Supplementary table 1. Search strategies

Database	Search strategies
MEDLINE	((febuxostat[tiab] OR "febuxostat" [Supplementary Concept])) NOT (animals[Mesh] NOT (humans[Mesh] AND animals[Mesh]))
Embase	('febuxostat'/exp OR febuxostat:ab,ti) NOT ('animal experiment'/de OR 'animal model'/de OR 'animal tissue'/de OR 'in vitro study'/de OR 'nonhuman'/de)
Cochrane	febuxostat:ti,ab,kw NOT (animals[Mesh] NOT (humans[Mesh] AND animals[Mesh]))
KoreaMed	Febuxostat[ALL]

Supplementary table 2. Assessment of methodological quality using GRADE

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Serum creatine	The mean serum creatine in the control groups was **serum Cr mg/dL**	The mean serum creatine in the intervention groups was **0.03 lower** (0.08 lower to 0.02 higher)		388 (4 studies)	⊕⊕⊕⊖ **moderate**	
eGFR	The mean egfr in the control groups was **eGFR**	The mean egfr in the intervention groups was **80.47 lower** (147.29 to 11.64 lower)		180 (2 studies)	⊕⊕⊕⊖ **moderate**	
Aluminuria(1month)	The mean aluminuria(1month) in the control groups was **albuminuria**	The mean aluminuria(1month) in the intervention groups was **1.65 higher** (0.38 to 2.91 higher)		322 (3 studies)	⊕⊕⊕⊖ **moderate**	
Serum uric acid(1-3month)	The mean serum uric acid(1-3month) in the control groups was **serum uric acid mg/dL**	The mean serum uric acid(1-3month) in the intervention groups was **0.92 lower** (1.29 to 0.56 lower)		388 (4 studies)	⊕⊕⊕⊖ **moderate**	
Albuminuria(3month)	The mean albuminuria(3month) in the control groups was **Albuminuria**	The mean albuminuria(3month) in the intervention groups was **1.42 higher** (2.78 lower to 5.62 higher)		180 (2 studies)	⊕⊕⊕⊖ **moderate**	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Supplementary table 3. Characteristics of included studies

	Goldfarb, 2013	Kim, 2014	Sezai, 2013	Tanaka, 2015
Journal	Clin J Am Soc Nephrol 8:1960-1967	J Korean Med Sci 29:1077-1081	Circ J 77:2043-2049	Clin Exp Nephrol 19:1044-1053
Design	Randomized controlled trial (multiracial, mostly Caucasian, US)	Randomized controlled trial (posthoc study, Korean)	Randomized controlled trial (Japanese)	Randomized controlled open label trial (Japanese)
Inclusion criteria	Men and women with higher uUA excretion (> 700 mg/24 hr) over the age of 18 yr with a recent (≤ 5 yr) history of kidney stones and one or more radio-opaque calcium kidney stone ≥ 3 mm in its longest in-plane diameter at screening were enrolled.	The subjects met the preliminary criteria of the American College of Rheumatology for gout and had serum urate concentrations ≥ 8.0 mg/dL at screening	The subjects were 141 outpatients with serum UA ≥ 8 mg/dL who were not on anti-hyperuricemic therapy, and who underwent cardiac surgery at Nihon University Hospital at least 1 yr previously. The age range of the eligible patients was ≥ 20 to < 90 yr	A total of 45 male and female adult subjects with hyperuricemia (serum UA C7.0 mg/dL) who were known to have CKD stage 3 (estimated glomerular filtration rate 30–59 mL/min/1.73 m2) was recruited. Patients treated with allopurinol were not excluded from the study.
Exclusion criteria	If the patients had any of the following criteria: gout, secondary hyperuricemia, or hyperparathyroidism; higher urinary calcium excretion (> 250 mg/d for women and >300 mg/d for men or > 4 mg/kg per day if body weight was ≥ 75 kg for men and ≥ 62.5 kg for women); a history of xanthinuria, inflammatory bowel disease, or bowel resection; renal tubular acidosis; cancer in the past 5 yr	The ineligibility criteria included a serum creatinine concentration > 1.5 mg/dL (133 μM/L), use of thiazide diuretics or medications containing aspirin or other salicylates, active liver disease, and an alcohol intake of more than 14 drinks/wk	Exclusion criteria were (1) renal dysfunction with an estimated glomerular filtration rate ≤ 20 mL · min−1 1.73 m−2; (2) hepatic dysfunction (aspartate aminotransferase > 39 U/L or alanine aminotransferase > 44 U/L); (3) treatment with mercaptopurine hydrate or azathiopurine; (4) pregnancy; and (5) other reasons that made patients unsuitable for this study as judged by the attending physician	Exclusion criteria were:(1) acute/chronic inflammatory disease and/or malignancy;(2) active gout; (3) severe cardiovascular/respiratory/digestive disease within the past 6 months; (4) pregnancy; (5) medication with febuxostat and/or benzbromarone within the past 3 months; (6) on immunosuppressive therapy; or (7) unable to give informed consent and/or other reasons making the patients unsuitable for the trial as judged by the attending physician.
Notes	Include patients having inclusion criteria regardless of renal function	Include patients with good renal function (creatinine level ≤ 1.5)	Include patients with moderate to good renal function (GFR > 20)	Include patients with CKD 3

Supplementary table 4. Lists of excluded studies

1. No full text (conference abstract only): 12 articles

Author	Title	Journal
Becker et al (2011)	Febuxostat (vs. allopurinol) in treating the hyperuricemia of gout in diabetic patients	Arthritis and Rheumatism 63(S10):1022.
Chohan et al (2010)	Urate-lowering (UL) efficacy and safety of febuxostat (FEB) and allopurinol (ALLO) in women with gout, an older subset of gout subjects with increased comorbidity	Arthritis and Rheumatism 62(S10): 165.
Filiopoulos et al (2014)	Efficacy and safety of oral febuxostat compared to allopurinol in subjects with moderate-to-severe chronic kidney disease	Nephrology Dialysis Transplantation 29: iii156-iii157.
Goldfarb et al (2012)	Prevention of recurrent calcium stones in subjects with hyperuricosuria: A randomized controlled trial of febuxostat vs allopurinol	Arthritis and Rheumatism 64: S67.
Goldfarb et al (2010)	Febuxostat in gout: Serum urate responses in uric acid overproducers vs. underexcretors	American Journal of Kidney Diseases 55(4): A59.
Ivanov and Ivanova (2013)	Febuxostat improves GFR and BP in non-diabetic adults with CKD 2-3	Nephrology Dialysis Transplantation 28: i48.
Jordan et al (2014)	Febuxostat head to head versus allopurinol achieves a higher serum uric acid (SUA) control in tumor lysis syndrome (TLS) prevention: Results of florence pivotal study	Supportive Care in Cancer 22:S37.
Krishnan et al (2010)	Febuxostat versus allopurinol in the treatment of gout in subjects 65 years of age: A subgroup analysis of the CONFIRMS trial	Arthritis and Rheumatism 62: 154.
Krishnan et al (2011)	Encore presentation febuxostat vs allopurinol in elderly gout subjects: Subgroup analysis of the confirms trial	Journal of the American Geriatrics Society 59:S56.
Nouvenne et al (2013)	New pharmacologic approach to patients with idiopathic calcium nephrolithiasis and high uricosuria: Febuxostat vs allopurinol. A pilot study	European Journal of Internal Medicine 24:e64.
Saag et al (2013)	Effect of febuxostat on serum urate levels in gout subjects with hyperuricemia and moderate-to-severe renal impairment: A randomized controlled trial	Arthritis and Rheumatism 65: S498-S499.
Spina et al (2014)	A randomized double-blind phase III pivotal study of febuxostat (FEB) versus allopurinol (ALL) in the prevention of tumor lysis syndrome (TLS): Florence study	Journal of Clinical Oncology 2014;32(5S): abstract 9641.

2. Duplication: 4 articles

Author	Title	Journal
Tatsuo and Iwao (2011)	A repeated oral administration study of febuxostat (TMX-67), a non-purine-selective inhibitor of xanthine oxidase, in patients with impaired renal function in Japan: pharmacokinetic and pharmacodynamic study	Journal of Clinical Rheumatology 17(4 Suppl 2): S27-34.
Naoyuki et al (2011)	An allopurinol-controlled, multicenter, randomized, open-label, parallel between-group, comparative study of febuxostat (TMX-67), a non-purine-selective inhibitor of xanthine oxidase, in patients with hyperuricemia including those with gout in Japan: phase 2 exploratory clinical study	Journal of Clinical Rheumatology 17(4 Suppl 2): S44-49.
Naoyuki et al (2011)	Placebo-controlled, double-blind study of the non-purine-selective xanthine oxidase inhibitor Febuxostat (TMX-67) in patients with hyperuricemia including those with gout in Japan: phase 3 clinical study	Journal of Clinical Rheumatology 17(4 Suppl 2): S19-26.
White et al (2012)	Cardiovascular safety of febuxostat and allopurinol in patients with gout and cardiovascular comorbidities	American Heart Journal 164:14-20.

3. Commentary: 4 articles

Author	Title	Journal
Chatham and Saag (2006)	Is febuxostat a more effective treatment for hyperuricemia and gout than allopurinol? Commentary	Nature Clinical Practice Rheumatology 2:240-241.
Maahs et al (2013)	Uric acid lowering to prevent kidney function loss in diabetes: The preventing early renal function loss (PERL) allopurinol study	Current Diabetes Reports 13:550-559.
Pohar and Murphy (2006)	Febuxostat for prevention of gout attacks	Issues in Emerging Health Technologies (87):1-4.
Zelicoff (2014)	Suggested statistical reappraisal of data from comparative study of febuxostat and allopurinol in chronic kidney disease	Clinical Rheumatology 33:1837.

4. No suitable outcome: 21 articles

Author	Title	Journal
Becker et al (2005)	Febuxostat compared with allopurinol in patients with hyperuricemia and gout	New England Journal of Medicine 353:2450-2461.
Becker et al (2010)	The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial	Arthritis Research & Therapy 12:R63.
Becker et al (2005)	Febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase: a twenty-eight-day, multicenter, phase II, randomized, double-blind, placebo-controlled, dose-response clinical trial examining safety and efficacy in patients with gout	Arthritis & Rheumatology 52:916-923.
Becker et al (2011)	Treating hyperuricemia of gout: safety and efficacy of febuxostat and allopurinol in older versus younger subjects	Nucleosides, Nucleotides & Nucleic Acids 30:1011-1017.
Becker et al (2013)	Diabetes and gout: Efficacy and safety of febuxostat and allopurinol	Diabetes, Obesity & Metabolism 15:1049-1055.
Chohan et al (2012)	Women with gout: efficacy and safety of urate-lowering with febuxostat and allopurinol	Arthritis Care & Research 64:256-261.
Chohan et al (2011)	Efficacy and safety of febuxostat and allopurinol in women with gout, an older subset with increased comorbidity	Journal of Rheumatology 38:1152.
Goldfarb et al (2011)	Febuxostat in gout: serum urate response in uric acid overproducers and underexcretors	Journal of Rheumatology 38:1385-1389.
Goldfarb et al (2010)	Febuxostat in gout: serum urate response in uric acid overproducers and underexcretors	NKF 2010 Spring Clinical Meetings Abstracts A59 109
Horikoshi et al (2013)	Febuxostat for hyperuricemia: experience with patients on chronic hemodialysis treatment	Clinical and Experimental Nephrology 17:149-150.
Hosoya et al (2011)	A repeated oral administration study of febuxostat (TMX-67), a non-purine-selective inhibitor of xanthine oxidase, in patients with impaired renal function in Japan: pharmacokinetic and pharmacodynamic study	Journal of Clinical Rheumatology 17:S27-34.
Huang et al (2014)	An allopurinol-controlled, multicenter, randomized, double-blind, parallel between-group, comparative study of febuxostat in Chinese patients with gout and hyperuricemia	International Journal of Rheumatic Diseases 17:679-686.
Jackson et al (2012)	The efficacy and safety of febuxostat for urate lowering in gout patients ≥ 65 years of age	BMC Geriatrics 12:11.
Kamatani et al (2011)	Placebo-controlled double-blind dose-response study of the non-purine-selective xanthine oxidase inhibitor febuxostat (TMX-67) in patients with hyperuricemia (including gout patients) in japan: late phase 2 clinical study	Journal of Clinical Rheumatology 17:S35-43.
Kamatani et al (2011)	An allopurinol-controlled, randomized, double-dummy, double-blind, parallel between-group, comparative study of febuxostat (TMX-67), a non-purine-selective inhibitor of xanthine oxidase, in patients with hyperuricemia including those with gout in Japan: phase 3 clinical study	Journal of Clinical Rheumatology 17:S13-18.

Author	Title	Journal
Kamatani et al (2011)	An allopurinol-controlled, multicenter, randomized, open-label, parallel between-group, comparative study of febuxostat (TMX-67), a non-purine-selective inhibitor of xanthine oxidase, in patients with hyperuricemia including those with gout in Japan: phase 2 exploratory clinical study	Journal of Clinical Rheumatology 17 (4 Suppl 2): S44-49.
Kamatani (2011)	Placebo-controlled, double-blind study of the non-purine-selective xanthine oxidase inhibitor Febuxostat (TMX-67) in patients with hyperuricemia including those with gout in Japan: phase 3 clinical study	Journal of Clinical Rheumatology 17 (4 Suppl 2):S19-26.
Park et al (2013)	The Urate-lowering Efficacy and Safety of Febuxostat in Korean Patients with Gout	Journal of Rheumatic Diseasese 20:223-230.
Wells et al (2012)	African American patients with gout: efficacy and safety of febuxostat vs allopurinol	BMC Musculoskeletal Disorders 13:15.
White et al (2012)	Cardiovascular safety of febuxostat and allopurinol in patients with gout and cardiovascular comorbidities	American Heart Journal 164:14-20.
Becker (2013)	Diabetes and gout: efficacy and safety of febuxostat and allopurinol	Diabetes, Obesity and Metabolism 15:1049–1055.

5. No RCT: 4 articles

Author	Title	Journal
Kuriyama et al (2014)	Clinical effects of febuxostat, an uric acid lowering agent	Therapeutic Research 35:677-686.
Miyaoka et al (2014)	Serum uric acid levels and long-term outcomes in chronic kidney disease	Heart Vessels 29:504-512.
Tausche et al (2014)	As compared to allopurinol, urate-lowering therapy with febuxostat has superior effects on oxidative stress and pulse wave velocity in patients with severe chronic tophaceous gout	Rheumatology International 34:101-109.
Sezai et al (2015)	Comparison of febuxostat and allopurinol for hyperuricemia in cardiac surgery patients with chronic kidney disease (NU-FLASH trial for CKD)	Journal of Cardiology 66:298-303.