National Clinical Guideline Centre

Acute Kidney Injury

Appendices (A-M)

Clinical guideline CG169

Methods, evidence and recommendations

10 July 2013

NICE's original guidance on acute kidney injury was published in 2013. It was updated in 2019.

See the NICE website for the guideline recommendations and evidence review for the 2019 update.

This document contains the appendices for the 2013 guideline.

Final draft

Commissioned by the National Institute for Health and Clinical Excellence

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Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

Funding
National Institute for Health and Clinical Excellence

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1 # Appendices

2 ## Appendix A: Scope

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SCOPE

1 Guideline title

Acute kidney injury: prevention, detection and management of acute kidney injury up to the point of renal replacement therapy

1.1 Short title

Acute kidney injury

2 The remit

The Department of Health has asked NICE: 'To produce a clinical guideline on the diagnosis and management up to the point of dialysis for acute kidney injury'.

3 Clinical need for the guideline

3.1 Epidemiology

a) Acute kidney injury (formerly known as acute renal failure) is a common condition in which there is a swift drop in the function of the kidneys over hours or days. It is mainly seen in acutely unwell patients, so about 90% of cases occur in hospital inpatients. It is predominantly seen in older people, people who already have kidney disease (also called chronic kidney disease), and people with a critical illness. However, it is also seen in primary care, in young people and children, after procedures including surgery, and in people with urological diseases (disorders of the rest of the urinary tract). Typically the mortality from acute kidney injury is in the range of 30–60%, depending on the patient group.

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b) Recently there has been much work to develop a standardised way to define acute kidney injury and its severity. This produced the RIFLE (risk, injury, failure, loss of kidney function and end-stage kidney disease) definition, which was then modified to produce the acute kidney injury network (AKIN) definition. A modified version of the RIFLE criteria has been developed for paediatrics (pRIFLE). The related AKIN definition has not been assessed in paediatric patients.

c) There is evidence that even small deteriorations in renal function are associated with increased mortality. Such modest drops in kidney function are now included in the AKIN definition. The more severe stages of acute kidney injury, that do or do not require dialysis, also have a very considerable risk of mortality.

d) The incidence of acute kidney injury in the UK has been best studied in relation to the need for renal replacement therapy (also known as dialysis). Typically some 300 adults per million need renal replacement therapy for acute kidney injury each year.

e) Studies of the incidence of all acute kidney injury have been hampered by the lack of an accepted definition. There have been no published UK studies using the RIFLE or AKIN definitions to determine the incidence of acute kidney injury. A retrospective study using the RIFLE definition in a large Australian hospital found that 18% of all adult admissions had acute kidney injury. The incidence in this study suggests that there are likely to be considerably more than 500,000 cases of acute kidney injury per year among hospitalised adult patients in England. There is extremely limited information on the incidence of acute kidney injury in the general paediatric inpatient population.

3.2 Current practice

a) Acute kidney injury is typically diagnosed based on either a fall in urine output or a rise in blood creatinine, the blood test commonly

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used to estimate kidney function. There is currently no 'gold standard' test to diagnose acute kidney injury in routine clinical practice. No test currently exists that provides non-invasive, inexpensive, real-time and continuous monitoring of kidney function.

b) The only current guidance on acute kidney injury for UK clinicians is produced by the Renal Association, which recently published its latest version of 'Clinical practice guidelines: acute kidney injury' (2011). The National Confidential Enquiry into Patient Outcome and Death (NCEPOD) published a landmark study in 2009 of the care of more than 500 adult patients who died in hospital with a primary diagnosis of acute kidney injury.

c) The bulk of adult inpatients who have or develop acute kidney injury are admitted under general medicine or elderly care, with a large range of medical and surgical specialties caring for small numbers of patients. Recent data from the USA suggest that acute kidney injury patients admitted at the weekend have an increased risk of death. Some 31% of patients dying of acute kidney injury were referred to nephrologists in the NCEPOD study, and assessors felt that a further 14% should have been referred.

d) If a person develops acute kidney injury in primary care, and is not admitted to hospital, their GP will often discuss the case with a secondary care physician or nephrologist.

e) It is well established that assessment of acute kidney injury in the UK is often suboptimal, and key steps in investigation and management are often lacking. NCEPOD showed a number of key deficiencies in care, including: the condition being avoidable in 14% of cases, recognition and care after admission often being poor, and senior reviews being inadequate in 24% of cases.

f) Patients with severe acute kidney injury (RIFLE 'Failure' category or AKIN stage 3) may need renal replacement therapy and/or

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critical care. In the NCEPOD study 20% of patients were transferred to renal or critical care, and a further 8% should have definitely received such 'step-up' care. It was not possible to determine the need for step-up care in a further 22% because of poor documentation. In the NCEPOD study 12% of patients received renal replacement therapy, and it was felt that a further 8% would have benefited from it but did not receive it. There have been few other studies of renal replacement therapy referral in acute kidney injury.

g) Children older than 1 month are affected by similar issues to adults in the prevention, detection and management of acute kidney injury. Although there are some differences in acute kidney injury in children, clinicians caring for children older than 1 month will benefit from guidance covering the areas set out in the scope.

h) This NICE guideline is needed to address the known and unacceptable variations in the recognition, assessment, initial treatment and usage of renal replacement therapy in acute kidney injury.

4 The guideline

The guideline development process is described in detail on the NICE website (see section 6, 'Further information').

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

The areas that will be addressed by the guideline are described in the following sections.

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4.1 Population

4.1.1 Groups that will be covered

a) Adults

b) Children older than 1 month.

c) Particular consideration will be given to the needs of:

- older patients (65 years and older)
- people at high risk of developing acute kidney injury, such as people with chronic kidney disease and urological disorders.

4.1.2 Groups that will not be covered

a) Children younger than 1 month (neonates). This group has physiologically different needs and care is very specialised. There is little information in this group on outcomes related to acute kidney injury.

b) Acute kidney injury in renal transplant patients. These patients have a different spectrum of causes of acute kidney injury.

c) Acute kidney injury in pregnant women. Acute kidney injury in pregnant women has a different spectrum of causes, with less morbidity and mortality than in the non-pregnant population.

4.2 Healthcare setting

a) All settings in which NHS care is received.

4.3 Clinical management

4.3.1 Key clinical issues that will be covered

a) Clinical risk assessment in the identification and ongoing assessment of acute kidney injury.

b) Serum creatinine and urine output in diagnosis and staging.

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c) Urinalysis to determine the underlying cause.

d) Preventing deterioration:

- nephrotoxic drugs in patients with, or at high risk of acute kidney injury
- methods to monitor the use of nephrotoxic and other potentially toxic drugs in patients with suspected or confirmed acute kidney injury.

e) Acetylcysteine and/or intravenous fluids to prevent contrast-induced nephropathy.

f) When to use ultrasound, and in which patients.

g) Timing of relief of urological obstruction by methods such as nephrostomy.

h) Pharmacological management with:

- low dose dopamine
- loop diuretics.

i) Criteria for involving nephrology services (note that ' Recognition of and response to acute illness in adults in hospital', NICE clinical guideline 50 [2007] covers referral of the acutely ill patients to critical care services).

j) At what stage renal replacement therapy should be considered

k) Information and support for patients and carers.

Note that guideline recommendations will normally fall within licensed indications; exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

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4.3.2 Clinical issues that will not be covered

a) Renal replacement therapy beyond timing of initiation. This includes method of dialysis used; type of dialysis membrane; dialysis dose; method of vascular access and dialysis anticoagulation.

b) Biomarkers. This is an important developing field in acute kidney injury but they are not widely available and there is insufficient published clinical evidence to support or refute their use, or to compare costs and benefits with standard care.

c) Intravenous fluid management in adults and paediatrics. A separate NICE guideline on intravenous fluid therapy in adults will be developed in parallel to cover this topic.

d) The specific management of less common causes of acute kidney injury, such as vasculitis and haemolytic uraemic syndrome.

4.4 Main outcomes

a) Mortality.

b) Need for renal replacement therapy.

c) Length of hospital stay.

d) Health-related quality of life.

4.5 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually be only from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see 'Further information').

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4.6 Status

4.6.1 Scope

This is the final scope.

4.6.2 Timing

The development of the guideline recommendations will begin in September 2011.

5 Related NICE guidance

5.1 Published guidance

- Chronic kidney disease. NICE quality standard (2011). Available from www.nice.org.uk/guidance/qualitystandards/chronickidneydisease/ckdqualitystandard.jsp
- Medicines adherence. NICE clinical guideline 76 (2009). Available from www.nice.org.uk/guidance/CG76
- Chronic kidney disease. NICE clinical guideline 73 (2008). Available from www.nice.org.uk/guidance/CG73
- Acutely ill patients in hospital. NICE clinical guideline 50 (2007). Available from www.nice.org.uk/guidance/CG50
- Nutrition support in adults. NICE clinical guideline 32 (2006). Available from www.nice.org.uk/guidance/CG32
- Preoperative tests. NICE clinical guideline 3 (2003). Available from www.nice.org.uk/guidance/CG3

5.2 Guidance under development

NICE is currently developing the following related guidance (details available from the NICE website):

- End of life care. NICE quality standard. Publication expected November 2011.
- Intravenous fluid therapy. NICE clinical guideline and quality standard. Publication date to be confirmed.

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6 Further information

Information on the guideline development process is provided in:

- 'How NICE clinical guidelines are developed: an overview for stakeholders the public and the NHS'
- 'The guidelines manual'.

These are available from the NICE website (www.nice.org.uk/GuidelinesManual). Information on the progress of the guideline will also be available from the NICE website (www.nice.org.uk).

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Appendix B: Declarations of interest

B.1 Introduction

All members of the GDG, expert co optees and all members of the NCGC staff were required to make formal declarations of interest at the outset of each meeting, and these were updated at every subsequent meeting throughout the development process. No interests were declared that required any actions.

B.2 Mark Thomas (Chair)

GDG meeting	Declaration of Interests
First GDG meeting (14th September 2011)	Declared a Personal pecuniary interest: he has been paid expenses to attend the following meetings: - Amgen Darbepoetin 20060163 trial investigator meeting – October 2010 - SHARP trial results meeting (Oxford SHARP group – sponsored by MSD) – November 2010 Declared a Non-personal pecuniary interest: he or his department have had or will have trials from: - Amgen Darbepoetin 20060163 trial – a trial of Epoetin therapy in chronic kidney disease. - Vifor FIND CKD trial – a trial of iron therapy in chronic kidney disease. - An NIHR trial of Mycophenolate mofetil in glomerulonephritis (GLOMY). - The DOPPS study (Dialysis Outcomes and Practice Patterns Study) - supported by research grants from Amgen (since 1996), Kyowa Hakko Kirin (since 1999, in Japan), Genzyme (since 2009), Abbott (since 2009), and Baxter (since 2011) without restrictions on publications. Declared personal non-pecuniary interests: he has published in the field. He is also a member of the Renal Association.
Second GDG Meeting (15th September 2011)	No change
Third GDG Meeting (20th October 2011)	No change
Fourth GDG Meeting (7th December 2011)	Declared a personal non pecuniary interest: he has attended an unpaid advisory board run by Sunquest International in November 2011.
Fifth GDG Meeting (20th January 2012)	No change
Sixth GDG Meeting (6th March 2012)	No change
Seventh GDG Meeting (22nd May 2012)	No change

GDG meeting	Declaration of Interests
Eighth GDG Meeting (19th July 2012)	No change
Ninth GDG Meeting (6th September 2012)	No change
Tenth GDG Meeting (17th October 2012)	No change
Eleventh GDG Meeting (10th December 2012)	No change
Twelfth GDG Meeting (14th Jan 2013)	No change
Thirteenth GDG Meeting (15th May 2013)	No change
Actions	None required

B.3 Annette Davies

GDG meeting	Declaration of Interests
First GDG meeting (14th September 2011)	She declared a personal non-pecuniary interest – she has published the following in the last year: Davies A and Bench S (2011) The patient with an acute kidney injury in Critical Care Nursing: Learning from Practice (editors Bench S and Brown K) Blackwell Publishing She has also presented the following in the last year; Davies A (2011) Management of AKI – practical aspects (invited speaker) at Renal Association / British Renal Society Conference June 2011
Second GDG Meeting (15th September 2011)	No change
Third GDG Meeting (20th October 2011)	No change
Fourth GDG Meeting (7th December 2011)	No change
Fifth GDG Meeting (20th January 2012)	No change
Sixth GDG Meeting (6th March 2012)	No change
Seventh GDG Meeting (22nd May 2012)	Declared a personal pecuniary interest: she has written two e-learning modules: Management of the renal patient – Advanced for Capita on behalf of NHS South west. She has also contributed to editing AKI chapter of Renal Nursing (editor Nicola Thomas) publisher Wiley – Blackwell.
Eighth GDG Meeting (19th July 2012)	No change
Ninth GDG Meeting (6th September 2012)	No change
Tenth GDG Meeting (17th October 2012)	Did not attend
Eleventh GDG Meeting (10th December 2012)	No change

GDG meeting	Declaration of Interests
Twelfth GDG Meeting (14th Jan 2013)	No change
Thirteenth GDG Meeting (15th May 2013)	No change
Actions	None required

B.4 Anne Dawnay

GDG meeting	Declaration of Interests
First GDG meeting (14th September 2011)	Declared a personal pecuniary interest; she lectured on AKI at the invitation of the American Association for Clinical Chemistry (AACC) in July 2011 for which her travel and hotel expenses were reimbursed. At that meeting she agreed to make a Webinar on AKI in 2012, updating the lecture on laboratory alerts to changes in creatinine and novel biomarkers. Declared a personal non-pecuniary interest; I am a member of the Renal Association, the Royal College of Pathologists and the Association for Clinical Biochemistry. She is the lab scientist member for the North Central London and the London AKI networks. She is a collaborator on projects looking at novel AKI markers not included in this guideline but necessarily involving serum creatinine.
Second GDG Meeting (15th September 2011)	No change
Third GDG Meeting (20th October 2011)	No change
Fourth GDG Meeting (7th December 2011)	No change
Fifth GDG Meeting (20th January 2012)	No change
Sixth GDG Meeting (6th March 2012)	Declared personal non-pecuniary interest; she has spoken at the launch of the London AKI network 8/3/12
Seventh GDG Meeting (22nd May 2012)	No change
Eighth GDG Meeting (19th July 2012)	Did not attend
Ninth GDG Meeting (6th September 2012)	No change
Tenth GDG Meeting (17th October 2012)	No change
Eleventh GDG Meeting (10th December 2012)	No change
Twelfth GDG Meeting (14th Jan 2013)	Declared a personal non pecuniary interest: she has been invited to give a lecture on AKI at annual meeting of AKI for clinical biochemistry.
Thirteenth GDG Meeting (15th May 2013)	Declared a personal pecurinary interest: she gave a presentation on the guideline during the consultation period and was paid her train fare
Actions	None required

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B.5 Mark Devonald

GDG meeting	Declaration of Interests
First GDG meeting (14th September 2011)	Declared a personal pecuniary interest: he has received sponsorship from Janssen to attend an international nephrology conference in 2011 and is due to receive further sponsorship to attend another later this year. Declared a non-personal pecuniary interest: The unit in which he works has received funding from Amgen and MSD to pay part of the salary of a research nurse involved in multicentre studies funded by these companies. Declared a personal non-pecuniary interest: he is lead author for local AKI guidelines and chair the local AKI group. He leads a research group which has developed an electronic AKI alert system, which uses specific definitions of AKI. This alert has been published in abstract form and has been adapted for use in other hospitals. He is a member of the UK Renal Association, the American Society of Nephrology and the International Society of Nephrology. He is deputy chair of the NUH Drugs and Therapeutics Committee. He has published in the field of AKI and has a number of manuscripts in preparation which relate to clinical and basic scientific aspects of AKI.
Second GDG Meeting (15th September 2011)	No change
Third GDG Meeting (20th October 2011)	No change
Fourth GDG Meeting (7th December 2011)	No change
Fifth GDG Meeting (20th January 2012)	No change
Sixth GDG Meeting (6th March 2012)	No change
Seventh GDG Meeting (22nd May 2012)	Declared a personal pecuniary interest: he received funding from Janssen to attend American Society of Nephrology 2010-12 and World Congress of Nephrology
Eighth GDG Meeting (19th July 2012)	No change
Ninth GDG Meeting (6th September 2012)	No change
Tenth GDG Meeting (17th October 2012)	No change
Eleventh GDG Meeting (10th December 2012)	No change
Twelfth GDG Meeting (14th Jan 2013)	No change
Thirteenth GDG Meeting (15th May 2013)	Declared a non personal pecuniary interest: he organised the 'Nottingham Acute Kidney Injury Course' held on 20 April. It was supported in part by unrestricted educational grants from 4 companies: Amgen, Boehringer Ingelheim, Shire and MSD. The first 3 paid £400 direct to the venue to contribute to costs. MSD paid for a dinner for the speakers, as they were not paid a fee. He did not receive any fee from any of them.
Actions	None required

B.6 Coral Hulse

GDG meeting	Declaration of Interests
First GDG meeting (14th September 2011)	Declared a personal non-pecuniary interest: Assessment tool in use that she has introduced to Leighton Hospital (the Kidney HOUR Tool). It is an assessment and response tool based on AKIN and RIFLE classifications for AKI.
Second GDG Meeting (15th September 2011)	No change
Third GDG Meeting (20th October 2011)	No change
Fourth GDG Meeting (7th December 2011)	No change
Fifth GDG Meeting (20th January 2012)	No change
Sixth GDG Meeting (6th March 2012)	No change
Seventh GDG Meeting (22nd May 2012)	No change
Eighth GDG Meeting (19th July 2012)	No change
Ninth GDG Meeting (6th September 2012)	Did not attend
Tenth GDG Meeting (17th October 2012)	No change
Eleventh GDG Meeting (10th December 2012)	No change
Twelfth GDG Meeting (14th Jan 2013)	No change
Thirteenth GDG Meeting (15th May 2013)	No change
Actions	None required

B.7 Chris Laing

GDG meeting	Declaration of Interests
First GDG meeting (14th September 2011)	Declared personal pecuniary interest: Prior sponsorship by Otska pharmaceutical for educational events on SINDH Declared non pecuniary interest: 1) Guideline development locally (NCL AKI network) and local audit (London JCH) 2) Ongoing clinical research on AKI 1) remote ischaemic preconditioning after cardiac surgery (NIHR funded) and 2) remote ischaemic preconditioning to prevent AKI after coronary angiography.
Second GDG Meeting	No change

GDG meeting	Declaration of Interests
(15th September 2011)	
Third GDG Meeting (20th October 2011)	No change
Fourth GDG Meeting (7th December 2011)	Declared a non-personal pecuniary interest: he was paid honorarium by otsuka pharmaceuticals who make tolvaptan (used for SIADH). This was for chairing the hyponatraemia academy. He put has put the money into the hospital's fellows' fund
Fifth GDG Meeting (20th January 2012)	No change
Sixth GDG Meeting (6th March 2012)	Declared a non-personal pecuniary interest: He is a joint organiser of the launch of the London acute kidney injury network which has received sponsorship from Gambro, Fresenius, Baxter, Amgen and Gilead Sciences to cover venue costs. Fees were paid directly to the Wellcome collection which hosted the event. No speaker, delegate or organiser fees were paid.
Seventh GDG Meeting (22nd May 2012)	No change
Eighth GDG Meeting (19th July 2012)	Did not attend
Ninth GDG Meeting (6th September 2012)	No change
Tenth GDG Meeting (17th October 2012)	No change
Eleventh GDG Meeting (10th December 2012)	Declared a non-personal pecuniary interest: they received sponsorship from Gambro, Fresenius and the Binding Site towards an educational course on AKI which they organised on behalf of the AKI Network. The sponsorship was offset against venue and catering cost. The revenue gained was put into the network fund to be reinvested in open access AKI education
Twelfth GDG Meeting (14th Jan 2013)	No change
Thirteenth GDG Meeting (15th May 2013)	No change
Actions	None required

B.8 Andrew Lewington

GDG meeting	Declaration of Interests
First GDG meeting (14th September 2011)	Declared personal pecuniary interest: 1. Amgen-£500 towards travel/accommodation/registration at American Society of Nephrology conference October 2010 2. Roche-£500 towards travel/accommodation/registration at American Society of Nephrology conference October 2010 3. Baxter-consultancy on continuous renal replacement therapy-Berlin, Germany September 2011 Declared non-personal pecuniary interest: Renal Department Research Roche funded anaemia trial - Micera Amgen funded anaemia trial - Extend

GDG meeting	Declaration of Interests
	Roche funded research trial - GloMY LifeCycle Pharma funded research trial - LCP
Second GDG Meeting (15th September 2011)	No change
Third GDG Meeting (20th October 2011)	No change
Fourth GDG Meeting (7th December 2011)	No change
Fifth GDG Meeting (20th January 2012)	No change
Sixth GDG Meeting (6th March 2012)	Declared a personal pecuniary interest: he is an adviser to AM Pharma on clinical phase 1 trial for alkaline phosphatase as a drug therapy for AKI.
Seventh GDG Meeting (22nd May 2012)	No change
Eighth GDG Meeting (19th July 2012)	Declared a personal pecuniary interest: he received a £1000 honorarium for lectures on IV Fluids for Baxter at the Royal College of Surgeon. He will be putting the money towards attending conferences.
Ninth GDG Meeting (6th September 2012)	No change
Tenth GDG Meeting (17th October 2012)	Declared a personal pecuniary interest: he will receive a fee for his attendance at an advisory board meeting to discuss a new drug treatment for AKI which is currently in development. He has authored a book on iv fluids for B Braun for which he received an educational grant of £5500.
Eleventh GDG Meeting (10th December 2012)	No change
Twelfth GDG Meeting (14th Jan 2013)	No change
Thirteenth GDG Meeting (15th May 2013)	Declared a personal pecuniary interest. He has been an AM Pharma - Advisory Board Member for a Phase 2 Clinical Trial using recombinant alkaline phosphatase in treating sepsis and AKI . He has attended 2 meetigs in San Diego (November 2012 and 14.2.13) and received for £480 each meeting.
Actions	None required

1 ## B.9 Fiona Loud

GDG meeting	Declaration of Interests
First GDG meeting (14th September 2011)	Declared a personal pecuniary interest; NIHR funded CKM (Conservative Kidney Management) OPPS – patient advisor (fee and travel expenses) ongoing. HF funded Closing the Gap (Patient education CKD in Primary Care) - patient and service team leader (fee and travel expenses) ongoing. City University Kidney Research Education Initiative funded by British Kidney Patients Association (fee and travel expenses) ongoing.

GDG meeting	Declaration of Interests
	She has received expenses for speaking from a patient viewpoint to the following: - A group of salespeople at an internal meeting for Amgen on what it is like to be a kidney patient (June 2011) - group of patients and staff at Basildon renal unit at the invitation of Baxter to welcome the opening of the new unit on World Kidney Day (March 2011) -
Second GDG Meeting (15th September 2011)	No change
Third GDG Meeting (20th October 2011)	Declared a personal pecuniary interest: she received a fee and travel expenses for speaking about patient views to a group of transplant surgeons at a Novartis sponsored event on immunosuppression (October 2011)
Fourth GDG Meeting (7th December 2011)	Declared that the following have verbally offered funding towards World Kidney Day next March 2012. - Shire £10,000, - Fresenius £3,000, - Amgen £5,000, - Baxter £5,000 Transplant 2013 (a group set up to promote leadership of organ donation and transplantation in Parliament and other relevant institutions and facilitate communication and consensus within the transplant community in order to support the implementation of the Organ Donation Taskforce's recommendations) £1,000.
Fifth GDG Meeting (20th January 2012)	No change
Sixth GDG Meeting (6th March 2012)	Did not attend
Seventh GDG Meeting (22nd May 2012)	Declared the following non personal pecuniary interests: a further of £2,000 was donated from Pfizer for World Kidney day. She also gave an interview to a media company working for Shire, reflecting on her experiences as a kidney patient with regard to diet and medication; This is intended for use in an internal magazine, called i-media. If it is used, she has requested a donation to a local charity, the Lister Kidney Foundation. Declared personal pecuniary interest: Abbott funded her travel to Paris for meeting of 'Kidney Health for Life'Coalition in May 2012
Eighth GDG Meeting (19th July 2012)	No change
Ninth GDG Meeting (6th September 2012)	Declared a personal non-pecuniary interest; she attended a meeting in July 2012 "Kidney Health 2032". The meeting was funded by Abbott (who did not attend). No fees were received or offered. The subject was to discuss creating a road map for kidney care in next 20 years.
Tenth GDG Meeting (17th October 2012)	Declared personal pecuniary interest: she is due to chair an event on 3 December, run by SBK Healthcare (independent events company). The meeting is entitled 'Managing Improvement in Renal services' and she will receive a fee for this day. She will also receive a fee from the Welsh CKD

GDG meeting	Declaration of Interests
	framework for having trained CKD and practice nurses in how to enable self-care in September. This is follow-on to the Health Foundation Closing the Gap work but is separately funded. She received expenses from Roche Pharmaceuticals for a day's training in September 2012 on healthcare social marketing. She also declared a non-personal pecuniary interest: The Kidney Alliance (KA) is now inviting funding for its World Kidney Day 2013 national event which will be a parliamentary reception plus publicity. This will be against an agreed budget at the AGM in June 2012. The KA is also inviting funding for its 2013-2014 review of the National Service Framework, also against an agreed budget. She will forward details when sponsorship is agreed. She declared a personal non-pecuniary interest: she attended 2 events funded by Abbott Healthcare towards the Kidney Health 2032 project. They were small group meetings in August and October 2012. No expenses or fees were paid. The project is run by the National Clinical Director and is a think-tank considering future developments in kidney health.
Eleventh GDG Meeting (10th December 2012)	Declared a non-personal pecuniary interest: The Kidney Alliance is now inviting funding for its World Kidney Day 2013 national event which will be a parliamentary reception and publicity. This will be against an agreed budget at the AGM in June 2012. The KA is also inviting funding for its 2013-2014 review of the National Service Framework, also against an agreed budget. She will provide further details when sponsorship is agreed. She has also had confirmation of £5,000 funding from Amgen for the World Kidney Day 2013 event and has had meetings to discuss the above with: Baxter, Takeda, Fresenius, NxStage and Abbott
Twelfth GDG Meeting (14th Jan 2013)	No change
Thirteenth GDG Meeting (15th May 2013)	Did not attend
Actions	None required

B.10 David Milford

GDG meeting	Declaration of Interests
First GDG meeting (14th September 2011)	Did not attend
Second GDG Meeting (15th September 2011)	Declared a non-personal pecuniary interest: his department will participate in Roche Valcyte protocol NV25409 CMV Prophylaxis. He had expenses paid to attend Roche Valcyte protocol NV25409 trial investigator meeting – Rome May 2011. He also declared personal non-pecuniary interests: he has published in the field. He is also a member of the British Association for Paediatric Nephrology, the Renal Association and European and International Paediatric Nephrology Associations.
Third GDG Meeting (20th October 2011)	No change
Fourth GDG Meeting (7th December 2011)	No change
Fifth GDG Meeting	No change

GDG meeting	Declaration of Interests
(20th January 2012)	
Sixth GDG Meeting (6th March 2012)	No change
Seventh GDG Meeting (22nd May 2012)	No change
Eighth GDG Meeting (19th July 2012)	Declared a personal pecuniary interest; he received a fee of £125 for a survey on atypical haemolytic uraemic syndrome
Ninth GDG Meeting (6th September 2012)	No change
Tenth GDG Meeting (17th October 2012)	Did not attend
Eleventh GDG Meeting (10th December 2012)	No change
Twelfth GDG Meeting (14th Jan 2013)	Declared a personal pecuniary interest: he received £500 travel grant from Astellas to attend African Nephrology Congress, Ghana, to give a talk on Congenital abnormalities of Kidneys and Urinary Tract
Thirteenth GDG Meeting (15th May 2013)	No change
Actions	None required

B.11 Marlies Ostermann

GDG meeting	Declaration of Interests
First GDG meeting (14th September 2011)	Declared personal pecuniary interests: she has received lecture fees from Pfizer and Gilead. She has received sponsorship from Amgen to attend the American Society of Nephrology meeting in the USA. Declared non-personal pecuniary interest: she has received sponsorship from Bioporto to undertake research in the field of biomarkers for acute kidney injury. She has taken part in commercial research projects sponsored by Eli Lilly. She has received an educational grant from Fresenius to undertake research in the field of citrate based renal replacement therapy.
Second GDG Meeting (15th September 2011)	No change
Third GDG Meeting (20th October 2011)	No change
Fourth GDG Meeting (7th December 2011)	No change
Fifth GDG Meeting (20th January 2012)	Declared a non-personal pecuniary interest: she received an honorarium from Bioporto for giving a talk. She donated the money to the ICU research fund at St Thomas' hospital.
Sixth GDG Meeting (6th March 2012)	Declared a non-personal pecuniary interest: she is joint organiser of the launch of the London acute kidney injury network which has received sponsorship from Gambro, Fresenius, Baxter, Amgen and Gilead Sciences to

GDG meeting	Declaration of Interests
	cover venue costs. Fees were paid directly to the Welcome collection which hosted the event. No speaker, delegate or organiser fees were paid.
Seventh GDG Meeting (22nd May 2012)	Declared a non-personal pecuniary interest: she attended a consultancy meeting organised by Novartis. She donated her fee to the hospital research fund.
Eighth GDG Meeting (19th July 2012)	Declared a non- personal pecuniary interest: she contributed to the development of educational material for Fresenius and received £400 which was donated to the Critical Care research fund.
Ninth GDG Meeting (6th September 2012)	No change
Tenth GDG Meeting (17th October 2012)	Did not attend
Eleventh GDG Meeting (10th December 2012)	Declared a non-personal pecuniary interest: they received sponsorship from Gambro, Fresenius and the Binding Site towards an educational course on AKI which they organised on behalf of the AKI Network. The sponsorship was offset against venue and catering cost. The revenue gained was put into the network fund to be reinvested in open access AKI education. Also chaired an educational meeting on behalf of Alere (manufacturers of NGAL). She received £500 which was donated to the departmental research fund
Twelfth GDG Meeting (14th Jan 2013)	Declared a personal pecuniary interest: she attended a post conference dinner which was paid for by Fresenius.
Thirteenth GDG Meeting (15th May 2013)	No change
Actions	None required

B.12 Nicholas Palmer

GDG meeting	Declaration of Interests
First GDG meeting (14th September 2011)	None to declare
Second GDG Meeting (15th September 2011)	Did not attend
Third GDG Meeting (20th October 2011)	Did not attend
Fourth GDG Meeting (7th December 2011)	Did not attend
Fifth GDG Meeting (20th January 2012)	No change
Sixth GDG Meeting (6th March 2012)	No change
Seventh GDG Meeting (22nd May 2012)	Did not attend
Eighth GDG Meeting	No change

GDG meeting	Declaration of Interests
(19th July 2012)	
Ninth GDG Meeting (6th September 2012)	Did not attend
Tenth GDG Meeting (17th October 2012)	No change
Eleventh GDG Meeting (10th December 2012)	No change
Twelfth GDG Meeting (14th Jan 2013)	No change
Thirteenth GDG Meeting (15th May 2013)	Did not attend
Actions	None required

1

2 ## B.13 Sue Shaw

GDG meeting	Declaration of Interests
First GDG meeting (14th September 2011)	Declared Personal pecuniary interest: she is a member of the Renal Pharmacy Group committee. This group receives sponsorship for conferences and study days from a number of pharmaceutical companies.
Second GDG Meeting (15th September 2011)	No change
Third GDG Meeting (20th October 2011)	No change
Fourth GDG Meeting (7th December 2011)	No change
Fifth GDG Meeting (20th January 2012)	No change
Sixth GDG Meeting (6th March 2012)	No change
Seventh GDG Meeting (22nd May 2012)	No change
Eighth GDG Meeting (19th July 2012)	No change
Ninth GDG Meeting (6th September 2012)	No change
Tenth GDG Meeting (17th October 2012)	No change
Eleventh GDG Meeting (10th December 2012)	No change
Twelfth GDG Meeting (14th Jan 2013)	No change
Thirteenth GDG Meeting (15th May 2013)	No change
Actions	None required

B.14 John Lemberger (Co Opted member)

GDG meeting	Declaration of Interests
Tenth GDG Meeting (17th October 2012)	Nothing to declare
Actions	None required

B.15 Lyda Jadresic (Co Opted member)

GDG meeting	Declaration of Interests
Sixth GDG Meeting (6th March 2012)	Nothing to declare
Seventh GDG Meeting (22nd May 2012)	Nothing to declare
Tenth GDG Meeting (17th October 2012)	Nothing to declare
Actions	None required

B.16 Mark Downes (Co Opted member)

GDG meeting	Declaration of Interests
Fourth GDG Meeting (7th December 2011)	Declared a personal pecuniary interest: he has received sponsorship from GE Healthcare to attend meetings (payments were in line with ABPI).
Fifth GDG Meeting (20th January 2012)	No change
Actions	None required

B.17 Mark Rigby (Co Opted member)

GDG meeting	Declaration of Interests
Tenth GDG Meeting (17th October 2012)	Nothing to declare
Actions	None required

B.18 Rajib Pal (Co Opted member)

GDG meeting	Declaration of Interests
Tenth GDG Meeting (17th October 2012)	Nothing to declare
Actions	None required

B.19 Sheilagh O'Riordan (Co Opted member)

GDG meeting	Declaration of Interests
Tenth GDG Meeting (17th October 2012)	Nothing to declare
Actions	None required

B.20 Declarations of interests of the NCGC staff

GDG meeting	Declaration of Interests
First GDG meeting (14th September 2011)	Nothing to declare
Second GDG Meeting (15th September 2011)	No change
Third GDG Meeting (20th October 2011)	No change
Fourth GDG Meeting (7th December 2011)	No change
Fifth GDG Meeting (20th January 2012)	No change
Sixth GDG Meeting (6th March 2012)	No change
Seventh GDG Meeting (22nd May 2012)	No change
Eighth GDG Meeting (19th July 2012)	No change
Ninth GDG Meeting (6th September 2012)	No change
Tenth GDG Meeting (17th October 2012)	No change
Eleventh GDG Meeting (10th December 2012)	No change
Twelfth GDG Meeting (14th Jan 2013)	No change
Thirteenth GDG Meeting (15th May 2013)	No change
Actions	None required

Appendix C: Review protocols

C.1 Assessing risk

C.1.1 Adult risk assessment tools

Review question	Which risk assessment tools are the most accurate for predicting AKI in at risk adult patients?
Objectives	To determine if any of the validated tools for AKI accurately predict AKI in at risk patients
Criteria	Population: Patients at risk of AKI Subgroups: •General inpatients •General Surgery •Patients receiving iodinated contrast Risk scores: Validated risk scores for AKI Comparison: not applicable Outcomes: sensitivity (%) and specificity (%), statistical measures of discrimination and calibration including Area Under the Curve (AUC) Study design: Prospective cohort studies and external validation studies Exclusion criteria: •Number of people with AKI <100 •Risk scores looking only at patients undergoing cardiac surgery •CI-AKI measured at <24h •Scores for risk of mortality or RRT rather than AKI per se •Geographical considerations where causes of AKI different from those in UK
Search	The databases to be searched are Medline, Embase, the Cochrane Library and CINAHL. Studies will be restricted to English language only. No study design filters will be applied.
Review strategy	Criteria for individual studies: • Multivariate analysis (exclude if variables have not been controlled for in the analysis depending on the quantity and quality of the papers found) Hierarchy of evidence: • IPD meta-analysis (Gold standard) • Meta-analysis/ systematic reviews • Prospective cohort studies If no validated score found for any population then a search will be done for prospective cohort studies designed to look at the risk factors for AKI in that population. If there is a lack of evidence studies with number of people with AKI <100 will be considered.

C.1.2 Paediatric risk assessment tools

Review question	Which risk assessment tools are the most accurate for predicting AKI in at risk paediatric patients?
Objectives	To determine if any of the validated tools for AKI accurately predict AKI in at risk patients

Criteria	Population: Patients at risk of AKI Subgroups: •General inpatients •General Surgery •Patients receiving iodinated contrast Risk scores: Validated risk scores for AKI Comparison: not applicable Outcomes: sensitivity (%) and specificity (%), statistical measures of discrimination and calibration including Area Under the Curve (AUC) Study design: Prospective cohort studies and external validation studies
Search	The databases to be searched are Medline, Embase, the Cochrane Library and CINAHL. Studies will be restricted to English language only. No study design filters will be applied.
Review strategy	Criteria for individual studies: • Multivariate analysis (exclude if variables have not been controlled for in the analysis depending on the quantity and quality of the papers found) If no multivariate analysis univariate analysis will be considered. Hierarchy of evidence: • IPD meta-analysis (Gold standard) • Meta-analysis/ systematic reviews • Prospective cohort studies If no validated score found for any population then a search will be done for prospective cohort studies designed to look at the risk factors for AKI in that population. Exclusion criteria: •Risk scores looking only at patients undergoing cardiac surgery •CI-AKI measured at <24h •Scores for risk of mortality or RRT rather than AKI per se. •Geographical considerations where causes of AKI different from those in UK If there is a lack of evidence studies with number of people with AKI <100 will be considered.

C.2 Preventing acute kidney injury

C.2.1 Paediatric early warning scores

Review question	**What is the predictive accuracy of paediatric early warning scores in detecting acutely ill children in hospital whose clinical condition is deteriorating or who are at risk of deterioration?**
Objectives	To determine how accurate paediatric early warning scores are in detecting children who are at risk of becoming acutely ill and therefore becoming at higher risk of developing AKI
Criteria	**Population**: children in hospital **Intervention/s**: paediatric early warning scores **Comparison/s**: not applicable **Outcomes**: AKI, mortality, number needing critical care, length of stay in critical care **Statistical measures:** sensitivity, specificity, AUROC **Other statistical measures:** positive predictive value, negative predictive value **Study design**: prospective cohorts, if none consider retrospective cohorts
Search	The databases to be searched are Medline, Embase, the Cochrane Library and CINAHL.

	Studies will be restricted to English language only. No study design filters will be applied.
Review strategy	The methodological quality of each study will be assessed using NICE checklists and GRADE. Meta-analysis will be conducted if appropriate. If not appropriate, ranges of results will be reported for these outcomes. No minimum sample size.

1

2 ### C.2.2 Preventing contrast induced acute kidney injury (CI-AKI)

Review question	What is the comparative clinical and cost effectiveness of NAC and/or intravenous fluids in preventing CI-AKI in at risk adults?
Objectives	To estimate the effects and cost effectiveness of NAC and/or intravenous fluids in the prevention of CI-AKI
Criteria	**Population:** Adults who are at risk of contrast induced AKI **Subgroups:** a) People with CKD b) People with diabetes c) Older people **Interventions:** sodium chloride 0.9% and 0.45%, sodium bicarbonate, oral fluids, NAC (see matrix in full guideline section 6.2) **Comparisons:** All compared to each other and placebo (see matrix in full guideline section 6.2) **Outcomes:** **a)** contrast induced AKI (as defined by study) **b)** mortality **c)** number of patients needing RRT **d)** length of hospital stay **Study design:** RCT
Search	The databases to be searched are Medline, Embase and the Cochrane Library. Studies will be restricted to English language only. Systematic review and randomised controlled trial study design filters will be applied.
Review strategy	Cochrane Reviews will be quality assessed and presented Further meta-analyses will be conducted as appropriate If there is heterogeneity the following subgroups will be analysed separately: • People with CKD • People with diabetes • Older people Exclude studies N<80 Exclude studies in which the type of iodinated contrast used is not specified. Exclude studies where the fluids being compared are given at different volumes and over different schedules unless these are the only studies available for a particular comparison. Different doses of the same fluid will be combined for meta-analysis.

3

C.2.3 Computerised decision tools

Review question	What is the clinical and cost effectiveness of methods for preventing inappropriate use of nephrotoxic drugs in hospital inpatients?
Objectives	To estimate the effectiveness and cost effectiveness of methods for preventing inappropriate use of nephrotoxic drugs in hospital inpatients.
Criteria	Population: Hospital inpatients Intervention: Pharmacist review of all prescriptions, electronic prescribing or computerised decision tool which included a measure of the patient's renal function Comparison: Each other or standard medical care Outcomes: • Frequency of AKI due to nephrotoxic drugs • Mortality • Number of changes/interventions • Time to discontinuation/change in nephrotoxic drug • Incidence of adverse events • Length of stay Study design: RCT. If no RCTs then large prospective cohort studies will be considered.
Search	The databases to be searched are Medline, Embase, the Cochrane Library and CINAHL. Studies will be restricted to English language only. Systematic review, randomised controlled trial and observational study design filters will be applied.
Review strategy	Studies with less than 100 events will be excluded. Meta-analysis will be conducted where appropriate.

C.2.4 Stopping ACEI/ARB therapy

C.2.4.1 Stopping ACEI/ARB therapy– Sepsis and diarrhoea and vomiting

Review question	What is the clinical and cost effectiveness of stopping compared to continuing chronic ACEI and/or ARB therapy to prevent AKI due to diarrhoea and vomiting, or sepsis?
Objectives	To estimate the effectiveness and cost effectiveness of stopping versus continuing chronic/longterm ACEI/ARB therapy in patients at risk of AKI in the following situations: • Diarrhoea and vomiting • Sepsis
Criteria	Population: Adults and children taking ACEI and/or ARBs Intervention: Stopping ACEI/ARB Comparison: Continuing ACEI/ARB Outcomes: • Number of patients developing AKI • Cardiovascular events • All cause mortality • Number of patients needing RRT • Length of hospital stay Study design: RCTs, consider large prospective studies. SRs of either of these.
Search	The databases to be searched are Medline, Embase and the Cochrane Library. Studies will be restricted to English language only. No study design filters will be applied.
Review strategy	Cochrane Reviews will be quality assessed and presented Further meta-analyses will be conducted as appropriate If there is heterogeneity the following subgroups will be analysed separately:

	• People with CKD • Older people No minimum sample size.

C.2.4.2 Stopping ACEI/ARB therapy– surgery and iodinated contrast

Review question	What is the clinical and cost effectiveness of stopping compared to continuing chronic ACEI and/or ARB therapy in patients with CKD to prevent AKI due to surgery or iodinated contrast?
Objectives	To estimate the effectiveness and cost effectiveness of stopping versus continuing chronic/long term ACEI/ARB therapy in patients with CKD or left ventricular failure at risk of AKI in the following situations: • Administration of iodinated contrast • Surgery – cardiac and non-cardiac
Criteria	Population: Adults and children with CKD or left ventricular failure taking ACEI and/or ARBs Intervention: Stopping ACEI/ARB Comparison: Continuing ACEI/ARB Outcomes: Number of patients developing AKI Cardiovascular events All cause mortality Number of patients needing RRT Length of hospital stay Study design: RCTs, consider large prospective studies. SRs of either of these.
Search	The databases to be searched are Medline, Embase and the Cochrane Library. Studies will be restricted to English language only. Systematic review, randomised controlled trial and observational study design filters will be applied.
Review strategy	Cochrane Reviews will be quality assessed and presented Further meta-analyses will be conducted as appropriate If there is heterogeneity the following subgroups will be analysed separately: • People with CKD • People with left ventricular failure • Older people No minimum sample size.

C.3 Detecting acute kidney injury

C.3.1 Definitions and staging of acute kidney injury using AKIN/RIFLE/pRIFLE/ KDIGO

Review question	What is the clinical evidence that RIFLE (pRIFLE) or AKIN or KDIGO are useful in detecting and staging AKI and predicting patient outcomes (mortality and RRT)?
Objectives	To estimate the diagnostic accuracy of RIFLE/pRIFLE/AKIN and KDIGO and their usefulness in predicting patient outcomes in terms of mortality and the need for RRT.
Criteria	Population: Acutely unwell patients (including ICU and cardiac surgery). Index test: AKIN or KDIGO Comparator test: RIFLE or pRIFLE Outcomes: Diagnostic yield, diagnostic accuracy (sensitivity and specificity), all-cause mortality (Odds ratios, AUROC), number of patients needing RRT

	Study design: Prospective cohorts (or retrospective analysis of prospectively collected data).
Search	The databases to be searched are Medline, Embase and the Cochrane Library. Studies will be restricted to English language only. Observational study design filters will be applied.
Review strategy	Criteria for individual studies: • Multivariate analysis (exclude if variables have not been controlled for in the analysis depending on the quantity and quality of the papers found) Hierarchy of evidence: • IPD meta-analysis (Gold standard) • Meta-analysis/ systematic reviews • Prospective cohort studies Minimum number of AKI events = 100 Multivariable analysis was used where available. Analysis was required to be by stage of AKI (not just 'all AKI' versus 'no AKI') and with a reference of "no AKI". The initial search was for studies in which AKIN and RIFLE were compared in the same cohort. Studies which only looked at RIFLE or AKIN would be considered if further evidence was required. Adjusted odds ratios or hazard ratios with 95% confidence intervals were used in the generic inverse variance analysis, as these were not meta-analysed both were shown in the same forest plot.

C.4 Identifying the cause of acute kidney injury

C.4.1 Urinalysis

Review question	**What is the sensitivity and specificity of urine dipstick compared to urine microscopy and/or biopsy in the detection of proteinuria and haematuria as indicators of glomerulonephritis in AKI patients?**
Objectives	To estimate the diagnostic accuracy of urine dipsticks at detecting haematuria and proteinuria as indicators of acute glomerulonephritis in AKI patients.
Criteria	Population: Patients with AKI Intervention: Urinalysis, dipstick Comparison: No urinalysis Outcomes: Sensitivity (%) and specificity (%); Area under the ROC curve (AROUC) – measure of predictive accuracy, Positive/negative predictive value, Positive/negative diagnostic likelihood ratios Study design: Diagnostic accuracy studies
Search	The databases to be searched are Medline, Embase, the Cochrane Library and CINAHL. Studies will be restricted to English language only. No study design filters will be applied.
Review strategy	The methodological quality of each study will be assessed using NICE checklists and GRADE. Meta-analysis will be conducted if appropriate. If not appropriate, ranges of results will be reported for these outcomes.

C.4.2 Ultrasound

Review question	**Which patients should have ultrasound for the diagnosis of the cause of AKI?**
Objectives	To establish which patients should have ultrasound to diagnose the cause of AKI
Criteria	Population: Patients with AKI Subgroups:

	• General inpatients • General Surgery • Patients receiving iodinated contrast Intervention: Risk stratification models or decision tools for use of ultrasound Comparison: n/a Outcomes: Main outcomes: • Sensitivity (%) and specificity (%) • Area under the ROC curve (AUROC) – measure of predictive accuracy Other outcomes: • Positive/negative predictive value • Positive/negative diagnostic likelihood ratios Study design: Prospective cohort studies
Search	The databases to be searched are Medline, Embase, the Cochrane Library and CINAHL. Studies will be restricted to English language only. No study design filters will be applied.
Review strategy	The methodological quality of each study will be assessed using NICE checklists and GRADE. Meta-analysis will be conducted if appropriate. If not appropriate, ranges of results will be reported for these outcomes. Number of patients with AKI ≥100 If no prospective studies, retrospective studies will be considered

C.5 Managing acute kidney injury

C.5.1 Relieving urological obstruction

Review question	**In adults and children with AKI and upper tract urological obstruction, what is the clinical and cost effectiveness of early compared to delayed relief of obstruction by nephrostomy or stenting on mortality, severity of AKI, need for RRT and length of hospital stay?**
Objectives	To estimate the effectiveness and cost effectiveness of early compared to delayed relief of upper tract urological obstruction.
Criteria	Population: Adults and children with AKI and upper tract urological obstruction - special groups: pyonephrosis, solitary kidney Intervention: Nephrostomy or urological stenting Comparison: No or delayed nephrostomy or stenting Outcomes: • Mortality • Worsening of AKI (as defined by study) • Number of patients needing RRT • Length of hospital stay • Adverse events (including bleeding, infection or injury to the obstructed kidney or to nearby organs). Study Design: RCT, if no RCTs consider prospective cohort studies. SR of either of these.
Search	The databases to be searched are Medline, Embase and the Cochrane Library. Studies will be restricted to English language only. Systematic review, randomised controlled trial and observational study design filters will be applied.
Review	Cochrane Reviews will be quality assessed and presented

strategy	Further meta-analyses will be conducted as appropriate. No minimum sample size.

1

2 C.5.2 Pharmacological management

3 C.5.2.1 Loop diuretics

Review question	In adults and children with AKI, what is the clinical and cost effectiveness of loop diuretics compared to placebo on mortality, need for RRT, length of RRT, dialysis independence, length of hospital stay and hearing loss?
Objectives	To estimate the effectiveness and cost effectiveness of loop diuretics in improving patient outcomes in patients with or at high risk of AKI.
Criteria	Population: Inpatients with AKI Intervention: Loop diuretics Comparison: Placebo or usual care Outcomes: • Mortality •Number of patients needing RRT •Length of RRT •Dialysis independence •Length of hospital stay •Hearing loss Study design: Randomised controlled trials and systematic reviews
Search	The databases to be searched are Medline, Embase and the Cochrane Library. Studies will be restricted to English language only. Systematic review and randomised controlled trial study design filters will be applied.
Review strategy	Cochrane Reviews will be quality assessed and presented Further meta-analyses will be conducted as appropriate. No minimum sample size.

4 C.5.2.2 Dopamine

Review question	In adults and children with AKI, what is the clinical and cost effectiveness of low dose dopamine compared to placebo on mortality, need for RRT, length of RRT, dialysis independence, length of hospital stay and cardiac arrythmias?
Objectives	To estimate the effectiveness and cost effectiveness of low dose dopamine in improving patient outcomes in patients with or at high risk of AKI.
Criteria	Population: Inpatients with or at risk of AKI Intervention: Low dose dopamine (<5µg/kg/min) Comparison: Placebo or usual care Outcomes: • Mortality •Number of patients needing RRT •Length of RRT •Dialysis independence •Length of hospital stay •Cardiac arrhythmias Study design: Randomised controlled trials and systematic reviews
Search	The databases to be searched are Medline, Embase and the Cochrane Library. Studies will be restricted to English language only.

Review question	**In adults and children with AKI, what is the clinical and cost effectiveness of low dose dopamine compared to placebo on mortality, need for RRT, length of RRT, dialysis independence, length of hospital stay and cardiac arrythmias?**
	Systematic review and randomised controlled trial study design filters will be applied.
Review strategy	Cochrane Reviews will be quality assessed and presented Further meta-analyses will be conducted as appropriate. No minimum sample size.

1

2 ### C.5.3 Referring for renal replacement therapy

Review question	**In patients with AKI, what is the clinical and cost effectiveness of initiating early RRT compared to delayed RRT on mortality, renal recovery, duration of RRT, length of critical care stay and HRQoL?**
Objectives	To assess the benefits/harms of early vs. late dialysis
Criteria	Population: Patients with AKI Subgroups: • People with CKD • Older people Interventions: Early dialysis (as defined by study) Comparisons: Late dialysis (as defined by study) Outcomes: • Mortality • Renal recovery – define (as defined by study) • RRT duration • Length of ITU stay • HRQoL Study design: RCTs and consider large prospective cohort studies
Search	The databases to be searched are Medline, Embase and the Cochrane Library. Studies will be restricted to English language only. Systematic review, randomised controlled trial and observational study design filters will be applied.
Review strategy	The methodological quality of each study will be assessed using NICE checklists and GRADE. Meta-analysis will be conducted if appropriate. If not appropriate, ranges of results will be reported for these outcomes. No minimum sample size.

3

4 ### C.5.4 Referring to nephrology

Review question	**In patients with or suspected of having AKI, what is the clinical and cost effectiveness of early compared to delayed referral to a nephrologist?**
Objectives	To estimate the effectiveness and cost effectiveness of early compared to late referral to nephrology for patients with or suspected of having AKI.
Criteria	Population: adults, young people and children with or suspected of having AKI Intervention: early nephrology referral from time of diagnosis of AKI on laboratory tests (as defined by study)

	Comparison: late nephrology referral from time of diagnosis of AKI on laboratory tests (as defined by study) Outcomes: • Stage of AKI • Number of patients needing RRT • Mortality • Renal recovery (as defined by study) • Length of ICU stay • Length of hospital stay Study design: RCTs, consider large prospective cohort studies.
Search	The databases to be searched are Medline, Embase, the Cochrane Library and CINAHL. Studies will be restricted to English language only. No study design filters will be applied.
Review strategy	Cochrane Reviews will be quality assessed and presented Further meta-analyses will be conducted as appropriate No minimum sample size.

1

2 C.6 Information and support for patients and carers

Review question	**What information and support do patients with acute kidney injury and their carers require?**
Objectives	To obtain the views of AKI patients and/or their carers on what information was or would have been useful to help them manage aspects of the condition including: • Renal replacement therapy • Transfer to alternative hospital for treatment • Long term risk • Self management
Criteria	Patients (adults and children) with AKI and their carers Subgroups: • Older people • People with CKD Interventions Patient information and support (Any type of written or verbal information (about treatment or prophylaxis etc.) handed out or recorded) Outcomes • Patient /carer subjective reported outcomes • Patient/carer satisfaction • HRQoL • Patient preference Study design: Qualitative (interviews, focus groups, surveys etc.)
Search	The databases to be searched are Medline, Embase, the Cochrane Library, CINAHL and PsychInfo. Studies will be restricted to English language only. Qualitative study design filters will be applied.
Review strategy	• Cochrane Reviews will be quality assessed and presented. • Further meta-analyses will be conducted as appropriate. • Analysis of the data will be appropriate to the design of the studies identified.

	• No limitation on sample size.

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C.7 Economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify economic studies relevant to the review questions set out above.
Criteria	Populations, interventions and comparators as specified in the individual review protocols above. Must be a relevant economic study design (cost-utility analysis, cost-benefit analysis, cost-effectiveness analysis, cost-consequence analysis, comparative cost analysis).
Search strategy	An economic study search was undertaken using population specific terms and an economic study filter – see Appendix F.
Review strategy	Each study is assessed using the NICE economic evaluation checklist – NICE (2009) Guidelines Manual. **Inclusion/exclusion criteria** • If a study is rated as both 'Directly applicable' and 'Minor limitations' (using the NICE economic evaluation checklist) then it should be included in the guideline. An evidence table should be completed and it should be included in the economic profile. • If a study is rated as either 'Not applicable' or 'Very serious limitations' then it should be excluded from the guideline. It should not be included in the economic profile and there is no need to include an evidence table. • If a study is rated as 'Partially applicable' and/or 'Potentially serious limitations' then there is discretion over whether it should be included. The health economist should make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the GDG if required. The ultimate aim being to include studies that are helpful for decision making in the context of the guideline and current NHS setting. Where exclusions occur on this basis, this should be noted in the relevant section of the guideline with references. Also exclude: • unpublished reports unless submitted as part of a call for evidence • abstract-only studies • letters • editorials • reviews of economic evaluations • foreign language articles **Where there is discretion** The health economist should be guided by the following hierarchies. *Setting:* • UK NHS • OECD countries with predominantly public health insurance systems (e.g. France, Germany, Sweden) • OECD countries with predominantly private health insurance systems (e.g. USA, Switzerland) • Non-OECD settings (always 'Not applicable') *Economic study type:* • Cost-utility analysis • Other type of full economic evaluation (cost-benefit analysis, cost-effectiveness analysis, cost-consequence analysis) • Comparative cost analysis

	• Non-comparative cost analyses including cost of illness studies (always 'Not applicable') *Year of analysis:* • The more recent the study, the more applicable it is *Quality and relevance of effectiveness data used in the economic analysis:* • The more closely the effectiveness data used in the economic analysis matches with the studies included for the clinical review the more useful the analysis will be to decision making for the guideline.

(a) Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.

Appendix D: Literature search strategies

Search strategies used for the acute kidney injury guideline are outlined below and were run as per the NICE Guidelines Manual 2009 http://www.nice.org.uk/media/5F2/44/The_guidelines_manual_2009_-_All_chapters.pdf .

Searches for the **clinical reviews** were run in Medline (Ovid), Embase (Ovid) and the Cochrane Library. Additional searches were run in CINAHL (EBSCO) and PsychInfo (Ovid) for some questions. Usually, searches were constructed in the following way:

- A PICO format was used for **intervention** searches where population (P) terms were combined with intervention (I) and sometimes comparison (C) terms. An intervention can be a drug, a procedure or a diagnostic test. Outcomes (O) are rarely used in search strategies for interventions. Search Filters were also added to the search where appropriate.

- A PEO format was used for **prognosis** searches where population (P) terms were combined with exposure (E) terms and sometimes outcomes (O). Search filters were added to the search where appropriate.

Searches for the **health economic reviews** were run in Medline (Ovid), Embase (Ovid), the NHS Economic Evaluations Database (NHS EED), the Health Technology Assessment (HTA) database and the Health Economic Evaluation Database (HEED). HTA and NHS EED searches were carried out via the Centre for Reviews and Dissemination (CRD) interface. The HEED database was accessed via the Wiley interface. Searches in NHS EED, HTA and HEED were constructed only using population terms. For Medline and Embase an economic filter (instead of a study type filter) was added to the same clinical search strategy.

All searches were run up to 3 January 2013 unless otherwise stated. Any studies added to the databases after this date were not included unless specifically stated in the text.

The search strategies are presented below in the following order:

Section D.1	Population terms by database. The same searches were used for all questions unless otherwise indicated, and for both clinical and health economic searches.
Section D.2	Study filter terms by database. These include filters for epidemiological study designs, health economic studies, quality of life studies and excluded study designs.
Section D.3	Searches run for specific questions with the intervention or exposure terms by database. Order as presented in guideline
D.3.1	Assessing risk
Error! Reference source not found.	Track and trigger systems
D.3.2	Preventing CI-AKI
D.3.2.3	Computerised decision tools
D.3.2.4	Stopping ACEi/ARB therapy
D.3.3	AKIN/RIFLE
D.3.4	Urinalysis
D.3.4.2	Ultrasound
D.3.5	Relieving urological obstruction
D.3.5.3	Loop diuretics
D.3.5	Dopamine
D.3.5.4	Referring for renal replacement therapy

D.3.5.5	Referring to nephrology
D.3.6	Information and support for patients
Section D.4	Economics searches

D.1 Population search strategies

Medline search terms

1	exp Acute Kidney Injury/
2	((acute or early) adj (kidney or renal) adj (failure* or injur* or insufficien* or dysfunction* or impair*)).ti,ab.
3	(acute kidney necrosis or acute kidney tubul* necrosis).ti,ab.
4	or/1-3
5	limit 4 to english language

Embase search terms

1	acute kidney failure/ or acute kidney tubule necrosis/
2	((acute or early) adj (kidney or renal) adj (failure* or injur* or insufficien* or dysfunction* or impair*)).ti,ab.
3	(acute kidney necrosis or acute kidney tubul* necrosis).ti,ab.
4	or/1-3
5	limit 4 to english language

Cinahl search terms

S1	(MH "Kidney Failure, Acute+")
S2	acute kidney failure* OR acute kidney injur* OR acute kidney insufficien* OR acute kidney dysfunction* OR acute kidney impair* OR acute renal failure* OR acute renal injur* OR acute renal insufficien* OR acute renal dysfunction* OR acute renal impair*
S3	early kidney failure* OR early kidney injur* OR early kidney insufficien* OR early kidney dysfunction* OR early kidney impair* OR early renal failure* OR early renal injur* OR early renal insufficien* OR early renal dysfunction* OR early renal impair*
S4	acute kidney necrosis OR acute kidney tubul* necrosis
S5	S1 or S2 or S3 or S4

Cochrane search terms

#1	MeSH descriptor Acute Kidney Injury explode all trees
#2	((acute or early) NEAR (kidney or renal) NEAR (failure* or injur* or insufficien* or dysfunction* or impair*)):ti,ab,kw
#3	(acute kidney necrosis or acute kidney tubul* necrosis):ti,ab,kw
#4	(#1 OR #2 OR #3)

PsychInfo search terms

1	*kidney diseases/
2	*kidneys/
3	1 or 2
4	injuries/
5	3 and 4
6	((acute or early) adj (kidney or renal) adj (failure* or injur* or insufficien* or dysfunction* or impair*)).ti,ab.

7	(acute kidney necrosis or acute kidney tubul* necrosis).ti,ab.
8	or/5-7
9	limit 8 to english language

D.2 Study filter search terms

D.2.1 Systematic review search terms

Medline search terms

1	Meta-Analysis/
2	Meta-Analysis as Topic/
3	(meta analy* or metanaly* or metaanaly*).ti,ab.
4	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7	(search* adj4 literature).ab.
8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9	cochrane.jw.
10	((indirect or mixed) adj2 comparison*).ti,ab.
11	or/1-10

Embase search terms

1	systematic review/
2	meta-analysis/
3	(meta analy* or metanaly* or metaanaly*).ti,ab.
4	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7	(search* adj4 literature).ab.
8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9	((pool* or combined) adj2 (data or trials or studies or results)).ab.
10	cochrane.jw.
11	((indirect or mixed) adj2 comparison*).ti,ab.
12	or/1-11

D.2.2 Randomised controlled studies (RCTs) search terms

Medline search terms

1	randomized controlled trial.pt.
2	controlled clinical trial.pt.
3	randomi#ed.ab.
4	placebo.ab.
5	randomly.ab.

6	Clinical Trials as topic.sh.
7	trial.ti.
8	or/1-7

Embase search terms

1	random*.ti,ab.
2	factorial*.ti,ab.
3	(crossover* or cross over*).ti,ab.
4	((doubl* or singl*) adj blind*).ti,ab.
5	(assign* or allocat* or volunteer* or placebo*).ti,ab.
6	crossover procedure/
7	single blind procedure/
8	randomized controlled trial/
9	double blind procedure/
10	or/1-9

D.2.3 Diagnostic accuracy search terms

Medline search terms

1	exp "sensitivity and specificity"/
2	(sensitivity or specificity).ti,ab.
3	((pre test or pretest or post test) adj probability).ti,ab.
4	(predictive value* or PPV or NPV).ti,ab.
5	likelihood ratio*.ti,ab.
6	likelihood function/
7	(ROC curve* or AUC).ti,ab.
8	(diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
9	gold standard.ab.
10	or/1-9

Embase search terms

1	exp "sensitivity and specificity"/
2	(sensitivity or specificity).ti,ab.
3	((pre test or pretest or post test) adj probability).ti,ab.
4	(predictive value* or PPV or NPV).ti,ab.
5	likelihood ratio*.ti,ab.
6	(ROC curve* or AUC).ti,ab.
7	(diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
8	diagnostic accuracy/
9	diagnostic test accuracy study/
10	gold standard.ab.
11	or/1-10

D.2.4 Observational studies search terms

Medline search terms

1	Epidemiologic studies/
2	exp Case control studies/
3	exp Cohort studies/
4	Cross-sectional studies/
5	case control.ti,ab.
6	(cohort adj (study or studies or analys*)).ti,ab.
7	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
8	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.
9	or/1-8

Embase search terms

1	Clinical study/
2	exp Case control study/
3	Family study/
4	Longitudinal study/
5	Retrospective study/
6	Prospective study/
7	Cross-sectional study/
8	Cohort analysis/
9	Follow-up/
10	cohort*.ti,ab.
11	9 and 10
12	case control.ti,ab.
13	(cohort adj (study or studies or analys*)).ti,ab.
14	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
15	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.
16	or/1-8,11-15

D.2.5 Prognosis search terms

Medline search terms

1	Prognosis/
2	Predictive value of tests/
3	(predict* or prognos* or progression).ti,ab.
4	or/1-3

Embase search terms

1	*prognosis/
2	*predictive value/
3	*disease exacerbation/
4	(predict* or prognos* or progression).ti,ab.
5	or/1-4

D.2.6 Health economic search terms

Medline search terms

1	Economics/
2	Value of life/
3	exp "Costs and Cost Analysis"/
4	exp Economics, Hospital/
5	exp Economics, Medical/
6	Economics, Nursing/
7	Economics, Pharmaceutical/
8	exp "Fees and Charges"/
9	exp Budgets/
10	budget*.ti,ab.
11	cost*.ti.
12	(economic* or pharmaco?economic*).ti.
13	(price* or pricing*).ti,ab.
14	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
15	(financ* or fee or fees).ti,ab.
16	(value adj2 (money or monetary)).ti,ab.
17	or/1-16

Embase search terms

1	health economics/
2	exp economic evaluation/
3	exp health care cost/
4	exp fee/
5	budget/
6	funding/
7	budget*.ti,ab.
8	cost*.ti.
9	(economic* or pharmaco?economic*).ti.
10	(price* or pricing*).ti,ab.
11	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
12	(financ* or fee or fees).ti,ab.
13	(value adj2 (money or monetary)).ti,ab.
14	or/1-13

D.2.7 Quality of life search terms

Medline search terms

1	quality-adjusted life years/
2	sickness impact profile/
3	(quality adj2 (wellbeing or well being)).ti,ab.
4	sickness impact profile.ti,ab.
5	disability adjusted life.ti,ab.
6	(qal* or qtime* or qwb* or daly*).ti,ab.
7	(euroqol* or eq5d* or eq 5*).ti,ab.

8	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
9	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
10	(hui or hui1 or hui2 or hui3).ti,ab.
11	(health* year* equivalent* or hye or hyes).ti,ab.
12	discrete choice*.ti,ab.
13	rosser.ti,ab.
14	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
15	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
16	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
17	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
18	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
19	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
20	or/1-19

1 **Embase search terms**

1	quality adjusted life year/
2	"quality of life index"/
3	short form 12/ or short form 20/ or short form 36/ or short form 8/
4	sickness impact profile/
5	(quality adj2 (wellbeing or well being)).ti,ab.
6	sickness impact profile.ti,ab.
7	disability adjusted life.ti,ab.
8	(qal* or qtime* or qwb* or daly*).ti,ab.
9	(euroqol* or eq5d* or eq 5*).ti,ab.
10	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
11	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
12	(hui or hui1 or hui2 or hui3).ti,ab.
13	(health* year* equivalent* or hye or hyes).ti,ab.
14	discrete choice*.ti,ab.
15	rosser.ti,ab.
16	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
17	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
18	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
19	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
20	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
21	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
22	or/1-21

2 ### D.2.8 Economic modelling search terms

3 **Medline search terms**

1	exp models, economic/
2	*Models, Theoretical/
3	*Models, Organizational/
4	markov chains/
5	monte carlo method/

6	exp Decision Theory/
7	(markov* or monte carlo).ti,ab.
8	econom* model*.ti,ab.
9	(decision* adj2 (tree* or analy* or model*)).ti,ab.
10	or/1-9

Embase search terms

1	statistical model/
2	exp economic aspect/
3	1 and 2
4	*theoretical model/
5	*nonbiological model/
6	stochastic model/
7	decision theory/
8	decision tree/
9	monte carlo method/
10	(markov* or monte carlo).ti,ab.
11	econom* model*.ti,ab.
12	(decision* adj2 (tree* or analy* or model*)).ti,ab.
13	or/3-12

D.2.9 Excluded study designs and publication types

The following study designs and publication types were removed from retrieved results using the NOT operator.

Medline search terms

1	letter/
2	editorial/
3	news/
4	exp historical article/
5	Anecdotes as Topic/
6	comment/
7	case report/
8	(letter or comment*).ti.
9	or/1-8
10	randomized controlled trial/ or random*.ti,ab.
11	9 not 10
12	animals/ not humans/
13	Animals, Laboratory/
14	exp animal experiment/
15	exp animal model/
16	exp Rodentia/
17	(rat or rats or mouse or mice).ti.
18	or/11-17

Embase search terms

1	letter.pt. or letter/
2	note.pt.
3	editorial.pt.
4	case report/ or case study/
5	(letter or comment*).ti.
6	or/1-5
7	randomized controlled trial/ or random*.ti,ab.
8	6 not 7
9	animal/ not human/
10	nonhuman/
11	exp Animal Experiment/
12	exp Experimental Animal/
13	animal model/
14	exp Rodent/
15	(rat or rats or mouse or mice).ti.
16	or/8-15

Cinahl search terms

S1	PT anecdote or PT audiovisual or PT bibliography or PT biography or PT book or PT book review or PT brief item or PT cartoon or PT commentary or PT computer program or PT editorial or PT games or PT glossary or PT historical material or PT interview or PT letter or PT listservs or PT masters thesis or PT obituary or PT pamphlet or PT pamphlet chapter or PT pictorial or PT poetry or PT proceedings or PT "questions and answers" or PT response or PT software or PT teaching materials or PT website

D.3 Searches by specific questions

D.3.1 Assessing risk

Searches for the following two questions were run as one search

Which risk assessment tools are the most accurate for predicting AKI in at risk patients?

Which risk assessment tools are the most accurate for predicting AKI in at risk patients (paediatrics)?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
AKI	Risk assessment tools		Exclusions	No date restriction. Search run up to 03/01/2013

<u>Risk assessment tools search terms</u>

Medline search terms

1	((decision or predict* or assess* or screen* or score* or scoring or stratif* or prognos* or logistic*) adj2 (tool* or rule* or instrument*1 or index* or test* or technique* or analys* or model* or score*)).ti,ab.
2	(risk* adj2 (score* or stratif*)).ti,ab.

3	(logistic adj2 model).ti,ab.
4	(prognos* or predict*).ti,ab.
5	(risk* adj2 assessment*).ti,ab.
6	algorithm*.ti,ab.
7	algorithms/
8	logistic models/
9	Risk Assessment/
10	validat*.ti,ab.
11	or/1-10
12	risk*.ti,ab.
13	11 and 12

1 **Embase search terms**

1	((decision or predict* or assess* or screen* or score* or scoring or stratif* or prognos* or logistic*) adj2 (tool* or rule* or instrument*1 or index* or test* or technique* or analys* or model* or score*)).ti,ab.
2	(risk* adj2 (score* or stratif*)).ti,ab.
3	(logistic adj2 model).ti,ab.
4	(prognos* or predict*).ti,ab.
5	(risk* adj2 assessment*).ti,ab.
6	algorithm*.ti,ab.
7	validat*.ti,ab.
8	*algorithm/
9	*statistical model/
10	*risk assessment/
11	*scoring system/
12	or/1-11
13	risk*.ti,ab.
14	12 and 13

2 **Cinahl search terms**

S1	(MH "Risk Assessment")
S2	(MH "Logistic Regression+")
S3	(MH "Algorithms")
S4	validat* OR algorithm* OR risk* n2 assessment* OR prognos* OR predict* OR logistic* n2 model* OR risk* n2 score* OR risk* n2 stratif*
S5	decision n2 tool* OR decision n2 rule* OR decision n2 instrument* OR decision n2 index* OR decision n2 test* OR decision n2 technique* OR decision n2 analys* OR decision n2 model* OR decision n2 score*
S6	predict* n2 tool* OR predict* n2 rule* OR predict* n2 instrument* OR predict* n2 index* OR predict* n2 test* OR predict* n2 technique* OR predict* n2 analys* OR predict* n2 model* OR predict* n2 score*
S7	assess* n2 tool* OR assess* n2 rule* OR assess* n2 instrument* OR assess* n2 index* OR assess* n2 test* OR assess* n2 technique* OR assess* n2 analys* OR assess* n2 model* OR assess* n2 score*
S8	screen* n2 tool* OR screen* n2 rule* OR screen* n2 instrument* OR screen* n2 index* OR screen* n2 test* OR screen* n2 technique* OR screen* n2 analys* OR screen* n2 model* OR screen* n2 score*

S9	stratif* n2 tool* OR stratif* n2 rule* OR stratif* n2 instrument* OR stratif* n2 index* OR stratif* n2 test* OR stratif* n2 technique* OR stratif* n2 analys* OR stratif* n2 model* OR stratif* n2 score*
S10	prognos* n2 tool* OR prognos* n2 rule* OR prognos* n2 instrument* OR prognos* n2 index* OR prognos* n2 test* OR prognos* n2 technique* OR prognos* n2 analys* OR prognos* n2 model* OR prognos* n2 score*
S11	logistic* n2 tool* OR logistic* n2 rule* OR logistic* n2 instrument* OR logistic* n2 index* OR logistic* n2 test* OR logistic* n2 technique* OR logistic* n2 analys* OR logistic* n2 model* OR logistic* n2 score*
S12	score* n2 tool* OR score* n2 rule* OR score* n2 instrument* OR score* n2 index* OR score* n2 test* OR score* n2 technique* OR score* n2 analys* OR score* n2 model*
S13	scoring n2 tool* OR scoring n2 rule* OR scoring n2 instrument* OR scoring n2 index* OR scoring n2 test* OR scoring n2 technique* OR scoring n2 analys* OR scoring n2 model*
S14	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13

Cochrane search terms

#1	((decision or predict* or assess* or screen* or score* or scoring or stratif* or prognos* or logistic*) NEAR/2 (tool* or rule* or instrument*1 or index* or test* or technique* or analys* or model* or score*)):ti,ab,kw
#2	(risk* NEAR/2 (score* or stratif*)):ti,ab,kw
#3	(logistic NEAR/2 model):ti,ab,kw
#4	(prognos* or predict*):ti,ab,kw
#5	(risk* NEAR/2 assessment*):ti,ab,kw
#6	algorithm*:ti,ab,kw
#7	validat*:ti,ab,kw
#8	MeSH descriptor Algorithms, this term only
#9	MeSH descriptor Logistic Models, this term only
#10	MeSH descriptor Risk Assessment, this term only
#11	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)

D.3.2 Preventing AKI

D.3.2.1 Paediatric early warning scores

In acutely ill children in hospital, what is the clinical and cost effectiveness of "track and trigger" systems in detecting children who are at risk of developing acute kidney injury?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Children	Track and trigger systems		Exclusions	No date restriction. Search run up to 03/01/2013

Medline search terms

1	*Health Status Indicators/
2	exp *"Severity of Illness Index"/
3	*Sickness Impact Profile/

4	severity of illness ind*.ti,ab.
5	health status ind*.ti,ab.
6	sickness impact profile*.ti,ab.
7	((early or advance*) adj warning adj3 (tool* or score* or scoring or system*)).ti,ab.
8	(warning adj2 (scor* or system*)).ti,ab.
9	(ews or pews or pops or cpotts or pewt or paws).ti,ab.
10	(observation adj2 (score* or tool*)).ti,ab.
11	(pims or "p?ediatric ind* of mortality").ti,ab.
12	"track and trigger".ti,ab.
13	((trigger or calling or alert) adj5 criteria).ti,ab.
14	or/1-13
15	exp *Critical Care/
16	*critical illness/
17	critical care.ti,ab.
18	intensive care.ti,ab.
19	exp *Intensive Care Units/
20	exp *Emergency Service, Hospital/
21	hospital emergency service*.ti,ab.
22	medical emergency team*.ti,ab.
23	hospital emergency team*.ti,ab.
24	patient emergency team*.ti,ab.
25	exp *Patient Care Team/
26	patient care team*.ti,ab.
27	patient at risk*.ti,ab.
28	(outreach adj (service* or team*)).ti,ab.
29	shock team*.ti,ab.
30	or/15-29
31	exp child/
32	Pediatrics/
33	child*.ti,ab.
34	Infant/
35	infan*.ti,ab.
36	(baby or babies).ti,ab.
37	"Adolescent"/
38	(pediatric*1 or paediatric*1).ti,ab.
39	or/31-38
40	14 and 30 and 39

1 **Embase search terms**

1	exp *"named inventories, questionnaires and rating scales"/
2	*checklist/ or *clinical assessment tool/ or *scoring system/
3	severity of illness ind*.ti,ab.
4	health status ind*.ti,ab.
5	sickness impact profile*.ti,ab.
6	((early or advance*) adj warning adj3 (tool* or score* or scoring or system*)).ti,ab.

7	(warning adj2 (scor* or system*)).ti,ab.
8	(ews or pews or pops or cpotts or pewt or paws).ti,ab.
9	(observation adj2 (score* or tool*)).ti,ab.
10	(pims or "p?ediatric ind* of mortality").ti,ab.
11	"track and trigger".ti,ab.
12	((trigger or calling or alert) adj5 criteria).ti,ab.
13	or/1-12
14	*critical illness/
15	*intensive care/
16	critical care.ti,ab.
17	intensive care.ti,ab.
18	*intensive care unit/
19	*emergency health service/
20	hospital emergency service*.ti,ab.
21	medical emergency team*.ti,ab.
22	patient emergency team*.ti,ab.
23	hospital emergency team*.ti,ab.
24	*patient care/
25	patient care team*.ti,ab.
26	patient at risk*.ti,ab.
27	(outreach adj (service* or team*)).ti,ab.
28	shock team*.ti,ab.
29	or/14-28
30	exp child/
31	pediatrics/
32	child*.ti,ab.
33	infan*.ti,ab.
34	(baby or babies).ti,ab.
35	exp adolescent/
36	(pediatric*1 or paediatric*1).ti,ab.
37	or/30-36
38	13 and 29 and 37

1 **Cinahl search terms**

S1	(MM "Health Status Indicators") OR (MM "Severity of Illness Indices")
S2	(MM "Sickness Impact Profile")
S3	severity of illness ind* OR health status ind* OR sickness impact profile* OR ((early or advance*) n1 warning n3 (tool* or score* or scoring or system*)) OR (warning n2 (scor* or system*))
S4	ews OR pews OR pops OR cpotts OR pewt OR paws OR (observation n2 (score* or tool*)) OR pims OR pediatric ind* of mortality OR paediatric ind* of mortality OR "track and trigger" OR ((trigger or calling or alert) n5 criteria)
S5	S1 or S2 or S3 or S4
S6	(MM "Critical Care+") OR (MM "Critical Illness") OR (MM "Intensive Care Units+") OR (MM "Emergency Service+") OR (MM "Multidisciplinary Care Team+")
S7	critical care OR intensive care OR hospital emergency service* OR medical emergency team* OR hospital emergency team* OR patient emergency team* OR patient care team* OR patient

	at risk* OR outreach n1 service* OR outreach n1 team* OR shock team*
S8	S6 or S7
S9	S5 and S8
S10	(MH "Child+") OR (MH "Pediatrics") OR (MH "Adolescence+")
S11	child* OR infan* OR baby OR babies OR pediatric* OR paediatric*
S12	S10 or S11
S13	S9 and S12

1 **Cochrane search terms**

#1	severity of illness ind*:ti,ab
#2	health status ind*:ti,ab
#3	sickness impact profile*:ti,ab
#4	(warning NEAR/2 (scor* or system*)):ti,ab,kw
#5	"track and trigger":ti,ab,kw
#6	MeSH descriptor Health Status Indicators, this term only
#7	MeSH descriptor Severity of Illness Index explode all trees
#8	MeSH descriptor Sickness Impact Profile, this term only
#9	((early or advance*) NEXT warning NEAR/3 (tool* or score* or scoring or system*)):ti,ab,kw
#10	(ews or pews or pops or cpotts or pewt or paws):ti,ab,kw
#11	(observation NEAR/2 (score* or tool*)):ti,ab,kw
#12	(pims or "p*diatric ind* of mortality"):ti,ab,kw
#13	((trigger or calling or alert) NEAR/5 criteria):ti,ab,kw
#14	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13)
#15	MeSH descriptor Critical Care explode all trees
#16	MeSH descriptor Critical Illness, this term only
#17	critical care.ti,ab
#18	intensive care.ti,ab
#19	MeSH descriptor Intensive Care Units explode all trees
#20	MeSH descriptor Emergency Service, Hospital explode all trees
#21	hospital emergency service*:ti,ab
#22	medical emergency team*:ti,ab
#23	hospital emergency team*:ti,ab
#24	patient emergency team*:ti,ab
#25	MeSH descriptor Patient Care Team explode all trees
#26	patient care team*:ti,ab
#27	patient at risk*:ti
#28	(outreach NEXT (service* or team*)):ti,ab,kw
#29	shock team*:ti,ab,kw
#30	(#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29)
#31	(#14 AND #30)
#32	MeSH descriptor Child explode all trees
#33	MeSH descriptor Pediatrics, this term only
#34	child*:ti,ab
#35	MeSH descriptor Infant, this term only
#36	infan*:ti,ab

#37	(baby or babies):ti,ab
#38	MeSH descriptor Adolescent, this term only
#39	(pediatric* or paediatric*):ti,ab
#40	(#32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39)
#41	(#31 AND #40)

D.3.2.2 Preventing CI-AKI

What is the comparative clinical and cost effectiveness of NAC and/or iv fluids in preventing CI-AKI in at risk patients?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
CI-AKI	IV fluids/NAC		Exclusions. SRs RCTs (Medline and Embase only)	No date restriction. Search run up to 03/01/2013

CI-AKI search terms

Medline search terms

1	Contrast Media/ae [Adverse Effects]
2	(((contrast or radiocontrast) adj induc* adj2 (nephropath* or nephrotoxi* or aki or arf or acute kidney injury or acute renal failure)) or cin or ciaki or ciraf or ci-aki or ci-arf or ((contrast or radiocontrast) adj2 prophlya*)).ti,ab.
3	or/1-2

Embase search terms

1	contrast induced nephropathy/
2	(((contrast or radiocontrast) adj induc* adj2 (nephropath* or nephrotoxi* or aki or arf or acute kidney injury or acute renal failure)) or cin or ciaki or ciraf or ci-aki or ci-arf or ((contrast or radiocontrast) adj2 prophlya*)).ti,ab.
3	or/1-2

Cochrane search terms

#1	MeSH descriptor Contrast Media, this term only with qualifier: AE
#2	(((contrast or radiocontrast) NEAR induc* NEAR/2 (nephropath* or nephrotoxi* or aki or arf or acute kidney injury or acute renal failure)) or cin or ciaki or ciraf or ci-aki or ci-arf or ((contrast or radiocontrast) NEAR/2 prophlya*)):ti,ab,kw
#3	(#1 OR #2)

IV fluids/NAC search terms

Medline search terms

1	Acetylcysteine/
2	(acetylcysteine or n-acetylcysteine or n acetyl l cysteine or parvolex).ti,ab.
3	Saline Solution, Hypertonic/
4	Bicarbonates/
5	(saline or sodium chloride or bicarbonate or ((iv or intravenous*) adj2 fluid*)).ti,ab.

6	or/1-5

Embase search terms

1	acetylcysteine/
2	(acetylcysteine or n-acetylcysteine or n acetyl l cysteine or parvolex).ti,ab.
3	sodium chloride/
4	bicarbonate/
5	(saline or sodium chloride or bicarbonate or ((iv or intravenous*) adj2 fluid*)).ti,ab.
6	infusion fluid/
7	or/1-6

Cochrane search terms

#1	MeSH descriptor Acetylcysteine, this term only
#2	(acetylcysteine or n-acetylcysteine or n acetyl l cysteine or parvolex):ti,ab,kw
#3	MeSH descriptor Saline Solution, Hypertonic, this term only
#4	MeSH descriptor Bicarbonates, this term only
#5	(saline or sodium chloride or bicarbonate or ((iv or intravenous*) NEAR/2 fluid*)):ti,ab,kw
#6	(#1 OR #2 OR #3 OR #4 OR #5)

D.3.2.3 Computerised decision tools

What is the clinical and cost effectiveness of methods for preventing inappropriate use of nephrotoxic drugs in hospital inpatients?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
AKI OR nephrotoxicity	Computerised decision tools		Exclusions. SRs, RCTs or observational (Medline and Embase only)	No date restriction. Search run up to 03/01/2013

<u>Nephrotoxicity search terms</u>

Medline search terms

1	nephrotox*.ti,ab.
2	((kidney* or renal) adj2 (toxic* or toxin*)).ti,ab.
3	exp Renal Insufficiency/
4	((kidney or renal) adj (failure* or injur* or insufficien* or dysfunction* or impair*)).ti,ab.
5	or/1-4

Embase search terms

1	*nephrotoxicity/
2	nephrotox*.ti,ab.
3	((kidney* or renal) adj2 (toxic* or toxin*)).ti,ab.
4	*kidney failure/ or *chronic kidney failure/
5	((kidney or renal) adj (failure* or injur* or insufficien* or dysfunction* or impair*)).ti,ab.
6	or/1-5

Cinahl search terms

S1	(MH "Nephrotoxicity")
S2	nephrotox* OR kidney* n2 toxic* OR kidney* n2 toxin* OR renal n2 toxic* OR renal n2 toxin*
S3	(MH "Renal Insufficiency+")
S4	((kidney or renal) n1 (failure* or injur* or insufficien* or dysfunction* or impair*))
S5	S1 or S2 or S3 or S4

1 **Cochrane search terms**

#1	nephrotox*:ti,ab,kw
#2	((kidney* or renal) NEAR/2 (toxic* or toxin*)):ti,ab,kw
#3	MeSH descriptor Renal Insufficiency explode all trees
#4	((kidney or renal) NEAR (failure* or injur* or insufficien* or dysfunction* or impair*)):ti,ab,kw
#5	(#1 OR #2 OR #3 OR #4)

2 **Computerised decision tools search terms**

3 **Medline search terms**

1	Electronic Prescribing/
2	Drug Prescriptions/
3	"Drug Utilization Review"/
4	Clinical Pharmacy Information Systems/
5	*Drug Monitoring/
6	decision making, computer-assisted/ or drug therapy, computer-assisted/
7	Decision Support Systems, Clinical/
8	Pharmacists/
9	Pharmacy Service, Hospital/
10	exp Medication Systems/
11	(pharmac* adj4 (review* or monit* or prescri*)).ti,ab.
12	(electronic prescri* or eprescri* or e-prescri*).ti,ab.
13	(computer* adj3 (decision* or tool* or support* or prescri*)).ti,ab.
14	(drug* adj2 (review* or monit*)).ti,ab.
15	or/1-14

4 **Embase search terms**

1	exp computerized provider order entry/
2	*prescription/
3	*"drug use"/
4	medical information system/
5	*drug monitoring/
6	decision support system/
7	computer assisted drug therapy/
8	*pharmacist/
9	hospital pharmacy/
10	(pharmac* adj4 (review* or monit* or prescri*)).ti,ab.
11	(pharmac* adj4 (review* or monit* or prescri*)).ti,ab.
12	(electronic prescri* or eprescri* or e-prescri*).ti,ab.
13	(computer* adj3 (decision* or tool* or support* or prescri*)).ti,ab.
14	(drug* adj2 (review* or monit*)).ti,ab.

15	or/1-14

Cinahl search terms

S1	(MH "Prescribing Patterns")
S2	(MH "Drug Therapy, Computer Assisted") OR (MH "Prescriptions, Drug")
S3	(MH "Drug Utilization")
S4	(MH "Clinical Pharmacy Information Systems")
S5	(MM "Drug Monitoring")
S6	(MH "Decision Making, Computer Assisted") OR (MH "Decision Support Systems, Clinical")
S7	(MH "Pharmacists") OR (MH "Pharmacy Service")
S8	(MH "Medication Systems")
S9	pharmac* n4 review* OR pharmac* n4 monit* OR pharmac* n4 prescri*
S10	electronic prescri* OR eprescri* OR e-prescri*
S11	computer* n3 decision* OR computer* n3 tool* OR computer* n3 support* OR computer* n3 prescri*
S12	drug* n2 review* OR drug* n2 monit*
S13	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12

Cochrane search terms

#1	MeSH descriptor Electronic Prescribing, this term only
#2	MeSH descriptor Drug Prescriptions, this term only
#3	MeSH descriptor Drug Utilization Review, this term only
#4	MeSH descriptor Clinical Pharmacy Information Systems, this term only
#5	MeSH descriptor Drug Monitoring, this term only
#6	MeSH descriptor Decision Making, Computer-Assisted, this term only
#7	MeSH descriptor Drug Therapy, Computer-Assisted, this term only
#8	MeSH descriptor Decision Support Systems, Clinical, this term only
#9	MeSH descriptor Pharmacists, this term only
#10	MeSH descriptor Pharmacy Service, Hospital, this term only
#11	MeSH descriptor Medication Systems explode all trees
#12	(pharmac* NEAR/4 (review* or monit* or prescri*)):ti,ab,kw
#13	(electronic prescri* or eprescri* or e-prescri*):ti,ab,kw
#14	(computer* NEAR/3 (decision* or tool* or support* or prescri*)):ti,ab,kw
#15	(drug* NEAR/2 (review* or monit*)):ti,ab,kw
#16	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)

D.3.2.4 Stopping ACEi/ARB therapy

What is the clinical and cost effectiveness of stopping ACEi and ARB in patients at risk of AKI?

Searches for this question were run as two separate searches: one looking for patients on ACEi/ARBs and with sepsis, diarrhoea or vomiting; the other for patients with CKD or left ventricular failure and on ACEi/ARBs undergoing surgery or contrast.

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Sepsis, diarrhoea,	ACEi/ARB		Exclusions	No date

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
vomiting				restriction. Search run up to 03/01/2013

1 **ACEi/ARB search terms**

2 **Medline search terms**

1	exp angiotensin ii type 1 receptor blockers/ or angiotensin ii type 2 receptor blockers/
2	((angiotensin adj3 (receptor* adj2 (antagonist* or blocker*))) or arb or arbs).ti,ab.
3	(candesartan or amias or eprosartan or teveten or irbesartan or aprovel or coaprovel or losartan or cozaar or cozaar-comp or olmesartan or olmetec or sevikar or telmisartan or micardis or valsartan or diovan or co-diovan).ti,ab.
4	exp Angiotensin-Converting Enzyme Inhibitors/
5	((ace or acei or ((angiotensin adj converting adj2 enzyme*) or ace or kininase)) adj2 (inhibit* or antagonist*)).ti,ab.
6	(captopril or ecopace or kaplon or capoten or co-zidocapt or capto-co or capozide or cilazapril or vascace or enalapril or ednyt or innovace or innozide or fosinopril or imidapril or tanatril or lisinopril or zestril or carace or zestoretic or moexipril or perdix or perindopril or coversyl or quinapril or quinil or accupro or accuretic or ramipril or tritace or triapin or trandolapril or gopten or tarka).ti,ab.
7	or/1-6

3 **Embase search terms**

1	exp *angiotensin receptor antagonist/
2	((angiotensin adj3 (receptor* adj2 (antagonist* or blocker*))) or arb or arbs).ti,ab.
3	(candesartan or amias or eprosartan or teveten or irbesartan or aprovel or coaprovel or losartan or cozaar or cozaar-comp or olmesartan or olmetec or sevikar or telmisartan or micardis or valsartan or diovan or co-diovan).ti,ab.
4	exp *dipeptidyl carboxypeptidase inhibitor/
5	((ace or acei or ((angiotensin adj converting adj2 enzyme*) or ace or kininase)) adj2 (inhibit* or antagonist*)).ti,ab.
6	(captopril or ecopace or kaplon or capoten or co-zidocapt or capto-co or capozide or cilazapril or vascace or enalapril or ednyt or innovace or innozide or fosinopril or imidapril or tanatril or lisinopril or zestril or carace or zestoretic or moexipril or perdix or perindopril or coversyl or quinapril or quinil or accupro or accuretic or ramipril or tritace or triapin or trandolapril or gopten or tarka).ti,ab.
7	or/1-6

4 **Cochrane search terms**

#1	MeSH descriptor Angiotensin II Type 1 Receptor Blockers explode all trees
#2	MeSH descriptor Angiotensin II Type 2 Receptor Blockers, this term only
#3	((angiotensin NEAR/3 (receptor* NEAR/2 (antagonist* or blocker*))) or arb or arbs):ti,ab
#4	(candesartan or amias or eprosartan or teveten or irbesartan or aprovel or coaprovel or losartan or cozaar or cozaar-comp or olmesartan or olmetec or sevikar or telmisartan or micardis or valsartan or diovan or co-diovan):ti,ab
#5	MeSH descriptor Angiotensin-Converting Enzyme Inhibitors explode all trees
#6	((ace or acei or ((angiotensin NEXT converting NEAR/2 enzyme*) or ace or kininase)) NEAR/2 (inhibit* or antagonist*)):ti,ab
#7	(captopril or ecopace or kaplon or capoten or co-zidocapt or capto-co or capozide or cilazapril or vascace or enalapril or ednyt or innovace or innozide or fosinopril or imidapril or tanatril or

	lisinopril or zestril or carace or zestoretic or moexipril or perdix or perindopril or coversyl or quinapril or quinil or accupro or accuretic or ramipril or tritace or triapin or trandolapril or gopten or tarka):ti,ab
#8	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)

1 **Sepsis, diarrhoea, vomiting search terms**

2 **Medline search terms**

1	sepsis/ or exp bacteremia/ or shock, septic/
2	(sepsis or septic).ti,ab.
3	((toxic or endotoxic) adj shock*).ti,ab.
4	septic?emi*.ti,ab.
5	(blood stream adj2 infect*).ti,ab.
6	Diarrhea/
7	(diarrhoea* or diarrhea*).ti,ab.
8	Vomiting/
9	(vomit* or emesis).ti,ab.
10	or/1-9

3 **Embase search terms**

1	exp *sepsis/
2	(sepsis or septic).ti,ab.
3	((toxic or endotoxic) adj shock*).ti,ab.
4	septic?emi*.ti,ab.
5	(blood stream adj2 infect*).ti,ab.
6	(diarrhoea* or diarrhea*).ti,ab.
7	(vomit* or emesis).ti,ab.
8	exp *diarrhea/
9	*vomiting/
10	or/1-9

4 **Cochrane search terms**

#1	MeSH descriptor Sepsis explode all trees
#2	(sepsis or septic):ti,ab
#3	((toxic or endotoxic) NEXT shock*):ti,ab
#4	septic*mi*:ti,ab
#5	(blood stream NEAR/2 infect*):ti,ab
#6	MeSH descriptor Diarrhea, this term only
#7	MeSH descriptor Vomiting, this term only
#8	(diarrhoea* or diarrhea*):ti,ab
#9	(vomit* or emesis):ti,ab
#10	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)

5 Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
CKD, left ventricular failure patients	ACEi/ARBs		Exclusions SRs, RCTs, observational	No date restriction. Search run up to

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
undergoing surgery, contrast			(Medline and Embase only)	03/01/2013

1 **CKD, left ventricular failure AND surgery, contrast search terms**

2 **Medline search terms**

1	Renal insufficiency, Chronic/
2	exp Kidney failure, Chronic/
3	Kidney diseases/ and chronic.ti,ab.
4	((chronic or progressive) adj2 (renal or kidney)).ti,ab.
5	(chronic adj (kidney or renal) adj insufficienc*).ti,ab.
6	(end stage adj2 (kidney or renal)).ti,ab.
7	(CKD or ESRD).ti,ab.
8	Diabetic nephropathies/
9	exp Proteinuria/
10	exp Hypertension, Renal/
11	(diabetic adj (kidney or renal) adj (disease* or failure)).ti,ab.
12	((renal or renovascular) adj2 hypertensi*).ti,ab.
13	(nephropath* or proteinuria*).ti,ab.
14	exp Ventricular Dysfunction, Left/
15	(left adj1 ventric* adj3 (fail* or dysfunction* or insufficien*)).ti,ab.
16	or/1-15
17	exp Surgical Procedures, Operative/
18	(surger* or surgical or operation* or operativ*).ti,ab.
19	exp Contrast Media/
20	(radiocontrast* or contrast*).ti,ab.
21	or/17-20
22	16 and 21

3 **Embase search terms**

1	Chronic kidney disease/
2	Chronic kidney failure/
3	(kidney failure/ or kidney disease/) and chronic.ti,ab.
4	((chronic or progressive) adj2 (renal or kidney)).ti,ab.
5	(chronic adj (kidney or renal) adj insufficienc*).ti,ab.
6	(end stage adj2 (kidney or renal)).ti,ab.
7	(CKD or ESRD).ti,ab.
8	Diabetic nephropathy/
9	exp Proteinuria/
10	Renovascular hypertension/
11	(diabetic adj (kidney or renal) adj (disease* or failure)).ti,ab.
12	((renal or renovascular) adj2 hypertensi*).ti,ab.
13	(nephropath* or proteinuria*).ti,ab.
14	heart left ventricle failure/
15	(left adj1 ventric* adj3 (fail* or dysfunction* or insufficien*)).ti,ab.

16	or/1-15
17	exp *surgery/
18	(surger* or surgical or operation* or operativ*).ti,ab.
19	exp contrast medium/
20	(radiocontrast* or contrast*).ti,ab.
21	or/17-20
22	16 and 21

Cochrane search terms

#1	MeSH descriptor Renal Insufficiency, Chronic explode all trees
#2	MeSH descriptor Kidney Diseases, this term only
#3	chronic*:ti,ab,kw
#4	(#2 AND #3)
#5	((chronic or progressive) NEAR/2 (renal or kidney)):ti,ab
#6	(chronic NEAR (kidney or renal) NEAR insufficienc*):ti,ab
#7	(end stage NEAR/2 (kidney or renal)):ti,ab
#8	(CKD or ESRD):ti,ab
#9	MeSH descriptor Diabetic Nephropathies, this term only
#10	MeSH descriptor Proteinuria explode all trees
#11	MeSH descriptor Hypertension, Renal explode all trees
#12	(diabetic NEAR (kidney or renal) NEAR (disease* or failure)):ti,ab
#13	((renal or renovascular) NEAR/2 hypertensi*):ti,ab
#14	(nephropath* or proteinuria*):ti,ab
#15	MeSH descriptor Ventricular Dysfunction, Left explode all trees
#16	(left NEAR ventric* NEAR/3 (fail* or dysfunction* or insufficien*)):ti,ab
#17	(#1 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16)
#18	MeSH descriptor Surgical Procedures, Operative explode all trees
#19	(surger* or surgical or operation* or operativ*):ti,ab
#20	MeSH descriptor Contrast Media explode all trees
#21	(radiocontrast* or contrast*):ti,ab
#22	(#18 OR #19 OR #20 OR #21)
#23	(#17 AND #22)

D.3.3 Detecting AKI

D.3.3.1 Definitions and staging of acute kidney injury using AKIN/RIFLE/pRIFLE/ KDIGO

What is the clinical evidence that the staging elements of RIFLE/AKIN/pRIFLE are useful in predicting patient outcomes?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
AKI	AKIN/RIFLE		Exclusions, Observational (Medline and Embase only)	No date restriction. Search run up to 03/01/2013

AKIN/RIFLE search terms

Medline search terms

1	(Acute Kidney Injury Network or akin).ti,ab.
2	rifle.ti,ab.
3	prifle.ti,ab.
4	or/1-3

Embase search terms

1	(Acute Kidney Injury Network or akin).ti,ab.
2	rifle.ti,ab.
3	prifle.ti,ab.
4	or/1-3

Cochrane search terms

#1	(Acute Kidney Injury Network or akin):ti,ab
#2	rifle:ti,ab
#3	prifle:ti,ab
#4	#1 or #2 or #3

D.3.4 Identifying the cause of AKI

D.3.4.1 Urinalysis

What is the sensitivity and specificity of urine dipstick compared to urine microscopy and/or biopsy in the detection of proteinuria and heamaturia as indicators of glomerulo nephritis in AKI patients?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
AKI OR glomerulonephritis	Urinalysis		Exclusions	No date restriction. Search run up to 03/01/2013

Glomerulonephritis search terms

Medline search terms

1	exp Glomerulonephritis/
2	((glomerul* adj nephriti*) or glomerulonephriti*).ti,ab.
3	or/1-2

Embase search terms

1	((glomerul* adj nephriti*) or glomerulonephriti*).ti,ab.
2	exp glomerulonephritis/
3	or/1-2

Cinahl search terms

S1	(MH "Glomerulonephritis+")
S2	glomerul* n1 nephriti* OR glomerulonephriti*

S3	S1 or S2

Cochrane search terms

#1	((glomerul* NEXT nephriti*) or glomerulonephriti*):ti,ab,kw
#2	MeSH descriptor Glomerulonephritis explode all trees
#3	(#1 OR #2)

Urinalysis search terms

Medline search terms

1	Urinalysis/
2	Reagent Strips/
3	urinalys*.ti,ab.
4	(dipstick* or ((dip or reagent) adj (stick* or strip*))).ti,ab.
5	or/1-4

Embase search terms

1	*urinalysis/
2	test strip/
3	urinalys*.ti,ab.
4	(dipstick* or ((dip or reagent) adj (stick* or strip*))).ti,ab.
5	or/1-4

Cinahl search terms

S1	(MH "Urinalysis")
S2	(MH "Reagent Strips")
S3	urinalys* OR dipstick* OR dip n1 stick* OR dip n1 strip* OR reagent n1 stick* OR reagent n1 strip*
S4	S1 or S2 or S3

Cochrane search terms

#1	MeSH descriptor Urinalysis, this term only
#2	MeSH descriptor Reagent Strips, this term only
#3	(urinalys* or dipstick* or ((dip or reagent) NEAR (stick* or strip*))):ti,ab,kw
#4	(#1 OR #2 OR #3)

D.3.4.2 Ultrasound

Which patients should have US for the diagnosis of the cause of AKI?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
AKI	Ultrasound		Exclusions	No date restriction. Search run up to 03/01/2013

Ultrasound search terms

Medline search terms

1	Ultrasonography/

2	(ultrasound* or ultrason* or sonograph* or echograph*).ti,ab.
3	or/1-2

Embase search terms

1	echography/
2	(ultrasound* or ultrason* or sonograph* or echograph*).ti,ab.
3	or/1-2

Cinahl search terms

S1	(MH "Ultrasonography+")
S2	ultrasound* OR ultrason* OR sonograph* OR echograph*
S3	S1 or S2

Cochrane search terms

#1	MeSH descriptor Ultrasonography explode all trees
#2	(ultrasound* or ultrason* or sonograph* or echograph*):ti,ab,kw
#3	(#1 OR #2)

D.3.5 Managing urological obstruction

D.3.5.1 Relieving urological obstruction

In adults and children with AKI and upper tract urological obstruction, what is the clinical and cost effectiveness of early compared to delayed relief of obstruction by nephrostomy or stenting on mortality, severity of AKI, need for RRT and length of hospital stay?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Urological obstruction	Time factors		Exclusions. SRs RCTs and observational (Medline and Embase only)	No date restriction. Search run up to 03/01/2013

Medline search terms

1	Ureteral Obstruction/
2	(((obstruct* or block* or occlu*) adj3 (urin* or ureter* or urethra* or pelviuret* or renal or kidney)) or uto or puj or hydronephros*).ti,ab.
3	exp hydronephrosis/
4	or/1-3
5	Nephrostomy, Percutaneous/
6	Stents/
7	(nephrostom* or nephrolithotom* or stent*).ti,ab.
8	(relief or relieve* or remov*).ti,ab.
9	or/5-8
10	4 and 9
11	Time Factors/
12	(early or earlier or late* or time or timing or initiat* or criteri* or hour*).ti,ab.
13	or/11-12

14	10 and 13

Embase search terms

1	ureter obstruction/ or ureteropelvic junction obstruction/ or urethra obstruction/
2	hydronephrosis/
3	(((obstruct* or block* or occlu*) adj3 (urin* or ureter* or urethra* or pelviuret* or renal or kidney)) or uto or puj or hydronephros*).ti,ab.
4	or/1-3
5	nephrostomy/ or percutaneous nephrostomy/
6	stent/ or ureter stent/
7	(nephrostom* or nephrolithotom* or stent*).ti,ab.
8	(relief or relieve* or remov*).ti,ab.
9	or/5-8
10	therapy delay/
11	time/
12	(early or earlier or late* or time or timing or initiat* or criteri* or hour*).ti,ab.
13	or/10-12
14	4 and 9
15	14 and 13

Cochrane search terms

#1	MeSH descriptor Ureteral Obstruction explode all trees
#2	MeSH descriptor Hydronephrosis explode all trees
#3	(((obstruct* or block* or occlu*) NEAR/3 (urin* or ureter* or urethra* or pelviuret* or renal or kidney)) or uto or puj or hydronephros*):ti,ab,kw
#4	(#1 OR #2 OR #3)
#5	MeSH descriptor Nephrostomy, Percutaneous explode all trees
#6	MeSH descriptor Stents, this term only
#7	(nephrostom* or nephrolithotom* or stent*):ti,ab,kw
#8	(relief or relieve* or remov*):ti,ab,kw
#9	(#5 OR #6 OR #7 OR #8)
#10	(#4 AND #9)
#11	MeSH descriptor Time Factors, this term only
#12	(early or earlier or late* or time or timing or initiat* or criteri* or hour*):ti,ab,kw
#13	(#11 OR #12)
#14	(#10 AND #13)

D.3.5.2 Loop diuretics

In patients with AKI, what is the clinical and cost effectiveness of loop diuretics compared to placebo on mortality, number of RRT sessions, length of RRT, pulmonary oedema or other defined fluid overload and hearing loss?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
AKI	Loop diuretics		Exclusions SRs RCTs (Medline and Embase only)	No date restriction. Search run up to

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
				03/01/2013

Loop diuretic search terms

Medline search terms

1	exp Sodium Potassium Chloride Symporter Inhibitors/
2	(Furosemide or lasix or frusene or frusol or bumetanide or burinex or torasemide or torsemide or torem).ti,ab.
3	Furosemide/
4	Bumetanide/
5	loop diuretic*.ti,ab.
6	or/1-5

Embase search terms

1	exp loop diuretic agent/
2	(Furosemide or lasix or frusene or frusol or bumetanide or burinex or torasemide or torsemide or torem).ti,ab.
3	loop diuretic*.ti,ab.
4	or/1-3

Cochrane search terms

#1	MeSH descriptor Sodium Potassium Chloride Symporter Inhibitors explode all trees
#2	MeSH descriptor Furosemide, this term only
#3	MeSH descriptor Bumetanide, this term only
#4	(Furosemide or lasix or frusene or frusol or bumetanide or burinex or torasemide or torsemide or torem):ti,ab,kw
#5	(loop diuretic*):ti,ab,kw
#6	(#1 OR #2 OR #3 OR #4 OR #5)

D.3.5.3 Dopamine

In patients with AKI, what is the clinical and cost effectiveness of low dose dopamine compared to placebo on mortality, numbers needing RRT and adverse events such as tachyarrythmias, myocardial ischaemia) as well as HRQoL, length of critical care and hospital stay?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
AKI	Dopamine		Exclusions SRs RCTs (Medline and Embase only)	No date restriction. Search run up to 03/01/2013

Dopamine search terms

Medline search terms

1	Dopamine/
2	dopamine.ti,ab.
3	1 or 2

Embase search terms

1	dopamine/
2	dopamine.ti,ab.
3	1 or 2

Cochrane search terms

#1	MeSH descriptor Dopamine explode all trees
#2	dopamine:ti,ab,kw
#3	(#1 OR #2)

D.3.5.4 Referring for renal replacement therapy

In patients with AKI, what is the clinical and cost effectiveness of initiating early RRT compared to delayed RRT in reducing mortality and major complications of AKI such as hyperkalaemia, pulmonary oedema or other defined fluid overload?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
AKI	RRT		Exclusions SRs, RCTs, observational (Medline and Embase only)	No date restriction. Search run up to 03/01/2013

<u>RRT search terms</u>

Medline search terms

1	exp renal replacement therapy/
2	(((kidney or renal) adj1 replacement therap*) or RRT or CRRT or dialys* or h?emodialys* or h?emofiltrat* or h?emodiafiltrat* or CVVH or CAVH).ti,ab.
3	or/1-2
4	Time factors/
5	3 and 4
6	((((kidney or renal) adj1 replacement therap*) or RRT or CRRT or dialys* or h?emodialys* or h?emofiltrat* or h?emodiafiltrat* or CVVH or CAVH) adj5 (Early or earlier or late* or time or timing or initiat*)).ti,ab.
7	or/5-6

Embase search terms

1	exp renal replacement therapy/
2	(((kidney or renal) adj1 replacement therap*) or RRT or CRRT or dialys* or h?emodialys* or h?emofiltrat* or h?emodiafiltrat* or CVVH or CAVH).ti,ab.
3	or/1-2
4	time/
5	therapy delay/ or early intervention/
6	or/4-5
7	3 and 6
8	((((kidney or renal) adj1 replacement therap*) or RRT or CRRT or dialys* or h?emodialys* or h?emofiltrat* or h?emodiafiltrat* or CVVH or CAVH) adj5 (Early or earlier or late* or time or timing or initiat*)).ti,ab.

9	or/7-8

Cochrane search terms

#1	MeSH descriptor Renal Replacement Therapy explode all trees
#2	(((kidney or renal) NEAR replacement therap*) or RRT or CRRT or dialys* or h*modialys* or h*mofiltrat* or h*modiafiltrat* or CVVH or CAVH):ti,ab,kw
#3	MeSH descriptor Time Factors, this term only
#4	(#1 OR #2)
#5	(#3 AND #4)
#6	((((kidney or renal) NEAR replacement therap*) or RRT or CRRT or dialys* or h*modialys* or h*mofiltrat* or h*modiafiltrat* or CVVH or CAVH) NEAR/5 (Early or earlier or late* or time or timing or initiat*)):ti,ab,kw
#7	(#5 OR #6)

D.3.5.5 Referring to nephrology

In patients with or suspected of having AKI, what is the clinical and cost effectiveness of early (as defined by stage or increased creatinine levels) compared to late referral to nephrologist?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
AKI	Referring to nephrology		Exclusions	No date restriction. Search run up to 03/01/2013

Referring to nephrology search terms

Medline search terms

1	"referral and consultation"/ or remote consultation/
2	*nephrology/
3	((refer* or consult* or second opinion) adj5 (nephrolog* or renal)).ti,ab.
4	or/1-3

Embase search terms

1	*patient referral/
2	*nephrologist/
3	nephrology/ and patient referral/
4	((refer* or consult* or second opinion) adj5 (nephrolog* or renal)).ti,ab.
5	or/1-4

Cinahl search terms

S1	(MH "Referral and Consultation+") OR (MM "Nephrology")
S2	((refer* or consult* or second opinion) n5 (nephrolog* or renal))
S3	S1 or S2

Cochrane search terms

#1	MeSH descriptor Referral and Consultation, this term only
#2	MeSH descriptor Nephrology, this term only
#3	((refer* or consult* or second opinion) NEAR/5 (nephrolog* or renal)):ti,ab

#4	(#1 OR #2 OR #3)

D.3.6 Information and support for patients

In patients with AKI what is the effectiveness of patient information and support in improving outcomes such as mortality and worsening of AKI?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
AKI OR nephrotoxicity OR RRT	Patient information		Exclusions Qualitative	No date restriction. Search run up to 03/01/2013

Nephrotoxicity search terms

Medline search terms

1	nephrotox*.ti,ab.
2	((kidney* or renal) adj2 (toxic* or toxin*)).ti,ab.
3	or/1-2

Embase search terms

1	*nephrotoxicity/
2	nephrotox*.ti,ab.
3	((kidney* or renal) adj2 (toxic* or toxin*)).ti,ab.
4	or/1-3

Cinahl search terms

S1	(MH "Nephrotoxicity")
S2	nephrotox*
S3	((kidney* or renal) n2 (toxic* or toxin*))
S4	S1 or S2 or S3

Cochrane search terms

#1	nephrotox*:ti,ab
#2	((kidney* or renal) NEAR/2 (toxic* or toxin*)):ti,ab
#3	#1 OR #2

PsychInfo search terms

1	nephrotox*.ti,ab.
2	((kidney* or renal) adj2 (toxic* or toxin*)).ti,ab.
3	or/1-1

RRT search terms

Medline search terms

1	exp renal replacement therapy/
2	(((kidney or renal) adj1 replacement therap*) or RRT or CRRT or dialys* or h?emodialys* or h?emofiltrat* or h?emodiafiltrat* or CVVH or CAVH).ti,ab.
3	or/1-2
4	acute*.ti,ab.

5	3 and 4

1 **Embase search terms**

1	exp renal replacement therapy/
2	(((kidney or renal) adj1 replacement therap*) or RRT or CRRT or dialys* or h?emodialys* or h?emofiltrat* or h?emodiafiltrat* or CVVH or CAVH).ti,ab.
3	or/1-2
4	acute*.ti,ab.
5	3 and 4

2 **Cinahl search terms**

S1	(MH "Renal Replacement Therapy+")
S2	(((kidney or renal) n1 replacement therap*) or RRT or CRRT or dialys* or haemodialys* or hemodialys* or haemofiltrat* or hemofiltrat* or haemodiafiltrat* or hemodiafiltrat* or CVVH or CAVH)
S3	S1 or S2
S4	acute*
S5	S3 and S4

3 **Cochrane search terms**

#1	MeSH descriptor Renal Replacement Therapy explode all trees
#2	(((kidney or renal) NEAR replacement therap*) or RRT or CRRT or dialys* or h*modialys* or h*mofiltrat* or h*modiafiltrat* or CVVH or CAVH):ti,ab,kw
#3	#1 OR #2
#4	acute*:ti,ab
#5	#3 AND #4

4 **PsychInfo search terms**

1	exp dialysis/
2	(((kidney or renal) adj1 replacement therap*) or RRT or CRRT or dialys* or h?emodialys* or h?emofiltrat* or h?emodiafiltrat* or CVVH or CAVH).ti,ab.
3	or/1-2
4	acute*.ti,ab.
5	3 and 4

5 **Patient Information AND qualitative search terms**

6 **Medline search terms**

1	"patient acceptance of health care"/ or exp patient satisfaction/
2	Patient Education as Topic/
3	(information* adj3 (patient* or need* or requirement* or support* or seek* or access* or disseminat*)).ti,ab.
4	((client* or patient* or user* or carer* or consumer* or customer* or parent* or guardian*) adj2 (attitud* or priorit* or perception* or preferen* or expectation* or choice* or perspective* or view* or satisfact* or inform* or experience or experiences or opinion*)).ti,ab.
5	or/1-4
6	qualitative research/
7	exp Interviews as Topic/
8	exp Questionnaires/
9	health care surveys/

10	(qualitative or interview* or focus group* or theme* or questionnaire* or survey*).ti,ab.
11	or/6-10
12	5 and 11

1 **Embase search terms**

1	patient attitude/ or patient preference/ or patient satisfaction/ or consumer attitude/
2	patient information/ or consumer health information/
3	patient education/
4	(information* adj3 (patient* or need* or requirement* or support* or seek* or access* or disseminat*)).ti,ab.
5	((client* or patient* or user* or carer* or consumer* or customer* or parent* or guardian*) adj2 (attitud* or priorit* or perception* or preferen* or expectation* or choice* or perspective* or view* or satisfact* or inform* or experience or experiences or opinion*)).ti,ab.
6	or/1-5
7	qualitative research/
8	exp interview/
9	exp questionnaire/
10	health care survey/
11	(qualitative or interview* or focus group* or theme* or questionnaire* or survey*).ti,ab.
12	or/7-11
13	6 and 12

2 **Cinahl search terms**

S1	(MH "Consumer Satisfaction+") OR (MH "Patient Education+")
S2	(information* n3 (patient* or need* or requirement* or support* or seek* or access* or disseminat*))
S3	((client* or patient* or user* or carer* or consumer* or customer* or parent* or guardian*) n2 (attitud* or priorit* or perception* or preferen* or expectation* or choice* or perspective* or view* or satisfact* or inform* or experience or experiences or opinion*))
S4	S1 or S2 or S3
S5	(MH "Qualitative Studies+") OR (MH "Interviews+") OR (MH "Focus Groups") OR (MH "Surveys") OR (MH "Questionnaires+")
S6	(qualitative or interview* or focus group* or theme* or questionnaire* or survey*)
S7	S5 or S6
S8	S4 and S7

3 **Cochrane search terms**

#1	MeSH descriptor Patient Acceptance of Health Care, this term only
#2	MeSH descriptor Patient Satisfaction explode all trees
#3	MeSH descriptor Patient Education as Topic, this term only
#4	(information* NEAR/3 (patient* or need* or requirement* or support* or seek* or access* or disseminat*)):ti,ab
#5	((client* or patient* or user* or carer* or consumer* or customer* or parent* or guardian*) NEAR/2 (attitud* or priorit* or perception* or preferen* or expectation* or choice* or perspective* or view* or satisfact* or inform* or experience or experiences or opinion*)):ti,ab
#6	#1 OR #2 OR #3 OR #4 OR #5
#7	MeSH descriptor Qualitative Research, this term only
#8	MeSH descriptor Interviews as Topic explode all trees
#9	MeSH descriptor Questionnaires explode all trees

#10	MeSH descriptor Health Care Surveys, this term only
#11	(qualitative or interview* or focus group* or theme* or questionnaire* or survey*):ti,ab
#12	#7 OR #8 OR #9 OR #10 OR #11
#13	#6 AND #12

PsychInfo search terms

1	client education/
2	health education/
3	exp client attitudes/
4	(information* adj3 (patient* or need* or requirement* or support* or seek* or access* or disseminat*)).ti,ab.
5	((client* or patient* or user* or carer* or consumer* or customer* or parent* or guardian*) adj2 (attitud* or priorit* or perception* or preferen* or expectation* or choice* or perspective* or view* or satisfact* or inform* or experience or experiences or opinion*)).ti,ab.
6	or/1-5

D.4 Economics search

Economic searches were conducted in Medline, Embase, HEED and CRD for NHS EED and HTA.

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
AKI or CI-AKI			Economic, Quality of life, Economic modelling (Medline and Embase only	No date restriction. Search run up to 03/01/2013

CRD search terms

#1	MeSH Kidney Failure, Acute EXPLODE 1 2 3 4
#2	"acute kidney injur*"
#3	"acute renal injur*"
#4	"acute kidney failure*"
#5	"acute renal failure*"
#6	"acute kidney insufficiency*"
#7	"acute renal insufficiency*"
#8	"acute kidney tubular necrosis*"
#9	"acute tubular necrosis*"
#10	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
#11	MeSH DESCRIPTOR contrast media WITH QUALIFIER AE
#12	(contrast NEAR induc*) OR (radiocontrast NEAR induc*)
#13	(ciaki or ciraf or ci-aki or ci-arf) OR (contrast NEAR prophlya*) OR (radiocontrast NEAR prophlya*)
#14	#11 OR #12 OR #13
#15	#10 OR #14

HEED search terms

1	AX=(kidney injury or kidney injuries or renal injury or renal injuries)
2	AX=(kidney failure or kidney failures or renal failure or renal failures)
3	AX=(kidney insufficiency or renal insufficiency)
4	AX=tubular necrosis

5	CS=1 or 2 or 3 or 4
6	AX=acute
7	CS=5 and 6
8	AX='contrast induced' within 2
9	AX='radiocontrast induced' within 2
10	AX=ciaki or ciraf or ci-aki or ci-arf
11	AX=contrast AND prophlya*
12	AX=radiocontrast AND prophlya*
13	CS=8 or 9 or 10 or 11 or 12
14	CS=7 or 13

An additional economic search was carried out for the computerised decision tools question, using the same population and intervention as the clinical search combined with an economic filter in Medline and Embase. For CRD and HEED the search terms were as listed below.

Computerised decision tools search terms

CRD search terms

#1	MeSH DESCRIPTOR renal insufficiency EXPLODE ALL TREES
#2	("kidney injur*") OR ("renal injur*") OR ("kidney failure*") OR ("renal failure*") OR ("kidney insufficiency*")
#3	("renal tox*")
#4	("renal tox*") OR (("renal insufficiency*")) OR (("kidney impair*")) OR (("renal impair*")) OR ((nephrotox*))
#5	#1 OR #2 OR #3 OR #4
#6	MeSH DESCRIPTOR electronic prescribing
#7	MeSH DESCRIPTOR Drug Prescriptions
#8	MeSH DESCRIPTOR Drug Utilization Review
#9	MeSH DESCRIPTOR Clinical Pharmacy Information Systems
#10	MeSH DESCRIPTOR Drug Monitoring
#11	MeSH DESCRIPTOR decision making, computer-assisted
#12	MeSH DESCRIPTOR drug therapy, computer-assisted
#13	MeSH DESCRIPTOR Decision Support Systems, Clinical
#14	MeSH DESCRIPTOR Pharmacists
#15	MeSH DESCRIPTOR Pharmacy Service, Hospital
#16	MeSH DESCRIPTOR Medication Systems EXPLODE ALL TREES
#17	((pharmac* adj4 (review* or monit* or prescri*)))
#18	((electronic prescri* or eprescri* or e-prescri*)) OR ((computer* adj3 (decision* or tool* or support* or prescri*))) OR ((drug* adj2 (review* or monit*)))
#19	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
#20	#5 AND #19

HEED search terms

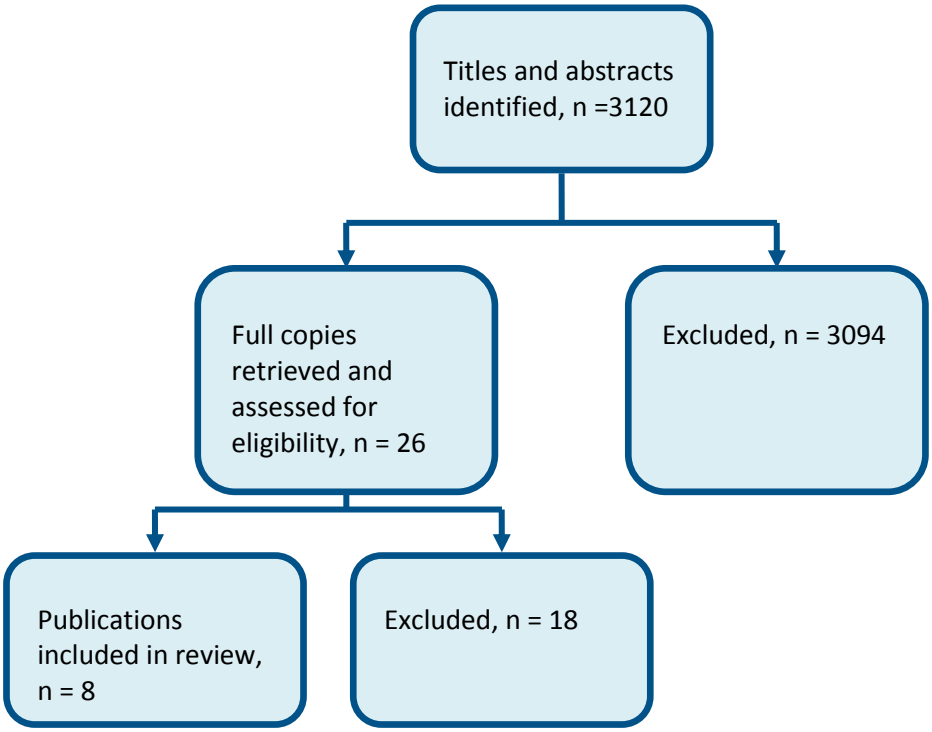
1	AX=kidney injury OR kidney injuries OR renal injury OR renal injuries
2	AX=kidney failure OR kidney failures OR renal failure OR renal failures
3	AX=kidney insufficiency OR renal insufficiency OR kidney impairment OR renal impairment
4	AX=tubular necrosis
5	AX=nephrotox*

6	CS=1 OR 2 OR 3 OR 4 OR 5
7	AX=electronic prescriptions OR electronic prescribing or eprescri* or e-prescri*
8	AX=decision* or tool* or support* or prescri*
9	AX=computer*
10	CS=8 AND 9
11	AX='drug review' within 2
12	AX='pharmacist review' within 2
13	AX= monit* or prescri*
14	AX=drug* or pharmac*
15	CS=13 AND 14
16	CS=7 OR 10 OR 11 OR 12 OR 15
17	CS=6 AND 16

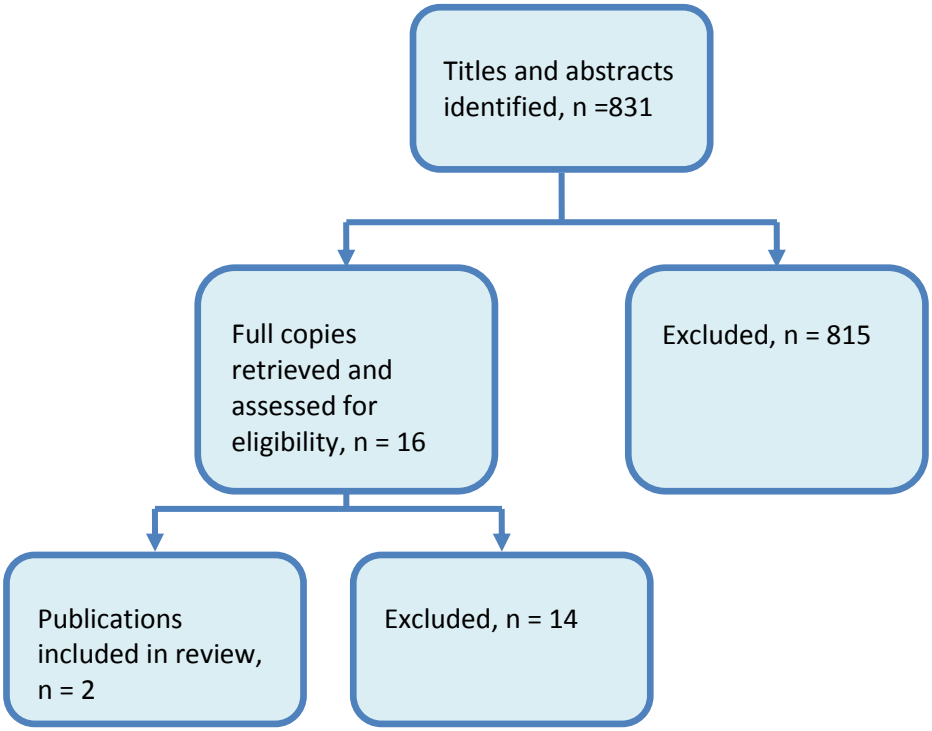
Appendix E: Clinical article selection

E.1 Assessing risk

E.1.1 Adult risk assessment

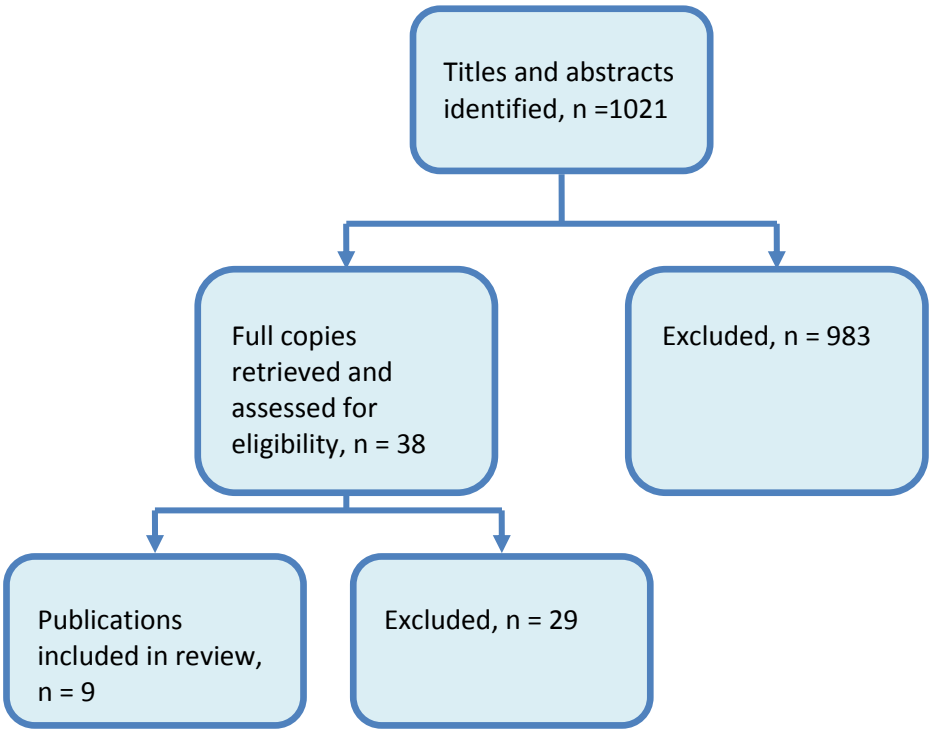


E.1.2 Paediatric risk assessment

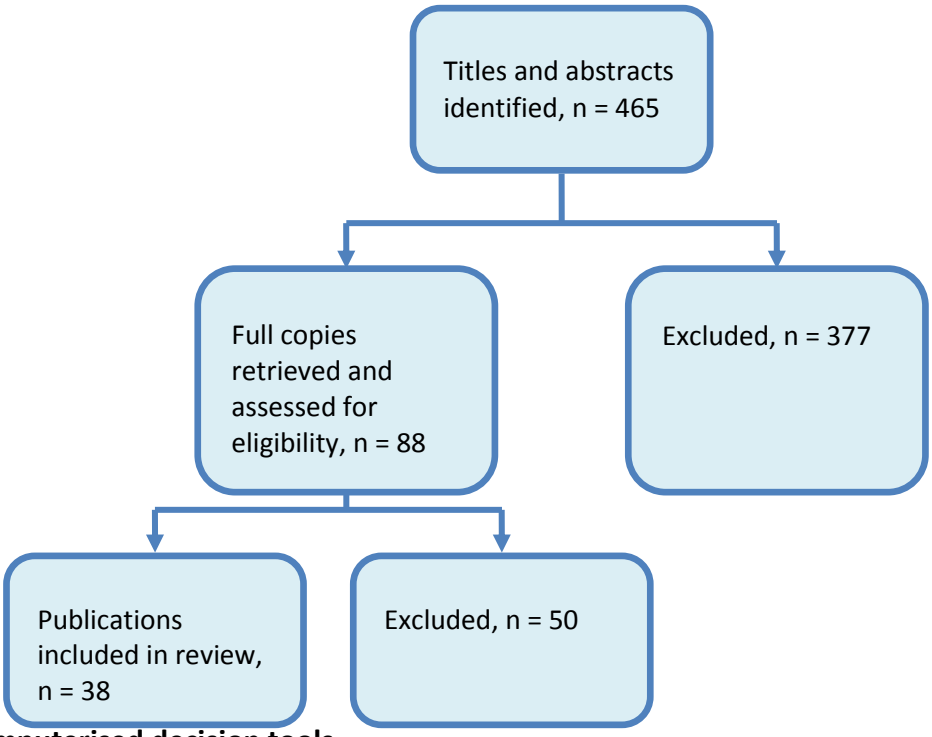


E.2 Preventing AKI

E.2.1 Paediatric early warning scores (PEWS)

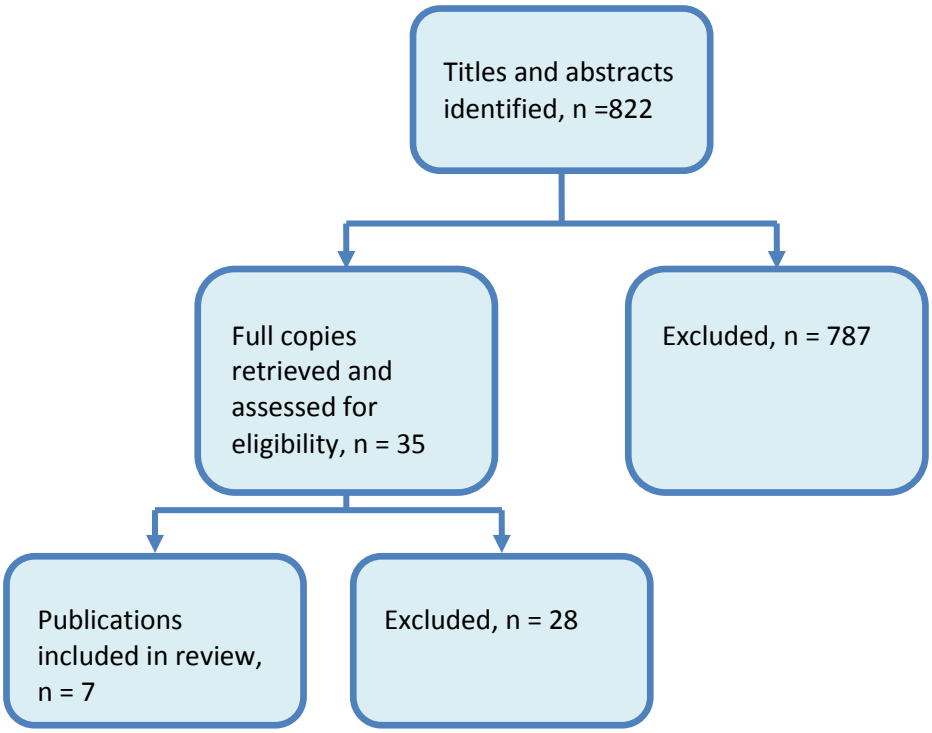


E.2.2 Preventing CI-AKI



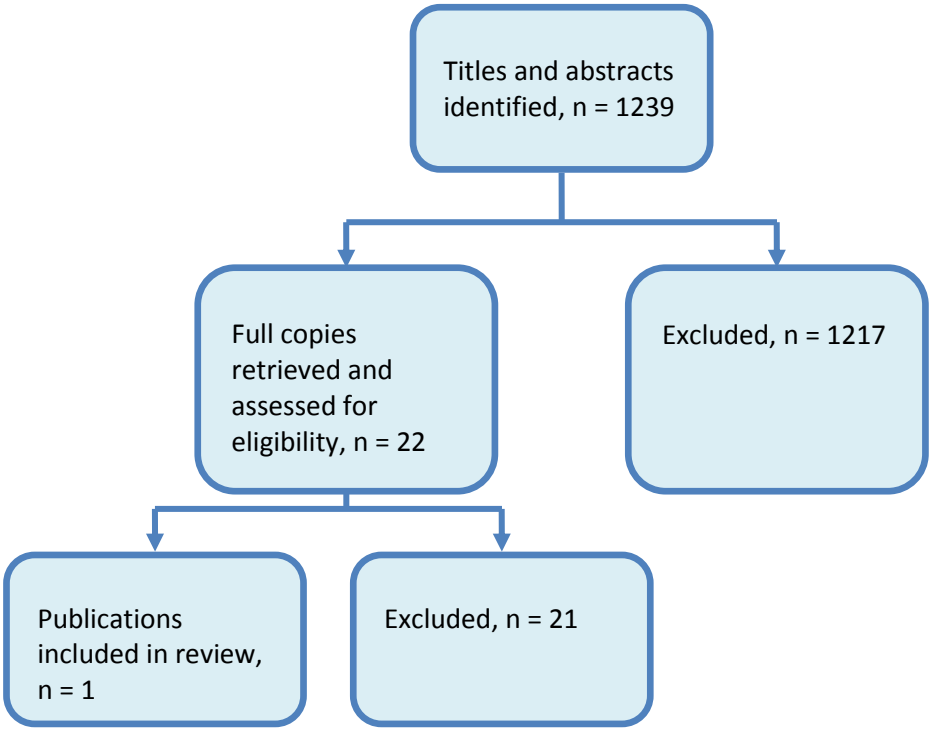
1

2 **E.2.3 Computerised decision tools**



3

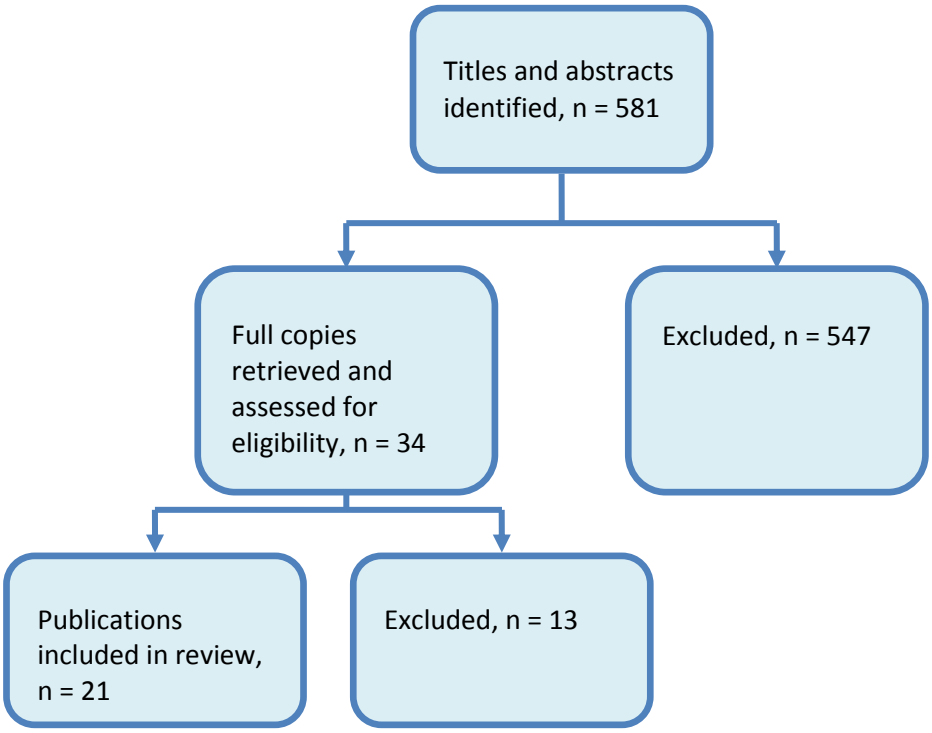
E.2.4 Stopping ACEI/ARB therapy



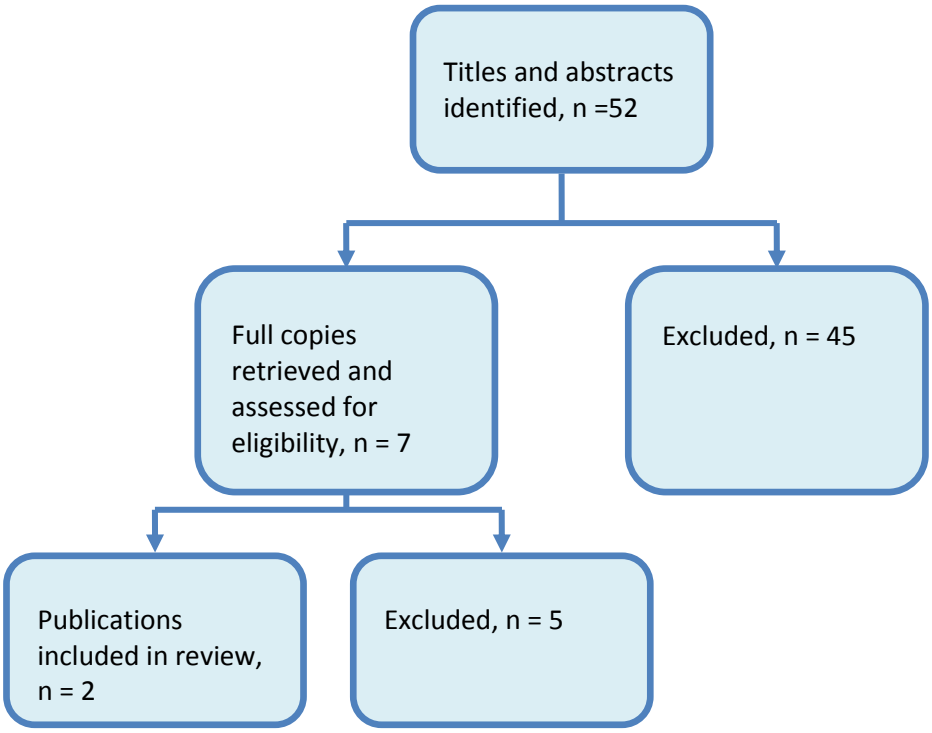
E.3 Detecting AKI

E.3.1 Definitions and staging of acute kidney injury using AKIN/RIFLE/pRIFLE/ KDIGO

Adults

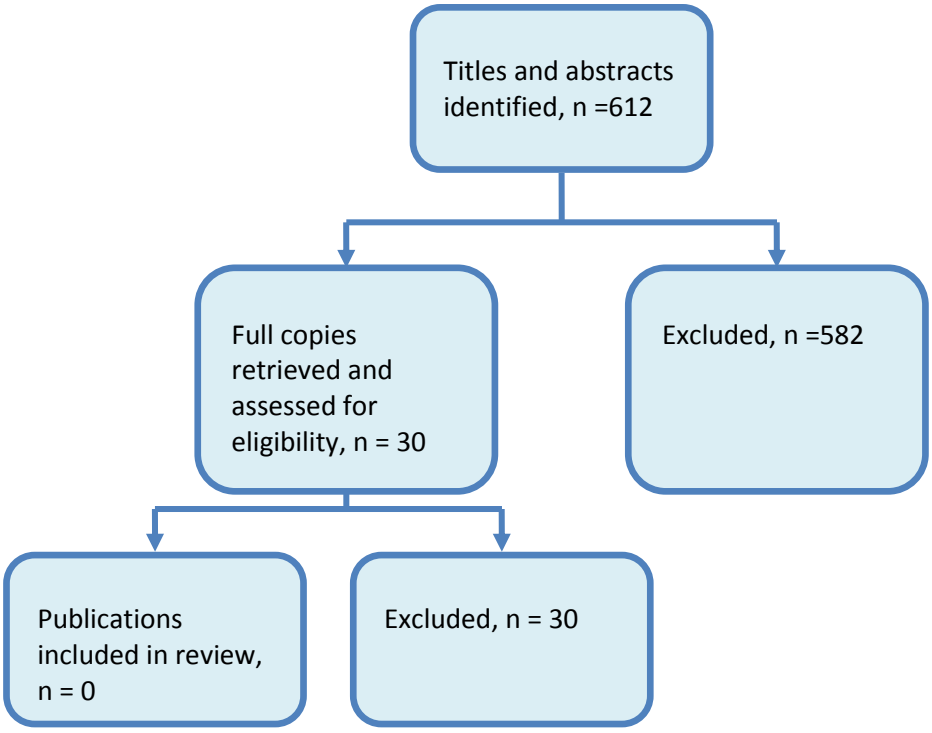


Paediatrics

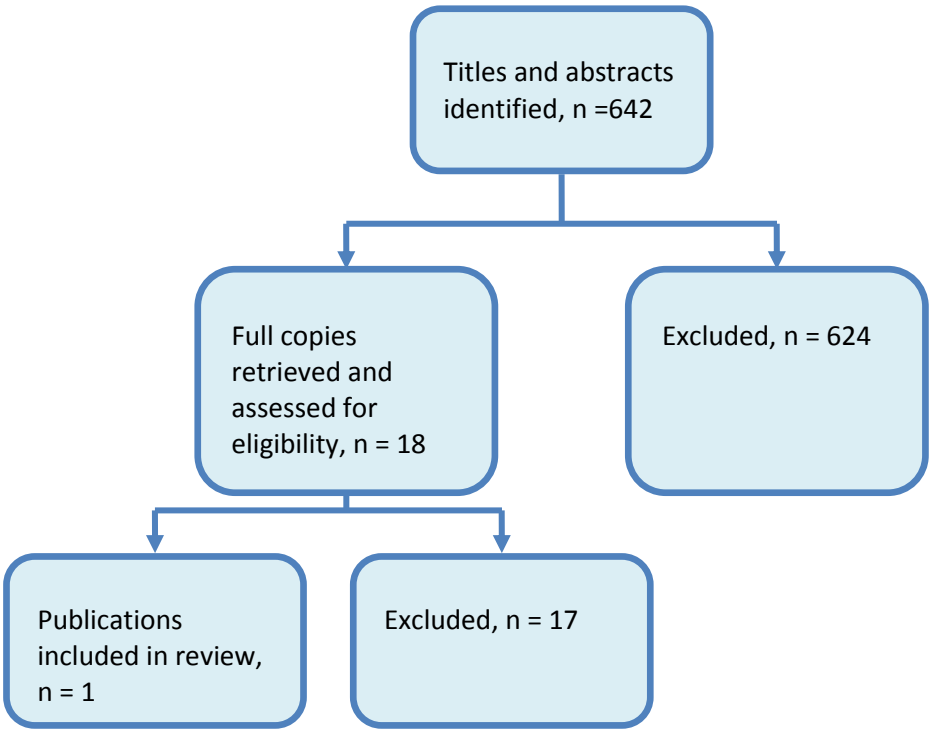


E.4 Identifying the cause of AKI

E.4.1 Urinalysis

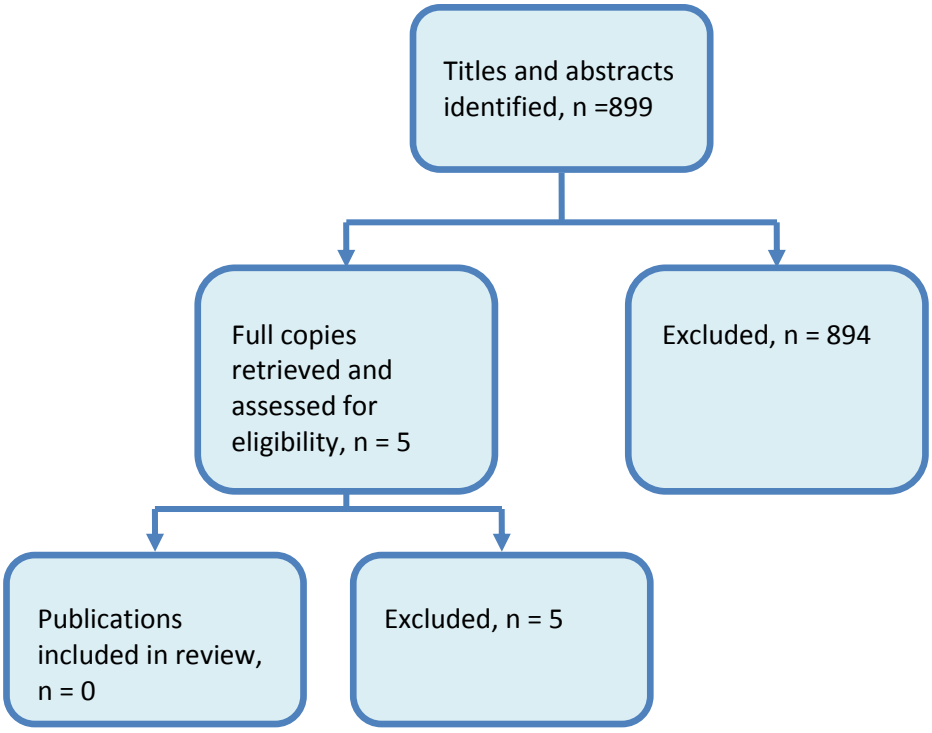


E.4.2 Ultrasound



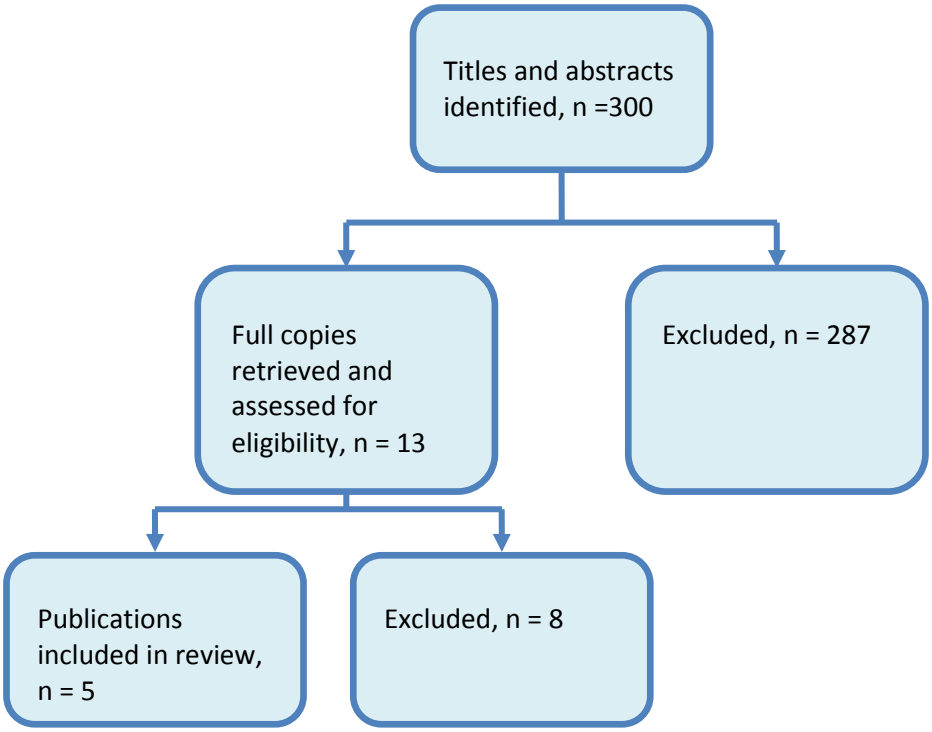
E.5 Managing AKI

E.5.1 Relieving urological obstruction

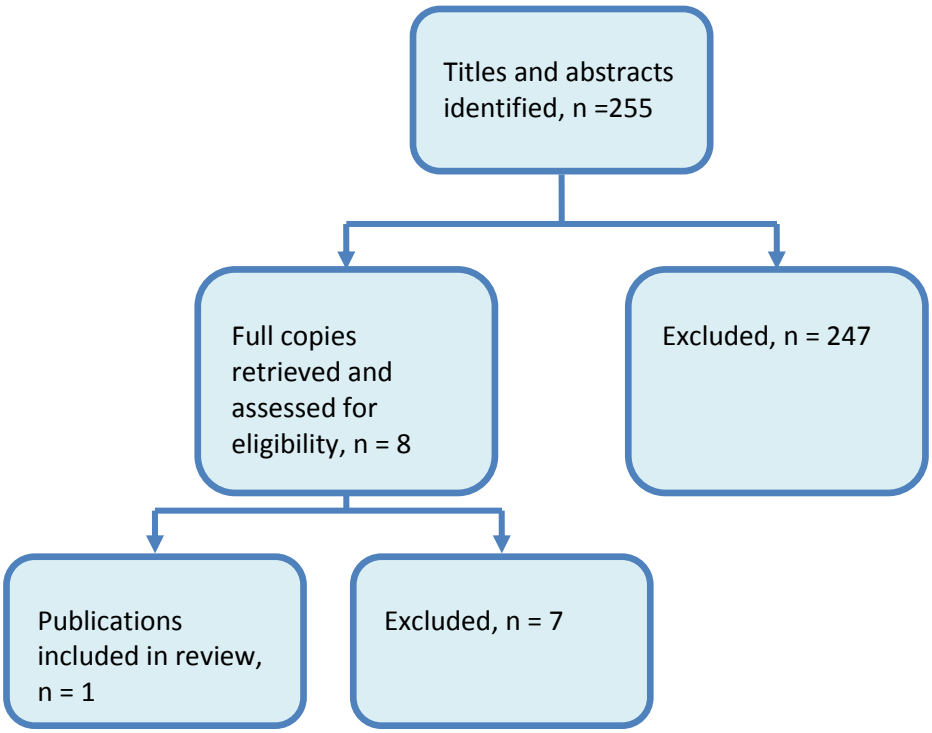


E.5.2 Pharmacological management

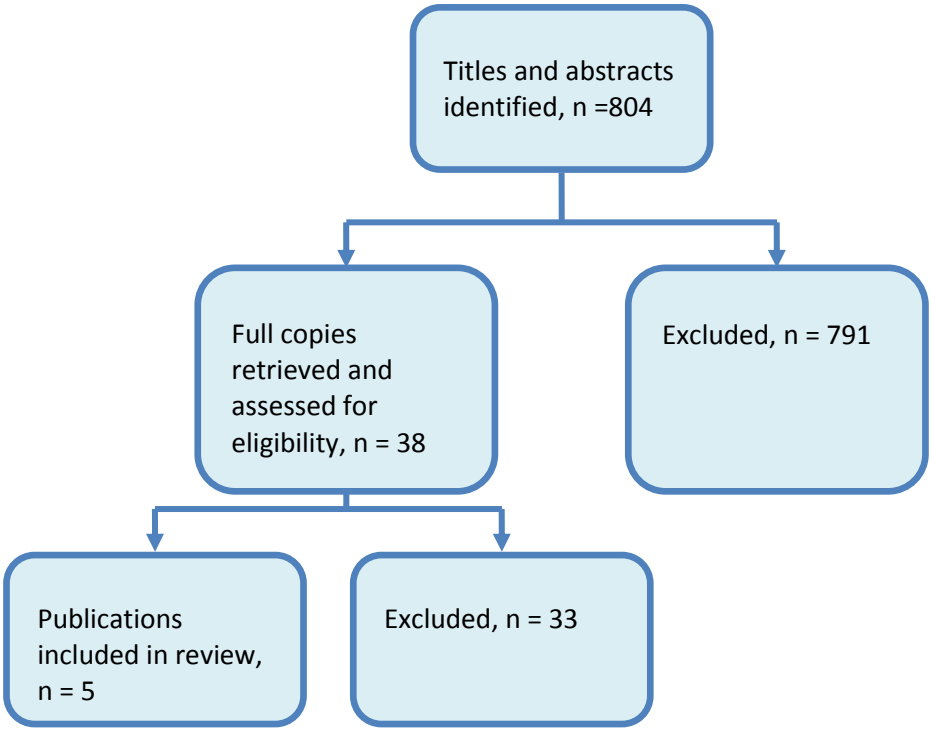
E.5.2.1 Loop diuretics



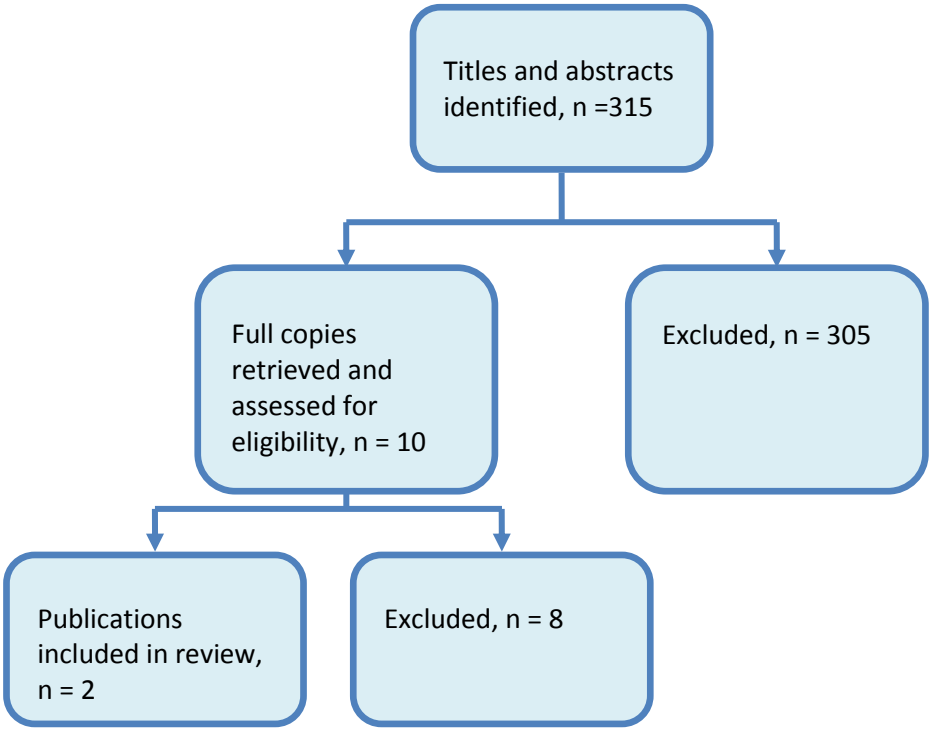
E.5.2.2 Dopamine



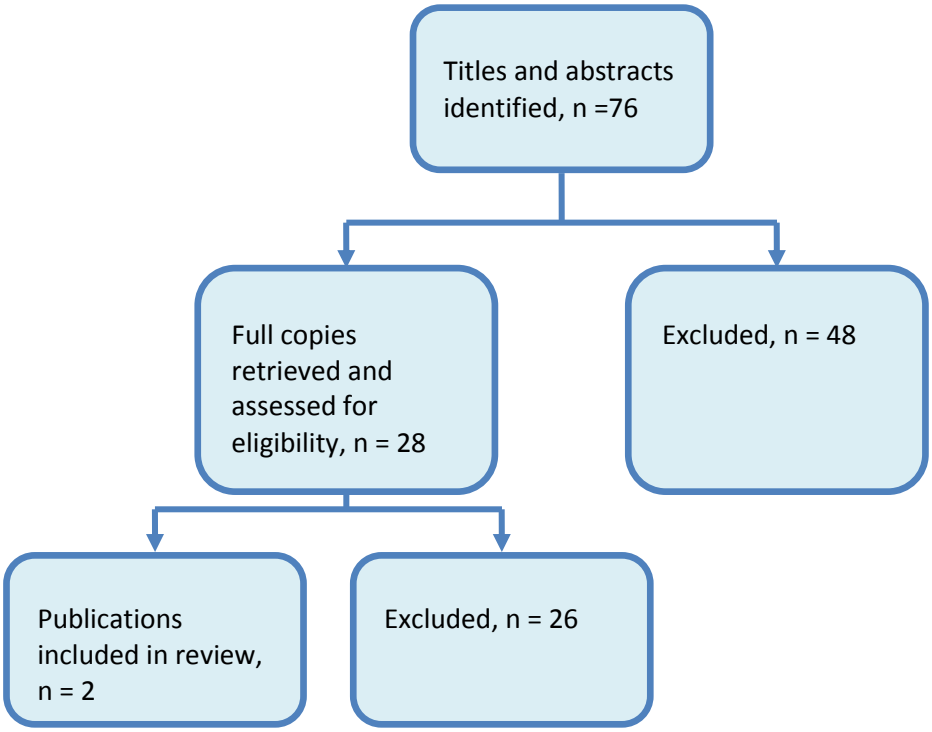
E.5.3 Referring for renal replacement therapy



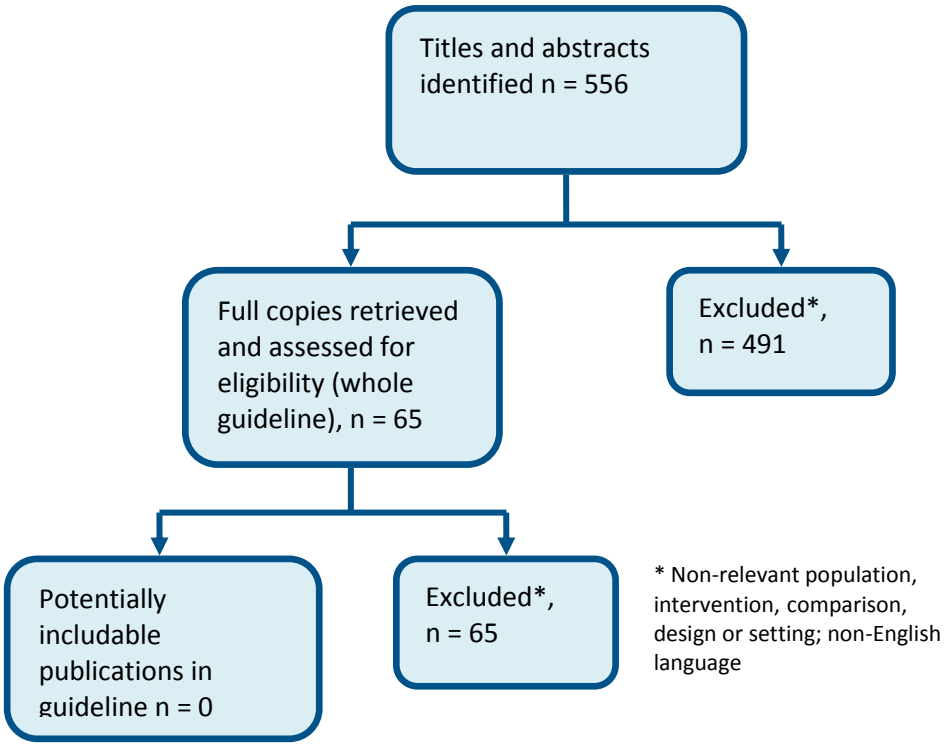
E.5.4 Referring to nephrology



E.6 Information and support for patients and carers



Appendix F: Economic article selection



Appendix G: Clinical evidence tables

G.1 Assessing risk

G.1.1 Risk assessment

Risk scores for CI-AKI

Table 1: MAIOLI 2010[259] and MAIOLI 2008[258]

SCORE: from Maioli 2010[259] Model with pre-procedure variables for CI-AKI					
Significant variables	**OR**	**95% CI**	**P value**	**Weighted score**	≤3: low risk (Incidence of CI-AKI 1.1% in this group) 4-6: moderate risk (Incidence of CI-AKI 7.5%) 7-8: high risk (Incidence of CI-AKI 22.3%) ≥9: very high risk (Incidence of CI-AKI 52.1%)
One procedure within past 72h	4.47	2.08-11.24	0.001	3	
Left ventricular EF ≤45%	3.46	2.08-5.78	0.001	2	
Preprocedure sCr≥baseline sCr	3.23	1.77-5.90	0.001	2	**Risk of bias:** Cutoffs for age and CrCl (continuous variables) used in score chosen on ROC curve analysis for "those most predictive of (CI-AKI)" pre-specified in methodology.
Baseline sCr ≥133µmol/l	3.10	1.63-5.89	0.001	2	
Diabetes mellitus	2.78	1.62-4.81	0.001	2	Methodology states that "the value of the OR rounded to nearest integer constituted the score for each factor…", however this does not agree with values reported.
CrCl† ≤ 44 ml/min	2.65	1.45-4.59	0.002	2	
Age ≥ 73	2.40	1.32-4.34	0.004	1	†CrCl calculated by Cockcroft-Gault formula

DERIVATION: Maioli 2010[259]								
Reference	**Number of patients**	**Population**	**Risk prediction tool**	**Outcomes/ condition**	**Length of follow-up**	**Outcome Statistics reported**	**Effect estimate (95%CI)**	**Comments**

SCORE: from Maioli 2010[259] Model with pre-procedure variables for CI-AKI								
Maioli 2010[259] **Country of study**: Italy **Study design:** Prospective cohort study. **Definition of CI-AKI:** Increase in sCr ≥ 44µmol/l within 5 days of administration of contrast	**Patient group (from Maioli 2010):** All patients undergoing coronary angiography or PCI from 1 June 2003 to 31 December 2004 1,384 patients were enrolled. Final number after exclusions: N= 1,218 patients Exclusion criteria: • ST-segment elevation acute MI • end stage renal failure requiring dialysis • unable to give informed consent	**Baseline characteristics (derivation cohort):** *Age (years) :* 69 ± 10 *Age ≥ 75* : 428 (35.1%) *M:F :* 818 (67.2%):400 (32.8%) *Diabetes*: 274 (22.5%) *sCr ≥ 133µmol/l:* 181 (14.9%) *Mean sCr:* 102 ± 32 *Mean CrCl:* 60 ± 21 CrCl <60: 684 (56.2%) *Mean LVEF*: 48 ± 12 *Mean contrast volume (ml) :*189 ± 97 *One procedure effected within past 72h*: 50 (4.1%) **All patients received:** • NAC 600mg bd day before and day of procedure. • Oral fluids if CrCL >60. • Saline 0.9% iv if CrCl<60. • Iodixanol (iso-osmolar) contrast	**Details of RFs included:** See score above. Categorical variables summarised as frequencies with percentages and compared by Pearson's chi-square or Fisher's exact test. Normal distribution tested using Kolmogorov-Smirnov test. Continuous variables compared by *t*-test or Mann-Whitney U-test. ROC curve analysis to establish cutoffs most predictive of CI-AKI. **Derivation of the tool:** univariable (odds ratios) and multivariable analysis, stepwise multiple logistic regression. Goodness of fit assessed using the Hosmer-Lemeshow statistic.	**Derivation set:** Incidence of CI-AKI (increase in sCr ≥ 44µmol/l within 5 days): 114/1218 (9.4%) CI-AKI (Baseline CrCl<60):100/684 (14.6%) CI-AKI (diabetes):44/274 (16.1%) CI-AKI (diabetes and CrCL <60): 23.2% **Other reported outcomes (NOTE: score not designed to detect these)** Inhospital mortality: All patients: 13/1218 (1.1%) Score ≥7: 11/250 (4.4%) Score ≤6: 2/968 (0.2%) OR: 22 [5-101] P=0.001 Need for RRT: 5/1218 (0.4%) all	10 days	AUC	85% 95% CI NR	NOTE: for serum creatinine NCGC calculated values in µmol/l from mg/dl given in study (x88.4) Continuous variables dichotomised No time to event data.

SCORE: from Maioli 2010[259] Model with pre-procedure variables for CI-AKI								
				had score ≥7 (ie high or very high risk) Length of Stay (days): Score ≥7: 8.6 ± 6.3 Score ≤6: 5.9 ± 3.3 P=0.004				
INTERNAL VALIDATION: Maioli 2010[259], population from Maioli 2008[258]								
Reference	**Number of patients**	**Population**	**Risk prediction tool**	**Outcomes/ condition**	**Length of follow-up**	**Outcome Statistics reported**	**Effect estimate (95%CI)**	**Comments**
Maioli 2010[259] and Maioli 2008[258] **Country of study**: Italy **Study design:** Validation cohort retrospective from Maioli 2008 **Definition of CI-AKI:** Increase in sCr ≥ 44µmol/l within 5 days of	**Patient group (from Maioli 2008):** All patients with estimated CrCl <60ml/min who underwent planned coronary angiography or PCI from January 2005 to March 2006 N=502 Exclusion criteria: • CrCl≥60ml/min • end stage renal disease • administration	**Baseline characteristics (validation cohort, Maioli 2008):** *Age (median, years) :* 74 *M:F :* 296(59.0%):206 (41.0%) *Diabetes*: 121 (24.1%) *sCr ≥ 133µmol/l:* NR *Mean sCr:* 106 ± 27 *Mean CrCl:* 43 ± 11 CrCl <60: NR CrCl <30: 75 (15.0%) *Median LVEF*: 47 *Mean contrast volume (ml) :*165 *One procedure effected within past 72h*: 0 (12 patients excluded due to contrast in past 10	**Details of RFs included (from Maioli 2010):** See score above. Categorical variables summarised as frequencies with percentages and compared by Pearson's chi-square or Fisher's exact test. Normal distribution tested using Kolmogorov-Smirnov test. Continuous variables compared by *t*-test or Mann-Whitney U-test. ROC curve analysis to establish cutoffs most	**Validation set:** Incidence of CI-AKI: 54/502 (10.8%) **Other reported outcomes (NOTE: score not designed to detect these)** Inhospital mortality: All patients: 7/502 (1.4%) Need for RRT: 2/502 (0.4%)	10 days	AUC	82% 95% CI NR	Used Mehran 2004[276] score in Maioli 2008, reported incidence of CI-AKI by level of risk, but no c-statistic/AUC. No time to event data. NOTE: for serum creatinine NCGC calculated values in µmol/l from mg/dl given in study (x88.4)

SCORE: from Maioli 2010[259] Model with pre-procedure variables for CI-AKI								
administration of contrast	of contrast within previous 10 days	days) **All patients received:** • NAC 600mg bd day before and day of procedure. • Oral fluids if CrCL >60. • Saline 0.9% iv or sodium bicarbonate iv if CrCl<60. • Iodixanol (iso-osmolar) contrast	predictive of CI-AKI. **Discrimination:** c-statistic All tests were two-tailed and statistical significance defined as P<0.05.					

Table 2: MEHRAN 2004[276], REUTER 2011[342], CAIXETA 2010A[65], SGURA 2010[363]

SCORE: from Mehran 2004[276] Pre and intraprocedural variables for risk of CI-AKI						
Significant variables	**Model coefficient**	**OR**	**95% CI**	**P value**	**Weighted score**	≤5: low risk (7.5% risk of CI-AKI in this group) 6-10: moderate risk (14.0% risk of CI-AKI) 11-15: high risk (26.1% risk of CI-AKI) ≥16: very high risk (57.3% risk of CI-AKI) **Risk of bias:** Patients were randomly assigned on 2:1 basis from entire database to development and validation datasets, increases likelihood score will agree in these populations **Notes:**
Model A - using serum creatinine as a criterion for renal function						
Hypotension*	0.9310	2.537	1.973-3.262	<0.0001	5	
Intra-aortic balloon pump (IABP) use	0.8910	2.438	1.677-3.544	<0.0001	5	
Congestive heart failure†	0.8111	2.250	1.682-3.011	<0.0001	5	
Serum creatinine >133µmol/l	0.7194	2.053	1.586-2.658	<0.0001	4	
Age >75 years	0.6133	1.847	1.509-2.260	<0.0001	4	
Anaemia‡	0.4705	1.601	1.328-1.930	<0.0001	3	
Diabetes	0.4109	1.508	1.260-1.806	<0.0001	3	

SCORE: from Mehran 2004[276] Pre and intraprocedural variables for risk of CI-AKI					
Contrast volume	0.2549	1.290	1.210-1.375	<0.0001	1 for 100ml
Model B – using eGFR as a criterion for renal function					
Hypotension*	0.9845	2.676	2.082-3.441	<0.0001	5
IABP use	0.9350	2.547	1.751-3.706	<0.0001	5
Congestive heart failure†	0.9923	2.698	2.019-3.603	<0.0001	5
Age >75 years	0.7861	2.195	1.780-2.706	<0.0001	4
Anaemia‡	0.6028	1.827	1.518-2.199	<0.0001	3
Diabetes	0.4681	1.597	1.335-1.910	<0.0001	3
Contrast volume	0.2434	1.276	1.197-1.360	<0.0001	1 for 100ml
eGFR (ml/min 1.73m^2)	0.1772	1.194	1.099-1.297	<0.0001	2 for 40-60 4 for 20-40 6 for <20

Assigned weighted integer based on OR, integer of 2 to each 0.5 value of OR, integer of 1 for each 100ml increment in contrast and an integer of 2,4 or 6 was assigned for eGFR as in the table.

Definitions:

* Systolic blood pressure < 80 mmHg for at least one hour requiring inotropic support with medications or IABP within 24 hr periprocedurally.

†NYHA functional class III or IV and/or history of pulmonary oedema.

‡Haematocrit < 39% for men or < 36% for women.

CKD defined as baseline sCr >133µmol/l (10.5% incidence) or eGFR <60 (26.4% incidence)

DERIVATION: Mehran 2004[276]

Reference	Number of patients	Population	Risk prediction tool	Outcomes/ condition	Length of follow-up	Outcome Statistics reported	Effect estimate (95%CI)	Comments
Mehran 2004[276] **Country of study**: USA **Study design:** Post hoc analysis of prospective	**Patient group:** Consecutive patients with documented serum creatinine before the procedure and at 48 hours after who underwent PCI N=8357/8443 divided into 5571 in development dataset and 2786 in validation dataset. Exclusion criteria (86 patients):	**Baseline characteristics:** *Age (years) :* 63.8 ± 11.2 *Age > 75* : 17.1% *M:F :* 71.2%: 28.8% *Diabetes*: 30.7% *sCr ≥133µmol/l:* 10.5%	**Details of RFs included:** See score above. **Derivation of the tool:** univariable (odds ratios) and multivariable logistic regression analysis. A	Incidence of CI-AKI 729/5571 (13.1%) **Other reported outcomes (NOTE: score not designed to detect these)**	48h for sCr, 1 year for mortality	AUC (Model A)	69% 95% CI NR	**Risk of bias:** Post hoc analysis: due to limited availability of data fields periprocedural hydration volume, proteinuria, urine output and nephrotoxic
						AUC (Model B)	70% 95% CI NR	

SCORE: from Mehran 2004[276] Pre and intraprocedural variables for risk of CI-AKI								
interventional cardiology database (Columbia university Medical Centre, New York) **Definition of CI-AKI:** Increase ≥25% and/or ≥44µmol/l in serum creatinine at 48 hours after PCI.	• acute MI • cardiogenic shock • end stage renal disease requiring RRT • administration of contrast within previous 7 days Multivariable analysis: N=4898/5571 (87.9%) (no missing covariate values) and included 646/729 (88.6%) of patients who developed CI-AKI.	*eGFR <60:* 26.5% *eGFR <20*: 0.7% *Congestive heart failure* : 6.0% *Hypertension:* 62.1% *Hypotension:* 8.3% *Anaemia:* 25.8% *Mean contrast volume (ml) :*260.9 ± 122 *Contrast >150ml:* 80.4% **All patients received:** • Saline 0.45% iv 1ml/kg/h for 4-12 hours before and 18-24 hours after PCI • No information on type of contrast	bootstrap method was used to select the best subset of risk factors (total 200 bootstrap samples). Variables that were selected in ≥90% of the bootstrap models were included in the final multivariable model. **Calibration:** Goodness of fit assessed using the Hosmer-Lemeshow statistic.	Number of patients needing RRT: Low risk: 0.04% Medium risk: 0.12% High risk: 1.09% Very high risk: 12.6% Mortality at 1 year: Low risk: 1.9% Medium risk: 5.5% High risk: 15.5% Very high risk: 31.2%		Cochran Armitage χ^2 Hosmer-Lemeshow statistic (Model A) Hosmer-Lemeshow statistic (Model B)	P<0.0001 8.05 (p=0.43) 8.13 (p=0.42)	medications could not be considered as parameters in derivation of score. NOTE: for serum creatinine NCGC calculated values in µmol/l from mg/dl given in study (x88.4) No time to event data.
INTERNAL VALIDATION: Mehran 2004[276]								
Reference	**Number of patients**	**Population**	**Risk prediction tool**	**Outcomes/ condition**	**Length of follow-up**	**Outcome Statistics reported**	**Effect estimate (95%CI)**	**Comments**
Mehran 2004[276] **Country of**	**Patient group:** Consecutive patients over a period of 6 years (dates not reported) with documented	**Baseline characteristics:** Not reported for validation set.	**Details of RFs included:** See score above.	Incidence of CI-AKI: 386/2786 (13.9%)	48h for sCr, 1 year for	AUC	67% 95% CI NR (unclear if this is for both	**Risk of bias:** Internal validation only - Patients

SCORE: from Mehran 2004[276] Pre and intraprocedural variables for risk of CI-AKI								
study: USA **Study design:** Post hoc analysis of prospective interventional cardiology database (Columbia university Medical Centre, New York) **Definition of CI-AKI:** Increase ≥25% and/or ≥44µmol/l in serum creatinine at 48 hours after PCI	serum creatinine before the procedure and at 48 hours after who underwent PCI N=8357/8443 divided into 5571 in development dataset and 2786 in validation dataset. Exclusion criteria (86 patients): • acute MI • cardiogenic shock • end stage renal disease requiring RRT • administration of contrast within previous 7 days	**All patients received:** • Saline 0.45% iv 1ml/kg/h for 4-12 hours before and 18-24 hours after PCI • No information on type of contrast	**Discrimination:** c-statistic	**Other reported outcomes (NOTE: score not designed to detect these)** Number of patients needing RRT: Low risk: 0% Medium risk:0% High risk:1.4% Very high risk: 13.4% Mortality at 1 year: Low risk: 2.0% Medium risk:5.7%% High risk: 13.5% Very high risk: 33.3%	mortality		models)	were randomly assigned to development and validation datasets, increases likelihood score will agree in these populations. Baseline characteristics not reported for validation set. NOTE: for serum creatinine NCGC calculated values in µmol/l from mg/dl given in study (x88.4)
EXTERNAL VALIDATION: Reuter 2011[342]								
Reference	**Number of patients**	**Population**	**Risk prediction tool**	**Outcomes/ condition**	**Length of follow-up**	**Outcome Statistics reported**	**Effect estimate (95%CI)**	**Comments**

SCORE: from Mehran 2004[276] Pre and intraprocedural variables for risk of CI-AKI								
Reuter 2011[342] **Country of study**: USA **Study design:** Retrospective cohort from 3 academic medical centres. **Definition of CI-AKI:** Increase ≥25% and/or ≥44µmol/l in serum creatinine at 48 hours after PCI	**Patient group:** Consecutive adult patients who underwent PCI at three academic medical centres in 2005. N=931 Exclusion criteria: • acute MI • end stage renal disease • administration of contrast within previous 7 days	**Baseline characteristics:** *Age (years)(median, IQR) :* 65 (56-75) *Age > 75* : 23.6% *M:F :* 68.1%: 31.9% *Diabetes*: 37.9% *sCr ≥133µmol/l:* 14.5% *sCr (Median, IQR):* 1.0 (0.9-1.2) *eGFR <60:* 30.2% *eGFR <20*: 0.2% *eGFR(Median, IQR):* 73 (57-89) *Congestive heart failure* : 11.1% *Hypertension:* 83.7% *Hypotension:* 1.3% *Anaemia:* 26.9% *Mean contrast volume (ml(Median, IQR)) :* 193 (135-258) *Contrast >150ml:* 67.1%	**Details of RFs included:** See score above. **Discrimination:** c-statistic	Incidence of CI-AKI: 114/931 (12.2%) Low risk: 29/508 (5.7%) Medium risk: 37/283 (13.1%) High risk: 35/114 (30.7%) Very high risk: 13/13 (50%) **Other reported outcomes (NOTE: score not designed to detect these)** Number of patients needing RRT: 4/931 (0.4%) All-cause mortality at 1 year: 84/931 (9.0%)	48h for sCr, 1 year for mortality	AUC	72% 95% CI: 67-77%	Abstract only. Further details gained via correspondence with author. . NOTE: for serum creatinine NCGC calculated values in µmol/l from mg/dl given in study (x88.4)
						Optimium cut-off point selected from ROC curve	6	
						Sensitivity at cut-off [95% CI]	0.72 [0.63 - 0.80]	
						Specificity at cut-off [95% CI]	0.62 [0.58 - 0.65]	
EXTERNAL VALIDATION: Caixeta 2010[65]								
Reference	**Number of patients**	**Population**	**Risk prediction tool**	**Outcomes/ condition**	**Length of follow**	**Outcome Statistics reported**	**Effect estimate (95%CI)**	**Comments**

SCORE: from Mehran 2004[276] Pre and intraprocedural variables for risk of CI-AKI								
					-up			
Caixeta 2010[65] **Country of study**: USA **Study design:** Post hoc analysis of prospective interventional cardiology database from ACUITY RCT* (large multicentre trial up to 600 centres in US, Europe, Australia and New Zealand)	**Patient group:** Consecutive patients with acute coronary syndrome (ACS) who underwent PCI. Patients 18 years of age or older with symptoms of unstable angina lasting at least 10 minutes within the preceding 24 hours were eligible for enrollment if one or more of the following criteria were met: new ST-segment depression or transient elevation of at least 1 mm; elevations in the troponin I, troponin T, or creatine kinase MB levels; known coronary artery disease; or all four other variables for predicting Thrombolysis in Myocardial Infarction (TIMI) risk scores for	**Baseline characteristics:** Not reported for this subset of patients from ACUITY trial	**Details of RFs included:** See score above.	Incidence of CI-AKI: 783/6731 (11.6%) Low risk: 415/4393 (9.4%) Medium risk: 259/1793 (14.4%) High risk: 96/495 (19.4%) Very high risk: 13/50 (26.0%)	48h for sCr, 1 year for mortality	AUC Cochrane-Armitage	NR 57%† P<0.0001	Abstract only NOTE: for serum creatinine NCGC calculated values in µmol/l from mg/dl given in study (x88.4) †calculated by NCGC by entering true positives and true negatives from study into John Hopkins online ROC curve calculator (available at http://www.rad.jhmi.edu/jeng/javarad/roc/JROCFITi.html)

SCORE: from Mehran 2004[276] Pre and intraprocedural variables for risk of CI-AKI								
Definition of CI-AKI: Increase ≥25% and/or ≥44µmol/l in serum creatinine at 48 hours after PCI	unstable angina. N=6731/13,819 who had serial serum creatinine measurements available. Exclusion criteria: • myocardial infarction associated with acute ST-segment elevation or shock • bleeding diathesis or major bleeding episode within 2 weeks before the episode of angina • thrombocytopenia; • a calculated creatinine clearance rate <30 ml/min • recent administrationof abciximab, warfarin, fondapar inux, fibrinolytic agents, bivalirudin, or ≥2doses of low-molecular-weight heparin • allergy to any of the study drugs or to iodinated contrast medium							* Stone et al 2004 Am Heart J. 2004 Nov;148(5):764-75 an stone et al 2006 N Engl J Med 2006;355:2203–16

EXTERNAL VALIDATION: Sgura 2010[363] – used Model B (eGFR)								
Reference	**Number of patients**	**Population**	**Risk prediction tool**	**Outcomes/ condition**	**Length of follow-up**	**Outcome Statistics reported**	**Effect estimate (95%CI)**	**Comments**
Sgura 2010[363] **Country of study**: Italy	**Patient group:** Consecutive patients (2002-2008) with STEMI who underwent PCI. Patients were included if they presented within 12 hours	**Baseline characteristics:** Age (mean ±SD): 63.9±13.1 Male sex: 522/891	**Details of RFs included:** See score above.	Incidence of CI-AKI: 126/891 (14.1%) Low risk: 68/562	sCr up to 72h. Mean	AUC	0.57 95% CI 0.52-0.62	Also external validated Marenzi risk score for CI-AKI in patients with STEMI: AUC 0.57 (95% CI, 0.51

SCORE: from Mehran 2004[276] Pre and intraprocedural variables for risk of CI-AKI								
Study design: Prospective cohort **Definition of CI-AKI:** Increase ≥25% and/or ≥44µmol/l in serum creatinine at 48 hours after PCI	from symptom onset. N=891/1046 Exclusion criteria (155 patients): • chronic peritoneal or hemodialysis • cardiogenic shock **Definitions:** Chronic renal insufficiency: eGFR <60 mL/min per 1.73 m^2 Anemia: baseline hemoglobin value <13 g/dL for men and <12 g/dL for women. Hypotension: blood pressure <80 mm Hg for at least 1 hour requiring inotropic support with medications or iIABP within 24 hours of theprocedure. Congestive heart failure: New York HeartAssociation functional classification III/IV and/or history of pulmonaryoedema. Diabetes: fasting plasma glucose ≥7.0 mmol/L or 2-hourplasma glucose ≥11.1 mmol/L	(77.56%) Diabetes: 128 (14.37%) Hypertension: 408 (45.79%) Hypotension : 47 (5.27%) Baseline sCr : 89.3 ± 27.4 eGFR: 80.91 ± 24.27 CKD: 169 (18.97%) Anemia: 165 (18.52%) Mean contrast volume (ml): 216.1±88.5 Contrast >300 mL : 153 (17.17%) Iodixanol: 682 (76.54%) IABP: 90 (10.10%) **All patients received:** NAC and sodium bicarbonate. Contrast type and dose and supportive pharmacological therapies were left to the discretion of the interventional cardiologist.	**Discrimination:** c-statistic	(12.10%) Medium risk: 32/217 (14.75%) High risk: 16/83 (19.28%) Very high risk: 10/29 (34.48%) **Other reported outcomes (NOTE: score not designed to detect these)** Inhospital mortality: 33/891 (3.7%)	25 months			to 0.62) i.e. almost same as for Mehran score in this population NOTE: for serum creatinine NCGC calculated values in µmol/l from mg/dl given in study (x88.4) Also assessed the use of the Mehran score in predicting major adverse cardiovascular and cerebrovascular events (MACCE) in both short- and long-term follow-up (score not designed for this purpose)

Risk scores for hospital acquired AKI

Table 3: MATHENY 2010[269]

SCORE: from Matheny 2010[269] Risk of hospital acquired AKI (using electronic health records)					
Risk Factor	**AKI Risk, OR (95% CI)**	**AKI Injury, OR (95% CI)**	**AKI Risk β coefficient (SE)**	**AKI Injury β coefficient (SE)**	Risk of AKI = $1/1+e^{-a}$, where $z= \beta_0 + \beta_1x_1 + \beta_2x_2 + \ldots + \beta_kx_k$ In this equation, each of the β variables is a beta coefficient for a variable in the model. β_0 is a special case called the intercept and represents the risk for the outcome in a case where all the risk factors are not present (β_0 = -4.13 [Risk] or -5.23 [Injury]). **Thresholds:** AKI Risk model: 0.372 for 50% of observed outcome incidence 0.847 for 150% of observed outcome incidence AKI Injury model: 0.477 for 50% of observed outcome incidence 0.831 for 150% of observed outcome incidence. **Risk of bias:** Baseline characteristics reported by admissions for all patients together (no separate derivation/ validation groups). Statistical significant difference between included and excluded patient groups in all baseline characteristics. Internal cross-validation only. "This method splits the data into 10 data sets each of 90% training data and 10% testing data, with a model fitted for each training data set, and applied to the testing data. Selection is random, but each observation is used in the testing data only one time."
Female	1.22 (1.07-1.4)	1.22 (1.02-1.4)	0.20	0.20	
Age 18-35	1.00	1.00			
Age 36-45	1.01 (0.81-1.25)	1.12 (0.85-1.48)	0.01	0.12	
Age 46-55	1.15 (0.94-1.41)	1.17 (0.90-1.53)	0.14	0.16	
Age 56-65	1.28 (1.04-1.57)	1.13 (0.85-1.49)	0.24	0.12	
Age ≥66	1.42 (1.17-1.73)	1.35 (1.04-1.75)	0.35	0.30	
Race: White	1.00	1.00			
African American	0.97 (0.81-1.17)	1.07 (0.84-1.37)	-0.03	0.07	
Race: Other	0.96 (0.61-1.49)	1.44 (0.88-2.34)	-0.05	0.36	
Race: Unknown	1.26 (1.04-1.52)	1.33 (1.04-1.69)	0.23	0.28	
Amphotericin B	8.04 (6.19-10.46)	8.39 (6.16-11.42)	2.08	2.13	
Ciclosporin	2.99 (2.33-3.84)	2.10 (1.51-2.92)	1.10	0.74	
Loop diuretics	2.08 (1.82-2.38)	2.24 (1.87-2.69)	0.73	0.81	
Thiazide diuretics	1.51 (1.23-1.85)	1.89 (1.48-2.42)	0.41	0.64	
Aminoglycosides	1.53 (1.27-1.85)	1.49 (1.18-1.89)	0.43	0.40	
NSAID	1.12 (0.99-1.28)	1.24 (1.05-1.47)	0.12	0.21	
Potassium sparing diuretic	1.21 (0.97-1.51)	1.19 (0.90-1.57)	0.19	0.17	
Aciclovir	0.98 (0.77-1.25)	0.66 (0.48-0.91)	-0.02	-0.41	
Cisplatin	0.62 (0.33-1.15)	0.37 (0.13-1.05)	-0.48	-1.01	
CT scan with contrast	0.92 (0.79-1.08)	0.85 (0.69-1.04)	-0.08	-0.17	
ARB	0.96 (0.70-1.33)	0.78 (0.49-1.25)	-0.04	-0.24	
ACE Inhibitor	0.80 (0.69-0.94)	0.70 (0.56-0.88)	-0.22	-0.36	
Mean admission	0.72 (0.51-1.03)	0.54 (0.33-0.87)	-0.32	-0.62	

SCORE: from Matheny 2010[269] Risk of hospital acquired AKI (using electronic health records)				
creatinine				
Bacterial infection (any antibiotic use)	1.74 (1.45-2.10)	2.84 (2.09-3.84)	0.56	1.04
Myocardial infarction *	1.11 (0.85-1.44)/ 0.89 (0.62-1.29)	1.45 (1.05-1.99)/ 1.10 (0.71-1.71)	0.10/0.10	0.37/0.10
Rhabdomyolysis*	0.98 (0.65-1.50)/ 1.00 (0.70-1.45)	0.93 (0.54-1.62)/ 0.75 (0.49-1.16)	-0.02/0.01	-0.07/-0,28
Acute hepatitis*	1.65 (1.28-2.12)/ 1.03 (0.78-1.36)	1.86 (1.38-2.52)/ 0.89 (0.60-1.31)	0.50/0.03	0.62/-0.12
Acute pancreatitis*	0.84 (0.64-1.11)/ 0.90 (0.73-1.10)	0.82 (0.59-1.15)/ 0.86 (0.67-1.12)	-0.17/-0.11	-0.20/-0.15
Hyperammonaemia *	1.38 (0.85-2.23)/ 0.85 (0.60-1.19)	1.86 (1.02-3.40)/ 1.06 (0.68-1.66)	0.32/-0.17	0.62/-0.12
AST:ALT >1.5*	1.86 (1.58-2.18)/ 1.01 (0.82-1.26)	1.73 (1.40-2.13)/ 0.88 (0.66-1.18)	0.62/0.01	0.55/-0.13
Thrombocytopenia*	1.76 (1.53-2.03)/ 0.84 (0.60-1.17)	2.11 (1.75-2.54)/ 1.00 (0.62-1.61)	0.57/-0.17	0.75/0.00
Leucocytosis*	1.00 (0.88-1.14)/ 0.97 (0.62-1.51)	1.09 (0.92-1.3)/ 1.25 (0.68-2.3)	0.00/-0.03	0.09/0.27
Hypercalcaemia (corrected)*	1.52 (1.06-2.18)/ 1.03 (0.84-1.26)	1.05 (0.62-1.79)/ 1.09 (0.83-1.42)	0.42/0.03	0.05/0.08
Mean glucose > 250 mg/dL (14mmol/l)	2.68 (2.06-3.5)	2.57 (1.76-3.75)	0.99	0.94
Mean glucose > 200-250 mg/dL (11-14mmol/l)	1.6 (0.82-3.12)	1.87 (1.37-2.57)	0.71	0.63
Mean glucose > 150-200 mg/dL (8-11mmol/l)	1.00 (0.88-1.14)	1.39 (1.13-1.72)	0.49	0.33
Mean glucose unknown	0.97 (0.62-1.51)	0.85 (0.24-3.00)	0.47	-0.17
*OR and β coefficients for yes/unknown for these risk factors				
DERIVATION: Matheny 2010[269]				

SCORE: from Matheny 2010[269] Risk of hospital acquired AKI (using electronic health records)								
Reference	**Number of patients**	**Population**	**Risk prediction tool**	**Outcomes/ condition**	**Length of follow-up**	**Outcome Statistics reported**	**Effect estimate (95%CI)**	**Comments**
Matheny 2010[269] **Country of study**: USA **Study design:** Retrospective analysis of clinical data acquired from electronic health records **Definition of AKI:** RIFLE criteria for 'Risk' and 'Injury'	**Patient group:** All adult hospital admissions to a tertiary care centre, academic hospital from 1 August 1999 to 31 July 2003 with a length of stay of at least 2 days. Total 61, 179 admissions. Final number after exclusions: N= 26,107 admissions in 21,074 patients (17,870 had only one admission) Excluded patients who: •Were missing data necessary for outcome determination e.g. no creatinine admission •Had evidence of moderate or severe chronic kidney dysfunction •Were experiencing acute kidney injury at the time of hospital admission •No sCr measurements available within 48h surrounding admission or no further sCr	**Baseline characteristics (FOR ALL PATIENTS, BY ADMISSIONS NOT NUMBER OF PATIENTS):** Age: *18-25:* 2365 (9.1%) *26-35:* 3044 (11.7%) *36-45:* 4382 (16.8%) *46-55:* 5027 (19.3%) *56-65:* 4614 (17.7%) *>65:* 6675 (25.6%) Female*:* 14,505 (55.6%) Race: *White:*19,329 (74.0%) *African American:* 3866 (14.8%) *Other:* 515 (2.0%) *Unknown:* 2397 (9.2%) Length of stay (days)(mean): 8.1 Mean sCr on admission: 72µmol/l Antibiotic: 19,672 (75.4%) Aminoglycoside: 2501 (9.6%) Aciclovir: 1508 (5.8%) Amphotericin B: 498 (1.9%) Ciclosporin: 578 (2.2%) ACEI: 5828 (22.3%)	**Details of RFs included:** See score above. Significance testing for hospitalisation characteristics using Fisher's exact test for binary variables and likelihood chi-square testing for categorical variables. **Derivation of the tool:** Two logistic regression models developed for RIFLE 'Risk' and 'Injury'. Performance of each model evaluated with ROC curve and Hosmer-Lemeshow goodness of fit. Adjustment made for repeated hospitalisations.	Incidence of AKI (derivation and validation)*: AKI (Risk Model): 1352/26102 (5.2%) AKI (Injury Model): 726/26102 (2.8%) *Calculated by NCGC from calibration performance table in which observed outcomes fro AKI Risk and AKI Injury models were reported.	In hospital. Serum Cr evaluate up to 30 days.			Statistical significant difference between included and excluded patient groups in all baseline characteristics. No time to event data. NOTE: for serum creatinine NCGC calculated values in µmol/l from mg/dl given in study (x88.4)

SCORE: from Matheny 2010[269] Risk of hospital acquired AKI (using electronic health records)								
	measurements after 24h of hospitalisation.	ARB: 866 (3.3%) Cisplatin: 303 (1.2%) Loop diuretic: 10,239 (39.2%) Thiazide diuretic: 2056 (7.9%) Potassium sparing diuretic: 1559 (6%) NSAID: 11,622 (44.5%) Radiocontrast: 4610 (17.7%)						
INTERNAL VALIDATION: Matheny 2010[269]								
Reference	**Number of patients**	**Population**	**Risk prediction tool**	**Outcomes/ condition**	**Length of follow-up**	**Outcome Statistics reported**	**Effect estimate (95%CI)**	**Comments**
Matheny 2010[269] **Country of study**: USA **Study design:** Retrospective analysis of clinical data acquired from electronic health records (administrative data, electronic prescribing and	**Patient group:** All adult hospital admissions to a tertiary care centre, academic hospital from 1 August 1999 to 31 July 2003 with a length of stay of at least 2 days. Total 61, 179 admissions. Final number after exclusions: N= 26,107 admissions in 21,074 patients (17,870 had only one admission)	**Baseline characteristics:** see derivation table below	**Details of RFs included:** See score above. 10-fold cross validation with 95% CI to estimate performance uncertainty and potential overfitting. Split data in 10 data sets each of 90% training data and 10% testing data, with a model fitted for each training set,	Incidence of AKI (derivation and validation)*: AKI (Risk Model): 1352/26102 (5.2%) AKI (Injury Model): 726/26102 (2.8%) *Calculated by NCGC from calibration performance table	In hospital. Serum Cr evaluate up to 30 days.	AUC (Risk model)	75% 95% CI: 73-76%	Baseline characteristics reported by admissions for all patients together (no separate derivation/ validation groups). Statistical significant difference between included and excluded patient groups in all baseline characteristics.
						AUC (Injury model)	78% 95% CI: 76-79%	
						Hosmer-Lemeshow test	P>0.05	
						Calibration χ^2 (Risk model)	9.7 (P=0.29)	

SCORE: from Matheny 2010[269] Risk of hospital acquired AKI (using electronic health records)								
laboratory tests) **Definition of AKI:** RIFLE criteria for 'Risk' and 'Injury'	Excluded patients who: •Were missing data necessary for outcome determination e.g. no creatinine admission •Had evidence of moderate or severe chronic kidney dysfunction •Were experiencing acute kidney injury at the time of hospital admission		and applied to the testing data. Selection random, but each observation is used in the testing data only one time. **Discrimination:** AUC **Calibration:** Calibration plots generated using observed and expected event rates per deciles as defined by the Hosmer-Lemeshow C statistic. Risk predictiveness curves.	in which observed outcomes from AKI Risk and AKI Injury models were reported		Calibration χ^2 (Injury model)	12.7 (P=0.12)	Internal cross-validation only.

Risk scores for AKI in patients undergoing general surgery

Table 4: Kheterpal 2009[222]

SCORE: from Kheterpal 2009[222] AKI risk in patients undergoing general surgery								
	Imputed Data Set*		Nonimputed Data Set*					Based on unweighted score:
Risk factor	**β coefficient**	**P value**	**β coefficient**	**P value**	**Adjusted HR (95% CI)**	**Unweighted score**	**Weighted score**	≤2: very low risk (0.2% risk of AKI in this group)

SCORE: from Kheterpal 2009[222] AKI risk in patients undergoing general surgery								
Intraperitoneal surgery	1.149	<0.0001	1.207	<0.0001	3.3 (2.4-4.7)	1	9	3: low risk (0.8% risk of AKI) 4: moderate risk (1.8% risk of AKI) 5: high risk (3.3% risk of AKI) ≥6: very high risk (8.9% risk of AKI) **Risk of bias:** Internal validation only - Patients were randomly assigned on 3:1 basis from entire database to development and validation datasets, increases likelihood score will agree in these populations Cutoff for age (continuous variable) used in score chosen on the maximal sum of sensitivity and specificity (prespecified in methodology). **Notes:** Assigned weighted integer by dividing β coefficient by the smallest β coefficient of the independent predictors, multiplying by 2, and rounding to the nearest integer (based on nonimputed data).
Renal insufficiency – moderate (≥177µmol/l)	1.126	<0.0001	1.172	<0.0001	3.2 (2.8-3.7)	1 for either (mutually exclusive)	9	
Renal insufficiency – mild (106-176µmol/l)	1.058	<0.0001	1.139	<0.0001	3.1 (2.5-3.9)		9	
Ascites	1.046	<0.0001	1.096	<0.0001	3.0 (2.2-4.0)	1	9	
Active congestive heart failure	0.724	<0.0001	0.705	<0.0001	2.0 (1.4-3.0)	1	6	
Emergency surgery	0.725	<0.0001	0.619	<0.0001	1.9 (1.5-2.3)	1	5	
Age ≥56† yr	0.617	<0.0001	0.555	<0.0001	1.7 (1.4-2.2)	1	4	
Diabetes – insulin therapy	0.550	<0.0001	0.545	<0.0001	1.7 (1.3-2.3)	1 for either (mutually exclusive)	4	
Diabetes – oral therapy	0.308	0.017	0.256	0.058	1.3 (1.0-1.7)		2	
Hypertension	0.388	<0.0001	0.402	<0.0001	1.5 (1.2-1.9)	1	3	
Male	0.377	<0.0001	0.333	<0.0001	1.4 (1.2-1.7)	1	3	
*Imputed data set included 57,075 patients. Preoperative sCr imputed using expectation-maximisation algorithm (tolerance 0.001 and convergence 0.0001). Nonimputed data set 49,929 patients with complete data (baseline sCr) available. i.e. 7167 (9.4%) of patients had missing data. † transformed into dichotomous variable by identifying the maximal sum of sensitivity and specificity.								

DERIVATION: Kheterpal 2009[222]

Reference	Number of patients	Population – Baseline characteristics			Risk prediction tool	Outcomes/ condition	Length of follow-up	Outcome Statistics reported	Effect estimate (95%CI)	Comments
Kheterpal 2009[222] **Country of study**: USA **Study design:**	**Patient group:** Consecutive patients in 2005-2006 American College of Surgeons National Surgical Quality Improvement Program. N=152,244. Final	**Risk Factor**	**No AKI N=56,519**	**AKI N=561**	**Details of RFs included:** See score above. **Derivation of the tool:** All patient and operative characteristics were compared using the Mann-Whitney U test for continuous	Incidence of AKI: 561/ 57,080 (1.0%)	30 days	AUC for general Surgery AKI Risk Index	80% 95% CI: 79-81%	**Risk of bias:** Post hoc analysis- due to limited availability of data fields periprocedural hydration and
								AUC (imputed data)	83% 95% CI: 82-84%	
		Age (mean	53.5 ±	64.8 ±				AUC (	83%	

SCORE: from Kheterpal 2009[222] AKI risk in patients undergoing general surgery										
Post hoc analysis of prospective general surgical database (121 centres in the US) **Definition of AKI:** Increase ≥177µmol/l (2mg/dl) in serum creatinine or need for RRT (due to impaired renal function) within 30 days of procedure	number after exclusions: 75,952 (49.9%). Derivation cohort N= 57,080 Exclusion criteria (76,292 patients): • vascular, cardiac, urology, ophthalmology, podiatry or obstetric procedures (21,064 patients) • outpatient procedures (53,591 patients) • RRT within 2 weeks before surgery or steadily increasing uraemia and sCr ≥265µmol/l within 24h of surgery (1637/152244 [1.1%])	**± SD)**	17.3	14.8	variables and χ^2 for categorical variables. Continuous variables (age) transformed into dichotomous ones by identifying the maximal sum of sensitivity and specificity. Missing Value Analysis module of SPSS version 16 used to assess impact of imputation of baseline sCr on the model. Showed preoperative sCr data were missing at random. Collinearity diagnostics and Pearson correlations evaluated for preoperative predictors. Bivariate correlation matrix identified no correlation issues. Multivariable logistic regression to identify significant predictors of AKI (P<0.05). Weighted and unweighted scores compared using c-statistic. **Calibration:** ROC area under curve/ c-statistic			nonimputed data)	95% CI: 82-84%	nephrotoxic medications could not be considered as parameters in derivation of score. Continuous variables dichotomised Additional outcomes: Also reported a propensity score matching based on preoperative AKI risk to determine risk of all cause 30 day mortality. NOTE: for serum creatinine NCGC calculated values in µmol/l from mg/dl given in study (x88.4)
		Male	21,959 (39%)	319 (57%)				AUC (weighted score)	82% 95% CI: 81-83%	
		Congestive heart failure	517 (0.9%)	46 (8.2%)				AUC (unweighted score)	81% 95% CI: 80-83%	
		Ascites	1,257 (2.2%)	75 (13%)				Omnibus test of model coefficients χ^2	1024.5 with 18 d.f. P<0.001	
		Hypertension	23,374 (41%)	387 (69%)						
		Mild renal insufficiency	4,215 (8.5%)	139 (27%)						
		Moderate renal insufficiency	916 (1.9%)	123 (24%)						

SCORE: from Kheterpal 2009[222] AKI risk in patients undergoing general surgery										
		Emergency surgery	11,260 (20%)	232 (41%)						
		Intraperitoneal surgery	40,975 (73%)	512 (91%)						
INTERNAL VALIDATION: Kheterpal 2009[222]										
Reference	**Number of patients**	**Population**	**Risk prediction tool**		**Outcomes / condition**	**Length of follow-up**	**Outcome Statistics reported**	**Effect estimate (95%CI)**	**Comments**	
Kheterpal 2009[222] **Country of study**: USA **Study design:** Post hoc analysis of prospective general surgical database (121 centres in the US) **Definition of AKI:** Increase	**Patient group:** See below. Randomly assigned 3:1 to derivation/validation cohorts. Total N= 152,244. Validation cohort N= 18,872 **Exclusion criteria**: see below. Details not reported separately for cohorts.	**Baseline characteristics:** Not reported separately for validation set. See below.	**Details of RFs included:** See score above. **Discrimination:** c-statistic Weighted and unweighted scores applied to validation cohort and c-statistic calculated.		Incidence of AKI: 201/18,872 (1.1%)	30 days	AUC for general Surgery AKI Risk Index	80% 95% CI: 78-82%	**Risk of bias:** Internal validation only - Patients were randomly assigned to development and validation datasets, increases likelihood score will agree in these populations. Baseline characteristics not reported for validation set. NOTE: for serum creatinine NCGC calculated values in µmol/l from mg/dl given in study (x88.4)	

SCORE: from Kheterpal 2009[222] AKI risk in patients undergoing general surgery								
≥177µmol/l (2mg/dl) in serum creatinine or need for RRT (due to impaired renal function) within 30 days of procedure								

G.1.2 Paediatric risk assessment

Table 5: Bailey 2007[30]

Study details	Patients	Condition or risk factor	Incidence/ Odds ratio	Comments
Bailey 2007[30] Country of study: Canada Study design: Prospective cohort Setting:	Patient group: Consecutive patients admitted to 22 bed PICU Inclusion criteria: See definition of AKI and exclusion criteria Exclusion criteria: <3 days of age or <40 weeks gestation (n=32)	Haemolytic uraemic syndrome	8 (18.2%)	Funding: None reported Limitations: PICU population only - ?indirect Additional outcomes: Mortality in patients with AKI vs without.
		Haemato-oncologic pathologies	8 (18.2%)	
		Cardiac surgery	5 (11.4%)	
		Sepsis	4 (9.1%)	
		Trauma	3 (6.8%)	

Study details	Patients	Condition or risk factor	Incidence/ Odds ratio	Comments
Tertiary care PICU (Single centre) Duration of study: 12 months, 2000-2001 Definition of AKI: doubling of sCr according to upper limit for age and gender or doubling of baseline Cr on admission to PICU, or 25% increase from baseline if known CKD, developing over 72h.	>18 years of age (n=10) Pregnancy or postpartum admission (n=2) Admission for renal transplantation (n=0) Brain death at entry to PICU (n=2) Expected PICU stay <24 hours (n=0) A priori decision to withhold or withdraw treatments (n=3) End stage renal failure (n=13) All patients N: 985/1047 screened Age: 72.3 ± 68.6 months M:F: 536 (54.4%) : 449 (45.6%) Baseline characteristics (those who developed AKI): N: 44/985 (4.5%) Age (mean): 111.0 ± 74.9 months M:F: 25 (56.8%): 19 (43.2%) PRISM score: 10.0 ± 9.2 Respiratory failure: 16 (36.4%) Shock: 1 (2.3%) Cardiac disease: 7 (15.9%) Infection: 9 (20.5%) Trauma: 2 (4.5%) Postsurgical: 30 (68.2%)	DKA	3 (6.8%)	Length of PICU stay and length of mechanical ventilation for patient with Aki vs without. Gender and duration of mechanical ventilation were not different between those with or without AKI. 61% of cases secondary to an extrarenal cause. Notes: Possible risk factors were identified and selected before the initiation of the study via consensus of 2 paediatric intensivists and 1 paediatric nephrologist based on literature and personal experience using the Delphi method.
		CKD	3 (6.8%)	
		Factors in multivariable analysis:		
		Thrombocytopenia (<50,000/mm3)	OR [95% CI]: 6.3 [2.5-16.2]	
		Age >12	OR [95% CI]: 4.9 [1.9-13.0]	
		Hypoxaemia (pulse oximetry saturation <90% or PaO2 60 mmHg)	OR [95% CI]: 3.2 [1.3-8.0]	
		Hypotension (decrease in systolic blood pressure below 2 SDs of the normal value for the age of the patient)	OR [95% CI]: 3.0 [1.2-7.5]	
		Coagulopathy (INR >2, prothrombin time >20s, APTT >60s, or D-dimer >0.5mg/ml)	OR [95% CI]: 2.7 [1.3-5.6]	
		Neurologic dysfunction (as defined by Proulx et al 1996)	OR [95% CI]: 1.6 [0.6-4.9]	
		Nephrotoxic drugs (aminoglycosides, vancomycin, acyclovir, foscarnet, calcineurin inhibitors)	OR [95% CI]: 1.2 [0.6–2.7]	

Study details	Patients	Condition or risk factor	Incidence/ Odds ratio	Comments
	Baseline characteristics (those who did not develop AKI): N: 941/985 (95.5%) Age (mean): 70.5 ± 67.9 months M:F: 511 (54.3%): 430 (45.7%) PRISM score: 5.5 ± 5.9 Respiratory failure: 268 (28.5%) Shock: 5 (0.53%) Cardiac disease: 186 (19.8%) Infection: 54 (5.7%) Trauma: 50 (5.3%) Postsurgical: 434 (46.1%) Study also reports baseline characteristics for all patients			

Table 6: Duzova 2010[119]

Study details	Patients	Outcome measures	Effect size	Comments
Duzova 2010[119] Country of study: Turkey	Patient group: All patients with AKI at time of admission or during treatment at the hospital. Inclusion criteria:	Known medical disorders prior to the diagnosis of AKI:		Funding: None reported Limitations: Tertiary care only
		Malignancy (leukaemia [39%], CNS tumours [22%] and non-Hodgkin lymphoma [10%])	41/318 (12.9%)	
		Congenital Heart Disease	39/318 (12.3%)	

Study details	Patients	Outcome measures	Effect size	Comments
Study design: Prospective cohort. Multicentre 17 paediatric nephrology centres in Turkey. Setting: Tertiary care Duration of study: 12 months, 2006-2007 Definition of AKI: An increase in sCr >26.5µmol/l or ≥50% from baseline or decrease in GFR ≥25% from baseline or urine output <0.5ml/kg for >8h. Classified by pRIFLE.	≤18 years old Exclusion criteria: None Baseline characteristics N: 472 Age (mean): Newborns (median age 3 days [1-24]): N= 154 (32.6%) Children >1 month (median age 2.99 years [1 month – 18 years]): N= 318 (67.4%) M:F: 264 (55.9%):208 (44.1%)			Only looked at children who had AKI so no comparison with a "no AKI" cohort Additional outcomes: Risk in neonates reported. Not extracted as this population excluded from the guideline. Need for RRT – 33.6% those aged 1month – 18 years. Mortality with stepswise multivariable regression analysis to determine independent risk factors for mortality in AKI. Problems and metabolic complications during AKI episode.
		Urologic disorders	19/318 (6.0%)	
		Mentally handicapped	16/318 (5.0%)	
		Renal diseases	12/318 (3.8%)	
		Gastrointestinal disorders	13/318 (4.1%)	
		Aetiology of AKI:		
		Hypoxic/ischaemic injury (hypoxia and/or hypotension/shock in the absence of sepsis)	65/318 (20.4%)	
		Sepsis (systemic inflammatory response plus suspected or proven infection)	49/318 (15.4%)	
		Glomerular disease (Haemolytic uraemic syndrome or glomerulonephritis)	49/318 (15.4%)	
		Acute gastroenteritis	38/318 (11.9%)	
		Low fluid intake without acute gastroenteritis (e.g. poor sucking, mental handicap, vomiting, iatrogenic)	46/318 (14.5%)	
		Nephrotoxic drugs (acyclovir, amikacin, amphotericin B, cisplatin, ciclosporin, radiocontrast)	29/318 (9.1%)	
		Acute tumour lysis syndrome	7/318 (2.2%)	
		Pyelonephritis	6/318 (1.9%)	
		Urinary tract obstruction	5/318 (1.6%)	
		Common clinical features at diagnosis of AKI:		
		Mechanical ventilation	92/318 (28.9%)	
		Hypoxia	65/318 (20.4%)	
		Hypotension	100/318 (31.4%)	

Study details	Patients	Outcome measures	Effect size	Comments
		Septic shock	53/318 (16.7%)	Notes:
		Heart failure	42/318 (13.2%)	
		Anuria	61/318 (19.2%)	
		Oliguria	100/318 (31.5%)	
		Dehydration	97/318 (30.5%)	
		Acute gastroenteritis	64/318 (20.1%)	

G.2 Preventing AKI

G.2.1 Paediatric early warning scores

Table 7: Duncan 2006[115]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Duncan 2006[115] Country of study: Canada Study design: Retrospective	Patient group: Patients admitted during a 28 month period ending march 2003 Age range: <18 years	All patients A PEWS score was developed using expert opinion synthesized by a modified Delphi method. The performance of the score was evaluated with a frequency-matched case-control design. Case patients were defined as	Sensitivity	100% for a score of 0 100% for a score of 1 95% for a score of 2 91% for a score of 3 83% for a score of 4 78% for a score of 5 68% for a score of 6 54% for a score of 7 45% for a score of 8	Funding: Sponsored by internal funding from The Department Of Critical Care Medicine and the Research Institute at The Hospital For Sick Children and partly funded by the Heart And Stroke Foundation Of Canada. Limitations: The validation of the PEWS score is not completely independent of the development

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
case control Who was blinded: NR Setting: Hospital PEWS tool: PEWS score developed by Duncan et al 2006	Cases: N= 87 Controls: N= 128 Inclusion criteria: <18years at admission No pre specified care limitations Exclusion criteria: NR	children who had code blue calls made as part of their care* Case patients were retrospectively identified from the resuscitation committee database for 28-month period ending March 2003. Control patients were defined as children who had no code blue event and were not admitted to PICU in the 48 hours after the period studied. The control patients were retrospectively identified from a list of children selected by matching the admission ward and age category of the code blue patients with other patients admitted to the hospital during the study period. The controls were selected from the first medical records available for review until a ratio of 1 control to 1 case patient was exceeded. Clinical data was abstracted, in case patients' data collection began 25 hours before the code blue call. In control patients data were collected for 24 hours beginning at the first 1:00AM of either hospitalization or after PICU discharge.	Specificity	2% for a score of 0 11% for a score of 1 40% for a score of 2 59% for a score of 3 80% for a score of 4 95% for a score of 5 97% for a score of 6 98% for a score of 7 100% for a score of 8	data set. Also the addition of 4 dynamic items could not be assessed because of incomplete or inconsistent documentation in the medical records Biased measurement endorsement, the use of extreme groups and the use of "most available" medical records to select controls may have inflated the differences between groups and artificially enhanced score performance. Additional outcomes: Number of false positive**, cases correctly identified, controls incorrectly identified, details of maximum PEWS scores during the study period for cases and controls, time related change in PEWS, details of how the PEWS tools was developed (initial analysis of clinical data and score components), AUROCC per age group Notes: * code blue calls: called for children who need additional and immediate medical assistance for the treatment of actual or impending cardiopulmonary arrest **assuming an incidence of code blue call of 0.31% of admissions ***for the largest component (dynamic items-vital signs, oxygen saturation, and on-going oxygen and fluid therapy) of the score
			PPV**	0.31% for a score of 0 0.34% for a score of 1 0.49% for a score of 2 0.68% for a score of 3 1.3% for a score of 4 4.2% for a score of 5 6.2% for a score of 6 9.6% for a score of 7 100% for a score of 8	
			NPV	NR	
			Area under ROC curve***	0.9 95% CI:NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments

Table 8: Edwards 2009 [121]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Edwards 2009[121] Country of study: UK Study design: Prospective cohort Who was blinded: NR Setting: Hospital PEWS Tool: The Cardiff	Patient group: All paediatric admissions to any of the paediatric wards at the University Hospital of Wales between 1 December 2005 and 30 November 2006 were eligible for inclusion Age range: 0–16 years N= 1000 Inclusion criteria:	All patients Nursing staff were trained to use a specifically developed paediatric observation chart to collect data. Charts were completed for all admissions between 1 December 2005 and 30 November 2006. The frequency of observations was determined by the current clinical care policy. The data were collated by the research nurse and entered into a database for analysis. The outcome measures defining an adverse outcome were respiratory arrest, cardiac arrest, PHDU	Sensitivity	Single parameter trigger: 89.0% (95% CI 80.5 to 94.1) Multiple trigger system*: 69.5% (95% CI 59.0 to 78.4)	Funding: NR Limitations: Use of “most available records” may not be representative for all admissions during this time. Missing data was assumed to be normal-, if this is not the case, the specificity and the PPV are likely to have been lower than measured Outcome measures used less reliable than ideal (death)- decision to admit patients to PICU may vary due to different criteria, decision to all MET may be subjective. Additional outcomes: Number of sets of adverse and no adverse observations according to PEW score. Number of patients with adverse event or not grouped by the number of abnormal sets of observation. Completeness of recording of the PEWS criteria.
			Specificity	Single parameter trigger: 63.9% (95% CI 63.8 to 63.9) Multiple trigger system*: 89.9% (95% CI 89.8 to 90.0)	
			PPV	Single parameter trigger: 2.2% (95% CI 2.0 to 2.3) Multiple trigger system*: 5.9% (95% CI 5.0 to 6.7)	
			NPV	Single parameter trigger: 99.8% (95% CI 99.7 to 99.9)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
and Vale paediatric early warning system	NR Exclusion criteria: Patients admitted directly to the PICU and PHDU. Patients presenting in cardiac or respiratory arrest.	admission, PICU admission and death		Multiple trigger system*: 99.7% (95% CI 99.6 to 99.8)	ROC curve Detailed report from ROC analysis: Sensitivity 100% for a score ≥0 89.02% for a score ≥1 69.51% for a score ≥2 47.56% for a score of ≥3 19.51% for a score of ≥4 9.76% for a score of ≥5 1.22% for a score of ≥6 0% for a score of ≥8 0% for a score of >8 Specificity 0% for a score ≥0 63.89% for a score ≥1 89.89% for a score ≥2 97.40% for a score of ≥3 99.27% for a score of ≥4 99.78% for a score of ≥5 99.94% for a score of ≥6 99.99% for a score of ≥8 100% for a score of >8 Correctly classified 0.90% for a score ≥0 64.12% for a score ≥1 89.71% for a score ≥2
			Area under ROC curve	Single parameter trigger: 0.86 95% CI: 0.82 to 0.91	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
					96.95% for a score of ≥3 98.55% for a score of ≥4 98.96% for a score of ≥5 99.05% for a score of ≥6 99.09% for a score of ≥8 99.10% for a score of >8 Notes: Sixteen children had an adverse outcome, 13 were admitted from the ward to the PHDU (four of these subsequently transferred PHDU to the PICU) and three were admitted from the ward to the PICU. There were no deaths, cardiac arrests, or respiratory arrests. Three of the 16 children (18.8%) had no abnormal observations before to the adverse outcomes. 810 of the 984 children (82.3%) who did not have an adverse outcome had at least one abnormal observation during the admission. Recording of the eight criteria in each set of observations was incomplete and ranged from 87% for heart rate to 8% for airways threat. Any missing criteria were assumed to be normal. *the score cut off that maximises the sensitivity and specificity from the ROC analysis; this score was 2

Table 9: Edwards 2011 [120]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Edwards 2011[120] Country of study: UK Study design: Prospective Cohort Who was blinded: NR Setting: Hospital PEWS Tool: Melbourne Activation Criteria of the Medical Emergency Team (MET)	Patient group: All paediatric admissions to any of the paediatric wards at the University Hospital of Wales between 1 December 2005 and 30 November 2006 were eligible for inclusion Age range: 0–16 years Mean (SD): 44 months (58 months) Median age: 18 months N= 1000 Inclusion criteria: NR Exclusion criteria:	All patients As in Edwards 2009[121] The outcome measures defining an adverse outcome were PHDU admission, PICU admission and death. Data were available from the original study Edwards 2009[121] to provide a measure of all nine of the Melbourne Activation Criteria required to trigger the MET	Sensitivity	68.3% (95% CI 57.7 to 77.3)	Funding: NR Limitations: As in Edwards 2009 and: Used data that was collected to evaluate another PEWS. Only 6/9 were identical measures Some MAC indicators were more subjective than indicators based on clearly defined physiological criteria. Additional outcomes: Number of sets of adverse and no adverse observations according to MAC score. Number of patients with adverse event or not grouped by the number of abnormal sets of observation that would have transgressed the MAC. Performance of the 9 MAC; number of patients who transgressed the criteria during admission, adverse outcome vs. no adverse outcome grouped by transgression of MAC, sensitivity, specificity, PPV and NPV. ROC curve Detailed report from ROC analysis: Sensitivity 100% for a score ≥0 68.29% for a score ≥1 48.78% for a score ≥2 23.17% for a score of ≥3 15.85% for a score of ≥4 10.98% for a score of ≥5
			Specificity	83.2% (95% CI 83.1 to 83.2)	
			PPV	3.6% (95% CI 3.0 to 4.0)	
			NPV	99.7% (95% CI 99.5 to 99.8)	
			Area under ROC curve	0.79 95% CI: CI 0.73 to 0.84	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Patients admitted directly to the PICU and PHDU. Patients presenting in cardiac or respiratory arrest.				2.44% for a score of ≥6 0% for a score of >6 Specificity 0% for a score ≥0 83.15% for a score ≥1 95.63% for a score ≥2 98.71% for a score of ≥3 99.63% for a score of ≥4 99.92% for a score of ≥5 100% for a score of ≥6 100% for a score of >6 Correctly classified 0.90% for a score ≥0 83.02% for a score ≥1 95.21% for a score ≥2 98.03% for a score of ≥3 98.88% for a score of ≥4 99.12% for a score of ≥5 99.12% for a score of ≥6 99.10% for a score of >6 Notes: Identical measurements were available for six out of the nine Melbourne activation criteria in the original observational chart used for data collection. Where the indicators were different clinical data recorded was used to precisely determine the Melbourne activation criteria.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
					Any missing criteria were assumed to be normal 16 children had an adverse outcome, 13 were admitted from the ward to PHDU (4 of these subsequently transferred from PHDU to PICU) and 3 were admitted from the ward to PICU. There were no deaths. 7 of the 16 children (43.8%) would not have transgressed the MAC prior to the adverse outcomes. 469 of the 984 children (47.7%) who did not have an adverse outcome would have transgressed the MAC at least once during the admission. A score of 1 maximises sum of sensitivity and specificity demonstrating that the MAC works best, as designed, as a single parameter tool

Table 10: Haines 2006 [168]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Haines 2006[168] Country of study: UK Study design: Prospective observational	Patient group: Sample of children admitted to the hospital during the 6 month period between September 2003 and February 2004	All patients Data collection; Inpatient wards (except A&E) were visited 3 days a week during the 6 month period. Staff were asked if any patients had recently or currently received high dependency nursing care (with explanation if required), or patients were identified through the admission book, the daily work/patient	Sensitivity	99%	Funding: NR Limitations: Specificity calculated incorrectly reported as below Original tool: 63% Modified tool:66% Observations obtained from documentation, thus no knowledge of how the child was assessed
			Specificity	11.4%#	
			PPV	0.22#	
			NPV	0.97#	
			Area under ROC curve		

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Who was blinded: NR Setting: Hospital PEWS Tool: Haines et al PEWS tool	Age range: <1 yr.- >12yr N= 360 180 controls Inclusion criteria: NR Exclusion criteria: NR	allocation book and completed CICA forms*. Children admitted to PICU from the ward and those discharged to the ward were analysed, the PICU staff also informed researchers if they had reviewed any children on wards. *** All children identified had their medical and nursing notes, and observational charts examined. Physiological observations and any relevant descriptions of the childs condition were noted. As well as care received over 24 hr. period so that the outcome of that patient was tracked. If the patient triggered any of the criteria this was documented together with any abnormal respiratory, circulatory, or neurological observations and patient outcome over a 24 hr. period, midnight to midnight. Data collection ceased after a maximum of 7 days or 24 hrs. following the child no longer triggering the tool. Outcomes included: requirement for enhanced level of care (e.g. additional monitoring on the ward, HDU and transfer to PICU), respiratory /cardiac arrest or	 Mortality	95% CI: 9/360	Subjective Population was those identified to be high dependency patients ideally the tool should have been applied to the whole inpatient population. Additional outcomes: Breakdown of what wards patients were located Nature of problem for emergency call outs Cause of death and ward Distribution of age categories Highest level of care reached by each of the 360 patients Total number of patient triggers by ward Notes: Literature review conducted. *the critically ill children's audit. ***control sample: on each day of the data collection five random bed space numbers were generated by an excel programme as a control sample. The control sample aimed to match the numbers (of positive triggers) that had been previously predicated for the study population using the CICA data. If a control patient were found to trigger the tool, then they would be entered into the study and physiological data collected. If the patient did not trigger they were followed up for a further 24 hr. to ensure that they remained a control i.e. a negative trigger. #NCGC calculated

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
		emergency call and death.			The PEWS tool was modified after the initial study to give a higher level of sensitivity and specificity. The results reported are related to the modified tool Diagnostic accuracy of original tool: Sensitivity:100% Specificity:20.9% #

Table 11: Parshuram 2011[313]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Parshuram 2011[313] Country of study: Canada and UK Study design: 1:2 frequency-matched case-control Who was blinded: NR Setting: 3 Canadian	Patient group: Patients admitted during August 2004 to January 2009, over 120 hospital months in 4 participating hospitals Age range: 0 - 227 months (18.9 yrs.) Median (IQR): 12 months (3.5 to 74) Total: N= 2,074 Cases: N= 686	All patients Eligible patients were cared for on an inpatient unit other than an ICU. Case patients were defined as those who experienced a clinical deterioration event resulting in either an immediate call to the resuscitation team or an urgent ICU admission without a resuscitation team call. An urgent ICU admission was defined as an admission to an ICU in an unscheduled fashion. Control patients were defined as those who were cared for on an inpatient unit without	Sensitivity	0.64 for a score of 7 0.57 or a score of 8	Funding: This work was in part supported by funds from the Heart and Stroke Foundation and the Centre for Safety Research at the Hospital for Sick Children. CSP is a career scientist at the Ontario Ministry of Health and Long-Term Care and recipient of an Early Researcher Award from the Ontario Ministry of Research and Innovation Limitations: Neonates <3months n=190 case patients and n= 333 control patients, case patients: median score (IQR) = 7 (4 to 10), AUCROC (95% CI) = 0.83 (0.79-.0.86) Grouping of “sick” and “well” patients not reflective of the complex clinical decision making. The definition of ‘well’ did not exclude children with complex clinical presentations, who may have been at significant on-going risk for adverse
			Specificity	0.91 for a score of 7 0.94 for a score of 8	
			PPV	NR	
			NPV	NR	
			Area under ROC curve	0.87 95% CI: 0.85 to 0.89 (when data from the hour immediately before the event were included, the AUCROC curve increased to 0.88 (95% CI: 0.87 to 0.90))	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
children's hospitals and 1 British children's hospital PEWS Tool: Bedside paediatric early warning system score	Controls: N= 1,388 Inclusion criteria: ≤18 years at the time of hospital admission Exclusion criteria: ICU admission episodes following: a scheduled procedure directly from an emergency department from outside the hospital children for whom care was either undergoing or anticipated to undergo medico legal review Children with care restrictions.	resuscitation team call or urgent ICU admission during the period studied or for the following 48 hours. The children were not studied while they were in an ICU, emergency department or operating room or if they were in the care of an anaesthetist for procedural sedation in another area. Clinical data were obtained by direct abstraction from medical records using standardized data collection forms*. Consenting nurses were interviewed to provide additional clinical data that was observed but not documented, and they completed a survey to describe their retrospective global rating of the risk of a clinical deterioration event. Responses were recorded on a five-point Likert scale			outcomes, and other 'stable children' with consistently abnormal vital signs. The classification of a child as 'sick' on the basis of urgent ICU admission or a code blue call has limitations. The severity of illness in the first hours after ICU admission varies and the decision to place an immediate call to a resuscitation team is complex, subjective and multifactorial. Patterns of missing data may differ between case and control patients and thus may have influenced the calculated scores. Of the 23,288 hours studied, only 5.1% had measurements on all 7 items, indicating that incomplete data were very common The patients for whom an immediate call was made to resuscitation teams may have been systematically different from other patients Additional outcomes: Retrospective rating by frontline nurses, Median (IQR) PEWS scores in case and control patients broken down by age, disease comorbidity and hospital Number of cases with risk factors present for cardiopulmonary arrest Change in PEWS score related to time PEWS score related to number of risk factors Notes: The primary outcome was the Bedside PEWS

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
					score. *Clinical data were abstracted by trained research nurses. The clinical data and age required to calculate the Bedside PEWS score were written into case report forms and entered into a custom-made Oracle database. Entered data were electronically checked for internal consistency of dates and manually rechecked for accuracy. Inconsistencies were resolved by reviewing case report forms and medical records as required. Clinical data were grouped into 1-hour blocks for 24 hrs. ending at the event for case patients or at the end of 12 hrs. of data collection for control patients. Where there were missing data, the most recent recorded data were used. The greatest sub score for each item within each hour was identified and used to calculate the Bedside PEWS score for that hour. The maximum PEWS score was calculated for the 12 hrs ending 1 hr before the clinical deterioration event and in the six 4-hr blocks preceding ICU admission in patients urgently admitted to the ICU. Repeated measures analysis showed that the Bedside PEWS scores increased over the 24 hours before urgent ICU admission or code blue event from a baseline mean. For each hour closer to the event, the

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
					maximum. Bedside PEWS score was 0.13 units higher (P < 0.0001). And were independent of the number of risk factors for cardiac arrest in case patients.

Table 12: Parshuram 2009[314]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Parshuram 2009 Country of study: Canada Study design: Prospective case-control. Who was blinded: NR Setting: One Canadian children's hospital.	Patient group: Patients admitted to the Hospital for Sick Children (no clear date given for case-control data collection). Age range: <1 yr – >12yrs Mean age: 72 mths. N = 180 Cases: 60 Controls: 120	Eligible patients were admitted to a hospital ward at the Hospital for Sick Children. Case patients • Admitted urgently to the paediatric intensive care unit (PICU) from hospital inpatient ward following urgent consultation with the PICU, but not following a call for immediate assistance (a 'code-blue' call). • Identified by prospective daily screening of PICU admissions. • Data collected for 24 hours ending at time of urgent admission to PICU.	Sensitivity	82% at a threshold score of 8.	Funding: Work supported by a Grant in Aid Funding from the Heart and Stroke Foundation of Ontario, and the Centre for Safety Research, the Department of Critical Care Medicine, and the Research Institute at the Hospital for Sick Children. Limitations: Study was conducted in a single centre, therefore may not be generalisable to other hospitals. Neonates included: <3mnths n=32. Clinical data contained many missing values – attempted to reduce this by asking nurses to recall clinical data they observed but didn't document, and grouped data into one hour blocks for score calculation. Accuracy of data abstraction not assessed.
			Specificity	93% at a threshold score of 8.	
			PPV	NR	
			NPV	NR	
			Area under ROC curve	0.91 (95%CI: 0.86-0.97)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
PEWS tool: Bedside Paediatric Early Warning System (PEWS) 7-item score	Inclusion criteria: Less than 18yrs of age on admission, no limitations on their care. Exclusion criteria: Patients with a 'code-blue' event.	Control patients • Admitted to an inpatient ward (not the PICU, neonatal ICU, outpatient area or ED) during the period of study, and in the 48 hours following inclusion did not have a 'code-blue' call and were not urgently admitted to the PICU. • Identified by frequently matching each case patient on the basis of age group, and type of ward. • Data collected for 12 hours. Study data obtained by abstracting from study patients' medical records. Consenting nurses were interviewed to provide additional clinical data that was observed but not documented, and they completed a survey (on 93% of patients) to describe their retrospective global rating of the risk of a clinical deterioration event. Responses were recorded on a five-point Likert scale. Prospective data was collected from patients seen by Critical			Bedside PEWS tool internally validated. Validation data not completely independent of development data set. Not clear when case-control data abstracted (prospective CCRT data collected between 1 May and 31 December, 2007). Additional outcomes: Retrospective rating by frontline nurses. Change in PEWS score related to time Notes: The primary outcome was the Bedside PEWS score. Clinical data were abstracted by trained research nurses and entered into an Oracle database. Clinical data were grouped into 1-hour blocks for 24 hrs ending at PICU admission in case patients or at the end of 12 hrs of data collection for control patients. The maximum PEWS score was calculated for the 11 hrs ending 1 hr before urgent ICU admission and for 12 hours in control patients who had no clinical deterioration event.The maximum Bedside PEWS score increased with increasing proximity to ICU admission. From mean maximum scores of 5.3-6.0 more than 12 hours before PICU admission, to 9.5, 0-3 hours before PICU admission (p<0.0001).

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
		Care Response Team (CCRT; a paediatric medical emergency team).			Four 'core items' that discriminated between sick and well with AUROC of >0.75 were heart rate, respiratory rate, respiratory effort and oxygen therapy. Parshuram (2009) added candidate items capillary refill time (CRT), transcutaneous oxygen saturation (Satn), systolic blood pressure (SBP) and temperature. Competing interests: KM is on salary as the Bedside PEWS research nurse co-ordinator. CP and KM are named inventors on a patent for the Bedside PEWS owned by the Hospital for Sick Children.

Table 13: Skaletzky 2012[374]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Skaletzky 2012[374] Country of study: USA Study design: Retrospective case control trial	Patient group: Patients admitted to the medical surgical wards during a 30 month period Age range: NR	All patients PEWS tool used: Modified version of the Brighton PEWS tool – a multiple parameter trigger tool(included behaviour, cardiovascular and respiratory components with a max score of 9)	Sensitivity for a PEWS score of 2.5	62%	Funding: NR Limitations: Retrospective design No baseline data given for each group Population – neonates have been included but exact proportion not given: Reported " no statistical difference in age of cases and controls (median [IQR] 2.5[0.6-14] vs. 3[0.6-12] years) The behavioural component of the PEWS may be subject to varying interpretations
			Specificity for a PEWS score of 2.5	89%	
			PPV	NR	
			NPV	NR	
			Area under ROC curve	0.81	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Retrospective chart review Who was blinded: NR Setting: hospital inpatients Duration of follow-up: 30 months	N= 350 Cases= 100 Controls = 250 Age range: NR Inclusion criteria: NR Exclusion criteria: No exclusion criteria	Cases Patients admitted to medical-surgical wards and subsequently transferred to PICU after a physicians' request, a rapid response team evaluation or a code blue. Controls Patients who were not admitted to PICU in the same period The maximum PEWS score was calculated for each case and control		95% CI:0.75-0.86	Missing data is not discussed Additional outcomes: Length of hospital stay Maximum PEWS score Notes: Data were recorded for the cases during the 48hr period before transfer to the PICU for the controls during the initial 48hrs following hospital admission. If the cases were transferred within 48hrs following hospital admission then the data were analysed from the time of admission to the time of transfer to the PICU. PEWS score of 2.5 was required for transfer to a higher level of care

Table 14: Tucker 2009[401]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Tucker 2009[401]	Patient group: All patients	All patients Registered nurses	Sensitivity	100% for a score 0-2 90.2% for a score of ≥3	Funding: NR

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Country of study: USA Study design: Prospective cohort Who was blinded: NR Setting: 24-bed Inpatient general medical unit-regional paediatric medical centre PEWS Tool: Paediatric Early Warning Score (adapted from Monaghan (2005))	admitted to the unit over a 1 year period Age range: new born – 22 yr Mean (SD): 2.28 (3.33) N= 2979 cases Inclusion criteria: NR Exclusion criteria: NR	were trained in the use of PEWS through learning modules and case studies. PEWS became a standard component of the assessment conducted every 4 hrs on all patients admitted to the unit PEWS was documented on in patients electronic records every 4 hrs for the duration of their stay. In addition to the PEWS scoring an algorithm was developed to prescribe actions to be taken based on PEWS (minimum required action)– tiered response to PEWS *		78.4% for a score of ≥4 70.6% for a score of ≥5 54.9% for a score of ≥6 33.3% for a score of ≥7 13.7% for a score of ≥8 7.8% for a score of 9	Limitations: The use of PICU transfer as a proxy measure of clinical deterioration. It is a rare event which limits its use as an outcome measure. PPV and NPV are greatly influenced by the prevalence of the outcome variable. By using a proxy outcome variable that has a very low prevalence, the predicative values were poor. Sensitivity false negatives - 4/5 did not clinically deteriorate in PICU, these patients were included in the analysis as false negatives therefore decreasing the sensitivity. Specificity false positives- some of the patients who scored high PEWS were not transferred to PCU as actions triggered by PEWS resulted in improvements, these patients were included in the analysis as false positives, there decreasing the specificity. Additional outcomes: Range of PEWS scores, inter-rater reliability, data on PICU transfers Notes: * a score of 0-2 required no additional intervention, a 3 required that a senior nurse assess the patient, a 4 required that the bedside nurse notify the paediatric resident of the patients PEWS, a 5 required that a senior nurse, paediatric resident, and senior resident assess the patient at the bedside, and a 7 or above required that the bedside nurse activate the hospitals
			Specificity	0% for a score 0-2 74.4% for a score of ≥3 82.4% for a score of ≥4 90.8% for a score of ≥5 97.6% for a score of ≥6 99.4% for a score of ≥7 99.8% for a score of ≥8 99.9% for a score of 9	
			PPV	1.7% for a score 0-2 5.8% for a score of ≥3 7.2% for a score of ≥4 11.8% for a score of ≥5 28.9% for a score of ≥6 48.6% for a score of ≥7 58.3% for a score of ≥8 80% for a score of 9	
			NPV	100% for a score 0-2 99.8% for a score of ≥3 99.5% for a score of ≥4 99.4% for a score of ≥5 99.2% for a score of ≥6 98.8% for a score of ≥7	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
		Transfer to PICU was chosen as an objective proxy measure of clinical deterioration.		98.5% for a score of ≥8 98.4% for a score of 9	medical emergency team. The bedside nurse based on clinical judgement could contact senior clinicians and activate the medical emergency team at any point regardless of PEWS score. While the PEWS required senior clinicians to assess the patient, the decision about interventions to implement at the bedside and the decision about whether to transfer a patient to the PICU were made at the discretion of the clinicians evaluating the patient, independent of PEWS. ANALYSIS: PEWS between 0-2 were considered collectively and each score 3 and above was analysed separately. False negative: 2 out of the 5 patients were transferred to PICU due to hospital protocol for PICU transfer based on lab results- the PEWS instrument is based on bedside assessment and not lab results. 2 out of 5 patients were transferred to PICU on the clinicians' request for increased monitoring due to the potential for deterioration based on neurological status or skin sloughing. And 1 patient was had non-sustained ventricular tachycardia who was transferred for more intense therapy for his arrhythmia. 4/5 did not deteriorate while in the unit.
			Area under ROC curve	0.89 95% CI: 0.84-0.94 P=<0.001	

Table 15: Tume 2007[403]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Tume 2007[403] Country of study: UK Study design: prospective chart review by two reviewers & a descriptive analysis Who was blinded: NR Setting: Hospital PEWS Tool: the Bristol Children's tool and the Royal Children's Hospital Melbourne, Australia tool	Patient group: 1 November 2004 to 28 February 2005. All children who were admitted as an unplanned admission to the ICU or HDU from the wards during this time were included in the audit. Age range: N=65 Inclusion criteria: NR Exclusion criteria: NR	All patients The audit involved a prospective chart review undertaken over the 4-month winter period by two reviewers. A descriptive analysis of the patient data was made, and the children's physiological data were retrospectively matched against two PEW tools (the Bristol Children's tool and the Royal Children's Hospital Melbourne, Australia tool) to ascertain whether they would have 'triggered' one of these tools. A formalized data collection tool was developed to ensure consistent data collection between the two reviewers.	Sensitivity Specificity PPV NPV Area under ROC curve	Bristol PEWS: 0.86# Melbourne PEWS:0.87# NR NR NR 95% CI:	Funding: NR Limitations: Large number of missing records and observation charts. The study period (winter) will have had an effect on the type of children in hospital at this time, which may have affected the main cause of ICU admission, respiratory distress. This audit has only looked at the children who were admitted to the PICU and HDU and not all children on the ward areas at this time, so there may have been children with abnormal physiological signs who did not come to ICU or HDU. The audit was only undertaken in a single centre (specialist children's hospital) and may not be applicable to all children in hospital. Additional outcomes: None Notes: #NCGC calculated Bristol PEWS tool 88% (n=29) of ICU admissions would have triggered the tool. Of these 25% (n=8) had multiple triggers and 25% (n=8) would have been triggered by tachypnoea alone. PHDU admissions 83% (n=27) would have triggered the

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
					tool. Of these 33% (n=11) had multiple triggers/trigger combinations and 10% (n=3) would have been triggered by tachypnoea, seizures and condition worrying. 16% did not trigger Melbourne PEW tool 88% (n=29) of ICU admissions would have triggered the tool. Of these 24% (n=8) had multiple triggers and 27% (n=9) would have been triggered by tachypnoea alone. 89% (n=28) of PHDU admissions would have triggered the tool. Of these 28% (n=9) had multiple triggers/trigger combinations and 28% (n=9) would have been triggered by tachypnoea alone and 12% (n=4) on seizures. 11% (n=4)did not trigger

G.2.2 Preventing CI-AKI

G.2.2.1 Sodium bicarbonate vs sodium chloride 0.9%

Table 16: Adolph 2008[6]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Adolph 2008[6] Country of study: Germany Study design: RCT – computer generated randomisation schedule. Hydrating solution uniformly labelled by pharmacist not involved in study. Who was blinded: Participants, healthcare staff and outcome assessors	Patient group: Patients with stable renal insufficiency undergoing elective diagnostic or interventional angiography (March 2005 – February 2006). Inclusion criteria: Two sCr levels >106µmol/l within 12 weeks of angiography that differed by <5% >18 years old Exclusion criteria: Acute MI requiring primary or rescue coronary intervention Allergy to trial medication Exposure to contrast medium in last 7 days Thyroid dysfunction Pregnancy Uncontrolled hypertension Life-limiting concomitant disease Pulmonary oedema Chronic RRT Administration of dopamine, mannitol, fenoldopam, NAC	Group 1 (Intervention) Sodium bicarbonate (154mEq/L in 5% dextrose) Route: iv pre contrast: 2ml/kg/h for 2h post contrast: 1ml/kg/h for 6h Group 2 (Comparison) Sodium chloride 0.9% (154mEq/L in 5% dextrose) Route: iv pre contrast: 2ml/kg/h for 2h post contrast: 1ml/kg/h for 6h Contrast Iso-osmolar Name: iodixanol	Mortality	NR	Funding: None reported Limitations: Underpowered relative to observed CI-AKI rate in the control group (assumed 13.6% in power calculation based on Merten et al 2004[279] which used low osmolar contrast and higher mean baseline sCr) Additional outcomes: sCr at 24 and 48h serum cystatin C plasma viscosity urinary alanine aminopeptidase and N-acetyl-β-D-glucosaminidase and α1microglobulin
			CI-AKI at 48 hours (increase in sCr ≥25% or 44µmol/l)	Group1: 3/71 (4.2%) Group 2: 2/74 (2.7%) Relative risk [95% CI]: NR p value: 0.614	
			CI-AKI at 72 hours	NR	
			Number of patients needing RRT	Group1: 0/71 Group 2: 0/74	
			Number of patients achieving dialysis independence	NR All patients sCr had returned to baseline within 12-14d of angiography	
			Length of hospital stay (days, mean ± SD)	CI-AKI: 5±2 No CI-AKI: 3±1	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Setting: Single centre, cardiology department Duration of follow-up: 48h, patients with primary endpoint had sCr rechecked between days 10 and 14 Definition of CI-AKI used:increase in sCr ≥25% or 44µmol/l within 48h of exposure to contrast medium	All patients N: 145/ 148 Age (mean±SD): 72 ± 6.7 Baseline serum creatinine (µmol/l) (mean±SD): 138 ± 38.9 Drop outs: 3 Group 1 N: 71/ 72 Age (mean±SD): 70.1 ± 8.4 Drop outs: 1 (lost to follow up) Baseline characteristics: M:F: 53 (74.6%); 18 (25.4%) Baseline serum creatinine* (µmol/l) (mean±SD): 136.1 ± 45.1 CKD: 71/71 (100%) Diabetes: 26/71 (36.6%) Hypertension: 59/71 (83.1%) ACEI: NR NSAIDs: NR Group 2 N: 74/76 Age (mean±SD): 72.7 ± 6.6 Drop outs: 2 (1 CABG, 1 lost to follow up) Baseline characteristics: M:F: 60 (81.1%) : 14 (18.9%) Baseline serum creatinine* (µmol/l) (mean±SD): 138.8 ± 31.8	Dose(ml) (mean ± SD): Group 1: 141 ± 50 Group 2: 138 ± 52 p=0.532 Both groups: Diuretics stopped on day of coronary angiography Blood pressure and body weight recorded before starting iv fluid			Notes: *calculated from mg/dl by NCGC (x88.4)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	CKD: 74/74 (100%) Diabetes: 23/74 (28.3%) Hypertension: 65/74 (87.8%) ACEI: NR NSAIDs: NR				

1 **Table 17: Brar 2008[58]**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Brar 2008[58] (longterm outcomes Brar 2010[59]) Country of study: USA Study design: RCT – "randomly assigned in a 1:1 ratio" stratified by "diabetes status and NAC use". Four computer generated concealed randomisatio	Patient group: Patients with moderate-severe stable CKD undergoing coronary angiography (Jan 2006-Jan 2007) Inclusion criteria: ≥18 years old eGFR ≤60 ml/min/1.73m2 AND one or more of: diabetes mellitus history of congestive heart failure hypertension ≥75 years old Exclusion criteria: Sodium bicarbonate infusion prior to randomisation Emergency cardiac catheterisation Intra-aortic balloon counterpulsation RRT	Group 1 (Intervention) Sodium bicarbonate (150mEq/L in 5% dextrose) Route: iv pre contrast: 3ml/kg/h for 1h during and post contrast: 1.5ml/kg/h during and for 4h after contrast Group 2 (Comparison) Sodium chloride 0.9% Route: iv pre contrast: 3ml/kg/h for 1h during and post contrast: 1.5ml/kg/h during and for 4h after contrast	Mortality (at 30 days)	Group1: 3/175 (1.7%) Group 2: 3/178 (1.7%) Relative risk [95% CI]: NR p value: Not sig	Funding: Kaiser Permanente, two people (non-administrative) from Kaiser Permanente helped with manuscript preparation and data collection. 7 of the 9 authors affiliated to Kaiser Permanente (although not the 2 authors involved in the analyses). Limitations: NAC was given at referring physicians discretion (600mg bd for 2 days before procedure) (~46% of patients had NAC, p=0.82 between
			Mortality (30d - 6 months)	Group1: 1/175 (0.6%) Group 2: 4/178 (2.3%) Relative risk [95% CI]: NR p value: NR	
			CI-AKI at 48 hours	NR	
			CI-AKI at 96 hours (≥25% decrease in eGFR)	Group1: 21/158 (13.3%) Group 2: 24/165 (14.6%) Absolute difference [95% CI]: 1.3 [-6.3-8.8] p value: 0.75	
			CI-AKI at 96 hours (increase in sCr ≥25% or 44*µmol/l)	Group1: 26/158 (16.5%) Group 2: 30/165 (18.2%) Absolute difference [95% CI]: 1.7 [-6.5–10.0] p value: 0.78	
			CI-AKI at 96h (severe	Group1: 2/10 (20%)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
n schedules each using permuted blocks of 4 with sealed opaque envelopes to allocate the sequential randomisation number. Who was blinded: Patients. Physicians performing procedure not blinded but laboratory personnel were. Investigators looking at long term outcomes were blinded. Setting: Single centre	Exposure to radiographic contrast media within preceding 2 days Allergy to contrast media Acutely decompensated heart failure Severe cardiac valvular abnormality Single functioning kidney History of renal or heart transplant Change in eGFR ≥7.5% per day or cumulative change of ≥15% over the prior 2 or more days All patients N: 353/392 eligible (90.1%) Age (median[IQR]): 71 [65-76] Drop outs: 0 lost to follow up Group 1 N: 175 Age (median[IQR]): 71 [65-75] Drop outs: 1 did not undergo angiography. 16 did not have eGFR data. Baseline characteristics: M:F: 109(62.3%): 66(37.7%) Baseline serum creatinine (µmol/l) (mean±SD): 131.7 ± 31.8 Baseline eGFR (ml/min per 1.73m2) (mean±SD): 47.7 ± 9.8 CKD: 100% Diabetes: 76/175 (43.4%)	Contrast low osmolar Name: ioxilan Dose (ml) (median[IQR]): Group 1: 126 [80-214] Group2: 137 [89-247] P=0.15 Both groups: For patients >100kg bolus and infusion rates limited to those used for someone weighing 100kg.	CKD subgroup – baseline eGFR ≤30ml/min)	Group 2: 4/11 (36.4%) p value: 0.64 (Fisher's exact test)	groups) Physicians performing procedure not blinded Additional outcomes: 4 of the patients receiving RRT had CI-AKI by the protocol definition. All 4 died by 6 months. 1/11 (9.1%) in Group 1 and 3/9 (33.3%) in Group2 developed CI-AKI after repeat PCI or CABG before 48h. Unclear if same fluid regime given for repeat procedure. Renal function at 2-8weeks in those with nephropathy showed persistent renal impairment in 18% Group1 and 20% Group 2 (p=0.99) BRAR2010 gives Kaplan-Meier survival curves for "Death or Dialysis" from 0-720 days. At 720 days rate is 7.6% in Group 1 and 10.3% in Group 2 (log-rank P=0.38). Data
			CIAKI at 96h (moderate – severe CKD and DM subgroup) (increase in sCr ≥25% or 44*µmol/l)	Group1: 16/68 (23.5%) Group 2: 16/77 (20.8%) Absolute difference [95% CI]: -3.6 [-18.1-10.9] p value: 0.69	
			CI-AKI at 96h (Contrast volume >150ml subgroup) (increase in sCr ≥25% or 44*µmol/l)	Group1: 10/68 (14.7%) Group 2: 15/76 (19.7%) Absolute difference [95% CI]: 5.0 [-7.3-17.3] p value: 0.51	
			Number of patients needing RRT (in 6 months)	Group1: 2/175 Group 2: 4/178 Relative risk [95% CI]: p value: (If no p-value: Sig/Not sig/NR)	
			Number of patients achieving dialysis independence	4 of the patients receiving RRT had CI-AKI by the protocol definition. All 4 died by 6 months.	
			Length of hospital stay	NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Duration of follow-up: 6 months[58] and 2 years[59] Definition of CI-AKI used: ≥25% decrease in eGFR on days 1-4 after contrast exposure	Hypertension: NR ACEI: 80/175 (45.7%) NSAIDs: NR Group 2 N: 178 Age (median[IQR]): 71 [65-76] Drop outs: 2 did not undergo angiography. 11 did not have eGFR data. Baseline characteristics: M:F: 116(65.2%): 62(34.8%) Baseline serum creatinine (µmol/l) (mean±SD): 131.7 ± 33.6 Baseline eGFR (ml/min per 1.73m2) (mean±SD): 48.3 ± 9.4 CKD: 100% Diabetes: 81/178 (45.5%) Hypertension: NR ACEI: 84/178 (47.2%) NSAIDs: NR				available for 98% of subjects. Notes: *calculated from mg/dl by NCGC (x88.4) Patients with repeat procedure were included in analysis (authors found no difference on sensitivity analysis).

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2 **Table 18: Merten 2004[279]**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Merten 2004[279]	Patient group: Patients with stable CKD undergoing diagnostic or interventional procedures	Group 1 (Intervention) Sodium bicarbonate (154mEq/L in 5%	Mortality CI-AKI at 48 hours (increase in sCr ≥25%)	NR Group1: 1/60 (1.7%) Group 2: 8/59 (13.6%)	Funding: Carolinas medical centre who supplied

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Country of study: USA Study design: RCT – computer generated randomisation schedule Who was blinded: Patients, laboratory personnel determining primary end point Setting: Single centre Duration of follow-up: 48h Definition of CI-AKI used: increase in sCr ≥25% within 48h	requiring radiocontrast (cardiac catheterisation, CT, diagnostic or therapeutic arteriography or transjugular intrahepatic portal systemic shunt placement). Inclusion criteria: ≥18 years old Stable sCr ≥97.2µmol/l Exclusion criteria: sCr >707µmol/l change in sCr ≥44.2µmol/l during the previous 24h pre-existing RRT multiople myeloma pulmonary oedema uncontrolled hypertension emergency catheterisation exposure to contrast within 2 days of the study allergy to radiocontrast pregnancy administration of dopamine, mannitol, fenoldapam or NAC during the intended time of the study All patients N: 119/137 randomised Age (mean±SD): Drop outs: 5 each arm excluded as no follow up laboratory tests, 4	dextrose and H2O) Route: iv Timing pre contrast: 3ml/kg/h for 1h Timing post contrast: 1ml/kg/h during contrast and for 6h post Group 2 (Comparison) Sodium chloride 0.9% (154mEq/L in 5% dextrose and H2O) Route: iv Timing pre contrast: 3ml/kg/h for 1h Timing post contrast: 1ml/kg/h during contrast and for 6h post Contrast low osmolar Name: iopamidol Dose(ml) (mean ± SD): Group 1: 130 ± 72 Group 2: 134 ± 63 p=0.75		p value: 0.02	contrast and fluids. No funding from manufacturers or suppliers. Limitations: Stopped early due to efficacy of sodium bicarbonate (not prespecified interim analysis). Safety monitor, who was not an investigator and was blinded to interim results, asked for interim analysis. Continued with a registry of patients after stopping trial. Additional outcomes: Change in MAP after initial bolus Urine pH after initial bolus Change in serum bicarbonate on day 1 Change in serum potassium on day 1 Change in serum Creatinine (highest level day 1or 2 used) Change in estimated
			CI-AKI at 72 hours	NR	
			Number of patients needing RRT	Group1: 0/60 Group 2: 0/59	
			Length of hospital stay	"All individuals with CI-AKIexperienced prolonged hospitalisation…". No other information reported.	
			Adverse events	No patients developed clinical heart failure or respiratory distress. One patient in the bicarbonate group had a blood pressure increase >30mmHG with the initial bolus, this responded to diuretics and patient did not develop CI-AKI or any other adverse events.	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
of exposure to contrast medium	each arm excluded for protocol violations Group 1 N: 60 Age (mean±SD): 66.7 ± 12 (range 37-88) Drop outs: 0 Baseline characteristics: M:F: 44 (73.3%) : 15 (26.7%) Baseline serum creatinine (µmol/l*) (mean±SD): 167.1 ± 61.0 (range 106.1- 459.7) Baseline GFR (ml/min per 1.73m2) (mean±SD): 41 ± 13 (range 12-80) CKD: 100% Diabetes: 30/60 (50%) Hypertension: NR ACEI: NR NSAIDs: NR Group 2 N: 59 Age (mean±SD): 69.2 ± 12 (range 32-87) Drop outs: 0 Baseline characteristics: M:F: 45 (76.3%) : 14 (23.7%) Baseline serum creatinine (µmol/l) (mean±SD): 151.2 ± 37.1 (range 97.2- 327.1)	Both groups: For patients >110kg fluid was limited to that of a patient weighing 100kg Diuretics withheld on day of contrast			GFR Notes: All cases of CI-AKI in patients undergoing cardiac catheterisation ?underpowered – calculated 260 patients required to detect 10% less CI-AKI in intervention group with power of 80% (α=0.05) *calculated from mg/dl by NCGC (x88.4)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Baseline GFR (ml/min per 1.73m2) (mean±SD): 45 ± 14 (range 13-88) CKD: 100% Diabetes: 45/59 (76.3%) Hypertension: NR ACEI: NR NSAIDs: NR				

G.2.2.2 Sodium chloride 0.9% vs sodium chloride 0.45%

Table 19: Mueller 2002[292]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Mueller 2002[292] Country of study: Germany and Switzerland Study design: RCT – " weekly randomly assigned in equal proportions with the use of a prespecified	Patient group: Patients scheduled for elective or emergency† coronary angioplasty Inclusion criteria: Patients scheduled for elective or emergency† coronary angioplasty Exclusion criteria: ESRD with regular haemodialysis Cardiogenic shock Mechanical ventilation All patients N: 1383/1620 randomised (85.4%)	Group 1 (Intervention) Sodium chloride 0.9% (154mmol/L of sodium) Dose: 1ml/kg/h Route: iv Timing pre contrast (elective): started at 8am on day of procedure Timing post contrast: until 8am the next morning Mean total fluid: 2022ml Group 2 (Comparison) Sodium chloride 0.45% (in 5% glucose, 77mmol/L of sodium)	Mortality (30 days, only for subgroup with coronary stent implantation)	Group1: 1/265 Group 2: 3/265 Relative risk [95% CI]: p value: (If no p-value: Sig/Not sig/NR)	Funding: None reported Limitations: Hydration protocol different for emergency and elective procedures, and within emergency group. No data given for CI-AKI in acute coronary syndrome subgroup of emergency patients. 15% not included in primary end-point analysis
			CI-AKI at 48 hours (increase in sCr ≥44µmol/l)	Group1: 5/685(0.7%) Group 2: 14/698 (2.0%) Relative risk [95% CI]: NR p value: 0.04	
			CI-AKI at 48 hours – Emergency† subgroup (increase in sCr ≥44µmol/l)	Group1: 3/393(0.8%) Group 2: 6/404 (1.5%) Relative risk [95% CI]: NR p value: 0.34	
			CI-AKI at 48 hours – Elective subgroup (increase in sCr ≥44µmol/l)	Group1: 2/292 (0.7%) Group 2: 8/294 (2.7%) Relative risk [95% CI]: NR p value: 0.06	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
randomisation sequence" Who was blinded: Open label study Setting: 2 centres, inpatient and outpatient Duration of follow-up: Inhospital, 30 days for coronary stent subgroup Definition of CI-AKI used: increase in sCr ≥44µmol/l within 48h of contrast being given.	Age (mean): 64 Drop outs: 237/1620 (14.6%) Group 1 N: 685 /809 (84.7%) Age (mean): 64 Drop outs: 124 (78 repeat catheterisation, 46 incomplete data) Baseline characteristics: M:F: 507 (74.0%): 178 (26.0%) Baseline serum creatinine (µmol/l) (mean[95% CI]): 81.3 [79.6-83.1] CKD: 138/685 (20.1%) Diabetes: 107/685 (15.6%) Hypertension: 445/685 (65.0%) ACEI: NR NSAIDs: NR Acute MI: 54/685 (7.9%) Emergency† procedure: 393/685 (57.4%) Group 2 N: 698 /811 (86.1%) Age (mean): 64 Drop outs: 113 (59 repeat catheterisation, 53 incomplete data, 1 bypass grafting) Baseline characteristics: M:F: 522 (74.8%): 176 (25.2%) Baseline serum creatinine (µmol/l)	Dose: 1ml/kg/h Route: iv Timing pre contrast (elective): started at 8am on day of procedure Timing post contrast: until 8am the next morning Mean total fluid: 2028ml Contrast low osmolar Name: iopromide and iomeprol Dose (ml) (mean ± sd): Group 1: 232 ± 6 Group 2: 236 ± 7 Both groups: NAC not used "(Elective) Patients were encouraged to drink plenty of fluids (tea and mineral water)" No protocol-defined prehydration for patients undergoing emergency procedures. The assigned infusion was	CI-AKI at 72 hours	NR	No blinding Additional outcomes: Risk factor analysis: OR for female = 3.9 OR for an increase in baseline Cr of 88µmol/l = 6.6 Baseline Cr >141µmol/l incidence of CI-AKI >10% Age, DM and contrast vol were not found to be independent risk factors Notes: predefined subgroups: elective procedures, women, DM, pre-existing renal dysfunction and >250ml contrast † Definition of: "Emergency" – patients with acute coronary syndrome and selected patients with stable coronary disease who had coronary angioplasty
			Number of patients needing RRT	Group1: 1/685 Group 2: 1/698 Relative risk [95% CI]: NR p value: 0.99	
			Number of patients achieving dialysis independence	NR	
			Length of hospital stay (mean in days [95% CI])	Group1: 4.8 [4.5-5.1] (N=685) SD*: 4.00 Group 2: 4.8 [4.6-5.1] (N=698) SD*: 3.37 Relative risk [95% CI]: NR p value: 0.87	
			Adverse events	Major adverse cardiac events (for stent subgroup) and peripheral vascular complications were reported. No significant difference between groups.	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	(mean[95% CI]): 82.2 [79.6-84.0] CKD: 148/698 (21.2%) Diabetes: 110/698 (15.8%) Hypertension: 425/698 (60.9%) ACEI: NR NSAIDs: NR Acute MI: 60/698 (8.6%) Emergency† procedure: 404/698 (57.9%)	started immediately on arrival in the catheter laboratory. The subgroup with acute coronary syndromes (about 40% of emergency group) received "500ml crystalloidal infusion …as their standard medical care before admission to hospital". (Ringers solution given, sodium concentration 147 mmol/L). The infusion rate during angioplasty was adjusted by operator as required. No changes in medication were allowed during the study			immediately post diagnostic procedure. "Elective" - Coronary angioplasty scheduled for 2 days post diagnostic procedure. *NCGC calculated from reported mean and 95% confidence intervals

G.2.2.3 Sodium chloride 0.9% vs. oral fluids

Table 20: Maioli 2011[260]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Maioli 2011[260]	Patient group: From July 2004 to December	Group 1	In hospital	Group1: 3/150 (2.0%)	Funding: None

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Country of study: Italy Study design: RCT - Computer-generated, open label randomization block (block size not reported) Who was blinded: "Open label", no further detail reported Setting: single centre Duration of follow-up: 72 hours Definition of CI-AKI used: increase in sCr ≥25% or 44µmol/l within 72hrs of exposure to contrast medium	2008, all consecutive patients with STEMI who were candidates for primary PCI Inclusion criteria: Adults with STEMI undergoing primary PCI Exclusion criteria: contrast medium administration within the previous 10 days, end-stage renal failure requiring dialysis, refusal to give informed consent All patients N: 461 Drop outs: 0 Group 1 N: 150/154 Age (mean±SD): 65±13 Age ≥ 75: 38 (25.3%) Drop outs: 4 – 3 no PCI, 1 emergency CABG Baseline characteristics: M:F: 115:35 Baseline serum creatinine (µmol/l) (mean±SD): 96±27 Baseline serum creatinine >133µmol/l: 13 (8.6%) Diabetes: 31 (20.7%) Hypertension: 66 (44.0%) ACEI or ARB: NR NSAIDs: NR Group 2	Sodium bicarbonate (154 mEq/L in dextrose and water) Route: iv Dose: bolus of 3 mL/kg of sodium bicarbonate solution in 1 hour, starting in the emergency room, followed by infusion of 1 mL/kg per hour for 12 hours after PCI Mean total volume (ml): 1157±228 Group 2 Sodium chloride 0.9% Route: iv Dose: 1ml/kg/h for 12hrs after PCI Mean total hydration volume (ml): 885±157 Group 3 No hydration (unclear if no iv hydration only or no hydration at all) Contrast Non-ionic, dimeric iso-osmolar Name: Iodixanol Dose(ml) (mean ± SD): All = 165.6±89.3 Group 1 = 208±92 Group 2 = 216±101	mortality	Group 2: 5/150 (3.3%) Group 3: 8/150 (5.3%) Relative risk [95% CI]: NR p value: 0.12	reported Limitations: Randomization occurred after "an open label assignment" Details of blinding not reported Additional outcomes: 3rd arm n=150 received saline for 12hr after PCI Reduction in eGFR>25% in 72hrs Notes: sCr converted from mg/dl to µmol/l by NCGC (x88.4)
			CI-AKI at 48 hours	NR	
			CI-AKI at 72 hours (increase in sCr ≥25% or 44µmol/l)	Group1: 18/150 (12%) Group 2: 34/150 (22.7%) Group 3: 41/150 (27.3%) Relative risk [95% CI]: NR p value: 0.001 (group 1 vs. group 3) 0.015 (group 1 vs. group 2)	
			Number of patients needing RRT (hemofiltration)	Group1: 2/150 (1.3%) Group 2: 1/150 (0.7%) Group 3: 1/150 (0.7%) Relative risk [95% CI]: NR p value: 0.54	
			Length of hospital stay (days, mean ± SD)	NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 150/154 Age (mean±SD): 66±12 Age ≥ 75: 36 (24.0%) Drop outs: 4 – no PCI Baseline characteristics: M:F: 109:41 Baseline serum creatinine (µmol/l) (mean±SD): 97±35 Baseline serum creatinine >133µmol/l: 14 (9.3%) Diabetes: 31 (20.7%) Hypertension: 71 (47.3%) ACEI or ARB: NR NSAIDs: NR Group 3 N: 150/153 Age (mean±SD): 64±12 Age ≥ 75: 29 (19.3%) Drop outs: 3 – 2 no PCI, 1 emergency CABG Baseline characteristics: M:F: 110:40 Baseline serum creatinine (µmol/l) (mean±SD): 95±27 Baseline serum creatinine >133 µmol/l: 11 (7.3%) Diabetes: 34 (22.7%) Hypertension: 66 (44.0%) ACEI or ARB: NR NSAIDs: NR	Group 3 = 224±94 p= 0.32 All groups: LVEF was measured before coronary procedures. Hydration rate was reduced to 0.5 ml/kg/h in patients with left ventricular ejection fraction (EF) ≤40% or New York Heart Association class III–IV in groups 1 and 2.			

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2 **Table 21: Wrobel 2010[428]**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Wrobel 2010[428] Country of study: Poland Study design: RCT Who was blinded: No one Setting: Single centre, cardiology department Duration of follow-up: 72h Definition of CI-AKI used:	Patient group: Diabetic patients undergoing coronary angiography and/or angioplasty. Inclusion criteria: Diabetes mellitus Cardiovascular disease Undergoing coronary angiography and/or angioplasty Exclusion criteria: Contraindication for invasive procedure Pregnancy or breastfeeding Symptoms and signs of infection Antibiotic treatment Participation in other studies in the preceding 30d History of hypersensitivity to contrast agents Comorbid cancer Acute renal failure of alternative aetiology All patients N: 102 Age (mean): 65.5	Group 1 (Intervention) Sodium chloride 0.9% Dose: 1ml/kg/h Route: iv Timing pre contrast: 6h Timing post contrast: 12h Fluid volume (ml) (mean ± SD): 1597.7 ± 226.0 Group 2 (Comparison) Oral mineral water or boiled water Dose: 1ml/kg/h Route: po Timing pre contrast: 6-12h Timing post contrast: 12h Fluid volume (ml) (mean ± SD): 1662.7 ± 338.7 P= Not significant for fluid volume between groups Contrast low osmolar Name: ioversol	Mortality	NR	Funding: None reported Limitations: Method used to randomise unclear Allocation concealment unclear No blinding Additional outcomes: Urea, uric acid, sodium and potassium at 72h post procedure Notes: *calculated from mg/dl by NCGC (x88.4)
			CI-AKI at 48 hours	NR	
			CI-AKI at 72 hours (increase in sCr ≥25% or 44µmol/l)	Group1: 3/52 (5.7%) Group 2: 2/50 (4%) Relative risk [95% CI]: NR p value: Not sig	
			Number of patients needing RRT	Group1: 0/52 Group 2: 0/50	
			Length of hospital stay	NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
increase in sCr ≥25% or 44µmol/l within 72h of exposure to contrast medium	M:F: 58 (56.9%):44(43.1%) Drop outs: 0 Group 1 N: 52 Age (mean±SD): 67.3 ± 7.76 Drop outs: 0 Baseline characteristics: M:F: only reported for all patients Baseline serum creatinine (µmol/l*) (mean±SD): 109.2 ±39.4 Baseline CrCl (ml/min) (mean±SD): 70.3 ± 21.2 CKD: NR (note mean sCr quite low) Diabetes: 100% Hypertension: NR ACEI: NR NSAIDs: NR Group 2 N: 50 Age (mean±SD): 63.7 ± 7.82 Drop outs: 0 Baseline characteristics: M:F: only reported for all patients Baseline serum creatinine (µmol/l*) (mean±SD): 103.6 ± 34.2 Baseline CrCl (ml/min) (mean±SD): 78.7 ± 19.9 CKD: NR (note mean sCr quite low) Diabetes: 100%	Dose(ml) (mean ± SD): Group 1: 101.1 ± 36.7 Group 2: 110.4 ± 45.3 P= Not Sig Both groups: Volume of fluid halved in patients with heart failure NAC not given			

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Hypertension: NR ACEI: NR NSAIDs: NR				

G.2.2.4 Sodium chloride 0.45% vs no hydration and NAC + sodium chloride 0.45% vs NAC + no hydration (evidence from same study)

Table 22: Chen 2008[87]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Chen 2008[87] Country of study: China Study design: RCT – pre-randomisation stratification into normal and abnormal sCr groups. Who was blinded:	Patient group: Patients with sCr <132.6µmol/l* and ≥132.6µmol/l* scheduled for elective percutaneous coronary intervention (PCI) Inclusion criteria: Myocardial ischemia (angina or positive exercise treadmill) Subgroups for normal and "abnormal" baseline renal function (see above) Exclusion criteria: Coronary anatomy not suitable for PCI Emergency CABG required Chronic peritoneal or haemodialysis	Group 1 (sCr ≥132.6µmol/l*) NAC Dose: 1200mg Route: po Timing pre contrast: 12h Timing post contrast: immediately post contrast Sodium chloride 0.45% Dose: 1ml/kg/h Route: iv Timing pre contrast: 12h Timing post contrast: 6h Group 2 (sCr ≥132.6µmol/l*) NAC	Mortality at 6 months	Groups 1+ 2: 13/276 Groups 3+ 4: 1/660 p value: NR	Funding: None reported Limitations: Method of randomisation used not described ?adequate allocation concealment ?selection bias - baseline characteristics only for "normal group" and "abnormal group" and for those who developed CI-AKI vs those without No blinding Protocol for "Non-hydaration" not fully described (unclear if
			CI-AKI at 48 hours (Increase in sCr >44.2 µmol/l*)	Group1: NR Group 2: NR p value:: Sig	
			CI-AKI at 48 hours (Increase in sCr >44.2 µmol/l*)	Group3: 22†/330 (6.67%) Group 4: 23†/330(6.97%) p value: Not sig	
			CI-AKI at 72 hours	NR	
			Number of patients needing RRT (haemofiltration performed if oligoanuria >48h despite administration of furosemide >1g iv per 24h)	Groups 1+ 2: 26/276 Groups 3+ 4: 0/660 p value: NR	
			Length of hospital stay	NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
No one Setting: 3 centres in China Duration of follow-up: 6 months Definition of CI-AKI used: Increase in sCr >44.2 µmol/l* at 48h after PCI	Acute MI on admission All patients N: 936 Drop outs: None reported Group 1 + Group 2 N: 276 Age (mean±SD): 63±11 Drop outs: None reported Baseline characteristics: M:F: 235† (85%): 41(15%) Baseline serum creatinine (µmol/l) (mean±SD): 221 ± 8.8 (for patients in this group significantly higher mean baseline sCr in those who got CI-AKI vs those without) CKD: 100% Diabetes:22% Hypertension: 73% ACEI: NR NSAIDs: NR Group 3 + Group 4 N: 330 +330 =660 Age (mean±SD): Drop outs: None reported Baseline characteristics: M:F: 541† (82%): 119(18%) Baseline serum creatinine (µmol/l) (mean±SD): 115 ± 26.5	Dose: 1200mg Route: po Timing pre contrast: 12h Timing post contrast: immediately post contrast "Non-hydration" – protocol for this not fully described (unclear if oral fluids allowed and if so how much) Group 3 (sCr <132.6µmol/l*) Sodium chloride 0.45% Dose: 1ml/kg/h Route: iv Timing pre contrast: 12h Timing post contrast: 6h Group 4 (sCr <132.6µmol/l*) "Non-hydaration" – see above Contrast Isosmolar Name: Not reported Dose(ml) (mean ± SD): Group 1+2: 298 ± 125			oral fluids allowed and if so how much) Additional outcomes: Clinical driven revascularisation (PCI or CABG) at 6 months Major bleeding requiring ≥2 units of blood Notes: Authors contacted for more information, no response received therefore only able to data for group 3 and 4 in the review. *calculated from mg/dl by NCGC (x88.4) †Calculated from percentage given in paper

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	CKD: 0% Diabetes:8% Hypertension: 59% ACEI: NR NSAIDs: NR	Group 3+4: 285 ± 107 Note: Significantly higher volumes given in patients who got CI-AKI vs those without Both groups: In patients with left ventricular dysfunction or overt heart failure fluid rate was reduced to 0.8ml/kg/h in the iv hydration groups. Use of β blockers, ACE inhibitors and diuretics was at cardiologists discretion.			

G.2.2.5 Sodium bicarbonate versus no (intravenous) hydration

See Table 11: Maioli 2011[260] located in G2.1.3 Sodium chloride 0.9% vs. oral fluids

G.2.2.6 Sodium chloride 0.9% + sodium bicarbonate vs sodium chloride 0.9%

Table 23: Motohiro 2011 [291]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Motohiro 2011 [291]	Patient group: Patients undergoing coronary	Group 1 (Intervention) Sodium chloride 0.9% +	Mortality CI-AKI at 48 hours	NR Group1: 2/78 (2.6%)	Funding: NR

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Country of study: Japan Study design: RCT Who was blinded: NR Setting: 2 Japanese hospitals Duration of follow-up: 1 month Definition of CI-AKI used: Absolute increase in the sCr concentration of ≥44.2µmol/l * or as a 25% increase from the baseline	angiography or intervention from November 2004 –May 2007 Inclusion criteria: ≥20 years old eGRF <60ml/min/1.73m² Exclusion criteria: sCr > 353.6 µmol/L* changes in sCr levels of ≥0.5mg/dl during the previous 24 hrs pre-existing dialysis pulmonary oedema uncontrolled hypertension (treated systolic blood pressure >160 mmHg or diastolic blood pressure > 100mmHg) emergency catheterization exposure to radiographic contrast within in the previous 2 days allergy to contrast no patients received dopamine, mannitol, fenoldopam or NAC during intended study period All patients N: 158 Age (mean±SD): NR Drop outs: 3	sodium bicarbonate Sodium chloride 0.90% Dose: 1 mL/kg/hr Route: IV Timing pre contrast: 12hrs Timing post contrast: 12hrs Sodium bicarbonate Dose: 154ml** 1ml/kg/hr Route: IV Timing pre contrast: 3 hrs Timing post contrast: 6hrs Group 2 (Comparison) Sodium chloride 0.9% Sodium chloride 0.90% Dose: 1 mL/kg/hr Route: IV Timing pre contrast: 12hrs Timing post contrast: 12hrs Contrast nonionic, low osmolar Name: Iopamidol	(Absolute increase in the sCr concentration of ≥44.2µmol/l* or as a 25% increase from the baseline value at 48 hrs after contrast exposure)	Group 2: 10/77 (13%) Relative risk [95% CI]: 0.176 [0.037 to 0.83] p value: 0.012	Limitations: Blinding not reported Allocation concealment unclear Additional outcomes: Mean sCr levels at day 1,2 and 1 month Mean eGFR at day 1,2 and 1 month Proportion of patients with CI-AKI requiring dialysis Notes: * Calculated from mg/dL by NCGC (x88.4) **1000 mEq/L to 846ml of 5% dextrose in water Indications for coronary angiography or intervention for each patient were left to the discretion of each clinical cardiologist Patients randomised to groups based on random numbers generated by computer Intention to treat analysis 10/12 patient with CI-AKI had
			CI-AKI at 72 hours	NR	
			Number of patients needing RRT	NR	
			Number of patients achieving dialysis independence	NR	
			Length of hospital stay	NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
value at 48 hrs after contrast exposure	Group 1 N: 79 Age (mean±SD): 71±9 Drop outs: 1 Baseline characteristics: M:F: 59 (76%)/20 (25.3%) Baseline serum creatinine (µmol/l) (mean±SD): 136.136±38.012* CKD: NR Diabetes: 44(56%) Hypertension: 67 (86%) ACEI: 62(79%) NSAIDs: NR Group 2 N: 79 Age (mean±SD): 74±7 Drop outs: 2 Baseline characteristics: M:F: 49(64%)/28 (36%) Baseline serum creatinine (µmol/l) (mean±SD): 137.02±38.896* CKD: NR Diabetes: 49(63%) Hypertension: 64 (83%) ACEI: 69(90%) NSAIDs: NR	Dose: NR Volume of contrast administered ml (mean±SD): Group 1: 140±50 Group2: 130±40 P value: NR Both groups: Diuretics stopped 24hrs before contrast administration and only restarted when renal function had been shown to be stable after procedure			diabetes Mean contrast dose in patients with CI-AKI was higher than that administered to those who did not develop CI-AKI (171±55 VS 132±45 P= <0.01)

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Table 24: Tamura 2009[388]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Tamura 2009[388] Country of study: Japan Study design: RCT Who was blinded: Single blinded (patients) Setting: 2 Japanese hospitals Duration of follow-up: 7 days Definition of CI-AKI used: increase in the sCr concentration of >44.2µmol/l	Patient group: Patients who were scheduled for elective coronary arteriography or percutaneous coronary intervention Inclusion criteria: >20 years old sCr >97.24 to <176.8 mg/dl* Exclusion criteria: Allergy to contrast Pregnancy History of dialysis Exposure to contrast medium within the previous 48 hrs ACS within the proceeding 1 month Serve symptoms of heart failure (New York heart association functional class IV) Left ventricular ejection fraction < 25% Severe chronic respiratory disease Single functioning kidney Administration of dopamine, theophylline, mannitol, fenoldopam or NAC All patients N: 144	Group 1 (Intervention) Sodium chloride 0.9% + sodium bicarbonate Sodium chloride 0.90% Dose: 1 mL/kg/hr (0.5 ml/kg/hr for patients with left ventricular ejection fraction <40%) Route: IV Timing pre contrast: 12hrs Timing post contrast: 12hrs Sodium bicarbonate Dose: 20ml** Route: single bolus IV Timing pre contrast: 5 minutes before exposure Timing post contrast: Group 2 (Comparison) Sodium chloride 0.9% Sodium chloride 0.90% Dose: 1 mL/kg/hr (0.5 ml/kg/hr for patients with left ventricular ejection fraction <40%) Route: IV	Mortality (7 days)	Group1: 0/72 Group 2: 0/72 Relative risk [95% CI]:NR p value:NR	Funding: NR Limitations: Single blinded (patients) Allocation concealment unclear Only included patients with mild renal insufficiency undergoing emergency coronary procedure Additional outcomes: Change in sCr levels Adverse clinincal events up to day7 including: acute pulmonary, acute renal failure requiring dialysis or hemofiltration and death eGFR Serum potassium Serum urea nitrogen Mehran risk score Notes: * Calculated from mg/dL by NCGC (x88.4) ** 20ml=20mEq Randomisation was performed using computer generated random numbers sCr was measured by an enzyme
			CI-AKI at 48 hours	NR	
			CI-AKI at 72 hours (increase in the sCr concentration of >44.2µmol/l* or >25% from the baseline value within 3 days after exposure)	Group1: 1/72 (1.4%) Group 2: 9/72 (12.5%) Relative risk [95% CI]:NR p value:0.0017	
			Number of patients needing RRT	Group1: 0/72 Group 2: 1/72 Relative risk [95% CI]:NR p value: NR	
			Number of patients achieving dialysis independence	NR	
			Length of hospital stay	NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
* or >25% from the baseline value within 3 days after exposure	Age (mean±SD): NR Drop outs: 0 Group 1 N: 72 Age (mean±SD): 72.3±9.9 Drop outs: 0 Baseline characteristics: M:F: 83.3%/16.7% Baseline serum creatinine (µmol/l) (mean±SD): 120.224 ±15.912 * CKD: NR Diabetes: 59.7% Hypertension: 84.7% ACEI: 25% NSAIDs: 0% Group 2 N: 72 Age (mean±SD): 73.3±7.7 Drop outs: 0 Baseline characteristics: M:F: 91.7%/8.3% Baseline serum creatinine (µmol/l) (mean±SD): 121.992 ±16.796* CKD: NR Diabetes: 56.9% Hypertension: 83.3% ACEI: 16.7% NSAIDs: 0%	Timing pre contrast: 12hrs Timing post contrast: 12hrs Contrast nonionic, low osmolar Name: Iohexol Dose: NR Volume of contrast administered ml (mean±SD): Group 1: 82.1±40.4 Group2: 87.8±44.9 P value: 0.31 Both groups: Saline hydration: for patients >80kg infusion rate was limited to 80 ml/hr (40 ml/hr for patients with left ventricular ejection fraction < 40%) Diuretics were routinely held on the day of the procedure and the decision as to when diuretics were restarted			method which means that sCr in the present study is lower by aprox 17.69 µmol/l* than that measured by the Jaffe method intention to treat analysis relatively small volume of contrast used

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
		was left to the discretion of the attending physician			

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4 **G.2.2.7 NAC + sodium bicarbonate vs NAC + sodium chloride 0.9%**

5 **Table 25: Briguori 2007[61]**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Briguori 2007[61] Country of study: Italy Study design: RCT Who was blinded: Double-blind Setting:	Patient group: Patients with CKD who underwent coronary and/or peripheral angiography and /or angioplasty from January 2005 to August 2006. Consecutive eligible patients scheduled for coronary and/ or peripheral angiography and/or angioplasty were considered for enrolment Inclusion criteria: ≥18 years of age stable sCr concentration ≥176.8 µmol/l* and/or glomerular filtration rate <40 mL · min $^{-1}$· 1.73 m^{-2}**	Group 1 (Intervention) NAC + sodium bicarbonate NAC Dose: 1200 mg X2 daily Route: oral Timing pre contrast/ post contrast: the day before and the day of administration of the contrast agent (total of 2 days) Sodium bicarbonate Dose: 154 mEq/L sodium bicarbonate in dextrose and H2O****	Mortality	NR	Funding: NR Limitations: 3 arm study Allocation concealment unclear Additional outcomes: increase in the sCr concentration ≥44.2µmol/l* at 48 hrs after contrast exposure decrease of estimated glomerular filtration rate ≥25% at 48 hours Median sCr concentration for all patients Notes:
			CI-AKI at 48 hours (increase in the sCr concentration ≥25% from the baseline value at 48 hrs after administration of the contrast)	Group1: 2 / 108 (1.9%) Group 2: 11/ 111 (9.9%) Relative risk [95% CI]: NR p value: 0.019	
			CI-AKI at 72 hours	NR	
			Number of patients needing RRT	Group1: 1/108(0.9%) Group 2: 1/111(0.9%) Relative risk [95% CI]: NR p value: NR	
			Number of patients achieving dialysis	NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
2-centre Secondary care Duration of follow-up: 5 days Definition of CI-AKI used: increase in the sCr concentration ≥25% from the baseline value at 48 hrs after administration of the contrast media or the need for dialysis	Exclusion criteria: sCr levels ≥8 mg/dL, history of dialysis, multiple myeloma, pulmonary edema, acute MI, recent exposure to radiographic contrast within 2 days of the study, pregnancy, administration of theophylline, dopamine, mannitol, or fenoldopam. All patients N: 351 *** Age (mean±SD): NR Drop outs: 25*** Group 1 N: 117 Age (mean±SD): 70±9 Drop outs: 9 Baseline characteristics: M:F: 95(81%)/ 22(19%) Baseline serum creatinine (µmol/l) (medians Q1 to Q3): 180.336 (166.194 to 208.624) CKD: All (117) Diabetes: 53 (49%) Hypertension: 99 (92%)	Route: IV Timing pre contrast: IV bolus 3 mL/kg/hr for 1 hour before contrast Timing post contrast: infusion of 1 mL/kg /hr during contrast exposure & for 6 hrs after the procedure. Group 2 (Comparison) NAC + 0.9% Saline NAC Dose: 1200 mg X2 daily Timing pre / post contrast: the day before and the day of administration of the contrast agent (total of 2 days) Sodium chloride 0.90% Dose: 1 mL/kg body weight/ hr (0.5 mL/kg for patients with left ventricular ejection fraction <40%) Route: IV Timing pre contrast: 12 hrs Timing post contrast: 12 hrs	independence Length of hospital stay	 NR	* Calculated from mg/dL by NCGC (x88.4) ** Estimated glomerular filtration rate was calculated by applying the level-modified Modification of Diet in Renal Disease formula: (186.3× sCr -1.154) × (age-0.203) × (0.742 if female). *** Including 3rd arm of study- saline plus ascorbic acid plus NAC group. Total minus ascorbic acid arm= 235 Dropouts minus ascorbic acid arm = 16 ****According to the protocol reported by Merten et al. Randomization in a 1:1:1 ratio, a randomization block was used (Plan Procedure of SAS, version 8.2, SAS Institute Inc, Cary, NC). Available case analysis The total volume of intravenous hydration: Group 1: 1081± 445 mL Group2: 156 2±585 mL P value: <0.001 Patients receiving sodium bicarbonate experienced urinary alkalinization Significant interaction between treatment strategies was observed in the Cr level 48 hrs after adjustment for baseline Cr level and risk score as covariates (F3.85; P0.022 by ANCOVA model) Sub analysis of the effectiveness of the 3 preventive strategies was performed according to the following variables:

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	ACEI: 63 (59%) NSAIDs: NR Group 2 N: 118 Age (mean±SD): 71±9 Drop outs: 7 Baseline characteristics: M:F: 90 (81%)/ 28 (24%) Baseline serum creatinine (µmol/l) (medians Q1 to Q3): 172.38 (149.396 to 199.784) CKD: All (118) Diabetes: 61 (55%) Hypertension: 96 (86.5%) ACEI: 64 (58%) NSAIDs: NR	Contrast nonionic, iso-osmolar Name: Iodixanol Dose: 320 mg iodine/mL Both groups: Diuretics were withheld on the day of contrast injection Volume of contrast administered (mean±SD): Group 1: 169 ±92 mL Group2: 179 ±102 mL P value: 0.69			volume of contrast media, risk score, and diabetes mellitus. Rate of CI-AKI was lower in the bicarbonate plus NAC group even in higher-risk subsets

Table 26: Hafiz 2012[167]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Hafiz 2012[167] Country of study: USA Study design: RCT – central randomisation . Adequate	Patient group: Patients with renal insufficiency scheduled for diagnostic or interventional angiography Inclusion criteria: sCr >141µmol/l in non-diabetics and >124µmol/l in diabetics or eGFR <50ml/min/1.73m2(MDRD) >18 years of age	Group 1 Sodium chloride 0.9% + NAC Route: iv pre contrast: 1ml/kg/h for 12h and oral NAC 1200mg 2-12 h before procedure post contrast: 1ml/kg/h for	Inhospital mortality	No deaths noted during the study period	Funding: None reported Limitations: No blinding Baseline characteristics only
			CI-AKI at 48 hours (increase in sCr ≥25% or 44µmol/l)	Group1: 8/81 (9.9%) Group 2: 11/80 (13.8%) Group 3: 8/80 (10%) Group4: 6/79 (7.6%) Relative risk [95% CI]: NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
allocation concealment. Who was blinded: Not blinded Setting: Single centre Duration of follow-up: 48h for sCr, in-hospital for other outcomes Definition of CI-AKI used: increase in sCr ≥25% or 44µmol/l within 48h of exposure to contrast medium	Exclusion criteria: RRT Change in sCr of >0.4mg/dl within 48h prior to index procedure Pulmonary oedema Serum bicarbonate >34mmol/l Fenoldopam, mannitol, dopamine or NAC within 48h prior to index procedure Cardiogenic shock Allergy to contrast media Pregnancy Unable to provide informed consent All patients N: 320 Age (median [IQR]): 73 [63-80] Baseline eGFR (median [IQR]): 41 [32-51] Drop outs: 0 Group 1 N: 81 Drop outs: 0 Baseline serum creatinine* (µmol/l) (median): 150 Group 2 N: 80 Drop outs: 0 Baseline serum creatinine* (µmol/l) (median): 141	12h and oral NAC 1200mg 6-12 h after procedure Group 2 Sodium chloride 0.9% (154mEq/L in 5% dextrose) Route: iv Fluid dose as for Group 1 Group 3 Sodium bicarbonate + NAC (154mEq/L in 5% dextrose) Route: iv pre contrast: 3ml/kg/h for 1h and oral NAC 1200mg 2-12 h before procedure post contrast: 1ml/kg/h for 6h and oral NAC 1200mg 6-12 h after procedure Group 4 Sodium bicarbonate (154mEq/L in 5% dextrose) Route: iv Fluid dose as for Group 3 Contrast Low osmolar Name: iodixanol, iopamidol, ioversol Dose(ml) (median [IQR]): 110 [80-150] Group 1 and 2: 100 [80-140] Group 3 and 4: 110 [75-155] p= “non-significant”		p value: not significant	reported for overall, Group 1+2 combined and Group 3+4 combined. Additional outcomes: Median sCr at 48h Multivariate logistic regression for factors associated with risk of CI-AKI Notes: sCr converted from mg/dl to µmol/l by NCGC (x88.4)
			CI-AKI at 72 hours	NR	
			Number of patients needing RRT	NR	
			Length of hospital stay (days, mean ± SD)	NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 1+2 N: 161 Age (median [IQR]): 73 [63-80] Baseline characteristics: M:F: 92:69 Baseline serum creatinine* (µmol/l) (median [IQR]): 141 [133-168] CKD: NR Diabetes: 73 (45.3%) Hypertension: 151 (93.8%) ACEI: 99 (61.5%) NSAIDs: NR Group 3 N: 80 Drop outs: 0 Baseline serum creatinine* (µmol/l) (median): 150 Group 4 N: 79 Drop outs: 0 Baseline serum creatinine* (µmol/l) (median): 150 Group 3+4 N: 159 Age (median [IQR]): 74 [65-80] Baseline characteristics: M:F: 90:69				

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Baseline serum creatinine* (µmol/l) (median [IQR]): 150 [133-186] CKD: NR Diabetes: 78 (49.1%) Hypertension: 151 (95.0%) ACEI: 88 (55.4%) NSAIDs: NR				

Table 27: Lee 2011 [242]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Lee 2011 [242] Country of study: Korea Study design: RCT Who was blinded: Single blinded (only patients) Setting: 9-centres	Patient group: from Feb 2008 –Aug 2009, patients scheduled for elective coronary or endovascular angioplasty/ intervention Inclusion criteria: sCr ≥97.24 µmol/l* Estimated GFR <60 ml/min/1.73m² Age ≥18 years Diabetes mellitus *** Exclusion criteria: Inability obtain informed consent sCr ≥707.2 µmol/l* Estimated GFR <15ml/min/1.73m² at rest	Group 1 (Intervention) NAC + sodium bicarbonate NAC Dose: 1200 mg X2 daily Route: oral Timing pre contrast/ post contrast: the day before and the day of administration of the contrast agent (total of 2 days) Sodium bicarbonate Dose: 154 mEq/L sodium bicarbonate in dextrose and water	Mortality (cumulative rates 6 months)	Group1: 6/193 (3.1%) Group 2: 2/189 (1.1%) Relative risk [95% CI]: NR p value:0.45	Funding: Supported by the cardiovascular research foundation, Seoul, Korea. And a grant from the ministry for health welfare and family affairs, Seoul, Republic of Korea, as part of the Korea Health 21 R&D Project. Limitations: Single blinded (only patients) Intravenous hydration volume was larger in group 2 than in group 1. Additional outcomes: eGFR pre and post contrast mean sCr concentration pre and post contrast continuous deterioration of renal
			CI-AKI at 48 hours (Absolute increase in the sCr concentration ≥44.2µmol/l* or ≥25% from the baseline value at 48 hrs after contrast exposure)#	Group1: 17/188 (9%) Group 2: 10/187 (5.3%) Relative risk [95% CI]: NR p value: 0.17	
			CI-AKI at 48 hours (Absolute increase in the sCr concentration	Group1: 16/188 (8.5%) Group 2: 9/187 (4.8%) Relative risk [95%	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Duration of follow-up: 6 month Definition of CI-AKI used: Absolute increase in the sCr concentration ≥25% or ≥44.2µmol/l * from the baseline value at 48 hrs after contrast exposure	end stage renal disease on hemodialysis multiple myeloma pulmonary oedema uncontrolled hypertension (systolic >160mmHg or diastolic >100mmHg) acute ST-segment elevation MI while undergoing primary PCI emergency coronary angioplasty/ angiography use of contrast media in the past 2 days/ medication: theophylline, dopamine, mannitol, fenoldopam and NAC All patients N: 382 Age (median): 68 Drop outs: 7**** Group 1 N: 193 Age (medians Q1 to Q3): 68.5 (63-73) Drop outs: 5**** Baseline characteristics: M:F: 57 (%) Baseline serum creatinine (µmol/l) (medians Q1 to Q3): 132.6 (114.92 - 167.96) CKD: ALL Diabetes: ALL	Route: IV Timing pre contrast: 3 mL/kg /hr for 1 hour before contrast Timing post contrast: 1 mL/kg /hr during contrast exposure & for 6 hrs after the procedure. Group 2 (Comparison) NAC + sodium chloride 0.9% NAC Dose: 1200 mg X2 daily Timing pre / post contrast: the day before and the day of administration of the contrast agent (total of 2 days) Sodium chloride 0.90% Dose: 1 mL/kg/ hr Route: IV Timing pre contrast: 12 hrs Timing post contrast: 12 hrs Contrast nonionic, iso-osmolar	≥44.2µmol/l* from the baseline value at 48 hrs after contrast exposure)	CI]:NR p value: 0.15	function (defined as ≥25% decrease in s Cr or permanent hemodialysis) at 1 month severe renal impairment eGFR= < 30 ml/min/1.73m² incidence of CI_AKI according to high contrast load (≥140 ml and > 5 times body weight per sCr mg/dl) adverse clinical outcomes at 1 & 6 months: MI and Stroke Independent predictors of CI-AKI development Notes: * ** GFR calculated using the Modification of Diet in Renal Disease study equation. ***diabetes mellitus was defined as use of hypglycemic agents or insulin. Fasting plasma glucose >126mg/dl, or random plasma glucose ≥ 200mg/dl Randomly assigned to 1:1using an interactive web response system Allocation sequence was computer generated, stratified according to participating centre, and blocked with block sizes of 6 and 10
			CI-AKI at 48 hours (relative increase in the sCr concentration >25% from the baseline value at 48 hrs after contrast exposure)	Group1: 13/188 (6.9%) Group 2: 9/187 (4.8%) Relative risk [95% CI]:NR p value: 0.39	
			CI-AKI at 72 hours	NR	
			Number of patients needing RRT (cumulative rates at 6 months)	Group1: 10/193 (5.2%) Group 2: 3/189 (1.6%) Relative risk [95% CI]: p value:	
			Number of patients achieving dialysis independence	NR	
			Length of hospital stay	NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Hypertension: 149 (77.2%) ACEI: 32 (16.6%) NSAIDs: NR Group 2 N: 189 Age (medians Q1 to Q3): 67.5 (62-72) Drop outs: 2**** Baseline characteristics: M:F: 135 (71.4%)/54 (28.6%) Baseline serum creatinine (µmol/l) (medians Q1 to Q3): 132.6 (114.92 - 150.28) CKD: ALL Diabetes: ALL Hypertension: 151 (79.9%) ACEI: 43 (22.8%) NSAIDs: NR	Name: Iodixanol Route: intraarterial Dose: 320 mg iodine/mL Both groups: Infusion rates reduced to 0.5 mL/kg for patients with left ventricular ejection fraction <45% Volume of contrast administered mL (medians Q1 to Q3): Group 1: 120 (79-223) Group2: 113 (80-220) P value: 0.89			****dropouts for the primary CI-AKI outcome Group 1 189 included in 1 month follow up 188 included 6 month follow up Group 2 193 included in 1 month follow up 192 included 6 month follow up # these figures used for CI-AKI in revman

Table 28: Maioli 2008 [258]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Maioli 2008 [258] Country of	Patient group: From January 2005 to March 2006 population of patients with chronic kidney dysfunction	Group 1 (Intervention) NAC + sodium bicarbonate NAC	Mortality (10 days)	Group1: 4/250 (1.6%) Group 2: 3/252 (1.2%) Relative risk [95% CI]: NR	Funding: NR Limitations:

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
study: Italy Study design: RCT Who was blinded: NR Setting: Secondary care Duration of follow-up: 10 days Definition of CI-AKI used: an absolute increase of at least 44.2µmol/l* over baseline sCr within 5 days after the administration of the contrast	who underwent planned coronary angiographic procedures Inclusion criteria: pre-angiographic estimated Cr clearance <60 ml/min Exclusion criteria: NR All patients N: 502 Age (mean±SD): NR Drop outs: 9 Group 1 N: 250 Age (medians Q1 to Q3): 74 (67–79) Drop outs: 5 Baseline characteristics: M: F: 143 (57%)/107 (43%) Baseline serum creatinine (µmol/l) (mean±SD): 106.964 ± 26.52* CKD: All (250) Diabetes: 62 (25%) Hypertension: 147 (59%) ACEI: 106 (42%) NSAIDs: NR Group 2	Dose: 1200 mg X2 daily Route: oral Timing pre / post contrast: the day before and the day of administration of the contrast agent Sodium bicarbonate Dose: 154 mEq/l in dextrose and water Route:IV Timing pre contrast: 3 ml/kg for 1 h before contrast medium Timing post contrast: an infusion of 1 ml/kg/h for 6 h after the procedure Group 2 (Comparison) NAC + sodium chloride 0.9% NAC Dose: 1200 mg X2 daily Route: oral Timing pre / post contrast: the day before and the day of administration of the contrast agent (total of 2 days)		p value: 0.99	Blinding unclear Allocation concealment unclear Additional outcomes: ≥25% relative increase in baseline serum creatinine at 5 days increase of at least 44.2µmol/l* over baseline sCr within 5 days sCr concentrations at baseline day 1, 2, 3, 5, 10 and peak sCr sCr concentrations in patients with CI-AKI at baseline, day 1, 2, 3, 5, 10, peak sCr and mean increase proportion of patients receiving ≥140 ml of contrast media contrast nephropathy risk score risk factor analysis incidence of CI-AKI in patients at high risk Notes: *Calculated from mg/dL by NCGC (x88.4) Randomization was performed by computerized open-label assignment in blinded envelopes used in a consecutive fashion. Intention to treat analysis Hydration rate was reduced to 0.5
			CI-AKI at 48 hours (CI-AKI was defined as ≥25% relative increase in baseline serum creatinine)	Group1: 25/250 (10%) # Group 2: 38/252 (15.1%) # Relative risk [95% CI]: NR p value: 0.09	
			CI-AKI at 72 hours	NR	
			Number of patients needing RRT	Group1: 1/250 Group 2: 1/252 Relative risk [95% CI]: NR p value: NR	
			Number of patients achieving dialysis independence	NR	
			Length of hospital stay	NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
medium	N: 252 Age (medians Q1 to Q3): 74 (70–79) Drop outs: 4 Baseline characteristics: M:F: 153 (61%)/ 99 (39%) Baseline serum creatinine (µmol/l) (mean±SD): 106.08 ± 26.52 * CKD: All (252) Diabetes: 59 (23%) Hypertension: 143 (57%) ACEI: 91 (36%) NSAIDs: NR	Sodium chloride (0.90%) Dose: 1 ml/kg/h Route: IV Timing pre contrast: 12hrs Timing post contrast: 12hrs Contrast nonionic, iso-osmolar Name: Iodixanol Dose: NR Both groups: Volume of contrast administered (medians Q1 to Q3): Group 1: 160 (120–220) Group2: 170 (120–230) P value: 0.80			ml/kg/h in both arms for patients with left ventricular ejection fraction 40% or New York Heart Association functional class III–IV # NCGC calculated from percentage given

G.2.2.8 NAC + sodium chloride 0.9% vs. 0.9% sodium chloride

See Table 18: Hafiz 2012[167] located in G.2.1.7 NAC + sodium bicarbonate vs NAC + sodium chloride 0.9%

Table 29: ACT Investigators[5]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
ACT Investigators[5] Protocol[4] Country of study: Brazil Study design: RCT – central Web-based randomisation, allocation in random permuted blocks stratified by site Who was blinded: Participants, healthcare staff, data collectors and outcome assessors	Patient group: Patients undergoing intravascular angiographic procedure with at least one risk factor for contrast induced AKI (September 2008-July 2010). Inclusion criteria: Patients undergoing coronary or peripheral arterial diagnostic intravascular angiography or percutaneous intervention and ≥1 of: Age >70 Chronic renal failure (sCr >132.6µmol/l) Diabetes mellitus Clinical evidence of congestive heart failure Left ventricular ejection fraction (LVEF) <0.45 Hypotension Exclusion criteria: RRT ST-segment elevation myocardial infarction undergoing primary angioplasty	Group 1 (Intervention) NAC Dose: 1200mg bd Route: po Timing pre contrast†: 2 doses, 12 hourly. Timing post contrast: 2 doses iv fluid - 0.9% Saline† Dose: 1ml/kg/h Route: iv Timing pre contrast†: 6-12h Timing post contrast: 6-12h Group 2 (Comparison) placebo Dose: matched placebo iv fluid - 0.9% Saline† Dose: 1ml/kg/h Route: iv Timing pre contrast: 6-	All-cause mortality at 30 days	Group1: 23/1171 (2.0%) Group 2: 24/1135 (2.1%) Hazard ratio [95% CI]: 0.97[0.54-1.73] p value: 0.92	Funding: Brazilian Ministry of Health Limitations: †Fluid regime "highly recommended" but type of fluid and amount could be altered by physician. Approximately 95% of patients received sodium chloride 0.9% and median duration was for 6 hours before and after procedure. Low, iso and high ismolar contrast given, with only post-hoc subgroup analysis for type of contrast. Additional outcomes: Doubling in sCr Elevation ≥44.2 and 13.3 µmol/l in sCr Adverse events (in separate online data
			CI-AKI at 48 hours	NR	
			CI-AKI at 96 hours (how was this measured: 25% elevation of sCr above baseline 48-96h after angiography.)	Group1: 147/1153 (12.7%) Group 2: 142/1119 (12.7%) Relative risk [95% CI]: 1.00 [0.81-1.25] p value: 0.97	
			CI-AKI at 96 hours – CKD subgroup	Group1: 12/188 (6.4%) Group 2: 10/179 (5.6%) Relative risk [95% CI]: 1.14 [0.51-2.58] p value (for homogeneity): 0.75	
			CI-AKI at 96 hours – Diabetes subgroup	Group1: 97/702 (13.8%) Group 2: 98/667 (14.7%) Relative risk [95% CI]: 0.94 [0.73-1.22] p value(for homogeneity): 0.42	
			CI-AKI at 72 hours – age >70 subgroup	Group1: 80/595 (13.4%) Group 2: 74/591 (12.5%) Relative risk [95% CI]: 1.07 [0.80-1.44] p value(for homogeneity): 0.52	
			CI-AKI at 72 hours – volume of contrast ≥140ml subgroup	Group1: 35/262 (13.4%) Group 2: 32/259 (12.4%) Relative risk [95% CI]: 1.08 [0.69-1.69]	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Setting: Multicentre – 46 centres in Brazil where angiography avaiable Duration of follow-up: 30 days Definition of CI-AKI used: 25% elevation of sCr above baseline 48-96h after angiography. Post hoc defined end point elevation ≥13.3µmol/l in sCr (AKIN criteria for AKI)	Pregnancy/breastfeeding Women aged <45 not using contraceptive methods All patients N: 2308 Drop outs: 36 (1.6%) had no follow up sCr 27 (1.2%) not submitted to angiography 7 (0.3%) died before 48-96h 2 (0.1%) lost to 30 day follow-up 19 (0.8%) did not receive study drug before angiography Group 1 (NAC) N: 1172 Age (mean±SD): 68.0 ± 10.4 Age >70: 601 (51.3%) Drop outs: 19 (1.6%) no follow up sCr, 15 (1.3%) not submitted to angiography, 4 (0.3%) died before 48-96h 1 (0.1%) lost to 30 day follow-up 12 (1.0%) did not receive study drug before angiography Baseline characteristics: M:F: 727(62.0%):445(38.0%) Baseline serum creatinine (µmol/l) (mean±SD): 106 ±44.2*	12h Timing post contrast: 6-12h Contrast High osmolar: 509/2281 Isosmolar: 67/2281 low osmolar: 1705/2281 Name: NR Dose(ml, median[IQR]): 100 [70-130] NB: 38 (3.2%) in Group 1 and 47 (4.1%) in Group 2 underwent additional angiography within 48-96h after first procedure Both groups: changes to total volume or speed of administration of fluid were permitted †Angiography could be performed anytime from 6 hours after first study drug to just before 3rd study drug dose		p value(for homogeneity): 0.79	supplement) – nausea, emesis, urticaria and bronchospasm. Incidence of adverse events was less in Group1 (NAC). Cardiovascular mortality Composite outcomes (1) death or RRT and (2) death, RRT or doubling in serum creatinine Post hoc subgroup analysis on type of contrast Notes: Available case analysis Outcomes extracted for pre-specified subgroups only. Sample size calculation: 2300 to detect 30% RR reduction (from 15%), with 90% power and 2-tailed α 5% *calculated from mg/dL by NCGC (x88.4)
			Number of patients needing RRT (at 30 days)	Group1: 3/1171 (0.3%) Group 2: 3/1135 (0.3%) Hazard ratio [95% CI]: 0.87[0.17-4.35] p value: 0.86	
			Length of hospital stay	NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	CKD: 180 (15.4%) Diabetes: 717 (61.2%) Hypertension: 1014 (86.5%) Hypotension: 3 (0.3%) Known heart failure: 116 (9.9%) ACEI: 698 (59.6%) NSAIDs >7d: 63 (5.4%) Group 2 (placebo) N: 1136 Age (mean±SD): 68.1 ± 10.4 Age >70: 601 (52.9%) Drop outs: 17 (1.5%) no follow up sCr, 12 (1.1%) not submitted to angiography, 3 (0.3%) died before 48-96h 1 (0.1%) lost to 30 day follow-up 7 (0.6%) did not receive study drug before angiography Baseline characteristics: M:F: 689(60.7%):447(39.3%) Baseline serum creatinine (µmol/l) (mean±SD): 106 ±44.2* CKD: 182 (16.0%) Diabetes: 678 (59.7%) Hypertension: 976 (85.9%) Hypotension: 2 (0.2%) Known heart failure: 104 (9.2%) ACEI: 661 (58.2%) NSAIDs >7d: 59 (5.2%)				

Table 30: Aslanger 2012[21]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Aslanger 2012[21] Country of study: Turkey Study design: RCT - Patients randomly assigned using computed generated random numbers, assigned in a 1:1:1 ratio Who was blinded: NR Setting: single centre Duration of follow-up: 72 hours Definition of CI-AKI used: increase in sCr ≥25% within 72h of exposure to contrast	Patient group: Patients with STEMI undergoing coronary angiography within 24h of symptom onset. Between January 2007 and January 2009 Inclusion criteria: ≥30 years of age Exclusion criteria: Known NAC hypersensitivity Chronic dialysis All patients: N: 220 Age (mean±SD): 56.4 ± 11 Drop outs: 18 M:F:241:89 Group 1 N: 110 Age (mean±SD): 56.1±12 Drop outs: 2 Baseline characteristics: M:F: 86:13 Baseline serum creatinine (µmol/l) (mean±SD):79.6±26.5 Creatinine clearance (CGF ml/min) (mean±SD):107±39 Creatinine clearance (MDRD ml/min)	Group 1 * Sodium chloride 0.9% + NAC Route: iv Dose: 1ml/kg/h for 12hrs (iv bolus NAC: 1200mg during the procedure and 1200mg of NAC orally twice /day for 48h after the procedure. (total 6g) Group 2 * Sodium chloride 0.9% + placebo Route: iv Dose: 1ml/kg/h for 12hrs Placebo: iv saline bolus of 12 ml during the procedure and then placebo capsules for 48h after. Contrast Low osmolar, ionic Name: ioxaglate Group 1: Dose(ml) (mean ± SD):193±57 Group 2: Dose(ml) (mean ± SD): 204±67 p= 0.443	Mortality CI-AKI at 72 hours (increase in sCr ≥25% or 44µmol/l) CI-AKI at 48 hours Number of patients needing RRT Length of hospital stay (days, mean ± SD)	NR Group1: 27/108(25%) Group 2: 23/99 (23%) Relative risk [95% CI]: NR p value: 0.64 NR NR NR	Funding: None reported Limitations: Blinding not reported Differential dropout rate (both less than incidence of CI-AKI) Timing of when saline is given in relation to contrast is not reported Additional outcomes: 3rd arm (additional N=110 randomised) received sodium chloride 0.9% 1ml/kg/h 12h and intra-renal NAC before PCI. Multivariate analysis for factors associated with risk of CI-AKI Notes: sCr converted from mg/dl to µmol/l by NCGC (x88.4) *The volume of isotonic infusion was

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
medium	(mean±SD): 95±29 Diabetes: 27(25%) Hypertension: 55 (51%) ACEI or ARB: 95(88%) NSAIDs: NR Group 2 N: 110 Age (mean±SD): 57.2±12 Drop outs: 11 Baseline characteristics: M:F: 73:35 Baseline serum creatinine (µmol/l) (mean±SD): 76.0±26.5 Creatinine clearance (CGF ml/min) (mean±SD):107±30 Creatinine clearance (MDRD ml/min) (mean±SD): 89.5±28 Diabetes: 16 (16%) Hypertension: 47(47%) ACEI or ARB: 90 (91%) NSAIDs: NR	Both groups: LVF was evaluated in all patients with 24hrs of admission. All patients were treated with STEMI therapy of aspirin, clopidegrel, tirofibian, enoxaparin, beta blockers, ACEi, and statins			halved in patients with congestive cardiac symptoms Available case analysis

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2 **Table 31: Castini 2010[77]**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Castini 2010[77] Country of	Patient group: Patients with stable serum creatinine levels ≥ 106µmol/l undergoing non-	Group 1 (Intervention) NAC Dose: 600mg bd	Mortality	NR	Funding: None reported
			CI-AKI at 48 hours	NR	
			CI-AKI at 5 days (how	Group1: 9/53 (17.0%)	

study: Italy Study design: RCT – randomised using computer-generated randomisation table Who was blinded: No one Setting: Single centre, cardiology unit Duration of follow-up: 5 days Definition of CI-AKI used: increase in sCr ≥25% baseline within 5 days from	emergency coronary angiography or PCI Inclusion criteria: sCr* ≥ 106µmol/l Age 18 years or older Exclusion criteria: sCr* >353.6µmol/l history of RRT multiple myeloma pulmonary oedema, cardiogenic shock or acute MI need for emergency cardiac catheterisation exposure to contrast in last 7 days allergy to contrast or NAC pregnancy administration of theophylline, mannitol, dopamine, dobutamine, NSAIDs or fenoldopam "previous enrollment in same or other protocols" All patients N: 156 Age (mean±SD): 71 ± 7.9 Drop outs: 0 Group 1 N: 53 Age (mean±SD): 70.5 ± 7.2 Baseline characteristics:	Route: po Twice daily on day before and day of administration of contrast iv fluid – sodium chloride 0.9% Dose: 1ml/kg/h Route: iv Timing pre contrast: 12h Timing post contrast: 12h Group 2 (Comparison) iv fluid – sodium chloride 0.9% Dose: 1ml/kg/h Route: iv Timing pre contrast: 12h Timing post contrast: 12h Group 3 (Comparison) iv fluid – sodium bicarbonate 154ml of 100mEq/L in 846ml of 5% dextrose in H2O Route: iv Timing pre contrast:	was this measured: increase in sCr ≥25% baseline)	Group 2: 7/51 (13.7%) Group 3: 7/52 (13.5%) Relative risk [95% CI]: NR p value: 0.85	Limitations: No blinding Additional outcomes: sCr concentration at 24h, 48h and 5d Serum bicarbonate at 24h, 48h and 5d Notes: *calculated from mg/dL by NCGC (x88.4)
			CI-AKI at 5 days (how was this measured: absolute increase in sCr* ≥44.2 µmol/l)	Group1: 5/53 (9.4%) Group 2: 4/51 (7.8%) Group 3: 6/52 (11.5%) Relative risk [95% CI]: NR p value: 0.82	
			Number of patients needing RRT	Group1: 0 Group 2: 0 Group 3: 0	
			Number of patients achieving dialysis independence	NR	
			Length of hospital stay	NR	

contrast exposure	M:F: 50(94.3%):3(5.7%) Baseline serum creatinine (µmol/l)* (mean±SD): 132 ± 27 CKD: 53/53 (100%) Diabetes: 14/53 (26.4%) Hypertension: 44/53 (83.0%) ACEI: 40/53 (75.5%) NSAIDs: 0 Group 2 N: 51 Age (mean±SD): 72.7 ± 8.2 Baseline characteristics: M:F: 43(84.3%):8(15.7%) Baseline serum creatinine (µmol/l)* (mean±SD): 139 ± 34 CKD: 51/51 (100%) Diabetes: 10/51 (19.6%) Hypertension: 40/51 (78.4%) ACEI: 37/51 (72.5%) NSAIDs: 0 Group 3 N: 52 Age (mean±SD): 70.0 ± 8.3 Baseline characteristics: M:F: 44(84.6%):8(15.4%) Baseline serum creatinine (µmol/l)* (mean±SD): 141 ± 34 CKD: 52/52 (100%) Diabetes: 18/52 (34.6%) Hypertension: 37/52 (71.2%) ACEI: 36/52 (69.2%)	3ml/kg for 1h immediately before contrast Timing post contrast: 1ml/kg/h during contrast exposure and for 6h post procedure Contrast Isosmolar Name: iodixanol Dose (ml) (mean ± SD): Group1: 210 ± 140.6 Group 2: 196.4 ± 127.7 Group 3: 179.2 ±125.1 All groups: “home therapy” continued for entire length of protocol except metformin which was stopped 24h preprocedure and reintroduced after 5 days if CI-AKI did not occur.			

	NSAIDs: 0				

Table 32: Fung 2004[147]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Fung 2004[147] Country of study: Hong Kong Study design: RCT – computer generated list maintained by someone independent of patient care and conduction of the study Who was blinded: "operating cardiologist blinded to the randomisation result"	Patient group: Patients with sCr 149 - 400µmol/l undergoing elective coronary angiography or PCI Inclusion criteria: sCr 149 - 400µmol/l 2 sCr measurements within one month of angiography with <15% change to confirm stable renal function Exclusion criteria: Known allergy to NAC or contrast agents Cardiogenic shock Current RRT Concomitant use of dopamine, theophylline or mannitol All patients N: 91 Drop outs: 0 Group 1	Group 1 (Intervention) NAC Dose: 400mg tds Route: po Timing: day before and day of contrast administation iv fluid – sodium chloride 0.9% Dose: 100ml/h Route: iv Timing pre contrast: 12h Timing post contrast: 12h Group 2 (Comparison) iv fluid – sodium chloride 0.9% Dose: 100ml/h Route: iv Timing pre contrast: 12h Timing post contrast:	Mortality	NR	Funding: None reported Limitations: ?adequately powered, calculation based on Tepel et al 2000[391] Additional outcomes: sCr at 48h GFR at 48h Compliance to NAC – 95% CI-AKI in patients with baseline GFR ≤30ml
			CI-AKI at 48 hours (how was this measured: increase in sCr ≥ 44µmol/l or reduction in GFR ≥25%)	Group1: 8/46 (17.4%) Group 2: 6/45 (13.3%) Relative risk [95% CI]: NR p value: 0.8	
			CI-AKI at 48 hours – Diabetes subgroup	Group1: 2/23 (8.7%) Group 2: 3/25 (12%) Relative risk [95% CI]: NR p value: 0.9	
			CI-AKI at 72 hours	NR	
			Number of patients needing RRT	Group1: 0 Group 2: 0	
			Number of patients achieving dialysis independence	NR	
			Length of hospital stay	NR	
			Adverse events (including allergic reaction, not including heart failure)	Group1: 0 Group 2: NR	
			Adverse events (clinical heart failure so could not complete	Group1: 6/46 (13.0%) Group 2: 7/45 (15.6%) p value: NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Setting: Cardiology department, university hospital Duration of follow-up: 48h Definition of CI-AKI used: increase in sCr ≥ 44µmol/l or reduction in eGFR ≥25% baseline value 48h after procedure	N: 46 Age (mean±SD): 68.2 ± 8.4 Baseline characteristics: M:F: 34(73.9%):12(26.1%) Baseline serum creatinine (µmol/l) (mean±SD): 201 ± 48 CKD: 46 (100%) Diabetes: 23/46 (50%) Hypertension: NR ACEI/ARB: 23/46 (50%) NSAIDs (Aspirin): 39/46 (84.8%) Group 2 N: 45 Age (mean±SD): 68.0 ± 8.8 Baseline characteristics: M:F: 30(66.7%):15(33.3%) Baseline serum creatinine (µmol/l) (mean±SD): 210 ± 54 CKD: 45 (100%) Diabetes: 25/45 (55.6%) Hypertension: NR ACEI/ARB: 26/45 (57.8%) NSAIDs (Aspirin): 32/45 (71.1%)	12h Contrast low osmolar Name: iopromide Dose(ml) (mean ± SD): Group1: 135.8 ± 66.6 Group 2: 121.0 ± 66.2 Both groups: Fasting 6h pre procedure, unrestricted oral fluids post procedure unless clinically indicated	sodium chloride infusion regimen)		

Table 33: Jaffery 2012[197]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Jaffery 2012[197] Country of study: USA Study design: prospective randomised single centre double blind placebo controlled trial Who was blinded: double blind(exactly who isn't reported) Setting: single centre Duration of follow-up: 72 hours Definition of CI-AKI used: increase in sCr ≥25% within 72h of exposure to contrast medium	Patient group: Patients with acute coronary syndrome undergoing coronary angiography or percutaneous coronary intervention. From January 2007- October 2010 Inclusion criteria: ≥18 years of age Primary diagnosis of acute coronary syndrome Scheduled for a coronary angiography or intervention during current hospitalisation Exclusion criteria: Known hypersensitivity to NAC or a history of life threatening contrast reaction ESRD requiring RRT All patients N: 398 Age (mean±SD): 65.4 ± 12.8 Drop outs: 0 Baseline characteristics: M:F: 252: 146 Baseline serum creatinine (µmol/l) (mean±SD): 95 ±3.5 Creatinine clearance (ml/min) (mean±SD): 89.7±42.5 Creatinine clearance <60ml/min: 98 (24.6%) Diabetes: 137(34.4%) Hypertension: 290 (72.9%) ACEI or ARB: NR NSAIDs: NR	Group 1 * Sodium chloride 0.9% + NAC Route: iv Dose: "the total volume of fluid administered was equal to 1 ml/kg/h for 24hrs" iv NAC: 1200 mg bolus followed by 200mg /h for 24hrs (iv solution consisted of 6g NAC in 500ml of 5% dextrose solution in water)) Group 2 * Sodium chloride 0.9% + placebo Route: iv Dose: "the total volume of fluid administered was equal to 1 ml/kg/h for 24hrs" Contrast Iso-osmolar, non-ionic Name: iodixanol Dose(ml) (mean ± SD): All = 165.6±89.3 Group 1 = 169.5±94.5 Group 2 = 161.3±83.4 p= 0.55	30 day mortality	Group1: 3/206(1.5%) Group 2: 3/192(1.6%) Relative risk [95% CI]: NR p value: 1.0	Funding: None reported Limitations: Lack of detail on when the drugs were administered before and after the procedure, exact volume of sodium chloride and details of the placebo Inconsistent reporting of numbers randomised between text, flow diagrams and results tables Unclear allocation concealment No mean volume of fluid per group reported Additional outcomes: Composite end point of in hospital mortality, mechanical ventilation and AKI requiring RRT Notes: *Patients with heart failure (volume overload) only received IV NAC or placebo. The exact
			In hospital mortality	Group1: 1/206 (0.5%) Group 2: 1/192(0.5%) Relative risk [95% CI]:NR p value: 1.0	
			CI-AKI at 48 hours	NR	
			CI-AKI at 72 hours (increase in sCr ≥25% from baseline)	Group1: 33/206(16%) Group 2: 25/192(13%) Relative risk [95% CI]: NR p value: 0.40	
			Number of patients needing RRT	NR	
			Length of hospital stay (days, mean ± SD)	Group1: 3.2±2.6 Group 2: 3.6±3.3 Relative risk [95% CI]: NR p value: 0.13	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 1 N: 206 Age (mean±SD): 65.6 ± 12.9 Drop outs: 0 Baseline characteristics: M:F: 138:68 Baseline serum creatinine (µmol/l) (mean±SD): 96 ±3.5 Creatinine clearance (ml/min) (mean±SD): 87.4.±40.7 Creatinine clearance <60ml/min: 57 (27.7%) Diabetes: 73(35.4%) Hypertension: 152(73.8%) ACEI or ARB: NR NSAIDs: NR Group 2 N: 192 Age (mean±SD): 65.1 ± 12.7 Drop outs: 0 Baseline characteristics: M:F: 114:78 Baseline serum creatinine (µmol/l) (mean±SD): 95 ±3.5 Creatinine clearance (ml/min) (mean±SD): 92.1±44.3 Creatinine clearance <60ml/min: 57 (27.7%) Diabetes: 41(21.4%) Hypertension: 138(71.9%) ACEI or ARB: NR				number of patients effected in each group isn't reported sCr converted from mg/dl to µmol/l by NCGC (x88.4)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	NSAIDs: NR				

Table 34: Kay 2003[210]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Kay 2003[210] Country of study: Hong Kong Study design: RCT – computer generated random numbers Who was blinded: Participants, healthcare staff and outcome assessors Setting: University hospital	Patient group: Patients with stable moderate renal insufficiency (CrCl <60ml/min) undergoing elective coronary angiography with or without intervention (May 2000-December 2001). Inclusion criteria: Adults with known stable chronic renal impairment and stable sCR concentrations with one of: sCr >106µmol/l CrCl <60ml/min Exclusion criteria: RRT Acute renal failure "Change in use" of diuretic or antihypertensive agents Received iodinated contrast media or nephrotoxic agents within 30 days Overt congestive heart failure, severe valvular disease or LVEF	Group 1 (Intervention) NAC Dose: 600mg bd Route: po Timing pre contrast: Started day before, 3 doses Timing post contrast: 1 dose iv fluid – sodium chloride 0.9% Dose: 1ml/kg/h Route: iv Timing pre contrast: 12h Timing post contrast: 6h Group 2 (Comparison) placebo Dose: matched placebo iv fluid – sodium chloride 0.9%	Mortality (in hospital)	Group1: 0 Group 2: 0	Funding: Zambon Group S.p.A, Milan, Italy (manufacturers of NAC) prepared NAC and placebo Additional outcomes: Change in sCr at 48h and 7d Change in CrCl at 48h and 7d Number of patients with oliguria Adverse cardiac events (cardiac death, nonfatal MI, or revascularisation of the target lesion) Subgroup analysis of CrCl at 48h for diabetes, LVEF 35-50% and contrast volume >100ml, presented in diagram form only
			CI-AKI at 48 hours (increase in sCr ≥25% 48h after contrast administration)	Group1: 4/102 (3.9%) Group 2: 12/98 (12.2%) Relative risk [95% CI]:0.32 [0.10-0.96] p value: 0.03	
			CI-AKI at 72 hours	NR	
			Number of patients needing RRT	Group1: 0 Group 2: 0	
			Number of patients achieving dialysis independence	NR	
			Length of hospital stay (days)	Group1: 3.4 ±0.9 Group 2: 3.9 ± 2.0 Mean difference[95% CI]: 0.52 [0.08-0.96] p value: 0.02	
			Adverse events due to study drug – nausea causing discontinuation of study drug	Group 1: 0 Group 2: 1/98 (1.0%)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Duration of follow-up: In hospital, sCR at 24h, 48h and 7d post contrast Definition of CI-AKI used: increase in sCr ≥25% 48h after contrast administration for which other explanations for renal impairment had been excluded	<35% COPD or asthma exacerbation Allergy to NAC All patients N: 200 Age (mean±SD): 68 ± 6.5 Drop outs: 8 Baseline serum creatinine (µmol/l) (mean±SD): 120.2 ± 38.9 Group 1 N: 102 Age (median[IQR]): 69 [50-81] Drop outs: 4 (1 urgent CABG, 3 declined follow up) Baseline characteristics: M:F: 61 (59.8%): 41 (40.2%) Baseline serum creatinine* (µmol/l) (median[IQR]): 109.6 [68.1-264.3] CKD: 102 (100%) Diabetes: 40 (39.2%) Hypertension: 39 (38.2%) ACEI:40 (39.2%) ARB: 8 (7.8%) NSAIDs:NR Group 2 N: 98 Age (median[IQR]): 69 [48-82]	Dose: 1ml/kg/h Route: iv Timing pre contrast: 12h Timing post contrast: 6h Contrast Non-ionic low osmolar Name: iopamidol Dose: at discretion of cardiologist Group 1(ml) (median[IQR]): 130[75-320] Group 2 (ml) (median[IQR]): 120[70-380] For all patients mean dose (ml) ± SD: 139 ± 53 Both groups: “Liberal intake” of oral fluids encourages except for 4h pre-procedure. Volume status and body weight monitored closely Metformin withheld before cardiac catheterisation and			Notes: *calculated from mg/dL by NCGC (x88.4)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Drop outs: 4 (2 urgent CABG, 2 declined follow up) Baseline characteristics: M:F: 62 (63.3%) : 36 (36.7%) Baseline serum creatinine* (µmol/l) (median[IQR]): 111.4 [66.3-321.8] CKD: 98 (100%) Diabetes: 35 (35.7%) Hypertension: 42 (42.9%) ACEI:39 (39.8%) ARB: 4 (4.1%) NSAIDs:NR	reinstituted after completeion of study (sulphonylurea po or insulin used instead)			

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Koc 2012[233] **Country of study:** Turkey **Study design:** RCT – "randomised" **Who was blinded:** NR **Setting:**	**Patient group:** Patients undergoing elective coronary angiography or percutaneous coronary intervention. **Inclusion criteria:** • ≥18 years of age • Creatinine clearance ≤60ml/min and /or baseline sCr ≥97µmol/l **Exclusion criteria:** • Contrast agent hypersensitvity • Pregnancy or lactation • Decompensated heart	**Group 1** **Sodium chloride 0.9% + NAC** (154mEq/L in 5% dextrose) Route: iv Dose: 1ml/kg/h "before, on and after the day of the coronary procedure" iv NAC: 600mg bd day before and day of procedure (total 2.4g) **Group 2** **Sodium chloride 0.9%**	Mortality	NR	**Funding:** None reported **Limitations:** • Difference in number of patients aged ≥70 (24% in Group 1 versus 40% in Group 2) • Blinding not reported • Unclear
			CI-AKI at 48 hours (increase in sCr ≥25% or 44µmol/l)	Group1: 2/80 (2.5%) Group 2: 13/80 (16.3%) Relative risk [95% CI]: NR p value: 0.006	
			CI-AKI at 72 hours	NR	
			Number of patients needing RRT	NR	
			Length of hospital stay (days, mean ± SD)	NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Multi centre **Duration of follow-up:** 48 hours **Definition of CI-AKI used:** increase in sCr ≥25% or 44µmol/l within 48h of exposure to contrast medium	failure • Pulmonary oedema • Emergency catheterisation • Acute kidney injury prior to procedure • ESRD **<u>All patients</u>** **N:** 160 **Baseline serum creatinine (µmol/l) (median [IQR]):** 115 [106-124] **Drop outs:** 0 **<u>Group 1</u>** **N:** 80 **Age (mean±SD):** 62 ± 10 **Age ≥ 70:** 19 (24%) **Drop outs:** 0 **Baseline characteristics:** **M:F:** 61:19 **Baseline serum creatinine (µmol/l) (median [IQR]):** 115 [106-133] **Creatinine clearance (ml/min) (mean±SD):** 59±16 **Creatinine clearance <50ml/min:** 21 (27%) **Diabetes:** 30 (38%) **Hypertension:** 49 (54%) **ACEI or ARB:** 60 (75%) **NSAIDs:** NR **<u>Group 2</u>**	(154mEq/L in 5% dextrose) Route: iv Dose: 1ml/kg/h "before, on and after the day of the coronary procedure" **Contrast** **Low osmolar, non-ionic** **Name:** iohexol **Dose(ml) (mean ± SD):** 138 ± 47 "The same contrast agent was given to all patients in similar amounts". p= NR **Both groups:** LVEF was measured before coronary procedures.			allocation concealment **Additional outcomes:** 3rd arm (additional N=60) received sodium chloride 0.9% 1ml/kg/h 12h before and post procedure. CI-AKI at 48h in this group was 6/60 (10%). Subgroup analysis age, LVEF, contrast dose >100ml, diabetes and baseline creatinine clearance. **Notes:** sCr converted from mg/dl to µmol/l by NCGC (x88.4)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 80 **Age (mean±SD):** 65 ± 11 **Age ≥ 70:** 32 (40%) **Drop outs:** 0 **Baseline characteristics:** **M:F:** 63:17 **Baseline serum creatinine (µmol/l) (median [IQR]):** 115 [106-124] **Creatinine clearance (ml/min) (mean±SD):** 58±16 **Creatinine clearance <50ml/min:** 24 (30%) **Diabetes:** 21 (26%) **Hypertension:** 38 (48%) **ACEI or ARB:** 50 (63%) **NSAIDs:** NR				
Study details	**Patients**	**Interventions**	Outcome measures	Effect size	**Comments**
Koc 2012[233] **Country of study:** Turkey **Study design:** RCT – "randomised" **Who was blinded:** NR	**Patient group:** Patients undergoing elective coronary angiography or percutaneous coronary intervention. **Inclusion criteria:** • ≥18 years of age • Creatinine clearance ≤60ml/min and /or baseline sCr ≥97µmol/l **Exclusion criteria:** • Contrast agent hypersensitvity • Pregnancy or lactation	**Group 1** **Sodium chloride 0.9% + NAC** (154mEq/L in 5% dextrose) Route: iv Dose: 1ml/kg/h "before, on and after the day of the coronary procedure" iv NAC: 600mg bd day before and day of procedure (total 2.4g) **Group 2**	Mortality	NR	**Funding:** None reported **Limitations:** • Difference in number of patients aged ≥70 (24% in Group 1 versus 40% in Group 2) • Blinding not reported
			CI-AKI at 48 hours (increase in sCr ≥25% or 44µmol/l)	Group1: 2/80 (2.5%) Group 2: 13/80 (16.3%) Relative risk [95% CI]: NR p value: 0.006	
			CI-AKI at 72 hours	NR	
			Number of patients needing RRT	NR	
			Length of hospital stay (days, mean ± SD)	NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Setting: Multi centre **Duration of follow-up:** 48 hours **Definition of CI-AKI used:** increase in sCr ≥25% or 44µmol/l within 48h of exposure to contrast medium	• Decompensated heart failure • Pulmonary oedema • Emergency catheterisation • Acute kidney injury prior to procedure • ESRD **<u>All patients</u>** **N:** 160 **Baseline serum creatinine (µmol/l) (median [IQR]):** 115 [106-124] **Drop outs:** 0 **<u>Group 1</u>** **N:** 80 **Age (mean±SD):** 62 ± 10 **Age ≥ 70:** 19 (24%) **Drop outs:** 0 **Baseline characteristics:** **M:F:** 61:19 **Baseline serum creatinine (µmol/l) (median [IQR]):** 115 [106-133] **Creatinine clearance (ml/min) (mean±SD):** 59±16 **Creatinine clearance <50ml/min:** 21 (27%) **Diabetes:** 30 (38%) **Hypertension:** 49 (54%) **ACEI or ARB:** 60 (75%) **NSAIDs:** NR	**Sodium chloride 0.9%** (154mEq/L in 5% dextrose) Route: iv Dose: 1ml/kg/h "before, on and after the day of the coronary procedure" **Contrast** **Low osmolar, non-ionic** **Name:** iohexol **Dose(ml) (mean ± SD):** 138 ± 47 "The same contrast agent was given to all patients in similar amounts". p= NR **Both groups:** LVEF was measured before coronary procedures.			• Unclear allocation concealment **Additional outcomes:** 3rd arm (additional N=60) received sodium chloride 0.9% 1ml/kg/h 12h before and post procedure. CI-AKI at 48h in this group was 6/60 (10%). Subgroup analysis age, LVEF, contrast dose >100ml, diabetes and baseline creatinine clearance. **Notes:** sCr converted from mg/dl to µmol/l by NCGC (x88.4)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 2 **N:** 80 **Age (mean±SD):** 65 ± 11 **Age ≥ 70:** 32 (40%) **Drop outs:** 0 **Baseline characteristics:** **M:F:** 63:17 **Baseline serum creatinine (µmol/l) (median [IQR]):** 115 [106-124] **Creatinine clearance (ml/min) (mean±SD):** 58±16 **Creatinine clearance <50ml/min:** 24 (30%) **Diabetes:** 21 (26%) **Hypertension:** 38 (48%) **ACEI or ARB:** 50 (63%) **NSAIDs:** NR				

Table 35: Koc 2012[233]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Koc 2012[233] Country of study: Turkey Study design: RCT – "randomised" Who was blinded: NR Setting: Multi	Patient group: Patients undergoing elective coronary angiography or percutaneous coronary intervention. Inclusion criteria: ≥18 years of age Creatinine clearance ≤60ml/min and /or baseline sCr ≥97µmol/l Exclusion criteria: Contrast agent hypersensitvity	Group 1 Sodium chloride 0.9% + NAC (154mEq/L in 5% dextrose) Route: iv Dose: 1ml/kg/h "before, on and after the day of the coronary procedure" iv NAC: 600mg bd day before and day of procedure (total 2.4g)	Mortality	NR	Funding: None reported Limitations: Difference in number of patients aged ≥70 (24% in Group 1 versus 40% in Group 2) Blinding not reported
			CI-AKI at 48 hours (increase in sCr ≥25% or 44µmol/l)	Group1: 2/80 (2.5%) Group 2: 13/80 (16.3%) Relative risk [95% CI]: NR p value: 0.006	
			CI-AKI at 72 hours	NR	
			Number of patients needing RRT	NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
centre Duration of follow-up: 48 hours Definition of CI-AKI used: increase in sCr ≥25% or 44µmol/l within 48h of exposure to contrast medium	Pregnancy or lactation Decompensated heart failure Pulmonary oedema Emergency catheterisation Acute kidney injury prior to procedure ESRD All patients N: 160 Baseline serum creatinine (µmol/l) (median [IQR]): 115 [106-124] Drop outs: 0 Group 1 N: 80 Age (mean±SD): 62 ± 10 Age ≥ 70: 19 (24%) Drop outs: 0 Baseline characteristics: M:F: 61:19 Baseline serum creatinine (µmol/l) (median [IQR]): 115 [106-133] Creatinine clearance (ml/min) (mean±SD): 59±16 Creatinine clearance <50ml/min: 21 (27%) Diabetes: 30 (38%) Hypertension: 49 (54%) ACEI or ARB: 60 (75%) NSAIDs: NR Group 2	Group 2 Sodium chloride 0.9% (154mEq/L in 5% dextrose) Route: iv Dose: 1ml/kg/h "before, on and after the day of the coronary procedure" Contrast Low osmolar, non-ionic Name: iohexol Dose(ml) (mean ± SD): 138 ± 47 "The same contrast agent was given to all patients in similar amounts". p= NR Both groups: LVEF was measured before coronary procedures.	Length of hospital stay (days, mean ± SD)	NR	Unclear allocation concealment Additional outcomes: 3rd arm (additional N=60) received sodium chloride 0.9% 1ml/kg/h 12h before and post procedure. CI-AKI at 48h in this group was 6/60 (10%). Subgroup analysis age, LVEF, contrast dose >100ml, diabetes and baseline creatinine clearance. Notes: sCr converted from mg/dl to µmol/l by NCGC (x88.4)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 80 Age (mean±SD): 65 ± 11 Age ≥ 70: 32 (40%) Drop outs: 0 Baseline characteristics: M:F: 63:17 Baseline serum creatinine (µmol/l) (median [IQR]): 115 [106-124] Creatinine clearance (ml/min) (mean±SD): 58±16 Creatinine clearance <50ml/min: 24 (30%) Diabetes: 21 (26%) Hypertension: 38 (48%) ACEI or ARB: 50 (63%) NSAIDs: NR				

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2 **Table 36: Marenzi 2006[265]**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Marenzi 2006[265] Country of study: Italy Study design: RCT (computer	Patient group: Patients with acute myocardial infarction (MI) undergoing primary angioplasty (February 2003 – May 2005) Inclusion criteria: ST-segment elevation acute MI Presented within 12h (18h in cases of cardiogenic shock) after onset of symptoms	Group 1a (Intervention) NAC Dose: 600mg Route: iv pre contrast, po post contrast Timing pre contrast: single bolus Timing post contrast: bd for 48h (4 doses)	Mortality (in hospital)	Group1a: 5/115 Group1b: 3/118 Group 2: 13/119 1a vs 2 Odds ratio [95% CI]: 1.85 [0.54-6.37] p=0.32 1b vs 2 Odds ratio [95% CI]: 5.43[1.24-23.81] p=0.03 p value: 0.02	Funding: Grant from Italian Ministry of Health Additional outcomes: Multivariate analysis Cardiac complications Major bleeding Composite endpoint –
			CI-AKI at 48 hours	NR	
			CIAKI at 72 hours	Group1a: 17/115	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
generated random numbers) Who was blinded: Participants, healthcare staff and outcome assessors Setting: Coronary Care Unit Duration of follow-up: In hospital Definition of CI-AKI used: increase in sCr ≥25% 72h after primary angioplasty	Exclusion criteria: Long-term RRT Known allergy to NAC All patients N: 354 Age (mean±SD): 62 ± 12 Drop outs: 2 (0.6%) Group 1a N: 116 Age (mean±SD): 62.5 ± 13 Drop outs: 1 (0.9%) (died during angioplasty) Baseline characteristics: M:F: 87 (75.7%); 28 (24.3%) Baseline serum creatinine* (µmol/l) (median[IQR]): 89.3 [77.8-103.4] CKD:NR Diabetes:16/115 (13.9%) Hypertension: 51/115 (44.3%) ACEI: NR NSAIDs:NR Group 1b N: 119 Age (mean±SD): 62.2 ± 11 Drop outs: 1 (0.8%)(emergency CABG)	iv fluid – sodium chloride 0.9% Dose: 1ml/kg/h (half if overt heart failure) Route: iv Timing pre contrast: NR Timing post contrast:12h Group 1b (Intervention) NAC Dose: 1200mg Route: iv pre contrast, po post contrast Timing pre contrast: single bolus Timing post contrast: bd for 48h (4 doses) iv fluid – sodium chloride 0.9% Dose: 1ml/kg/h (half if overt heart failure) Route: iv Timing pre contrast: NR Timing post contrast:12h Group 2 (Comparison) placebo Matched placebo iv fluid – sodium chloride	(increase in sCr ≥25% at 72h)	Group1b: 10/118 Group 2: 39/119 Relative risk [95% CI]: NR p value: <0.001	death, RRT or mechanical ventilation Notes: *calculated from mg/dL by NCGC (x88.4)
			CI-AKI at 72 hours (increase in sCr ≥44µmol/l at 72h)	Group1a: 7/115 Group1b: 4/118 Group 2: 22/119 Relative risk [95% CI]:NR p value: <0.001	
			Number of patients needing RRT	Group1a: 2/115 Group1b: 1/118 Group 2: 6/119 Relative risk [95% CI]:NR p value: 0.14	
			Length of hospital stay	NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Baseline characteristics: M:F: 100 (84.7%) : 18 (15.3%) Baseline serum creatinine* (µmol/l) (median[IQR]): 90.2 [81.3-102.5] CKD:NR Diabetes:20/118 (16.9%) Hypertension: 58/118 (49.2%) ACEI: NR NSAIDs:NR Group 2 N: 119 Age (mean±SD): 62.6 ± 12 Drop outs: 0 Baseline characteristics: M:F: 97 (81.5%): 22(18.5%) Baseline serum creatinine* (µmol/l) (median[IQR]): 93.7 [81.3-106.1] CKD:NR Diabetes: 18/119 (15.1%) Hypertension:49/119 (41.2%) ACEI: NR NSAIDs:NR	0.9% Dose: 1ml/kg/h (half if overt heart failure) Route: iv Timing pre contrast: NR Timing post contrast:12h Contrast Nonionic low osmolar Name: iohexol Dose (ml) (mean±SD): Group 1a:264 ± 146 Group 1b: 253 ± 108 Group 2: 274 ± 113 Both groups: Echocardiogram within 24h of admission Bolus 5000iU heparin with additional intraprocedural boluses to maintain APTT 300s Post stenting aspirin + clopidogrel or ticlopidine at “standard doses”			

1

1 **Table 37: Rashid 2004[336]**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Rashid 2004[336] Country of study: UK Study design: RCT – "randomisation performed by the hospital clinical trials pharmacist" Who was blinded: Patient and doctor Setting: Tertiary centre-vascular surgery department Duration of	Patient group: Patients with peripheral vascular disease undergoing elective angiography or angioplasty Inclusion criteria: As above Normal sCr subgroup (men <120µmol/l, women < 97 µmol/l) Raised sCr subgroup. Exclusion criteria: None reported. All patients N: 94/103 randomised Drop outs: 9/103 (8.7%) - 7 cancelled after received randomisation number due to unavailability of hospital beds or time in the angiography suite, 2 patients refused due to difficulty collecting 24h urine. Group 1 N: 46 Age (mean±SD): 72.1 ± 12.3 Drop outs: NR Baseline characteristics: M:F: 27 (58.7%): 19 (41.3%) Baseline serum creatinine (µmol/l) (mean±SD): 109.9 ± 41.2	Group 1 (Intervention) NAC Dose: 1000mg Route: iv Timing pre contrast: given in the bag of sodium chloride 0.9% Timing post contrast: given in the bag of sodium chloride 0.9% iv fluid – sodium chloride 0.9% Dose: 500ml over 4-6h (pre and post) Route: iv Timing pre contrast: 6-12h Timing post contrast: given over 4-6h Group 2 (Comparison) placebo Bags prepared by hospital clinical trials pharmacist, nothing added to sodium chloride 0.9% for placebo group	Mortality (7 days)	Group1: 1/46 (2.2%) (partly due to complications of renal failure) Group 2: 0/48 Relative risk [95% CI]: NR p value: NR	Funding: None reported Limitations: Method of randomisation not fully described - "randomisation performed by the hospital clinical trials pharmacist" Additional outcomes: Change in sCr at 24h,48h and 7d Change in CrCl at 24h, 48h and 7d Re-analysed data using 20% rise in sCr within 1-7 days of contrast administration Notes: *calculated from mg/dL by NCGC (x88.4)
			CI-AKI at 48 hours (increase in sCr* ≥ 44.2 µmol/l or ≥25% 48h after contrast)	Group1: 3/46 (6.5%) Group 2: 3/48 (6.3%) Relative risk [95% CI]: NR p value: NR	
			CI-AKI at 48 hours (normal sCr subgroup)	Group1: 0 Group 2: 0	
			CI-AKI at 48 hours (raised sCr subgroup)	Group1: 3/17 (17.6%) Group 2: 3/21 (14.3%) Relative risk [95% CI]: NR p value: 1.000	
			CI-AKI at 72 hours	NR	
			Number of patients needing RRT	Group1: ?1/46 (2.2%)(if person who died required RRT) Group 2: 1/48 (2.1%) Relative risk [95% CI]:NR p value: NR	
			Number of patients achieving dialysis independence	NR	
			Length of hospital stay	NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
follow-up: 7 days Definition of CI-AKI used: increase in sCr* ≥ 44.2 µmol/l or ≥25% 48h after contrast.	CKD: 17/46 (37.0%) Diabetes: 17/46 (37.0%) Hypertension: NR ACEI: NR NSAIDs: NR Group 2 N: 48 Age (mean±SD): 68.8 ± 12.3 Drop outs: NR Baseline characteristics: M:F: 33 (68.75%): 15 (31.25%) Baseline serum creatinine (µmol/l) (mean±SD): 124.3 ± 63.5 CKD: 21/48 (43.8%) Diabetes: 13/48 (27.1%) Hypertension: NR ACEI: NR NSAIDs: NR	iv fluid – sodium chloride 0.9% Dose: 500ml over 4-6h (pre and post) Route: iv Timing pre contrast: 6-12h Timing post contrast: given over 4-6h Contrast low osmolar Name: Iohexol (Omnipaque 300) Dose(ml) (mean±SD): 143.2 ± 69.4 Group 1: 135.4 ± 62.7 Group 2: 151.2 ± 75.6			

1 **Table 38: Thiele 2010[395]**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Thiele 2010[395] Country of study: Germany	Patient group: Patients with ST elevation myocardial infarction (MI) undergoing primary angioplasty with moderate contrast volumes (November 2006 – February 2008)	Group 1 (Intervention) NAC Dose: 1200mg bd Route: iv Timing pre contrast: single bolus	Mortality (at 6 months)	Group1: 12 Group 2: 12 +2 Relative risk [95% CI]: NR p value: NR	Funding: None reported Limitations: Only patients blinded
			CI-AKI at 48 hours	NR	
			CI-AKI at 72 hours	Group1: 18/126 (14.3%)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Study design: RCT – "single blinded" computer generated random numbers in 1:1 ratio Who was blinded: Patients. CCU physicians aware of group assignment, but blinded to all laboratory, ECG and MRI measurements Setting: Single centre cardiology deparment/ CCU Duration of	Inclusion criteria: MI symptoms <12h ST segment elevation ≥0.1mV in ≥2 extremity leads or ≥0.2mV in ≥2 precordial leads Exclusion criteria: Previous fibrinolysis <12h Known NAC allergy Chronic RRT Pregnancy Contraindication to MRI All patients N: 251/258 screened (97.3%) Drop outs: 3 = no informed consent, 1= hepatitis C and 3= technical reasons Group 1 N: 126 Age (median[IQR]): 68 [57-75] Drop outs: 0 Baseline characteristics: M:F: 89 (70.6%) : 37 (29.4%) Baseline serum creatinine (µmol/l) (median[IQR]): 81 [69-97] CKD: NR Diabetes: 32/126 (25.4%) Hypertension: 89/126 (70.6%)	Timing post contrast: 48h (4 doses) iv fluid – sodium chloride 0.9% Dose: 1ml/kg/h (0.5ml/kg/h in overt heart failure) Route: iv Timing pre contrast: not given Timing post contrast: 12h Group 2 (Comparison) placebo Matched placebo (10ml sodium chloride 0.9%) iv fluid – sodium chloride 0.9% Dose: 1ml/kg/h (0.5ml/kg/h in overt heart failure) Route: iv Timing pre contrast: not given Timing post contrast: 12h Contrast low osmolar Name: iopromide	(how was this measured: increase in sCr ≥25%)	Group 2: 25/123 (20.3%) Relative risk [95% CI]: NR p value: 0.28	Additional outcomes: Myocardial reperfusion injury Markers of oxidative stress Infarct size Early ST segment resolution Major cardiovascular events within 6 months after randomisation Changes in sCr at 72h Changes in CrCl at 72h
			Number of patients needing RRT	Group1: 4/126 Group 2: 1/123 Relative risk [95% CI]: NR p value: 0.37	
			Number of patients achieving dialysis independence	NR	
			Length of hospital stay	NR	
			Adverse events during NAC administration	Group1: 0 Group 2: 0	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
follow-up: 6 months from randomisation Definition of CI-AKI used: increase in sCr ≥25% 72h after PCI.	ACEI: 124/126 (98.4%) NSAIDs (aspirin): 125/126 (99.2%) Group 2 N: 123/125 (2/125 [1.6%] died during catheterisation) Age (median [IQR]): 68 [56-76] Drop outs: 0 Baseline characteristics: M:F: 82 (65.6%) : 43 (34.4%) Baseline serum creatinine (µmol/l) (median[IQR]): 78 [67-90] CKD: NR Diabetes: 41/125 (32.8%) Hypertension: 92/125 (73.6%) ACEI: 122/125 (97.6%) NSAIDs (aspirin): 124/125 (99.2%)	Dose (ml) (median[IQR]): Group 1: 180 [140-230] Group 2: 160 [120-220] p= 0.20 Both groups: Additional use of thrombectomy where indicated All patients received 500mg aspirin and heparin (60iU/kg iv) before PCI, plus clopidogrel 600mg po during PCI and then 75mg od for ≥12 months. Aspirin continued indefinitely at a dose of 100mg/d.			

Table 39: Webb 2004[421]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Webb 2004[421] Country of study: Canada	Patient group: Patients with "renal dysfunction" undergoing cardiac catheterisation or PCI Inclusion criteria:	Group 1 (Intervention) NAC Dose: 500mg (in 50ml of 5% dextrose saline) Route: iv Timing pre contrast:	Inhospital mortality	Group1: 10/194 (5.2%) Group 2: 9/204 (4.4%) Relative risk [95% CI]: NR p value: NR	Funding: Tyco Canada Inc (suppliers of ioversol [Optiray 320]), Shiley Canada Inc, Vancouver Hospital Interventional Trust
			CI-AKI at 48 hours	NR	
			CI-AKI at "72 hours"	Group1: 46/194 (23.7%)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Study design: RCT – block random assignment using sealed envelopes, assignment by research co-ordinator not involved in patient recruitment Who was blinded: "Study personnel" and patients Setting: Inpatient/outpatient tertiary care cardiac unit Duration of follow-up: In hospital, telephone call at 2 days post procedure	Screening GFR <50ml/min Exclusion criteria: Acute renal failure Creatinine >400µmol/l Concurrent RRT Unstable clinical status NAC administration within 48h Age <18 Inability to comply with follow up Recent creatinine elevation after diagnostic angiogram All patients N: 398 (available case analysis)/487 (enrolled) Drop outs: 89 (18.3%) (40 no follow up Cr, 38 sCr outside 2-8 day window, 10 had exclusion criteria, 1 did not receive study drug) Group 1 N: 194/242 Age (mean±SD): 70.8 ± 10.3 Drop outs: 48/242 (19.8%) Baseline characteristics: M:F: 144/242 (59.5%): 98/242 (40.5%) Baseline serum creatinine (µmol/l) (median [IQR]): 141 [125-	over 15 mins within 1h of procedure Timing post contrast: not given iv fluid – sodium chloride 0.9% Route: iv pre contrast: 200ml post contrast: 1.5ml/kg/h for 6h Group 2 (Comparison) placebo Dose: 50ml of 5% dextrose saline Route: iv Administered as for NAC iv fluid – sodium chloride 0.9% Route: iv pre contrast: 200ml post contrast: 1.5ml/kg/h for 6h Contrast low osmolar	(reduction in CrCl from baseline of >5ml/min day 2-8, median 3 days) CI-AKI at "72 hours" (increase in sCr ≥25% or ≥44µmol/l day 2-8, median 3 days) Number of patients needing RRT Number of patients achieving dialysis independence Length of hospital stay	Group 2: 43/204 (21.1%) Relative risk [95% CI]: NR p value: 0.55 Group1: 37/194 (19.1%) Group 2: 34/204 (16.7%) Relative risk [95% CI]: NR p value: NR Group1: 0 Group 2: 0 NR NR	and the St Paul's Hospital Foundation Limitations: Terminated early after blinded interim analysis showed "futility" 18% drop out rate NAC only given precontrast Additional outcomes: (list additional outcomes reported in paper but not recorded in this table) Notes: GFR estimated using MDRD equation Pre-defined subgroups for analysis: Age >70, sex, pre-existing hypertension, diabetes mellitus,

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
for outpatients Definition of CI-AKI used: reduction in CrCl from baseline of >5ml/min day 2-8	166] CKD: NR Diabetes: 74/242 (30.6%) Hypertension: NR ACEI/ARB: 165/242 (68.1%) NSAIDs: NR Group 2 N: 204/245 Age (mean±SD): 70.0 ± 9.4 Drop outs: 41/245 (16.7%) Baseline characteristics: M:F: 152/245 (62.0%): 93/245 (38.0%) Baseline serum creatinine (µmol/l) (median [IQR]): 142 [124-167] CKD: NR Diabetes: 96/245 (39.2%) Hypertension: NR ACEI/ARB: 171/245 (70.0%) NSAIDs: NR	Name: ioversol Dose(ml) (median [IQR]): 120 [80-175]			impaired LVEF volume of contrast (≥100ml vs <100ml) unable to extract from figure but none of the p values significant Sample size calculation: 918 patients to detect a relative reduction in CI-AKI of 50% with α 0.05 and power 80%.

G.2.2.9 NAC + sodium chloride 0.45% vs sodium chloride 0.45%

Table 40: Allaqaband 2002[15]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Allaqaband	Patient group:	Group 1 (Intervention)	Mortality	NR	Funding:

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
2002[15] Country of study: USA Study design: Prospective RCT Who was blinded: NR Setting: Clinical Secondary Care Duration of follow-up: 48 hours Definition of CI-AKI used: An absolute increase in serum creatinine level of at least 44.2	Prospectively enrolled 123 patients who were scheduled to undergo cardiovascular interventions requiring the use of radio contrast Inclusion criteria: Baseline creatinine ≥136.8 µmol/l** or an estimated creatinine clearance of ≤60 ml/min (calculated on the basis of sex, weight and age) Exclusion criteria: NR All patients N: 123* Age (mean±SD): 71±10 Drop outs: 0 Group 1 N: 45 Age (mean±SD): 70±10 Drop outs: 0 Baseline characteristics: M:F: 28/17 Baseline serum creatinine (µmol/l) (mean±SD): 194.48±64.532** CKD: NR Diabetes:70% Hypertension:80%	NAC Dose:600mg Route: oral Timing pre contrast/ Timing post contrast: twice daily starting the day before the procedure and continuing through the day of the procedure iv fluid –sodium chloride 0.45% Dose: 1ml/kg/hr Route: IV Timing pre contrast:12 hr Timing post contrast:12 hr Group 2 (Comparison) IV fluid iv fluid sodium chloride 0.45%Dose: 1ml/kg/hr Route: IV Timing pre contrast:12 hr Timing post contrast:12 hr Contrast low osmolar non ionic	CI-AKI at 48 hours (absolute increase in serum creatinine level of at least 44.2 µmol/l** with 48 hr of the injection) CI-AKI at 72 hours (how was this measured) Number of patients needing RRT Length of hospital stay	Group1: 17.7% Group 2: 15.3% Relative risk [95% CI]:NR p value: 0.919 NR NR NR	NR Limitations: Blinding unclear Allocation concealment unclear Larger proportion of diabetic patients in NAC arm of the study 43% v 70% Additional outcomes: Absolute change in serum creatinine concentration at 24 hrs and 48 hrs Incidence of CI-AKI in patients using ACEI or calcium channel antagonists Cardiac interventional procedure undertaken Notes: *Total number of patients enrolled including fenoldopam arm of the study, total number of patients for the sodium chloride and NAC arms only =85 A random allocation table was used to assign patients to one of three arms of the study. No patient received aminophylline, theophylline or dopamine during the study period. **calculated from mg/dL by NCGC

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
µmol/l** with 48 hr of the injection of the radiocontrast medium	ACEI:50% NSAIDs: NR Group 2 N: 40 Age (mean±SD): 71±10 Drop outs: 0 Baseline characteristics: M:F: 24/16 Baseline serum creatinine (µmol/l) (mean±SD): 179.452 ±42.432** CKD: NR Diabetes: 43% Hypertension: 92% ACEI: 65% NSAIDs: NR	Name: Ioversol/ Iodixanol Dose: (ml/kg) Group1: 1.52 ±0.81 Group 2: 1.47±0.90 P value: 0.806			(x88.4) Incidence of CI-AKI according to diabetic status Group1: 5/8 Group 2: 3/6 (denominator is the total number of patients developing CI-AKI in the NAC/sodium chloride group)

1 **Table 41: Boccalandro 2003[52]**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Boccalandro 2003[52] Country of study: USA Study	Patient group: All consecutive patients between August 2000 and December 2001 with serum creatinine >106.8 µmol/l** or a creatinine clearance of <50 ml* who underwent elective cardiac catheterization and received >1cc/kg of radiographic contrast agent	Group 1 (Intervention) NAC Dose:600 mg Route: oral Timing pre contrast/ Timing post contrast: twice a day the day before and the day of	Mortality CI-AKI at 48 hours (an increase in the serum creatinine concentration of >44.2 µmol/l** from the baseline value at 48 hr after the procedure)	NR Group1: 10/75 (13%) Group 2: 13/106 (12%) Relative risk [95% CI]: p value: 0.84	Funding: NR Limitations: Randomisation unclear Blinding unclear Allocation concealment unclear Powered to find a 10% relative risk

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
design: Prospective RCT Who was blinded: NR Setting: Clinical Secondary Care Duration of follow-up: 48hr Definition of CI-AKI used: An increase in the serum creatinine concentration of >44.2 µmol/l** from the baseline value at 48 hr after the procedure	Inclusion criteria: As above Exclusion criteria: Acute renal failure End stage renal disease Receiving oral theophylline, mannitol, furosemide or dopamine Undergoing renal angioplasty or renal angiogram All patients N: 179 Age (mean±SD): NR Drop outs: 0 Group 1 N: 73 Age (mean±SD): 66±13 Drop outs: 0 Baseline characteristics: M:F: 49/24 Baseline serum creatinine (µmol/l) (mean±SD): 159.12±53.04** CKD: NR Diabetes: 49 (67%) Hypertension: 64 (87%) ACEI: 40(54%)	catheterization iv fluid sodium chloride 0.45% Dose: 75 cc/hr Route:IV Timing pre contrast:12hr Timing post contrast:12hr Group 2 (Comparison) IV fluid iv fluid sodium chloride 0.45% Dose: 75 cc/hr Route: IV Timing pre contrast:12hr Timing post contrast:12hr Contrast low osmolar non ionic Name: Iodixanol Dose: NR	CI-AKI at 72 hours Number of patients needing RRT Length of hospital stay	NR NR NR	reduction in incidence of CI-AKI 10% more diabetics in NAC arm 10% more patients using ACEI in sodium chloride arm Additional outcomes: Serum creatinine at 48 hrs Absolute change in serum creatinine Subgroup analysis Treatment effect in patients with elevated baseline serum creatinine or patients who underwent percutaneous intervention Baseline measures and associated risk of CI-AKI Notes: *Calculated using the formula of Cockcroft and Gault Intention to treat analysis The amount of contrast used was at the discretion of the operator. Contrast administer ed(cc) Group 1:192±142 Group2:191±120 P value:0.959 Contrast administer (cc/kg) Group 1:2.2±1.7 Group2:2.3±1.5 P value:0.678

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	NSAIDs: NR Group 2 N: 106 Age (mean±SD): 65±11 Drop outs: 0 Baseline characteristics: M:F: 59/47 Baseline serum creatinine (µmol/l) (mean±SD): 163.2±53.04** CKD: NR Diabetes: 61 (57%) Hypertension: 91(85%) ACEI: 68 (64%) NSAIDs: NR				Total fluid volume pre procedure (cc) Group 1:899±401 Group2:896±392 P value:0.960 Total fluid volume post procedure (cc) Group 1:933±402 Group2:992±397 P value:0.332 **calculated from mg/dL by NCGC (x88.4)

1 **Table 42: Briguori 2002[62]**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Briguori 2002[62] Country of study: Italy Study design: Prospective	Patient group: From September 2000, 183 consecutive patients with impairment of renal function (serum creatinine concentration >106.8 µmol/l** and/or estimated creatinine clearance <70 ml/min) undergoing elective coronary and/or peripheral angiography and/or angioplasty	Group 1 (Intervention) NAC Dose: 600 mg Route: oral Timing pre contrast/ Timing post contrast: Twice daily, on the day before and on the day of administration of the contrast agent, for a total	Mortality CI-AKI at 48 hours (increase in the serum creatinine concentration of ≥25% of the baseline value at 48 h or the need for dialysis after administration)	NR Group1: 6 / 92 (6.5%) Group 2: 10 / 91 (11%) Relative risk [95% CI]:NR p value: 0.22	Funding: NR Limitations: Randomisation unclear Blinding unclear Allocation concealment unclear Approximately 10% more diabetics in sodium chloride arm

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
RCT Who was blinded: NR Setting: Clinical secondary care Duration of follow-up: 48 hours Definition of CIAKI used: An early contrast agent-induced reduction in renal function was defined as an increase in the serum creatinine concentration of ≥25% of the baseline value at 48 h	Inclusion criteria: As above Exclusion criteria: NR All patients N: 183 Age (mean±SD): NR Drop outs: 0 Group 1 N: 92 Age (mean±SD): 64 ±9 Drop outs: 0 Baseline characteristics: M: F: 77 (84%) / 15 (16%) Baseline serum creatinine (µmol/l) (mean±SD): 134.368 ± 38.012 ** CKD: NR Diabetes: 40 (43%) Hypertension: 66 (72%) ACEI: 52 (56.5%) NSAIDs: NR Group 2 N: 91 Age (mean±SD): 64±9	of two iv fluid sodium chloride 0.45% Dose: 1 ml/kg body weight/ hr Route: IV Timing pre contrast: 12 hr Timing post contrast: 12hr Group 2 (Comparison) IV fluid iv fluid sodium chloride 0.45% Dose: 1 ml/kg body weight/ hr Route: IV Timing pre contrast: 12 hr Timing post contrast: 12hr Contrast low osmolar nonionic Name: Iopromide Dose: 0.769 mg/ml, 370	CI-AKI at 72 hours	NR	Additional outcomes: Serum creatinine at 48 hr Proteinuria levels Macroalbuminuria rate Post-hoc sub group analysis Volume of contrast administered predicative of contrast associated nephrotoxicity Baseline serum creatinine range predicative of contrast associated nephrotoxicity Notes: None of the patients received theophylline dopamine, mannitol or furosemide during the study The amount of contrast agent administered was similar between the two groups (194 ± 127 ml in group 1 vs. 200 ± 144 ml in group 2; p = 0.80). The amount of contrast dye was significantly higher in the 22 patients who had ad-hoc PCI (347 ± 182 ml vs. 321 ± 125 ml for PCI alone, 135 ± 72 ml for coronary angiography alone and 114 ± 43 ml for peripheral angiography; p = 0.001) Intention to treat analysis
			Number of patients needing RRT	Group1: 0/92 Group 2: 1/91 (1.1%) Relative risk [95% CI]: NR p value: NR	
			Length of hospital stay	NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
or the need for dialysis after administration of the contrast media	Drop outs: 0 Baseline characteristics: M: F: 81 (89%)/ 10 (11%) Baseline serum creatinine (µmol/l) (mean±SD): 136.136 ± 31.824** CKD: NR Diabetes: 29 (32.5%) Hypertension: 65 (72%) ACEI: 60 (55%) NSAIDs: NR	mg iodine/ml			

G.2.2.10 NAC + sodium bicarbonate versus sodium bicarbonate

See Table 43: Hafiz 2012[167] located in G.2.1.7

G.2.2.11 NAC + sodium bicarbonate vs NAC + sodium chloride 0.9%

Table 44: Carbonell 2007[70]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Carbonell 2007[70] Country of study: Spain	Patient group: High-risk* coronary patients with normal renal** function undergoing coronary angiography. Data collected from March 1st 2002 – July 31st 2005	Group 1 (Intervention) NAC Dose:600mg diluted in 50 ml of 0.9% saline Route:IV Timing pre	Mortality (in hospital)	Group1: 2.8% Group 2: 4.6% Relative risk [95% CI]: NR p value: Not significant	Funding: NR Limitations: Allocation concealment unclear Short follow up – insufficient to
			CI-AKI at 48 hours (acute increase in	Group1: 11/107 (10.3%) Group 2: 11/109 (10.1%)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Study design: Prospective RCT Who was blinded: Double blind Physicians and patients Setting: Tertiary care Duration of follow-up: Data collection continued until discharge (a few days) Definition of CI-AKI used: Acute increase in serum creatinine concentration of	Inclusion criteria: Exclusion criteria: Chronic renal failure Acute renal dysfunction Hemodynamic instability (systolic blood pressure <90 mmHg) Know allergy to NAC or to contrast agents Untreated GI bleeding Previous treatment with theophylline, mannitol or nephrotoxic antibiotics All patients N: 216 Age (mean±SD): NR Drop outs: 0 Group 1 N: 107 Age (mean±SD): 63.1±13.7 Drop outs: 0 Baseline characteristics: M:F:86/21 Baseline serum creatinine (µmol/l) (mean±SD): 83.096±14.144 CKD: NR Diabetes: 30 (27.5%)	contrast/Timing post contrast: IV for 30 mins twice daily for 4 doses, starting at east during the 6 hrs before the administration of contrast media iv fluid sodium chloride 0.45% Dose: 1 ml/kg/h*** Route: IV Timing pre contrast:6hr Timing post contrast:12 hr Group 2 (Comparison) placebo Dose:50 ml sodium chloride 0.9% Route: IV Timing pre contrast/ Timing post contrast: for 30 mins iv fluid sodium chloride 0.45% Dose: 1 ml/kg/h*** Route: IV Timing pre contrast:6hr Timing post contrast:12 hr	serum creatinine concentration of 44µmol/l or 25% increase above baseline level at 48 hrs after contrast dosing)	Relative risk [95% CI]: NR p value:0.5	calculate mid/long term morbidity/ mortality Measure used to detect renal dysfunction; serum creatinine concentrations can inaccurately estimate glomerular filtration rate Additional outcomes: Notes: Normal renal function arm of the main study * high risk –diagnosed with angina at rest or post-myocardial infarction or received thrombolytic therapy with failed recanalization so the cardiac catheterisation was an emergency procedure. ** normal renal function-stable serum creatinine <123.76µmol/l or a creatinine clearance of >60 ml/min according to the Cockroft-Gault formula *** patients with congestive heart failure received a reduced hydration volume. 16 patients received 1/3 of the volume due
			CIAKI at 72 hours	NR	
			Number of patients needing RRT	NR	
			Length of hospital stay	NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
44µmol/l or 25% increase above baseline level at 48 hrs after contrast dosing	Hypertension: 56 (52.3%) ACEI: 67 (62.6%) NSAIDs: 96 (89.7%) Group 2 N: 109 Age (mean±SD):60.7 ±11.7 Drop outs: 0 Baseline characteristics: M:F: 79/30 Baseline serum creatinine (µmol/l) (mean±SD): 84.864±15.028 CKD: NR Diabetes: 30 (27.5%) Hypertension: 63(57.8%) ACEI: 58 (53.3%) NSAIDs: 91 (83.5%)	Contrast Non ionic low osmolar Name: iopromide Dose: 370 mg iodine/ml Both groups:			to the presence of pulmonary oedema Randomisation was carried out with computer generated random numbers (C4- study design pack program) Intention to treat analysis

1

2 **Table 45: Carbonell 2010[71]**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Carbonell 2010[71] Country of study:	Patient group: As in Carbonell 2007. Data collected from March 1st 2002 – December 31st 2006	As in Carbonell 2007	Mortality (in hospital)	Group1: 4/39 (%) Group 2: 7/42(%) Relative risk [95% CI]: NR p value: 0.65	Funding: NR Limitations:
			Mortality (1 year)	Group1: 6/39 (15.4%)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Spain Study design: Prospective RCT Who was blinded: Double blind Physicians and patients Setting: Tertiary care Duration of follow-up: As in Carbonell 2007 Definition of CI-AKI used: As in Carbonell 2007	Inclusion criteria: Patients with chronic renal disease described as; stable serum creatinine ≥123.76µmol/L or <60 mL/ min creatinine clearance calculated with the Cockcroft-Gault Exclusion criteria: Hemodynamic instability (systolic blood pressure <90 mmHg) Know allergy to NAC or to contrast agents Untreated GI bleeding Previous treatment with theophylline, mannitol or nephrotoxic antibiotics All patients N: 81 Age (mean±SD): NR Drop outs: 0 Group 1 N: 39 Age (mean±SD): 69±11 Drop outs: 0 Baseline characteristics: M:F: 31/8 Baseline serum creatinine (µmol/l) (mean±SD): 177.684±68.068			Group 2:9/42 (21.4%) Relative risk [95% CI]: NR p value: 0.67	Additional outcomes: Notes: Chronic renal disease arm of the main study Randomisation was carried out with computer generated random numbers (C4-study design pack program) Intention to treat analysis
			CI-AKI at 48 hours (acute increase in serum creatinine concentration of 44µmol/l or 25% increase above baseline level at 48 hrs after contrast dosing)	Group1: 2/39(5.1%) Group 2: 10 /42(23.8%) Relative risk [95% CI]: NR p value: 0.027	
			CI-AKI at 72 hours (how was this measured)	NR	
			Number of patients needing RRT(whilst in care of cardiac unit)	Group1: 0/39(0%) Group 2: 1/42 (2%) Relative risk [95% CI]: NR p value: 0.15	
			Length of hospital stay Median [95% CI]	Group1: 10(1-42) Group 2: 10 (2-76) Relative risk [95% CI]: NR p value: 0.20	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	CKD: 42(100%) Diabetes: 18 (43%) Hypertension: 31(80%) ACEI: 15(38%) NSAIDs: 27(69%) Group 2 N: 42 Age (mean±SD): 70±10 Drop outs: 0 Baseline characteristics: M:F:34/8 Baseline serum creatinine (µmol/l) (mean±SD): 165.308±61.88 CKD: 42(100%) Diabetes: 20(51%) Hypertension: 30(71%) ACEI: 15 (36%) NSAIDs: 27(64%)				

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2 **Table 46: Durham 2002 [117]**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Durham 2002 [117] Country of study:	Patient group: Patients referred for cardiac angiography at Winthrop-University Hospital, including both diagnostic and therapeutic	Group 1 (Intervention) NAC (mixed with 6ml of orange juice*) Dose: 1200 mg (total 2400 mg)	Mortality CI-AKI at 48 hours (An increase serum creatinine of 0.5 mg/dL at 48 hours	NR Group1: 10/38 (22%) Group 2: 9/41 (26.3%) Relative risk [95% CI]: NR	Funding: NR Limitations: Number of drop outs per arm

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
New York, USA Study design: RCT Who was blinded: NR Setting: Inpatient Duration of follow-up: 48 hours Definition of CI-AKI used: An increase serum creatinine of 44.2 µmol/l# at 48 hours after angiography	procedures. Patients were enrolled between December 2000 and November 2001 Inclusion criteria: Baseline serum creatinine >1.7mg/dL Exclusion criteria: Less than 18 years old, The renal disease was determined by a nephrologist to have a reversible component, Patient unwilling or unable to provide informed consent, Adequate time prior to angiography was not available to perform the study procedures, Patient had any evidence of active atheroembolic disease, including but not limited to blue toes, livedo reticularis or eosinophilia, Known prior insensitivity to acetylcysteine, Severe asthma, Breast feeding women, Severe peptic ulcer disease, Respiratory depression Serum creatinine measurements varied by more than 15% in the 3 days prior to angiography. Women of child bearing potential not using an approved method of contraception	Route: oral Timing pre contrast: 1 hr Timing post contrast: 3 hrs following cardiac catheterization iv fluid: sodium chloride 0.45% Dose: 1.0 mL/kg/h Route:IV Timing pre contrast: 12 hours Timing post contrast: up to 12 hours Group 2 (Comparison) placebo: orange juice Dose: 12 mL orange juice Route: oral Timing pre contrast: 1 hr Timing post contrast: 3 hrs iv fluid; sodium chloride 0.45% Dose: 1.0 mL/kg/h Route:IV Timing pre contrast: 12	after angiography) CI-AKI at 72 hours Number of patients needing RRT Length of hospital stay	p value: Not sig NR NR NR	of study not reported. Unclear allocation concealment Unclear blinding Additional outcomes: Any side effect(s) due to NAC Blood urea nitrogen Serum creatinine immediately after cathetheterization, and at 48 hours, Total volume of contrast administered, Total IV hydration administered, Type of catheterization procedure performed. CI-AKI in patients diagnosed with diabetes CI-AKI in patients with elevated baseline serum creatinine (>2.5mg/dL) Notes: Randomization was performed using a computer generated randomization list by the research pharmacy. Eligible patients were randomized on a 1:1 basis * Study drug was prepared as a mixture of 6 mL NAC

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	All patients N: 81 Age (mean±SD): NR Drop outs: 2 Group 1 N: 38 (excluding drop outs) Age (mean±SD): 71.4±12.2 Drop outs: NR Baseline characteristics: M:F: 24/14 Baseline serum creatinine (µmol/l) (mean±SD): 194.48±35.36# CKD: NR Diabetes: 50% Hypertension: 57% ACEI: NR NSAIDs: NR Group 2 N: 41 (excluding drop outs) Age (mean±SD): 69.8±9.7 Drop outs: NR Baseline characteristics: M:F: 28/13 Baseline serum creatinine (µmol/l) (mean±SD): 203.32±44.2# CKD: NR Diabetes: 46.3 % Hypertension: 64.4 %	hours Timing post contrast: up to 12 hours Contrast Iow osmolar nonionic Name: Omnipaque (iohexol) Dose: NR Duration: see below Both groups: The actual rate and duration of contrast was at the discretion of the nephrologist or cardiologist, who were permitted to modify the regimen depending on the clinical status of the patient			20% solution with 6 mL of orange juice. The juice was added to mask the sulfurous odor of NAC. A series of “taste tests” were conducted to ensure blinding. #calculated from mg/dL by NCGC (x88.4)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	ACEI: NR NSAIDs: NR				

1 **Table 47: Goldenburg 2004 [157]**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Goldenburg 2004 [157] Country of study: Israel Study design: Prospective RCT Who was blinded: Double blind. Patients and physicians Setting: Clinical	Patient group: 80 consecutive patients who underwent coronary angiography and had serum creatinine of concentrations ≥1.5mg/dl or creatinine clearance of < 50 ml/ml. All patients had a known history of chronic renal failure with stable creatinine concentrations. Enrolled from june 2002 through march 2003 Inclusion criteria: As above Exclusion criteria: Acute renal failure Acute myocardial infarction requiring primary or rescue coronary intervention within less than 12 hrs Cardiogenic shock Current peritoneal or	Group 1 (Intervention) NAC Dose:600 mg t.i.d Route: oral Timing pre contrast:24 hrs Timing post contrast:24 hrs iv fluid-sodium chloride 0.45% Dose:1 ml/kg / hr Route: IV Timing pre contrast:12hrs Timing post contrast:12 hrs Group 2 (Comparison) placebo Matched placebo iv fluid-sodium chloride	Mortality	NR	Funding: NR Limitations: Allocation concealment unclear 10 patients excluded, number per arm of study not reported Small sample Additional outcomes: Clinical adverse events including; need for dialysis, overt congestive heart failure following coronary angiography, transient hypotension (systolic blood pressure <100mmHg), peri-procedural acute MI, emergency cardiac surgery, cardiac arrhythmias, the need for intra-aortic counter-pulsation, in hospital death and length of hospital stay. (group1 = 2, group2 = 3 p=0.47)
			CI-AKI at 48 hours (Increase in serum creatine concentrations of ≥44.2 µmol/l 48 h after administration of contrast)	Group1: 4/41 (10%) Group 2: 3/39 (8%) Relative risk [95% CI]: NR p value: 0.52 Unadjusted odds ratio [95% CI]: 1.30 (0.27-6.21)	
			CI-AKI at 72 hours	NR	
			Number of patients needing RRT	NR	
			Number of patients achieving dialysis independence	NR	
			Length of hospital stay Median (inter quartile range)	Group1: 4 (2-4) Group 2: 2 (2-4) Relative risk [95% CI]: NR p value: 0.44	

Duration of follow-up: 7 days Definition of CI-AKI used: Increase in serum creatine concentrations of ≥44.2 µmol/l 48 h after administration of contrast	haemodialysis Planned post contrast dialysis Known allergy to NAC All patients N: 80 Age (mean±SD): NR Drop outs: 0 Group 1 N: 41 Age (mean±SD): 71±9 Drop outs: 0 Baseline characteristics: M:F: 35/6 Baseline serum creatinine (µmol/l) (mean±SD): 176.8±35.36# CKD: NR Diabetes: 16 (39%) Hypertension: NR ACEI: 27 (66%) NSAIDs: NR Group 2 N: 39 Age (mean±SD): 69±10 Drop outs: 0 Baseline characteristics: M:F: 31/8 Baseline serum creatinine (µmol/l) (mean±SD): 167.96±26.52 CKD: NR Diabetes: 19 (49%)	0.45% Dose:1 ml/kg / hr Route: IV Timing pre contrast:12hrs Timing post contrast:12 hrs Contrast Non ionic low osmolar Name: Iopamidol Dose: boluses of 8-15 ml (0.755g of iopromide/ml iodine content was 370 mg/ml) Volume (ml): Group 1: 111±43 Group 2: 121±49 Both groups:	Serum creatinine at 7 days (µmol/l) (mean±SD)	Group1: 185.64-39.78# Group 2: 165.308-27.404# Relative risk [95% CI]: NR p value: 0.13	Notes: Randomisation carried out with computer generated random numbers. Intention to treat analysis #calculated from mg/dL by NCGC (x88.4)
			Serum creatinine at 48 hrs (µmol/l) (mean±SD)	Group1: 176.8-45.084# Group 2: 165.308-31.824# Relative risk [95% CI]: NR p value: 0.14	

	Hypertension: NR ACEI: 24 (62%) NSAIDs: NR				

1 **Table 48: Miner 2004[282]**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Miner 2004[282] Country of study: Canada Study design: RCT Who was blinded:	Patient group: March 2001 to October 2002 Patients with previous diagnostic angiography undergoing planned PCI or urgent coronary angiography with high likelihood of ad hoc PCI Inclusion criteria: Patients without diabetes and a calculated creatinine clearance of <50 mL/min Patients with diabetes and a calculated creatinine clearance of <100mL/min	Group 1 (Intervention) NAC Dose: 2000mg Route: oral Timing pre contrast /Timing post contrast: Prior day patients received their first dose 8pm the night before the procedure with subsequent doses at 8am and 8pm the day of their procedure. Same day patients received their first dose at 8am	Mortality (in hospital)	Group1: 0/95 Group 2: 2/85** Relative risk [95% CI]: NR p value: Not significant	Funding: NR Limitations: Randomization unclear Allocation concealment unclear Blinding unclear Number of drop outs per arm of study not reported. 1 patient assigned to placebo was mistakenly given open label NAC. This patient did not have CIN and was included in the placebo group for analysis. Patients enrolled at different
			Mortality (composite incidence of death-6 months*)	Group1: 4/95 Group 2: 3/85 Relative risk [95% CI]: NR p value: Not significant	
			CI-AKI at 48 hours (incidence of CIN: increase in serum creatinine of ≥25% , 48-72 following procedure***)	Group1: 9.6% Group 2: 22.2% Relative risk [95% CI]: NR Odds Ratio: 0.37 (95% CI: 0.14-0.93) p value: 0.04	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Double blind Setting: Tertiary care Duration of follow-up: 3 days (in hospital) 6 months (long term) * Definition of CI-AKI used: Increase ≥25% in the baseline serum creatinine concentration 48 to 72 hours following the procedure	Any patient with an absolute serum creatinine of > 200µmol/L Exclusion criteria: RRT (dialysis or transplantation) Reactive airway disease requiring oral steroids Baseline systolic blood pressure <80 mmHg Active congestive heart failure Acute MI Enrolment in another clinical trial Inability to give informed consent Ongoing need for IV nitroglycerin and treatment with NAC within 72 hrs of PCI Women of child bearing age All patients N: 180 Age (mean±SD): Drop outs: 25 (in hospital phase) 9 (long term follow up) Group 1 N: 95 Age (mean±SD): 71±8 Drop outs: NR Baseline characteristics: M:F: 68%/32% Baseline serum creatinine (µmol/l) (mean±SD): 124±49	and 8 pm on the same day. NAC total dose: prior day patients received a total of 6000mg and same day patients a total of 4000mg iv fluid; sodium chloride 0.45% Dose:75 ml/hr Route: IV Timing pre contrast/ Timing post contrast: 24 hrs beginning at time of enrolment. Group 2 (Comparison) placebo Dose: Route: Timing pre contrast: Timing post contrast: iv fluid; sodium chloride 0.45% Dose:75 ml/hr Route: IV Timing pre contrast/ Timing post contrast: 24 hrs beginning at time of enrolment.	CI-AKI at 72 hours	NR	points, the day prior or same day as procedure Difference in hydration Difference in total NAC dose 14% loss to follow up Additional outcomes: CIN defined as absolute increase in serum creatinine concentration >44µmol/L Change in serum creatinine 48 to 72 hours post procedure Non-fatal MI (defined as increase in serum creatinine kinase concentrations >2X upper limit of normal) in hospital and long term Adverse events Repeat hospitalisations Notes: Intention to treat analysis *Follow up telephone survey for long term clinical outcomes was conducted by the research coordinator at least 6 months post-PCI, mean follow up was 9.5±2.7 months
			Number of patients needing RRT (in hospital)	Group1: 1/95 Group 2: 0/85 Relative risk [95% CI]: NR p value: Not significant	
			Number of patients needing RRT (6 months*)	Group1: 1/95 Group 2: 1/85 Relative risk [95% CI]: NR p value: Not significant	
			Number of patients achieving dialysis independence	NR	
			Length of hospital stay	NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	CKD: NR Diabetes: 68% Hypertension: 72% ACEI: NR NSAIDs: NR Group 2 N: 85 Age (mean±SD): 69±11 Drop outs: NR Baseline characteristics: M:F: 66%/34% Baseline serum creatinine (µmol/l) (mean±SD): 130±58 CKD: NR Diabetes: 67% Hypertension: 77% ACEI: NR NSAIDs: NR	Contrast Iow osmolar nonionic Name: Omnipaque Dose: NR Both groups: Changes in hydration were allowed at the discretion of the cardiologist			**2 deaths in the placebo group were unrelated to acute renal dysfunction ***reduction in CI-AKI was limited to those patients enrolled the day prior to the procedure (OR: 0.16, 95% CI: 0.03-0.63 P= 0.005)

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2 **Table 49: Oldemeyer 2003[301]**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Oldemeyer 2003[301] Country of	Patient group: Consecutive patients referred for elective coronary angiography	Group 1 (Intervention) NAC Dose: 1500mg NAC Route: orally in 120 mL	Mortality	NR	Funding: NR Limitations:
			CI-AKI at 48 hours Absolute increase in serum creatinine of ≥0.5 mg/dL or a	Group1: 4/49 Group 2: 3/47 Relative risk [95% CI]:NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
study: Nebraska, USA Study design: prospective, randomized, double-blind, placebo-controlled trial Who was blinded: double-blind Setting: Hospital inpatient Duration of follow-up: 48 hours Definition of CI-AKI used: Absolute increase in serum creatinine of	Inclusion criteria: ≥19 years of age Baseline calculated creatinine clearance <50 mL/min Serum creatinine >1.2 mg/dL, Scheduled for coronary angiography with or without concomitant coronary intervention, An anticipated use of ≥75 mL of contrast. Exclusion criteria: In acute kidney failure, Undergoing dialysis, Unstable renal function as evidenced by a change in serum creatinine of ≥0.5 mg/dL or ≥25% in the prior 10 days, Known allergy to contrast or acetylcysteine, Administration of mannitol, intravenous catecholamines, parenteral diuretics, theophylline, or a contrast agent within 7 days of study entry, Mechanical ventilation, Cardiogenic shock, or emergent angiography. All patients N: 96	of carbonated beverage, using the 10% acetylcysteine inhalation solution Timing pre contrast: starting the evening before angiography and every 12 hours for 4 doses Timing post contrast: iv fluid-sodium chloride 0.45% Dose: 1 mL/kg Route: NR Timing pre contrast: 12 hrs Timing post contrast: 12 hrs Group 2 (Comparison) placebo Dose: equivalent volume of normal saline in 120 mL of carbonated beverage Route: Oral Timing pre contrast: NR Timing post contrast:NR iv fluid-sodium chloride	relative increase of ≥25% in serum creatinine compared with baseline	p value: 0.74	Unclear allocation concealment Sample size Brief period of monitoring for changes in renal function after angiography The ability to truly blind NAC therapy Additional outcomes: Changes in serum creatine and BUN concentrations at baseline, 24hrs and 48 hrs after procedure CI-AKI occurrence in diabetic/ non- diabetic patients Adverse events of NAC Hospital charges Notes: Patients were randomly assigned, through the use of a computer- generated 1:1 randomization sequence #calculated from mg/dL by NCGC (x88.4)
			CI-AKI at 72 hours	NR	
			Number of patients needing RRT	Group1: 0/49 Group 2: 0/47 Relative risk [95% CI]: NR p value: NR	
			Number of patients achieving dialysis independence	NR	
			Length of hospital stay (mean ± SD)	Group1: 4.8 ± 3.8 days Group 2: 4.9±4.0 days Relative risk [95% CI]: NR p value: NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
≥44.2 µmol/l# or a relative increase of ≥25% in serum creatinine at 24 or 48 hours after the procedure compared with baseline	Age (mean): NR Drop outs: NR Group 1 N: 49 Age (mean±SD): 77 ±9 Drop outs: NR Baseline characteristics: M:F: 27/22 Baseline serum creatinine (µmol/l) (mean±SD): 144.09± 71.60 # CKD: NR Diabetes: 20 (41%) Hypertension: 23 (69%) ACEI: NR NSAIDS: NR Group 2 N: 47 Age (mean): 75± 8 Drop outs: NR Baseline characteristics: M:F: 26/21 Baseline serum creatinine (µmol/l) (mean±SD): 146.74± 57.46 # CKD: NR Diabetes: 23 (49%) Hypertension: 35 (74%) ACEI: NR	0.45% Dose: 1 mL/kg Route: NR Timing pre contrast: 12 hrs Timing post contrast: 12 hrs Contrast low-osmolar, nonionic Name: Isovue; iopamidol Dose: 0.76 mg/mL, 370 mg iodine/mL Duration: NR			

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	NSAIDS: NR				

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2 **Table 50: Poletti 2007[327]**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Poletti 2007[327] Country of study: Geneva Switzerland Study design: RCT Who was blinded: Double blind - Patients and investigators Setting: Inpatient hospital emergency department Duration of	Patient group: 100 adult patients admitted consecutively to the emergency department during daytime hours Inclusion criteria: Serum Cr concentration greater than 106 µmol/L Emergency CT needed within 12 hours of admission. Exclusion criteria: Pregnancy End-stage renal failure necessitating dialysis, Suspicion of acute renal obstruction (complicated renal colic), Asthma, Severe cardiac failure or hemodynamically unstable condition contraindicating IV hydration Non-urgent indications for CT.	Group 1 (Intervention) NAC Dose pre contrast: 900 mg of NAC diluted in a 50-mL solution of 5% glucose Dose post contrast: 900 mg of NAC mixed into the sodium chloride 0.45% perfusion- 1 mL/kg body weight per hr Route: administered IV Timing pre contrast: 1 hr Timing post contrast: 12 hr iv fluid-sodium chloride 0.45% Dose pre contrast: 5mL/kg body weight Dose post contrast: : 1 mL/kg body weight	Mortality	NR	Funding: Supported by a grant for Research and Development of the University Hospital of Geneva. Limitations: Allocation concealment unclear. Number of drop outs per arm of study not reported. Additional outcomes: Severe nephrotoxicity: defined as 50%> increase in serum Cr / cystatin C concentrations from baseline CI-AKI: defined as 25% or greater increase from baseline of Cycstatin C CI-AKI at 96 hours Notes: Baseline figures reported on total number of patients
			CI-AKI at 48 hours 25% or greater increase from baseline of serum Cr	Group1: 2/44 Group 2: 7/43 Relative risk [95% CI]:NR p value: 0.09	
			CI-AKI at 72 hours	NR	
			Number of patients needing RRT	NR	
			Number of patients achieving dialysis independence	NR	
			Length of hospital stay	NR	

follow-up: 4 days Definition of CI-AKI used: 25% or greater increase from baseline of serum Cr	All patients N: 87 Age (mean): NR Drop outs: 7 (3 died, 1 transferred hospitals, 3 lost to follow up) M/F: 55 (63%)/32 (37%) Group 1 N: 44 Age (mean): 69.5 ± 18.7 Drop outs: NR M/F: 26 (59)/ 18 (41) Baseline factors: Baseline serum creatinine (µmol/l) (mean ±SD): 146 ± 35 CKD: NR Diabetes: 9 (18%) Hypertension: NR ACEI: 5 (10%) NSAIDS: 11 (22%) Group 2 N: 43 Age (mean): 72.7 ± 17.2 Drop outs: NR M/F: 29 (67%)/ 14 (33%) Baseline factors: Baseline serum creatinine (µmol/l) (mean ±SD): 148 ± 36 CKD: NR Diabetes: 6 (12%) Hypertension: NR	Route: iv Timing pre contrast: 1hr Timing post contrast: 12 hr Group 2 (Comparison) placebo: the same procedure was performed, but with placebo Dose: placebo (50 mL of sodium chloride 0.9%) Route: iv Timing pre contrast: 1 hr Timing post contrast: 12 hr iv fluid-sodium chloride 0.45% Dose pre contrast: 5mL/kg body weight Dose post contrast: : 1 mL/kg body weight Route: iv Timing pre contrast: 1hr Timing post contrast: 12 hr Contrast nonionic low-osmolality iodine contrast medium Name: iopromide, Ultravist 300, Schering			screened for study not the actual number of patients included for the study. Patients were randomized to two groups by serial enrolment Intention to treat analysis

	ACEI: 12 (24%) NSAIDS: 5 (10%)	Dose: A bolus of 2 mL/kg body weight was used for nonneurologic indications, and a standard dose of 100 mL was used for brain imaging or suspicion of pulmonary embolism. Duration: Injection was performed at a rate of 3 mL/s			

1 **Table 51: Shyu 2002[370]**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Shyu 2002[370] Country of study: Taiwan Study design: Prospective RCT Who was blinded: Double blind cardiologist and patient	Patient group: Patients scheduled for cardiac angiography Inclusion criteria: Serum creatinine >176.8 µmol/l and <530.4 µmol/l# Rates of creatinine clearance < 40 ml/min and >8 ml/min history of chronic renal failure with a stable serum creatinine concentrations* Exclusion criteria: Acute MI requiring primary or rescue coronary intervention, Use of vasopressors before the procedure	Group 1 (Intervention) NAC Dose: 400mg Route: Oral Timing pre contrast: twice a day a day prior Timing post contrast: twice a day on the day of the procedure iv fluid; sodium chloride 0.45% Dose:1 ml/kg/hr Route:IV Timing pre contrast: 12hrs Timing post contrast: 12 hrs	Mortality	NR	Funding: Funded by the research committee of Shin Kong Wu Ho-Su memorial Hospital Limitations: Additional outcomes: Serum creatinine concentration at 48 hrs & 7 days BUN concentration at 48 hrs , & 7 days Notes: *A difference of ≤0.1 mg/dl between baseline serum creatinine at 12 -24 hrs before
			CI-AKI at 48 hours (increase in serum creatinine of at least 44.2 µmol/l at 48 hrs after contrast)	Group1: 2/60 (3.3%) Group 2: 15/61 (24.6%) Relative risk [95% CI]: 0.13 [0.08-0.20] p value: <0.001	
			CI-AKI at 72 hours	NR	
			Number of patients needing RRT	NR	
			Number of patients achieving dialysis independence	NR	
			Length of hospital stay	NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Setting: Clinical Duration of follow-up: 48 hours Definition of CI-AKI used: An increase in serum creatinine of at least 44.2 µmol/l at 48 hrs after injection of the radio contrast medium	Cardiogenic shock Current peritoneal dialysis or hemodialysis Planned post contrast dialysis Allergy to study medications All patients N: 121 Age (mean±SD): NR Drop outs: Group 1 N: 60 Age (mean±SD): 70±7 Drop outs: Baseline characteristics: M:F: 42/18 Baseline serum creatinine (µmol/l) (mean±SD): 247.52±70.72# CKD:NR Diabetes: 38 (63%) Hypertension: 42 (70%) ACEI: 24 (40%) NSAIDs: NR Group 2 N: 61 Age (mean±SD): 70±7 Drop outs:	Group 2 (Comparison) placebo Dose: NR Route: NR Timing pre contrast: NR Timing post contrast: NR iv fluid; sodium chloride 0.45% Dose:1 ml/kg/hr Route: IV Timing pre contrast: 12hrs Timing post contrast: 12 hrs Contrast nonionic, low-osmolar Name: Iopamidol (Iopamiro) Dose: NR –decided by each patients cardiologist ipamidol content was 0.755 mg/ml and iodine content was 370 mg/ml Both groups:			coronary angiography and serum creatinine measured 1-2 weeks before angiography sCr calculated from mg/dL by NCGC (x88.4)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Baseline characteristics: M:F: 40/21 Baseline serum creatinine (µmol/l) (mean±SD): 247.52±70.72# CKD: NR Diabetes: 39 (64%) Hypertension: 41 (67%) ACEI: 26(43%) NSAIDs: NR	Patients were encouraged to drink if thirsty. Patients who underwent coronary angioplasty received a bolus of 10,000 U heparin during the procedure followed by an additional bolus if deemed necessary.			

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2 **Table 52: Tepel 2000[391]**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Tepel 2000[391] Country of study: Germany Study design: Prospective RCT Who was	Patient group: Prospectively studied 83 patients who underwent elective CT for the evaluation of an abdominal or thoracic illness. Inclusion criteria: Serum creatinine concentration above 1.2 mg per deciliter (106 µmol per litre) Creatinine clearance of less than 50 ml per minute (0.8 ml per second)* Only patients known to have a	Group 1 (Intervention) NAC Dose: 600 mg twice daily Route: Oral Timing pre contrast /Timing post contrast: day before and on the day of administration of the contrast agent, for a total of two days. iv fluid sodium chloride 0.45% Dose: 1 ml per kilogram	Mortality	NR	Funding: NR Limitations: Randomization unclear Allocation concealment unclear Additional outcomes: Serum creatinine and urea nitrogen were measured repeatedly during the week before administration of the
			CI-AKI at 48 hours (increase in the serum creatinine 0.5 mg per deciliter 48 hours after administration of the contrast agent)	Group1: 1/41 (2%) Group 2: 9/42(21%) Relative risk [95% CI]: 0.1 [0.02-0.9] p value: 0.01	
			CI-AKI at 72 hours	NR	
			Number of patients needing RRT	Group1: 0/41 Group 2: 0/42 Relative risk [95% CI]: NR p value: NR	
			Number of patients achieving dialysis	NR	

blinded: NR Setting: Inpatient Duration of follow-up: 6 days Definition of CI-AKI used: An increase in the serum creatinine concentration of at least 44 µmol per litre 48 hours after administration of the contrast agent	history of chronic renal failure and with stable serum creatinine concentrations were included. Exclusion criteria: Acute renal failure All patients N: 83 Age (mean±SD): NR Drop outs: 0 Group 1 N: 41 Age (mean±SD): 66±11 Drop outs: Baseline characteristics: M:F:24/17 Baseline serum creatinine (µmol/l) (mean±SD): 221±114.92# CKD: NR Diabetes: 13 (32%) Hypertension: NR ACEI: 8 (20%) NSAIDs: NR Group 2 N: 42 Age (mean±SD): 65±15 Drop outs: Baseline characteristics: M:F:23/19 Baseline serum creatinine (µmol/l)	of body weight per hour Route: IV Timing pre contrast: 12 hrs Timing post contrast: 12 hrs Group 2 (Comparison) placebo Dose: NR Route: NR Timing pre contrast: NR Timing post contrast: NR iv fluid sodium chloride 0.45% Dose: 1 ml per kilogram of body weight per hour Route: IV Timing pre contrast: 12 hrs Timing post contrast: 12 hrs Contrast non-ionic low-osmolar Name: iopromide Dose: 75 ml infusion contained 0.623 g of iopromide per ml, and the iodine content was 300 mg per ml Duration: NR	independence Length of hospital stay	 NR	contrast agent,and immediately before, 48 hours after, and 6 days after administration of the contrast agent CI-AKI in patients diagnosed with diabetes CI-AKI in patients with elevated baseline serum creatinine (>2.5mg/dL) Adverse events Notes: *Creatinine clearance was estimated on the basis of the serum creatinine concentration, weight, age, and sex intention-to-treat analysis #calculated from mg/dL by NCGC (x88.4)

	(mean ±SD): 212.16±114.92# CKD: NR Diabetes: 14 (33%) Hypertension: NR ACEI: 5 (12%) NSAIDs: NR	Both groups: All patients were encouraged to drink if they were thirsty			

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5 **Table 53: Wan Mohd Izani Wan Mohamed 2008 [196]**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Wan Mohd Izani Wan Mohamed 2008 [196] Country of study: Malaysia Study design: RCT Who was blinded: Patients and	Patient group: Patients electively admitted for coronary angiography between April 2006- march 2007 Inclusion criteria: Creatinine clearance between 40-90 ml/min ≥18 years Exclusion criteria: Severe renal failure Severe peptic ulcer disease History of allergy to NAC Severe asthma Pregnant / breast feeding women	Group 1 (Intervention) NAC (mixed with orange drink) Dose:600 mg twice daily for four doses Route:oral Timing pre contrast:12 hrs Timing post contrast: iv fluid: sodium chloride 0.45% Dose:1 ml/kg/hr Route:iv Timing pre contrast:12hrs Timing post	Mortality	NR	Funding: short term grant of the university of science Malaysia Limitations: Additional outcomes: Association between variables and CIN by univariate analysis Changes in creatinine at 24 hrs and 48 hrs Notes: Randomisation performed using computed generated randomisation list
			CI-AKI at 48 hours (Increase in serum creatinine of more than 25% from baseline)	Group1: 2/49 (4.1%) Group 2: 6/51 (11.8%) Relative risk [95% CI]: p value: 0.269	
			CI-AKI at 72 hours	NR	
			Number of patients needing RRT	NR	
			Number of patients achieving dialysis independence	NR	
			Length of hospital stay	NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
operators of coronary angiography Setting: Tertiary hospital Duration of follow-up: 48 hrs Definition of CI-AKI used: Increase in serum creatinine of more than 25% from baseline	All patients N: 108 Age (mean±SD): NR Drop outs: 8 Group 1 N: 53 Age (mean±SD): 57.64 ±8.40 Drop outs: 4 Baseline characteristics: M:F: 42:7 Baseline serum creatinine (µmol/l) (mean±SD):123.7 ± 17.08 CKD: NR Diabetes: 24 (49%) Hypertension: 45 (91.8%) ACEI: 40 (81.6%) NSAIDs: NR Group 2 N: 55 Age (mean±SD): 56.4±6.78 Drop outs: 4 Baseline characteristics: M:F: 42:9 Baseline serum creatinine (µmol/l) (mean±SD): 124.4 ± 21.89 CKD: NR Diabetes: 23 (45.1%)	contrast:12hrs Group 2 (Comparison) IV fluid iv fluid: sodium chloride 0.45% Dose: 1ml/kg/hr Route: IV Timing pre contrast:12 hrs Timing post contrast:12hrs Contrast low osmolar non- ionic Name: Iohexol Dose: 350mg I/ml Both groups: Adjunctive drug therapy and amount of contrast used during the procedure was left to the discretion of the attending cardiologist Contrast volume (mean±SD)			

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Hypertension: 46 (90.2%) ACEI: 38 (74.5%) NSAIDs: NR	Group1: 136.73±100.23 Group 2: 126.67±94.37 p value: 0.606			

G.2.3 Computerised decision tools

Table 54: Chertow 2001[89]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Chertow 2001[89] Country of study: USA Study design: Prospective cohort – time series Setting: Tertiary care teaching hospital Duration of study: 8	Patient group: Inpatients with renal insufficiency Inclusion criteria: All patients admitted to medical, surgical, neurology and obstetrics and gynaecology screened. Renal insufficiency defined as estimated CrCl<80ml/min. Exclusion criteria: Admissions that straddled a study period boundary All patients N: 14440 orders in 7490 patients with renal impairment out of	Group 1 Electronic prescribing plus a computerised decision tool for adjusting drug dose and frequency in patients with renal insufficiency. Alerts gave information on potential harms and a suitable substitute if appropriate. Group 2 Electronic prescribing alone.	Rates of inappropriate orders – dose or frequency	Group1: 2714/5490 (49%) Group 2: 6298/8950 (70%) p value: <0.001	Funding: 4 authors employees of Partners HealthCare System, Boston (not for profit organisation). Last author on paper multiple conflicts of interest with companies developing Electronic prescribing and computerised decision tools. Limitations: Higher mean estimated CrCl in intervention vs control at baseline (P<0.001), however not clinically significant. Additional outcomes: Estimated hospital/ pharmacy costs
			Rates of inappropriate orders – dose	Group1: 1211/3689 (33%) Group 2: 2743/5964 (46%) p value: <0.001	
			Rates of inappropriate orders –frequency	Group1: 1689/4136 (41%) Group 2: 4456/6814 (65%) p value: <0.001	
			Length of hospital stay (days) (mean ± SD)	Group1: 4.3 ± 4.5 Group 2: 4.5 ± 4.8 p value: 0.009 "Median (interquartile	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
months – consecutive 2 month intervals alternating control and intervention	19982 patients admitted Age (mean): 52.5 Drop outs: 2154/19982 patients (10.8%) excluded on basis of exclusion criteria. 11386/108537 orders for nephrotoxic/ renally cleared medications excluded from analysis due to missing dose amount, frequency interval or unable to estimate CrCl (usually because of missing data regarding weight). Group 1 N: 7887 patients admitted Age (mean): 52.5 ± 18.4 M:F: 38.6% : 61.4% Mean estimated CrCl (ml/min): 90.9 Group 2 N: 9941 patients admitted Age (mean): 52.5 ± 18.3 M:F: 38.2% : 61.8% Mean estimated CrCl (ml/min): 84.7			range) for intervention and control is 3 (2-6), although Wilcoxon rank-sum tests are significant due to differences in distribution". In-hospital mortality Group1: 1.8% Group 2: 1.9% p value: 0.61	– no difference found. Sensitivity analysis on effect of excluding those patients whose admissions that straddled a study period boundary for length of stay and costs only. Risk of selection bias: multivariable regression of log transformed data used in analysis, but then reported the unadjusted untransformed data in the table. Did not carry out any multivariable logistic regression analyses for the dichotomous outcomes.

1 **Table 55: Evans 1998[131]**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Evans	Patient group: Consecutive	Group 1	Alerts for excess drug	Group1: 87 in 398	Funding:

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
1998[131] Country of study: USA Study design: Prospective cohort (pre and post intervention). Setting: Intensive care unit Duration of study: 12 months (intervention). 24 months (control).	patients on intensive care. Inclusion criteria: All patients Exclusion criteria: None All patients N: 1681 Age (mean): 47.5 Drop outs: 0 Group 1 N: 545 Age (mean): 48 Drop outs: 0 M:F: 322 (59%) : 223 (41%) Group 2 N: 1136 Age (mean): 47 Drop outs: 0 M:F: 670(59%) : 466 (41%)	Computerised decision tool linked to computer based patient records for the management of anti-infective agents Group 2 'Usual care' without computer management program Group 1a- Computer regimen followed (203/398 patients) Group 1b – Computer regimen overridden (195/398 patients)	dosing in relation to patient's renal function	patients Group 2: 405 in 755 patients p value: <0.01	Intermountain healthcare Limitations: Unequal length of follow up for control and intervention No definitions given for renal impairment Additional outcomes: Cost of anti-infective agents and hospital stay Number of anti-infective drugs ordered and doses. Length of ICU stay Notes: Drugs included: antibiotics and other anti-infective agents.
			Number of days dose of anti-infective agent remained excessive	Group1: 2.7 days Group 2: 5.9 days p value: <0.002	
			Mortality in patients receiving anti-infective agents	Group1: 88/398(22.1%) Group 2: 172/755 (22.5%) p value: Not sig	
			Length of hospital stay (days)	Group1a: 11.5 ± 10.7 Group 1b: 17.9 ± 16.0 Group 2: 14.1 ± 14.5 p value: NR	
			Adverse drug reaction to anti-infective agents	Group1: 4 in 398 patients (1.0%) Group 2: 28 in 755 patients (3.7%) p value: 0.018	

Table 56: Falconnier 2001[133]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Falconnier 2001[133] Country of study: Switzerland Study design: Prospective cohort with retrospective control Setting: 39 bed unit of university hospital. Duration of study: 12 months, 1995-1996. Control group retrospective from 1993.	Patient group: Patients with estimated CrCl ≤50ml/min from wards specialising in infectious diseases, kidney disorders including post-transplant care, and oncology. (Consecutive patients evaluated for inclusion). Inclusion criteria: CrCl ≤50ml/min ≥1 pharmacologically active drug Exclusion criteria: None as long as inclusion criteria met All patients N: 213/1648 screened (17%) Drop outs: 0 Group 1 N: 143/806 (all who met inclusion criteria) Age (mean): 68.8 ± 17.6 Drop outs: 0 M:F: 73 (51%): 70 (49%) CrCl (mean ± SD): 23.9 ± 14.1 Severity of renal impairment*: Mild: 53/143 (37%) Moderate: 55/143 (38%) Severe: 35/143 (25%) No. of drugs prescribed per patient	Group 1 Clinical pharmacist alert in paper chart if estimated CrCl <50 Explicit recommendation for dose adjustments (for renally excreted drugs adjusted to individual renal function) if changes not made within 24h. Group 2 No alerts/ recommendations.	Percentage of dosage regimens adjusted to renal function (by number of patients receiving renally excreted drugs) Percentage of dosage regimens adjusted to renal function (by no. of drugs) Length of hospital stay (days) (mean ± SD)	Group1: 19/26 (73%) (8 after 1st part, 11 more after 2nd) Group 2: NR Group1: 155/192 (81%) Group 2: 23/70 (33%) p value: <0.001 Group1: 20.9 ± 16.0 Group 2: 23.1 ± 25.8 p value: Not sig	Funding: Senglet Stiftung Basel, Fonds Golaz of the Schweizerische Apothekerverein Bern-Liebefeld, Freiwillige Akademische Gesellschaft Basel, Mr and Mrs Wilhelm VT Martius-Fasser, Wissenschaftliche Kredit of University Hospital Basel and BMBF grant 01EC9902 Limitations: Possible selection bias: Intervention group mean age significantly less (P<0.005) with more drugs prescribed per patient (P<0.005) Additional outcomes: Intervention required approximately 4h/day of one pharmacist's time. Notes: Renally excreted drugs were: digoxin, β lactam antibiotics, antivirals, antifungals, ACEi, β blockers, fibrates, H2 antagonists. Aminoglycosides were not included in the study as there was already a successful dose optimisation program in place for these. *Severity of renal impairment: Mild (CrCl 31-50ml/min)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	(mean ± SD): 8.9 ± 4.1 Group 2 N: Random sample of 70/140 who met inclusion criteria out of 842 screened Age (mean): 75.7 ± 13.9 Drop outs: 0 M:F: 37 (53%): 33 (47%) CrCl (mean ± SD): 26.0 ± 14.2 Severity of renal impairment*: Mild: 27/70 (39%) Moderate: 31/70 (44%) Severe: 12/70 (17%) No. of drugs prescribed per patient (mean ± SD): 7.0 ± 3.6				Moderate (10-30ml/min) Severe (<10ml/min)

1

2

3 **Table 57: Galanter 2005[148]**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Galanter 2005[148] Country of study: USA Study design:	Patient group: Inpatients with renal insufficiency (estimated CrCl) Inclusion criteria: All inpatients, alerts generated at	Group 1 Electronic prescribing with a computerised decision tool and alerts if patients CrCl less than the minimum safe CrCl	Likelihood of patient receiving ≥1 dose of a contraindicated drug	Group1: 47% Group 2: 87% p value: <0.0001	Funding: Cerner Corporation – developers and suppliers of the computerised decision tool used "Discern Expert" (one of the authors was an employee and Cerner

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Prospective cohort Setting: Teaching hospital Duration of study: 18 months – 4 months control, 14 months intervention	different CrCl for different drugs Exclusion criteria: None All patients N: NR Age (mean): 66 Drop outs: NR Group 1 N: 323 alerts in 233 patients Age (mean): 66 ± 14 Drop outs: NR M:F: 25% : 75% Group 2 N: 87 occasions alert would have been generated. Number of patients not reported. Age (mean): 66 ± 12 Drop outs: NR M:F: 16% : 87%	for the medication ordered. Group 2 Electronic prescribing without alerts			"supported his efforts") Limitations: Number of patients in Group 2 not reported Unequal length of follow up in control and intervention cohorts Additional outcomes: Compliance with alerts – staff and patient factors Notes: Drugs included: NSAIDs, metformin, nitrofurantoin, ribavarin, sotalol, various drugs that suppress rheumatic disease process.

Table 58: McCoy 2010[272]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
McCoy 2010	Patient group: Inpatients with	Group 1	Drug modification or	Group1: 52.6 per 100 events	Funding:

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
[272] Country of study: USA Study design: Prospective cohort Setting: Tertiary care university hospital Duration of study: 17 months (10 months control, 7 months intervention – with 2 month pilot between the two, no data included from the pilot period)	increase in sCr following an order for nephrotoxic or renally cleared medication. Inclusion criteria: ≥44µmol/l increase in sCr over 48 hours following an active recurring order for ≥1 of 122 nephrotoxic or renally cleared medications. Adult patients only Exclusion criteria: Baseline GFR <30ml/min/1.73m2 RRT Transfer to external facility Death within study period Discharge within 24 hours after first change in sCr All patients N: 1598 Age (mean): 57.9 Group 1 N: 745 patients with 1598 orders Age (mean): 57.9 ± 17.1 Drop outs: 197 (RRT, death, transfer or discharge) M:F: 55.7% : 41.7% (2.6% not recorded) Surgical: 23.7% ICU: 46.2%	Electronic prescribing with a computerised decision tool consisting of passive, non-interactive alerts regarding increasing sCr on computer and printed reports and second interruptive alert if attempt made to exit from ordering session without adjusting the medication as suggested in patients with: Increasing sCr levels Medications to be avoided or adjusted Baseline sCr >30ml/min Patient not receiving RRT Group 2 Electronic prescribing alone.	discontinuation rate	Group 2: 35.2 per 100 events p value: <0.001	National Library of Medicine grants Limitations: Control and intervention different lengths of time Additional outcomes: Kaplan Meier curves for time to response NSAIDs and antigout drugs were the most frequently altered due to the intervention Response to alerts Notes: Drugs divided into those to avoid in AKI, adjust in AKI and to review in prolonged AKI.
			Drug modification or discontinuation rate – drugs to avoid	Group1: 59.5 per 100 events Group 2: 33.9 per 100 events p value: <0.001	
			Drug modification or discontinuation rate – drugs to adjust	Group1: 46.4 per 100 events Group 2: 36.2 per 100 events p value: 0.001	
			Drug modification or discontinuation rate – drugs to review	Group1: 40.4 per 100 events Group 2: 36.3 per 100 events p value: 0.08	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 2 N: 914 patients with 1920 orders Age (mean): 57.9 ± 18 Drop outs: 225 (RRT, death, transfer or discharge) M:F: 56.6% : 41.2% (2.2% not recorded) Surgical: 23.9% ICU: 46.2%				

1

2 **Table 59: Rind 1994[344]**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Rind 1994[344] Rind 1991[343] Country of study: USA Study design: Prospective cohort (time series). Assigned to control or intervention based on	Patient group: Inpatients who develop worsening renal function during treatment with nephrotoxic or renally excreted drugs. Inclusion criteria: ≥18 years old Initial creatinine ≤265µmol/l Exclusion criteria: Pre-existing moderate to severe renal impairment (sCr > 265µmol/l)	Group 1 Computerised decision tool consisting of alerts via email to physicians about rising sCr levels (within minutes) in inpatients receiving nephrotoxic or renally excreted drugs. No suggestion made for course of action. Physician could reply to say alert "taken care of". All physicians that had looked up information	Number of events*†	Group1: 728 (generating 534 alerts to 648 physicians) Group 2: 845	Funding: Grants from John A. Hartford Foundation, Agency of Health Care Policy and Research, and research funds from Center for Clinical Computing, Harvard Medical School Limitations: Only results for patients with events*†. Additional outcomes: "No difference" between groups for length of stay, mortality, pharmacy charges or total hospital charges.
			Number of admissions with an event*†	Group1: 439 in 267 patients Group 2: 483 in 295 patients	
			Patients with events*† developing serious renal impairment	Group1: 9/267 (3.4%) Group 2: 22/295 (7.5%) Relative risk [95% CI]: 0.45 [0.22-0.94]	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
admission date and stayed in that group for length of admission. Setting: Teaching hospital Duration of study: 18 months (3 month control, 6 month intervention, 3 month control, 3 month intervention, 3 month control)	All patients N: 562/ 14130 (20228 admissions) had events Drop outs: Only included data for patients with events*†. Group 1 N: 267 (439 admissions) Age (mean): 66.6 ± 18.9 Drop outs: not reported M:F: 53.6% : 46.4% Baseline creatinine (µmol/l)(mean): 203 ± 80 Group 2 N: 295 (483 admissions) Age (mean): 65.8 ± 18.6 Drop outs: not reported M:F: 56.2% : 43.8% Baseline creatinine (µmol/l)(mean): 203 ± 88	about the patient in the preceding 3 days and the patient's consultant were emailed and continued to be sent in 3 days following event if medication not changed and alert not marked "taken care of". Group 2 Standard practice – abnormal lab results flagged with an asterix, critically abnormal values with an exclamation mark, and significant changes in values with a pound sign.	(x2 increase in sCr)	p value: 0.034	Day 3 and Day 7 mean sCr levels. Mean time interval to change for ACEi, aminoglycosides and NSAIDs - P>0.1 for all (very wide CI). Survey of physicians opinions of alerts. Notes: Rind 1991[343] published outcomes of this study after 1 year. These are not reported here as GDG interested in longer follow-up and events would be included in the data from Rind 1994. *Definition used in study of an event for patient on nephrotoxic medication: an increase in sCr ≥44µmol/l †Definition used in study of an event for patient on renally excreted medication: an increase in sCr ≥50% to ≥177µmol/l. NOTE: multiple medications produce multiple events in the same patient, although only recorded once for each drug during a single admission.
			Mean interval to change in medication for nephrotoxic drug (hours)	Group1: 86.6 ± 187.7 Group 2: 95.5 ± 168.8 p value: 0.07	
			Mean interval to change in medication for renally excreted drug (hours)	Group1: 64.7 ± 93.3 Group 2: 99.4 ± 134.3 p value: 0.0001	

G.2.4 Stopping ACEi/ARB therapy

Table 60: Rosenstock 2008 [350]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Rosenstock 2008[350] Country of study: USA; Single centre Study design: RCT – randomised by coin flip Who was blinded: Physicians performing procedure Setting: Tertiary care Duration of follow-up: 24 to 72h for CI-AKI	Patient group: People with CKD (GFR 15-60 ml/min/1.73m2) on ACEI or ARB therapy undergoing elective coronary angiography. Inclusion criteria: ≥1 month continuous therapy with am ACEI or ARB GFR ≤60 ml/min as calculated by abbreviated MDRD Exclusion criteria: Acute ST elevation myocardial infarction within 2 weeks NYHA class IV heart failure AKI pre angiography (increase in sCr > 44µmol from baseline) Hyperkalaemia >5.0meq/l GFR ≤15ml/min Prior cardiac catheterisation in last month Systolic BP <90 mmHg on 2 consecutive readings or need for pressors Poorly controlled hypertension (systolic BP >180 mmHg on 2 consecutive readings) Patients on ACEI and ARB combination therapy All patients N: 283	Group 1 (Discontinuation) ACEI/ARB withheld the morning of procedure until 24h post procedure Group 2 (Continuation) Continued on usual dose and timings of ACEI or ARB (Stopped post procedure in patients who developed CI-AKI) Group 3 – People with CKD not on ACE/ARBs All patients: Preprocedural hydration determined by physician/centre protocol. No patients received sodium bicarbonate. See baseline characteristics.	CI-AKI (25% or 44µmol rise in sCr from baseline within 72h)	Group1: 4/107 (3.7%) Group 2: 7/113 (6.2%) Group 3: 4/63 (6.3%) p value: 0.66	Funding: None reported Limitations: sCr measured at baseline and 24h in all patients but only subsequently if "clinically indicated". Differences in fluid regimes between groups (see baseline characteristics). Additional outcomes: mean sCr post contrast mean GFR post contrast Notes: sCr converted from mg/dl to µmol/l multiplying by 88.4
			CI-AKI (increase in sCr 27µmol/l above baseline)	Group1: 8/107 (7.4%) Group 2: 14/113 (12.4%) Group 3: 8/63 (12.6%) p value: 0.32	
			Number of patients needing RRT	Group1: 1/107 (0.9%) Group 2: 0/113 p value: NR	
			All cause mortality (in hospital)	Group1: 0/107 Group 2: 1/113 (0.9%) – sepsis unrelated to study p value: NR	
			Recovery of renal function back to baseline	Group1: 100% Group 2: 100%	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Definition of CI-AKI used: 25% or 44µmol rise in sCr from baseline within 72h of contrast administration	Drop outs: 0 Group 1 (Discontinuation) N: 107 Age (mean): 71.8 ± 11.2 Drop outs: 0 M:F: 66 (62%) : 41 (38%) Baseline sCr (mean, µmol/l): 141 ± 35 GFR (mean): 43.4 ± 10.4 Hypertension: 103 (96%) Diabetes: 59 (55%) ACEI:ARB: 65 (61%): 42 (39%) Statins: 77 (72%) NAC: 83 (78%) Sodium chloride 0.45%: 84 (79%) Sodium chloride 0.9%: 17 (27%) Group 2 (Continuation) N: 113 Age (mean): 71.8 ± 10.2 Drop outs: 0 M:F: 61 (54%) : 52 (46%) Baseline sCr (mean, µmol/l): 133 ± 35 GFR (mean): 44.6 ± 10.4 Hypertension: 110 (97%) Diabetes: 61 (54%) ACEI:ARB: 71 (63%) : 42 (37%) Statins: 83 (74%) NAC: 83 (74%) Sodium chloride 0.45%: 77 (68%)	All patients who received NAC had 1.2g po bd 48h. Metformin and diuretics withheld Contrast: Iso-osmolar contrast: Group 1: 99/107 (93%) Group 2: 95/113 (84%) Group 3: 57/63 (91%) (P=0.12 between groups) Contrast volume (mean ± SD, ml): Group 1: 149 ± 90 Group 2 : 142 ± 76 Group 3: 125 + 75 (P=0.19 between groups)			

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Sodium chloride 0.9%: 21 (20%) Group 3 (ACEI/ARB naïve) N: 63 Age (mean): 68.5 ± 11.9 Drop outs: 0 M:F: 40 (63%): 23 (37%) Baseline sCr (mean, µmol/l): 141 ± 35 GFR (mean): 44.3 ± 10.6 Hypertension: 55 (87%) Diabetes: 19 (30%) Statins: 43 (68%) NAC: 50 (79%) Sodium chloride 0.45%: 45 (71%) Sodium chloride 0.9%: 36 (32%)				

G.3 Detecting AKI

G.3.1 Definitions and staging of acute kidney injury using AKIN/RIFLE/pRIFLE/ KDIGO

Table 61: Bagshaw 2008[29]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Bagshaw 2008[29] **Country of study:** Australia and New Zealand **Study design:** Retrospective analysis of prospectively collected data **Setting:** 57 ICUs (from ANZICS database) included tertiary referral, metropolitan, regional/rural and private hospitals.	**Patient group:** Adults admitted to ICU January 2000-December 2005. Assessed first 24 hours of ICU admission only. **Inclusion criteria:** • Age ≥18 years • ICU admission for ≥24h **Exclusion criteria:** • End stage kidney disease on chronic RRT • Prior end stage kidney disease • Patients admitted following kidney transplant **<u>All patients</u>** **N:** 120,123/124,088 (96.8%) had satisfactory data for analysis **Age (mean):** 61.6 ± 17.5 **M:F:** 59.5% : 40.5% **"Comorbidities disease":** 28.6% **Surgical admission:** 49.7% **Sepsis/septic shock:** 27.8% **Estimated baseline creatinine† (µmol/l) (median [IQR]):** 98 (68-130) **Urine output (l/24h) (mean ± SD):**	**RIFLE (standard sCr and modified* UO criteria)** **Risk (R):** Increase in sCr ≥1.5X baseline or decrease in GFR ≥25% or UO <35ml/h **Injury (I):** Increase in sCr ≥2.0X baseline or decrease in GFR ≥50% or UO <21 ml/h **Failure (F):** Increase in sCr ≥3.0X baseline or decrease in GFR ≥75% or an absolute sCr ≥354 µmol/L with an acute rise of at least 44 µmol/L or UO <4ml/h **AKIN (standard sCr and modified* UO criteria)** **Stage 1:** Increase in serum creatinine ≥26.2 µmol/L or increase to ≥ 1.5- to 1.9-fold)from baseline or UO <35ml/h **Stage 2:** Increase in	**No AKI**	**AKIN:** 75,570/120,123 (62.9%) **RIFLE:** 76,728/120,123 (63.9%)	**Funding:** The Austin Hospital Anaesthesia and Intensive Care Trust Fund. No conflicts of interest declared. **Conflicts of interest:** Third author member of ADQI Workgroup for RIFLE classification. **Limitations:** UO data only available for 111,091 patients (92.4%). *This was only as a 24h cumulative output and patient weight had not been recorded. Therefore assumed an average weight of 70kg and modified UO criteria (see "Interventions"). Focuses on occurrence of AKI at or within the first 24h of admission to ICU only. Therefore
			RIFLE R/AKIN 1	**AKIN:** 21,741/120,123 (18.1%) **RIFLE:** 19,547/120,123 (16.2%)	
			RIFLE I/AKIN 2	**AKIN:** 12,160/120,123 (10.1%) **RIFLE:** 16,344/120,123 (13.6%)	
			RIFLE F/ AKIN 3	**AKIN:** 10,652/120,123 (8.9%) **RIFLE:** 7,504/120,123 (6.3%)	
			AKI total	**AKIN:** 44,553/120,123 (37.1%) **RIFLE:** 43,395/120,123 (36.1%)	
			All cause mortality (inhospital)	**RIFLE criteria** / **AKIN criteria** **No AKI** 8.9% / **No AKI** 8.5% **RIFLE R** 17.9% / **AKIN 1** 18.5%	

Study details	Patients	Interventions	Outcome measures	Effect size				Comments
Duration of follow-up: First 24h of ICU admission for AKI, In hospital for mortality **Definition of AKI used:** AKIN and RIFLE sCr and UO criteria	2.1 ± 1.3	serum creatinine to >2–2.9 fold from baseline or UO <21 ml/h **Stage 3:** Increase in sCr to ≥3-fold from baseline or sCr ≥354 µmol/L with an acute rise of at least 44 µmol/L or initiation of RRTor UO <4ml/h		**RIFLE I**	27.7%	**AKIN 2**	28.1%	may underestimate true incidence of AKI. No information given on how multivariable analysis undertaken. **Additional outcomes:** • Subgroup analysis or septic patients. • ICU length of stay (dead and alive) • Hospital length of stay (dead and alive) **Notes:** †Baseline sCr unavailable and estimated by the MDRD equation.
				RIFLE F	33.2%	**AKIN 3**	32.6%	
				Any AKI	24.2%	**Any AKI**	24.5%	
			All cause mortality (Odds ratio [95% CI]) • Logistic regression analysis • P<0.001 for all compared to patients with no AKI	**RIFLE R**	2.24 [2.1-2.3]	**AKIN 1**	2.45 [2.3-2.6]	
				RIFLE I	3.95 [3.8-4.1]	**AKIN 2**	4.23 [4.0-4.4]	
				RIFLE F	5.13 [4.9-5.4]	**AKIN 3**	5.22[5.0 -5.5]	
			All cause mortality (AUROC)	**AKIN:** 0.6695 **RIFLE:** 0.6610 **95% CIs not reported**				
			Number of patients needing RRT	No data available from database for proportion of patients receiving acute RRT.				

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
					For analysis patients were assigned to their worst RIFLE or AKIN category according to **either** sCr or UO criteria.

Table 62: Bastin 2013[40]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Bastin 2013[40] **Country of study:** UK **Study design:** Retrospective analysis of prospectively collected data	**Patient group:** Adults undergoing cardiac surgery necessitating cardiopulmonary bypass (CPB). May 2006-April 2008. **Inclusion criteria:** • Age >16 years **Exclusion criteria:** • Need for ventricular assist device or extracorporeal membrane oxygenation • Cardiac transplantation	**RIFLE** Standard sCr criteria **AKIN** Standard sCr criteria **KDIGO** Standard sCr criteria	**No AKI**	**AKIN/KDIGO:** 1394/1881 (74.1%) **RIFLE:** 1412/1881 (75.1%)	**Funding:** Academic funding only **Limitations:** • Single centre • UO criteria not used. • No multivariable analysis. • RRT only reported overall, not reported by stage.
			RIFLE R/AKIN or KDIGO 1	**AKIN/KDIGO:** 317/1881 (16.9%) **RIFLE:** 336/1881 (17.9%)	
			RIFLE I/AKIN or KDIGO 2	**AKIN/KDIGO:** 34/1881 (1.8%) **RIFLE:** 98/1881 (5.2%)	

Study details	Patients	Interventions	Outcome measures	Effect size				Comments
Setting: Single centre, Tertiary care **Duration of follow-up:** 7 days for maximum stage AKIN, RIFLE or KDIGO, inhospital for other outcomes. **Definition of AKI used:** AKIN, KDIGO and RIFLE sCr criteria	• Need for >1 episode of CPB during the same admission • RRT before surgery • Death within 24 hours of surgery. **<u>All patients</u>** **N:** 1881 **Age (median [IQR]):** 66 [56-74] **M:F:** 1340 (71.2%): 541 (28.8%) **Preoperative eGFR (median [IQR]):** 68 [56-80] **Preoperative sCr, µmol/l(median [IQR]):** 92 [80-107] **Diabetes:** NR **Nonelective surgery:** 341 (18.1%)		**RIFLE F/ AKIN or KDIGO 3**	**AKIN/KDIGO:** 136/1881 (7.2%) **RIFLE:** 35/1881 (1.9%)				**Additional outcomes:** • Length of ICU stay by stage • Length of hospital stay by stage.
			AKI total	**AKIN:** 487/1881 (25.9%) **RIFLE:** 469/1881 (24.9%)				
			All cause mortality (inhospital)	**RIFLE criteria**		**AKIN/KDIGO criteria**		
				No AKI	5/1412 (0.4%)	**No AKI**	4/1394 (0.3%)	
				RIFLE R	13/336 (3.8%)	**AKIN 1**	1/317 (0.3%)	
				RIFLE I	4/98 (4.1%)	**AKIN 2**	0/34 (0%)	
				RIFLE F	2/35 (5.7%)	**AKIN 3**	19/136 (14.0%)	
				Any AKI	19/469 (4.1%)	**Any AKI**	20/487 (4.1%)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
			All cause mortality (OR [95% CI])	**No multivariable analysis reported.** **Univariable logistic regression analysis (not by stage):** **AKIN: 4.3 [2.9-6.3] P<0.0001** **RIFLE: 2.7 [1.8-3.9] P<0.0001**	
			All cause mortality (AUROC [95% CI])	**AKIN:** 0.86 [0.85-0.88] **RIFLE:** 0.78 [0.76-0.80] **P=**0.0009	
				RIFLE R 63% **AKIN 1** 63% **RIFLE I** 42% **AKIN 2** 44% **RIFLE F** 0% **AKIN 3** 0% **RIFLE R** 75% **AKIN 1** 74% **RIFLE I** 90% **AKIN 2** 88% **RIFLE F** 100% **AKIN 3** 100%	
			Number of patients needing RRT	122/1881 (6.5%)	

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1 **Table 63: Chang 2010[81]**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Chang 2010[81] **Country of study:** Taiwan **Study design:** Retrospective cohort **Setting:** Single centre ICU **Duration of follow-up:** 6 months (telephone interview), Mortality inhospital.	**Patient group:** Adults admitted to medical ICU with septic shock, acute respiratory distress syndrome or hepatic cirrhosis March 2003-February 2006. **Inclusion criteria:** • Age >18 years **Exclusion criteria:** • Chronic uraemic patients undergoing RRT • Patients whose hospital stay was <24h • Readmitted patients **<u>All patients</u>** **N:** 291 **Age (mean):** 62 ± 1 **M:F:** 204 (70.1%): 87 (29.9%) **Creatinine on 1st ICU day (µmol/l):** 194.5 ± 8.8***** **Diabetes:** 80/291 (27.5%) **Sepsis:** 160/291 (55.0%) **Cirrhosis:** 122/291 (41.9%) **ARDS:** not reported, only PaO_2/FiO_2 ratio	**RIFLE** Standard sCr and UO criteria **AKIN** Standard sCr and UO criteria **Simple model for mortality:** Non-AKI and AKIN 0 (0 points) RIFLE-R and AKIN 1 (1 point) RIFLE-I and AKIN 2 (2 points) RIFLE-F and AKIN 3 (3 points) for day 1 of ICU admission	**No AKI**	**AKIN:** 93/291 (32.0%) **RIFLE:** 114/291 (39.2%)	**Funding:** None reported **Limitations:** • Selected ICU patients only (see 'Patient group') • Single centre • Baseline UO not reported **Additional outcomes:** • AKI classification and length of stay for survivors vs nonsurvivors • Compared with APACHE II and SOFA for ability to predict mortality (calibration
			RIFLE R/AKIN 1	**AKIN:** 57/291 (19.6%) **RIFLE:** 38/291 (13.1%)	
			RIFLE I/AKIN 2	**AKIN:** 49/291 (16.8%) **RIFLE:** 52/291 (17.9%)	
			RIFLE F/ AKIN 3	**AKIN:** 92/291 (31.6%) **RIFLE:** 87/291 (29.9%)	
			AKI total	**AKIN:** 198/291 (68.0%) **RIFLE:** 177/291 (60.8%)	
			All cause mortality (inhospital)	**RIFLE criteria**: **No AKI** 42/114 (36.8%) **AKIN criteria**: **AKIN 0** 36/93 (38.7%)	

Study details	Patients	Interventions	Outcome measures	Effect size				Comments
Definition of AKI used: AKIN and RIFLE sCr and UO criteria				**RIFLE R**	24/38 (63.2%)	**AKIN 1**	30/57 (52.6%)	and discrimination and sensitivity and specificity) • Youden index for cut-off points for sensitivity and specificity • Cumulative survival rates (graphs) **Notes:** *NCGC calculated. (For conversion from mg/dL to µmol/L multiplied by 88.4).
				RIFLE I	36/52 (69.2%)	**AKIN 2**	33/49 (67.3%)	
				RIFLE F	75/87 (86.2%)	**AKIN 3**	78/92 (84.8%)	
				Any AKI	135/177 (76.3%)	**Any AKI**	141/198 (71.2%)	
			All cause mortality (Odds ratio [95% CI]) • univariable analysis	**RIFLE R**	2.94 [1.37-6.29]	**AKIN 1**	1.76 [0.9-3.43]	
				RIFLE I	3.86 [1.91-7.78]	**AKIN 2**	3.07 [1.5-6.31]	
				RIFLE F	10.71 [5.22-21.98]	**AKIN 3**	9.50 [4.62-19.53]	
			All cause mortality (AUROC ± SE [95% CI])	**AKIN:** 0.720 ± 0.030 [0.680-0.796] **RIFLE:** 0.738 ± 0.030 [0.680-0.796]				
			Sensitivity for predicting all cause inhospital mortality	**No AKI**	76%	**No AKI**	78%	
				RIFLE R	63%	**AKIN 1**	63%	

Study details	Patients	Interventions	Outcome measures	Effect size				Comments
				RIFLE I	42%	**AKIN 2**	44%	
				RIFLE F	0%	**AKIN 3**	0%	
			Specificity for predicting all cause inhospital mortality	**No AKI**	63%	**No AKI**	50%	
				RIFLE R	75%	**AKIN 1**	74%	
				RIFLE I	90%	**AKIN 2**	88%	
				RIFLE F	100%	**AKIN 3**	100%	
			Number of patients needing RRT	Not reported				

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2 **Table 64: Englberger 2011[125]**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Englberger 2011[125] **Country of study:** USA **Study design:**	**Patient group:** Consecutive patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) from 2005-2007 **Inclusion criteria:** • Adults (≥18 years) undergoing cardiac surgery	**RIFLE** Standard sCr or eGFR (MDRD) criteria **AKIN** Standard sCr criteria only	**No AKI**	**AKIN:** 3564/4836 (73.7%) **RIFLE:** 3921/4836 (81.1%) **p value:** NR	**Funding:** Division of cardiovascular surgery, Mayo Clinic, USA and lead author had grant from Clinic for cardiovascular Surgery, Berne, Switzerland. **Limitations:**
			RIFLE R/AKIN 1	**AKIN:** 1141/4836 (23.6%) **RIFLE:** 715/4836 (14.8%) **p value:** NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Retrospective analysis of prospectively collected data **Setting:** Tertiary care, single centre **Duration of follow-up:** 7 days post op for sCr, 30 days for mortality and RRT **Definition of AKI used:** AKIN sCr criteria and RIFLE sCr and eGFR criteria only	**Exclusion criteria:** • RRT prior to surgery • Baseline sCr > 265µmol/l • Preoperative extracorporeal membrane oxygenation • Patients undergoing cardiac/lung transplantation, assist device insertion or thoracoabdominal aortic repair • Patients who denied access to medical records for purposes of research • Patients who died intra-operatively or within 48h of procedure (N=30) • Missing data (pre op sCr) (N=1) **<u>All patients</u>** **N:** 4836/4839 (Post hoc 3 patients excluded who had RRT planned postoperatively) **Age (mean):** 64.4 ± 14.2 **M:F:** 3203 (66%): 1633 (34%) **Diabetes:** 981 (20%) **History of "renal failure":** 172 (4%) **Baseline sCr (µmol/l):** 100 ± 25.6 **Baseline eGFR:** 68 ± 19 **eGFR<60:** 1646/4836 (34%) **Congestive heart failure:** 775 (16%)	Note: CPB with haemodilution leads to postoperative positive fluid balance. As s Cr was not corrected for fluid accumulation this will effect AKIN where there is a 48h "moving window" for diagnosis due to some patients having a lower measured sCr postop than preop leading to possible false positives.	**RIFLE I/AKIN 2**	**AKIN:** 57/4836 (1.2%) **RIFLE:** 169/4836 (3.5%) **p value:** NR	• only used sCr criteria, no information on UO • 3 patients excluded post hoc due to postoperative planned RRT • No information given on how multivariable analysis undertaken. **Additional outcomes:** • Prolonged intubation(>24 h) • Length of ICU and hospital stay • Agreement of RIFLE and AKIN definitions reported as 4x4 table • Outcomes by RRT or no-RRT • Comparison of outcomes , age and baseline
			RIFLE F/ AKIN 3	**AKIN:** 74/4836 (1.5%) **RIFLE:** 31/4836 (0.64%) **p value:** NR	
			AKI total	**AKIN:** 1272/4836(26.3%) **RIFLE:** 915/4836(18.9%) **p value:** <0.0001	
			All cause mortality at 30 days	**RIFLE criteria** / **AKIN criteria** **No AKI** 25/3921 (0.64%) / **No AKI** 19/3564 (0.53%) **RIFLE R** 27/715 (3.8%) / **AKIN 1** 30/1141 (2.6%) **RIFLE I** 31/169 (18.1%) / **AKIN 2** 7/57 (12.3%) **RIFLE F** 6/31 (19.4%) / **AKIN 3** 33/74 (44.6%)	
			All cause mortality (Odds ratio [95% CI])	**AKIN:** 5.3 [4.3-6.6] P<0.001 **RIFLE:** 4.5 [3.6-5.6] P<0.001	

<table>
<tr><th>Study details</th><th>Patients</th><th>Interventions</th><th>Outcome measures</th><th colspan="4">Effect size</th><th>Comments</th></tr>
<tr><td rowspan="5"></td><td rowspan="5"></td><td rowspan="5"></td><td>• Multivariable logistic regression analysis
• Only reported per 1 class/stage increase of AKI</td><td colspan="4"></td><td rowspan="5">sCr in patients detected

Notes:

*NCGC calculated. (For conversion from mg/dL to µmol/L multiplied by 88.4).

If >1 cardiac procedure in study period only first episode included. (N=42)

Baseline sCr was taken as last recorded value before surgery.</td></tr>
<tr><td>All cause mortality (AUROC [95% CI])</td><td colspan="4">AKIN: 0.82 [0.77-0.87]

RIFLE: 0.80 [0.75-0.85]</td></tr>
<tr><td rowspan="4">Number of patients needing RRT (defined as need for RRT in entire postoperative hospital stay or within 30 days of operation – all who had RRT in first 7 days postop classified as AKIN 3)

From univariable analysis</td><td>RIFLE criteria</td><td></td><td>AKIN criteria</td><td></td></tr>
<tr><td>No AKI</td><td>8/3921 (0.2%)</td><td>No AKI</td><td>4/3564 (0.1%)</td></tr>
<tr><td>RIFLE R</td><td>33/715 (4.6%)</td><td>AKIN 1</td><td>24/1141 (2.1%)</td></tr>
<tr><td>RIFLE I</td><td>37/169 (21.9%)</td><td>AKIN 2</td><td>5/57 (1.2%)</td></tr>
<tr><td></td><td>RIFLE F</td><td>18/31 (58.1%)</td><td>AKIN 3</td><td>63/74 (85.1%)</td></tr>
<tr><td></td><td></td><td></td><td></td><td colspan="4"></td></tr>
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Table 65: Garner 2012[151]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Garner 2012[151] **Country of study:** UK **Study design:** Retrospective analysis of clinical biochemistry database **Setting:** Single centre, district general hospital **Duration of follow-up:** 30 days	**Patient group:** Patients admitted to DGH during October 2008 **Inclusion criteria:** • Inpatients • >18 years old **Exclusion criteria:** • No sCr test available **<u>All patients</u>** **N:** 1315/2822 had multiple sCr tests **Age (median[range]):** 61 [18-98] **M:F:** 1401/2822 (49.6%): 1421/2822 (50.4%)	**RIFLE** Standard sCr criteria only **AKIN** Standard sCr criteria only Waikar and Bonventre (– Stage 1: sCr increase ≥26.4µmol/l within 24h or ≥44µmol/l within 48h Stage 2: ≥44µmol/l within 24h or ≥88µmol/l within 48h Stage 3: ≥88µmol/l within 24h or ≥132µmol/l within 48h Delta check (only AKI or not, no stages) >26µmol/l between two successive sCr results over a period of 30 days	**No AKI***	**AKIN:** 1190/1315 (90.5%) **RIFLE:** 1221/1315 (92.9%)	**Funding:** None **Limitations:** • Clinical biochemistry database only – limited baseline characteristics • No information on mortality or RRT • sCr criteria only • Very low rates of AKI due to general hospitalised population **Additional outcomes:** Outcomes for Waikar and Bonventre and delta check definitions.
			RIFLE R/AKIN 1	**AKIN:** 95/1315 (7.2%) **RIFLE:** 64/1315 (4.9%)	
			RIFLE I/AKIN 2	**AKIN:** 20/1315 (1.5%) **RIFLE:** 20/1315 (1.5%)	
			RIFLE F/ AKIN 3	**AKIN:** 10/1315 (0.8%) **RIFLE:** 10/1315 (0.8%)	
			AKI total*	**AKIN:** 125/1315 (9.5%) **RIFLE:** 94/1315 (7.1%)	
			All cause mortality	**Not reported**	
			Number of patients needing RRT	**Not reported**	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Definition of AKI used: AKIN, RIFLE and Waikar Bonventre and delta check sCr criteria only					Median time to detection of AKI – 6 days **Notes:** *Calculated by NCGC

Table 66: Haase 2009[166]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Haase2009[166] **Country of study:** Australia **Study design:** Prospective cohort	**Patient group:** Consecutive patients undergoing cardiac surgery with cardiopulmonary bypass .June 2007-December 2007. **Inclusion criteria:** • Adults (age >18) undergoing cardiac surgery (CABG, valve surgery and thoracic aortic surgery)	**RIFLE** Standard sCr (7 days) and UO (in ICU only) criteria **AKIN** Standard sCr (and RRT) and UO criteria (first 48h post op) **All patients:**	**No AKI**	**AKIN:** 156/282 (55.3%) **RIFLE:** 153/282 (54.2%)	**Funding:** Grant from Australian and New Zealand College of Anaesthetists and the Austin Hospital Anaesthesia and Intensive Care Trust Fund. **Conflicts of interest:** Second author member of ADQI Workgroup for
			RIFLE R/AKIN 1	**AKIN:** 95/282(33.7%) **RIFLE:** 85/282 (30.1%)	
			RIFLE I/AKIN 2	**AKIN:** 19/282 (6.7%) **RIFLE:** 34/282(12.1%)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Setting: Single centre, tertiary care. **Duration of follow-up:** 3 months - 48 hours for AKIN, 7 days for RIFLE, inhospital for mortality. **Definition of AKI used:** AKIN and RIFLE sCr criteria only	**Exclusion criteria:** • End stage renal disease undergoing chronic haemodialysis • Patients undergoing renal transplantation • Patients enrolled in a conflicting research study **<u>All patients</u>** **N:** 282 NOTE: Baseline characteristics only reported by stage of AKIN/RIFLE. **Age (mean):** 66.4-76.4years **Female:** 10.0%-36.8% **Pre-operative kidney disease (eGFR <60):** 18.6%-60.0% **Diabetes:** 16.7% - 42.1% **Baseline sCr† (µmol/l)(mean) :** 102 ± 27	UO maintained at 0.5-1ml/kg/h post op (with fuids or furosemide if required) Criteria for RRT, ≥1 of: • Oliguria unresponsive to fluid resuscitation • Potassium >6.5mmol/l • pH <7.2 • clinically significant organ oedema in the setting of renal failure.			RIFLE classification. **Limitations:** Baseline characteristics only reported by stage of AKIN/RIFLE. Confounders not considered in analysis. Differences between RIFLE and AKIN on length of time sCr measured over (as per standard criteria). All patients needing RRT classified as AKIN 3 no further information on predictive value of AKIN for this outcome. Creatine measured preoperatively – assume this was taken as baseline
			RIFLE F/ AKIN 3	**AKIN:** 12/282 (4.3%) **RIFLE:** 10/282 (3.5%)	
			AKI total	**AKIN:** 126/282 (44.7%) **RIFLE:** 129/282 (45.7%)	
			All cause mortality (inhospital)	**RIFLE criteria** / **AKIN criteria** **No AKI** 0/153 (0%) / **No AKI** 0/156 (0.0%) **RIFLE R** 1/85 (1.2%) / **AKIN 1** 1/95 (1.1%) **RIFLE I** 3/34 (8.8%) / **AKIN 2** 0/19 (0.0%) **RIFLE F** 2/10 (20.0%) / **AKIN 3** 5/12 (41.7%)	
			All cause mortality (Odds ratio [95% CI])	**Not reported**	
			All cause mortality (AUROC)	**AKIN:** 0.94 **RIFLE:** 0.91	

Study details	Patients	Interventions	Outcome measures	Effect size				Comments
				p value: 0.6				
			Number of patients needing RRT	**RIFLE criteria**		**AKIN criteria**		**Additional outcomes:** • length of ICU and hospital stay • AUROC by stage of AKI and by UO and sCr criteria • RIFLE L (n=2) • RIFLE E (n=1)
				No AKI	0/153 (0%)	**No AKI**	0/156 (0.0%)	
				RIFLE R	1/85 (1.2%)	**AKIN 1**	0/95 (0.0%)	
				RIFLE I	2/34 (5.9%)	**AKIN 2**	0/19 (0.0%)	
				RIFLE F	6/10 (60.0%)	**AKIN 3**	9/12 (75%)	**Notes:** * NCGC calculated. (For conversion from mg/dL to µmol/L multiplied by 88.4).

Table 67: Joannidis 2009[203]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Joannidis	**Patient group:** Patients admitted to	**RIFLE**	**No AKI**	**AKIN:** 10,263/14,356 (71.5%)	**Funding:** supported by

Study details	Patients	Interventions	Outcome measures	Effect size				Comments
2009[203] **Country of study:** Worldwide (not Africa, China or Japan) – SAP 3 cohort **Study design:** Retrospective analysis of prospectively collected data **Setting:** Multicentre, 303 ICUs **Duration of follow-up:** 48 hours for sCr,30 days for mortality	ICU **Inclusion criteria:** • Adults • Admission ≥48h **Exclusion criteria:** • Chronic renal supportive therapy for irreversible renal disease or history of chronic renal insufficiency at a sufficient level to provoke visceral effects • Renal transplantation • Patients with missing values for AKIN/RIFLE classification **<u>All patients</u>** **N:** 14,356/ 16,784 screened **Age (median [IQR]):** 63 [49-74] **M:F:** 8725 (60.8%): 5631 (39.2%) **Serum creatinine on ICU admission (µmol/l) (median [IQR]):** 88 [71-115] **Diabetes:** 1229 (8.6%) **Chronic heart failure (NYHA Class II-IV):** 1310 (9.1%)	Standard sCr criteria. UO criteria modified so <0.5ml/kg/h assigned RIFLE I. **AKIN** Standard sCr criteria without including a requirement of RRT in the analysis. UO criteria modified so <0.5ml/kg/h assigned AKIN 2.		**RIFLE:** 9263/14,356 (64.5%)				a grant from the Fund of the Austrian National Bank **Conflicts of interest:** First author AKIN participant for AKIN classification, however last author member of ADQI Workgroup for RIFLE classification. **Limitations:** UO criteria only available for 24h, therefore modified criteria. No information on RRT. No information given on how multivariable analysis undertaken. **Additional outcomes:**
			RIFLE R/AKIN 1	**AKIN:** 1077/14,356 (7.5%) **RIFLE:** 1092/14,356 (7.6%)				
			RIFLE I/AKIN 2	**AKIN:** 1033/14,356 (7.2%) **RIFLE:** 1596/14,356 (11.1%)				
			RIFLE F/ AKIN 3	**AKIN:** 1983/14,356 (13.8%) **RIFLE:** 2405/14,356 (16.8%)				
			AKI total	**AKIN:** 4093/14356 (28.5%) **RIFLE:** 5093/14356 (35.5%)				
			All cause mortality at 30 days	**RIFLE sCr or UO criteria**		**AKIN sCr or UO criteria**		
				No AKI	1261/9263 (13.6%)	**No AKI**	1630/10,263 (15.9%)	

Study details	Patients	Interventions	Outcome measures	Effect size				Comments
Definition of AKI used: AKIN and RIFLE sCr and UO criteria (not including RRT)				**RIFLE R**	319/1092 (29.2%)	**AKIN 1**	372/1077 (34.5%)	• Agreement of RIFLE and AKIN definitions reported as 4x4 table • Mortality for UO criterion alone and sCr criterion alone • Standardised mortality ratios – mean with 95% CI, figure only actual values not reported • 30 day survival curves **Notes:** *NCGC calculated. (For conversion from mg/dL to µmol/L multiplied by 88.4).
				RIFLE I	515/1596 (32.3%)	**AKIN 2**	300/1033 (29.0%)	
				RIFLE F	1024/2405 (42.6%)	**AKIN 3**	817/1983 (41.2%)	
			All cause mortality (Odds ratio [95% CI]) • Multivariable logistic regression analysis • P<0.001 for all	**RIFLE R**	1.38 [1.17-1.63]	**AKIN 1**	2.07 [1.77-2.43]	
				RIFLE I	1.90 [1.65-2.18]	**AKIN 2**	1.93 [1.63-2.28]	
				RIFLE F	2.99 [2.66-3.36]	**AKIN 3**	2.99 [2.64-3.38]	
			All cause mortality (AUROC)	**Not reported**				
			Number of patients needing RRT	**Not reported**				

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1 **Table 68: Lassnigg 2008[241]**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Lassnigg 2008[241] **Country of study:** Switzerland **Study design:** Prospective cohort **Setting:** Single centre, tertiary care. **Duration of follow-up:** 48 hours for sCr,30 days for mortality. Mean follow up 22 ±14 months.	**Patient group:** Consecutive patients undergoing cardiac surgery over a 46 month period. **Inclusion criteria:** • Adults (age >18) undergoing cardiac surgery **Exclusion criteria:** • Death within 48h after surgery (n=50) • Incomplete patient data (n=145) • Chronic RRT before surgery or baseline sCr >354µmol/l (n=36) • Need for thromboenarterectomy of the pulmonary arteries • Sole insertion of cardiac assist device • Cardiac transplantation **<u>All patients</u>** **N:** 7241 (3123 + 4118 patients from a previous study from same group (Lassnigg et al 2004) with significant differences in baseline characteristics,	**RIFLE** Standard sCr criteria only **AKIN** Standard sCr (and RRT) criteria only	**No AKI**	**AKIN:** 6644/7241 (91.8%) **RIFLE:** 7023/7241 (97%)	**Funding:** None reported **Conflicts of interest:** First author AKIN participant for AKIN classification. **Limitations:** • only used sCr criteria, no information on UO • Confounders not considered in analysis • Combines 2 populations with significant differences in baseline characteristics, surgery and timing of initiation of RRT
			RIFLE R/AKIN 1	**AKIN:** 463/7241 (6.4%) **RIFLE:**160/7241 (2.2%)	
			RIFLE I/AKIN 2	**AKIN:** 3/7241 (0.04%) **RIFLE:** 43/7241 (0.6%)	
			RIFLE F/ AKIN 3	**AKIN:** 131/7241 (1.8%) **RIFLE:** 15/7241 (0.2%)	
			AKI total	**AKIN:** 597/7241 (8.2%) **RIFLE:** 218/7241 (3%)	
			All cause mortality at 30 days	**RIFLE criteria**: **No AKI** 252/7023 (3.6%) **AKIN criteria**: **No AKI** 184/6644 (2.8%)	

Study details	Patients	Interventions	Outcome measures	Effect size				Comments
Definition of AKI used: AKIN and RIFLE sCr criteria only	surgery and timing of initiation of RRT) **LASSNIGG 2008 (Zurich) (N=3123)** **Age (mean):** 63 ± 11 **M:F:** 2354 (75%): 769 (25%) **Congestive heart failure:** 362 (12%) **Diabetes:** 505 (16%) **Baseline sCr† (µmol/l)(mean) :** 102 ± 27 **Mortality**: 100 (3.2%) **CABG-CPB:** 1781 (57%) **Off pump CABG:** 211 (6%) **Valve surgery:** 650 (20%) **Emergent surgery:** 71 (2.3%) **RRT:** 85 (3%) **RRT within 48h**: 60/85 (71%) **LASSNIGG 2004 (Vienna) (N=4118)** **Age (mean):** 64 ± 13 (P<0.01) **M:F:** 2672 (65%): 1446 (35%) (P<0.001) **Congestive heart failure:** 656 (16%) (P<0.001) **Diabetes:** 865 (21%) (P<0.001) **Baseline sCr† (µmol/l) (mean) :** 102 ± 30 (NS) **Mortality**: 212 (5.2%) (P<0.001) **CABG-CPB:** 1608 (39%) (P<0.001) **Off pump CABG:** 415 (10%) (P<0.001) **Valve surgery:** 1294 (32%) (P<0.001) **Emergent surgery:** 227 (5.5%) (P<0.001) **RRT:** 236 (6%) (P<0.001) **RRT within 48h:** 64/236 (27%) (P<0.001)			**RIFLE R**	47/160 (29.4%)	**AKIN 1**	76/463 (16.4%)	**Additional outcomes:** • Kaplan-Meier survival plots for ΔCreatinine groups only • Hazard ratios for 30 day mortality for ΔCreatinine groups only **Notes:** * NCGC calculated. (For conversion from mg/dL to µmol/L multiplied by 88.4). † Baseline sCr defined as value recorded just before surgery.
				RIFLE I	8/43 (18.6%)	**AKIN 2**	2/3 (66.7%)	
				RIFLE F	5/15 (33.3%)	**AKIN 3**	50/131 (38.2%)	
			All cause mortality (Odds ratio [95% CI])	**Not reported**				
			All cause mortality (AUROC)	**Not reported**				
			Number of patients needing RRT	**RIFLE criteria**		**AKIN criteria**		
				No AKI	247/7023 (3.5%)	**No AKI**	129/6644 (1.9%)	
				RIFLE R	40/160 (25%)	**AKIN 1**	62/463 (13.4%)	
				RIFLE I	23/43 (53.5%)	**AKIN 2**	3/3 (100%)	
				RIFLE F	11/15 (73.3%)	**AKIN 3**	127/131 (96.9%)	

Table 69: Lopes 2008[253]

Study details	Patients	Interventions	Outcome measures	Effect size		Comments
Lopes 2008[253] **Country of study:** Portugal **Study design:** Retrospective cohort **Setting:** Single centre ICU **Duration of follow-up:** inhospital	**Patient group:** Patients admitted to intensive care January 2003 – December 2006. Assessed whole ICU admission. **Inclusion criteria:** • Adults admitted to intensive care **Exclusion criteria:** • Chronic kidney disease undergoing RRT • Renal transplant **<u>All patients</u>** **N:** 662 **Age (mean):** 58.6 ± 19.2 **M:F:** 392 (59.2%): 270 (40.8%) **History of cardiovascular disease:** 53.2% **Medical admission:** 76.4% **Sepsis:** 40.9% **Estimated baseline creatinine† (µmol/l):** 96.9 ± 37.2	**RIFLE** Standard sCr and UO criteria **AKIN** Standard sCr and UO criteria	**No AKI**	**AKIN:** 328/662 (49.5%) **RIFLE:** 372/662 (56.2%) **p value:** NR		**Funding:** None **Limitations:** Single centre, retrospective study CKD prevalence in cohort unknown **Additional outcomes:** • Mean length of stay (RIFLE only) • Number of patients classified by creatinine criteria or UO criteria or both • All cause mortality OR for sCr or UO
			RIFLE R/AKIN 1	**AKIN:** 140/662 (21.1%) **RIFLE:** 97/662 (14.7%) **p value:** 0.003		
			RIFLE I/AKIN 2	**AKIN:** 67/662 (10.1%) **RIFLE:** 73/662 (11%) **p value:** 0.655		
			RIFLE F/ AKIN 3	**AKIN:** 127/662 (19.2%) **RIFLE:** 120/662 (18.1%) **p value:** 0.672		
			AKI total	**AKIN:** 334/662 (50.4%) **RIFLE:** 290/662 (43.8%) **p value:** 0.018		
			All cause mortality	**RIFLE criteria**	**AKIN criteria**	

Study details	Patients	Interventions	Outcome measures	Effect size				Comments
Definition of AKI used: AKIN and RIFLE sCr and UO criteria			**(inhospital)**	**No AKI**	11%	**No AKI**	8.5%	criteria alone **Notes:** †Baseline sCr unavailable and estimated by the MDRD equation. Daily sCr and hourly UO were available. For analysis patients were assigned to their worst RIFLE or AKIN category according to **either** sCr or UO criteria. Factors considered in multivariable analysis: age, gender, race, history of cardiovascular disease, medical admission, sepsis diagnosis, SAPS II, need for vasopressors or mechanical ventilation.
				RIFLE R	30.9%	**AKIN 1**	30.7%	
				RIFLE I	32.8%	**AKIN 2**	32.8%	
				RIFLE F	55%	**AKIN 3**	53.5%	
				Any AKI	41.3%	**Any AKI**	39.8%	
			All cause mortality (Odds ratio [95% CI]) • Multivariable ogistic regression analysis • P<0.001 for all compared to patients with no AKI	**RIFLE R**	2.69 [1.49-4.88]	**AKIN 1**	3.54 [1.97-6.37]	
				RIFLE I	2.01 [1.03-3.89]	**AKIN 2**	2.71 [1.33-5.53]	
				RIFLE F	3.59 [2.01-6.42]	**AKIN 3**	4.66 [2.47-8.73]	
			All cause mortality (AUROC)	**AKIN:** 0.750 **RIFLE:** 0.733 **95% CIs not reported**				
			Number of patients needing RRT	**RIFLE criteria**		**AKIN criteria**		
				RIFLE R	2%	All RRT AKJN 3 by		

Study details	Patients	Interventions	Outcome measures	Effect size			Comments
				RIFLE I	12.3%	definition therefore not analysed in study	
				RIFLE F	56.7%		
				Any AKI	27.2%		
			Number of patients needing RRT (AUROC)	**RIFLE (Cr and UO criteria):** 0.829 (83%) **RIFLE (sCr criteria):** 0.818 (82%) **RIFLE (UO criteria):** 0.787 (79%) **95% CIs not reported**			

Table 70: Ostermann 2011[305]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Ostermann 2011[305] **Country of study:** UK and Germany	**Patient group:** Patients admitted to ICU June 1989-October 1999. **Inclusion criteria:** • Adults (age ≥18) **Exclusion criteria:** • RRT dependent end-stage	**RIFLE** Standard sCr criteria only **AKIN** Standard sCr (and RRT) criteria only	**No AKI**	**AKIN:** 26597/41172 (64.6%)† **RIFLE:** 26391/41172 (64.1%)†	**Funding:** Departmental funds only, no conflicts of interest. **Limitations:** • No 6h urine results available **Additional outcomes:**
			RIFLE R/AKIN 1	**AKIN:** 7864/41172 (19.1%)† **RIFLE:** 7082/41172 (17.2%)†	
			RIFLE I/AKIN 2	**AKIN:** 1565 /41172 (3.8%)†	

Study details	Patients	Interventions	Outcome measures	Effect size				Comments
Study design: Retrospective analysis of prospectively collected data **Setting:** Multicentre, 22 ICUs **Duration of follow-up:** 48h for sCr, inhospital for mortality **Definition of AKI used:** AKIN, RIFLE (and ARI,ARFS and SARFS) criteria	renal failure (n=797) • Missing data (n=3) **<u>All patients</u>** **N:** 41172/ 41972 **Age (mean):** 63.7			**RIFLE:** 4525/41172 (10.99%)†				• Out comes for ARI,ARFS and SARFS criteria **Notes:** †Calculated by NCGC from percentages reported in study Factors considered in multivariable analysis: cardiac surgery, age, male gende, APACHE II and SOFA score on admission to ICU, pre-existing chronic diseases, maximum number of failed organs, ventilation, emergency surgery, non-surgical admission.
			RIFLE F/ AKIN 3	**AKIN:** 5147/41172 (12.5%)† **RIFLE:** 3129/41172 (7.6%)†				
			AKI total	**AKIN:** 14575/41172 (35.4%)† **RIFLE:** 14781/41172 (35.9%)†				
			All cause mortality (inhospital)†	**RIFLE criteria**		**AKIN criteria**		
				No AKI	NR	**No AKI**	NR	
				RIFLE R	1480/7082 (20.9%)	**AKIN 1**	2351/7864 (29.9%)	
				RIFLE I	2063/4525 (45.6%)	**AKIN 2**	560/1565 (35.8%)	
				RIFLE F	1777/3129 (56.8%)	**AKIN 3**	2980/5147 (57.9%)	
			All cause mortality (Odds ratio [95% CI])	**RIFLE R**	1.40 [1.28-	**AKIN 1**	0.98 [0.90-	

Study details	Patients	Interventions	Outcome measures	Effect size				Comments
			• Multivariable logistic regression analysis		1.53]		1.08]	
				RIFLE I	1.96 [1.80-2.14]	**AKIN 2**	1.11 [0.94-1.31]	
				RIFLE F	1.59 [1.43-1.76]	**AKIN 3**	2.01 [1.71-2.36]	
			All cause mortality (AUROC [Hosmer Lemeshow χ^2])	**AKIN:** 0.84 [40.987; P<0.0001] **RIFLE:** 0.897 [48.32; P<0.001] 95% CI not reported				
			Number of patients needing RRT	**Not reported**				

Table 71: Robert 2010[346]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Robert 2010[346]	**Patient group:** Patients undergoing CABG or valve surgery between	**RIFLE** Standard sCr criteria only	**No AKI**	**AKIN:** 17356/24747 (70.1%) **RIFLE:** 17017/24747 (68.8%)	**Funding:** Grant from Agency for Healthcare

<table>
<tr><th>Study details</th><th>Patients</th><th>Interventions</th><th>Outcome measures</th><th colspan="4">Effect size</th><th>Comments</th></tr>
<tr><td rowspan="8">Country of study: USA

Study design:
Retrospective analysis of prospectively collected data

Setting:
Cardiothoracic surgery departments in 8 medical centres

Duration of follow-up:
Inhospital (unclear if sCr limited to 48h)</td><td rowspan="8">January 2001 and December 2007

Inclusion criteria:
• Adults undergoing CABG or valve surgery

Exclusion criteria:
• Preoperative RRT (n=339)

<u>All patients</u>
N: 24747/25086 screened
Age (mean): 66 ± 11
M:F†: 17521 (70.8%): 7226 (29.2%)
Diabetes†: 7894 (31.9%)
Baseline sCr (µmol/l)*(mean): 97 ± 88</td><td rowspan="8">AKIN
Standard sCr (and RRT) criteria only</td><td></td><td colspan="4"></td><td rowspan="8">Research and Quality.

Limitations:
• Univariable analysis only
• UO criteria not used, no information on UO

Additional outcomes:
None

Notes:
* NCGC calculated. (For conversion from mg/dL to µmol/L multiplied by 88.4).

†Calculated by NCGC from percentages reported in study

Baseline sCr defined as last sCr collected before surgery.</td></tr>
<tr><td>RIFLE R/AKIN 1</td><td colspan="4">AKIN: 5659/24747 (22.9%)
RIFLE: 5357 /24747 (21.7%)</td></tr>
<tr><td>RIFLE I/AKIN 2</td><td colspan="4">AKIN: 852/24747 (3.4%)
RIFLE: 1473/24747 (5.9%)</td></tr>
<tr><td>RIFLE F/ AKIN 3</td><td colspan="4">AKIN: 880/24747 (3.6%)
RIFLE: 900/24747 (3.6%)</td></tr>
<tr><td>AKI total</td><td colspan="4">AKIN: 7391/24747 (29.9%)
RIFLE: 7730 /24747 (31.2%)</td></tr>
<tr><td rowspan="3">All cause mortality (inhospital)</td><td colspan="2">RIFLE criteria</td><td colspan="2">AKIN criteria</td></tr>
<tr><td>No AKI</td><td>235/17017 (1.4%)</td><td>No AKI</td><td>228/17356 (1.3%)</td></tr>
<tr><td>RIFLE R</td><td>175/5357 (21.7%)</td><td>AKIN 1</td><td>229/5659 (4.1%)</td></tr>
</table>

Study details	Patients	Interventions	Outcome measures	Effect size				Comments
Definition of AKI used: AKIN and RIFLE sCr criteria only				**RIFLE I**	164/1473 (11.1%)	**AKIN 2**	121/852 (14.2%)	
				RIFLE F	328/900 (36.4%)	**AKIN 3**	324/880 (36.8%)	
			All cause mortality (Odds ratio [95% CI]) • Univariable analysis, no AKI as reference	**RIFLE R**	2.41 [1.98-2.94]	**AKIN 1**	3.17 [2.63-3.82]	
				RIFLE I	8.94 [7.27-11.00]	**AKIN 2**	12.43 [9.85-15.69]	
				RIFLE F	40.94 [33.95-49.36]	**AKIN 3**	43.77 [36.22-52.89]	
			All cause mortality (AUROC)	**AKIN:** 0.79 [0.77-0.80] **RIFLE:** 0.78 [0.76-0.80] $\mathbf{X^2}$=0.81, **p**=0.369				
			Number of patients needing RRT	**Not reported**				

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1 **Table 72: Valette 2012[409]**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Valette 2012[409] **Country of study:** France **Study design:** Prospective cohort **Setting:** single centre, surgical ICU **Duration of follow-up:** 72h for sCr and UO, in-ICU for mortality	**Patient group:** Consecutive patients in surgical ICU who had received intravenous and intra-arterial contrast medium. May 2007-June2008. **Inclusion criteria:** • Stable sCr before injection of contrast medium **Exclusion criteria:** • Chronic or acute RRT • Other aetiology for new AKI • Increase in sCr >44µmol/l within 48h before injection of contrast medium **<u>All patients</u>** **N:** 101 **Age (mean):** 56 ± 18 **M:F:** 67 (66%) :34 (34%) **Diabetes:** 10/101 (10%) **CKD:** 2/101 (2%) **CrCl <60ml/min:** 20/101 (20%) **Chronic heart failure:** 0/101 (0%) **Aminoglcosides**: 19/101 (19%) **NSAIDs**: 0/101 (0%)	**RIFLE** Standard sCr and UO criteria **AKIN** Standard sCr and UO criteria	**No CI-AKI**	**AKIN:** 82/101 (81%) **RIFLE:** 82/101 (81%)	**Funding:** None **Limitations:** • Small sample size • No multivariable analysis • Mortality and RRT only reported for no CI-AKI vs CI-AKI not by stage **Additional outcomes:** • Outcomes for Barrett and Parfrey criteria • Univariable analysis (no ORs) diabetes, CrCL<60 and aminoglycoside administration to be associated with CI-AKI by
			RIFLE R/AKIN 1	**Not reported**	
			RIFLE I/AKIN 2	**Not reported**	
			RIFLE F/ AKIN 3	**Not reported**	
			CI-AKI total	**AKIN:** 19/101 (19%) **RIFLE:** 19/101 (19%)	
			All cause ICU mortality	**RIFLE criteria**: **No AKI** 10/82 (12.2%); **RIFLE R** 5/19 (26.3%) **AKIN criteria**: **No AKI** 9/82 (11%); **AKIN 1** 6/19 (31.6%)	
			All cause mortality (Odds ratio [95% CI])	**Not reported**	
			All cause mortality (AUROC)	**Not reported**	

Study details	Patients	Interventions	Outcome measures	Effect size				Comments
Definition of AKI used: AKIN, RIFLE and Barrett and Parfrey criteria within 72h of contrast administration	**ACEI:** 3/101 (3%) **Previous contrast media injection within 72h of enrolment:** 33/101 (33%) **CT with low osmolar contrast:** 74/101 (73%) **Arteriography with iso-osmolar contrast:** 22/101 (22%) **Arteriography with low-osmolar contrast:** 5/101 (5%) **Mean volume of contrast for CT:** 100 ± 18ml **Mean volume of contrast for arteriography:** 110 ± 72ml		**Number of patients needing RRT**	**RIFLE criteria**		**AKIN criteria**		• RiFLE classification but only diabetes by AKIN classification • Effect of excluding UO criteria on association with RRT and mortality **Notes:** * NCGC calculated. (For conversion from mg/dL to µmol/L multiplied by 88.4). Baseline sCr was defined as the value just before contrast medium injection
				No CI-AKI	4/82 (4.9%)	**No CI-AKI**	3/82 (3.6%)	
				CI-AKI	6/19 (31.6%)	**CI-AKI**	7/19 (36.8%)	

Table 73: Perez valdivieso 2008 [321]

Study details	Patients	Interventions	Outcome measures	Effect size		Comments
Perez valdivieso	Patient group: Patients who had a nephrology	All patients: Patients were assessed	Mortality	No AKI	4.2% (N=11#)	Funding: NR
				RIFLE R	20.5%(N=23#	

Study details	Patients	Interventions	Outcome measures	Effect size		Comments
2008 [321] Country of study: Spain Study design: Prospective cohort Who was blinded: NR Setting: Tertiary care hospital, single centre Duration of follow-up: Cohort followed from Jan 98- Apr 06 Definition of AKI used: RIFLE sCr criteria (unclear if UO	consultation requested because of suspicion of AKI between January 1998 – April 2006* Inclusion criteria: As above Exclusion criteria: Presented with oliguria but did not show an adequate sCr increase to qualify for one of the creatinine RIFLE criteria Age less than 16 years Missing data All patients N: 903 Age (mean): NR Drop outs: 0 Baseline data given according to RIFLE category: No AKI N: 259 Age (median (IQR)): 62(19.75) Drop outs: 0 M/F (%):72.8/27.2 Diabetes (%): 11.6	using the RIFLE criteria – sCr criteria used, unclear if urine output criteria used. Cox proportional hazards model was used to asses the relationship between RIFLE categories and hospital mortality. The multivariate adjusted model included the following variables selected through descriptive analysis of potential confounders; Liano score** prior food intake***, need for RRT, chronic renal failure, the cause of AKI, admission type (surgical or not), Karnofsky score and oncologic disease.		)		Limitations: The RIFLE criterion- urine output on a 6 h basis was not used Unclear if urine output criteria used. Data collection was started before definitions used in the study were clearly defined Single centre- cannot be generalised to other populations Additional outcomes: HR for the additive effects of the exposures of hospital mortality and Liano score values and RIFLE scores. Cumulative survival rates within 60 days after nephrology consultation Calibration curves for RIFLE criteria ROC curve for RIFLE criteria, Liano score, and RIFLE + Liano score Notes: *In the event of multiple admissions only the initial admission was considered to avoid bias
				RIFLE I	27.0%(N=50#)	
				RIFLE F	33.4%(N=116#)	
			Need for RRT	No AKI	1.8% (N=5#)	
				RIFLE R	11.9% (N=13#)	
				RIFLE I	24.6% (N=46#)	
				RIFLE F	41.4% (N=144#)	
			Incidence of in hospital mortality (multivariate adjusted HR (95% CI))- using no AKI as the reference group	No AKI	1 (reference)	
				RIFLE R	2.77(1.15-6.66)	
				RIFLE I	3.23(1.42-7.37)	
				RIFLE F	3.52(1.59-7.80)	
			Incidence of in hospital mortality (multivariate adjusted HR (95% CI)) – using RIFLE R as the reference group	No AKI	Patients excluded	
				RIFLE R	1 (reference)	
				RIFLE I	1.15(0.63-2.09)	
				RIFLE F	1.22(0.69-2.17)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
criteria used)	Chronic renal failure (%):65.9 RIFLE R N: 112 Age (median (IQR)): 60(20.25) Drop outs: 0 M/F (%):73.7/26.3 Diabetes (%): 8.5 Chronic renal failure (%):26.3 RIFLE I N: 185 Age (median (IQR)): 62(18.00) Drop outs: 0 M/F (%):69.1/30.9 Diabetes (%): 9.4 Chronic renal failure (%):12.0 RIFLE F N: 347 Age (median (IQR)): 63(18.00) Drop outs: 0 M/F (%):69.1/30.9 Diabetes (%): 8.9 Chronic renal failure (%):28.0				**Liano score equation: 0.032*age in decades-0.086 *male gender-0.109*nephrotoxic+0.109*oliguria+0.116*hypotension+0.122*jaundice+0.150*coma-0.154*consciousness +0.182*assisted respiration+0.210 *** classified as appropriate when it was optimal, mild malnutrition when it had been inadequate for less than 3 days, moderate malnutrition when it had been inadequate for 3-7 days and severe malnutrition when it had been inadequate for more than 7 days Baseline creatinine in patients with no history of chronic renal disease was calculated using modification of diet in renal disease equation assuming a GFR of 75ml/min per 1.73m². For patients with a history of chronic renal disease the baseline sCr was assumed to be the one that was measured at admission. #NCGC calculated

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3 **Table 74: Bihorac 2009[51]**

Study details	Patients	Interventions	Outcome measures	Effect size		Comments
Bihorac 2009[51] Country of study: USA Study design: Retrospective cohort Who was blinded: N/A Setting: Hospital ICU Duration of follow-up: 5 years Definition of AKI used: RIFLE criteria using the	Patient group: Critically ill adult surgical patients between January 1 1992 – December 31 2002. Inclusion criteria: Admitted to surgical ICU for >24 hrs after any kind of operative procedure and who survived to be discharged home. Exclusion criteria: Trauma, burn orthopaedic, ear nose and throat, urological and kidney transplantation patients History of CKD at any stage All patients N: 10518 Age (mean): NR Drop outs: NR Baseline data given according to RIFLE category: No AKI N: 7192	All patients Patients were assessed using the RIFLE criteria – **Patients with AKI were stratified according to the maximum RIFLE class reached during hospital stay. This was determined by comparing the highest sCr during hospitalization with the baseline sCr. RIFLE R: corresponds to a 150% increase in sCr RIFLE I: corresponds to a 200% increase in sCr RIFLE F: corresponds to a 300% increase in sCr Cox proportional hazards model was used to assess the relationship between RIFLE categories and mortality following hospital discharge. The multivariate adjusted	Need for RRT	No AKI	NR	Funding: NR Limitations: CKD excluded Dependence on ICD-9-CM codes for assessing pre existing co morbidities and other post operative complications, cannot be sure that there is accurate coding and there may be difference in coding between centres-also data was entered by non-clinicians therefore some complications which are dependent on physician judgement (e.g. sepsis) may be under represented Single centre study- cannot readily generalise to other populations Mortality rate may be affected by surgical technique at the centre No information given about medical treatment post discharge which would impact on long term mortality also.
				RIFLE R	1 (0.07%)	
				RIFLE I	4 (0.43%)	
				RIFLE F	191 (22%)	
				All AKI patients	195(6%)	
			RRT dependence (no recovery)	No AKI	NR	
				RIFLE R	0 (0%)	
				RIFLE I	0 (0%)	
				RIFLE F	99 (11%)	
				All AKI patients	99 (3%)	
			Mortality following hospital discharge (multivariate adjusted HR (95% CI))	No AKI	NR	
				RIFLE R	1.18(1.08-1.29)	
				RIFLE I	1.43 (1.29-1.59)	
				RIFLE F	1.57(1.40-1.75)	
				All AKI patients	NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
change in sCr during hospitalisation compared with baseline sCr(lowest value measured at admission/expected sCr*)	Age (mean ±SD): 55±16 Drop outs: NR M/F (%): 3925(55)/3267(45) Hypertension (%): 2682(37) Diabetes (%): 861(12) Congestive heart failure (%): 548(8) Sepsis (%): 217(3) RIFLE R N: 1535 Age (mean±SD): 63±14 Drop outs: NR M/F (%): 859(56)/676(44) Hypertension (%): 731(48) Diabetes (%): 317(21) Congestive heart failure (%): 288(19) Sepsis (%):100 (7) RIFLE I N: 928 Age (mean±SD): 62±15 Drop outs: NR M/F (%):494 (53)/434(47) Hypertension (%): 469(51) Diabetes (%): 223(24) Congestive heart failure (%): 204(22) Sepsis (%): 107(12) RIFLE F	model included the following variables; age, gender, race, type of surgery, co morbidities, other postoperative complications, discharge facility, and LOS.			Additional outcomes: HR for mortality following discharge associated with other co-morbidities, age, gender, type of surgery, discharge site, LOHS and postoperative complications Kaplan Meier plots for survival in patients with AKI vs. no AKI up to 14 years. Notes: * calculated with the modification of diet in renal disease equation assuming a GFR of 75ml/min per 1.73m^2 The number of patients lost to follow up contributed to a maximum of 250 patient years – these patients were taken into account in the analysis until the last recording.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 863 Age (mean ±SD): 61-±14 Drop outs: NR M/F (%):502 (58)/361(42) Hypertension (%): 473(55) Diabetes (%): 206(24) Congestive heart failure (%): 274(32) Sepsis (%):168(19)				

1 **Table 75: Clec'h 2011[97]**

Study details	Patients	Interventions	Outcome measures	Effect size		Comments
Clec'h 2011[97] Country of study: France Study design: Retrospective cohort Who was blinded: N/A Setting: Hospital ICU-13 French	Patient group: Critically ill patients admitted to ICU. Data collected from multiple-centre database (OUTCOMEREA) from January 1997 to June 2009* Inclusion criteria: As above Exclusion criteria: Patients with CKD (assessed according to the APACHE II definitions) and patients with a nonorganic (pre renal) cause of renal dysfunction patients with RRT for extra renal	All patients Patients were classified according to the maximum RIFLE class. For patients who received RRT, the maximum RIFLE class was that reached before RRT initiation. Also GFR criteria was only used as urine output data was not recorded, GFR criteria were determined according to changes in serum creatinine level from baseline values, using the Modification of Diet in Renal Disease	Incidence of hospital mortality (multivariate adjusted HR (95% CI))	No AKI	1	Funding: NR Limitations: Excluded patients with CKD Data did not include information about urine output - did not utilise urine criteria in the RIFLE Additional outcomes: Association of AKI with hospital mortality and non renal SOFA score per point, McCabe class 3 and respiratory failure – adjusted and unadjusted HR Notes: Baseline creatinine values
				RIFLE R	1.58 (1.32 to 1.88)	
				RIFLE I	3.99 (3.43 to 4.65)	
				RIFLE F	4.12 (3.55 to 4.79)	
			Need for RRT	No AKI	0 (these patients were excluded from the analysis)	
				RIFLE R	41(7.5%)	
				RIFLE I	110(20.2)	
				RIFLE F	394(72.3%)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
ICUs Duration of follow-up: 12 years Definition of AKI used: RIFLE criteria	indications patients for whom the decision to withhold or withdraw life-sustaining treatments All patients N: 8,639 Age (mean): NR Drop outs: NR Baseline data given according to RIFLE category: No AKI N: 5,793 Age (mean±SD): 55.6 (18.5) Drop outs: NR M/F (%):3,609/2184 Uncomplicated diabetes mellitus (%):431 (7.4) Complicated diabetes mellitus (%):124 (2.1) RIFLE R N: 1,025 Age (mean±SD): 67.6 (15.8) Drop outs: NR M/F :588 /437 Uncomplicated diabetes mellitus (%):125 (12.2) Complicated diabetes mellitus	equation. RIFLE criteria: RIFLE R: Increase in serum creatinine ≥1.5 × baseline or decrease in GFR ≥25% and UO: <0.5 ml/kg/hour for ≥6 hours RIFLE I: Increase in serum creatinine ≥2 × baseline or decrease in GFR ≥ 50% and UO: <0.5 ml/kg/hour for ≥12 hours RIFLE F: Increase in serum creatinine ≥3 × baseline or decrease in GFR ≥75% or serum creatinine ≥350 µmol/L with an acute rise of at least 44 µmol/L and UO: <0.3 ml/kg/hour for ≥24 hours or anuria ≥12 hours A multivariate analysis was conducted and adjusted for the following predefined potential confounding factors: baseline characteristics			assessed by the MDRD equation *A random sample of patients older than 16 years of age and staying in the ICU for >24 hours are entered into the database each year. Participating centres can choose between two modes of patient selection: (1) consecutive admissions in "n" ICU beds for the whole year or (2) consecutive admissions in a particular month. The allocation of beds (or a particular month) is decided yearly by the database's steering committee. Only the first ICU stay was included in the analysis.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	(%):45 (4.4) RIFLE I N: 830 Age (mean±SD): 66.7 (15.7) Drop outs: NR M/F:502 /328 Uncomplicated diabetes mellitus (%):90 (10.8) Complicated diabetes mellitus (%):40 (4.8) RIFLE F N: 991 Age (mean±SD): 64.9 (16.0) Drop outs: NR M/F:582 /409 Uncomplicated diabetes mellitus (%):105 (10.6) Complicated diabetes mellitus (%):63 (6.4)	(non renal SOFA score, McCabe class, admission category and transfer from ward) and other organ failures (assessed on the basis of a specific SOFA component>2) occurring before AKI.			

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2 **Table 76: Gammelager 2012[149]**

Study details	Patients	Interventions	Outcome measures	Effect size		Comments
Gammelager 2012[149] Country of	Patient group: All adult residents (aged 15 years or older) with a first-time ICU admission from 1 January 2005 -	All patients Classified patients according to the maximum RIFLE class	Need for RRT	No AKI RIFLE R RIFLE I RIFLE F	482 (1.9%) 206 (10.4%) 220 (16.8%) 561 (37.5%)	Funding: NR Limitations:

Study details	Patients	Interventions	Outcome measures	Effect size		Comments
study: Denmark Study design: retrospective cohort Who was blinded: N/A Setting: Hospital ICU-national database Duration of follow-up: 1 year Definition of AKI used: RIFLE defined AKI	31 December 2010 using the Danish National Registry of Patients Inclusion criteria: As above Exclusion criteria: chronic dialysis treatment, previous kidney transplant, lacking information on creatinine level on the day of ICU admission, and on the day before and the day after admission All patients N: 30762 Age (median): 65 yrs Drop outs: NR Baseline data given according to RIFLE category: No AKI N: 25969 Age (median (IQR)): 64 (49, 75) Drop outs: NR M/F (%):14,797 (57.0%)/ 11,172 (43.0%) Primary diagnosis of septicaemia at current admission (%):232	(class R, class I or class F) reached during their hospital stay. The creatinine level was used to classify patients according to the RIFLE criteria: RIFLE R: defined as a 50-100% increase in creatinine from the baseline RIFLE I defined as a 100-200% increase RIFLE F: defined as an increase of 200% or more or creatinine values ≥ 354 µmol/l, with an acute rise > 44 µmol/l up to seven days before ICU admission Cox proportional hazards regression, was used adjusting for Age, gender, Charlson comorbidity index score (nonrenal), CKD (eGFR <60), RRT, mechanical ventilation, inotropes/vasopressors, surgical admission (emergency, elective, cardiac, non cardiac),	Mortality 1 year	No AKI	22.1% (21.6% - 22.7%)	data did not include information about urine output - did not utilize urine criteria in the RIFLE classification of AKI Additional outcomes: Cumulative 1 year survival by AKI level Unadjusted HR for mortality Cumulative 30-day and 31-365 day mortality and corresponding adjusted hazard ratios for age, Charlson co morbidity index score, surgical status, primary diagnosis during current hospitalization, CKD and ICU treatments Notes: * Baseline creatinine was defined as the most recent creatinine measurement from an outpatient clinic or general practitioner in the period from 1 year - 7 days before the current hospitalization. Creatinine assessments up to seven days before the current hospitalization were not considered
				RIFLE R	48.7% (46.5% - 50.9%)	
				RIFLE I	57.4% (54.8% - 60.1%)	
				RIFLE F	54.7% (52.1% - 57.2%)	
			Incidence of mortality at 0-30 days (multivariate adjusted HR (95% CI))	No AKI	1(ref.)	
				RIFLE R	1.96 (1.80-2.13)	
				RIFLE I	2.60 (2.38-2.85)	
				RIFLE F	2.41 (2.21-2.64)	
			Incidence of mortality at 30-365 days (multivariate adjusted HR (95% CI))	No AKI	1 (reference)	
				RIFLE R	1.33 (1.17-1.51)	
				RIFLE I	1.60 (1.37-1.87)	
				RIFLE F	1.64 (1.42-1.90)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	(0.9%) RIFLE R N: 1986 Age (median (IQR)): 72 (61, 80) Drop outs: NR M/F (%):1,108 (55.8%) / 878 (44.2%) Primary diagnosis of septicaemia at current admission (%): 100 (5.0%) RIFLE I N: 1311 Age (median (IQR)): 71 (59, 80) Drop outs: NR M/F (%):666 (50.8%)/ 645 (49.2%) Primary diagnosis of septicaemia at current admission (%):127 (9.7%) RIFLE F N: 1496 Age (median (IQR)): 69 (59, 78) Drop outs: NR M/F (%):839 (56.1%)/ 657 (43.9%) Primary diagnosis of septicaemia at current admission (%):187 (12.5%)	primary diagnosis (sepsis, CV, respiratory, GI or liver, malignancy, trauma, endocrine, other), length of hospital stay			For patients with no baseline creatinine level and without CKD, it was estimated using the 4-variable version of the Modification of Diet in Renal Disease equation Assumption made that all patients were Caucasian

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3 **Table 77: Hobson 2009[182]**

Study details	Patients	Interventions	Outcome measures	Effect size		Comments
Hobson 2009[182] Country of study: USA Study design: Retrospective cohort Who was blinded: N/A Setting: Hospital ICU Duration of follow-up: inhospital Definition of AKI used: RIFLE defined AKI**	Patient group: adult patients who were admitted to a surgical ICU for at least 24 hours after any kind of general/gastrointestinal, vascular, cardiothoracic, or neurosurgical operative procedure and who survived to discharge from the hospital were identified through a search of the billing database between the years 1992 and 2002 Inclusion criteria: patients who underwent any kind of cardiothoracic procedure with subsequent admission to a cardiothoracic surgery ICU Survived to be discharged Exclusion criteria: Patients with a history of CKD of any stage* Baseline characteristics Baseline data given according to RIFLE category:	All patients Patients were assessed using the RIFLE criteria – Patients with AKI were stratified according to the maximum RIFLE class reached during hospital stay. This was determined by comparing the highest sCr during hospitalization with the baseline sCr. RIFLE R: corresponds to a 100% increase in sCr RIFLE I: corresponds to a 200% increase in sCr RIFLE F: corresponds to a 3 fold increase in sCr Cox proportional hazards model was used to asses the relationship between RIFLE categories and mortality following hospital discharge.	Need for RRT	No AKI	NR	Funding: University of Florida College of Medicine, Departments of Surgery, Medicine, and Anaesthesiology. Limitations: No UO criteria used Excluded patients with CKD. Single centre Additional outcomes: HR for mortality following discharge associated with other co-morbidities, age, gender, ethnicity, type of cardiac surgery, discharge site, LOHS and postoperative complications HR for mortality stratified by degree of renal recovery Kaplan Meier plots for survival in patients with AKI vs. no AKI according to type of cardiac surgery up to 10 years. Kaplan Meier plots for survival in patients with AKI vs. no AKI stratified by degree of renal recovery
				RIFLE R	0 (0%)	
				RIFLE I	0 (0%)	
				RIFLE F	75 (31%)	
				All AKI patients	75 (6%)	
			RRT dependence (no recovery)	No AKI	NR	
				RIFLE R	0 (0%)	
				RIFLE I	0 (0%)	
				RIFLE F	35 (14%)	
				All AKI patients	35 (3%)	
			Mortality following hospital discharge (multivariate adjusted HR (95% CI))	No AKI	NR	
				RIFLE R	1.23(1.06 - 1.42)	
				RIFLE I	1.45(1.22-1.72)	
				RIFLE F	2.14(1.73-2.66).	
				All AKI patients	1.39(1.23-1.57)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	No AKI N: 1708 Age (mean ±SD): 60 ±13 Drop outs: NR M/F (%):1156 (68)/ 552 (32%) Hypertension (%):762 (45%) Diabetes (%):309 (18%) Congestive heart failure (%):294 (17%) RIFLE R N: 1265 Age (mean ±-SD): 64±12 Drop outs: NR M/F (%): 1060(68)/ 205 (32%) Hypertension (%):314 (49%) Diabetes (%):150 (24%) Congestive heart failure (%):175 (27%) RIFLE I N: 386 Age (mean ±SD): 64 ±13 Drop outs: NR M/F (%): 224(57)/ 162 (42%) Hypertension (%):207 (54%) Diabetes (%):97 (25%) Congestive heart failure (%):122 (32%) RIFLE F	These factors were chosen a priori, based on both the literature on AKI in surgery patients and on investigators clinical experience with AKI in these patients.			Notes: * History of CKD was established through review of all relevant clinical notes and sCr values before surgery and by analysis of ICD-9-CM codes for end-stage renal disease and CKD. **The change in sCr during hospitalization compared with baseline sCr. For the baseline sCr, the lowest of 2 values was used: The lowest measured sCr at the hospital admission or the expected sCr value calculated with the abbreviated Modification of Diet in Renal Disease equation

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 242 Age (mean±SD): 64±13 Drop outs: NR M/F (%):142 (59)/ 100 (41%) Hypertension (%):127 (52%) Diabetes (%):50 (21%) Congestive heart failure (%):55 (23%)				

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2 **Table 78: Hoste 2006 [187]**

Study details	Patients	Interventions	Outcome measures	Effect size		Comments
Hoste 2006 [187] Country of study: USA Study design: retrospective cohort Who was blinded: N/A	Patient group: All adult hospitalizations during a 12 month period (1 July 2000–30 June 2001) at the University of Pittsburgh Medical Centre that were admitted to one of its seven ICUs during their hospital stay* Inclusion criteria: As above Exclusion criteria: patients receiving chronic haemodialysis	All patients Classified patients according to the maximum RIFLE class (class R, class I or class F) reached during their hospital stay. Loss and End stage kidney disease were not investigated The RIFLE class was determined based on the worst of either glomerular filtration rate criteria or urine output criteria. The change in	Need for RRT P=0.001	No AKI	1 (0.1%)	Funding: conducted without external financial support Conflicts of interest: Some of the research group were involved in the consensus process by which RIFLE was developed and by which MDRD recommendations were made. Limitations: A true baseline is often unknown for patients admitted to the ICU- the use of the MDRD equation only a substitute for
				RIFLE R	0 (0%)	
				RIFLE I	4 (0.3%)	
				RIFLE F	214 (14.2%)	
			In hospital mortality P=0.001	No AKI	97 (5.5%)	
				RIFLE R	59 (8.8%)	
				RIFLE I	163 (11.4%)	
				RIFLE F	398 (26.3%)	
			Incidence of in hospital mortality (multivariate adjusted HR(95% CI))	No AKI	1(reference)	
				RIFLE R	1.0 (0.68–1.56)	
				RIFLE I	1.4 (1.02–1.88)	
				RIFLE F	2.7 (2.03–3.55)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Setting: Hospital ICU Duration of follow-up: inhospital Definition of AKI used: RIFLE UO and sCr	All patients N: 5,383 Age (mean): Drop outs: Baseline characteristics Baseline data given according to RIFLE category: No AKI N: 1,766 Age (mean ±-SD): 56.6 ±18.2 Drop outs: NR M/F (%): Chronic kidney insufficiency (%):17 (1.0%) In hospital before ICU admission: 527 (29.8%) RIFLE R N: 670 Age (mean -SD): 63.4±17.0 Drop outs: NR M/F (%):372 (55.5%)/(45.5%) Chronic kidney insufficiency (%):4 (0.6%) In hospital before ICU admission: 243 (36.3%) RIFLE I N: 1,436	sCr level and urine output to were used to classify patients according to the RIFLE criteria.** Cox proportional hazards regression analysis was used to examine whether the maximum RIFLE class and the incidence of AKI (defined as patients who fulfilled one of the RIFLE classes) were associated with mortality. Variables included: age, gender, race, the main reason for ICU admission, the medical or surgical admission category and the non renal SOFA score on ICU admission or at the maximum RIFLE class in the model			the actual glomerular filtration rate. The study is relatively large and included seven ICUs, it was conducted at a single medical centre whose case mix and referral patterns may not be representative of other centres. Additional outcomes: Severity of illness scores – APAHE III and SOFA regression analyses examining the impact of the different baseline characteristics on the appearance of acute kidney injury and maximum RIFLE class F Impact of baseline characteristics on the occurrence of acute kidney injury (multivariate logistic regression analysis) Association of Risk, Injury, Failure, Loss, and End-stage Kidney (RIFLE) criteria with mortality Notes: * only considered the first admission for patients who were readmitted to the ICU during the study period

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Age (mean -SD): 62.6 ±16.6 Drop outs: NR M/F (%):841 (58.6%)/595(41.2%) Chronic kidney insufficiency (%):17 (1.2%) In hospital before ICU admission: 476 (33.1%) RIFLE F N: 1,511 Age (mean -SD): 62.1 ±16.4 Drop outs: NR M/F (%):570 (57.0%)/941(43%) Chronic kidney insufficiency (%):121 (8.0%) In hospital before ICU admission: 592 (39.2%)				* *For patients without chronic kidney insufficiency as reported in the medical history- sCr level was calculated with the modification of diet in renal disease equation assuming a GFR of 75ml/min per 1.73m² the lowest creatinine value among the hospital admission creatinine, the ICU admission creatinine or the MDRD creatinine (used for half of all patients) was used as the baseline value

Table 79: Kim 2012[223]

Study details	Patients	Interventions	Outcome measures	Effect size		Comments
Kim 2012[223] Country of study: South Korea	Patient group: all consecutive patients with severe sepsis and septic shock who had been admitted to the medical ICU between January 2005 and December 2006*	All patients Patients were classified according to the maximum RIFLE class (no AKI, Risk, Injury or Failure) reached	Incidence of hospital mortality (multivariate adjusted OR (95% CI))	No AKI		Funding: NR Limitations: Small, single centre
				RIFLE R	0.84 (0.28-2.51) P= 0.76	
				RIFLE I	5.58 (2.23-13.93)	

Study details	Patients	Interventions	Outcome measures	Effect size		Comments
Study design: Retrospective cohort Who was blinded: N/A Setting: Hospital ICU Duration of follow-up: 1 year Definition of AKI used: AKI was defined according to the RIFLE criteria	Inclusion criteria: As above Exclusion criteria: receiving long-term dialysis or their stay in the ICU was less than 24 hours All patients N: 291 Age (mean±SD): 62.1 ± 14.0 Drop outs: NR M/F:198 /93 Malignancy (%):92 (31.6) Baseline data given according to maximum RIFLE category: No AKI N: 43 Age (mean±SD): 63.5 ± 13.9 Drop outs: NR M/F:28 /15 Malignancy (%):13 (30.2) RIFLE R N: 50 Age (mean±SD): 59.5 ± 13.2	during their ICU stay. Loss and End stage kidney disease were not investigated Patients were categorized on sCr or urine output or both; the criteria that led to the worst classification was used** Variables which were statistically significant (P < 0.25) by univariable analysis were included in multivariable analysis by applying a multiple logistic regression based on enter method. Variables adjusted for included age, sex, APACHE II score, SOFA score, and presence of malignancy			P= <0.00	Selected population - generalizing to others even ICU patients is limited Notes: * The diagnosis of severe sepsis and septic shock was based on the modified consensus criteria of the American College of Chest Physicians and Society of Critical Care Medicine. Only the first was considered ** Baseline renal function was defined as the lowest known creatinine value during the preceding 3 months. For patients without known prior creatinine, the baseline creatinine was estimated using the simplified modification of diet in renal disease formula, assuming a glomerular filtration rate of 75 mL/ min per 1.73 m2
			RIFLE F	7.64 (3.08-19.00) P=<0.00		
			Need for RRT	No AKI	0 (0)	
				RIFLE R	3 (6.0)	
				RIFLE I	27 (30.0)	
				RIFLE F	67 (62.0)	
			AuROC curve (95% CI)	0.58(0.52-0.65)		

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Drop outs: NR M/F:31 /19 Malignancy (%):20 (40.0) RIFLE I N: 90 Age (mean±SD): 63.3 ± 13.8 Drop outs: NR M/F:61 /29 Malignancy (%):28 (31.1) RIFLE F N: 108 Age (mean±SD): 61.7 ± 11.8 Drop outs: NR M/F:78 /30 Malignancy (%):31 (28.7)				

1 **Table 80: Mandelbaum 2011[262]**

Study details	Patients	Interventions	Outcome measures	Effect size		Comments
Mandelbaum2011[262] Country of study: USA Study	Patient group: Adult ICU patients admitted between 2001 and 2007 Inclusion criteria: ICU length of stay >24 hrs Had at least 2 sCr measurements available and 1 6 hr urine output	All patients Categorized using AKIN into stages 1,2 or 3 using sCr and UO measurements* Variables adjusted for in the multivariable	Incidence of in hospital mortality (multivariate adjusted OR(95% CI))	No AKI	1 (reference)	Funding: National institute of health grant Limitations: Database did not have a accurate coding system for RRT
				AKIN 1	1.380 (1.201-1.586)	
				AKIN 2	1.259 (1.058-1.499)	
				AKIN 3	2.484 (1.979-3.119)	
			Incidence of ICU	No AKI	NR	

Study details	Patients	Interventions	Outcome measures	Effect size		Comments
design: Retrospective cohort Who was blinded: N/A Setting: Hospital ICU-7 adult ICUs Duration of follow-up: 6 years Definition of AKI used: As defined by AKIN	observation period Exclusion criteria: Patients with end stage renal disease All patients N: 14524 Age (median (Q1,Q3)): 65.8 (55.2,77.8) Drop outs: NR M/F:/6161 (42.4%) Sequential organ failure assessment (non renal) (median (Q1, Q3)): 5(2,8) Baseline data given according to maximum AKIN category: No AKI N: 6252 Age (median (Q1,Q3)): 61.7(48.6, 75.7) Drop outs: NR M/F: 3706/ 2546 Sequential organ failure assessment (non renal) (median (Q1-Q3)): 3 (1,7)	analysis included: age, sex, SOFA score on admission, AKI stage, and co morbidities including diseases of the respiratory and gastrointestinal systems, sepsis, cirrhosis, GI bleeding, malignancy, CHF, diabetes mellitus, coronary artery disease, and peripheral vascular disease.	mortality (multivariate adjusted OR (95% CI))	AKIN 1 AKIN 2 AKIN 3	1.27 (NR) 1.26(NR) 3.71(NR)	Changes in medical management during the study may have impacted on the results Additional outcomes: OR for in hospital mortality for other co variants Kaplan mier survival plot Length of hospital stay and ICU stay Notes: * The lowest sCr level was considered to be equivalent to the patients' pre hospital baseline sCr level. The worst UO or sCr were examined in 48hr periods.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	AKIN 1 N: 5595 Age (median (Q1,Q3)): 68.8 (55.6, 79.2) Drop outs: NR M/F:3274/ 2321 Sequential organ failure assessment (non renal) (median (Q1-Q3)): 6(3,8) AKIN 2 N: 2046 Age (median (Q1,Q3)): 68.8 (56.5, 78.6) Drop outs: NR M/F:1046/1000 Sequential organ failure assessment (non renal) (median (Q1-Q3)): 7(4,9) AKIN 3 N: 631 Age (median (Q1,Q3)): 65.2 (52,76.5) Drop outs: NR M/F:337/294 Sequential organ failure assessment (non renal) (median (Q1-Q3)): 7(5,10)				

1 **Table 81: Uchino 2006[405]**

Study details	Patients	Interventions	Outcome measures	Effect size		Comments
Uchino 2006[405] Country of study: Australia Study design: Retrospective cohort Who was blinded: N/A Setting: Tertiary hospital Duration of follow-up: 2 years Definition of AKI used: As defined by RIFLE	Patient group: All hospitalised patients admitted between January 2000 and December 2002.* Inclusion criteria: As above. Exclusion criteria: < 15 years of age Chronic dialysis Kidney transplant Length of hospital stay < 24 hrs All patients N: 20126 Age (mean): 63.7±18.8 M/F: 11069(55%)/9057 (45%) Drop outs: NR ICU admission (%):14.7% Cardiology admission (%): 11.9	All patients Patients were classified according to the maximum RIFLE class RIFLE R: Increase in serum creatinine 1.5 × or decrease in GFR ≥25% and UO: <0.5 ml/kg/hour for ≥6 hours RIFLE I: Increase in serum creatinine 2 × or decrease in GFR ≥ 50% and UO: <0.5 ml/kg/hour for ≥12 hours RIFLE F: Increase in serum creatinine 3 × or decrease in GFR ≥75% or serum creatinine ≥4mg/dl with an acute rise of 44 µmol/L and UO: <0.3 ml/kg/hour for ≥24 hours or anuria ≥12 hours ** Patients were categorised on GFR only. The multivariate analysis used the following	Incidence of ICU mortality (multivariate adjusted OR (95% CI))	No AKI	1	Funding: Austin Hospital anesthesia and intensive care trust fund Potential conflict of interest: would favour RIFLE Limitations: Single centre- generalisability is a concern UO criteria not used Additional outcomes: Distribution of hospital mortality and RIFLE criteria - graph Notes: * In the case of multiple admissions only the first was considered. Peak creatinine was defined as the highest sCr during the hospital stay. For patients with 2 admissions the baseline sCr was defined as the measurement at hospital discharge from the previous
				RIFLE R	2.536(2.152-2.988) P=<0.0001	
				RIFLE I	5.412(4.547-6.442) P=<0.0001	
				RIFLE F	10.124(8.318-12.32) P=<0.0001	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
		variables: age, gender, emergency admission, ICU admission mechanical ventilation, baseline sreatinine and admission units			admission or calculate using the MDRD equation

G.4 Identifying the cause of AKI

G.4.1 Urinalysis

No relevant clinical studies comparing urine dipstick tests with microscopy and or biopsy were identified.

G.4.2 Ultrasound

Table 82: Licurse 2010[247]

Risk factors used in the multivariable model using the derivation sample: Licurse 2010[247]						
Risk factor	% of patients with HN	Adjusted odds ratio (95% CI, adjusted)				Comments
		Model 1	P value	Model 2	P value	
Nonblack	53.7	2.1 (1.0-4.4)	0.06	2.2 (1.0-4.6)	0 .046	* Diagnosis consistent with possible obstruction: benign prostatic hyperplasia, abdominal or pelvic cancer, neurogenic bladder, single functional kidney, or previous pelvic
Black	39.2	1 [Reference group] #	-	1 [Reference group]	-	
History of recurrent urinary tract infections - Yes	76.0	2.7 (0.8-8.5)	0.10	2.3 (0.7-7.1)	0.16	

History of recurrent urinary tract infections- No	46.3	1 [Reference group]	-	1 [Reference group]	-	surgery. ** History of HN: documented history of HN in the medical record or any imagining history of HN in the 2 years prior to the current RUS. ***Nephrotoxic medications: aspirin (81 mg/d), diuretic, angiotensin-converting enzyme inhibitor, or intravenous vancomycin. # Reference group: the reference group in a multivariate model has an adjusted odds ratio of 1 which means the risk factor does not affect odds of the outcome (HN)
Diagnosis consistent with possible obstruction*- Yes	67.4	2.4 (1.2-4.6)	0.01	2.4 (1.2-4.7)	0.009	
Diagnosis consistent with possible obstruction*- No	36.0	1 [Reference group]	-	1 [Reference group]	-	
History of HN** - Yes	90.3	11.1 (3.0-41.3)	<0.001	11.7 (3.0-45.2)	<0.001	
History of HN** - No	42.6 1	1 [Reference group]	-	1 [Reference group]	-	
History of CHF - No	52.7	2.1 (0.8-5.2)	0.12	2.0 (0.8-5.0)	0.14	
History of CHF - Yes	37.1	1 [Reference group]	-	1 [Reference group]	-	
History of prerenal AKI, use of pressors or history of sepsis - No	53.0	2.3 (0.9-6.2)	0.10	NA	NA	
History of prerenal AKI, use of pressors or history of sepsis - Yes	35.3	1 [Reference group]	-	NA	NA	
History of prerenal AKI, use of pressors, history of sepsis, or hypotension - No	60.2	NA	NA	2.1 (0.9-3.6)	0.04	
History of prerenal AKI, use of pressors, history of sepsis, or hypotension - Yes	40.2	NA	NA	1 [Reference group]	-	
Exposure to nephrotoxic medications prior to AKI - No***	62.2	2.1 (1.0-3.85)	0.05	3 1.8 (0.9-3.6)	0.09	
Exposure to nephrotoxic medications prior to AKI	38.2	1 [Reference group]	-	1 [Reference group]	-	

– Yes***						

DERIVATION STUDY DETAILS: Licurse 2010[247]

Reference	Population characteristics	Protocol and statistics	Model	Comments
Licurse 2010[247] Country of study: USA Study design: Cross sectional Definition of AKI: An abrupt decline in renal function, indicated either by increased sCr level (>0.3mg/dL or 50% above baseline) or decreased urine production (<0.5mL/kg/h over 6	Patient group: Hospitalised patients with suspected AKI from January 1 2005 to May 1 2009, who underwent RUS. Inclusion criteria: >18 years underwent RUS Exclusion criteria: did not meet the definition of AKI: a peak rise in sCr level of at least 0.3 mg/dL from baseline* during inpatient admission pregnancy, history of renal transplant previous diagnosis of HN within 30 days prior to RUS (considered follow-up studies, rather than primary diagnostic evaluations) Construction of derivation sample: 2097 RUS studies considered (January 1, 2005– December 31, 2007)of which 1 RUS study	Assessment of risk factors Risk factors were chosen based on clinical relevance and description in the salient medical literature. All data were abstracted from medical records (discharge summaries and clinical notes) by 4 trained reviewers****. Medical chart reviewers were blinded to the RUS result for each patient. There were 36 variables## Assessment of outcomes The study outcomes were HN and HNRI: Any RUS report that described "hydronephrosis" in the findings section was considered an outcome event. HNRI was defined as a RUS-diagnosed HN followed by either placement of a urologic stent or nephrostomy tube after the RUS date. Statistical analysis The association between risk factors and presence of HN on RUS was assessed using bivariate logistic regression analysis.	Consists of 7 variables: 1. history of HN (high-risk group) 2. recurrent urinary tract infections (1 point) 3. diagnosis consistent with possible obstruction (1 point) 4. nonblack race (1 point) And absence of the following: 5. exposure to inpatient nephrotoxic medications (1 point), 6. congestive heart failure (1 point), 7. pre-renal AKI (1 point). Results of derivation – prevalence of HN assessed for each score Three distinct risk groups emerged: Low (<2 points, 1%-20% prevalence of HN), Medium (3 points, 20% 40% prevalence of HN), High (>3 points, >40% prevalence of HN).	Funding: Doris Duke Charitable Foundation Additional outcomes: Number needed to screen to find 1 case of HN Estimated cost associated with a positive finding according to Medicare reimbursement Limitations: Only those patients who underwent RUS were included, rather than all patients with AKI Notes: A derivation sample was analysed using the presence of HN on RUS as a dependent variable. Strata were created based on the presence of risk factors associated with HN. * Baseline sCr level was defined as the lowest value in the 3 months prior to admission (if unavailable, then in the following order: lowest value 12 months prior to admission, baseline value described in the admission note, or lowest value during the current admission) **Nephrotoxic medications: aspirin (>81 mg/d), diuretic, ACE inhibitor, or intravenous vancomycin. *** Diagnosis consistent with possible

hours)	was randomly selected per patient until n = 100 with HN and n = 100 without HN (in order to maximise power in the derivation sample) Baseline characteristics All patients Total N: 200 Age (mean): 65.6 Male: 56.5% Race black: 25.5% Patients without HN N:100 Age < 55y: 28 Male sex: 56 Race, nonblack: 69 Mean absolute rise in sCr, mg/dL: 1.97 Urine output, <500 mL/d: 11 History of HN on previous imaging, CT or RUS: 3 Hematuria:4 Congestive heart failure:22 Sepsis, mentioned directly in medical chart:19 Cirrhosis:5 Hypertension:68 Diabetes:45 CKD:34 Exposure to nephrotoxic	Clinically relevant variables with a P value <0.20 from the bivariate analysis were evaluated in a logistic regression model# Multivariable logistic regression and stepwise regression was conducted until the model's quality was optimised (according to the C statistic and AIC). The most accurate model (ie, discrimination) was applied it to the validation sample. For a sensitivity analysis, a second model, differing from the main model only in the definition of a single clinical variable ("prerenal status"), which showed poorer discrimination Risk score: A risk score was developed based on the individual OR of each covariate. Each covariate was awarded 1 risk point. Any patient with a history of HN was assigned a priori to the high-risk group. Using this scoring system patients were segregated into 3 risk groups based on the prevalence of HN among patients with each risk score. This stratification was then applied to a validation sample. The sample size (N=800) was		obstruction: benign prostatic hyperplasia, abdominal, or pelvic cancer, neurogenic bladder, single functional kidney, or previous pelvic surgery ****The abstraction form was piloted and refined on a sample of 50 patients. Interobserver agreement was calculated for 10% of the derivation sample across 36 total variables, each treated as an independent unit. The average proportion of identically abstracted variables between one reviewer and each of the other 3 reviewers was 95%. #benign prostatic hyperplasia was also included owing to its clinical significance; P=.38 and some clinically related variables were collapsed into single composite variables ##Variables included: age, sex, race, documented history of HN, history of HN on previous imaging, CT or RUS, abdominal or pelvic cancer, recurrent uritis, mentioned by name in medical chart, or >2 in year prior to current admission, benign prostatic hyperplasia, 1 functional kidney, neurogenic bladder, pelvic surgery, flank pain, hematuria, history of HN-diagnosis consistent with obstruction, documented history of HN in notes, clinical history consistent with non-obstructive AKI; congestive heart failure, hypotension, sepsis, cirrhosis hypertension, diabetes, chronic kidney disease, hospital-acquired AKI, AKI for which the maximum sCr value was reached >2 d after admission date, history of pre-renal status, history of pre-renal status with hypotension, medications and

	medications**:63 History of HN***:3 Hospital-acquired AKI, AKI for which the maximum sCr value was reached >2 d after admission date: 46 Patients with HN N:100 Age < 55y: 17 Male sex:56 Race, nonblack:80 Mean absolute rise in sCr, mg/dL:2.67 Urine output, <500 mL/d:12 History of HN on previous imaging, CT or RUS:28 Hematuria:13 Congestive heart failure:13 Sepsis, mentioned directly in medical chart:10 Cirrhosis:3 Hypertension:61 Diabetes:33 CKD:28 Exposure to nephrotoxic medications**:39 History of HN***:28 Hospital-acquired AKI, AKI for which the maximum serum CR value was reached >2 d after admission date: 35	calculated a priori and provided 80% power to detect a prevalence of HNRI in the low-risk group of 0.3% to 0.5%.		nephrotoxic exposures within 10 days prior to maximum sCr value, IV contrast, angiography or cardiac catheterization, aspirin, NSAID, diuretic or ACE inhibitor, pressor, vancomycin, any IV antibiotic, exposure to nephrotoxic medications Clinical variables were only coded if they were available and known by the clinical team prior to the maximum sCr value and RUS date. All data were constructed as categorical variables, except for the mean rise in sCr level, age, and white blood cell count, which were constructed as continuous variables. Age and white blood cell count were subsequently dichotomised based on preliminary bivariate analysis. Pre renal AKI was coded 2 ways: In the primary model- history of sepsis or use of pressors during current admission. In secondary model(designed for sensitivity analysis), this variable also included history of hypotension prior to the onset of AKI, defined as at least 2 consecutive blood pressure measurements below 80mm Hg systolic or below 60 mm Hg diastolic.

Validation: Licurse 2010[247]				
Reference	Population characteristics	Protocol and statistics	Results per model*	Comments
Licurse 2010[247] Country of study: USA Study design: Cross sectional Definition of AKI: An abrupt decline in renal function, indicated either by increased sCr level (>0.3mg/dL or 50% above baseline) or decreased urine production (<0.5mL/kg/h over 6	Patient group As above Inclusion As above Exclusion As above Baseline characteristics All patients Total N: 797 Age (mean): 65.6 Male: 54.6% Race black: 22.8% Incidence of HN: 10.6% HN requiring intervention: 31.7% (3.3% of total N)	As above	Model 1 ** Risk stratification –(N=797) Low risk: N=223 (27.8%) Medium risk / high risk N= 574 (72.02%) Medium risk: N=267 # High risk: N=307# Incidence of HN and HNRI according to risk group Low risk: 7/223 (3.1% had HN (1 patient, or 0.4% [0.01%-2.5%] had HNRI)). Medium risk: 29/267# (10.7% had HN) High risk: 49/307# (16.1% had HN) Medium risk / high risk: 26/574 (4.5% had HNRI) Test performance for detecting HN low risk vs. high + medium NPV: 96.9% (CI: 7%-98.1%) Sensitivity: 91.8% (CI: 89.9%- 93.7%) Specificity: 30.4% (CI: 27%-34%) # NLR: 0.27# PLR: 1.3# PPV: 13.6# Test performance for detecting HN high risk vs. low + medium# NPV: 92.7# Sensitivity: 57.6 (CI: 46%-68%) # Specificity: 63.8 (CI: 60%-67%) # NLR: 0.66# PLR: 1.6# PPV: 15.9# Test performance for detecting HNRI low risk vs. high +	*Difference between models was the definition of pre renal status: Model 1 definition of pre renal status: history of sepsis or use of pressors during current admission. Model 2 definition of pre-renal status: also included history of hypotension prior to the onset of AKI, defined as at least 2 consecutive blood pressure measurements below 80mm Hg systolic or below 60 mm Hg diastolic. ** model 1 more sensitive for HN but included fewer patients in the low-risk group (i.e. less specific). Model 2 was less sensitive but more specific for HN. Incidental findings on RUS(n=797) 8 incidental findings (1%) unknown to the clinical team: 2 horseshoe kidneys, 4 extra renal pelvises, and 2 complex cysts. Of these, none were found in low-risk patients. #NCGC calculated Could not calculate values separately for high, medium, and low risk groups for model 2 and HNRI as insufficient data was reported.

hours)			medium NPV: 99.6% (CI, 99.1%-100%) Sensitivity: 96.3% (95% CI, 94.9%-97.6%) Specificity: 28.8% (26%-32%)# NLR: 0.13 PLR:1.4# PPV:4.5# Model 2** Risk stratification – (N=797) Low risk: N=331 (41.5%) Medium risk / high risk N= 466 (58.5%) Incidence of HN and HNRI according to risk group Low risk: 17/331 (5.1% had HN (1 patient [0.3%] had HNRI) Medium risk / high risk: 68/466 (14.6% had HN (26/466 (5.6%) had HNRI) Test performance for detecting HN low risk vs. high + medium NPV: 94.9 % (CI: 93.3%-96.4%) Sensitivity: 80.0% (CI: 77.2%-82.8%) Specificity: 44.1 %(40%-48%) # NLR: 0.45 PLR:1.4# PPV:14.6# Test performance for detecting HNRI low risk vs. high + medium NPV: 99.7% (CI: 99.3%-100.1%) Sensitivity: 96.3% (CI: 94.9%-97.6%) Specificity: 42.9(39%-46%) # NLR: 0.09 PPV:5.6# PLR:1.7#	

G.5 Managing AKI

G.5.1 Relief of urological obstruction

No clinical evidence was identified in the systematic review for timing of relief of upper tract urological obstruction.

G.5.2 Pharmacological management

G.5.2.1 Dopamine

Table 83: BELLOMO 2000[45]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Bellomo 2000[45] Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group Setting: Mulicentre, intensive	Patient group: Critically ill adults at risk of "renal failure". (March 1996-April 1999). Inclusion criteria: Presence of central venous catheter (CVC) ≥2 pathophysiological changes of the systemic inflammatory response syndrome (SIRS) over 24h One of: Urine output averaging <0.5mL/kg/h over 4 hours or longer Serum creatinine >150 µmol/L in the absence of premorbid renal dysfunction Rise in serum creatinine >80 µmol/L in <24h in absence of creatinine kinase >5000IU/L or	Group 1 Low dose dopamine 2µg kg-1 min-1 Continuous infusion via central venous catheter Infused for a mean of 113h (SD 157) Group 2 Placebo (vehicle without active	Survival to hospital discharge	Group1: 92/161 (57.1%) Group 2: 97/163 (59.5%) *Relative risk [95% CI]: 0.96 [0.80, 1.15] p value: 0.66	Funding: ANZICS and the Austin and Repatriation Anaesthesia and Intensive Care Trust Fund Limitations: Only ICU patients - ?generalisability. Clinicians could still give loop diuretics or vasoactive drugs as they thought necessary. Unclear duration of follow up, although outcomes
			Mortality at hospital discharge (NCGC)	Group1: 69/161 (42.9%) Group 2: 66/163 (40.5%) *Relative risk [95% CI]: 1.06 [0.82, 1.37] *p value: 0.67	
			Number needing RRT	Group1: 35/161 (21.7%) Group 2: 40/163 (24.5%)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
care (ICU) setting Study design: RCT – stratified blocks of 10 Who was blinded: patient, research nurse, investigator, ICU nursing and medical staff Duration of follow-up: not stated in protocol but all patients followed up until death or hospital discharge. Definition of AKI used: UO or serum	myoglobin in the urine Exclusion criteria: Age <18 years An episode of ARF within the previous 3 months Previous renal transplantation Use of dopamine in any dose during the current hospital stay Baseline serum creatinine >300 µmol/L Enrolling physician's belief that the drug could not be administered for ≥8h Unsuitability for use of RRT All patients N: 328 (328/467 screened = 70.2%) Drop outs: 4 withdrawn and not included in analyses (1 preparation error, 1 withdrew consent and 2 incorrect enrolment) No patients had renal parenchymal disease or urological obstruction. Group 1 N: 161 (161/163) Age (mean): 63 (±15) Drop outs: 2 M/F: 94 (58.4%) / 67 (41.6%) Pre-renal renal dysfunction: 152 (94.4%) Nephrotoxic component: 9 (5.6%) Baseline creatinine: 183 (±85) Oliguria: 109 (67.7%)	drug) Equivalent volume to 2µg kg-1 min-1 Continuous infusion via central venous catheter Infused for a mean of 125h (SD 166) Both groups: Drug was infused until: RRT given Death Serious adverse event SIRS and renal dysfunction resolved ≥24h Discharge from ICU 90 patients (≈55%) in each group had simultaneous administration of a loop diuretic.		*Relative risk [95% CI]: 0.89 [0.60, 1.32] *p value: 0.55	probably not biased by this. Additional outcomes: No. of patients with creatinine concentration >300 µmol/L Peak creatinine Urine output (ml/h) at baseline and 1h,24h and 48h Peak urea (mmol/L) Increase in creatinine Increase in urea Duration of mechanical ventilation Time to renal recovery (Kaplan-Meier) – no difference found between groups Notes: Each centre had a pharmacist or nurse independent of patient care and site investigator who was responsible for allocation, preparation and accounting of trial infusion. All statistical analysis done with masking maintained. 90% power to detect difference >25% in peak serum creatinine between
			Length of RRT	Not reported	
			Dialysis independence	Not reported	
			Length of hospital stay (days)	Group1: 29 (SD 27) Group 2: 33 (SD 39) *Mean difference[95% CI]: -4.00 [-11.30, 3.30] p value: 0.29	
			Cardiac arrhythmias (No. of patients who experienced arrhythmias)	Group1: 53/161 (32.9%) Group 2: 54/163 (33.1%) *Relative risk [95% CI]: 0.99 [0.73, 1.35] *p value: 0.97	
				*NCGC calculated	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
creatinine as defined in inclusion criteria	Type of admission: Respiratory (medical): 32% General surgical: 30% Vascular surgery: 19% Cardiac surgery: 12% Multiple trauma: 8% Cardiac (medical): 4% General medical: 13% Haematology/oncology: 8% Gastrointestinal (medical): 7% Thoracic surgery: 5% Other medical: 8% Other surgical: 15% Group 2 N: 163 (163/165) Age (mean): 61 (±17) Drop outs: 2 M/F: 102 (62.6%) / 61 (37.4%) Pre-renal renal dysfunction: 154 (94.5%) Nephrotoxic component: 9 (5.5%) Baseline creatinine (µmol/L): 182 (±81) Oliguria: 113 (69.3%) Type of admission: Respiratory (medical): 25% General surgical: 35% Vascular surgery: 16% Cardiac surgery: 12% Multiple trauma: 14% Cardiac (medical): 12%				the 2 groups at an α of 0.05 (assuming a normal distribution with SD equal to 60% of its mean, and estimated mean value of 250 µmol/L for the control group)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	General medical: 6% Haematology/oncology: 7% Gastrointestinal (medical): 6% Thoracic surgery:6% Other medical: 9% Other surgical: 15%				

G.5.2.2 Loop diuretics

Table 84: Brown 1981[63]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Brown 1981[63] Study design: Open label RCT "selective randomisation by decades of age". Who was blinded: no one Setting: Inpatient, renal unit in UK Duration of follow-up: Unclear	Patient group: Established ARF (ATN) following surgery or trauma. Inclusion criteria: See "AKI definition used" Oligo-anuria was not essential if shock or hypotension were absent or had been corrected before entry. Exclusion criteria: None stated Baseline characteristics:	Group 1 1g furosemide iv over 4 hours, then continued iv infusion of 2mg/min or orally at 3g/d to maintain UO 150-200ml/h and/or until plasma Cr <300µmol/l. Maximal daily dose of furosemide=3g. Group 2 1g furosemide iv over 4 hours then stopped	Mortality	Group1: 18/28 (64.3%) Group 2: 16/28 (57.1%) Relative risk: 95% CI: p value: Not sig	Funding: Furosemide supplied by Hoechst Pharmaceutical Ltd. Limitations: ?indirect population – all ATN (not AKI generally) and 55/56 required dialysis No blinding ?adequate randomisation Unclear allocation concealment Unclear follow up
			Number of patients needing RRT	Group 1: 28/28 (100%) Group 2: 27/28 (96.4%) Relative risk: 95% CI: p value: NR	
			Length of RRT	Not reported	
			Dialysis independence	Not reported	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Definition of AKI used: Acute tubular necrosis (ATN) defined by: a)Urine/plasma osmolality ≤1.1 b)Urine/plasma urea ≤10 c)Urine[Na+] ≥20mmol/l d)Absence of pre-existing CRF, obstructive uropathy, glomerulonephritis or systemic disease involving the kidney	All patients N: 56 Drop outs: 0 Group 1 N: 28 Age (mean) males: 55 Age (mean) females: 54 Drop outs: 0 M/F: 13(46.4%)/15(53.6%) Initial UO ≤500ml/h: 22/28 (78.6%) Group 2 N: 28 Age (mean) males: 53 Age (mean) females: 48 Drop outs: 0 M/F: 18(64.3%)/10(35.7%) Initial UO ≤500ml/h: 21/28 (75%)	All patients Dialysed by peritoneal or haemodialysis on daily or alternate day basis to maintain serum urea <30mmol/l and serum Cr <800µmol/l. Oral or iv nutrition to provide 3500-4000 calories/d and 80-150g/d of protein.	Length of hospital stay	Not reported	Additional outcomes: Subgroups of initially oliguric vs non oliguric for prevention/reversal of oliguria Time to reach UO 1000ml/d and 2000ml/d Oliguria reversed or prevented. Duration of oliguria. Time spent on furosemide for 8/28 (28.6%) patients – average =13.25 (range 8-21 days) Time to reach Cr of 150/300 µmol/l (in recovered patients)
			Hearing loss	Group1: 2/28 (7.1%) Group 2: 0/28 Relative risk: 95% CI: p value: (If no p-value: Sig/Not sig/NR)	
			Permanent hearing loss	Group 1: 1/28 (3.6%) (dosing error) Group2: 0/28	
				*Calculated by NCGC	

Table 85: Cantarovich 1971[68]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Cantarovich 1971[68]	Patient group: Severely ill patients with ARF of varied	Group 1a-fixed dose Conventional treatment plus iv	Mortality	Group 1a: 9/19 (48%) Group 1b: 7/15 (54%)	Funding: Not reported.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Study design: Open label RCT Setting: Inpatient – renal unit, Central Military Hospital, Argentina Duration of follow-up: Unclear Definition of AKI: See inclusion criteria	aetiology. Inclusion criteria: Urine output < 400ml/d Clear cut aetiology for ARF Many patients had failure of treatment with mannitol or peritoneal dialysis and frusemide elsewhere prior to inclusion. Exclusion criteria: diuresis after the rapid infusion of mannitol to a total of 60g within 24 h. Shock (unless corrected before randomisation). All patients N: 47 Age (mean): NR Drop outs: 0 Group 1a -Fixed dose N: 19 (40.4%) Age (mean): NR Drop outs: 0 Post surgery/trauma: 4/19 (21.1%) Obstetric (post C-section or septic abortion): 10/19 (52.6%) Sepsis: 1/19 (5.3%)	furosemide 600mg/d. (Given for an average of 14 days) Group 1b-progressive dose Conventional treatment plus iv furosemide 100-3200mg/d in geometric progression on successive days. [infused over 30 min (100mg) to 10 hr (3200mg)]. Average dose 1240mg/d for 7 days. Maximum daily dose 3200mg Group 2-control Conventional treatment only. All patients: Repeated RRT of short duration, started as early as possible and with unrestricted diet. Indications for RRT ≥1 of: Plasma urea >150mg/100ml Plasma potassium >6mg/100ml Serum creatinine >8mg/100 ml Intervention groups only: Furosemide continued until diuresis=2000 ml/d. Furosemide restarted if sustained		Group 2: 6/13 (40%) 95% CI:NR p value: NR	Limitations: All patients on RRT (?indirect population) 22 (47%) were obstetric (septic abortion and post caesarean) – (?indirect) Unequal numbers of patients randomised to groups Baseline characteristics of age and sex not reported Different average length of treatment: Group 1a 14 days vs Group 1b 7 days. Unclear follow up Additional outcomes: Urinary output Serum furosemide levels Furosemide detectable in urine Furosemide in blood Duration of anuria Diuresis of 400ml/d and 2000ml/d Blood urea Serum creatinine1.5 and 3mg/100ml Average number of RRT sessions Largest subgroup; septic abortion, analysed separately. Results in the survivors of this group followed the same pattern as the whole series.
			Number of patients needing RRT	Not reported	
			Length of RRT	Not reported	
			Dialysis independence	Not reported	
			Length of hospital stay	Not reported	
			Hearing loss/tinnitus	Tinnitus in patients given 3200mg in <4h, all resolved in few hours of stopping. No hearing loss.	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Other: 4/19 (21.0%) Group 1b -Progressive dose N: 15 (31.9%) Age (mean): NR Drop outs: 0 Post surgery/trauma: 4/15 (26.7%) Obstetric (post C-section or septic abortion): 7/15 (46.7%) Sepsis: 0/15 Other: 4/15 (26.7%) Group 2 -Control N: 13 (27.7%) Age (mean): NR Drop outs: 0 Post surgery/trauma: 3/13 (23.1%) Obstetric (post C-section or septic abortion): 5/13 (38.5%) Sepsis: 1/13 (7.7%) Other:4/13 (30.8%)	fall in UO followed by a persistent increase in plasma urea and creatinine. Daily blood and urine furosemide levels. In some patients a catheter was placed in the renal veins to determine the concentration of furosemide in renal venous blood to compare with the concentration in peripheral venous blood taken simultaneously. Appropriate adjustments in fluid and electrolyte balance made.			Notes: SD, CI or p values NR for any of the results.

1 **Table 86: Cantarovich 2004[69]**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Cantarovich 2004[69] Setting: 23	Patient group: Patients with "Acute renal failure requiring dialysis therapy". (Consecutive patients November 1992-	Group 1 Initially furosemide 25mg/kg/d iv over 6 hours (maximum 2g/d)	Mortality (at one month)	Group1: 59/166 (35.5%) Group 2: 50/164 (30.5%) p value: NR	Funding: Aventis Pharmaceuticals (manufacturers of
			Number of patients	Group1: 166/166 (100%)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
centres in France (ICU and nephrology wards) Study design: RCT. Stratification according to severity at presentation. Randomisation according to random plan. Who was blinded: "double blinded" – no further details given except that Aventis provided the study drug and matched placebo	December 1998) Inclusion criteria: RRT requirement defined as plasma urea >30mmol/L, oligoanuria for 48 hours, or uraemic syndrome Exclusion criteria: Pre-existing advanced CRF (serum Cr >150µmol/L or renal atrophy) Dehydration and pre-renal failure Obstructive uropathy Glomerulonephritis or systemic disease involving the kidney Malignant disease with a life expectancy <6 months Known auditory defect or history of hypersensitivity to the study drug Pregnancy or lack of adequate contraception Inability to obtain written informed consent All patients N: 330/338 (8 patients showed spontaneous recovery predialysis and so were excluded post-randomisation). Drop outs: 0 Group 1 N: 166	after intermittent RRT. [Changed to 35 mg/kg/d orally once a day after RRT if tolerated. On recovery of renal function this dose was tapered over 3 days prior to discontinuation)]. Group 2 Matched placebo (details not defined). All patients: Day 0 (pre-randomisation): 15mg/kg iv infusion of furosemide over 4 hours. Illness severity determined using Simplified Acute Physiology Scores (SAPS). Day 1: If serum Cr increased further patient randomly assigned to group 1 or 2. After randomisation patients could enter an optional predialysis period for a maximum of	needing RRT	Group 2: 164/164 (100%) (Population was AKI requiring RRT therefore not included in meta-analysis)	Lasix [furosemide]) provided an unrestricted grant and the furosemide and matched placebo. Two of the authors were employed by Aventis Pharma at the time of study initiation. Limitations: Blinding of assessors unclear Sig difference in serum Cr at randomisation and sepsis between groups (biased to control as intervention group more severe at randomisation) Unclear follow up Additional outcomes: Time to reach a 2L/day diuresis for 2 consecutive days. Time to achieve serum Cr <200 µmol Other side effects: pancreatitis, agranulocytosis, allergic reaction, heart arrest, pneumonia, hypoxia, peritonitis, GI
			Length of RRT: Time on dialysis therapy (days from start to end of RRT)	Group1: 11.4 (SD 8.6) Group 2: 12.4 (SD 8.7) p value: 0.21	
			Dialysis independence	Not reported	
			Length of hospital stay	Not reported	
			Hearing loss (patients systematically questioned and hearing tests performed when necessary)	Group1: 3/166 (1.8%) Group 2: 1/164 (0.6%) p value: Not significant	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Duration of follow-up: One month Definition of AKI used: ARF requiring RRT defined as plasma urea >30mmol/L, oligoanuria for 48 hours, or uraemic syndrome	Age (mean): 58.5 ± 16.3 Drop outs: 0 M/F: 111 (66.9%) / 55 (33.1%) Serum Cr at randomisation (mg/dL): 4.87±2.61 Serum Cr before 1st dialysis (mg/dL): 6.14±3.13 Serum Cr at randomisation (μmol/L)*: 430.5±230.7 Serum Cr before 1st dialysis (μmol/L)*: 542.8±276.7 SAPS: 15.4±5.3 Sepsis: 72/166 (43.4%) Sepsis and shock: 55/166 (33.1%) Group 2 N: 164 Age (mean): 58.6 ± 16.1 Drop outs: 0 M/F: 112 (68.3%) / 52 (31.7%) Serum Cr at randomisation (mg/dL): 4.31±2.78 Serum Cr before 1st dialysis (mg/dL): 6.05±3.19 Serum Cr at randomisation (μmol/L)*: 381.0±245.8 Serum Cr before 1st dialysis (μmol/L)*: 534.8±282.0 SAPS: 15.6±5.6 Sepsis: 54/164 (32.9%) Sepsis and shock: 33/164 (20.1%)	48 hours. Blood drawn before and after each intermittent RRT session. Continuous RRT interrupted if sustained decrease in serum Cr.			disorders, hypokalaemia and polyuria. Only polyuria significant (p=0.015). Notes: Sample size calculation: 122 patients per arm for power of 80% to detect 15% difference between groups for survival (assuming a 45% baseline value). *NCGC calculated. (For conversion from mg/dL to μmol/L multiplied by 88.4).

Study details	Patients	Interventions	Outcome measures	Effect size	Comments

1

2 **Table 87: Kleinknecht 1976[230]**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Kleinknecht 1976[230] Study design: Open label RCT Setting: Inpatient – renal unit (France). Duration of follow-up: NR Defintion of AKI: See inclusion criteria	Patient group: Patients with acute established oliguric renal failure. (1971 -1974). Inclusion criteria: ≥one of: Urinary output <500ml/d or <20ml/h with no response to volume expansion, when performed Urine/plasma urea <10 sodium concentration >30 mEq/l urine/plasma osmolality <1.1 Exclusion criteria: Pre-existing chronic renal failure, obstructive uropathy, glomerulonephritis or systemic disease involving the kidney. Shock or hypotension (unless corrected before randomisation). All patients N: 66 Age (mean): NR Drop outs: NR	Group 1- Intervention 3mg/kg furosemide iv over a few minutes and followed every 4h by equal doses if UO 20-100 ml/h. 6mg/kg if UO < 20ml/h, 1.5mg/kg if UO 100-150ml/h, 0mg/kg if UO >150ml/h. Maximum daily dose 1200mg. Urinary losses of water and electrolytes were systematically compensated by a standard solution of 5% dextrose containing 6g/l NaCl and 1.5g/l KCl, adjusted to UO. Group 2- Control Not defined - ?low dose	Mortality	Group1: 13/33 (39.4%) Group 2: 12/33 (36.4%) 95% CI: NR p value: >0.5	Funding: NR Limitations: Method of randomisation not described. 56/66 (84.8%) patients had RRT (haemodialysis or peritoneal dialysis). Details of treatment for control group not described. Results not reported for all patients. 15/66 (22.7%) post obstetric. ?Urinary losses compensated in intervention group only Unclear follow up Additional outcomes: Anuria Oligura UO 1500ml/d Spontaneous decrease in blood urea Diuretic response to furosemide
			Number of patients needing RRT	Not reported	
			Length of RRT	Not reported	
			Dialysis independence	Not reported	
			Length of hospital stay	Not reported	
			Hearing loss or tinnitus	“several conscious patients had a transient hearing loss and/or tinnitus”	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	M/F: 31(47.0%) /35(53.0%) Group 1 - Intervention N: 33 Age (mean): NR Drop outs: NR M/F: 13 (39.4%)/20 (60.6%) Post surgery/trauma:17/33 (51.5%) Obstetric (post partum or post abortum): 8/33 (24.2%) Medical: 8/33 (24.2%) Oliguria before admission: ≤ 2days: 13/33 (39.4%) >2 days: 20/33 (60.6%) Group 2 - Control N: 33 Age (mean): NR Drop outs: 0 M/F: 18 (54.5%)/15 (45.5%) Post-surgery/trauma: 15/33 (45.5%) Obstetrical (post-partum or post arboretum): 7/33 (21.2%) Medical: 11/33 (33.3%) Oliguria before admission: ≤ 2days: 18/33 (54.5%) >2 days: 15/33 (45.5%)	furosemide as diuretic response to furosemide reported for this group. All patients Blood urea levels remained or were maintained by RRT <200mg/100ml. Protein intake ≥1g/kg/d and caloric intake ≥30cal/kg/d were given whenever possible. Intervention Group: Furosemide temporarily discontinued if no diuretic response was observed after 3 successive injections (UO < 20 ml/h). Further treatment was attempted every 5 days until diuresis occurred.			(more than 500ml/day) Number of RRT sessions No benefit was found giving or not giving furosemide within the first 48h after onset of ARF. Normal urinary output (>1500 ml/d) was more rapidly obtained in treated than non-treated patients, once diuresis had occurred (p<0.01).

Table 88: Van der Voort 2009[411]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
van der Voort 2009[411] Study design: RCT (placebo controlled) Who was	Patient group: Mechanically ventilated critically ill patients in the recovery phase of haemofiltration (CVVH) dependent acute renal failure Inclusion criteria: CVVH ended Written informed consent from	Group 1 Furosemide 0.5mg/kg/h continuous iv infusion Group 2 Matched placebo All patients	Mortality	Group1: 13/36 (36.1%) Group 2: 11/35 (31.4%) *Relative risk [95% CI]: 1.15 [0.60, 2.21] p value: 0.8	Funding: Sponsored by funds from the ICU where the study was performed, "not commercially funded". Limitations: Indirect population
			Number of patients needing RRT	Not reported	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
blinded: patients and individuals administering care Setting: 13 bed ICU in a teaching hospital in the Netherlands. Duration of follow-up: 2 months after hospital discharge. Definition of AKI used: Haemofiltration dependent ARF.	nearest relative Exclusion criteria: Age <18 years Chronic renal failure (defined as pre-ICU admission recorded serum Cr >2mg/dL or chronic dialysis or Cr clearance <30mL/min) Pregnancy Known furosemide allergy ARF caused by glomerulonephritis Baseline characteristics: All patients N: 71 /136 screened Drop outs: 0 Group 1 N: 36 Age (mean): 72 ± 8.8 Drop outs: 0 M/F: 23(63.9%)/13(36.1%) Sepsis: 16/36 (44.4%) APACHE II: 25 (SD 7.3)	At the end of CVVH 4 hour urine sample (with concomitant blood sample) was collected to measure creatinine clearance (CrCl). Study medication was started at the end of the 4h collection period. Rate of fluid infusion was adapted hourly to match urinary production of the previous hour. Criteria to restart CVVH, one of: Serum urea >40mmol/L Fluid overload with hypoxia Serum potassium >6.0mmol/L Metabolic acidosis Uraemic syndrome Study medication restarted after this new session of	Length of RRT: No. of days on CVVH [median (IQR)]	Group1: 8.2 (12) Group 2: 7.0 (10) 95% CI:NR p value: 0.74	Unclear if assessors of outcomes blinded Method of randomisation unclear Unclear follow up Additional outcomes: Sodium excretion (p=0.001) Fluid balance over study episode Serum Chloride Creatinine clearance ICU mortality Renal recovery (defined as Cr clearance >30mL/min or stable serum creatinine without RRT) at discharge and at 2 months post discharge Urinary volume Long term RRT

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	SOFA: 10.2 (SD 2.7) Serum Cr (μmol/L): 122 (SD 48) Cr Clearance(mL/min)(median): 13.5 (IQR 29) No. of CVVH at entry (median): 6 (IQR 6) Preadmission serum Cr (μmol/L) (median):93 (IQR 61) Group 2 N: 35 Age (mean): 66 ± 10.0 Drop outs: 0 M/F: 20(57.1%)/15(52.9%) Sepsis: 16/35 (45.7%) APACHE II: 23 (SD 7.0) SOFA: 8.6 (SD 2.3) Serum Cr (μmol/L): 114 (SD 57) Cr Clearance(mL/min)(median): 16.4 (IQR 20) No. of CVVH at entry (median): 6 (IQR 6) Preadmission serum Cr (μmol/L) (median):84 (IQR 38)	CVVH. Patients given inotropes to maintain mean arterial pressure of 60mmHg. Aminoglycosides, ACE inhibitors and ARBs were prohibited. Study medication stopped when CrCl >30mL/min, recovery of renal function or new haemofiltration session started. Also if UO <400mL/d. Recovery of renal function defined as: CrCl >30mL/min OR Stable serum Cr level for ≥3 days while CrCl <30mL/min	Dialysis independence	Not reported	dependency Notes: Not enough information given to be able to convert median (IQR) into mean (SD). Unable, therefore, to meta-analyse these data.
			Length of hospital stay: Length of ICU stay (days) [median (IQR)]	Group1: 24 (18) Group 2: 20 (24) 95% CI: NR p value: NR	
			Hearing loss	Not reported	

G.5.3 Referring for renal replacement therapy

1 **Table 89: Bagshaw 2009[28]**

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Bagshaw 2009[28] Country of study: Multinational 23 countries Study design: Prospective observational study Who was blinded: NR Setting: 53 ICUs in 23 countries Duration of follow-up: NR Definition of AKI used:	Patient group: Critically ill ICU patients with severe AKI who were treated with RRT. Inclusion criteria: >12 years Evidence of severe AKI Admitted to ICU Teated with RRT Exclusion criteria: Pre-existing end stage renal disease receiving chronic RRT Treated with RRT before ICU admission/ treated for drug toxicity not associaited with AKI All patients N: 1238 Age (mean±SD): 61.6 ±16 Drop outs: 0 M/F: 799/439* Urea at RRT initiation Group 1 N: 618 Age (mean): 59.9±19.9 Drop outs: 0	The timing of RRT was assessed using several approaches; Serum biomarker values Early/late RRT based on urea / sCr at the time of initiation of RRT where early represented initiation at values below the median and late at values above the median. Based on median urea at start of RRT Early: ≤24.2 mmol/L Late: >24.2 mmol/L Based on median sCr at start of RRT Early: ≤309µmol/l Late: >309µmol/l Acute changes to kidney function Median change in urea/sCR from ICU admission to start of RRT Based on median	Urea at RRT initiation ≤24.2 vs. >24.2		Funding: Funded in part by an unrestricted grant from the Austin hospital intensive care trust fund Limitations: Confounding factors may impact on the allocation to groups Groups not comparable at baseline Interventions not standardised Blinding not reported Additional outcomes: Co variate adjusted mortality sensitivity analysis restricted to severe AKI and mortality Notes: Available case analysis Median change in sCr : prehospital sCr values only available for 79% of the cohort (n=977) the n per arm is not reported * NCGC calculated using percentages reported
			Mortality (crude hospital mortality)	Group1(EARLY): 392/618* Group 2(LATE): 380/619* Relative risk [95% CI]:NR OR [95% CI]: 0.92 [0.73-1.15] p value: 0.48	
			RRT dependence (defined as: in those surviving till hospital discharge)	Group1:20/226(9%)* Group 2: 58/239(24.4%)* Relative risk [95% CI]:NR OR [95% CI]: 3.3 [1.89-5.60] p value: <0.0001	
			Duration of RRT (median (IQR))	Group1: 6 (2-15) Group 2: 4 (2-13) Relative risk [95% CI]:NR p value: 0.004	
			Length of ICU stay (median (IQR))	Group1: 1 (0-2) Group 2: 2 (1-7) Relative risk [95% CI]: NR p value: <0.0001	
			Length of hospital stay (median (IQR))	Group1: 15 (6-30) Group 2: 23 (12-44) Relative risk [95% CI]: NR p value: <0.0001	
			sCr at RRT initiation: ≤309µmol/l vs. >309µmol/l		
			Mortality (crude hospital mortality)	Group1(EARLY): 441/618* Group 2(LATE): 330/618* Relative risk [95% CI]: NR OR [95% CI]: 0.46[0.36-0.58]	

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
AKI defined as; presence of azotemia (>30mmol/L)and/or urine output of less than 200mL in 12hrs DEFINITION of EARLY vs LATE used: see intervention	M/F:61.9%/38.1% Group 2 N: 619 Age (mean): 63.3±14.9 Drop outs: 0 M/F:67.3%/32.7% sCr at RRT initiation Group 1 N: 618 Age (mean): 62.4±15.7 Drop outs: 0 M/F:59.4%/40.6% Group 2 N: 618 Age (mean): 60.8 Drop outs: 0 M/F:69.6%/30.4% Median change in urea Group 1 N: 618 Age (mean):NR Drop outs: 0 Group 2 N: 619 Age (mean): NR	change in urea; Early: ≤3.1mmol/l Late: >3.1mmol/l Based on median change in sCr; Early: ≤163µmol/l Late: >163µmol/l Start of RRT relative to the date of ICU admission Evaluated as a continuous variable and stratified in to 3 groups: RRT at admission / within 2 days = EARLY(Group 1) RRT from 2-5 days inclusive = DELAYED (Group 2) RRT later than 5 days after ICU admission = LATE (Group 3)		P value: <0.0001	
			RRT dependence (defined as: in those surviving till hospital discharge)	Group1: 12/177(6.9%)* Group 2: 66/288(23%)* Relative risk [95% CI]: NR OR [95%CI]: 4.04[2.13-7.66] P value:<0.0001	
			Duration of RRT (median (IQR))	Group1: 6[2-15] Group 2: 5[2-13] Relative risk [95% CI]: NR P value: <0.06	
			Length of ICU stay (median (IQR))	Group1: 1(1-5) Group 2: 2(0-4) Relative risk [95% CI]: NR P value: 0.24	
			Length of hospital stay (median (IQR))	Group1:18[9-38] Group 2: 19[11] Relative risk [95% CI]: NR P value:<0.86	
			Median change in urea between ICU admission and initiation of RRT: ≤3.1mmol/l vs. >3.1mmol/l		
			Mortality (crude hospital mortality)	Group1(EARLY): 387/618* Group 2(LATE): 384/619* Relative risk [95% CI]: NR P value:	
			RRT dependence (defined as: in those surviving till hospital discharge)	NR	

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
	Drop outs: 0 M/F: NR Median change in sCr Group 1 N: NR Age (mean): NR Drop outs: NR M/F:NR Group 2 N: NR Age (mean): NR Drop outs: NR M/F: NR Start of RRT relative to the date of ICU admission Group 1 N: 785 Age (mean): 60.5±16.7 Drop outs: 0 M/F:62.7%/37.3% Group 2 N: 174 Age (mean): 63.3 ±15.7 Drop outs: 0 M/F: 68.4%/31.6%		Duration of RRT	Group1: 5[2-12] Group 2: 5[2-16] Relative risk [95% CI]: NR p value: 0.01	
			Length of ICU stay (median (IQR))	Group1: 1[0-1] Group 2: 4[2-8] Relative risk [95% CI]: NR p value:<0.0001	
			Length of hospital stay (median (IQR))	Group1: 15[6-29] Group 2: 22.5[11-44] Relative risk [95% CI]: NR p value:<0.001	
			Median change in sCr between ICU admission and initiation of RRT: ≤163µmol/l vs. >163µmol/l		
			Mortality (crude hospital mortality)	Group1: 70.3% Group 2: 55.6% Relative risk [95% CI]: NR p value:NR	
			RRT dependence (defined as: in those surviving till hospital discharge)	NR	
			Duration of RRT (median (IQR))	Group1: 5[2-14] Group 2:6[2-16] Relative risk [95% CI]: NR p value:0.05	
			Length of ICU stay (median (IQR))	Group1: 1[1-4] Group 2: 2[1-6]	

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 3 N: 268 Age (mean):63.9 ±13.7 Drop outs: 0 M/F: 67.5%/32.5%			Relative risk [95% CI]: NR p value: <0.01	
			Length of hospital stay	NO DIFFERENCES WERE EVIDENT BETWEEN THE GROUPS	
			Start of RRT relative to the date of ICU admission <2days vs. 2-5days vs. >5days		
			Mortality (crude hospital mortality)	Group1(EARLY): 462/785* Group 2(DELAYED): 108/174* Group 3(LATE): 195/268* Relative risk [95% CI]:NR OR[95% CI]: 2.20[1.44-3.37] p value: <0.001	
			Renal recovery (defined as: in those surviving till hospital discharge- RRT dependence)	Group1: 55/323[16.9%]* Group 2: 10/66[15.6%]* Group 3:13/73[18.3%]* Relative risk [95% CI]: NR p value:0.92	
			Duration of RRT (median (range))	Group1: 5[2-13] Group 2: 6[2-12] Group 3:7[3-19] Relative risk [95% CI]:NR p value:<0.001	
			Length of ICU stay	NR	
			Length of hospital stay (median (range))	Group1: 20[10-42] Group 2: 26[14-51] Group 3:38[22-62] Relative risk [95% CI]:NR p value:<0.001	

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2 **Table 90: Bouman 2002[56]**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Bouman 2002[56] Country of study: Netherlands Study design: RCT Who was blinded: NR Setting: Multidisciplinary ICU at The Academic Medical Centre (university hospital) and Onze lieve Vrouwe Gasthuius	Patient group: 372 ICU admissions between May 1998 and March 2000 who received continuous venovenous hemofiltration. Of which 248 patients had oliguric ARF Inclusion criteria: Urine output <30ml/hr for >6 hrs despite aggressive fluid resuscitation (pulmonary artery occlusion pressure/ central venous pressure of >12mmHg) Hemodynamic optimization with dopamine/ dobutamine (>5µg.kg^{-1}), phosphodiesterase inhibitors or norepinephrine in any dose and the administration of high dose diuretics (> 500 mg of furosemide infusion in 6 hrs) Creatinine clearance of < 20ml/min(calculated from a 3 hr urine proportion) Mechanical ventilation 18-90 yrs Intention to provide full intensive treatment for at least 3 days Exclusion criteria: Prexisiting renal disease with	Group 1 (EARLY) Treatment started within 12 hrs after time of inclusion (time at which ALL inclusion criteria were met). Blood flow rate maintained at 100-150 ml/min and minimal ultrafiltrate production was 24L/day and 36 at maximum. The hemofilter and tubing set were changed when signs of clotting of the extra corporeal system occurred. Treatment was allowed to be interrupted for a maximum of 12 hrs between 2 runs. Group 2 (LATE) Treatment started when the patient fulfilled the conventional criteria for RRT*. Blood flow rate maintained at 150 ml/min and minimal ultrafiltrate production	Mortality	NR	Funding: NR Limitations: Unclear method of randomisation Blinding not reported Small sample size Inconsistencies in reporting figures Additional outcomes: Hemofiltration treatment characteristics Severity of illness scores at ICU admission and at study inclusion Notes: 3 arm study; extra arm early high volume hemofiltration: treatment started within 12 hrs after time of inclusion (time when ALL inclusion criteria were met). Blood flow rate maintained at 200 ml/min and minimal ultrafiltrate production was 72L/day. The hemofilter and tubing set were changed routinely every 24 hrs to prevent decay. Treatment was allowed to be interrupted for a maximum of 12 hrs between 2 runs.
			Survival (28 days)	Group1: 24/35 #(68.8% (72.2% also reported)) Group 2: 37/36 #(75%) Relative risk [95% CI]:NR p value: 0.80	
			Survival (ICU)	Group1: 22/35 #(62.9%) Group 2: 25/36 # (69.4%) Relative risk [95% CI]:NR p value: 0.73	
			Survival (hospital)	Group1:17/35# (48.6%) Group 2: 22/36#(61.15%) Relative risk [95% CI]:NR p value: 0.42	
			Duration of renal failure (medians and quartiles)	Group1: 5.7 (2.6-12.7) Group 2: 6.6 (2.9-12.2) Relative risk [95% CI]:NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
(teaching hospital) Duration of follow-up: 28 days Definition of AKI used: NR DEFINITION of EARLY vs LATE used: NR	creatinine clearance of <30 ml/min(according to Cockcroft & Gault) ARF caused by permanent occlusion or surgical lesion of the renal artery ARF caused by glomerulonephritis, interstitial nephritis or vasculitis ARF caused by post renal obstruction CHILD class C liver cirrhosis AIDS with CD4 count <0.05X10^9/L Non witnessed arrest with Glasgow coma score of <5 Hematologic malignancy with neutrophiles of <0.05X10^9/L No hemofiltration machine free for use at the moment of inclusion All patients N: 71 (106 inc 3rd arm) Age (mean): NR Drop outs: 6 Group 1 N: 35 Age (mean): 70±10 Drop outs: 0 M/F: 20/15#	was 24L/day and 36 at maximum. The hemofilter and tubing set were changed when signs of clotting of the extra corporeal system occurred. Hemofiltration Performed using computer controlled fully automated hemofiltration machines. The extra corporeal circuit was anticoagulated with heparin or nadroparin. In cases of severe contraindication antigoagulation wasn't used, in cases of heparin induced thrombocytopenia danaparoid was used. Hours between study inclusion and first session of hemofiltration (medians and quartiles): Group 1:7 (5-10) Group 2: 41.8(21.4-72)		p value: 0.55	* Conventional criteria for RRT: plasma urea >40mmol/l, potassium of >6.5mmol/L, or severe pulmonary oedema defined as central venous pressure or pulmonary artery occlusion pressure of >16mmHg and lung oedema on radiograph in all quadrants, with positive end expiratory pressure of ≥10cm H2O an PO2/FIO2 ratio of <150mmHg. In all treatment groups hemofiltration was allowed to be discontinued when urine output recovered (≥60ml/hr). Treatment was restarted if renal clearance remained insufficient (blood urea: >50mmol/l). When the second period of oligouria occurred the patient remained in the same group. The definite time to recovery was taken as the time of final recovery. Intention to treat analysis # NGCG calculated using percentages reported
			Length of ICU stay (medians and quartiles)	Group1: 13 (5-21) Group 2: 13.5 (6-21.8) Relative risk [95% CI]:NR p value: 0.96	
			Length of hospital stay (medians and quartiles)	Group1: 27 (12-53) Group 2: 35.5 (11.3-63.3) Relative risk [95% CI]:NR p value: 0.72	
			HRQoL	NR	
			Duration of RRT	NR	
			Renal recovery	Group1: 100% of all survivors Group 2: 100% of all survivors Relative risk [95% CI]:NR p value: NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Type of admission Cardiosurgical:74.3% Postoperative surgical/medical:25.7% Days between ICU admission at study inclusion(median(quartiles)): 1.6(0.7-2.0) Creatinine clearance and study inclusion (ml/min) (mean±SD): 5±4 Group 2 N: 36 Age (mean): 67±13 Drop outs: 6 (2=died 4=renal function recovered) M/F: 22/14 Type of admission Cardiosurgical: 50% Postoperative surgical/medical: 50% Days between ICU admission and study inclusion (median(quartiles)): 1.2(0.7-1.6) Creatinine clearance at study inclusion (ml/min) (mean±SD): 6±5	Days between ICU admission and study inclusion: Group 1:7 (5-10) Group 2: 41.8(21.4-72)			

1 **Table 91: Liu 2006[252]**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Liu 2006[252] Country of study: USA Study design: Observational study Who was blinded: NR Setting: Five academic medical centres (University of California San Diego, Cleveland Clinic Foundation, Maine Medical Center, Vanderbilt University, and	Patient group: During a 31 month period (February 1999 to August 2001), all patients who underwent consultation for AKI in the ICU by nephrology team were considered for study inclusion. *** Inclusion criteria: AKI was defined as an increase in serum creatinine ≥0.5 mg/dl and baseline serum creatinine <1.5mg/dl or an increase in serum creatinine ≥1.0 mg/dl and baseline serum creatinine ≥1.5 mg/dl and <5.0 mg/dl Exclusion criteria: Baseline serum creatinine ≥5.0 mg/dL <18 years, previous dialysis, kidney transplantation, ARF from urinary tract obstruction and hypovolemia responsive to fluids, prisoners and pregnant patients, eGFR <30 ml/min per 1.73 m² at the time of hospital admission**	The modality and the intensity of dialysis and other co-interventions were determined by the treating physician Group 1 (EARLY) patients with a relatively low degree of azotemia, whose BUN was ≤76 mg/dl at dialysis initiation Group 2 (LATE) patients with a high degree of azotemia, whose BUN was >76 mg/dl at dialysis initiation The rate of dialysis initiation ranged from 36%-59% between sites There was variation ranging from 46 to 57% of the mean BUN at dialysis initiation between sites Patients who started	Mortality	NR	Funding: Research grants: National Institutes of Health RO1-DK53412, RO1-DK53411, RO1-DK53413, R33-DK67645, and K12-HD049077 Limitations: Within-site variation with protocol, patient selection, dialysis care (frequency and dose)-interventions not standardized Number of dropouts per arm not reported Additional outcomes: Developed a propensity score using dialysis initiation at a high BUN as the dependent variable Notes: supplementary paper: Mehta R, Pascual M, Soroko S, Savage B, Himmelfarb J, Ikizler T, Paganini E, Chertow G: Spectrum of acute renal failure in the intensive care unit: The PICARD experience. Kidney Int 66: 1613–1621, 2004 * Adjusted for age, hepatic failure, sepsis, thrombocytopenia, and serum
			Renal recovery	NR	
			Duration of RRT	NR	
			Length of ICU stay	NR	
			HRQoL	NR	
			Survival (14 days)	Group1: 0.80 Group 2: 0.75 Relative risk [95% CI]:NR p value: 0.09	
			Survival (28 days)	Group1: 0.65 Group 2: 0.59 Relative risk [95% CI]:NR p value: 0.09	
			Adjusted*RR for death associated with dialysis initiation	Group1: NR Group 2: 1.85 (95% CI 1.16 to 2.96) p value: NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
University of California San Francisco) Duration of follow-up: 28 days Definition of AKI used: increase in sCr ≥0.5 mg/dl and baseline sCr <1.5mg/dl or an increase in sCr ≥1.0 mg/dl and baseline sCr ≥1.5 mg/dl and <5.0 mg/dl DEFINITION of EARLY vs LATE used: early: low degree of azotemia (BUN: ≤76 mg/dl), late: high degree	All patients N: 250 Age (mean): NR Drop outs: 7 BUN (median):76mg/dl M/F: NR Group 1: Low degree of azotemia N: 122 (excluding dropouts) Age (mean): 54.4 Drop outs: NR BUN (mean ± SD): 47.4±17.9 mg/dl M/F: 65(53%)/57(47%) Surgery before/at ICU admission: 55% No. failed organ systems (median [IQR]): 4 (3 to 4) Sepsis or septic shock: 37% Median urine output (mL): 423 Mean creatinine (mg/dl) 3.4 Mean BUN (mg/dl) 47.4 Parenteral or enteral nutrition support:33% Initial dialysis with CRRT:69% Group 2 : High degree of azotemia N: 121 (excluding dropouts) Age (mean): 57.7 Drop outs: NR	dialysis later were more likely to be treated with intermittent hemodialysis than with continuous RRT (P < 0.0001); this difference persisted after controlling for differences in modality assignment by site			creatinine and stratified by site and initial dialysis modality **A total of 398 (64%) of the 618 enrolled patients received dialysis during their ICU stay. To give patients in the analysis an equal "opportunity" to receive dialysis with a low and high degree of azotemia, individuals with an estimated GFR (eGFR) of <30 ml/min per 1.73 m2 at the time of hospital admission were excluded, reflecting National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) stage IV chronic kidney disease or significant/evolving AKI ***Given the large number of ICU beds at Cleveland Clinic Foundation, one in six AKI patients were randomly assigned for possible study inclusion, to avoid single-centre overrepresentation. Independent predictors of dialysis initiation with a high BUN included: a history of chronic obstructive pulmonary disease (odds ratio [OR] 2.78; 95% CI 1.20 to 6.49) higher sCr (OR1.43; 95% CI 1.21 to 1.69 per mg/dl). higher plasma bicarbonate concentrations (OR 1.05; 95% CI 0.99

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
of azotemia (BUN: >76 mg/dl)	BUN (mean ± SD): 144.8±28.5 mg/dl M/F: 85(70%)/30(36%) Surgery before/at ICU admission: 55% No. failed organ systems (median [IQR]): 3 (2 to 4) Sepsis or septic shock: 46% Median urine output (mL): 424 Mean creatinine (mg/dl) 4.7 Mean BUN (mg/dl) 114.9 Parenteral or enteral nutrition support: 65% Initial dialysis with CRRT: 43%				to 1.10 per mmol/L) patients who did not have a pulmonary artery catheter in place at the time dialysis was initiated (OR 1.59; 95% CI 0.85 to 2.99) Tachycardia was associated with a lower likelihood of dialysis initiation at a high BUN (OR 0.89; 95% CI 0.77 to 1.04 per 10 beats/min).

Table 92: Sugahara 2004[381]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Sugahara 2004[381] Country of study: Japan	Patient group: 486 patients who underwent cardiac surgery at Saitama Medical School during the period from January 1st 1995 to dec 31st 1997	Group 1 (EARLY) Patients received dialysis when the hourly urinary output became less than 30ml/hr for 3 consecutive hrs (or daily urinary output was	Mortality (day 14)	Group1: 2/14 Group 2: 12/14 Relative risk [95% CI]:NR p value: NR	Funding: NR Limitations: Method of randomisation unclear "all patients were divided randomly into two groups"
			Survival rates (Kaplan –Meier	Group1: 0.7 Group 2: 0.17	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Study design: RCT Who was blinded: NR Setting: Saitama Medical School Duration of follow-up: 14 days following start of continuous hemodialysis Definition of AKI used: sCr elevated by 0.5mg/dl/day or more DEFINITION of EARLY vs LATE used:	Inclusion criteria: Patients who developed acute renal failure* after coronary artery bypass graft surgery. Patients entered into the study once hourly urine output became 30 ml/hr or less and serum creatinine increased at the rate of 0.5 mg/dl/day or more. Exclusion criteria: Pregnant Severe hepatic dysfunction (serum bilirubin level of ≥5mg/dl) Mental disorders Cancers Proteninuria ≥2g daily sCr ≥1.4mg/dl before surgery All patients N: 36 Age (mean): NR Drop outs: 8 M/F: NR Group 1 N: 14 (excludes dropouts) Age (mean±SD): 65±3 Drop outs: 0 M/F: 9/5 Diabetes mellitus: 42%	aprox 750ml/less) Group 2 (LATE) Patients received dialysis when the hourly urinary output became less than 20ml/hr for 2 consecutive hrs (or daily urinary output was aprox 500ml/less) Continuous hemodialysis: patients were accessed through double-lumen catheters which were inserted into the right or left femoral vein and connected to a continuous hemodialyzer. An anticoagulant, nafamostat mesilate was used at 30IU/hr. dialysis started under condition of water elimination rate of 60ml/hr and a dialysate flow rate of 1l/hr. the variables were adjusted to the clinical conditions of the patient. The dialyzers used were	curves) (day 14)** Renal recovery Duration of RRT*** Length of ICU stay HRQoL	Relative risk [95% CI]:NR p value: <0.01 NR NR NR NR	Blinding not reported Allocation concealment unclear Small sample size Additional outcomes: At the start of dialysis: BP, sCr, urine volume, APACHE II score, days after surgery Changes in BP, urinary output and sCr after the initiation of dialysis Notes: *AFR was diagnosed when sCr was elevated by 0.5mg/dl/day or more 8 patients were excluded from the study because they were either patients in the early start treatment group whose urinary output recovered to more than 30ml/hr during the 3 hr observation, or patients in the late start group, whose urinary output either remained between 30-20ml/hr or was higher than 30 ml/hr for longer than 2 hr. 4 of these patients later received continuous hemodialysis and another 4 didn't because their urinary output recovered. Available case analysis used Comparisons between two groups used analysis of variance for hourly changes and students t test for other variables.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
NR	Hypertension: 57% sCr (mg/dl) (mean±SD): 0.8±0.1 GFR (ml/min) (mean±SD):78±3 Total cholesterol (mg/dl) (mean±SD):220±17 Ejection fraction (%) (mean±SD): 58±2 Group 2 N: 14 (excludes dropouts) Age (mean±SD): 64±2 Drop outs: 0 M/F: 9/5 Diabetes mellitus: 35% Hypertension: 57% sCr (mg/dl) (mean±SD): 0.9±0.1 GFR (ml/min) (mean±SD): 80±4 Total cholesterol (mg/dl) (mean±SD): 216±14 Ejection fraction (%) (mean±SD): 56±3	Panflow APF-S and Hemofeel SH			And Survival rates were analysed using Kaplan meier method GFR calculated using cockroft and gault equation ** read of graph ***the two survivors in the late treatment group were weaned from dialysis on the 7th and 10th days respectively. In the early start group two patients remained on dialysis on the 14th day

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2 **Table 93: Sutherland 2010[384]**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Sutherland 2010[384] Country of	Patient group: Prospective paediatric CRRT registry cohort. 297 children receiving CRRT.	All decisions regarding the initiation, prescription, termination and CRRT	Mortality (give timepoint if reported)	Group1: 45/153[29.4%] Group 2: 22/51[43.1%] Group 3:61/93[65.6%] Relative risk [95% CI]:NR	Funding: Unrestricted grant funding from 2001-2005 from Gambo Renal Products, Dialysis Solutions Inc, Baxter

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
study: USA Study design: Prospective observational cohort Who was blinded: NR Setting: Multicentre collaborative Duration of follow-up: NR Definition of AKI used: NR DEFINITION of EARLY vs. LATE used: based on fluid overload see	Inclusion criteria: NR Exclusion criteria: Missing data All patients N: 297 Age (mean±SD): 8.5±7 Drop outs: 0 M/F (%): 58.6%/41.4% Sepsis (%):32 Multiorgan dysfunction syndrome (%):78.5 Oncologic process (%):23.9 Inborn error of metabolism or intoxication diagnosis (%):6.1 Inotrope no. at CRRT initiation (mean±SD):1.2±1.2 eGFR at CRRT initiation (ml/min/1.73m²):42.8±41.6 CRRT indication included fluid overload(%):77.4 CRRT modality (convective)(%):53.2 CRRT modality (diffusive)(%): 46.8 Weight(kg): 34.3±29.7 Group 1	modality are made by care provider at local institutions Patients divided into three groups according to severity of fluid overload, the degree of fluid overload developed from ICU admission to CRRT initiation (percentage of fluid overload) was calculated using the following formula: (fluid in – fluid out)/(ICU admission weight) X 100% Group 1 Fluid overload <10% Group 2 Fluid overload ≥10%-<20% Group 3 Fluid overload ≥20%		p value: <0.001	healthcare and B. Braun Inc. One author received a grant from the national kidney foundation One author received salary and grant support from the foundation de recherché en santé du quebec, the kidney research scientist core education and national raining program and the McGill University health centre. 3 authors held consultancies with Gambo Renal Products, Dialysis Solutions Inc and 2 received honoraria from Gambo One author received grant support from dialysis solutions inc 2 authors are currently a members of Gambos speakers bureau Limitations: Generalisability Patients not randomly assigned to groups Care wasn't standardised among centres which determined CRRT intervention independently Increased fluid overload may have merely identified more critically ill / hemodynamically unstable and required greater fluid administration
			Length of ICU stay (mean±SD)	Group1: 15.7±17.1 Group 2: 24.8±30 Group 3:29.5±36.9 Relative risk [95% CI]:NR p value: <0.001	
			HRQoL	NR	
			Renal recovery	NR	
			Duration of RRT	NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
interventions	N: 153 Age (mean): 10.4±7 Drop outs: 0 M/F: 62.1%/37.9% Sepsis (%):24.8 Multiorgan dysfunction syndrome (%):64.7 Oncologic process (%):30.1 Inborn error of metabolism or intoxication diagnosis (%):10.5 Inotrope no. at CRRT initiation (mean±SD):0.9±1.1 eGFR at CRRT initiation (ml/min/1.73m²):47.5±51 CRRT indication included fluid overload(%):69.3 CRRT modality (convective)(%):60.1 CRRT modality (diffusive)(%): 39.9 Weight(kg): 43.4±32.1 Group 2 N: 51 Age (mean): 7.5±6.8 Drop outs: 0 M/F:54.9%/45.1% Sepsis (%):37.3 Multiorgan dysfunction syndrome (%):86.3 Oncologic process (%):21.6				Additional outcomes: Notes: Supplementary paper: Goldstein SL, Somers MJ, Brophy PD, et al. the prospective pediatric Continuous Renal replacement Therapy(ppCRRT) registry; design, development and data assessed. Int J Artific Organs. 2004;27(1):9-14 60.9% of patients were receiving diuretics at CRRT initation

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Inborn error of metabolism or intoxication diagnosis (%):2 Inotrope no. at CRRT initiation (mean±SD):1.4±1 eGFR at CRRT initiation (ml/min/1.73m²):44.4±33 CRRT indication included fluid overload(%):82.4 CRRT modality (convective)(%):49 CRRT modality (diffusive)(%): 51 Weight(kg): 29.1±23.2 Group 3 N: 93 Age (mean): 6.1±6.2 Drop outs: 0 M/F:54.8%/45.2% Sepsis (%):40.9 Multiorgan dysfunction syndrome (%):96.8 Oncologic process (%):15.1 Inborn error of metabolism or intoxication diagnosis (%):1.1 Inotrope no. at CRRT initiation (mean±SD):1.7±1.2 eGFR at CRRT initiation (ml/min/1.73m²):33.9±23.9 CRRT indication included fluid overload(%):88.2 CRRT modality (convective)(%):44.1 CRRT modality (diffusive)(%): 55.9				

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Weight(kg): 22.1±23.1				

G.5.4 Referring for nephrology

Table 94: Meier 2011[278]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Meier 2011[278] Country of study: Switzerland Study design: Retrospective cohort Setting: Tertiary care Duration of follow-up: Inhospital for most	Patient group: Noncritically ill patients admitted under medical or surgical services (2004-2008) Inclusion criteria: Noncritically ill patients with HA-AKI using AKIN criteria Exclusion criteria: AKI acquired in ICU Patients discharged from ICU who did not have a stable sCr for at least 48 hours prior to diagnosis of AKI Patients requiring a transfer to ICU regardless of cause of transfer Patients with insufficient sCr or urinary output data (9216 patients)	Group 1 – early referral Patients referred ≤5 days after development of HA-AKI (Mean 3.6 ± 1.2 days) Group 2 – delayedreferral Patients in whom the diagnosis of HA-AKI was made by non-nephrologists and referred >5 days after the development of AKI. (Mean 7.8 ± 3.4 days) Group 3 – non referral Patients with undiagnosed of missed HA-AKI by the non-	Inhospital mortality	Group1: 100/834 (12%) Group 2: 526/2504 (21%) Group 3: 211/958 (22%) p value: 0.01	Funding: Intramural funds from Centre HospitalierUniversitaire Vaudois and the Centre Hospitalier du Centre du Valais Sion (both public funds). Limitations: "Missing data represented approximately 6% of all collected data and were censored." Additional outcomes: AKIN Stage Multivariable analysis of the risk factors
			Inhospital mortality and time to consultation (unadjusted)	≤5 days: Reference: 6-10 days: OR [95% CI] 1.81 [1.36-2.42] 11-15 days :OR[95% CI] 2.44 [1.89-3.15] >15 days :OR[95% CI] 3.45 [2.68-4.43]	
			Number of patients needing RRT	Group1: 200/834 (24%) Group 2: 776/2504 (31%) Group 3: not assessed Relative risk [95% CI]: NR p value: 0.02	
			Length of hospital stay (mean, days)	Group1: 15 ± 3 (N= 834) Group 2: 24 ± 6 (N=2504) Group 3: 10 ± 5 (N= 958)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
outcomes (6 months for need for long term RRT) Definition of AKI used: Hospital acquired AKI (HA-AKI)using AKIN classification	RRT before admission or within 48 hours of hospitalisation (2693 patients) All patients N: 4296/116,181 screened Age (mean): 61 ± 15 years Drop outs: 0 Group 1 (early referral) N: 834 Age (mean): 60 ± 17 Drop outs: 0 M:F: 467 (56%): 367 (44%) Medical: 275 (33%) Surgical: 559 (67%) Diabetes: 192 (23%) Cardiovascular disease: 183 (22%) Acute infection: 158 (19%) Median (range) baseline sCr (µmol/l): 131 (71-256) Median (range) baseline eGFR: 60 (123-24) Median (range) sCr at first nephrology evaluation: 292 (143-1845) Group 2 (delayedreferral) N: 2504 Age (mean): 61 ± 13 Drop outs: 0	nephrologists and patients with proven or diagnosed HA-AKI not referred to nephrology		p value: 0.001 (0.01 for group 1 vs group 2 only)	associated with inhospital mortality Notes: *NCGC calculated numbers of patients from percentages reported in study. † NCGC calculated numbers of patients from percentages to nearest interger from figure in study, no further information available from text.
			Number of patients with complete renal recovery at discharge (>75% ΔsCr)	Group1: 375/834 (45%)* Group 2: 701/2504 (28%)* Group 3: 144/958 (15%)* p value: NR	
			Number of patients with no renal recovery at discharge (<25% ΔsCr)	Group1: 133/834 (16%)* Group 2: 1077/2504 (43%)* Group 3: 604/958 (63%)* p value: 0.001	
			Number of patients needing RRT at hospital discharge	Group1: 42/834 (5%)† Group 2: 376/2504 (15%)† p value: 0.001	
			Number of patients needing RRT (HD or PD) long term (>6 months)	Group1: 22/834 (2.6%) Group 2+3: 249/3462 (7.2%) p value: 0.001	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	M:F: 1402 (55%): 1127 (45%) Medical: 1527 (61%) Surgical: 977 (39%) Diabetes: 626 (25%) Cardiovascular disease: 526 (21%) Acute infection: 551 (22%) Median (range) baseline sCr (µmol/l): 121 (68-237) Median (range) baseline eGFR: 61 (103-29) Median (range) sCr at first nephrology evaluation: 345 (127-1542) Group 3 (non referral) N: 958 Age (mean): 62 ± 16 Drop outs: 0 M:F: 546 (57%): 412 (43%) Medical: 642 (67%) Surgical: 316 (33%) Diabetes: 240 (25%) Cardiovascular disease: 220 (23%) Acute infection: 172 (18%) Median (range) baseline sCr (µmol/l): 131 (75-246) Median (range) baseline eGFR: 59 (121-24)				

Table 95: Ponce 2011[328]

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Ponce 2011[328] Country of study: Brazil Study design: Prospective cohort Setting: ICU Duration of follow-up: inhospital Definition of AKI used: AKIN	Patient group: ICU patients who developed AKI (July2008 – May 2010) Inclusion criteria: Patients on adult ICU who developed AKI by AKIN criteria Exclusion criteria: Basal sCr >354µmol/l (6 patients) Previous RRT (20 patients) End-stage disease (tumour) (0 patients) ICU stay <48h (30 patients) Patients admitted to ICU with AKI (10 patients) All patients N: 148 Age (mean): 59.4 years Drop outs: 0 Group 1 – Early referral N: 29 Age (mean): 62.4 ± 16.7 M:F: 20 (68%): 9 (32%)* Surgical: 18 (62%)* Sepsis: 15 (53%)* Basal sCr> 133µmol/l: 9 (32%)* Group 2 –Delayedreferral N: 48	Group 1 – Early referral <48h from laboratory diagnosis of AKI day. Median 1.5 days (range 1-2days) Group 2 – Delayedreferral ≥48h from laboratory diagnosis of AKI day. Median 4.7 days (range 3-11 days) Group 3 – No referral All groups: Criteria for nephrology consultation were based on intensivists individual criteria. After a nephrologist was called they would see the patient within 6 hours.	In-ICU mortality	Group1: 19/29(65.4%)* Group 2: 42/48 (88.2%)* Group 3: 54/71 (76.3%)* p value:<0.001 (for Group 1 vs Group 2)	Funding: None declared Limitations: ICU population only Additional outcomes: AKIN stage Multivariable analyses of factors associated with nephrology consultation and delayed consultation. Notes: *NCGC calculated numbers of patients from percentages reported in study.
			Inhospital mortality and time to consultation (covariate adjusted)	≤ 2 days (N=29): OR[95% CI] 0.73 [0.47-0.97] >3 days (N=48): OR [95% CI] 1.32 [1.16-2.9]	
			Number of patients needing RRT	Group1: 20/29(68%)* Group 2: 36/48 (76%)* Group 3: 0/71 (0%)* p value: 0.11	
			Length of ICU stay (days)	Group1: 12.0 ± 2.4 Group 2: 14.4 ± 3.8 Group 3: 10.3 ± 2.8 p value: 0.08 (for Group 1 vs Group 2)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Age (mean): 59.4 ± 16.1 M:F: 33 (69%):15 (31%)* Surgical: 28 (58%)* Sepsis: 28 (58%)* Basal sCr > 133µmol/l: 16 (34%)* Group 3 – No referral N: 71 Age (mean): 58.4 ± 15.7 M:F: 45(63%): 26 (37%)* Surgical: 38 (53%)* Sepsis: 31 (44%) * Basal sCr> 133µmol/l: 20 (28%) *				

G.6 Information and support for patients and carers

Table 96: Coupe 1998[100]

Study	Coupe 1998[100]		
Aim	Audit and evaluation for a pre-dialysis education programme. (Patients views regarding decision making about dialysis options)		
Population	297 patients' referred for the education programme. Patients with chronic renal failure attending the renal unit at the university hospital of Wales NHS trust in the UK.		
Methods	Retrospective patient audit. Mailed questionnaires 2-3 months after commencing dialysis. 75% response rate (172 returned)		
Themes with findings	[Poor quality study that does not present a	Key issues which help with decision making	Work and life style and how treatment will adapt around this Information gained through the renal multi disciplinary team Visiting the dialysis unit: "gut reaction" "knowing instantly" when they visited as to which dialysis method

Study	Coupe 1998[100]		
	thematic analysis. Only information directly relevant to the question on patient information and support reported here]		they would be suited to Past experience, including what they have seen or heard during a hospital stay Social circumstance and family influences The need for control and autonomy or independence Talking with other patients Issues related to bad image
		Satisfaction with amount of information received	Patients received information on how the kidney works, what happens when they fail, haemodialysis, peritoneal dialysis, medication, access (every topic area isn't listed in the paper) – patients felt they did not receive enough information on tests and investigations and adaptations to everyday life with dialysis Contact with the education nurse increased patient satisfaction with the amount of information received. (74% vs. 27%)
		Did patients feel they had enough information	Contact with the education nurse increased patient satisfaction with the amount of information received to make their decision. Patients with end stage renal failure had less time then others and a significant proportion of them felt they didn't receive enough information or perceived they had no choice in their treatment option All literate patients found written information to be useful
		Information patients didn't know before starting treatment which would have effected their decision making	Only 9 patients responded: Physical effects of haemodialysis The flexibility or time commitment for CAPD The procedure for insertion of the CAPD catheter. Early complications
		Things which happened which the patients weren't prepared for	48 responded: Physical effects of haemodialysis Early complications of CAPD such as catheter migration
Limitations	No details of participants other than their diagnosis. Mailed questionnaire only. No thematic analysis. Does not give any patient quotes No details regarding type of questions included in the questionnaire.		

Study	Coupe 1998[100]
	Insufficient information given regarding the patient education programme- amount and detail on the type of information given to patients

1

2 **Table 97: Mitchell 2009[283]**

Study	Mitchell 2009[283]		
Aim	A qualitative positive psychology approach to examine patients' views on what helps during patients transition onto haemodialysis. Positive psychology focuses on peoples' strengths and their abilities to adapt and flourish in the face of life's challenges		
Population	Hospital-based haemodialysis of patients who attended a specialist unit for treatment, usually three times a week for three to four hours (excluding those beginning other methods of renal replacement therapy and participants were excluded if they were judged to be too ill to take part, or if they had significant co-morbidity such that their predominant treatment was for another illness). 10 participants were identified. 5 male, 5 female aged between 20 -80 years. Who had been on haemodialysis for between one week and six months. 90%were unemployed.		
Setting	Medium-sized NHS Renal Unit in the UK. Treatment is provided for approximately 600 renal patients (predialysis, CAPD, haemodialysis and post-transplant), of whom about 250 were receiving haemodialysis at the time of the study.		
Methods	A purposive sampling strategy was used to identify and recruit patients aged over 18 who had started haemodialysis within the previous six months.(the paper states: Selection criteria ensured that the sample reflected the diverse characteristics of the wider haemodialysis patient population with respect to age, gender, marital status, employment status, previous treatment and acute or gradual onset of kidney failure). Individual semi-structured interviews were conducted with all participants by two interviewers sharing the questioning to make the interview informal and conversational. The interviews were supervised by an experienced researcher, who was a member of the research group. Interviews were carried out during their dialysis, in a side treatment room for privacy. The interviews covered participants' experiences of daily activities, thoughts, feelings, and social life, focussing on what, if anything had helped them cope across these domains. The participants dictated the order and pace of the interviews, which lasted between 30 and 50 minutes All interviews were audio-taped and transcribed verbatim, with the influence of any pre-existing ideas held by the researchers minimised through discussion and reflection between the research team. The interpretive content analysis of the text was supported by three researchers reading all the transcripts and developing an initial categorisation with supporting quotations. All authors discussed and amended the categories or definitions. Data analysis continued until no further modifications emerged and all relevant text was coded. The study states the authors attempted to ensure that the analysis was coherent, that it accounted for all relevant data and that it usefully identified implications for clinical practice and research.		
Themes with findings	Preparation	Education	Patients emphasised the importance of having questions addressed, with clear and honest explanations about the nature of the illness, its management, treatment and what could go wrong: 'She was very, very good because she came to my house and explained things first of all... I think it's a good idea because it doesn't come as such a shock then' (Ian).

Study	Mitchell 2009[283]		
			Participants noted that sometimes staff found it difficult to provide answers: '...once or twice you meet a member of staff who perhaps doesn't feel secure in telling me. There is this, has always been, this sort of reluctance hasn't there, to share with the patient...' (Gina). Some patients that they had to push for information '...unless you ask questions and unless you push, you'll get neglected for one reason and the other' (Charles). Patients who underwent acute transition onto haemodialysis recognised that a visit to the unit, before starting treatment, would have been useful. 'Make sure people get a look around first. That was one of the things I meant to tell you, and about them not telling you about what can go wrong' (Fiona).
		Choice	Retaining a sense of personal autonomy and choice over decision making was highlighted as beneficial by all the older participants who underwent a gradual transition 'Then [the home care nurse] said 'Well you haven't got to go on. We'll make it quite peaceful for you to pass on.' They can tell you, but it's your body. It's up to me to decide what I want to do' (Alice).
	Cognitive Style - term used in to describe peoples' preferred approach to explaining events and solving problems. There are a range of cognitive styles (listed).	Positive reappraisal	Participants who underwent a gradual transition onto haemodialysis highlighted several ways in which they positively reappraised their future on haemodialysis, often recognising that they would be dead without haemodialysis. 'So I'm just really, really, lucky, or I could be pushing up the daisies' (Edward).
		Optimism	All participants who underwent a gradual transition onto haemodialysis highlighted the value of hope and an optimistic outlook towards their future: 'I never moan...Life is sweet, isn't it. There's always something to look forward to, if you look for it' (Fiona). For some, optimism was directed towards resuming daily activities such as walking, gardening and swimming or special family events: '..we've got a family party one weekend and the friends the next weekend. So I've got a goal you see' (Gina-planning a golden wedding anniversary). Others looked forward to receiving a possible transplant, which may or may not be forthcoming. Sometimes, the optimism was on behalf of other patients with whom they spoke rather than for themselves directly: 'I know damn well I'm not going to get a transplant but the younger ones, the lady I talk to, she's hoping that she will be in for a transplant...' (David).
		Realistic expectations	Patients stayed optimistic within realistic expectations: 'I'm optimistic that I'm getting back — not the normal sort of life, but somewhere near it' (Bill). Realistic expectations required readjustments due to the restrictions and limitations imposed by haemodialysis. 'I think you've got to be realistic...I've just got to readjust my life and do what I can' (Gina).
		Acceptance	Accepting their situation was evident for all participants, whether the transition was sudden or gradual:

Study	Mitchell 2009[283]		
			'I was a bit shocked at first but then you've got to put up with these things, haven't you? You've got to live with it....No good saying you won't do this and you won't do that. It's for your own good. You've just got to accept it like that' (Hazel). Acceptance was not only directed towards the demands imposed during the transition to haemodialysis, but also associated with a growing sense of mortality. This was evident among younger as well as older participants. 'Your life doesn't go on...I'm well aware of my life expectancy but it's things you want to do and it's a fact...All the regrets, you put things into perspective' (Charles). For some of the younger participants, however, acceptance seemed tempered by an active avoidance of more painful aspects of their situation. 'You kind of put a block to it and you just think "Oh, I'm going to get on with it" and there's all these issues you just don't go there because it's too painful to even disturb' (Charles).
		Social comparisons	All participants highlighted the benefit of knowing other haemodialysis patients, enabling them to make comparisons with their own situation. Some participants felt reassured by making comparisons with patients seen as coping effectively with the demands of haemodialysis. 'You only had to look at [patient], fit as a fiddle. I said, 'Well that's it for me. If it does it for him, it will do it for me' (David). Participants were appreciative of their own state when comparing themselves with fellow patients who seemed to be in a worse situation. 'A lot of them are in a worse state than I am in, so I've got to be thankful for that too...it does help because you feel sorry for them' (Bill)
	Social Support - importance of support from a range of other people—neighbours, friends and family, staff and other patients	Instrumental support (practical help)	Receiving practical help was highlighted by all participants as being particularly helpful. 'My next door neighbour, she's very good...if ever I want any help or anything, I've only got to pick up the phone' (Alice). Neighbours were mentioned more often than family as a source of practical support. This arises possibly as a consequence of reluctance by patients to rely on family members, in case they become a burden. 'I don't want to start leaning on [daughter]...I don't find it easy, to be honest...I don't want to make her life a misery' (Fiona). A fear of becoming a burden was also expressed by several participants with respect to neighbours, but this time largely with respect to talking about emotional problems rather than potentially seeking practical support. 'I don't say a lot [to neighbour]. She's got enough of her own worries' (Hazel).
		Emotional	Emotional support was identified as important, especially by younger participants. A marked difference of opinion arose between the younger and older participants with respect to the usefulness of emotional support. Younger participants highlighted benefits arising from having someone to talk to about their emotional difficulties.

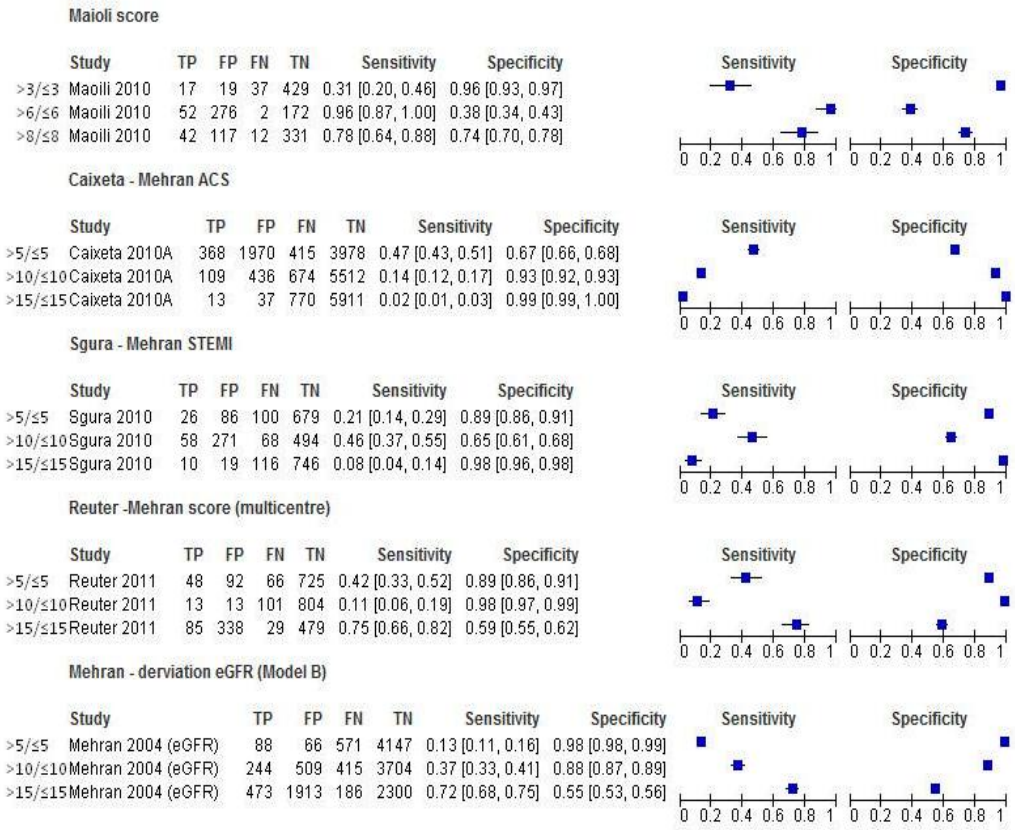
Study	Mitchell 2009[283]		
			'There's got to be people that can't talk to anyone, there definitely should be some way of giving them someone to talk, just to go on about it. Talking does help; let it all out, so basically you're out on the queries and worries that you have' (Jean). It was not generally felt that emotional support needed to be provided by professionals, unless someone lacked friends or family to provide such support. 'I have a whole series of people that I can talk to...so I have in a way got my own counsellors haven't I,... but perhaps if I ...lived alone and didn't know which way to turn, then possibly I might have someone but it would be a professional wouldn't it' (Jean). Older participants were wary of emotional support being provided intrusively by professionals. 'You can embarrass people by saying 'How do you feel?', we don't need any counsellors, we counsel ourselves' (Bill).
Limitations	Only one method of data collection used. Interviews weren't transcribed and study does not state in detail the methods used to code or identify themes. Patients acting as researchers interpreting interviews could introduce bias (patients on the collaborative research group who oversaw the study). Interviewer bias/ interpretation bias. Only selected responses reported. Unclear how participants were selected Small sample sizes, caution is needed before generalising results from numerically small qualitative studies to a wider population Conducted within a single dialysis unit thus; the findings may, in part, reflect specific aspects of the service provided in this unit. This is especially likely with respect to participants who partook of the preparation period, which meant these patients had received a range of services to prepare for haemodialysis. The study focuses on positives about how patients adapted to treatment however potentially overlooking important negative aspects/ difficulties adapting to the treatment/lifestyle changes Haemodialysis patients not specially AKI.		

Appendix H: Forest plots

H.1 Assessing risk

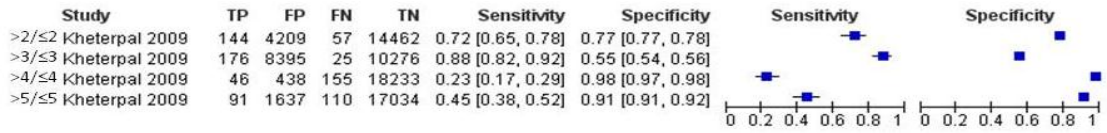
H.1.1 Risk assessment

Figure 1: Risk scores for CI-AKI



Please see evidence tables for further details on level of risk associated with a particular score

Figure 2: General surgery risk scores – internal validation from Kheterpal 2009



Please see evidence tables for further details on level of risk associated with a particular score.

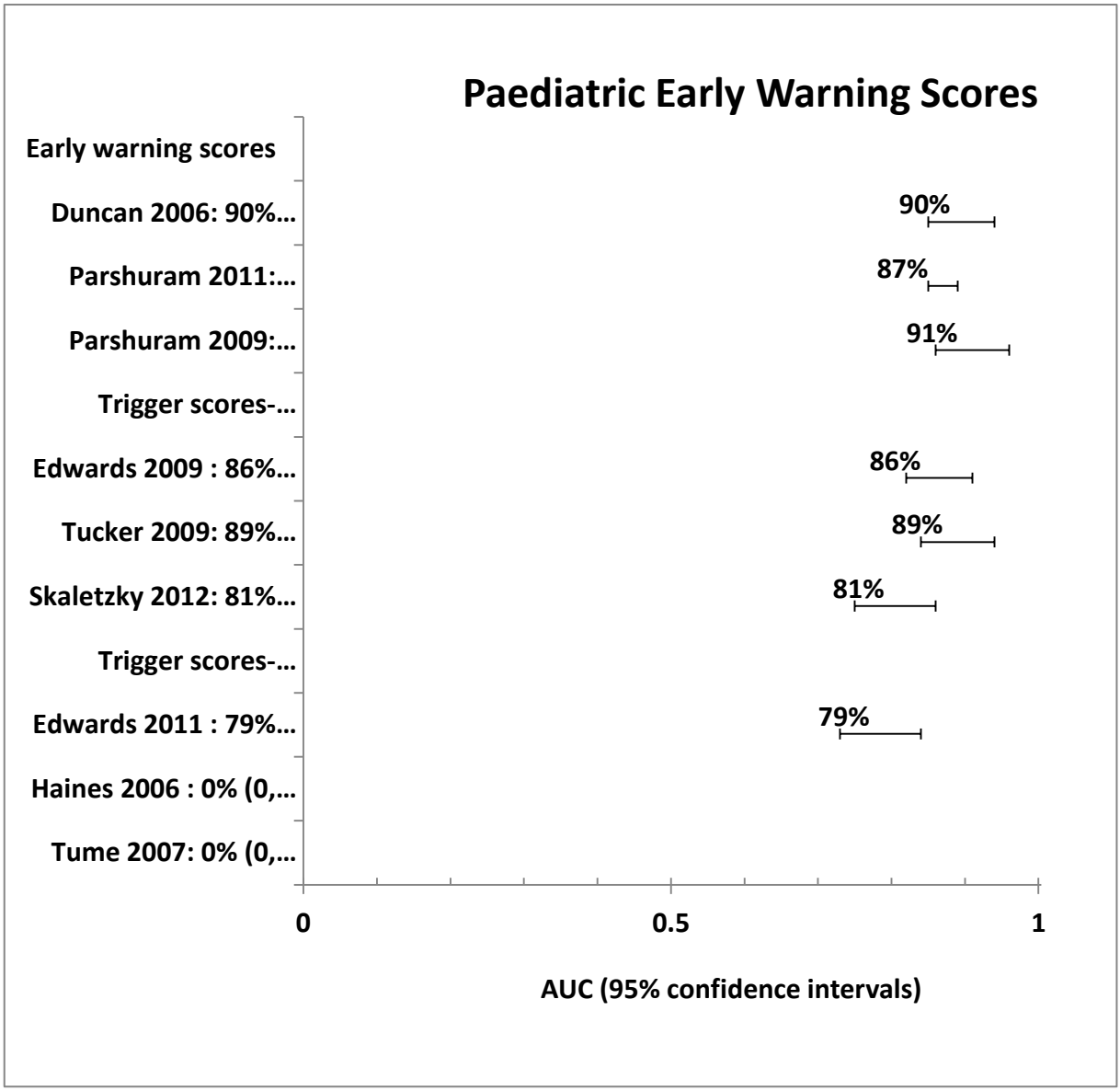
H.1.2 Paediatric risk assessment

None found in chapter

H.2 Preventing AKI

H.2.1 Paediatric early warning scores

Figure 3: Summary of results for AUC



H.2.2 Preventing CI-AKI

H.2.2.1 Sodium bicarbonate vs sodium chloride 0.9%

Figure 4: CI-AKI (as reported by study)

Study or Subgroup	Sodium bicarbonate Events	Total	Sodium chloride 0.9% Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Adolph 2008	3	71	2	74	5.0%	1.56 [0.27, 9.08]
Brar 2008	26	158	30	165	74.5%	0.91 [0.56, 1.46]
Merten 2004	1	60	8	59	20.5%	0.12 [0.02, 0.95]
Total (95% CI)		**289**		**298**	**100.0%**	**0.78 [0.50, 1.20]**
Total events	30		40			

Heterogeneity: Chi² = 4.11, df = 2 (P = 0.13); I² = 51%
Test for overall effect: Z = 1.13 (P = 0.26)

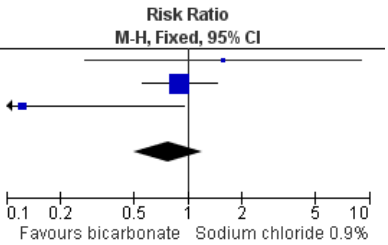


Figure 5: Mortality at 30 days

Study or Subgroup	sodium bicarbonate Events	Total	sodium chloride 0.9% Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Brar 2008	3	175	3	178	100.0%	1.02 [0.21, 4.97]
Total (95% CI)		**175**		**178**	**100.0%**	**1.02 [0.21, 4.97]**
Total events	3		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.02 (P = 0.98)

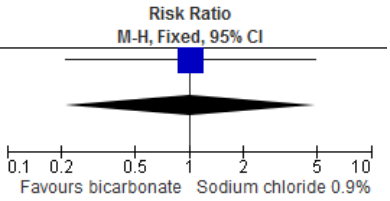


Figure 6: Number of patients needing RRT

Study or Subgroup	Sodium bicarbonate Events	Total	Sodium chloride 0.9% Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Adolph 2008	3	71	2	74	5.0%	1.56 [0.27, 9.08]
Brar 2008	26	158	30	165	74.5%	0.91 [0.56, 1.46]
Merten 2004	1	60	8	59	20.5%	0.12 [0.02, 0.95]
Total (95% CI)		**289**		**298**	**100.0%**	**0.78 [0.50, 1.20]**
Total events	30		40			

Heterogeneity: Chi² = 4.11, df = 2 (P = 0.13); I² = 51%
Test for overall effect: Z = 1.13 (P = 0.26)

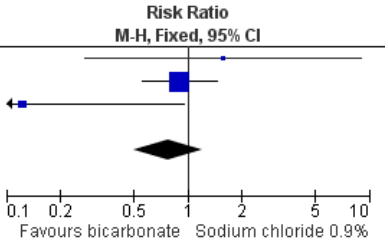
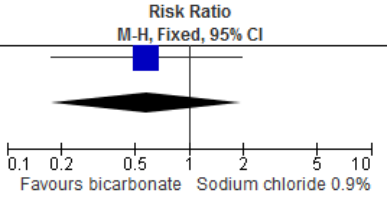


Figure 7: Mortality at 6 months

Study or Subgroup	sodium bicarbonate Events	Total	sodium chloride 0.9% Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Brar 2008	4	175	7	178	100.0%	0.58 [0.17, 1.95]
Total (95% CI)		**175**		**178**	**100.0%**	**0.58 [0.17, 1.95]**
Total events	4		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.88 (P = 0.38)



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2 **H.2.2.2 Sodium chloride 0.9% vs sodium chloride 0.45%**

Figure 8: CI-AKI (as defined by study)

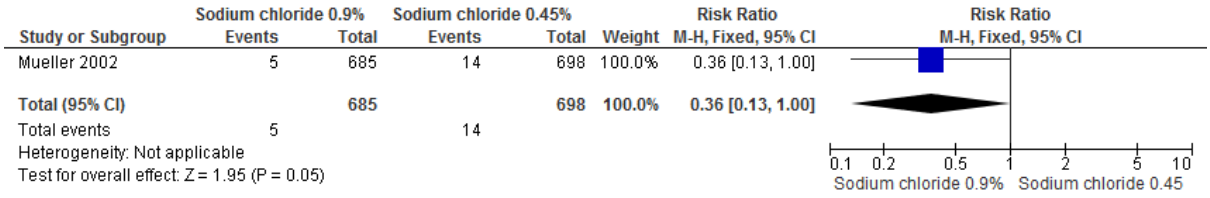

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Figure 9: Mortality at 30 days

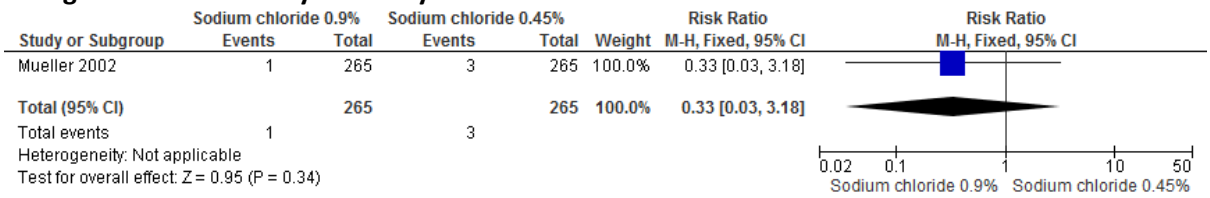

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Figure 10: Number of patients needing RRT

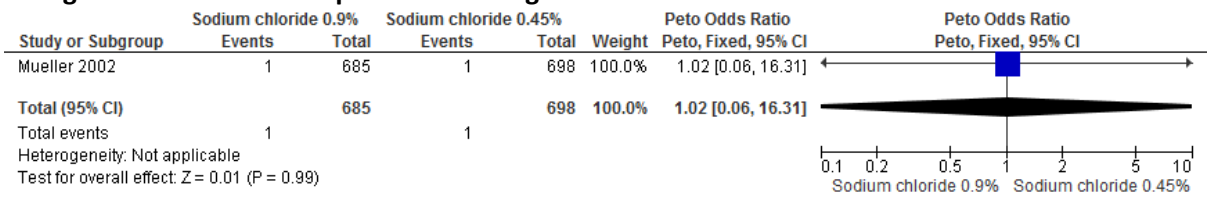

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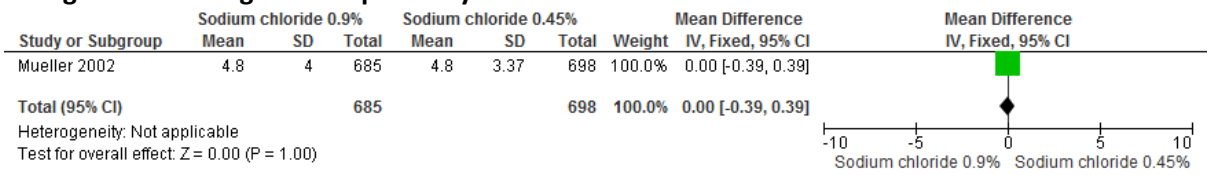
Figure 11: Length of hospital stay



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H.2.2.3 Sodium chloride 0.9% vs oral fluids

Figure 12: CI-AKI (as defined by study)

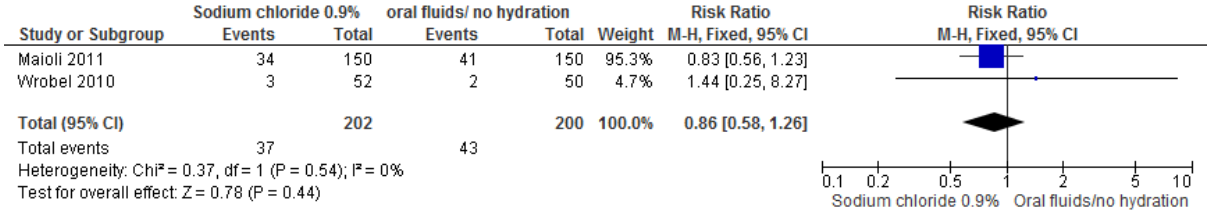


Figure 13: In hospital mortality

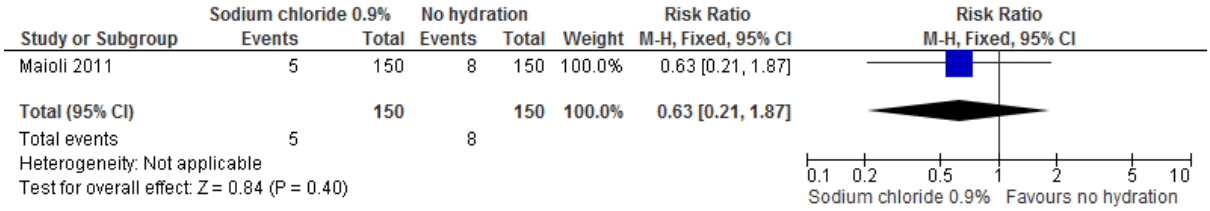
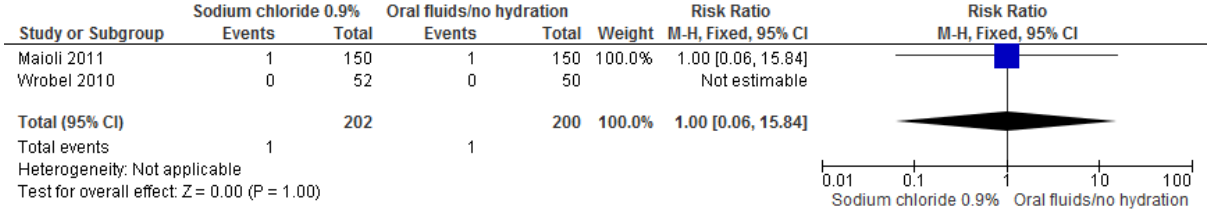
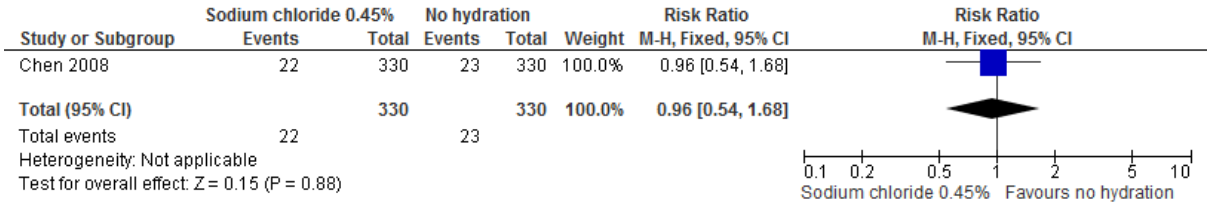


Figure 14: Number of patients needing RRT



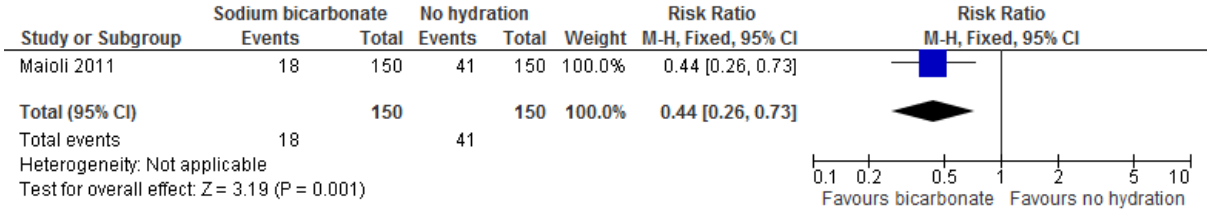
H.2.2.4 Sodium chloride 0.45% versus no (intravenous) hydration

Figure 15: CI-AKI (as defined by study)



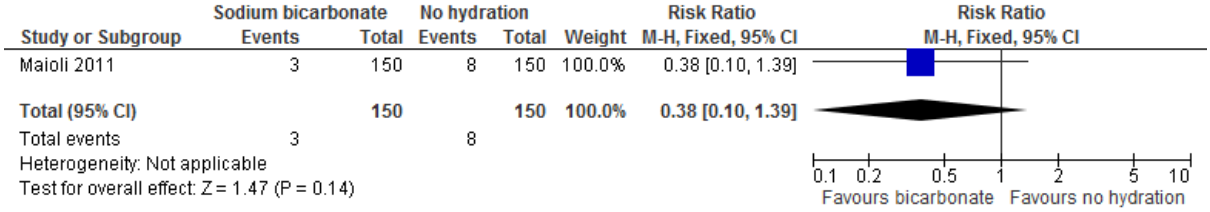
1 **H.2.2.5 Sodium bicarbonate versus no (intravenous) hydration**

Figure 16: CI-AKI (as defined by study) at 72 hours



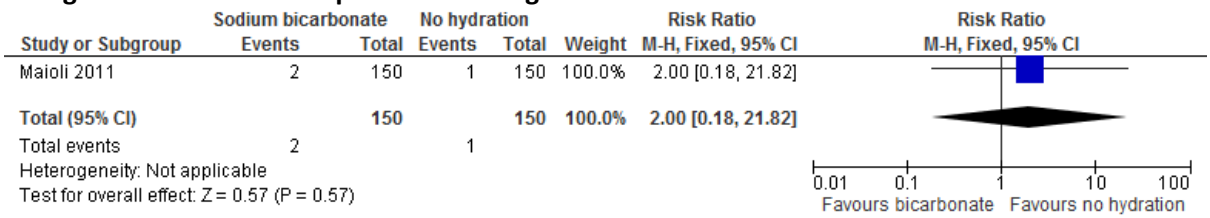
2

Figure 17: In hospital mortality



3

Figure 18: Number of patients needing RRT



4

H.2.2.6 NAC + sodium bicarbonate vs NAC + sodium chloride 0.9%

Figure 19: CI-AKI (as reported by study)

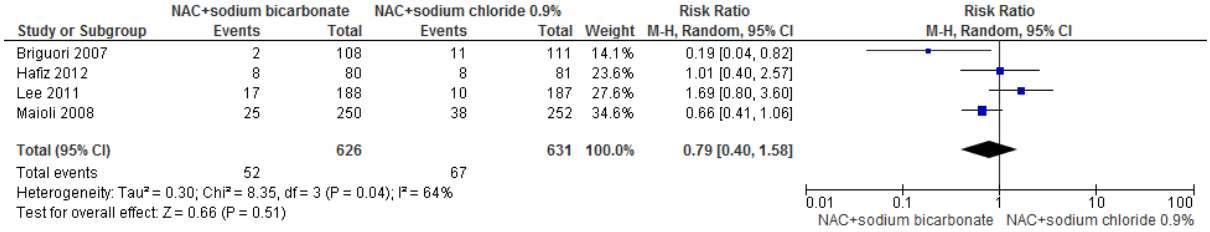


Figure 20: Mortality (10 days)

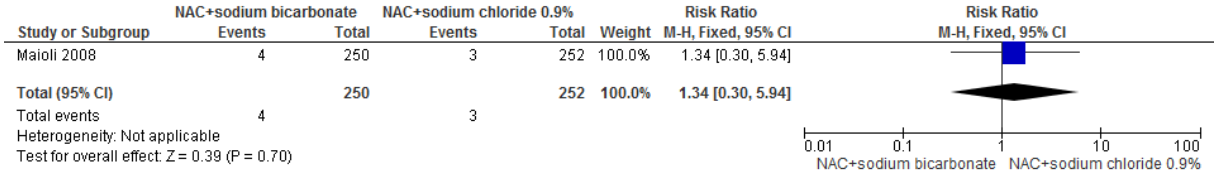


Figure 21: Number needing RRT

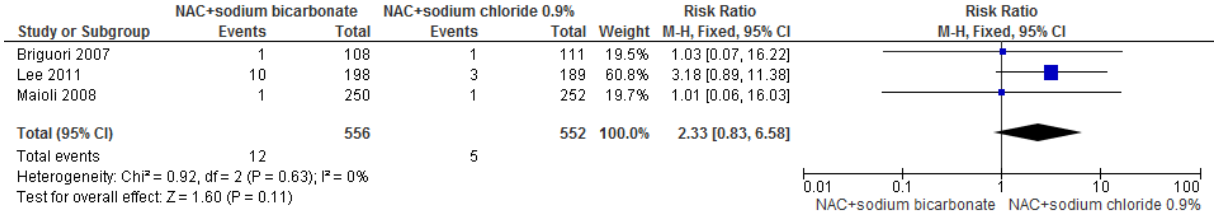
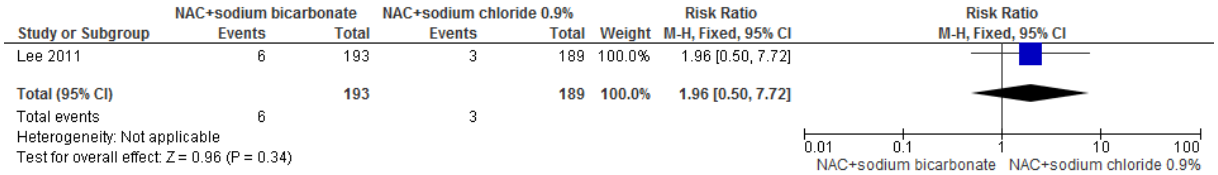


Figure 22: Mortality (6 months)



H.2.2.7 Sodium chloride 0.9% + sodium bicarbonate vs. sodium chloride 0.9%

Figure 23: CI-AKI (as reported by study)

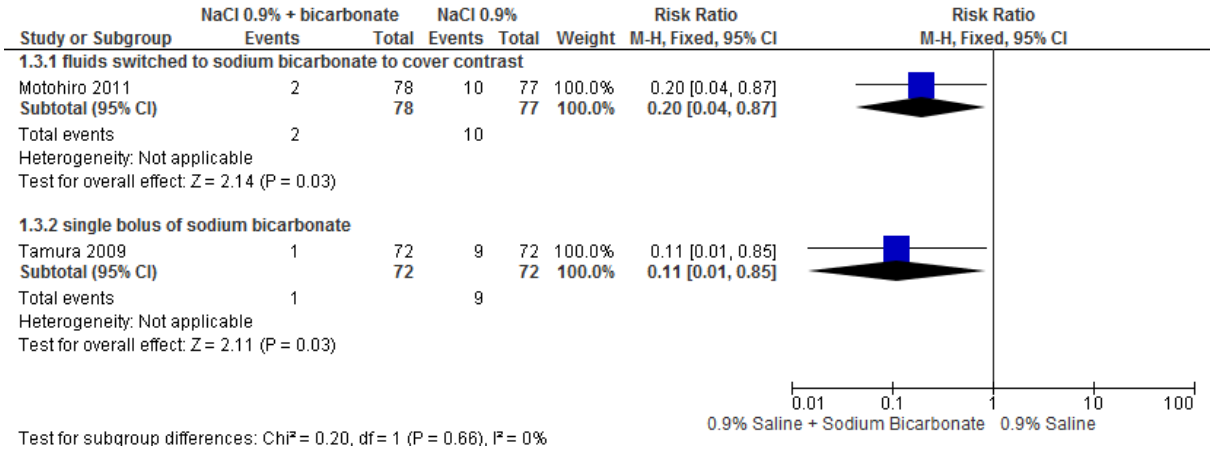
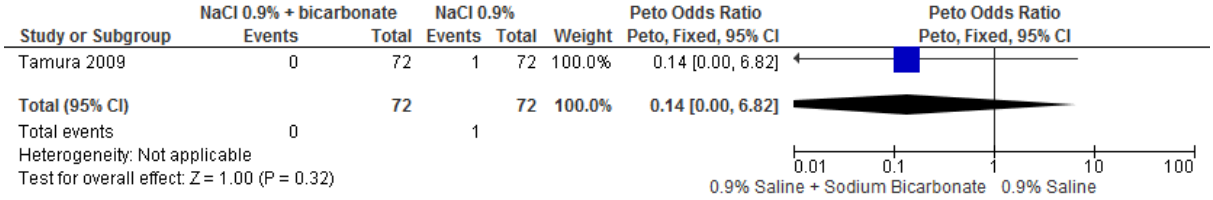


Figure 24: Number needing RRT



H.2.2.8 NAC + sodium chloride 0.9% vs sodium chloride 0.9%

Figure 25: Contrast induced AKI (as defined by study)

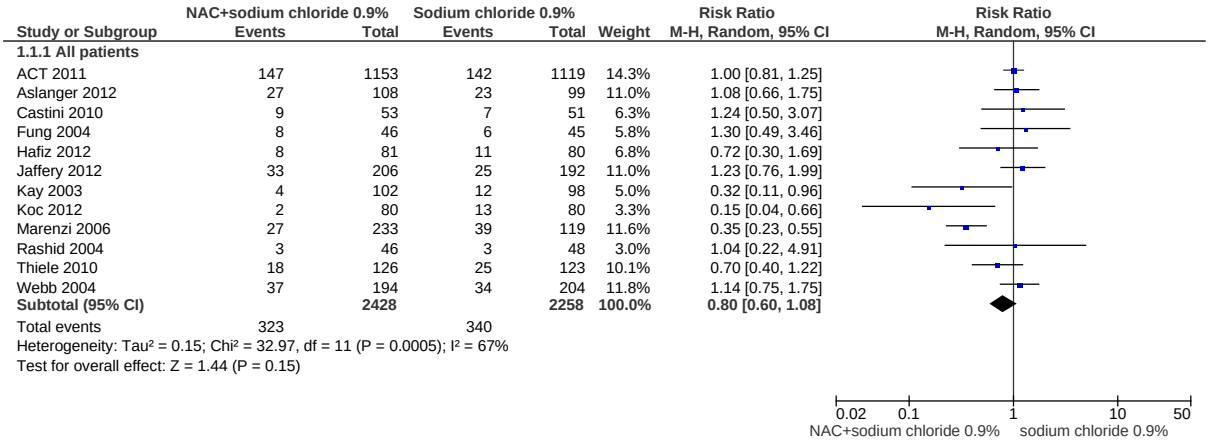


Figure 26: In hospital mortality

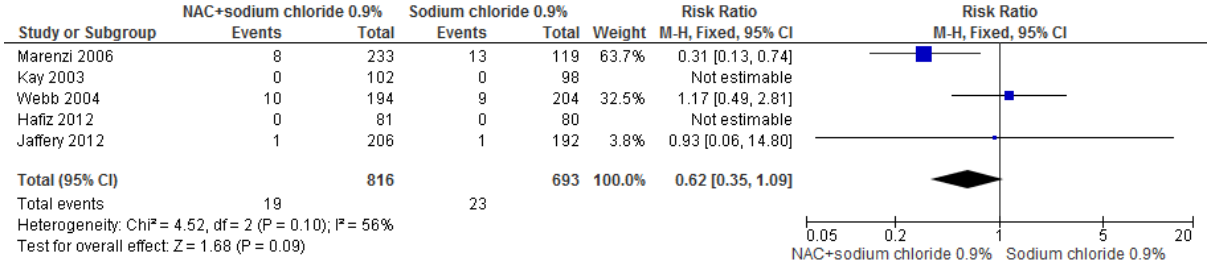
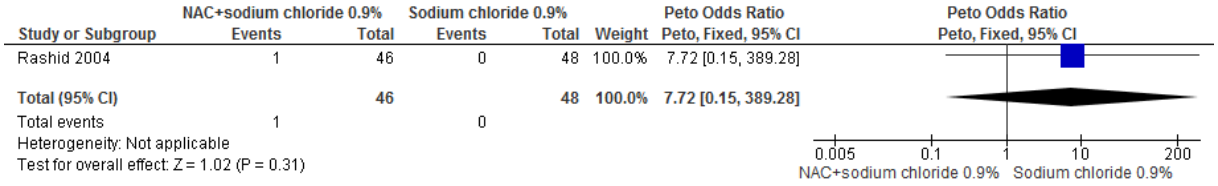
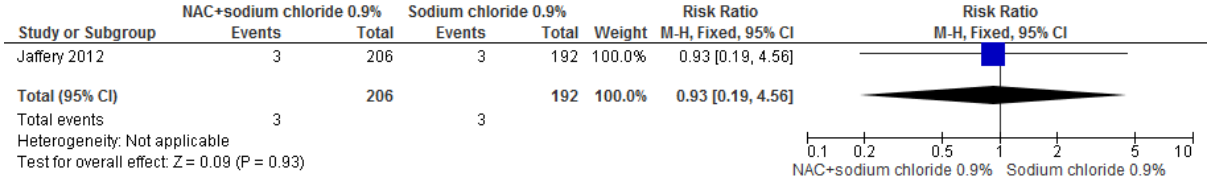


Figure 27: Mortality at 7 days



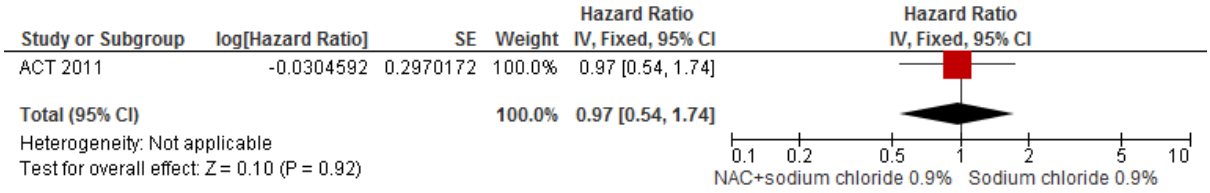
1

Figure 28: Mortality at 30 days



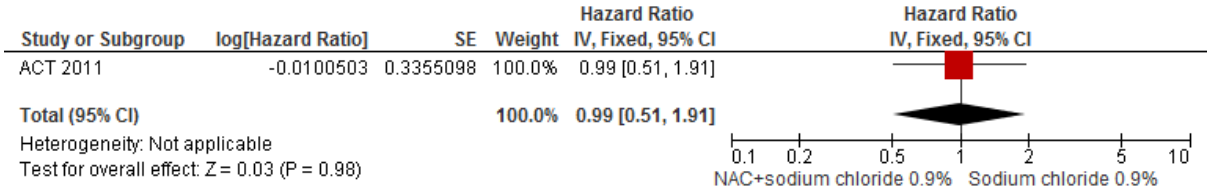
2

Figure 29: All-cause mortality at 30 days



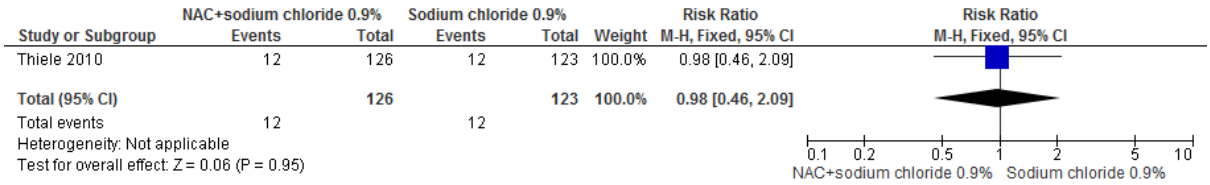
3

Figure 30: Cardiovascular mortality at 30 days (Hazard ratio)



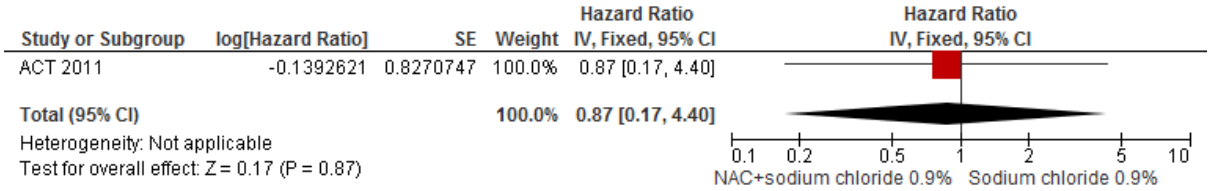
1

Figure 31: Mortality at 6 months



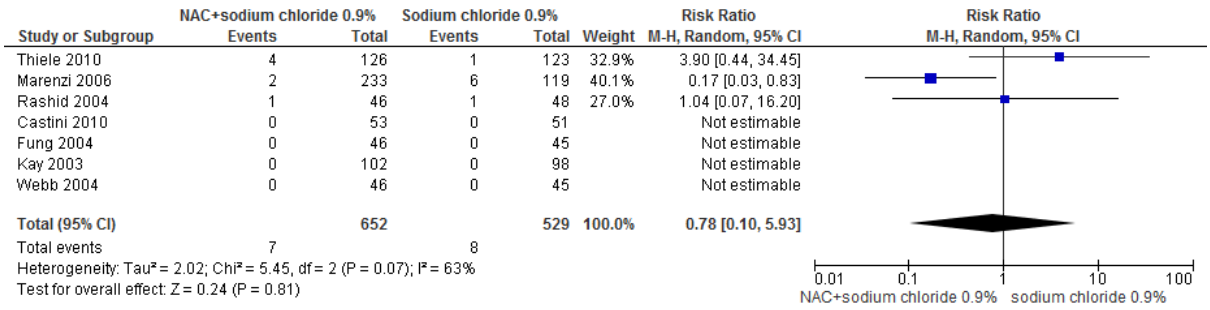
2

Figure 32: Number of patients needing RRT (at 30 days)



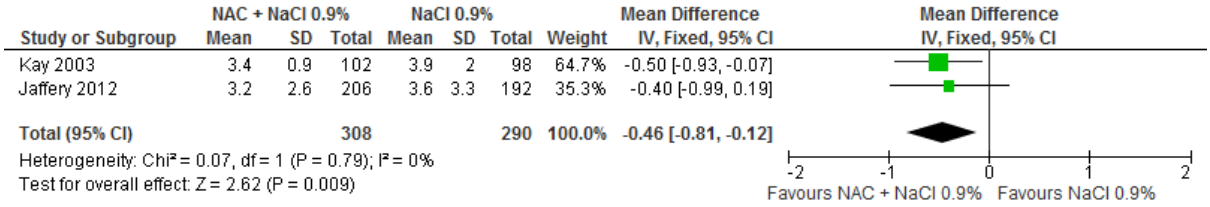
3

Figure 33: Number of patients needing RRT



4

Figure 34: Length of hospital stay

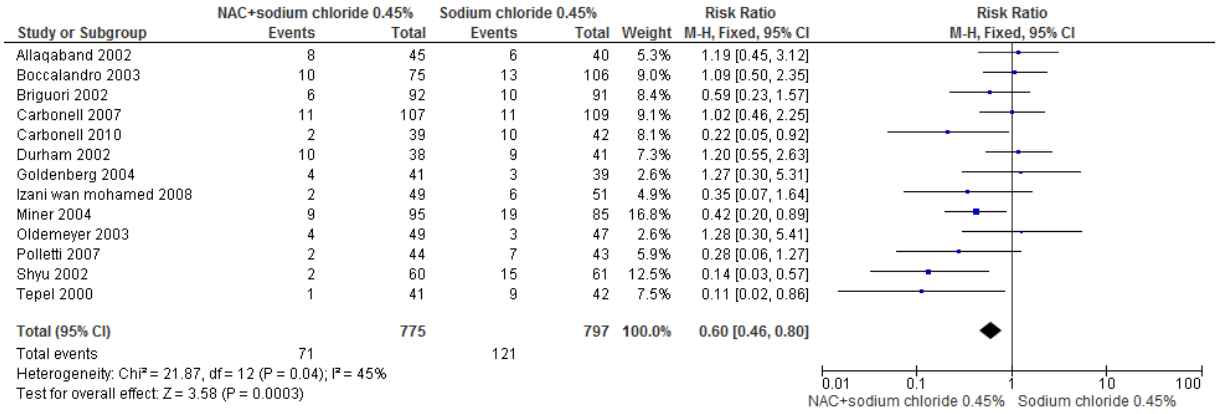


1

2

3 **H.2.2.9 NAC + sodium chloride 0.45% vs. sodium chloride 0.45%**

Figure 35: Contrast induced AKI (as defined by study)



4

5

Figure 36: Inhospital mortality

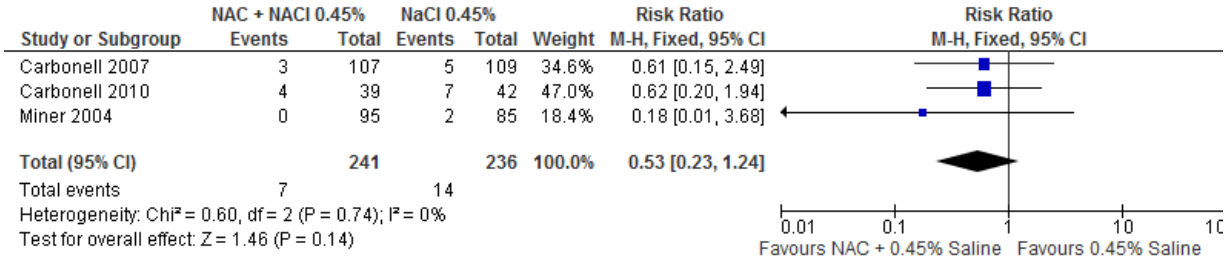


Figure 37: Number of patients needing RRT

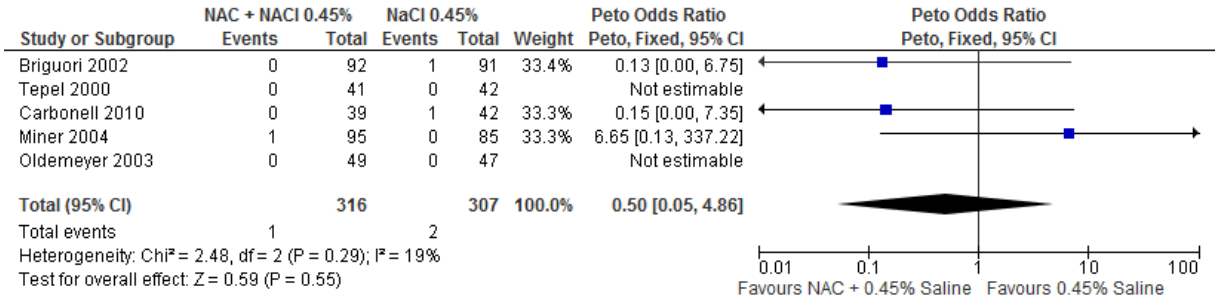


Figure 38: Length of hospital stay

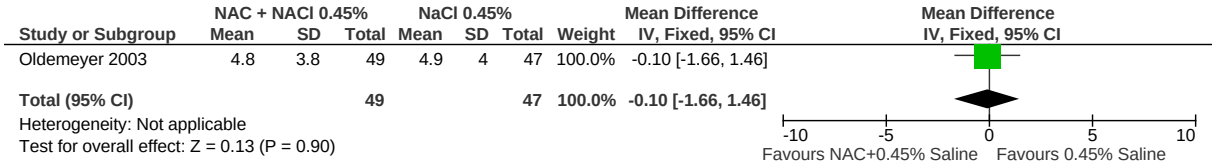


Figure 39: Mortality at 6 months

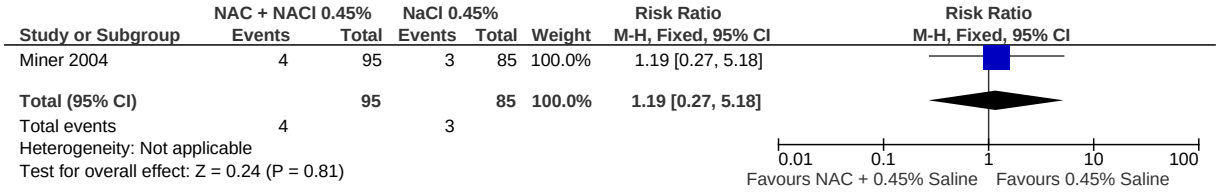
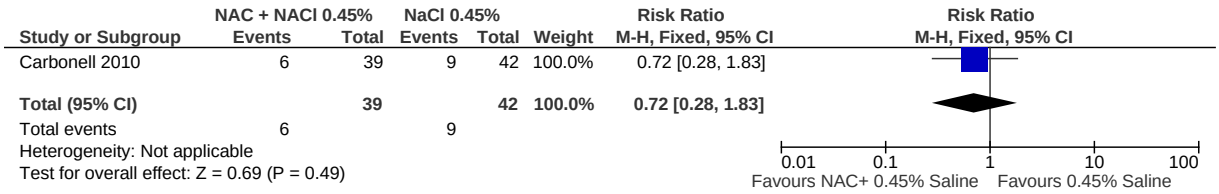
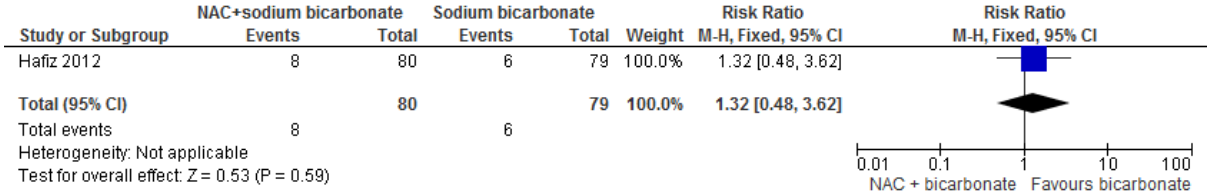


Figure 40: Mortality at 1 year



H.2.2.10 NAC + sodium bicarbonate vs. sodium bicarbonate

Figure 41: CI-AKI (as defined by study)



H.2.3 Computerised decision tools

Figure 42: Pharmacist review vs. standard medical care; dosage regimens adjusted to renal function (by number of drugs)

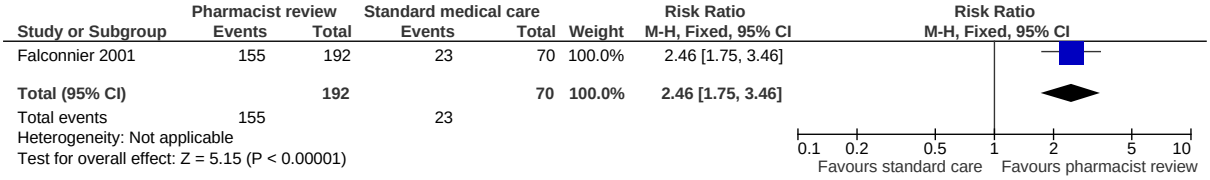


Figure 43: Pharmacist review vs. standard medical care; length of hospital stay

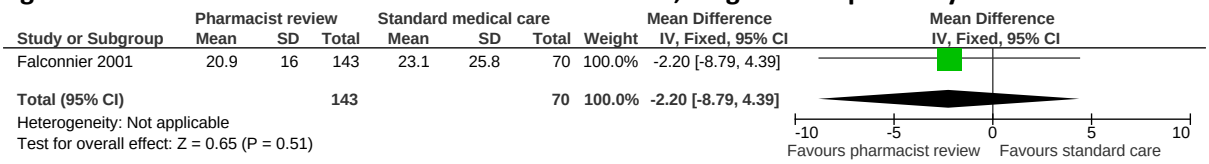


Figure 44: Computerised decision tool vs. standard medical care; number of patients with a rise in serum creatinine who developed serious renal impairment

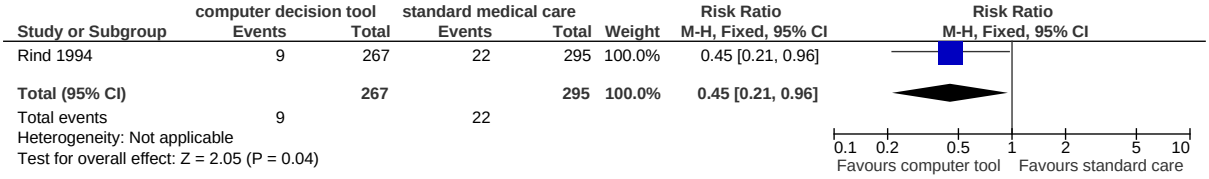


Figure 45: Computerised decision tool vs. standard medical care; mean interval to change in medication for nephrotoxic drugs

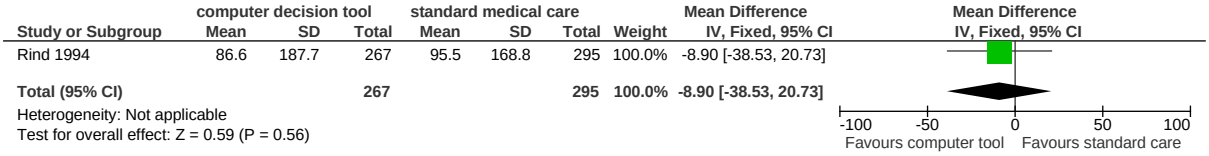
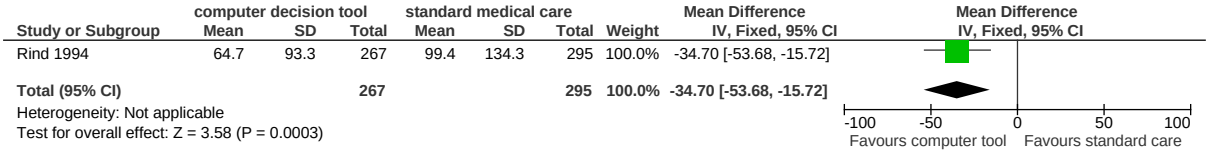


Figure 46: Computerised decision tool vs. standard medical care; mean interval to change in medication for renally excreted drugs



1

Figure 47: Computerised decision tool vs. standard medical care; alerts for excess drug dosing in relation to patient's renal function

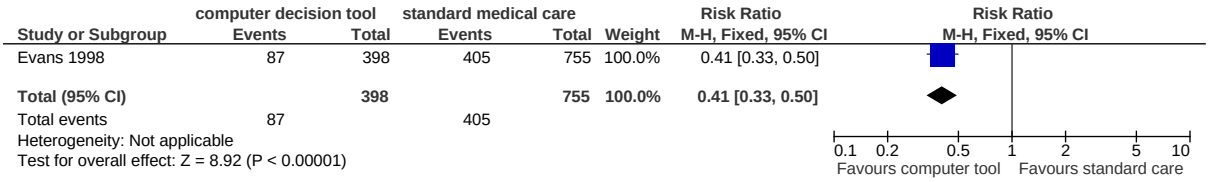


Figure 48: Computerised decision tool vs. standard medical care; adverse drug reaction to anti-infective agents

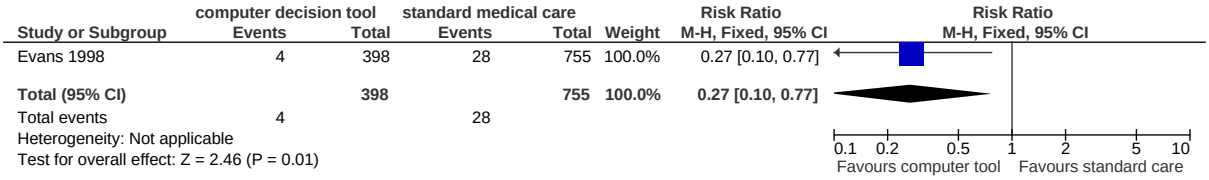
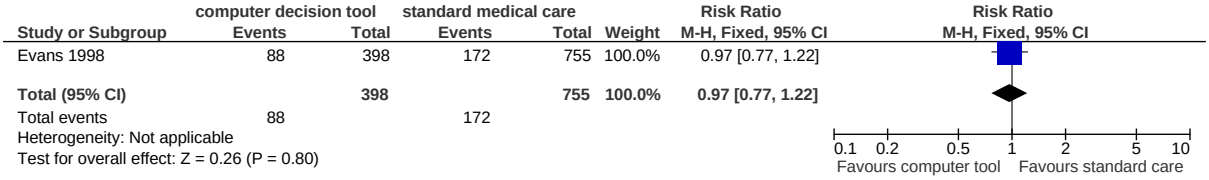


Figure 49: Computerised decision tool vs. standard medical care; mortality in patients receiving anti-infective agents



1

Figure 50: Electronic prescribing and computerised decision tool vs. electronic prescribing alone; Inappropriate orders (dose or frequency) by number of orders

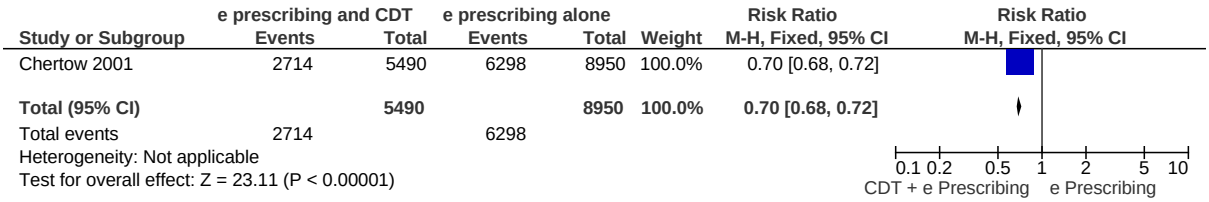


Figure 51: Electronic prescribing and computerised decision tool vs. electronic prescribing alone; Inappropriate orders (dose) by number of orders

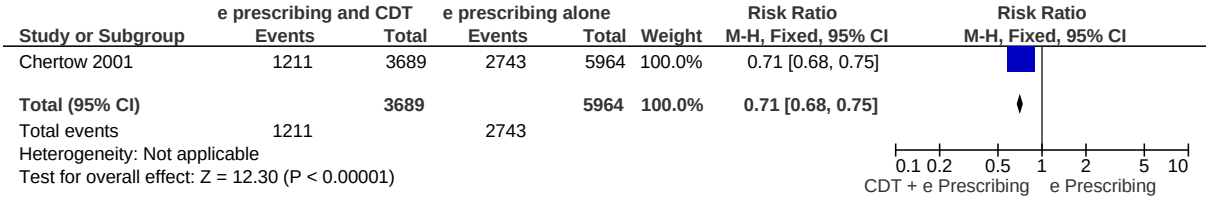


Figure 52: Electronic prescribing and computerised decision tool vs. electronic prescribing alone; Inappropriate orders (frequency) by number of orders

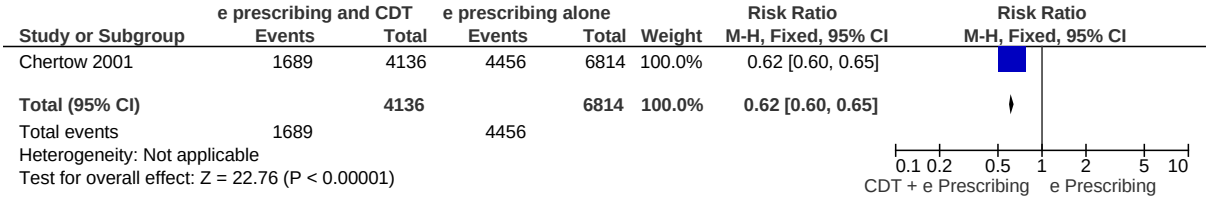


Figure 53: Electronic prescribing and computerised decision tool vs. electronic prescribing alone; length of hospital stay

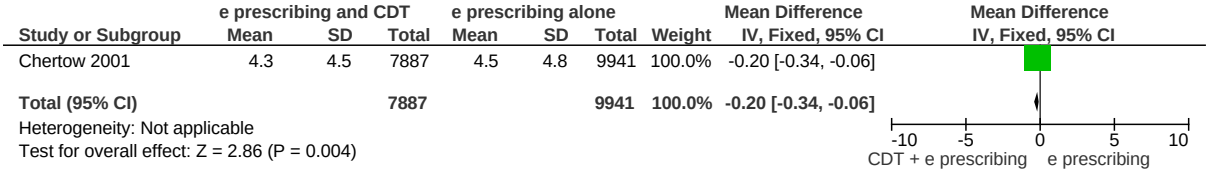
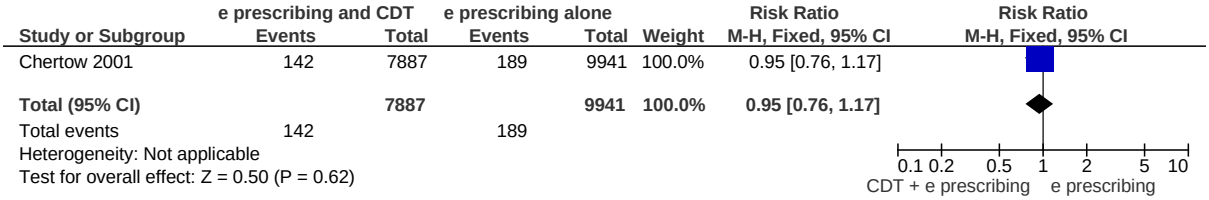


Figure 54: Electronic prescribing and computerised decision tool vs. electronic prescribing alone; in hospital mortality



H.2.5 Stopping ACEI/ARB therapy

Figure 55: CI-AKI in stopping vs. continuing ACEI/ARBs in people to be administered radiocontrast

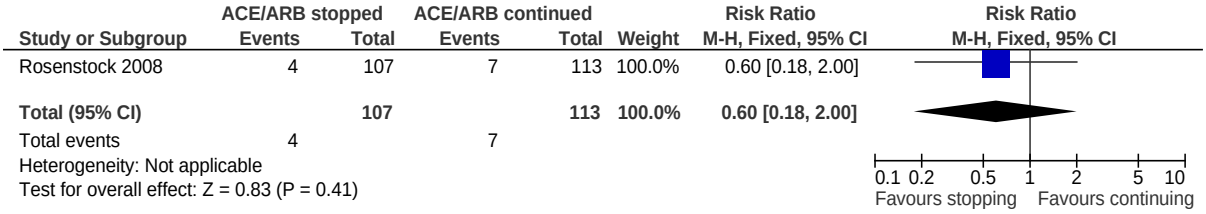


Figure 56: Number of people needing RRT in stopping vs. continuing ACEI/ARBs in people to be administered radiocontrast

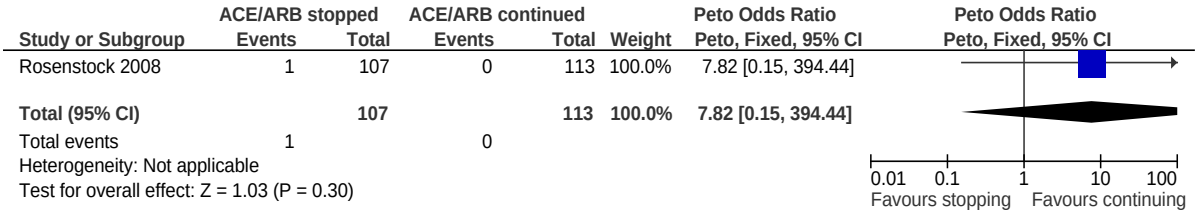
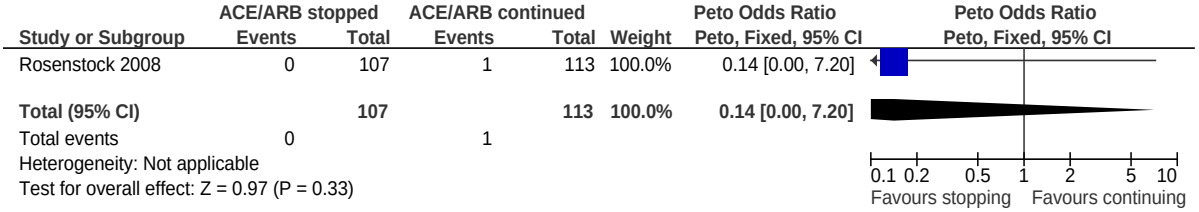


Figure 57: All-cause mortality (inhospital) in stopping vs. continuing ACEI/ARBs in people to be administered radiocontrast



H.3 Detecting AKI

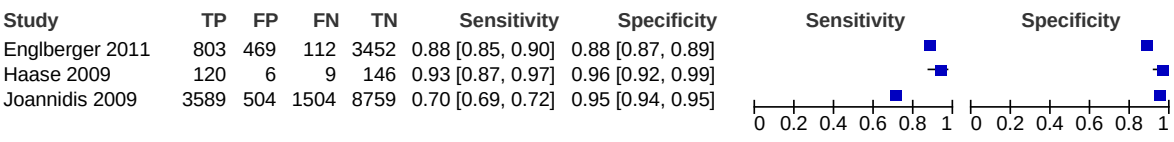
H.3.1 Diagnostics (Adults)

Table 98: Diagnostic yield by study

	No AKI (RIFLE)	RIFLE R	RIFLE I	RIFLE F		No AKI (AKIN)	AKIN 1	AKIN 2	AKIN 3
ICU population									
Bagshaw 2008	63.9%	16.2%	13.6%	6.3%		62.9%	18.1%	10.1%	8.9%
Chang 2010	39.2%	13.1%	17.9%	29.9%		32.0%	19.6%	16.8%	31.6%
Joannidis 2009	64.5%	7.6%	11.1%	16.8%		71.5%	7.5%	7.2%	13.8%
Lopes 2008	56.2%	14.7%	11.0%	18.1%		49.5%	21.1%	10.1%	19.2%
Osterma nn 2011	64.1%	17.2%	10.99%	7.6%		64.6%	19.1%	3.8%	12.5%
Cardiac surgery population									
Bastin 2013[a]	75.1%	17.9%	5.2%	1.9%		74.1%	16.9%	1.8%	7.2%
Englberg er 2011	81.1%	14.8%	3.5%	0.64%		73.7%	23.6%	1.2%	1.5%
Haase 2009	54.2%	30.1%	12.1%	3.5%		55.3%	33.7%	6.7%	4.3%
Lassnigg 2008	97.0%	2.2%	0.6%	0.2%		91.8%	6.4%	0.04%	1.8%
Robert 2010	68.8%	21.7%	5.9%	3.6%		70.1%	22.9%	3.4%	3.6%
Hospital inpatients									
Garner20 12	92.9%	4.9%	1.5%	0.8%		90.5%	7.2%	1.5%	0.8%
Patients receiving iodinated contrast									
Valette 2012	81.0%					81.0%			

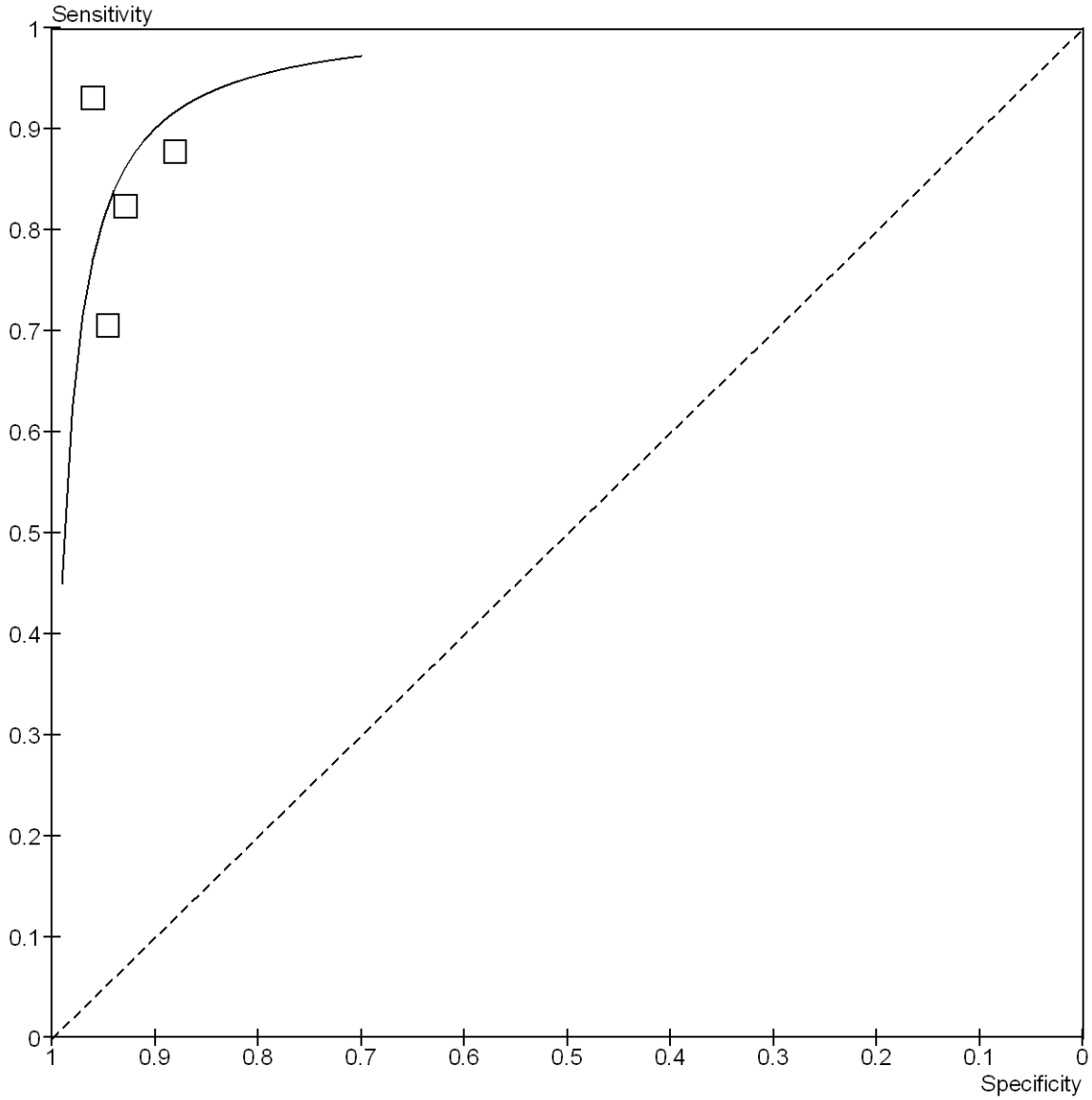
a This study found KDIGO performed identically to AKIN. It was the only study to include KDIGO.

Figure 58: Sensitivity and specificity of AKIN (RIFLE as reference standard)



1

Figure 59: ROC curve for AKIN (RIFLE as reference standard)



2

1 H.3.2 Prognostics (Adults)

Figure 60: **AUROC for all cause mortality**

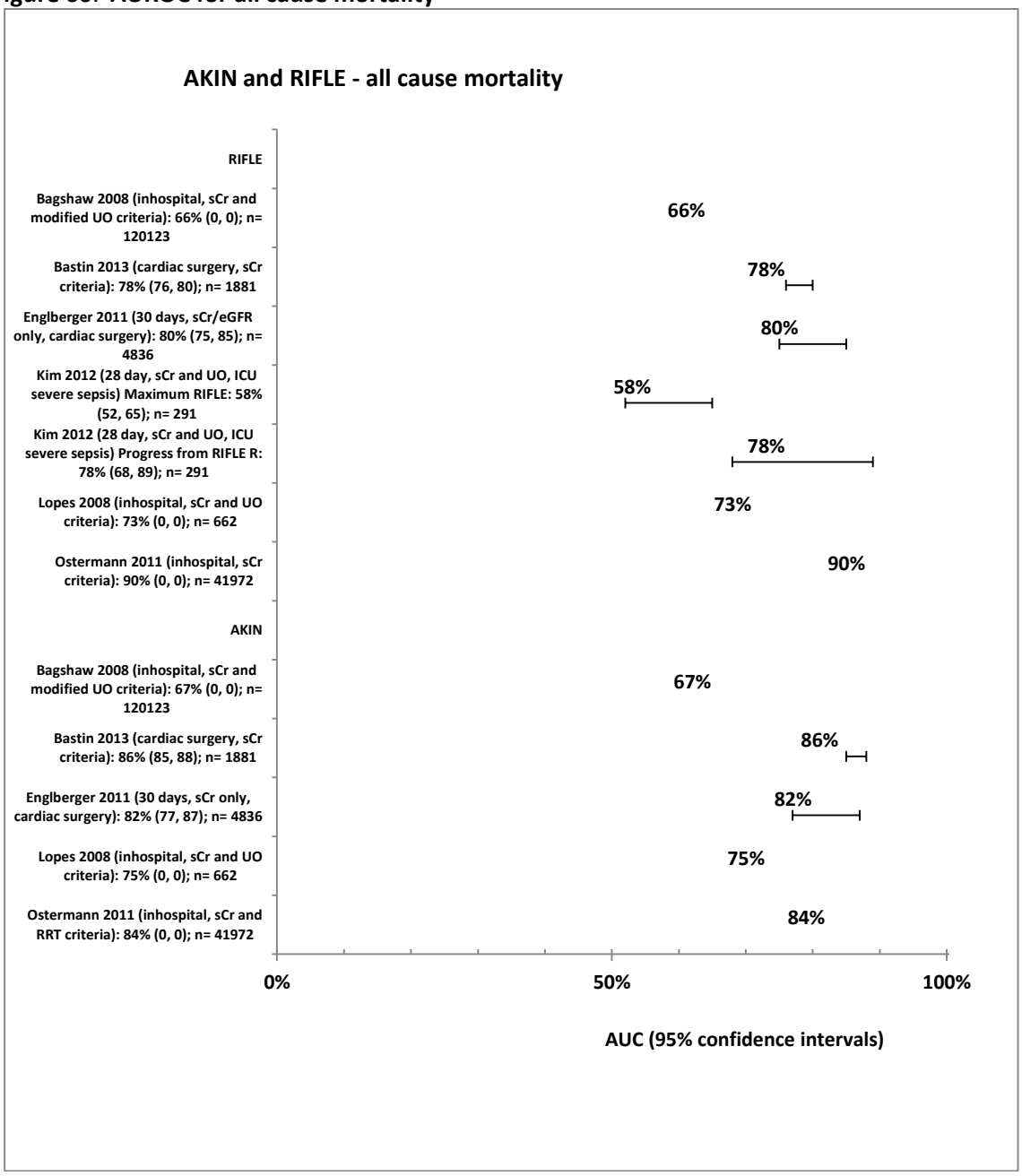
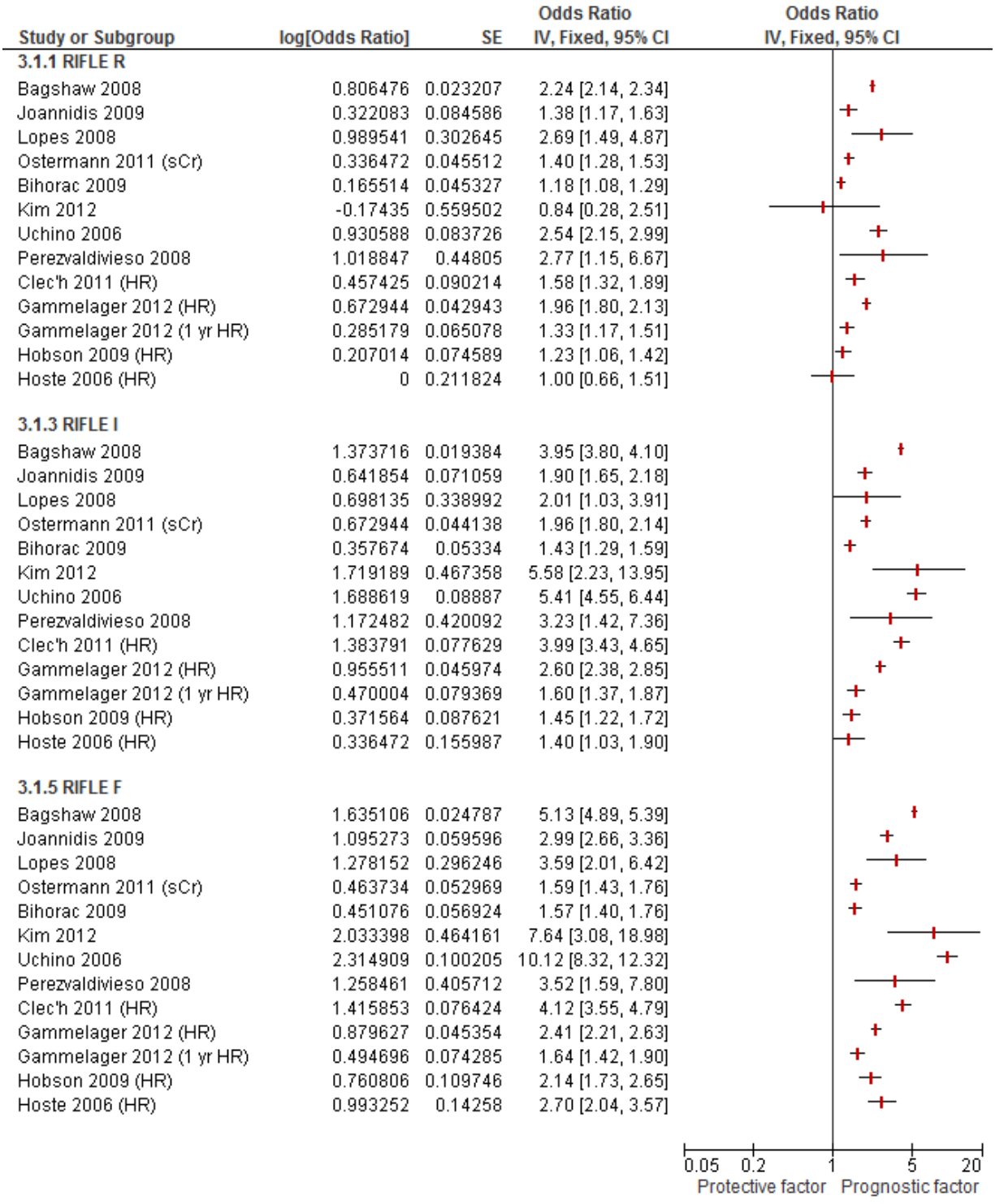
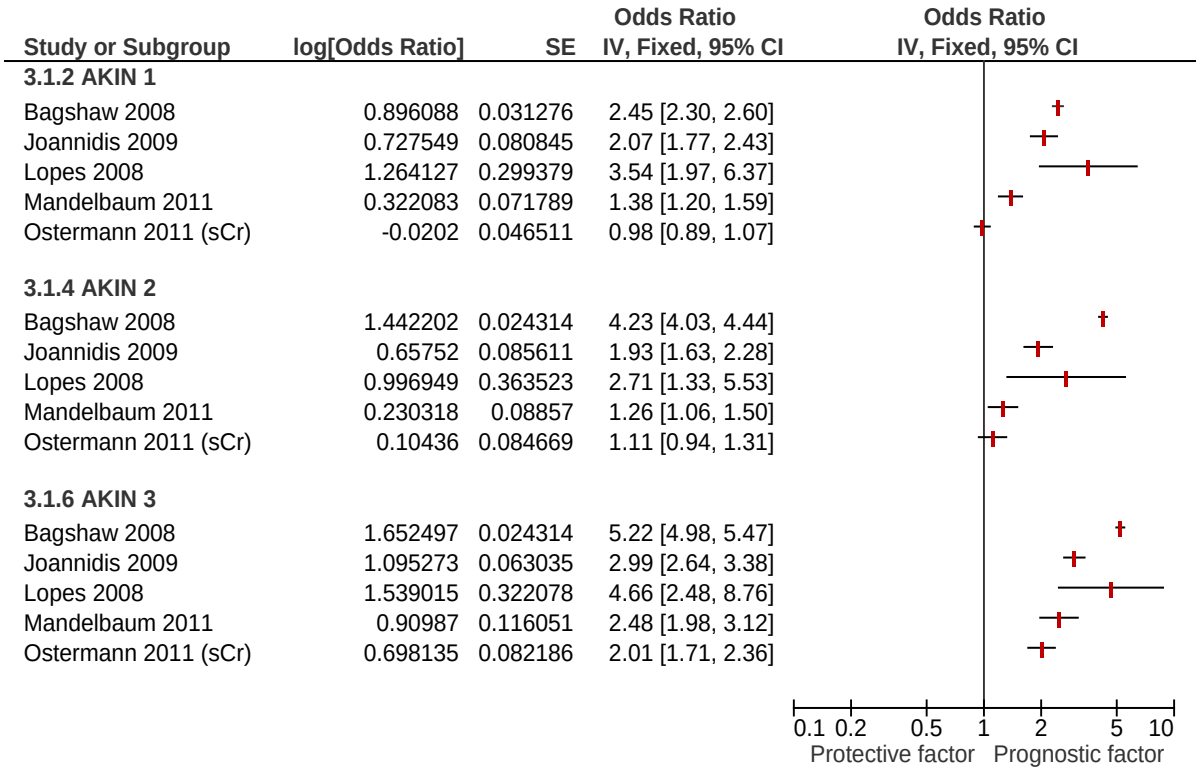


Figure 61: All cause mortality prognosis by RIFLE stage (HR signifies hazard ratio)



1

Figure 62: All cause mortality prognosis by AKIN stage (sCr signifies serum creatinine criteria only)



1

2

Figure 63: Mortality (AKIN versus RIFLE)

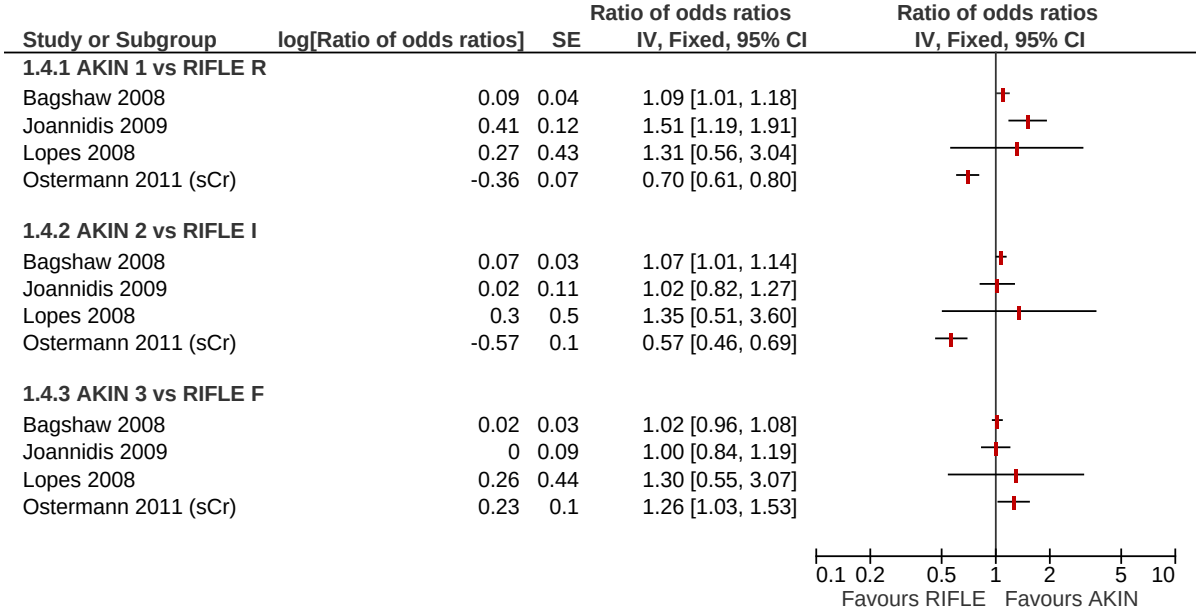
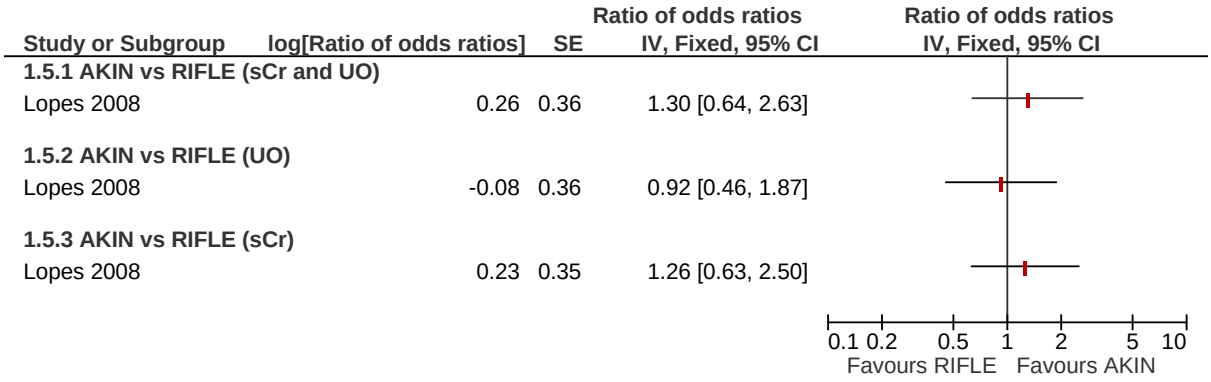


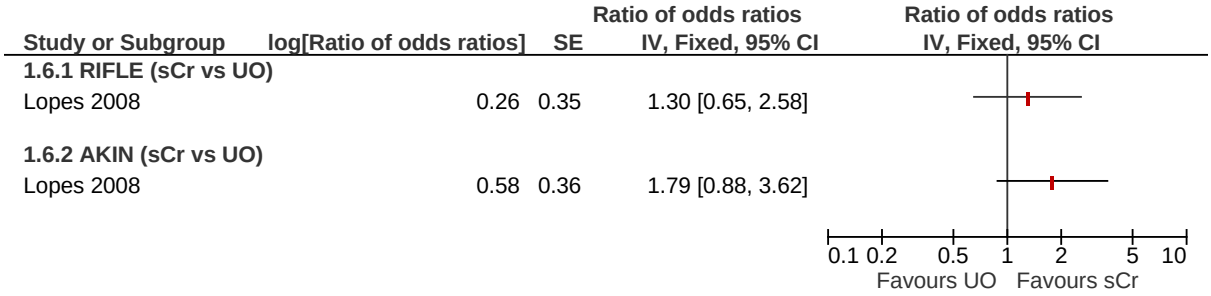
Figure 64: **Mortality by sCr and UO criteria (AKIN versus RIFLE)**



1

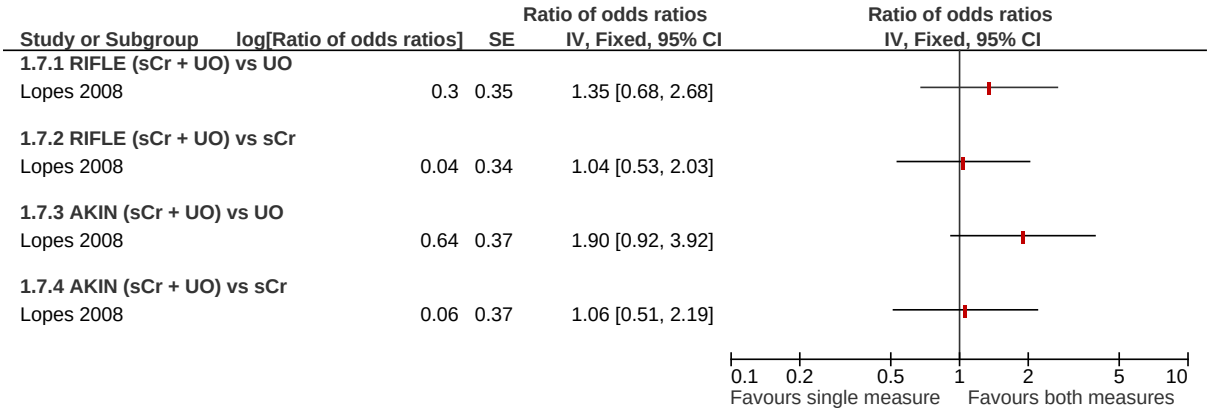
2

Figure 65: **Mortality by sCr and UO criteria (within RIFLE or AKIN)**



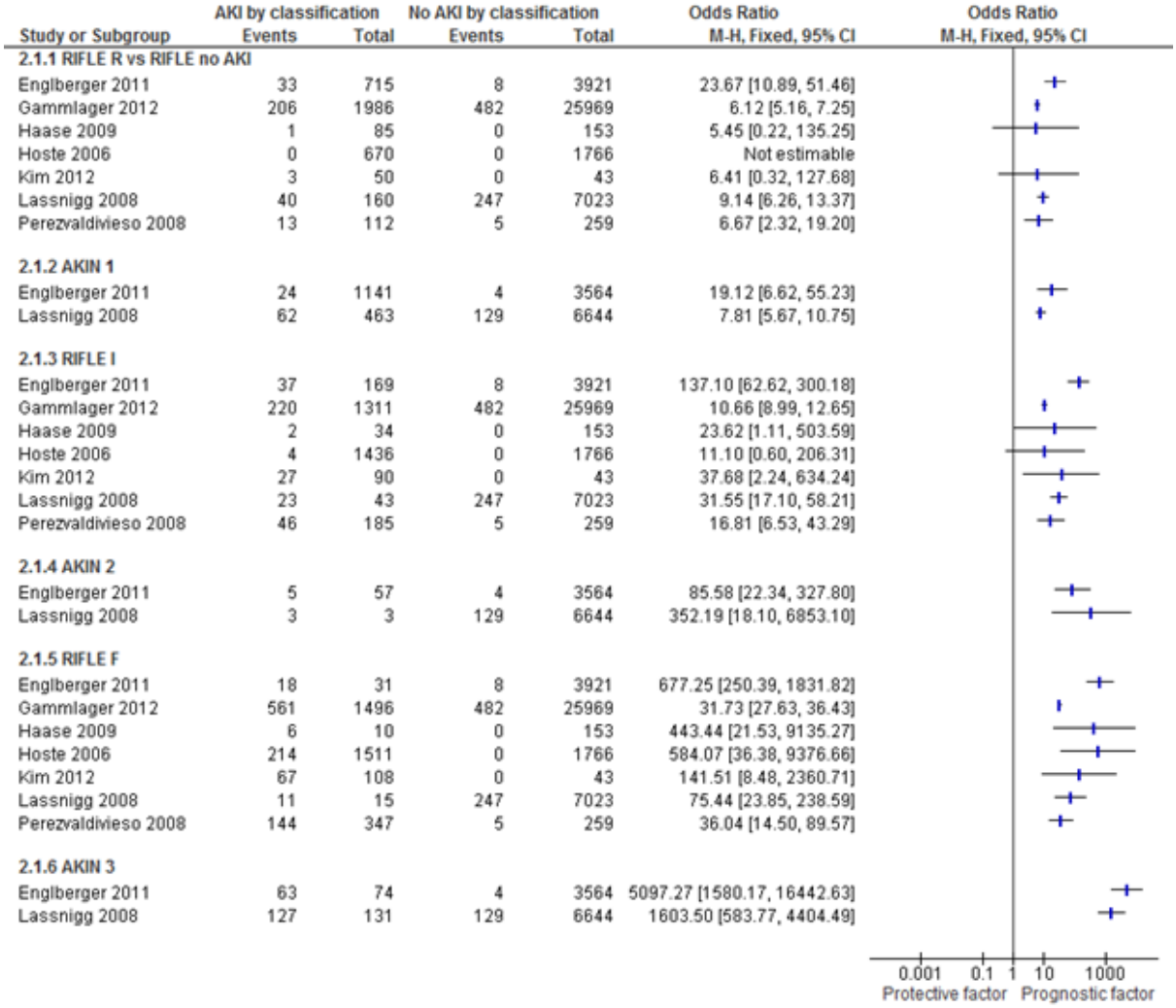
3

Figure 66: **Mortality by sCr and UO together versus either UO or sCr alone**



1

Figure 67: Renal replacement therapy (RRT) by RIFLE or AKIN stage versus no AKI by same classification (unadjusted odds ratios)



H.3.3 Prognostics (Paediatrics)

Figure 68: All cause mortality – adjusted odds ratios

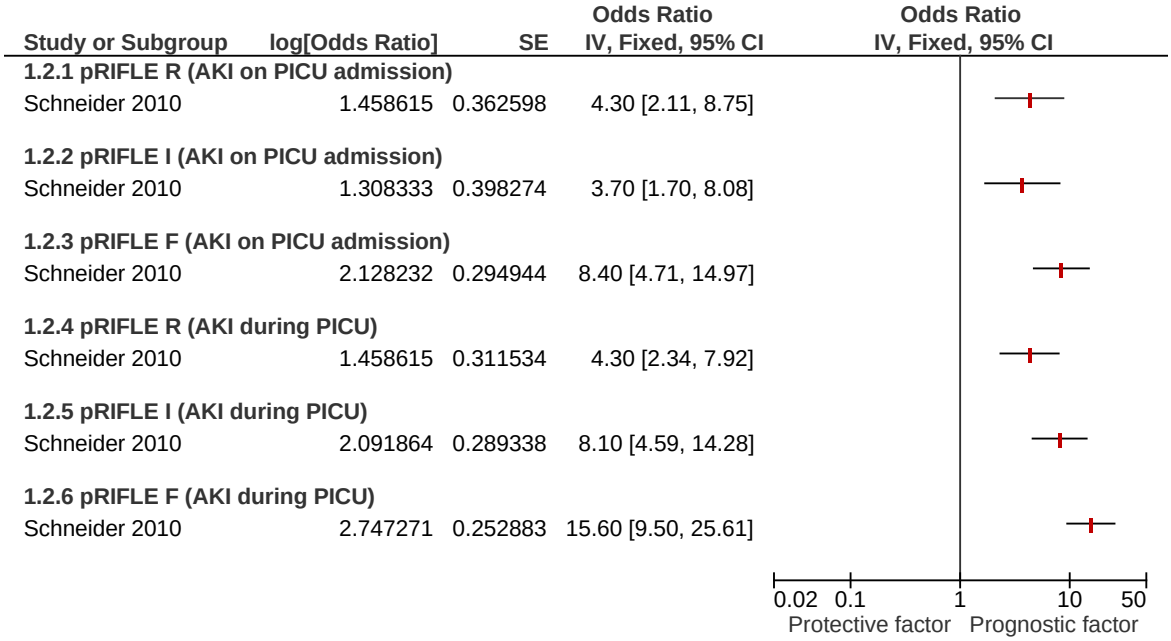
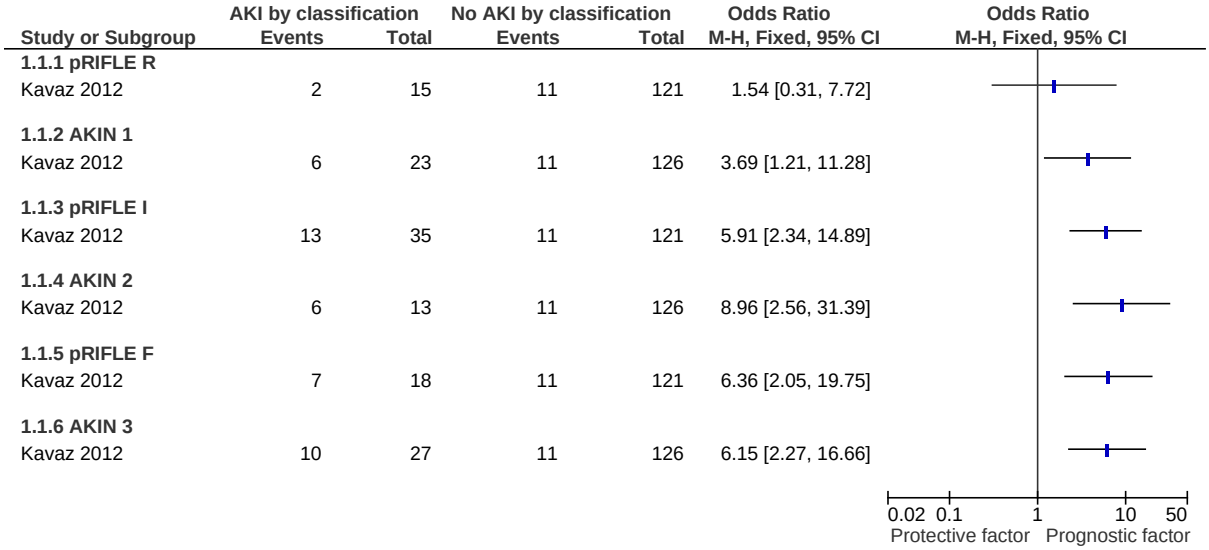


Figure 69: All cause mortality – unadjusted odds ratios



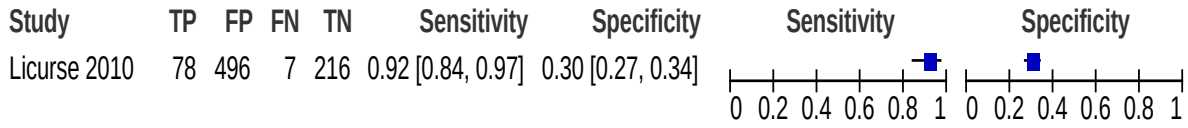
H.4 Identifying the cause of AKI

H.4.1 Urinalysis

No relevant clinical studies comparing urine dipstick tests with microscopy and or biopsy were identified

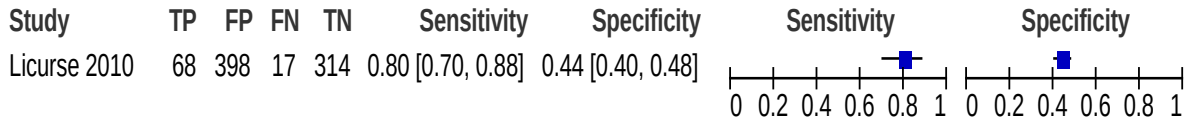
H.4.2 Ultrasound

Figure 70: Detecting hydronephrosis using model 1 (low risk group vs. high + medium risk group in patients with AKI who have had a RUS)



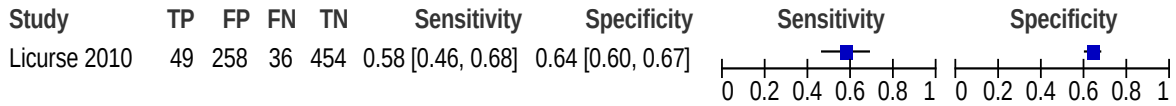
As reported by Licurse et al, see extraction tables for further details on each model

Figure 71: Detecting hydronephrosis using model 2 (low risk group vs. high + medium risk group in patients with AKI who have had a RUS)



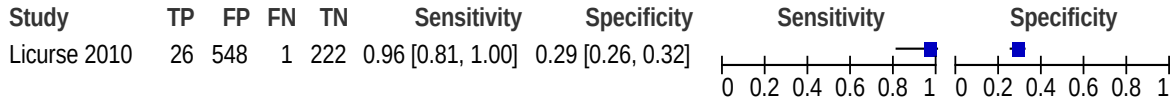
As reported by Licurse et al, see extraction tables for further details on each model

Figure 72: Detecting HN using model 1 (high risk group vs. low + medium risk group in patients with AKI who have had a RUS)



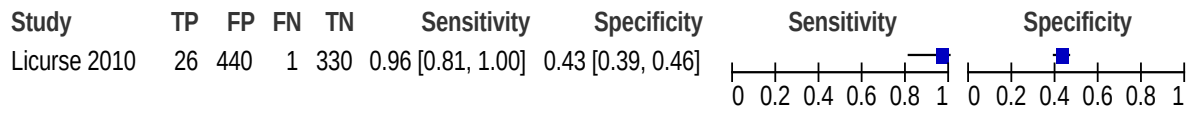
NCGC calculated, see extraction tables for further details on each model

Figure 73: Detecting patients with hydronephrosis requiring intervention using model 1 (low risk group vs. high + medium risk group in patients with AKI who have had a RUS)



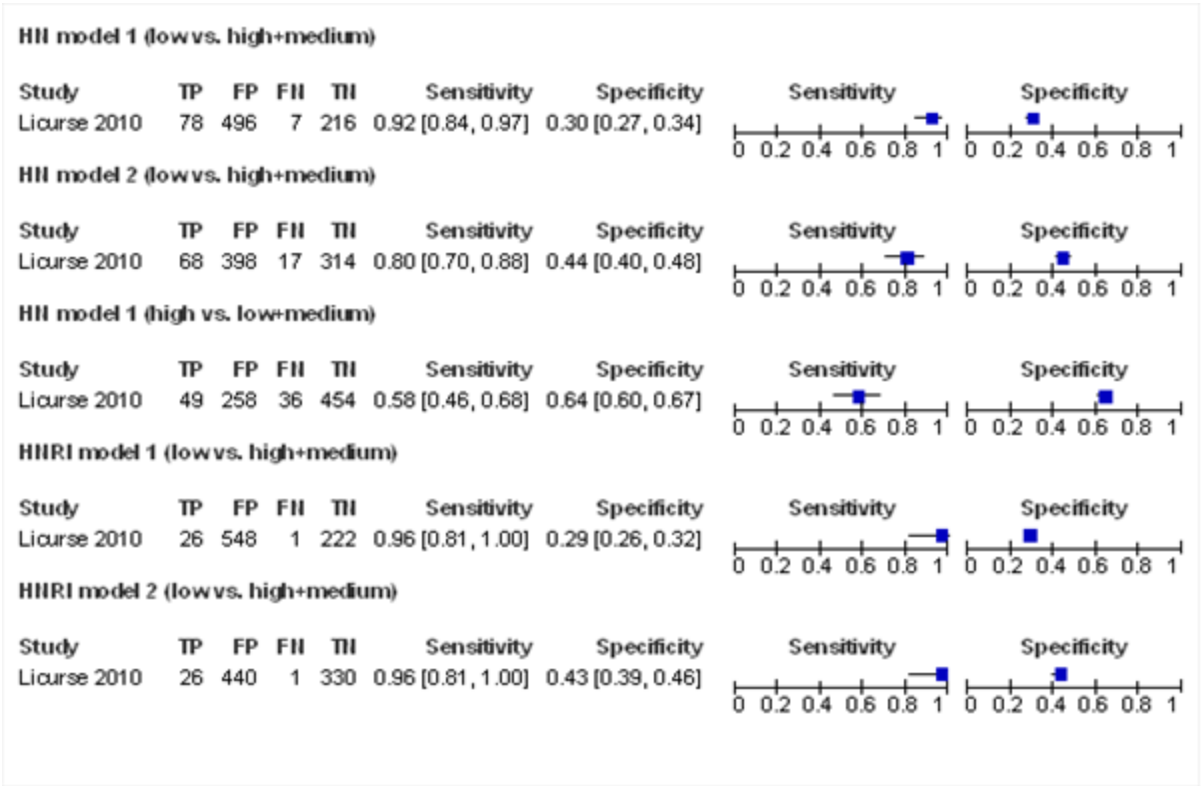
As reported by Licurse et al, see extraction tables for further details on each model

Figure 74: Detecting patients with hydronephrosis requiring intervention using model 2 (low risk group vs. high + medium risk group in patients with AKI who have had a RUS)



As reported by Licurse et al, see extraction tables for further details on each model

Figure 75: Summary of the diagnostic accuracy data reported by Licurse 2010[247]



As reported by Licurse et al, see extraction tables for further details on each model.
HN: Hydronephrosis, HNRI: Hydronephrosis requiring intervention

H.5 Managing AKI

H.5.1 Relieving urological obstruction

No clinical evidence was identified in the systematic review for timing of relief of upper tract urological obstruction

H.5.2 Pharmacological management

H.5.2.1 Loop diuretics

Figure 76: loop diuretics vs. placebo/usual care in inpatients with AKI: Mortality (up to 1 month)

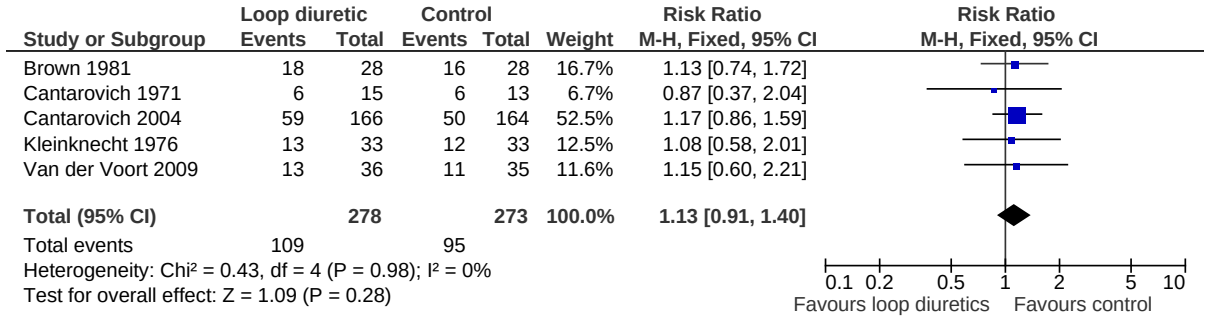


Figure 77: loop diuretics vs. placebo/usual care in inpatients with AKI: Number of patients needing RRT

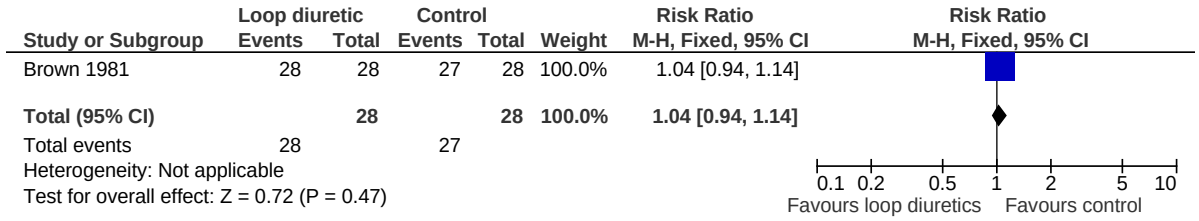


Figure 78: loop diuretics vs. placebo/usual care in inpatients with AKI: Length of RRT

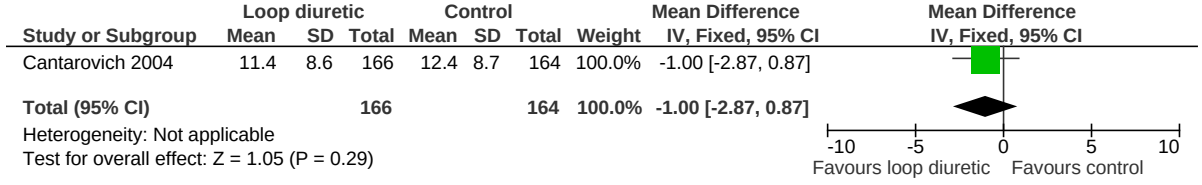
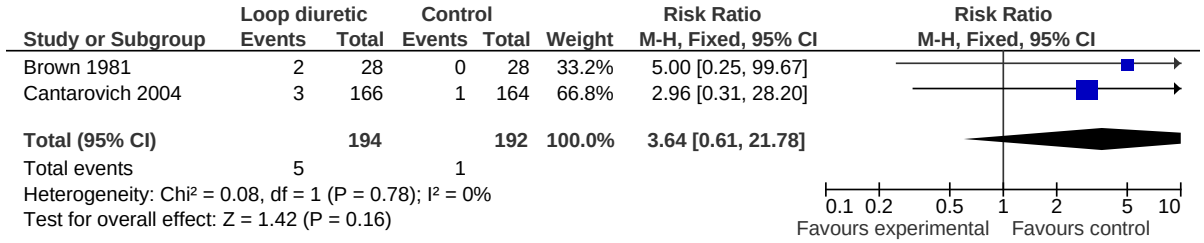


Figure 79: loop diuretics vs. placebo/usual care in inpatients with AKI: Hearing loss



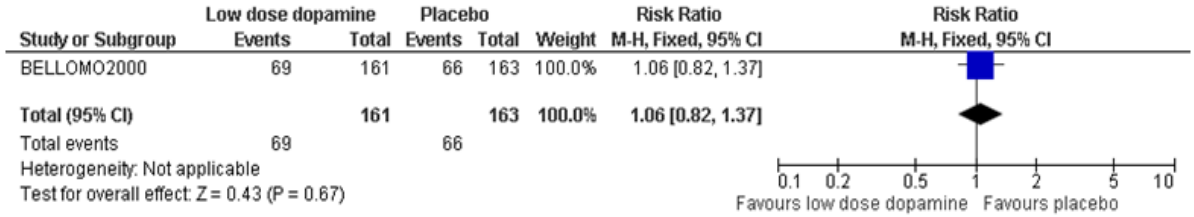
1

2

3

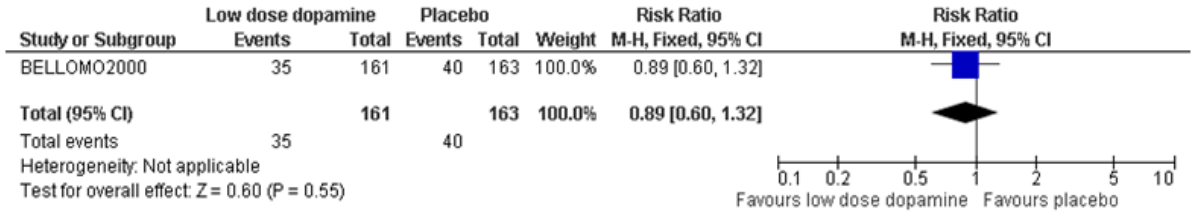
4 **H.5.2.2 Dopamine**

Figure 80: Low dose dopamine vs. placebo in patient with/at risk of AKI; Mortality by hospital discharge



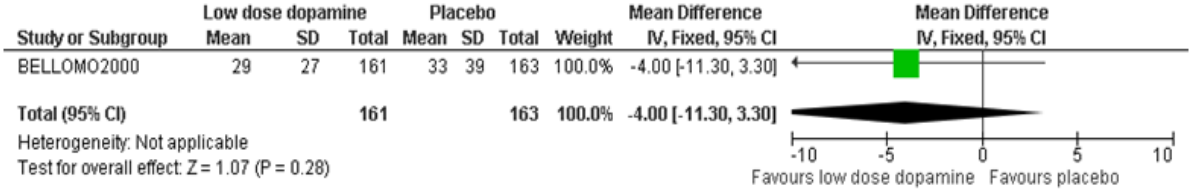
5

Figure 81: Low dose dopamine vs. placebo in patient with/at risk of AKI; Number of patients needing RRT



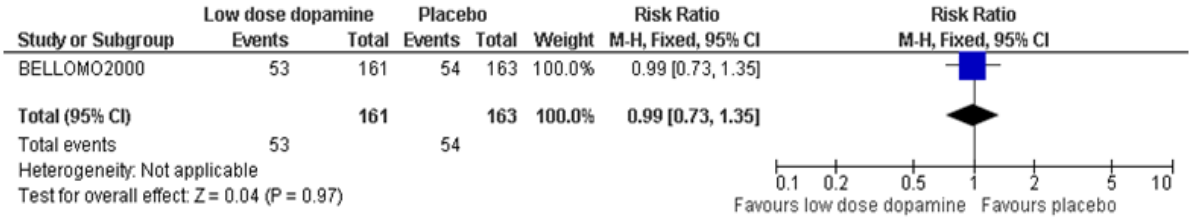
6

Figure 82: Low dose dopamine vs. placebo in patient with/at risk of AKI; Length of hospital stay (days)



1

Figure 83: Low dose dopamine vs. placebo in patient with/at risk of AKI; Cardiac arrhythmias



2

3 **H.5.3 Referring for renal replacement therapy**

Figure 84: Early RRT vs. Late RRT in patients with AKI; Mortality

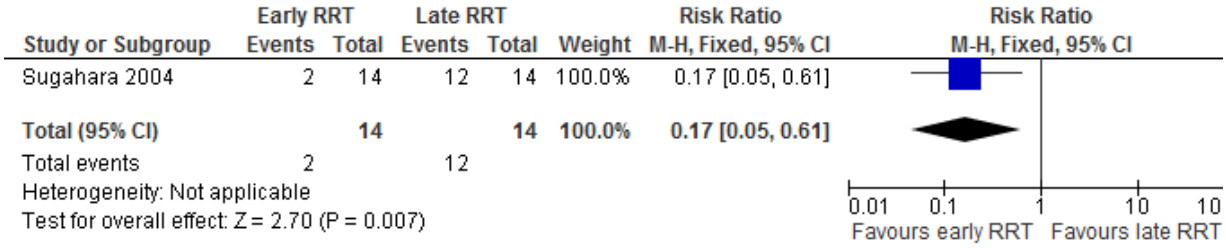


Figure 85: Early RRT vs. Late RRT in patients with AKI; Survival (at 28 days)

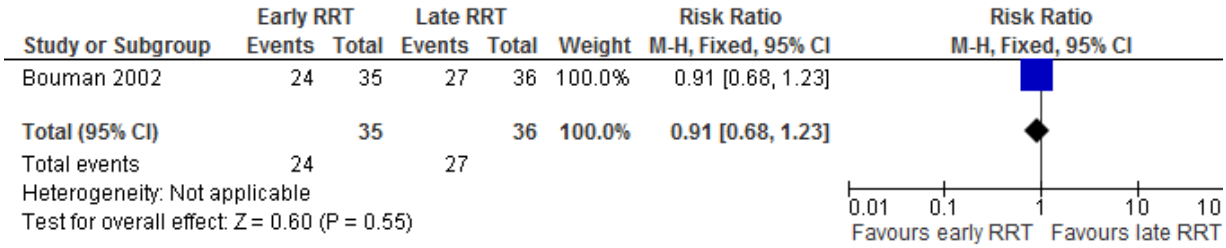


Figure 86: Early RRT vs. Late RRT in patients with AKI; Survival (ICU)

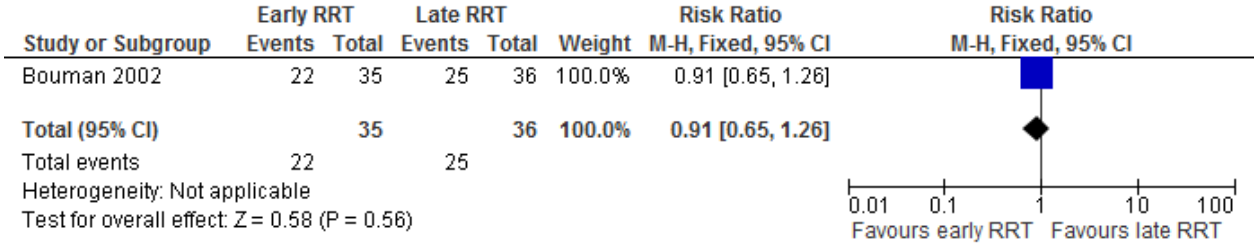
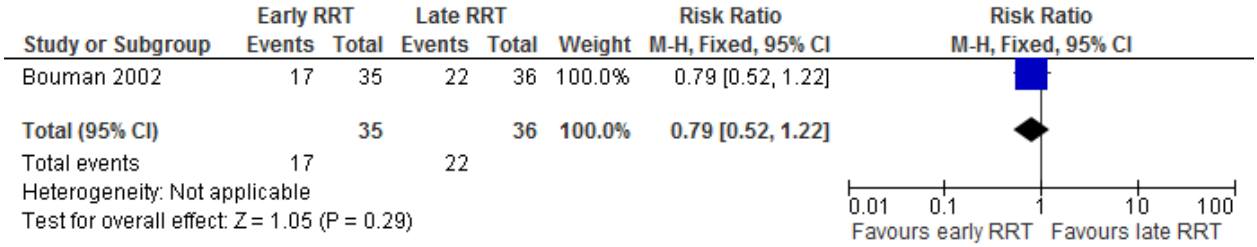


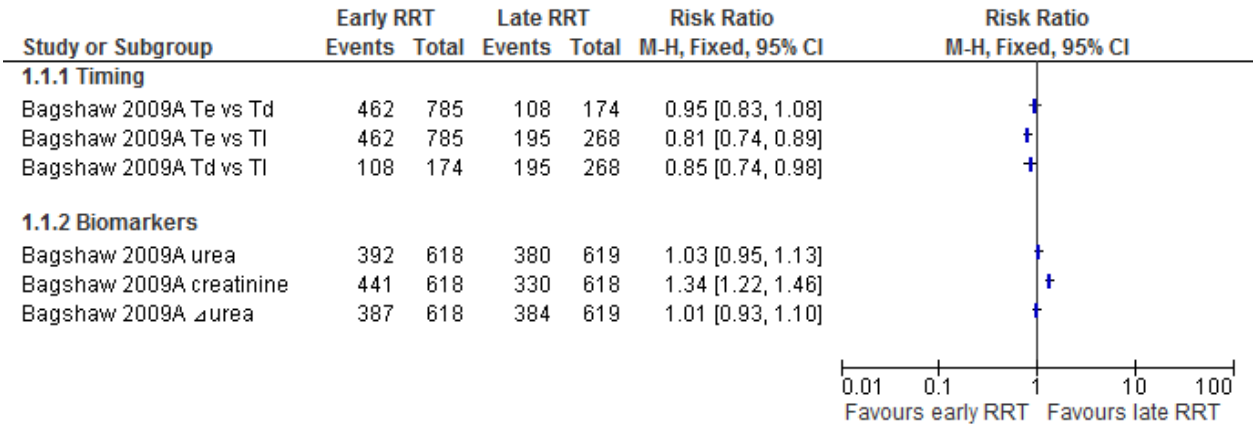
Figure 87: Early RRT vs. Late RRT in patients with AKI; Survival (hospital)



Forest plots for observational studies:

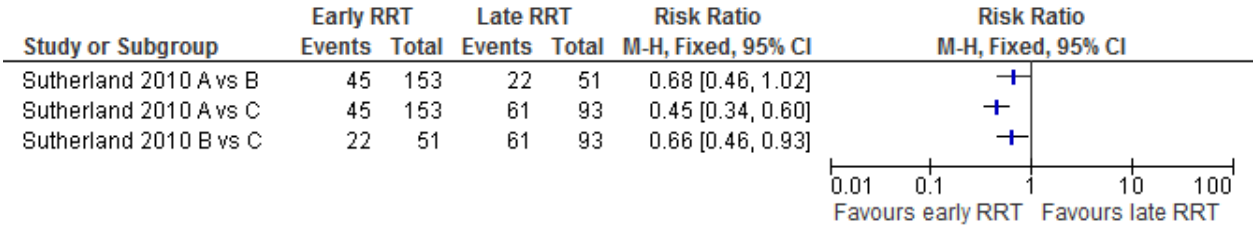
The following data was not meta-analysed due to the heterogeneous manner in which definitions of early vs. late RRT have been reported.

Figure 88: Early RRT vs. Late RRT in patients with AKI; Mortality (adult)



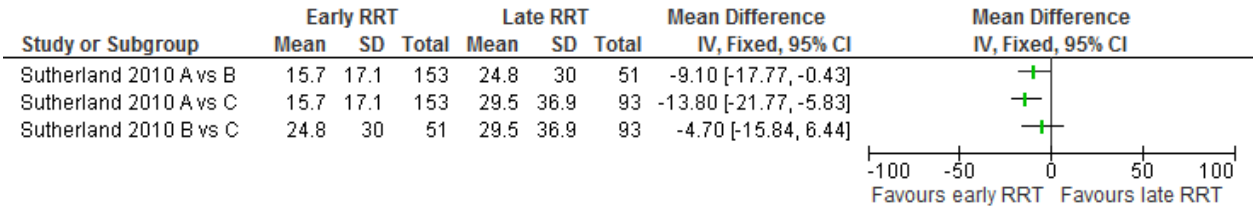
Definitions: Te: Early, Td: delayed, Tl: late, Creatinine: median creatinine at RRT initiation, Urea: median urea at RRT initiation, Δ change in urea from baseline to RRT initiation

Figure 89: Early RRT vs. Late RRT in patients with AKI; Mortality (paediatric)



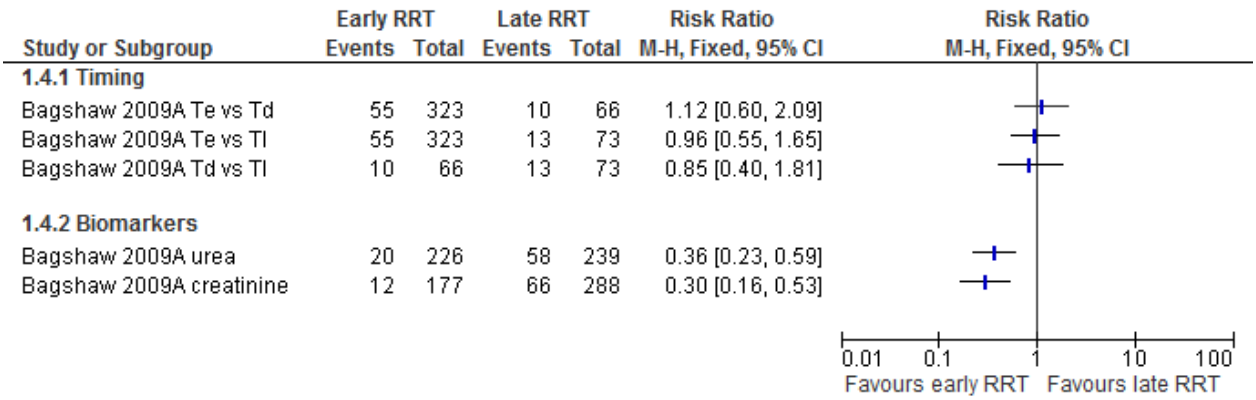
Definitions: A = <10% fluid overload, B = ≥10-20% fluid overload, C= ≥20% fluid overload

Figure 90: Early RRT vs. Late RRT in patients with AKI; Length of ICU stay



Definitions: A = <10% fluid overload, B = ≥10-20% fluid overload, C= ≥20% fluid overload

Figure 91: Early RRT vs. Late RRT in patients with AKI; Renal recovery (RRT dependence)



Definitions: Te: Early, Td: delayed, Tl: late, Creatinine: median creatinine at RRT initiation, Urea: median urea at RRT initiation, Δ change in urea from baseline to RRT initiation

H.5.4 Referring to nephrology

Figure 92: Late vs. early referral; Mortality (Inverse Variance)

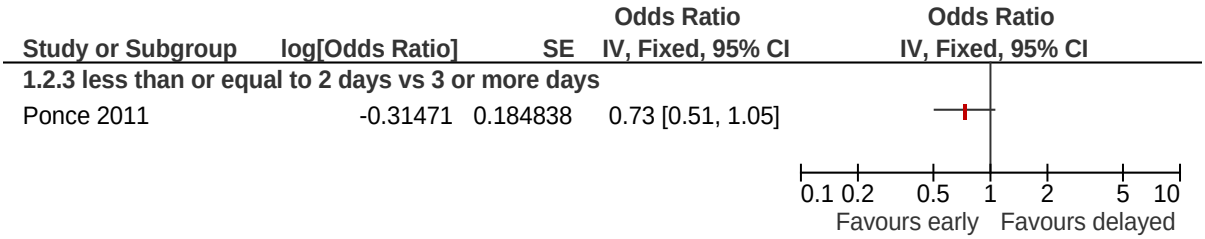


Figure 93: Late vs. early referral; Mortality

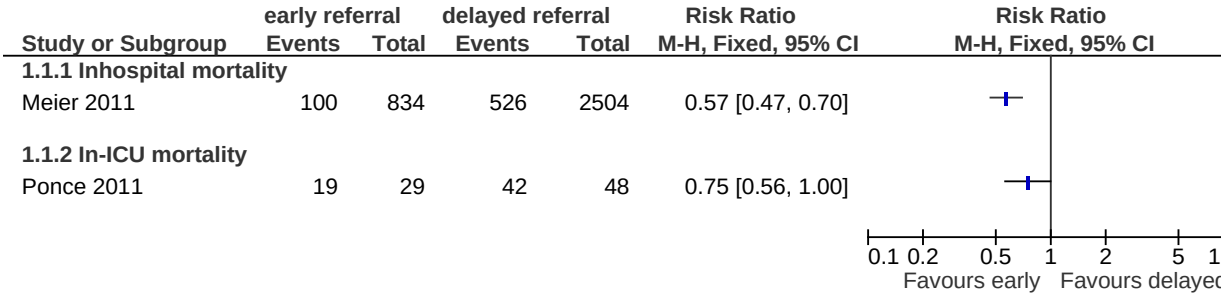


Figure 94: Late vs. early referral; Number of people needing RRT

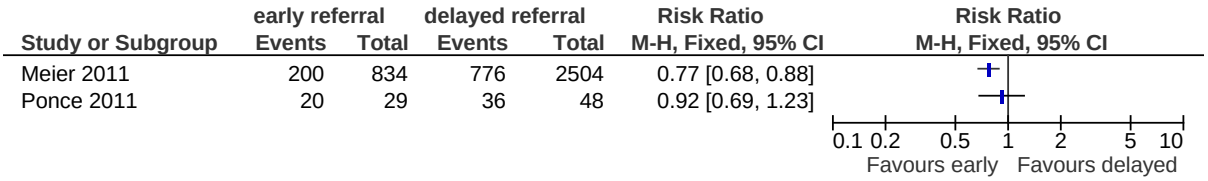


Figure 95: Late vs. early referral; Recovery of renal function

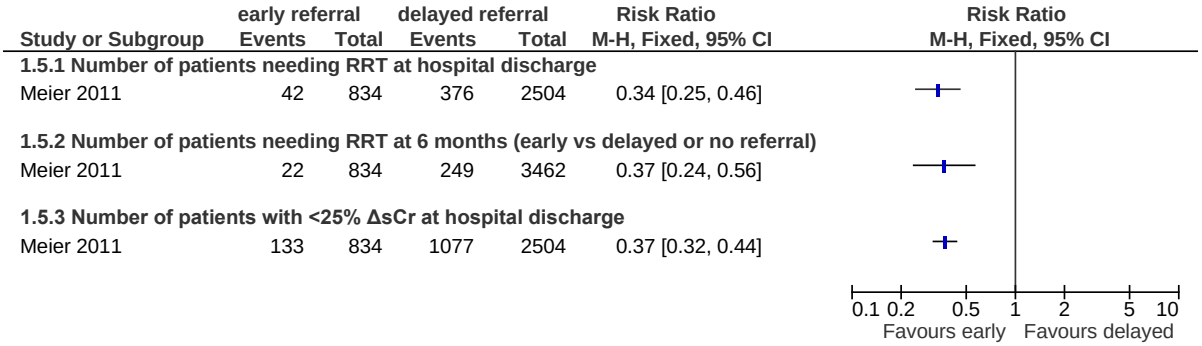
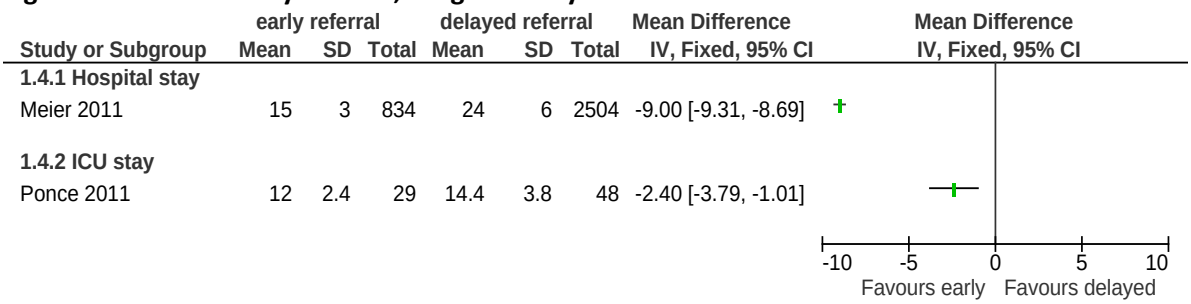


Figure 96: Late vs. early referral; Length of stay



H.6 Information and support for patients and carers

No forest plots were created due to the data found in the studies being qualitative

Appendix I: Excluded clinical studies

I.1 Assessing risk

I.1.1 Risk assessment tools

Reference	Reason for exclusion
Antunes 2009[20]	Cardiac surgery risk score
Bartholomew 2004[39]	CI AKI measured at <48h
Candelatoha 2008[67]	Cardiac surgery risk score
Costaesilva 2009[99]	Looks at prognostic value of physiological scores, not AKI risk scores
Drawz 2008[111]	Retrospective case control study and event rate of AKI <100 in validation sample
Englberger 2010[126]	Cardiac surgery risk score
Fortescue 2000[142]	Cardiac surgery risk score
Huerta 2005[192]	Study looks at relative risks not the development and validation of a score
Rajamanickam 2011[335]	Abstract only. Risk of haemodialysis not risk of AKI
Skelding 2007[375]	CI AKI measured at <48h and event rate of CI-AKI <100
Thakar 2003[394]	Cardiac surgery risk score
Thakar2005[393]	Cardiac surgery risk score
Uchino 2005 [406]	Score to predict mortality in AKI not risk of AKI
Wijeysundera 2007[422]	Cardiac surgery risk score
Heise 2010[173]	Cardiac surgery risk score
Knapik 2008[232]	Cardiac surgery risk score
Eriksen 2003[128]	Cardiac surgery risk score
Vives 2011[418]	Cardiac surgery risk score

I.1.2 Paediatric risk assessment tools

Reference	Reason for exclusion
Duzova 2011[118]	Abstract only
Jamal 2004[198]	Geographical considerations
Mangia 2011[263]	Incidence and outcome of septic AKI only
Mckamy 2011[274]	Retrospective cohort
Moffett 2011[285]	Retrospective case-control
Patzer 2008[317]	Non-systematic review (educational feature)

Reference	Reason for exclusion
Pundziene 2010[330]	Retrospective review of medical records
Vachvanichsanong 2006[408]	Retrospective review of medical records
Vanbiljon 2008[410]	Retrospective review of medical records
Waters 2007[419]	Identified cases (retrospective) from 2 centres and from UK section of European Pediatric Registry for diarrhoea negative HUS
Williams 2002[423]	Retrospective review of medical records
Zappitelli 2008a[435]	Non-systematic review
Zappitelli 2011[436]	Retrospective cohort study.

I.2 Preventing AKI

I.2.1 Paediatric early warning scores

Reference	Reason for exclusion
Adshead 2009[7]	Non-systematic review
Bhal 2006[49]	SICK score -Not a PEWS
Bradman 2008[57]	A&E warning score
Chamberlain 1998[79]	PRISA score -Not a PEWS
Chamberlain 2004[78]	PRISA score- Not a PEWS
Chamberlain 2005[80]	PRISA score -Not a PEWS
Chapman 2010[84]	Review- all relevant studies have been included
Dryden 2010[113]	Abstract
Duncan 2007[114]	Non-systematic review
Egdell 2008[122]	PAWS- Not a PEWS
Gravel 2003[161]	PRISA score -Not a PEWS
Monaghan 2005[289]	Study on the development of tool not validation
Oldroyd 2011[302]	Non-systematic review
Oliver 2010[303]	Does not address PICO - not a validation study of PEWS
Tume 2004[404]	Non-systematic review
Winberg 2008[425]	Systematic review of paediatric rapid response systems
Alessandrini 2012[11]	A&E warning score
Anon 2012[3]	Conference abstract – no PEWS
Bonafide 2012[55]	Not a validation study
Carmichael 2011[73]	A&E warning score
Duncan 2012[116]	Implementation of PEWS no a validation study
Fernandez 2012[136]	Paediatric mortality score – Not a PEWS
Imamura 2012[193]	Paediatric mortality score – Not a PEWS
Keyes 2012[216]	PEWS and interhospital facility transport
Leteurtre 2012[244]	Paediatric mortality score – Not a PEWS
Mohkam 2011[287]	Testing of AKI definitions in neonates

Reference	Reason for exclusion
Reini 2012[340]	MEWS in adults
Shore 2012[368]	Paediatric mortality score – Not a PEWS
Green 2012[162]	A&E warning score

I.2.2 Preventing CI-AKI

Reference	Reason for exclusion
Amini 2009[16]	More than one type of contrast allowed in study design
Anderson 2011[17,18]	Meta analysis, all included studies assessed separately
Awal 2011[23]	CIN measured at 24h only. Type of contrast used not reported. Patients were "divided in two groups", no randomisation reported.
Azmus 2005[24]	More than one type of contrast allowed in study design
Baker 2003[31]	Different fluid regimens in timing and volume for intervention and control arms.
Balderramo 2004[35]	N<80
Baranska 2007[36]	Results reported per cardiac catheterisation rather than per patient (112 procedures in 97 patients). Also indirect population (after orthotopic heart transplantation).
Boccalandro 2010[53]	Poster only
Chen 2008[87]	Did not match protocol - inappropriate study comparison.
Cho 2010[93]	N<40 per arm (4 arm study)
Coyle 2006[101]	Contrast used not specified in study, just states "selection and volume of contrast at the discretion of the operator".
Droppa 2011[112]	Post hoc analysis of Thiele et al. 2010.[395]
Gomes 2005[159]	Used low osmolar ionic contrast medium.
Heng 2008[175]	N<80
Hoste 2010[186]	Meta analysis, all included studies assessed separately
Hsu 2007[190]	N<80
Jang 2011[200]	Meta analysis, all included studies assessed separately.
Jang 2012[201]	Meta analysis, all included studies assessed separately.
Kefer 2003[211]	Does not match protocol, sCr only checked at 24h post procedure.
Khalili 2006[218]	N<80
Kitzler 2012[227]	N<80
Klima 2012[231]	Different fluid regimens in timing and volume for intervention and control arms.
Kotlyar 2005[236]	N<80
Kunadian 2011[238]	Meta-analysis, all included studies assessed separately.
Li 2001[245]	Meta analysis, all included studies assessed separately.
MacNeill 2003[257]	N<80
Masuda 2008[268]	N<80
Masuda 2007[267]	N<80
Meguro 2010[275]	Conference abstract only

Reference	Reason for exclusion
Ochoa 2004[299]	More than one type of contrast allowed in study design
Ozcan 2007[309]	Used low osmolar ionic contrast medium.
Ratcliffe 2009[337]	N<40 per arm (4 arm study)
Recio-Mayoral 2007[338]	NAC only given pre-contrast in intervention group and volume and timing of fluids given was different for intervention and control.
Reinecke 2007[339]	
Rocha 2009[348]	Conference abstract only
Sadat 2011[351]	N<80
Sagara 2009[352]	N<80
Sandhu 2006[355]	More than one type of contrast used
Sar 2010[356]	N<80
Seyon 2007[362]	N<80
Shavit 2009[365]	Non-randomised study
Shemirani 2012[366]	Does not match protocol – incorrect intervention/comparison
Silva 2010[373]	N<80
Tanaka 2011[389]	N<80
Trivedi 2003[399]	N<80
Trivedi 2010[398]	Meta-analysis, all included studies assessed separately.
Ueda 2011[407]	N<80
Vasheghani-Farahani 2009[413]	Included 110 patients that did not meet inclusion criteria and 25 patients did not have sCr measured at 48h, insufficient data for ACA. 8 patients given high osmolar, 2 iso osmolar and 254 low osmolar (1 patient not accounted for). No information regarding CI-AKI by contrast subgroup.
Vasheghani-Farahani 2010[412]	N<80
Zaraca 2011[438]	Meta-analysis, all included studies assessed separately.

I.2.3 Computerised decision tools

Reference	Reason for exclusion
Bakris 1993[33]	Non-systematic review
Bates 2007[43]	Non-systematic review
Belaiche 2011[44]	Conference abstract
Bhardwaja 2011[50]	Outpatient population - Not PICO
Briceland 1999[60]	No control group
Castelino 2011[76]	No control group
Chang 2011[82]	Systematic review, includes studies not our PICO
Colpaert 2006[98]	Less than 100 events
Eslami 2006[130]	Abstract only
Faynor 1984[134]	Non-systematic review - ciclosporin

Reference	Reason for exclusion
Fernandez 2010[137]	Abstract only
Field 2009[138]	Not our population - long term care
Frolich 2011[146]	Prescriptions on discharge from surgery
Geerts 2012[153]	No control group
Golightly 1993[158]	No control group
Hassan 2009[171]	Poor applicability to clinical question
Hou 2011[188]	Retrospective cohort
Houshmand 1996[189]	Less than 100 events
Kaushal 2003[208]	Systematic review, includes studies not our PICO
Matsumura 2009[270]	Less than 100 events
Milani 2011[281]	Antithrombotic treatment only
Nash 2005[293]	No baseline characteristics or patient numbers
Quartarolo 2007[333]	Poor applicability to clinical question, looks at recognition of CKD and discharge prescribing in this population
Roberts 2010a[347]	Less than 100 events
Schetz 2005[358]	Non-systematic review
Shuster 2006[369]	Protocol/design only
Tawadrous 2011[390]	Systematic review, includes studies without controls
Terrell 2010[392]	Prescriptions on discharge from ED

I.2.4 Stopping ACEI/ARB therapy

Reference	Reason for exclusion
Diarrhoea and vomiting	
Stirling 2003[379]	Very small retrospective study
Wynckel 1998[431]	Does not answer review question
Flynn 2008[141]	Safety efficacy study of valsartan, does not answer review question
Schaefer 2010[357]	Safety efficacy study of candesartan, does not answer review question
Tullus 2011[402]	Review article only – used to identify other possibly relevant studies
Radiocontrast	
Cirit 2006[95]	Study design – prospective cohort study
Gupta 1999[165]	Does not answer review question . Acute administration of ACEI, not chronic use
Hashemi 2005[170]	Does not answer review question . Acute administration of ACEI, not chronic use
Kiski 2010 [225]	Study design - Post hoc analysis of prospective cohort study.
Li 2012[246]	MA - most acute administration of ACEI, other studies considered separately.
Onuigbo 2011[304]	Non-systematic review
Patel 2011[315]	Unavailable from any UK source
Shemirani 2012[366]	Does not match protocol – incorrect population as excluded patients with serum creatinine > 133µmol/l or GFR <60ml/min.

Reference	Reason for exclusion
Surgery	
Benedetto 2008[47]	Does not answer the review question- indirect population and incorrect intervention
Cittanova 2001[96]	Does not answer the review question- indirect population and incorrect intervention
Kheterpal 2008[221]	Does not answer the review question- indirect population and incorrect intervention
Ozaydin 2010[307]	Does not answer the review question- data not extractable
Rady 1998[334]	Does not answer the review question- indirect population and incorrect intervention
Sun 2011[383]	Non-systematic review
Sepsis	
Mortensen 2007[290]	Does not answer the review question – indirect population
Ng 2008[296]	Does not answer the review question

I.3 Detecting AKI

Reference	Reason for exclusion
Adults	
Ali 2007[14]	Study design – retrospective cohort
Barrantes 2008[38]	Does not match protocol (multivariable analysis not by stage of AKI)
Bentley 2011[48]	Short cut review -all studies considered separately
Che 2011[86]	Does not match protocol (multivariable analysis not by stage of AKI)
Chen 2009[88]	Does not match protocol (no multivariable analysis)
Cruz 2010[102]	Incorrect study design: Non-systematic review
Cruz 2007[103]	Does not match protocol (reference not 'no AKI')
Kuitunen 2006[237]	Does not match protocol (multivariable analysis not by stage of AKI)
Kwon 2010[239]	Does not match protocol (reference not 'no AKI')
Lakhal 2011[240]	Study design – retrospective cohort
Macedo 2011[255]	Does not match review question
Rodrigues 2010[349]	Abstract only
Zhou 2012[440]	Does not match protocol (reference not 'no AKI')
Paediatrics	
Mian 2009[280]	Abstract only
Ozcakar 2009[308]	Does not match protocol (reference not 'no AKI')
Plotz 2008[326]	Does not match protocol (retrospective cohort, no multivariable analysis and stage of AKI not reported separately for pRIFLE I and F)
Riyuzo 2010[345]	Abstract only
Zappitelli 2008[437]	Does not match review question

I.4 Identifying the cause of AKI

I.4.1 Urinalysis

Reference	Reason for exclusion
Ahsan 2001[8]	Does not address clinical question.
Alavi 2012[10]	Population does not match protocol. Excludes patients with AKI.
Anderson 2004[17]	Review. Ordered for background reading.
Bakr 2007[32]	Screening study in healthy children.
Carroll 2000[74]	Ordered for background reading.
Cassidy 1990[75]	Does not address the clinical question.
Chawla 2008[85]	Only looks at urine microscopy
Cho 2010[92]	Abstract only.
Cho 2001[91]	Population does not match protocol. Screening study in children.
Cho 2007[90]	Population does not match protocol. Screening study in children.
Dasilvamagro 2004[106]	Does not include correct index and reference test under investigation.
Hicks 2007[177]	Does not address the clinical question. Only looks at macroscopic haematuria in emergency department patients.
Hicks 2008[178]	Does not address the clinical question. Only looks at macroscopic haematuria in emergency department patients.
Hisano 1991[179]	Does not address clinical question. Screening study in children.
Ito 2006[194]	Does not address clinical question. Population does not match protocol. Children with mixed connective tissue disease
James 2010[199]	Does not address the clinical question. Looks at eGFR and proteinuria in AKI prognosis
Kanbay 2010[206]	Systematic review.
Kawamura 1995[209]	Population does not match protocol. Screening study in adults.
Kitagawa 1985[226]	Population does not match protocol. Screening study in children.
Lee 2006[243]	Population does not match protocol. Not clear how many had AKI.
Lin 2001[249]	Population does not match protocol. Screening study in children.
Lin 2001[248]	Population does not match protocol. Screening study in children.
Lins1986[250]	Population does not match protocol.
Marcussen 1995[264]	Does not include correct index and reference test under investigation. Only includes microscopy.
Perazella 2008[320]	No comparison of index and reference tests. Only looks at Microscopy.
Perazella 2010[319]	No comparison of index and reference tests. Only looks at Microscopy.
Szwed 1982[386]	Not clear if samples from AKI patients were included.
Yamagata 1996[432]	Population does not match protocol. Screening study in adults.
Yap 2005[433]	Population does not match protocol. Screening study in adults.
Siedner 2008[371]	Population does not match protocol. Only lupus nephritis patients.

I.4.2 Ultrasound

Reference	Reason for exclusion
Barozzi 2007[37]	Review of ultrasound changes
Chang 1985[83]	Ultrasound findings only no diagnostic accuracy
Endo 2011[124]	Abstract of Licurse 2010[247]
Fiorini 2007[140]	Review of the role of ultrasound techniques
Geddes 2005[152]	Review of ultrasound in renal impairment
Glatstein 2010[156]	Paper looks at using ultrasound in diagnosing haemolytic uremic syndrome.
Herbert 1983[176]	Review of ultrasound findings only
Huang 2005[191]	Investigates the usefulness of portable renal sonographer in ICU. No diagnostic accuracy data
Kalantarinia 2009[205]	Review of imaging techniques
Kenney 1986[215]	Ultrasound findings only no diagnostic accuracy
Keyserling 2002[217]	Ultrasound findings only no diagnostic accuracy
Khati 2005[220]	Review of ultrasound findings only
Liu 2010[251]	Abstract and comment on Licurse 2010[247]
Oneill 2006[297]	Review of technical aspects of sonography
Paton 2011[316]	Abstract only
Platt 1991[325]	Study looking at the role of duplex Doppler in distinguishing between acute pre-renal failure and acute tubular necrosis
Vergesslich 1987[416]	Doesn't answer the clinical question, only gives ultrasound findings no diagnostic accuracy and excludes children with hydronephrosis

I.5 Managing AKI

I.5.1 Relieving urological obstruction

Reference	Reason for exclusion
Mohan 2009[286]	Abstract only.
Mokhmalji 2001[288]	RCT of nephrostomy vs. stents, no information on timing.
Schneider 1989[359]	Sensitivity of USS in diagnosis of pyonephrosis in children. Not PICO/inclusion criteria.
Sood 2006[377]	Not PICO/inclusion criteria.
Watson 2001[420]	Prospective case series of stenting, no information on timing.

I.5.2 Pharmacological management

I.5.2.1 Loop diuretics

Reference	Reason for exclusion
Bagshaw 2007[26]	Meta-analysis of 5 studies including Cantarovich 2004 and Kleinknecht 1976, includes 3 other studies that do not meet our criteria.
Bagshaw 2010[27]	Protocol for a phase II trial - recruitment complete June 2011 and

Reference	Reason for exclusion
	results available by December 2011.
Ho 2006[181]	Meta-analysis of 9 studies included 3 studies of intraoperative furosemide in patients with normal renal function pre-op and other studies that did not meet our criteria.
Ho 2010[180]	Meta-analysis of 11 studies included 3 studies of intraoperative furosemide in patients with normal renal function pre-op.
Kellum 1997[212]	SR includes studies not in our PICO, relevant studies looked at separately by NCGC.
Mitchell 2005[284]	Cochrane renal group report. Cantarovich 2004 is the only referenced study for loop diuretics.
Parapiboon 2011[312]	Cochrane protocol- corresponded with authors, expected completion late 2012 to early 2013.
Sampath 2007[353]	Meta-analysis of 13 studies includes 8 non randomised studies, RCTs looked at separately by NCGC.

I.5.2.2 Dopamine

Reference	Reason for exclusion
Andreoli 2009[19]	Non-systematic review of AKI in paeds - only adult studies included - KELLUM2001, MARIK2002 and FRIEDRICH2005. Extrapolation to paediatric population from these studies
Basu 2011 [41]	SR of AKI in paediatrics for intensivists (includes Bellomo 2000, Andreoli 2009, Filler 2001).
Filler 2001[139]	Non-systematic review of AKI in paeds.
Friedrich 2005[145]	Meta-analysis (61 RCTS and quasi-RCTs). Random effects analysis due to between study heterogeneity. Includes Bellamo 2000, other studies included not our population.
Kellum 2001[213]	Meta analysis of 17 RCT and 7 observational. Search Jan 1966-Dec 1999 (so Bellomo 2000 not included). Includes populations not in our PICO.
Kellum 2011[214]	BMJ Clinical evidence SR - included 3 studies Kellum2001, Marik 2002 and Bellomo 2000.
Marik 2002[266]	Meta-analysis (15 RCTs) of low dose dopamine - includes Bellomo 2000, other studies included not our population. Analysed using random effects ?because of heterogenity of populations.

I.5.3 Referring for renal replacement therapy

Reference	Reason for exclusion
Bagshaw 2009[25]	Algorithm for initiation of RRT. Does not fit our review question.
Basu 2011A[42]	Non-systematic review of paediatric acute RRT
Belsha 1995[46]	Survey
Bock 2005[54]	Systematic review of RRT in general. Studies on initiation reviewed separately.
Bouman 2002[56]	Retrospective
Carl 2010[72]	Retrospective

Reference	Reason for exclusion
Chou 2011[94]	Retrospective
Demirkilic 2004[108]	Retrospective
Elahi 2004[123]	Retrospective
Faber 2009[132]	General review on RRT for nurses
Gettings 1999[154]	Retrospective
Gibney 2008[155]	Non-systematic review - relevant studies included separately
Iyem 2009[195]	Retrospective
Ji 2011[202]	Retrospective
Karvellas 2011[207]	Includes retrospective cohorts in meta-analysis. Relevant studies included separately
Konopka 2011[235]	Retrospective
Macedo 2011[254]	Non-systematic review
Maclaren 2009[256]	Non-systematic review of paediatric CRRT not just for AKI
Manche 2008[261]	Retrospective
Ostermann 2009[306]	Retrospective
Palevsky 2008[310]	Non-systematic review
Pannu 2008[311]	Systematic review
Payen 2008[318]	Retrospective
Perez 2011[322]	Incorrect intervention and abstract only. The study identifies for septic shock patients on CRRT, doesn't look at early vs. late RRT
Pursnani 1997[331]	Not sure about comparison- early vs. conservative. Not clear what is meant by conservative. Very low N= 35
Piccinni 2006[324]	Retrospective
Seabra 2008[360]	Systematic review
Shiao 2009[367]	Retrospective
Soubrier 2006[378]	Retrospective cohort on epidemiology and prognostic factors
Sugahara 2004[381]	Retrospective
Vats 2011[415]	Retrospective
Wu 2007[430]	Retrospective
Zarbock 2009[439]	Non-systematic review

I.5.4 Referring to nephrology

Reference	Reason for exclusion
Ali 2011[13]	Incorrect intervention/comparison – does not look at early versus delayed referral.
Balasubramanian 2011[34]	Incorrect intervention -Early blanket 'referral' based on automated laboratory alerts.
Feest 1993[135]	Incorrect intervention/comparison – does not look at early versus delayed referral.
Khan 1997[219]	Incorrect intervention/comparison – does not look at early versus delayed referral.

Reference	Reason for exclusion
Mehta 2002[277]	Definition of early versus delayed does not fit review question and no information on serum creatinine levels at time of nephrology referral.
Perezvaldivieso 2007[323]	Definition of early versus delayed does not fit review question, no indication of time to nephrology referral.
Siew 2012a[372]	Incorrect intervention/comparison – does not look at early versus delayed referral.
Paediatrics	
Akl 2008 [9]	All referrals not just AKI. Only looked at reason for referral.

I.6 Information and support for patients and carers

Reference	Reason for exclusion
Anon 2008[1]	Conference abstracts- no relevant abstracts
Anon 2009[2]	Conference abstracts- no relevant abstracts
Alexander 1998[12]	Doesn't answer the clinical question – patients preference of type of medical practitioner, based in USA not applicable to the UK
Buck 2007[64]	Doesn't answer the clinical question
Calvin 2004[66]	Doesn't answer the clinical question – qualitative study on decisions regarding end of life for patients on RRT, the process of decision making
Curtin 2002[104]	Doesn't answer the clinical question – looking at the symptoms of RRT patients and relation to QOL scores
Freeman 1991[143]	Doesn't answer the clinical question – investigating the decision making process of doctors to place a patient on RRT
Gopal 1997[160]	doesn't answer the clinical question & incorrect population
Guerin 2002[163]	Doesn't answer the clinical question- survey on doctors on the current practice of RRT in ARF
Hejaili 2009[174]	Doesn't answer the clinical question – abstract, questionnaire looking at QOL nothing on patient information and support
Holley 1993[183]	Doesn't answer the clinical question – survey on patients regarding their opinions on advance directive.
Holley 1997[184]	Doesn't answer the clinical question - survey assessing how patients use their nephrologists for their primary care needs
Hossli 1989[185]	Doesn't answer the clinical question – nurse perceptions
Maynard 2003[271]	Doesn't answer the clinical question – looking at QOL and relationship to clinical data at admission
Obolensky 2010[298]	Doesn't answer the clinical question – interviews with patients regarding the treatment escalation plan
Prasad 2004[329]	Doesn't answer the clinical question – survey on patients opinions on calcineurin inhibitors
Sharp 2005[364]	Doesn't answer the clinical question – RCP testing cognitive behavioural therapy and adherence to fluid resuscitation therapy
Swartz 2004[385]	Doesn't answer the clinical question – prospective review of patients with ARF requiring RRT and life support withdrawal

Reference	Reason for exclusion
Tong 2011[396]	Doesn't answer the clinical question – systematic review of the opinions of transplant patients and taking medicine
Tourtier 2010[397]	Doesn't answer the clinical question – interviews with patients regarding their opinions on advance directive.
Troidle 2006[400]	Doesn't answer the clinical question – survey on doctor opinions of chronic peritoneal dialysis therapy for end stage renal disease patients
Vasudevan 2012[414]	Doesn't answer the clinical question – survey on doctors choice of RRT
Williams 2009[424]	Study looking at the development of a patient education leaflet, abstract
Wolfsen 1989[427]	Doesn't answer the clinical question – systematic review on nurse perceptions
Yu 2010[434]	Indirect Chinese study differences in care given to AKI patients.
Ziroyannis 2006[441]	doesn't answer the clinical question- review on patient compliance

Appendix J: Excluded economic studies

Study title	Reason for exclusion
ASPELIN2005[22] - Cost-effectiveness of iodixanol in patients at high risk of contrast-induced nephropathy	Intervention does not match protocol
GUEST2000[164] - The cost associated with managing nephrotoxicity among vancomycin-treated patients in an intensive care unit	Costing study; Intervention does not match protocol
ERSTAD1999[129] - Pharmacoeconomic comparison of an albumin-furosemide complex versus sequential therapy for renal insufficiency	Intervention does not match protocol
GARBINO2006[150] - Invasive aspergillosis: is treatment with 'inexpensive' amphotericin B cost saving if 'expensive' voriconazole is only used on demand?	Intervention does not match protocol
HAMEL1997[169] - Outcomes and cost-effectiveness of initiating dialysis and continuing aggressive care in seriously ill hospitalized adults. SUPPORT Investigators. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments	Intervention does not match protocol
KLARENBACH2006[229] - Cost-effectiveness of hemofiltration to prevent contrast nephropathy in patients with chronic kidney disease	Intervention does not match protocol
KLARENBACH2009[228] - Economic evaluation of continuous renal replacement therapy in acute renal failure	Intervention does not match protocol
MCCULLOUGH2008[273] - Acute kidney injury with iodinated contrast.	Review article
QUANTIN1999[332] - Modelling of high-cost patient distribution within renal failure diagnosis related group	Not CEA/CUA
SANABRIA2006[354] - Decision-making analysis for selection of antibiotic treatment in intra-abdominal infection using preference measurements	Population does not match protocol
SMITH2011[376] - An economic evaluation of a laboratory monitoring program for Renin-Angiotensin system agents	Intervention does not match protocol
WINGARD2005[426] - Caspofungin versus amphotericin B for candidemia: a pharmacoeconomic analysis	Intervention does not match protocol
SUBRAMANIAN2007[380] - Economic burden of contrast-induced nephropathy: implications for prevention strategies	Not CEA/CUA

Appendix K: Cost-effectiveness analysis – Fluid regimens for the prevention of Contrast Induced Acute Kidney Injury

K.1 Introduction

The model presented here is designed to answer the clinical question: What is the clinical and cost effectiveness of intravenous (IV) fluids with or without N-Acetylcysteine (NAC) for the prevention of contrast induced acute kidney injury (CI-AKI)?

The area was prioritised for new economic evaluation because of the lack of economic evidence in the area and because it is an area of great uncertainty.

K.2 Methods

K.2.1 Model overview

K.2.1.1 Comparators

The interventions compared are types of fluid regimens used to prevent CI-AKI, with or without NAC. Patients are infused with fluids and can take NAC, before after or during a contrast scan. This is designed to prevent the nephrotoxic contrast agent from causing damage to the kidneys and inducing an acute kidney injury (AKI) episode. The mode of action varies between fluids and is not well understood. The comparators in the model are all commonly used strategies for prevention of CI-AKI for which effectiveness data were available. These were:

1. Sodium chloride 0.9%
2. Sodium chloride 0.45%
3. Oral fluids
4. Sodium bicarbonate
5. Sodium bicarbonate and sodium chloride 0.9%
6. Sodium chloride 0.9% and NAC
7. Sodium chloride 0.45% and NAC
8. Sodium bicarbonate and NAC

The data obtained from the clinical review allows all of these interventions to be compared against each other. Sodium chloride 0.9% strategy was chosen as the baseline intervention as the GDG felt that while there is much variation in current practice, this is the closest intervention to a “usual care” comparator.

K.2.1.2 Population

Contrast scans are done in a large variety of patients and for a variety of conditions. The overwhelming majority of evidence, however, in patients at medium to high risk (chronic kidney disease with or without diabetes) is in cardiac patients undergoing a cardiac angiography, catheterisation or primary coronary intervention. While there are differences between this

population and for example those undergoing a CT scan, the results are likely to be fairly equivalent and can therefore be extrapolated. The risk of CI-AKI in patients without a pre-existing renal condition or diabetes is very low. The base case patient was therefore considered to be a patient with stage 3–4 chronic kidney disease (CKD). Diabetes, the other major risk factor for CI-AKI was considered in a subgroup analysis, where all patients have diabetes, giving them an increased risk of CI-AKI. The sex distribution was considered to be 50% male. The studies analysed in the review had an average patient age of around 65–75, the base-case patient was therefore 70 and the risk of CI-AKI was applied over a lifetime. Because the probability of progressing from one CKD stage to another is dependent on age, the age that a person enters the model was also tested in a sensitivity analysis.

K.2.1.3 Time horizon, perspective, discount rates used

In keeping with the NICE reference case[294] a lifetime horizon is used. The perspective used is that of the National Health Service (NHS) and Personal Social Services (PSS). The discount rate used is 3.5% per year in the base case on both costs and outcomes. This is varied in a sensitivity analysis between 0-6% on both costs and outcomes.

K.2.2 Approach to modelling

The model is built in Windows Excel® and evaluates the use of different methods for the prevention of CI-AKI in patients with pre-existing CKD with or without diabetes, on the basis of costs and outcomes which are attached to health states relevant to the condition. The model is a cost–utility analysis, meaning that attached to the outcomes from the model are quality of life weights that have been elicited from patients and the general population using preference based measures. The treatments are evaluated over a lifetime with the probability of repeat scans built into the model.

K.2.2.1 Model structure

The model takes a Markov model structure with four health states:

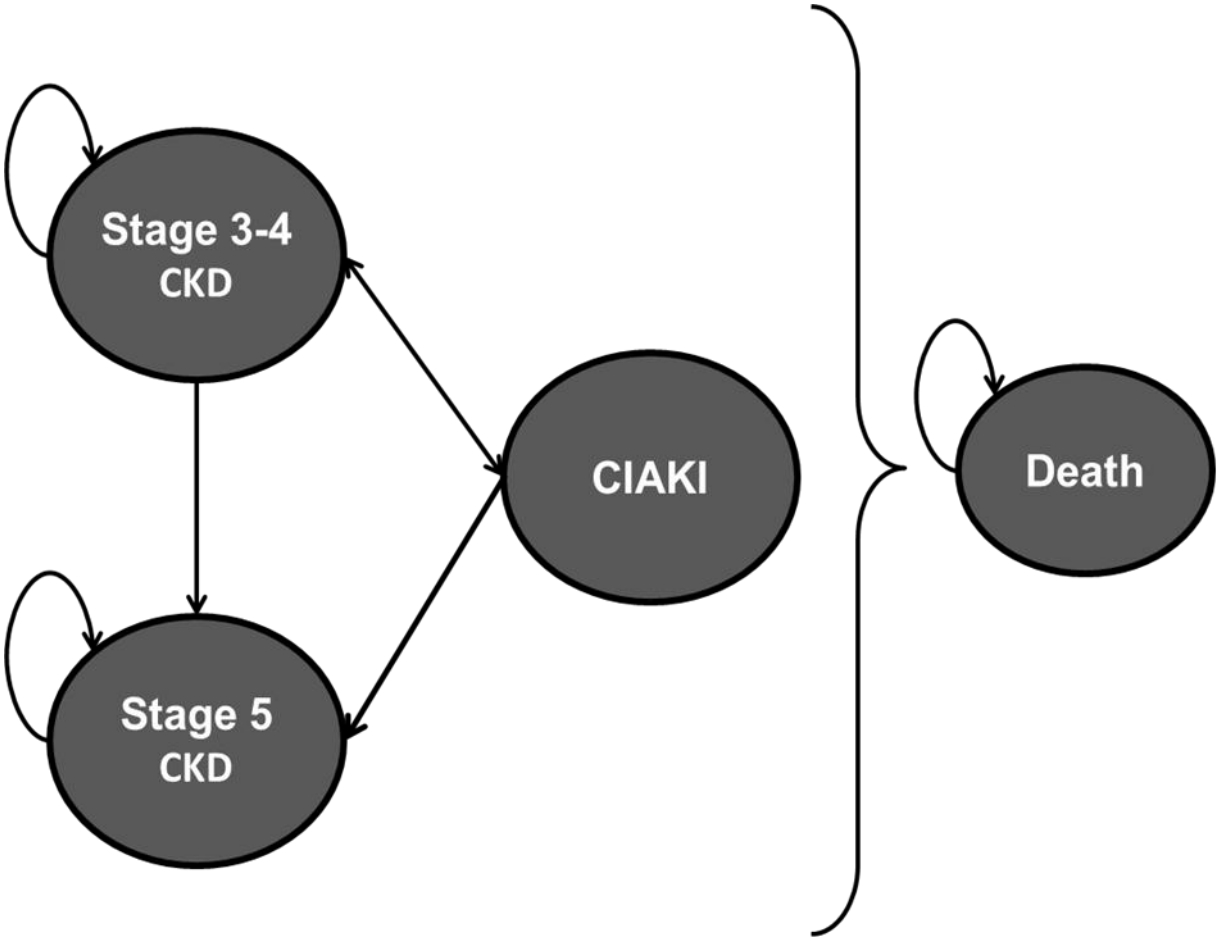
1. Stage 3–4 CKD (beginning state),
2. CI-AKI,
3. Stage 5 CKD and
4. Death (absorptive state).

A schematic of the model structure can be found in Figure 97, the ovals represent health states and the arrows represent the possible transition between them. The probability of moving between each state is taken from the clinical review and GDG recommended sources from the literature on CI-AKI and CKD. The cycle length for the model is 3 months, meaning that every 3 months patients have a probability of transitioning between health states. This cycle length is based on the classification of AKI and CKD as a patient can only be classified as AKI after 3 months. At the commencement of the model, a hypothetical cohort of patients is found in the 'stage 3–4 CKD' health state. Every one of these patients has a scan at the beginning of the model, which determines a probability of transitioning to the CI-AKI health state. Those patients that do not get CI-AKI will either remain in 'stage 3–4 CKD' or will transition to 'stage 5 CKD' as the natural progression of their CKD. Those patients that transition to CI-AKI will incur the costs and utility loss associated with CI-AKI for one cycle only. In the following cycle these patients will then either go back to 'stage 3–4 CKD' or will progress to 'stage 5 CKD' again incurring the costs and quality of life weight associated with these health states. After stage 1, there is also a continuous risk of transitioning from 'stage 3–4 CKD' to CI-

AKI. This is the risk of CI-AKI associated with repeat scans. Patients may receive more than one scan throughout their lifetime[361], this is captured in the model and the impact that it has will be tested in a sensitivity analysis. Once in 'stage 5 CKD', patients cannot return to either 'stage 3–4 CKD', which is in keeping with natural progression in the chronic disease pathway, nor can they return to CI-AKI. Patients in 'stage 5 CKD' can experience episodes of AKI; however, this is not included in the model. This is for two reasons: firstly the majority of patients in 'stage 5 CKD' would be receiving renal replacement therapy (RRT), so that the interventions compared would not be necessary to prevent CI-AKI as the RRT would perform this protective function; secondly, the data on the relative effectiveness between treatments in the small number of patients not receiving RRT is not available from the clinical review.

At any point in the model the patients can progress to the death state. The mortality data is taken from standard UK sources and is discussed later.

Figure 97: Model Structure showing health states and potential transitions



Note: This table shows the health states in the model and the transitions between them. The straight arrows denote direction of travel between health states and the circular arrows represents the probability of remaining within the health state. At any point during the model, a patient may transition to the death state; this is indicated by the curly bracket.

K.2.2.2 Uncertainty

The model is built probabilistically to take account of the uncertainty around parameter point estimates. In a probabilistic sensitivity analysis (PSA), each parameter is assigned a distribution reflecting its uncertainty; random draws are then taken from each distribution to calculate expected costs and quality-adjusted life years (QALYs). This process is repeated 1000 times and a model result, which represents an average of the simulations, is computed.

In order to conduct a PSA, a probability distribution is defined for each model input so that when the model is run, a value for each input gets randomly selected from its respective probability distribution simultaneously. Statistical distributions were selected based on the nature of the data, so for example probabilities were given a beta distribution, which is bounded by zero and one (Table 99). The number of simulations used (1000) was chosen considering the Monte Carlo error of the incremental costs, QALYs and net monetary benefit using the methods as described by Koehler et al. 2009.[234] It is set to ensure that the Monte Carlo error is not more than 5% of the standard error for these parameters.

Table 99 - Types of distributions used in the model

Parameter	Type of distribution	Properties of distribution	Parameters for the distribution
Proportion and probabilities	Beta	Bounded on 0 – 1 interval. Derived from sample size, number of patients experiencing events.	α = events β = sample size – α
Cost	Gamma	Bounded at 0. Derived from mean and standard error.	α = (mean/SEM)2 λ = mean/SEM2
Number of resources used	Triangular	Derived from expert opinion or reported in data source.	Min = minimum value Likeliest = mean Max = maximum value
Utility values	Normal	Derived from mean and SE.	Mean SE
Relative risk (RR)	Lognormal	Bounded at 0. Derived from log (mean) and standard error.	μ = ln(RR) SD(μ) = (ln[UpperCI] – ln[lowerCI])/1.96*2

All of the types of variables that were probabilistic in the model and their distributional parameters are detailed in Table 100. Some parameters (discount rate and cost-effectiveness threshold) are subject to non-sampling uncertainty as they are prescribed by the NICE reference case of methods. The best approach to handle such non-sampling uncertainty is via univariate analyses rather than PSA.

Univariate, deterministic (one-way) sensitivity analyses were undertaken to test the robustness of model assumptions and data sources. In these, one or more inputs are changed and the analysis is rerun to see the impact on results. This was done using the deterministic (non-probabilistic) data.

K.2.3 Model inputs

K.2.3.1 Summary table of model inputs

Model inputs were based on clinical evidence identified in the systematic review undertaken for the guideline, supplemented by additional data sources as required. Model inputs were validated with clinical members of the GDG. A summary of the model inputs used in the base-case (primary) analysis is provided in Table 100 below. More details about sources, calculations and rationale for selection can be found in the sections following this summary table.

Table 100: Summary of base-case model inputs

Input	Point estimate	Probability distribution	Distribution parameters	Source
Transition probabilities – per cycle				
Stage3-4 CKD to CI-AKI in cycle 1 only	2.17%	Beta	α = 14.89, β = 670	Mueller2002[292]
Repeat scan	2.84%	Beta	α = 102, β = 789	Serruys2009[361]
CI-AKI risk	0.87%	CI-AKI * repeat scan		
Proportion of patients in stage 1 CI-AKI	83%			James2010[199]
Proportion of patients in stage 2–3 CI-AKI	17%			James2010[199]
CI-AKI stage1 to stage 5 CKD (83%)	1.5%	Beta	α = 24.8, β = 1585	James2010[199]
CI-AKI stage2 and 3 to stage 5 CKD (17%)	10.9%	Beta	α = 36.8, β = 302	James2010[199]
CI-AKI to stage 5 CKD	3.28%	Pooled average stages 1,2 and 3 CI-AKI to stage 5 CKD		
CKD Stage 3–4 to CKD Stage 5 (<69 years)	0.018%	Beta	α = 5.5 β = 3042	Eriksen 2006[127]
CKD Stage 3–4 to CKD Stage 5 (70–79 years)	0.10%	Beta	α = 3.1 β = 3044	Eriksen 2006[127]
CKD Stage 3–4 to CKD Stage 5 (>79 years)	0.08%	Beta	α =2.3 β = 3045	Eriksen 2006[127]
Remaining in CKD stage 3–4 cycle 1 only	97.64%	100% - (risk of CI-AKI + risk of stage 5)		
Remaining in CKD stage 3–4	99.75%	100% - (risk of CI-AKI + risk of stage 5)		
Returning to stage 3–4 after CI-AKI	96.84%	100% – (risk of stage 5 from CI AKI)		
Remaining in stage 5 CKD	100%			
Mortality – per cycle				
CI-AKI stage 1 to Death (83%)	13.6%	Beta	α =220, β = 1405	James2010[199]
CI-AKI stage 2 and 3 to Death (17%)	37.8%	Beta	α =144, β = 237	James2010[199]
CI-AKI to Death	18.2%	Pooled average stages 1,2 and 3		

Input	Point estimate	Probability distribution	Distribution parameters	Source
		CI-AKI to Death		
CKD Stage 3–4 (<69 years) SMR*	M: 3.6 F: 2.7	Standardised mortality ratio (SMR) multiplied by the age dependant standardised UK mortality		Eriksen 2006[127]
CKD Stage 3–4 (70-79 years) SMR	M: 2.4 F: 1.8			Eriksen 2006[127]
CKD Stage 3–4 (>79) SMR	M: 2.3 F: 2.1			Eriksen 2006[127]
Stage 5 to death	7.2	Multiplied by the age dependant standardised UK mortality		Villar 2007[417]
Relative treatment effects				
Sodium chloride 0.45%	2.78	Lognormal	SE: 0.30	Clinical Review
Oral fluids	0.69	Lognormal	SE: 0.89	Clinical Review
Sodium bicarbonate	0.78	Lognormal	SE: 0.22	Clinical Review
Sodium bicarbonate + Sodium chloride 0.9%	0.20	Lognormal	SE: 0.79	Clinical Review
NAC + Sodium chloride 0.9%	0.80	Lognormal	SE: 0.15	Clinical Review
NAC + Sodium chloride 0.45%	1.72	Lognormal	SE: 0.37	Clinical Review
NAC + Sodium bicarbonate	1.03	Lognormal	SE: 0.56	Clinical Review
Utilities – per cycle				
Stage 3–4	0.168	Normal	0.027	Tajima 2010[387] and Kind 1998[224]
Stage 5 CKD	0.156	Normal	0.021	Tajima 2010[387] and Kind 1998[224]
CI-AKI	0.131	Normal	0.033	Sullivan 2011[382]
Costs – per scan/cycle				
Sodium chloride 0.9% iv (1000ml Bag)	£0.70	Gamma	$\alpha = 4; \beta = 0.315$	Personal communication from the Commercial Medicines Unit UK
Sodium chloride 0.45% iv (500ml bag)	£0.90	Gamma	$\alpha = 4; \beta = 0.225$	
Sodium bicarbonate 1.26% iv (1000ml bag)	£7.71	Gamma	$\alpha = 4; \beta = 0.490$	Fresenius Kabi - 2011 price list for the NHS[144]
Acetylcysteine – Oral (600 mg pill)	£1.30	Gamma	$\alpha = 4; \beta = 0.256$	Prescription Cost Analysis 2012[172]
CKD stage 3–4	£176	Combined costs – see section K.2.3.6		
CKD Stage 5 Cycle 1	£6,585			
CKD Stage 5 Cycle 2 onwards	£5,512			
AKI	£2,013			

SMR = Standardised Mortality Ratio

K.2.3.2 Initial cohort settings

The base case cohort is stage 3–4 CKD outpatients that are 50% male. The base case patient is aged 70 with no diabetes.

K.2.3.3 Baseline events

The baseline treatment that the others were compared to was the sodium chloride 0.9% strategy.

Probability of progressing from stage 3–4 CKD to CI-AKI

One study from the meta-analysis, Mueller 2002,[292] that gave the baseline probability of progressing to CI-AKI from stage 3–4 CKD was selected for this purpose. The study was selected on the basis that it was the largest study in the meta-analysis (n=1,383) and that it had a low risk of bias and no serious imprecision. This study showed that out of the 685 patients randomised to the sodium chloride 0.9% arm, 5 patients (0.7%) had CI-AKI. This incidence is however quite low when compared against other literature in the area.[107,276] This low event rate is in part due to the fact that only 20% of patients had CKD and the average estimated glomerular filtration rate (eGFR) was quite high. The study however also broke down the patients in the trial into patients with and without renal insufficiency. In patients with renal insufficiency the incidence of CKD was higher: 2.2% (3/138) of patients receiving sodium chloride 0.9%. While this estimate is based on a much smaller number of patients, it gives a more accurate reflection of the patient population and was used in the base case. This point estimate is still very low, considering other literature that indicates the probability of CI-AKI associated with CKD as much higher. Univariate sensitivity analysis will be carried out to explore the uncertainty around this input and details are discussed in the section on sensitivity analysis (K.2.4). The rates of CI-AKI that will be applied in the model can be found in Table 104.

Probability of progressing from CKD stage 3–4 to CKD stage 5

The baseline transition probability associated with the progression of CKD stage 3–4 to stage 5 CKD is taken from a ten year cumulative incidence rate in a cohort study of 3,047 patients by Eriksen et al. 2006.[127] This study gave the rate of progression of patients with an average eGFR of 55.1. While this eGFR was high for stage 4 patients, it was used in this population as the data was not forthcoming for patients in stage 4. The study provided the rate of progression for three age periods: <69, 70–79, >80 years old. It was therefore possible to define the 3-month probability of progressing from stage 3–4 to stage 5 as an age dependant variable (Table 101) using the formula:

I (–LN(1-10 year rate))/40

This will give the 3 month rate then it has to be converted to the probability by exponentiating the rate:

II 1-EXP(rate)*1

In order to incorporate this age dependant variable, each transition matrix is repeated 3 times for each age category.

Table 101: Age dependant disease specific progression from Stage 3–4 to stage 5 CKD

Age category	10 year cumulative incidence (a)	3 month probability (See calculation in text)	Distribution type	Distributional parameters (a)
<69	0.07	0.0018	Beta	α = 5.5 β = 3041.5
70–79	0.04	0.0010	Beta	α = 3.1 β = 3043.9
>79	0.03	0.0008	Beta	α =2.3 β = 3044.7

(a) Source: Eriksen et al. 2005

Mortality

The mortality associated with CKD stage 3–4 is also taken from the study by Eriksen et al. 2006.[127] The study provides an age and sex-dependent standardised mortality ratio (SMR) that can be found in Table 102. SMRs were then multiplied by the age dependant mortality from the life tables (standard UK mortality rates by age) provided by the Office of National Statistics.[300] Mortality is applied at each cycle prior to the transition probabilities for the other health states.

Table 102: Age dependent standardised mortality ratios in stage 3–4 CKD for men and women by age from Eriksen et al. 2006[127]

Age category	Men (SMR)	Women (SMR)
<69	3.6	2.7
70–79	2.4	1.8
>79	2.3	2.1

Death from stage 5 CKD was taken from Villar et al. 2007[417]; this also gave an age dependant SMR that can be found in Table 103.

Table 103: Age dependant SMR for Stage 5 CKD

Age Category	Men (SMR)	Women (SMR)
18-64	8.88	13.86
>65	4.88	7.96

The mortality from CI-AKI is taken from the study by James et al. 2010.[199] This study is a large retrospective cohort of 14,782 adults undergoing coronary angiography; of these, 1,420 patients had CI-AKI. In this study CI-AKI was divided into stages 1, 2 and 3 to denote severity, with 83% (n=1,610) of patients having the less severe form of CI-AKI, stage 1, and 17% (n=339) having either stage 2 or 3 CI-AKI. These categories gave the probability of death following CI-AKI as 13.6% for stage 1 and 37.8% for stage 2 and 3. The probabilities of death in each of these stages of CI-AKI were therefore weighted by the number of people in that stage and then the mortality was pooled to give 18.2% per patient with CI-AKI.

Probability of stage 5 CKD in patients with CI-AKI

The transition probability for the risk of stage 5 CKD following CI-AKI is taken from the study by James et al. 2010.[199] The study divided up the rate of stage 5 CKD following CI-AKI into stage 1 AKI (1.55 per 100 person years) and stage 2–3 AKI (11.5 per 100 person years), when these were pooled according

to percentage of patients in each, 83% and 17% respectively, and converted to probabilities. They gave a probability of going to stage 5 CKD of 3.3% per patient undergoing a scan (Table 104). The probability of remaining in stage 3–4 CKD is simply the residual from the combined probability of progression to CI-AKI and stage 5 CKD. Once the individual is in stage 5 CKD, the probability of remaining in this state is 100% after death has been removed from the equation, i.e. no other transition other than death is possible.

Probability of a repeat scan

The probability of a repeat percutaneous coronary intervention (PCI) was given in a trial of 1,800 patients with coronary artery disease by Serruys et al. 2009[361] over 5 years. Repeat PCI was used in the model as a surrogate for repeat scans. The trial gave the probability of requiring a repeat PCI of 11.4% per year. This probability can then be divided by the cycle length to give the probability per cycle (3%); the probability of repeat scan per cycle is then multiplied by the probability of CI-AKI to give the risk per cycle of CI-AKI (0.07% in the base case). The population of this study is not specific to CKD but is indicative of the probability of repeat scans. Due to the uncertainty over this parameter it will be tested in a sensitivity analysis.

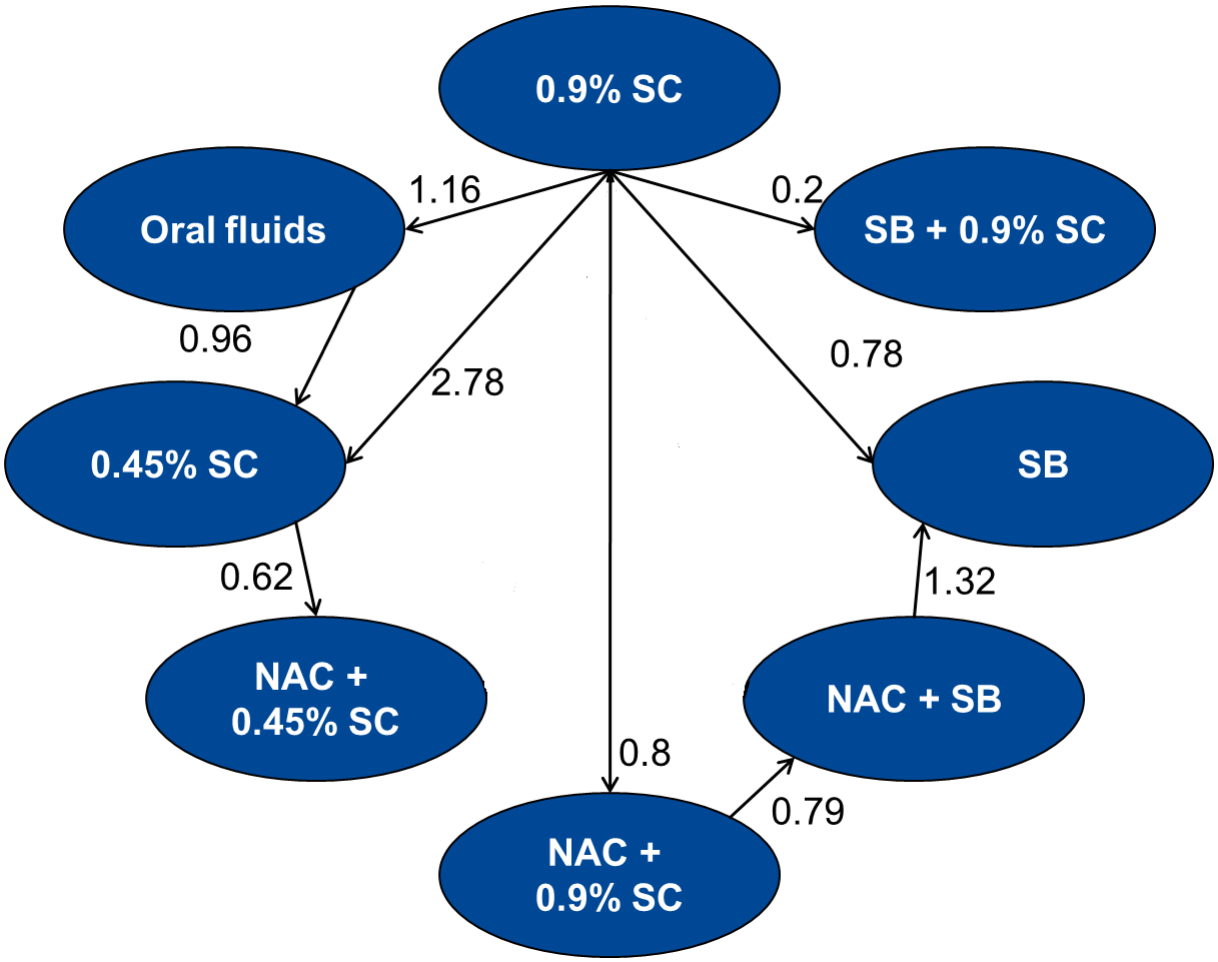
Table 104: Baseline Events

Baseline Risk /per cycle	Point estimate	Probability distribution	Distribution parameters	Source
Stage3–4 CKD to CI-AKI	2.17%	Beta	α = 14.89, β = 670	Mueller2002[292]
Repeat scan	3%	Beta	α = 102, β = 789	Serruys2009[361]
CI-AKI risk	0.07%	Stage 3–4 CKD to CI-AKI * repeat scan		
Proportion of patients in stage 1 CI-AKI	83%			James2010[199]
Proportion of patients in stage 2–3 CI-AKI	17%			James2010[199]
CI-AKI stage1 to stage 5 CKD	1.5%	Beta	α = 24.8, β = 1585	James2010[199]
CI-AKI stage2 and 3 to stage 5 CKD	10.9%	Beta	α = 36.8, β = 302	James2010[199]
CI-AKI to stage 5 CKD	3.1%	CI-AKI stage 1 to stage 5 CKD * % stage 1 + CI-AKI stage 2-3 to stage 5 CKD * % stage 2–3		
CKD stage 3–4 to CKD stage 5 (mean–age dependant)	0.1%	Beta	α = 3.1, β = 3044	Eriksen2006[127]
Remaining in CKD stage 3–4 cycle 1 only	97.64%	100% – (Risk of CI-AKI + risk of stage 5)		
Remaining in CKD stage 3–4	99.75%	100% – (Risk of CI-AKI + risk of stage 5)		
Returning to stage 3–4 after CI-AKI	96.84%	100% – (Risk of stage 5 from CI-AKI)		
Remaining in stage 5 CKD	100%	100%		
CI-AKI stage 1 to Death (83%)	13.6%	Beta	α =220, β = 1405	James2010[199]
CI-AKI stage 2 and 3 to Death (17%)	37.8%	Beta	α =144, β = 237	James2010[199]
CI-AKI to Death	18.2%	CI-AKI stage 1 to Death * % stage 1 + CI-AKI stage 2–3 to Death * % stage 2-3		

K.2.3.4 Relative treatment effects

The clinical review was used to compare the effectiveness of the various interventions. The clinical review compared the various strategies that can be found in the section on comparators (K.2.1.1). The review was made up of head to head trials between the various strategies which were used to generate a network of direct comparisons. A diagram of this can be found in Figure 98, the numbers represent the relative risks compared with the other comparators with the arrow denoting the direction of the comparison that the relative risk is for.

Figure 98: Comparisons of relative treatment effects available from meta-analysis of trials – direct comparisons



Source/Note: *SC = Sodium chloride; NAC = N-Acetylcysteine; SB = Sodium bicarbonate. Direction of the relative risk comparison given by the arrow, number represents the relative risk.*

From this diagram it is possible to note that there are closed loops which could potentially allow us to conduct a network meta-analysis. However, the evidence presented too much inconsistency to do this and a network meta-analysis would not be a solution this issue. Quite the opposite, a network meta-analysis would be meaningless if based on unreliable evidence. In the section below we have

explained why the GDG considered the evidence on oral fluids vs. sodium chloride 0.9% and the evidence on NAC plus sodium chloride 0.9% vs. NAC plus sodium bicarbonate to be unreliable. As it can be seen in Figure 98, once this two comparisons are removed from the diagram there are no closed loops and a network meta-analysis cannot be conducted.

Since we planned to estimate the relative risk of each treatment compared with sodium chloride 0.9%, we had to estimate the relative risk (RR) of NAC plus sodium bicarbonate and NAC plus sodium chloride 0.45% compared to sodium chloride 0.9% using indirect evidence. For each intervention (A) this was calculated by using the following formula:

III RR (A vs. B) = RR (A vs. C) * RR (C vs. B)

Where:

- A is the intervention for which the RR compared to sodium chloride 0.9% is unknown
- B is sodium chloride 0.9%
- C is an intervention for which we have both its RR compared to intervention A and compared to sodium chloride 0.9%.

The standard error (SE) which gives the uncertainty around the estimated RR is calculated using the following equations:

IV SE(C vs. A) = √(〖SE(B vs. A)〗^2)+√(〖SE(C vs. B)〗^2)

Where:

- SE(B vs. A) is the SE of the relative risk of B vs. A
- SE(C vs. B) is the SE of the relative risk of C vs. B

This process was conducted for three interventions in the model:

- NAC plus sodium bicarbonate (where the intermediate strategy was sodium bicarbonate)
- NAC plus sodium chloride 0.45% (where the intermediate strategy was sodium chloride 0.45%)
- oral fluids (where the intermediate strategy was sodium chloride 0.45%).

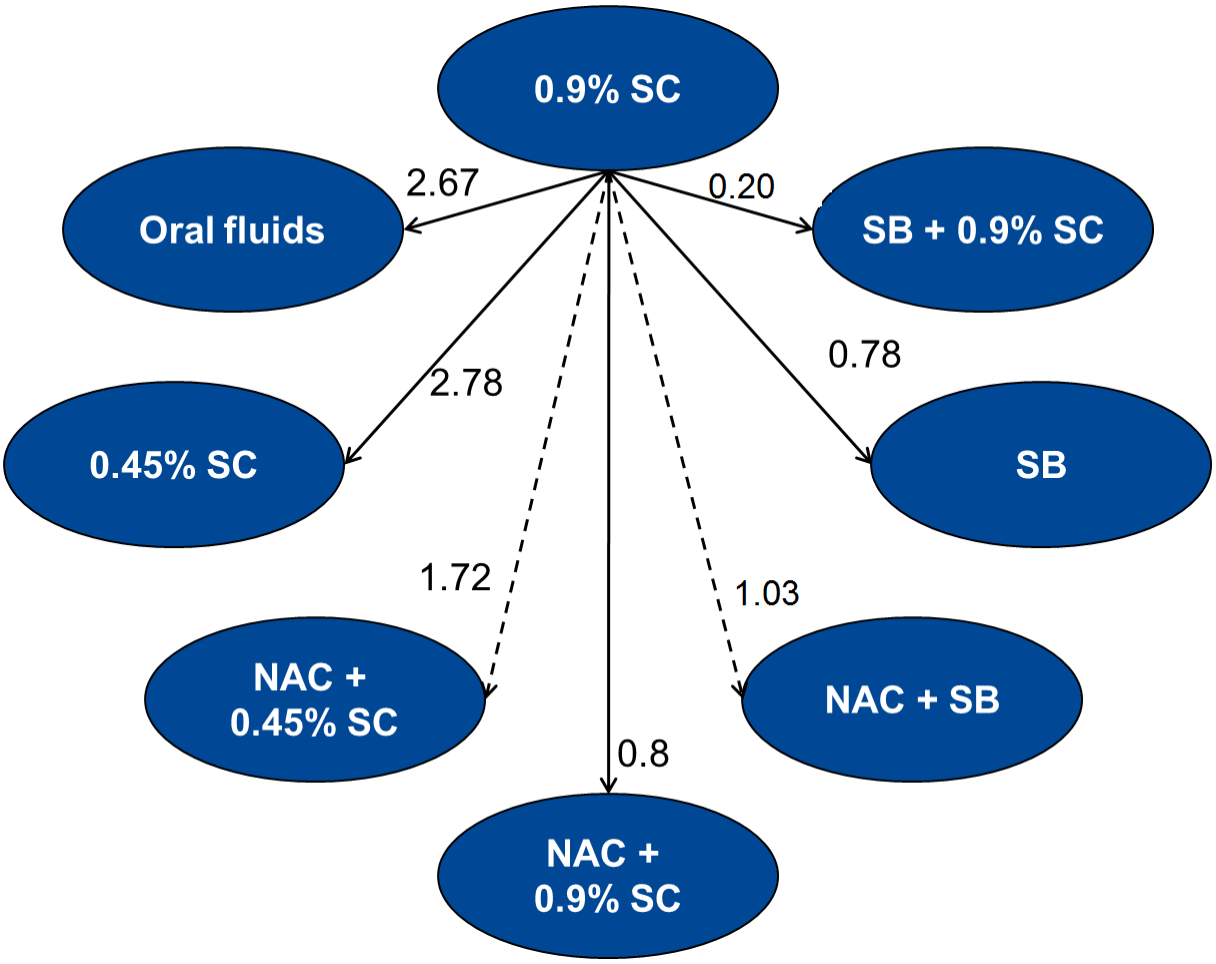
While a direct comparison of oral fluids vs. sodium chloride 0.9% is available, the GDG decided they had more confidence in the indirect comparison data than in the direct comparison data. The direct comparison shows oral fluids as better than sodium chloride 0.9% whereas the indirect route shows oral fluids as the worst comparator in terms of effectiveness. The second scenario was judged by the GDG to be more realistic. The GDG felt that oral fluids, particularly the oral fluids provided in the study (i.e. no rehydration therapy), was unlikely to be more effective than IV infused sodium chloride 0.9%. In addition, the one study used to inform the direct comparison of sodium chloride 0.9% with oral fluids has major flaws in its design. The study by Wrobel et al. 2009[429,429] is of very low quality (no blinding and unclear allocation concealment), and was conducted in a small number of patients, in an inappropriate population (no CKD) and had very low event rates. Therefore an indirect comparison was made to give the relative risk of oral fluids compared with sodium chloride 0.9%. A sensitivity analysis was carried out using the direct comparison of oral fluids with sodium chloride 0.9%.

The RR of NAC plus sodium bicarbonate vs. sodium chloride 0.9% could have been estimated using two different routes: one that used the NAC plus sodium chloride 0.9% as intermediate, and one that

used sodium bicarbonate as intermediate. We considered using both sets of data by conducting a network meta-analysis but due to the inconsistency of data we excluded this option. The GDG decided that sodium bicarbonate vs. NAC plus sodium bicarbonate was the most meaningful comparison and that the effectiveness of the addition of NAC to sodium bicarbonate should be estimated by comparing this strategy (NAC plus sodium bicarbonate) with the same fluid without the addition of NAC (sodium bicarbonate). If we had to use the data on NAC plus sodium chloride 0.9%, the difference in effectiveness could be due more to the type of fluid than to the addition of NAC, which instead is the main focus of the question. Furthermore, the evidence on the comparison NAC plus sodium bicarbonate vs. NAC plus sodium chloride 0.9% was judged of worse quality than the evidence on the comparison NAC plus sodium bicarbonate vs. sodium bicarbonate. Therefore, the study by Hafiz et al. 2012[167] was selected over the meta-analysis based on the studies by Briguori et al. 2007, Hafiz et al. 2012, Maioli et al. 2008 and Lee et al. 2011.[61,167,242,258]

The relative risks calculated through direct and indirect comparisons can be found in Figure 99 and Table 105.

Figure 99: Comparisons of relative treatment effects available from meta-analysis of trials – all interventions compared through sodium chloride 0.9% allowing indirect comparison of all interventions.



SC = Sodium chloride; NAC = N-Acetylcysteine; SB = Sodium bicarbonate. Direction of the relative risk comparison given by the arrow, numbers represent the relative risks.

These relative risks are applied to the baseline risk of CI-AKI to either increase or decrease this risk compared to sodium chloride 0.9%.

Table 105: Relative treatment effects summary

Comparator	Relative Risk vs. sodium chloride 0.9%	Standard Error	Probability distribution
Sodium chloride 0.45%	2.78	0.30	Lognormal
Oral fluids	2.89 (a)	0.89	Lognormal
Sodium bicarbonate	0.78	0.22	Lognormal
Sodium bicarbonate + Sodium chloride 0.9%	0.20	0.79	Lognormal
NAC + Sodium chloride 0.9%	0.80	0.15	Lognormal
NAC + Sodium chloride 0.45%	1.72 (b)	0.37	Lognormal
NAC + Sodium bicarbonate	1.03 (c)	0.56	Lognormal

(a) Obtained using the relative risk of oral fluids vs. sodium chloride 0.45% (0.62) and the relative risk of sodium chloride 0.45% vs. sodium chloride 0.9% (2.78) in equation III.
(b) Obtained using the relative risk of NAC + sodium chloride 0.45% vs. sodium chloride 0.45% (1.042) and the relative risk of sodium chloride 0.45% vs. sodium chloride 0.9% (2.78) in equation III.
(c) Obtained using the relative risk of NAC + sodium bicarbonate vs. sodium bicarbonate (1.32) and the relative risk of sodium bicarbonate vs. sodium chloride 0.9% (0.78) in equation III.

K.2.3.5 Utilities

A systematic review of the quality of life literature in CKD and AKI revealed several sources from which utilities could be obtained. The utilities are measures by which it is possible to weight a time period by the quality of life during that period. The utility for CI-AKI could be taken from Sullivan et al. 2011[382] who provide a catalogue of UK EQ-5D based utilities, including "renal failure" (kidney injury) with a utility of 0.525 (n=194). The utilities for CKD stages 3–4 and stage 5 were identified in a Japanese study by Tajima et al. 2010.[387] This study was chosen as it is the largest (n=569) EQ-5D based study. In order to make the utilities more relevant to a UK population, they were all multiplied by the UK population utility average for people aged 65–75 (0.780).[224] The utility of each stage of CKD (U_stage) were obtained using the data from the Japanese study (weight_stage) and the general utility of the UK population (genUtility):

U_stage = weight_stage * genUtility

So for example for stage 5 the utility was: U_stage5 =0.798 * 0.780 = 0.622

The Stage 3–4 CKD utilities, on the other hand, had to be combined. This was done by taking the two utilities, stage 3 (0.883) and stage 4 (0.839) and multiplying them by the UK population average utility, then averaging them:

0.883*0.780=0.689

0.839*0.780=0.654

((0.689+0.654))/2=0.672

The standard error was calculated by combining the square roots of the standard errors from both utilities:

√(〖SE(0.013)〗^2)+√(〖SE(0.023)〗^2)=0.027

Quality of life weights attached to the three health states included in the model can be found in Table 106. However, due to the Japanese data set being used, rather than a UK data set, a sensitivity analysis will be done to examine the impact that quality of life would have on the cost effectiveness of different strategies.

Table 106: Utilities

Health state	Utility per year	Standard Error	Utility per cycle	Probability distribution	Source
UK population average (Age 65–75)	0.780			Normal	Kind 1998[224]
Stage 3–4 CKD Tajima2010	0.861	0.027		Normal	Tajima 2010[387]
Stage 3-4 CKD (UK average * stage 3–4 Tajima 2010)	0.672	0.027	0.168	Normal	Tajima 2010[387] and Kind 1998[224]
Stage 5 CKD Tajima 2010	0.798	0.021		Normal	Tajima 2010[387]
Stage 5 CKD (UK average * stage 5 Tajima 2010)	0.622	0.021	0.156	Normal	Tajima 2010[387] and Kind 1998[224]
CI-AKI	0.525	0.033	0.131	Normal	Sullivan 2011[382]

K.2.3.6 Resource use and cost

The resource use and costs can be divided up into two categories, firstly the cost of the fluid strategy for prevention of CI-AKI and secondly the cost of each health state. An assumption was made that applied across all costs categories, that is, if a cost did not have an error estimate, it was assumed that it had a standard error of 50% the mean, in order to make the cost probabilistic.

Fluid Strategy resource use and costs

A list price for larger quantities (500ml, 1l) of sodium chloride is not available from sources such as the NHS drug tariff or the British National Formulary (BNF). The cost was therefore provided by the Commercial Medicines Unit of the UK Department of Health. The cost of sodium bicarbonate was taken from the manufacturer's list price (Freseius Kabi - 2011 price list for the NHS[144]). However, this price is likely to be higher than what most trusts would be likely to pay for them due to price negotiations. A list of the unit costs can be found in Table 107. All of these costs were taken from list prices; however different hospitals and trusts will negotiate prices from manufacturers for individual products so the list price offers no measure of this variability in practice.

Table 107: Unit costs of fluids

Fluid	ml or mg per unit	Cost per unit	SE cost (50% mean cost)	Gamma distribution parameters	Source
Sodium chloride 0.9% iv	1000ml	£0.70	0.350	α = 4; β = 0.175	Personal communication from the Commercial Medicines Unit UK
Sodium chloride 0.9% iv	500ml	£0.63	0.315	α = 4; β = 0.158	
Sodium chloride 0.45% iv	500ml	£0.90	0.450	α = 4; β = 0.225	
Sodium bicarbonate 1.26% iv	500ml	£7.71	3.855	α = 4; β = 0.490	Freseius Kabi - 2011 price list for the NHS[144]
Acetylcysteine – oral tablets	600mg	£1.30	0.650	α = 4; β = 0.256	Prescription Cost Analysis 2012[172]

The fluid regimens and the dose of NAC are based on the actual strategies used in the RCTs or on the current practice in the UK and costs are attached to the resources associated with each strategy (Table 108). The strategies in the trials differed in length; some involved only day cases while in others a night in hospital was required. Sodium chloride 0.9% and sodium bicarbonate can be delivered within 8 hours and therefore may not require admission. Strategies which involve the use of sodium chloride 0.45% or a combination of sodium bicarbonate and sodium chloride 0.9% require a longer time of administration and therefore the cost of an excess bed day is added to those strategies in the base case. The cost of a bed day used was £266 which is the cost of an excess bed day for coronary angiography.[109] We changed the assumptions on resource use in a sensitivity analysis, where sodium bicarbonate and sodium chloride 0.9% regimes were assumed to require 2 litres of fluid over 18 hours and therefore require admission (see K.2.4 for more details).

Table 108: Fluid infusion strategy costs

Strategy	Fluid/NAC cost [(a)]	Additional cost of one night admission to hospital [(b)]	Total cost of fluid regime
Sodium chloride 0.9% - 1 litre over 8 hours (no admission)	£0.70	-	£0.70
Sodium chloride 0.45% - 2 litres over 24 hours (requires admission)	£3.60	£266	£270
Oral fluids (glass of water)	£0.00	-	£0.00
Sodium bicarbonate – 1 litre over 8 hours (no admission)	£15.42	-	£15.42
Sodium bicarbonate + sodium chloride 0.9% - 1 litre of sodium bicarbonate over 9 hours + 1.5 litres of sodium chloride over 15 hours (requires admission)	£16.75	£266	£283
NAC + sodium chloride 0.9% - 2.4 g of NAC and 1 litre over 8 hours (no admission)	£5.91	-	£5.91

Strategy	Fluid/NAC cost [(a)]	Additional cost of one night admission to hospital [(b)]	Total cost of fluid regime
NAC + sodium chloride 0.45% - 2.4 g of NAC and 2 litres over 24 hours (requires admission)	£8.81	£266	£275
NAC + Sodium bicarbonate - 2.4 g of NAC and 1 litre over 8 hours (no admission)	£20.63	-	£20.63

(a) See Table 107
(b) Source: NHS Reference Costs [109]

Costs of health states

The health states could for the most part be costed using relevant national data sources: NHS reference costs 2010/12, unit cost of health and social care 2012 produced by the Personal Social Services Research Unit (PSSRU 2012)[105], the BNF 62[204] and other NICE guidance. However in order to establish resource use, it was often necessary to turn to the GDG to make assumptions on the basis of expert opinion.

CKD stage 3–4

If a patient remains in stage 3–4 CKD they incur the cost of 3 monthly consultations with a nephrologist (GDG assumption), and this would include an eGFR measurement. The cost of an eGFR measurement was considered to be the cost of lab resources combined with the cost of 5 minutes of phlebotomist time. The other costs would include 9% of patients requiring Epoetin for the treatment of anaemia.[295] The dose (1,788 units per week) of Epoetin alpha was taken from CG114[295] but the cost was updated using the BNF 62[204]. The calculations can be found in Table 109. This came to a cost of £11 per cycle. In order to consider the proportion of patients requiring diuretics, the GDG assumed that 26% patients were in stage 4 and of these patients around 60% would be on 40mg of Furosemide per day. This gave a cost of £4 per cycle. The cost of drugs for stage 3–4 can be found in Table 109. The cost of stage 3–4 CKD is £176 in total.

Table 109: Cost of stage 3–4 CKD

Cost of care					
Unit	**Unit Cost**	**Resource use percycle**	**Cost per cycle**	**Parameter distribution**	**Source**
Nephrologist appointment	£157	1	£157	(Gamma distribution: α = 7; β = 24)	NHS reference costs 2010/11 [110]
Biochemistry	£1.26	1	1.26	(Gamma distribution: α = 7.62; β = 0.16)	NHS reference costs 2010/11[110]
Phlebotomist time	£3.42	5 min	3.42	Fixed salary cost	PSSRU 2012[105]
eGFR measurement	£4.67	Phlebotomist cost + biochemistry cost			
Drug costs					

Drug	Dose	Frequency	% of patients	BNF cost per dose	Cost per cycle	Distribution & parameters (SE=50%)	Source
Diuretics Stage 4	40mg	1 per day	60%	£0.26	£4	Gamma (SE=50%): $\alpha = 4$; $\beta = 9.51$	BNF 62[204] and GDG assumption
Epoetin α Stage 3–4	1,788 units	Per week	9%	£9.1	£11	Normal: SE for dose: 37	BNF 62[204] and CG114[295]

Stage 5 CKD

In addition to the drug costs outlined in Table 109, patients that enter stage 5 CKD will incur costs associated with either RRT or conservative management (CM), defined as management of stage 5 CKD without RRT. They will also incur costs such as RRT access procedures, anaemia management, specialist appointments, eGFR measurements and diuretics. The costs for stage 5 CKD were calculated differently for cycle 1 and for cycle 2 onwards.

In cycle 1, patients are initiating treatment and therefore will be receiving care with increased intensity than later on. For this cycle, the GDG made an assumption that 90% of patients will be receiving RRT and 10% will be on CM. This was tested in a sensitivity analysis in order to examine the effect of this assumption. To estimate the cost of RRT, a pooled average was taken from the NHS reference costs comparing national usage of different treatment modalities with the costs per session of each modality. The modalities included are, haemodialysis or hemofiltration, either peritoneal or via fistula or graft, with or without a blood borne virus; these costs can be found in Table 110.

Table 110: RRT modality – NHS reference costs 2010/11

RRT Modality (LD01-12)	National usage Weight by modality	Unit cost	Weighted cost per session
Haemodialysis			
Hospital Haemodialysis/Filtration with access via haemodialysis catheter	23.2%	£167	£38.76
Hospital Haemodialysis/Filtration with access via arteriovenous fistula or graft	29.6%	£160	£47.34
Hospital Haemodialysis/Filtration with access via haemodialysis catheter with blood borne virus	0.7%	£130	£0.94
Hospital Haemodialysis/Filtration with access via arteriovenous fistula or graft with blood borne virus	2.0%	£82	£1.66
Satellite Haemodialysis/Filtration with access via haemodialysis catheter	17.5%	£182	£31.82
Satellite Haemodialysis/Filtration with access via arteriovenous fistula or graft	22.7%	£136	£31.03
Satellite Haemodialysis/Filtration with access via haemodialysis catheter with blood borne virus	0.2%	£481	£0.93
Satellite Haemodialysis/Filtration with access via arteriovenous fistula or graft with blood borne virus	0.3%	£236	£0.67
Home Haemodialysis/Filtration with access via	1.4%	£115	£1.56

haemodialysis catheter			
Home Haemodialysis/Filtration with access via arteriovenous fistula or graft	2.4%	£128	£3.05
Pooled average cost of haemodialysis per session			***£157.76***
Peritoneal dialysis			
Continuous Ambulatory Peritoneal Dialysis (CAPD)	43%	£51	£21.83
Automated Peritoneal Dialysis (API)	57%	£57	£32.87
Pooled average cost of peritoneal dialysis per day			***£54.70***
Frequency		**Source**	
Frequency of haemodialysis per week	3 days	Renal Registry[341]	
Frequency of peritoneal dialysis per week	7 days	Renal Registry[341]	
Proportion of patients receiving each strategy			
Haemodialysis	79%		
Peritoneal dialysis	21%		
	Cost per week (frequency * cost per day)	**Per 3-month cycle**	**Weighted cost per cycle (cost per cycle * proportion)**
Haemodialysis	£473	£5,676	£4,541
Peritoneal dialysis	£383	£4,596	£919
TOTAL COST OF RRT	***£5,460***		

In the first cycle, every patient undergoing RRT will receive a procedure that allows permanent access for RRT, known as access procedures, which varied depending on the type of dialysis they are undergoing (see Table 111).

Table 111: RRT access procedures for cycle 1

Procedure	Cost	Distribution & parameters	Source	Proportion	Weighted cost (cost * proportion)
Peritoneal access	£1,160	Gamma, α = 3.19; β = 364	NHS Reference Costs 2010/11[109]	21%	£244
Haemodialysis vascular access	£1,366	Gamma, α = 3.19; β = 364	NHS Reference Costs 2010/11[109]	79%	£1,079
				Total	***£1,323***

In cycle 2 and beyond the main difference is that there would be fewer vascular access procedures. There is huge variability in the number of vascular access procedures per patient that are required. The GDG made the assumption that patients would receive anywhere between one access procedure per year to one every five years; the midpoint was taken for the base case and a uniform distribution was applied for the probabilistic analysis.

CKD stage 5 patients also required drugs and check-ups. It was assumed that all patients with CKD stage 5, CM and RRT, in cycle 1 and cycle 2 onwards would have 2 appointments with a nephrologist every 3 months and their eGFR measured weekly. In addition, a third of the patients would be receiving Epoetin at the cost and dose outlined in Table 109. The 10% of patients on CM would be receiving monthly home visit and weekly telephone calls from a specialist nurse. The GDG also assumed that 90% of CM patients would be on diuretics. The most commonly prescribed for this indication is 80mg per day of Furosemide (Table 109). The cost break down for stage 5 CKD can be found in Table 112.

Table 112: CKD Stage 5 Costs

Patients on RRT - Cycle 1				
Resource	**frequency**	**Cost per cycle**	**Distribution & Parameters**	**Source of cost**
Nephrologist appointment	2 per cycle	£374	Gamma α = 7.86; β = 27.62	NHS reference costs 2010/11[109]
eGFR	12 per cycle	£56	Table 109	NHS reference costs 2010/11[109] and PSSRU 2012[105]
Epoetin alpha	1,788 units per week (£0.005 per unit)	£39	Table 109	BNF 62[204] and CG114[295]
Access procedure	1	£1,323	Table 111	NHS reference costs 2010/11[109]
RRT		£5,460	Pooled average of RRT modalities (Table 110)	
Sub Total		***£7,252***		
Patients on Conservative Management (CM) – Cycle 1 and subsequent cycles				
Nephrologist appointment	2 per month	£374	Gamma α = 6.63; β = 23.69	NHS reference costs 2010/11[109]
Phone call	12 per cycle	£64	Fixed	PSSRU 2012[105]
Home visits	3 per cycle	£66	Fixed	PSSRU 2012[105]
eGFR	12 per cycle	£56	Table 109	NHS reference costs 2010/11[109] & PSSRU 2012[105]
Diuretics	80mg per day	£43	Table 109	BNF 62[204] +GDG assumption
Epoetin alpha	1,788 units per week	£39	Table 109	BNF 62[204] & CG114[295]
Sub Total		***£642***		
Patients on RRT cycle 2 onwards				
Nephrologist appointment (no initial consultation)	2 per cycle	£314	Gamma α = 6.63; β = 23.69	NHS reference costs 2010/11[109]
eGFR	12 per cycle	£59	Table 109	NHS reference costs 2010/11[109] & PSSRU 2012[105]
Epoetin alpha	1,788 units per week	£39	Table 109	BNF 62[204] & CG114[295]
Access procedure	0.15 per cycle	£199	Table 111	NHS reference costs 2010/11[109]
RRT		£5,460	Pooled average of RRT modalities (Table 110)	
Sub Total		***£6,284***		

Totals		
Cycle 1	90% RRT/10% CM	£6,585
Cycle 2 onwards	90% RRT/10% CM	£5,512

CI-AKI

In order to establish the cost of the CI-AKI health state, we took a pooled average of the costs of AKI from the NHS reference costs (Table 113). The reference cost included 7% of patients requiring "interventions," these interventions included RRT as a result of AKI as well as any other procedures that might be required. Due to the disaggregated form of this cost and the possibility for miscoding/misreporting inherent in any nationally collected data source, this cost will be varied in a sensitivity analysis to assess the impact that this cost has on the results.

Table 113: Costs of CI-AKI

AKI code	Weight (A)	Unit cost (B)	Weighted cost (A*B)
LA07C Acute Kidney Injury without CC	5%	£1,257	£57.35
LA07D Acute Kidney Injury with Major CC with Interventions	4%	£5,111	£213.50
LA07E Acute Kidney Injury with Major CC without Interventions	43%	£2,266	£978.21
LA07F Acute Kidney Injury with Intermediate CC with Interventions	3%	£3,350	£91.71
LA07G Acute Kidney Injury with Intermediate CC without Interventions	45%	£1,483	£672.67
Pooled average	**Distribution and parameters: Gamma: α = 8; β = 238**		**£2,013**

The total cost for each health state are summarised in Table 114.

Table 114: Cost of health states

Health State	Health state cost (3 months)
CKD stage 3–4	£176
CKD Stage 5 Cycle 1	£10,927
CKD Stage 5 Cycle 2 onwards	£9,845
AKI	£2,013

K.2.4 Sensitivity analyses

The model was built probabilistically. However, some assumptions and data sources carry greater uncertainty than others and need to be investigated individually in univariate sensitivity analyses.

Sensitivity analysis 1

A sensitivity analysis will be carried out by changing the assumptions around the resource use/administration time of strategies involving sodium bicarbonate and sodium chloride 0.9%. While in current practice these two fluid regimens are ideally given over 8 hours, it is not uncommon for these fluids to require a longer administration time and a larger volume. Table 115 reports the assumptions and costs used in this sensitivity analysis.

Table 115: Fluid infusion strategy costs in sensitivity analysis 1

Strategy	Fluid/NAC cost [(a)]	Additional cost of one night admission to hospital [(b)]	Total cost of fluid regimen
Sodium chloride 0.9% - 2 litres over 18 hours (requires admission)	£1.40	£226	£267
Sodium chloride 0.45% - 2 litres over 24 hours (requires admission)	£3.60	£266	£270
Oral fluids (glass of water)	£0.00	-	£0.00
Sodium bicarbonate – 2 litres over 18 hours (requires admission)	£30.84	£266	£297
Sodium bicarbonate + sodium chloride 0.9% - 1 litre of sodium bicarbonate over 9 hours + 1.5 litres of sodium chloride over 15 hours (requires admission)	£16.75	£266	£283
NAC + sodium chloride 0.9% - 2.4 g of NAC and 2 litres over 18 hours (requires admission)	£6.61	£266	£273
NAC + sodium chloride 0.45% - 2.4 g of NAC and 2 litres over 24 hours (requires admission)	£8.81	£266	£275
NAC + sodium bicarbonate - 2.4 g of NAC and 2 litres over 18 hours (requires admission)	£36.05	£266	£302

(a) See Table 107
(b) Source: NHS Reference Costs [109]

Sensitivity analysis 2

In the base case we assume that the population entering our model does not require admission for other causes and they are admitted only if the fluid regime requires it (outpatient population). In a sensitivity analysis we will explore the changes to results when we consider an inpatient population. The fluid strategy costs used in this sensitivity analysis are reported in Table 116.

Table 116: Fluid infusion strategy costs in sensitivity analysis 2

Strategy	Total cost of fluid regime [(a)]
Sodium chloride 0.9% - 2 litres over 18 hours (requires admission)	£0.70

Strategy	Total cost of fluid regime [(a)]
Sodium chloride 0.45% - 2 litres over 24 hours (requires admission)	£3.60
Oral fluids (glass of water)	£0.00
Sodium bicarbonate – 2 litres over 18 hours (requires admission)	£15.42
Sodium bicarbonate + sodium chloride 0.9% - 1 litre of sodium bicarbonate over 9 hours + 1.5 litres of sodium chloride over 15 hours (requires admission)	£16.75
NAC + sodium chloride 0.9% - 2.4 g of NAC and 2 litres over 18 hours (requires admission)	£5.91
NAC + sodium chloride 0.45% - 2.4 g of NAC and 2 litres over 24 hours (requires admission)	£8.81
NAC + sodium bicarbonate - 2.4 g of NAC and 2 litres over 18 hours (requires admission)	£20.63

(a) Only the cost of fluid/NAC is considered – admission is assumed to be the same for all the strategy and should not be counted as an incremental.

Sensitivity analysis 3

The starting age at which patients enter the model will be analysed as age has a large impact on CKD progression and on the incidence of CI-AKI in a susceptible population. The base case age at the start of the model is 70 and the age range will be varied from 60 to 85.

Sensitivity analysis 4

In the model it is assumed that around 11% of patients will have a repeat scan every year, however, this estimate is based on repeat percutaneous coronary intervention (PCI) in a coronary artery disease population, who do not necessarily have CKD. In order to test this value, the probability of having a repeat scan is set to zero, that is patients receive a contrast scan at the beginning of the model, then never again. No values above the base case were tested as 11% per year was already considered by the GDG to be quite high.

Sensitivity analysis 5

The trial used to form the base line progression from stage 3–4 CKD to CI-AKI had a low CI-AKI event rate, due in part to the low prevalence of CKD in the base line population. A sensitivity analysis was therefore carried out on the incidence of CI-AKI. A prospective cohort study by Dangas et al. 2005[107,107] in patients undergoing PCI showed that patients with CKD (defined as eGFR 42-48 ml per min per 1.73m^2) have a probability of CI-AKI of 19% (n=1,980). Another prospective cohort study by Mehran et al. 2004[107,276] shows that patients undergoing PCI with CKD (defined as eGFR<60ml per min per 1.73m^2) had an incidence of CI-AKI of 30% (n=1,473). The incidence from these two studies will be used in a one-way sensitivity analysis as high and medium values of probability of CI-AKI from stage 3–4. However in both of these studies patients received sodium chloride 0.45% before

undertaking the contrast scan as this is used as the baseline event rate, the relative risk with sodium chloride 0.9% compared with sodium chloride 0.45% will also be applied to the incidence.

Sensitivity analysis 6

The cost of an episode of CI-AKI is quite uncertain as the cost obtained from the NHS reference costs[109] was based on AKI not specifically contrast induced AKI. Therefore the highest available cost and the lowest available cost were used as the upper and lower bounds of the sensitivity analysis.

Sensitivity analysis 7

Diabetes in combination with CKD is a considered to be a strong risk factor for CI-AKI. Therefore the increased risk of CI-AKI with diabetes was taken from the study outlined above by Mehran et al. 2004.[276] This was a study in 8,357 patients and evaluated the risks of CI-AKI in patients with diabetes and CKD undergoing a primary coronary intervention. It gave an odds ratio of 1.73 compared to patients with no diabetes.

Sensitivity analysis 8

The data for oral fluids is particularly uncertain due to the inconsistency in the network of relative risks (meaning that there is more than one comparison that can be used to populate this arm). Therefore the data that was considered to be lower quality by the GDG will be used in that sensitivity analysis to test how important this factor is in assessing the cost effectiveness of the various options. This data gives oral fluids a relative risk of 1.16 compared with sodium chloride 0.9%.

Sensitivity analysis 9

The data on utilities in stage 3–4 CKD and stage 5 CKD made use of Japanese EQ-5D data combined with UK population averages. This is a technique that should provide the best estimate of utilities but has great uncertainty inherent in it. Therefore the effect of using the Japanese EQ-5D data without combining it with UK population averages was tested.

Sensitivity analysis 10

In keeping with the NICE reference case, the base case discount rate is 3.5% per year. However, this is varied between 0 and 6% on both costs and outcomes. An additional analysis was performed, whereby the discount rate is set at 1.5% on outcomes and maintained at 3.5% on costs.

Sensitivity analysis 11

In a sensitivity analysis the relative risk of NAC plus sodium bicarbonate vs. sodium chloride 0.9% was estimated using the comparison between NAC plus sodium bicarbonate vs. NAC plus sodium chloride 0.9%, and NAC plus sodium chloride 0.9% vs. sodium chloride 0.9%. The relative risk thus obtained was 0.63.

K.2.5 Model validation

The model was developed in consultation with the GDG; model structure, inputs and results were presented to and discussed with the GDG for clinical validation and interpretation.

The model was systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given inputs. The model was peer reviewed by a second experienced health economist from the NCGC; this included systematic checking of many of the model calculations.

K.2.6 Interpreting results

The threshold applied in the model is £20,000 per QALY. This threshold is used implicitly in the calculation of costs and outcomes. When multiple comparators are used, the traditional incremental cost effectiveness ratio (ICER) faces many difficulties in presentation. Negative ICERs are hard to interpret and confusing, the incremental nature is complicated and dominance and extended dominance are particularly tough to establish. A more intelligible way to present multiple comparators is to rearrange the ICER equation to include the threshold. We do this by costing the gained QALYs at the threshold: £20,000 per QALY per patient. Then if we remove the costs in the treatment arm, we are left with only the increased effects but costed at the threshold. The treatment arm with the highest number of QALYs, net of cost, will have the highest "net monetary benefit (NMB)" allowing comparison and ranking.

ICER: ΔCost/(ΔQALYs)<or>threshold

Rearranged to:

NMB: threshold*QALYs-Cost=NMB

So if a treatment has the highest NMB it is given the highest rank and is considered the cost effective option.

K.3 Results

K.3.1 Base case

The overall ranking of strategies by net monetary benefit can be found in Table 117. This table also displays the costs and QALYs resulting from each strategy, and the probability that any given strategy is cost effective at a threshold of £20,000 per QALY. The probability is defined by using the 1000 probabilistic simulations to give the proportions of simulations where each strategy is the most cost effective at the £20,000 per QALY threshold. The results of the model show that the most cost effective strategy for the prevention of CI-AKI in the base case is the strategy that involves infusion with sodium chloride 0.9% and treatment with NAC. The most effective strategy is sodium chloride 0.9% with sodium bicarbonate; however it is also more costly than other strategies ranking 1 to 4 by NMB and its additional effectiveness does not justify the additional cost (i.e. the ICER is above the £20,000 per QALY threshold).

The key driver of this model is the effectiveness of the treatments combined with the cost of admission when required.

Table 117: Base case analysis - probabilistic results per patient

Strategy	Costs	QALYs	NMB	Rank by NMB	Probability CE at £20,000 per QALY
NAC + sodium chloride 0.9%	£3,261	2.543	47597	1	43%
Sodium bicarbonate	£3,274	2.543	47585	2	30%
Sodium chloride 0.9%	£3,268	2.541	47544	3	4%
NAC + sodium bicarbonate	£3,314	2.538	47442	4	17%
Sodium bicarbonate + sodium chloride 0.9%	£3,631	2.549	47352	5	6%
NAC + sodium chloride 0.45%	£3,726	2.531	46888	6	0%
Oral fluids	£3,437	2.515	46853	7	0%
Sodium chloride 0.45%	£3,800	2.518	46553	8	0%

Figure **100** shows the relationship between the strategies in terms of costs (vertical axis) and QALYs (horizontal axis) in the probabilistic analysis. The deterministic analysis yields similar results. Oral fluids, sodium chloride 0.45% and NAC with sodium chloride 0.45% are less effective and more costly than the strategies on the right-bottom of the picture: sodium chloride 0.9%, sodium bicarbonate, NAC with sodium chloride 0.9% and NAC with sodium bicarbonate. Sodium bicarbonate with sodium chloride 0.9% is the strategy that generates the most QALYs, however it is also more costly than the strategies just listed on the right-bottom of the picture. When and incremental analysis is conducted, its ICER compared to sodium bicarbonate is £67,209 per QALY (see Table 118).

Figure 100: Costs and effectiveness of different prevention strategies

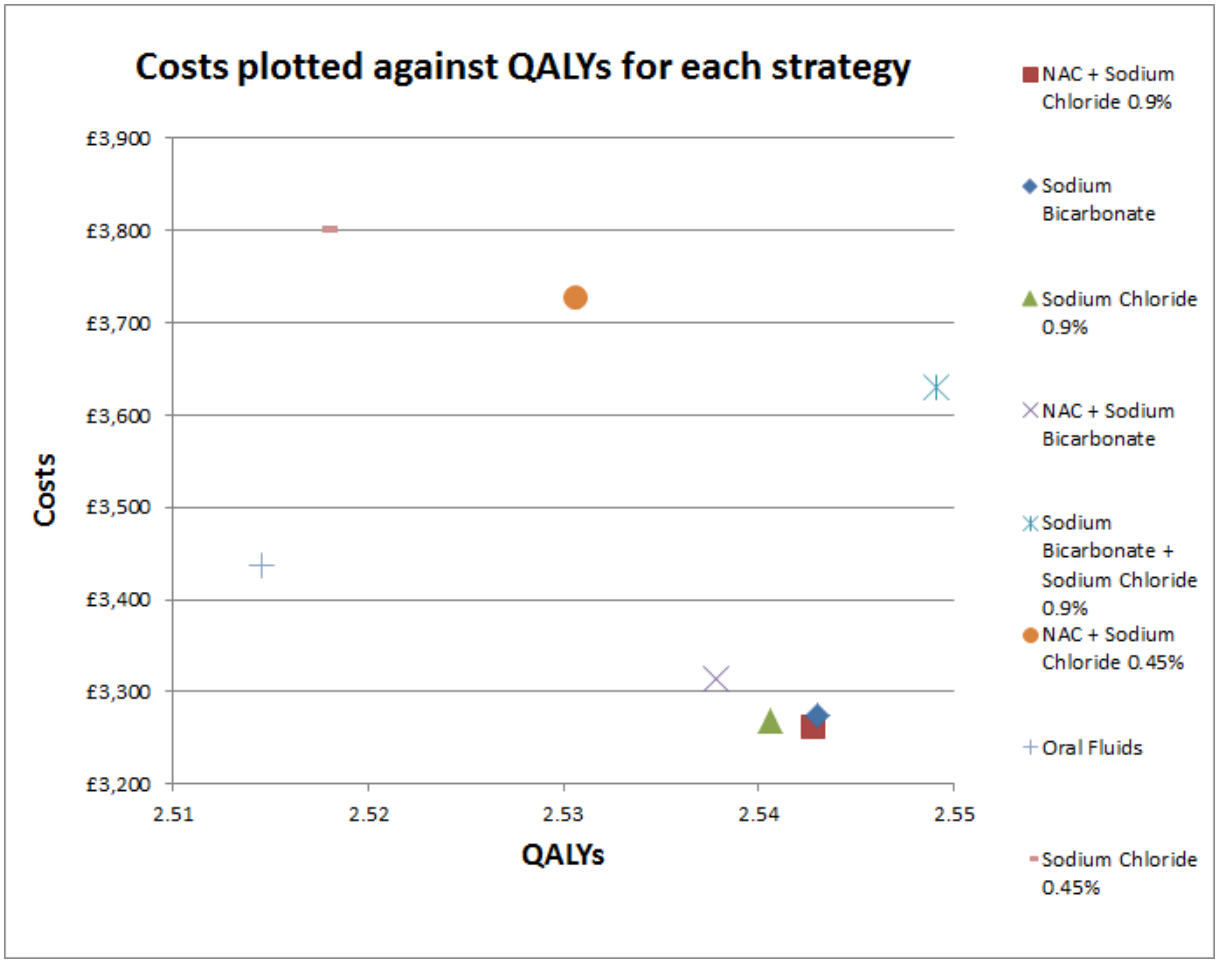


Table 118: Incremental analysis – deterministic results per patient

Strategy	Costs	QALYs	ICER (£ per QALY)
Sodium bicarbonate + sodium chloride 0.9%	£3,876	2.460	67,209
Sodium bicarbonate	£3,583	2.456	
NAC + sodium bicarbonate	£3,589	2.456	dominated
NAC + sodium chloride 0.9%	£3,589	2.454	dominated
Sodium chloride 0.9%	£3,606	2.451	dominated
NAC + sodium chloride 0.45%	£3,975	2.444	dominated
Sodium chloride 0.45%	£4,002	2.439	dominated
Oral fluids	£3,752	2.430	dominated

In Table 119 a breakdown of costs and outcomes is reported. This table shows where the biggest differences between the strategies are found and the key drivers of cost effectiveness.

The costs also are not very different between strategies per patient. The cost breakdown indicates that some interventions (sodium chloride 0.45% with or without NAC and sodium bicarbonate with sodium chloride 0.9%) are associated with higher initial costs. The cost of stage 3–4 is fairly similar between strategies as are the cost of stage 5 CKD. Similarly, there is not a big difference in the total cost per patient. Together with the effectiveness of strategies, the cost of admission is a key driver of the results in the model.

Table 119: Breakdown of costs and outcomes per patient

	Costs						Outcomes	
Component	Fluids/ admission	CI-AKI	Stage 3–4	Stage 5 (Cycle1)	Stage 5	Total cost	Life years	QALYs
Sodium chloride 0.9%	£1.01	£61.47	£2,644	£108	£454	£3,268	4.208	2.541
Sodium chloride 0.45%	£383.7	£176.91	£2,610	£118	£512	£3,800	4.173	2.518
Oral fluids	£0.00	£192.87	£2,606	£119	£520	£3,437	4.168	2.514
Sodium bicarbonate	£22.01	£49.42	£2,648	£107	£448	£3,273	4.212	2.543
Sodium bicarbonate + Sodium chloride 0.9%	£404.5	£17.91	£2,657	£104	£432	£3,615	4.221	2.549
NAC + sodium chloride 0.9%	£8.57	£49.93	£2,647	£107	£448	£3,261	4.212	2.543
NAC + sodium chloride 0.45%	£392.1	£113.21	£2,629	£112	£479	£3,726	4.193	2.531
NAC + sodium bicarbonate	£29.54	£74.95	£2,640	£109	£461	£3,314	4.204	2.538

Some important considerations can be made on the basis of the results: sodium chloride 0.45% with or without NAC and oral fluids are both more costly and less effective than other strategies, therefore, while there is not a big difference between the top strategies in terms of costs and effectiveness and they could be all considered cost-effective, oral fluids and sodium chloride 0.45% would never be considered cost-effective

Another interesting result is that sodium bicarbonate alone or with NAC is the same cost and virtually the same effectiveness of sodium chloride alone or with NAC. Sodium chloride 0.9% with NAC was

the most cost-effective strategy in only 43% of the 1,000 simulations of the model; from these uncertain results it is difficult to conclude which intervention is the most cost effective among the top four.

K.3.2 Sensitivity analyses

Various sensitivity analyses were carried out on the inputs and point estimates. The sensitivity analyses performed are described in section K.2.4. The model on the whole remained robust to any changes made by the sensitivity analyses with the exception of sensitivity analysis 1 and 2. The changes that occurred can be found in Table 120.

Table 120: Sensitivity analysis results

Sensitivity analysis	Changes to base case results observed
1: change in fluid regimens	Sodium bicarbonate plus sodium chloride 0.9% was the most cost-effective strategy in 70% of the simulations. The ranking of the other strategies remained unvaried with the exception of oral fluids which ranked higher than NAC plus sodium chloride 0.45%.
2: inpatient population	Sodium bicarbonate plus sodium chloride 0.9% was the most cost-effective strategy in 90% of the simulations. The ranking of the other strategies remained unvaried with the exception of oral fluids which ranked last.
3: starting age	No changes to conclusions
4: repeat scans	No changes to conclusions
5: incidence of CI-AKI	No changes to conclusions
6: cost of AKI	No changes to conclusions
7: diabetes	No changes to conclusions
8: oral fluids alternative data	No changes to conclusions – oral fluids ranked fourth by NMB
9: utilities for stage 5 CKD and stages 3-4 CKD	No changes to conclusions
10: discount rate	No changes to conclusions
11: NAC plus sodium bicarbonate alternative data	NAC plus sodium bicarbonate was the most cost-effective strategy in 48% of the simulations. The ranking of the other strategies remained unvaried.

The only sensitivity analyses (SA) that led to a change to the overall result were SA1, SA2 and SA11. In SA1 it was assumed that in order to receive any strategy containing either sodium chloride 0.9% or sodium bicarbonate patients would have to spend an extra night in hospital. This showed that sodium bicarbonate with sodium chloride 0.9% was the most effective and had an ICER of £6,372 per QALY compared with oral fluids, while other strategies were dominated. The detailed results can be found in Table 121.

Table 121: Results of Sensitivity Analysis 1 – change in fluid regimes

Strategy	Costs	QALYs	NMB	Rank by NMB	probability CE at £20,000 per QALY

Sodium bicarbonate + sodium chloride 0.9%	£3,649	2.54762295	47304	1	70%
NAC + sodium chloride 0.9%	£3,660	2.541203518	47164	2	2%
Sodium bicarbonate	£3,709	2.541359979	47118	3	1%
Sodium chloride 0.9%	£3,666	2.538933934	47112	4	0%
NAC + sodium bicarbonate	£3,729	2.536847331	47008	5	3%
Oral fluids	£3,438	2.514622135	46854	6	24%
NAC + sodium chloride 0.45%	£3,740	2.528701772	46834	7	0%
Sodium chloride 0.45%	£3,811	2.515901087	46507	8	0%

In sensitivity analysis 2, we assumed that every patient was already admitted in hospital and the cost of the extra bed day for those strategies which take a longer time was not added to the strategy cost as this is not an additional cost anymore. Similarly to sensitivity analysis 1, sodium bicarbonate with sodium chloride 0.9% was the optimal strategy in 90% of the simulations (Table 122). Among the other strategies, there was not much difference in terms of costs and QALYs between NAC with sodium chloride 0.9%, NAC with sodium bicarbonate, sodium bicarbonate and sodium chloride 0.9%.

Table 122: Results of Sensitivity Analysis 2 – inpatient population

Strategy	Costs	QALYs	NMB	Rank by NMB	probability CE at £20,000 per QALY
Sodium bicarbonate + sodium chloride 0.9%	£3,224	2.54807528	47738	1	90%
NAC + sodium chloride 0.9%	£3,247	2.541831485	47590	2	4%
Sodium bicarbonate	£3,262	2.541888937	47576	3	3%
Sodium chloride 0.9%	£3,254	2.539573004	47537	4	1%
NAC + sodium bicarbonate	£3,297	2.537541591	47453	5	3%
NAC + sodium chloride 0.45%	£3,329	2.529870725	47269	6	0%
Sodium chloride 0.45%	£3,401	2.517386837	46946	7	0%
Oral fluids	£3,416	2.514376252	46872	8	0%

In sensitivity analysis 11, using alternative data to estimate the relative risk of NAC with sodium bicarbonate compared to sodium chloride 0.9%, the former came up much more effective than the latter. This shifted NAC with sodium bicarbonate to the top of the optimal strategies list (Table 123).

Table 123: Results of Sensitivity Analysis 11 – alternative data on NAC with sodium bicarbonate

Strategy	Costs	QALYs	NMB	Rank by NMB	probability CE at £20,000 per QALY
NAC + sodium bicarbonate	£3,239	2.545	47670	1	48%
NAC + sodium chloride 0.9%	£3,227	2.544	47650	2	25%
Sodium bicarbonate	£3,242	2.544	47639	3	21%
Sodium chloride 0.9%	£3,234	2.542	47598	4	2%
Sodium bicarbonate + sodium chloride 0.9%	£3,610	2.550	47399	5	3%
Oral fluids	£3,392	2.516	46932	6	0%
NAC + sodium chloride 0.45%	£3,700	2.531	46926	7	0%
Sodium chloride 0.45%	£3,767	2.519	46617	8	0%

K.4 Discussion

K.4.1 Summary of results

When no admission is required for strategies including sodium bicarbonate and sodium chloride 0.9%, these two fluids with or without NAC are acceptable interventions for the prevention of CI-AKI. Strategies with sodium chloride 0.45%, NAC with sodium chloride 0.45% or oral fluids were not cost-effective in any of the analyses.

Admitting a patient for fluid infusion prior to a contrast scan would increase costs and could be avoided by using a strategy where the infusion is given for 8 hours. Although sodium bicarbonate with sodium chloride 0.9% was the most effective strategy, its incremental cost due mainly to the extra admission to hospital is too high for the QALY gain. If a patient is already admitted, the most cost-effective strategy is sodium bicarbonate with sodium chloride 0.9%.

K.4.2 Limitations & interpretation

Sodium bicarbonate and sodium chloride together proved to be the most effective option but not cost effective and sodium chloride 0.9% is cost effective compared with sodium chloride 0.45%.

The results suggest that there is uncertainty around the improvement with NAC, as some studies reported an increased effectiveness of the fluid when administered with NAC while other reported decreased effectiveness (higher incidence of CI-AKI) when NAC was added to the fluid. There are also some concerns about the possible adverse reaction due to NAC which the model did not account for, and some concerns about practicalities such as the availability of NAC and the fact that it is an unlicensed medicine and consent needs to be sought. Given that the potential QALY gained showed in the model when NAC is added to sodium chloride 0.9% is so small, and that other factors mentioned above were not incorporated into the model, the GDG did not think the clinical and economic evidence was convincing enough to conclude that NAC is cost effective. There is also uncertainty around the data sources and although sodium bicarbonate with sodium chloride 0.9% was the most cost-effective strategy in the inpatient population, the GDG had some concerns over the data used to establish its effectiveness. The effectiveness data of this strategy was quite limited and only two studies were available, one of which had an odd regime as a small dose was given during the procedure, and overall the effectiveness was based on very low event rates. For this reason, the GDG did not feel that sodium bicarbonate with sodium chloride 0.9% should be considered a cost-effective strategy even in the inpatient population.

The comparators that the analysis is based on also have some inconsistencies. While there are no relative risks calculated that have inconsistencies in the opposite direction, the effect size can be very different between direct and indirect evidence. For example using the indirect evidence on oral fluids the relative risk compared to sodium chloride is 2.68 whereas using the direct evidence this is 1.14.

K.4.3 Generalisability to other populations / settings

The model is relevant to an NHS and PSS care setting.

K.4.4 Comparisons with published studies

There were no cost effectiveness studies identified that looked at the use of fluids in the prevention of CI-AKI.

Appendix L: Research recommendations

L.1 Long-term outcomes of acute kidney injury

Research question:

What are the long-term outcomes of acute kidney injury in adults, children and young people?

Why this is important:

Long-term follow-up studies, predominantly from North America, have shown that acute kidney injury is associated with an increased risk of chronic kidney disease (CKD) or exacerbation of underlying CKD. This can lead to end-stage renal disease (ESRD) and long-term dialysis. About a quarter to a third of the costs associated with acute kidney injury in adults are due to ESRD. Older adults with comorbidities are at particular risk.

Although acute kidney injury is traditionally regarded as 'reversible,' the psychological effects are not well studied. Some studies of adults who have recovered from acute kidney injury suggest a reduced quality of life, including higher rates of depression. People also often need more social care or discharge to institutional care.

The factors associated with the long-term complications of acute kidney injury are poorly understood. A large, prospective epidemiological or cohort study is needed with a control group (for example, patients admitted to hospital as an emergency case with an acute illness, but without acute kidney injury). In adults follow-up should be for at least 2–3 years, and the study should be adequately powered to detect factors predictive of the two most costly outcomes in adults, new ESRD and new need for institutional care or the inability to live independently in the community. In children and young people, longer follow-up beyond puberty is needed. Important long-term complications for children and young people include hypertension, proteinuria and reduced renal function.

Criteria for selecting high-priority research recommendations:

PICO question	What are the long-term outcomes of acute kidney injury patients? Outcomes: - Health Related Quality of LIFE (HRQOL) - New CKD of stage 3b or worse - New end stage renal disease - New hypertension in children - New requirement for adult placement in an institution or inability to live independently in the community (requiring a package of care, level to be defined)
Importance to patients or the population	The long-term effects of AKI have not been studied in the NHS. The majority of existing data stem from different healthcare systems, predominantly from North America. A better understanding of long-term effects is essential to provide

	appropriate follow up arrangements for survivors of AKI and allow meaningful counselling. The long term outcome of AKI in a population of children has not been reported. Knowledge of long term risks is essential to identifying predictors of long term outcome and determining the frequency and duration of follow-up.
Relevance to NICE guidance	Long term outcome data in adults and children who have suffered an episode of AKI will help in focussing future NICE guidance on strategies to minimise the occurrence of AKI and to reduce the risk of long term complications.
Relevance to the NHS	Increasing data predominantly from large databases suggest that patients who have survived an episode of AKI have an increased risk of chronic kidney disease, including end-stage renal failure. The risk is particularly high in patients who already had pre-existing CKD before an episode of AKI. It is not clear whether regular follow up of AKI survivors in specialist clinics or any particular investigations or interventions reduce this risk and are cost-effective. A better understanding of the long-term complications of AKI will aid future planning and allocation of resources and may improve patients' long-term prognosis. Children who have suffered an episode of AKI will become adults at risk of the complications of AKI. Any new guidance, informed by a better understanding of long term risks gained from research, is likely to impact positively on the long term health of children who have suffered an episode of AKI with a consequent reduction in consumption of health resource.
National priorities	The National Service Framework standard for Renal Services (part 2, 2009) included quality requirement two: that people at increased risk of developing chronic kidney disease are identified, assessed, and their condition managed to preserve their kidney function.
Current evidence base	Current evidence is predominantly based on data from large databases and renal registries from North America, where obviously both primary and secondary care function quite differently. Hence it is not known how these data apply or relate to NHS healthcare. Recommendation 50 highlights that information should be provided about long-term treatment options, monitoring, self-management and support to people following acute kidney injury (and/or their parent or carer, if appropriate) in collaboration with a multidisciplinary team appropriate to the person's individual needs. 'Give patients needing dialysis after discharge information about dialysis sessions and the preparation needed (such as having a fistula or peritoneal catheter).' This is in line with recommendations in 'Chronic kidney disease' (NICE clinical guideline 73). Recommendation 48 highlights the importance of long term follow up of children who have suffered AKI, and emphasises the importance of continuing follow-up until after puberty. There are no large long term studies examining the consequence of loss of nephrons from an episode of AKI in childhood. This is of importance in children because it is recognised that hyperperfusion and hyperfiltration changes, as a consequence of reduced nephron numbers [due to the previous AKI], are later exacerbated by increased body mass following a pubertal growth spurt.
Equality	This research focuses attention on children, a group presently not adequately studied.

Study design	The study in children should be a longitudinal cohort study, extending through to completion of puberty. In adults, the study should ideally also be a longitudinal cohort study. Other potential designs would be retrospective analyses of different databases, i.e. linkage of ICU and renal registry data.
Feasibility	The main challenge to undertaking the study in children is funding to allow follow up. As discussed this should take place over some years until completion of puberty, a considerable time span for young children who develop AKI. An adequately sized follow up study with appropriate duration of follow up is necessary to provide valid data. The main challenges will be funding and achieving completion of follow up in a high percentage of the enrolled children and young people. Nevertheless, it was felt that the UK should be capable of such a study with follow up that is longer term.
Other comments	None
Importance	The study is of high importance because there is presently no well-designed, long term, multi-centre study of the outcome of AKI in adults and children. There is increasing evidence that both have a risk of CKD following AKI but the magnitude of that risk is not known. Furthermore, there is no good understanding of predictors of long term outcome to inform the required frequency and duration of follow-up and whether there are any effective strategies to improve long-term outcome and reduce the risk of end-stage renal failure. There is also no good understanding of the extent of resources needed to provide cost-effective follow up.

L.2 Rapid referral to nephrology services for moderate to severe acute kidney injury

Research question:

What is the clinical and cost effectiveness of rapid referral (within 12 hours) to nephrology services for adults with moderate to severe (stage 2 to 3) acute kidney injury not needing critical care?

Why this is important:

There is national variation in referral of patients with moderate to severe acute kidney injury to nephrology services. Evidence is lacking on the effect of rapid referral (within 12 hours) on major outcomes, including the need for renal replacement therapy, mortality, length of hospital stay and health–related quality of life at 6 months. In most patients acute kidney injury is managed by correcting volume depletion and hypotension and avoiding further renal insults, including nephrotoxic drugs. This does not usually require specialist input from nephrology or critical care services.

In a proportion of patients, renal function may deteriorate further because of primary renal diseases needing specialist treatment (for example, immunosuppressive therapy), progressive organ failure needing treatment with adverse effects on the kidneys (for example, high-dose diuretics in congestive heart failure) or inadequate correction of volume depletion and hypotension.

The optimal timing for referral to nephrology services is not known. Rapid referral of all patients with stage 2 to 3 acute kidney injury may allow earlier detection of primary renal diseases and avoid delay in starting appropriate therapy. It may also ensure more rapid correction of volume depletion and hypotension and initiation of targeted investigations. Potential benefits also include prevention of progressive acute kidney injury, avoidance of renal replacement therapy, avoidance of a delayed transfer to critical care, improved chances of renal recovery, a shorter hospital stay and better long-term outcomes.

The challenge would be to provide rapid referral (within 12 hours) out of hours. This would be a particular problem in hospitals without a renal unit on site. Another downside of rapid referral of all patients with stage 2 to 3 acute kidney injury would be the costs associated with referring patients whose renal function recovers quickly with basic general management alone.

A randomised controlled trial is needed to evaluate the clinical and cost effectiveness of rapid referral (within 12 hours) to nephrology services for all adult patients with moderate to severe (stage 2 to 3) acute kidney injury compared with referral based on clinical judgement (that is, standard care). Outcomes should include need for renal replacement therapy, mortality, length of hospital stay and health-related quality of life at 6 months.

Criteria for selecting high-priority research recommendations:

PICO question	What is the clinical and cost effectiveness of rapid referral (within 12 hours) to nephrology services for management of adults with moderate to severe (stage 2 to 3) AKI on outcomes including need for RRT, mortality, length of hospital stay and health related quality of life at 6 months?
Importance to patients or the population	AKI is common, in particular in hospitalised patients outside renal and critical care services. The optimal time for referral to nephrology service is not known and data are necessary to guide non-renal clinicians. Earlier consultation by a nephrologist would be expected to be acceptable to patients if it was associated with better short- and long-term outcomes, in particular a shorter stay in hospital, faster recovery of renal function and avoidance of complications. If earlier referral to nephrology service was not more effective than a referral policy based on the individual clinician's decision, patients would benefit from the reduced number of consultations.
Relevance to NICE guidance	Evidence based guidance whether to refer patients with AKI stage 2-3 to nephrology services within 12 hours will help in focussing future NICE guidance on achieving best outcomes for patients without causing an unacceptable increase in use of healthcare resources and expenses.
Relevance to the NHS	The practice of referring patients with AKI to nephrology service is very variable across the NHS. Guidance on whether early referral is effective and results in better short- and long-term outcomes for patients would ensure equitable care across the NHS and ensure cost-effective use and allocation of resources.
National priorities	Preventing CKD has been a high priority for the government, Department of Health and NHS for many years. Identifying AKI at an early stage and slowing down its progress through timely initiation of effective management and avoidance of further nephrotoxic insults is key to reducing the impact of AKI and subsequent CKD on people's lives. Quality requirement three of the National Service Framework for Renal Services,

	Part II (2009) recommends that people suffering from acute renal failure are managed in partnership with specialised renal teams. Markers of good practice are timely identification and referral to renal services for specialist input, culturally appropriate advice and assessment. The time frame for referral is not defined in this document. Further research is necessary to define "timely referral".
Current evidence base	The evidence base is largely retrospective, dividing cohorts of AKI patients into those referred 'early' and 'late'. It is very difficult to interpret these studies due to various sorts of bias, affecting the speed of referral. The evidence base of prospective studies is very limited, and does not include any in a healthcare system comparable to the NHS.
Equality	The main group suffering AKI are frail elderly patients, and reducing the impact of AKI is likely to reduce any decline in health, prevent increasing disability and improve QOL. Hence the recommendation may reduce inequality for the elderly.
Study design	A cluster randomised trial would be the most suitable design for such service delivery / health services research.
Feasibility	It can be carried out in a realistic timescale and at an acceptable cost.
Other comments	None
Importance	High – as determined by GDG vote. The research is essential to inform future updates of key recommendations in the guideline

L.3 Definition of acute kidney injury – system for staging and detection

Research question:

Can a simplified definition and staging system, based on Système International (SI) units, be used to predict short- to medium-term outcomes in acute kidney injury?

Why this is important:

Definitions of acute kidney injury have evolved fairly rapidly in recent years, from RIFLE (2004), through AKIN (2007), to KDIGO (2012) (a merger of RIFLE and AKIN, but with less rigorous requirements for detection in those with CKD). All three are complex and rely on non-SI units for creatinine.

Absolute creatinine rises have been shown to be independently associated with mortality, but the evidence comes from US studies that used non-SI units for creatinine. Stage 1 acute kidney injury is currently defined by a rise in creatinine of 0.3 mg/dl within 48hours, which translates awkwardly to 26.4 µmol/l in SI units (note that laboratories report creatinine as an integer value only). The current definitions are complex and difficult to use for non-specialists in healthcare systems that use SI units for creatinine measurement (including the UK).

A large, prospective epidemiological or cohort study is needed to investigate whether a simplified system, derived from KDIGO, would be useful for detecting and staging acute kidney injury in the NHS. The study should investigate the relationship of acute kidney injury, as defined by creatinine

rise in SI units, with outcomes, adjusted for comorbidity. It also needs to investigate whether the same absolute rise in creatinine equally reflects outcomes among patients with and without CKD. The study should include a control group (for example, patients admitted to hospital as an emergency with an acute illness, but without acute kidney injury) and be adequately powered to show the effect of acute kidney injury on mortality, length of stay, and dialysis for acute kidney injury at 6 months.

Criteria for selecting high-priority research recommendations:

PICO question	Can a simplified staging and definition system for AKI, based on Système International (SI) Units, be used to predict short to medium term outcomes in acute kidney injury?
Importance to patients or the population	Improved recognition and hence management of AKI in the NHS.
Relevance to NICE guidance	Such evidence would directly inform future updates of NICE AKI guidance.
Relevance to the NHS	Improved recognition and management of AKI in the NHS may reduce costs.
National priorities	It is relevant to Recording, coding and commissioning of acute kidney injury (AKI) activity (NHS Kidney Care, 2012).
Current evidence base	The evidence base is entirely retrospective and uses databases from North America.
Equality	The main group suffering AKI are frail elderly patients, and improving the diagnosis of AKI is likely to reduce any decline in health, prevent increasing disability and improve QOL. Hence the recommendation may reduce inequality for the elderly.
Study design	A prospective cohort study would be the most appropriate design.
Feasibility	It can be carried out in a realistic timescale and at an acceptable cost. The feasibility of such work in the UK has recently been demonstrated by the NHS Kidney Care AKI audit.
Other comments	None.
Importance	High – as determined by GDG vote.

L.4 Introducing renal replacement therapy

Research question:

What is the clinical and cost effectiveness of early versus later introduction of renal replacement therapy in patients with acute kidney injury stages 2 and 3, when there is no urgent need for such therapy?

Why this is important:

In some patients renal replacement therapy is a lifesaving intervention (for example, in those with hyperkalaemia). For other patients, there may be no clear indicators of when renal replacement

therapy should be started because oliguria, fluid overload and uraemia are common and ill-defined indications. An early introduction of renal replacement therapy might reduce the incidence of uraemic or other complications of acute kidney injury, but might also expose the patient to more risks from the therapy itself. Later introduction might increase the incidence of uraemic or other complications of acute kidney injury, but might also reduce the risks associated with renal replacement therapy.

A prospective study is needed of adult in patients with acute kidney injury AKIN stages 2 and 3, who are likely to need renal replacement therapy within a given timeframe (for example, 72 hours), but have no urgent need for therapy. Units participating in the study should be logistically capable of providing early or later dialysis for these patients. Mortality, length of stay, incidence of complications of acute kidney injury, incidence of complications of renal replacement therapy and usage of dialysis should be compared in patients having early therapy and those having later renal replacement therapy. Possible indicators for early renal replacement therapy could, be weight gain less than10%,urea less than 25 mmol/l and oliguria 0.5 ml/kg/hour or less for at least 24 hours (see trial design, below).

Criteria for selecting high-priority research recommendations:

PICO question	In patients with AKI stages 2 and 3, what is the clinical and cost effectiveness of an earlier versus later start strategy for RRT, when there is no compelling or absolute requirement for RRT?
Importance to patients or the population	Patients with severe AKI treated with RRT have an increased risk of dying, a significantly longer stay in hospital and a higher risk of complications, including infections. Survivors are at increased risk of chronic kidney disease and end-stage renal failure, including long-term dialysis. The healthcare costs and complications for severe AKI are high. If an adequately powered study showed that earlier or later initiation had a beneficial effect on either mortality, chance of renal recovery, length of stay in hospital, patient wellbeing or risk of chronic kidney disease, this would be of immediate benefit to individual patients, may save lives and reduce short and long-term healthcare costs. If the study showed no benefit between both strategies, earlier RRT and the associated costs and risk could be avoided. At present, management of RRT is very variable with no clear consensus. Data of an adequately powered study would serve to design appropriate guidelines which would benefit patients and reduce the variability of clinical practice.
Relevance to NICE guidance	Such evidence would directly inform future updates of NICE AKI guidance.
Relevance to the NHS	See above for comments on possible effects on costs. 'Acute dialysis' is a costly and intensive intervention. If early dialysis was shown to be beneficial this might well require improved service delivery by Renal Units. Health economic analysis should be included as a key outcome in any study.
National priorities	Yes – the National Service Framework for Renal Services (Part Two: Chronic Kidney Disease, Acute Renal Failure and End of Life Care, 2009) – quality requirement 3.

Current evidence base	Evidence base is limited, see chapter 9.
Equality	The main group suffering severe AKI are frail elderly patients, and improving the use of dialysis is likely to reduce any decline in health, prevent increasing disability and improve QOL. Hence the recommendation may reduce inequality for the elderly.
Study design	A randomised controlled trial would be the most appropriate design. The GDG did not want to confine the trial to its definition of earlier versus later dialysis, but possible indicators of earlier or later dialysis for example could be: • Weight gain: <10% versus ≥10% • Urea: <25 versus ≥ 25 mmol/L • Oliguria – < 0.5 ml/kg/hr for at least 24 hr versus at least 48 hr
Feasibility	It can be carried out in a realistic timescale and at an acceptable cost. A technical and ethical issue is informed consent of the patient and/or next of kin within the timeframe required for rapid randomisation, followed by rapid access placement and dialysis for those in the early dialysis group.
Other comments	None.
Importance	High – as determined by GDG vote. Also the GDG again noted that 'Acute dialysis' is a costly and intensive intervention, and its effective usage, as shown by such a study, would have a high impact.

L.5 Preventing deterioration

Research question:

What is the clinical and cost effectiveness of continuing ACE inhibitor or ARB treatment, versus stopping treatment 24 hours before cardiac surgery and resuming 24 hours after, in people with CKD and an estimated GFR of less than 30ml/min/1.73 m^2?

Why this is important:

People who need cardiac surgery are often receiving ACE inhibitors or ARBs for their cardiac disease. It is unclear whether these people should stop ACE inhibitors or ARBs around the time of cardiac surgery when their blood pressure will be most unstable. Stopping ACE inhibitors or ARBs might cause deterioration of cardiac disease, which is often a concern for cardiology clinicians, but trials of ACE inhibitors and ARBs in cardiac disease have typically excluded patients undergoing cardiac surgery whose condition is unstable. Stopping ACE inhibitors or ARBs at the time of surgery may prevent exacerbation of acute kidney injury in patients whose condition is unstable.

A randomised controlled trial is needed in patients on ACE inhibitors or ARBs undergoing cardiac surgery to compare continuing treatment with stopping treatment for 48 hours (24 hours before and after surgery). Outcomes should include the incidence of acute kidney injury, cardiovascular events, all cause mortality, number of patients needing renal replacement therapy and length of hospital stay.

Criteria for selecting high-priority research recommendations:

PICO question	In people with CKD and an estimated GFR of less than 30ml/min/1.73m2 on ACEI or ARB therapy what is the clinical and cost effectiveness of continuing versus stopping this treatment 24 hours before and after cardiac surgery?
Importance to patients or the population	Obviously new guidance would directly impact the care of many patients undergoing cardiac surgery. Evidence as to the best approach could reduce cardiac events or AKI in cardiac patients.
Relevance to NICE guidance	NICE guidance on AKI and perioperative care would change and be much more specific as a result of such a study.
Relevance to the NHS	Reduced costs, potentially due to reduced cardiac events or AKI in cardiac patients.
National priorities	Yes – the National Service Framework for Renal Services (Part Two: Chronic Kidney Disease, Acute Renal Failure and End of Life Care, 2009) – quality requirement 3, which includes appropriate peri-operative interventions for people at risk of AKI.
Current evidence base	See chapter 6.
Equality	No specific issues addressed, although older patients undergoing cardiac surgery are both more likely to be using ACEI/ARB and are more at risk of AKI and its consequences.
Study design	A pragmatic randomised controlled trial.
Feasibility	It may not be feasible to switch all patients to one ACEI or ARB, nor is it likely to be feasible to use one placebo. Therefore blinded end points assessment may be needed to avoid bias.
Other comments	None.
Importance	Medium.

L.6 Additional research recommendations

1. In people with CKD and an estimated GFR of less than 30ml/min/1.73m2 on ACEI or ARB therapy what is the clinical and cost effectiveness of continuing versus stopping this treatment 24 hours before and after administration of iodinated contrast?

Why this is important:

Prior treatment with ACEI/ARB is common in people with CKD. It is unclear if patients should stop ACEI or ARB therapy around the time of procedures giving iodinated contrast when the risk of CI-AKI could be increased in these people. Variation in practice exists and no evidence was identified in the systematic review. A randomised controlled trial is required in patients on ACEI or ARB therapy receiving iodinated contrast to compare continuing on ACEI/ARB with stopping for 48 hours (24 hours before and after the procedure). The outcomes should include incidence of AKI, cardiovascular events, all cause mortality, number of patients needing RRT and length of hospital stay.

2. What is the clinical and cost effectiveness of oral rehydration salts versus iv fluids (0.9% saline or sodium bicarbonate) for the prevention of CI-AKI in high risk patients with an estimated GFR of less than 30ml/min/1.73m2 who are receiving iodinated contrast for elective procedures?

Why this is important:

Fluid administration has been shown to reduce the incidence of CI-AKI in at risk individuals. The effectiveness of the oral route of administration of an appropriate fluid (such as oral rehydration salts) remains unclear. A randomised controlled trial comparing these routes of fluid administration is required. It is important that the fluids being compared are given over the same time period and in the same total absorbed volume so that it is clear it is the type of fluid being administered and not the amount given that the study is assessing. The main outcome would be CI-AKI at 48- 72hours defined as rise in serum creatinine greater or equal to x1.5 baseline value; all cause mortality, number of patients needing RRT and length of hospital stay, progression of CKD would also be important outcomes.

3. What is the clinical and cost effectiveness for outpatients with CKD stage 4/5 of an intensive tailored package of advice/care on prevention of AKI versus standard care on outcomes including incidence of AKI, mortality, need for RRT and hospital admission at 3 years?

Why this is important:

People with CKD are at increased risk of AKI compared to the general population. It is unknown if providing tailored advice on nephrotoxic drugs, avoiding dehydration/hypovolaemia, what steps to take when acutely unwell would benefit patients in terms of long term outcomes including reduced incidence of AKI, mortality, need for RRT and hospital admission.

4. In acutely ill children what are the indicators for developing AKI?

Why this is important:

There is currently no track and trigger system for children at risk of developing AKI, consequently some children present with AKI late in their clinical course. In many cases, early intervention can reverse or ameliorate the development of AKI by correcting physiological and pharmacological factors that contribute to the development of AKI. A large multicentre, cohort study in which children at risk of AKI (as per the list in recommendation 2) are identified and are then monitored using PEWS with other indicators including urine output, urine testing and serum creatinine. The data collected could then be used to identify which parameters are useful for predicting the development of AKI.

5. Research question:

In children who have had an episode of AKI what are outcomes at 5 years regarding new onset CKD and progression of CKD?

Why this is important:

Long term outcomes, including the risk of developing AKI and the impact on quality of life, after an episode of AKI in children are not known. Children with a reduction in nephron number, such as may occur after AKI, are known to be at risk of progressive nephron loss through glomerulosclerosis secondary to hyperperfusion and hyperfiltration. The process of nephron loss is often noted to be

accelerated at the time of puberty, presumably because this is a time of increased demand on the kidneys as a result of a marked increase in body mass associated with the pubertal growth spurt. Accurate assessment of risk can only be provided by a large, multicentre cohort study.

Appendix M: References

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