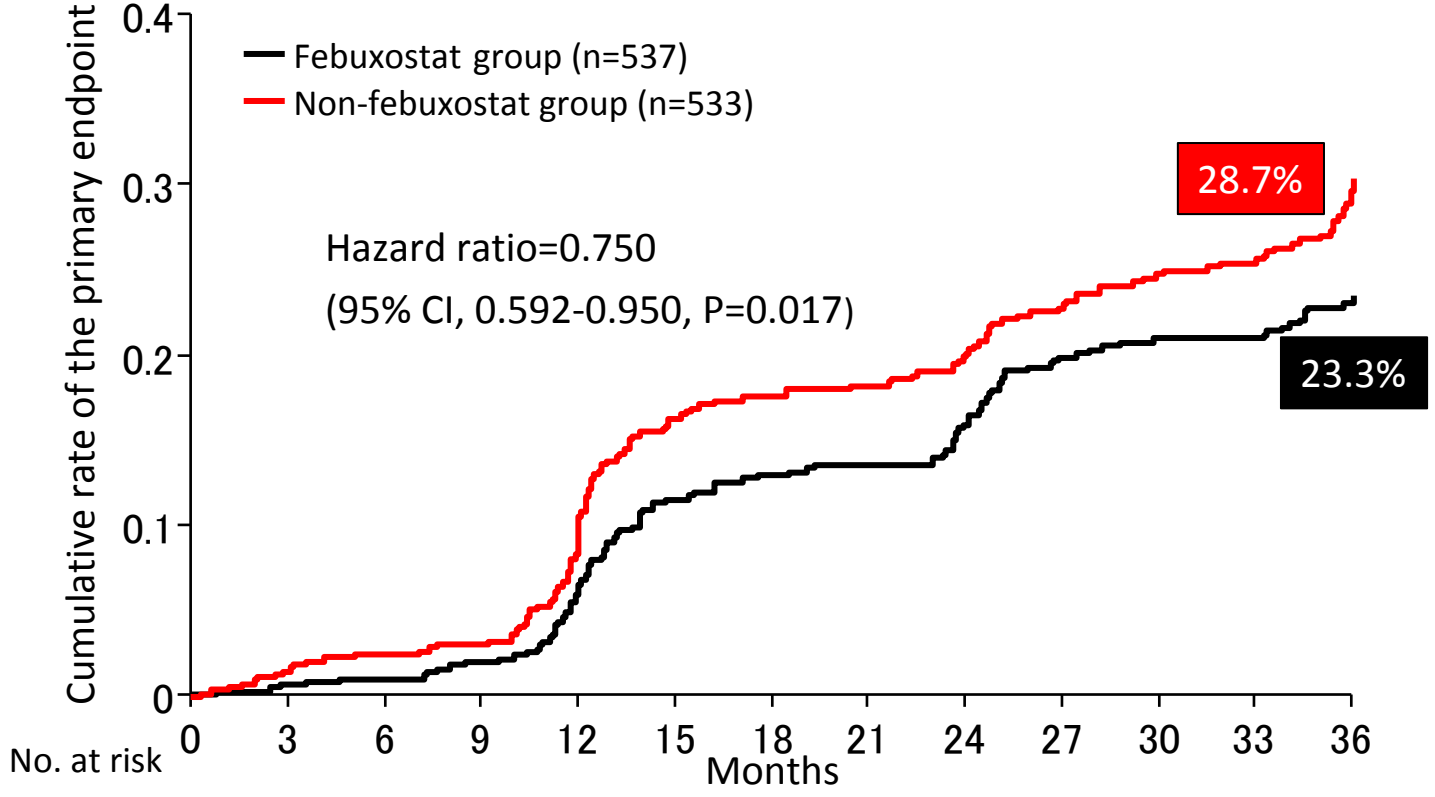
Visit	Febuxostat group (n=537)	Non-febuxostat group (n=533)
8 weeks	394/503 (78.3)	65/482 (13.5)
12 weeks	430/499 (86.2)	76/487 (15.6)
6 months	426/489 (87.1)	88/491 (17.9)
12 months	412/471 (87.5)	81/455 (17.8)
18 months	351/392 (89.5)	87/362 (24.0)
24 months	344/381 (90.3)	65/341 (19.1)
30 months	292/317 (92.1)	68/294 (23.1)
36 months	290/322 (90.1)	82/293 (28.0)

Values are presented as n (%)

Primary End Point

FREED

(Composite of death due to any cause, cerebrovascular disease, non-fatal coronary artery disease, heart failure requiring hospitalization, arteriosclerotic disease requiring treatment, renal impairment, atrial fibrillation)

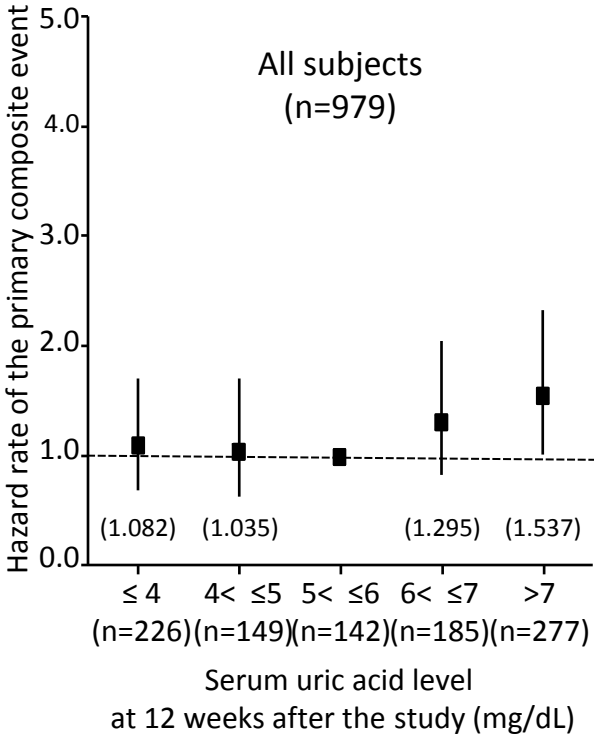


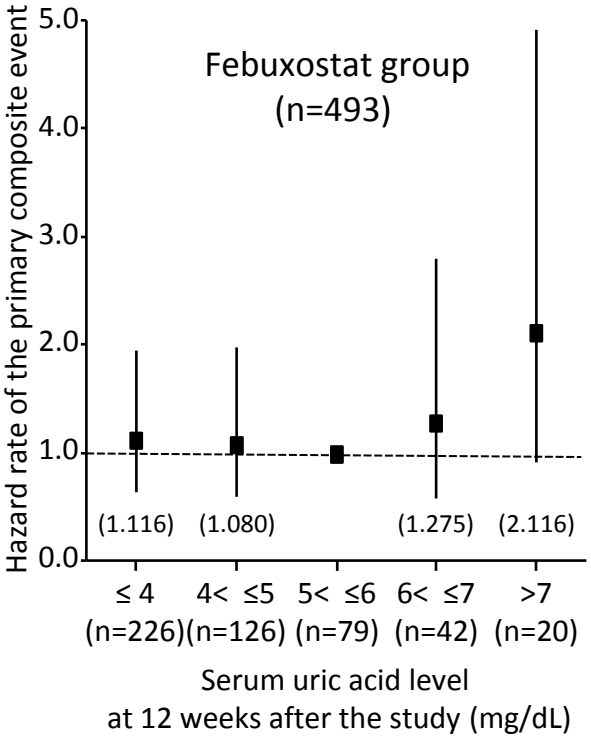
No. at risk							
Febuxostat	537	515	473	429	399	372	209
Non-febuxostat	533	501	451	391	370	341	188

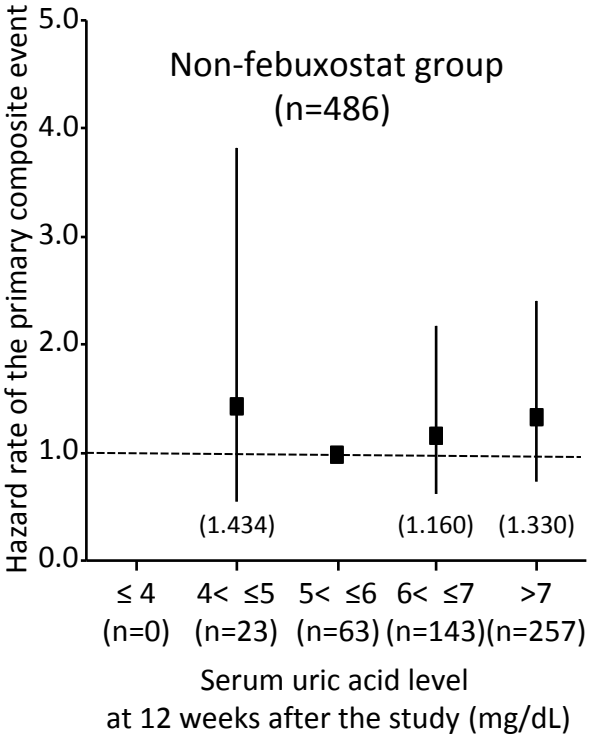
Secondary End Point

	Febuxostat group (n=537)		Non-febuxostat group (n=533)		Hazard ratio (95% confidence interval)	P value
Death due to cerebral, cardiovascular and renal disease	6	(1.1)	6	(1.1)	0.958 (0.314-2.926)	0.940
Cerebrovascular disease	9	(1.7)	7	(1.3)	1.271 (0.479-3.371)	0.630
Non-fatal coronary artery disease	4	(0.7)	7	(1.3)	0.559 (0.167-1.869)	0.345
Heart failure requiring hospitalization	9	(1.7)	12	(2.3)	0.699 (0.290-1.689)	0.427
Arteriosclerotic disease requiring treatment	2	(0.4)	3	(0.6)	0.644 (0.107-3.873)	0.631
Renal impairment	87	(16.2)	109	(20.5)	0.745 (0.562-0.987)	0.041
Atrial fibrillation	4	(0.7)	3	(0.6)	1.320 (0.292-5.968)	0.719
Death due to other cause	4	(0.7)	6	(1.1)	0.635 (0.179-2.253)	0.482
Hard end point (composite of death due to any cause, cerebrovascular disease, or non-fatal coronary artery disease)	23	(4.3)	26	(4.9)	0.861 (0.492-1.506)	0.600

Primary Composite Event according to Achieved Serum Uric Acid Level at 12 weeks







Summary

- The present FREED study demonstrated that febuxostat significantly decreased serum uric acid levels, and its effect was associated with reduction of cerebral, cardiovascular, and renal events as the primary composite end point in patients aged 65 years or older with hyperuricemia compared with conventional therapy with lifestyle modification.
- In a primary composite end point, a renal event was clearly reduced by febuxostat treatment.
- Febuxostat treatment could not decrease hard end point events during the study period.
- More than 7 mg/dL in serum uric acid level at 12 weeks after treatment was a stronger risk factor for the primary composite endpoint compared to 5< to ≤6 mg/dL in serum uric acid level. Patients whose serum uric acid levels were 6< to ≤7 mg/dL, 4< to ≤5 mg/dL, ≤4 mg/dL showed a higher hazard ratio than that in those with 5< to ≤6 mg/dL in serum uric acid level.

Conclusion

- Uric acid level lowering by febuxostat provides clinical benefit for prevention of cerebral, cardiovascular, and renal events in elderly patients with hyperuricemia.
- Febuxostat may be expected to prevent the development and progression of chronic kidney disease.
- However, excessive lowering treatment by febuxostat may be avoided.

Full List of the FREED Study Investigators

FREED

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(Listed in prefectural and alphabetical order)

Hard End Point

(composite of death due to any cause, cerebrovascular disease, or non-fatal coronary artery disease)