

Uric acid and CKD

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 @Badves

Case

- Mr J, 52 Male, referred in June 2015
- DM type 2 (4 years), HTN, diabetic retinopathy, diabetic neuropathy, PVD, BMI 38, OSA, no gout.
- Rx: ACEi, nondihydropyridine CCB, thiazide, statin+ezetimibe, sulfonylurea+metformin

	2012	2013	2015	2016	2017
eGFR (mL/min/1.73 m ²)	90	73	58	48	40
Urine ACR (mg/mmol)	37	114	393	556	590
HbA1c (%)	5.8	5.7	5.6	-	6.6
Urate (mmol/L)	-	0.55	0.56	***	***

Question 1

- Has hyperuricaemia played a causative role in the progression of CKD in this patient?
- Answer:
 1. Certainly yes.
 2. Possibly yes.
 3. No.
 4. I don't know.

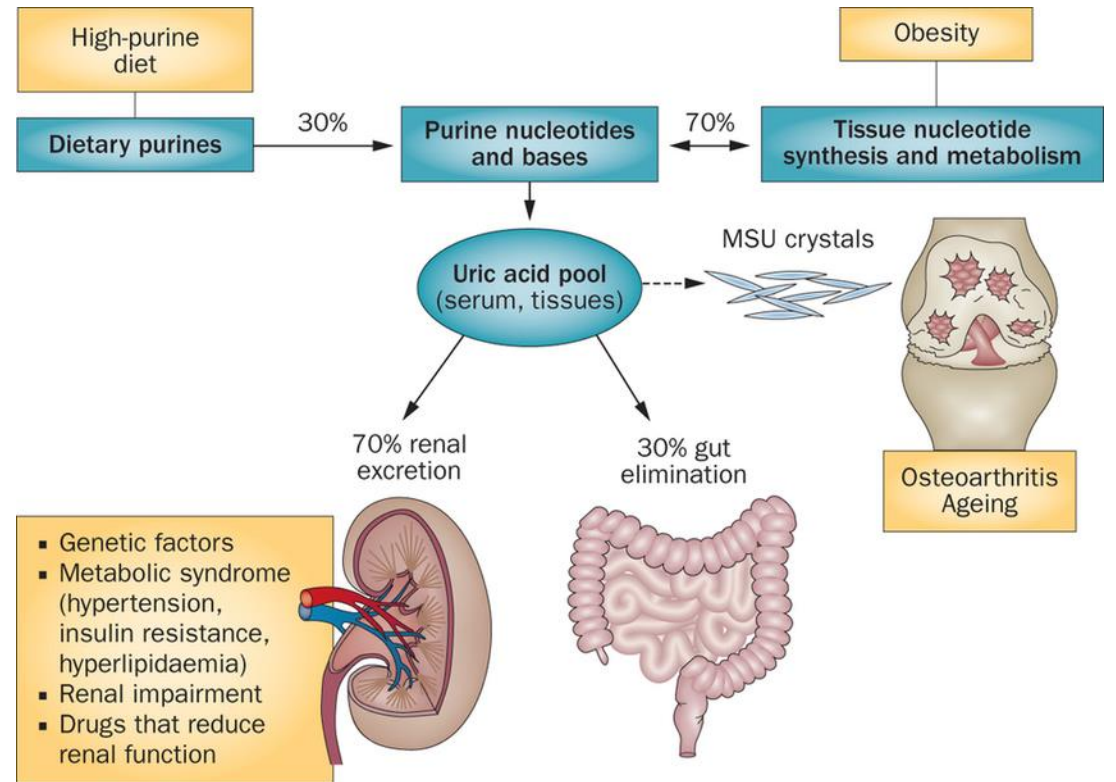
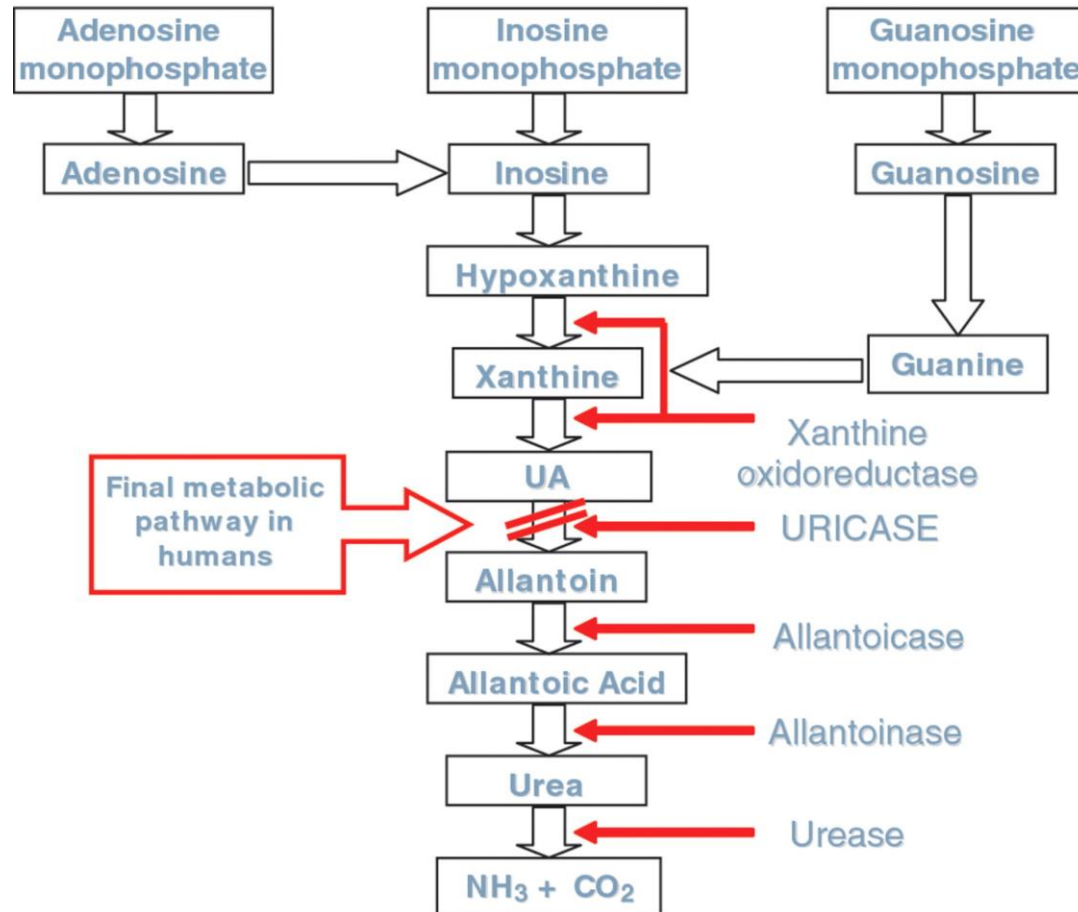
Question 2

- Will you prescribe a uric-acid lowering medication to this patient to slow the progression of CKD?
- Answer:
 1. I always prescribe a uric-acid lowering medication for asymptomatic hyperuricaemia.
 2. I sometimes prescribe if other measures are not effective.
 3. I am not convinced and need more data.
 4. Never.

Question 3

- What is the highest daily dose of allopurinol that you prescribe in patients with eGFR <30 mL/min/1.73 m²?
- Answer:
 1. 100 mg.
 2. 200 mg.
 3. 300 mg.
 4. I am comfortable with doses >300 mg/day.

Hyperuricaemia in humans



Evolutionary advantages of the loss of uricase

1. Uric acid is one of the most potent antioxidant
2. Greater longevity- antioxidant action
3. To maintain blood pressure during low salt ingestion
4. Intelligence
5. Neuroprotection

Hyperuricemia: consequences

General

- Gout
- Asymptomatic monosodium urate crystal deposition
- Non-crystal deposition disorders: hypertension, obesity, dyslipidemia, hypertension, insulin resistance, endothelial dysfunction, possibly cardiovascular diseases

Renal

- Acute uric acid nephropathy: uric acid precipitation within the tubules
- Chronic uric acid nephropathy: deposition of sodium urate crystals in the medullary interstitium
- Uric acid nephrolithiasis: increased urinary uric acid excretion
- Uromodulin kidney disease (familial juvenile nephropathy): hyperuricemia, gout and by progressive renal impairment

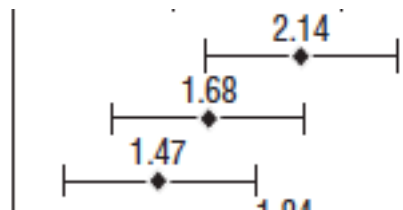
Observational study: #1

- 3,499 apparently healthy adults (aged 35–54 years) from Thailand
- Follow-up for 12 years
- Outcome: incident CKD (GFR <60 ml/min/1.73 m²)

Input Variable		Odds Ratio (95% CI)	
		Unadjusted	Adjusted
Serum uric acid (mg/dl)	mmol/L		
first quartile (1.50 to 4.49)	0.09 – 0.27	1	1
second quartile (4.50 to 5.39)	0.28 – 0.32	0.99 (0.59 to 1.67)	0.89 (0.52 to 1.53)
third quartile (5.40 to 6.29)	0.33 – 0.36	1.24 (0.76 to 2.04)	1.10 (0.65 to 1.84)
fourth quartile (6.30 to 14.50)	0.37 – 0.86	2.31 (1.45 to 3.66) ^b	1.82 (1.12 to 2.98) ^b

Observational study: #2

- 177,570 individuals from Northern California (1964-1973)
- Initiation of ESRD treatment: through December 31, 2000.
- **Outcome: incident ESKD= 842 cases**



			mmol/L
Quartile 4 (vs quartile 1)	} Uric acid	6.00-14.9	>0.36
Quartile 3 (vs quartile 1)		5.10-5.99	0.30-0.35
Quartile 2 (vs quartile 1)		4.18-5.09	0.25-0.29
		0.10-4.17	<0.24

Adjusted Hazard Ratio (95% Confidence Interval) for End-Stage Renal Disease

Observational study: #3

- 13,338 patients from the Atherosclerosis Risk in Communities and Cardiovascular Health Studies, follow-up: 8.5 years
- Outcome: incident CKD (GFR <60 ml/min/1.73 m²)

Table 2. Sequentially built logistic regression models for the primary study outcome of incident kidney disease^a

Parameter	Model 1 (Uric Acid Only)	Model 2 (Model 1 + Kidney Function)	Model 3 (Model 2 + Demographic Data)	Model 4 (Model 3 + History and Labs)	Model 5 (Model 4 + SBP and Hypertension)	Model 6 (Model 5 + BMI and Diuretic Use)
eGFR	1.16 (1.11 to 1.22)	1.09 (1.04 to 1.15)	1.12 (1.06 to 1.19)	1.12 (1.05 to 1.18)	1.07 (1.01 to 1.14)	1.07 (1.01 to 1.15)
Creatinine	1.29 (1.20 to 1.39)	1.13 (1.04 to 1.22)	1.15 (1.06 to 1.25)	1.15 (1.06 to 1.25)	1.11 (1.02 to 1.21)	1.11 (1.01 to 1.22)

^aOR and 95% CI are those associated with each 1-mg/dl rise in baseline serum uric acid in each model.

Table 3. Multivariable model for incident kidney disease^a

Parameter	Creatinine Based (OR [95% CI])	eGFR Based (OR [95% CI])
Serum uric acid (per 1-mg/dl increase)	1.11 (1.02 to 1.21)	1.07 (1.01 to 1.14)

1 mg/dL = 0.059 mmol/L

J Am Soc Nephrol 2008;19:1204-11

Observational study: #4

- 5,899 healthy individuals from Japan, 68% women, Follow-up 5 years
- Outcome: incident CKD (GFR <60 ml/min/1.73 m²); HTN (≥ 140 or ≥90)

		Crude			Model 1*			Model 2†			Model 3‡		
		OR	95% CI	P Value	OR	95% CI	P Value	OR	95% CI	P Value	OR	95% CI	P Value
Total (n=5899)													
Hypertension (n=396, 6.7%)	Hyperuricemia	2.708	2.023–3.625	<0.001	2.049	1.508–2.785	<0.001	2.112	1.548–2.882	<0.001	1.915	1.399–2.620	<0.001
	per SUA 1 mg/dL	1.481	1.370–1.601	<0.001	1.409	1.271–1.562	<0.001	1.450	1.303–1.613	<0.001	1.388	1.246–1.546	<0.001
→ CKD (n=664, 11.3%)	Hyperuricemia	1.969	1.519–2.553	<0.001	1.801	1.363–2.379	<0.001	0.828	0.589–1.163	0.276	0.817	0.581–1.150	0.247
	per SUA 1 mg/dL	1.260	1.183–1.343	<0.001	1.296	1.189–1.412	<0.001	0.864	0.779–0.958	0.006	0.858	0.774–0.953	0.004

*Model 1: Data adjusted for age, sex, and smoking and drinking habits.

†Model 2: Data adjusted for age, sex, body mass index, smoking and drinking habits, and baseline estimated GFR.

‡Model 3: Data adjusted for age, sex, body mass index, smoking and drinking habits, baseline estimated GFR, and body mass index.

Hyperuricemia: >7.0 mg/dL (0.42 mmol/L) of SUA in men
and ≥6.0 mg/dL (0.36 mmol/L) in women

Hypertension 2017;69:1036-1044

Observational study: #5

- 13,070 individuals from Japan, Follow-up 5 years
- Outcome: the highest quartile of change in eGFR (>20.56 ml/min/1.73 m² over 5 years)

	Serum uric acid, mg/dL		Number	OR	95% CI	p value
<i>Total</i>		mmol/L				
1st quartile	-4.2	<0.25	1,630	Reference		
2nd quartile	4.3–5.1	0.26 – 0.30	1,617	1.060	0.857–1.311	0.592
3rd quartile	5.2–6.2	0.31 – 0.37	1,502	1.182	0.923–1.513	0.186
4th quartile	6.3–	>0.38	1,540	2.238	1.656–3.023	<0.001
Serum uric acid change	Per 1 increase			3.711	3.298–4.178	<0.001

1 mg/dL = 0.059 mmol/L

Observational study: #6 (post-hoc MDRD)

- 838 CKD patients, baseline GFR 33 ± 12 ml/min/1.73 m², follow-up: 10 years, outcome: dialysis or transplantation

	0.10-0.41 mmol/L	0.42-0.49 mmol/L	0.50-0.93 mmol/L
	Tertile 1 (1.7-6.9 mg/dL) (n = 276)	Tertile 2 (7.0-8.3 mg/dL) (n = 288)	Tertile 3 (8.4-15.6 mg/dL) (n = 274)
Kidney failure			
Unadjusted	1.00 (reference)	1.23 (0.99-1.51)	1.16 (0.94-1.43)
Model 1*	1.00 (reference)	1.21 (0.98-1.49)	1.08 (0.87-1.33)
Model 2†	1.00 (reference)	1.18 (0.96-1.46)	1.10 (0.89-1.36)
Model 3‡	1.00 (reference)	1.11 (0.90-1.37)	1.12 (0.90-1.39)
Model 4§	1.00 (reference)	1.18 (0.94-1.47)	1.20 (0.95-1.51)

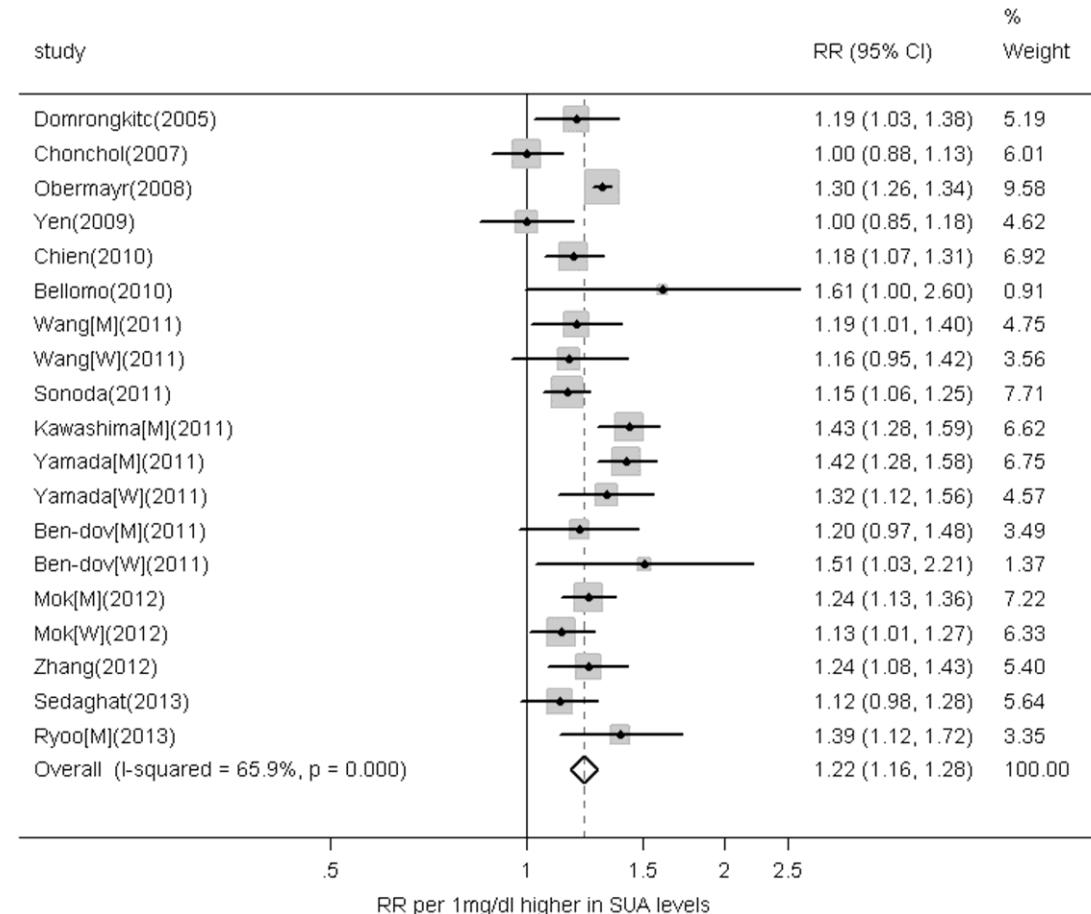
Observational study: #6 (post-hoc MDRD)

For each 1 mg/dL increase in serum uric acid:

Outcome	Adjusted HR
All-cause mortality	1.17 (95% CI 1.07 – 1.30)
Cardiovascular mortality	1.16 (95% CI 1.01 – 1.33)
Kidney failure	1.02 (95% CI 0.97 – 1.07)

1 mg/dL = 0.059 mmol/L

Meta-analysis: #1 Outcome: CKD

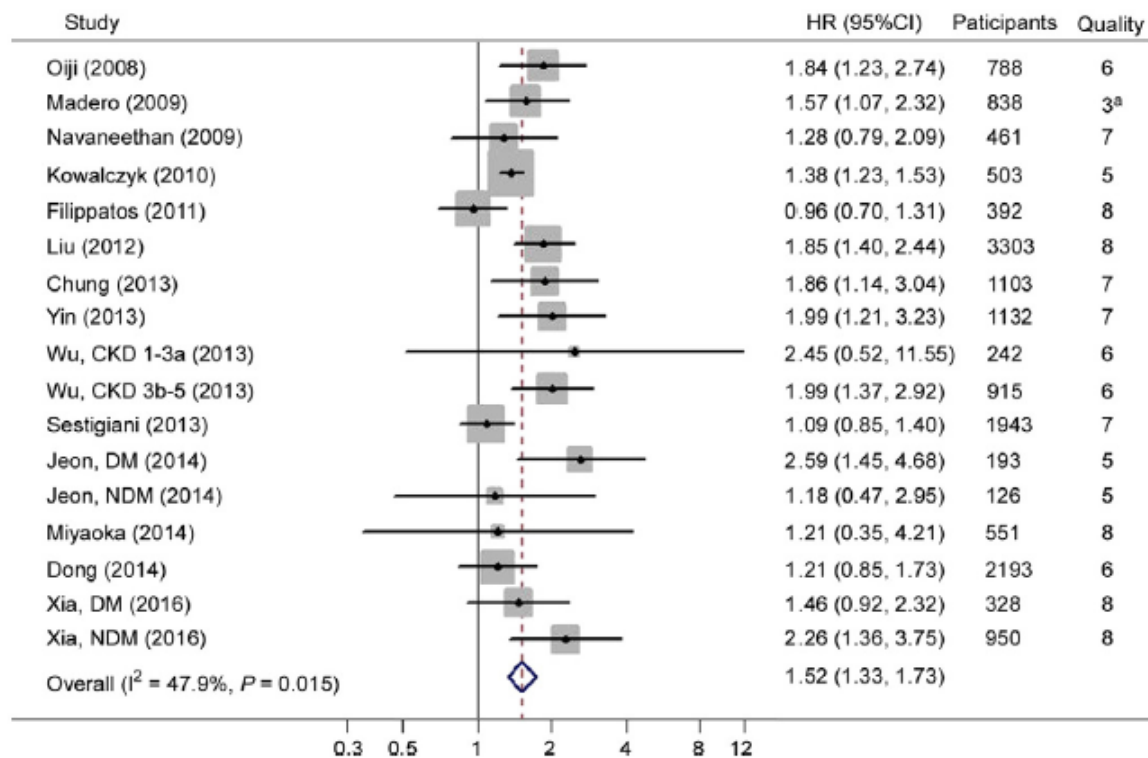


RR for the association
between SUA (for
each 1 mg/dL
increase) and the
incidence of CKD

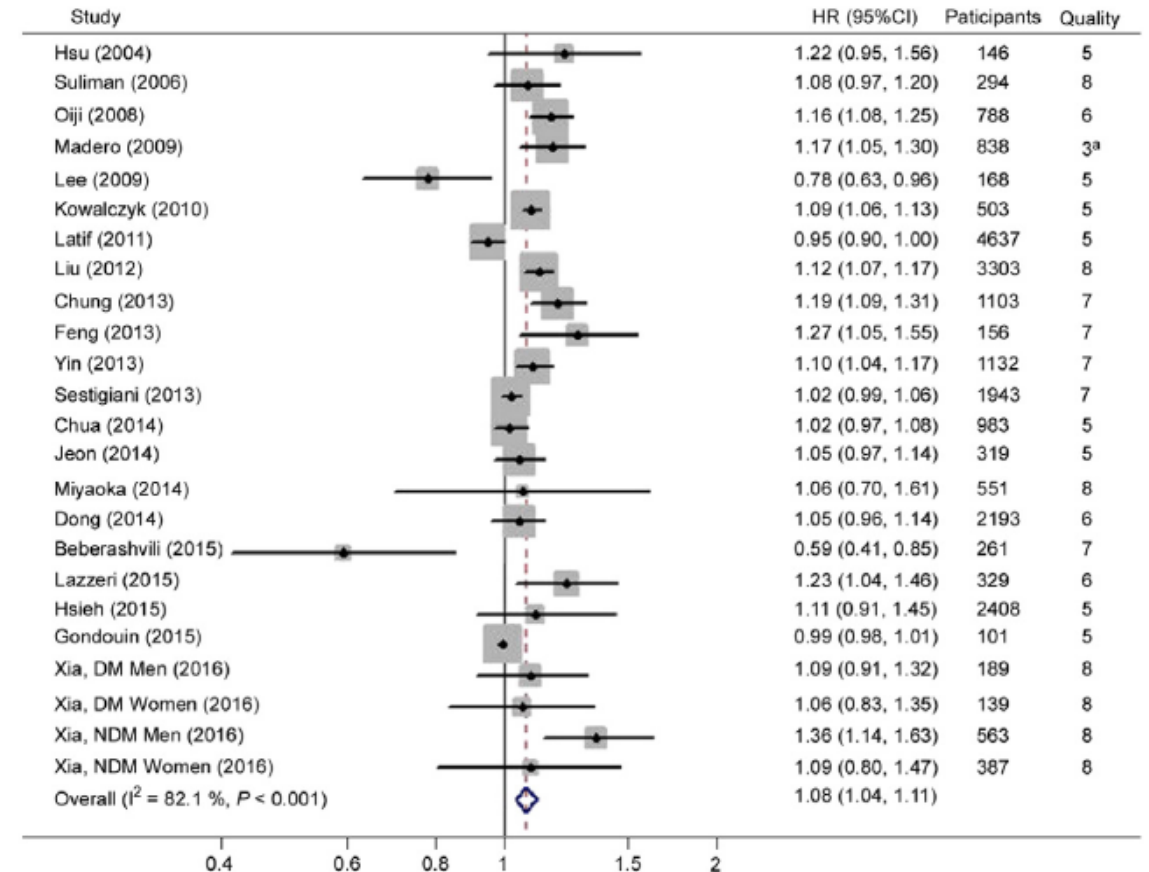
1 mg/dL = 0.059 mmol/L

Meta-analysis: #2 Outcome: Mortality in CKD

Highest vs lowest SUA level



For each 1 mg/dL increase in SUA

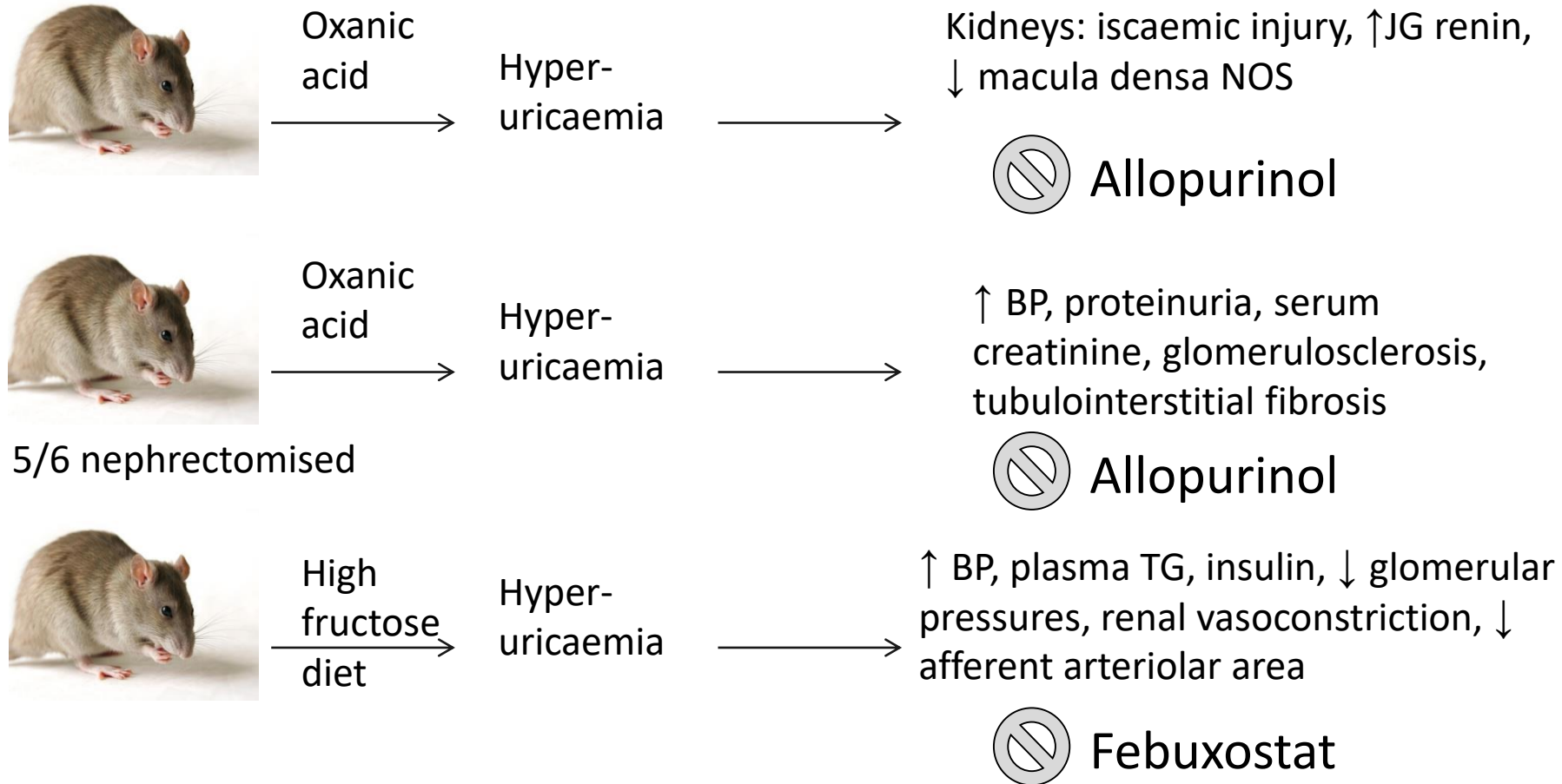


1 mg/dL = 0.059 mmol/L

Interim summary

- Epidemiological studies: asymptomatic hyperuricaemia *may be associated* with CKD and progression of CKD.

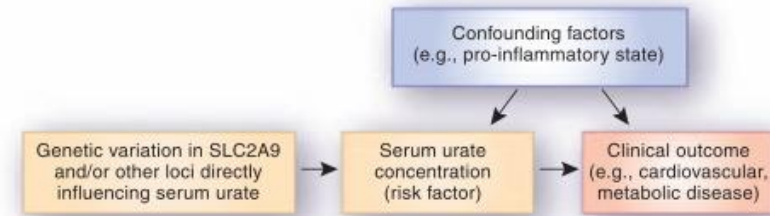
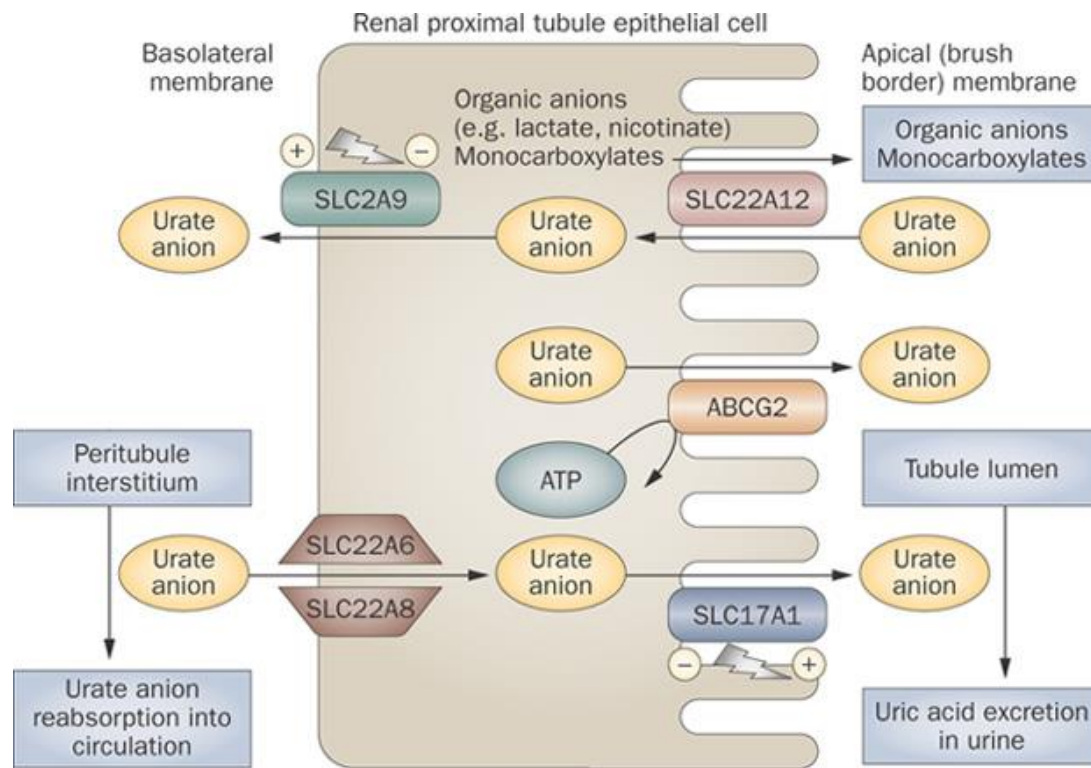
Pre-clinical studies



Interim summary

- Epidemiological studies: asymptomatic hyperuricaemia *may be associated* with CKD and progression of CKD.
- Pre-clinical studies: uric acid *may* play a causative role.

Mendelian randomisation



Mendelian randomisation 1

- 7979 patients of the Atherosclerosis Risk in Communities and Framingham Heart studies.
- Instrumental variable: uric acid transporter genetic risk score, 5 SNPs
- Risk factor: serum urate
- Outcomes: serum creatinine and eGFR

Table 1 | Association between uric acid transporter genetic risk score and SU

	SU transporter genetic risk score	
	F-statistic ^a	R ² ^a
<i>ARIC</i>		
Overall	114.81	0.0215
Men	63.05	0.0256
Women	99.25	0.0335
<i>FHS</i>		
Overall	73.32	0.0259
Men	27.56	0.0215
Women	94.73	0.0593
<i>Combined</i>		
Overall	190.74	0.0231
Men	90.6	0.0242
Women	185.14	0.0409

Abbreviations: ARIC, Atherosclerosis Risk in Communities; FHS, Framingham Heart Study; SU, serum urate.

Single-nucleotide polymorphisms rs11942223, rs2231142, rs1183201, rs2078267, and rs3825018 were used for both ARIC and FHS for SLC2A9, ABCG2, SLC17A1, SLC22A11, and SLC22A12, respectively.

^aF-statistic represents the strength, and R² the percent variance in SU explained, of the association between the genetic risk score and SU.

Mendelian randomisation 1

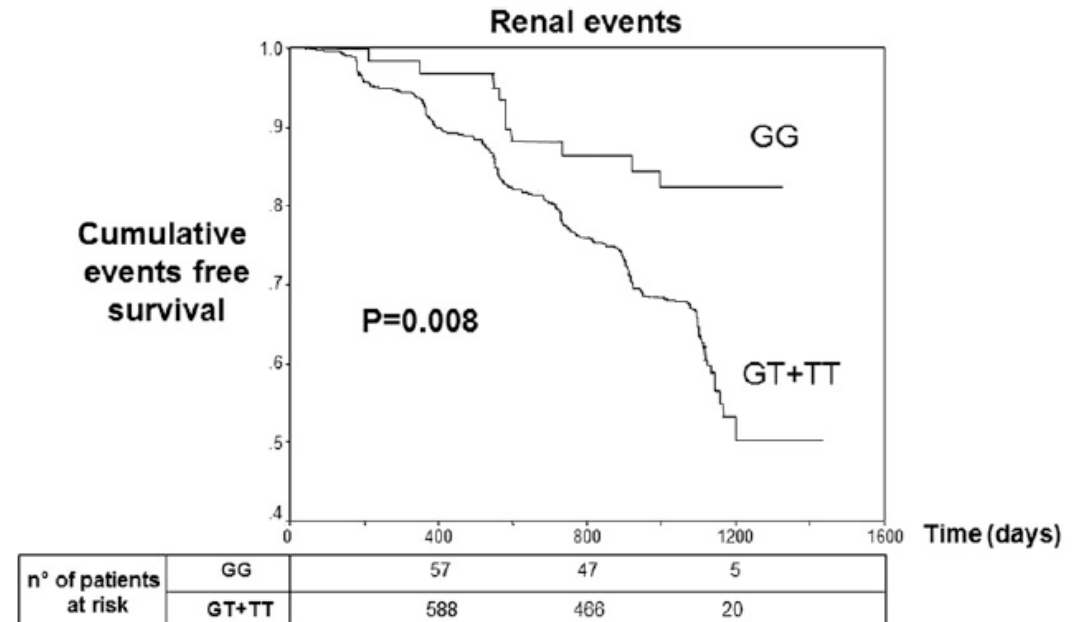
- There was evidence for a causal role for SU in determining SCr and eGFR in males.
- Each unit increase in SU attributable to the genetic risk score was associated with 45.06 $\mu\text{mmol/L}$ decrease in SCr ($P=0.02$) and 39.26 ml/min/1.73m^2 increase in eGFR ($P=0.045$).
- Using a uric acid transporter genetic risk score as an instrumental variable, there was evidence that increased SU caused by genetic variation in uric acid transporters improved renal function in males.

Table 2 | Mendelian randomization analysis of SU against eGFR/SCr using uric acid transporter genetic risk score as instrumental variable

		Ordinary least square regression			Two-stage least square			
		β^a	SE ^b	P	β^a	SE	P	DH P
SCr								
All								
Crude ^c		87.20	1.70	4.01E – 305	– 13.15	13.49	0.33	<0.0001
Adjusted ^d		37.14	2.04	1.42E – 72	– 19.23	10.76	0.07	<0.0001
Males								
Crude		35.75	2.76	1.18E – 37	– 46.52	19.90	0.019	<0.0001
Adjusted		38.32	3.08	7.33E – 35	– 45.06	19.42	0.020	<0.0001
Females								
Crude		32.31	2.44	2.22E – 39	– 3.04	12.37	0.81	0.0029
Adjusted		37.14	2.74	6.31E – 41	1.05	12.50	0.93	0.0025
eGFR								
All								
Crude		– 11.20	1.79	4.05E – 10	14.75	12.08	0.22	0.10
Adjusted		– 37.04	2.33	4.01E – 56	12.20	12.09	0.31	<0.0001
Males								
Crude		– 30.60	2.95	6.03E – 25	37.11	20.49	0.07	0.001
Adjusted		– 35.04	3.16	3.89E – 28	39.26	19.54	0.045	<0.0001
Females								
Crude		– 34.61	3.17	2.56E – 27	– 0.84	16.04	0.96	0.11
Adjusted		– 36.73	3.45	4.33E – 26	– 6.34	15.65	0.69	0.11

Mendelian randomisation 2

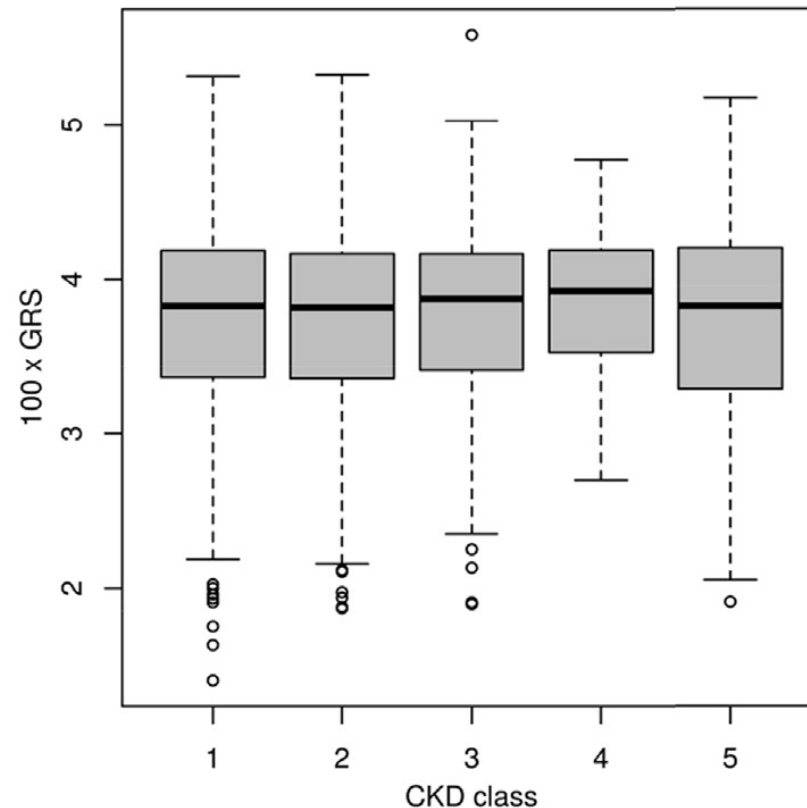
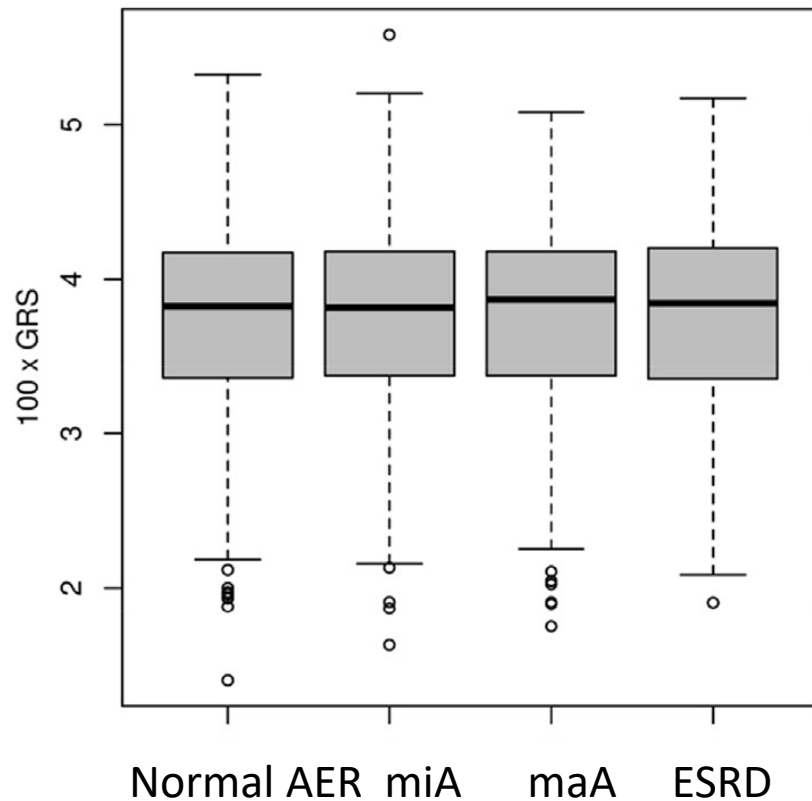
- rs734553 single-nucleotide polymorphism (SNP) of the GLUT9 urate transporter gene
- 755 CKD patients, baseline GFR 36 ± 13 ml/min/1.73 m²
- Follow-up: 23 months
- Renal outcome: composite of >30% decrease in the GFR, dialysis or transplantation
- Homozygotes (TT) and heterozygotes (GT) for the T allele [vs. patients without such an allele (GG)] was associated with 2.35 times higher risk of CKD progression.



HR 2.35; 95% CI, 1.25 – 4.42

Mendelian randomisation 3

- 2720 patients with type 1 diabetes mellitus from the FinnDiane Study



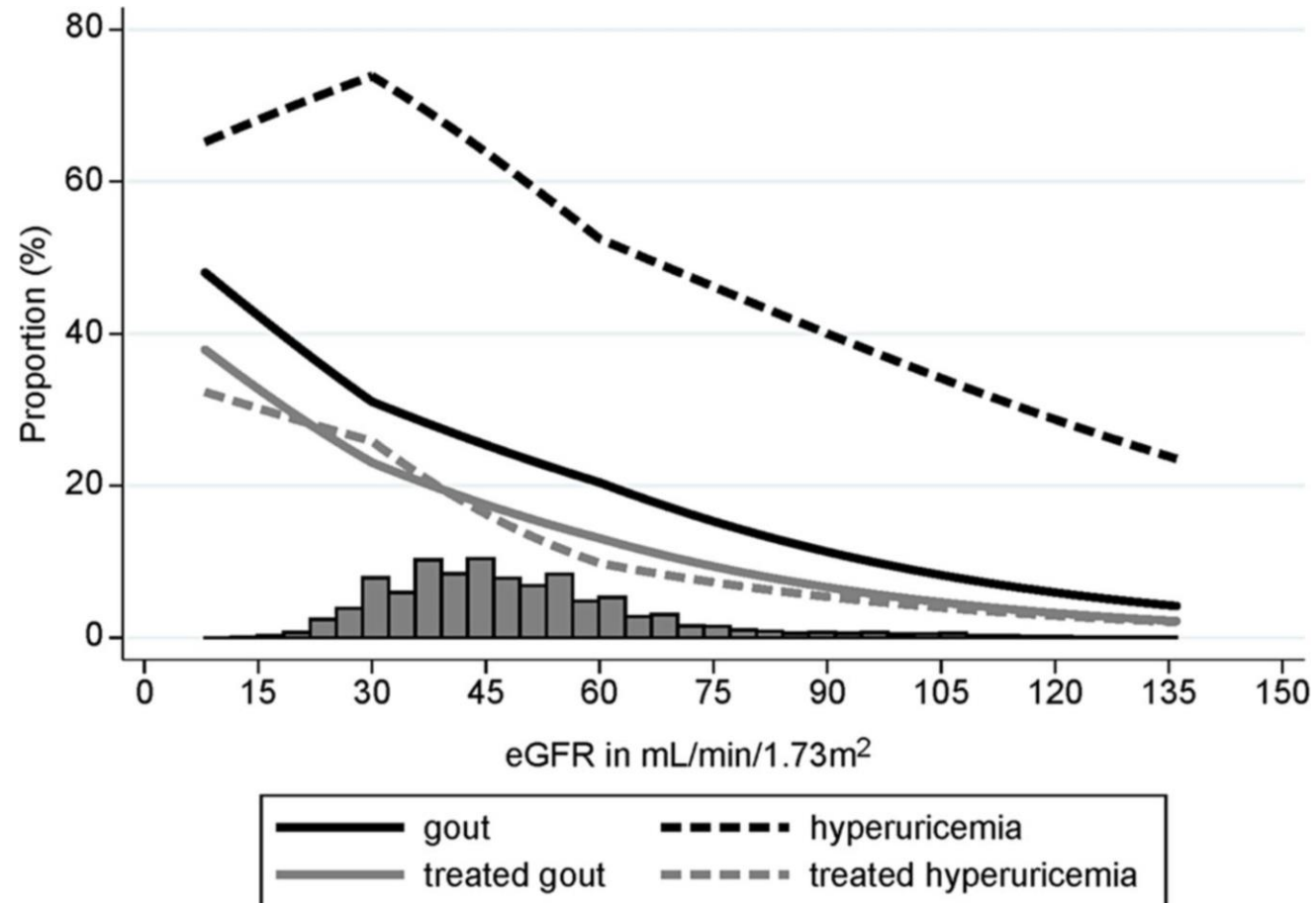
Genetic risk score based on
23 SNPs

No causal effect of serum uric
acid on the renal outcomes

Interim summary

- Epidemiological studies: asymptomatic hyperuricaemia *may be associated* with CKD and progression of CKD.
- Pre-clinical studies: uric acid *may* play a causative role.
- Mendelian randomisation studies: conflicting results on causative role of uric acid and renal outcomes.

Hyperuricaemia: a ubiquitous finding in CKD



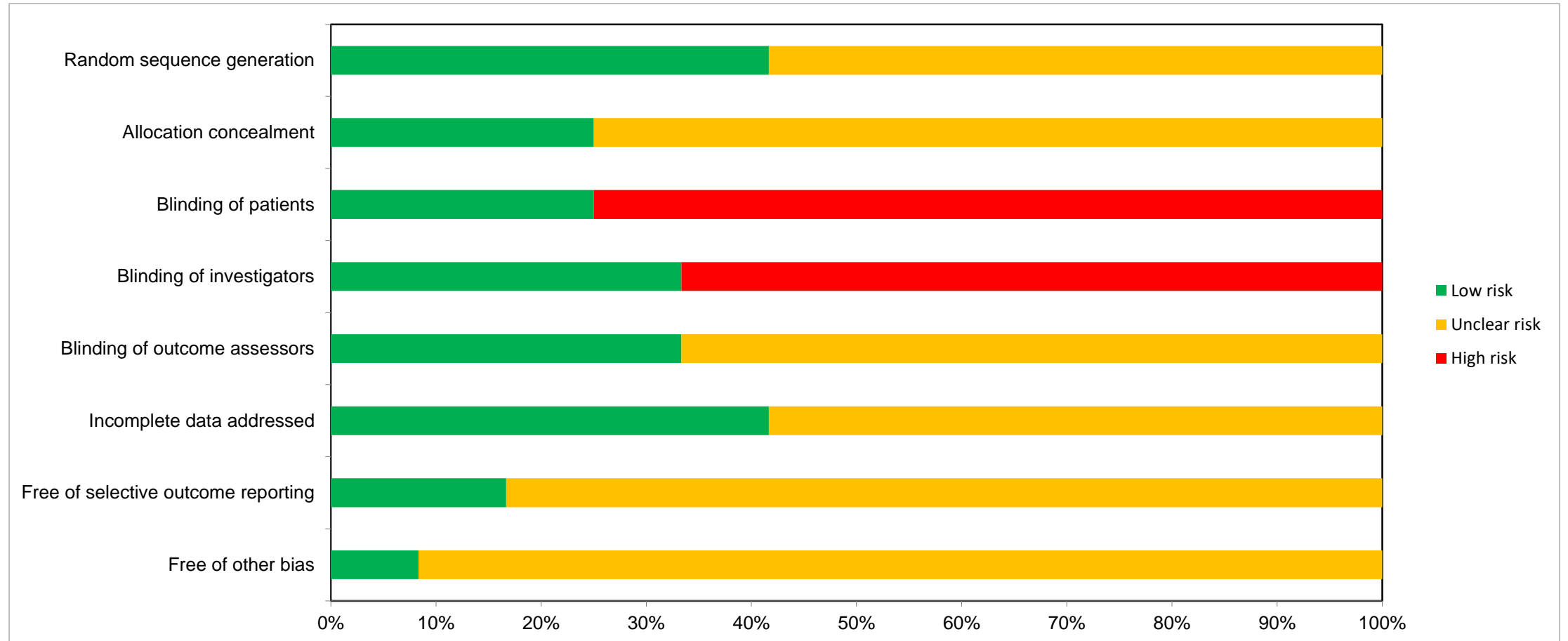
Effects of uric acid-lowering therapy on renal outcomes: a systematic review and meta-analysis

Bhadran Bose^{1,*}, Sunil V. Badve^{1,2,*}, Swapnil S. Hiremath³, Neil Boudville^{2,4}, Fiona G. Brown^{2,5}, Alan Cass^{2,6}, Janak R. de Zoysa^{2,7}, Robert G. Fassett^{2,8}, Randall Faull^{2,9}, David C. Harris^{2,10}, Carmel M. Hawley^{1,2}, John Kanellis^{2,5}, Suetonia C. Palmer^{2,11}, Vlado Perkovic^{2,12}, Elaine M. Pascoe², Gopala K. Rangan^{2,10}, Robert J. Walker^{2,13}, Giles Walters^{2,14} and David W. Johnson^{1,2}

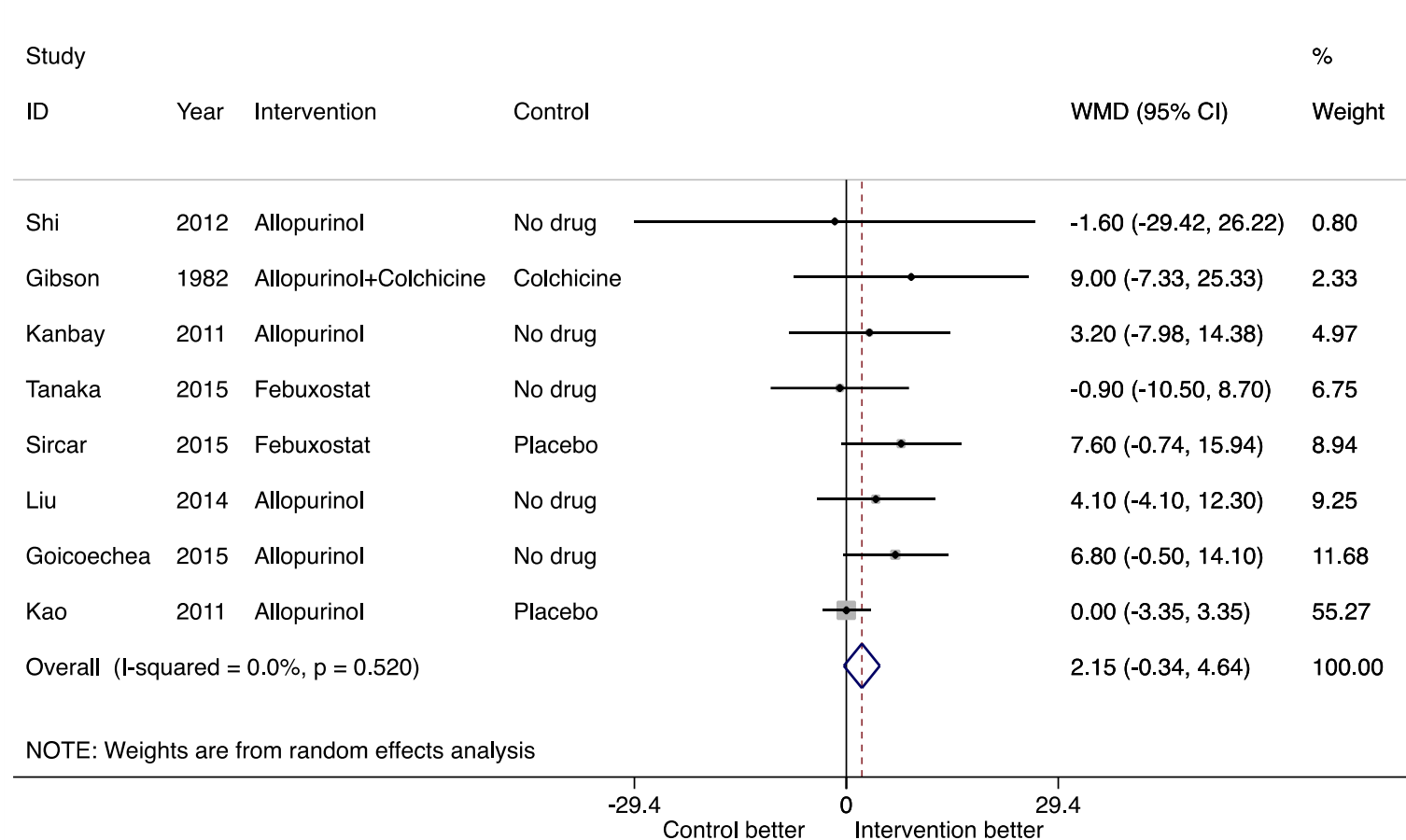
Urate-lowering therapy and renal outcomes

- Trials with follow-up >3 months were included.
- 12 trials involving 870 participants (median sample size 63; median follow-up 8 months)
- 9 trials in 592 CKD patients; 3 trials in 278 patients with normal or mildly decreased kidney function
- Allopurinol- 9 trials; febuxostat- 2 trials; 1 trial- allopurinol vs febuxostat
- Allopurinol dose: 100-300 mg daily
- Febuxostat dose: 10-60 mg daily
- Only 3 trials were placebo-controlled studies.

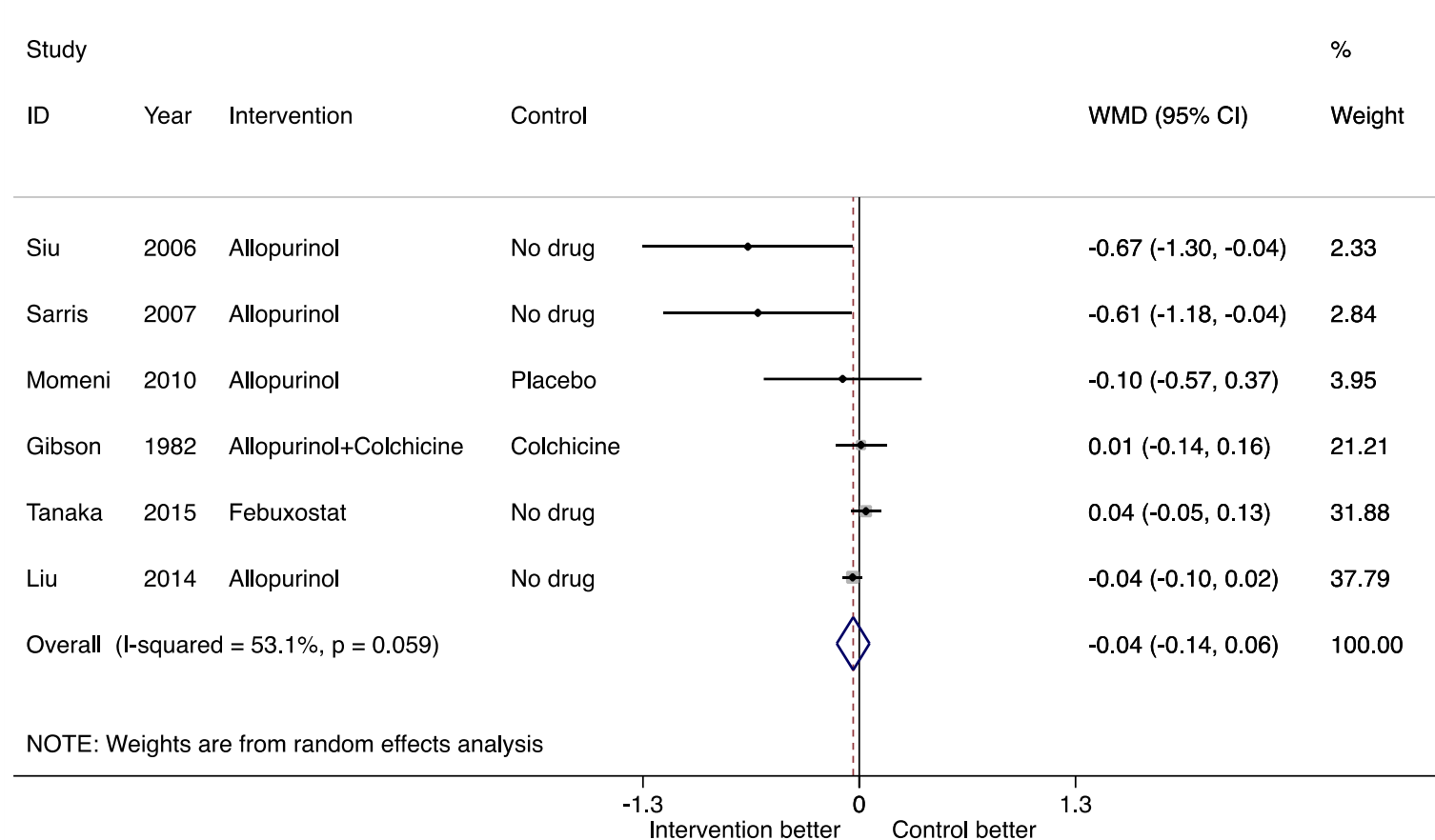
Risk of bias assessment



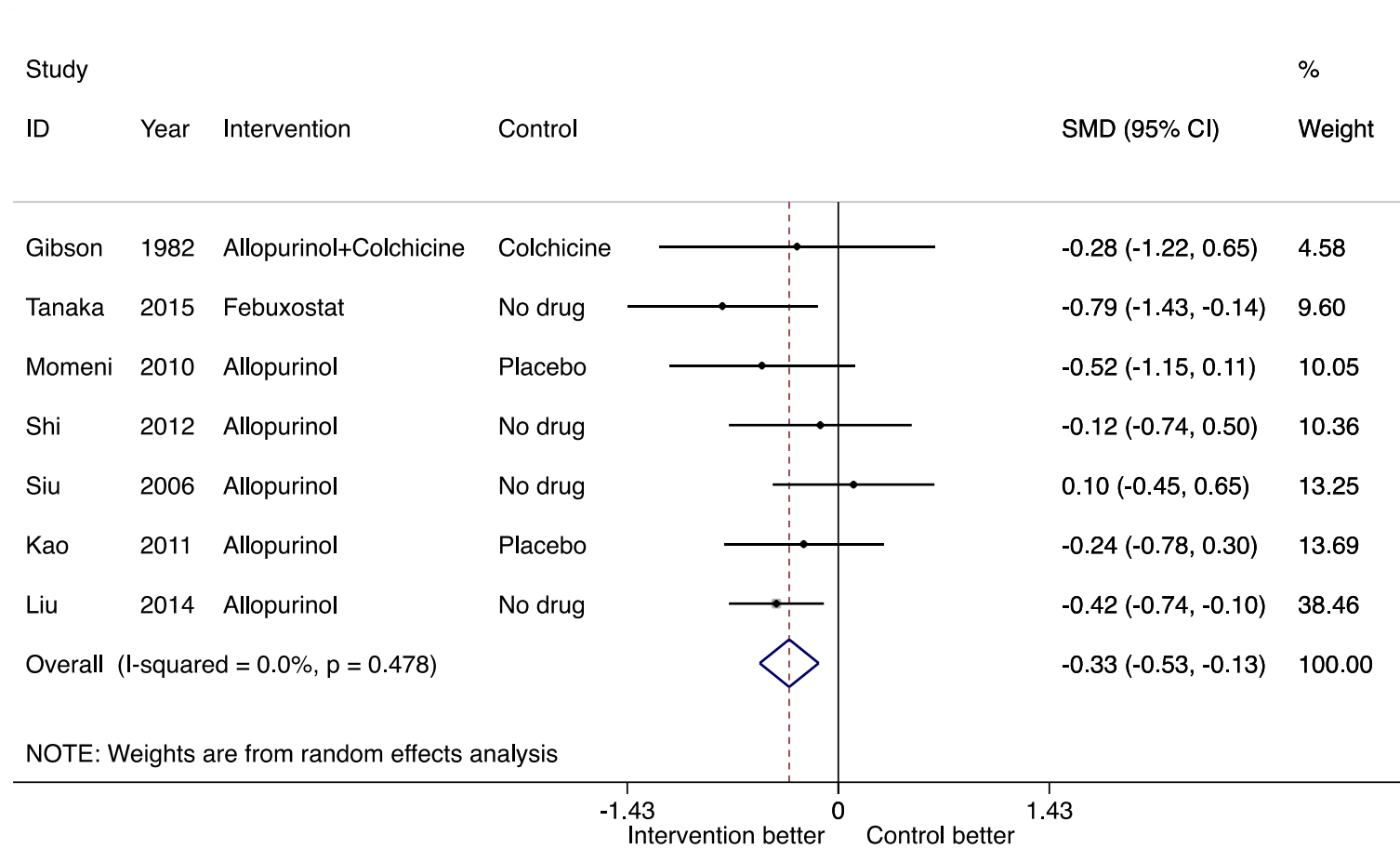
Effect of uric acid-lowering therapy on change in GFR (mL/min/1.73 m²) from baseline



Effect of uric acid-lowering therapy on change in serum creatinine (mg/dL) from baseline



Effect of uric acid-lowering therapy on change in proteinuria from baseline



Summary estimates of other outcomes #1

Outcome	Number of trials	MD, 95% CI; P
SBP (mm Hg)	7	-3.11, (-5.79, -0.42); 0.023
DBP (mm Hg)	7	-2.42 (-4.41, -0.44); 0.017
Uric acid (mg/dL)	11	-2.38 (-2.86, -1.91); 0.001

Summary estimates of other outcomes #2

Outcome	Number of trials	RR (95% CI); P
Progression to ESKD	2	0.56 (0.25, 1.25); 0.159
Death	1	0.88 (0.51, 1.51); 0.640
Medication discontinuation	9	0.91 (0.61, 1.36); 0.648
Any adverse event	8	2.73 (1.25, 5.97); 0.012

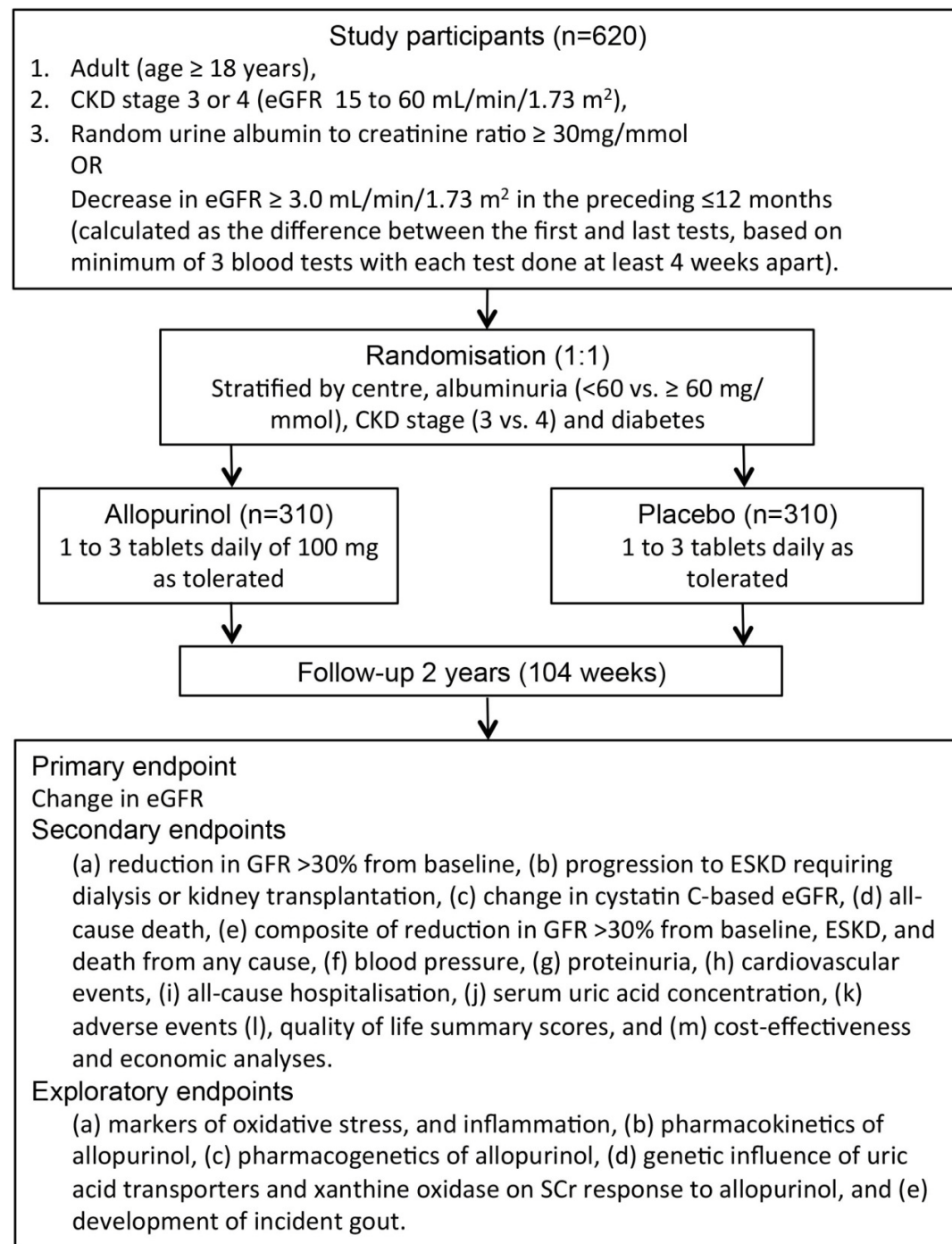
Systematic review: Conclusion

- The available RCT evidence evaluating the safety and efficacy of uric-acid lowering therapy as a renoprotective agent in patients with CKD is limited to a small number of single-centre studies with suboptimal methodology.
- There is insufficient evidence to currently recommend widespread use of uric acid-lowering therapy to slow the progression of CKD.
- Adequately powered randomised trials are required to evaluate the benefits and risks of uric acid-lowering therapy in CKD.

Trial 1: The CKD-FIX Study



- Controlled trial of slowing of Kidney Disease progression From the Inhibition of Xanthine oxidase
- Investigator-initiated, international, multicentre, prospective, randomised, double-blind, 1:1 placebo-controlled, parallel group superiority trial



Current status

- Funding: NHMRC project grant APP1043203 and NZ HRC grant
- Recruitment: March 2014 to December 2016
- Patients screened: 10,485
- Total randomised: 368 (only 3.5% of screened)!
- Planned follow-up: December 2018.
- Results expected in 2019.

Trial 2: The PERL Consortium

- Pilot international (USA, Canada, Denmark), placebo-controlled RCT (NIH sponsored)
- Study population (n=400): age 18-70 years, type 1 DM ≥ 8 years, micro- or macroalbuminuria, eGFR 45-100 mL/min/1.73 m², SUA ≥ 4.5 mg/dL
- Comparators: Allopurinol vs. placebo 100-400 mg/d \rightarrow target SUA 2.5-4.5 mg/dL, with reduction $\geq 30\%$ from baseline
- Duration: 3 years
- Primary outcome: Measured GFR (plasma clearance of non-labelled iohexol)

Trial 3: The FEATHER Study

- Japanese placebo-controlled RCT (Teijin Pharma)
- Study population (n=400): age ≥ 20 years, SUA 7.1-10 mg/dL, eGFR 30-59 mL/min/1.73 m²
- Comparators: Febuxostat vs. placebo 10 mg/d 1-4 weeks → 20 mg/d 5-8 weeks → 40 mg/d
- SUA checked in central lab, SUA ≥ 12 mg/dL → discontinue study
- Duration: 108 weeks
- Primary outcome: Annual rate of eGFR decline (eGFR slope)