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MALADIE-INVALIDITÉ
SERVICE DES SOINS DE SANTÉ
Comité d'évaluation des pratiques
médicales en matière de médicaments

THE RATIONAL USE OF DRUGS IN CHRONIC KIDNEY DISEASE

Systematic literature review: full report

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ABBREVIATIONS

ACE-I = Angiotensin converting enzyme inhibitor
ACR= Albumin-to-creatinine ratio
AE = adverse events
AER = Albumin excretion rate
AKI= Acute kidney injury
ARA= American Rheumatology Association
ARB= Angiotensin II receptor blocker
ARR = absolute risk reduction
BB= beta blocker
BMI = Body Mass Index
BP = Blood pressure
$CHADS_2$ = Congestive heart failure, hypertension, age > 75, diabetes mellitus, and prior stroke or transient ischemic attack score
CI = confidence interval
CKD = Chronic kidney disease
CO = crossover RCT
CV= cardiovascular
DB = double blind
DBP= diastolic blood pressure
DKD= Diabetic kidney disease
DM = Diabetes mellitus
eGFR = Estimated GFR
$eGFR_{CG}$= eGFR according to the Cockroft-Gault formula
ESRD = end-stage renal disease
GFR = Glomerular filtration rate
HbA1c = Glycosylated hemoglobin
HDL-C = High density lipoprotein cholesterol
HR = hazard ratio
HTN = hypertension
INR = International normalized ratio
ITT = intention-to-treat analysis
LDL-C = Low density lipoprotein cholesterol
MA = meta-analysis
MI= myocardial infarction
n = number of patients
NA= not applicable
NR = not reported
NS = not statistically significant
NSAID = non-steroidal inflammatory drug
NT= no statistical test
NYHA= New York Heart Association
OL = open label
PCR = protein-to-creatinine ratio

PG = parallel group
PO = primary outcome
RCT = Randomized clinical trial.
RR= relative risk
RRT = Renal replacement therapy
SB = single blind
SCr = serum creatinine
SO = secondary outcome
sUA= serum urate concentration
TC = total cholesterol
TG = triglycerides
UACR= urinary albumin /creatinine ratio

1 Methodology

1.1 Introduction and scope

This systematic literature review was conducted in preparation of the consensus conference on 'Rational use of drugs in kidney disease' which will take place on November 27th , 2014.

1.1.1 Questions to the jury

The questions to the jury, as they were phrased by the organising committee of the RIZIV/INAMI are

Question 1. Evaluation de la fonction rénale

Vraag 1. Evaluatie van de nierfunctie

Q 1.1. Quelles sont les méthodes les plus performantes pour l'évaluation de la fonction rénale ?

V 1.1. Welke zijn de meest performante methodes om de nierfunctie te evalueren?

Q 1.2. Existe-t-il des circonstances et/ou des caractéristiques particulières pour un patient (âge par exemple) justifiant une autre méthode d'évaluation, plus fiable ?

V 1.2. Zijn er omstandigheden en/of specifieke karakteristieken van een patiënt (bijvoorbeeld de leeftijd) die een andere, meer betrouwbare methode rechtvaardigen?

Question 2. Médicaments et fonction rénale

Vraag 2. Geneesmiddelen en de nierfunctie

Q 2.1. Quelles sont les notions pharmacologiques générales (pharmacocinétique, pharmacodynamique) indispensables en médecine de première ligne pour la bonne gestion d'une prescription médicamenteuse en cas d'insuffisance rénale connue ?

V 2.1. Welke zijn de algemene farmacologische begrippen (farmacokinetiek, farmacodynamiek) die in de eerstelijnsgeneeskunde onontbeerlijk zijn voor het correct voorschrijven van geneesmiddelen in geval van vastgestelde nierinsufficiëntie?

Q 2.2. Quelles sont les notions pharmacologiques générales (pharmacocinétique, pharmacodynamique) indispensables en médecine de première ligne pour la bonne gestion d'une prescription médicamenteuse en cas d'insuffisance rénale survenant dans le cadre d'une situation-piège – hors médicaments identifiés comme néphrotoxiques (point 3.5.) ?

V 2.2. Welke zijn de algemene farmacologische begrippen (farmacokinetiek, farmacodynamiek) die in de eerstelijnsgeneeskunde onontbeerlijk zijn voor het correct voorschrijven van geneesmiddelen in geval van nierinsufficiëntie die zich voordoet bij een mogelijke valkuil – behalve de geneesmiddelen die als nefrotoxisch worden beschouwd (punt 3.5.)?

Question 3. Domaines thérapeutiques et classes médicamenteuses particuliers

Vraag 3. Therapeutische domeinen en bijzondere medicamenteuze klassen

Q 3.1. **Les antidiabétiques oraux**

V 3.1. ***Orale antidiabetica***

Quels sont les choix préférentiels pour un traitement d'un diabète de type 2 en cas d'insuffisance rénale chronique (suivant le grade KDIGO[2] de celle-ci) et dans des circonstances particulières ?

Welke keuzes zijn doorslaggevend voor een behandeling van een type 2-diabetes in geval van chronische nierinsufficiëntie (volgens de KDIGO[2]-graad van die chronische nierinsufficiëntie) en in bijzondere omstandigheden?

Q 3.2. **Les anticoagulants**

V 3.2. ***De anticoagulantia***

Quels sont les choix préférentiels pour un traitement anticoagulant (oral ou non) en cas d'insuffisance rénale chronique (suivant le grade KDIGO[2] de celle-ci) et dans des circonstances particulières ?

Welke keuzes zijn doorslaggevend voor een (al dan niet orale) behandeling met anticoagulantia in geval van chronische nierinsufficiëntie (overeenkomstig de KDIGO[2]-graad van die chronische nierinsufficiëntie) en in bijzondere omstandigheden?

Q 3.3. **Les médicaments cardiovasculaires (hors anticoagulants)**

V 3.3. ***Cardiovasculaire geneesmiddelen (behalve de anticoagulantia)***

Quels sont les choix préférentiels pour un traitement à visée cardiovasculaire (HTA, angor/post infarctus, insuffisance cardiaque, artérite périphérique, hyperlipidémies) en cas d'insuffisance rénale chronique (suivant le grade KDIGO[2] de celle-ci) et dans des circonstances particulières ?

Welke keuzes zijn doorslaggevend voor een cardiovasculaire behandeling (arteriële hypertensie, angina na infarct, hartinsufficiëntie, perifere arteritis, hyperlipidemieën) in geval van chronische nierinsufficiëntie (overeenkomstig de KDIGO[2]-graad van die chronische nierinsufficiëntie) en in bijzondere omstandigheden?

Q 3.4. **Les analgésiques/ anti-inflammatoires et les médicaments particuliers posant problème dans la pratique (hors points 3.1. à 3.3.)**

V 3.4. ***Analgetica/anti-inflammatoire middelen en die geneesmiddelen die in de praktijk problemen veroorzaken (andere dan vermeld in 3.1. tot 3.3.)***

Quels sont les analgésiques/ anti-inflammatoires et autres médicaments particuliers qui, dans la pratique courante, posent problème en relation avec la fonction rénale ?

Quels sont les choix préférentiels pour un traitement analgésique/anti-inflammatoire en cas d'insuffisance rénale chronique (suivant le grade KDIGO[2] de celle-ci) et dans des circonstances particulières ?

Welke analgetica/anti-flogistica en andere geneesmiddelen veroorzaken in de praktijk problemen met de nierfunctie?

Welke keuzes zijn doorslaggevend voor een analgetische/anti-inflammatoire behandeling in geval van chronische nierinsufficiëntie (overeenkomstig de KDIGO[2]-graad van die chronische nierinsufficiëntie) en in bijzondere omstandigheden?

Q 3.5. **Médicaments néphrotoxiques : suivi particulier en première ligne de soins**

V 3.5. ***Nefrotoxische geneesmiddelen: gerichte opvolging in de eerstelijnsgezondheidszorg***

Quel suivi doit-il être assuré en première ligne de soins en cas de prescription d'un médicament dont la néphrotoxicité (aiguë ou chronique) est identifiée ?

Welke opvolging moet in de eerstelijnsgezondheidszorg worden gegarandeerd wanneer een geneesmiddel wordt voorgeschreven dat bekend staat om zijn (acute of chronische) nefrotoxiciteit?

Question 4. Rôle du pharmacien dans le suivi des traitements médicamenteux en cas d'insuffisance rénale

Vraag 4. Rol van de apotheker bij de opvolging van geneesmiddelen die door een patiënt met nierinsufficiëntie worden gebruikt

Quel rôle le pharmacien d'officine peut-il jouer dans l'accompagnement d'un traitement médicamenteux en cas d'insuffisance rénale connue/suspectée ?

Welke rol kan de apotheker spelen bij de opvolging van een medicamenteuze behandeling in geval van reeds vastgestelde of veronderstelde nierinsufficiëntie?

1.1.2 Research task of the literature group

The organising committee has specified the research task for the literature review as follows:

- To discuss selected guidelines regarding jury questions numbers 1.1, 2.2 (considering only risk of AKI in CKD and contrast nephropathy), 3 and 4.
- To search for systematic reviews, meta-analyses and RCT's for the selected drug groups with **possible benefits on the renal function** in patients with chronic kidney disease (CKD), as found in the handbooks and main guidelines. The groups that will be considered in this manner, are: certain classes of antihypertensive agents, oral antidiabetic drugs and uric acid lowering drugs (for more details: see 1.1.2.2. Interventions).
- To search for systematic reviews, meta-analyses and RCT's from 2009 (date of literature search of the renal drug handbook) for the selected drug groups **with possible harm on the renal function** in patients with CKD (as found in the handbooks, main guidelines or SPC's). These groups are: colchicine, new oral anticoagulants, NSAID's, paracetamol (acetaminophen), methotrexate, lithium, lipid lowering therapies and phosphate containing bowel preparations.
- For other selected medication groups which do **not harm nor benefit** the progression of the renal insufficiency, only handbooks and guidelines will be discussed, with special attention to dosing, follow-up and toxicity symptoms. Groups considered here are: vitamin K antagonists, LMWHs, narcotic analgesics, sotalol and digoxin.
- To search for systematic reviews, meta-analyses and RCT's for the association of RAAS inhibitors, NSAIDs and diuretics.
- To discuss selected guidelines and handbooks on the association of statins and fibrates.
- To search for large observational studies when systematic reviews, meta-analyses and RCT's are missing for certain interventions or endpoints.

Populations

The following populations are to be evaluated.

- Adults with chronic kidney disease (CKD), defined as a GFR < 60 ml/min and/or with signs of kidney damage, as defined by KDIGO. [2]
- Special attention is given to diabetic patients concerning antihypertensive drugs and antidiabetic agents.
- No special attention is given to the elderly population, because in this population therapy is primarily adjusted to renal function, independently of age.

Excluded from the literature search are:

- renal transplant patients
- patients with end stage renal failure (ESRD)
- patients on dialysis
- children.

1.1.2.1 Interventions

Only products with a registered indication in Belgium will be considered. According to the demand of the organising committee, the following molecules will be considered (see also 1.1.2 for research task depending on drug group) :

- Antidiabetic drugs (insulin excluded): metformin, incretin mimetics, DPP4- inhibitors, glinides, thiazolidinediones, sulfonylurea, acarbose
- Antihypertensive drugs: ACE-inhibitors (ACE-Is), angiotensin II receptor antagonists (ARBs), aliskiren, dual RAAS inhibition, beta blockers, calcium channel blockers, diuretics
- Lipid lowering drugs: statins, fibrates
- Drugs used in the management of gout: allopurinol, febuxostat, colchicine
- Anticoagulants: LMWH, vitamin K antagonists, new oral anticoagulants
- Analgesics: NSAIDs, acetaminophen, narcotic analgesics
- Specific drugs: sotalol, digoxin, methotrexate, lithium, phosphate containing bowel preparations
- Associations: fibrates+statins, NSAIDs+diuretics+ACE-Is

Supplementary interventions considered are:

- Strict vs standard blood pressure control
- Strict vs standard glycemic control

1.1.2.2 Endpoints

The following endpoints are to be reported from RCT's and in case of lack of RCT's, from observational cohort studies for the aforementioned drugs studied:

- All-cause mortality
- Cardiovascular events including CVA
- Doubling of serum creatinine
- Number of patients progressing to end-stage renal disease

For defined classes of medication, additional endpoints are to be studied:

<u>Oral antidiabetics</u>

- Lactic acidosis
- Hypoglycaemia
- HbA1c
- Incretin mimetics: gastrointestinal side effects

<u>Antihypertensive drugs</u>

- Blood pressure (BP), mean change in BP (compared to baseline), number of patients achieving target BP
- Micro/macro albuminuria; proteinuria
- Hyperkalaemia

<u>Drugs used in the management of gout</u>

Colchicine

- Gastro-intestinal side effects

Allopurinol

- Skin rash
- Bone marrow depression

<u>New Oral Anticoagulants</u>

- Major bleeding
- Minor bleeding
- Haemorrhagic stroke

<u>NSAIDs</u>

- gastro-intestinal bleeding
- composite bleeding risk

<u>Phosphate containing bowel preparations</u>

- electrolyte disturbances (hyperphosphatemia, hypocalcaemia)

<u>Association ACE inhibitors + NSAIDs + diuretics</u>

- hyperkalaemia
- BP, mean change in BP (compared to baseline), number of patients achieving target BP

1.1.2.3 Study criteria

The following study criteria were to be used as inclusion criteria:

- All type of studies
    - Research question in selected publication matched research question for this literature review
    - Reporting of clinically relevant outcomes
    - Some publications were excluded for practical reasons:
        - Publications unavailable in Belgian libraries
        - Publications in languages other than Dutch, French, German and English

- RCT
    - Preferably double blind
    - Because short term effects are also to be considered, no study duration was specified.
    - Minimum number of participants: minimum 40 per study arm. For studies with multiple treatment arms, we looked at the number of participants in comparisons relevant to our search.
    - Phase III trials (no phase II trials)

- Observational studies
    - If RCT's are lacking
    - Only cohortstudies
    - Only studies with small confidence intervals

- Other sources for safety and dosing
    - Commentaren Medicatiebewaking 2014/2015 [5]
    - Renal Drug Handbook 3th. Ed. 2009 [6]

1.1.2.4 Guidelines

Only guidelines that report Levels of evidence/Grades of recommendation are selected.
Only guidelines from 2009 onwards are selected.
Guidelines were selected and agreed upon through discussion with the organising committee, based on relevance for the Belgian situation.
Similarities and discrepancies between guidelines are to be reported.
The literature group will also report whether the guideline was developed together with other stakeholders (other healthcare professionals: pharmacists, nurses,… or patient representatives) and whether these guidelines are also targeting these groups.

Each guideline will be appraised on base of the AGREE II scoring system, with special attention to the evidence supporting the Levels of evidence and the Grades of recommendation.

In order to make an assessment on the rigour of development of the guidelines, guidelines were scored according to Agree II score, for the domain “Rigour of development”. More information can be found on http://www.agreetrust.org/. [7]

Table 1 gives an overview of the items assessed in this domain according to the Agree II score.[7]

No.	Description of the item
7	Systematic methods were used to search for evidence
8	The criteria for selecting the evidence are clearly described
9	The strengths and limitations of the body of evidence are clearly described
10	The methods for formulating the recommendations are clearly described
11	Health benefits, side effects, and risks have been considered in formulating the recommendations.
12	There is an explicit link between the recommendations and the supporting evidence.
13	The guideline has been externally reviewed by experts prior to its publication
14	A procedure for updating the guideline is provided

Table 1. Items assessed by the domain "Rigour of development" in AgreeIIscore.

Domain scores are calculated by summing up all the scores of the individual items in a domain and by scaling the total as a percentage of the maximum possible score for that domain. The domain score “Rigour of development” can be used to assess the process used to gather and synthesize the evidence, the methods to formulate the recommendations, and to update them, though be careful with the interpretation because this scoring is also subjective and the resulting scores can thus be disputable.

In the section about the guidelines, the Domain scores like assessed by the literature group, are given for each guideline.

1.2 Search strategy

1.2.1 Principles of systematic search

Relevant literature was searched in a stepwise approach.

- Firstly, sources that report and discuss data from systematic reviews, meta-analyses and original trials, like Clinical Evidence were consulted. Guidelines were consulted to look up additional relevant references.
- In a second step we have searched for large systematic reviews from reliable EBM-producers (NICE, AHRQ, the Cochrane library) that answer our research questions. For the subjects where we didn't find systematic reviews in this manner, Pubmed was searched using the query and limited to systematic reviews. To only use good quality systematic reviews as a basic source, systematic reviews with an Amstar score ≤ 3, were excluded. One or more systematic reviews were selected as our basic source. From these sources, references of relevant publications were screened manually.
- In a third step, we conducted a systematic search for RCT's, meta-analyses and smaller systematic reviews that were published after the search date of our selected systematic reviews.
- In absence of systematic reviews, meta-analyses or RCT's, a systematic search for cohort studies was conducted.

The following electronic databases have been searched

- Medline (PubMed)
- Cochrane Library

A number of other sources were consulted additionally: relevant publications, indices of magazines available in the library of vzw Farmaka asbl: mainly independent magazines that are a member of the International Society of Drug Bulletins (ISDB) such as Geneesmiddelenbulletin (The Netherlands), Folia Pharmacotherapeutica (Belgium), La Revue Prescrire (France), Drug & Therapeutics Bulletin (UK), Therapeutics Letter (Canada), Geneesmiddelenbrief (Belgium), Arzneimittelbrief (Germany),…

Guidelines were searched through the link "evidence-based guidelines" on the website of vzw Farmaka asbl (www.farmaka.be) and on the website of CEBAM (www.cebam.be). These contain links to the national and most frequently consulted international guidelines, as well as links to 'guideline search engines', like National Guideline Clearinghouse and G-I-N.

1.2.2 Search strategy details

As a source document, the following systematic reviews or meta-analyses were selected

Glycemic control

- Fink HA, Ishani A, Taylor BC, Greer NL, MacDonald, R, Rossini D, Sadiq S, Lankireddy S, Kane RL, Wilt TJ. Chronic Kidney Disease Stages 1–3: Screening, Monitoring, and Treatment. Comparative Effectiveness Review No. 37. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. HHSA 290-2007-10064-I.) AHRQ Publication No. 11(12)-EHC075-EF. Rockville, MD: Agency for Healthcare Research and Quality. January 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm. (search date January 2011)[8]
- National Kidney Foundation. *KDOQI™ Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic KidneyDisease*.Am J Kidney Dis 49:S1-S180, 2007 (suppl 2) [9] + National Kidney Foundation. KDOQI ClinicalPractice Guideline for Diabetes and CKD: 2012 update. *Am J Kidney Dis*. 2012;60(5):850-886. (search date oktober 2010) [10]

Antihypertensive drugs

- Fink HA, Ishani A, Taylor BC, Greer NL, MacDonald, R, Rossini D, SadiqS, Lankireddy S, Kane RL, Wilt TJ. Chronic Kidney Disease Stages 1–3: Screening, Monitoring, and Treatment. Comparative Effectiveness Review No. 37. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. HHSA 290-2007-10064-I.) AHRQ Publication No. 11(12)-EHC075-EF. Rockville, MD: Agency for Healthcare Research and Quality. January 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm. (search date January 2011)[8]

Since the AHRQ report included only patients with CKD stages 1-3, this document was compared to

- National Clinical Guideline Centre. Chronic kidney disease (partial update). Clinical Guideline 182, July 2014. www.nice.org.uk (search date November 25, 2013)[11]
- KDIGO Management of Blood Pressure in Chronic kidney disease (search date February 2012)[12]

in order to retrieve trials in patients with CKD stage 4.

Lipid lowering drugs and anticoagulants

- National Clinical Guideline Centre. Chronic kidney disease (partial update). Clinical Guideline 182, July 2014. www.nice.org.uk (search date November 25, 2013)[11]

Drugs used in hyperuricemia

- Bose B, Badve SV, Hiremath SS, et al. Effects of uric acid-lowering therapy on renal outcomes: a systematic review and meta-analysis. Nephrol Transplant 2014;29:406-13. (search date December 2012)[13]. Since this meta-analysis uses clinical heterogeneous studies, with CKD and non-CKD subgroups, the pooled analysis has not been used but reference list was checked to find relevant publications.

Analgesics

- Nderitu P, Doos L, Jones PW, et al. Non-steroidal anti-inflammatory drugs and chronic kidney disease progression: a systematic review. Fam Pract 2013;30:247-55. (search date September 2011).[14]

A search strategy was developed in Pubmed to find relevant RCT's and observational studies that appeared after the search date of above publications (http://www.ncbi.nlm.nih.gov/pubmed/).

The search strategy that was used can be found in Appendix 1.

1.3 Selection procedure

Selection of relevant references was conducted by two researchers independently. Differences of opinion were resolved through discussion. A first selection of references was done based on title and abstract. When title and abstract were insufficient to reach a decision, the full article was read to decide on inclusion or exclusion.

In– and exclusion criteria of the different types of studies are found in chapter 1.1.2 with relevant populations, interventions, endpoints and study criteria

1.4 Assessing the quality of available evidence

To evaluate the quality of the available evidence, the GRADE system was used. In other systems that use 'levels of evidence', a meta-analysis is often regarded as the highest level of evidence. In the GRADE system, however, only the quality of the original studies is assessed. Whether the results of original studies were pooled in a meta-analysis is of no influence to the quality of the evidence.
The GRADE-system is outcome-centric. This means that quality of evidence is assessed for each endpoint, across studies.

The GRADE system[15-17] assesses the following items:

Study design		+ 4	RCT
		+ 2	Observational
		+ 1	Expert opinion
Study quality		- 1	Serious limitation to study quality
		- 2	Very serious limitation to study quality
Consistency		- 1	Important inconsistency
Directness		- 1	Some uncertainty about directness
		- 2	Major uncertainty about directness
Imprecision		- 1	Imprecise or sparse data
Publication bias		- 1	High probability of publication bias
For observational studies	Evidence of association	+ 1	Strong evidence of association (RR of >2 or <0.5)
		+ 2	Very strong evidence of association (RR of >5 or <0.2)
	Dose response gradient	+ 1	Evidence of a dose response gradient (+1)
	Confounders	+ 1	All plausible confounders would have reduced the effect
SUM		4	HIGH quality of evidence
		3	MODERATE quality of evidence
		2	LOW quality of evidence
		1	VERY LOW quality of evidence

Table 2. Items assessed by the GRADE system

In this literature review the criteria 'publication bias' has not been assessed. The GRADE system has only been used in this literature review to assess RCT's, so the criteria specifically intended for observational studies (see table above) has not been assessed. This adapted version of GRADE therefore evaluates the following criteria:

Study design	+ 4	RCT
Study quality	- 1	Serious limitation to study quality
	- 2	Very serious limitation to study quality
Consistency	- 1	Important inconsistency
Directness	- 1	Some uncertainty about directness
	- 2	Major uncertainty about directness
Imprecision	- 1	Imprecise or sparse data
SUM	4	HIGH quality of evidence
	3	MODERATE quality of evidence
	2	LOW quality of evidence
	1	VERY LOW quality of evidence

Table 3 GRADE system adapted by literature group

In assessing the different criteria, we have applied the following rules:

Study design

In this literature review RCT's and observational studies are included but GRADE was only applied to the RCT's.

Study quality

To assess the methodological quality of RCT's, we considered the following criteria:

- **Randomization**: If the method of generating the randomization sequence was described, was it adequate (table of random numbers, computer-generated, coin tossing, etc.) or inadequate (alternating, date of birth, hospital number, etc.)?
- **Allocation concealment:** If the method of allocation was described, was it adequately concealed (central allocation, …) or inadequate (open schedule, unsealed envelopes, etc.)?
- **Blinding**: Who was blinded? Participants/personnel/assessors. If the method of blinding was described, was it adequate (identical placebo, active placebo, etc.) or inadequate (comparison of tablet vs injection with no double dummy)?
- **Missing outcome data:** Follow-up, description of exclusions and drop-outs, ITT
- **Selective outcome reporting**

If a meta-analysis or a systematic review is used, quality of included studies was assessed. It is not the quality of the meta-analysis or systematic review that is considered in GRADE assessment, but only the quality of RCTs that were included in the meta-analysis/systematic review.

Application in GRADE:
Points were deducted if one of the above criteria was considered to generate a high risk of bias for a specific endpoint.
For example:

- Not blinding participants will not decrease validity of the results when considering the endpoint 'mortality', but will decrease validity when considering a subjective endpoint such as pain, so for the endpoint pain, one point will be deducted.
- A low follow-up when no ITT analysis is done, will increase risk of bias, so one point will be deducted in this case.

Consistency

Good "consistency" means that several studies have a comparable or consistent result. If only one study is available, consistency cannot be judged. This will be mentioned in the synthesis report as "NA" (not applicable).

Consistency is judged by the literature group and the reading committee based on the total of available studies, whilst taking into account

- Statistical significance
- Direction of the effect if no statistical significance is reached. E.g. if a statistically significant effect was reached in 3 studies and not reached in 2 others, but with a non-significant result in the same direction as the other studies, these results are considered consistent.
- Clinical relevance: if 3 studies find a non-significant result, whilst a 4th study does find a statistically significant result, that has no clinical relevance, these results are considered consistent.
- For meta-analyses: Statistical heterogeneity. In the NICE report, statistical heterogeneity was assessed by considering the chi-squared test for significance at $p<0.1$ or an I-squared inconsistency statistic of >50% to indicate significant heterogeneity[11]; Fink used I^2 statistic (≥50% indicates moderate heterogeneity and ≥75% indicates high heterogeneity).[8]

Directness

Directness addresses the extent in which we can generalise the data from a study to the real population (external validity). If the study population, the studied intervention and the control group or studied endpoint are not relevant, points can be deducted here. When indirect comparisons are made, a point is also deducted.

Imprecision

If we include systematic reviews or meta-analyses that include studies with <40 patients per study-arm (for a cross-over study: <40 patients in the complete study), a point is deducted for imprecision. For meta-analyses and in comparisons with only one study: a point is deducted when power is inadequate (depends also on the sample size).

Application of GRADE when there are many studies for 1 endpoint:

Points are only deducted if the methodological problems have an important impact on the result. If 1 smaller study of poor quality confirms the results of 2 large good quality studies, no points are deducted.

More information on the GRADE Working Group website: http://www.gradeworkinggroup.org[16]

1.5 Synopsis of study results

The complete report contains per research question

- (Comprehensive) summary of selected guidelines
- Evidence tables (English) of systematic reviews or RCT's on which the answers to the study questions are based
- A short synopsis, consisting of a summary table and a text, with a quality assessment using an adjusted version of the GRADE system (English)

The synopsis report contains per research question

- (Brief) summary of selected guidelines
- A short synopsis, consisting of a summary table and a text, with a quality assessment using an adjusted version of the GRADE system.

The conclusions have been discussed and adjusted through discussions between the authors of the literature search and the reading committee of the literature group.

2 Critical reflections of the literature group and reading committee

2.1 Population

The majority of the clinical trials was performed in patients with early stages of CKD (1-3). Information on patients with CKD stage 4 is lacking.
Trials used heterogeneous entrance criteria for renal function and damage, which were based on different definitions of CKD stages. The meta-analyses in this report pooled this diverse data. Moreover, trials rarely reported outcomes stratified by CKD stage or other CKD markers. This makes it difficult to determine if clinical benefits applied to patients within individual CKD stages or eGFR or albuminuria categories. Only limited data addressed whether the relative effectiveness of treatment differed between patients with and without CKD or between patients with different stages of CKD. Incomplete reporting of patient characteristics in many included trials also limits our ability to judge applicability of study results to specific CKD patient populations. [8]
For the section on antihypertensive drugs, besides heterogeneity of renal function, some of the studies included normotensive patients, some hypertensive patients and other did not specified blood pressure parameters. This means that studies of hypertensive and normotensive patients were pooled together in the AHRQ report.[11]

2.2 Intervention

Many studies on antihypertensive drugs, with the exception of those in the ARB versus placebo comparisons, compared drugs at doses that are considered subtherapeutic, and would not be expected to be of benefit. This represents a limitation in the evidence for these comparisons. In some other trials, final achieved doses were not provided, so it is unclear if the doses compared were equivalent.[11]

2.3 Outcomes

2.3.1 Composite outcomes

The composite vascular and composite renal outcomes reported in the trials are very heterogeneous. Although the AHRQ report[8] performed a pooled analysis on these outcomes, we choose not to report these outcomes because no clinical conclusions can be drawn from them.

2.3.2 Adverse effects

Few trials reported adverse events. When reported, adverse events often did not appear to be predefined, were not systematically collected or reported, and often were not reported separately by treatment group. Although limitations in reporting impeded the quantitative synthesis of withdrawal and adverse events data from different studies, adverse events reported were generally consistent with known safety profiles of these treatments (e.g., hypotension with antihypertensives; cough with ACEIs; edema with calcium channel blockers; hyperkalemia with ACEIs, ARBs, and aldosterone). [11]

2.4 Study design and quality[18, 19]

For certain medication groups, especially statins and antithrombotic drugs, the available trials are of very poor quality: mostly post-hoc subgroup analyses. These post-hoc analysis do not guarantee that randomization is preserved and groups are big enough to draw conclusions.
A few predefined subgroupanalyses were found, but no correction was made for the use of multiple comparisons. Caution is warranted in the interpretation of these analyses, because the more subgroupanalyses are performed, the bigger the chance that the result found is caused by accident.

2.5 Guidelines

The majority of the current recommendations in the guidelines are mainly based on weak level of evidence, reflecting the lack of good quality studies in CKD patients. Sometimes, guidelines are based on studies that are carried out in a normal population, while it is emphasized that it is not clear if this can be extrapolated to a CKD population. Guidelines mention frequently the lack of data in CKD patients, especially when GFR < 30ml/min. Therefore a considerable part of the recommendations are based on expert consensus.

2.6 Handbooks

The handbooks considered in this literature review are not totally evidence based but use new literature to update their information. Dose adjustments and advice on use of drugs in CKD in the books are primarily based on pharmacokinetic models and expert opinion instead of convincing evidence. But as noted above, good studies on patients with renal insufficiency are scarce.
This explains the frequent contradictions that exist between different pharmacology compendia.

2.7 Lack of studies

We already pointed to the lack of studies in CKD stage 4 and to the poor quality of the existing trials in the other stages. Furthermore, for some drug groups, no studies at all in CKD patients were identified.
To conclude, the literature group feels that there is an important lack of evidence in the use of drugs in patients with CKD, which can hopefully be resolved by future trials, specifically targeting this important patient population.

3 General information on selected guidelines

3.1 Selected guidelines

The selected guidelines and their abbreviations like used in this report can be found in table 4.

Abbreviation	Guideline
KDIGO CKD 2012	KDIGO Clinical practice guideline for the evaluation and management of chronic kidney disease [2]
KDIGO AKI 2012	KDIGO Clinical practice guideline for acute kidney injury[3]
KDIGO BP in CKD 2012	KDIGO Clinical practice guideline for the management of blood pressure in chronic kidney disease[12]
KDIGO lipid in CKD 2013	KDIGO Clinical practice guideline for lipid management in chronic kidney disease[20]
KDOQI DM and CKD 2012	KDOQI Clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. [10]
NICE CKD 2014	NICE Chronic kidney disease - early identification and management of chronic kidney disease in adults in primary and secondary care.[11]
NICE AKI 2013	NICE Acute kidney injury. Prevention, detection and management of acute kidney injury up to the point of renal replacement therapy. Clinical guideline.[1]
ACP CKD 2013	Screening, Monitoring, and Treatment of Stage 1 to 3 Chronic Kidney Disease: A Clinical Practice Guideline From the American College of Physicians[21]
Domus Medica CNI 2012	Richtlijn voor goede medische praktijkvoering: Chronische nierinsufficiëntie. Domus Medica [4]
ACR gout 2012	American College of Rheumatology guidelines for management of gout [22, 23]
CCS atrial fibrillation 2012	Focused 2012 update of the Canadian cardiovascular society atrial fibrillation guidelines: Recommendations for stroke prevention and rate/rhythmcontrol.[24]
SIGN Antithrombotics 2013	SIGN Antithrombotics: indications and management. A national clinical guideline. Updated 2013. [25]

Table 4 Selected guidelines and their abbreviations like used in this report.

3.2 Grades of recommendation and levels of evidence

Grades of recommendation and levels of evidence like defined in each guideline, can be found in tables 5 to 11.

KDIGO CKD 2012 [2] **KDIGO AKI 2012** [3] **KDIGO BP in CKD 2012** [12] **KDIGO lipid in CKD 2013** [20] **KDOQI DM and CKD 2012** [10] (This guideline updates the Clinical practice guideline from 2007. "Evaluation of renal function" and "antihypertensive drugs" were not updated and the authors refer to the original 2007 guideline, which we used for the recommendations concerning this subject [9])			
Grades of recommendation			For Clinicians
	1 ("We recommend")		Most patients should receive the recommended course of action.
	2 ("We suggest")		Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.
	Not graded		Is used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence.
Level of evidence	Grade	Quality	Meaning
	A	High	The authors are confident that the true effect lies close to that of the estimate of the effect.
	B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
	C	Low	The true effect may be substantially different from the estimate of the effect.
	D	Very Low	The estimate of effect is very uncertain, and often will be far from the truth.

Table 5 Grades of recommendation and levels of evidence of KDIGO and KDOQI guidelines.

NICE CKD 2014 [11] **NICE AKI 2013** [1]		
Grades of recommendation	Interventions that must (or must not) be used	If there is a legal duty to apply the recommendation or occasionally if the consequences of not following the recommendation could be extremely serious or potentially life threatening.
	Interventions that should (or should not) be used (strong recommendation) "offer"; "refer"; "advise"	For the vast majority of patients, an intervention will do more good than harm, and be cost effective. Similar forms of words (for example, 'Do not offer…') are used when they are confident that an intervention will not be of benefit for most patients.

	Interventions that could be used	An intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences.
Level of evidence	High	Future research unlikely to change confidence in estimate of effect.
	Moderate	Further research likely to have an important impact on confidence in estimate of effect and may change the estimate.
	Low	Further research very likely to have a significant impact on the estimate of effect and is likely to change the estimate.
	Very Low	The estimate of effect is very uncertain.

Table 6 Grades of recommendation and Levels of evidence of NICE guidelines.

ACP CKD 2013 [21]				
Uses ACP's guideline grading system, adopted from the classification of the GRADE workgroup.				
Level of evidence		High	Moderate	Low
Grade of recommendation	Benefits clearly outweigh risks and burden or risks and burden clearly outweigh benefits.	Strong	Strong	Strong
	Benefits finely balanced with risks and burden.	Weak	Weak	Weak

Table 7 Grades of recommendation and Levels of evidence of ACP guidelines.

Domus Medica CNI 2012 [4]

This guideline is developed following the ADAPTE procedure using following guidelines:

- NICE: National Collaborating Centre for Chronic Conditions. Chronic kidney disease: national clinical guideline for early identification and management in adults in primary and secondary care. London: Royal College of Physicians 2008.[26]
- SIGN: Scottish intercollegiate Guidelines Network. Diagnosis and management of chronic kidney disease; 2008.[27]

The Grades of recommendation are based on the evidence scheme developed by the Grade Working Group and adapted by the Grading system. The original guideline used only a classification of evidence level. This was translated to "Quality of evidence", completed by a grade of recommendation to become a Grade.

Grades of recommendation	1	Strong recommendation
	2	Weak recommendation
Level of evidence	A	High
	B	Moderate
	C	Low

Table 8 Grades of recommendation and Level of evidence of Domus Medica guidelines.

ACR gout 2012 [22, 23]		
Grades of recommendation	No grades of recommendation	
Level of evidence	A	Supported by multiple (i.e.,>1) randomized clinical trials or meta-analyses.
	B	Derived from a single randomized trial or nonrandomized studies.
	C	Consensus opinion of experts, case studies, or standard of care.

Table 9 Grades of recommendation and Level of evidence of ACR guidelines.

CCS atrial fibrillation 2012 [24]		
Grades of recommendation	Strong	
	Conditional	
	Weak	
Level of evidence	High	Future research is unlikely to change confidence in estimate of effect; e.g., multiple well-designed, well-conducted clinical trials.
	Moderate	Further research is likely to have an important impact on confidence in estimate of effect and may change the estimate; e.g., limited clinical trials, inconsistency of results or study limitations.
	Low	Further research very likely to have a significant impact on the estimate of effect and is likely to change the estimate; e.g., small number of clinical studies or cohort observations.
	Very low	The estimate of effect is very uncertain; e.g., case studies, consensus opinion.

Table 10 Grades of recommendation and Level of evidence of CCS guidelines.

SIGN Antithrombotics 2013 [25]		
Grades of recommendation	A	At least one meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+ directly applicable to the target population, and demonstrating overall consistency of results.
	B	A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+.
	C	A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++.
	D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+.
Level of evidence	1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.
	1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias.
	1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias.

	2++	High quality systematic reviews of case control or cohort studies; or High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.
	2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal.
	2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal.
	3	Non-analytic studies (e.g., case reports, case series).
	4	Expert opinion.

Table 11 Grades of recommendation and Levels of evidence of SIGN guidelines.

3.3 Agree II score

Information about the Agree II score can be found in the section "Methodology".
A summary of the assessment by the literature group of the individual items of the domain score can be found for each guideline in table 12. The total domain score is also reported in this table.

Rigour of development item	7	8	9	10	11	12	13	14	Total	Domain score
KDIGO CKD 2012 [2]	5	5	7	1	7	7	7	5	**44**	**75%**
KDIGO AKI 2012 [3]	6	7	7	1	7	7	6	7	**48**	**83%**
KDIGO BP in CKD 2012 [12]	6	7	7	1	7	7	6	5	**46**	**79%**
KDIGO Lipid in CKD 2013 [20]	6	7	7	1	7	7	6	7	**48**	**83%**
KDOQI DM and CKD 2012 [10]	5	7	7	2	7	7	4	1	**40**	**66%**
NICE CKD 2014 [11]	7	7	7	5	7	7	7	5	**52**	**92%**
NICE AKI 2013 [1]	7	7	7	5	7	7	7	5	**52**	**92%**
ACP CKD 2013 [21]	6	7	7	1	7	7	2	2	**39**	**65%**
Domus Medica CNI 2012 [4]	3	4	5	1	5	7	7	5	**37**	**60%**
ACR Gout 2012 [22, 23]	3	2	1	7	6	4	1	1	**25**	**35%**
CCS Atrial Fibrillation 2012 [24]	2	1	2	7	7	7	1	1	**28**	**42%**
SIGN Antithrombotics 2013 [25]	6	1	4	5	7	7	7	1	**38**	**63%**

Table 12. Score given to the items of the domain "Rigour of development", for the selected guidelines. In the last column the Domain score can be found.

3.4 Included populations - interventions - main outcomes

In table 13 – 23, the populations, interventions and main outcomes considered in the selected guidelines are represented.

KDIGO CKD 2012 [2]	
Population	- Adults and children identified with CKD who are not on RRT
Interventions	- Diagnostic interventions - Pharmacological interventions: Blood pressure targets and agents, ARBs, ACE-Is, glycemic control, statins, antiplatelet therapy, bicarbonate supplementation, vaccination, contrast agents, bowel preparations, agents to lower serum uric acid, vitamin D and bisphosphonates, herbal remedies. - Non-pharmacological interventions: Lowering protein and salt intake, physical activity, weight, smoking cessation, dietary advice, referral, renal replacement therapy, bone mineral density measurement - Advance care planning, end-of-life and palliative care
Outcomes	- Sensitivity, specificity, and accuracy of diagnostic tests - Rates of CKD progression - Risk of cardiovascular disease - Risk of end-stage renal disease - Mortality - Quality of life - Risk of hypertension, gout attacks, and proteinuria

Table 13 Included population, intervention and main outcomes of KDIGO guideline CKD. [2]

KDIGO AKI 2012 [3]	
Population	- Adults and children at risk for or with acute kidney injury
Interventions	- Risk Assessment/Evaluation, prevention - Pharmacological interventions: isotonic crystalloids, vasopressors, insulin, theophylline for neonates, anticoagulation, diuretics, vasodilators, growth factor interventions, N-acetyl cysteine - Non-pharmacological interventions: Nutritional intake, prophylactic intermittent hemodialysis or hemofiltration, coronary artery bypass surgery - Protocol-based hemodynamic and oxygenation parameters - Assessment of risk and prevention of contrast-induced AKI - Renal replacement therapy (RRT)
Outcomes	- Development of AKI - Need for or dependence on RRT - All-cause mortality.

Table 14 Included population, intervention and main outcomes of KDIGO guideline AKI [3]

KDIGO BP in CKD 2012 [12]	
Population	- All non-dialysis-dependent CKD patients and kidney transplant recipients
Interventions	- Non-pharmacological: advice on lifestyle - Pharmacological agents that reduce BP - Blood pressure targets
Outcomes	- Kidney outcomes (kidney function and albuminuria) - Cardiovascular outcomes

Table 15 Included population, intervention and main outcomes of KDIGO guideline BP in CKD [12]

KDIGO Lipid in CKD 2013 [20]	
Population	- Adults and children with known CKD
Interventions	- Lipid lowering therapies (pharmacological and lifestyle)
Outcomes	- Mortality, cardiovascular mortality, cardiovascular or cerebrovascular events - ESRD, graft failure, doubling of SCr or halving of GFR - Change in TC, LDL-C, or HDL-C or TGs - Adverse events

Table 16 Included population, intervention and main outcomes of KDIGO guideline lipid in CKD [20].

KDOQI DM and CKD 2012 [10]	
Population	- Patients with diabetes mellitus with or without CKD
Interventions	- Target HbA1c - LDL-C lowering medicines - ACE-I or ARB in normotensive patients with diabetes and albuminuria
Outcomes	- All-cause mortality, cardiovascular death, non-fatal cardiovascular events - ESRD - Clinically significant retinopathy including vision loss, amputations - Symptomatic hypoglycemia of sufficient severity to require the assistance

Table 17 Included population, intervention and main outcomes of KDOQI guideline DM and CKD [10]

NICE CKD 2014 [11]	
Population	- Adults aged 18 and over. Specific consideration is given to older people, black and minority ethnic people and people at high risk of developing CKD
Interventions	- Measurement of kidney function and markers of kidney damage, frequency of monitoring, classification of CKD. - Non-pharmacological interventions: Diet, self-management support systems - Pharmacological therapy: renin-angiotensin-aldosterone system antagonists, antiplatelet and antithrombotic therapy, uric acid lowering therapy, vitamin D and bicarbonate supplementation
Outcomes	- Diagnostic: accuracy, bias, precision, sensitivity/specificity, area under curve - CKD progression, acute kidney injury - Mortality (all cause and cardiovascular) - Hospitalization - Side effects

Table 18 Included population, intervention and main outcomes of NICE guideline CKD [11]

NICE AKI 2013 [1]	
Population	- Adults, children older than 1 month and young people up to 18 years. - Particular consideration is to the needs of older patients and people at high risk of acute kidney injury, such as people with CKD and urological disorders
Interventions	- Investigation and identification of acute kidney injury, monitoring and preventing deterioration in patients with or at high risk of AKI - Assessment of risk factors and prevention of AKI in adults having iodinated contrast agents or surgery - Identification of causes of AKI - Managing AKI - Information and support for patients and carers
Outcomes	- Sensitivity, specificity, positive/negative predictive value, likelihood ratio - Incidence of acute kidney injury - Cardiovascular events - All-cause mortality - Number of patients needing renal replacement therapy - Length of hospital stay - Cost-effectiveness

Table 19 Included population, intervention and main outcomes of NICE guideline AKI [1]

ACP CKD 2013 [21]	
Population	- Adults with CKD stage 1 to 3, defined as: o Stage 1 Kidney damage with GFR >90 mL/min/1.73 m^2 o Stage 2 Kidney damage with GFR of 60–89 mL/min/1.73 m^2 o Stage 3 GFR of 30–59 mL/min/1.73 m^2
Interventions	- Screening and monitoring tests - Pharmacological interventions: ACE-Is, ARBs, beta blockers, calcium-channel blockers, thiazide diuretics, statins, intensive diabetes control) - Non-pharmacological interventions: low-protein diet, multicomponent interventions
Outcomes	- All-cause mortality, cardiovascular mortality, cardiovascular events - Composite renal outcomes (including but not limited to doubling of serum creatinine, need for dialysis, and reduction of GFR by 50%) - ESRD - Quality of life, physical function, activities of daily living

Table 20 Included population, intervention and main outcomes of ACP guideline CKD [21]

Domus Medica CNI 2012 [4]	
Population	- Adult patients (older than 18 years) with a chronic decreased renal function. Acute forms are not included.
Interventions	- Those aiming to slow down of progression of the disease. - Treatment of the symptomatology - The causal treatment is not considered
Outcomes	- Not described.

Table 21 Included population, intervention and main outcomes of Domus Medica guideline CKD [4]

ACR Gout 2012 [22, 23]	
Population	- Patients with gout
Interventions	- Assessment of comorbidities, of use of uric acid elevating medicines, of risk of allopurinol hypersensitivity syndrome - History and physical examination, investigations, imaging, referral - Non-pharmacological counseling - Pharmacological interventions: allopurinol, febuxostat, probenecid, fenofibrate, losartan, urine alkalization, combination therapy, pegloticase) - Uric acid monitoring during drug titration
Outcomes	- Risk and frequency of gout attacks - Changes in serum uric acid levels, efficacy in achieving serum uric acid target - Tophus size - Time to treatment response - Adverse effects - Health-related quality of life

Table 22 Included population, intervention and main outcomes of ACR guidelines Gout [22, 23]

SIGN Antithrombotics 2012 [25]	
Population	- Adult patients on antithrombotic therapy
Interventions	- Antiplatelet agents: aspirin, dipyridamole, clopidogrel - Parenteral anticoagulation: unfractionated heparin and low molecular weight heparin, fondaparinux, danaparoid - Oral anticoagulation with vitamin K antagonists: warfarin - Novel antithrombotic agents - Combination therapy - Assessment of risk factors using $CHADS_2$ or CHA_2DS_2-VASc - Patient education on self-monitoring and computer-assisted dosing
Outcomes	- Positive and negative predictive value of diagnostic tests - Risk factor score ($CHADS_2$ or CHA_2DS_2-VASc) - Rate of major bleeding episodes, including intracranial bleeding - Risk of myocardial infarction, stroke, systemic embolism, and other cardiovascular events - Adverse effects of antithrombotic therapy - Mortality

Table 23 Included population, intervention and main outcomes of SIGN guideline Antithrombotics [25]

3.5 Members of development group – target audience

Members of the development group that produced the guidelines, and the target audience for who the guidelines are intended, can be found in table 24-35.

KDIGO CKD 2012 [2]	
Development group	Experts, including individuals with expertise in internal medicine, nephrology, diabetology/endocrinology, clinical chemistry, epidemiology.
Target audience	Nephrologists, primary care physicians, non-nephrology specialists (e.g., cardiologists, diabetologists, etc.), clinical chemists and other practitioners caring for adults and children with CKD. The guideline is also expected to be suitable for use in public policy and other health-care arenas. The target health-care settings include primary, secondary, and tertiary care.

Table 24 Members of development group and target audience of KDIGO guideline CKD [2]

KDIGO AKI 2012 [3]	
Development group	Domain experts, including individuals with expertise in nephrology, critical care medicine, internal medicine, pediatrics, cardiology, radiology, infectious diseases and epidemiology, and a professional evidence review team.
Target audience	Practitioners caring for adults and children at risk for or with AKI, including contrast-induced acute kidney injury (CI-AKI).

Table 25 Members of development group and target audience of KDIGO guideline AKI [3]

KDIGO BP in CKD 2012 [12]	
Development group	Experts, including individuals with expertise in internal medicine, nephrology, cardiology, pharmacology, epidemiology, and endocrinology.
Target audience	Health care professionals caring for individuals with CKD, including nephrologists, nurses, and pharmacists, as well as physicians involved in the care of patients with diabetes and primary care providers.

Table 26 Members of development group and target audience of KDIGO guideline BP in CKD [12]

KDIGO Lipid in CKD 2013 [20]	
Development group	Kidney specialists, diabetologists, cardiologists, epidemiologists, lipidologists and a professional evidence review team.
Target audience	Nephrologists, primary care physicians, non-nephrology specialists (e.g., cardiologists, diabetologists, etc.), clinical chemists and other practitioners caring for adults and children with CKD worldwide. The guideline is also expected to be suitable for use in public policy and other healthcare arenas.

Table 27 Members of development group and target audience of KDIGO guideline Lipid in CKD [20]

KDOQI DM and CKD 2012 [10]	
Development group	Multidisciplinary team (endocrinologists, nephrologists, pediatrics,…).
Target audience	The practitioner caring for patients with diabetes and CKD.

Table 28 Members of development group and target audience of KDOQI guideline DM and CKD [10]

NICE CKD 2014 [11]	
Development group	Multidisciplinary, comprising professional group members and consumer representatives of the main stakeholders.
Target audience	Health care professionals and others.

Table 29 Members of development group and target audience of NICE guideline CKD [11]

NICE AKI 2013 [1]	
Development group	Multidisciplinary, comprising professional group members and 3 consumer representatives of the main stakeholders.
Target audience	The guideline is primarily aimed at generalist clinicians.

Table 30 Members of development group and target audience of NICE guideline AKI [1]

ACP CKD 2013 [21]	
Development group	Not described in detail.
Target audience	Internists, family physicians and other clinicians.

Table 31 Members of development group and target audience of ACP guideline CKD [21]

Domus Medica CNI 2012 [4]	
Development group	Family physicians.
Target audience	Family physicians.

Table 32 Members of development group and target audience of Domus Medica guideline CKD [4]

ACR Gout 2012 [22, 23]	
Development group	Rheumatologists, primary care physicians, nephrologist, patient representative.
Target audience	Rheumatologists and other health care providers, including other subspecialists, primary care practitioners, nurse practitioners, physician assistants, and allied health professionals

Table 33 Members of development group and target audience of ACR guidelines Gout [22, 23]

CCS Atrial fibrillation 2012 [24]	
Development group	Wide representation from primary and specialty care (internal medicine, cardiology, neurology, and emergency medicine).
Target audience	Specialists and allied health professionals.

Table 34 Members of development group and target audience of CCS guideline Atrial fibrillation [24]

SIGN Antithrombotics 2013 [25]	
Development group	Specialists, lay representatives, general practitioner, nurses, pharmacist…
Target audience	Healthcare professionals including general practitioners, surgeons, nurses, physicians, pharmacists and dentists. It may also be of interest to patients and their carers, members of the voluntary sector and those involved in the development of research strategies in pharmacotherapy.

Table 35 Members of development group and target audience of SIGN guideline Antithrombotics [25]

3.6 Method of reporting of the recommendations and notes

For a large part of the selected chapters, no recommendations were found in the guidelines. For these items, sometimes a declaration on the drugs and their use in renal insufficiency was found in the plain text or tables of the guidelines. This information is also summarized in this document, but these parts must in no case be considered as recommendations because there are neither grades of recommendation nor levels of evidence given. To make a difference with the recommendations, this supplemental information is written in smaller letters in *italics*, while the recommendations are written **boldfaced**.

4 General information on the selected handbooks

The handbooks that were selected by the organizing committee and the literature group are:

- Commentaren Medicatiebewaking Update maart 2014 [5]
- Renal Drug Handbook 3 th ed. 2009 [6]

4.1 Information on the sources of the handbooks

4.1.1 Commentaren Medicatiebewaking 2014/2015 [5]

This handbook is based on other handbooks, Summary of Product Characteristics and publications in primary literature. The advices of the handbook are preferentially in accordance with international guidelines. There is no systematic review of literature used to write this summary. The information is yearly reviewed and updated.

4.1.2 The Renal Drug Handbook 3th ed. 2009[6]

The monographs of the Renal Drug Handbook are formed from the clinical experience of the authors and the UK Renal Pharmacy Group. The information has been largely practice-based, but is slowly evolving into an increasingly evidence-based resource. It is not based on a systematic review of literature. All drug monographs are periodically reviewed, with the date of the most recent review noted on each monograph.

4.2 Information on interpretation of contra-indications in Commentaren Geneesmiddelenbewaking[5]

Relative contra-indication: Advise the patients to contact the physician in case of symptoms
Important contra-indication: Negative influence on the syndrome
Absolute contra-indication: Avoid use of this medication

4.3 Information on cut-offs GFR as represented in the tables of the handbooks

Cut-offs for GFR differed from handbook to handbook, from drug to drug. To summarize the information in an intelligible way, we display the information according to a standard of 3 cut-off values of GFR.

5 Results: evaluation of the kidney function (guidelines only)

5.1 KDIGO CKD 2012[2]

Evaluation of GFR

KDIGO recommends using serum creatinine and a GFR estimating equation for initial assessment. *(1A).* KDIGO recommends that clinicians *(1B)*:

- **use a GFR estimating equation to derive GFR from serum creatinine ($eGFR_{creat}$) rather than relying on the serum creatinine concentration alone.**
- **understand clinical settings in which $eGFR_{creat}$ is less accurate.** *(some examples: AKI, race/ethnicity other than US and European black and white, extremes of muscle mass or body size, diet and nutritional status (high protein diet, creatine supplement), muscle wasting diseases, ingestion of cooked meat, drugs (trimethoprim, cimetidine, fenofibrate, antibiotics), dialysis, large volume losses of extracellular fluid, interference with creatinine assay (e.g., bilirubin, some drugs, glucose, ketones),…)*

KDIGO suggests using additional tests (such as cystatin C or a clearance measurement) for confirmatory testing in specific circumstances when eGFR based on serum creatinine is less accurate. *(2B)*

KDIGO suggests measuring cystatin C in adults with $eGFR_{creat}$ 45–59 ml/min/1.73 m^2 who do not have markers of kidney damage if confirmation of CKD is required. *(2C)*

- **If $eGFR_{cys}$/$eGFR_{creat-cys}$ is also <60 ml/min/1.73 m2, the diagnosis of CKD is confirmed.**
- **If $eGFR_{cys}$/$eGFR_{creat-cys}$ is ≥60 ml/min/1.73 m2, the diagnosis of CKD is not confirmed.**

If cystatin C is measured, KDIGO suggests that health professionals *(2C)*:

- **use a GFR estimating equation to derive GFR from serum cystatin C rather than relying on the serum cystatin C concentration alone.**
- **understand clinical settings in which $eGFR_{cys}$ and $eGFR_{creat-cys}$ are less accurate.** *(some examples: AKI, race/ethnicity other than US and European black and white, disorders of thyroid function, corticosteroids, factors affecting extra-renal elimination of cystatin C (e.g. by severe decrease in GFR), interference with cystatin C assay (e.g. heterophilic antibodies),…)*

KDIGO suggests measuring GFR using an exogenous filtration marker under circumstances where more accurate ascertainment of GFR will impact on treatment decisions. *(2B)*

Assess GFR at least annually in people with CKD. Recognize that small fluctuations in GFR are common and are not necessarily indicative of progression. *(Not Graded)*

Evaluation of albuminuria

KDIGO suggests using the following measurements for initial testing of proteinuria (in descending order of preference, in all cases an early morning urine sample is preferred) *(2B)*:

1) urine albumin-to-creatinine ratio (ACR);
2) urine protein-to-creatinine ratio (PCR);
3) reagent strip urinalysis for total protein with automated reading;
4) reagent strip urinalysis for total protein with manual reading.

KDIGO recommends that clinical laboratories report ACR and PCR in untimed urine samples in addition to albumin concentration or proteinuria concentrations rather than the concentrations alone. *(1B)* The term micro-albuminuria should no longer be used by laboratories. *(Not Graded)*

Clinicians need to understand settings that may affect interpretation of measurements of albuminuria and order confirmatory tests as indicated *(Not Graded)*:

- **Confirm reagent strip positive albuminuria and proteinuria by quantitative laboratory measurement and express as a ratio to creatinine wherever possible.**
- **Confirm ACR ≥30 mg/g (≥3mg/mmol) on a random untimed urine with a subsequent early morning urine sample.**
- **If a more accurate estimate of albuminuria or total proteinuria is required, measure albumin excretion rate or total protein excretion rate in a timed urine sample.**

If significant non-albumin proteinuria is suspected, use assays for specific urine proteins (e.g., a1-microglobulin, monoclonal heavy or light chains (''Bence Jones'' proteins)). *(Not Graded)*

Assess albuminuria at least annually in people with CKD *(Not Graded).*

Definition and staging of CKD

CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health. *(Not Graded)*

Criteria for CKD: either of the following present for > 3 months

- **Markers of kidney damage:**
  - **Albuminuria (AER ≥30mg/24 hours; ACR ≥30mg/g [≥3 mg/mmol])**
  - **Urine sediment abnormalities**
  - **Electrolyte and other abnormalities due to tubular disorders**
  - **Abnormalities detected by histology**
  - **Structural abnormalities detected by imaging**
  - **History of kidney transplantation**
- **Decreased GFR: GFR < 60 ml/min/1.73 m2 (GFR categories G3a-G5)**

KDIGO recommends that CKD is classified based on cause, GFR category, and albuminuria category. *(1B)*

Assign cause of CKD based on presence or absence of systemic disease and the location within the kidney of observed or presumed pathologic-anatomic findings. *(Not Graded)*

Assign GFR categories as follows *(Not Graded)*:

GFR categories in CKD

GFR category	GFR (ml/min/1.73 m^2)	Terms
G1	≥90	Normal or high
G2	60–89	Mildly decreased*
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.
*Relative to young adult level
In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.

Figure 1 GFR categories in CKD as defined by KDIGO, copied from KDIGO guideline CKD[2]

Assign albuminuria categories as follows *(Not Graded)*:

Albuminuria categories in CKD

Category	AER (mg/24 hours)	ACR (approximate equivalent) (mg/mmol)	ACR (approximate equivalent) (mg/g)	Terms
A1	<30	<3	<30	Normal to mildly increased
A2	30-300	3-30	30-300	Moderately increased*
A3	>300	>30	>300	Severely increased**

Abbreviations: AER, albumin excretion rate; ACR, albumin-to-creatinine ratio; CKD, chronic kidney disease.
*Relative to young adult level.
**Including nephrotic syndrome (albumin excretion usually >2200 mg/24 hours [ACR >2220 mg/g; >220 mg/mmol]).

Figure 2 albuminuria categories as defined by KDIGO, copied from KDIGO guideline CKD[2]

In people with GFR < 60 ml/min/1.73 m2 (GFR categories G3a-G5) or markers of kidney damage, review past history and previous measurements to determine duration of kidney disease. *(Not Graded)*

- **If duration is > 3 months, CKD is confirmed. Follow recommendations for CKD.**
- **If duration is not > 3 months or unclear, CKD is not confirmed. Patients may have CKD or acute kidney diseases (including AKI) or both and tests should be repeated accordingly.**

5.2 KDOQI Diabetes and CKD 2007 [9]

Screening *(in diabetic patients)* **should include:**

- **Measurements of urinary albumin-creatinine ratio (ACR) in a spot urine sample; *(B)***
- **An elevated ACR should be confirmed in the absence of urinary tract infection with 2 additional first-void specimens collected over the next 3 to 6 months. *(B)* Micro-albuminuria is defined as an ACR between 30-300 mg/g. Macro-albuminuria is defined as an ACR>300 mg/g. 2 of 3 samples should fall within the micro-albuminuric or macro-albuminuric range to confirm classification.**
- **Measurement of serum creatinine and estimation of GFR. *(B)***

5.3 NICE CKD 2014 [11]

Evaluation of GFR

Offer testing for CKD using $eGFR_{creat}$ and ACR to people with risk factors.

Clinical laboratories should report an estimate of glomerular filtration rate ($eGFR_{creat}$ or $eGFR_{cys}$) using a prediction equation in addition to reporting the serum creatinine or cystatin result. Apply a correction factor to GFR value for people of African–Caribbean or African family origin (multiply eGFR by 1.159).

Clinical laboratories should report GFR either as a whole number if it is 90 ml/min/1.73 m_2 or less, or as 'greater than 90 ml/min/1.73 m^{2}'. If GFR is greater than 90 ml/min/1.73 m^2, use an increase in serum creatinine concentration of more than 20% to infer significant reduction in kidney function.
Interpret eGFR values of 60 ml/min/1.73 m^2 or more with caution, bearing in mind that estimates of GFR become less accurate as the true GFR increases.

Confirm an eGFR result of less than 60 ml/min/1.73 m^2 in a person not previously tested by repeating the test within 2 weeks. Allow for biological and analytical variability of serum creatinine (±5%) when interpreting changes in eGFR.

In people with extremes of muscle mass – for example, in bodybuilders, an amputation or muscle wasting disorders – interpret $eGFR_{creat}$ with caution. (Reduced muscle mass will lead to overestimation and increased muscle mass to underestimation of the GFR.) **Advise people not to eat any meat in the 12 hours before having a blood test for $eGFR_{creat}$. Avoid delaying the dispatch of blood samples to ensure that they are received and processed by the laboratory within 12 hours of venipuncture. Interpret $eGFR_{cys}$ with caution in people with uncontrolled thyroid disease because values may be falsely elevated in people with hypothyroidism and reduced in people with hyperthyroidism.**

Consider using $eGFR_{cys}$ at initial diagnosis to confirm or rule out CKD in people with:

- **an $eGFR_{creat}$ of 45–59 ml/min/1.73 m^2, sustained for at least 90 days and**
- **no proteinuria (ACR less than 3 mg/mmol) or other marker of kidney disease.**

Do not diagnose CKD in people with:

- **an $eGFR_{creat}$ of 45–59 ml/min/1.73 m^2 and**
- **an $eGFR_{cys}$ of more than 60 ml/min/1.73 m^2 and**
- **no other marker of kidney disease.**

Where a highly accurate measure of GFR is required – for example, during monitoring of chemotherapy and in the evaluation of renal function in potential living donors – consider a reference standard measure (inulin, ^{51}Cr-EDTA, ^{125}I-iothalamate or iohexol).

Evaluation of proteinuria

Quantify urinary albumin or urinary protein loss for:

- **people with diabetes**
- **people without diabetes with a GFR of less than 60 ml/min/1.73 m^2.**

Quantify by laboratory testing the urinary albumin or urinary protein loss of people with a GFR of 60 ml/min/1.73 m^2 or more if there is a strong suspicion of CKD.

Do not use reagent strips to identify proteinuria unless they are capable of specifically measuring albumin at low concentrations and expressing the result as an ACR.

To detect and identify proteinuria, use urine ACR in preference to protein: creatinine ratio (PCR), because it has greater sensitivity than PCR for low levels of proteinuria. For quantification and monitoring of high levels of proteinuria (ACR 70mg/mmol or more), PCR can be used as an alternative. ACR is the recommended method for people with diabetes.

For the initial detection of proteinuria, if the ACR is between 3 mg/mmol and 70 mg/mmol, this should be confirmed by a subsequent early morning sample. If the initial ACR is 70 mg/mmol or more, a repeat sample need not be tested.

Regard a confirmed ACR of 3 mg/mmol or more as clinically important proteinuria.

Evaluation of hematuria

When testing for the presence of hematuria, use reagent strips rather than urine microscopy.

- **Evaluate further if there is a result of 1+ or more.**
- **Do not use urine microscopy to confirm a positive result.**

Definition and staging of CKD

Classify CKD using a combination of GFR and ACR categories (as in KDIGO, see above 2.1.1.3).
Do not determine management of CKD solely by age.
In people with a new finding of reduced GFR, repeat the GFR within 2 weeks to exclude causes of acute deterioration of GFR – for example, acute kidney injury or starting renin–angiotensin system antagonist therapy.

5.4 ACP CKD 2013 [21]

ACP recommends against screening for chronic kidney disease in asymptomatic adults without risk factors for chronic kidney disease. ***(weak recommendation, low quality evidence)***

ACP recommends against testing for proteinuria in adults with or without diabetes who are currently taking an angiotensin-converting enzyme inhibitor or an angiotensin II– receptor blocker. ***(weak recommendation, low-quality evidence)***

Criteria for CKD include markers of kidney damage (albuminuria, as indicated by an albumin excretion rate of 30mg/24 h or greater and an albumin– creatinine ratio of 3 mg/mmol or greater [>30 mg/g]); urine sediment abnormalities; electrolyte and other abnormalities due to tubular disorders; abnormalities detected by histologic examination; structural abnormalities detected by imaging; history of kidney transplantation or presence of kidney damage; or kidney dysfunction that persists for 3 or more months, as shown by structural and functional abnormalities (most often based on increased albuminuria) or a glomerular filtration rate (GFR) less than 60 mL/min/1.73 m2 for 3 or more months. Traditionally, CKD is categorized into 5 stages that are based on disease severity defined by GFR. These stages are identical to the GFR categories of KDIGO, except that there is no difference between stade 3a and stade 3b, which form together stage 3 with a GFR of 30-59 ml/min/1.73m^2. Stage 1 is normal renal function with kidney damage. Stages 1 to 3 are considered to be early-stage CKD.

No population-based studies have tested the sensitivity or specificity of 1-time CKD screening using either estimated GFR or albuminuria or the validity and reliability of repeated screening. Although no studies have compared GFR estimated from serum creatinine values with direct GFR measurement, estimation is believed to be reasonably accurate. There are many sources of variability when measuring urinary albumin loss and the method of collection and measurement of urinary albumin and creatinine has yet to be standardized.

5.5 Domus Medica CNI 2012 [4]

For screening of renal insufficiency, Domus Medica recommends following laboratory measurements:

- **Creatinine with eGFR (calculated according to the MDRD-formula)** ***(1A).***
- **In non-diabetic patients, the corrected proteinuria** ***(1B).***
- **In diabetic patients, the corrected albuminuria** ***(consensus)***

To diagnose chronic kidney disease, measure eGFR minimum three times in 90 days. ***(consensus)*** **Diagnose chronic kidney disease if eGFR <60 ml/min/1,73 m² during minimum 90 days. Think at the possibility of acute renal insufficiency in case of suddenly strong decreased renal function.**

Measure the corrected albuminuria or corrected proteinuria in eGFR <60 ml/min/1,73 m^2 ***(1C).***

CKD categories ***(consensus)*** **are assigned as in the GFR categories of KDIGO, with stage 1 a normal GFR with signs of kidney damage.**

5.6 Summary of guidelines on evaluation of renal function

All guidelines recommend an eGFR based on serumcreatinine as first test of GFR. [2, 4, 9, 11] Some guidelines suggest using an eGFR based on cystatin C to confirm CKD in patients with eGFR $_{creat}$ of 45-59 ml/min, without kidney damage. An exogenous filtration marker can be used if an exact estimate of GFR is necessary. [2, 11] To test for proteinuria, most guidelines recommend using ACR, because of higher sensitivity. [2, 9, 11]Only Domus Medica prefers PCR in non-diabetic patients, also considering the price of the tests.[4] Testing of proteinuria happens preferably on an early morning testing. [2, 4, 9, 11] Reagent strip urinalysis is not a preferred test and needs confirmation, just as AER is not preferred as first test. [2] The guidelines define CKD as presence of markers of kidney damage or/and an eGFR of < 60 ml/min/ 1.73m^2 [2, 4, 11, 21], present for minimum 3 months. [2, 4, 21] Most guidelines follow the categorization of KDIGO. [2, 4, 11] Table 36 gives an overview of the recommendations with their grades of recommendation. [2, 4, 9, 11, 21]

Evaluation of renal function				**KDIGO CKD**	**KDOQI DM CKD**	**NICE CKD**	**ACP CKD**	**Domus Medica CNI**
AGREE Domain score Rigour of development				**75%**	**66%**	**92%**	**65%**	**60%**
Definition of CKD	Kidney damage or eGFR<60ml/min			NG	-	Rec	Txt	CONS
	No diagnosis if eGFR$_{creat}$ 45-60 and eGFR$_{cys}$/eGFR$_{creat-cys}$ ≥60 and no kidney damage			2C	-	Rec	-	-
Test of GFR	Serum creatinine only			-	-	-	-	-
	eGFR based on serum creatinine			1A	B	Rec	-	1A
	eGFR base on serum cystatin C or based on both serum creatinine and cystatin		If eGFR$_{creat}$ is less accurate	2B	-	-	-	-
			if eGFR$_{creat}$ 45-59ml/min if no kidney damage	2C	-	Rec	-	-
	GFR based on exogenous filtration marker		If eGFR$_{creat}$ is less accurate	2B	-	Rec	-	-
			Need accurate GFR	2B	-	-	-	txt
Tests for albuminuria	AER	Need for more accurate estimate		NG	-	-	-	-
	ACR	preferential test	diabetic	2B	B	Rec	-	CONS
			non diabetic	2B	-	Rec	-	-
	PCR	preferential test	diabetic	-	-	-	-	-
			non diabetic	-	-	-	-	1B
		As an alternative		2B	-	Rec	-	-
	early morning urine sample			NG	B	Rec	-	txt
	Reagentstrip urinalysis	Alternative but confirmation needed by quantitative analyses		NG	-	-	-	-
Definition albuminuria	≥ 30 mg/24h			NG	B	-	Txt	-
	≥ 3mg/mmol			-	-	Rec	-	-
Chronicity	3months			NG	-	-	Txt	CONS

Table 36 Summary of recommendations on evaluation of renal function. Txt= no recommendation but in text or table, is not graded; 1, 2 on a scale of 1 to 2; A= High quality; B = Moderate quality; C= Low quality of evidence; on a scale of A to D; NG= recommendation but not graded; Rec= recommendation of NICE, no GOR found; CONS= recommendation based on consensus

6 Results: Glycemic control (insulin excluded) in CKD

6.1 Guidelines: glycemic control

6.1.1 KDIGO CKD 2012 [2]

KDIGO recommends a target hemoglobin A1c (HbA1c) of ~7.0% (53mmol/mol) to prevent or delay progression of the microvascular complications of diabetes, including diabetic kidney disease. ***(1A)***

KDIGO recommends not treating to an HbA1c target of <7.0% (<53mmol/mol) in patients at risk of hypoglycemia. ***(1B)***

KDIGO suggests that target HbA1c be extended above 7.0% (53mmol/mol) in individuals with comorbidities or limited life expectancy and risk of hypoglycemia. ***(2C)***

In people with CKD and diabetes, glycemic control should be part of a multifactorial intervention strategy addressing blood pressure control and cardiovascular risk, promoting the use of angiotensin-converting enzyme inhibition or angiotensin receptor blockade, statins, and antiplatelet therapy where clinically indicated. ***(Not Graded)***

KDIGO recommends that metformin be continued in people with GFR ≥45ml/min/1.73 m^2 (GFR categories G1-G3a); its use should be reviewed in those with GFR 30–44ml/min/1.73 m^2 (GFR category G3b); and it should be discontinued in people with GFR <30 ml/min/1.73 m^2 (GFR categories G4-G5). ***(1C)***

KDIGO notes to suspend metformin in people who become acutely unwell and suggests to avoid sulfonylureas that are mainly renal excreted (e.g., glyburide/ glibenclamide). Other agents that are mainly metabolized in the liver may need reduced dose when GFR <30 ml/min/1.73 m^2 (e.g., gliclazide, gliquidone).

6.1.2 KDOQI diabetes and CKD 2012 [10]

Hyperglycemia is a fundamental cause of vascular target organ complications, including diabetic kidney disease (DKD). Intensive treatment of hyperglycemia prevents elevated albuminuria or delays its progression, but patients treated by approaches designed to achieve near normal glycaemia may be at increased risk of severe hypoglycemia. Evidence that intensive treatment has an effect on loss of glomerular filtration rate (GFR) is sparse.

KDOQI recommends a target hemoglobin A1c (HbA1c) of ~7.0% to prevent or delay progression of the microvascular complications of diabetes, including DKD. ***(1A)*** **KDOQI recommends not treating to an HbA1c target of <7.0% in patients at risk of hypoglycemia** ***(1B)*** *Risk of hypoglycemia is amplified in CKD, especially if kidney function is substantially reduced (CKD stages 4 -5).*

KDOQI suggests that target HbA1c be extended above 7.0% in individuals with co-morbidities or limited life expectancy and at risk of hypoglycemia ***(2C).***

Notes KDOQI gives on the use of antidiabetic agents in CKD:

Second-generation sulfonylureas (e.g., glipizide, glyburide, and glimepiride)

- *Glipizide is the preferred agent; has no active metabolites and does not increase the risk of hypoglycemia in patients with CKD. No dose adjustment.*
- *Glimepiride: start low dose*
- *Glyburide: avoid use*
- *Gliclazide: No dose adjustment.*

Repaglinide

- *When the GFR ≤30 mL/min/1.73 m^2, it can accumulate. Start at low dose with meals and titrate upwards cautiously*
- *hypoglycemia has not been demonstrated to increase substantially with progressive falls of eGFR*

Metformin

- *is cleared by the kidneys, thus its use in CKD is restricted*
- *Does not cause hypoglycemia.*
- *Lactic acidosis is a rare and serious side effect of metformin use, which can occur when toxic levels of metformin accumulate. At present the exact GFR cutoff for metformin use to avoid lactic acidosis is controversial. A United States FDA mandated black-box warning exists regarding the risk of lactic acidosis. The FDA indicates that metformin should not be used in men with a SCr of ≥1.5 mg/dl or in women with a SCr of ≥1.4 mg/dl. (or a GFR cutoff of <60ml/min). According to KDOQI, lactic acidosis is still exceedingly rare in studies of patients continuing to receive metformin with GFR levels in the 30-60 mL/min/1.73 m^2 range. KDOQI refers to a recent review that proposed that metformin use be reevaluated when GFR is <45 mL/min/1.73 m^2 and stopped when <30 mL/min/1.73 m^2; this advice was adopted by the British National Formulary and the Japanese Society of Nephrology.*

Thiazolidinediones: pioglitazone

- *Do not lead to hypoglycemia*
- *are metabolized by the liver, and thus can be used in CKD.*
- *Fluid retention is a major side effect, thus should not be used in advanced heart failure and CKD.*
- *have been linked with increased fracture rates and bone loss; thus the appropriate use in patients with underlying bone disease (such as renal osteodystrophy) needs to be considered.*

Acarbose, a disaccharidase inhibitor

- *is only minimally absorbed, but with reduced kidney function, serum levels of the drug and its metabolites increase significantly.*
- *No adverse effects have been reported*
- *Avoid in patients with a GFR <30mL/min/ 1.73 m^2.*

DPP4 inhibitors: sitagliptin saxagliptin, linagliptin, and vildagliptin

- *All can be used in CKD patients*
- *Linagliptin needs no dose adjustment; sitagliptin, saxagliptin and vildagliptin need dose adjustments*

Incretinmimetics: Exenatide and liraglutide

Exenatide

- *Is excreted by the kidneys*
- *not recommended for use with a GFR <30 mL/min/1.73 m^2*
- *Associated with acute kidney injury or acceleration of CKD progression in case reports.*

Liraglutide

- *kidneys are not a major organ of elimination.*
- *few data on long term use and manufacturer recommends avoidance in GFR <60 mL/min/1.73m^2*

6.1.3 Domus Medica CNI 2012 [4]

Use metformin and sulfonylurea in chronic kidney disease with the necessary prudence *(1C).*

Domus Medica notes that in case of use of metformin, from an eGFR <50ml/min, there is a chance on lactic acidosis by accumulation. In an eGFR 30-50 ml/min lower the start dose; in 30ml/min: contra-indicated.

For sulfonylureumderivates, there is an elevated chance on severe hypoglycemia by accumulation from an eGFR <50ml/min. In <50ml/min, half the start dose or switch to insulin or tolbutamide.

6.1.4 Summary of guidelines on glycemic control

Most guidelines use an HbA1c target of ~7.0%. [2, 4]

Considering the different antidiabetic drugs, the guidelines give only recommendations on metformin. An overview is given in table 37, with the grades of recommendation of each recommendation.[2, 4, 10]

Glycemic control in CKD		**KDIGO CKD**	**Domus Medica CNI**	**KDOQI DM and CKD**
AGREE domainscore Rigour of development		**75%**	**60%**	**66%**
HbA1c target	~7.0 % (53mmol/mol) in most patients	1A	-	1A
	Not <7.0% in patients at risk of hypoglycemia	1B	-	1B
	> 7.0% if comorbidities or limited life expectancy and risk of hypoglycemia	2C	-	2C
Metformin	Stop if GFR<60 ml/min	-	-	Controversial
	Continued if GFR ≥ 45 ml/min	1C	-	Controversial
	Reviewed if GFR 30-44 ml/min	1C	-	Controversial
	Dose adjustment if GFR 30-50 ml/min	-	txt	-
	Stop if GFR <30ml/min	1C	txt	Controversial

Table 37 Summary of recommendations on glycemic control. *Txt= no recommendation but in text or table, is not graded; 1, 2 on a scale of 1 to 2; A= High quality; B = Moderate quality; C= Low quality of evidence; on a scale of A to D; controversial = no recommendation because still controversial*

6.2 Handbooks: glycemic control

6.2.1 Metformin

Dose in renal impairment		
GFR	**Renal Drug handbook[6]**	**Commentaren medicatiebewaking[5]**
30-50 ml/min	25% of dose if GFR 30-40 ml/min; 50% of dose if GFR 40-50 ml/min	Lowering of starting dose to 2x 500mg
10-30 ml/min	25% of dose	Contra-indicated
<10 ml/min	Avoid	Contra-indicated
Comments		
Renal Drug Handbook[6] Lactic acidosis is a rare but serious metabolic complication that can occur due to metformin accumulation. Reported cases have occurred primarily in diabetic patients with significant renal impairment. As metformin is renally excreted, eGFR values should be determined before initiating treatment and regularly thereafter: at least annually in patients with normal renal function, at least 2–4 times a year in patients with an eGFR at the lower limit of normal and in elderly subjects. Special caution should be exercised in the elderly in situations where renal function may become impaired, e.g. initiating therapy with antihypertensive drugs, diuretics or NSAIDs. Commentaren medicatiebewaking[5] Metformin can increase the risk of lactic acidosis in renal insufficiency. If GFR is 30-50 ml/min, the patient must be advised to consult the physician in case of intercurrent diseases with risk of dehydration about temporary stopping the metformin.		

6.2.2 Incretin mimetics

Only information on exenatide is found in the handbooks.

Dose in renal impairment		
GFR	**Renal Drug handbook[6]**	**Commentaren medicatiebewaking[5]**
30-50 ml/min	Increase dose of exenatide with caution.	No information
10-30 ml/min	Avoid	Exenatide is contra-indicated
<10 ml/min	Avoid	Exenatide is contra-indicated
Comments		
Renal Drug Handbook[6] Clearance of exenatide is reduced by 84% in patients with established renal failure; increased gastrointestinal side effects in patients with severe renal impairment and on dialysis; may cause renal failure including proteinuria. Avoid in patients with preexisting renal impairment.		

6.2.3 DPP4-inhibitors

Dose in renal impairment		
GFR	**Renal Drug handbook[6]**	**Commentaren medicatiebewaking[5]**
30-50 ml/min	Avoid (vildagliptin) Or Lowering of the dose (sitagliptin)	Lowering of the dose (vildagliptin, sitagliptin and saxagliptin)
10-30 ml/min	Avoid (vildagliptin) Or Lowering of the dose (sitagliptin)	Lowering of the dose (vildagliptin, sitagliptin and saxagliptin)
<10 ml/min	Avoid (vildagliptin) Or Lowering of the dose (sitagliptin)	No information
Comments		
Renal Drug Handbook[6] Use of vildagliptin is contraindicated in renal impairment due to lack of data. In severe renal impairment (GFR<30 mL/min) the AUC of sitagliptin was increased 4-fold.		

6.2.4 Glinides

Dose in renal impairment		
GFR	**Renal Drug handbook[6]**	**Commentaren medicatiebewaking[5]**
30-50 ml/min	Dose as in normal renal function	Dose as in normal renal function
10-30 ml/min	Start at a low dose and gradually increase according to response	Start at a low dose and increase according to response
<10 ml/min	Start at a low dose and gradually increase according to response	Start at a low dose and increase according to response
Comments		
No comments		

6.2.5 Glitazones

Dose in renal impairment		
GFR	**Renal Drug handbook[6]**	**Commentaren medicatiebewaking[5]**
30-50 ml/min	Dose as in normal renal function	Dose as in normal renal function
10-30 ml/min	Dose as in normal renal function	Dose as in normal renal function
<10 ml/min	Dose as in normal renal function	Dose as in normal renal function
Comments		
No comments		

6.2.6 Sulfonylureas

Dose in renal impairment		
GFR	**Renal Drug handbook[6]**	**Commentaren medicatiebewaking[5]**
30-50 ml/min	Lowering of the starting dose (to 25-50%) Monitor closely (most sulfonylureas) Or Dose as in normal renal function (glimepiride)	Lowering of the starting dose (to 50%) (most sulfonylureas) Or Dose as in normal renal function (gliclazide)
10-30 ml/min	Lowering of the starting dose (to 25-50%) Monitor closely (most sulfonylureas) Or Dose as in normal renal function (glimepiride)	Lowering of the starting dose (to 50%) (most sulfonylureas) Or Dose as in normal renal function (gliclazide)
<10 ml/min	Lowering of the starting dose (to 25-50%). Use cautiously, monitor closely (most sulfonylureas including glimepiride)	Lowering of the starting dose (to 50%) (most sulfonylureas) Or Dose as in normal renal function (gliclazide)
Comments		
Renal Drug Handbook[6] *Glibenclamide*: If creatinine clearance <10 mL/min, accumulation of active metabolite and unchanged drug in plasma may cause prolonged hypoglycemia; company information states that use is contraindicated in severe renal impairment; compensatory excretion via bile in faeces occurs in renal impairment. *Gliclazide:* Manufacturer contraindicates prescribing of Diamicron in severe renal impairment, which they define as creatinine clearance below 40 mL/min. *Glipizide*: Manufacturer does not recommend the use of Glibenese in patients with renal insufficiency; renal or hepatic insufficiency may cause elevated blood levels of glipizide (increased risk of serious hypoglycemic reactions)		

6.3 Evidence tables and conclusions: Glycemic control

6.3.1 Intensive vs standard glycemic control

No clinical trial was designed to compare the efficacy and safety of intensive versus standard glycemic control in a population consisting exclusively of patients with type 2 diabetes and chronic kidney disease. Trials in type 2 diabetic patients reporting outcomes according to a pre-specified stratification of kidney function, are scarce too.

The KDOQI Guideline for diabetes and CKD[9, 10] included 3 small RCTs with patients with CKD and microalbuminuria. In this trials intensive versus standard glycemic control consisted of intensive insulin treatment with multiple injections/d compared to standard treatment with less frequent insulin injections. Since insulin treatment is out of scope for our literature review, this subject will not be discussed any further.

The only available evidence comes from a pre-specified subgroup analysis of the VADT trial (Duckworth 2009)[28] which included patients with suboptimal response to therapy for type 2 diabetes. On a total population of 1791 persons, 491 patients had microalbuminuria at the start of the trial. Trial participants allocated to the intensive control group were started on maximal doses of oral therapy, and insulin was added as needed to achieve a target HbA1c <6%. Participants assigned to standard control were started on one-half of maximal doses of oral therapy and insulin was added as needed to achieve a target HbA1c <9%. After a median follow up of 5.6 years, 7.6% in the group with intensive treatment and 12.1% in the group with standard treatment progressed from micro-to macroalbuminuria (p= 0.10; NS). No other outcomes were reported for this subgroup with CKD.

Intensive versus standard glycemic control			
Bibliography: Duckworth 2009 (VADT)[28]			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Progression from micro- to macroalbuminuria	491 (1 study) 5.6 y	7.6% (intensive) vs 12.1% (standard) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 for subgroup Consistency: NA Directness: OK Imprecision: -1 for sparse data

Table 38

Intensive glycemic control (target HbA1c <6%) is not significantly better than standard glycemic (target HbA1c <9%) control for preventing the progression from micro- to macroalbuminuria in patients with type 2 diabetes and early CKD.
GRADE: LOW quality of evidence

In diabetic patients with CKD, we found insufficient evidence regarding whether there is a difference between intensive and standard treatment (not insulin) in risk of mortality or ESRD.

6.3.2 Metformin, glinides, glitazones, incretin mimetics

No RCT's of sufficient quality could be found on the efficacy and safety of these antidiabetic drugs in patients with chronic kidney disease.

Although there are several observational studies examining the effect of antidiabetic treatment on the development of kidney disease, trials in patients already having CKD are very scarce. Only 1 cohort study fulfilled the inclusion criteria of this literature review.

Ekström 2012[29]					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Retrospective cohort study Sweden 4 y follow up	N= 51.675	- type 2 diabetes - CKD - treatment with oral antidiabetics or insulin - 58% male - mean age 65y	use of other oral antidiabetics (OAD) or insulin vs metformin use	Any cardiovascular event	30≤eGFR<45 HR= 1.00 (0.83-1.19) 45≤eGFR<60 HR= 0.94 (0.84 to 1.05)
				Any acidosis/ serious infection	30≤eGFR<45 HR= 0.98 (0.79-1.21) 45≤eGFR<60 HR= 0.85 (0.74-0.97) **SS in favour of metformin**
				All-cause mortality	30≤eGFR<45 HR= 1.02 (0.84-1.24) 45≤eGFR<60 HR= 0.87 (0.77-0.99) **SS in favour of metformin**
*adjusted for : age, sex, diabetes duration, HbA1c, non-HDL-C, BMI, smoking, eGFR, multidose dispensation, previous hospitalisation, history of CVD and CHF, microalbuminuria, and treatment with antihypertensive agents, lipid-lowering agents and cardiac glycosides					

Table 39

An observational cohort study performed in Sweden with a follow-up of 4 years compared the use of metformin to the use of other oral antidiabetics or insulin in patients with type 2 diabetes and CKD. Metformin, compared with any other treatment, showed reduced risk of all-cause mortality (HR 0.87, 95% CI 0.77 to 0.99), in patients with eGFR between 45 and 60 ml/min/1.73 m^2, and no increased risks of all-cause mortality, acidosis/serious infection or CVD were found in patients with eGFR between 30 and 45 ml/min/1.73 m^2.

GRADE: not applied

6.3.3 DPP-4 inhibitors versus placebo

6.3.3.1 Clinical evidence profile: DPP4 inhibitor vs placebo

Study details	n/Population	Comparison	Outcomes		Methodological
McGill 2013[30] Design: RCT Duration of follow-up: - 12w and 52w (efficacy) - 52 w (safety)	n= 133 Mean age: 64 y Previous CV event: NR Hypertension: NR Diabetes: 100% Hypercholesterolemia: NR Smoking: NR <u>Inclusion</u> - type 2 diabetes (HbA1c 7.0–10.0%) AND - **severe** RI (eGFR <30 mL/min/1.73 m^2) <u>Exclusion</u> - CV in previous 6 m - any requirement for acute dialysis within the previous 3 months - renal transplantation - impaired hepatic function	Linagliptine 5 mg/d Vs Placebo Added to existing background therapy	Efficacy		- RANDO: unclear - ALLOCATION CONC: unclear - BLINDING : unclear - FOLLOW-UP at 52w: 73% - ITT: no Other important methodological remarks - 2 week placebo run-in Sponsor: Boehringer Ingelheim
			Mean change in HbA1c at 12 w	Lina= -0.76% Pla= - 0.15% Between-treatment difference= 0.60% **P<0.0001, SS in favor of lina**	
			Mean change in HbA1c at 52 w	Lina= -0.71% Pla= +0.01% Between-treatment difference= 0.72% **P<0.0001, SS in favor of lina**	
			Safety		
			Total adverse events	94.1 vs 92.3% "similar" (NT)	
			Mortality	4.4 vs 4.6% "similar" (NT)	
			Hypoglycemia	Lina= 63.2% Pla= 49.2% (NT)	
			eGFR	Lina= -0.8 mL/min/1.73m^2 pla= -2.2 mL/min/1.73m^2 NT, "clinically not meaningful"	
			Cardiovascular events	"similar" (NT)	

Table 40

Study details	n/Population	Comparison	Outcomes		Methodological
Nowicki 2011[31] Design: RCT Duration of follow-up: 12 weeks	n= 170 Mean age: 67 y Previous CV event: NR Hypertension: NR Hypercholesterolemia: NR Smoking: NR <u>Inclusion</u> - Type 2 DM - HbA1c 7–11% - creatinineclearance <50 ml/min <u>Exclusion</u> - current or anticipated need for peritoneal dialysis or expected kidney transplant within 3 months of enrolment; - abnormal liver function tests - anaemia - significant CV disease - ≥2 major hypoglycaemic events in past 3 months	saxagliptin 2.5mg/d vs pla added to existing background therapy	Efficacy		- RANDO: unclear - ALLOCATION CONC: unclear - BLINDING : unclear - FOLLOW-UP: 76% - ITT: no Other important methodological remarks - Oral antihyperglycaemic drugs and insulin therapy present at enrolment were continued throughout the study. - A 2-week, single-blind, placebo lead-in period Sponsor: AstraZeneca
			Mean change in HbA1c	<u>Overall</u> Saxa= -0.86% Pla= -0.44% Between-treatment difference= 0.42% **p=0.007, SS in favor of saxa** <u>Moderate renal impairment</u> Saxa= -0.64% (95% CI -0.90 to -0.37) Pla= -0.05% (95% CI -0.33 to 0.22) NS <u>Severe renal impairment</u> Saxa= -0.95% (95% CI -1.41 to -0.49) Pla= -0.50% (95% CI -0.90 to -0.09) NS
			Safety		
			Total adverse events	57.6 vs 54.1% "similar" (NT)	
			Mortality	0 in both groups	
			Reported hypoglycemia	20 vs 22% "similar" (NT)	

Table 41

This trial was followed by a 52-week non-randomised follow up[32]. The authors conclude: "Saxagliptin 2.5 mg once daily offers sustained efficacy and good tolerability for patients with T2DM and renal impairment."

Study details	n/Population	Comparison	Outcomes		Methodological
Chan 2008[33] Design: RCT Duration of follow-up: 54 weeks	n= 91 Mean age: 67y Previous CV event: 40% Hypertension: 89% Diabetes: % Hypercholesterolemia: 30% Smoking: NR Moderate CKD: 57% Severe CKD: 43% Dialysis: 12% <u>Inclusion</u> - type 2 diabetes - moderate [creatinine clearance (CrCl) ≥ 30 to <50 ml/min] or severe renal insufficiency [CrCl <30 ml/min including patients with end-stage renal disease (ESRD) on dialysis]. <u>Exclusion</u> - type 1 diabetes - acute renal disease - history of renal transplant - liver disease - recent CV event	Sitagliptin 50 mg/d for moderate CKD or 25 mg/d for severe CKD For 54 w Vs Pla for 12 w followed by glipizide2.5-20 mg/d for 42 w Added to existing background therapy	Efficacy		- RANDO: adequate - ALLOCATION CONC: unclear - BLINDING : yes - FOLLOW-UP: 73% - ITT: no Other important methodological remarks - open label insulin rescue therapy if necessary Sponsor: Merck
			Mean change in HbA1c at 12 w	sita= -0.6% Pla= -0.2% Between-treatment difference= 0.4% **SS in favor of sitagliptin**	
			Mean change in HbA1c at 52 w	Sita= -0.7% Pla/glip= -1.0% Between-treatment difference: no statistical test	
			Safety		
			Total adverse events, severe adverse events	"similar" (no statistical test reported)	
			Mortality	"similar" (no statistical test reported)	
			Renal and urinary disorders	Sita= 7.7% Pla/glip= 11.5% NS	
			Cardiovascular disorders	Sita= 12.3% Pla/glip= 23.1% NS	
			hypoglycemia	Sita= 4.6% Pla/glip= 23.1% **SS in favor of siragliptin**	

Table 42

Study details	n/Population	Comparison	Outcomes		Methodological
Lukashevich 2011[34] Design: RCT Duration of follow-up: 24 weeks	n= 515 Mean age: 65y Previous CV event: NR Hypertension: >90% Diabetes: 100% >Most patients receiving background insulin therapy). Hypercholesterolemia: NR Smoking: NR <u>Inclusion</u> Patients with T2DM and moderate or severe kidney failure <u>Exclusion:</u> - FPG ≥15 mmol/l - A history of renal transplant - significant CV history within 6 months - active liver disease or abnormal liver tests	Vildagliptin 50mg qd vs Placebo Added to existing background therapy	Efficacy		- RANDO: unclear - ALLOCATION CONC: unclear - BLINDING : unclear - FOLLOW-UP: 88% - ITT: NR Other important methodological remarks - There was a 2-week single-blind, placebo run-in period - Rescue medication (insulin addition or intensification) was administered after Week 4 if FPG 15 mmol/l, at Week 8 if FPG 13.3 mmol/l and at Week 16, if FPG 12.2 mmol/l. Sponsor: Novartis
			Mean change in HbA1c	<u>Moderate CKD</u> Vilda= -0.7% Pla= -0.2% Between-treatment difference= 0.5% **p<0.0001, SS in favor of of vildagliptin** <u>Severe CKD</u> Vilda= -0.9% Pla= -0.3% Between-treatment difference: -0.6% **p<0.0001, SS in favor of of vildagliptin**	
			Safety		
			Total adverse events	67.5 vs 72.9% and 72.6 vs 74.2% "similar" (NT)	
			Mortality	0.6 vs 0.8% and 2.4 vs 4.1% "similar" (NT)	
			Hypoglycemia	17.2 vs 11.6% and 15.3 vs 12.4% "similar" (NT)	
			Cardiac events	<u>Moderate CKD</u> Vilda: 4.9% Placebo: 8.5% "Numerically lower" (NT) <u>Severe CKD</u> Vilda: 12.1% Placebo: 12.4% (NT)	

Table 43

This study was followed by a non-randomized 52 week-extension (Kothny 2012)[35]. The authors conclude: "In patients with T2DM and moderate or severe RI, vildagliptin added to ongoing antidiabetic therapy had a safety profile similar to placebo during 1-year observation. Furthermore, relative to placebo, a clinically significant decrease in A1C was maintained throughout 1-year treatment with vildagliptin."

6.3.3.2 Summary and conclusions. DPP4 inhibitors versus placebo in patients with CKD.

DPP 4-inhibitors versus placebo			
Bibliography: McGill 2013[36], Nowicki 2011[31], Chan 2008[33], Lukashevich 2011[34]			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mean change in HbA1c	909 (4 studies) 12w-1y	Between treatment difference 0.4-0.6% according to study **SS in favour of DPP4-inhibitors**	⊕⊕⊖⊖ **LOW** Study quality: -1 for unclear blinding and alloc concealment Consistency: OK Directness: OK Imprecision: -1 for sparse data
Adverse events	909 (4 studies) 12w-1y	"similar" No major safety concerns	⊕⊕⊖⊖ **LOW** Study quality: -1 for unclear blinding and alloc concealment, -1 for no statistical test Consistency: OK Directness: OK Imprecision: -1 for sparse data

Table 44

Four RCTs compared DPP4-inhibitors (linagliptin, saxagliptin, sitagliptin, vildagliptin) with placebo, added to existing background therapy in patients with type 2 diabetes and CKD. The largest trial was performed with vildagliptin.

Addition of a DPP4-inhibitor to existing antidiabetic treatment leads to an extra decrease in HbA1c of about 0.5%, compared with placebo.
GRADE: LOW quality of evidence

Although treatment with a DPP4-inhibitor seems safe in patients with CKD, safety information is very limited.
GRADE: VERY LOW quality of evidence

6.3.4 DPP4-inhibitor versus sulfonylurea

6.3.4.1 Clinical evidence profile

Study details	n/Population	Comparison	Outcomes		Methodological
Arjona Ferreira 2013[37] Design: RCT Duration of follow-up: 54 weeks	n= 426 Mean age: 64y >50% Asian Previous CV event: 25% Hypertension: NR Diabetes: 100% Hypercholesterolemia:NR Smoking: NR <u>Inclusion</u> - type 2 diabetes - moderate to severe CKD (eGFR<50 mL/min/1.73 m^2 Not on dialysis <u>Exclusion</u> - type 1 diabetes - Acute renal disease or history of transplantation - recent CV event - liver disease	Sitagliptine 50 mg/d for moderate CKD Or 25 mg/d or severe CKD vs glipizide 2.5-20 mg/d Added to existing background therapy	Efficacy		- RANDO: adequate - ALLOCATION CONC: unclear - BLINDING : yes - FOLLOW-UP: 79% - ITT: no Other important methodological remarks - 2 w placebo run-in - If necessary insulin rescue therapy and discontinuation of glipizide or matching placebo Sponsor: Merck
			Mean change in HbA1c	sita= -0.8% glip= -0.6% Between-treatment difference= 0.2% Non-inferior	
			Safety		
			Total adverse events	68.1 vs 72.2% "similar" (NT)	
			Symptomatic hypoglycemia	Sita= 6.2% Glip= 17.0% **p=0.001, SS less frequent with sitagliptin**	
			eGFR	sita= -3.9 mL/min/1.73m^2 glip= -3.3 mL/min/1.73m^2 "similar" (NT)	
			Cardiovascular events	"similar" (NT)	

Table 45

6.3.4.2 Summary and conclusions. Sitagliptine versus glipizide in patients with CKD

Sitagliptine versus glipizide			
Bibliography: Arjona Ferreira 2013[38]			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mean change in HbA1c	426 (1 study) 54 w	Between treatment difference= 0.2% NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -1 Consistency: NA Directness: -1 for >50% Asian Imprecision: -1 for sparse data
Symptomatic hypoglycemia	426 (1 study) 54 w	6.2 vs 17.0% **SS less frequent with sitagliptin**	⨁⊖⊖⊖ **VERY LOW** Study quality: -1 Consistency: NA Directness: -1 for >50% Asian Imprecision: -1 for sparse data

Table 46

One RCT assessed the efficacy and safety of addition of sitagliptin or glipizide to existing antidiabetic therapy in patients with type 2 diabetes and moderate to severe CKD.

There is no significant difference between sitagliptin and glipizide concerning the degree of glycemic control.
GRADE: VERY LOW quality of evidence

Sitagliptin is associated with a lower risk of symptomatic hypoglycemia, compared with glipizide.
GRADE: VERY LOW quality of evidence

7 Results: Anticoagulants in CKD

7.1 Guidelines: LMWHs, Vitamin K antagonists and New oral anticoagulants

7.1.1 KDIGO CKD 2012 [2]

Low-molecular-weight heparins

- *Halve the dose when GFR <30 ml/min/1.73 m^2*
- *Consider switch to conventional heparin or alternatively monitor plasma anti-factor Xa in those at high risk for bleeding*

Warfarin

- *Increased risk of bleeding when GFR <30 ml/min/1.73 m^2*
- *Use lower doses and monitor closely when GFR <30 ml/min/1.73 m^2*

7.1.2 NICE CKD 2014[11]

Consider apixaban in preference to warfarin in people with a confirmed eGFR of 30-50 ml/min/1.73 m^2 and non-valvular atrial fibrillation who have 1 or more of the following risk factors:

- **prior stroke or transient ischemic attack**
- **age 75 years or older**
- **hypertension**
- **diabetes mellitus**
- **symptomatic heart failure**

7.1.3 CCS Atrial Fibrillation 2012 [24]

CCS recommends that patients with atrial fibrillation who are receiving oral anticoagulants:

- **Have their renal function assessed at least annually by measuring serum creatinine and calculating eGFR *(Strong Recommendation, Moderate-Quality Evidence).***
- **Be regularly considered for the need for alteration of OAC drug and/or dose changes based on eGFR *(Strong Recommendation, Moderate-Quality Evidence).***

For antithrombotic therapy of CKD patients, therapy should relate to eGFR as follows:

- **eGFR > 30 ml/min: CCS recommends that such patients receive antithrombotic therapy according to their $CHADS_2$ score as for patients with normal renal function *(Strong Recommendation, High-Quality Evidence).*** *Note that for patients with normal renal function, CCS recommends dabigatran, apixaban and rivaroxaban in preference to warfarin.*
- **eGFR 15-30 ml/min and not on dialysis: CCS suggests that such patients receive antithrombotic therapy according to their $CHADS_2$ score as for patients with normal renal function. The preferred agent for these patients is warfarin *(Conditional Recommendation, Low-Quality Evidence).***

This recommendation places a relatively higher value on prevention of ischemic stroke than on bleeding complications associated with antithrombotic therapy, as well as the limited data available for new OACs in CKD patients. No therapy may be appropriate for some patients with eGFR 15-30 mL per minute (not on dialysis), with a stronger preference for avoiding bleeding complications than preventing ischemic stroke. Clinical trials of antiplatelet agents or OACs in AF have not systematically enrolled patients with GFR < 30 ml/min. With respect to stroke risk, multiple studies have found that chronic kidney disease is associated with higher rates of stroke in dialysis patients and patients with even mildly reduced renal function, but not all studies have found this relationship. On the other hand, severe chronic kidney disease is also associated with higher rates of bleeding complications, including hemorrhagic stroke and GI bleeding. So it is not clear how to balance the utility of preventing a stroke versus preventing a major bleeding.
Therapeutic choices in patients with CKD and stroke risk factors ($CHADS_2 \geq 1$) are given in table 47.

GFR	***Warfarin***	***Dabigatran***	***Rivaroxaban***	***Apixaban***
Excretion	*Minimally (<1%) renal, largely by the liver.*	*largely renal*	*Largely renal*	*Only ~ 25% renal*
GFR ≥ 60 ml/min	*Dose adjusted for INR*	*2x 150 or 110 mg*	*20 mg daily*	*2x 5 mg*
GFR 50-59 ml/min	*Dose adjusted for INR*	*2x 150 or 110 mg*	*20 mg daily*	*2x 5 mg*
GFR 30-49 ml/min	*Dose adjusted for INR*	*2x 150 or 110 mg*	*15 mg daily*	*2x 5mg. Consider 2x 2.5 mg*
GFR 15-29 mL/min (not on dialysis)	*No RCT data. Dose adjusted warfarin has been used, but observational data regarding safety and efficacy is conflicting*	*No RCT data (Modelling studies suggest that 2x 75 mg might be safe, but this has not been validated)*	*No RCT data. Product monographs suggest contra-indication*	*2x 5 mg if GFR> 25 ml/min. Consider 2x 2.5 mg if GFR ≤ 25 ml/min (if age >80year or <60 kg)*
GFR < 15 ml/min (on dialysis)		*No RCT data. Product monographs suggest contra-indication*		*No RCT data*

Table 47 Excretion and dosing of different oral anticoagulants.

<u>Warfarin, vitamin K inhibitor</u>

- *CKD is associated with lower dose requirements, a higher risk for over-anticoagulation, and higher risk for hemorrhage*
- *initiate at lower doses and monitor more frequently in patients with moderate or severe CKD*

What the efficacy and safety of the NOACs in the trials of normal populations mean for patients with CKD, is not clear. Data from RCTs of stroke/STE prevention support OAC use in patients with mild to moderate CKD, but there are essentially no randomized controlled trial data on those with severe CKD (GFR < 30 ml/min).
<u>Dabigatran, oral direct thrombin inhibitor</u>

- *Net clinical benefit for the subgroup of patients with GFR <50 ml/min was not reported.*
- *CCS explains that, though pharmacokinetic studies provide a rationale for dose reduction of dabigatran in moderate CKD, and though a similar approach has been demonstrated to be safe in the context of orthopedic surgery, currently published data do not clearly show that dabigatran 110mg 2x/d is superior to dabigatran 150mg bid in patients with moderate CKD (GFR > 30 ml/min).*

Rivaroxaban, oral Factor Xa inhibitor

- *Effect of rivaroxaban is consistent for those with and without CKD. The dose reduction of 15 mg/day in patients with moderate CKD (GFR 30-49 ml/min) compared with 20 mg/day in patients with mild CKD or normal renal function (GFR > 50 ml/min) yielded overall results in terms of safety and efficacy that were consistent with the overall trial.*

Apixaban, oral Factor Xa inhibitor

- *The results were similar in the subgroups with and without CKD, but the results of the patients with GFR 25-29ml/min were not reported as a distinct subgroup. To date, there are no published studies that support an apixaban dose in severe CKD with GFR < 25 ml/min.*

7.1.4 SIGN Antithrombotics 2013 [25]

LMWH should be used with caution for those in whom standard or weight-adjusted dosing is likely to be unreliable, especially in patients with acute kidney injury or stage 4-5 chronic kidney disease. *(D)* When LMWH is to be continued after hospital discharge there should be a record of the patient's renal function. *(not graded)*

A baseline renal function test should be obtained prior to starting oral anticoagulants.

Low molecular weight heparin

- *Excreted principally by the kidneys.*
- *Most randomized trials of LMWH have excluded patients with renal insufficiency.*
- *Increased bleeding complications have been reported with LMWH in patients with renal insufficiency. There were insufficient studies to assess the risk of major bleeding for LMWHs other than enoxaparin.*
- *A reduced dose should be given with careful observation for bleeding.*
- *Monitoring of the anti-Xa activity should be considered*

Fondaparinux

- *Renally excreted*
- *Use with caution in patients with GFR 30-50 ml/min*
- *Generally avoided in patients with GFR <30 ml/min*

Dabigatran and rivaroxaban

- *In a general population (not specifically CKD patients), SIGN states that dabigatran or rivaroxaban can be considered as an alternative to warfarin in the management of patients with atrial fibrillation with one or more risk factors for stroke. (GRADE A). But in selecting those drugs, consideration should be given to the limited data on use in patients with renal impairment, in addition to the lack of experience of long term use, lack of experience with rapid reversal of the anticoagulant effect, and higher rates of gastro intestinal bleeding.*
- *Dabigatran is mainly (80%) eliminated by the renal route and consequently there is a risk of accumulation in severe renal impairment. Rivaroxaban is less dependent on renal clearance (around 60%) but caution is required in severe renal impairment.*

(In a normal population,) **apixaban can be considered as an alternative to warfarin in the management of patients with atrial fibrillation with one or more risk factors for stroke*. (A)*** *Note that this recommendation did not specifically applied to CKD patients, but renal impairment is not mentioned as a special consideration in the section of apixaban (in contrast with rivaroxaban and dabigatran, which are also considered as an alternative to warfarin in a normal population, but in this case SIGN warns that special consideration should be given to the limited data on use in CKD patients)*

In selecting apixaban consideration should be given to:

- *the relative lack of experience of long term use compared with a VKA or aspirin*
- *the lack of a licensed product for rapid reversal of the anticoagulant effect of apixaban*
- *The limited data on use in patients at the extremes of body weight and those with hepatic impairment.*

7.1.5 Summary of guidelines on anticoagulants

According to SIGN, LMWH should be used with caution in patients with AKI or CKD stage 4-5. [25]
If eGFR > 30 ml/min, guidelines recommend apixaban as preferred agent [11, 24] or as an alternative to warfarin if antithrombotic therapy is needed. [25]
If eGFR <30 ml/min, the guidelines state that there is insufficient data on the new oral anticoagulants.

7.2 Handbooks: LMWHs, Vitamin K antagonists and New oral anticoagulants

7.2.1 LMWHs

Dose in renal impairment		
GFR	**Renal Drug handbook[6]**	**Commentaren medicatiebewaking[5]**
		50-60 ml/min therapeutic doses: Start with normal dose (except if bridging therapy) and give then 75% of normal dose. If use > 3 days: monitor anti-Xa levels
30-50 ml/min	Dose as in normal renal function (dalteparin, tinzaparin) Or Dose as in normal renal function and monitor carefully (enoxaparin)	Prophylactic doses Dose as in normal renal function Therapeutic doses Start with normal dose (except if bridging therapy) and give then 75% of normal dose. If use > 3 days: monitor anti-Xa levels
10-30 ml/min	Prophylactic doses 20-30 ml/min Dose as in normal renal function 10-20 ml/min Dose as in normal renal function and monitoring for anti-Xa levels to determine appropriate dose. (dalteparin) Or 20mg daily (enoxaparin) Therapeutic doses 1 mg/kg daily. Monitor (enoxaparin).	Prophylactic doses Dose as in normal renal function Therapeutic doses Start with normal dose (except if bridging therapy) and give then 50% of normal dose. If use > 3 days: monitor anti-Xa levels
<10 ml/min	Prophylactic doses Dose as in normal renal function and monitoring for anti-Xa levels to determine appropriate dose. (dalteparin) Or 20mg daily (enoxaparin) Therapeutic doses 1 mg/kg daily. Monitor (enoxaparin).	Prophylactic doses Dose as in normal renal function Therapeutic doses No information

Comments
Renal Drug Handbook[6] Low molecular weight heparins are renally excreted and hence accumulate in severe renal impairment. While the doses recommended for prophylaxis against DVT and prevention of thrombus formation in extracorporeal circuits are well tolerated in patients with end stage renal failure, the doses recommended for treatment of DVT and PE have been associated with severe, sometimes fatal, bleeding episodes in such patients. Hence the use of unfractionated heparin would be preferable in these instances. Rhone-Poulenc Rorer (enoxaparin) advise monitoring of the antifactor-Xa activity, whatever the severity of the renal impairment, when treatment doses are being used. They also advise monitoring patients if given prolonged treatment with prophylactic dose. Information from Leo Pharma (tinzaparin) states that tinzaparin can be used safely in elderly patients with a GFR>20 mL/min for 10 days without any accumulation. Heparin can suppress adrenal secretion of aldosterone leading to hypercalcaemia, particularly in patients with chronic renal impairment and diabetes mellitus. *Dalteparin*: Target anti-Xa range is 0.5-1.5 IU/m Commentaren medicatiebewaking[5] According to the guideline of the Dutch federation of nephology 2012, in general LMWH are preferred above unfractionated heparins because of better effectivitey, safety and user friendliness. LMWH must not be used for therapeutic use in case of severe renal impairment if there is no possibility to estimate anti-Xa levels. Only LMWH with known pharmacokinetic and clinical data in renal insufficiency must be used. On theoretical grounds, the clearance of a LMWH with relatively high weight (like dalteparin and tinzaparin), would be a little less influenced by a deterioration of kidney function comparing to enoxaparin and nadroparin. A twice daily dosing scheme instead of once daily can be used to avoid high anti-Xa levels. Intravenous UFH seems to be preferred above subcutaneous LMWH, if the patient is instable, possibly will undergo an urgent intervention or has an elevated bleeding risk. This because UFH can be stopped rapidly, had a short half-life and can be antagonized eventually.

7.2.2 Vitamin K antagonists

Dose in renal impairment		
GFR	**Renal Drug handbook[6]**	**Commentaren medicatiebewaking[5]**
30-50 ml/min	Dose as in normal renal function	No information
10-30 ml/min	Dose as in normal renal function	Start at a low dose
<10 ml/min	Dose as in normal renal function	No information
Comments		
Renal Drug Handbook[6] Reduced protein binding in renal impairment, in uremia. Inactive metabolites are renally excreted and may accumulate in renal impairment (warfarin). Commentaren medicatiebewaking[5] In renal impairment, the risk on an INR outside the target zone is increased.		

7.2.3 New oral anticoagulants

7.2.3.1 Thrombin inhibitors (dabigatran)

Dose in renal impairment		
GFR	**Renal Drug handbook[6]**	**Commentaren medicatiebewaking[5]**
30-50 ml/min	No information	Prophylaxis of VTE after surgery Dose adjustment Prophylaxis of CVA or embolism in AF Dose as in normal renal function, except if there is an increased risk of bleeding
10-30 ml/min	No information	Contra-indicated
<10 ml/min	No information	Contra-indicated
Comments		
Commentaren medicatiebewaking[5] For dabigatran, it is advised to control renal function annually. In severe renal impairment, there are very little data and bleeding complications are described.		

7.2.3.2 Factor Xa inhibitors (apixaban, rivaroxaban)

Dose in renal impairment		
GFR	**Renal Drug handbook[6]**	**Commentaren medicatiebewaking[5]**
30-50 ml/min	No information	Prophylaxis of VTE after surgery Dose as in normal renal function (apixaban) Prophylaxis of CVA or embolism in AF Dose as in normal renal function (apixaban) Or Dose adjustment needed (rivaroxaban) Treatment DVT/prevention after DVT or LE Dose as in normal renal function (apixaban) Or Dose adjustment needed (rivaroxaban)
10-30ml/min	No information	Prophylaxis of VTE after surgery Dose as in normal renal function (apixaban) Or Dose adjustment needed (rivaroxaban) Prophylaxis of CVA or embolism in AF Dose adjustment (apixaban, rivaroxaban) Treatment DVT/prevention after DVT or LE No information (apixaban) Or Dose adjustment needed (rivaroxaban <15ml/min: rivaroxaban contra-indicated
<10 ml/min	No information	No information (apixaban) Or Contra-indicated (rivaroxaban)

Comments
Commentaren medicatiebewaking[5] The experience with rivaroxaban in renal impairment is limited. Caution is needed in moderate renal insufficiency (GFR 15-50 ml/min).

7.3 Evidence tables and conclusions: New oral anticoagulants

7.3.1 Clinical evidence profile

Study details	n/Population	Comparison	Outcomes		Methodological
Agnelli 2013[39] AMPLIFY-EXT RCT Follow up 1y	Symptomatic deep vein thrombosis or pulmonary embolism Total n= 2486 ±25% CKD	Apixaban 2.5 mg/d vs pla	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : yes FOLLOW-UP: 98% ITT: yes Prespecified subgroup analysis Sponsor: Bristol-Myers Squibb and Pfizer.
			All-cause mortality or symptomatic recurrent venous thromboembolism	Apix= 5.4% Pla= 13.8% **RR 0.39 (0.20 to 0.73) SS**	
			Major bleeding or clinically relevant non-major bleeding	Apix=5% Pla= 2.1% **RR= 2.31 (0.82-6.5) SS**	
		Apixaban 5 mg/d vs pla	All-cause mortality or symptomatic recurrent venous thromboembolism	Apix= 3.8% Pla= 13.8% **RR= 0.28 (0.13 to 0.58) SS**	
			Major bleeding or clinically relevant non-major bleeding	Apix= 36.2% Pla= 2.1% **RR= 2.9 (1.06 to 7.95) SS**	
Alexander 2011[40] RCT Follow up 241 days	Patients with recent acute coronary syndrome and ≥2 risk factors for recurrent ischaemic events. Total n=7392 28% CKD	Apixaban 2x5 mg/d vs pla	Cardiovascular mortality, MI, ischaemic stroke	<u>Mild renal impairment</u> RR= 1.04 (0.79-1.37) <u>Moderate or severe renal impairment</u> RR= 0.94 (0.69-1.29)	RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : yes FOLLOW-UP: 80% ITT: yes Prespecified subgroup analysis Sponsor: Bristol-Myers Squibb
			Major bleeding	<u>Mild renal impairment</u> RR= 1.3 (0.57-2.96) <u>Moderate or severe renal impairment</u> **RR= 4.94 (1.42-17.22) SS**	

Eikelboom 2012[41] AVERROES Follow up 1.1y	Permanent or paroxysmal atrial fibrillation and at least 1 additional risk factor for stroke. N= 1697 with CKD stage 3	Apixaban 2x5 mg/d vs aspirin 81-324 mg/d	All-cause mortality	6.9 vs 7.9% HT= 0.86 (1.61-1.21) NS	RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : yes FOLLOW-UP: 80% ITT: yes **Post hoc subgroup analysis** Sponsor: Bristol-Myers Squibb and Pfizer
			Cardiovascular/cerebrovascular events	1.8 vs 5.6% HR= 0.32 (0.18-0.57) **SS in favour of apixaban**	
			Major bleeding	2.8 vs 2.4% HR= 1.2 (0.65-2.22) NS	
Fox 2011[42] ROCKET-AF Follow up 2y	ECG documented non-valvular atrial fibrillation and at moderate to high risk of stroke. Total n= 14.264 20.7% moderate CKD (CrCl 30-49 mL/min)	Rivaroxaban 15 mg/d vs warfarin (target INR 2-3)	Stroke and systemic embolism (primary outcome)	2.32 vs 2.77% HR= 0.84 (0.57-1.23) NS	RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : yes FOLLOW-UP: 77% ITT: yes Subgroup analysis (unclear if pre-specified) Sponsor: Johnson & Johnson Pharmaceutical Research and Development and Bayer HealthCare.
			Ischaemic stroke	1.98 vs 1.78% HR= 1.11 (0.71-1.73) NS	
			Haemorrhagic stroke	0.29 vs 0.52% HR= 0.56 (0.21-1.51) NS	
			Major bleeding	4.49 vs 4.70% HR= 0.95 (0.72-1.25) NS	
Hijazi 2014[43] RE-LY Follow up 2y	People with atrial fibrillation and at least one additional risk factor for stroke. Total n= 17.951 eGFR 50 to <80 mL/min: 47.6% eGFR 30-50 mL/min: 19.8%	Dabigatran 2x110 mg/d or 2x150 mg/d vs Warfarin (target INR 2-3)	Stroke or systemic embolism	<u>eGFR 50 to <80 mL/min</u> 3.3 vs 3.5% HR= 0.94 (0.73-1.21) NS <u>eGFR 30-50 mL/min</u> 3.3 vs 4.1% HR= 0.79 (0.51-1.19) NS	RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : no FOLLOW-UP: 99.9% ITT: NR Prespecified subgroup analysis Sponsor: Boehringer Ingelheim
			All cause mortality	<u>eGFR 50 to <80 mL/min</u> 6.6 vs 6.4% HR= 0.88 (0.74-1.05) NS <u>eGFR 30-50 mL/min</u> 12.1 vs 12.2% HR= 0.97 (0.77-1.22) NS	

			Major bleeding	<u>eGFR 50 to <80 mL/min</u> 5.5 vs 6.7% **HR= 0.82 (0.68-0.99)** **SS in favour of dabigatran** <u>eGFR 30-50 mL/min</u> 9.9 vs 11.7% HR= 1.02 (0.78-1.33) NS	
Hohnloser 2012[44] ARISTOTLE Follow up 1.8y	Atrial fibrillation or flutter at enrolment and at least 1 additional risk factor for stroke Total n= 18.201 15% with eGFR 15-50 mL/min/1.73m^2	Apixaban 2.5 or 5 mg twice daily vs warfarin (target INR 2-3)	All cause mortality	10.7 vs 13.4% HR= 0.78 (0.63-0.97) **SS in favour of apixaban**	RANDO: Adequate ALLOCATION CONC: unclear BLINDING : yes FOLLOW-UP: 98% ITT: yes Prespecified subgroup analysis Sponsor: Bristol-Myers Squibb and Pfizer.
			Stroke or systemic embolism	2.3 vs 3.7% HR= 0.61 (0.39-0.95) **SS in favour of apixaban**	
			Major bleeding	5.1 vs 10.1% HR= 0.48 (0.37-0.62) **SS in favour of apixaban**	
MEGA 2012[45] ATLAS ACS 2 – TIMI 51 Follow up 13 m	Patients with acute coronary syndrome and creatinine clearance < 50ml/min. Total n= 15.526 N=1054 with CrCl<50 mL/min	Rivaroxaban 2x2.5 mg/d vs placebo	Cardiovascular mortality, MI or stroke	11.7 vs 13.3% HR= 0.88 (0.62-1.25) NS	RANDO: Adequate ALLOCATION CONC: unclear BLINDING : yes FOLLOW-UP: 74% ITT: 'modified' ITT Prespecified subgroup analysis Sponsor: Johnson & Johnson and Bayer Healthcare
			Bleeding outcomes	NR for subgroup <u>Total study</u> • Major and intracranial bleeding: SS worse with rivaroxaban • Fatal bleeding: NS	

Table 48

An additional post hoc analysis (Hori 2013)[46], reporting outcomes for Japanese people in the ROCKET trial, was excluded from this analysis because this subgroupanalysis was carried out in an exclusively Japanese population.

7.3.1.1 Summary and conclusion. New oral anticoagulants in patients with CKD.

There are no trials designed to assess the efficacy and safety of NOAC in a population consisting exclusively of patients with CKD. The available data are based on subgroup analyses performed within subsets of patients with CKD from larger trial populations not originally limited to subjects with CKD.
Because this literature group totally agrees with the conclusions as formulated by the NICE working group[11] and the levels of quality of evidence assigned by them, we copy their conclusions.

Apixaban versus placebo (Agnelli 2013[39] AMPLIFY-EXT, Alexander 2011[40])

- *Moderate quality evidence* showed apixaban at doses of 2.5 or 5mg to be more effective than placebo at reducing the risk of all-cause mortality and venous thromboembolism or death due to venous thromboembolism in people with mild, moderate or severe renal impairment who also had symptomatic deep vein thrombosis or pulmonary embolism. However, in people with recent acute coronary syndrome and at least 2 risk factors for recurrent ischaemic events, *low and very low quality evidence* suggested there was no difference between placebo and apixaban in people with renal impairment.
- *Low quality evidence* suggested that there was a greater risk of major bleeding or clinically relevant non-major bleeding at both doses of apixaban compared to placebo in people with symptomatic deep vein thrombosis or pulmonary embolism, and major bleeding in people with acute recent coronary syndrome and moderate or severe renal impairment.

Apixaban versus aspirin (Eikelboom 2012[41] AVERROES)

Very low quality evidence suggested that there is no difference between 5mg apixaban twice daily and aspirin (at varying doses) in people with stage 3 CKD and permanent or paroxysmal atrial fibrillation and at least one additional risk factor for stroke, in reducing the risk of all-cause mortality or major bleeding, however *low quality evidence* showed that apixaban was more effective than aspirin at reducing the risk of stroke or systemic embolism in this population.

Apixaban versus warfarin (Hohnloser 2012[44] ARISTOTLE)

Apixaban at doses of 2.5 or 5mg twice daily also appears to be more effective than warfarin at reducing the risk of all-cause mortality, stroke and systemic embolism and major bleeding or clinically relevant non-major bleeding in people with an eGFR 15-50 ml/min/1.73 m^2 and atrial fibrillation or flutter. This was suggested by *low and very low quality evidence.*

Dabigatran versus warfarin (Hijazi 2014[43] RE-LY)

- In people with atrial fibrillation and at least one additional risk factor for stroke, *low and very low quality evidence* showed no difference between dabigatran 100 or 150 mg twice daily and warfarin in terms of reducing mortality at eGFR of 30-80 ml/min/1.73 m^2 or occurrence of major bleeding at doses of 110mg and eGFR of 30-50 ml/min/1.73 m^2 or 150mg at eGFR of 50-80 ml/min/1.73 m^2.

- The evidence suggested that dabigatran 150 mg twice daily was more effective than warfarin in reducing mortality in people without renal impairment (eGFR >80 ml/min/1.73 m^2), but at 110 mg twice daily there was more uncertainty about the effect. *Low and very low quality evidence* showed that dabigatran 110 and 150 mg twice daily was more effective than warfarin at reducing occurrence of major bleeding, and suggested that 150mg twice daily was more effective that warfarin in terms of reducing occurrence stroke and systemic embolism at all levels of renal impairment, but there was uncertainty about the magnitude of these effects. *Very low quality evidence* suggested that dabigatran 150mg twice daily was less effective than warfarin in people with eGFR of 30-50 ml/min/1.73 m^2.

Rivaroxaban versus placebo (MEGA 2012[45] ATLAS ACS 2–TIMI 51)

Very low quality evidence demonstrated no difference in efficacy between rivaroxaban (2.5mg) and placebo in terms of reducing cardiovascular mortality, myocardial infarction or stroke in people with acute coronary syndrome and eGFR less than 50ml/min/1.73 m^2.

Rivaroxaban versus warfarin (Fox 2011[42] ROCKET-AF)

In people with ECG documented non-valvular atrial fibrillation who were at moderate to high risk or stroke and had an eGFR of 30-49 ml/min/1.73 m^2, *very low and low quality evidence* suggested that there was no clinically effective difference between 15mg rivaroxaban and warfarin in terms of reducing risk of ischemic stroke or haemoglobin drop, transfusion, clinical organ or fatal bleeding. The evidence suggested that rivaroxaban may be more effective in terms of reducing haemorrhagic stroke, undetermined stroke and intracranial haemorrhage, but there was uncertainty in the magnitude and direction of this effect.

8 Results: Antihypertensive drugs in CKD

8.1 Guidelines: antihypertensive drugs

For comparison of albuminuria, which is stated in guidelines as 24hours excretion or as corrected albuminuria/proteinuria, we refer to the table in section 5.1.1.1.

8.1.1 KDIGO CKD 2012 [2]

KDIGO recommends that all people with CKD be considered at increased risk for cardiovascular disease. *(1A)* KDIGO recommends that the level of care for ischemic heart disease offered to people with CKD should not be prejudiced by their CKD. *(1A)* They suggest that the level of care for heart failure offered to people with CKD should be the same as is offered to those without CKD. *(2A)* In people with CKD and heart failure, any escalation in therapy and/or clinical deterioration should prompt monitoring of eGFR and serum potassium concentration. *(Not Graded)*
Recommendations considering the different antihypertensive drugs and target blood pressure in this guideline are excerpted from the KDIGO Clinical Practice Guideline for the Management of Blood Pressure in CKD. For convenience, we do not mention them twice and refer to this guideline in section 2.3.1.2. We only mention the cautionary notes on this drug category.

RAAS antagonists (ACE-Is, ARBs, aldosterone antagonists, direct renin inhibitors)

- *Avoid in people with suspected functional renal artery stenosis*
- *Start at lower dose in people with GFR <45 ml/min/1.73 m^2*
- *Assess GFR and measure serum potassium within 1 week of starting or following any dose escalation*
- *Temporarily suspend during intercurrent illness, planned IV radiocontrast administration, bowel preparation prior to colonoscopy, or prior to major surgery*
- *Do not routinely discontinue in people with GFR <30 ml/min/1.73 m^2 as they remain nephroprotective*

Beta-blockers: *Reduce dose by 50% in people with GFR <30 ml/min/1.73 m^2*

8.1.2 KDIGO BP in CKD 2012[12]

Individualize BP targets and agents according to age, co-existent cardiovascular disease and other co-morbidities, risk of progression of CKD, presence or absence of retinopathy (in CKD patients with diabetes) and tolerance of treatment. *(Not Graded)* Inquire about postural dizziness and check for postural hypotension regularly when treating CKD patients with BP-lowering drugs. *(Not Graded)*

<u>For both diabetic and non-diabetic adults with CKD,</u> KDIGO recommends if urine albumin excretion <30 mg per 24 hours (or equivalent) in CKD patients whose office BP is consistently >140mmHg systolic or >90mmHg diastolic, to treat them with BP-lowering drugs to maintain a BP that is consistently ≤140mmHg systolic and ≤90mmHg diastolic. *(1B)*

For non-diabetic adults with CKD

KDIGO suggests if urine albumin excretion of

- **30 to 300 mg per 24 hours *(2D)* (or equivalent) or;**
- **>300 mg per 24 hours *(2C)* (or equivalent)**

whose office BP is consistently >130mmHg systolic or >80mmHg diastolic be treated with BP-lowering drugs to maintain a BP that is consistently ≤130mmHg systolic and ≤80mmHg diastolic

KDIGO suggests/recommends that an ARB or ACE-I be used if albumin excretion of

- **30 to 300 mg per 24 hours (or equivalent) *(2D)* or;**
- **>300 mg per 24 hours (or equivalent). *(1B)***

in whom treatment with BP-lowering drugs is indicated

For CKD patients with diabetes mellitus, KDIGO suggests if urine albumin excretion >30 mg per 24 hours (or equivalent) whose office BP is consistently >130mmHg systolic or >80mmHg diastolic be treated with BP lowering drugs to maintain a BP that is consistently ≤130mmHg systolic and ≤80mmHg diastolic. *(2D)*

KDIGO suggests/ recommends that an ARB or ACE-I be used if urine albumin excretion of

- **30 to 300 mg per 24 hours. *(2D)***
- **>300 mg per 24 hours (or equivalent). *(1B)***

Tailor BP treatment regimens in elderly patients with non-diabetic CKD by carefully considering age, co-morbidities and other therapies, with gradual escalation of treatment and close attention to adverse events related to BP treatment, including electrolyte disorders, acute deterioration in kidney function, orthostatic hypotension and drug side effects. *(Not Graded)*

According to KDIGO, with the exception of ARBs or ACE-Is in CKD patients with high levels of urinary albumin or protein excretion, there is no strong evidence to support the preferential use of any particular agent(s) in controlling BP in CKD; nor are there data to guide the clinician in the choice of second- and third-line medications. Treatment choices described in the guideline were based on comorbidities like in non-CKD patients, but it is not possible to make any recommendations for CKD patients in particular, since the data are largely from studies of non-CKD patients

ACE-Is and ARBs.

- *are indicated if urinary albumin excretion is elevated*
- *give a higher risk of side effects like hyperkalemia and reduction in GFR, particularly when used with NSAIDs, COX-2 inhibitors, or potassium-sparing diuretics. If hyperkalemia occurs in CKD patients taking a renal excreted ACE-I, possible interventions include dietary advice, reducing the dose, switching to fosinopril or trandolapril, or adding a potassium-losing diuretic.*
- *In renal-artery stenosis or reduced intravascular volume, risk of hyperkalemia is high and ACE-I and ARBs or should be used with caution or even avoided.*
- *Hypotension may cause an acute decline in GFR in patients with CKD taking ACE-Is or ARBs. Reducing the dose or holding off on using ACE-Is or ARBs until recovery is sensible in patients who develop inter-current illnesses (e.g., dehydration, hypovolemia or sepsis)*
- *are titrated according to clinical effect rather than kidney function.*
- *lead to a reversible reduction in GFR of up to 30% and in urine albumin excretion. This results in some degree of long-term renoprotection, at least in patients with albuminuria. Greater reductions in GFR may indicate underlying renal artery stenosis.*

Aldosterone antagonists.

- *can be used adjunct to other antihypertensive agents in treating resistant hypertension.*
- *Because of the risk of hyperkalemia and reduction in GFR, they should be used with caution in CKD. Plasma potassium levels and kidney function should be monitored closely during the introduction of aldosterone antagonists and during intercurrent illnesses*
- *In CKD, there is an impaired renal excretion of aldosterone antagonists or active metabolites of spironolactone and eplerenone*
- *In patients with CKD, aldosterone antagonists have been shown to decrease urine albumin excretion when added to ACE-I or ARB therapy. Small reductions in GFR and systolic BP have been reported. It is premature to conclude whether they reduce the rate of decline in kidney function in the long term.*
- *are potassium sparing diuretics, thus may be combined with thiazide or loop diuretics that enhance urinary potassium loss. Be careful if combined with ACE-Is, ARBs, or other potassium-sparing diuretics.*

Direct renin inhibitors.

- *Dose is not modified in CKD. Their place in the management of BP in CKD has yet to be determined.*

Diuretics

- *potentially have an important role in hypertension in CKD, because salt and water retention are major factors contributing to high BP in CKD patients and to morbidity and mortality through systemic or pulmonary edema.*

  Thiazides.

  - *Of the available antihypertensive agents, thiazides diuretics are most often used and have been assessed in many RCTs involving CKD patients*
  - *are excreted by the kidney*
  - *No dose adjustment is recommended in patients with reduced GFR*
  - *As the GFR <30–50 ml/min/1.73m^2, the ability of thiazides to overcome fluid retention is diminished, although their antihypertensive benefit may be preserved. Most clinicians switch to a loop diuretic in patients with CKD 4, particularly if the BP is becoming resistant to therapy or edema becomes a problem.*
  - *are often one of the first 2 or 3 drugs used for BP lowering in CKD, particularly if there is edema or if ACE-Is or ARBs have already been prescribed. They can potentiate the effect of other antihypertensive agents, particularly ACE-Is and ARBs and may reduce the risk of hyperkalemia.*

  Loop diuretics.

  - *In primary hypertension effective in the short term but less so than thiazides in the long term.*
  - *particularly useful when treating edema and high BP in CKD 4–5 patients in addition or as an alternative to thiazide diuretics.*

  Potassium-sparing diuretics

  - *usually avoided in patients with CKD because of the risk of hyperkalemia.*
  - *less effective in reducing extracellular fluid volume than thiazides or loop diuretics.*

Beta-blockers

- *Pay attention to accumulation of beta-blockers or active metabolites in patients with advanced CKD, which could exacerbate concentration-dependent side effects such as bradyarrhythmias. Such accumulation occurs with atenolol and bisoprolol, but not carvedilol, propranolol or metoprolol. The combination of atenolol or bisoprolol with other bradycardia-inducing drugs is not recommended.*

Calcium-channel blockers

- *Most do not accumulate in patients with impaired kidney function, with the exception of nicardipine and nimodipine.*

Dihydropyridines

- *Are more selective for vascular smooth muscle (vasodilatation) with less action on the myocardium. Accordingly, the side effects may include fluid retention and ankle edema, which can be problematic in patients with CKD. So avoiding other vasodilators may be sensible.*
- *Most act on L-channel receptors (predominantly on the afferent arteriole) and hence have the effect of increasing urine albumin excretion. (This in contrast to T-channel blockade that leads to a reduction in intraglomerular pressure, and accordingly a fall in urine albumin levels). Later generation Dihydropyridines (e.g., manipine, cilnidipine) are less prone to increasing albumin excretion and may even reduce it. It is wise to avoid dihydropyridines in CKD patients with already increased urinary albumin excretion, particularly if there is not concomitant use of an ACE-I or ARB.*

Non-dihydropyridines

- *tend <u>not</u> be associated with an increase of albumin excretion*
- *combination with beta-blockers can lead to severe bradycardia*

Centrally acting alpha-adrenergic agonists

- *Dosing is limited by side effects and caution is advised when using alpha-agonists in the elderly, in patients with advanced CKD and in those taking sedating drugs.*
- *Since they interact minimally with other antihypertensive drugs, they are valuable as adjunct therapy for resistant hypertension in CKD patients. Combination with thiazides is probably advantageous to reduce vasodilatation induced fluid retention.*
- *Doses of methyldopa or clonidine are not generally reduced in patients with impaired kidney function. Moxonidine is extensively excreted by the kidney and accordingly it has been recommended that the dosage should be reduced in the presence of a low GFR. Although side effects are common (in 10-15% of the patients), moxonidine can be used in advanced CKD.*

Alpha-blockers

- *are not considered a first-line choice because of the common side effects of postural hypotension, tachycardia and headache. But can be used as adjunctive treatment for elevated BP in CKD patients in whom other antihypertensive drugs have failed or are not tolerated.*
- *Start a low dosage to avoid a first-dose hypotensive reaction.*
- *do not require dose modification in cases of kidney failure, are excreted via the liver.*
- *may be advantageous if symptoms of prostatic hypertrophy are present*

Direct vasodilators

- *do not require dose adjustment in patients with impaired kidney function.*
- *Hydralazine has little value in the management of chronically elevated BP in CKD. Minoxidil is generally used in patients with very resistant hypertension and thus may be helpful in patients with CKD. However, its side effects) limit its use to the most resistant cases.*

8.1.3 KDOQI diabetes and CKD 2012 [10]

KDOQI recommends not using an ACE-I or an ARB for the primary prevention of DKD in normotensive normoalbuminuric patients with diabetes. ***(1A)***

KDOQI suggests using an ACE-I or an ARB in normotensive patients with diabetes and albuminuria levels >30 mg/g who are at high risk of DKD or its progression. ***(2C)***

Not updated, from 2007:

Hypertensive people with diabetes and CKD stages 1-4 should be treated with an ACE inhibitor or an ARB, usually in combination with a diuretic. (A)

Target blood pressure in diabetes and CKD stages 1-4 should be < 130/80 mmHg. (B)

8.1.4 NICE CKD 2014[11]

In people with CKD aim to keep the systolic blood pressure below 140 mmHg (target range 120–139 mmHg) and the diastolic blood pressure below 90 mmHg.

In people with CKD and diabetes, and also in people with an ACR of 70 mg/mmol or more, aim to keep the systolic blood pressure below 130 mmHg (target range 120–129 mmHg) and the diastolic blood pressure below 80 mmHg.

Offer a low-cost renin-angiotensin system antagonist to people with CKD and

- **diabetes and an ACR ≥ 3 mg/mmol (ACR category A2 or A3)**
- **hypertension and an ACR ≥ 30 mg/mmol (ACR category A3)**
- **an ACR ≥ 70 mg/mmol (irrespective of hypertension or cardiovascular disease).**

Do not offer a combination of renin-angiotensin system antagonists to people with CKD.

Follow the treatment recommendations of NICE clinical guideline Hypertension (127) for people with CKD, hypertension and an ACR <30 mg/mmol (ACR categories A1 and A2), if they do not have diabetes.

To improve concordance, inform people who are prescribed renin-angiotensin system antagonists about the importance of:

- **achieving the optimal tolerated dose of renin-angiotensin system antagonists and**
- **monitoring eGFR and serum potassium in achieving this safely.**

In people with CKD, measure serum potassium concentrations and estimate the GFR before starting renin–angiotensin system antagonists. Repeat these measurements between 1 and 2 weeks after starting renin–angiotensin system antagonists and after each dose increase. Do not routinely offer a renin–angiotensin system antagonist to people with CKD if their pretreatment serum potassium concentration is >5.0 mmol/l. When hyperkalemia precludes use of renin-angiotensin system antagonists, assessment, investigation and treatment of other factors known to promote hyperkalemia should be undertaken and the serum potassium concentration rechecked. Concurrent prescription of drugs known to promote hyperkalemia is not a contraindication to the use of renin-angiotensin system antagonists, but be aware that more frequent monitoring of serum potassium concentration may be required. Stop renin-angiotensin system antagonists if the serum potassium concentration increases to 6.0 mmol/l or more and other drugs known to promote hyperkalemia have been discontinued.

If there is a decrease in eGFR or increase in serum creatinine after starting or increasing the dose of renin-angiotensin system antagonists, but it is less than 25% (eGFR) or 30% (serum creatinine) of baseline, repeat the test in 1–2 weeks. Do not modify the renin-angiotensin system antagonist dose if the change in eGFR is less than 25% or the change in serum creatinine is less than 30%.

If the eGFR change is 25% or more, or the change in serum creatinine is 30% or more:

- **investigate other causes of a deterioration in renal function, such as volume depletion or concurrent medication (for example, NSAIDs)**
- **if no other cause for the deterioration in renal function is found, stop the renin-angiotensin system antagonist or reduce the dose to a previously tolerated lower dose, and add an alternative antihypertensive medication if required**

8.1.5 NICE AKI 2013[1]

Investigate for acute kidney injury, by measuring serum creatinine and comparing with baseline, in adults with acute illness if use of drugs with nephrotoxic potential (such as ACE-Is, ARBs and diuretics) within the past week, especially if hypovolemic.
Consider temporarily stopping ACE-Is and ARBs in patients with diarrhea, vomiting or sepsis until their clinical condition has improved and stabilized.

8.1.6 ACP CKD 2013 [21]

ACP recommends that clinicians select pharmacologic therapy that includes either an angiotensin-converting enzyme inhibitor *(moderate-quality evidence)* or an angiotensin II–receptor blocker *(high-quality evidence)* in patients with hypertension and stage 1 to 3 chronic kidney disease. *(Strong recommendation)*

8.1.7 Domus Medica CNI 2012[4]

There are no reasons to differ in patients with CKD from the approach following the cardiovascular algorithm *(1A).*
Aim at a systolic blood pressure between 120 and 139 mmHg and a diastolic blood pressure between 60 and 89 mmHg in all patients with CKD *(1B)*.
An ACE inhibitor (ACE-I) is preferred as antihypertensive in all diabetic patients with CKD and in all patients with a corrected proteinuria of more than 270 mg/g (30 mg/mmol) *(2B)*.
Give an ACE-I to all diabetic patients with a corrected albuminuria of more than 20 mg/g (2,5 mg/mmol) in man and more than 30 mg/g (3,5 mg/mmol) in woman and this regardless the blood pressure *(2B).*
Give an ACE-I to all patients with a corrected proteinuria of more than 900 mg/g (100 mg/mmol) and this regardless the blood pressure *(1B).*
Monitor serum potassium before and after the start of an ACE-I or ARB. Control in case of hyperkalemia first if there are medical causes and consider afterwards to restrict the potassium intake by diet measures *(1C)*.

Notes Domus Medica gives on the use of antihypertensive agents in CKD patients

Atenolol

- *If eGFR <30 ml/min, there exists an elevated chance on side effects.*
- *Switch to metoprolol or half the normal dose*

Bisoprolol

- *If eGFR <30 ml/min, the excretion declines slightly*
- *Half the normal dose*

Furosemide/Bumetanide

- *Adjustment if eGFR <30 ml/min*
- *Bumetanide has a better biological availability than furosemide*
- *Start with normal dose, increase according to effect, with a lower maximum dose*

Nebivolol

- *If eGFR <30 ml/min, elevated chance on side effects.*
- *Dose according to side effects.*

RAAS inhibitors

- *If eGFR <30/50ml/min, there is an elevated chance on side effects, depending on the substance*
- *Dose adjustments can be necessary depending on the substance. Until 10 ml/min no adjustment needed for fosinopril and angiotensin-II-antagonists (except olmesartan).*

Spironolacton

- *If eGFR <50ml/min, risk of hyperkalemia. Control twice a year serum potassium.*

Thiazide diuretics

- *If eGFR < 30 ml/min, monotherapy of thiazide is insufficient, but can be combined with a loop diuretic.*
- *If eGFR 30-50 ml/min, adjust the dose, start at low dose and increase according to effect; often a higher dose than normal is necessary.*

Triamterene

- *If eGFR <30 ml/min, risk of hyperkalemia. If eGFR < 30ml/min, triamterene is contra-indicated.*
- *Give 50% of normal dose, control serum potassium regularly.*

8.1.8 Summary of guidelines on antihypertensive agents and RAAS inhibition

The guidelines recommend a blood pressure target of </≤140/90 or </≤ 130/80, depending on the presence or absence of diabetes and depending on the presence or absence of a certain proteinuria. Table 49 compares the different guidelines with their grades of recommendation for each patient group and each target. [4, 10-12]

Blood pressure target in CKD patients			**KDIGO BP in CKD**	**KDOQI DM and CKD**	**NICE CKD**	**Domus medica CNI**
AGREE domainscore Rigour of development			**79%**	**66%**	**92%**	**60%**
	Proteinuria	Target BP (mmHg)				
Non diabetic	UAE <30 mg/24h	≤140/90	1B	-	Rec	1B
		≤130/80	-	-	-	-
	UAE 30-300 mg/24h	≤140/90	-	-	Rec	1B
		≤130/80	2D	-	-	-
	UAE >300 mg/24h	≤140/90	-	-	-	1B
		≤130/80	2C	-	-	-
	ACR >70mg/mmol	≤140/90	-	-	-	1B
		≤130/80	-	-	Rec	-
Diabetic	UAE <30 mg/24h	≤140/90	1B	-	-	1B
		≤130/80	-	B	Rec	-
	UAE 30-300 mg/24h	≤140/90	-	-	-	1B
		≤130/80	2D	B	Rec	-
	UAE >300 mg/24h	≤140/90	-	-	-	1B
		≤130/80	2D	B	-	-
	ACR >70mg/mmol	≤140/90	-	-	-	1B
		≤130/80	-	B	Rec	-

Table 49 Recommendations on blood pressure targets in CKD patients. 1, 2 on a scale of 1 to 2; A= High quality; B = Moderate quality; C= Low quality of evidence; on a scale of A to D; Rec= recommendation of NICE, no GOR found
For convenience, ≤140/90 and ≤130/80 is used for the targets. Beware that NICE sets targets < 140/90 or <130/80

All guidelines agree that in hypertensive CKD patients with a certain degree of proteinuria, an ACE-I or ARB is the preferential choice for antihypertensive treatment. [4, 10-12, 21] Most guidelines recommend that in diabetic patients with proteinuria above certain level, an ACE-I or ARB is started regardless of the blood pressure. [4, 10-12] The guidelines differ in their choices of from which degree of proteinuria an ACE-I or ARB should be started.
The guidelines do not agree about well or not starting an ACE-I or ARB in antihypertensive patients without proteinuria.
Table 50 is an overview of the indications for ACE-I or ARBs with the grades of recommendation of the guidelines considered. [4, 10-12, 21]

Indications for ACE-I or ARB			KDIGO BP in CKD	NICE CKD	Domus Medica CNI	ACP CKD	KDOQI DM and CKD
AGREE domainscore			**79%**	**92%**	**60%**	**65%**	**66%**
Non diabetic	If antihypertensive is needed	without albuminuria*	-	-	-	Strong	-
		With albuminuria* above a threshold**	1B/2D	Rec	2B	Strong	-
	Regardless of the blood pressure	without albuminuria*	-	-	-	-	-
		With albuminuria* above a threshold**	-	Rec	1B	-	-
Diabetic	If antihypertensive is needed	without albuminuria*	-	-	2B	Strong	A
		With albuminuria* above a threshold**	2D/1B	Rec	2B	Strong	A
	Regardless of the blood pressure	without albuminuria*	-	-	-	-	-
		With albuminuria* above a threshold**	2D/1B	Rec	1B/2B	-	2C

Table 50 Indications for ACE-inhibitors and ARBs in patients with CKD. *or proteinuria for guideline of Domus Medica **exact threshold value varies depending on guideline; 1, 2 on a scale of 1 to 2; A= High quality; B = Moderate quality; C= Low quality of evidence; D= very low quality of evidence; on a scale of A to D; Rec= recommendation of NICE, no GOR found, Strong = strong recommendation on a scale of Strong or Weak

8.2 Handbooks: antihypertensive drugs

8.2.1 ACE inhibitors

Dose in renal impairment		
GFR	**Renal Drug handbook[6]**	**Commentaren medicatiebewaking[5]**
30-50 ml/min	Start at a low dose – adjust according to response (captopril, cilazapril, lisinopril, perindopril, quinapril) Or Dose as in normal renal function (enalapril, fosinopril, ramipril)	Adjustment of starting doses (most ACE inhibitors) Further dosing according to response and control of serum creatinine and potassium
10-30 ml/min	Start at a low dose – adjust according to response (most ACE inhibitors) Or Dose as in normal renal function (enalapril, ramipril and fosinopril if GFR 10-20ml/min)	Start at a low dose – adjust according to response and control of serum creatinine and potassium
<10 ml/min	Start at a low dose – adjust according to response (most ACE inhibitors) Normal doses have been used in CKD stadium 5 (perindopril, ramipril)	No information.

Comments
Renal drug handbook[6] Start at a low dose and adjust according to response. For some molecules (e.g. captopril, fosinopril) hepatic elimination route becomes increasingly more significant as renal function declines. Adverse reactions, especially hyperkalemia and sometimes metabolic acidosis (enalapril) are more common in patients with renal impairment. Renal failure has been reported in association with ACE inhibitors in patients with renal artery stenosis, post renal transplant, or in those with congestive heart failure. Close monitoring of renal function during therapy is necessary in those with renal insufficiency. Commentaren medicatiebewaking[5] ACE-inhibitors are important in the treatment of patients with renal insufficiency, not only because of their antihypertensive effect, but also because of lowering of the intra-glomerular pressure in the kidney by post-glomerular vasodilatation. This causes a decline in proteinuria and in a lot of cases a slowing down of the deterioration of the renal function. Furthermore, the ACE inhibitors have anti-proliferative and anti-fibrotic nephroprotective effects. The nephroprotective effect of ACE inhibitors has been shown in a number of studies. ACE inhibitors cause by their hemodynamic effect some (completely reversible) decline in glomerular function and increase in serum creatinine. ACE inhibitors can cause and worsen hyperkalemia. That is why ACE inhibitors are relatively contra-indicated in renal impairment. Control of the renal function before start of the therapy and after two weeks is necessary. In case of considerable increase in serum creatinine (>20%), the therapy must be adjusted or stopped. This can be a sign of renal artery stenosis. Bilateral renal artery stenosis or renal artery stenosis in a solitary functioning kidney is an absolute contra-indication for ACE inhibitors. It should always be taken into account that ACE inhibitors and their eventually active metabolites are cleared mostly renal. (only fosinopril is mostly eliminated hepatically). In renal insufficiency, dose adjustment is therefore always necessary.

8.2.2 Angiotensin-II receptor antagonists

Dose in renal impairment		
GFR	**Renal Drug handbook[6]**	**Commentaren medicatiebewaking[5]**
30-50 ml/min	Dose as in normal renal function	In general, no dose adjustment needed because dosing is guided by the response and adverse effects
10-30 ml/min	20-30ml/min: Dose as in normal renal function 10-20 ml/min: Start at a low dose and increase according to response (candesartan, losartan, olmesartan, valsartan) Or Dose as in normal renal function (eprosartan, irbesartan, telmisartan)	In general, no dose adjustment needed because of dosing is guided by the response and adverse effects (most Angiotensin-II receptor antagonists) Or Maximum dose adjustment (olmesartan)
<10 ml/min	Start at a low dose and increase according to response (most Angiotensin-II receptor antagonists) Or Normal dose (irbesartan)	No information.

Comments
Renal drug handbook[6] In patients with renal impairment C_{max} and AUC are increased: e.g. for candesartan respectively with 50 % and 70% in mild/moderate renal impairment, with 50% and 110% in severe renal impairment; for olmesartan AUC is increased with 62% in mild renal impairment, 82% in moderate renal impairment and 179% in severe renal impairment. Adverse reactions, especially hyperkalemia, are more common in patients with renal impairment. Renal failure has been reported in association with angiotensin-II receptor antagonists in patients with renal artery stenosis, post renal transplant, and in those with congestive heart failure. Close monitoring of renal function during therapy is necessary in those with renal insufficiency. Commentaren medicatiebewaking[5] Renal artery stenosis is a contra-indication for the use of Angiotensin-II receptor antagonists. The instructions are identical to those described for the ACE-inhibitors. In diabetic nephropathy, irbesartan and losartan are nephroprotective.

8.2.3 Renin inhibitors

Dose in renal impairment		
GFR	**Renal Drug handbook[6]**	**Commentaren medicatiebewaking[5]**
30-50 ml/min	Dose as in normal renal function	Adjustment of the starting dose is not needed
10-30 ml/min	Dose as in normal renal function	Adjustment of the starting dose is not needed
<10 ml/min	Dose as in normal renal function	No information
Comments		
Renal drug handbook[6] Potassium should be monitored in patients with renal impairment. Commentaren medicatiebewaking[5] The instructions are identical to those described for the ACE-inhibitors. Adjustment of the starting dose is not necessary.		

8.2.4 Diuretics

Dose in renal impairment		
Potassium wasting diuretics		
GFR	**Renal Drug handbook[6]**	**Commentaren medicatiebewaking[5]**
30-50 ml/min	Dose as in normal renal function	No information
10-30 ml/min	Dose as in normal renal function (most potassium wasting diuretics) Or Avoid (chlortalidone) Or Increased doses may be required (furosemide if GFR 10-20ml/min)	Important contra-indication (thiazides) Or Can have effect in high dose (loop diuretics)

<10 ml/min	Dose as in normal renal function (most potassium wasting diuretics) Or Avoid (chlortalidone) Or Increased doses may be required (furosemide)	Important contra-indication (thiazides) Or Can have effect in high dose (loop diuretics)
Potassium sparing diuretics		
GFR	**Renal Drug handbook[6]**	**Commentaren medicatiebewaking[5]**
30-50 ml/min	Dose as in normal renal function (Eplerenon, triamterene) Or 50% of normal dose (spironolactone)	Contra-indicated (canreonate) Or Dose adjustment according to response and kaliemia (most potassium sparing diuretics)
10-30 ml/min	Dose as in normal renal function (Eplerenon) Or 50% normal dose (spironolactone) Or Dose as in normal renal function if GFR = 20-30ml/min, avoid if GFR= 10-20 ml/min (Triamterene)	Contra-indicated (canreonate) Or Advise against (amiloride, triamterene) Or Dose adjustment according to response and kalemia (spironolactone, eplerenon)
<10 ml/min	Dose as in normal renal function (Eplerenon) Or Use with caution (spironolactone) Or Avoid (triamterene)	Absolute contra-indicated
Comments		

Renal drug handbook[6]

Thiazide diuretics: are unlikely to be of use once GFR <30ml/min.

Indapamide: If pre-existing renal insufficiency is aggravated – stop. Caution if hypokalemia develops. Indapamide is ineffective in established renal failure.

Bumetanide: In patients with severe chronic renal failure receiving high doses, there are reports of musculoskeletal pain and muscle spasm. Use with caution in patients receiving nephrotoxic drugs.

Furosemide: Furosemide is excreted by tubular secretion; therefore in severe renal impairment (GFR 5-10 mL/min) higher doses may be required due to a reduction in the number of functioning nephrons.

Torasemide: In patients with renal failure, the renal clearance is reduced but total plasma clearance is not significantly altered. Approximately 80% of dose is excreted renally as parent drug and metabolites

Potassium sparing diuretics: Monitor potassium levels regularly in patients with renal impairment. They are weak diuretics and are ineffective in moderate to severe renal failure. Because these patients are at an increased risk of hyperkalemia, spironolactone should be used with caution. It has active metabolites with long half-lives. Hyperkalemia is common with triamterene when GFR <30 ml/min. May cause renal failure.

Commentaren medicatiebewaking[5]

Use of diuretics can increase renal impairment by a decrease of the circulating blood volume. This is especially the case for loop diuretics.

In severe renal impairment (GFR <30 ml/min), thiazides and related molecules are only effective in very high doses (important contra-indication). Indapamide should be avoived. High doses of bumetanide (max. 10 mg) or furosemide (dosing according to response) can be effective in this case. Because hyperkalemia is common in renal impairment, potassium sparing diuretics can only be administered with the needed precautions in patients with severe renal impairment.

8.2.5 Beta-blockers

Dose in renal impairment		
Lipophilic agents (betaxolol, bisoprolol, carvedilol, labetolol, metoprolol, nebivolol, pindolol, propranolol)		
GFR	**Renal Drug handbook[6]**	**Commentaren medicatiebewaking[5]**
30-50 ml/min	Dose as in normal renal function Or Start at a low dose and adjust according to response (nebivolol)	Dose as in normal renal function (most lipophilic agents) Or Dose adjustment (nebivolol)
10-30 ml/min	Dose as in normal renal function Or Start at a low dose and titrate in accordance with response (metoprolol and propranolol if GFR 10-20ml/min) Or Start at a low dose and adjust according to response (nebivolol)	Dose as in normal renal function (most lipophilic agents) Or Dose adjustment needed (bisoprolol, nebivolol)
<10 ml/min	Dose as in normal renal function Or Start at a low dose and adjust according to response (metoprolol, nebivolol, propanolol)	No information
Hydrophilic agents (acebutolol, atenolol, celiprolol, esmolol)		
GFR	**Renal Drug handbook[6]**	**Commentaren medicatiebewaking[5]**
30-50 ml/min	Dose as in normal renal function Or Dose as in normal renal function, but frequency should not exceed once daily in renal impairment (acebutolol)	Dose as in normal renal function (most hydrophilic agents)
10-30 ml/min	Dose as in normal renal function Or Dose as in normal renal function, but frequency should not exceed once daily in renal impairment (acebutolol)	Dose as in normal renal function (celiprolol and esmolol) Or Dose adjustment needed (acebutolol and atenolol)

<10 ml/min	Dose as in normal renal function Or Start low – adjust according to response (celiprolol) Or Dose as in normal renal function, but frequency should not exceed once daily in renal impairment (acebutolol)	No information
Comments		
Renal Drug Handbook[6] *Hydrophilic agents:* *Esmolol:* has an active renally excreted metabolite; hyperkalemia can occur in CKD 5; titrate dose according to blood pressure response. *Acebutolol:* Administration of high doses in severe renal failure cautioned due to accumulation; dose frequency should not exceed once daily in renal impairment; has an active metabolite – diacetolol. *Lipophilic agents:* Labetolol: no adverse effects on renal function; no accumulation in renal impairment Metoprolol: almost all the drug is excreted as inactive metabolites. Accumulation of the metabolites will occur in renal failure, but does not seem to cause any side effects Nebivolol: 38% of the dose is excreted in the urine as active metabolites; in a trial of 10 patients with renal artery stenosis given nebivolol 5 mg daily, plasma renin activity significantly decreased, although serum aldosterone levels did not change to any great extent. In addition, there was no change in effective renal plasma flow, GFR, renal blood flow, or renal vascular resistance. Renal function remained well-preserved. Propranolol: non-selective active metabolites accumulate in renal impairment. Consider metoprolol or atenolol; may reduce renal blood flow in severe renal impairment. Commentaren medicatiebewaking[5] The acute effects of beta blockers are a slowing down of the renal blood flow and a decrease of the glomerular filtration rate. In nonselective beta blockers this also happens in chronic use. The cardioselective agents atenolol and metoprolol don't cause a decrease of the glomerular filtration rate if orally administered. In CKD, use of beta blockers has to be done carefully. Lipophilic agents are preferred above hydrophilic agents. Hydrophilic agents are mostly excreted by the kidneys and need dose adjustments.		
For sotalol: see 6.1		

8.2.6 Calcium-channel blockers

Dose in renal impairment		
GFR	**Renal Drug handbook[6]**	**Commentaren medicatiebewaking[5]**
30-50 ml/min	Dose as in normal renal function (diltiazem, most dihydropiridines) Or Dose as in normal renal function. Monitor carefully (verapamil) Or Use small doses and titrate according to response (isradipine, lercanidipine)	Dose as in normal renal function Or Contra-indicated (barnidipine)

10-30 ml/min	Dose as in normal renal function (diltiazem, some dihydropiridines) Or Dose as in normal renal function. Monitor carefully (verapamil) Or Use small doses and titrate according to response (isradipine, lercanidipine, nicardipine, nifedipine)	Dose as in normal renal function Or Contra-indicated (barnidipine)
<10 ml/min	Dose as in normal renal function (diltiazem, some dihydropiridines) Or Dose as in normal renal function. Monitor carefully (verapamil) Or Use small doses and titrate according to response (isradipine, lercanidipine, nicardipine, nifedipine)	Dose as in normal renal function Or Contra-indicated (barnidipine)
Comments		
Renal drug Handbook[6] *Verapamil*: monitor BP and ECG; active metabolites may accumulate in renal impairment. *Dihydropyridines*: The blood levels of some molecules may be elevated in some renal impaired patients. Therefore, start with a low dose and titrate to BP and response. The dose interval may also need to be extended. For nifedipine: protein binding decreased in severe renal impairment; acute renal dysfunction reported. Commentaren medicatiebewaking[5] Dihydropyridine calcium-channel blockers don't have an effect (nor negative nor positive) on the proteinuria. Non-Dihydropyridine calcium-channel blockers (diltiazem, verapamil, which have a positive effect on the proteinuria), are preferred.		

8.3 Evidence tables and conclusions: antihypertensive drugs

General introduction

The evidence tables for this chapter are based on the AHRQ CER report, with an additional search for trials published after the search date of AHRQ.

AHRQ Comparative Effectiveness Review (CER) 37. Chronic kidney disease stages 1-3: screening, monitoring and treatment. January 2012[8]

Search strategy

The data sources were MEDLINE® and Cochrane Database of Systematic Reviews electronic databases, hand searches of references from relevant systematic reviews and eligible trials, and references from expert consultants. Search date January 2011.

Inclusion criteria

- RCT
- Adult population >18 years
- Only full articles
- Patients: adults with CKD stages 1–3. Again, studies whose definitions of CKD stages 1–3 at least closely approximated the current KDOQI and KDIGO definitions were considered eligible.
- Outcomes: We restricted the review to studies that reported clinical outcomes or harms.
- Publication bias: Grey literature was searched for relevant trials and other material to estimate the likelihood of publication bias.

The AHRQ-report was compared by this literature group with NICE and KDIGO as not to miss trials in patients with CKD stage 4.

8.3.1 Blood pressure targets

8.3.1.1 Clinical evidence profile: Strict vs standard bloodpressure target

Ref	Comparison	Results		
AHRQ-CER37[8]	**Strict Versus Standard Blood Pressure Target Treatment**	**Strict BP** Mean (SD) or event rate	**Usual BP** Mean (SD) or event rate	**RR (95% CI)**
Mortality				
Ruggenenti (REIN-2) 2005[47], Shulman (HDFP) 1989[48], Toto 1995[49] Wright (AASK) 2002[50]		Total (N=4, n=1806)		
		Strict BP=96/908 (10.6%)	Standard BP=103/895 (11.5%)	RR=0.86 (0.68-1.09) NS I^2:0%
Cardiovascular mortality				
Ruggenenti (REIN-2) 2005[47], Shulman (HDFP) 1989[48]		Total (N=2, n=332)		
		Strict BP=33/326 (10.1%)	Standard BP=35/306 (11.4%)	RR=0.83 (0.54-1.26) NS I^2:0%
CV events: MI (fatal)				
Ruggenenti (REIN-2) 2005[47]		Total (N=1, n=335)		
		Strict BP=1/167 (0.6%)	Standard BP=1/168 (0.6%)	RR=1.01 (0.06-15.95) NS
CV events: stroke (fatal)				
Ruggenenti (REIN-2) 2005[47], Shulman (HDFP) 1989[48]		Total (N=2, n=632)		
		Strict BP=6/326 (1.8%)	Standard BP=5/306 (1.6%)	RR=1.09 (0.34-3.47) NS I^2:0%

Doubling of sCr			
Not reported			
End-stage renal disease			
Ruggenenti (REIN-2) 2005[47], Toto 1995[49], Wright (AASK) 2002[50]	Total (N=3, n=1506)		
	Strict BP=126/749 (16.8%)	Standard BP=126/757 (16.6%)	RR=1.03 (0.77-1.38) NS I^2:22%
Progression from micro-to macroalbuminuria			
Not reported			
Blood pressure			
Not reported			
Any or serious adverse events leading to study withdrawal			
Ruggenenti (REIN-2), 2005[47]	Total (N=1, n=338)		
	Strict BP=6/169 (3.6%)	Standard BP=3/169 (1.8%)	NT

Table 51

8.3.1.2 Characteristics of included studies in the above mentioned meta-analysis, from evidence profile

Study details	Inclusion / exclusion criteria	Patients characteristics	Intervention	Study quality
Ruggenenti 2005[47] REIN-2 Multi-center Italy Followup period (median): 19 months	Inclusion Criteria - Age 18–70 years - nondiabetic nephropathy - persistent proteinuria (urinary proteinexcretion >1 g/24 - no ACEI therapy for at least 6 weeks. - Patients with proteinuria of 1–3 g /24 hr were included if their creatinine clearance was less than 45 mL/min per 1·73m^2; those with a proteinuria >3 g /24 h were included if their creatinine clearance was less than 70 mL/min per 1·73 m^2.	N= 338 Age (yr): 53.8 Gender (Male %): 74.9 Race/Ethnicity (%): NR BP (mm Hg): 137/84 MAP (mm Hg): 101.6 Proteinuria (g/day): 2.85 Serum creatinine (mg/dL): 2.7 Creatinine Clearance (ml/min/1.73m^2): 38.8	Conventional BP control (n=169), with target DBP <90 mmHg, irrespective of SBP Vs Intensified BP control (n=169), with target <130/80 mm Hg, using felodipine, initially at 5 mg/day then titrated up as needed to 10mg/day.	- Allocation Concealment: adequate. - Randomization: adequate - Blinding: No. - Intention to Treat Analysis (ITT): 'modified' ITT - Withdrawals/Dropouts adequately described: Yes - Study withdrawals (%): 15.4

	Exclusion Criteria - Urinary tract Infection - NYHA class III or IV heart failure - CV event in past 6m - severe uncontrolled hypertension - evidence or suspicion of renovascular disease - obstructive uropathy - type 1 DM - cancer - "higher" serum aminotransferase concentrations - chronic cough	Measured GFR (ml/min/1.73m^2):35.0 Diabetes (%): NR		Other methodological remarks: - After randomization, adjustment of concomitant BP meds (excluding ACEI, ARB, or dihydropiridine CCB other than felodipine) allowed to meet BP target/avoid hypotension. Funding: Industry and other (nonprofit research institute)
Wright, 2002[50] AASK Multi-center USA Followup period: median 3.8 yrs (median 4.1 yr in ramipril and metoprolol groups, and 3.0 yr in amlodipine group)	Inclusion Criteria - African Americans - hypertension - aged 18 to 70 yr - GFR 20 to 65 mL/min per 1.73 m2, - no other identified causes of renal insufficiency. Exclusion Criteria - DBP 95 mm Hg, - known history of diabetes mellitus - urinary protein to creatinine ratio >2.5 - malignant hypertension - secondary hypertension - evidence of non–BP-related causes of chronic kidney disease - serious systemic disease - heart failure	N=1094 Age (yr): 54.6 Gender (Male %): 61.2 Race/Ethnicity (%): African American 100 BP (mm Hg): 151/96 MAP (mm Hg): 114 Proteinuria (g/24h): 0.53 Urine protein/creatinine ratio: 0.33 Serum creatinine (mg/dL): 2.0 Creatinine Clearance (ml/min/1.73m^2): NR Measured GFR (ml/min/1.73m^2): 45.6 Diabetes (%): 0	Target MAP 102-107 mm Hg (n=554) Vs Target MAP <92 mm Hg (n=540)	- Allocation Concealment Unclear - Blinding: No - Intention to Treat Analysis (ITT): Yes - Withdrawals/Dropouts adequately described: Yes - Study withdrawal: 8% Other methodological remarks: Study was 3x2 factorial design, including 2 target BP groups and 3 BP drug groups (amlodipine, metoprolol or ramipril Funding Source: Industry and Government

Toto 1995[49] Multi-center USA Followup period (Mean): 3.4 years	Inclusion Criteria - Age 25 to 73 yr - hypertensive nephrosclerosis - DBP >95 mm Hg serum creatinine >1.6 mg/dl - GFRf <70 ml/min/1.73 m^2 - longstanding hypertension - urinary protein excretion rate <2 g/day patients Exclusion Criteria - Diabetes mellitus - recent history (<4 months) of malignant hypertension, stroke or AMI - acute renal failure of any cause, polycystic kidney disease, rapidly progressive glomerulonephritis - significant hepatic dysfunction - renovascular hypertension - serum creatinine >7.0 mg/dl	N= 77 Age (yr): 55.7 Gender (Male %): 62.3 Race/Ethnicity (%): Black 75.3, Nonblack 24.7 Systolic BP (mm Hg): 123 Diastolic BP (mm Hg): 76 MAP (mm Hg) 92 Proteinuria (mg/day): 359 Serum creatinine (mg/dL): 2.3 Creatinine Clearance (ml/min/1.73m^2): NR Measured GFR (ml/min/1.73m^2): 37.8 Diabetes (%): 0	Conventional target DBP 85-95 mm Hg (n=35) vs Strict target DBP 65-80 mm Hg (n=42)	- Allocation Concealment Unclear - Blinding: Double - Intention to Treat Analysis (ITT): Yes - Withdrawals/Dropouts adequately described: Unclear - Study withdrawals (%): R Other methodological remarks: - 3-6 m run-in before randomization Funding Source Government and Industry

Shulman 1989[48] HDFP Location United States Followup period: 5 yrs	<u>Inclusion Criteria</u> - 30 to 69 years - average home screening DBP of 95 mm Hg or above - confirmed follow-up average diastolic pressure of 90 mm Hg or above. <u>Exclusion Criteria</u>: - Terminally ill and institutionalized persons - Treated hypertensives with DBP below 95.	N=297 (subgroup analysis of subjects with baseline serum creatinine ≥1.7 mg/dl from overall study of N=10, 940) Age (yr): NR Gender (Male %): 68.4 Race/Ethnicity (%): White 40.4, Black 59.6 Systolic BP (mm Hg): NR Diastolic BP (mm Hg): NR MAP (mm Hg): NR CKD stage: NR Serum creatinine (mg/dL): NR Creatinine clearance (mL/min): NR Albuminuria: NR Proteinuria (1+) : 35.0 % Albumin/creatinine ratio (mg/g): NR Estimated GFR (ml/min/1.73m2): NR Diabetes (%): 15.8	Stepped care (n= 5,485; of which n=159 had creatinine ≥1.7 mg/dl). Target goal DBP ≤90 mm Hg for those entering trial on BP drug treatment or with baseline DBP >100 mm Hg, or goal 10mm Hg DBP decrease if baseline DBP 90-99 mm Hg. vs Referred care (n=5,455; of which n=138 had creatinine ≥1.7 mg/dl)	- Allocation Concealment Adequate - Blinding: No - Intention to Treat Analysis (ITT): No - Withdrawals/Dropouts adequately described: No - Study withdrawals (%): NR **Post hoc analysis** Funding Source: Government

Table 52

8.3.1.3 Summary and conclusion. Strict versus standard blood pressure target in patients with CKD.

Strict blood pressure target versus standard blood pressure target			
Bibliography: meta-analysis AHRQ CER 37[8]			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	1806 (4 studies) 2-5 y	RR=0.86 (0.68-1.09) NS	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: OK Directness: -1 (>50% of participants are African Americans) Imprecision: OK
Cardiovascular mortality	332 (2 studies)	RR=0.83 (0.54-1.26) NS	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: OK Directness: OK Imprecision: -1 for sparse data
Myocardial infarction (fatal)	335 (1 study)	RR=1.01 (0.06-15.95) NS	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: NA Directness: OK Imprecision: -1 for sparse data
Stroke (fatal)	632 (2 studies)	RR=1.09 (0.34-3.47) NS	⊕⊕⊖⊖ **LOW** Study quality: OK Consistency: -1 Directness: OK Imprecision: -1 for sparse data
ESRD	1506 (3 studies)	RR=1.03 (0.77-1.38) NS	⊕⊕⊖⊖ **LOW** Study quality: OK Consistency: -1 Directness: -1 (>70% of participants are African Americans) Imprecision: OK

Table 53

In this meta-analysis, a strict blood pressure target was compared to a standard blood pressure target. In general, studies established blood pressure targets for their strict control group about 10-15 mm Hg lower than for their standard control group, though there was variability between trials in the absolute blood pressure targets selected. The specific antihypertensive agents utilized to achieve these blood pressure targets varied between trials. Few study participants had diabetes.

Compared with standard blood pressure control, there was no significant reduction in risk of all-cause or cardiovascular mortality with strict blood pressure control.
GRADE: MODERATE quality of evidence

Compared with standard blood pressure control, there was no significant reduction in risk of fatal myocardial infarction with strict blood pressure control.
GRADE: MODERATE quality of evidence

Compared with standard blood pressure control, there was no significant reduction in risk of fatal stroke with strict blood pressure control.
GRADE: LOW quality of evidence

Compared with standard blood pressure control, there was no significant reduction in risk of end-stage renal disease with strict blood pressure control.
GRADE: LOW quality of evidence

Due to a lack of data, it is unclear if the degree of blood pressure control has an effect on the progression from micro-to macroalbuminuria.

8.3.2 ACE inhibitors versus placebo

8.3.2.1 Clinical evidence profile: ACE-I vs placebo

Ref	Comparison	Results		
AHRQ-CER37[8]	ACEI vs placebo (N=16) /no treatment (N=1) **N=17, n=11661**	**ACEI** Event rate	**placebo** Event rate	**RR (95% CI)**
Mortality				
Perkovic 2007[51], Asselberghs 2004[52], Marre 2004[53], Katayama 2002[54], Bojestig 2001[55], Gerstein 2001[56], O'Hare 2000[57], Muirhead 1999[58], Ruggenenti 1999[59], Crepaldi 1998[60], GISEN Group 1997[61], Maschio 1996[62], Laffel 1995[36], Sano 1994[63], Lewis 1993[64], Ravid 1993[65]		Total (N=16)		
		ACEI= 667/5786 (11.5%)	Pla= 686/5750 (11.9%)	RR=0.94 (0.80-1.12) NS I^2:33%
		Diabetic nephropathy (N=11)		
		ACEI= 439/3584	Pla= 460/3580	RR=0.91 (0.70-1.18) NS I^2:38%
		Non-diabetic or mixed nephropathy (N=5)		
		ACEI= 228/2202	Pla= 226/2170	RR=1.01 (0.72-1.43) NS I^2:40%
Cardiovascular mortality				
Perkovic 2007, Asselberghs 2004, Marre 2004		Total (N=3)		
		ACEI= 231/3769 (6.1%)	Pla= 222/3764 (5.9%)	RR=1.03 (0.86-1.23) NS I^2:0%
		- Diabetic nephropathy (N=1)		
		ACEI= 141/2443	Pla= 133/2469	RR=1.07 (0.85-1.35) NS

	- Non-diabetic or mixed nephropathy (N=2)		
	ACEI= 90/1326	Pla= 89/1295	RR=0.97 (0.74-1.29) NS I^2:0%
CV events: MI (any)			
Marre 2004, Crepaldi 1998, Trevisan 1995[66]	Total = Diabetic nephropathy (N=3)		
	ACEI= 62/2535 (2.4%)	Pla= 80/2565 (3.1%)	RR=0.79 (0.57-1.09) NS I^2:0%
CV events: stroke (any)			
Perkovic 2007, Asselbergs 2004, Marre 2004, REIN 1999	Total (N=4)		
	ACEI= 232/3868 (6.0%)	Pla= 278/3851 (7.2%)	RR=0.80 (0.52-1.23) NS I^2:68%
	Diabetic nephropathy (N=1)		
	ACEI= 118/2443	Pla= 116/2469	RR=1.03 (0.80-1.32) NS
	Non-diabetic or mixed nephropathy (N=3)		
	ACEI= 114/1425	Pla= 162/1382	RR=0.51 (0.13-2.09) NS I^2:52%
Doubling of sCr			
Marre 2004, Katayama 2002, Gerstein 2001, REIN 1997, Maschio 1996, Lewis 1993, Ravid 1993	Total (N=7)		
	ACEI= 129/3682 (3.5%)	Pla= 202/3710 (5.5%)	**RR=0.60 (0.40-0.89) SS I^2: 58%**
	Diabetic nephropathy (N=5)		
	ACEI= 98/3304	Pla= 135/3330	RR=0.69 (0.44-1.09) NS I^2:55%

	Non-diabetic or mixed nephropathy (N=2)		
	ACEI= 31/378	Pla= 67/371	RR=0.31 (0.07-1.35) NS I^2:58%
End-stage renal disease			
Marre 2004, Gerstein 2001, REIN 1999, REIN 1997, Maschio 1996, Lewis 1993, Ravid 1993	Total (N=7)		
	ACEI= 63/3729 (1.7%)	Pla= 97/3761 (2.6%)	**RR=0.65 (0.49-0.88) SS better with ACEI I^2:0%**
	Diabetic nephropathy (N=4)		
	ACEI= 36/3252 (1.1%)	Pla= 49/3303 (1.4%)	RR=0.73 (0.48-1.10) NS I^2:0%
	Non-diabetic or mixed nephropathy (N=3)		
	ACEI= 27/477	Pla= 48/458	**RR=0.59 (0.39-0.89) SS I^2:0%**
Progression from micro-to macroalbuminuria			
Bojestig 2001, Gerstein 2001, O'Hare 2000, Muirhead 1999, Crepaldi 1998, Laffel 1995, Ravid 1993	Total (N=7)		
	ACEI= 123/855 (13.9%)	Pla= 174/827 (21.4%)	**RR=0.48 (0.27-0.85) SS better with ACEI**
Blood pressure			
Not reported			
Any or serious adverse events leading to study withdrawal			
Asselberghs 2004, Marre 2004, Katayama 2002, Bojestig 2001, Gerstein 2001, O'Hare 2000, Muirhead 1999, REIN 1999, Crepaldi 1998, REIN 1997, Maschio 1996, Trevisan 1995, Laffel 1995, ,Ravid 1993	Total (N=14; n=7.336)		
	ACEI= 20.7%	Pla= 18.7%	**RR=1.12 (1.02-1.23) SS more frequent with ACEI**

Renal adverse events leading to study withdrawal			
REIN 1999, Crepaldi 1998, REIN 1997, Maschio 1996	Total (N= 4; n=1.001)		
	ACEI= 0.8%	Pla= 1.7%	NT
Cough			
Marre 2004, Bojestig 2001, Gerstein 2001, Muirhead 1999, REIN 1999, Maschio 1996, Trevisan 1995, Laffel 1995, Sano 1994, Ravid 1993	Total (N= 10; n=7.361)		
	ACEI= 4.7%	Pla= 1.8%	**RR=2.33 (1.49-3.63) SS more frequent with ACEI**
Hyperkalemia			
REIN 1999, REIN 1997, Maschio 1996, Laffel 1995, Sano 1994 Lewis 1993	Total (N=8; n= 2.758)		
	1.3%	0.9%	RR=1.08 (0.53-2.23) NS

Table 54

8.3.2.2 Characteristics of included studies in the above mentioned meta-analysis, from the evidence profile

Study details	Inclusion / exclusion criteria	Patients characteristics	Intervention	Study quality
Perkovic 2007[51] PROGRESS Multinational (Europe, Asia, Australia) Followup period: mean 4 years	Inclusion criteria - history of cerebrovascular disease (ischemic stroke, hemorrhagic stroke, or transient ischemic attack but not subarachnoid hemorrhage) within the previous 5 years. Exclusion criteria not described.	N=1757 patients with CKD (Baseline GFR <60 ml/min/ 1.73m2) of 6105 randomized. Age (yr): 70 Gender (Male %): 55 Race/Ethnicity (%): Asian 37 BP (mm Hg): 149/84 Serum creatinine (mg/dL): 1.2 Creatinine clearance 50 ml/min/1.73m2 Estimated GFR (ml/min/1.73m2): NR Diabetes (%): 11	Perindopril 4 mg/d (n=895) vs Placebo (n=862)	- Allocation Concealment: adequate - Blinding: double - Intention to Treat Analysis: yes - Study withdrawals (%): NR **post hoc analysis** Funding Source: industry and other
Asselbergs 2004[52] PREVEND IT The Netherlands Followup period: mean 3.8 years	Inclusion criteria - persistent microalbuminuria - BP <160/100 mm Hg and no use of antihypertensive medication Exclusion criteria - creatinine clearance <60% of the normal age adjusted value - use of ACEI or ARB antagonists.	N=864 Age (yr): 51 Gender (Male %): 65 Race/Ethnicity (%): white 96 BP (mm Hg): 130/76 Albuminuria (mg/24 h): 23 Serum creatinine (mg/dL): 1 Estimated GFR (ml/min/1.73m2): NR Diabetes (%): 2.5	Fosinopril 20 mg/d (n=431) Placebo (n=433)	- Allocation Concealment: Unclear - Blinding: double - Intention to Treat Analysis: yes - Withdrawals/Dropouts adequately described: yes - Study withdrawals (%): 28 Note: 2 x 2 factorial design with pravastatin Funding Source: Industry

Marre 2004[53] DIABHYCAR Multinational (Europe and North Africa) Followup period: median 4 years	Inclusion criteria - persistent microalbuminuria or proteinuria - <50 years of age - type 2 diabetes Exclusion criteria - serum creatinine concentration >150 mmol/L - treatment with insulin, an ACEI or ARB blocker - recent AMI intolerance to an ACE inhibitor.	N=4,912 Age (yr): 65 Gender (Male %): 70 Race/Ethnicity (%): NR BP (mm Hg): 145/82 Microalbuminuria (%): 74 Proteinuria (%): 26 Serum creatinine (mg/dL): 1.0 Estimated GFR (ml/min/1.73m2): NR Diabetes (%): 100	Ramipril 1.25 mg/d (n=2443) Placebo (n=2469)	- Allocation Concealment: Adequate - Blinding: double - Intention to Treat Analysis: yes - Withdrawals/Dropouts adequately described: yes - Study withdrawals (%): 17 Funding Source: Industry
Katayama 2002[54] JAPAN-IDDM Sarafidis review Japan Followup period: mean 1.5 years	Inclusion criteria - UAE >30 mg/24 h - onset of type 1 diabetes before 20 year - aged between 20 and 50 years Exclusion criteria none stated.	N=53 (imdapril arm excluded) Age (yr): 33 Gender (Male %): 35 Race/Ethnicity (%): NR SBP (mm Hg): 127/78 Albumin excretion rate (mg/day): 711 Serum creatinine (mg/dL): 0.76 Creatinine clearance (ml/min): 98.4 Estimated GFR (ml/min/1.73m2): NR Diabetes (%): 100	Captopril 37.5 mg (n=26) vs Placebo (n=27)	- Allocation Concealment: Adequate - Blinding: double - Intention to Treat Analysis: no - Withdrawals/Dropouts adequately described: yes - Study withdrawals (%): 30 Funding Source: Other

Bojestig 2001[55] Sarafidis review Sweden Followup period: 2 years	Inclusion criteria - microalbuminuria - type 1 diabetes - normotensive Exclusion criteria - Patients treated with any form of hypertensive medication.	N=55 Age (yr): 40 Gender (Male %): 75 Race/Ethnicity (%): NR Systolic BP (mm Hg): 126 (clinic) Diastolic BP (mm Hg): NR Albumin excretion rate (µg/min): median 69-103 Estimated GFR (ml/min/1.73m2): median 100-108 Diabetes (%): 100	Ramipril 1.25 mg/d (n=19) Ramipril 15 mg/d (n=18) Placebo (n=18)	- Allocation Concealment: Unclear - Blinding: double - Intention to Treat Analysis: yes - Withdrawals/Dropouts adequately described: yes - Study withdrawals (%): 7 Funding Source: Industry
Gerstein 2001[56] HOPE Multinational (North and South America and in Europe) Followup period: median 4.5 years	Inclusion criteria - ≥55 years of age; - history of CV disease - history of DM; - plus at least one other CV risk factor (total cholesterol >200 mg/dL, high-density lipoprotein cholesterol ≤35mg/dL, HTN, known microalbuminaria, or current smoker. Exclusion criteria - heart failure; - serum creatinine concentration >200 mmol/L (2.3 mg/dL) - dipstick-positive proteinuria (>+1)	N=1.140 patients with diabetes and microalbuminuria from the larger HOPE trial. Patient characteristics not described for microalbuminuric subjects	Ramipril 10 mg/d (n=553) Placebo (n=587)	- Allocation Concealment: adequate - Blinding: double - Intention to Treat Analysis: yes - Study withdrawals (%): NR Note: 2 x 2 factorial design with vitamin E. **post hoc analysis** Funding Source: Industry

O'Hare 2000[57] ATLANTIS UK and Ireland Followup period: 2 years	Inclusion criteria - microalbuminuria - type 1 diabetes - untreated blood pressure <150/90 mmHg for patients <50 years of age and <165/90 mmHg for patients 50–65 years of age. Exclusion criteria - other known renal diseases or raised creatinine levels (>120 µmol/L) - liver function twice that of normal on repeat testing	N=140 Age (yr): 40 Gender (Male %): 71 Race/Ethnicity (%): NR BP (mm Hg): 132/76 Diastolic BP (mm Hg): 76 Albumin excretion rate (µg/min): 53 Estimated GFR (ml/min/1.73m2): 104 Diabetes (%): 100	Ramipril 1.25 mg/d (n=47) Ramipril 5 mg/d (n=45) Placebo (n=48)	- Allocation Concealment: Adequate - Blinding: double - Intention to Treat Analysis: no - Withdrawals/Dropouts adequately described: yes - Study withdrawals (%): 30 Funding Source: Industry
Muirhead 1999[58] Kunz review Canada Follow-up period: 1 year	Inclusion criteria - incipient diabetic nephropathy, defined as AER between 20 to 300 µg/min and a GFR 60 ≥ ml/min/1.73m2 - aged ≥18 years - type 2 DM Exclusion criteria - "brittle" diabetes (increased risk of hypoglycemia	N=60 (excluding valsartan arms) Age (yr): 56 Gender (Male %): 82 Race/Ethnicity (%): white 87 BP (mm Hg): 136/84 Serum creatinine (mg/dL): NR Albumin excretion rate (µg/min): 53.4 Estimated GFR (ml/min/1.73m2): 87 Diabetes (%): 100	Captopril 75 mg/d (n=29) Placebo (n=31)	- Allocation Concealment: Unclear - Blinding: double - Intention to Treat Analysis: no - Withdrawals/Dropouts adequately described: yes - Study withdrawals (%): 18 Funding Source: Industry
Ruggenenti 1999[59] REIN, proteinuria stratum 1: ≥1 g to <3g/24 h Italy Followup period: median 2.6 years	Inclusion criteria - chronic nephropathy - persistent proteinuria (≥1 g to <3g) - aged 18 to 70 years Exclusion criteria - treatment with corticosteroids, NSAIDs or immunosuppressive drugs; - recent AMI or cerebrovascular accident - severe uncontrolled hypertension - renovascular disease - type 1 diabetes	N=186 Age (yr): 50 Gender (Male %): 75 Race/Ethnicity (%): NR BP (mm Hg): 143/89 Urinary protein excretion (g/day): 1.7 Serum creatinine (mg/dL): 2.0 Creatinineclearance (ml/min/1.73m^2):52 Estimated GFR (ml/min/1.73m2): 46 Diabetes (%): NR	Ramipril 1.25 mg/d (n=99) Placebo (n=87)	- Allocation Concealment: adequate - Blinding: double - Intention to Treat Analysis: yes - Withdrawals/Dropouts adequately described: yes - Study withdrawals (%): 22 Funding Source: Industry

Crepaldi 1998[60] Sarafidis review Italy Followup period: 3 years	Inclusion criteria - overt albuminuria - GFR ≥80 ml/min/1.73m2 - aged 18 to 70 years - onset of insulin-dependent DM before age 35 and insulin treatment within 3 years of diagnosis - standing systolic BP ≥115 and ≤145 mmHg and diastolic BP ≥75 and ≤90 mmHg. Exclusion criteria - impaired renal function (defined as serum creatinine >10% above the upper limit of normal (125 µmol/L) and median AER >200 µg/min - nondiabetic renal disease - clinically significant liver or hematological disease - arrhythmias; unstable angina; recent AMI - hyperkalemia	N=96 (66 included in the baseline characteristics and nifedipine arm excluded) Age (yr): 37 Gender (Male %): 67 Race/Ethnicity (%): NR BP (mm Hg): 128/83 Albumin excretion rate (µg/min): 71.5 Serum creatinine (mg/dL): 0.98 Creatinine clearance (ml/min/1.73m2): 114 Estimated GFR (ml/min/1.73m2): 114 Diabetes (%): 100	Lisinoprol 2.5-20 mg/d (n=47) Placebo (n=49)	- Allocation Concealment: Unclear - Blinding: double - Intention to Treat Analysis: no - Withdrawals/Dropouts adequately described: yes - Study withdrawals (%): 32 Funding Source: None stated
The GISEN Group 1997[61] REIN proteinuria stratum 2: ≥3 g/ 24 h Italy Followup period: mean 1.3 years	Inclusion criteria - chronic nephropathy - persistent proteinuria (≥3 g) - aged 18 to 70 years Exclusion criteria - recent AMI or cerebrovascular accident - severe uncontrolled hypertension - renovascular disease - type 1 diabetes - cancer, higher serum aminotransferase concentrations, or chronic cough	N=166 Age (yr): 49 Gender (Male %): 78 Race/Ethnicity (%): NR BP (mm Hg): 149/92 Urinary protein excretion (g/day): 5.3 Serum creatinine (mg/dL): 2.4 Creatinine clearance (ml/min/1.73m2): 45 Estimated GFR (ml/min/1.73m2): 39 Diabetes (%): NR	Ramipril 1.25 mg/d (n=78) Placebo (n=88)	- Allocation Concealment: Adequate - Blinding: double - Intention to Treat Analysis: yes - Withdrawals/Dropouts adequately described: yes - Study withdrawals (%): 21 Funding Source: Industry

Maschio 1996[62] Europe Followup period: median 3 years	Inclusion criteria - chronic renal insufficiency caused by various - aged 18 to 70 years -serum creatinine concentration of 1.5 to 4.0 mg/dL and a 24-hour estimated creatinine clearance of 30 to 60 ml/min Exclusion criteria - therapy-resistant oedema - treatment with corticosteroids, NSAIDs, or immunosuppressive drugs; - urinary protein excretion over 10 g/24 h and serum albumin under 25 g/L - renovascular hypertension - cardiovascular disease; congestive heart failure - insulin-dependent DM	N=583 Age (yr): 51 Gender (Male %): 72 Race/Ethnicity (%): NR BP (mm Hg): 143-87 Urinary protein excretion (g/day): 1.8 Serum creatinine (mg/dL): 2.1 Creatinine clearance (ml/min): 43 Estimated GFR (ml/min/1.73m2): NR Diabetes (%): 4 (n=21) have diabetic Nephropathy Severity of renal dysfunction: Creatinine clearance 46 to 60 ml/min) (%): 39 Creatinine clearance 30 to 45 ml/min) (%): 61	Benazepril 10 mg/d (n=300) Placebo (n=283)	- Allocation Concealment: Unclear - Blinding: double - Intention to Treat Analysis: yes - Withdrawals/Dropouts adequately described: yes - Study withdrawals (%): 23 Funding Source: Industry
Trevisan 1995[66] Italy Followup period: 6 months	Inclusion criteria - persistent microalbuminuria - aged 18 to 65 years - stable type 2 diabetes Exclusion criteria - systolic blood pressure was ≥180 mm Hg or diastolic blood pressure ≥105 mm Hg - unstable angina, heart failure serum creatinine >1.5 mg/dL - high serum potassium levels (>5.5 mEq/L - liver, gastrointestinal, and connective tissue diseases.	N=122 Age (yr): 57 Gender (Male %): 77 Race/Ethnicity: NR Systolic BP (mm Hg): 149 Diastolic BP (mm Hg): 91 Albumin excretion rate (µg/min): 67 Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m2): NR Diabetes (%): 100	Ramipril 1.25 mg/d (n=60) Placebo (n=62)	- Allocation Concealment: Unclear - Blinding: double - Intention to Treat Analysis: no - Withdrawals/Dropouts adequately described: yes - Study withdrawals (%): 11 Funding Source: Industry

Laffel 1995[36] North American Microalbuminuria Study Sarafidis review USA and Canada Followup period: 2 years	Inclusion criteria - microalbuminaria - aged 14 to 57 years - at least 4 years insulin-dependent DM - normotensive Exclusion criteria - HbA1c ≥11.5%; - serum creatinine and potassium levels beyond normal ranges - antihypertensive therapy; - histories of renal, cardiac, hepatic, gastrointestinal, or autoimmune diseases.	N=143 Age (yr): 33 Gender (Male %): 50 Race/Ethnicity (%): white 92 BP (mm Hg): 140/90 Albumin excretion rate (µg/min): 62 Serum creatinine (mg/dL): 1.1 Estimated GFR (ml/min/1.73m2): NR Creatinine clearance (ml/min/1.73m2): 80 Diabetes (%): 100	Captopril 100 mg (n=70) Placebo (n=73)	-Allocation Concealment: Unclear - Blinding: double - Intention to Treat Analysis: no - Withdrawals/Dropouts adequately described: yes - Study withdrawals (%): 30 Funding Source: Industry
Sano 1994[63] Sarafidis review Japan Followup period: 2 years	Inclusion criteria - noninsulin dependent DM - persistent microalbuminuria - aged 50 to 76 years - serum creatinine <1.2 mg/dL; systolic BP <150 mmHg and diastolic <90 mmHg - no history of nondiabetic renal disease Exclusion criteria none stated.	N=52 (48 included in the baseline characteristics) Age (yr): 64 Gender (Male %): NR Race/Ethnicity (%): NR BP (mm Hg): 136/74 Albumin excretion rate (mg/day): 72 Estimated GFR (ml/min/1.73m2): NR Creatinine clearance (ml/min): 90 Diabetes (%): 100	Enalapril (n=26) No enalapril (n=26)	- Allocation Concealment: Unclear - Blinding: no - Intention to Treat Analysis: no - Withdrawals/Dropouts adequately described: yes - Study withdrawals (%): 8 Funding Source: none stated

Lewis 1993[64] USA Followup period: median 3 years	Inclusion criteria - urinary protein excretion of ≥ 500 mg/24 h - serum creatinine concentration of ≤ 2.5 mg/dL - aged 18 to 49 years - insulin-dependent - diabetic retinopathy; Exclusion Criteria - CHF NYHA class III or worse - serum potassium ≥6 mmol/L.	N=409 Age (yr): 35 Gender (Male %): 53 Race/Ethnicity (%): white 89; black 7 BP (mm Hg): 138/85 Urinary protein excretion (g/day): 2.7 Serum creatinine (mg/dL): 1.3 Estimated GFR (ml/min/1.73m2): NR Creatinine clearance (ml/min): 82 HbA1c (%): 11.7 Diabetes (%): 100	Captopril 75 mg (n=207) Placebo (n=202)	- Allocation Concealment: Unclear - Blinding: double - Intention to Treat Analysis: yes - Withdrawals/Dropouts adequately described: yes - Study withdrawals (%): 26 Funding Source: Industry and Other
Ravid 1993[65] Sarafidis review Israel Followup period: 5 years	Inclusion criteria - microalbuminuria - type 1 diabetes <10 years - no evidence of systemic, renal, cardiac, or hepatic disease - age <50 years; BMI <27 - normal BP Exclusion criteria none stated.	N=108 (94 included in the baseline characteristics) Age (yr): 44 Gender (Male %): 45 Race/Ethnicity (%): NR Mean BP (mm Hg): 98 Proteinuria (mg/day): 133 Serum creatinine (mg/dL): 1.2 Estimated GFR (ml/min/1.73m2): NR Diabetes (%): 100	Enalapril 10 mg (n=56) Placebo (n=52)	- Allocation Concealment: Unclear - Blinding: double - Intention to Treat Analysis: no - Withdrawals/Dropouts adequately described: yes - Study withdrawals (%): 13 Funding Source: other

Table 55

8.3.2.3 Summary and conclusion. ACE-I versus placebo in patients with CKD

ACE inhibitors (ACE-I) versus placebo			
Bibliography: meta-analysis AHRQ CER 37[8]			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
All-cause mortality	11536 (16 studies) 6m - 5y	RR= 0.94 (0.80-1.12) NS Diabetic (N=11) RR= 0.91 (0.70-1.18) NS Non diabetic RR= 1.01 (0.72-1.43)	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK
Cardiovascular mortality	7533 (3 studies)	RR=1.03 (0.86-1.23) NS Diabetic (N=1) RR= 1.07 (0.85-1.35) NS Non diabetic RR= 0.97 (0.74-1.29) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1 for posthoc analysis Consistency: OK Directness: OK Imprecision: OK
Myocardial infarction (any)	5100 (3 studies)	Diabetic (N=3) RR=0.79 (0.57-1.09) NS Non diabetic NR	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK
Stroke (any)	7719 (4 studies)	RR= 0.80 (0.52-1.23) NS Diabetic (N=1) RR= 1.03 (0.80-1.32) NS Non diabetic (N=3) RR= 0.51 (0.13-2.09) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 for posthoc analysis Consistency: -1 Directness: OK Imprecision: OK
Doubling of serum creatinine	7392 (7 studies)	**RR= 0.60 (0.40-0.89)** **SS in favour of ACEI** Diabetic RR= 0.69 (0.44-1.09) Non diabetic RR= 0.31 (0.07-1.35)	⊕⊕⊕⊖ **MODERATE** Study quality: -1 for posthoc analysis Consistency: OK Directness: OK Imprecision: OK
ESRD	7490 (7 studies)	**RR=0.65 (0.49-0.88)** **SS in favour of ACEI** Diabetic (N=4) RR= 0.73 (0.48-1.10) Non diabetic (N=3) **RR= 0.59 (0.39-0.89)**	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK

Progression from micro- to macroalbuminuria	1682 (7 studies)	**RR=0.48 (0.27-0.85)** **SS in favour of ACEI**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 for posthoc analysis Consistency: OK Directness: OK Imprecision: OK
Any or serious adverse events leading to study withdrawal	7336 (14 studies)	**RR=1.12 (1.02-1.23)** **SS more frequent with ACEI**	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: -1 Directness: OK Imprecision: OK
Cough	7361 (10 studies)	**RR=2.33 (1.49-3.63)** **SS more frequent with ACEI**	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK
Hyperkalemia	2758 (8 studies)	RR=1.08 (0.53-2.23)	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK

Table 56

In this meta-analysis, ACE inhibitors (ACE-Is) were compared to placebo in patients with CKD (mostly early stage disease). The majority of the trials was performed in diabetic patients with albuminuria. Included patients could be normotensive or hypertensive.

Treatment with ACE-I does not significantly reduce risk of all-cause mortality in patients with or without diabetes, compared to placebo.
GRADE: HIGH quality of evidence

Treatment with ACE-I does not significantly reduce risk of cardiovascular mortality in patients with or without diabetes, compared to placebo.
GRADE: MODERATE quality of evidence

Patients with diabetic CKD randomized to ACE-Is did not have a significantly reduced risk of myocardial infarction compared with those assigned placebo. There are no data on patients with non-diabetic CKD.
GRADE: HIGH quality of evidence

Patients with CKD, diabetic and non-diabetic, randomized to ACE-Is did not have a significantly reduced risk of stroke compared with those assigned placebo.
GRADE: LOW quality of evidence

CKD patients overall assigned ACE-I treatment had a significantly reduced risk for doubling of baseline serum creatinine, compared with placebo. In subgroup analysis according to diabetic status, this effect was not statistically significant.
GRADE: MODERATE quality of evidence

In CKD patients overall, ACE-Is significantly reduced the risk of ESRD, compared with placebo. This effect was significant in patients without diabetes but not in the subgroup with diabetic CKD.
GRADE: HIGH quality of evidence

CKD patients overall assigned ACE-I treatment had a significantly reduced risk for progression from microalbuminuria to macroalbuminuria, compared with placebo.
GRADE: MODERATE quality of evidence

Patients allocated to an ACE-I were significantly more likely to withdraw from treatment due to any or a serious adverse event than patients assigned placebo.
GRADE: MODERATE quality of evidence

Cough was significantly more likely in patients treated with ACE-Is, compared to placebo.
GRADE: HIGH quality of evidence

Hyperkalemia was not significantly increased with use of an ACE-I, compared to placebo.
GRADE: HIGH quality of evidence

8.3.3 Angiotensin II receptor antagonists versus placebo

8.3.3.1 Clinical evidence profile: ARBs vs placebo

Ref	Comparison	Results		
AHRQ-CER37[8] MA	Angiotensin II receptor blockers (ARB) versus placebo All patients have diabetes	**ARB** Event rate	**placebo** Event rate	**RR (95% CI)**
Mortality				
Tobe 2011 (TRANSCEND)[67], Brenner 2001 (RENAAL)[68], Parving 2001 (IRMA-2)[69], Lewis 2001 (IDNT)[70]		Total (N=4; n=5242)		
		ARB=432/2711 (15.9%)	Pla=415/2531 (16.4%)	RR=1.04 (0.92-1.18) NS I^2:0%
Cardiovascular mortality				
Tobe 2011 (TRANSCEND)[67]		Total (N=1; n=1991)		
		ARB=114/992 (11.5%)	Pla=112/999 (11.2%)	RR=1.03 (0.80-1.31) NS
CV events: MI (any)				
Brenner 2001 (RENAAL)[68]		Total (N=1; n=1513)		
		ARB=50/751 (6.7%)	Pla=68/762 (8.9%)	RR= 0.75 (0.53-1.06) NS
CV events: stroke (any)				
Not reported				
Doubling of sCr				
Tobe 2011 (TRANSCEND)[67], Brenner 2001 (RENAAL)[68], Lewis 2001 (IDNT)[70]		Total (N=3; n= 4652)		
		ARB=275/2322 (11.8%)	Pla=354/2330 (15.2%)	**RR=0.78 (0.68-0.90) SS** **SS I^2:1%**

End-stage renal disease			
Tobe 2011 (TRANSCEND)[67], Brenner 2001 (RENAAL)[68], Lewis 2001 (IDNT)[64]	Total (N=3; n=4652)		
	ARB=232/2322 (10.0%)	Pla=301/2330 (12.9%)	**RR=0.77 (0.66-0.90) SS I^2:0%**
Progression from micro-to macroalbuminuria			
Makino 2007[71], Parving 2001 (IRMA-2)[69]	Total (N= 2; n=1104)		
	ARB=96/729 (13.2%)	Pla=117/375 (31.2%)	**RR=0.42 (0.33-0.52) SS I^2:0%**
Blood pressure			
Not reported			
Any or serious adverse events leading to study withdrawal			
Not reported			
Renal adverse events leading to study withdrawal			
Not reported			
Hyperkalemia necessitating discontinuation of study medication			
	Total (N=3; n=4652)		
	ARB=3.2%	Pla= 1.3%	**RR=2.38 (1.57-3.61) SS**

Table 57

8.3.3.2 Characteristics of included studies in the above mentioned meta-analysis, from the evidence profile

Study details	Inclusion / exclusion criteria	Patients characteristics	Intervention	Study quality
Tobe, 2011 TRANSCEND[67] Location Multinational Study duration: median 4.7 years (all subjects)	Inclusion criteria - patients intolerant to ACEI - coronary artery, peripheral vascular or CVD - diabetes with endorgan damage. Exclusion criteria - heart failure, - valvular or cardiac outflow tract obstruction - systolic BP >160 mm Hg - creatinine levels >265 µmol/L - proteinuria - hepatic dysfunction.	N=5926 total were randomized, 1480 had a GFR <60 ml/min/1.73m^2 and an additional 511 had micro or macroalbuminuria with a GFR ≥60 ml/min/ 1.73m^2. N=1991 Age (yr): 68.7 Gender (Male %): 51 Race/Ethnicity(%): European 59,Asian 23 BP (mm Hg): 143/82 Albuminuria-to-creatinine ratio (ACR): 6.8 Serum creatinine (mg/dL): 1.2 Estimated GFR (ml/min/1.73m2): 57. Diabetes (%): 41	Telmisartan 80mg/day vs placebo	- Allocation Concealment : adequate - Blinding: double - Intention to Treat Analysis (ITT): yes - Withdrawals/Dropouts adequately described: yes - Study withdrawals (%): 24% Note: Post-hoc analysis
Makino 2007[71] Location Japan Followup period: median 1.3 +/- 0.5 years	Inclusion criteria - Age 30 to 74 - type 2 DM - urinary albumin-to-creatinine ratio 100-300 mg/g - serum creatinine <1.5 mg/dl (men) and <1.3 mg/dl (women). Exclusion criteria - DM type 1 - hypertension - definable chronic kidney disease other than diabetic nephropathy	N=527 Age (yr): 61.7 Gender (Male %): NR Race/Ethnicity (%): NR BP (mm Hg): 137/77 Albuminuria: see Inc. criteria Serum creatinine (mg/dL): see Inc. criteria Estimated GFR (ml/min/1.73m2): NR Diabetes (%): 100	n= 168 to Telmisartan 80mg/day n= 172 to Telmisartan 40mg/day n= 174 to placebo	- Allocation Concealment Unclear - Blinding: Double blinded - Intention to Treat Analysis (ITT): No - Withdrawals/Dropouts adequately described: Yes - Study withdrawals:2.4% Funding Source: NR

Brenner 2001[68] RENAAL Location Multinational Followup period: median 3.4 years	Inclusion criteria - Age 31 to 70 years - type 2 DM -nephropathy Exclusion criteria - Type 1 DM or nondiabetic renal disease including renal-artery stenosis. - recent MI , CABG, CVA or TIA	N=1513 Age (yr): 60 Gender (Male %): 63.2 Race/Ethnicity (%): 50% white, 18% BP (mm Hg): 153/82 Albuminuria: Median ACR: 1250 mg/g Serum creatinine (mg/dL): 1.9 Estimated GFR (ml/min/1.73m^2): NR Diabetes (%): 100	Losartan 50-100 mg/day Vs Placebo	- Allocation Concealment Adequate - Blinding: Double blind - Intention to Treat Analysis (ITT): Yes - Withdrawals/Dropouts adequately described: Yes - Study withdrawals (%): 7.8 Funding Source Industry
Parving 2001[69] IRMA-2 Location: 96 centers Worldwide Followup period: median 2 years	Inclusion criteria - hypertension - age 30 to 70 - type 2 DM - persistent microalbuminuria Exclusion criteria - Nondiabetic kidney Disease - cancer, life-threatening disease	N=590 Age (yr): 58 Gender (Male %): 68.5 Race/Ethnicity (%): White: 97.3, BP (mm Hg): 153/90 Diastolic BP (mm Hg): 90 Albuminuria: 55.5 µg/min Serum creatinine (mg/dL): 1.18 Estimated GFR (ml/min/1.73m^2):NR Diabetes (%): 100	n= 201 placebo n= 195 Irbesartan 150mg n= 194 Irbesartan 300mg	- Allocation Concealment: unclear - Blinding: Double blind - Intention to Treat Analysis (ITT): Yes - Withdrawals/Dropouts adequately described: Yes - Study withdrawals (%): 13 Funding Source Industry
Lewis, 2001[70] IDNT Location USA Followup period: median 2.6 years	Inclusion criteria - Age 30 – 70 - type 2 DM - hypertension - proteinuria (urinary protein excretion > 900 mg per 24 hours) - serum creatinine 1.0 - 3.0 mg/dL in women and 1.2 - 3.0 mg/dL in men Exclusion criteria None stated	N=1.148 Age (yr): 59 Gender (Male %): 68 Race/Ethnicity (%): White 74.3 BP (mm Hg): 159/87 Albuminuria: NR Median UrineProtein Excretion 2.9g/24h Median Urine AER 1.9g/24h Serum creatinine (mg/dL): 1.68 Estimated GFR (ml/min/1.73m^2): NR Diabetes (%): 100%	n= 579 Irbesartan 300 n= 569 Placebo Additional antihypertensives (excluding ACEI, ARB or CCB) allowed to maintain SBP <135mmHg (or 10mmHg less than baseline if SBP >145) and DBP <85.	- Allocation Concealment : Adequate - Blinding: Patients, investigators, and assessors - Intention to Treat Analysis (ITT): Yes - Withdrawals/Dropouts adequately described: yes - Study withdrawals (%): 0.8 Funding Source: Industry

Table 58

8.3.3.3 Characteristics of extra studies in the evidence profile, not reported in a meta-analysis

Study details	n/Population	Comparison	Outcomes		Methodological
Imai 2011[72] Design: RCT Duration of follow-up: mean 3.2 years	n= 577 (Japanese and Chinese) Mean age: 59 y CV disease: 85% Hypertension: 94% Diabetes: 100% Smoking: 25% <u>Inclusion</u> - Type 2 diabetes - UACR >33.9 g/mmol) - SCr concentration 88.40–221.00 µmol/l in women and 106.08–221.00 µmol/l in men <u>Exclusion</u> - type 1 diabetes - recent CV event or revascularization - heart failure III-IV - rapidly progressive renal disease - severe orthostatic hypotension - serum potassium level ≤3.5 mmol/l or ≥5.5 mmol/l.	10-40 mg 1x/d Vs Placebo Added to existing background antihypertensive therapy	Efficacy		- RANDO: Adequate - ALLOCATION CONC: Adequate - BLINDING : Adequate - FOLLOW-UP: 98% - ITT: Yes Other important methodological remarks - 6 w placebo run-in Sponsor: Daiichi Sankyo.
			Composite outcome of doubling of SCr, ESRD (SCr >442.01 µmol/l [5 mg/dl]), chronic dialysis, transplantation and all-cause death (= primary outcome)	Olm=41.1% Pla= 45.4% HR: 0.97 (95% CI 0.75 to 1.24) NS	
			Doubling of SCR	37.6 vs 42.3% HR= 1.09 (0.78-1.49) NS	
			All-cause mortality	6.7 vs 7.0% HR= 0.99 (0.53-1.86) NS	
			ESRD	0 in both groups	
			Safety		
			Adverse events	Olm= 26% Pla=23% NT	
			Hyperkalemia	Olm= 9% Pla= 5% NT	

Table 59

8.3.3.4 Summary and conclusion. Angiotensin II antagonists versus placebo in patients with CKD

Angiotensin II receptor antagonists (ARB) versus placebo			
Bibliography: meta-analysis AHRQ CER 37[8], Imai 2011[72]			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	5242+577 (4+1 studies) 1-4.5 y	RR= 1.04 (0.92-1.18) NS	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK
Cardiovascular mortality	1991 (1 study)	RR=1.03 (0.80-1.31) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 for post hoc analysis only available study Consistency: NA Directness: OK Imprecision: OK
Myocardial infarction (any)	1513 (1 study)	RR= 0.75 (0.53-1.06) NS	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: NA Directness: OK Imprecision: -1
Doubling of sCr	4652+577 (3+1 studies)	**RR=0.78 (0.68-0.90)** **SS in favour of ARB**	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK
ESRD	4652 (3 studies)	**RR=0.77 (0.66-0.90)** **SS in favour of ARB**	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK
Progression from micro-to macroalbuminuria	1104 (2 studies)	**RR=0.42 (0.33-0.52)** **SS in favour of ARB**	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK
Hyperkalemia necessitating discontinuation of study medication	4652 (3 studies)	**RR=2.38 (1.57-3.61)** **SS more frequent with ARB**	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK

Table 60

In this meta-analysis and an additional RCT, angiotensin II receptor blockers (ARB) were compared to placebo in patients with diabetic CKD and albuminuria. The majority of patients were hypertensive at baseline.

Treatment with ARB does not significantly reduce risk of all-cause mortality compared with placebo.
GRADE: HIGH quality of evidence

Treatment with ARB does not significantly reduce risk of cardiovascular mortality compared with placebo.
GRADE: LOW quality of evidence

Treatment with ARB does not significantly reduce risk of myocardial infarction compared with placebo.
GRADE: MODERATE quality of evidence

Treatment with ARB significantly reduces risk of doubling of sCr and risk of progression from micro- to macro-albuminuria.
GRADE: HIGH quality of evidence

Treatment with ARB significantly reduces risk of ESRD.
GRADE: HIGH quality of evidence

Hyperkalemia necessitating discontinuation of study medication was more frequent in patients treated with ARB, compared to placebo.
GRADE: HIGH quality of evidence

There are no data on the following outcomes: stroke and other adverse events than hyperkalemia.

8.3.4 Beta blocker versus placebo

8.3.4.1 Clinical evidence profile: Betablocker (BB) versus placebo

Ref	Comparison	Results		
AHRQ-CER37 MA	N=2 (post hoc analyses) n=2173	**BB** Event rate	**placebo** Event rate	**RR (95% CI)**
Mortality				
Cohen-Solal 2009[73], Ghali 2009[74]		Total (N=2)		
		BB= 134/1083 (12.4%)	Pla= 197/1090 (18.1%)	**RR=0.69 (0.53-0.91) SS in favour of BB I^2:45%**
Cardiovascular mortality				
Cohen-Solal 2009		Total (N=1)		
		BB= 49/348	Pla= 67/356	RR=0.75 (0.53-1.05) NS
Heart failure hospitalisation				
Ghali 2009		BB= 90/735 (12.2%)	Pla= 147/734 (20%)	**RR= 0.61 (0.48-0.78) SS in favour of BB**
CV events: MI (any)				
Not reported				
CV events: stroke (any)				
Not reported				
Doubling of sCr				
Not reported				
End-stage renal disease				
Not reported				

Progression from micro-to macroalbuminuria			
Not reported			
Blood pressure			
Not reported			
Any adverse events			
Cohen-Solal 2009	Total (N=1; n=886)		
	BB= 23/440 (5.2%)	Pla= 11/446 (2.5%)	NT

Table 61

8.3.4.2 Characteristics of included studies in the above mentioned meta-analysis, from the evidence profile

Study details	Inclusion / exclusion criteria	Patients characteristics	Intervention	Study quality
Cohen-Solal 2009[39] SENIORS Country Europe (11 countries) Followup period: 21 months	Inclusion criteria: - age ≥70 years - clinical history of chronic heart failure with at least one of the following: a)hospital admission in past 12 months with discharge diagnosis of CHF or b) LVEF ≤35% in past 6 months Exclusion criteria: - heart failure due primarily to uncorrected valvular heart disease - significant hepatic or renal dysfunction - recent cerebrovascular accident	n=704 (this is subgroup with GFR ≤55.5 ml/min/1.73m^2 from larger study of 2,135 patients) Age (yr): 77.4 Gender (Male %): 59.2 Race/Ethnicity (%): NR BP (mm Hg): 134/78 Serum creatinine (umol/L): 137.8 (=1.56 mg/dL) Creatinine clearance (mL/min): NR Albuminuria (µg/min): NR Proteinuria (mg/day): NR Albumin/creatinine ratio (mg/g): NR GFR (ml/min/1.73m^2): 43.5 Diabetes (%): 29.4	Nebivolol, 1.25-10 mg/d vs Placebo	- Allocation Concealment: Adequate - Blinding: double blind - Intention to Treat Analysis (ITT): no - Withdrawals/Dropouts adequately described: unclear - Study withdrawals: NR Other methodological remarks: **post hoc analysis** Funding Source: Private Industry

Ghal, 2009[74] MERIT-HF Country U.S., Sweden Norway, multisite Followup period: 1 year	<u>Inclusion criteria:</u> - aged 40-80 y - supine resting heart rate ≥68/min. - symptomatic heart failure NYHA II-IV - receiving optimum standard therapy - stable clinical condition - leftventricular ejection fraction of 0.40 or lower. - Patients with ejection fraction 0.36 to 0.40 included only if their maximum walking distance was 450 m or less in a 6 min walk test. <u>Exclusion criteria:</u> - recent acute myocardial infarction or unstable angina - heart failure secondary to systemic disease or alcohol abuse - atrioventricular block - use of calcium antagonists or amiodarone	n=1469 (this is subgroup with GFR ≤60 ml/min/1.73m2 from larger MERIT study of 3,991 patients) Age (yr): 68.1 Gender (Male %): 68.3 Race/Ethnicity (%): NR BP (mm Hg): 130/77 Serum creatinine (umol/L): 134.1 (=1.52 mg/dL) Creatinine clearance (mL/min): NR Albuminuria (µg/min): NR Proteinuria (mg/day): NR Albumin/creatinine ratio (mg/g): NR GFR (ml/min/1.73m2): 47.7 Diabetes (%): 29.3	Metoprolol CR/XL, 12.5 mg daily for NYHA III-IV pts and 25.0 mg daily for NYHA II pts, to a targeted 200 mg daily over 8 weeks vs Placebo	Allocation Concealment: Adequate - Blinding: double blind Intention to Treat Analysis (ITT): Yes - Withdrawals/Dropouts adequately described: unclear - Study withdrawals: NR - Other methodological remarks: **post hoc analysis** Funding Source: NA

Table 62

8.3.4.3 Summary and conclusion. Beta-blockers versus placebo in patients with CKD.

Beta blockers versus placebo			
Bibliography: AHRQ Fink CER 37[8]			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	2173 (2 studies) 1-2 years	**RR=0.69 (0.53-0.91)** **SS in favour of BB**	⊕⊖⊖ ⊖ **VERY LOW** Study quality: -2 for only post hoc analyses Consistency: OK Directness: -1 for only heart failure patients included Imprecision: OK
Cardiovascular mortality	704 (1 study)	RR=0.75 (0.53-1.05) NSdir	⊕⊖⊖⊖ **VERY LOW** Study quality: -2 for only post hoc analyses Consistency: NA Directness: -1 for only heart failure patients included Imprecision: OK
Heart failure hospitalization	1469 (1 study)	**RR= 0.61 (0.48-0.78)** **SS in favour of BB**	⊕⊖⊖ ⊖ **VERY LOW** Study quality: -2 for only post hoc analyses Consistency: NA Directness: -1 for only heart failure patients included Imprecision: OK

This meta-analysis includes two post hoc analyses of patients with CKD, selected from bigger trials with heart failure patients. Patients on optimal medical therapy for heart failure were randomized to beta blocker or placebo.

There was a significant reduction in the risk of all-cause mortality in patients treated with beta blockers compared to patients treated with placebo.
GRADE: VERY LOW quality of evidence

There was a significant reduction in the risk of cardiovascular mortality in patients treated with beta blockers compared to patients treated with placebo.
GRADE: VERY LOW quality of evidence

There was a significant reduction in the risk of hospitalization for heart failure in patients treated with beta blockers compared to patients treated with placebo.
GRADE: VERY LOW quality of evidence

No data for the following outcomes: AMI, stroke, renal outcomes, blood pressure, adverse events.

8.3.5 Calcium channel blocker versus placebo

8.3.5.1 Clinical evidence profile: CCB versus placebo

Ref	Comparison	Results		
AHRQ-CER37 MA	N=2 Lewis (IDNT) 2001, Crepaldi 1998	**CCB** Mean (SD) or event rate	**placebo** Mean (SD) or event rate	**RR (95% CI)**
Mortality				
Lewis (IDNT) 2001[70], Crepaldi 1998[60]		Diabetic nephropathy (N=2)		
		CCB= 84/608 (13.8%)	Pla= 93/618 (15.0%)	RR=0.90 (0.69-1.19) NS I^2:0%
Cardiovascular mortality				
Lewis (IDNT) 2001, Crepaldi 1998		Diabetic nephropathy (N=2)		
		CCB= 38/608 (6.3%)	Pla= 46/618 (7.4%)	RR=0.83 (0.55-1.25) NS I^2:0%
CV events: MI (any)				
Lewis (IDNT) 2001, Crepaldi 1998		Total = Diabetic nephropathy (N=2)		
		CCB= 27/608 (4.4%)	Pla= 47/618 (7.6%)	**RR=0.58 (0.37-0.92)** **SS in favour of CCB** **I^2:0%**
CV events: stroke (any)				
Lewis (IDNT) 2001		Diabetic nephropathy (N=1)		
		CCB= 15/567 (2.6%)	Pla= 26/569 (4.6%)	RR=0.58 (0.31-1.08) NS

Doubling of sCr			
Lewis (IDNT) 2001	Diabetic nephropathy (N=1)		
	CCB= 144/567 (25.4%)	Pla= 135/569 (23.7%)	RR=1.07 (0.87-1.31) NS
End-stage renal disease			
Lewis (IDNT) 2001	Diabetic nephropathy (N=1)		
	CCB= 104/567 (18.3%)	Pla= 101/569 (17.8%)	RR=1.03 (0.81-1.32) NS
Progression from micro-to macroalbuminuria			
Crepaldi 1998	Total (N=1)		
	CCB= 2/26 (7.7%)	Pla= 7/34 (20.6%)	RR=0.37 (0.08-1.65) NS
Blood pressure			
Not reported			
Any or serious adverse events leading to study withdrawal			
Not reported			
Renal adverse events leading to study withdrawal			
Not reported			

Table 63

8.3.5.2 Characteristics of included studies in the above mentioned meta-analysis, from the evidence profile

Study details	Inclusion / exclusion criteria	Patients characteristics	Intervention	Study quality
Lewis 2001[70] IDNT International Multi-site Followup period: 2.5 years (mean)	Inclusion Criteria - ages 30-70 - type 2 DM - hypertension - proteinuria (urinary protein excretion >900 mg/24h) - serum creatinine between 1.0 and 3.0 mg/dL (women) and 1.2-3.0 mg/dL (men) Exclusion criteria: none stated	N=1.136 Age (yr): 58.7 Gender (Male %): 67 Race/Ethnicity (%): 71.0% white, BP (mm Hg): 158/87 Serum creatinine (mg/dL): 1.7 Creatinine clearance (mL/min): NR Albuminuria (gday): 1.9 Proteinuria (g/day): 2.9 Albumin/creatinine ratio (mg/g): NR GFR (ml/min/1.73m2): NR Diabetes (%): 100	amlodipine (titrated from 2.5 to 10 mg/day) vs placebo Antihypertensives other than ACEIs, ARBs, and CCBs used as needed;	- Allocation Concealment: Adequate - Blinding: Double blind - Intention to Treat Analysis (ITT): Yes - Withdrawals/Dropouts adequately described: Yes - Study withdrawals: 0.5% Funding Source: Industry

Crepaldi 1998[60] Italy Multi-site Followup period: 3 years	Inclusion criteria - ages 18 to 65 years; - onset of insulin-dependent diabetes mellitus before age 35; insulin treatment within 3 years of diagnosis; - standing SBP from 115 to 140 mm Hg (without antihypertensives) - median albumin excretion rate between 20 and 200 µg/min - GFR ≥80 ml/min/1.73m2 Exclusion criteria: - impaired renal function; serum creatinine >10% above upper limit of normal laboratory - history of any nondiabetic renal disease - clinically significant liver or hematological disease - arrhythmias, unstable angina, or history of myocardial infarction - autonomic neuropathy - systematic malignancy	N= 90 (baseline data reported for 60 patients who were not excluded during run-in phase) Age (yr): 36.6 Gender (Male %): 70 Race/Ethnicity (%): NR BP (mm Hg): NR Albumin (g/dl): 4.4 Serum creatinine (µmol/L): 85.8 (=0.97 mg/dL) Creatinine clearance (mL/min): 107.8 Albuminuria (µg/min): 80.2 Albumin/Creatinine ratio (mg/mmol): NR GFR (ml/min/1.73m2): 111.8 Diabetes (%): 100	10 mg nifedipine vs placebo Antihypertensives other than ACEIs, ARBs, and CCBs used as needed;	- Allocation Concealment: Unclear - Blinding: Double blind - Intention to Treat Analysis (ITT): No - Withdrawals/Dropouts adequately described: Yes - Study withdrawals (%): 32.2 Funding Source: None reported

8.3.5.3 Summary and conclusion. Calcium channel blockers versus placebo in patients with CKD.

Calcium channel blockers (CCB) versus placebo			
Bibliography: AHRQ Fink CER 37[8]			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
All cause mortality	1226 (2 studies) 2.5-3 years	RR=0.90 (0.69-1.19) NS	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: OK Directness: OK Imprecision: -1 for sparse data
Cardiovascular mortality	1226 (2 studies)	RR=0.83 (0.55-1.25) NS	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: OK Directness: OK Imprecision: -1 for sparse data
Myocardial infarction (any)	1226 (2 studies)	**RR=0.58 (0.37-0.92)** **SS in favour of CCB**	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: OK Directness: OK Imprecision: -1 for sparse data
Stroke (any)	1136 (1 study)	RR=0.58 (0.31-1.08) NS	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: OK Directness: OK Imprecision: -1 for sparse data
Doubling of sCr	1136 (1 study)	RR=1.07 (0.87-1.31) NS	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: OK Directness: OK Imprecision: -1 for sparse data
End-stage renal disease	1136 (1 study)	RR=1.03 (0.81-1.32) NS	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: OK Directness: OK Imprecision: -1 for sparse data
Progression from micro-to macroalbuminuria	60 (1 study)	RR=0.37 (0.08-1.65) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: -1 Consistency: NA Directness: OK Imprecision: -1 for sparse data

This meta-analysis included 2 trials in patients with diabetes and CKD. Patients in the largest trial (n=1136) had type 2 diabetes and were hypertensive; patients in the smallest trial (n=60)had type 1 diabetes and were normotensive.

Treatment with CCB does not significantly reduce the risk of all-cause and cardiovascular mortality compared with placebo.
GRADE: MODERATE quality of evidence

Patients treated with CCB had a significantly lower risk of myocardial infarction compared to those treated with placebo.
GRADE: MODERATE quality of evidence

Treatment with CCB does not significantly reduce the risk of stroke compared with placebo.
GRADE: MODERATE quality of evidence

Treatment with CCB does not significantly reduce the risk of doubling of sCR and the risk of ESRD compared with placebo.
GRADE: MODERATE quality of evidence

Treatment with CCB does not significantly reduce the risk of progression from micro-to macroalbuminuria compared with placebo.
GRADE: VERY LOW quality of evidence

No data are available for the following outcomes: blood pressure, total, serious or renal adverse events.

8.3.6 Diuretics versus placebo

No trials fulfilled the inclusion criteria of this literature review.

8.3.7 ACE inhibitors versus angiotensin II receptor antagonists

8.3.7.1 Clinical evidence profile

Ref	Comparison	Results		
AHRQ-CER37[8] MA	ACEI vs ARB N=6 , n=4799	**ACEI** Event rate	**ARB** Event rate	**RR (95% CI)**
Mortality				
Barnett 2004[75], Lacourcière 2000[76], Menne 2008[77], Muirhead 1999[58]		Total (N=4 ; n=534)		
		ACEI= 7/257 (2.7%)	ARB= 5/277 (1.8%)	RR=1.04 (0.37-2.95) NS I^2: 0%
Cardiovascular mortality				
Barnett 2004[75], Lacourcière 2000[76], Menne 2008[77], Muirhead 1999[58]		Total (N=4; n=534)		
		ACEI= 3/257 (1.2%)	ARB= 3/277 (1.1%)	RR= 0.88 (0.19-4.13) NS I^2: 0%
CV events: stroke (non-fatal and fatal)				
Lacourcière 2000[76]		Total (N=1; n=103)		
		ACEI= 0/51	ARB= 0/52	NR
CV events: MI (non-fatal)				
Barnett 2004[75], Lacourcière 2000[76]		Total (N= 2; n=353)		
		ACEI= 6/181 (3.3%)	ARB= 9/172 (5.2%)	RR= 0.62 (0.23-1.68) NS I^2: not applicable
Doubling of sCr				
Not reported				
End-stage renal disease				
Not reported				

Progression from micro-to macroalbuminuria			
Sengul 2006[78]	Total (N=1; n=219)		
	ACEI= 0/110	ARB= 0/109	
Blood pressure			
Not reported			
Any study withdrawal			
Barnett 2004[75], Lacourcière 2000[76], Menne 2008[77], Muirhead 1999[58], Sengul 2006[78]	Total (N= 5; n=753)		
	ACEI= 74/366 (20.2%)	ARB= 70/387 (18.1%)	RR=1.07 (0.80-1.42) NS I^2: 0%
Study withdrawal due to AE			
Barnett 2004[75], Lacourcière 2000[76], Menne 2008[77], Muirhead 1999[58]	Total (N=4 ; n=534)		
	ACEI= 37/257 (14.4%)	ARB= 27/277 (9.7%)	RR= 1.35 (0.86-2.13) NS I^2: 0%
Cough			
Lacourcière 2000[76], Menne 2008[77], Muirhead 1999[58]	Total (N= 3; n=284)		
	ACEI= 15/127 (11.8%)	ARB= 4/157 (2.5%)	**RR= 4.10 (1.47-11.48) SS more frequent with ACEI I^2: 0%**
Hyperkalemia			
Menne 2008[77]	Total (N=1; n=90)		
	ACEI= 1/47 (2.1%)	ARB= 1/43 (2.3%)	NT

Table 64

8.3.7.2 Characteristics of included studies in the above mentioned meta-analysis, from the evidence profile

Study details	Inclusion / exclusion criteria	Patients characteristics	Intervention	Study quality
Menne, 2008[77] VALERIA Germany and Hungary Follow up period: 2.5 years	Inclusion criteria - microalbuminuria - aged 18 to 75 years - essential hypertension Exclusion criteria: - primary kidney disease - renal impairment - serum potassium values >5.5mmol/L - heart failure, significant arrhythmias or bradycardia - type I DM, uncontrolled type II DM with HbA1c >8.0%; - history of MI; recent PTCA or stroke - unstable angina pectoris; - renal transplantation; - severe hepatic disease - malignant concomitant diseases - systemic inflammatory diseases	N= 90 Age (yr): 58 Race/ethnicity (%): NR Gender (male%): 69 BP: 153/91 mmHg Urinary protein excretion (g/24 h): NR Urine albumin creatinine ratio (mg/min): 9.4 Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m²): NR Creatinine clearance (mg/min): 112 Diabetes (%): 74	Lisinopril 40 mg/d (n=47) versus Valsartan 320 mg/d (n=43)	- Allocation concealment: adequate - Blinding: double - Intention to treat (ITT) analysis: no - Withdrawals/dropouts adequately described: yes - Follow-up: 86% Funding: Industry

Sengul, 2006[78] Turkey Followup period: 1 year	Inclusion criteria - Type 2 diabetes - microalbuminuria - aged 40 to 65 years - previously diagnosed HTN despite receiving ACE inhibitor monotherapy for ≥6 month Exclusion criteria - type 1 DM; BMI ≥40 - any non-diabetic cause of secondary HTN (including bilateral renal artery stenosis) - chronic liver disease - overt carcinoma - any recent cardiovascular event - serum creatinine ≥ 150 mmol/L - serum potassium ≥ 5.5 mmol/L	N= 219 Age (yr): 57 Race/ethnicity (%): NR Gender (male%): 37 BP: 151/89 mmHg Urinary protein excretion (g/24 h): 260 Serum creatinine (mg/dL): 1 Estimated GFR (ml/min/1.73m²): NR Creatinine clearance (mg/min): 97 Diabetes (%): 100	Lisinopril 20 mg/d (n=110) versus Telmisartan 80 mg/d (n=109)	- Allocation concealment: unclear - Blinding: open-label - Intention to treat (ITT) analysis: no - Withdrawals/dropouts adequately described: yes - Follow-up: 88% Other methodological remarks: no Funding: none stated
Barnett, 2004[75] DETAIL Europe Followup period: 5 years	Inclusion criteria - urinary albumin excretion rate 11-999 µg per minute, - aged 35 to 80 years - type 2 diabetes - mild-to-moderate hypertension - normal renal morphology - serum creatinine <1.6 mg/dL - GFR >70 ml/min/1.73m2. Exclusion criteria - any condition (other than cardiovascular disease) that could restrict long-term survival	N= 250 Age (yr): 61 Race/ethnicity (%): white 98 Gender (male%): 73 BP: 152/86 mmHg Urinary protein excretion (g/24 h): NR Urinary AER (µg/min): median 46 to 60 Serum creatinine (mg/dL): 1 Estimated GFR (ml/min/1.73m²): 93 Creatinine clearance (mg/min): NR Diabetes (%): 100	Enalapril 20 mg/d (n=130) versus Telmisartan 80 mg/d (n=120)	- Allocation concealment: adequate - Blinding: double - Intention to treat (ITT) analysis: yes - Withdrawals/dropouts adequately described: yes - Follow-up: 67% Funding: industry

Lacourcière, 2000[76] Canada Followup period: 1 year	Inclusion criteria - early nephropathy characterized by a UAE rate 20 to 350 µg/min without evidence of urinary tract infection - type 2 diabetes - mild to moderate hypertension Exclusion criteria - renovascular disease; - history of malignant hypertension; - recent CVA, TIA or AMI - arrhythmias; unstable angina; history of heart failure - serum creatinine ≥ 200 mmol/L; - serum potassium ≥ 5.5 mmol/L or ≤ 3.5 mmol/L	N= 103 Age (yr): 59 Race/ethnicity (%): white 96; asian: 3; black: 1 Gender (male%): 81 BP: 160/96 mmHg Urinary protein excretion (g/24 h): NR Urinary AER (µg/min): 69 Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m²): 96 Creatinine clearance (mg/min): NR Diabetes (%): 100	Enalapril 5 mg/d (n=51) versus Losartan 50 mg/d (n=52)	- Allocation concealment: unclear - Blinding: double blind - Intention to treat (ITT) analysis: no - Withdrawals/dropouts adequately described: yes - Follow-up: 89% Funding: Industry
Muirhead, 1999[58] Kunz review Canada Followup period: 1 year	Inclusion criteria - incipient diabetic nephropathy, defined as AER between 20 to 300 µg/min and a GFR 60 ≥ ml/min/1.73m² - aged ≥ 18 years - type 2 DM Exclusion criteria - "brittle" diabetes (increased risk of hypoglycemia) or patients with a history of non compliance with medical regimens.	N= 91 Age (yr): 56 Race/ethnicity (%): white: 90; black: 1; asian: 4 Gender (male%): 67 BP: 136/83 mmHg Urinary protein excretion (g/24 h): NR Urinary AER (µg/min): 54 Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m²): 91 Creatinine clearance (mg/min): NR Diabetes (%): 100	Captopril 75 mg/d (n=29) Versus Valsartsan 80 mg/d (n=31) versus Valsartsan 160 mg/d (n=31)	- Allocation concealment: unclear - Blinding: double - Intention to treat (ITT) analysis: no - Withdrawals/dropouts adequately described: yes - Follow-up: 87% Funding: Industry

Table 65

8.3.7.3 Summary and conclusion. ACE inhibitors versus Angiotensin II receptor antagonists in patients with CKD.

ACE inhibitors (ACEI) versus angiotensin receptor II antagonists (ARB)			
Bibliography: AHRQ Fink CER 37[8]			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	534 (4 studies) 1-5 years (mean 2.5 y)	RR=1.04 (0.37-2.95) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 Consistency: OK Directness: OK Imprecision: -1 for sparse data
Cardiovascular mortality	534 (4 studies)	RR= 0.88 (0.19-4.13) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 Consistency: OK Directness: OK Imprecision: -1 for sparse data
Stroke (any)	103 (1 study)	0 in both groups	⊕⊕⊖⊖ **LOW** Study quality: -1 Consistency: NA Directness: OK Imprecision: -1 for sparse data
Myocardial infarction (non fatal)	353 (2 studies)	RR= 0.62 (0.23-1.68) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 Consistency: OK Directness: OK Imprecision: -1 for sparse data
Progression from micro-to macroalbuminuria	219 (1 study)	0 in both groups	⊕⊕⊖⊖ **LOW** Study quality: -1 Consistency: NA Directness: OK Imprecision: -1 for sparse data
Any study withdrawal	753 (5 studies)	RR=1.07 (0.80-1.42) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 Consistency: OK Directness: OK Imprecision: -1 for sparse data
Study withdrawal due to AE	534 (4 studies)	RR= 1.35 (0.86-2.13) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 Consistency: OK Directness: OK Imprecision: -1 for sparse data
Cough	284 (3 studies)	**RR= 4.10 (1.47-11.48)** **SS more frequent with ACE-I**	⊕⊕⊖⊖ **LOW** Study quality: -1 Consistency: OK Directness: OK Imprecision: -1 for sparse data

In this meta-analysis, ACE-I were compared to ARB in patients with early stages of CKD. The majority of included patients had diabetes and albuminuria. Nearly all patients were hypertensive at baseline. Overall, trials were small and of low methodological quality.

Between patients assigned to ACE-I versus those assigned to ARB, there is no significant difference in risk for total mortality, cardiovascular mortality, myocardial infarction or stroke.
GRADE: LOW quality of evidence

Between patients assigned to ACE-I versus those assigned to ARB, there is no significant difference in risk of progression from micro- to macro-albuminuria.
GRADE: LOW quality of evidence

There was no significant difference between ACE-I and ARB for total study withdrawal or withdrawal due to adverse events.
GRADE: LOW quality of evidence

Cough was more frequent in patients treated with ACE-I compared with ARB.
GRADE: LOW quality of evidence

No data are available for the following outcomes: doubling of sCr and end-stage renal disease.

8.3.8 ACE inhibitors versus beta blockers

8.3.8.1 Clinical evidence profile: ACEI versus BB

Ref	Comparison	Results		
AHRQ-CER37[8] MA	ACEI vs BB	**ACEI** Event rate	**BB** Event rate	**RR (95% CI)**
Mortality				
Hannedouche 1994[79], Norris 2006 (AASK)[80], van Essen 1997[81]		Total (N=3; n = 1080)		
		ACEI= 37/540 (6.9%)	BB= 52/540 (9.6%)	RR= 0.71 (0.48-1.07) NS I^2: 0%
Cardiovascular mortality				
Norris 2006[80], van Essen 1997		Total (N=1; n=980)		
		ACEI= 14/488 (2.9%)	BB= 13/492 (2.6%)	RR= 1.08 (0.51-2.28) NS I^2: 0%
CV events: MI (any)				
Not reported				
CV events: stroke (any)				
Norris 2006[80]		Total (N=1; n=877)		
		ACEI= 23/436 (5.3%)	BB= 23/441 (5.2%)	RR= 1.01 (0.58-1.78) NS
Doubling of sCr				
Not reported				
End-stage renal disease				
Hannedouche 1994[79], Norris 2006[80], van Essen 1997[81]		Total (N=3; n = 1080)		
		ACEI= 77/540 (14.3%)	BB= 92/540 (17.0%)	RR= 0.81 (0.50-1.33) NS I^2: 40%

Progression from micro-to macroalbuminuria			
Not reported			
Blood pressure			
Not reported			
Any or serious adverse events leading to study withdrawal			
Hannedouche 1994[79], van Essen 1997[82], Wright 2002[50]	Total (N3=; n=1080)		
	ACEI= 2.2%	BB= 1.5%	P=0.39 (NS)
Renal adverse events leading to study withdrawal			
	NR		
Cough			
Wright 2002[50]	Total (N= 1; n=877)		
	ACEI= 54.9% per patient year	BB= 41.5% per patient year	NT
Hyperkalemia			
Van Essen 1997[81], Wright 2002[50]	Total (N=2; n=980)		
	ACEI= 2.9%	BB= 0.0%	NT

Table 66

8.3.8.2 Characteristics of included studies in the above mentioned meta-analysis, from the evidence profile

Study details	Inclusion / exclusion criteria	Patients characteristics	Intervention	Study quality
Wright 2002[50] Norris 2006[80] AASK USA Followup period: 4 years	Inclusion criteria - African Americans with hypertension - aged 18 to 70 years - GFR between 20 and 65 mL/min/1.73 m² - no other identified causes of renal insufficiency. Exclusion criteria - diastolic BP <95 mm Hg - diabetes - urinary protein to creatinine ratio >2.5 - malignant or secondary hypertension - evidence of non-BP-related cause of CKD - serious systemic disease	N= 877 (minus amlodipine arm of 1094 randomized) Age (yr): 55 Race/ethnicity (%): NR Gender (male%): 61.5 BP: 150.5/95.5 mmHg Urinary protein excretion (g/24 h): NR Serum creatinine (mg/dL): 2.15 Estimated GFR (ml/min/1.73m²): 45.6 Creatinine clearance (mg/min): NR Diabetes (%): 0	Ramipril 2.5-10.0 mg/d (n=436) versus Metoprolol 50-200 mg/d (n=441)	- Allocation concealment: adequate - Blinding: adequate - Intention to treat (ITT) analysis: yes - Withdrawals/dropouts adequately described: yes - Follow-up: 100% Funding: Industry and others
Van Essen 1997[81] Followup period: median 3.9 years	Inclusion criteria - modest CKD defined as a creatinine clearance of 30-90 mL/min - aged 18 to 65 years old - no need for immunosuppressive agents or NSAIDS - no proven renal artery stenosis - Both patients with and without proteinuria could be included. Exclusion criteria NR	N= 103 Age (yr): 50 Race/ethnicity (%): NR Gender (male%): 64 BP: 152/90 mmHg Urinary protein excretion (g/24 h): median 3.3 Serum creatinine (mg/dL): 1.8 Estimated GFR (ml/min/1.73m²): 53 Creatinine clearance (ml/min/1.73m²): 55 Diabetes (%): 0	Enalapril 10 mg/d (n=52) versus Atenolol 50 mg/d (n=51)	- Allocation concealment: unclear - Blinding: double - Intention to treat (ITT) analysis: no - Withdrawals/dropouts adequately described: yes - Follow-up: 86% Funding: Industry

Hannedouche 1994[79] France Followup period: 3 years	Inclusion criteria - aged 18 to 70 years - chronic renal failure as defined by a serum creatinine concentration of 200-400 µmol/L Exclusion criteria -nephrotic syndrome - systemic diseases including diabetes, malignant hypertension, serious extrarenal disorders including malignancy, heart failure,	N= 100 Age (yr): 51 Race/ethnicity (%): NR Gender (male%): 53 BP: 167/102 mmHg Urinary protein excretion (g/24 h): 2.2 Serum creatinine (mg/dL): 3.0 Estimated GFR (ml/min/1.73m²): NR Creatinine clearance (mg/min): NR Diabetes (%): 0	Enalapril 5-10 mg/d (n=52) versus Acebutolol 400 mg/d or Atenolol 100 mg/d (n=48)	- Allocation concealment: adequate - Blinding: open label - Intention to treat (ITT) analysis: yes - Withdrawals/dropouts adequately described: yes - Follow-up: 77% Funding: Industry

Table 67

8.3.8.3 Summary and conclusion. ACE-inhibitors versus betablockers in patients with CKD.

ACE inhibitors versus beta blockers			
Bibliography: meta-analysis AHRQ CER 37[8]			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	1080 (3 studies) 3-4 y	RR= 0.71 (0.48-1.07) NS	⊕⊕⊖⊖ **LOW** Study quality: OK Consistency: OK Directness: -1 (mainly data on African Americans) Imprecision: -1 for sparse data
Cardiovascular mortality	980 (2 studies)	RR= 1.08 (0.51-2.28) NS	⊕⊕⊖⊖ **LOW** Study quality: OK Consistency: OK Directness: -1 (mainly data on African Americans) Imprecision: -1 for sparse data
Stroke	877 (1 study)	RR= 1.01 (0.58-1.78) NS	⊕⊕⊖⊖ **LOW** Study quality: OK Consistency: OK Directness: -1 (mainly data on African Americans) Imprecision: -1 for sparse data
ESRD	1080 (3 studies)	RR= 0.81 (0.50-1.33) NS	⊕⊕⊖⊖ **LOW** Study quality: OK Consistency: OK Directness: -1 (mainly data on African Americans) Imprecision: -1 for sparse data
Any or serious adverse events leading to study withdrawal	1080 (3 studies)	2.2 vs 1.5% P= 0.39 (NS)	⊕⊕⊖⊖ **LOW** Study quality: OK Consistency: OK Directness: -1 (mainly data on African Americans) Imprecision: -1 for sparse data

In this meta-analysis, ACEI were compared to beta blockers in patients with CKD without diabetes. The largest trial was performed in Afro-Americans with moderate CKD (stage 3). The majority of included patients were hypertensive at baseline.

When comparing ACEI with beta blockers, no significant differences were found for the incidence of all-cause or cardiovascular mortality.
GRADE: LOW quality of evidence

When comparing ACEI with beta blockers, no significant differences were found for the risk of stroke.
GRADE: LOW quality of evidence

When comparing ACEI with beta blockers, no significant differences were found for the risk of ESRD.
GRADE: LOW quality of evidence

When comparing ACEI with beta blockers, no significant differences were found for the total incidence of adverse events, nor for the occurrence of serious adverse events.
GRADE: LOW quality of evidence

There are no data available for the following outcomes: myocardial infarction, doubling of sCR, progression of micro- to macroalbuminuria, blood pressure, cough and hyperkalemia.

8.3.9 ACE inhibitors versus calcium channel blockers

8.3.9.1 Clinical evidence profile: ACEI versus CCB

Ref	Comparison	Results		
AHRQ-CER37[8] MA	N = 6 ACEI vs CCB n = 4357	**ACEI** Event rate	**CCB** Event rate	**RR (95% CI)**
Mortality				
Crepaldi 1998[60], Fogari 2002[83], Marin 2001[84], Norris 2006 (AASK)[80], Zucchelli 1992[85, 86]		Total (N=5; n=1307)		
		ACEI= 42/774 (5.4%)	CCB= 33/533 (6.2%)	RR= 0.75 (0.48-1.16) NS I^2: 0%
Cardiovascular mortality				
Marin 2001[84], Norris 2006[80], Zucchelli 1992[85, 86]		Total (N=3; n=1011)		
		ACEI= 16/625 (2.6%)	CCB= 13/386 (3.4%)	RR= 0.75 (0.36-1.57) NS I^2: 0%
CV events: Any and fatal myocardial infarction				
Crepaldi 1998[60]		Total (N=1; n=58)		
		ACEI= 0/32	CCB= 0/26	Not determined
CV events: stroke (any)				
Marin 2001[84], Norris 2006[80], Rahman 2006[87]		Total (N=3; n=3943)		
		ACEI= 123/2098 (5.9%)	CCB= 111/1845 (6.0%)	RR= 1.00 (0.78-1.28) NS I^2: 0%
Doubling of sCr				
Not reported				

End-stage renal disease			
Norris 2006[80], Rahman 2006[87], Zucchelli 1992[85, 86]	Total (N=3; n=3823)		
	ACEI= 124/2029 (6.1%)	CCB= 111/1794 (6.2%)	RR= 0.82 (0.57-1.19) NS I^2: 46%
Progression from micro-to macroalbuminuria			
Agodoa 2001[82], Rahman 2006[87]	N=2; n=3702		
	ACEI= 80/1969 (4.1%)	CCB= 48/1733 (2.8%)	NT
Blood pressure			
Not reported			
Any or serious adverse events leading to study withdrawal			
Fogari 2002[83], Wright 2002[50], Marin 2001[84], Crepaldi 1998[60], Zucchelli 1995[86]	Total (N=5)		
	ACEI= 3.2%	CCB= 4.7%	p=0.77 NS
Renal adverse events leading to study withdrawal			
Fogari 2002[83], Wright 2002[50], Crepaldi 1998	Total (N=3 ; n=504)		
	ACEI= 6/263 (2.3%)	CCB= 3/241 (1.2%)	NT
Cough			
Fogari 2002[83], Marin 2001[84], Zucchelli 1995[86]	Total (N=3 ; n=567)		
	7/291 (2.4%)	CCB= 0/276 (0.0%)	NT

Table 68

8.3.9.2 Characteristics of included studies in the above mentioned meta-analysis, from the evidence profile

Study details	Inclusion / exclusion criteria	Patients characteristics	Intervention	Study quality
Rahman 2006[87] ALLHAT USA and CANADA Followup period: mean 4.9 years	Inclusion criteria - aged 55 years or older - stage 1 or stage 2 hypertension - at least 1 additional risk factor for CHD events Exclusion criteria - heart failure and/or a known left ventricular ejection fraction <35% - serum creatinine level > 2 mg/dL	N= 3049 for patients with a baseline GFR <60 ml/min/ 1.73m² (of a total of 17118 randomized and minus the chlorthalidone arm) Subgroup analysis with diabetic patients: n=1007 Age (yr): 70 Race/ethnicity (%): white: 58; black 25; Hispanic: 13 Gender (male%): 48 BP: 147/83 mmHg Urinary protein excretion (g/24 h): NR Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m²): 50 Creatinine clearance (mg/min): NR Diabetes (%): 33	Lisinopril up to 40 mg/d (n=1533) versus Amlodipine up to 10 mg/d (n=1516)	- Allocation concealment: adequate - Blinding: double - Intention to treat (ITT) analysis: yes - Withdrawals/dropouts adequately described: not reported for CKD subgroup - Follow-up: % study withdrawals : not reported for CKD subgroup Other methodological remarks: - 3 x 2 factorial design - **post hoc analysis** Funding: Industry and other
Fogari, 2002[83] Italy Followup period: 4 years	Inclusion criteria - microalbuminuria; - essential hypertension - type 2 DM - UAE ≥30 and ≤300 mg/24 h - serum creatinine <1.5 mg/dL. Exclusion criteria - history of previous CHD, stroke, heart failure - cancer; smoking - total cholesterol >240 mg/dL - use of diuretics or beta blockers.	N= 205 (minus the combination artm) Age (yr): 63 Race/ethnicity (%): NR Gender (male%): 58 BP: 160/97 mmHg Urinary protein excretion (g/24 h): NR Urinary AER (µg/min): 97 Serum creatinine (mg/dL): 1 Estimated GFR (ml/min/1.73m²): NR Creatinine clearance (mg/min): 90 Diabetes (%): 100	Fosinopril 10-30 mg/d (n=102) versus Amlodipine up to 10 mg/d (n=103) *Combination arm*	- Allocation concealment: adequate - Blinding: open label - Intention to treat (ITT) analysis: no - Withdrawals/dropouts adequately described: yes - Follow-up: 68% Other methodological remarks: no Funding: Industry and other

Agodoa, 2001[82] Wright, 2002[50] Norris, 2006[80] AASK USA Followup period: mean 4 years (Norris 2006)	Inclusion criteria - African Americans with hypertension - aged 18 to 70 years - GFR between 20 and 65 mL/min/1.73 m^2 - no other identified causes of renal insufficiency. Exclusion criteria - diastolic BP of <95 mm Hg - diabetes - urinary protein to creatinine ratio >2.5 - malignant or secondary hypertension - evidence of non–BP-related causes of chronic kidney disease - serious systemic disease	N= 653 (minus metoprolol arm of 1094 randomized) Age (yr): 54 Race/ethnicity (%): 100 African American Gender (male%): 61 BP: 151/96 mmHg Urinary protein excretion (g/24 h): 0.5 Serum creatinine (mg/dL): 2.21 for men and 1.76 for women Estimated GFR (ml/min/1.73m2): 46.3 Creatinine clearance (mg/min): NR Diabetes (%): 0	Ramipril 2.5-10 mg/d (n=436) Versus Amlodipine 5-10 mg/d (n=217)	- Allocation concealment: : adequate - Blinding: double blinded - Intention to treat (ITT) analysis: yes - Withdrawals/dropouts adequately described: yes - Follow-up: 100% - Other methodological remarks: 3 x 2 factorial design with lower and usual blood pressure goal arms The CCB treatment arm was stopped early . Funding: Industry and other
Marin, 2001[84] ESPIRAL Spain Followup period: Minimum 3 years	Inclusion criteria - aged 18 to 75 year - serum creatinine values between 1.5 and 5 mg/dl - hypertension - proven progression of chronic renal failure in the previous 2 years (increase by more than 25% or > 0.5 mg/dl in serum creatinine). Exclusion criteria - diabetes -recent history of cardiovascular disease	N= 241 Age (yr): 56 Race/ethnicity (%): NR Gender (male%): 59 BP: 156/96 mmHg Urinary protein excretion (g/24 h): 1.7 Serum creatinine (mg/dL): 2.8 Estimated GFR (ml/min/1.73m²): NR Creatinine clearance (ml/min/1.73m²): 36 Diabetes (%): 0	Fosinopril 10-30 mg/d (n=129) versus Nifedepine 30-60 mg/d (n=112)	- Allocation concealment: unclear - Blinding: open label - Intention to treat (ITT) analysis: yes - Withdrawals/dropouts adequately described: yes - Follow-up: 66% Funding: none stated

Crepaldi, 1998[60] (Sarafidis review) Italy Followup period: 3 years	Inclusion criteria - age 18 to 70 y - onset of insulin-dependent DM before age 35 and insulin treatment within 3 years of diagnosis - median AER value 20 to 200 µg/min - GFR ≥80 ml/min/1.73m^2 - systolic BP ≥115 and ≤145 mmHg (without HTN therapy) and diastolic BP ≥75 and ≤90 mmHg. Exclusion criteria - impaired renal function (defined as serum creatinine >10% above the upper limit of normal (125 µmol/L) and median AER >200 µg/min - nondiabetic renal disease; - liver or hematological disease - arrhythmias; unstable angina; recent AMI - systemic malignancy - hyperkalemia	N= 88 (58 included in the baseline characteristics and nifedipine arm excluded) Age (yr): 37 Race/ethnicity (%): NR Gender (male%): 69 BP: 128/83 mmHg Urinary protein excretion (g/24 h): NR Albumin excretion rate (µg/min): 61.2 Serum creatinine (mg/dL): 0.96 Estimated GFR (ml/min/1.73m²): 120 Creatinine clearance (ml/min/1.73m²): 109 Diabetes (%): 100	Lisinoprol 2.5-20 mg/d (n=48) versus Nifedepine 10-20 mg/d (n=41)	- Allocation concealment: unclear - Blinding: double - Intention to treat (ITT) analysis: no - Withdrawals/dropouts adequately described: yes - Follow-up: 63% Funding: none stated
Zucchelli 1992[85]/1995[86] Italy Followup period: 3 years	Inclusion criteria - age 18 to 70 y - established chronic renal failure (SCr ranging between 1.8 to 5 mg/dL); - hypertension - good general health Exclusion criteria: - diabetes - potentially reversible renal disease - systemic diseases - severe cardiac or hepatic dysfunction - peripheral edema; - proteinuria >5 g/24 h.	N= 121 Age (yr): 55 Race/ethnicity (%): NR Gender (male%): 58 BP: 165/100 mmHg Urinary protein excretion (g/24 h): 1.8 Serum creatinine (mg/dL): 3.0 Estimated GFR (ml/min/1.73m²): NR Creatinine clearance (mg/min): NR Diabetes (%): 0	Captopril 25-100 mg/d (n=60) versus Nifedepine 20-40 mg/d (n=61)	- Allocation concealment: unclear - Blinding: none stated - Intention to treat (ITT) analysis: yes - Withdrawals/dropouts adequately described: yes - Follow-up: 74% - Other methodological remarks: no Funding: none stated

Table 69

8.3.9.3 Summary and conclusion. ACE-inhibitors versus calcium channel blockers in patients with CKD

ACE inhibitors versus calcium channel blockers			
Bibliography: meta-analysis AHRQ CER 37[8]			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	1307 (5 studies) 3-5 y	RR= 0.75 (0.48-1.16)	⊕⊕⊖⊖ **LOW** Study quality: -1 Consistency: OK Directness: -1 for mostly African Americans Imprecision: OK
Cardiovascular mortality	1011 (3 studies)	RR= 0.75 (0.36-1.57)	⊕⊕⊖⊖ **LOW** Study quality: -1 Consistency: OK Directness: -1 for mostly African Americans Imprecision: OK
Myocardial infarction (any)	58 (1 study)	0 in both groups	⊕⊕⊖⊖ **LOW** Study quality: -1 Consistency: NA Directness: OK Imprecision: -1 for sparse data
Stroke (any)	3943 (3 studies)	RR= 1.00 (0.78-1.28)	⊕⊕⊕⊖ **MODERATE** Study quality: -1 for post hoc analysis Consistency: OK Directness: OK Imprecision: OK
ESRD	3823 (3 studies)	RR= 0.82 (0.57-1.19)	⊕⊕⊕⊖ **MODERATE** Study quality: -1 for post hoc analysis Consistency: OK Directness: OK Imprecision: OK
Any or serious adverse events leading to study withdrawal	1307 (5 studies)	3.2 vs 4.7% (NS)	⊕⊕⊕⊖ **MODERATE** Study quality: -1 Consistency: OK Directness: OK Imprecision: OK

In this meta-analysis ACE-I were compared to calcium channel blockers in patients with CKD, mostly non-diabetic. The largest included study is a post hoc analysis performed in the subset of 3,049 individuals with GFR <60 ml/min/ 1.73m^2 from the larger Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Another large trial in this analysis included only African Americans. All patients had hypertension at baseline

When comparing ACEI with calcium channel blockers, no significant differences were found for the incidence of total and cardiovascular mortality and for the risk of myocardial infarction.
GRADE: LOW quality of evidence

When comparing ACE-I with calcium channel blockers, no significant differences were found for the risk of stroke.
GRADE: MODERATE quality of evidence

When comparing ACE-I with calcium channel blockers, no significant differences were found for the risk ESRD.
GRADE: MODERATE quality of evidence

No significant differences were found between ACE-I and calcium channel blockers for the total incidence of adverse events and the occurrence of serious adverse events.
GRADE: MODERATE quality of evidence

There are no data available for the following outcomes: doubling of sCr, progression from micro- to macroalbuminuria, blood pressure, cough and hyperkalemia.

8.3.10 ACE inhibitors versus diuretics

8.3.10.1 Clinical evidence profile: ACEI versus diuretics

Ref	Comparison	Results		
AHRQ-CER37[8] MA	N=2 ACEI versus diuretics n=4716	**ACEI** Event rate	**Diuretics** Event rate	**RR (95% CI)**
All-cause mortality= cardiovascular mortality				
Marre 2004[88] Remark: all deaths were cardiovascular deaths		Total (N=1; n=570)		
		ACE= 1/286 (0.3%)	Diur= 2/284 (0.7%)	RR= 0.50 (0.05-5.44) NS
CV events: MI (fatal)				
Marre 2004[88]		Total (N=1; n=570)		
		ACE= 0/286	Diur= 1/284 (0.3%)	NT
CV events: stroke (any)				
Rahman 2006[87]		Total (N=1; n=4146)		
		ACE= 99/1533 (6.5%)	Diur= 157/2613 (6.0%)	RR= 1.07 (0.84-1.37) NS
		Diabetes patients (N=1; n=1382)		
		ACE= 33/501 (6.6%)	Diur= 63/881 (7.2%)	NT
Doubling of sCr				
Not reported				

End-stage renal disease			
Rahman 2006[87]	Total (N=1; n =4146)		
	ACE= 70/1533 (4.6%)	Diur= 124/2613 (4.7%)	RR= 0.96 (0.72-1.28) NS
	Diabetes patients (N=1; n=1382)		
	ACE= 41/501 (8.2%)	Diur= 68/881 (7.7%)	NT
Progression from micro- to macroalbuminuria			
Marre 2004[88]	Total (N=1; n=570)		
	ACE= 18/286 (6.3%)	Diur= 26/283 (9.2%)	RR= 0.69 (0.38-1.22) NS
Blood pressure			
Not reported			
Any or serious adverse events leading to study withdrawal			
Marre 2004[88]	Total (N=1; n=570)		
	ACE= 15/286 (5.2%)	Diur= 14/286 (4.9%)	NT
Cough			
Not reported			
Hyperkalemia			
Not reported			

Table 70

8.3.10.2 Characteristics of included studies in the above mentioned meta-analysis, from the evidence profile

Study details	Inclusion / exclusion criteria	Patients characteristics	Intervention	Study quality
Rahman 2006[87] ALLHAT USA and Canada Followup period: mean 4.9 years	Inclusion criteria -aged 55 years or older - stage 1 or stage 2 Hypertension - at least 1 additional risk factor for CHD Exclusion criteria - history of symptomatic heart failure and/or a known left ventricular ejection fraction <35% - serum creatinine level > 2 mg/dL	N= 4146 for patients with a baseline GFR <60 ml/min/ 1.73m² (of a total of 17118 randomized and minus the amlodipine arm) Subgroupanalysis for diabetes patients:1382 Age (yr): 71 Race/ethnicity (%): white: 57, black: 26, Hispanic: 12 Gender (male%): 49 BP: 147/83 mmHg Urinary protein excretion (g/24 h): NR Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m²): 50 Creatinine clearance (mg/min): NR Diabetes (%): 33	Lisinopril up to 40 mg/d (n=1533) versus Chlorthalidone up to 25 mg/d (n=2613)	- Allocation concealment: adequate - Blinding: double - Intention to treat (ITT) analysis: yes - Withdrawals/dropouts adequately described: NR for CKD subgroup - Follow-up: NR for CKD subgroup Other methodological remarks: - 3 x 2 factorial design **- Post hoc analysis** performed within subset of participants with CKD from the ALLHAT trial Funding: Industry and others
Marre 2004[88] NESTOR France Followup period: 1 year	Inclusion criteria - aged between 35 and 80 years - type 2 DM - persistent micro-albuminuria - essential hypertension Exclusion criteria - severe hypertension - ventricular rhythm disorders - plasma creatinine >150 µmol/l - kalaemia < 3.5 mmol/l > 5.5 mmol/l - uric acid > 536 µmol/l	N= 570 Age (yr): 60 Race/ethnicity(%): white 86, black 4, asian 2 Gender (male%): 65 BP: 161/94 mmHg Urinary protein excretion (g/24 h): NR Albumin excretion rate (µg/min): 58 Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m²): NR Creatinine clearance (ml/min/1.73m²): 92 Diabetes (%): 100	Enalapril 10 mg/d (n=286) versus Indapamide 1.5 mg/d (n=284)	- Allocation concealment: unclear - Blinding: double - Intention to treat (ITT) analysis: 'modified' ITT - Withdrawals/dropouts adequately described: yes - Follow-up: 89% Funding: Industry

Table 71

8.3.10.3 Summary and conclusion. ACE-inhibitors verus diuretics in patients with CKD

ACE inhibitors versus diuretics			
Bibliography: meta-analysis AHRQ CER 37[8]			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Cardiovascular mortality= all cause mortality	570 (1 study) 1 y	RR= 0.50 (0.05-5.44)NS	⊕⊖⊖⊖ **VERY LOW** Study quality: -1 allocation Consistency: NA Directness: OK Imprecision: -1 for sparse data, -1 for wide CI
Myocardial infarction (fatal)	570 (1 study)	NT (0 vs 0.3%)	⊕⊖⊖⊖ **VERY LOW** Study quality: -1 Consistency: NA Directness: OK Imprecision: -1 for sparse data, -1 for wide CI
Stroke (any)	4146 (1 study) 5 y	RR= 1.07 (0.84-1.37) NS	⊕⊕⊖⊖ **LOW** Study quality: -2 for posthoc analysis of only available trial Consistency: NA Directness: OK Imprecision: OK
ESRD	4146 (1 study)	RR= 0.96 (0.72-1.28) NS	⊕⊕⊖⊖ **LOW** Study quality: -2 for posthoc analysis of only available trial Consistency: NA Directness: OK Imprecision: OK
Progression from micro- to macroalbuminuria	570 (1 study)	RR= 0.69 (0.38-1.22) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: -1 allocation concealment unclear, -1 for wide CI Consistency: NA Directness: OK Imprecision: -1 for limited data
Any or serious adverse events leading to study withdrawal	570 (1 study)	NT (5.2% vs 4.9%)	⊕⊖⊖⊖ **VERY LOW** Study quality: -1 allocation concealment unclear, -1 for wide CI Consistency: NA Directness: OK Imprecision: -1 for limited data

In this meta-analysis ACE-I were compared to diuretics in patients with CKD. The largest trial is a post hoc analysis of the ALLHAT trial; diabetic and non-diabetic patients were included in this analysis. The other trial included patients with diabetic CKD. All patients had hypertension at baseline.

When comparing ACE-I with diuretics, no significant differences were found for the incidence of all-cause and cardiovascular mortality.
GRADE: VERY LOW quality of evidence

When comparing ACE-I with diuretics, no significant differences were found for the risk of myocardial infarction.
GRADE: VERY LOW quality of evidence

When comparing ACE-I with diuretics, no significant differences were found for the risk of stroke.
GRADE: LOW quality of evidence

When comparing ACE-I with diuretics, no significant differences were found for the risk of ESRD.
GRADE: LOW quality of evidence

When comparing ACE-I with diuretics, no significant differences were found for the risk of progression from micro- to macroalbuminuria.
GRADE: VERY LOW quality of evidence

No significant differences were found between ACEI and diuretics for the total incidence of adverse events and the occurrence of serious adverse events.
GRADE: VERY LOW quality of evidence

There are no data for the following outcomes: myocardial infarction, doubling of sCr, blood pressure, cough and hyperkalemia.

8.3.11 Angiotensin-II receptor antagonists versus calcium channel blockers

8.3.11.1 Clinical evidence profile: ARB versus CCB

Ref	Comparison	Results		
AHRQ-CER37[8]	ARB vs CCB	**ARB** Event rate	**CCB** Event rate	**RR (95% CI)**
Mortality				
Lewis 2001[70], Ogawa 2007[89]		Total (N=2; n=1204)		
		ARB= 87/619 (14.1%)	CCB= 83/585 (14.2%)	RR= 1.03 (0.79-1.35) NS I^2: not applicable
Cardiovascular mortality				
Not reported				
CV events: MI (any)				
Not reported				
CV events: stroke (any)				
Saruta 2009[90]		Total (N=1; n=2720)		
		ARB= 44/1376 (3.2%)	CCB= 40/1344 (3.0%)	RR= 1.07 (0.70-1.64) NS
Doubling of sCr				
Lewis 2001[70]		Total (N=1; n=1146)		
		ARB= 98/579 (17.0%)	CCB= 144/567 (25.4%)	**RR= 0.67 (0.53-0.84) SS**
End-stage renal disease				
Lewis 2001[70]		Total (N=1; n=1146)		
		ARB= 82/579 (14.2%)	CCB= 104/567 (18.3%)	RR= 0.77 (0.59-1.01) NS

Progression from micro-to macroalbuminuria			
Ogawa 2007[89]	Total (N=1; n=58)		
	ARB= 4/40 (10.0%)	CCB= 5/18 (27.8%)	RR= 0.36 (0.11-1.18) NS
Blood pressure			
Not reported			
Any or serious adverse events leading to study withdrawal			
Ogawa 2007[89]	Total (N=1; n=58)		
	ARB= 0/40	CCB= 0/18	NA
Renal adverse events leading to study withdrawal			
Not reported			
Hyperkalemia			
Lewis 2001[70]	Total (N=1; n=1146)		
	ARB= 11/579 (1.9%)	CCB= 3/567 (0.5%)	**SS** **P < 0.05**

Table 72

8.3.11.2 Characteristics of included studies in the above mentioned meta-analysis, from the evidence profile

Study details	Inclusion / exclusion criteria	Patients characteristics	Intervention	Study quality
Saruta 2009[90] CASE-J Japan Followup period: 36 months	Inclusion criteria - SBP >180mmHg or DBP >110mmHg - type II diabetes, history of stroke or TIA - left ventricular hypertrophy - angina pectoris or a history of myocardial infarction - proteinuria or a serum creatinine >1.3mg/dL -arteriosclerotic peripheral artery obstruction. Exclusion criteria - SBP ≥200 mmHg or DBP ≥120 mmHg - Type I DM, - recent AMI or CVA - CHF NYHA II-IV - atrial fibrillation or atrial flutter, - serum creatinine ≥3 mg/dL - malignancy <5 years before enrollment	N= 2720 (subset with GFR <60ml/min/1.73m² from among larger study cohort of 4728) Age (yr): 65 Race/ethnicity (%): NR Gender (male%): 51.8 BP: 163/91 mmHg Urinary protein excretion (g/24 h): NR Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m²): NR Creatinine clearance (mg/min): NR Diabetes (%): 42.4	Candesartan 4 to 12mg daily titrated to target BP (n=1376) versus Amlodipine 2.5 to 10mg daily titrated to target BP (n=1344) Doses titrated to goal BP <130/85 for ages <60 years <140/90 for ages 60-69 <150/90 for ages 70-79 <160/90 for ages >80	- Allocation concealment: not defined - Blinding: Assessor -Intention to treat (ITT) analysis: Yes - Withdrawals/dropouts adequately described: inadequate - Follow-up: % study withdrawals: NR - sungroup analysis, unclear if predefinied Funding: Industry and government

Ogawa 2007[89] Japan Followup period: median 56 weeks	Inclusion criteria - type 2 DM - untreated moderate hypertension (130/80 – 200/110 mmHg) - microalbuminuria - HbA1c<8% - serum creatinine < 1.2 mg/dl Exclusion criteria - other renal diseases - severe cerebral or cardiovascular diseases or liver dysfunction - active retinopathy.	N= 58 Age (yr): 6.7 Race/ethnicity (%): NR Gender (male%): 46.6 BP: 152/90 mmHg Urinary protein excretion (g/24 h): NR Serum creatinine (mg/dL): 0.74 Estimated GFR (ml/min/1.73m²): NR Creatinine clearance (mg/min): NR Diabetes (%): 100	Candesartan 4 - 8mg/d (n=40) Versus Nifedipine 20 - 40mg/d (n=18) .	- Allocation concealment: not defined - Blinding: Patient only - Intention to treat (ITT) analysis: Unclear - Withdrawals/dropouts adequately described: Yes - Follow-up: % study withdrawals: 3.4% Funding: NR
Lewis 2001[70] IDNT USA Followup period: 2.6 years	Inclusion criteria - Age 30 - 70 yrs, - type 2 DM - hypertension - proteinuria - serum creatinine 1.0 -3.0 mg/dL in women and 1.2 - 3.0 mg/dL in men Exclusion criteria Not stated	N= 1146 Age (yr): 59 Race/ethnicity (%): white: 72.1, Hispanic: 5.0, Black: 13.0, Asian: 5.1, Other: 4.7 Gender (male%): 64.3 BP: 160/87 mmHg Urinary protein excretion (g/24 h): 2.9 (median) Estimated GFR (ml/min/1.73m²): NR Creatinine clearance (mg/min): NR Diabetes (%): 100	Irbesartan 300 mg daily (n=579) versus Amlodipine 10mg daily (n=567) Additional antihypertensives (excluding ACEI, ARB or CCB) allowed to maintain SBP <135mmHg (or 10mmHg less than baseline if SBP >145) and DBP <85.	- Allocation concealment: yes - Blinding: Patients, investigators, assessors - Intention to treat (ITT) analysis: yes - Withdrawals/dropouts adequately described: Adequate - Follow-up: % study withdrawals: 0.6 Funding: Industry

Table 73

8.3.11.3 Summary and conclusion. Angiotensin II receptor antagonists versus calcium channel blockers in patients with CKD

Angiotensin II receptor antagonists (ARB) versus calcium channel blockers (CCB)			
Bibliography: meta-analysis AHRQ CER 37[8]			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	1204 (2 studies) 1.8 to 3.2 y	RR= 1.03 (0.79-1.35) NS	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: OK Directness: OK Imprecision: -1 for sparse data
Stroke	2720 (1 study)	RR= 1.07 (0.70-1.64) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 only subgroup Consistency: NA Directness: -1 only Japanese Imprecision:
Doubling of sCr	1146 (1 study)	**RR= 0.67 (0.53-0.84)** **SS in favour of ARB**	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: NA Directness: OK Imprecision: -1 for sparse data
ESRD	1146 (1 study)	RR= 0.77 (0.59-1.01) NS	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: NA Directness: OK Imprecision: -1 for sparse data
Progression from micro-to macroalbuminuria	58 (1 study)	RR= 0.36 (0.11-1.18) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: -1 Consistency: NA Directness: -1 only Japanese Imprecision: -1 for sparse date
Hyperkalemia	1146 (1 study)	**1.9 vs 0.5%** **SS more frequent with ARB (p<0.05)**	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: NA Directness: OK Imprecision: -1 for sparse data

In this meta-analysis, angiotensin II receptor blockers (ARB) were compared to calcium channel blockers (CCB) in patients with diabetic CKD, albuminuria and hypertension.

When comparing ARB with CCB, no significant difference was found for the incidence of total mortality.
GRADE: MODERATE quality of evidence

When comparing ARB with CCB, no significant difference was found for the risk of stroke.
GRADE: LOW quality of evidence

Patients treated with ARB were significantly less likely to develop a doubling of their baseline sCr than patients treated with CCB.
GRADE: MODERATE quality of evidence

The risk of developing hyperkalemia is higher with ARB, compared with CCB
GRADE: MODERATE quality of evidence

No data are available for the following outcomes: cardiovascular mortality, myocardial infarction, blood pressure, total incidence of adverse events.

8.3.12 Dual inhibition of the RAS

8.3.12.1 Clinical evidence profile: dual inhibition of RAS

Study details	n/Population	Comparison	Outcomes		Methodological
Parving 2012[91] ALTITUDE RCT Duration of follow-up: 33 months Trial was stopped prematurely	n= 8561 Mean age: 64y Previous CV event: 42% known CV diseases other than hypertension. Hypertension: 95% Diabetes: 82% Hypercholesterolemia: NR Smoking: 13% CKD: 98% Proteinuria: 84% <u>Inclusion</u> - type 2 diabetes - evidence of micro/macroalbuminuria, or cardiovascular disease <u>Exclusion</u> -Serum potassium >5.0 mmol/L - Congestive heart failure III-IV - renal transplant - CV event in prior 3m	Aliskiren 300 mg/d Vs Placebo As an adjunct to ACE-I or sartan	Efficacy		RANDO: unclear ALLOCATION CONC: unclear BLINDING : yes FOLLOW-UP: % in safety analysis % in efficacy analysis FOLLOW-UP: 97% ITT: yes Other important methodological remarks - trial was stopped prematurely Sponsor: Novartis
			Time to CV death or a first occurrence of cardiac arrest with resuscitation; nonfatal MI or stroke; unplanned hospitalization for heart failure; ESRD, death attributable to kidney failure, or the need for RRT with no dialysis or transplantation available or initiated; or doubling of the baseline SCr level = primary outcome	Aliskiren= 18.3% Pla= 17.1% HR= 1.08 (0.98-1.20) NS	
			Total mortality	Aliskiren= 8.8% Placebo= 8.4% HR= 1.06 (0.92-1.23) NS	
			Cardiovascular mortality	Aliskiren= 5.8% Placebo= 5.0% HR= 1.16 (0.96-1.39) NS	
			ESRD mortality	Aliskiren= 2.8% Placebo= 2.6% HR= 1.08 (0.84-1.40) NS	
			Doubling of sCr	Ali= 4.9% Pla= 5.1% HR= 0.97 (0.80-1.17) NS	
			Safety		
			Discontinuation due to adverse events	Aliskiren= 13.2% Placebo= 10.2% **P<0.001 in favour of placebo**	
			Hyperkalemia	Aliskiren= 39.1% Placebo= 29.0% **P<0.001 in favour of placebo**	

			Hypotension	Aliskiren= 12.1% Placebo= 8.3% **P<0.001 in favour of placebo**	

Table 74

Study details	n/Population	Comparison	Outcomes		Methodological
Fried 2013[92] VA NEPHRON-D RCT Duration of follow-up: 2.2y Trial was stopped prematurely owing to safety concerns.	n= 1448 Mean age: Previous CV event: % Hypertension: % Diabetes: % Cholesterol: mean total 158 mg/dl Smoking: NR <u>Inclusion</u> - veterans with type 2 diabetes - eGFR 30.0-89.9 mL/min/1.73 m^2 <u>Exclusion</u> - non-diabetic kidney disease - serum potassium >5.5 mmol/L	Losartan 100 mg/d (all patients) and Lisinopril 10-40 mg/d (= ass.) vs placebo (= mono)	Efficacy		RANDO: adequate ALLOCATION CONC: unclear BLINDING : yes FOLLOW-UP: NR ITT: NR Other important methodological remarks - Trial was stopped prematurely owing to safety concerns. - Initial run-in with losartan Sponsor: Veterans Affairs Office
			Change in eGFR (a decline of ≥30ml/ min/1.73 m^2 if initial eGFR was ≥60 ml/ min/1.73m^2 or a decline of ≥50% if initial eGFR was <60 ml /min/1.73 m^2), ESRD, or death = primary outcome	Ass= 18.2% Mono= 21.0% HR= 0.88 (0.70-1.12) NS	
			First occurrence of a decline in eGFR or ESRD (= secondary renal end point)	Ass= 10.6% Mono= 14.0% HR= 0.78 (0.58-1.05) NS	
			ESRD	Ass= 3.7% Mono= 5.9% HR= 0.66 (0.41-1.07) NS	
			Total mortality	Ass= 8.7% Mono= 8.3% HR= 1.04 (0.73-1.49) NS	
			Safety		
			Hyperkalemia	Ass= 9.9% Mono= 4.4% HR= 2.8 (1.8-4.3) **P<0.001, SS more frequent with association**	
			Acute kidney injury	Ass= 18.0% Mono= 11.0% HR= 1.7 (1.3-2.2) **P<0.001, SS more frequent with association**	
			Serious adverse events	Not reported	

Table 75

8.3.12.2 Summary and conclusion. Dual inhibition of the renin-angiotensin system in patients with CKD

Dual ACEI-ARB therapy arose around 2000 from the concept that monotherapy resulted in incomplete blockade of the renin-angiotensin system. Several studies demonstrated that patients with the greatest reduction in proteinuria had the lowest rates of progression to end-stage renal disease and supported the idea that reducing proteinuria should be a target of treatment. Despite improvement in proteinuria, overwhelming evidence now demonstrates significant harm with dual therapy without any benefit in mortality or kidney function[93].

Most trials assessing the efficacy and safety of dual inhibition of the RAS are very small and of short duration. Here we discuss only the 2 major RCT's.

Dual versus single inhibition of the RAS			
Bibliography: Parving 2012[91], Fried 2013[92]			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	10.009 (2 studies) 2-3 y	NS	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK
ESRD	10.009 (2 studies) 2-3 y	NS	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK
Hyperkalemia	10.009 (2 studies) 2-3 y	**SS more frequent with dual therapy**	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK
Acute kidney injury	1448 (1 study)	HR= 1.7 (1.3-2.2) **SS more frequent with dual therapy**	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: NA Directness: OK Imprecision: -1

Two large trials assessed the efficacy and safety of dual RAS inhibition compared to the use of a single RAS-inhibiting agent. The largest trial compared aliskiren versus placebo, in patients already treated with an ACE or an ARB. The second trial compared the association of losartan and lisinopril to losartan alone. Both trials were stopped prematurely due to safety concerns.

Dual inhibition of the RAS is not significantly superior to the use of a single agent for the prevention of mortality or progression to ESRD.
GRADE: HIGH quality of evidence

Dual inhibition of the RAS is associated with a higher risk for hyperkalemia compared to the use of a single agent.
GRADE: HIGH quality of evidence

Dual inhibition of the RAS is associated with a higher risk for acute kidney injury compared to the use of a single agent.
GRADE: MODERATE quality of evidence

In May 2014 the European Medicines Agency advised against the use of dual inhibition of the renin-angiotensin system in patients with CKD.

- Where combination of these medicines (dual blockade) is considered absolutely necessary, it must be carried out under specialist supervision with close monitoring of kidney function, fluid and salt balance and blood pressure. This would include the licensed use of the ARBs candesartan or valsartan as add-on therapy to ACE-inhibitors in patients with heart failure who require such a combination.
- The combination of aliskiren with an ARB or ACE-inhibitor is strictly contraindicated in those with kidney impairment or diabetes.

9 Results: Lipid lowering drugs in CKD

9.1 Guidelines: statins and fibrates

9.1.1 KDIGO CKD 2012 [2]

KDIGO recommends that all people with CKD be considered at increased risk for cardiovascular disease. ***(1A)***

Cautionary notes

- *No increase in toxicity for simvastatin dosed at 20 mg per day or simvastatin 20 mg/ezetimide 10 mg combinations per day in people with GFR < 30 ml/min/1.73 m^2 or on dialysis. Other trials of statins in people with GFR <15 ml/min/1.73 m^2 or on dialysis also showed no excess toxicity.*
- *Fenofibrate increases SCr by approximately 0.13 mg/dl (12µmol/l)*

9.1.2 KDIGO Lipid in CKD 2013[20]

In adults aged ≥50 years with eGFR <60 ml/min/1.73 m^2 but not treated with chronic dialysis or kidney transplantation (GFR categories G3a-G5), KDIGO recommends treatment with a statin or statin/ezetimibe combination. ***(1A)***

In adults aged ≥50 years with CKD and eGFR ≥60 ml/min/1.73 m^2 (GFR categories G1-G2) we recommend treatment with a statin. ***(1B)***

According to KDIGO, the risk of future coronary events in patients aged ≥50 years with CKD is markedly increased, as compared to those without CKD.

In adults aged 18–49 years with CKD but not treated with chronic dialysis or kidney transplantation, KDIGO suggests statin treatment in people with one or more of the following ***(2A):***

- **known coronary disease (myocardial infarction or coronary revascularization)**
- **prior ischemic stroke**
- **diabetes mellitus**
- **estimated 10-year incidence of coronary death or non-fatal myocardial infarction >10%**

In adults with CKD (including those treated with chronic dialysis or kidney transplantation) and hypertriglyceridemia, we suggest that therapeutic lifestyle changes be advised. ***(2D)***

In the judgment of KDIGO, there is insufficient evidence to recommend for or against the use of fibric acid derivatives in people with CKD. There are currently no published randomized trials of fibric acid derivatives in CKD populations and too few participants with CKD were included in previous trials to provide reliable information. Given that evidence of clinical benefit is greater for statins than for fibrates, KDIGO recommends that statins be prescribed in preference to fibrates.

9.1.3 KDOQI diabetes and CKD 2012 [10]

Dyslipidemia is common in people with diabetes and CKD. Cardiovascular events are a frequent cause of morbidity and mortality in this population. Lowering low-density lipoprotein cholesterol (LDL-C) with statin-based therapies reduces risk of major atherosclerotic events, but not all-cause mortality, in patients with CKD including those with diabetes.

KDOQI recommend using LDL-C lowering medicines, such as statins or statin/ezetimibe combination, to reduce risk of major atherosclerotic events in patients with diabetes and CKD, including those who have received a kidney transplant. ***(1B)***

9.1.4 ACP CKD 2013[21]

ACP recommends that clinicians choose statin therapy to manage elevated low-density lipoprotein in patients with stage 1 to 3 chronic kidney disease. ***(Strong recommendation, moderate-quality evidence)***

9.1.5 Domus Medica CNI 2012 [4]

Domus Medica notes that there is insufficient scientific evidence that the routine use of statins influences the progression of CKD in a positive way. The use of statins in patients with CKD is appropriate in the prevention of cardiovascular diseases. **There are no reasons to differ in patients with CKD from the approach following the cardiovascular algorithm** ***(1A).***

9.1.6 Summary of guidelines on lipid management in CKD

Guidelines differ in their approach of lipid management in CKD.

Following KDIGO, CKD patients above 50 years, in secondary prevention, with diabetes or with high cardiovascular risk, are candidate for statin therapy [2]; ACP recommends statin for all CKD patients with elevated LDL-C [21], whereas Domus Medica chooses to follow the normal cardiovascular algorithm to decide to start a statin. [4]

9.2 Handbooks: statins and fibrates

9.2.1 Statins

Dose in renal impairment		
GFR	**Renal Drug handbook[6]**	**Commentaren medicatiebewaking[5]**
30-50 ml/min	Dose as in normal renal function (most statins) Or Do not use high doses (rosuvastatin)	Dose as in normal renal function (most statins Or Start at a low dose and adjust according to effect to max. 20 mg (rosuvastatin)
10-30ml/min	Dose as in normal renal function (most statins) Or Use only at a low dose (rosuvastatin)	Dose as in normal renal function (most statins Or Start at a low dose and adjust according to effect to max. 10 mg (rosuvastatin)
<10 ml/min	Dose as in normal renal function (atorvastatin, fluvastatin, pravastatin) Or Use only at a low dose (rosuvastatin, simvastatin)	No information
Comments		

Renal Drug Handbook[6]

The Committee on Safety of Medicines has advised that rhabdomyolysis associated with lipid-lowering drugs, such as the fibrates and statins, appears to be rare (approx. 1 case in every 100 000 treatment years), but may be increased in those with renal impairment and possibly in those with hypothyroidism

Rosuvastatin: In renal impairment, doses above 20 mg should not be used due to risk of myopathy. Do not use doses greater than 20 mg in Asian patients. Always start at a dose of 5 mg. The 40 mg dose should only be used under specialist supervision.

There is an increased risk of proteinuria with doses above 40 mg.

fluvastatin: Manufacturers literature indicates fluvastatin is contraindicated in patients with severe renal impairment (creatinine greater than or equal to 160 μ mol/L).

Pravastatin: Rhabdomyolysis with acute renal failure, secondary to statin-induced myoglobinaemia, has been reported. Inactive polar metabolite accumulates but is readily removed by hemodialysis.

Commentaren medicatiebewaking[5]

In rosuvastatin, renal insufficiency increases the risk on myopathy and rhabdomyolysis.

9.2.2 Fibrates

Dose in renal impairment		
GFR	**Renal Drug handbook[6]**	**Commentaren medicatiebewaking[5]**
30-50 ml/min	Dose as in normal renal function (ciprofibrate) Or Dose adjustment (bezafibrate) Or Max 134mg daily (fenofibrate)	Contra-indicated (bezafibraat) Or Adjustment of the dose (ciprofibraat) Or No information (fenofibrate)
10-30ml/min	Dose reduction or frequency reduction	Contra-indicated (Bezafibrate, ciprofibrate) Or No information (fenofibrate)
<10 ml/min	Avoid	Contra-indicated (Bezafibrate, ciprofibrate) Or No information (fenofibrate)
Comments		
Renal Drug Handbook[6] *Bezafibrate:* Contra-indicated in nephrotic syndrome. Modified-release preparation is not appropriate in renal impairment. *Ciprofibrate:* Increased risk of rhabdomyolysis in doses of 200 mg or greater. Approximately 30–75% of a single dose administered to volunteers was excreted in the urine in 72 hours, either as unchanged ciprofibrate (20–25% of the total excreted) or as a conjugate. Subjects with moderate renal impairment excreted on average 7% of a single dose as unchanged ciprofibrate over 96 hours, compared with 6.9% in normal subjects. In subjects with severe insufficiency this was reduced to 4.7% *Fenofibrate:* Avoid use of fibrate in patients with GFR<10 mL/min due to increased risk of rhabdomyolysis		

9.3 Evidence tables and conclusions

9.3.1 Statins versus placebo

9.3.1.1 Clinical evidence profile: Statins vs placebo

Ref	Comparison	Results		
AHRQ-CER37[8]		**STATINS** Event rate	**placebo** Event rate	**RR (95% CI)**
Mortality all-cause				
Kendrick 2010 (AFCAPS/TexCAPS)[94], Ridker 2010 (JUPITER)[95], Nakamura 2009 (MEGA)[96], Colhoun 2009 (CARDS)[97], Koren 2009 (ALLIANCE)[98], Rahman 2008 (ALLHAT-LLT)[99], Huskey 2009 (4S Trial)[100], Kjekshus 2007 (CORONA)[101], Lemos 2005 (LIPS) [102], Asselbergs 2005 (PREVEND IT)[52], Tonelli 2004 (WOSCOPS/CARE/LIPID)[103], Tonelli 2003 (CARE)[104] Asselbergs= only dedicated RCT		Total (N=8, n=13 964)		
		Statins= 492/6922 7.1%	Pla= 8.7%	**RR= 0.80 (0.68-0.95)** **SS** I^2=22%
Cardiovascular mortality		Total (N=4, n=2057)		
Kendrick 2010 (AFCAPS/TexCAPS)[94], Koren 2009 (ALLIANCE)[98], Asselbergs 2005 (PREVEND IT)[52], Lemos 2005 (LIPS) [102],		Statins= 24/1014 2.4%	Pla= 35/1043 3.4%	RR= 0.71 (0.43-1.17) I^2=0%
CV events: MI (any)				
Kendrick 2010 (AFCAPS/TexCAPS)[94], Tonelli 2003 (CARE)[104]		Total (N=2, n=2015)		
		Statins= 67/989 6.8%	Pla= 96/1026 9.4%	**RR= 0.72 (0.54-0.98) SS**
CV events: stroke (any)				
Nakamura 2009 (MEGA)[96], Colhoun 2009 (CARDS)[97], Tonelli 2003 (CARE)[104], Ridker 2010 (JUPITER)[95], Koren 2009 (ALLIANCE)[98], Asselbergs 2005 (PREVEND IT)[52],		Total (N=6, n= 10 369)		
		Statins= 71/5154 1.4%	Pla= 120/5215 2.3%	**RR= 0.62 (0.41-0.95) SS** I^2=42%

Doubling of sCr			
Not reported			
End-stage renal disease			
Rahman 2008 (ALLHAT-LLT)[99]	Total (N=1, n=1557)		
	Statins= 32/779 4.1%	Pla= 31/778 4.0%	RR= 1.03 (0.64-1.67) NS
Progression from micro-to macroalbuminuria			
Not reported			
Any or serious adverse events leading to study withdrawal			
NR			

Table 76

9.3.1.2 Characteristics of studies in the above mentioned meta-analysis, from the evidence profile

Study details	Inclusion / exclusion criteria	Patients characteristics	Intervention	Study quality
Asselbergs 2004[52] PREVEND IT Netherlands Study duration 46m	<u>Inclusion criteria</u> - persistent microalbuminuria - BP<160/100 mmHg - no use of antihypertensive drugs - no use of lipid lowering drugs <u>Exclusion criteria</u> - Cr clear<60% of normal age adjusted value - use of ACEI or ARB	n= 864 Age (yr): 54 Gender (male%): 65% BP: 130/75 mmHg Albuminuria (mg/24 h): 22 Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m2): Creatinine clearance (mg/min): Diabetes (%): 2	Pravastatin Vs placebo	- Allocation concealment: unclear - Blinding: yes - Intention to treat (ITT) analysis: NR - Withdrawals/dropouts adequately described: yes - Follow-up: >80% Other methodological remarks: -2x2 factorial design with fosinopril Funding: Dutch Kidney Foundation and Bristol-Myers Squibb.

Table 77

9.3.1.3 Summary and conclusion. Statins versus placebo in patients with CKD

Statins versus placebo			
Bibliography: meta-analysis AHRQ CER 37[8]			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	13.694 (8 studies) 2-5y	**RR= 0.80 (0.68-0.95)** **SS in favour of statin**	⊕⊕⊕⊖ **MODERATE** Study quality: -2 for mostly post hoc Consistency: OK Directness: OK Imprecision: +1 for large dataset
Cardiovascular mortality	2057 (4 studies)	RR= 0.71 (0.43-1.17) NS	⊕⊕⊖⊖ **LOW** Study quality: -2 for mostly post hoc Consistency: O Directness: OK Imprecision: OK
Myocardial infarction	2015 (2 studies)	**RR= 0.72 (0.54-0.98)** **SS in favour of statin**	⊕⊕⊖⊖ **LOW** Study quality: -2 for mostly post hoc Consistency: O Directness: OK Imprecision: OK
Stroke	10.639 (6 studies)	**RR= 0.62 (0.41-0.95)** **SS in favour of statin**	⊕⊕⊖⊖ **LOW** Study quality: -2 for mostly post hoc Consistency: O Directness: OK Imprecision: OK
ESRD	1557 (1 study)	RR= 1.03 (0.64-1.67) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 for only post hoc Consistency: O Directness: OK Imprecision: -1

This meta-analysis compares statins with placebo in patients with CKD. Only one RCT was designed to examine prospectively the efficacy and safety of statins in patients with microalbuminuria (Asselbergs 2004[52]). The rest of the data are based on post hoc analyses performed within subsets of patients with CKD from larger trial populations not originally limited to subjects with CKD. Study populations were heterogeneous for initial cardiovascular risk: about half of the patients were hypertensive and about 50% had coronary heart disease.

Statins significantly lower the incidence of all-cause mortality, compared to placebo.
GRADE: MODERATE quality of evidence

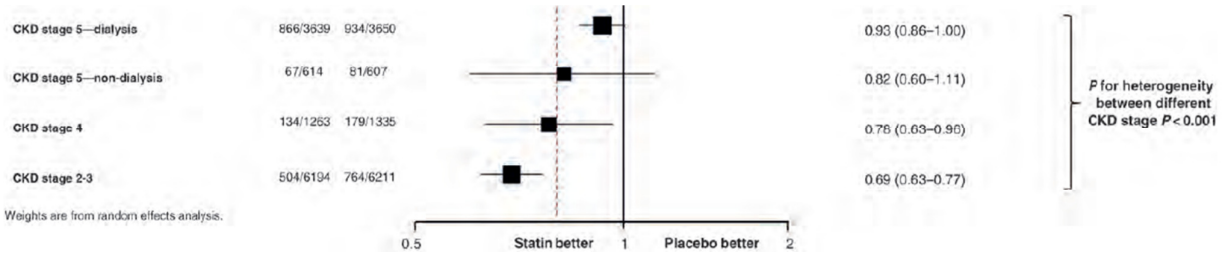
Statins have no effect on the incidence of cardiovascular mortality, compared to placebo.
GRADE: LOW quality of evidence

Statins significantly lower the risk of myocardial infarction or stroke, compared to placebo.
GRADE: LOW quality of evidence

Statins have no effect on the risk of ESRD, compared to placebo.
GRADE: LOW quality of evidence

No data are available for the following outcomes: doubling of sCR, progression from micro- to macroalbuminuria and adverse events.

A recent meta-analysis (Hou 2013[105]) pooled mostly the same available trials. Subgroup analysis demonstrated that the relative effects of statins in CKD were significantly reduced in people with advanced CKD (p<0.001).



9.3.2 Statin-ezetimibe association vs placebo

Study details	n/Population	Comparison	Outcomes		Methodological
Baigent 2011[106] (SHARP) RCT Duration of follow-up: 4.9 years	n= 9270 Mean age: 62y Previous CV event: 15% On dialysis: 33% Diabetes: 23% Smoking: 13% Mean total cholesterol 4.9 mmol/L Mean LDL: 2.77 mmol/L Mean blood pressure 139/79 mmHg CKD stage 3: 36% CKD stage 4: 43% CKD stage 5: 20% <u>Inclusion</u> - CKD - no known history of AMI or coronary revascularisation - > 40 y <u>Exclusion</u> - Functioning renal transplant or living donor renal transplant planned - abnormal liver function - active inflammatory muscle disease	Simvastatin 20 mg/d + ezetimibe 10 mg/d vs placebo	Efficacy		- RANDO: adequate - ALLOCATION CONC: adequate - BLINDING : yes Remarks on blinding method: Double dummy method - FOLLOW-UP: 65% - ITT: yes Other important methodological remarks - 6 w placebo run-in to identify potential non-compliers - change in primary outcome before unblinding - outcome ESRD mentioned in protocol, but not reported in final publication Sponsor: Merck + Independent sponsor: University of Oxford
			Major atherosclerotic event (non-fatal AMI, cardiac death, stroke, arterial revascularization excluding dialysis access procedures)= primary outcome	Sim/eze= 11.3% Pla= 13.4% **RR= 0.83 (0.74-0.94)** **SS in favor of active treatment**	
			Non-fatal coronary events	Sim/eze= 2.9% Pla= 3.4% RR= 0.84 (0.66-1.05) NS	
			Cardiac death	Sim/eze= 2.0% Pla= 1.9% RR= 1.01 (0.75-1.35) NS	
			Non-haemorrhagic stroke	Sim/eze= 2.8% Pla= 3.8% **RR= 0.75 (0.60-0.94)** **SS in favor of active treatment**	
			Revascularization procedures	Sim/eze= 6.1% Pla= 7.6% **RR= 0.79 (0.68-0.93)** **SS in favor of active treatment**	
			All-cause mortality	Sim/eze= 24.6% Pla= 24.1% RR= 1.02 (0.94-1.11) NS	
			Safety		
			Any hepatitis	0.5 vs. 0.4% NS	
			Cancer	9.4 vs 9.5% NS	
			Muscle pain	21.3 vs 20.8% NS	
			Discontinuation due to muscle pain	Sim/eze= 1.1% Pla= 0.6% **P= 0.02, SS worse with active treatment**	

Table 78

9.3.2.1 Summary and conclusion. Simvastatine +ezetimibe versus placebo in patients with CKD.

Simvastatine + ezetimibe versus placebo			
Bibliography: Baigent (SHARP) 2011[106]			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Major atherosclerotic event*	9270 (1 study) 4.9 y	**RR= 0.83 (0.74-0.94)** **SS in favor of active treatment**	⊕⊕⊖⊖ **LOW** Study quality: -1 for incomplete reporting Consistency: NA Directness: 1/3 on dialysis Imprecision: OK
All-cause mortality	9270 (1 study) 4.9 y	RR= 1.02 (0.94-1.11) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 for incomplete reporting Consistency: NA Directness: 1/3 on dialysis Imprecision: OK
Cardiac death	9270 (1 study) 4.9 y	RR= 1.01 (0.75-1.35) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 for incomplete reporting Consistency: NA Directness: 1/3 on dialysis Imprecision: OK
Non-haemorrhagic stroke	9270 (1 study) 4.9 y	**RR= 0.75 (0.60-0.94)** **SS in favor of active treatment**	⊕⊕⊖⊖ **LOW** Study quality: -1 for incomplete reporting Consistency: NA Directness: 1/3 on dialysis Imprecision: OK
Revascularization procedures	9270 (1 study) 4.9 y	**RR= 0.79 (0.68-0.93)** **SS in favor of active treatment**	⊕⊕⊖⊖ **LOW** Study quality: -1 for incomplete reporting Consistency: NA Directness: 1/3 on dialysis Imprecision: OK
Any hepatitis	9270 (1 study) 4.9 y	0.5 vs. 0.4% NS	⊕⊕⊖⊖ **LOW** Study quality: -1 for incomplete reporting Consistency: NA Directness: 1/3 on dialysis Imprecision: OK
Discontinuation due to muscle pain	9270 (1 study) 4.9 y	1.1 vs 0.6% **P= 0.02, SS more frequent with active treatment**	⊕⊕⊖⊖ **LOW** Study quality: -1 for incomplete reporting Consistency: NA Directness: 1/3 on dialysis Imprecision: OK

*major atherovascular event= primary outcome= non-fatal AMI, cardiac death, stroke, arterial revasularisation excluding dialysis access procedures

In this large trial, patients with no history of AMI or revascularization and CKD (mostly stages 3 and 4) were randomized to simvastatin 20 mg/d + ezetimibe 10 mg/d or to placebo. Follow up was almost 5 years. About 1/3 patients was on dialysis. As this trial had no simvastatin-only arm, an eventual surplus value of the association compared to statin only cannot be established.

Treatment with simvastatin+ezetimibe was associated with a lower risk of major atherosclerotic events, non-haemorrhagic stroke and need for revascularization procedures, compared with placebo.
GRADE: LOW quality of evidence

The association of simvastin+ezetimibe was not superior to placebo for the risk of all-cause and cardiac mortality.
GRADE: LOW quality of evidence

The association of simvastin+ezetimibe seemed to be safe concerning the general risk of hepatitis, but discontinuation due to muscle pain was more frequent compared to placebo.
GRADE: LOW quality of evidence

The outcome ESRD was mentioned in the protocol, but not reported in the final publication.

9.3.3 Fibrates versus placebo

A meta-analysis published in 2012 (Jun 2012)[107] pooled the available evidence for the efficacy and safety of fibrates in patients with CKD. Included trials were of short duration, limited quality or concerned fibrates not available in Belgium.
Because of the low quality of evidence, results of the studies with fenofibrate are discussed only very briefly here. The only available evidence is based on post hoc analysis of larger trials.

Fenofibrate is superior to placebo for diminishing the rate of CV events and CV deaths, but not the total mortality.
GRADE: VERY LOW quality of evidence

Fenofibrate is superior to placebo for obtaining a regression in microalbumiuria in patients with CKD.
GRADE: VERY LOW quality of evidence

Fenofibrate is not superior to placebo for stopping the progression to ESRD.
GRADE: VERY LOW quality of evidence

10 Results: Analgesics in CKD

10.1 Guidelines: NSAIDs, paracetamol and narcotic analgesics

10.1.1 KDIGO CKD 2012 [2]

KDIGO recommends temporary discontinuation of potentially nephrotoxic and renally excreted drugs in people with a GFR <60 ml/min/1.73 m^2 (GFR categories G3a-G5) who have serious intercurrent illness that increases the risk of AKI. These agents include NSAIDs. ***(1C)***

NSAIDs:

- *Avoid in people with GFR <30 ml/min/1.73 m^2*
- *Prolonged therapy is not recommended in people with GFR <60 ml/min/1.73 m^2*
- *Should not be used in people taking lithium or RAAS blocking agents*

Opioids

- *Reduce dose when GFR <60 ml/min/1.73 m^2*
- *Use with caution in people with GFR <15 ml/min/1.73 m^2*

10.1.2 NICE CKD 2014 [11]

Monitor GFR at least annually in people prescribed drugs known to be nephrotoxic, such as NSAIDs. In people with CKD the chronic use of NSAIDs may be associated with progression and acute use is associated with a reversible decrease in GFR. Exercise caution when treating people with CKD with NSAIDs over prolonged periods of time. Monitor the effects on GFR, particularly in people with a low baseline GFR and/or in the presence of other risks for progression.

10.1.3 NICE AKI 2013 [1]

Investigate for acute kidney injury, by measuring serum creatinine and comparing with baseline, in adults with acute illness if use of drugs with nephrotoxic potential (such as NSAIDs) within the past week, especially if hypovolemic.

10.1.4 Domus Medica CNI 2012 [4]

Morphine

- *If eGFR is <50ml/min, accumulation of the active metabolite morphine-6-glucuronide can occur*
- *Dose as usual according to effect and side effects, a lower dose can be necessary. Switch to fentanyl is also possible, a dose adjustment is not necessary in this case*

NSAID's

- *If eGFR is <30 ml/min, acute renal injury can occur.*
- *Use paracetamol if possible and avoid NSAIDs. If necessary, give only for short duration with control of renal function before and one week after start of treatment.*
- *NSAID promote deterioration of the renal function.*

Tramadol

- *If eGFR is <30ml/min, higher chance on side effects because of lengthening of half-life.*
- *Lower the dose frequency in a normal preparation to max. 2-3 times a day, give max. 200mg per day tramadol with regulated release.*

10.1.5 Summary of guidelines on analgesics in CKD

All guidelines warn for the nephrotoxic potential of NSAIDs, and recommend or note to

- temporary discontinue NSAIDs in CKD with intercurrent illness [2]
- avoid NSAIDs in CKD <30 ml/min [2, 4]
- investigate for acute injury in acute illness if NSAIDs are used in the past week [1]
- monitor GFR at least annually if using NSAIDs [11]

10.2 Handbooks: NSAIDs, paracetamol and narcotic analgesics

10.2.1 NSAIDs

Dose in renal impairment		
GFR	**Renal Drug handbook[6]**	**Commentaren medicatiebewaking[5]**
30-50 ml/min	Dose as in normal renal function but use with caution (most nsaids) Or Maximum 60 mg/d (ketorolac)	Contra-indicated (important CI) Use only under control of kidney function and electrolytes
10-30ml/min	Dose as in normal renal function but avoid if possible if GFR 10-20ml/min (most nsaids) Or Avoid if possible. Use small doses and monitor closely (Ketorolac in GFR 10-20 ml/min) Or Lowering of the dose but avoid if possible (nabumetone in GFR 10-20 ml/min)	Contra-indicated (important CI) Use only under control of kidney function and electrolytes
<10 ml/min	Dose as in normal function but only if on dialysis. (most nsaids) Or Ketorolac: Avoid if possible. Use small doses and monitor closely (ketorolac) Or Lowering of the dose but only use of on dialysis (nabumetone)	Contra-indicated (important CI) Use only under control of kidney function and electrolytes

Comments
Renal Drug Handbook[6] Use with caution in uremic patients predisposed to gastrointestinal bleeding or uremic coagulopathies. Inhibition of renal prostaglandin synthesis by NSAIDs may interfere with renal function, especially in the presence of existing renal disease – avoid if possible; if not, check serum creatinine 48–72 hours after starting NSAID therapy – if raised, discontinue NSAID therapy. *Ketoprofen* is associated with nephrotic syndrome, interstitial nephritis, hyperkalemia and sodium retention. *Ibuprofen* is eliminated to a large extent (95%) as metabolites by urinary excretion via glomerular filtration. Remainder is excreted via the faeces. *Nabumetone* is absorbed from the gastro-intestinal tract and rapidly metabolized in the liver to the principal active metabolite 6-methoxy-2-naphthylacetic acid (6-MNA). The metabolite is a potent inhibitor of prostaglandin synthesis. Excretion of the metabolite is predominantly in the urine. The Summary of Product Characteristics recommends a dose reduction if creatinine clearance <30 mL/minute; however, another article concluded that dosage adjustments may not be necessary with decreased renal function. Commentaren medicatiebewaking[5] NSAIDs, especially high doses and when used in combinations, can cause papilnecrosis, followed by interstitial nephrite. They are nephrotoxic and can cause both acute and chronic kidney injury. NSAIDs can only be used in renal impairment under good control of kidney function and electrolytes (important contra-indication). NSAIDs work by the inhibition of the enzyme cyclooxygenase, which promotes the syntheses of prostaglandins. These prostaglandins influence the normal physiology of the kidney, like regulation of the blood flow, glomerular filtration, renal resistance, transport of electrolytes through the tubulus cells, renal resorption and excretion of water and production of renin. The selective COX2-inhibitors have the same effect on the blood flow in the kidney and therefore renal impairment is also an important contra-indication..

10.2.2 Paracetamol (acetaminophen)

Dose in renal impairment		
GFR	**Renal Drug handbook[6]**	**Commentaren medicatiebewaking[5]**
30-50 ml/min	Dose as in normal renal function	Dose as in normal renal function
10-30ml/min	Dose as in normal renal function	Dose as in normal renal function
<10 ml/min	500mg – 1g every 6-8 hours	Lengthening of the interval between two doses to 6-8h.

Comments
Renal Drug Handbook[6] Beware of the sodium content of soluble tablets. Paracetamol is nephrotoxic in overdose due to a reactive alkylating metabolite. Metabolites may accumulate in CKD 5; normal doses are used in CKD 5. Commentaren medicatiebewaking[5] Paracetamol, especially high doses and when used in combination with NSAIDs, can cause papilnecrosis, followed by interstitial nephritis.

10.2.3 Opioid analgesics

Dose in renal impairment		
GFR	**Renal Drug handbook[6]**	**Commentaren medicatiebewaking[5]**
30-50 ml/min	Dose as in normal renal function (buprenorphine, hydromorphone, methadone, oxycodone, pethidine, tramadol) Or Titrate according to response (fentanyl) Or 75% of normal dose (Morphine)	Dosing according to response, monitor for toxicity; a lower dose can be necessary
10-30ml/min	20-30 ml/min: see 30-50 ml/min 10-20 ml/min Dose as in normal renal function, (Methadone, oxycodone) but avoid very large doses (buprenorphine) Or Reduce dose and titrate according to response (hydromorphone, fentanyl). Extend also dosing intervals (Morphine, tramadol, pethidine)	Dosing according to response, monitor for toxicity; a lower dose can be necessary. Or lowering of the dose (tramadol)
<10 ml/min	Reduce dose and increase as tolerated; avoid very large single doses. Transdermal: Dose as in normal renal function (buprenorphine) Or Reduce dose. Titrate according to response (fentanyl, Methadone, hydromorphone). Extend also dosing intervals (Morphine, tramadol) Or	No information

	Start with small doses (oxycodone) Or Avoid if possible. If not, use small doses and increase dosing interval (pethidine)	

Comments

Renal Drug Handbook[6]

Fentanyl: Renal impairment may have a moderate effect on the elimination of fentanyl; however, as fentanyl is titrated to response the usual dose and method of administration remains valid.

Hydromorphone is metabolized to mainly hydromorphone- 3-glucuronide and some hydromorphone-6-glucuronide, which also have opioid activity, and which accumulate in renal failure. May cause neuroexcitation and cognitive impairment

Methadone: Risk of QT interval prolongation especially with high doses and concomitant risk factors. Extreme caution with all opiates in patients with impaired renal function. Potential accumulation of morphine-6- glucuronide (a renal excreted active metabolite, more potent than morphine)

and morphine-3-glucuronide. Half-life of morphine-6-glucuronide is increased from 3‑5 hours in normal renal function to about 50 hours in ERF.

Ensure that naloxone is readily available as an antidotum.

Sometimes slow release oral preparations are avoided, as any side effects may be prolonged.

Oxycodone has been used in CKD 5 patients; start with lowest dose and gradually increase dose according to response. Limited accumulation of metabolites in renal failure compared with morphine. Increased volume of distribution in renal failure.

Pethidine has a risk of CNS and respiratory depression or convulsions, particularly in established renal failure patients receiving regular doses, due to accumulation of active metabolite, norpethidine. Norpethidine levels can be measured.

Commentaren medicatiebewaking[5]

Use of opioids in renal impairment has to be done carefully. There is an increased risk of strong sedation, respiratory depression and hypotension. Opioid analgesics are metabolized in the liver. Some molecules are converted to active metabolites (codeine, morphine) but also to renal excreted toxic metabolites, who don't have an analgesic function. An impaired kidney function can fortify the effect of narcotic analgesics both by accumulation of the mother molecule but also of the working of toxic metabolites.

The dosing is guided by response, also in renal impairment.

In normal doses, like used in primary care, codeine is not contra-indicated in renal impairment.

The half-life of tramadol is lengthened in renal impairment.

10.3 Evidence tables and conclusions: NSAIDs and paracetamol

10.3.1 NSAIDs versus placebo

There are no RCT's of good quality assessing the efficacy and safety of NSAIDs in patients with CKD. A very small trial (n=29) (Murray 1995)[108] is the only RCT ever performed in patients with CKD.
The only available evidence comes from observational studies.

10.3.1.1 Clinical evidence profile

Nderitu 2013[14]					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Design: MA of 3 cohort studies Yarger 2011[109] Gooch 2006[110] Hemmelgarn 2007[111] Search date: From 1966 to 30/09/2011. Study duration >6m.	N=3 n=54 663	- CKD 3-5 - selective and non-selective NSAIDS, including aspirin	Regular dose NSAID use Vs no NSAID use	Accelerated CKD progression°= eGFR decline ≥15ml/min /1.73m^2 over a 2-y period)	OR: 0.96 (95% CI 0,86 to 1,07) p=0,43 NS
	N=2 n= 44 479	- CKD 3-5 - selective and non-selective NSAIDS, including aspirin	High dose NSAID use Vs no NSAID use	Accelerated CKD progression°	**OR: 1.26 (95% CI 1.06 to 1.50)** **p=0,009** **SS more frequent with high NSAID use**
		- CKD 3-5 - selective and non-selective NSAIDS, including aspirin	Overall NSAID use Vs No NSAID use	Accelerated CKD progression°	Total: OR: 1.04 (95% CI 0,90 to 1,20) p=0,63 NS
*adjusted for : age, gender and at least one co-morbidity					

Table 79

Moller 2013[112]					
Design	**n**	**Population**	**Risk factor**	**Outcome**	**Results***
Design: longitudinal cohort study Swiss 1996-2007	n=4101 (1362 'NSAID naïve' and 2739 'NSAID users')	Patients with rheumatoid arthritis diagnosis	NSAID naïve Vs NSAID users	Decline in $eGFR_{CG}$	Total population: -0.83 mL/min/y with no significant differences between users and non-users
					CKD 1-3 -1.27 mL/min/y with no significant differences between users and non-users
					CKD 4-5 -9.98 mL/min/y **eGFR decline significantly faster on NSAID therapy** **p=0.045 SS**

*adjusted for : age, sex, arterial hypertension, heart disease, renal and cardiovascular disease, hypertension, diabetes. The RA disease activity score, body mass index and antirheumatic RA therapies other than NSAIDs were included in the model only if they were found to be substantial confounders using the 10% change in estimate criteria.

Table 80

10.3.1.2 Summary and conclusion. NSAIDs versus placebo in patients with CKD.

The only available evidence comes from observational studies.

- The meta-analysis of Nderitu 2013[14] performed a pooling of 3 cohort studies with a total > 50.000 patients with CKD stage 3-5. Regular-dose NSAID use did not significantly affect the risk of accelerated CKD progression, but high-dose NSAID use significantly increased the risk of accelerated CKD progression. The publication reported no standard definition for 'high dose'.
  GRADE: not applied
- Another cohort(Moller 2013[112]) followed >4000 patients with rheumatoid arthritis for >10 years and compared NSAID users with NSAID naïve users. Use of NSAID did not significantly affect the risk of decline in eGFR in patients with CKD 1-3, but it significantly accelerated the decline in eGFR in patients with CKD 4-5.
  GRADE: not applied

10.3.2 Paracetamol (acetaminophen)

No RCT's nor observational studies of sufficient quality on the use of paracetamol (acetaminophen) in patients with CKD, that met our inclusion criteria were identified. (from 2009)

11 Results: Drugs used in the management of gout and CKD

11.1 Guidelines: drugs used in gout

11.1.1 KDIGO CKD 2012 [2]

There is insufficient evidence to support or refute the use of agents to lower serum uric acid concentrations in people with CKD and either symptomatic or asymptomatic hyperuricemia in order to delay progression of CKD. ***(Not Graded)***

11.1.2 NICE CKD 2014 [11]

There was a lack of good quality evidence on the effectiveness of uric acid lowering therapy in asymptomatic patients in the management of CKD which made the GDG unable to make a clinical recommendation.

11.1.3 Domus Medica CNI 2012 [4]

Colchicine

- If eGFR is <50ml/min, lower the dose to max 0.5 mg/day

Allopurinol

- *If eGFR is < 80, there is an elevated chance on toxic side effects. Adapt the dose:*
  - *50- 80 ml/min 300 mg/day*
  - *30- 50 ml/min 200 mg/day*
  - *10- 30 ml/min 100 mg/dag*[419]

11.1.4 ACR Gout 2012[22, 23]

In patients with prior gout attacks and current hyperuricemia, CKD stage 2-5 or end stage renal disease is an appropriate indication for pharmacological uric lowering therapy. ***(C)***

The Task Force Panel (TFP) recommends xanthine oxidase inhibiting therapy with either allopurinol or febuxostat as the first-line pharmacologic approach ***(A).*** *The panel did not preferentially recommend either xanthine oxidase inhibiting drug over the other because of the lack of published safety data for febuxostat in the setting of stage 4 or worse CKD.*

Starting dosage of allopurinol should be no greater than 100 mg/day for any patient, and start at 50 mg/day in stage 4 or worse CKD ***(B).*** **Gradually titrate maintenance dose upward every 2–5 weeks to appropriate maximum dose in order to treat to chosen serum uric acid target** ***(C).*** **Dose can be raised above 300 mg daily, even with renal impairment, as long as it is accompanied by adequate patient education and monitoring for drug toxicity (e.g., pruritus, rash, elevated hepatic transaminases).** ***(B)***

Concurrent thiazide use and renal impairment have been implicated as risk factors for allopurinol hypersensitivity syndrome. A widely employed risk management strategy has been a non–evidence-based algorithm for allopurinol maintenance dosing, calibrated to renal impairment ***(C).*** The TFP did not recommend this strategy.

The TFP did not vote on specific quantitative renal function impairment-adjusted dosing of oral colchicine. Specific quantitative colchicine dose adjustment in CKD is the decision of the treating clinician.

Pay attention to the result of the Rigour of development score that was given to this guideline, which was rather poor (35%).

11.1.5 Summary of guidelines on drugs used in gout

Guidelines do not support nor refute treatment of asymptomatic hyperuricemia in CKD patients, because lack of evidence. [2, 11]

In symptomatic patients, the ACR recommends xanthine oxidase inhibiting therapy. Allopurinol should be started at low dose in CKD and gradually titrated. [22]

11.2 Handbooks: drugs used in gout

11.2.1 Colchicine

Dose in renal impairment		
GFR	**Renal Drug handbook[6]**	**Commentaren medicatiebewaking[5]**
30-50 ml/min	Dose as in normal renal function	Normal dose for acute gout max 1x/2weeks
10-30ml/min	Dose as in normal renal function	Normal dose for acute gout max 1x/2weeks
<10ml/min	Dose adjustment max 1 course in 3 days	No information
Comments		
Renal drug handbook[6] In CKD stage 5, colchicine can be administered concurrently with allopurinol, but seek specialist advice. If nausea, vomiting or diarrhea occur, stop therapy. Commentaren medicatiebewaking[5] Because of the nephrotoxic effect of colchicine, it must be administered carefully (important contra-indication).		

11.2.2 Allopurinol

Dose in renal impairment		
GFR	**Renal Drug handbook[6]**	**Commentaren medicatiebewaking[5]**
	In all grades of renal impairment commence with 100 mg/day and increase if serum and/or urinary urate response is unsatisfactory. Doses less than 100 mg/day may be required in some patients.	
30-50 ml/min	200–300 mg daily (even till GFR 20ml/min)	Dose adjustment
10-30ml/min	100–200 mg daily (for GFR 10-20ml/min)	Dose adjustment (100mg daily)
<10ml/min	100 mg daily or 100 mg on alternate days	No information
Comments		
Renal Drug handbook[6] Main active metabolite: oxipurinol is renally excreted Increased incidence of skin rash in patients with renal impairment Commentaren medicatiebewaking[5] The dose of allopurinol should be lowered in renal impairment (important contra-indication)		

11.2.3 Febuxostat

No information was found in the handbooks.

11.3 Evidence tables and conclusions: drugs used in gout

Data on efficacy and safety of urate-lowering drugs are limited. Most RCTs have a small sample size, a limited study duration and are of low methodological quality. Only 2 RCTs fulfilled the selection criteria of this literature search. No observational studies fulfilled the selection criteria for this literature review.

11.3.1 Allopurinol versus control

A recent Health Technology Assessment (Fleeman 2014[113]) examined the possible efficacy of allopurinol for the *treatment* of CKD. The authors concluded: There is limited evidence that allopurinol reduces CKD progression or cardiovascular events. It appears that AEs and in particular serious adverse events attributable to allopurinol are rare. However, the exact incidence of AEs in patients with CKD is unknown." This conclusion is predominantly based on the results of Goicoechea 2010[114].

11.3.1.1 Clinical evidence profile

Study details	n/Population	Comparison	Outcomes		Methodological
Goicoechea 2010[114] Design: RCT Duration of follow-up: 24m	n= 113 Mean age 72y 65% male BP 146/76 Diabetes: 20% SCr (mg/dL): 155 eGFR (ml/min/1.73m^2): 40 sUA, mean (mmol/l): 0.45 <u>Inclusion criteria</u> - moderate CKD (eGFR <60ml/min). - Stable clinical condition - No CV events in past 3m -Stable renal function <u>Exclusion criteria</u> - Active infections or inflammatory diseases - HIV infection - Chronic hepatopathy - Immunosuppressive therapy	Allopurinol 100 mg/d Vs control (usual treatment)	Efficacy		- Allocation concealment: unclear - Randomization: adequate - Blinding: only assessor -Intention to treat (ITT) analysis: yes - Follow-up: 80% Sponsor: NR Remark: Concomitant use of statins, antiplatelets and RAS-inhibitors.
			Hospitalization	Allo= 12 events Control= 22 events **P= 0.032 SS in favour of allopurinol**	
			CV events	Allo= 7 events Control= 15 events **P= 0.039 SS in favour of allopurinol**	
			ESRD	1 in each group	
			Mortality	N=2 in control group	
			Change in eGFR	Allo= +1.3 ml/min Control= -3.3 ml/min **P= 0.018 SS in favour of allopurinol**	
			Change in serum urate	Allo= -1.6 mg/dl Control= +0.3 mg/dl **SS in favour of allopurinol**	
			Safety		
			Serious adverse events	none	

Table 81

11.3.1.2 Summary and conclusion. Allopurinol versus placebo in patients with CKD.

Allopurinol vs control			
Bibliography: Goicoechea 2010[114]			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Hospitalization	113 (1 study) 24 m	**P= 0.032 SS in favour of allopurinol**	⊕⊖⊖⊖ **VERY LOW** Study quality: -1 for lack of blinding, -1 for alloc concealm Consistency: NA Directness: OK Imprecision: -1 for sparse data
CV events	113 (1 study) 24 m	**P= 0.039 SS in favour of allopurinol**	⊕⊖⊖⊖ **VERY LOW** Study quality: -1 for lack of blinding, -1 for alloc concealm Consistency: NA Directness: OK Imprecision: -1 for sparse data
Change in eGFR	113 (1 study) 24 m	**P= 0.018 SS in favour of allopurinol**	⊕⊖⊖⊖ **VERY LOW** Study quality: -1 for lack of blinding, -1 for alloc concealm Consistency: NA Directness: OK Imprecision: -1 for sparse data

In this small trial, treatment with allopurinol 100 mg/d was compared with usual treatment in patients with CKD (eGFR 40 ml/min).

Addition of allopurinol to usual treatment can reduce the risk for hospitalization and the risk for cardiovascular events.
GRADE: VERY LOW quality of evidence

Addition of allopurinol to usual treatment can diminish the decline in eGFR.
GRADE: VERY LOW quality of evidence

There are no reliable data available for: mortality, ESRD, adverse events.

11.3.2 Febuxostat versus placebo

No RCT's nor observational studies of sufficient quality on the use of febuxostat versus placebo in patients with CKD, that met our inclusion criteria were identified.

11.3.3 Febuxostat versus allopurinol

11.3.3.1 Clinical evidence profile

Study details	n/Population	Comparison	Outcomes		Methodological
Becker 2010[115] CONFIRMS RCT Duration of follow-up: 6m	N total= 2269 Of which - 48% with mild CKD - 18% with moderate CKD Mean age: 53y CV disease: 57% Hypertension: 53% Diabetes: 14 % Hypercholesterolemia: 7% sUA 8-15 mg/dL <u>Inclusion</u> - 18-85 y - gout (ARA criteria) - sUA ≥ 8.0 mg/dL <u>Exclusion</u> - secondary hyperuricemia - severe CKD - elevated liver enzymes	Febuxostat 40/80 mg/d vs Allopurinol 300 mg/d in normal renal function or mild CKD or 200 mg/d in moderate CKD	Efficacy		- RANDO: adequate - ALLOCATION CONC: adequate - BLINDING : yes - FOLLOW-UP: 82% - ITT: yes Other important methodological remarks - 30-d washout period - concomitant prophylaxis with colchicine - predefined subgroup analysis Sponsor: Takeda
			sUA < 6.0 mg/dL at 6 m= primary endpoint total group	Feb 40= 45.2% Feb 80= 67.1% Allo= 42.1% → feb 40 vs allo: NS **→ feb 80 SS better than feb 40 or allo P<0.001**	
			sUA < 6.0 mg/dL at 6 m in patients with mild or moderate CKD	Feb 40= 49.7% Feb 80= 71.6% Allo= 42.3% **→ feb 40 SS better than allo p= 0.021** **→ feb 80 SS better than feb 40 or allo P<0.001**	
			Safety		
			Adverse events in total group	56%: NS between treatment groups	
			Adverse events in patients with CKD	Feb 40= 56% Feb 80= 54% Allo= 58% → 'similar' to rates in total population (NT)	
			Rash	6 vs 7% NS	
			Liver function abnormalities	2 vs 1% NS	
			CV events	5 vs 6% NS	

Table 82

11.3.3.2 Summary and conclusion. Febuxostat 80mg versus allopurinol

Febuxostat 80 mg/d versus allopurinol			
Bibliography: Becker 2010[115]			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Serum urate < 6.0 mg/dL at 6 m	2269 (1 study) 6m	49.7 vs 42.3% **SS in favour of febuxostat**	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: NA Directness: OK Imprecision: OK
Adverse events	2269 (1 study) 6m	- NS between febuxostat and allopurinol in total treatment group - adverse events in patients with CKD 'similar' to rates in total population (NT)	⊕⊕⊕⊖ **MODERATE** Study quality: -1 for NT Consistency: NA Directness: OK Imprecision: OK

This trial included 2269 patients with gout, 66% of them had mild to moderate CKD. Here we report only the results of the predefined subgroup with CKD.

Urate-lowering efficacy of febuxostat exceeds that of allopurinol
GRADE: HIGH quality of evidence

Febuxostat seems as safe as allopurinol in patients with gout and CKD.
GRADE: MODERATE quality of evidence

Remark: no information on clinical endpoint as gout flares.
There are no reliable data available for mortality and renal endpoints.

11.3.4 Colchicine

No RCT's nor observational studies of sufficient quality on the use of colchicine in patients with CKD, that met our inclusion criteria were identified. (from 2009)

12 Results: Specific drugs in CKD

12.1 Sotalol in CKD

12.1.1 Guidelines: sotalol

12.1.1.1 Domus Medica CNI 2012 [4]

If eGFR <50, there exists an elevated chance on side effects. Reduce dose and double the dose interval.

12.1.2 Handbooks: sotalol

Dose in renal impairment		
GFR	**Renal Drug handbook[6]**	**Commentaren medicatiebewaking[5]**
30-50 ml/min	50% of normal dose	Adjustment of maximum dose to 50%
10-30ml/min	25% of normal dose (if GFR 20-30 ml/min: 50%)	Adjustment of maximum dose to 25%
<10 ml/min	25% of normal dose and use with caution	No information
Comments		
Renal Drug Handbook[6] Sotalol prolongs the QT interval, which predisposes to the development of *torsades de pointes.* Commentaren medicatiebewaking[5] Dose adjustment of sotalol is needed in renal impairment to prevent intoxications, causing severe brady-arrithmies or *torsades de pointes.*		

12.2 Digoxin in CKD

12.2.1 Guidelines: digoxin

12.2.1.1 KDIGO CKD 2012[2]

KDIGO recommends temporary discontinuation of digoxin in people with a GFR <60 ml/min/1.73 m^2 (GFR categories G3a-G5) who have serious intercurrent illness that increases the risk of AKI. ***(1C)***

Reduce digoxin based on plasma concentrations

12.2.1.2 Domus Medica CNI 2012 [4]

Avoid use of digoxin because of the higher risk on intoxication. If use is necessary in patients with CKD, lower doses are used. ***(2C)***

- *Measure digoxin level in case of suspicion on digoxin intoxication.*
- *If eGFR is <50 ml/min, risk of toxicity (nausea, vomiting, visus distortion, delirium) and arrhythmias.*
- *Half loading dose. Initial maintenance dose after loading: 0,125 mg/day. Adjust dose afterwards according to plasma concentrations and the clinical context.*

12.2.2 Handbooks: digoxin

Dose in renal impairment		
GFR	**Renal Drug handbook[6]**	**Commentaren medicatiebewaking[5]**
30-50 ml/min	125–250 micrograms per day	Adjustment of starting dose to 50% of normal dose Further adjustments based on serum level (important contra-indication)
10-30ml/min	125–250 micrograms per day. Monitor levels if GFR<20 ml/min.	Adjustment of starting dose to 50% of normal dose Further adjustments based on serum level (important contra-indication)
<10 ml/min	Dose commonly 62.5 micrograms alternate days, or 62.5 micrograms daily. Monitor levels	Adjustment of starting dose to 50% of normal dose Further adjustments based on serum level (important contra-indication)
Comments		
Renal Drug Handbook[6] Dose reduction in function of GFR. Monitoring of digoxin levels if GFR <20ml/min. Steady-state plasma monitoring advisable. Complex kinetics in renal impairment: volume of distribution and total body clearance reduced in CKD. Hypokalemia, hypomagnesaemia, marked hypercalcaemia and hypothyroidism increase toxicity Commentaren medicatiebewaking[5] Digoxin is mainly excreted by the kidney.		

12.3 Methotrexate in CKD

12.3.1 Guidelines: methotrexate

12.3.1.1 KDIGO CKD 2012[2]

- *Reduce dose when GFR <60 ml/min/1.73 m^2*
- *Avoid if possible when GFR <15 ml/min/1.73 m^2*

12.3.2 Handbooks: Methotrexate

Dose in renal impairment		
GFR	**Renal Drug handbook[6]**	**Commentaren medicatiebewaking[5]**
30-50 ml/min	50–100% of normal dose	Lowering of start dose and adjustment of the dose according to effect and adverse effects (blood tests, liverfunction)
10-30ml/min	20-30ml/min 50-100% of normal dose 10-20ml/min 50% of normal dose	Lowering of start dose and adjustment of the dose according to effect and adverse effects (blood tests, liverfunction)
<10 ml/min	Contra-indicated	No information

Comments
Renal Drug Handbook[6] An approximate correction for renal function may be made by reducing the dose in proportion to the reduction in creatinine clearance based on a normal creatinine clearance of 60 mL/minute/m2 Alternative dose regimen: CrCl (mL/min) Dose >80 : 100% 60: 65% 45: 50% <30: Avoid Renal function should be closely monitored throughout treatment. Excreted primarily by the kidneys (>90%), although small amounts via the bile. High-dose methotrexate may cause precipitation of methotrexate or its metabolites in renal tubules. A high fluid throughput and alkalinisation of urine, using sodium bicarbonate if necessary, is recommended. Commentaren medicatiebewaking[5] Regular control of renal function is advised.

12.3.3 Evidence tables and conclusions: Methotrexate

No RCT's nor observational studies of sufficient quality on the use of methotrexate in patients with CKD, that met our inclusion criteria were identified. (from 2009)

12.4 Lithium in CKD

12.4.1 Guidelines: Lithium

12.4.1.1 KDIGO CKD 2012[2]

KDIGO recommends temporary discontinuation of lithium in people with a GFR <60 ml/min/1.73 m^2 (GFR categories G3a-G5) who have serious intercurrent illness that increases the risk of AKI. ***(1C)***

KDIGO recommends that all people taking potentially nephrotoxic agents such as lithium should have their GFR, electrolytes and drug levels regularly monitored. ***(1A)***

- *Nephrotoxic and may cause renal tubular dysfunction with prolonged use even at therapeutic levels.*
- *Monitor GFR, electrolytes, and lithium levels 6 monthly or more frequently if the dose changes or the patient is acutely unwell*
- *Avoid using concomitant NSAIDs*
- *Maintain hydration during intercurrent illness*
- *Risk-benefit of drug in specific situation must be weighed*

12.4.1.2 Domus Medica CNI 2012 [4]

- *If eGFR is < 50 ml/min, higher chance on toxic side effects (small therapeutic spectrum)*
- *Replace lithium if possible by an anti-epileptic drug (lamatrigine, carbamazepine, valproate) and/or an atypical antipsychotic drug.*
- *If this is not possible, halve the normal dose. Adjust dose concerning plasma levels.*

12.4.1.3 NICE CKD 2014 [11]

Monitor GFR at least annually in people prescribed drugs known to be nephrotoxic, such as lithium.

12.4.2 Handbooks: Lithium

Dose in renal impairment		
GFR	**Renal Drug handbook[6]**	**Commentaren medicatiebewaking[5]**
30-50 ml/min	Avoid if possible, or reduce dose and monitor plasma concentration carefully	Avoid if possible (important contra-indication). If replacement is not possible, start with 50% of normal dose and adjust according to serum levels of lithium
10-30ml/min	Avoid if possible, or reduce dose and monitor plasma concentration carefully	Avoid if possible (important contra-indication). If replacement is not possible, start with 50% of normal dose and adjust according to serum levels of lithium
<10 ml/min	Avoid if possible, or reduce dose and monitor plasma concentration carefully	Avoid if possible (important contra-indication). If replacement is not possible, start with 50% of normal dose and adjust according to serum levels of lithium
Comments		
Renal Drug Handbook[6] Lithium generally should not be used in patients with severe renal disease because of increased risk of toxicity. Doses are adjusted to achieve lithium plasma concentrations of 0.4–1.0 mmol/L. Long-term treatment may result in permanent changes in kidney histology and impairment of renal function. High serum concentration of lithium, including episodes of acute lithium toxicity, may aggravate these changes. The minimum clinically effective dose of lithium should always be used.		

12.4.3 Evidence tables and conclusions: Lithium

No RCT's nor observational studies of sufficient quality on the use of lithium in patients with CKD, that met our inclusion criteria were identified. (from 2009)

12.5 Phosphate containing bowel preparations in CKD

12.5.1 Guidelines: phosphate containing bowel preparations

12.5.1.1 KDIGO CKD 2012[2]

KDIGO recommends not to use oral phosphate-containing bowel preparations in people with a GFR <60 ml/min/1.73 m^2 or in those known to be at risk of phosphate nephropathy. *(1A)*[2 1]

Case reports exist of acute and late irreversible renal failure with biopsy-proven phosphate deposition in a small number of people although the condition is likely to be under recorded. Phosphate nephropathy causes irreversible kidney injury in addition to electrolyte disturbances like hyperphosphatemia, hypocalcaemia, hypo- and hypernatremia, and hypokalemia. People with GFR <60ml/min are said to be at particular risk although the link to kidney injury is associative in many cases and firm evidence is lacking. As there are non-phosphate-containing bowel preparations available, these should be used in GFR <60ml/min.
Next to people with GFR<60ml/min/1.73m^2, risk factors include >60 years of age, female, hypertension, diabetes, chronic heart failure, dehydration, active colitis, concurrent use of RAAS blocking agents, diuretics, lithium, NSAIDs, large and/or repeat dosing of oral phosphate preparations, hypoparathyroidism.

12.5.2 Handbooks: phosphate containing bowel preparations

Dose in renal impairment
Comments
Renal Drug Handbook[6] No information. Commentaren medicatiebewaking[5] Oral administration of natriumphosphate laxatives can cause acute renal injury due to intrarenal/tubular calciumphosphate depositions, caused by high phosphate serumlevels. Risk factors are old age, dehydration and short dosing intervals.

12.5.3 Evidence tables and conclusions: phosphate containing bowel preparations

No RCT's of sufficient quality on the use of phosphate containing bowel preparations in patients with CKD, that met our inclusion criteria were identified. (from 2009)

An observational trial with 1105 Korean patients evaluated an eventual relationship between oral sodium phosphate laxatives and acute renal failure. 13.3% of the study population had CKD (stage not defined). The authors found an elevated risk of acute kidney failure 0-12 weeks after the administration of oral sodium phosphate in patients with and patients without CKD. A comparison between persons with CKD and persons without CKD was not reported (Choi 2014)[116].

13 Results: Associations in CKD

13.1 Fibrates and statins association in CKD

13.1.1 Guidelines: Fibrates and statins association

13.1.1.1 KDIGO CKD 2012[2]

Patients with CKD appear to be at increased risk of adverse events when statins and fibrates are used in combination. For this reason, KDIGO recommends that fibrates not be used concomitantly with statins in patients with CKD.

13.1.2 Handbooks: Fibrates and statins association

Comments
Renal Drug Handbook[6] Fibrates in combination with statins: increased risk of myopathy; do not exceed 10 mg of simvastatin, except with fenofibrate. Avoid use of fibrate in patients with GFR<10 mL/min due to increased risk of rhabdomyolysis (fenofibrate). Commentaren medicatiebewaking[5] Fibrates in combination with statins can cause severe rhabdomyolysis.

13.2 NSAIDs and diuretics and ACE-inhibitors association in CKD

13.2.1 Guidelines: NSAIDs and diuretics and ACE-inhibitor association

No guidelines on this triple therapy in CKD were identified. For the completeness of this report, we give the information on dual therapy.

13.2.1.1 Domus Medica CNI 2012 [4]

Domus Medica advises against the use of NSAIDs after the start of ACE inhibitors.

13.2.2 Handbooks: NSAIDs and diuretics and ACE-inhibitor association

No information of this triple therapy was identified in the handbooks. For the completeness of this report, we give the information on dual therapy like found in Renal drug handbook. Commentaren Medicatiebewaking does not provide specific information on combinations.

Comments
Renal Drug Handbook[6] Combination of ACE-inhibitors with analgesics: antagonism of hypotensive effect and increased risk of renal impairment with NSAIDs; hyperkalemia with ketorolac and other NSAIDs. Combination of ACE-inhibitors with diuretics: enhanced hypotensive effect; hyperkalemia with potassium-sparing diuretics. Combination of diuretics with analgesics: increased risk of nephrotoxicity with NSAIDs; antagonism of diuretic effect.

13.2.3 Evidence tables and conclusions: NSAIDs and diuretics and ACE-inhibitor association

No RCT's nor observational studies of sufficient quality on the use of this triple association in patients with CKD, that met our inclusion criteria were identified. (from 2009)

An large observational recent study in a general population, was found. Because this observational study was not carried out in patients with CKD, it did not met our inclusioncriteria. For completeness, we included the results in the table below.

Lapi 2013[117]					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Design: Retrospective cohort UK Follow up: 6y	n= 487.372	General practice Exclusion: renal disorders	Diuretic or ACEI or ARB (= single) vs Diuretic or ACEI or ARB +NSAID (= double)	**Acute kidney injury** Diur+NSAID vs diur alone	RR= 1.02 (0.81-1.28)
				Acute kidney injury ACEI/ARB +NSAID vs ACEI/ARB alone	RR= 0.89 (0.69-1.15) NS
			Vs diuretic + ACEI or ARB +NSAID (= triple)	Acute kidney injury Triple vs double	**RR= 1.31 (1.12-1.53)** **SS worse for triple therapy**
*adjusted for : comorbidity known to be associated with acute kidney injury) e.g. antihypertensive drug use, rhythm disorders, diabetes), blood pressure, other drugs.					

Table 83

There are no RCTs on the concurrent use of diuretics, RAS-inhibiting agents and NSAIDs .

The only available evidence comes from a large cohort trial with about half a million users of antihypertensive drugs (Lapi 2013[117]). This trial was not performed in patients with CKD, and therefore did not fulfill our inclusion criteria, but for reasons of completeness, the results are reported in brief. Data were collected from general practices in the UK and patients were followed for 6 years.
Double therapy with
- an association of diuretic + NSAID compared to diuretic alone
- an association of ACEI or ARB + NSAID compared to ACEI or ARB alone
did not significantly increase the risk of acute kidney injury.

Triple therapy with diuretic + ACEI or ARB + NSAID significantly increased the risk of acute kidney injury.
GRADE: not applied

14 Results: Pitfalls in CKD (guidelines only)

14.1 CKD and risk of AKI, precautions

14.1.1 KDIGO CKD 2012[2]

KDIGO recommends that all people with CKD are considered to be at increased risk of AKI. ***(1A)***

KDIGO recommends temporary discontinuation of potentially nephrotoxic and renally excreted drugs in people with a GFR <60 ml/min/1.73 m^2 (GFR categories G3a-G5) who have serious intercurrent illness that increases the risk of AKI. These agents include, but are not limited to: RAAS blockers (including ACE-Is, ARBs, aldosterone inhibitors, direct renin inhibitors), diuretics, NSAIDs, metformin, lithium, and digoxin. ***(1C)***

14.1.2 KDIGO AKI 2012[3]

KDIGO recommends that patients be stratified for risk of AKI according to their susceptibilities and exposures. ***(1B)*** **Manage patients according to their susceptibilities and exposures to reduce the risk of AKI** (see table). ***(Not Graded)***

Test patients at increased risk for AKI with measurements of SCr and urine output to detect AKI. Individualize frequency and duration of monitoring based on patient risk and clinical course. ***(Not Graded)***

Exposures	Susceptibilities
Sepsis	Dehydration or volume depletion
Critical illness	Advanced age
Circulatory shock	Female gender
Burns	Black race
Trauma	CKD
Cardiac surgery (especially with CPB)	Chronic diseases (heart, lung, liver)
Major noncardiac surgery	Diabetes mellitus
Nephrotoxic drugs	Cancer
Radiocontrast agents	Anemia
Poisonous plants and animals	

CKD, chronic kidney disease; CPB, cardiopulmonary bypass.

Figure 3 Exposures and susceptibilities for AKI, copied from KDIGO guideline AKI 2012 [3]

14.1.3 NICE CKD 2014 [11]

Monitor people for the development or progression of CKD for at least 2–3 years after acute kidney injury, even if serum creatinine has returned to baseline. Advise people who have had acute kidney injury that they are at increased risk of CKD developing or progressing.

14.1.4 NICE AKI 2013[1]

Investigate for acute kidney injury, by measuring serum creatinine and comparing with baseline, in adults with acute illness if any of the following are likely or present:

- **chronic kidney disease (adults with an eGFR < 60 ml/min/1.73 m^2 are at particular risk)**
- **heart failure**
- **liver disease**
- **diabetes**
- **history of acute kidney injury**
- **oliguria (urine output less than 0.5 ml/kg/hour)**
- **neurological or cognitive impairment or disability, which may mean limited access to fluids because of reliance on a carer**
- **hypovolemia**
- **use of drugs with nephrotoxic potential (such as NSAIDs, aminoglycosides, ACE inhibitors, ARBs and diuretics) within the past week, especially if hypovolemic**
- **use of iodinated contrast agents within the past week**
- **symptoms or history of urological obstruction, or conditions that may lead to obstruction**
- **sepsis**
- **deteriorating early warning scores**
- **age 65 years or over**

Assess the risk of acute kidney injury in adults before surgery. Be aware that increased risk is associated with:

- **emergency surgery, especially when the patient has sepsis or hypovolemia**
- **intraperitoneal surgery**
- **chronic kidney disease (adults with an eGFR < 60 ml/min/1.73 m^2 are at particular risk)**
- **diabetes**
- **heart failure**
- **age 65 years or over**
- **liver disease**
- **use of drugs with nephrotoxic potential in the perioperative period (in particular, NSAIDs after surgery).**

Use the risk assessment to inform a clinical management plan.

Be aware that in adults, children and young people with chronic kidney disease and no obvious acute illness, a rise in serum creatinine may indicate acute kidney injury rather than a worsening of their chronic disease.

Ensure that acute kidney injury is considered when an adult, child or young person presents with an illness with no clear acute component and has any of the following:

- **chronic kidney disease, especially stage 3B, 4 or 5, or urological disease**
- **new onset or significant worsening of urological symptoms**
- **symptoms suggesting complications of acute kidney injury**
- **symptoms or signs of a multi-system disease affecting the kidneys and other organ systems (for example, signs or symptoms of acute kidney injury, plus a purpuric rash)**

14.1.5 Domus Medica CNI 2012 [4]

In case of a suddenly decreased renal function, think about the possibility of an acute renal insufficiency and consult if necessary a nephrologist. ***(consensus based)***

14.1.6 Summary of guidelines on AKI in CKD

The guidelines say that people with CKD are at an increased risk of AKI. [1-3]

They point at the possibility of AKI in CKD in case of a suddenly decreased renal function, rather than worsening of their chronic disease. [1, 4]

Patients must be assessed and investigated for risk of AKI according to their risk factors, exposures and susceptibilities. [1, 3]

14.2 Contrast-induced nephropathy

14.2.1 KDIGO CKD 2012[2]

Balance the risk of acute impairment in kidney function due to contrast agent use against the diagnostic value and therapeutic implications of the investigation. ***(Not Graded)***

KDIGO recommends that all people with GFR <60ml/min/1.73 m^2 (GFR categories G3a-G5) undergoing elective investigation involving the intravascular administration of iodinated radiocontrast media should be managed as follows:

- **Avoidance of high osmolar agents** ***(1B);***
- **Use of lowest possible radiocontrast dose** ***(Not Graded);***
- **Withdrawal of potentially nephrotoxic agents before and after the procedure** ***(1C);***
- **Adequate hydration with saline before, during, and after the procedure** ***(1A);***
- **Measurement of GFR 48–96 hours after the procedure** ***(1C).***

KDIGO recommends not using gadolinium-containing contrast media in people with GFR <15 ml/min/1.73 m^2 (GFR category G5) unless there is no alternative appropriate test. ***(1B)***

KDIGO suggests that people with a GFR <30 ml/min/1.73 m^2 (GFR categories G4-G5) who require gadolinium containing contrast media are preferentially offered a macrocyclic chelate preparation. ***(2B)***

14.2.2 KDIGO AKI 2012[3]

Assess the risk for CI-AKI and, in particular, screen for pre-existing impairment of kidney function in all patients who are considered for a procedure that requires intravascular (i.v. or i.a.) administration of iodinated contrast medium. ***(Not Graded)***

Consider alternative imaging methods in patients at increased risk for CI-AKI. Use the lowest possible dose of contrast medium in patients at risk for CI-AKI. ***(Not Graded)***

KDIGO recommends using either iso-osmolar or low-osmolar iodinated contrast media, rather than high-osmolar iodinated contrast media in patients at increased risk of CI-AKI. ***(1B)***

KDIGO recommends IV volume expansion with either isotonic sodium chloride or sodium bicarbonate solutions, rather than no IV volume expansion, in patients at increased risk for CI-AKI. ***(1A).*** **They recommend not using oral fluids alone in patients at increased risk of CI-AKI.** ***(1C)*** **They suggest using oral NAC, together with IV isotonic crystalloids, in those patients** ***(2D).*** **KDIGO suggests not using theophylline to prevent CI-AKI** ***(2C)*** **and recommends not using fenoldopam to prevent CI-AKI.** ***(1B)*** **KDIGO suggests not using prophylactic intermittent hemodialysis or hemofiltration for contrast-media removal in patients at increased risk for CI-AKI.** ***(2C)***

Define and stage AKI after administration of intravascular contrast media. ***(Not Graded)*** **In individuals who develop changes in kidney function after administration of intravascular contrast media, evaluate for CI-AKI as well as for other possible causes of AKI.** ***(Not Graded)***

14.2.3 NICE AKI 2013[1]

Before offering iodinated contrast agents to adults for non-emergency imaging, investigate for CKD by measuring eGFR or by checking an eGFR result obtained within the past 3 months.

Before offering iodinated contrast agents to adults for emergency or nonemergency imaging, assess their risk of acute kidney injury. Be aware that increased risk is associated with:

- **chronic kidney disease (adults with an eGFR <40 ml/min/1.73 m^2 are at particular risk)**
- **diabetes but only with CKD (adults with an eGFR < 40 ml/min/1.73 m^2 are at particular risk)**
- **heart failure**
- **renal transplant**
- **age 75 years or over**
- **hypovolemia**
- **increasing volume of contrast agent**
- **intra-arterial administration of contrast agent.**

Ensure that risk assessment does not delay emergency imaging.

Include the risks of developing acute kidney injury in the routine discussion of risks and benefits of the imaging procedure.

Offer intravenous volume expansion to adults having iodinated contrast agents if:

- **they are at increased risk of contrast-induced acute kidney injury, or**
- **they have an acute illness.**

Offer either isotonic sodium bicarbonate or 0.9% sodium chloride.

Discuss care with a nephrology team before offering iodinated contrast agent to adults with contraindications to intravenous fluids if:

- **they are at increased risk of contrast-induced acute kidney injury, or**
- **they have an acute illness, or**
- **they are on renal replacement therapy.**

Consider temporarily stopping ACE inhibitors and ARBs in adults having iodinated contrast agents if they have chronic kidney disease with an eGFR less than 40 ml/min/1.73 m^2.

Investigate for acute kidney injury, by measuring serum creatinine and comparing with baseline, in adults with acute illness if use of iodinated contrast agents within the past week.

14.2.4 Domus Medica CNI 2012[4]

Measure eGFR before each contrast investigation, if there is no recent (last 12 months) level available. *(1B)* Pass the renal function tot the person who performs the investigation or operation and discuss about the necessary preventive actions. *(1B)*

Spread the investigation if possible in time (interval of minimum two weeks) and control again and again the eGFR before a new investigation. *(1B)*

14.2.5 Summary of guidelines on contrast induced nephropathy

The guidelines recommend to balance the risk of acute impairment in kidney function due to contrast agent use against the benefits [1, 2].

All guidelines recommend to measure eGFR before each contrast investigation or check a recent GFR and pass it to the radiologist. [1, 3, 4]

Before offering iodinated contrast agents, assess the risk of acute kidney injury, with risk factors like described above[3].

The guidelines recommend in people with GFR <60ml/min/1.73 m^2 undergoing elective investigation involving the intravascular administration of iodinated radio contrast media, precautions have to be taken:

- Avoidance of high osmolar agents [2, 3]
- Use of lowest possible radiocontrast dose [2, 3]
- Withdrawal of potentially nephrotoxic agents before and after the procedure including ACE-I or ARBs [1, 2]
- Adequate hydration with saline [1-3]
- Measurement of GFR with definition and staging of AKI after the procedure [2, 3]

15 Follow up by the pharmacist (guidelines only)

15.1 KDIGO CKD 2012 [2]

KDIGO recommends that adults with CKD seek medical or pharmacist advice before using over-the-counter medicines or nutritional protein supplements. ***(1B)***

KDIGO recommends not using herbal remedies in people with CKD. (*1B)*

15.2 NICE AKI 2013 [1]

Seek advice from a pharmacist about optimizing medicines and drug dosing in adults, children and young people with or at risk of acute kidney injury.

Based on the very low quality of evidence it was not possible to distinguish between e-prescribing, CDT or pharmacist review as the best method for prevention of deterioration for patients at risk of AKI who are prescribed nephrotoxic drugs. However a trend was shown that any intervention is better than none at all. Though the evidence was limited, the GDG felt that CDTs (either alone or with electronic prescribing) or pharmacist review could reduce the incidence of inappropriate prescribing of either nephrotoxic drugs or drugs excreted by the kidneys as long as they are used in combination with clinical judgment.

16 Appendix: Search strategy

Search in the Cochrane library

Kidney disease, renal impairment, renal insufficiency

Search in Pubmed

16.1 Glycemic control

16.1.1 RCT's

(kidney insufficienc*[tiab] OR kidney disease*[tiab] OR renal disease*[tiab] OR Renal insufficienc*[tiab] OR Renal impairment*[tiab] OR "Renal insufficiency" [Mesh] OR nephropath* [tiab] OR "Diabetic Nephropathies"[Mesh] OR kidney failure [tiab] OR renal failure [tiab]) AND (Metformin*[tiab] OR biguanid*[tiab] OR Glibenclamid*[tiab] OR glyburid*[tiab] OR Gliclazid*[tiab] OR Glimepirid*[tiab] OR Glipizid*[tiab] OR Gliquidon*[tiab] OR sulfonylure*[tiab] OR sulphonylure*[tiab] OR repaglinid*[tiab] OR glinid*[tiab] OR meglitinid*[tiab] OR Pioglitazon*[tiab] OR Thiazolidinedion*[tiab] OR glitazon*[tiab] OR Sitagliptin*[tiab] OR Saxagliptin*[tiab] OR Vildagliptin*[tiab] OR linagliptin*[tiab] OR dpp-4*[tiab] OR dpp4*[tiab] OR dpp-iv*[tiab] OR dppiv*[tiab] OR Dipeptidyl-Peptidase IV Inhibit* [tiab] OR Dipeptidyl-Peptidase 4 Inhibit* [tiab] OR dipeptidylpeptidase 4 inhibit*[tiab] OR dipeptidylpeptidase iv inhibit* [tiab] OR gliptin*[tiab] OR "Acarbose"[Mesh] OR acarbose [tiab] OR ((hypoglycemic agent*[tiab] OR hypoglycemic drug* [tiab] OR antihyperglycemic* [tiab] OR antidiabetic*[tiab]) NOT "Insulin"[Mesh]) OR oral glucose-lowering drug*[tiab] OR oral glucose lowering agent*[tiab] OR glucagon-like peptide 1 [tiab] OR Exenatid* [tiab] OR Liraglutid*[tiab] OR GLP-1[tiab] OR glp1[tiab] OR incretin mimetic*[tiab] OR "Dipeptidyl-Peptidase IV Inhibitors"[Mesh] OR "Thiazolidinediones"[Mesh] OR "Glipizide"[Mesh] OR "Gliclazide"[Mesh] OR "Metformin"[Mesh] OR "Glyburide"[Mesh] OR "Sulfonylurea Compounds"[Mesh] OR ("Hypoglycemic Agents"[Mesh] NOT "Insulin"[Mesh]) OR ("Diabetes Mellitus, Type 2"[Mesh] AND (glycemic control [tiab] OR glycaemic control [tiab] OR glucose control [tiab] OR target* [tiab]) AND ("2011/10/25"[PDAT] : "2014/04/30"[PDAT]))) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo[tiab] OR systematic[sb] OR medline[TIAB])

16.1.2 Observational studies

(kidney insufficienc*[tiab] OR kidney disease*[tiab] OR renal disease*[tiab] OR Renal insufficienc*[tiab] OR Renal impairment*[tiab] OR “Renal insufficiency” [Mesh] OR nephropath* [tiab] OR "Diabetic Nephropathies"[Mesh] OR kidney failure [tiab] OR renal failure [tiab]) AND (Metformin*[tiab] OR biguanid*[tiab] OR Glibenclamid*[tiab] OR glyburid*[tiab] OR Gliclazid*[tiab] OR Glimepirid*[tiab] OR Glipizid*[tiab] OR Gliquidon*[tiab] OR sulfonylure*[tiab] OR sulphonylure*[tiab] OR repaglinid*[tiab] OR glinid*[tiab] OR meglitinid*[tiab] OR Pioglitazon*[tiab] OR Thiazolidinedion*[tiab] OR glitazon*[tiab] OR Sitagliptin*[tiab] OR Saxagliptin*[tiab] OR Vildagliptin*[tiab] OR linagliptin*[tiab] OR dpp-4*[tiab] OR dpp4*[tiab] OR dpp-iv*[tiab] OR dppiv*[tiab] OR Dipeptidyl-Peptidase IV Inhibit* [tiab] OR Dipeptidyl-Peptidase 4 Inhibit* [tiab] OR dipeptidylpeptidase 4 inhibit*[tiab] OR dipeptidylpeptidase iv inhibit* [tiab] OR gliptin*[tiab] OR "Acarbose"[Mesh] OR acarbose [tiab] OR ((hypoglycemic agent*[tiab] OR hypoglycemic drug* [tiab] OR antihyperglycemic* [tiab] OR antidiabetic*[tiab]) NOT "Insulin"[Mesh]) OR oral glucose-lowering drug*[tiab] OR oral glucose lowering agent*[tiab] OR glucagon-like peptide 1 [tiab] OR Exenatid* [tiab] OR Liraglutid*[tiab] OR GLP-1[tiab] OR glp1[tiab] OR incretin mimetic*[tiab] OR "Dipeptidyl-Peptidase IV Inhibitors"[Mesh] OR "Thiazolidinediones"[Mesh] OR "Glipizide"[Mesh] OR "Gliclazide"[Mesh] OR "Metformin"[Mesh] OR "Glyburide"[Mesh] OR "Sulfonylurea Compounds"[Mesh] OR ("Hypoglycemic Agents"[Mesh] NOT "Insulin"[Mesh])) AND (Cohort*[tiab] OR Longitudinal[TIAB] OR Prospective[TIAB] OR Retrospective[TIAB] OR "Observational Study" [Publication Type])

16.2 Anticoagulants

16.2.1 RCT's

(kidney insufficienc*[tiab] OR kidney disease*[tiab] OR renal disease*[tiab] OR Renal insufficienc*[tiab] OR Renal impairment*[tiab] OR "Renal insufficiency" [Mesh] OR nephropath* [tiab] OR Kidney Failure*[tiab] OR Renal Failure*[tiab] OR "Diabetic Nephropathies"[Mesh]) AND ("Antithrombins"[Mesh] OR oral anticoagul*[tiab] OR factor Xa inhibit*[tiab] OR thrombin inhibit*[tiab] OR anti thrombin*[tiab] OR antithrombin*[tiab] OR dabigatran*[tiab] OR apixaban*[tiab] OR rivaroxaban*[tiab] OR NOAC*[tiab]) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo[tiab] OR systematic[sb] OR medline[TIAB]) AND ("2009/01/01"[PDAT] : "2014/04/30"[PDAT])

16.2.2 Observational studies

(kidney insufficienc*[tiab] OR kidney disease*[tiab] OR renal disease*[tiab] OR Renal insufficienc*[tiab] OR Renal impairment*[tiab] OR "Renal insufficiency" [Mesh] OR nephropath* [tiab] OR Kidney Failure*[tiab] OR Renal Failure*[tiab] OR "Diabetic Nephropathies"[Mesh]) AND ("Antithrombins"[Mesh] OR oral anticoagul*[tiab] OR factor Xa inhibit*[tiab] OR thrombin inhibit*[tiab] OR anti thrombin*[tiab] OR antithrombin*[tiab] OR dabigatran*[tiab] OR apixaban*[tiab] OR rivaroxaban*[tiab] OR NOAC*[tiab]) AND (Cohort*[tiab] OR Longitudinal[TIAB] OR Prospective[TIAB] OR Retrospective[TIAB] OR "Observational Study" [Publication Type]) AND ("2009/01/01"[PDAT] : "2014/04/30"[PDAT])

16.3 Antihypertensive drugs (only RCT's)

(kidney insufficienc*[tiab] OR kidney disease*[tiab] OR renal disease*[tiab] OR Renal insufficienc*[tiab] OR Renal impairment*[tiab] OR "Renal insufficiency" [Mesh] OR nephropath* [tiab] OR "Diabetic Nephropathies"[Mesh]) AND ("Diuretics"[Mesh] OR "Sodium Chloride Symporter Inhibitors"[Mesh] OR "Thiazides"[Mesh] OR "Sodium Potassium Chloride Symporter Inhibitors"[Mesh] OR "Diuretics, Potassium Sparing"[Mesh] OR "Carbonic Anhydrase Inhibitors"[Mesh]OR "Chlorthalidone"[Mesh] OR "Indapamide"[Mesh] OR "Bumetanide"[Mesh] OR "Furosemide"[Mesh] OR "Canrenoic Acid"[Mesh] OR "Spironolactone"[Mesh] OR "Triamterene"[Mesh] OR "Acetazolamide"[Mesh] OR "Amiloride"[Mesh] OR Mineralocorticoid Receptor Antagon*[tiab] OR Mineralocorticoid Receptor inhib*[tiab] OR Diuretic*[tiab] OR Sodium Chloride Symporter Inhibit*[tiab] OR Thiazid*[tiab] OR Sodium Potassium Chloride Symporter Inhibit*[tiab] OR Carbonic Anhydrase Inhibit* [tiab] OR Chlorthalidon* [tiab] OR Indapamid* [tiab] OR Bumetanid*[tiab] OR Furosemid*[tiab] OR torsemid*[tiab] OR torasemid*[tiab] OR Canrenoic Acid*[tiab] OR canreonate* [tiab] OR eplerenon* [tiab] OR spironolacton*[tiab] OR Triamteren*[tiab] OR Acetazolamid*[tiab] OR althiazid*[tiab] OR Amilorid*[tiab] OR "Angiotensin-Converting Enzyme Inhibitors"[Mesh] OR "Angiotensin Receptor Antagonists"[Mesh] OR "Captopril"[Mesh] OR "Cilazapril"[Mesh] OR "Enalapril"[Mesh] OR "Fosinopril"[Mesh] OR "Lisinopril"[Mesh] OR "Perindopril"[Mesh] OR "Ramipril"[Mesh] OR "Losartan"[Mesh] OR Angiotensin-Converting Enzyme Inhibit*[tiab] OR Angiotensin converting Enzyme antagonist*[tiab] OR ACE inhibit* [tiab] OR sartan*[tiab] OR (Angiotensin[tiab] AND receptor [tiab] AND (block*[tiab] OR antagonist*[tiab] OR inhibit*[tiab])) OR benazepril [tiab] OR Captopril[tiab] OR Cilazapril[tiab] OR Enalapril[tiab] OR Fosinopril[tiab] OR Lisinopril[tiab] OR Perindopril[tiab] OR quinapril[tiab] OR Ramipril[tiab] OR zofenopril[tiab] OR candesartan*[tiab] OR eprosartan[tiab] OR irbesartan[tiab] OR Losartan[tiab] OR olmesartan [tiab] OR telmisartan[tiab] OR valsartan[tiab] OR aliskiren [tiab] OR renin inhibit* [tiab] OR "Adrenergic beta-Antagonists"[Mesh] OR "Acebutolol"[Mesh] OR "Atenolol"[Mesh] OR "Betaxolol"[Mesh] OR "Bisoprolol"[Mesh] OR "Labetalol"[Mesh] OR "Metoprolol"[Mesh] OR "Pindolol"[Mesh] OR "Propranolol"[Mesh] OR beta antagonist* [tiab] OR beta block* [tiab] OR betablock*[tiab] OR b-block* [tiab] OR b-antagonist* [tiab] OR Acebutolol [tiab] OR Atenolol[tiab] OR Betaxolol[tiab] OR Bisoprolol[tiab] OR carvedilol[tiab] OR Celiprolol[tiab] OR celiprolol[tiab] OR esmolol[tiab] OR Labetalol[tiab] OR Metoprolol[tiab] OR nebivolol[tiab] OR Pindolol[tiab] OR Propranolol[tiab] OR "Calcium Channel Blockers"[Mesh] OR Calcium channel block* [tiab] OR "Dihydropyridines"[Mesh] OR "Amlodipine"[Mesh] OR "Felodipine"[Mesh] OR "Isradipine"[Mesh] OR "Nicardipine"[Mesh] OR "Nifedipine"[Mesh] OR "Nimodipine"[Mesh] OR "Nisoldipine"[Mesh] OR "Nitrendipine"[Mesh] OR "Verapamil"[Mesh] OR "Diltiazem"[Mesh] OR Dihydropyridin*[tiab] OR Amlodipin*[tiab] OR mepirodipin*[tiab] OR barnidipin*[tiab] OR Felodipin*[tiab] OR Isradipin*[tiab] OR lacidipin*[tiab] OR lercanidipin*[tiab] OR Nicardipin*[tiab] OR Nifedipin*[tiab] OR Nimodipin*[tiab] OR Nisoldipin*[tiab] OR Nitrendipin*[tiab] OR Verapamil*[tiab] OR Diltiazem*[tiab]) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo[tiab] OR systematic[sb] OR medline[TIAB]) AND ("2010/12/01"[PDAT] : "2014/04/30"[PDAT])

16.4 Analgetics

16.4.1 RCT's

(kidney insufficienc*[tiab] OR kidney disease*[tiab] OR renal disease*[tiab] OR Renal insufficienc*[tiab] OR Renal impairment*[tiab] OR "Renal insufficiency" [Mesh] OR nephropath* [tiab] OR Kidney Failure*[tiab] OR Renal Failure*[tiab] OR "Diabetic Nephropathies"[Mesh]) AND ((("Acetaminophen"[Mesh] OR Acetaminophen*[tiab] OR paracetamol [tiab]) AND ("2009/01/01"[PDAT] : "2014/04/30"[PDAT])) OR (("Anti-Inflammatory Agents, Non-Steroidal"[Mesh] OR "Diclofenac"[Mesh] OR "Ketorolac"[Mesh] OR "Ibuprofen"[Mesh] OR "Ketoprofen"[Mesh] OR "Naproxen"[Mesh] OR "Indomethacin"[Mesh] OR "Piroxicam"[Mesh] OR "Cyclooxygenase 2 Inhibitors"[Mesh] OR "Niflumic Acid"[Mesh] OR ((nonsteroidal [tiab] OR non steroidal [tiab]) AND (antiinflammatory[tiab] OR anti inflammatory[tiab]) AND (agent*[tiab] OR drug*[tiab])) OR nsai* [tiab] OR aryl acetic acid* [tiab] OR arylacetic acid*[tiab] OR aceclofenac [tiab] OR Diclofenac[tiab] OR Ketorolac[tiab] OR aryl propionic acid* [tiab] OR arylpropionic acid*[tiab] OR dexketoprofen [tiab] OR Ibuprofen[tiab] OR Ketoprofen[tiab] OR Naproxen[tiab] OR oxaprozin* [tiab] OR Indomethacin*[tiab] OR indometacin*[tiab] OR proglumetacin* [tiab] OR oxicam*[tiab] OR meloxicam [tiab] OR Piroxicam[tiab] OR tenoxicam [tiab] OR Cyclo-oxygenase 2 Inhibit*[tiab] OR cyclooxygenase 2 inhibit* [tiab]OR coxib* [tiab] OR celecoxib [tiab] OR etoricoxib [tiab] OR parecoxib [tiab] OR nabumeton*[tiab] OR biphenylylacetic acid [tiab] OR etofenamate [tiab] OR Niflumic Acid[tiab]) AND ("2011/08/30"[PDAT] : "2014/04/30"[PDAT]))) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo[tiab] OR systematic[sb] OR medline[TIAB])

16.4.2 Observational studies

(kidney insufficienc*[tiab] OR kidney disease*[tiab] OR renal disease*[tiab] OR Renal insufficienc*[tiab] OR Renal impairment*[tiab] OR "Renal insufficiency" [Mesh] OR nephropath* [tiab] OR Kidney Failure*[tiab] OR Renal Failure*[tiab] OR "Diabetic Nephropathies"[Mesh]) AND ((("Acetaminophen"[Mesh] OR Acetaminophen*[tiab] OR paracetamol [tiab]) AND ("2009/01/01"[PDAT] : "2014/04/30"[PDAT])) OR (("Anti-Inflammatory Agents, Non-Steroidal"[Mesh] OR "Diclofenac"[Mesh] OR "Ketorolac"[Mesh] OR "Ibuprofen"[Mesh] OR "Ketoprofen"[Mesh] OR "Naproxen"[Mesh] OR "Indomethacin"[Mesh] OR "Piroxicam"[Mesh] OR "Cyclooxygenase 2 Inhibitors"[Mesh] OR "Niflumic Acid"[Mesh] OR ((nonsteroidal [tiab] OR non steroidal [tiab]) AND (antiinflammatory[tiab] OR anti inflammatory[tiab]) AND (agent*[tiab] OR drug*[tiab])) OR nsai* [tiab] OR aryl acetic acid* [tiab] OR arylacetic acid*[tiab] OR aceclofenac [tiab] OR Diclofenac[tiab] OR Ketorolac[tiab] OR aryl propionic acid* [tiab] OR arylpropionic acid*[tiab] OR dexketoprofen [tiab] OR Ibuprofen[tiab] OR Ketoprofen[tiab] OR Naproxen[tiab] OR oxaprozin* [tiab] OR Indomethacin*[tiab] OR indometacin*[tiab] OR proglumetacin* [tiab] OR oxicam*[tiab] OR meloxicam [tiab] OR Piroxicam[tiab] OR tenoxicam [tiab] OR Cyclo-oxygenase 2 Inhibit*[tiab] OR cyclooxygenase 2 inhibit* [tiab]OR coxib* [tiab] OR celecoxib [tiab] OR etoricoxib [tiab] OR parecoxib [tiab] OR nabumeton*[tiab] OR biphenylylacetic acid [tiab] OR etofenamate [tiab] OR Niflumic Acid[tiab]) AND ("2011/08/30"[PDAT] : "2014/04/30"[PDAT]))) AND (Cohort*[tiab] OR Longitudinal[TIAB] OR Prospective[TIAB] OR Retrospective[TIAB] OR "Observational Study" [Publication Type])

16.5 Drugs used in gout

16.5.1 RCT's

(kidney insufficienc*[tiab] OR kidney disease*[tiab] OR renal disease*[tiab] OR Renal insufficienc*[tiab] OR Renal impairment*[tiab] OR "Renal insufficiency" [Mesh] OR nephropath* [tiab] OR Kidney Failure*[tiab] OR Renal Failure*[tiab] OR "Diabetic Nephropathies"[Mesh]) AND ((("Gout Suppressants"[Mesh] OR Gout Suppress*[tiab] OR anti gout agent* [tiab] OR antigout agent* [tiab] OR anti gout drug* [tiab] OR antigout drug* [tiab] OR "Colchicine"[Mesh] OR Colchicin*[tiab]) AND ("2009/01/01"[PDAT] : "2014/04/30"[PDAT])) OR (("Allopurinol"[Mesh] OR xanthine oxidase inhib* [tiab] OR Allopurinol[tiab] OR febuxostat [tiab]) AND ("2012/11/01"[PDAT] : "2014/04/30"[PDAT]))) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo[tiab] OR systematic[sb] OR medline[TIAB])

16.5.2 Observational studies

(kidney insufficienc*[tiab] OR kidney disease*[tiab] OR renal disease*[tiab] OR Renal insufficienc*[tiab] OR Renal impairment*[tiab] OR "Renal insufficiency" [Mesh] OR nephropath* [tiab] OR Kidney Failure*[tiab] OR Renal Failure*[tiab] OR "Diabetic Nephropathies"[Mesh]) AND ((("Gout Suppressants"[Mesh] OR Gout Suppress*[tiab] OR anti gout agent* [tiab] OR antigout agent* [tiab] OR anti gout drug* [tiab] OR antigout drug* [tiab] OR "Colchicine"[Mesh] OR Colchicin*[tiab]) AND ("2009/01/01"[PDAT] : "2014/04/30"[PDAT])) OR (("Allopurinol"[Mesh] OR xanthine oxidase inhib* [tiab] OR Allopurinol[tiab] OR febuxostat [tiab]) AND("2012/11/01"[PDAT] : "2014/04/30"[PDAT]))) AND (Cohort*[tiab] OR Longitudinal[TIAB] OR Prospective[TIAB] OR Retrospective[TIAB] OR "Observational Study" [Publication Type])

16.6 Specific medications

16.6.1 Methotrexaat

16.6.1.1 RCT's

(kidney insufficienc*[tiab] OR kidney disease*[tiab] OR renal disease*[tiab] OR Renal insufficienc*[tiab] OR Renal impairment*[tiab] OR "Renal insufficiency" [Mesh] OR nephropath* [tiab] OR Kidney Failure*[tiab] OR Renal Failure*[tiab] OR "Diabetic Nephropathies"[Mesh]) AND ("Methotrexate"[Mesh] OR Methotrexate [tiab]) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo[tiab] OR systematic[sb] OR medline[TIAB]) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo[tiab] OR systematic[sb] OR medline[TIAB]) AND ("2009/01/01"[PDAT] : "2014/04/30"[PDAT])

16.6.1.2 Observational studies

(kidney insufficienc*[tiab] OR kidney disease*[tiab] OR renal disease*[tiab] OR Renal insufficienc*[tiab] OR Renal impairment*[tiab] OR "Renal insufficiency" [Mesh] OR nephropath* [tiab] OR Kidney Failure*[tiab] OR Renal Failure*[tiab] OR "Diabetic Nephropathies"[Mesh]) AND ("Methotrexate"[Mesh] OR Methotrexate [tiab]) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo[tiab] OR systematic[sb] OR medline[TIAB]) AND (Cohort*[tiab] OR Longitudinal[TIAB] OR Prospective[TIAB] OR Retrospective[TIAB] OR "Observational Study" [Publication Type]) AND ("2009/01/01"[PDAT] : "2014/04/30"[PDAT])

16.6.2 Lithium

16.6.2.1 RCT's

(kidney insufficienc*[tiab] OR kidney disease*[tiab] OR renal disease*[tiab] OR Renal insufficienc*[tiab] OR Renal impairment*[tiab] OR "Renal insufficiency" [Mesh] OR nephropath* [tiab] OR Kidney Failure*[tiab] OR Renal Failure*[tiab] OR "Diabetic Nephropathies"[Mesh]) AND ("Lithium"[Mesh] OR Lithium [tiab]) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo[tiab] OR systematic[sb] OR medline[TIAB]) AND ("2009/01/01"[PDAT] : "2014/04/30"[PDAT])

16.6.2.2 Observational studies

(kidney insufficienc*[tiab] OR kidney disease*[tiab] OR renal disease*[tiab] OR Renal insufficienc*[tiab] OR Renal impairment*[tiab] OR "Renal insufficiency" [Mesh] OR nephropath* [tiab] OR Kidney Failure*[tiab] OR Renal Failure*[tiab] OR "Diabetic Nephropathies"[Mesh]) AND ("Lithium"[Mesh] OR Lithium [tiab]) AND (Cohort*[tiab] OR Longitudinal[TIAB] OR Prospective[TIAB] OR Retrospective[TIAB] OR "Observational Study" [Publication Type]) AND ("2009/01/01"[PDAT] : "2014/04/30"[PDAT])

16.6.3 Phosphate containing bowel preparations

16.6.3.1 RCT's

(kidney insufficienc*[tiab] OR kidney disease*[tiab] OR renal disease*[tiab] OR Renal insufficienc*[tiab] OR Renal impairment*[tiab] OR "Renal insufficiency" [Mesh] OR nephropath* [tiab] OR Kidney Failure*[tiab] OR Renal Failure*[tiab] OR "Diabetic Nephropathies"[Mesh]) AND ((Phosphate [tiab] AND laxativ* [tiab]) OR (phosphate [tiab] AND "Laxatives"[Mesh]) OR (phosphate [tiab] AND bowel preparation [tiab])) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo[tiab] OR systematic[sb] OR medline[TIAB]) AND ("2009/01/01"[PDAT] : "2014/04/30"[PDAT])

16.6.3.2 Observational studies

(kidney insufficienc*[tiab] OR kidney disease*[tiab] OR renal disease*[tiab] OR Renal insufficienc*[tiab] OR Renal impairment*[tiab] OR "Renal insufficiency" [Mesh] OR nephropath* [tiab] OR Kidney injur*[tiab] OR Kidney Failure*[tiab] OR Renal Failure*[tiab] OR ESRD[tiab] OR "Diabetic Nephropathies"[Mesh]) AND ((Phosphate [tiab] AND laxative* [tiab]) OR (phosphate [tiab] AND "Laxatives"[Mesh]) OR (phosphate [tiab] AND bowel preparation [tiab])) AND (Cohort*[tiab] OR Longitudinal[TIAB] OR Prospective[TIAB] OR Retrospective[TIAB] OR "Observational Study" [Publication Type]) AND ("2009/01/01"[PDAT] : "2014/04/30"[PDAT])

16.6.4 Association NSAIDs + ACE-I + diuretics

16.6.4.1 RCT's

(kidney insufficienc*[tiab] OR kidney disease*[tiab] OR renal disease*[tiab] OR Renal insufficienc*[tiab] OR Renal impairment*[tiab] OR "Renal insufficiency" [Mesh] OR nephropath* [tiab] OR Kidney injur*[tiab] OR Kidney Failure*[tiab] OR Renal Failure*[tiab] OR ESRD[tiab] OR "Diabetic Nephropathies"[Mesh]) AND (("Diuretics"[Mesh] OR "Sodium Chloride Symporter Inhibitors"[Mesh] OR "Thiazides"[Mesh] OR "Sodium Potassium Chloride Symporter Inhibitors"[Mesh] OR "Diuretics, Potassium Sparing"[Mesh] OR "Carbonic Anhydrase Inhibitors"[Mesh]OR "Chlorthalidone"[Mesh] OR "Indapamide"[Mesh] OR "Bumetanide"[Mesh] OR "Furosemide"[Mesh] OR "Canrenoic Acid"[Mesh] OR "Spironolactone"[Mesh] OR "Triamterene"[Mesh] OR "Acetazolamide"[Mesh] OR "Amiloride"[Mesh]OR Mineralocorticoid Receptor Antagon*[tiab] OR Mineralocorticoid Receptor inhib*[tiab] OR Diuretic*[tiab] OR Sodium Chloride Symporter Inhibit*[tiab] OR Thiazid*[tiab] OR Sodium Potassium Chloride Symporter Inhibit*[tiab] OR Carbonic Anhydrase Inhibit* [tiab] OR Chlorthalidon* [tiab] OR Indapamid* [tiab] OR Bumetanid*[tiab] OR Furosemid*[tiab] OR torsemid*[tiab] OR torasemid*[tiab] OR Canrenoic Acid*[tiab] OR canreonate* [tiab] OR eplerenon* [tiab] OR spironolacton*[tiab] OR Triamteren*[tiab] OR Acetazolamid*[tiab] OR althiazid*[tiab] OR Amilorid*[tiab]) AND ("Angiotensin-Converting Enzyme Inhibitors"[Mesh] OR "Angiotensin II Type 1 Receptor Blockers"[Mesh] OR "Angiotensin Receptor Antagonists"[Mesh] OR "Captopril"[Mesh] OR "Cilazapril"[Mesh] OR "Enalapril"[Mesh] OR "Fosinopril"[Mesh] OR "Lisinopril"[Mesh] OR "Perindopril"[Mesh] OR "Ramipril"[Mesh] OR "Losartan"[Mesh] OR Angiotensin-Converting Enzyme Inhibit*[tiab] OR Angiotensin-Converting Enzyme antagonist*[tiab] OR ACE inhibit* [tiab] OR sartan*[tiab] OR (Angiotensin[tiab] AND receptor [tiab] AND (block*[tiab] OR antagonist*[tiab] OR inhibit*[tiab])) OR benazepril [tiab] OR Captopril[tiab] OR Cilazapril[tiab] OR Enalapril[tiab] OR Fosinopril[tiab] OR Lisinopril[tiab] OR Perindopril[tiab] OR quinapril[tiab] OR Ramipril[tiab] OR zofenopril[tiab] OR candesartan*[tiab] OR eprosartan[tiab] OR irbesartan[tiab] OR Losartan[tiab] OR olmesartan [tiab] OR telmisartan[tiab] OR valsartan[tiab]) AND ("Anti-Inflammatory Agents, Non-Steroidal"[Mesh] OR "Diclofenac"[Mesh] OR "Ketorolac"[Mesh] OR "Ibuprofen"[Mesh] OR "Ketoprofen"[Mesh] OR "Naproxen"[Mesh] OR "Indomethacin"[Mesh] OR "Piroxicam"[Mesh] OR "Cyclooxygenase 2 Inhibitors"[Mesh] OR "Niflumic Acid"[Mesh] OR ((nonsteroidal [tiab] OR non steroidal [tiab]) AND (antiinflammatory[tiab] OR anti inflammatory[tiab]) AND (agent*[tiab] OR drug*[tiab])) OR nsai* [tiab] OR aryl acetic acid* [tiab] OR arylacetic acid*[tiab] OR aceclofenac [tiab] OR Diclofenac[tiab] OR Ketorolac[tiab] OR aryl propionic acid* [tiab] OR arylpropionic acid*[tiab] OR dexketoprofen [tiab] OR Ibuprofen[tiab] OR Ketoprofen[tiab] OR Naproxen[tiab] OR oxaprozin* [tiab] OR Indomethacin*[tiab] OR indometacin*[tiab] OR proglumetacin* [tiab] OR oxicam*[tiab] OR meloxicam [tiab] OR Piroxicam[tiab] OR tenoxicam [tiab] OR Cyclo-oxygenase 2 Inhibit*[tiab] OR cyclooxygenase 2 inhibit* [tiab]OR coxib* [tiab] OR celecoxib [tiab] OR etoricoxib [tiab] OR parecoxib [tiab] OR nabumeton*[tiab] OR biphenylylacetic acid [tiab] OR etofenamate [tiab] OR Niflumic Acid[tiab])) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo[tiab] OR systematic[sb] OR medline[TIAB])

16.6.4.2 Observational studies

(kidney insufficienc*[tiab] OR kidney disease*[tiab] OR renal disease*[tiab] OR Renal insufficienc*[tiab] OR Renal impairment*[tiab] OR “Renal insufficiency” [Mesh] OR nephropath* [tiab] OR Kidney injur*[tiab] OR Kidney Failure*[tiab] OR Renal Failure*[tiab] OR ESRD[tiab] OR "Diabetic Nephropathies"[Mesh]) AND (("Diuretics"[Mesh] OR "Sodium Chloride Symporter Inhibitors"[Mesh] OR "Thiazides"[Mesh] OR "Sodium Potassium Chloride Symporter Inhibitors"[Mesh] OR "Diuretics, Potassium Sparing"[Mesh] OR "Carbonic Anhydrase Inhibitors"[Mesh]OR "Chlorthalidone"[Mesh] OR "Indapamide"[Mesh] OR "Bumetanide"[Mesh] OR "Furosemide"[Mesh] OR "Canrenoic Acid"[Mesh] OR "Spironolactone"[Mesh] OR "Triamterene"[Mesh] OR "Acetazolamide"[Mesh] OR "Amiloride"[Mesh]OR Mineralocorticoid Receptor Antagon*[tiab] OR Mineralocorticoid Receptor inhib*[tiab] OR Diuretic*[tiab] OR Sodium Chloride Symporter Inhibit*[tiab] OR Thiazid*[tiab] OR Sodium Potassium Chloride Symporter Inhibit*[tiab] OR Carbonic Anhydrase Inhibit* [tiab] OR Chlorthalidon* [tiab] OR Indapamid* [tiab] OR Bumetanid*[tiab] OR Furosemid*[tiab] OR torsemid*[tiab] OR torasemid*[tiab] OR Canrenoic Acid*[tiab] OR canreonate* [tiab] OR eplerenon* [tiab] OR spironolacton*[tiab] OR Triamteren*[tiab] OR Acetazolamid*[tiab] OR althiazid*[tiab] OR Amilorid*[tiab]) AND ("Angiotensin-Converting Enzyme Inhibitors"[Mesh] OR "Angiotensin II Type 1 Receptor Blockers"[Mesh] OR "Angiotensin Receptor Antagonists"[Mesh] OR "Captopril"[Mesh] OR "Cilazapril"[Mesh] OR "Enalapril"[Mesh] OR "Fosinopril"[Mesh] OR "Lisinopril"[Mesh] OR "Perindopril"[Mesh] OR "Ramipril"[Mesh] OR "Losartan"[Mesh] OR Angiotensin-Converting Enzyme Inhibit*[tiab] OR Angiotensin-Converting Enzyme antagonist*[tiab] OR ACE inhibit* [tiab] OR sartan*[tiab] OR (Angiotensin[tiab] AND receptor [tiab] AND (block*[tiab] OR antagonist*[tiab] OR inhibit*[tiab])) OR benazepril [tiab] OR Captopril[tiab] OR Cilazapril[tiab] OR Enalapril[tiab] OR Fosinopril[tiab] OR Lisinopril[tiab] OR Perindopril[tiab] OR quinapril[tiab] OR Ramipril[tiab] OR zofenopril[tiab] OR candesartan*[tiab] OR eprosartan[tiab] OR irbesartan[tiab] OR Losartan[tiab] OR olmesartan [tiab] OR telmisartan[tiab] OR valsartan[tiab]) AND ("Anti-Inflammatory Agents, Non-Steroidal"[Mesh] OR "Diclofenac"[Mesh] OR "Ketorolac"[Mesh] OR "Ibuprofen"[Mesh] OR "Ketoprofen"[Mesh] OR "Naproxen"[Mesh] OR "Indomethacin"[Mesh] OR "Piroxicam"[Mesh] OR "Cyclooxygenase 2 Inhibitors"[Mesh] OR "Niflumic Acid"[Mesh] OR ((nonsteroidal [tiab] OR non steroidal [tiab]) AND (antiinflammatory[tiab] OR anti inflammatory[tiab]) AND (agent*[tiab] OR drug*[tiab])) OR nsai* [tiab] OR aryl acetic acid* [tiab] OR arylacetic acid*[tiab] OR aceclofenac [tiab] OR Diclofenac[tiab] OR Ketorolac[tiab] OR aryl propionic acid* [tiab] OR arylpropionic acid*[tiab] OR dexketoprofen [tiab] OR Ibuprofen[tiab] OR Ketoprofen[tiab] OR Naproxen[tiab] OR oxaprozin* [tiab] OR Indomethacin*[tiab] OR indometacin*[tiab] OR proglumetacin* [tiab] OR oxicam*[tiab] OR meloxicam [tiab] OR Piroxicam[tiab] OR tenoxicam [tiab] OR Cyclo-oxygenase 2 Inhibit*[tiab] OR cyclooxygenase 2 inhibit* [tiab]OR coxib* [tiab] OR celecoxib [tiab] OR etoricoxib [tiab] OR parecoxib [tiab] OR nabumeton*[tiab] OR biphenylylacetic acid [tiab] OR etofenamate [tiab] OR Niflumic Acid[tiab])) AND (Cohort*[tiab] OR Longitudinal[TIAB] OR Prospective[TIAB] OR Retrospective[TIAB] OR "Observational Study" [Publication Type])

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