Medical therapies to reduce chronic kidney disease progression and cardiovascular risk: uric acid-lowering agents

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GUIDELINES

a. We suggest that use of uric acid lowering agents (such as allopurinol, rasburicase or febuxostat) should not be routinely recommended in people with early (stages 1-3) chronic kidney disease who have asymptomatic hyperuricaemia (2C).

UNGRADED SUGGESTIONS FOR CLINICAL CARE

There are no ungraded statements.

IMPLEMENTATION AND AUDIT

No recommendations.

BACKGROUND

Chronic kidney disease (CKD) represents a major, rapidly growing, public health burden worldwide. In Australia, CKD affects approximately 1 in 7 (or more than 2 million) adults over the age of 25, and contributes to nearly 10% of all deaths and over 1.1 million hospitalisations annually. [1, 2] Several studies, in various populations[3-22], have demonstrated that:

- CKD is a potent, independent cardiovascular (CV) risk factor, with CV events occurring between 10 to 100 times more frequently in the CKD population, and
- CKD has a multiplicative impact on other chronic diseases.

CKD is expensive. In 2000-01, the estimated total recurrent health expenditure on CKD in Australia was $647 million. [23] A recent analysis of the health economic impact of end-stage kidney disease (ESKD) in Australia estimated that, at the end of 2007, hospital dialysis cost around $189 million per year. [24]

Taken together, CKD is a significant contributor of morbidity and mortality, and represents a major expense to the health care system. Early intervention with appropriate medical therapies is essential to address this public health burden and may reduce the progression of CKD and CV risk by up to 50%. [25] The objective of this guideline is to review currently available evidence in this regard and provide appropriate clinical recommendations. Recommendations in other guidelines, and the evidence underpinning these recommendations, have also been reviewed.

Numerous epidemiological studies, comprehensively reviewed elsewhere[26, 27], have established that asymptomatic hyperuricaemia is associated with both CKD and ESKD. However, hyperuricaemia is a ubiquitous finding in CKD[28] and could be a consequence of reduced excretion, diuretic therapy, or oxidative stress. Although it is not clear whether urate plays a causative role or is an indirect marker of kidney function, uric acid lowering therapy has emerged as a potentially novel therapeutic treatment for slowing the progression of CKD[27]

SEARCH STRATEGY

Databases searched: Text words for chronic kidney disease were combined with MeSH terms and text words for uric acid, allopurinol, rasburicase and febuxostat. The search was carried out in Medline (1994 – October 2009). No language restrictions were placed on the search. The conference proceedings of the American Society of Nephrology from 1994 - 2011 were also searched for trials. A search update was conducted in Medline (2009 – May 2012) using the same MeSH terms and text words.

Date of search/es: November 2009 and May 2012.

WHAT IS THE EVIDENCE?

Recent, indirect evidence (2 cohort studies) suggests that allopurinol may be beneficial in retarding CKD progression. Kanbay et al. [29] performed a 3-month study of 41 patients who were treated with allopurinol 300 mg/d and compared them with 18 healthy controls. In the allopurinol group, there was an improvement of creatinine clearance from 79.2 ± 31.9 to 92.9 ± 36.8 ml/min ($P < 0.05$). Talaat et al. [30] examined the effect of allopurinol withdrawal from 50, stage 3-4 CKD patients who had been on chronic allopurinol therapy for mild hyperuricaemia. Allopurinol withdrawal was associated with significant worsening of hypertension and acceleration of the rate of loss of kidney function.

Four RCTs have examined the effect of allopurinol on CKD progression. Siu et al. [31] compared 12 months of allopurinol therapy with 'usual therapy' and found that allopurinol was safe and helped preserve kidney function. 4 of 25 patients (16%) in the allopurinol group experienced deteriorating renal function or became dialysis-dependent, compared to 12 of 26 patients (46.1%) in the control group ($P < 0.05$). 'Usual therapy' was ill-defined in this small, open-label study.

Goicoechea et al[32] conducted a prospective, randomized trial of 113 patients with estimated GFR (eGFR) <60 ml/min randomised to treatment with allopurinol 100 mg/d (n = 57) or to continue usual therapy (n = 56) for a period of 24 months. eGFR decreased by 3.3 ± 1.2 ml/min/1.73 m^2 in the control group and increased by 1.3 ± 1.3 ml/min/1.73 m^2 in the allopurinol group after 24 months (p=0.018). Using multivariable Cox regression analysis, allopurinol treatment slowed renal disease progression (defined as an eGFR decrease >0.2 ml/min/ 1.73 m^2 per month) compared with controls (HR 0.53, 95% CI 0.28-0.99, p=0.048). The study was limited by small sample size, short follow-up duration, open-label design, and failure to consider dietary factors.

Momeni et al[33] conducted a double-blind RCT of allopurinol 100 mg daily versus placebo for 4 months in 40 CKD patients with type 2 diabetes mellitus, proteinuria >0.5 g/d and serum creatinine <229 µmol/L. After 4 months of treatment, proteinuria was significantly reduced in the allopurinol group compared with controls (1011±767 vs 1609±1071 mg/d, p=0.049). The study was limited by small sample size, short follow-up duration, lack of assessment of volume status and reliance on surrogate outcome measures.

A randomised, double-blind, placebo-controlled, parallel-group study of allopurinol 300 mg daily versus placebo in 53 patients with stage 3 CKD and left ventricular hypertrophy for 9 months found that allopurinol significantly reduced left ventricular hypertrophy (p=0.036), improved endothelial function (p=0.009), and improved the central augmentation index (p=0.015)[34] The study was limited by small sample size, short follow-up duration, failure to adjust for multiple statistical comparisons and reliance on surrogate outcome measures.

All of these studies had generally suboptimal methodologic quality and none adequately evaluated (or was adequately powered to evaluate) the safety of allopurinol therapy in CKD.

Dosing of allopurinol requires adjustment in patients with CKD to minimise the risk of adverse reactions. This may also attenuate the urate-lowering effect of allopurinol. The advent of two novel, urate-lowering agents, febuxostat (a selective xanthine oxidase inhibitor) and rasburicase (recombinant urate oxidase) may provide alternative approaches in patients with CKD. Both agents have demonstrated better efficacy than allopurinol in lowering uric acid with a more favourable safety profile, particularly in patients with impaired renal function. [35, 36] No studies have evaluated the effect of febuxostat on CKD progression. One recent RCT compared rasburicase with placebo in elderly (65 – 85 yrs) patients with CKD and hyperuricaemia. [37] In this small (38 patients), 8-week study, patients managed with rasburicase + diet treatment had a decrease in serum creatinine of 0.68 (60 µmol/L) vs an increase of 0.16 mg/dL (14 µmol/L) in the placebo group, ($P < 0.001$). The treatment group had an increase in

creatinine clearance of 12.7 vs a decrease of 1.10 ml/min/24 h for the placebo group, (P < 0.001). There was no significant difference in mean baseline serum creatinine (rasburicase group: 2.66 ± 0.55 mg/dl (235 ± 49 μmol/l) vs placebo group: 2.44 ± 0.61 mg/dl (216 ± 54 μmol/l).

SUMMARY OF EVIDENCE

Recent small, single-centre, short-duration trials of suboptimal methodologic quality have provided suggestive signals of a benefit of uric acid-lowering agents on surrogate markers of CKD progression. However, there are no adequately powered, high quality randomised controlled trials examining patient-level outcomes to permit recommendation of the routine use of uric acid lowering agents in patients with early (stages 1-3) CKD with asymptomatic hyperuricaemia. There has also not been an adequate assessment of the safety of allopurinol therapy under such circumstances.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.
UK Renal Association: No recommendation.
Canadian Society of Nephrology: No recommendation.
European Best Practice Guidelines: No recommendation.
International Guidelines:
National Institute for Clinical Excellence (NICE):[38]
R60 There is insufficient evidence to recommend the routine use of drugs to lower uric acid in people with CKD who have asymptomatic hyperuricaemia.

SUGGESTIONS FOR FUTURE RESEARCH

A double-blind randomised placebo-controlled trial to assess the safety and efficacy of uric acid lowering therapy on slowing the progression of chronic kidney disease and reducing cardiovascular events in patients with CKD is warranted. The Australasian Kidney Trials Network is currently planning such a study with allopurinol (the CKD-FIX study).

CONFLICT OF INTEREST

Richard Phoon has a level II b. conflict of interest for receiving speaker fees and honoraria from several companies related to anaemia, CKD-MBD and cardiovascular disease between 2008 and 2012.

David Johnson has a level II b. conflict of interest for receiving speaker honoraria and advisor's fees from several companies related to anaemia, CKD-MBD, hypertension and cardiovascular disease between 2008 and 2012.

REFERENCES

1. Green F and C R, *An Overview of Chronic Kidney Disease in Australia*. 2009, Australian Institute of Health and Welfare: Canberra.
2. *National Chronic Kidney Disease Strategy*. 2006, Kidney Health Australia.
3. Anavekar NS, McMurray JJ, Velazquez EJ et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *New England Journal of Medicine*. 2004; **351**: 1285-1295.
4. Brantsma AH, Bakker SJL, Hillege HL et al. Cardiovascular and renal outcome in subjects with K/DOQI stage 1-3 chronic kidney disease: the importance of urinary albumin excretion. *Nephrology Dialysis Transplantation*. 2008; **23**: 3851-8.
5. Chien K-L, Hsu H-C, Lee Y-T et al. Renal function and metabolic syndrome components on cardiovascular and all-cause mortality. *Atherosclerosis*. 2008; **197**: 860-7.
6. Farbom P, Wahlstrand B, Almgren P et al. Interaction between renal function and microalbuminuria for cardiovascular risk in hypertension: the nordic diltiazem study. *Hypertension*. 2008; **52**: 115-22.
7. Foley RN, Parfrey PS, and Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *American Journal of Kidney Diseases*. 1998; **32**: S112-9.
8. Go AS, Chertow GM, Fan D et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *New England Journal of Medicine*. 2004; **351**: 1296-305.
9. Keith DS, Nichols GA, Gullion CM et al. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Archives of Internal Medicine*. 2004; **164**: 659-63.
10. Kurth T, de Jong PE, Cook NR et al. Kidney function and risk of cardiovascular disease and mortality in women: a prospective cohort study. *BMJ*. 2009; **338**: b2392.
11. Luthi J-C, Flanders WD, Burnier M et al. Anemia and chronic kidney disease are associated with poor outcomes in heart failure patients. *BMC Nephrology*. 2006; **7**: 3.
12. Manjunath G, Tighiouart H, Coresh J et al. Level of kidney function as a risk factor for cardiovascular outcomes in the elderly. *Kidney International*. 2003; **63**: 1121-9.
13. McCullough PA, Li S, Jurkovitz CT et al. CKD and cardiovascular disease in screened high-risk volunteer and general populations: the Kidney Early Evaluation Program (KEEP) and National Health and Nutrition Examination Survey (NHANES) 1999-2004. *American Journal of Kidney Diseases*. 2008; **51**: S38-45.
14. McDonald SP, Maguire GP, and Hoy WE. Renal function and cardiovascular risk markers in a remote Australian Aboriginal community. *Nephrology Dialysis Transplantation*. 2003; **18**: 1555-61.
15. Nakamura K, Okamura T, Hayakawa T et al. Chronic kidney disease is a risk factor for cardiovascular death in a community-based population in Japan: NIPPON DATA90. *Circulation Journal*. 2006; **70**: 954-9.
16. Nickolas TL, Khatri M, Boden-Albala B et al. The association between kidney disease and cardiovascular risk in a multiethnic cohort: findings from the Northern Manhattan Study (NOMAS). *Stroke*. 2008; **39**: 2876-9.
17. Parikh NI, Hwang S-J, Larson MG et al. Chronic kidney disease as a predictor of cardiovascular disease (from the Framingham Heart Study). *American Journal of Cardiology*. 2008; **102**: 47-53.
18. Rashidi A, Sehgal AR, Rahman M et al. The case for chronic kidney disease, diabetes mellitus, and myocardial infarction being equivalent risk factors for cardiovascular mortality in patients older than 65 years. *American Journal of Cardiology*. 2008; **102**: 1668-73.
19. Remuzzi G and Remuzzi A. Is regression of chronic nephropathies a therapeutic target? *Journal of the American Society of Nephrology*. 2005; **16**: 840-2.
20. Shara NM, Resnick HE, Lu L et al. Decreased GFR estimated by MDRD or Cockcroft-Gault equation predicts incident CVD: the strong heart study. *Journal of Nephrology*. 2009; **22**: 373-80.
21. Tsagalis G, Akrivos T, Alevizaki M et al. Renal dysfunction in acute stroke: an independent predictor of long-term all combined vascular events and overall mortality. *Nephrology Dialysis Transplantation*. 2009; **24**: 194-200.

22. Weiner DE, Tighiouart H, Stark PC et al. Kidney disease as a risk factor for recurrent cardiovascular disease and mortality. *American Journal of Kidney Diseases*. 2004; **44**: 198-206.
23. AIHW, *Chronic Kidney Disease in Australia*, in *Cat.No. PHE68*. 2005, Australian Institute of Health and Welfare: Canberra.
24. Cass A, Craig J, Howard H et al, *The Economic Impact of End-Stage Kidney Disease in Australia*. 2006.
25. Johnson DW. Evidence-based guide to slowing the progression of early renal insufficiency. *Internal Medicine Journal*. 2004; **34**: 50-7.
26. Avram Z and Krishnan E. Hyperuricaemia—where nephrology meets rheumatology. *Rheumatology*. 2008; **47**: 960-964.
27. Badve SV, Brown F, Hawley CM et al. Challenges of conducting a trial of uric-acid-lowering therapy in CKD. *Nature Reviews Nephrology*. 2011; **7**: 295-300.
28. Sturm G, Kollerits B, Neyer U et al. Uric acid as a risk factor for progression of non-diabetic chronic kidney disease? The Mild to Moderate Kidney Disease (MMKD) Study. *Experimental gerontology*. 2008; **43**: 347-52.
29. Kanbay M, Ozkara A, Selcoki Y et al. Effect of treatment of hyperuricemia with allopurinol on blood pressure, creatinine clearence, and proteinuria in patients with normal renal functions. *International Urology and Nephrology*. 2007; **39**: 1227-1233.
30. Talaat KM and El-Sheikh AR. The effect of mild hyperuricemia on urinary transforming growth factor beta and the progression of chronic kidney disease. *American Journal of Nephrology*. 2007; **27**: 435 - 440.
31. Siu YP, Leung KT, Tong MKH et al. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. *American Journal of Kidney Diseases*. 2006; **47**: 51 - 59.
32. Goicoechea M, de Vinuesa SG, Verdalles U et al. Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. *Clinical Journal of The American Society of Nephrology: CJASN*. 2010; **5**: 1388-93.
33. Momeni A, Shahidi S, Seirafian S et al. Effect of allopurinol in decreasing proteinuria in type 2 diabetic patients. *Iranian journal of Kidney Diseases*. 2010; **4**: 128-32.
34. Kao MP, Ang DS, Gandy SJ et al. Allopurinol benefits left ventricular mass and endothelial dysfunction in chronic kidney disease. *Journal of the American Society of Nephrology*. 2011; **22**: 1382-9.
35. Mayer MD, Khosravan R, Vernillet L et al. Pharmacokinetics and Pharmacodynamics of Febuxostat, a New Non-purine Selective Inhibitor of Xanthine Oxidase in Subjects with Renal Impairment. *American Journal of Therapeutics January/February*. 2005; **12**: 22-34.
36. Schumacher HR, Becker MA, Wortmann RL et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: A 28-week, phase III, randomized, double-blind, parallel-group trial. *Arthritis Care & Research*. 2008; **59**: 1540-1548.
37. Malaguarnera M, Vacante M, Russo C et al. A single dose of rasburicase in elderly patients with hyperuricaemia reduces serum uric acid levels and improves renal function. *Expert Opinion on Pharmacotherapy*. 2009; **10**: 737-742.
38. National Collaborating Centre for Chronic Conditions, *Chronic kidney disease: National clinical guideline for early identification and management in adults in primary and secondary care.* 2008, Royal College of Physicians: London.

APPENDICES

Table 1. Characteristics of included studies

Study ID	N	Study design	Participants	Follow up	Comments and results
Kanbay et al (2007) [29]	69	Cohort	Participants with GFR > 60 ml/min and hyperuricemia (uric acid level > 7.0mg/dL) were recruited. Patients in the treatment group received allopurinol 300 mg/day	3 months	• In the allopurinol group, serum uric acid levels, GFR, systolic and diastolic blood pressure, and C-reactive protein (CRP) levels improved significantly (P < 0.05). GFR improved from 79.2 ± 31.9 to 92.9 ± 36.8 ml/min (P < 0.05) compared to the control group (from 89.4 ± 3.0 to 91.0 ± 6.1; P = NS)
Talaat et al (2007) [30]	50	Cohort	Participants with stage 3 and 4 chronic kidney disease and with mild hyperuricemia	1 year	• Withdrawal of allopurinol treatment resulted in significant worsening of hypertension, significant acceleration of the rate of loss of kidney function and significant increase in the urinary excretion of transforming growth factor beta-1 (TGF-ß1) in patients not receiving renin-angiotensin system blockers.
Siu et al (2006) [31]	54	RCT	Participants with chronic kidney disease were randomised to treatment (allopurinol) or control (usual treatment) group	1 year	• Serum uric acid levels were significantly decreased in subjects treated with allopurinol, from 9.75 ±1.18 mg/dL to 5.88 ± 1.01 mg/dL (P < 0.001) • There was a trend toward a lower serum creatinine level in the treatment group compared with controls but was not statistically significant (P = 0.08) • 4 of 25 patients (16%) in the allopurinol group had significant loss in renal function or became dialysis-dependent compared with 12 of 26 (46.1%) in the control group (P = 0.015) • Serum creatinine levels did not change significantly for the treatment group (from 1.64 ± 0.63 mg/dL to 1.99 ± 0.92 mg/dL; P = 0.15) compared to the control group (from 1.86 ± 0.69 mg/dL to 2.89 ± 0.96 mg/dL; P = 0.003)
Goicoechea et al (2010)[32]	113	RCT	Patients with eGFR <60 mL/min/1.73m^2 were randomly assigned to all allopurinol (100 mg/day) or to usual therapy. Single centre, Spain	24 months	• After 24 months of treatment, there was a decrease in eGFR in the control group eGFR 3.3 ± 1.2 mL/min/1.73m^2 but an increase of 1.3 ± 1.3 mL/min/1.73m^2 in eGFR the intervention group (P = 0.018) • Allopurinol treatment slowed kidney disease progression HR 0.53 (95%CI: 0.28 – 0.99; P = 0.048) • 15 patients suffered a cardiovascular event in the control group and 7 in the intervention group. Allopurinol treatment reduced the risk of cardiovascular events in 71% (HR 0.29, 95%CI: 0.09 – 0.86; P = 0.026) • 22 patients in the control group were hospitalized compared with 12 in the intervention group (P = 0.032)
Momeni et al (2010)[33]	40	RCT	Patients with type 2 diabetes and diabetic nephropathy were randomized to either intervention (allopurinol, 100 mg/day) or placebo. Multicentre, Isfahan, Iran.	4 months	• Serum levels of uric acid were significantly lower in the intervention group compared with placebo (5.31 ± 0.79 vs 6.44 ± 1.97 mg/dL; P = 0.02) • 24-hour urine protein was also lower in the treatment group compared to placebo (1,011 ± 767mg vs 1,609 ± 1,071 mg; P = 0.049)

Study ID	N	Study design	Participants	Follow up	Comments and results
Kao et al (2011)[34]	67	RCT	Patients with stage 3 CKD and left ventricular hypertrophy (LVH) were randomized to allopurinol (300mg/day) or placebo. Single centre, Dundee, UK	9 months	• Left ventricular hypertrophy decreased significantly in the treatment group (P = 0.036) • Allopurinol significantly improved endothelial function (P = 0.009) and significantly improved the central augmentation index (P = 0.015)
Schumacher et al (2008) [36]	1,072	RCT	Participants 18 to 85 years old, with gout, hyperuricemia and normal or impaired renal function. Participants were randomised to febuxostat, allopurinol or placebo	28 weeks	• Higher percentages of participants treated with febuxostat 80 mg (48%), 120 mg (65%) and 240 mg (69%) attained serum urate levels < 6.0 mg/dL compared with allopurinol (22%) and placebo (0%) (P ≤ 0.05) • A significantly higher percentage of participants with impaired renal function and treated with febuxostat achieved serum urate levels < 6.0 mg/dL: febuxostat 80 mg (44% [4 of 9]), 120 mg (45% [5 of 11]), 240 mg (60% [3 of 5]) compared with those treated with allopurinol 100 mg (0% [0 of 10]) • Adverse events were similar across groups, although diarrhoea and dizziness were more frequent in the febuxostat 240 mg group
Malaguarnera et al (2009) [37]	38	RCT	Participants 65 to 85 years old with hyperuricaemia were randomised to rasburicase plus diet treatment or placebo plus diet.	8 weeks	• There was a significant reduction of urate (from 10.9 ± 2.9 to 7.6 ± 3.9 mg/ml; P < 0.05) and creatinine (from 2.76 ± 0.48 to 2.08 ± 0.44 mg/ml; P < 0.001) in the rasburicase group, whereas there were no significant changes in the placebo group. • The rasburicase group also had a significant increase in creatinine clearance (from 51.8 ± 9.7 to 64.5 ± 10.8; P < 0.001) and urate clearance (from 4.9 ± 3.1 to 10.6 ± 3.9 ml/min/24 hr; P < 0.001) • There were no significant changes in the creatinine and urate clearance in the placebo group

Table 1a. Characteristics of included randomised trials

Study ID (author, year)	N	Study Design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Siu et al (2006) [31]	54	Randomised controlled clinical trial	Single centre, China	Patients with chronic kidney disease	Allopurinol	Control	12	
Goicoechea et al (2010)[32]	113	Randomised controlled clinical trial	Single centre, Spain	Patients with eGFR <60 mL/min/1.73m^2	Allopurinol (100 mg/day)	Standard therapy	24	
Momeni et al (2010)[33]	40	Randomised controlled clinical trial	Multicentre, Isfahan, Iran	Patients with type 2 diabetes and diabetic nephropathy	Allopurinol (100 mg/day)	Placebo	4	
Kao et al (2011)[34]	67	Randomised controlled clinical trial	Single centre, Dundee, UK	Patients with stage 3CKD and left ventricular hypertrophy	Allopurinol (300 mg/day)	Placebo	9	
Schumacher et al (2008) [36]	1,072	Randomised controlled clinical trial	Multicentre, US	Participants with gout, hyperuricemia and normal or impaired renal function	Febuxostat or Allopurinol	Placebo	7	Trial consisting of 5 arms, (allopurinol, placebo and 3 different doses of febuxostat)
Malaguarnera et al (2009) [37]	38	Randomised controlled clinical trial	Single centre, Italy	Participants with hyperuricaemia	Rasburicase + diet	Placebo + diet	2	Pilot randomised clinical trial

Table 2a. Methodological quality of randomised trials

Study ID (author, year)	Method of allocation concealment *	Blinding			Intention-to-treat analysis †	Loss to follow up (%)	Comments ‡
		(participants)	(investigators)	(outcome assessors)			
Siu et al (2006) [31]	Computer	Yes	Yes	Unclear	No	3.7	Ø
Goicoechea et al (2010)[32]	Computer generated	Unclear	Yes	Yes	Yes	8.0	Ø
Momeni et al (2010)[33]	Not specified	Yes	Yes	Unclear	Unclear	Unclear	-
Kao et al (2011)[34]	Not specified	Unclear	Yes	Yes	Unclear	1.9	-
Schumacher et al (2008) [36]	Central	Yes	Yes	Yes	Yes	6.7	+
Malaguarnera et al (2009) [37]	Envelopes containing randomization codes	Yes	Yes	Yes	Yes	Unclear	Ø

* Choose between: central; third party (e.g. pharmacy); sequentially labelled opaque sealed envelopes; alternation; not specified.

† Choose between: yes; no; unclear.

‡ Quality score – "How successfully do you think the study minimised bias?" Choose between: very well (+); okay (Ø); poorly (–).

Table 3a. Results and quality rating for dichotomous outcomes

Outcomes	Study ID (author, year)	Intervention group (no. of patients with events/no. of patients exposed)	Control group (no. of patients with events/no. of patients exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]	Importance**
Cardiovascular event	Goicoechea et al (2010)[32]	7/57	15/56	0.46 [0.20, 1.04]	-0.15 [-0.29, -0.00]	Critical
Death	Goicoechea et al (2010)[32]	0/57	2/56	0.20 [0.01, 4.00]	-0.04 [-0.09, 0.02]	Critical
Hospitalization	Goicoechea et al (2010)[32]	12/57	22/56	0.54 [0.29, 0.98]	-0.18 [-0.35, -0.02]	Important

- Methodological quality, consistency across studies and directness of the evidence (generalisability/applicability).

** The GRADE system uses the following 3 categories to rank the importance of end points:

- critical for decision making
- important but not critical for decision making
- not important for decision making (of lower importance to patients)

* NA – not applicable

Table 3b. Results and quality rating for continuous outcomes

Outcomes	Study ID (author, year)	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means (95% CI)	Importance**
Uric acid (mg/dL)	Siu et al (2006) [31]	5.88 (1.01)	10.08 (1.68)	-4.20 (-4.96, -3.44)	Important
	Momeni et al (2010)[33]	5.31 (0.79)	6.44 (1.97)	-1.13 [-2.06, -0.20]	
Serum creatinine (µmol/L)	Siu et al (2006) [31]	176 (81)	255 (85)	-79.0 (-124.56, -33.44)	Important
Proteinuria (g/day)	Siu et al (2006) [31]	2.53 (4.85)	2.16 (1.93)	0.37 (-1.67, 2.41)	Important
	Momeni et al (2010)[33]	1.011 (0.767)	1.609 (1.071)	-0.60 [-1.18, -0.02]	
Urate (mg/ml)	Malaguarnera et al (2009) [37]	7.6 (3.9)	9.7 (3.4)	-2.10 (-4.42, 0.22)	Important
Serum urate levels (< 6.0 mg/dL)	Schumacher et al (2008) [36]	*NA	NA	NA	Important
Creatinine (mg/ml)	[Malaguarnera et al (2009) [37]	2.08 (0.44)	2.71 (0.96)	-0.63 (-1.11, -0.15)	Important
Creatinine clearance (ml/min/24hr)	Malaguarnera et al (2009) [37]	64.5 (10.8)	54.8 (9.7)	9.7 (3.18, 16.22)	Important
Left ventricular muscle index (g/m^2)	Kao et al (2011)	-1.42 (4.67)	1.28 (4.45)	-2.70 [-5.16, -0.24]	Important
Endothelial function [Flow mediated dilatation (%)]	Kao et al (2011)	1.26 (3.06)	1.05 (2.84)	0.21 [-1.38, 1.80]	Important
Central arterial stiffness [Augmentation index (%)]	Kao et al (2011)	-4.70 (9.30)	0.77 (6.06)	-5.47 [-9.68, -1.26]	Important

- Methodological quality, consistency across studies and directness of the evidence (generalisability/applicability).

** The GRADE system uses the following 3 categories to rank the importance of end points:

- critical for decision making
- important but not critical for decision making
- not important for decision making (of lower importance to patients)

* NA – not applicable