Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Badve SV, Pascoe EM, Tiku A, et al. Effects of allopurinol on the progression of chronic kidney disease. N Engl J Med 2020;382:2504-13. DOI: 10.1056/NEJMoa1915833

Supplementary Appendix

Effect of Allopurinol on the Progression of Chronic Kidney Disease

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Committees, Leadership and Investigators

Trial Steering Committee

David W. Johnson (Chair), Sunil V. Badve, Anushree Tiku, Neil Boudville, Fiona G. Brown, Alan Cass, Philip Clarke, Nicola Dalbeth, Richard O. Day, Janak R. de Zoysa, Bettina Douglas, Randall Faull, David C. Harris, Carmel M. Hawley, Graham R.D. Jones, John Kanellis, Suetonia C. Palmer, Elaine M. Pascoe, Vlado Perkovic, Gopala K. Rangan, Donna Reidlinger, Laura Robison, Robert J. Walker, Giles Walters.

Data and safety monitoring board

Bruce Neal (Chair), The George Institute for Global Health, UNSW Sydney, Australia; Andrew Forbes, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia; David C. Wheeler, Department of Renal Medicine, University College London, London, the United Kingdom; and Christoph Wanner, Department of Medicine, University Hospital, Wuerzburg, Germany.

Project management team

The Australasian Kidney Trials Network, Brisbane, Australia: Carmel M. Hawley (Chair), David W. Johnson, Sunil V. Badve, Elaine Pascoe, Donna Reidlinger, Laura Robison, Liza A. Vergara, Peta-Anne Paul-Brent, and Julie Varghese, Alicia T. Morrish, Anish Scaria, Andrea K. Viecelli, Charani Kiriwandeniya, Hayley B. Candler, Magid A. Fahim, Rathika Krishnasamy and Yeoungjee Cho.

The Australasian Kidney Trials Network Executive Committee Members

Carmel M Hawley (Chair), Department of Nephrology, Princess Alexandra Hospital, Woolloongabba, Australia and Australasian Kidney Trials Network, The University of Queensland, Brisbane, Australia; David W Johnson (Deputy Chair), Department of Nephrology, Princess Alexandra Hospital, Woolloongabba, Australia and Australasian Kidney Trials Network, The University of Queensland, Brisbane, Australia and Translational Research Institute, Brisbane, Australia; Sunil V Badve, Department of Renal Medicine, St George Hospital, Sydney, Australia and Renal and Metabolic Division, the George Institute for Global Health, University of New South Wales Medicine, Sydney, Australia; Neil Boudville, Sir Charles Gairdner Hospital, Perth, Australia and Medical School, University of Western Australia, Perth, Australia; Alan Cass, Menzies School of Health Research, Charles Darwin University, Darwin, Australia; Meg J. Jardine, Concord Repatriation and General Hospital, Concord, Australia and The George Institute for Global Health, UNSW, Sydney, Australia; Alicia Morrish, Australasian Kidney Trials Network, The University of Queensland, Brisbane, Australia; Vlado Perkovic, The George Institute for Global Health, UNSW, Sydney, Australia; Elaine Pascoe, Australasian Kidney Trials Network, The University of Queensland, Brisbane, Australia; Donna Reidlinger, Australasian Kidney Trials Network, The University of Queensland, Brisbane, Australia.

Ancillary studies

Economic and cost-effectiveness: Philip Clarke, University of Melbourne, Melbourne, Australia and Health Economics Research Centre, Nuffield Department of Population Health, University of Oxford, Oxford, UK; Pharmacokinetic studies: Richard O Day, University of New South Wales and St. Vincent's Hospital, Sydney, Australia; Pharmacogenomic and genetic studies: Tony Merriman, University of Otago, Dunedin, New Zealand, and Elizabeth

Phillips, Vanderbilt University Medical Center, Nashville TN, USA and Centre for Clinical Pharmacology & Infectious Diseases, Institute for Immunology & Infectious Diseases, Murdoch University, Murdoch, WA, Australia; and Incident gout study: Nicola Dalbeth, School of Medicine, The University of Auckland, Auckland, New Zealand.

Collaborating sites and investigators

Australia: Australian Capital Territory: Canberra Hospital (Giles Walters, Patricia Johnson); **New South Wales**: Gosford Renal Research (Simon Roger, Liz Bohringer), John Hunter Hospital (Emmanuel D'Almeida, Leanne Garvey, Theresa Brown); Nepean Hospital (Bhadran Bose, Nelson Ubera, Craig Lawlor); Prince of Wales Hospital (Grant Luxton, Jacqueline Pearse, Zuzana Gray, Natalie Murphy, Maham Amin); St George Hospital (George Mangos, Sunil V. Badve, Kylie Turner, Paula Williamson); Westmead Hospital (Gopala Rangan, David Harris, Penelope Murie, Myrna Llapitan); Wollongong Hospital (Jane Holt, Mikki Smyth); **Queensland:** Gold Coast University Hospital (Siddharth Sharma, Helen McEvoy); Hervey Bay Hospital (Krishan Madhan, Leanne Brown, Ada Stevenson); Logan Hospital (Ken-Soon Tan, Erica Lennan); Nambour General Hospital and Sunshine Coast University Hospital (Carolyn Clark, Rathika Krishnasamy, Andrea Pollock, Gerald Hilder); Princess Alexandra Hospital (David Johnson, Amanda Coburn, Joanna Sudak); Toowoomba Hospital (Sree Krishna Venuthurupalli, Ian Fox); **South Australia:** Flinders Medical Centre (George Passaris, Susan Murray, Margaret Pummeroy); Royal Adelaide Hospital (Randall Faull, Jenny Latte); **Tasmania:** Royal Hobart Hospital (Lisa Jeffs, Matthew Jose); **Victoria:** Austin Health (Kathy Paizis, Marieke Veenendaal); Monash Medical Centre (Fiona Brown, Teresa Gilley); Melbourne Renal Research Group (David Packham, Robyn Gibbs); The Alfred Hospital (Scott Wilson, Jacquie Dixon, Claire Galbraith); Western Health (Craig Nelson, Jason Bennier); **Western Australia:** Fiona Stanley Hospital (Ashley Irish, Monika Chang); Sir Charles Gairdner Hospital and Medical School, University of Western Australia (Neil Boudville).

New Zealand: Auckland City Hospital (John Collins, Michael Collins, Andrew Pilmore); Christchurch Hospital (Jenny Usher, Nick Cross, Suetonia Palmer); North Shore Hospital (Janak de Zoysa, Erin Baker, Beula Vincent); Taranaki Base Hospital (Ashik Hayat, Lynette Knuth); Dunedin Hospital (Rob Walker, Liz Berry, Ines Becker), Waikato Hospital (Kannaiyan Rabindranath, Deborah Peek, Tania Smith); Renal Service, Northland District Health Board (Walaa Saweirs, Christine Johnson).

Figure S1. Study Flow Diagram

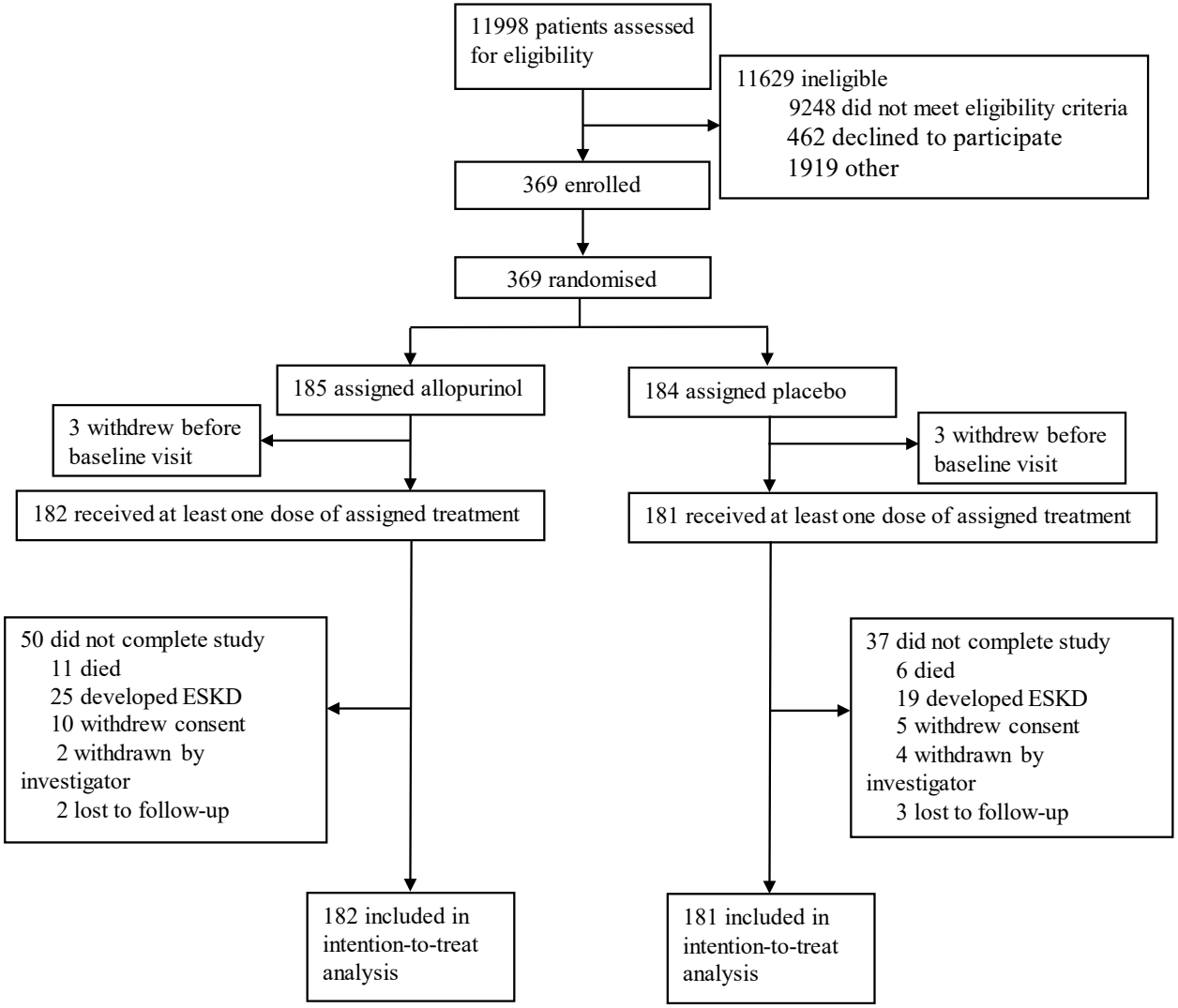

Figure S2. Effects of Allopurinol on Change in eGFR in Subgroups

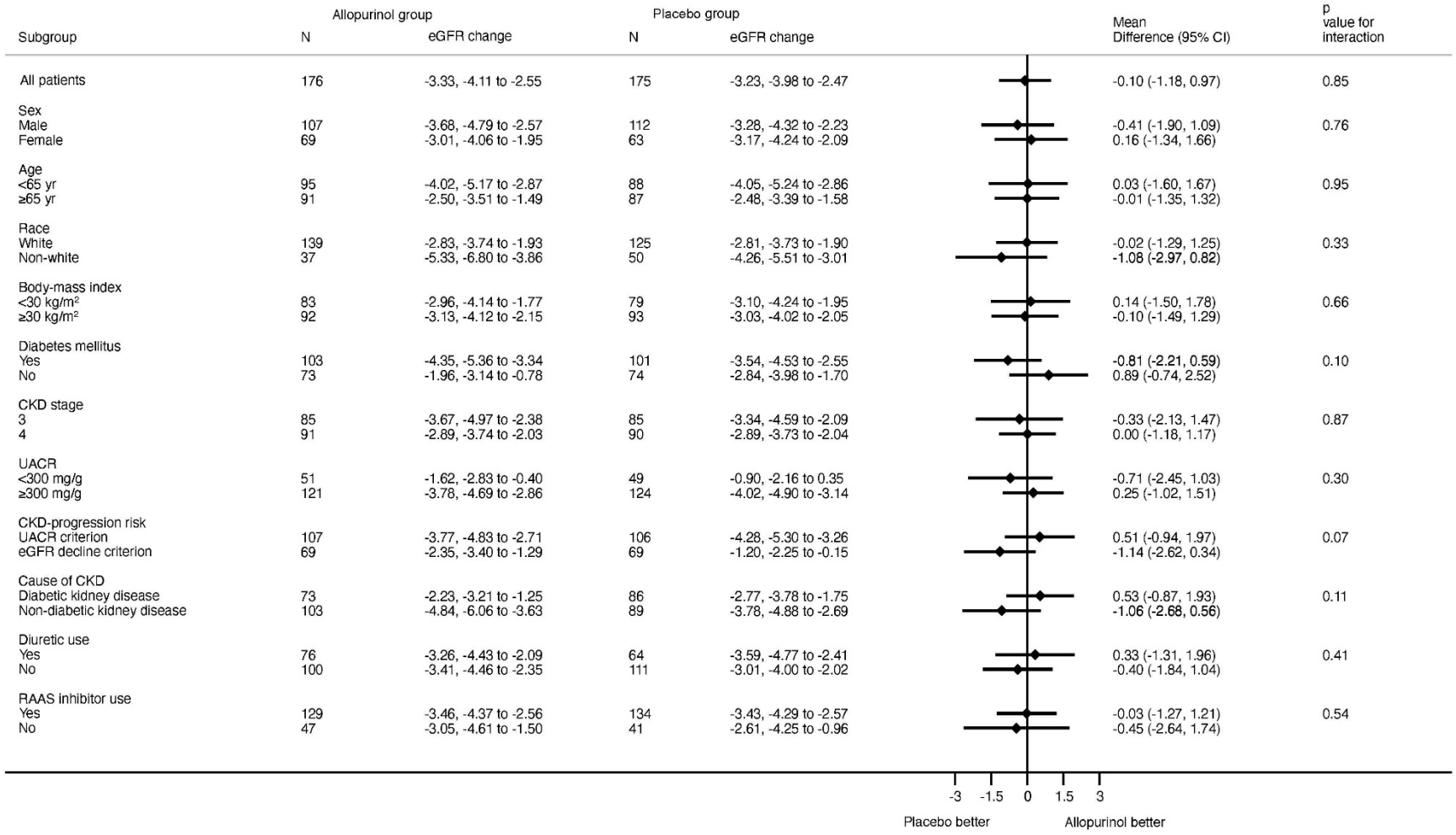

Figure S3. Effect of Allopurinol on Systolic Blood Pressure

Error bars indicate 95% confidence interval.

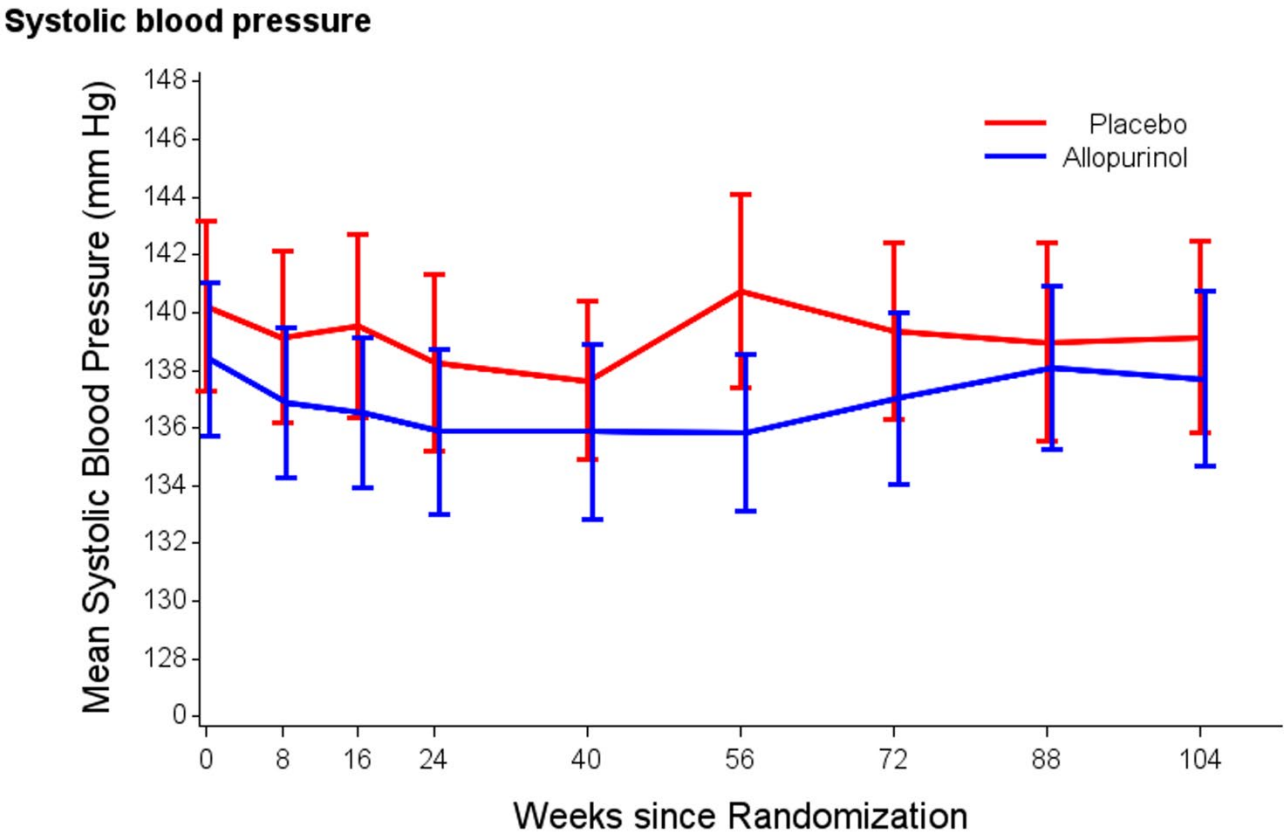

Figure S4. Effect of Allopurinol on Diastolic Blood Pressure

Error bars indicate 95% confidence interval.

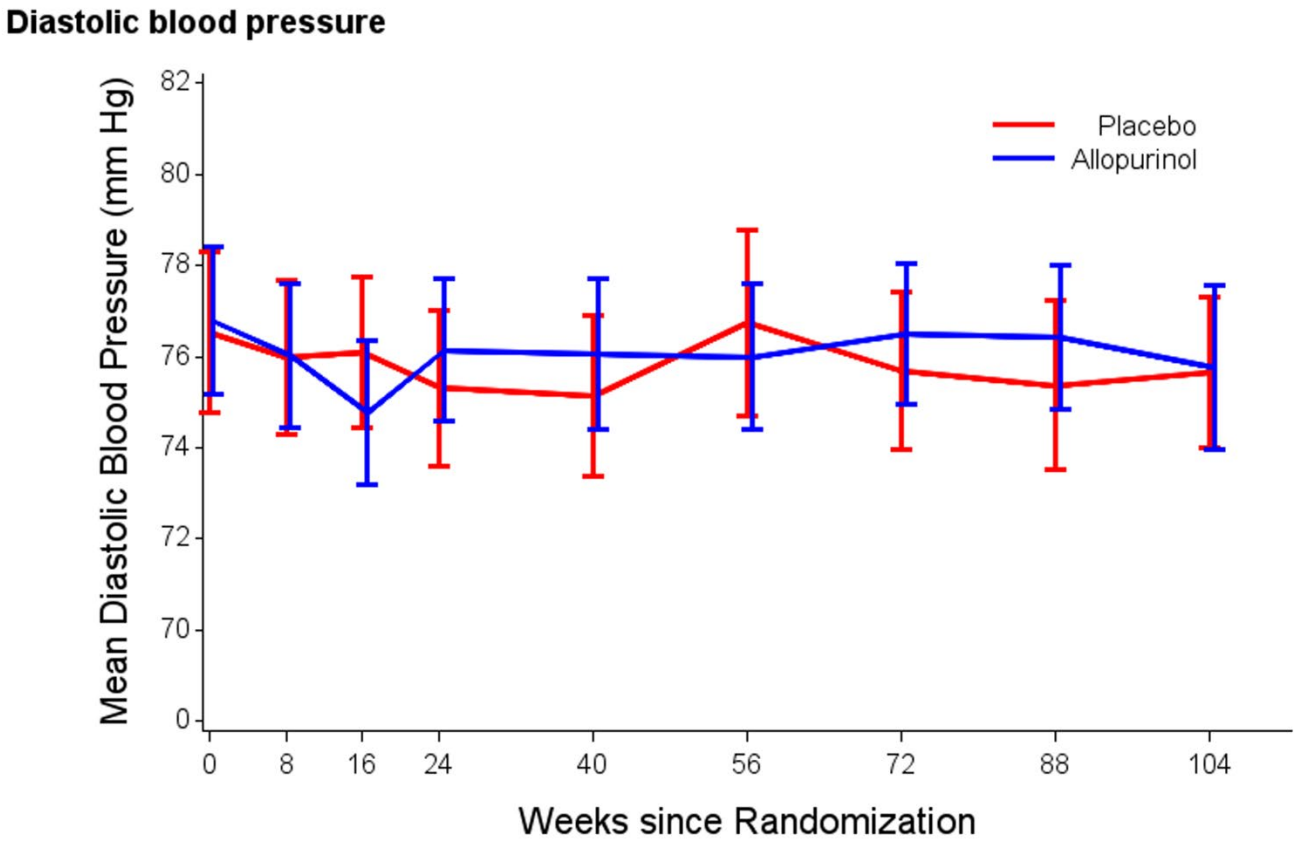

Table S1. Trial Eligibility Criteria

Inclusion criteria

1. Adult (age ≥ 18 years);
2. CKD stage 3 or 4 (eGFR 15 to 59 mL/min/1.73 m^2 inclusive); and,
3. Random urine albumin to creatinine ratio ≥265 mg/g (≥30 mg/mmol)
   OR
   Evidence of progression of CKD (decrease in eGFR ≥ 3.0 mL/min/1.73 m^2 in the preceding ≤ 12 months, calculated as the difference between the first and last tests, based on minimum of 3 blood tests with each test done at least 4 weeks apart).

Exclusion criteria

1. History of clinically established gout;
2. History of hypersensitivity to allopurinol;
3. Kidney transplant recipients;
4. Concurrent treatment with azathioprine, 6-mercaptopurine, theophylline, cyclophosphamide, cyclosporine, probenecid, phenytoin, or chlorpropamide;
5. Indication for allopurinol, including tophus or tophi on clinical examination or imaging study, uric acid nephropathy, uric acid nephrolithiasis or urolithiasis;
6. Current non-skin cancer malignancy;
7. Unresolved acute kidney injury in last 3 months;
8. Current pregnancy or breast feeding;
9. Any uncontrolled psychological illness or condition which interferes with their ability to understand or comply with the requirements of the study; or
10. Elective or imminent initiation of maintenance dialysis or kidney transplantation expected in the next 6 months.

Table S2. Criteria for Study Medication Dose Adjustment

1. No new onset skin rash or reaction;
2. Haemoglobin >80 g/L;
3. Neutrophil count >2.0 x 10^9/L;
4. Eosinophil count ≤0.60 x 10^9/L or <20% of previous value if baseline eosinophil count >0.60 x 10^9/L;
5. Platelet count >100 x 10^9/L;
6. Alanine transaminase (use aspartate transaminase if alanine transaminase is not available) <3 times upper limit of normal;
7. Serum creatinine >20% increase of previous value; and,
8. The treating physician feels increasing dose is safe based on the clinical circumstances.

Table S3. Causes of Discontinuation of Study Medication

Cause	Allopurinol	Placebo
Total	54	45
Physician request	11	14
Patient request	20	15
Adverse event	20	16
Other	3	0

Table S4. Demographic and Clinical Characteristics of the Patients at Baseline.

Characteristic	Allopurinol (N=182)	Placebo (N=181)	Total (N=363)
Age - yr	62.3±12.6	62.6 (12.9)	62.4±12.7
Female sex - n (%)	70 (38.5%)	65 (35.9%)	135 (37.2%)
Race or ethnic group - n (%)			
White	143 (78.6%)	129 (71.3%)	272 (74.9%)
Australian Aboriginal/ Torres Strait Islander	2 (1.1%)	2 (1.1%)	4 (1.1%)
New Zealand Māori	13 (7.1%)	15 (8.3%)	28 (7.7%)
Asian	8 (4.4%)	11 (6.1%)	19 (5.2%)
Other	16 (8.8%)	24 (13.3%)	40 (11.0%)
Weight - kg †	90.3±22.4	90.0±22.3	90.0±22.3
Body-mass index - kg/m^2 (IQR) †	30 (26, 36)	31 (27, 35)	30 (26, 36)
Blood pressure †			
Systolic - mm Hg	138.4±18.2	140.2±20.0	139.3±19.1
Diastolic - mm Hg	76.8±11.1	76.5±12.2	76.7±11.6
Primary cause of kidney disease - n (%)			
Diabetic kidney disease	75 (41.2%)	90 (49.7%)	165 (45.5%)
Hypertension/vascular	31 (17.0%)	19 (10.5%)	50 (13.8%)
Glomerulonephritis	22 (12.1%)	16 (8.8%)	38 (10.5%)
Reflux nephropathy	5 (2.7%)	4 (2.2%)	9 (2.5%)
Polycystic kidney disease	19 (10.4%)	9 (5.0%)	28 (7.7%)
Other	24 (13.2%)	27 (14.9%)	51 (14.0%)
Unknown	6 (3.3%)	16 (8.8%)	22 (6.1%)
Diabetes mellitus - n (%)	104 (57.1%)	106 (58.6%)	210 (57.9%)
Hypertension - n (%)	171 (94%)	173 (95.6%)	344 (94.8%)
Cardiovascular disease - n (%)	58 (31.9%)	64 (35.4%)	122 (33.6%)

Characteristic	Allopurinol (N=182)	Placebo (N=181)	Total (N=363)
Peripheral artery disease - n (%)	21 (11.5%)	18 (9.9%)	39 (10.7%)
Cerebrovascular disease - n (%)	18 (9.9%)	18 (9.9%)	36 (9.9%)
Hyperlipidemia - n (%)	132 (72.5%)	136 (75.1%)	268 (73.8%)
Previous cancer (not skin) - n (%)	19 (10.4%)	20 (11.0%)	39 (10.7%)
Current smoker - n (%)	14 (7.7%)	23 (12.7%)	37 (10.2%)
eGFR - mL/min/1.73 m^2	31.6±11.7	31.9±12.4	31.7±12.0
CKD stage - n (%)			
Stage 3	88 (48.4%)	90 (49.7%)	178 (49.0%)
Stage 4	94 (51.6%)	91 (50.3%)	185 (51.0%)
Urine ACR - mg/g (IQR) †	716.9 (237.2, 1947)	716.9 (246.0, 1857)	716.9 (244.3, 1857)
<30 - n (%)	21 (11.7%)	16 (8.9%)	37 (10.3%)
≥30-300 - n (%)	33 (18.4%)	34 (19.0%)	67 (18.7%)
≥300 - n (%)	125 (69.8%)	129 (72.1%)	254 (70.9%)
Serum urate mg/dL †	8.2±1.8	8.2±1.7	8.2±1.8
Hemoglobin g/dL †	12.5±1.7	12.5±1.7	12.5±1.7
Total cholesterol - mg/dL †	181.7±49.9	174.4±53.4	178.0± 51.7
Triglyceride - mg/dL (IQR) †	159.3 (115.1, 239.0)	177.0 (106.2, 256.7)	168.2 (106.2, 256.7)
Medications - n (%)			
ACE inhibitor	71 (39%)	75 (41.4%)	146 (40.2%)
ARB	63 (34.6%)	67 (37.0%)	130 (35.8%)
Spironolactone	7 (3.8%)	14 (7.7%)	21 (5.8%)
Diuretics (including loop and thiazide)	79 (43.4%)	67 (37.0%)	146 (40.2%)

Plus–minus values are means ±SD. IQR, interquartile range. ACE, angiotensin-converting enzyme; ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

† some missing data.

Table S5. Effect of allopurinol on the primary outcome of change in eGFR

Outcome	Change in eGFR (mL/min/1.73 m^2/year)		Mean difference
	Allopurinol (n=182)	Placebo (n=181)	
CKD-EPI creatinine equation			
Adjusted for baseline eGFR	-3.33, -4.11 to -2.55	-3.23, -3.98 to -2.47	-0.10, -1.18 to 0.97
Adjusted for baseline eGFR and primary cause of kidney disease	-3.09, -3.84 to -2.34	-3.08, -3.81 to -2.34	-0.01, -1.06 to 1.04
Adjusted for baseline eGFR and minimisation variables	-3.34, -4.12 to -2.56	-3.24, -4.00 to -2.48	-0.10, -1.18 to 0.98
Adjusted for baseline eGFR, minimisation variables and region	-3.08, -3.83 to -2.33	-3.08, -3.82 to -2.34	0.00, -1.05 to 1.05
CKD-EPI cystatin C equation			
Adjusted for baseline eGFR	-2.31, -2.94 to -1.67	-2.46, -3.09 to -1.83	0.15, -0.74 to 1.05
CKD-EPI cystatin C and creatinine equation			
Adjusted for baseline eGFR	-2.86, -3.55 to -2.17	-2.84, -3.52 to -2.16	-0.02, -0.97 to 0.94
MDRD creatinine equation			
Adjusted for baseline eGFR	-3.05, -3.82 to -2.28	-2.91, -3.66 to -2.15	-0.14, -1.21 to 0.92

Footnotes

Data are mean, 95% confidence interval. † treatment x time interaction p value.

CKD-EPI: Chronic Kidney Disease Epidemiology; MDRD: Modification of Diet in Renal Disease

Table S6. Serious Adverse Events by Body System

Body system	Allopurinol (n=182)	Placebo (n=181)	Total (n=363)
Cardiovascular	**33 (19%)**	**44 (26%)**	**77 (23%)**
Acute coronary disorder	4	18	22
Heart failure	7	11	18
Accelerated, malignant or vascular hypertension	1	0	1
Arrhythmia	7	3	10
Peripheral vascular event	5	2	7
Hypotension	4	1	5
Hypertension	1	3	4
Syncope	2	1	3
Other cardiovascular	2	5	7
Respiratory	**15 (9%)**	**18 (11%)**	**33 (10%)**
COPD exacerbation	2	4	6
Lower respiratory or lung infection	9	6	
Other respiratory	4	6	10
Gastrointestinal	**19 (11%)**	**21 (13%)**	**40 (12%)**
Nausea/vomiting	1	6	7
Diarrhea	2	3	5
Abdominal pain	5	1	6
Gastrointestinal bleeding	3	2	5
Other gastrointestinal	8	9	17
Renal	**39 (23%)**	**30 (18%)**	**69 (20%)**
Acute kidney injury	8	6	14
Peripheral edema	1	4	5
Noncardiac pulmonary edema	1	2	3

Body system	**Allopurinol (n=182)**	**Placebo (n=181)**	**Total (n=363)**
Hyperkalemia	3	3	6
Urinary tract infection	3	2	5
Calculi	4	0	4
Elective procedure	14	10	24
Other renal	5	3	8
Neurological	**11 (6%)**	**6 (4%)**	**17 (5%)**
Altered conscious state	0	1	1
Headache	0	1	1
Stroke	5	4	9
Other neurological	6	0	6
Musculoskeletal	**11 (6%)**	**17 (10%)**	**28 (8%)**
Pain	3	3	6
Fracture	3	6	9
Infection	3	4	7
Other musculoskeletal	2	4	6
Endocrine	**6 (4%)**	**3 (2%)**	**9 (3%)**
Hyperglycemia	3	2	5
Hypoglycemia	2	0	2
Other endocrine	1	1	2
Cancer/ neoplasm	**6 (4%)**	**7 (4%)**	**13 (4%)**
Hematologic	**4 (2%)**	**2 (1%)**	**6 (2%)**
Anemia requiring investigation	3	1	4
Other hematologic	1	1	2
Skin	**10 (6%)**	**10 (6%)**	**20 (6%)**
Skin rash	1	1	2

Body system	**Allopurinol (n=182)**	**Placebo (n=181)**	**Total (n=363)**
Erythema multiforme	1	0	1
Infection	7	6	13
Other skin	1	3	4
Other	**16 (9%)**	**9 (5%)**	**25 (7%)**
Elective procedure	12	7	19
Infection	2	0	2
Other	2	2	4
Total	**170 (100%)**	**167 (100%)**	**337 (100%)**

Values are number of events (%).

Table S7. Non-Serious Adverse Drug Reactions

Adverse drug reaction	**Allopurinol (n=182)**	**Placebo (n=181)**	**Total (n=363)**
Skin rash	14 (41%)	13 (30%)	27 (35%)
Pruritus	4 (12%)	6 (14%)	10 (13%)
Musculoskeletal pain	2 (6%)	5 (12%)	7 (9%)
Upper respiratory tract infection	1 (3%)	3 (7%)	4 (5%)
Abdominal pain	1 (3%)	2 (5%)	3 (4%)
Edema	3 (9%)	0	3 (4%)
Fall	0	3 (7%)	3 (4%)
Gout	2 (6%)	1 (2%)	3 (4%)
Headache	2 (6%)	1 (2%)	3 (4%)
Anemia	0	2 (5%)	2 (3%)
Diarrhea	0	2 (5%)	2 (3%)
Hypertension	2 (6%)	0	2 (3%)
Hypotension	1 (3%)	0	1 (1%)
Acute kidney injury	0	1 (2%)	1 (1%)
Other	2 (6%)	4 (9%)	6 (8%)
Total †	**34 (100%)**	**43 (100%)**	**77 (100%)**

Values are number of events (%). A non-serious adverse drug reaction was defined as any unfavorable and unintended response that are judged by the investigator to be at least possibly related to study medication. † Events are from 32/182 (18%) participants in the allopurinol group and 29/181 (16%) participants in the placebo group (chi-square P =0.69).