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LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Allopurinol for chronic kidney disease

HTA 12/45

20th November 2012

UNIVERSITY OF LIVERPOOL
LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 TITLE OF PROJECT

Allopurinol for chronic kidney disease

2 TAR TEAM AND PROJECT 'LEAD'

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For details of expertise within the TAR team, see section 6.

3 PLAIN ENGLISH SUMMARY

Evidence of kidney damage that occurs over time is known as chronic kidney disease. Its severity can be classified as ranging from stage 1 to stage 5, with stage 5 being the most severe condition (end-stage renal failure). Some patients with stage 5 chronic kidney disease may require kidney dialysis or transplantation. However, people with chronic kidney disease have an increased risk of cardiovascular disease and are more likely to die from causes related to cardiovascular disease than they are to progress to end-stage renal failure.

Hyperuricaemia is a condition in which a person has high levels of uric acid in the blood. Uric acid is created when the body breaks down substance called purines. It develops when there's an excess production of uric acid (e.g. diet rich in purines, metabolic complications that can occur after cancer), decreased excretion of uric acid (e.g. drugs) or a combination of both (e.g. beer). Hyperuricaemia is associated with both chronic kidney disease and cardiovascular disease. However it is not fully known if hyperuricaemia is a cause, consequence or coincidental to either disease.

Allopurinol is a drug commonly used to treat hyperuricaemia in patients with gout. Evidence is emerging that it may also have a role to play in slowing down the progression of chronic kidney disease and reducing the risk of cardiovascular disease.

The aim of this review is to consider whether allopurinol is clinically useful for people with chronic kidney disease, primarily in reducing mortality, slowing down chronic kidney disease progression and risk of cardiovascular disease. Other outcomes will also be considered including outcomes that may be indicators of chronic kidney disease and cardiovascular disease (levels of uric acid, serum creatinine and albuminuria, numbers of patients with endothelial dysfunction and/or left ventricular hypertrophy), changes in number of blood pressure medications, the number and type of adverse events and quality of life. The review will compare allopurinol with usual therapy. Based on the evidence from this review, recommendations for future clinical practice and/or research will be made.

4 DECISION PROBLEM

4.1 Clarification of research question and scope

Allopurinol is a drug that is used to treat hyperuricaemia, commonly in people with gout. The aim of this systematic review is to address the following research question: Does allopurinol reduce mortality, the progression of chronic kidney disease (CKD) or cardiovascular risk in people with CKD?

4.2 Background

Abnormally elevated levels of uric acid in the blood are known as hyperuricaemia. Hyperuricaemia develops when there's an excess production of uric acid, decreased excretion of uric acid or a combination of both. High blood concentrations of uric acid may result in gout. Uric acid is also associated with hypertension, metabolic syndrome, cardiovascular disease (CVD) and CKD. However, the extent to which uric acid is a cause, effect or indeed a coincidental factor for these diseases remains unknown.[1-4]

Chronic kidney disease is defined according to the presence or absence of kidney damage and level of kidney function. It is measured by a decrease in glomerular filtration rate (GFR). There are no obvious symptoms of worsening kidney function and hence diagnosis often occurs via the screening of patients with conditions which increase the risk for CKD. In the UK, the National Institute for Health and Clinical Excellence (NICE) recommends screening for the following conditions: diabetes; hypertension; cardiovascular disease (ischaemic heart disease, chronic heart failure, peripheral vascular disease and cerebral vascular disease); structural renal tract disease, renal calculi or prostatic hypertrophy, multisystem diseases with potential kidney involvement (e.g. systemic lupus erythematosus), family history of stage 5 CKD or hereditary kidney disease and opportunistic detection of haematuria or proteinuria.[5] Chronic kidney disease may also be identified when it leads to one of its recognised complications such as cardiovascular disease, anaemia or pericarditis.

Traditionally serum creatinine measurements were the mainstay for initial identification of CKD. Higher levels of creatinine indicate a lower GFR (decreased renal function). However, in early stages of CKD, creatinine levels may be within the normal range. Partly for this reason, it is commonly recommended that all clinical biochemistry laboratories should provide a calculated estimate of GFR (eGFR) using a formula to identify affected people. In the UK, the laboratories typically use the Modification of Diet in Renal Disease (MDRD) formula, which takes into account a patient's age, sex and ethnicity alongside serum creatinine levels.

Chronic kidney disease is classified from stage 1, usually causing few symptoms, to stage 5 resulting in poor life expectancy (see Table 1). Stage 3 CKD is commonly referred to as moderate CKD.

Table 1: Stages of CKD

Stage [a]	GFR (mL/min/1.73m^2)	Description
1	≥90	Normal or increased GFR, with other evidence of kidney damage
2	60 to 89	Slight decrease in GFR, with other evidence of kidney damage
3A 3B	45 to 59 30 to 44	Moderate decrease in GFR, with or without other evidence of kidney damage
4	15 to 29	Severe decrease in GFR, with or without other evidence of kidney damage
5	<15	Established renal failure

GFR= glomerular filtration rate
[a] the suffix (p) is used to denote the presence of proteinuria when staging CKD in order to underline the importance of proteinuria/albuminuria as an independent risk factor for adverse outcomes

No specific treatment has been found to unequivocally slow the worsening of CKD but the control of blood pressure helps[6] and there is emerging evidence that treatment with sodium bicarbonate also slows down progression.[7] Thus where an underlying cause can be identified, treatment tends to focus on this underlying cause in order to attempt to reduce progression of renal failure. More advanced stages of CKD may also require treatments for anaemia and bone disease. Severe CKD requires renal replacement therapy, which may involve a form of dialysis, but ideally constitutes transplantation of a new kidney in suitable patients. People with CKD have an increased prevalence of CVD and are more likely to die from a CVD-related cause than they are to progress to established end-stage renal failure.[5] Recently, clinical evidence has emerged that allopurinol, a drug commonly used to treat hyperuricaemia in patients with gout, may slow the progression of CKD[8, 9] and may also reduce cardiovascular risk in these subjects.[9, 10] In the absence of the use of drugs to control hypertension, there is also evidence that following allopurinol withdrawal, a significant worsening of hypertension, significant acceleration of the rate of loss of kidney function and a significant increase in the urinary excretion of TGF-1β_1 may occur.[11]

4.3 Epidemiology

A systematic review of 26 population studies conducted worldwide (but none from the UK) published in 2008 found that CKD prevalence varied widely among the study populations investigated, strongly depending on how GFR was measured or calculated.[12] However, in all populations, prevalence rates increased with age, the median prevalence rate being 7.2% in persons aged 30 and over, while in persons aged 64 and over it was between 23.4% and 35.8%.[12] The 2009 Health Survey for England has estimated the prevalence of stages 3-5 CKD in persons aged 16 and over in England to be 6% (male: 7%, female: 5%), ranging from 1% of males and 2% of females aged 16-54 to 31% of males and 36% of females aged 75 and over.[13] For all stages of CKD, the prevalence was 14% in males and 13% in females.[13] According to the New Opportunities for Early Renal Intervention by Computerised Assessment (NEOERICA) project, based on data from three primary care trusts in England, the age-standardised prevalence of stages 3-5 CKD was 8.5% (male: 5.8%, female: 10.6%).[14] It has been

recently found in the United States that the prevalence of stages 3-5 CKD is increasing most rapidly in those aged 60 and over. Between 1988–1994 and 2003–2006, data from the National Health and Nutrition Examination Survey suggests a rise from 18.8% to 24.5% in this age group while the prevalence of stages 3-5 CKD in people between the ages of 20 and 39 remained consistently below 0.5%.[15] To date, incidence estimates have been less commonly reported in the literature.

The incidence and prevalence of hyperuricaemia are not commonly studied. In a relatively recent study of the US population in 2007-2008, prevalence rates for hyperuricaemia were reported to be 21.4% (men: 21.2%, women: 21.6%) compared to 3.9% for gout (men: 5.9%, women: 2.0%) in the same study.[16] A recent systematic review conducted in China has estimated the prevalence of hyperuricaemia to be similar to the US rate for men (21.6%) but not women (8.6%).[17]

4.4 The technology

Allopurinol (Zyloprim, Aloprim, Allohexal, Allosig, Milurit, Alloril, Progout, Zyloprim, Zyloric, Zyrik and Aluron) inhibits conversion of hypoxanthine to xanthine to uric acid, resulting in a decrease in the production of uric acid. In the UK allopurinol has the following indications:[18]

Adults

- All forms of hyperuricaemia not controllable by diet including secondary hyperuricaemia of differing origin and in clinical complications of hyperuricaemic states, particularly manifest gout, urate nephropathy and for the dissolution and prevention of uric acid stones.
- The management of recurrent mixed calcium oxalate stones in concurrent hyperuricaemia when fluid, dietary and similar measures have failed.

Children and adolescents

- Secondary hyperuricaemia of differing origin.
- Uric acid nephropathy during the treatment of leukaemia.
- Hereditary enzyme deficiency disorders, Lesch-Nyhan syndrome (partial or total hypoxanthin-guanin phosphoribosyl deficiency) and adenine phosphoribosyl transferase deficiency.

It is also approved by the US Food and Drug Administration (FDA) with the following indications:[19]

- The management of patients with signs and symptoms of primary or secondary gout (acute attacks, tophi, joint destruction, uric acid lithiasis, and/or nephropathy).
- The management of patients with leukemia, lymphoma and malignancies who are receiving cancer therapy which causes elevations of serum and urinary uric acid levels. Treatment with allopurinol should be discontinued when the potential for over production of uric acid is no longer present.

- The management of patients with recurrent calcium oxalate calculi whose daily uric acid excretion exceeds 800 mg/d in male patients and 750 mg/d in female patients. Therapy in such patients should be carefully assessed initially and reassessed periodically to determine in each case that treatment is beneficial and that the benefits outweigh the risks.

The dose required to lower serum uric acid to normal or near-normal levels varies with the type of patient and severity of the disease. In the UK, a dose of 100 mg/d to 200 mg/d is recommended for mild conditions, 300 mg/d to 600 mg/d for moderately severe conditions and 700 mg/d to 900 mg/d in severe conditions.[18] In the US 200 mg/d to 300 mg/d is recommended for people with mild gout, 400 mg/d to 600 mg/d for those with moderately severe tophaceous gout and a maximum dose of 800 mg/d for those with severe conditions.[19] Allopurinol may be taken once daily, preferably after food.[18, 19] However, if the daily dosage exceeds 300 mg/d, gastrointestinal intolerance (GI) is evident and so a divided dosage regimen may be appropriate.[18, 19] A maximum dose of 400 mg/d is recommended for children and adolescents for the treatment of malignant conditions.[18]

Since allopurinol and its metabolites are primarily eliminated only by the kidney, accumulation of the drug can occur in renal failure.[18, 19] Hence the FDA recommends that the dose of allopurinol should be reduced in people with CKD:[19] The Medicines and Healthcare products Regulatory Agency (MHRA), which granted the UK licence, is more explicit and states that in patients with impaired renal function, a starting dose of 100 mg/d should be employed and only increased if the serum/urinary response is unsatisfactory.[18] Both the MHRA and FDA recommend a dose of 200 mg/d for people with a creatinine clearance of 10 to 20 mL/min and when the creatinine clearance is <10 mL/min the dose should not exceed 100 mg/d. With extreme renal impairment (creatinine clearance < 3 mL/min) the interval between doses may also need to be lengthened.[18, 19]

As shown in Table 2, according to adverse event (AE) data submitted to the FDA between the first quarter of 2004 and the first quarter of 2012, renal failure, pyrexia and rash (with and without eosinophilia and systemic symptoms and including Stevens-Johnson Syndrome and toxic epidermal necrolysis) are the most common of reported AEs at a frequency of 1-2%). Skin reactions to allopurinol can be severe, sometimes fatal and so treatment with allopurinol should be discontinued immediately if a rash develops. The incidence of skin rash may be increased in the presence of renal insufficiency. As is also evident from Table 2, gastrointestinal intolerance (GI) as characterised diarrhoea or vomiting is also relatively common. These AEs are thought to be causally related to allopurinol and dose dependent. Allopurinol is contraindicated in patients with hypersensitivity to allopurinol. People with the HLA-B*5801 gene variant who are treated with allopurinol have been identified to be at increased risk of allopurinol-induced hypersensitivity, Stevens–Johnson syndrome, and toxic epidermal necrolysis.[20]

Table 2: Most common (≥0.5%) allopurinol-related adverse events reported to the FDA, 2004-2012

Adverse event	Number (%)
Renal failure acute	344 (1.85%)
Pyrexia	338 (1.82%)
Drug rash with eosinophilia and systemic symptoms	330 (1.78%)
Stevens-Johnson syndrome	289 (1.56%)
Renal failure	223 (1.20%)
Rash	203 (1.09%)
Toxic epidermal necrolysis	192 (1.03%)
Drug interaction	175 (0.94%)
Pruritus	168 (0.90%)
Alanine aminotransferase increased	150 (0.81%)
Diarrhoea	149 (0.80%)
Dyspnoea	147 (0.79%)
Dehydration	131 (0.71%)
Hypotension	129 0(.69%)
Blood creatinine increased	115 (0.62%)
Eosinophilia	113 (0.61%)
Asthenia	112 (0.60%)
Pneumonia	112 (0.60%)
Aspartate aminotransferase increased	111 (0.60%)
Renal impairment	110 (0.59%)
Pancytopenia	108 (0.58%)
Thrombocytopenia	108 (0.58%)
Sepsis	106 (0.57%)
Malaise	105 (0.57%)
Anaemia	102 (0.55%)
Interstitial lung disease	101 (0.54%)
Oedema peripheral	100 (0.54%)
Vomiting	98 (0.53%)

Source: FDA[21]

4.5 Guidelines on the treatment of CKD

The recent NICE guideline makes some recommendations for the treatment of people with CKD.[5] These echo the recommendations of the UK Renal Association[22] which do not differ significantly to those elsewhere in the world. In general, the aim is to control blood pressure and complications such as diabetes. Hence it is recommended that treatment should consist of both lifestyle support (e.g. dietary advice, encouragement to exercise and smoking cessation interventions) and drugs, in particular drugs to control hypertension. In addition, patients will be encouraged to avoid nephrotoxic medications such as nonsteroidal anti-inflammatory drugs. The precise regimen of treatment will therefore depend to some extent on a patient's albumin:creatinine ratio and comorbidities.

There are no specific guidelines for using allopurinol to treat CKD. In the UK, allopurinol is highlighted as a drug that if people are already taking this drug and they are diagnosed with CKD, the dose should be reduced.[23] The NICE guideline states that "There is insufficient evidence to recommend the routine use of drugs to lower uric acid in people with CKD who have asymptomatic hyperuricaemia."[5] Similarly, in the US, FDA dosing guidelines for the use of allopurinol for CKD unequivocally advocate initiation and maintenance dose reductions.[24]

4.6 The use of allopurinol in clinical practice

According to data presented to NICE in 2008, allopurinol is the most commonly used urate lowering drug in the UK (89% of gout treatments), with most cases (98%) using doses of ≤300 mg/d.[25] Similarly, it was recently reported that in the US over 90% of urate lowering prescriptions are for allopurinol but again rarely (<5% of patients) prescribed at doses exceeding 300 mg/d.[26] However such doses may not be effective for the treatment of gout.[24] While it is generally recommended that doses be increased from a low dose,[18, 19] it has been reported that in practice this rarely happens.[25] Allopurinol is not commonly used for the slowing down of the progression of CKD.

4.7 Objectives of the systematic review

The aim of this review is to consider the clinical effectiveness of allopurinol for people with CKD. Primarily, the review will consider the evidence in terms of effects on mortality, progression of CKD and effects on cardiovascular risk. The effects on mortality will be measured by all-cause deaths. Progression of CKD will be measured by the proportion of deaths attributable to CKD, patients requiring dialysis and/or transplantation and change in eGFR levels. Cardiovascular risk will be measured by the proportion of patients dying due to cardiovascular disease, experiencing cardiovascular events and with cardiovascular risk factors (see Table 3 for more detail about these events and risk factors). In addition to the primary outcomes, evidence will be sought for the effects on disease markers (levels of uric acid, serum creatinine and albuminuria, number of patients with endothelial dysfunction and/or left ventricular hypertrophy), number of blood pressure medications, AEs and quality of life. If the data allow, subgroups based on stage of CKD, age, gender, ethnicity and co-morbidities will also be considered. Based on the evidence from the systematic review, recommendations for future practice and/or research will be made.

4.8 Key factors to be considered

Allopurinol to treat hyperuricaemia is not recommended in patients with CKD in the absence of gout or uric acid kidney stones. However it is possible that patients included within studies may be treated for asymptomatic hyperuricaemia.

All patients with CKD are likely to receive drugs to control hypertension as part of their treatment. These may also impact on outcomes (e.g. losartan which is an angiotensin receptor blocker is also a uricosuric and so would be expected to impact on both levels of uric acid and blood pressure).

Many of the end points for which data are to be synthesised may be defined differently across studies. This will pose challenges for data synthesis.

Analysis of the data in relation to severity of CKD may be complicated by the fact that it is unclear if hyperuricaemia is a cause, effect or indeed a coincidental factor of CKD.

It may be difficult to determine whether cardiovascular events and/or risk factors develop following treatment or existed prior to treatment.

5 METHODS FOR SYNTHESISING EVIDENCE

A review of the evidence for clinical effectiveness will be undertaken systematically following the general principles recommended in the PRISMA statement.[27]

5.1 Search strategy

The major electronic databases including Medline, EMBASE and The Cochrane Library will be searched for relevant published literature. Search terms will include a combination of index terms (for the disease) and free text words for the technologies involved (generic and trade names of the drugs) but will not include methodological filters to limit results to a specific study design. Information on studies in progress, unpublished research or research reported in the grey literature will be sought by searching a range of relevant databases including ClinicalTrials.gov and Controlled Clinical Trials. Additional evidence may be derived from contact with experts in the field. Although allopurinol is now off-patent, manufacturers of the drug will be approached for data on any trials they may have conducted. Bibliographies of previous systematic reviews and retrieved articles will also be examined. No date or language limits will be applied to the search strategy although studies in languages other than English which cannot be translated may be excluded. A database of the identified literature will be held in the Endnote X5 software package.

5.2 Study selection strategy

The citations identified by the search strategy will be assessed for inclusion through two stages. Firstly, two reviewers will independently screen (stage 1) all relevant titles and abstracts identified via electronic searching to identify potentially relevant studies for inclusion in the review. Secondly, full text copies of these potentially relevant studies will be obtained and assessed independently (stage 2) by two reviewers using the inclusion criteria outlined in Table 3. Any disagreements between reviewers will be resolved by discussion at each stage and, if necessary, a third reviewer will be consulted.

Studies that do not meet the inclusion criteria at stage 2 will be excluded and their bibliographic details listed with reasons for exclusion. In the absence of any universally agreed guidelines for using allopurinol in slowing the progression of CKD, studies which use allopurinol at any dose will be included in this review and at any point along the treatment pathway. Included studies should also compare allopurinol to usual therapy (however defined, see also section 4.5). Only people with CKD should be included in the analyses. Efficacy data will be derived from randomised controlled trials (RCTs), data for AEs or quality of life from non-randomised studies will also be included. The identification and use of such data will be described in the final report.

Table 3: Eligibility criteria

	Included	Excluded
Population	Studies which include people with CKD (eGFR<60mls/min/1.73m^2)	Studies which do not include any people with CKD
Intervention	Studies where patients in at least one treatment arm are treated with allopurinol of any dose	Studies in which patients are not treated with allopurinol
Setting	Any healthcare setting (including the community and the home)	Non-healthcare settings
Comparator	Usual therapy or placebo	Any treatment that cannot be considered to include usual therapy

Outcomes	**Primary:**
	• All-cause mortality
	• Progression of CKD as defined by individual studies but likely to include:
	  o Mortality directly attributable to CKD
	  o Number of patients requiring transplantation
	  o Number of patients requiring dialysis
	  o Change in eGFR (ml/min per 1.73 m^2)
	• Cardiovascular risk as defined by individual studies but likely to include measures of:
	  o Mortality directly attributable to cardiovascular events [a]
	  o Non-fatal cardiovascular events [a]
	  o Number of patients with risk factors for cardiovascular disease [b]
	Secondary:
	• Change in uric acid levels (mg/dl)
	• Change in serum creatinine levels (µmol/l)
	• Change in albuminuria levels (mg/d)
	• Number of patients with endothelial dysfunction
	• Number of patients with left ventricular hypertrophy
	• Change in number of blood pressure medications
	• AEs
	• Quality of life
		No study will be excluded from inclusion based on its outcomes
		Included studies may however be excluded from the analysis if they are not those that match the inclusion criteria

Study design	RCTs for evidence of efficacy Observational studies for AE and quality of life data	Animal models Preclinical and biological studies Narrative reviews, editorials, opinions Non-English language papers Reports published as meeting abstracts only, where insufficient methodological details are reported to allow critical appraisal of study quality Letters, commentaries and editorials

AE=adverse event; CKD=chronic kidney disease; eGFR= estimated glomerular filtration rate; RCT=randomised controlled trial

[a] Cardiovascular events include: coronary heart disease (including myocardial infarction, unstable angina, acute coronary syndromes with coronary intervention, heart failure of whatever cause resulting in new diagnosis and/or admission), cerebrovascular disease (including strokes and transient ischaemic attacks), arrhythmias (including atrial fibrillation) and cardiac arrest, ischaemic heart disease, peripheral vascular disease, deep vein thrombosis and pulmonary embolism

[b] Risk factors include: high blood pressure (hypertension), high levels of low density lipoprotein (LDL) cholesterol, high levels of total cholesterol, high triglyceride levels, raised blood glucose levels (diabetes)

5.3 Data extraction strategy

Data relating to study design, findings and quality will be extracted by one reviewer and independently checked for accuracy by a second reviewer. Study details will be extracted using a standardised data extraction form. If time permits, attempts will be made to contact authors for missing data. Data from studies presented in multiple publications will be extracted and reported as a single study with all relevant other publications listed. The types of data extracted will include, but not necessarily be limited to, those listed in the appendix.

5.4 Quality assessment strategy

The quality of the individual studies will be assessed by one reviewer, and independently checked for agreement by a second. Disagreements will be resolved through consensus and, if necessary, a third reviewer will be consulted. The quality of the clinical-effectiveness studies will be assessed according to criteria based on the CRD's guidance for undertaking reviews in healthcare[28] and will therefore include an assessment of the risk of bias according to the Cochrane Collaboration (see Appendix).[29]

5.5 Methods of analysis/synthesis

The results of the data extraction and quality assessment for each study will be presented in structured tables and as a narrative summary. The possible effects of study quality on the effectiveness data and review findings will be discussed. All summary statistics will be extracted for each outcome and where possible, data will be pooled using a standard meta-analysis.[30] Consideration will be given to the manner in which outcomes are derived, e.g. definitions for cardiovascular risk factors such as heart disease, how GFR is estimated.

Meta-analysis will be carried out using fixed or random effects models using an appropriate software package. Heterogeneity will be explored through consideration of the study populations, methods and interventions, by visualisation of results and, in statistical terms, by the χ^2 test for homogeneity and the I^2 statistic.[31] If the data allow, subgroups based on stage of CKD, age, gender, ethnicity, concomitant medication and co-morbidities will also be considered. If appropriate and if data allows, sensitivity analyses will be conducted excluding trials of low quality to assess the robustness of the findings.

6 EXPERTISE IN THIS TAR TEAM AND TAR TEAM MEMBERS' CONTRIBUTIONS

The Liverpool Reviews and Implementation Group (LRiG) was established at the University of Liverpool in April 2001. It is a multi-disciplinary research group whose purpose, in the first instance, is to conduct Technology Assessment Reviews commissioned by the HTA programme. The team has substantial expertise in systematic reviewing, literature searching and assessing clinical outcomes and is well practised in applying this expertise to health technology evaluations. In addition, for the specific purposes of this review, LRiG has approached a Consultant Nephrologist, Consultant Cardiologist and Consultant Physician and Rheumatologist, all based at the Royal Liverpool University Hopsital to provide clinical input. Hence, it is expected that this TAR team will be made up of the following individuals:

- Mr Nigel Fleeman (Research Fellow, LRiG): Team lead /Main systematic reviewer
- Mrs Gerlinde Pilkington: Secondary reviewer
- Dr Yenal Dundar: Literature review searches
- Dr Kerry Dwan: Medical statistician
- Dr Hameed Anijeet: Clinical advisor (Consultant Nephrologist)
- Dr Jason Pyatt: Clinical advisor (Consultant Cardiologist)
- Dr Tom Kennedy: Clinical advisor (Consultant Physician and Rheumatologist)

The role of the Team lead /Main systematic reviewer will be to maintain day-to-day running of the review. He has compiled the study protocol (with input from all the other team members) and will carry out the study selection and data extraction (with assistance from the secondary reviewer) and data synthesis (with assistance from the medical statistician). It is also intended that he/she will draft the methods, narratives for included trials, and part of the results and discussion of the final report with other members of the TAR team contributing as appropriate. In addition, the Director of LRiG, Dr Rumona Dickson, will provide assistance into all aspects of the review as and when necessary and the Associate Director, Dr Angela Boland will also provide feedback on drafts of the report.

7 COMPETING INTERESTS

No member of the research team has any competing interests to declare. Any competing interests relating to the external reviewers will be declared in the final report.

8 PROJECT TIMELINES

Milestone	Date
Literature searches	December 2012
Article screening	December 2012
Data extraction	December 2012 and January 2012
Quality assessment	December 2012 and January 2012
Data analyses	January and February 2012
Final draft of report for peer review	February 2013
Submission of final report to NETSCC	March 2013

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10 APPENDIX: TYPE OF DATA TO EXTRACT AND ASSESSMENT OF RISK OF BIAS

It is anticipated that clinical effectiveness data will be extracted and entered under the following headings:

Study details

- Author and Year of publication/abstract/data source (e.g. Jones et al 2012)
- Endnote reference (endnote reference number)
- Study design:
    - Method of randomisation
    - Allocation concealment
    - Blinding
    - Number of patients randomised
    - Number of patients excluded
    - Loss to follow-up
    - Type of analysis conducted (e.g. ITT, per-protocol or non-inferiority analysis)
    - Methods for handling missing data
    - Rationale for study sample size (e.g. use of power calculation)
- Inclusion/exclusion criteria (summary of trial inclusion/exclusion criteria)
- Follow-up duration
- Geographic location(s) of study
- Setting(s) of study
- Sponsor of study
- Sub-groups analysed (if any)

Intervention and comparator details

- Intervention (i.e. drug name[s])
- Dose(s) of intervention(s)
- Concomitant medications (summary for reported medications, e.g. diuretics, statins, etc)

Participant characteristics

- Number of participants enrolled (summary)
- Number of participants lost to follow up (summary)
- Average age (mean/median, range, standard deviation)
- Proportion of males and females (summary)
- Body weight (kg) (summary)
- Baseline disease characteristics (summary):
    - Stage of CKD
    - Renal pathology (summary for each pathology, e.g. diabetes, vascular nephrology, etc)
    - Comorbidities (summary for each reported disease, e.g. diabetes, gout, etc)
    - Number of blood pressure medications
    - C cystatine (mg/l)
    - Serum creatinine (µmol/l)
    - eGFR (ml/min per 1.73 m2)
    - Uric acid (mg/dl)
    - hsCRP (mg/l)
    - Serum fibrinogen (mg/dl)
    - Erythrocyte sedimentation rate (mm/h)
    - Haemoglobin (g/dl)
    - Serum albumin (g/dl)
    - Albuminuria (mg/d)
    - Blood pressure (mmHg)
        - Systolic
        - Dystolic
    - Smoking status

Outcomes: Definitions and measures

- Primary outcome (description of outcome as reported)
- Secondary outcomes (description of outcomes as reported)
- Adverse events (description of outcomes as reported)
- Quality of life (description of outcomes as reported)

Outcomes: Results

- All-cause mortality
- Progression of CKD as defined by individual studies but likely to include:
    - Mortality directly attributable to CKD
    - Number of patients requiring transplantation
    - Number of patients requiring dialysis
    - Change in eGFR (ml/min per 1.73 m^2)
- Cardiovascular risk as defined by individual studies but likely to include measures of:
    - Mortality directly attributable to cardiovascular events
    - Non-fatal cardiovascular events:
        - coronary heart disease (including myocardial infarction, unstable angina, acute coronary syndromes with coronary intervention, heart failure of whatever cause resulting in new diagnosis and/or admission)
        - cerebrovascular disease (including strokes and transient ischaemic attacks)
        - arrhythmias (including atrial fibrillation) and cardiac arrest
        - other (including ischaemic heart disease, peripheral vascular disease, deep vein thrombosis and pulmonary embolism)
    - Number of patients with risk factors for cardiovascular disease:
        - high blood pressure (hypertension)
        - high levels of low density lipoprotein (LDL) cholesterol
        - high levels of total cholesterol
        - high triglyceride levels
        - raised blood glucose levels (diabetes)
- Change in uric acid levels (mg/dl)
- Change in serum creatinine levels (µmol/l)
- Change in albuminuria levels (mg/d)
- Endothelial dysfunction (however defined)
- Change in number of blood pressure medications
- AEs
- Quality of life

Assessment of risk of bias will be conducted by addressing the following questions:

1. Was randomisation carried out appropriately?
2. Was the concealment of treatment allocation adequate?
3. Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?
4. Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?
5. Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?
6. Is there any evidence to suggest that the authors measured more outcomes than they reported?
7. Did the analysis include an Intention-To-Treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?