Clinical Practice Guideline on management of patients with diabetes and chronic kidney disease stage 3b or higher (eGFRr<45ml/min)
1. Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>CKD</td>
<td>Chronic Kidney Disease</td>
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<tr>
<td>ACE-I</td>
<td>Angiotensin Converting Enzyme Inhibitor</td>
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<td>ERA-EDTA</td>
<td>European Renal Association – European Dialysis and Transplant Association</td>
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<tr>
<td>ERBP</td>
<td>European Renal Best Practice</td>
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<tr>
<td>MD</td>
<td>Mean Difference</td>
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<td>OR</td>
<td>Odds Ratio</td>
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<td>RR</td>
<td>Relative Risk</td>
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<td>95% CI</td>
<td>95% Confidence Interval</td>
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2. Foreword

Diabetes mellitus is a devastating disease, that is becoming increasingly prevalent, and is considered a rapidly growing concern for health care systems. Besides the cardiovascular complications, diabetes mellitus is associated with chronic kidney disease (CKD). This might be attributable to true diabetic nephropathy, but can also be caused indirectly by diabetes, e.g. because of polynuropathic bladder dysfunction, increased incidence of relapsing urinary tract infections, or because of macrovascular angiopathy.

On the other hand, many patients with another cause of their underlying chronic kidney disease than diabetes, will develop or already have diabetes mellitus. Last, many drugs that are used for management of chronic kidney diseases, eg corticosteroids or calcineurin inhibitors, can cause diabetes.

Despite the strong interplay between diabetes and chronic kidney disease, the management of patients with diabetes and CKD stage 3b or higher (eGFR<45ml/min) remains problematic. Many guidance providing documents have been produced on the management of patients with diabetes to prevent or delay the progression to chronic kidney disease (mostly defined as presence of micro and macro-albuminuria), but none deals specifically with patients with CKD stage 3b or higher (eGFR<45ml/min). There is a paucity of well-designed, prospective studies in this population, as many studies exclude either patients with diabetes, or with CKD stage 3b or higher (eGFR<45ml/min), or both. This limits the evidence-base to these approaches.

Available previous guidance has often been experience, or practice-based, without a systematic approach to evaluation and lacking a clear, patient-centred focus. The guidance has been difficult to follow in day-to-day clinical practice, especially by doctors in training who are managing patients in the ‘front line’. Here, the requirement is for clear, concise and practical advice on what to do. The guidance has used a biochemical focus rather than a patient centered approach, failing to prioritise clinical status in decisions on treatment options.

In addition, some new developments in this area made that the advisory board of ERBP decided that a guideline on management of patients with diabetes and CKD stage 3b or higher (eGFR<45ml/min) was needed and timely:

1. The clear recognition of the importance of evidence-based approaches to patient care to enhance quality, improve safety and establish a clear and transparent framework for service development and health-care provision.
2. The advent of new diagnostics and therapeutics in this area, highlighting the need for a valid, reliable and transparent process of evaluation to support key decisions.

In addition to a rigorous approach to methodology and evaluation, we were keen to ensure the document focused on patient-important outcomes and had utility for clinicians involved in every-day practice.

3. Composition of the Guideline Development Group

After approval of the project concept by the advisory board of ERBP, a working group convened in May 2011 and decided on the composition of the guideline development group, taking into account the clinical and research expertise of each proposed candidate. It was decided that, next to the
actual members of the guideline development group, additional external experts would be approached for their expertise in specific areas

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see also appendix 1 for more complete biography and declaration of interest

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4. Conflict of Interest

4.1. Conflict of interest policy

We required all participants in the Guideline Development Group to fill out a detailed ‘Declaration of Interest Statement’ including all current and future conflicts of interest as well as past interest restricted to the two years before joining the guideline development process. Because it was felt that excluding every individual with some degree of potential conflict of interest would make assembling a guideline development group impossible, we allowed members of the guideline development group to have past financial and/or intellectual conflicts of interest. We did not attach any consequences to the stated interests, but rather insisted on transparency. All members of the guideline development group were allowed to participate in all the discussions and had equal weight in formulating the statements. All were allowed equal involvement in data extraction and writing the rationales.

4.2. Guideline development group declaration of interest

The declaration of interest forms are available from http://www.european-renal-best-practice.org/content/ERBP-Workgroup-Diabetes-0 and are updated on a regular basis. They can also be found in the supplementary material appendix 1.
5. Purpose and Scope of this guideline

5.1. Why was this guideline produced?

The purpose of this Clinical Practice Guideline was to provide guidance on the management and treatment of adult individuals with diabetes mellitus and CKD stage 3b or higher (eGFR<45ml/min). It was designed to provide information and assist decision-making related to topics in this specific patient population. It was not intended to define a standard of care, and should not be construed as one. It should not be interpreted as prescribing an exclusive course of management.

5.2. Who is this guideline for?

This guideline was meant to support clinical decision making for any health care professional dealing with patients with diabetes and CKD stage 3b or higher (eGFR<45ml/min), i.e. for general practitioners, internists, surgeons and other physicians dealing with this specific patient population in both an outpatient and an in-hospital setting. The guideline was also developed for policymakers for informing standards of care and for supporting the decision making process.

5.3. What is this guideline about?

This section defines what this guideline intended to cover, and what the guideline developers considered. The scope was determined at a first meeting held in Brussels in May 2011 with a steering group assembled for this purpose by the ERBP advisory board. This steering group defined a set of healthcare questions related to the management of patients with diabetes mellitus and CKD stage 3b or higher (eGFR<45ml/min) 3b-5. An electronic survey was done amongst all members of ERA-EDTA to prioritise these questions.

5.3.1. Population

The guideline covers adults with diabetes mellitus and CKD stage 3b or higher (eGFR<45ml/min), as defined by the recent KDIGO classification. The guideline does not cover interventions in patients with diabetes and chronic kidney disease stages 1-2 to prevent or retard development of micro- or macro-albuminuria.

5.3.2. Conditions

The guideline specifically covers management and treatment of patients with diabetes mellitus and CKD stage 3b or higher (eGFR<45ml/min), and this in 4 major areas: 1/ selection of renal replacement modality; 2/ management of glycaemic control; 3/ management and prevention of cardiovascular comorbidity

5.3.3. Healthcare setting

This guideline targets primary, secondary and tertiary healthcare settings dealing with patients with diabetes and CKD stage 3b or higher (eGFR<45ml/min).

5.3.4. Clinical management

The guideline deals with topics related to the management of patients with diabetes and CKD stage 3b or higher (eGFR<45ml/min). It intended to provide an evidence based rationale for the day to day...
management of these patients, and to develop pathways of care in this area by systematically compiling available evidence in this area. It provides an evidence based rationale on why treatment and management of patients with diabetes and CKD stage 3b or higher (eGFR<45ml/min) should or should not be different from patients with diabetes without CKD stage 3b or higher (eGFR<45ml/min), or patients with CKD stage 3b or higher (eGFR<45ml/min) but without diabetes. In line with the mission statement of ERBP, the guideline document intends to inform all involved stakeholders and stimulate shared decision making[1].
6. Methods for Guideline Development

6.1. Establishment of the guideline development group

As defined by the methodology of ERBP[2], the advisory board of ERBP installed a steering group, which, after selection of the topics, selected further members of the guideline development group. In the selection of the steering group and the further members of the guideline development group, the clinical and research expertise of the proposed candidates was taken into account, besides their willingness to invest the necessary time and effort to perform the task according to the proposed deadlines and the agreed methodology. The guideline development group consisted of content experts, which included individuals with expertise in endocrinology and diabetes, general internal medicine, and clinical nephrology. In addition, experts in epidemiology and systematic review methodology were added to the guideline development group. The ERBP methods support team provided methodological input and practical assistance throughout the guideline development process.

6.2. Developing clinical questions

From the final scope of the guideline, specific research questions, for which a systematic review would be conducted, were identified. They all addressed issues related to one of the following four areas:

1/ renal replacement modality selection in patients with diabetes with end stage renal disease
2/ glycaemic control in patients with diabetes and chronic kidney disease stage 3b or higher (eGFR<45ml/min)
3/ management of cardiovascular risk in patients with diabetes and chronic kidney disease stage 3b or higher (eGFR<45ml/min)

6.3. Development of Review Questions

The methods support team assisted in developing review questions, i.e. framing the clinical questions into a searchable format. This required careful specification of the patient group (P), the intervention (I), the comparator (C) and the outcomes (O) for intervention questions and the patient group, index tests, reference standard and target condition for questions of diagnostic test accuracy [3]. For each question the guideline development group agreed upon explicit review question criteria including study design features. (See Appendices for Detailed Review Questions and PICO tables).

6.4. Assessment of the Relative Importance of the Outcomes

For each intervention question, the guideline development group compiled a list of outcomes, reflecting both benefits and harms of alternative management strategies. The guideline development group ranked the outcomes as critical, highly or moderately important according to their relative importance in the decision-making process. (Table 1).

6.5. Target Population Perspectives

An effort was made to capture the target population’s perspectives by adopting different strategies. European Renal Best Practice has a permanent patient representative on its advisory board. Although he was not included in the guideline development group or in the evidence review process, drafts of the guideline document were sent out for his review and his comments were taken into account in revising and drafting the final document.
6.6. Searching for Evidence

6.6.1. Sources

The ERBP methods support team searched The Cochrane Database of Systematic Reviews (May 2014), DARE (May 2014), CENTRAL (May 2014) and Medline (1946 to May, week 4, 2014) for all questions. The search strategies combined subject headings and text words for the patient population, index test and target condition for the diagnostic questions and subject headings and text words for the population and intervention for the intervention questions. The detailed search strategies are available from Appendix 3.

Reference lists from included publications were screened to identify additional papers. The methods support team also searched guideline databases and organisations including the National Guideline Clearinghouse, Guidelines International Network, Guidelines Finder, Centre for Reviews and Dissemination, National Institute for Clinical Excellence, and professional societies of Nephrology and Endocrinology for guidelines to screen the reference lists.

6.6.2. Selection

For the diagnostic questions, we included every study that compared any of the predefined clinical or biochemical tests with a golden standard reference test. For the question on treatment strategies, we included every study in which one of the predefined interventions was evaluated in humans. We excluded case-series that reported on benefit if the number of participants ≤ 5, but included even individual case-reports if they reported an adverse event. No restriction was made based on language.

We used the Early Reference Organisation Software (EROS) [http://www.eros-systematic-review.org] to organise the initial step of selection of papers. Title and abstract of all papers retrieved by the original search were made available to the responsible screener through this system. For each question, a member of the ERBP methods support team and one member of the guideline development group dedicated to this question screened all titles and abstracts to discard the clearly irrelevant ones based on title and abstract. All abstracts that did not meet the inclusion criteria were discarded. Any discrepancies at this stage were resolved by consensus. The methods support team retrieved full texts of potentially relevant studies and examined them for eligibility together with the member of the guideline development group dedicated to the specific question, and this independently of each other. Any discrepancies were resolved by consensus. If no consensus could be reached, the disagreement was settled by group arbitrage. The flow of the paper selection is presented for each question in appendix 5

6.6.3. Data extraction and critical appraisal of individual studies

For each included study, we collected relevant information on design, conduct, and relevant results through a tailor made online software system. For each question, two reviewers extracted all data independently of each other. We produced tables displaying the data extraction of both reviewers. Both reviewers checked all data independently. Any discrepancies were resolved by consensus and if no consensus could be reached, disagreements were resolved by a third independent referee. From these tables, we produced merged consensus evidence tables for informing the recommendations. The evidence tables are available from Appendix 6.

Risk of bias of the included studies was evaluated using various validated checklists, as recommended by the Cochrane Collaboration. These were AMSTAR for Systematic Reviews [4], the Cochrane Risk of Bias tool for randomised controlled trials [5], the Newcastle Ottawa scale for cohort
and case-control studies [6] and QUADAS for diagnostic test accuracy studies [7]. Data were compiled centrally by the ERBP methods support team.

6.6.4. **Evidence Profiles**

The evidence for outcomes on therapeutic interventions from included systematic reviews and randomised controlled trials was presented using the ‘Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox’ developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The evidence profiles include details of the quality assessment as well as summary – pooled or unpoold - outcome data, an absolute measure of intervention effect when appropriate and the summary of quality of evidence for each outcome. Evidence profiles were constructed by the methods support team and reviewed and confirmed with the rest of the guideline development group. Evidence profiles were constructed for research questions addressed by at least two randomised controlled trials. If the body of evidence for a particular comparison of interest consisted of only one randomised controlled trial or of solely observational data, the summary tables provided the final level of synthesis.

6.7. **Rating the Quality of the Evidence for Each Outcome across Studies**

In accordance with GRADE, the guideline development group initially categorized the quality of the evidence for each outcome as high if it originated predominantly from randomised controlled trials and low if it originated from observational data. We subsequently downgraded the quality of the evidence one or two levels if results from individual studies were at serious or very serious risk of bias, there were serious inconsistencies in the results across studies, the evidence was indirect, the data were sparse or imprecise or publication bias thought to be likely. If evidence arose from observational data, but effect sizes were large, there was evidence of a dose-response gradient, or all plausible confounding would either reduce a demonstrated effect or suggest a spurious effect when results showed no effect, we would upgrade the quality of the evidence (Table 2). Uncontrolled case-series and case-reports automatically received downgrading from ‘low’ to ‘very low’ level of evidence for risk of bias, so that no other reasons for downgrading were marked. By repeating this procedure, we would obtain an overall quality of the evidence for each outcome and each intervention. See Table 3 for the list of definitions.

6.8. **Formulating Statements and Grading Recommendations**

6.8.1. **Recommendations**

After the summary tables and evidence profiles had been prepared, revised and approved by the guideline development group, two full day plenary meetings were held to formulate and grade the recommendations. Recommendations can be for or against a certain strategy. The guideline development group drafted the recommendations based on their interpretation of the available evidence. Judgements around four key factors determined the strength of a recommendation: the balance between desirable and undesirable consequences of alternative therapeutic or diagnostic strategies, the quality of the evidence, the variability in values and preferences. We did not conduct formal decision or cost analysis. In accordance to GRADE, we classified the strength of the recommendations as strong, coded ‘1’ or weak, coded ‘2’ (Table 4, figure 1) [8]. Individual statements were made and discussed
in an attempt to reach group consensus. If we could not reach consensus, we held a formal open vote by show of hands. An arbitrary 80% had to cast a positive vote for a statement to be accepted. Voting results and reasons for disagreement were specified in the rationale when applicable.

6.8.2. Ungraded statements
We decided to use an additional category of ungraded statements for areas where formal evidence was not sought and statements were based on common sense, or expert experience alone. They were termed ‘statement’ to differentiate them from graded recommendations and do not hold an indicator for the quality of the evidence. The ungraded statements were generally written as simple declarative statements but were not meant to be stronger than level 1 or 2 recommendations.

6.8.3. Optimizing implementation
Recommendations often fail to reach implementation in clinical practice partly because of their wording[9]. Care was therefore taken to produce the evidence in clear, unambiguous wordings. Preferentially data were presented either as flowcharts with decision points, or as tables.

We also provided additional advice for clinical practice. The advice is not graded, and is only for the purpose of improving practical implementation. It contains some elaboration on one of the statements, clarifying how the statement can be implemented in clinical practice.

6.9. Writing Rationale
We collated recommendations and ungraded statements for each of the clinical questions in separate chapters structured according to a specific format. Each question resulted in one or more specific boxed statements. Within each recommendation the strength was indicated as level 1 or level 2 and the quality of the supporting evidence as A, B, C or D as prescribed by the GRADE methodology (Table 4).

These statements are followed by advice for clinical practice where relevant and the rationale of the statement. The rationale contains a brief section on ‘why this question’ with relevant background and justification of the topic, followed by a short narrative review of the evidence in ‘what did we find’ and finally a justification of how the evidence translated in the recommendations made in ‘how did we translate the evidence into the statement’.

When areas of uncertainty were identified, the guideline development group considered making suggestions for future research based on the importance to patients or the population, and on ethical and technical feasibility.

6.10. Internal and External Review
6.10.1. Internal review
A first draft of the guideline was sent to internal reviewers from the ERA-EDTA council and the ERBP advisory board. Internal reviewers were asked to comment on the statements and the rationale within free text-fields. All these comments and suggestions were discussed during an ERBP advisory board meeting, during a meeting of the ERBP Methods Support team, and during an additional teleconference meeting of the guideline development group. For each comment or suggestion, the guideline development group evaluated if it was needed to adapt the statement, again taking into account the balance between desirable and undesirable consequences of the alternative management strategies, the quality of the evidence, and the variability in values and preferences.
6.10.2. External review

The guideline was sent to the Endocrine Society of Australia (ESA), the European Society of Endocrinology, Kidney Health Australia – Caring for Australasians with Renal Impairment (KHA-CARI) and American Society of Nephrology (ASN), with the request to have the guideline evaluated by two of their members. In addition, it was send to all members of the European Renal Association – European Dialysis Transplant Association (ERA-EDTA), who received an online questionnaire in Survey Monkey format to evaluate the guideline using the AGREE evaluation. In addition, a free text field was provided to allow for additional comments. All these valid comments and suggestions were discussed with the guideline development group by e-mail, and during a final meeting of the co-chairs of the guideline development group, the methods support team and the chair of ERBP.

6.11. Timeline and Procedure for Updating the Guideline

It was decided to update the guideline at least every five years. New evidence requiring additional recommendations or changes to existing statements could instigate an earlier update. At least every five years, the ERBP methods support team will update its literature searches. Relevant studies will be identified and their data extracted using the same procedure as for the initial guideline. During a one-day meeting, the guideline development group will decide whether or not the original statements require updating. An updated version of the guideline will be published online describing the changes made. During the five-year interval, the guideline development group co-chairs will notify the ERBP chair of new information that may justify changes to the existing guideline. If the chair decides an update is needed, an update version of the guideline will be produced using the same procedures as for the initial guideline.

6.12. Funding

ERBP completely sponsored the production of this guideline, according to the statutes of ERA-EDTA and the bylaws of ERBP[10]. Activities of ERBP and its methods support team are supervised by an advisory board[10] (see www.european-renal-best-practice.org for details and declaration of interests). ERBP is an independent part of ERA-EDTA. The Council of ERA-EDTA approves and provides the annual budget based on a proposition made by the chair of ERBP. ERA-EDTA receives money and is partly funded by industrial partners, but its council is not involved with and does not interfere with question development or any other part of the guideline development process. The guideline development group did not receive any funds directly from industry to produce this guideline.
7. Chapter 1: Issues related to renal replacement modality selection in patients with diabetes and end stage renal disease
Chapter 1.1. Should patients with diabetes and CKD stage 5 start with peritoneal dialysis or haemodialysis as a first modality?

**Statements**

1.1.1 We recommend to give priority to patient condition and preference to select on option of renal replacement therapy, and this in view of the absence of evidence of superiority of one modality over the other in patients with diabetes and CKD stage 5 (1C).

1.1.2 We recommend to provide patients with unbiased information about the different available treatment options (1A).

1.1.3 In patients opting to start haemodialysis, we suggest to prefer high flux over low flux when this is available (2C).

1.1.4 We suggest diabetes has no influence on the choice between haemodialysis or haemodiafiltration (2B).

**Advice for clinical practice**

Making sure that all the different renal replacement therapy modalities (peritoneal dialysis, in centre haemodialysis, satellite haemodialysis, home haemodialysis, nocturnal dialysis, different modalities of transplantation) can be made equally available for all patients is indispensable to allow free modality choice.

**Rationale**

- **Why this question?**
  
  It is unclear whether in patients with diabetes and CKD stage 3b or higher (eGFR<45ml/min), the modality of renal replacement therapy (different modalities of haemodialysis (HD) or peritoneal dialysis (PD), or transplantation...) selected as first choice treatment may have an impact on major outcomes, metabolic profile, diabetes complications and technique survival of the replacement therapy.

- **What did we find:**
  
  To answer this question, we refer to the systematic literature review specifically performed for this guideline[11]. This systematic review included 25 from an initial 426 records retrieved through database searching. All studies but one[12] were observational. None included only patients with diabetes; the percentage of patients with diabetes ranged from 9% to 61%. The total number of patients with diabetes included was 828 573, of which 721 783 on HD and 106 790 on PD. Not enough treatment details were available to allow reliable analysis of the benefit of subcategories of
HD or PD (eg haemodialysis vs haemodiafiltration or manual vs automated PD). The overall study
quality assessed by the Newcastle-Ottawa scale was moderate to high.
Because of their observational design, none of the included studies was free from selection bias.
There was some heterogeneity in the length of follow-up among studies (from 1 to 8 years) which
may hamper the generalizability of results.
None of the reviewed studies provided data on quality of life, patient satisfaction, major and minor
morbid events, hospital admissions, deterioration of residual renal function, functional status,
glycaemic control, access to transplantation or survival of the technique. Twenty four cohort studies
analysed the risk of death. Only one cohort study considered the risk of infectious complications.
In intention-to-treat analyses (i.e. patients are assigned to their initial treatment and not to the
treatment eventually received), most studies found a survival benefit for PD over HD in the beginning
of treatment, that disappeared with length of time on treatment (supplementary data extraction
tables). The duration of this advantage varied from 6 months to 3 years after the start of dialysis,
depending on the underlying comorbidities (congestive heart failure, coronary heart disease), gender
and age of the observed cohort, region and time-period.
In “as treated” analyses (i.e. patients are considered at risk as long they are treated in the modality),
heterogeneity was even more expressed, with some studies reporting PD was associated with
improved survival in all patients [13], or only in patients under 60yrs during the first 2 years[14],
patients under 65 years[15], during the first year[16]. In patients aged over 44 years, Yeates et al.
showed a higher risk of death in patients with diabetes on PD[17]. Stack et al.[18] reported adjusted
mortality to be higher for PD patients with congestive heart failure who remained on this therapy
during the follow-up and for patients who switched compared to those who remained on HD. In the
subgroup without congestive heart failure, the mortality was similar for patients who remained
either on HD or PD but was higher for those who switched. This study is however biased by the
exclusion of patients who died in the first 90 days.
Only one small cohort study reported on infectious complications, with higher infection rates
(hospitalisation or access-related infections) being observed in PD patients with diabetes (1.28 vs
0.84 / year, p<0.004) but this difference lost its statistical significance after adjustment for albumin,
age, race and gender (RR 1.13; 95% CI 0.76-1.67)[19].
A systematic review (26 studies) on the impact of dialysis modality (centre-HD and PD) on quality of
life [20] was retrieved. The authors concluded that there was no significant difference in QOL
between HD and PD patients. PD patients tend to rate their QOL higher than HD patients. Worsening
of physical component of QOL was more marked in PD patients.
Another systematic review (52 articles) on the impact of RRT modality (HD, PD and TX) on quality of
life as assessed by the SF-36 score [21] concluded that scores of HD compared with PD patients were
not statistically different. Results are similar when restricting the analyses to articles that reported the % of patients with diabetes. A third systematic review (27 articles) based on utility measures to assess preference-based quality of life (HD, PD and TX)[22] concluded that there was no statistically significant difference in utilities between HD and PD patients. Mean quality of life tended to be higher among PD patients. A fourth systematic review (190 articles) based on utility-based quality of life (HD, PD, TX, CKD, conservative treatment)[23] concluded that there was no statistically significant difference in utilities between HD and PD patients. Mean utility estimate tended to be higher among PD patients.

We found one meta analysis on the impact of haemodialysis vs haemodiafiltration, showing no interaction for presence of diabetes [24].

• How did we translate the evidence into the statement? (Which considerations were taken into account? (GRADE)

In view of the numerous methodological pitfalls in the various observational studies, no firm conclusion can be drawn. If anything, the observed differences in survival between the different modalities seem to be small, suggesting they all can be considered "equally adequate treatments" in general terms, when applied in the current indications and with the current technology.

In view of this, the guideline development group judges that patient preference should be the driving factor for renal replacement modality choice. Therefore, the guideline group judges that availability of all different renal replacement therapy options and good, well balanced education on the different modalities, for example the Yorkshire dialysis decision aid (YODDA)(see link on website www.european-renal-best-practice.org) are essential first steps.

In patients opting for haemodialysis, it is suggested that high flux dialysis is preferred when this is available and affordable, consistent with the ERBP recommendation on the use of high flux vs low flux membranes [25].

In a recent meta-analysis of haemodiafiltration (HDF) vs haemodialysis (HD), no interaction for diabetes and HDF vs HD was observed[24]. Consequently, the choice for HD vs HDF should not be influenced by the diabetes status of the patient.

What do the other guidelines say?

We did not find other guidelines providing guidance on this area

Suggestions for future research

1/ establish and validate patient decision aids on modality selection; test whether use of these
decision aids results in improved outcomes, QoL and patient satisfaction.

2/ Analyse outcomes on PD vs HD in different subgroups such as elderly patients with diabetes, and this taking into account differences in practices in different centres and countries (e.g., impact of assisted care).

3/ Development and validation of decision-making tools for the timely transfer to HD/PD after PD/HD start.

4/ Develop and validate statistical models that can take into account modality transfers and thus allow to explore different patient trajectories rather than HD vs PD.
Chapter 1.2: Should patients with diabetes and CKD stage 5 start dialysis earlier, i.e. before becoming symptomatic, than patients without diabetes?

Statements

1.2.1. We recommend to initiate dialysis in patients with diabetes on the same criteria as in patients without diabetes (1A)

advice for clinical practice:

* Distinguishing complaints due to longstanding diabetes (polyneuropathy, gastroparesis vs nausea on uraemia etc) from uraemic complaints might be cumbersome in clinical practice
* In patients opting for haemodialysis, take into account and discuss with the patient the following factors to determine decision on and optimal timing of vascular access creation:
  1. speed of deterioration of renal function
  2. projected probability that a functioning vascular access will be achieved
  3. projected life expectancy

Rationale

• Why this question?
  We aimed to clarify whether the starting of dialysis without clinical symptoms of uraemia at a predefined fixed point of clearance may produce favourable outcomes in patients with diabetes as compared to waiting to start renal replacement until patients do have uraemic complaints (as is recommended for patients without diabetes [26, 27]).

• What did we find?
  We found twelve papers reporting eleven studies on the association between some form of early vs. late start of dialysis and survival/mortality on dialysis. One study was a randomized controlled trial, three studies were prospective cohorts and the remaining studies were retrospective cohorts. The RCT was the IDEAL study by Cooper et al.[28], which was performed in 828 patients in Australia and New Zealand. Although initially patients randomized to late start were to start dialysis between 5-7mL/min/1.73m$^2$ of creatinine clearance as estimated by Cockcroft and Gault (eGFR$_{CG}$), and the early start group was supposed to start between 10 and 14 ml/min/1.73m$^2$, in reality eGFR$_{CG}$ at start of dialysis was 9.8 and 12.0 ml/min/1.73m$^2$ in the late and early start group, respectively. So, the difference in eGFR$_{CG}$ at start of dialysis was only 2.2 ml/min/1.73m$^2$. This difference did not appear to result in a change in survival between early and late start. However, patients in the late start group started on average six months later than patients in the early start group. The IDEAL study provided a subgroup analysis for the 34% of patients with diabetes and in those patients there was also no difference in survival between early and late start of dialysis in patients with diabetes.
  There were three prospective studies. Contreras-Velazquez et al [29] performed a study in 98 patients
with the aim to identify peritoneal anatomical changes in incident PD patients, their role in peritoneal permeability, technique failure, and mortality on PD. There was no data on the subgroup of 24% PD patients with diabetes. Tang et al.[30] performed a prospective cohort study in 233 Asian patients. The comparison was between patients that accepted PD and were immediately started and patients that declined PD and were followed up on the low clearance clinic. Again there were no separate data provided on the subgroup of patients with diabetes.

The remaining studies were all retrospective cohort studies. Chandna et al.[31] compared survival in patients whose start of dialysis was planned (n=163) versus survival in patients in whom start of dialysis was unplanned (n=129). A comparison in survival between patients with (n=59) versus without diabetes (n=229) was presented, showing no difference between the two groups, but no separate results for patients with diabetes were presented. Only in 25% of patients with diabetes dialysis was unplanned versus 49% in patients without diabetes, indicating that the comparison of planned vs. unplanned dialysis is maybe different in patients with vs without diabetes. Lastly, planned versus unplanned start of dialysis can probably not be considered the same as early vs. late start of dialysis.

Coronel et al.[32] compared survival in 100 patients with diabetes that started PD either below or equal and higher to 7.7 ml/min/1.73m², finding that starting early (i.e. ≥ 7.7 ml/min/1.73m²) was significantly associated with better survival at 3 years (61% vs. 39%). However, this is an observational retrospective study, and patients who started at an eGFR below 7.7 ml/min/1.73m² were not comparable to patients who start at higher levels. Kazmi et al [33] studied the effect of comorbidity on the association between eGFR at start of dialysis and survival on dialysis in more than three hundred thousand people in the United States. They found that the higher levels of eGFR at the start of dialysis were associated with significantly worse survival on dialysis, even after adjustment for comorbidity. However, there was no formal subgroup analysis in patients with diabetes alone. Lassalle et al [34] analyzed more than eleven thousand patients in the French REIN registry, looking at the association between eGFR at start of dialysis and survival on dialysis with extensive adjusting for confounders. Results showed that, even after adjustment, higher eGFR levels at the start of dialysis were associated with poor survival on dialysis. Traynor et al [35] studied the effect of lead-time bias in 235 European patients by calculating when these patients reached eGFR=20ml/min/1.73m² and using this point as the start of follow-up. They demonstrated that lead-time bias can partly explain the effect between eGFR at the start of dialysis and survival on dialysis. Higher levels of eGFR at the start of dialysis were associated with poor survival on dialysis, but there was no formal subgroup analysis in patients with diabetes. Wright et al [36] also studied the effect of early and late start of dialysis on survival on dialysis in almost nine hundred thousand patients in the United States. They also showed that higher levels of eGFR at the start of dialysis are associated with
poor survival on dialysis. In the subgroup analysis in patients with diabetes they showed a similar result. Beddu et al.[37] also investigated timing of start of dialysis, modeled as renal function at the start of dialysis in a continuous fashion, in incident hemo- and peritoneal dialysis patients. They found that every increase in eGFR (MDRD) at baseline with 5 ml/min led to a 14% increased risk of dying on dialysis (HR=1.15 (1.06-1.14)). Hwang et al.[38] demonstrated that there was a dose-response relation between the level of eGFR at the start of dialysis and risk of mortality on dialysis, even after adjustment for potential confounders (Q1 as reference: Q2: HR\textsubscript{Adj} = 1.18 (95% CI: 1.01-1.37), Q3: HR\textsubscript{Adj} = 1.21 (95% CI: 1.04-1.41), Q4: HR\textsubscript{Adj} = 1.66 (95% CI: 1.43-1.93), and Q5: HR\textsubscript{Adj} = 2.44 (95% CI: 2.11-2.81). Clark et al.[39] found that 8,441 patients in the CORR cohort who started dialysis early (eGFR (MDRD) > 10.5 ml/min) had 18% more risk of dying on dialysis (HR=1.18 (95% CI: 1.13-1.23) compared to late start of dialysis (eGFR (MDRD) ≤ 10.5 ml/min) in 17,469 incident haemodialysis patients. Jain et al.[40] did not detect a survival difference between patients starting dialysis early (n=2,994) (eGFR (MDRD) > 10.5 ml/min) (HR=1.08 (95% CI 0.96-1.23)) mid-start of dialysis (n=2,670) (eGFR (MDRD) 7.5-10.5) (HR= 0.96 (95% CI 0.86-1.09)) versus late (eGFR (MDRD) < 7.5 ml/min).

For all these studies, it is likely that remaining confounding induced by the use of estimated rather than measured GFR explains the worse outcome of start at higher eGFR. Indeed, eGFR is based on creatinine, which itself is negatively impacted by malnutrition and poor food intake, and is diluted by fluid overload. Both these conditions will result in an overestimation of true GFR by eGFR, and also result in worse outcomes.

**How did we translate the evidence into the statement? (Which considerations were taken into account? -GRADE)**

Based on one randomised controlled trial, there appears to be no evidence to support the hypothesis that in patients with diabetes, start of dialysis based on predefined levels of eGFR before they become symptomatic vs when they become symptomatic is of any benefit in terms of mortality or quality of life. As such, the same recommendations as made previously by ERBP[26] for the general CKD5 population can be maintained for CKD5 patients with diabetes. In patients with diabetes, it might be cumbersome to distinguish whether polyneuropathy, nausea, concentration disturbances, sleepiness are to be attributed as "uraemic" or as "diabetes related" symptoms. To the knowledge of the guideline development group, there are no strict and clear criteria that can be forwarded to assist making this distinction. Therefore, it can be that in reality, patients with diabetes start at somewhat higher eGFR levels as compared to patients without diabetes. Although this was already mentioned in the original guidance published by ERBP[26] after publication of the IDEAL trial, (guideline 1.3: High-risk patients e.g. with diabetes and those whose renal...
function is deteriorating more rapidly than eGFR 4 mL/min/year require particularly close supervision. Where close supervision is not feasible and in patients whose uraemic symptoms may be difficult to detect, a planned start to dialysis while still asymptomatic may be preferred, the re-assessment in the current guidance production process, makes clear that there is no reason to start patients with diabetes at higher levels of eGFR just because they have diabetes, but only (as for those without diabetes) because they are symptomatic. The new statement abolishes eventual ambiguity arising from the original statements, and should be seen as an addition to them.

The guideline development group also wants to stress that in the IDEAL trial, all patients had been followed by a nephrology centre for a substantial period of time, and most had a functioning access in place at start of renal replacement therapy. Therefore, discussion of the different renal replacement modalities and selection of a preferred dialysis modality in a shared decision making process should be started timely.

As creation of vascular access might be problematic, and as maturation failure might be prevalent in patients with diabetes, the guideline group judges that it is advisable to timely discuss, in patients opting for haemodialysis, the creation of a vascular access. In this discussion, the speed of deterioration of renal function should be taken into account, as not all patients might be progressive. Also the general condition of the patient, and the likelihood of death before ESRD rather than evolution to ESRD should be evaluated.

What do the other guidelines say
We did not find other guidelines providing guidance on this topic

Suggestions for future research
1/ develop and validate clinical/biochemical scores to distinguish uraemic and diabetes related complaints.
Chapter 1.3: In patients with diabetes and CKD stage 5, should a native fistula, a graft or a tunnelled catheter be preferred as initial access?

<table>
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<tr>
<th>Statements</th>
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<tbody>
<tr>
<td>1.3.1 We recommend reasonable effort is done to avoid tunnelled catheters as primary access in patients with diabetes starting haemodialysis as renal replacement therapy (1C)</td>
</tr>
<tr>
<td>1.3.2 We recommend that the advantages, disadvantages and risks of each type of access are discussed with the patient.</td>
</tr>
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</table>

Advice for clinical practice:
- when deciding to create a native vascular access or not, the following points should be considered:
  - expected life expectancy of the patient
  - expected quality of life of the patient
  - probability of success of native access creation, as predicted based on ultrasound and Doppler results (figure 2).

Rationale

- Why this question?
  From observational trials, it is clear that haemodialysis patients with a native vascular access have a better outcome as compared to those starting with a catheter. However, "not having a native fistula" can be a marker of severity of disease, especially in patients who also have diabetes. In addition, in patients with diabetes, creation of vascular access, and especially at the more distal parts of the arm, can be cumbersome in view of presence of vascular disease. This might result in repetitive attempts to create native vascular access without clinical success.

It is important to clarify the most advisable strategy of vascular access planning (type of vascular access (central venous catheter (CVC) or arteriovenous fistula (AVF) or graft (AVG) and position) in this patient group, and define whether, and to what extent, it should be different from patients without diabetes.

- What did we find?
  The full results of this systematic review are published in a separate document[41]. In this systematic review, we identified 262 records, of which 213 were excluded based on title and abstract. As a result, 49 full-text articles were accessed and evaluated, resulting in a further exclusion of 36 articles. So, finally, 13 studies were included in the data extraction table: 2 prospective cohort studies, but which dated from an older era [42, 43], 10 retrospective cohort studies [44-52] and 1 case-control study [53]. We did not retrieve any randomized clinical trial.

We also included one systematic review on the topic of vascular access in the general dialysis population[54], starting from the hypothesis that, if any difference at all exists with the population
without diabetes, it was most likely that success of vascular access will be worse in patients with diabetes. This systematic review identified 3965 citations, of which 67 (62 cohort studies comprising 586,337 participants) were data extracted. In a random-effects meta-analysis, compared with persons with fistulas, those individuals using catheters had higher risks for all-cause mortality (risk ratio=1.53, 95% CI=1.41–1.67), fatal infections (2.12, 1.79–2.52), and cardiovascular events (1.38, 1.24–1.54). Similarly, compared with persons with grafts, those individuals using catheters had higher odds of mortality (1.38, 1.25–1.52), fatal infections (1.49, 1.15–1.93), and cardiovascular events (1.26, 1.11–1.43). Compared with persons with fistulas, those individuals with grafts had increased all-cause mortality (1.18, 1.09–1.27) and fatal infection (1.36, 1.17–1.58), but no higher risk for cardiovascular events (1.07, 0.95–1.21). The authors note that the risk for selection bias was high in all studies.

Patient survival:
In a retrospective cohort study of incident, >65year-old, HD patients (total N=764, 200 patients with diabetes), Chan et al.[44] reported a similar mortality rate and vascular access patency among patients with AVF vs AVG. Dhingra et al.[46] reported in a retrospective cohort study of incident and prevalent HD patients (total N= 5189 patients, 31% with diabetes) that all-cause and CV mortality was higher in CVC vs. AVF and all-cause and infection mortality was higher in AVG vs. AVF. In a prospective single centre cohort study including incident and prevalent HD patients (total N= 218, 63 with diabetes), Saxena et al [43] reported a lower rate of vascular access-related sepsis among patients with AVF compared to those with AVG or dialysis catheter; patients with femoral catheters presented a higher sepsis-related mortality in comparison to those with AVF and AVG.

Survival of the access:
In a retrospective single centre cohort study including ESRD patients who underwent proximal AVF creation (total N=293, 68 with diabetes ) Murphy et al [50] reported apparently similar results for age and better results in males vs females, but no statistical significance was reported. Field et al.[47] reported a better survival of proximal versus distal AVF in patients with diabetes in a retrospective single-centre cohort study including 289 incident HD patients (103 with diabetes,36%), but also here no statistical significance was reported. In a prospective single centre cohort study including 197 incident HD patients (43 with diabetes, 22%) who underwent AVF creation by nephrologists[42], similar cumulative patency rates between distal versus proximal AVF were observed. Konner et al. [49] reported in their retrospective single centre cohort study (total 247 patients, 78 with diabetes (22.5%)) a higher mortality and lower primary patency rate in patients with diabetes; no separate data were provided amongst patients with diabetes for distal vs. proximal AVF. Also, a lower primary
patency rate in non-perforating proximal AVF versus perforating proximal AVF and distal AVF was reported; the cumulative patency rates among the three study groups was similar but thrombosis rate was lower among those with a proximal perforating AVF. This study has a high risk of selection bias, and all procedures were performed by one expert. Hammes et al. [48] reported in a retrospective single centre cohort study (total N= 127, 52 with diabetes) that patients with vs without diabetes had lower prevalence of cephalic arch stenosis, but the interpretation of these data is cumbersome, as there is a high risk of indication bias. Diehm et al. [52] found lower patency rates in a retrospective single-centre cohort study (total N= 244, 62 with diabetes) in patients with diabetes, and this using a mixture of different AV fistula types. Yeager et al[53] report the risk factors associated with finger gangrene after placement of an AV fistula in a case-control single-centre study (total 222 patients, 121 with diabetes (54%)): diabetes, peripheral and coronary artery disease and age less than 55 years at the start of dialysis.

While awaiting a formal systematic literature review and guidance from the update of the EBPG guideline on vascular access from 2007, we used recent updates of the CARI guideline[55] to support technical details of vascular access creation.

- **How did we translate the evidence into the statement?**

There has been a general awareness in the nephrology community of the too high rates of prevalent dialysis patients on catheters. Over the last years, there was a general consensus that efforts should be made to reduce these high rates, as from different large observational studies [54], there was a clear link between catheter use and higher mortality and infection rates. Based on this consensus, several initiatives, e.g. "the fistula first" initiative, have been launched, and some countries even linked reimbursement to vascular access type. Whereas these initiatives were successful in increasing the percentage of prevalent patients dialysing with a native fistula, it became clear that this growth was lower than expected, and came at the expense of enormous efforts and costs for the society and suffering for the patient[56-58]. The major underlying explanation appears to be that there is selection bias in the observational trials because of the association between (cardiovascular) status and the propensity to have a functioning fistula. Although the evidence is scanty, creation of vascular access is more cumbersome and results more often in non-maturation in patients with vs without diabetes, and this particularly in women and in the elderly. Factors predicting non-maturation in the general dialysis population, such as the diameter of the feeding artery < 2mm and/or of the draining vein <2.5mm, or absence of flow increase with fist exercise, should certainly raise concern on the probability that a functioning access can be created in such a patient[55]. In addition, life expectancy in some patients is low, and protracted and persisting efforts to create vascular access might cause a
substantial decrease in quality of life, without adding any substantial benefit (figure 2).

**What do the other guidelines say?**
No guideline provides specific recommendations for patients with diabetes. KDOQI, CARI, CSN and UK-RA all recommend to use a native fistula as preferred access, when feasible. Three of them recommend to try placing a graft rather than a tunnelled catheter in case a native fistula is deemed not possible. In their respective discussions, they all highlight that creation of native vascular access might be more problematic in patients with vs without diabetes.

**Suggestions for future research**
1/ detailed observational studies to associate practices concerning vascular access creation with outcomes, and this using advanced statistical techniques to adjust for comorbidities such as age, gender, diabetes status, cardiovascular disease and for surgical technique.
2/ based on the above, randomised controlled trials should be designed to explore potential hypotheses.
chapter 1.4 Is there a benefit to undergo renal transplantation for patients with diabetes and CKD stage 5?

1.4.1 We recommend education on the different options of transplantation and their expected outcomes for patients with diabetes and CKD stage 4 or 5 and who are deemed suitable for transplantation (see table)(1D)

**Statements only for patients with type 1 diabetes**
1.4.2 We suggest living donation kidney transplantation or simultaneous pancreas kidney transplantation to improve survival of suitable patients with type 1 diabetes and CKD Stage 5 (2C).
1.4.3 We suggest against islet transplantation after kidney transplantation with the aim to improve survival (2C).
1.4.4 We suggest pancreas grafting to improve survival after kidney transplantation (2C).

**Statements only for patients with type 2 diabetes**
1.4.5 We recommend against pancreas or simultaneous kidney pancreas transplantation (1D)
1.4.6 We recommend diabetes per se should not be considered a contra-indication to kidney transplantation in patients who otherwise comply with in and exclusion criteria for transplantation. (1C)

**advice for clinical practice:**
- Successful simultaneous pancreas kidney transplantation improves quality of life, neuropathy, glycaemic control and diabetic retinopathy in type 1 diabetes (ungraded statement).
- Take into account that peri-operative comorbidity of simultaneous pancreas kidney transplantation can be substantial (ungraded statement)
- We refer to the ERBP guideline[59] on kidney transplant donor and recipient evaluation and peri-operative management to decide whether or not a patient is deemed suitable for transplantation.

**Rationale**
- **Why this question?**
The guideline development group wants to provide a recommendation on whether transplantation is a viable option in patients with diabetes, and whether some subgroups or some types of transplantation (cadaveric kidney, living donor kidney, simultaneous pancreas kidney, pancreas after kidney) might be preferred. The answer to this question is however hampered by the fact that only observational data are available, and that accordingly, selection bias might potentially blur the interpretation of what we find in the literature. As such, having an idea whether there is selection bias to accept only the most optimal patients with diabetes for waitlisting for transplantation might be important in the later interpretation of the observational data. This analysis, together with the analysis of the outcome of transplantation, can help us to formulate an advise whether we should promote more transplantation in patients with diabetes, or rather refrain from doing so.
Patients with diabetes and CKD stage 3b or higher (eGFR<45ml/min) mostly have complex comorbidity. In the post-transplantation period, immuno-suppressive medication can deteriorate their glycaemic control and worsen already existing vascular comorbidity. On the other hand, survival and QoL when remaining on dialysis might also be grim. Therefore, we need to ascertain whether patients with diabetes benefit from kidney transplantation, in terms of major outcomes. It is also important to elucidate whether a specific type of transplantation has better outcomes over another.

- **What did we find?**

We retrieved 12 studies allowing to evaluate a potential selection bias for patients to be waitlisted for transplantation (supplementary data extraction tables). Most studies are consistent with the hypothesis that patients with vs without diabetes have a lower probability to be waitlisted. Most guidelines recommend more extensive screening in patients with diabetes [59-61]

No randomised controlled data for any form of transplantation in patients with diabetes and CKD stage 5 were identified.

We found 21 papers exclusively reporting observational data. After reading the full papers and manually searching the references therein, and from personal knowledge of the literature, 8 additional studies were added to the data extraction table. The majority of the studies suffers from methodological limitations and are at high risk of different forms of bias. The studies reporting on hard end points (mortality/graft outcome) were mostly large registry-based patient populations. Some reported single-centre data[62, 63] [64-67] [68] with a high potential of centre bias. Some registry studies did not discriminate between type 1 or type 2 diabetes in their evaluation of outcome of transplantation vs. remaining on dialysis[69] or in the outcome of a pancreas graft[62]. Most importantly, most studies suffer especially from a high risk of selection bias as patients remaining on the waiting list might have different characteristics from those actually transplanted (such as non-compliance, smoking, increased cardiovascular comorbidity, or high immunization) which can affect their outcome and which mostly is not accounted for in the survival analysis.

Only few studies focus on the outcome after kidney transplantation stratified according to diabetes status[70-72], whereby the adjusted mortality risk is higher in patients with versus without diabetes, although the risk difference is apparently steadily getting smaller because of a reduction of cardiac events and infectious deaths[72, 73]. Patient survival is better after transplantation in CKD stage 5 patients with diabetes versus those remaining on the waiting list[69, 72].

The studies dealing with the different options for **type 1 diabetes** are summarized in table 5. This table intends to help physicians to discuss the different options and their pro/cons with the patient
to support shared decision making. Patients receiving pancreas after kidney transplantation had better graft survival vs as compared to those who were eligible but did not receive a pancreas graft or only after a long-term period (>5 year). Other analyses have demonstrated superior outcome of pancreas transplantation after Living Donor Kidney vs. Simultaneous Pancreas Kidney [74]. The survival benefit of Simultaneous Pancreas Kidney over kidney transplantation alone in patients with type 1 is not consistent and also depends on the modality of kidney transplantation (cadaveric vs. living), the time point of assessment, and the adjustment for confounders. Changes in patient selection criteria, donor criteria, surgical and immunosuppressive treatment can also explain changes in outcome according to time period[67]. Early survival benefit in Simultaneous Pancreas Kidney vs. Kidney Transplant Alone often is not observed with even increases in early post-transplantation mortality[75]. Long term outcome is in most, but not all, studies better with Simultaneous Pancreas Kidney than with kidney transplantation alone[64, 66-68, 75]. In an older UNOS analysis, Simultaneous Pancreas Kidney recipients had a higher mortality hazard than living donor kidney recipients through the first 18 months post-transplantation, but they had a lower relative hazard thereafter thereafter[76]. In the univariate survival analysis, no difference in outcome for patient and graft[77] was observed between patients receiving a Simultaneous Pancreas Kidney vs a living donation kidney alone. In contrast, long-term patient and graft survival in the multivariate model was inferior in the Simultaneous Pancreas Kidney versus the living donation kidney group. Longer term survival is reported to be superior with Simultaneous Pancreas Kidney vs solitary renal transplantation in other studies[78, 79]. Pancreas graft failure the first year seems to attenuate or even abolish the beneficial long-term effects of SPK vs. kidney transplantation alone[80] as it decreases both graft and patient survival[81], and also having preserved kidney graft function at year one seems to be an important modulating factor [76].

Analyses of quality of life or intermediate endpoints such as neuropathy[82], retinopathy [83] or cardiovascular surrogate markers [84-86] without exception have small patient numbers and/or are unadjusted for confounders [82, 84, 85, 87-91]. They compare different patient populations (for instance Simultaneous Pancreas Kidney with failed vs. functioning pancreas graft)[88, 91] with –in the quality of life studies- numerous and not always consistent use of valid assessments of physical state, cognitive functioning and mental health. Comparing quality of life of patients receiving Simultaneous Pancreas Kidney with that of patients losing or refusing their pancreatic graft [88] might overestimate the differences in perceived quality of life between the groups.

- How did we translate this into the statement?

Only observational data are available to support guidance in this area. There is a high risk for selection bias in the observational data, as the access to the waiting list is
hampered for patients with diabetes. This is consistent with the observation that most guidelines recommend more intense screening, especially for cardiovascular disease [59], in patients with diabetes. As a result, it should be taken into account that for patients with diabetes the outcome results observed after transplantation are only valid for those without substantial comorbidity, i.e. who have passed our current pre-transplant screening procedures [59]. For this type of patients with type 2 diabetes, the presence of diabetes appears to be no additional risk factor per se; as a consequence, the guideline development group judged that diabetes per se should not be a contraindication for transplantation, provided patient complies with current pre-transplant screening recommendations.

The same risk of selection bias might be at play in the observed results of simultaneous pancreas kidney transplantation for patients with type 1 diabetes. Simultaneous pancreas kidney is mostly performed at high-volume centres, and this most likely affects generalizability of outcomes by referral bias. The healthiest patients are also likely to be allocated to simultaneous pancreas kidney, receive the highest quality organs [92] and get more often a pre-emptive transplant [66].

A potential decision flow chart for transplantation modality selection in patients with type 1 diabetes is provided in figure 3. When a living donor is available, the guideline development group judges that pre-emptive living donation should be preferred, as it increases the donor pool, and the results are not inferior to simultaneous pancreas kidney transplantation. If no living donor is available, a simultaneous pancreas kidney transplant should be preferred, provided the patient is considered fit enough to survive the increased peri-operative risk.

What do the other guidelines say?
We did not find any guidelines providing guidance on this topic

Suggestions for future research
1/ Detailed prospective multicenter observational studies with assessment of hard endpoints after living donor kidney transplantation for subjects with diabetes type 1 versus Simultaneous Pancreas Kidney with appropriate adjustment for comorbidity.
2/ Prospective, adequately powered multicenter studies to assess the effect of transplantation (vs. remaining on the waiting list) in patients with type 1 or 2 diabetes on prespecified (surrogate) endpoints, such as cardiovascular events, vascular stiffness, intima media thickness and retinopathy
8. Chapter 2: Issues related to glycaemic control in patients with diabetes and CKD stage 3b or higher (eGFR<45ml/min)
Chapter 2.1.

A. Should we aim to lower HbA1C by more tight glycaemic control in patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min).

B. Is an aggressive treatment strategy (in number of injections and controls and follow up) superior to a more relaxed treatment strategy in patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min) and using insulin

<table>
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<th>Statements</th>
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<tbody>
<tr>
<td>2.1.1 We recommend against more tight glycaemic control if this results in or increases the risk for severe hypoglycaemic episodes (1B)</td>
</tr>
<tr>
<td>2.1.2 We recommend vigilant attempts to tighten glycaemic control with the intention to lower HbA1C when values are &gt;8.5% (69 mmol/mol) (1C)</td>
</tr>
<tr>
<td>2.1.3 We suggest vigilant attempts to tighten glycaemic control with the intention to lower HbA1C according to the flow chart in figure 4 in all other conditions (2D)</td>
</tr>
<tr>
<td>2.1.4 We recommend intense self monitoring only to avoid hypoglycaemia in patients at high risk for hypoglycaemia (2D)</td>
</tr>
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Advice for clinical practice

- Severity of hypoglycaemic episodes are defined as follows:
  - Grade 1: its existence can be detected biochemically but it does not produce symptoms.
  - Grade 2: produces only mild symptoms and can be easily treated by the affected person.
  - Grade 3: produces more severe symptoms and requires the assistance of another person.
  - Grade 4: very severe, producing unconsciousness, coma and/or convulsions and requiring emergency treatment in hospital.

- The most important concern is to avoid episodes of hypoglycaemia.
- Empower patients at risk for hypoglycaemia to perform regular follow up of blood glucose level by using validated point of care devices.
- Patients and conditions at low, moderate and high risk for hypoglycaemic episodes are depicted in figure 5

Rationale

- Why this question?

It is unclear whether in this specific patient cohort, aiming at a lower HbA1C value by tightening glycaemic control results in improved outcomes, in terms of mortality and morbidity. There is some concern that excess mortality and morbidity can be induced by increasing the risk for (severe) hypoglycaemia.

It is unclear whether maintaining or promoting intensive glucose control by regular auto-control, more regular follow-up visits and educational or patient empowerment programs helps to decrease diabetes specific complications in this specific patient population. These programs are labour
intensive and expensive and have thus an important impact on health care resources.

**What did we find?**

We found one recent systematic review in (haemo)dialysis patients[93] on the association between HbA1C and outcome that included 10 studies (83,684 participants) (9 observational studies and one secondary analysis of a randomized trial). After adjustment for confounders, patients with baseline HbA1c levels >69 mmol/mol (8.5%) vs 48-57 mmol/mol (6.5-7.4%) had increased mortality (HR, 1.14; 95% CI, 1.09-1.19). Likewise, patients with a mean HbA1c value >69mmol/l (8.5%) had a higher adjusted risk of mortality (HR,1.29; 95% CI, 1.23-1.35). In incident patients, mean HbA1c levels <36mmol/mol (5.4%) also were associated with increased mortality risk (HR, 1.29; 95% CI, 1.23-1.35). A recent randomised trial demonstrated that adding saxagliptin to existing treatment, resulted in a decrease of HbA1C and a higher percentage of patients reaching a HbA1C<7%, but not in an improvement in cardiovascular outcomes[94].

We did not retrieve any other data collected specifically in patients with diabetes and with CKD stage 3b or higher (eGFR<45ml/min). Effort was done to extract data specifically on patients with diabetes and CKD stage 3b or higher (eGFR<45ml/min) in general diabetes studies, but this was hampered by the fact that in most studies, presence of CKD 3B or higher (eGFR<45ml/min) is an exclusion criterion, or data were not reported separately for patients with CKD stage 3b or higher (eGFR<45ml/min).

A high quality systematic review demonstrated lack of benefit of more tight glycaemic control <7 (53 mmol/mol) or 7.5 % (59 mmol/mol) [95], whereas there was a clear risk for enhanced hypoglycaemia episodes when glycaemic control is tightened[95].

We found one high quality systematic review assessing the effectiveness of self-monitoring blood glucose levels in people with non-insulin treated type 2 diabetes compared with clinical management without self monitoring[96]. Although there was an improvement in HbA1C levels in the self-monitoring group (-2.7mmol/mol), there was no convincing clinically meaningful effect.

**How did we translate the evidence into the statement? (which considerations were taken into account? -GRADE)**

As data in our target population (patients with diabetes and CKD stage 3b or higher) are scant, the guideline group considered a two tiered approach: 1/ evaluate the available evidence in the general population with diabetes; 2/ evaluate which considerations made our target population special in this regard, and would impact on translation of the data from the general diabetes population.
In the general population, tight glycaemic control does not result in improvement of all cause and cardiovascular mortality, but results in an increased risk for hypoglycaemia. As in CKD stage 3b or higher (eGFR<45ml/min), the risk of hypoglycaemia is enhanced, and the survival benefit is probably lower due to the general lower life expectancy, tight HbA1C control is probably even less relevant in this patient cohort. On the other hand, observational data show that lower HbA1C is associated with better outcome, so at least one should (cautiously) try to lower HbA1C, if this can be obtained without increasing the risk for hypoglycaemia.

Therefore, the guideline development group judged that a balanced approach, taking into account the specific condition of the individual patient, should be recommended (see figure 4).

Under these conditions, an intense self monitoring with the sole aim to attain lower glycaemic values is difficult to defend, as it is linked with uncertain benefit. In addition, using intense self-monitoring did not result in an improvement of HbA1C values, and accordingly, self-monitoring can thus not be recommended if the only aim is to reduce HbA1C. However, in patients at risk for hypoglycaemia (figure 5), i.e. mostly those taking active medication with a high risk of hypoglycaemia, e.g. insulin, regular monitoring should be performed to avoid overshooting and hypoglycaemia.

- **What do other guidelines say?**

  No guideline specifically targets patients with diabetes and chronic kidney disease stage 3b or higher (eGFR<45ml/min).

  In their 2012 position statement[97], the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) also promote to take into account individual patient characteristics to determine the most optimal level of glycaemic control.

  In their 2012 update of their clinical practice guideline on diabetes and chronic kidney disease, KDOQI[98] recommends a target hemoglobin A1c (HbA1c) of around 7.0% to prevent or delay progression of the micro-vascular complications of diabetes, including Diabetic Kidney Disease; they further recommend not treating to an HbA1c target of <7.0% in patients at risk of hypoglycemia, and suggest that the target HbA1c can be extended above 7.0% in individuals with co-morbidities or limited life expectancy and risk of hypoglycaemia. In their rationale, they explain that the risk for hypoglycaemia outweighs the potential benefits of reduced micro-vascular complications in patients with advanced stages of chronic kidney disease.

- **Suggestions for further research:**

  1/ Evaluate whether it is glycaemic variability and specifically hypoglycaemia that contributes to
cardiovascular risk, rather than average blood glucose level

2/ A study of intensive control vs. standard control (HbA1c <53mmol/mol vs <69mmol/mol) specifically in patients with diabetes and chronic kidney disease stage 3b or higher is warranted, and this specifically using drugs with low hypoglycaemia risk.
Chapter 2.2.
Are there better alternatives than HbA1c to estimate glycaemic control in patients with diabetes and chronic kidney disease stage 3b or higher (eGFR <45 mL/min/1.73m²)?

Statements:

2.2.1 We recommend the use of HbA1C as a routine reference to assess longer term glycaemic control in patients with CKD stage 3b or higher (eGFR<45ml/min/1.73m²) (1C)

Advice for clinical practice:

- Continuous glucose measurement devices can be considered in high risk patients in whom a very tight control of glycaemia is deemed of benefit.
- The association between HbA1C and longer term glycaemic control might be different in patients with vs without chronic kidney disease stage 3b or higher (eGFR<45ml/min), and this both for the absolute value as for the slope of the association curve.
- The following factors are potentially associated with a lower than expected HbA1C:
  - decreased red blood cell survival
  - increased red blood cell formation (use of iron, RhuEpo)
- The following factors are potentially associated with a higher than expected HbA1C:
  - accumulation of uraemic toxins

Rationale

- **Why this question?:**
  
  Although in many countries measurement of HbA1c is the cornerstone for diagnosis and management of diabetes mellitus in routine clinical practice, the role of this biomarker in reflecting long-term glycaemic control in patients with chronic kidney disease stage 3b or higher (eGFR<45ml/min) has been questioned. As a different association between glycaemic control and morbidity/mortality might be observed in patients with and without chronic kidney disease stage 3b or higher (eGFR<45ml/min), we wanted to summarise the current knowledge and evidence of the use of HbA1C and of alternative glycaemic markers (glycated albumin, fructosamine, 1.5-anhydroglucitol and continuous glucose monitoring) in this specific patient population.

- **What did we find?**
  
  The guideline development group conducted a narrative review[99] to explore different methods to assess longer term glycaemic control, and their accuracy in patients with chronic kidney disease stage 3b or higher (eGFR<45ml/min). The findings are summarized in table 6.
• How did we translate this into the statements?
Due to the availability of relatively inexpensive and routinely measured HbA1c assays and the inconsistent or limited data to prove superiority of other glycaemic markers (glycated albumin, fructosamine, 1,5-AG and continuous glucose monitoring) at this moment, the guideline development group judges that HbA1c remains the reference standard for glycaemic monitoring in patients with diabetes and CKD stage 3b or higher (eGFR<45ml/min).
In the future, continuous subcutaneous glucose monitoring seems to be a promising method to correctly evaluate glycaemic control in patients with diabetes undergoing haemodialysis and in whom more intense glycaemic control is judged to be of relevance.

What do the other guidelines say
None of the other guidelines provides guidance in this area for this specific patient group of patients with diabetes and CKD stage 3b or higher.

Suggestions for future research
1. Prospective studies testing pre-specified diabetes control targets based on glycated albumin and continuous glucose measurements in order to determine whether morbidity and mortality would be reduced with intensive glycaemic control using these measurements as reference target, and this specifically in patients with diabetes and chronic kidney disease stage 3b or higher (eGFR<45ml/min).
2. Evaluate the role, if any, of continuous glucose monitoring systems for determining therapeutic adjustments for patients with diabetes treated with renal replacement therapy.
Chapter 2.3.
A. Is any oral drug superior to another in terms of mortality/complications/glycaemic control in patients with diabetes type 2 and with chronic kidney disease stage 3b or higher (eGFR <45 mL/min/1.73m²)?
B. In patients with diabetes type 2 and chronic kidney disease stage 3b or higher (eGFR <45 mL/min/1.73m²), is maximal oral therapy better than starting/adding insulin in an earlier stage?

Statements

2.3.1 We recommend metformin in a dose adapted to renal function as a first line agent when lifestyle measures alone are insufficient to get HbA1C in the desired range according to figure 4(1B)

2.3.2 We recommend to add on a drug with a low risk for hypoglycaemia (fig 5, 6 and 7) as an additional agent when improvement of glycaemic control is deemed appropriate according to figure 4 (1B)

2.3.3 We recommend instructing patients to temporarily withdraw metformin in conditions of pending dehydration, when undergoing contrast media investigations, or when there is a risk for AKI (1C)

advice for clinical practice
- Consider to instruct patients by using credit-card type flyers on when to temporarily withdraw metformin.
- Conditions considered as low, moderate or high risk for hypoglycaemia are depicted in figure 5
- Hypoglycaemia risk for different drugs is presented in figure 5 and figure 7
- in patients with diabetes type 2 and CKD stage 3b or higher (eGFR <45ml/min) who are on metformin, the decision to withhold the drug 48 hours before and after administration of contrast media should be taken by the treating physician, balancing the probability of emergence of contrast induced nephropathy (type and amount of contrast, intravenous vs intra-arterial), and presence of other co-existing factors that might cause sudden deterioration of kidney function (dehydration, use of NSAID, use of inhibitors of the RAAS system) against the potential harms by stopping the drug (which should be considered low in view of the short period that it should be withheld).
- As renal clearances of different glycaemia lowering agents might differ, combining different glycaemia lowering drugs in a one pill formulation can lead to overdosing of one of the constituents in patients with CKD stage 3b or higher.

Rationale

- Why this question?
The achievement of a good glycaemic control is postulated to be one of the cornerstones for preventing and delaying progression of micro-vascular and macro-vascular complications in patients with both diabetes and chronic kidney disease. New research suggests that commonly prescribed drugs for type 2 diabetes may not all be equally effective at preventing death and cardiovascular diseases, such as heart attacks and stroke.

Each drug category has unique advantages and disadvantages and with this question we aim to place them into the context of rational, evidence based therapeutic strategies. This question also specifically addresses whether adding another oral hypoglycaemic therapy provides a better
efficacy/safety profile rather than starting/adding insulin, and whether specific types of drugs should be preferred to others.

- **What did we find?**

  We did not retrieve any randomised controlled trial evaluating our question on superiority of one drug over the other in the specific population of patients with diabetes and CKD stage 3b or higher (eGFR<45ml/min). Some drugs need dose adaptation when administered in patients with renal insufficiency (see table 6).

  One study[100] showed a high rate of hypoglycaemia when using insulin as compared to glyburide in patients with CKD, but apparently, the reported risk was lower than in patients with normal kidney function. One study showed high rate of hypoglycemia in patients with CKD treated with sulphonylureas[101].

  Tree studies analyzing the effects of DPP4 inhibitors in patients with CKD (one sitagliptin[102], one vildagliptin[103], two saxagliptin[104, 105]) were retrieved. Most of these studies only analyzed surrogate endpoints, mostly reduction of HbA1C levels. None of these studies reported on higher incidence of side effects as compared to no CKD patients. Only one study was performed in ESRD patients (saxagliptin), demonstrating no effect on total nor on cardiovascular comorbidity[94]. One study [106] evaluated the effect of liraglutide in CKD, reporting an increased frequency of nausea.

  One study[107] demonstrated that risk of hypoglycemia was lower with meglitinides as compared to insulin in patients on HD. One study[108] demonstrated that use of mitiglinide resulted in a mean decrease of HbA1C of 0.8%.

  With regard to the second line add-on treatment, we found in our target cohort of patients with diabetes and eGFR<45ml/min 11 manuscripts reporting on 10 studies: 3 RCT’s, 5 prospective observational, and 2 retrospective observational cohorts. The study by Lukashevic [103] is a double blind randomized study on vildagliptin vs placebo added to already existing glycaemia lowering treatment. In patients with diabetes and moderate (CKD3; vildagliptin 165/placebo 129) or severe (CKD 5; vildagliptin 124/placebo 97) renal impairment, vildagliptin resulted in lower Hba1C than placebo after a follow-up of 24 weeks. No hard endpoints were reported. After 1 year, the between-treatment difference in adjusted mean change in HbA1C was -0.4 ± 0.2% (p = 0.005) in moderate CKD (baseline = 7.8%) and -0.7 ± 0.2% (p < 0.0001) in severe CKD (baseline = 7.6%). In patients with moderate CKD, similar proportions of patients experienced any adverse event (AE) (84 vs. 85%), any serious adverse event (SAE) (21 vs. 19%), any AE leading to discontinuation (5% vs. 6%) and death
(1% vs. 0%) with vildagliptin and placebo, respectively. This was also true for patients with severe CKD: AEs (85% vs. 88%), SAEs (25% vs. 25%), AEs leading to discontinuation (10% vs. 6%) and death (3% vs. 2%). The first authors of these papers are employees of the pharmaceutical company producing the drug.

Nowicki et al [104] present one randomized double blind prospective study (12 weeks) and its long term follow up (52 weeks) conducted in 170 patients with type 2 diabetes and CKD randomized to saxagliptin (n=85) or placebo (n=85). The DPPIV inhibitor saxagliptin confers sustained improvement in HbA1c in patients with diabetes and retains a good safety profile when compared with placebo in patients with diabetes and creat clearance < 50 ml/min. The study by McGill[109] is a prospective (1 year) double blind randomized study conducted in 133 patients with type 2 diabetes randomized to linagliptin (n=68) or placebo (n=65). Linagliptin demonstrated significant improvement in glycaemic control with a risk of hypoglycaemia similar to placebo.

In the general population with diabetes, several meta-analysis comparing different combinations of oral glycemia lowering drugs or insulin and providing data on all cause mortality, cardiovascular events, risk for hypoglycemia, weight gain and HbA1C control were retrieved and summarized (see figure 7 and supplementary data extraction tables of chapter 2.3). Only one of these systematic reviews explicitly mentioned they included patients with chronic kidney disease stage 3b or higher. In none of the others, interaction of CKD vs no CKD on the reported outcomes was take into account. Metformin was the only drug that has a proven beneficial impact on all cause and cardiovascular mortality. Risk of hypoglycaemia was reported to be low with metformin, glipizide, acarbose, all DPP-IV inhibitors, and the SGLT2 inhibitors. Metformin, acarbose, exenatide, liraglutide, lixisenatide, pramlintidine and SGL-T2 inhibitors were reported to be weight neutral, whereas DPP4-inhibitors, gliclazide, repaglinide and nateglinide were reported to slightly increase weight.

Based on a Cochrane review, there is no evidence to underpin the notion that CKD stage 3b or higher per se enhances the risk for lactic acidosis associated with metformin [110]. Although this Cochrane review did not restrict to patients with CKD stage 3b or higher, it did also not exclude this patient group.

Based on a systematic review of case reports on lactic acidosis, we did not find any evidence to support a consistent association between metformin and lactic acidosis (supplementary data extraction tables). There was a signal that in most of the case reports, overdosing of metformin was present, although there was no consistent association between metformin levels and metabolic acidosis or lactate levels in case reports that reported these values. Overdosing was either
intentional, or accidental due to inappropriate adaptation of dose to renal function. In the latter case, this was mostly due to an abrupt decrease of glomerular filtration rate due to an intercurrent event.

**How did we translate the evidence into the statement (GRADE)**

As there is insufficient data from our specific target population with diabetes type 2 and CKD stage 3b or higher (eGFR<45ml/min), the guideline group decided, in line with the initial planned methodology, to evaluate how data from the general population with diabetes could be translated for use in our target population of patients with diabetes type 2 and CKD stage 3b or higher (eGFR<45ml/min).

The guideline development group therefore decided that a first step was to evaluate whether drugs needed adaptation of dose in relation to renal function. Accordingly, a review of pharmacokinetic data of glycaemia lowering drugs was done, and published as a separate document[111]. Based on these data, the table in figure 6 was constructed to guide dose adaptation in function of CKD stages.

As a second step, the guideline group wanted to evaluate which aspects of the treatment would be different in patients with diabetes type 2 with vs without eGFR<45ml/min. Based on interpretation of the available evidence, the guideline development group judged that especially the higher risk for hypoglycaemia and the lower likelihood of improving hard endpoints by tightening the glycaemic control should be taken into account.

Therefore, the guideline development group considered that the first concern should always be not to increase the risk for severe hypoglycaemia. As a consequence, preference should go to drugs with a low risk for hypoglycaemia when administered in a dose adapted to renal function. Additional glycaemia lowering drugs should only be started after careful consideration of their expected benefit, and taking into account their potential to cause hypoglycaemia (figure 5 and 7).

There is little doubt in general guidelines on management of type 2 diabetes that metformin should be the first line glycaemia lowering drug[97], because of its beneficial impact on all cause and cardiovascular mortality. In addition, metformin has a low risk for hypoglycaemia. As a consequence, the guideline development group considered that metformin should be the first line drug for all patients with type 2 diabetes until a clearance of 30ml/min because of its association with improved cardiovascular comorbidity, the very low risk of hypoglycaemia and its weight lowering properties.

This position is also in agreement with recent insights in metformin therapy[112] Of course, metformin dose should be adapted to renal function. The guideline development group acknowledged that, despite its proven value, the use of metformin in patients with chronic kidney disease remains controversial, and evokes substantial emotion. Even below this threshold of
30ml/min, the guideline development group considers the cost-benefit of metformin to be positive[113], but as less data are available[114], some caution remains warranted. A recent systematic review published after the end of our official literature search confirmed the absence of any evidence for an increased risk of lactic acidosis, even in patients with eGFR<30ml/min[115]. In a systematic review, Kajbaf et al[116] report widely varying recommendations on the use of metformin in patients with renal failure in 51 different guidance documents. Some guidelines used qualitative criteria, whereas others used quantitative criteria, either serum creatinine or eGFR. Seventeen guidance documents provide a cut-off below which metformin should simply not be used (nothing or all). The more logic recommendation to adapt the dose of metformin according to renal function, as is done for other drugs excreted by the kidneys, only appeared in 8 guidance documents. The guideline development group explicitly wanted to highlight in the current guideline this important change in paradigm to adapt the dose to renal function rather than to stop metformin.

As it is unclear whether metformin per se is associated with enhanced risk for lactic acidosis at all[112, 115], the guideline development group judges that a recommendation to use metformin in doses adapted to glomerular filtration rate in stable chronic kidney disease is more safe than switching to other glycaemia using drugs such as insulin, which might bear a bigger risk e.g. because of hypoglycaemia.

However, there is indirect evidence that a sudden drop of glomerular filtration rate can lead to a sudden accumulation of metformin. Therefore, patients should be instructed to reduce or stop metformin in conditions with enhanced risk of acute kidney injury, e.g. severe bouts of diarrhea, or deshydration or fever. The guideline development group feels that this patient information is an essential part of good clinical management in this regard, and therefore recommends to provide a patient information card/leaflet that should be handed over to patients with CKD stage 3b or higher(eGFR<45ml/min) on metformin.

With regard to the glitazones, the guideline development group preferred not to make an official statement, as these drugs are currently under regulatory scrutiny and are no longer available on most markets. A major concern of the guideline development group was that not all information might be publically available, and that, by lack of access to all information, an incorrect statement would be made.

One should carefully weigh the expected benefits and drawbacks before upgrading glycaemia lowering therapy in our target population of patients with type 2 diabetes and CKD stage 3b or higher (eGFR<45ml/min), as there is no clear expected advantage in terms of mortality, and there might be
an increased risk for adverse effects, such as hypoglycaemia and weight gain.

When cost is an issue, a short acting second generation sulphonylurea with no active metabolites could be considered, as they are commonly cheaper than other classes of drug. Reduced effect over time is common, due to islet cell exhaustion. Many of these drugs require progressive does dose reduction with progression of CKD, and some are contraindicated in CKD stage 5, as depicted in figure 6 [117]. Glipizide, repaglinide, and gliquidone however do not require specific dose reduction. In dialysis patients, the glinides should generally be avoided.

In other cases, if improvement of glycaemic control is considered of benefit, adding a GLP-1 agonist rather than insulin to metformin might offer the advantages of lower risk for hypoglycaemia and better control of body weight [118]. However, the guideline group wants to point out that CKD patients appear to have a normal incretin production, but a reduced incretin effect, suggesting a reduced β-cell response to incretin in CKD[119]. A well performed study with GLP1 agonists in patients with diabetes and renal insufficiency would be needed to provide evidence for the role of GLP1 agonists in this population. Liraglutide is highly protein bound, and is not eliminated through a kidney mediated pathway, and only a small fraction of its metabolites were recovered in urine[120]. From a pharmacokinetic or pharmacodynamic perspective, the drug should thus be considered as safe in patients with renal insufficiency, even at advanced stages. One should however pay attention to avoid dehydration as a consequence of the gastro-intestinal side effects, as this might lead to decreased renal function. Exenatide is cleared by proteolytic activity after glomerular filtration, and its clearance is therefore strongly diminished in patients with impaired renal function, and its use is thus not recommended in CKD stage 3b or higher (eGFR<45ml/min)[117]. Pancreatitis is a rare complication of GLP-1 RA[121].

Beneficial effects of DPP-4 inhibitors have only been documented for surrogate markers, and data on hard endpoints such as all cause mortality, or cardiovascular, macrovascular and microvascular events are scarce[118]. A recent large RCT published after our search and data extraction was closed, demonstrated no improvement in cardiovascular outcomes in patients receiving saxagliptin vs placebo as add on therapy[94]. As a consequence, the guideline group judges that, whereas adding a DPP4-I to metformin seems to be safe in terms of hypoglycaemia risk ,and does not result in an increase of weight[122-124], the expected benefit is very low. Sitagliptin, vildagliptin, alogliptin and saxagliptin all require dose reduction in CKD, whereas linagliptin does not[117]. Whereas some guideline group members consider renal clearance of a drug a disadvantage, others argued that in this way a lower dosing (and thus cost reduction) can be achieved.

Of note, these drugs are often marketed in combination pills with metformin in one formulation. The guideline development group wants to draw attention to the fact that these formulations should be avoided in patients with CKD stage 3b or higher (eGFR<45ml/min), as the two components have
differing dose adaptation requirements.

Although gastro-intestinal tolerance might be problematic, adding an alfa glucosidase inhibitor as second line therapy to metformin might be considered as the risk of hypoglycaemia is very low[125, 126], and they result in a modest weight decrease[127, 128]. However, also here, data on patient relevant outcomes such as all cause mortality or cardiovascular effects are largely lacking.

Triple therapy further increased the risk for hypoglycaemia[129], especially when insulin vs another oral glycaemia lowering agent was added as a third agent[130]. When administered to patients with insufficient glycaemic control under metformin and a sulphonylurea, both biphasic insulin and bolus insulin were associated with weight gain, whereas DPP-4 inhibitors and alpha-glucosidase inhibitors were weight-neutral, and GLP-1 analogues were associated with modest weight loss[129, 130].

What do the other guidelines say
No other guidelines provide specific recommendations on this topic for this patient group

Suggestions for future research
1/ Ideally, glycaemia lowering drugs should be investigated and compared for their effects on hard end-points, e.g. cardiovascular disease, death, microvascular complications, Qol, and risk for severe hypoglycaemia.

2/ A study as described under 1 should be done specifically for metformin. This study should not only assess hard endpoints, as described in 1, but also whether it is useful to monitor plasma metformin levels on a regular basis.
9. Chapter 3: Issues related to management of cardiovascular risk in patients with diabetes and CKD stage 3b or higher
Chapter 3.1.

In patients with diabetes and CKD stage 3b or higher (eGFR < 45 mL/min/1.73m²) or on dialysis and coronary artery disease, is Percutaneous Coronary Intervention (PCI) or Coronary Artery Bypass Grafting (CABG) or conservative treatment to be preferred?

Statements

3.1.1 We recommend not omitting coronary angiography with the sole intention of avoiding potential contrast related deterioration of kidney function in patients with diabetes and CKD stage 3b or higher (eGFR < 45 mL/min) in whom a coronary angiography is indicated (1D).
3.1.2 We recommend that optimal medical treatment should be considered as preferred treatment in patients with stable CAD and diabetes, unless there are large areas of ischaemia or significant left main or proximal LAD lesions (1C).
3.1.3 We recommend, when a decision is taken to consider revascularization, CABG is preferred over PCI in patients with multivessel or complex (SYNTAX score > 22) coronary artery disease (1C).
3.1.4 We recommend that patients with diabetes and CKD stage 3b or higher (eGFR < 45 mL/min) who present with an acute coronary event should be treated no differently to patients with CKD stage 3b or higher (eGFR < 45 mL/min) without diabetes or patients with diabetes without CKD stage 3b or higher (eGFR < 45 mL/min) (1D).

Advice for clinical practice:

* For patients with stable CAD,
  - optimal medical treatment is the preferred treatment
  - When there are large areas of ischaemia, or indications of significant left main or proximal LAD lesions, elective CABG is the preferred treatment.

* For patients presenting with ST Elevation Myocardial Infarction (STEMI), primary PCI is recommended over fibrinolysis if it can be performed within the recommended time limits.

* For patients presenting with Non STEMI
  - CABG results in improved outcomes (mortality, MACE) as compared to PCI when they have main stem lesions and/or advanced multivessel disease.
  - Pharmacological treatment, including anti-thrombotic therapy, has a place provided the doses of the medications are adapted to renal function.

Rationale

- **Why this question?**

Chronic kidney disease and diabetes are two of the most important risk factors for poor outcomes in patients with coronary artery disease (CAD), but it is unknown whether the combination of CKD stage 3b or higher (eGFR < 45 mL/min) and diabetes influences the efficacy of treatment strategies of coronary artery disease. Percutaneous Coronary Intervention (PCI) or Coronary Artery Bypass Grafting (CABG) may improve the major outcomes and survival but also increase the risk of specific complications, such as bleeding, further deterioration of renal function and infections. The question investigates whether maintaining conservative medical therapy or promoting potentially aggressive interventions (either PCI or CABG) would help to improve survival in this specific subpopulation.
What did we find?

Both diabetes and chronic kidney disease (CKD) are associated with a poorer prognosis in patients with acute and stable coronary artery disease (CAD)[131-134]. In large registry cohorts, these conditions are also associated with less and delayed diagnostic and therapeutic interventions[135].

In general three different clinical scenarios can be considered for patients with coronary artery disease (CAD), CKD stage 3b or higher and diabetes: patients with stable CAD, patients with ST-Elevation Myocardial Infarction (STEMI) and patients with non-STEMI.

The guidelines of the European Society of Cardiology (ESC) describe extensively the different treatment options in general for patients with stable CAD, ST-elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (non-STEMI)[136]. Also, specific ESC guidelines have been developed for patients with diabetes[137] but not for patients with CKD stage 3b or higher or the combination of both.

Specific randomized clinical trials for the treatment of CAD in patients with diabetes are scarce, and for patients with CKD stage 3b or higher or the combination of CKD stage 3b or higher and diabetes, we did not find any RCTs. For this specific patient group, only very limited, indirect evidence from subgroup analyses from RCTs in the general population or from real-life observational registries is currently available. Therefore, very specific recommendations for treatment of CAD in these patients are difficult to formulate. For this chapter the currently available evidence is summarized, starting from the ESC guidelines. We did an additional systematic search on available studies (Chapter 3.1 supplementary table).

Patients with stable CAD

The ESC guideline on management of cardiovascular disease in patients with diabetes[137] recommends that optimal medical treatment should be considered as preferred treatment in patients with stable CAD and diabetes, unless there are large areas of ischaemia or significant left main or proximal LAD lesions. This recommendation was largely based on the BARI 2D trial[138]. In this trial however, patients with a creatinine level > 2 mg/dl (>177µmol/l) were excluded as well as patients who required immediate revascularization or had left main disease, class III-IV heart failure patients and patients who had undergone PCI or CABG within the previous 12 months.

When a decision is taken to consider revascularization, CABG is recommended over PCI in patients with multi-vessel or complex (SYNTAX score > 22) CAD, as this improved survival free from major cardiovascular events (subgroup analyses of the BARI 2D[138], SYNTAX[139], FREEDOM[140] trial and recent larger registries and meta-analyses[141-144]). PCI for symptom control may be considered as an alternative to CABG in patients with diabetes and less complex multi-vessel CAD (Syntax score ≤
Patients with STEMI

In patients with diabetes who present with STEMI, primary PCI is recommended over fibrinolysis if available and performed within recommended time limits [147]. As a consequence of the higher absolute risk, the number needed to treat (NNT) to save one live at 30 days was significantly lower for diabetes patients (NNT 17; 95% CI 11-28) than for non-diabetes patients (NNT 48; 95% CI 37-60). As it is the case for patients without diabetes, a subgroup analysis of patients with diabetes in the Occluded Artery Trial (OAT) [148] showed no benefit of revascularization of an occluded infarct-related artery 3-28 days after myocardial infarction. In patients with milder degrees of chronic kidney disease, results from registries suggest that primary PCI is associated with a better outcome, but this finding is uncertain for those with CKD stage 3b or higher or on dialysis.

Patients with non-STEMI

Patients with diabetes have a high risk for mortality and unfavourable course, and as such require aggressive pharmacological as well as early invasive management when presenting with non-STEMI. In case of main stem lesions and/or advanced multi-vessel disease CABG should be favoured over PCI, although most of the data supporting this recommendation come from studies with chronic stable diabetes patients and it is unclear whether these data can be extrapolated to patients with non-STEMI. Patients with non-STEMI and CKD stage 3b or higher should receive the same first-line antithrombotic treatment as patients without CKD stage 3b or higher, with appropriate dose adjustments according to the severity of renal dysfunction. It is unclear however if an invasive strategy has an impact on clinical endpoints in these patients as most trials of revascularization in non-STEMI excluded patients with more advanced stages of chronic kidney disease. Data from registries and observational studies suggest that an early invasive therapy is associated with a better outcome in earlier stages of chronic kidney disease, but the benefit decreases with worsening renal function and is uncertain in those with CKD stage 3b or higher or on dialysis. In general, ESC
guidelines on non-STEMI state that CABG or PCI is recommended in patients with chronic kidney disease amenable to revascularization after careful assessment of the risk-benefit ratio in relation to the severity of renal dysfunction. Data from the Korean Registry Study [149] with 5,185 patients in total, compared early invasive (EI), deferred invasive (DI), and conservative strategies in patients with acute non-ST-segment elevation myocardial infarction (NSTEMI) and chronic kidney disease (CKD). At 1-year follow-up, mortality rates in the conservative group were significantly higher than in the invasive groups except for the severe CKD group. The benefit of the early over the delayed intervention strategy, although there were no significant differences between the 2 groups, tended to decrease as renal function decreased. Data presented by the USRDS registry in a 2002[150] report showed that in diabetic ESRD, there was no significant difference in all-cause death risk for stent (RR 0.99, 95% CI 0.91 to 1.08) but a 19% reduction for CABG surgery (RR 0.81, 95% CI 0.75 to 0.88) compared with PTCA. In patients with diabetes and on dialysis, there was also no significant reduction in cardiac death risk for stent (RR 0.99, 95% CI 0.89 to 1.11) compared with PTCA alone. In contrast, the risk for cardiac death in patients with diabetes and on dialysis was 27% lower after CABG surgery (RR 0.73, 95% CI 0.66 to 0.81) compared with PTCA.

More recently, a 2012 USRDS report[151] showed that when CABG is compared with PCI, CABG is associated with significantly lower risks for both death (HR=0.87, 95% CI=0.84–0.90) and the composite of death or myocardial infarction (HR=0.88, 95% CI=0.86–0.91). Subgroup analysis showed no evidence that age, race, diabetes, duration of ESRD, MI on index presentation, dialysis modality, stent era, or index year significantly modified the association of CABG and PCI on death. Similar results were obtained after the release of the FREEDOM trial[140] results, a randomized trial that enrolled 1900 patients with diabetes and multi-vessel coronary artery disease to undergo either PCI with drug-eluting stents or CABG. For patients with diabetes and advanced coronary artery disease, CABG was superior to PCI in that it significantly reduced rates of death and myocardial infarction but with a higher rate of stroke. A subgroup analysis of 129 patients with chronic kidney disease showed no difference between CABG vs PCI for primary outcome. However, the greater benefit of CABG versus PCI was consistent across all prespecified subgroups.

A very recent meta-analysis for patients with diabetes in general demonstrated a beneficial effect for CABG over PCI[152].

**What do the other guidelines say**

Guidance in this part is largely based on the European Society of Cardiology guidelines. The KH-CARI guideline on management of cardiovascular risk in CKD recommends that in patients with chronic kidney disease (CKD), end stage renal failure (ESRF) and after kidney transplantation, guidelines for revascularisation of the general population be adhered to (1D).
None of the other nephrology guidelines provides guidance in this area

**Suggestions for future research**

1/ A randomised controlled trial of conservative vs PCI vs CABG in diabetic patients with CKD stage 3b or higher (eGFR<45ml/min) presenting either with stable coronary artery disease or non STEMI on hard outcomes such as mortality, ESRD, QoL
Chapter 3.2.
In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²) or on dialysis and with a cardiac indication (heart failure, ischemic heart disease, hypertension) should we prescribe inhibitors of the RAAS system as cardiovascular prevention?

Statements

3.2.1 We recommend that adults with CKD stage 3b or higher (eGFR <45 mL/min/1.73m² or on dialysis) and diabetes who have a cardio-vascular indication (heart failure, ischemic heart disease) be treated with an ACE-I at maximally tolerated dose (1B).

3.2.2 We suggest there is insufficient evidence to justify the start of an angiotensin receptor blocker in adults with CKD stage 3b or higher (eGFR <45 mL/min/1.73m² or on dialysis) and diabetes who have a cardio-vascular indication (heart failure, ischemic heart disease) but intolerance for ACE-I (2B)

3.2.3 We recommend not combining different classes of Renin angiotensin blocking agents (ACE-I, angiotensin receptor blockers or direct renin inhibitors) (1A)

Advice for clinical practice:
* There is insufficient evidence whether or not RAAS inhibitors should be stopped in patients with CKD progressing to CKD stage 5. A trial of stopping the RAAS inhibitor with the aim to delay start of need for renal replacement therapy can be discussed with the patient

Rationale

• Why this question?
In patients with CKD stage 3-5, death is more likely an outcome than progression to ESRD. Diabetes is a multiplier of CVD risk. Therefore in this particular population drugs that would slow progression of renal disease and at the same time would be cardioprotective appear as a theoretical “first-line” therapy. Blockers of the RAA system are both renoprotective and cardioprotective in the general population. However in patients with diabetes and CKD stage 3b or higher, this potential benefit may be more limited or be counterbalanced by the need to start dialysis earlier (e.g. because of hyperkalaemia, or sudden deterioration of renal function). It can thus be questioned whether in this specific subpopulation, starting a RAAS blocker in patients who have a cardiac indication, is justified. As many patients will already be on these drugs before they develop CKD stage 3b or higher, the question should also be asked whether withdrawing these drugs is justified.
This question does not handle patients who only have a renal indication (proteinuria) or hypertension.

• What did we find?
**Effects on cardiovascular end points and mortality:**

We found 11 randomized controlled studies examining the outcomes after using inhibitors of the RAAS system or aldosteron receptor antagonists as cardiovascular prevention in patients with chronic kidney disease (eGFR <60 mL/min/1.73m² or on dialysis) and diabetes and with a cardiovascular indication (heart failure, ischemic heart disease, vascular disease) [153-164].

Unfortunately, in none of these studies data were presented by categories of patients according to staging of chronic kidney disease, making it impossible to make a statement specifically about inhibitors of the RAAS system or aldosteron receptor antagonists in the eGFR<45 mL/min/1.73m² or on dialysis category. Results varied widely between studies (see supplementary data). For the the major end-point of mortality, the overall analysis shows no difference between intervention and controls, with a hazard ratio ranging from 0.64 to 1.05 (4 studies pro, 3 studies contra, with comparable populations).

A pooled analysis of the included studies showed a favourable trend for RAAS-blocking agents. They also reduce by 10% non-fatal CV events in populations including both patients with and without diabetes. The dichotomous composite outcome asserting CKD progression (need for RRT or doubling of serum creatinine), showed a 22% difference in favour of RAAS-blocking agents for patients with diabetes (moderate quality of evidence).

No effect on a composite outcome of cardiovascular death, non-fatal myocardial infarction or stroke (289/1719 vs 299/1675, RR: 0.91, 95% CI:0.76-1.09 in the pooled analysis of the subgroup of patients with diabetes) was observed in a systematic review[165] including atherosclerotic normotensive (systolic RR<130mmHg) patients. Only patients treated with maximally tolerated doses of ACE-I vs placebo, had survival benefit (RR 0.78, 95%CI 0.61-0.98), but not those treated at lower doses of ACE-I (RR1.18, 95%CI 0.41-3.44) or with Angiotensin receptor blockers (RR: 0.99, 95% CI 0.85-1.17) in a Cochrane review[166].

The TRANSCEND[167] (Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease, N= 5927 patients) compared telmisartan to placebo in patients at high vascular risk and intolerant for angiotensin-converting enzyme (ACE) inhibitors. Telmisartan had no effect on the primary cardio-vascular outcome (15.7% vs 17.0% HR 0.92, 95% CI 0.81–1.05) nor on the secondary outcomes—a composite of cardiovascular death, myocardial infarction, or stroke (13.0%vs 14.8%, HR 0.87, 95%CI 0.76–1.00, but p=0.068 after adjustment for multiplicity of comparisons and overlap with primary outcome). In a post hoc analyses of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[158] (N= 33 357) treatment with a calcium channel blocker, an angiotensin-converting enzyme inhibitor or a diuretic was compared in high-risk hypertensive patients with a reduced glomerular filtration rate (GFR) for a composite end point including ESRD, 50% or greater decline in GFR, or death from any cause. The RR’s for patients taking amlodipine compared with those taking chlorthalidone for this end point was 1.02 (95% CI,
0.90-1.15; P=0.78) and lisinopril compared with chlorthalidone was 1.02 (95% CI, 0.90-1.15; P=0.80) in the GFR of less than 60 mL/min per 1.73 m² stratum. Estimated GFRs were similar between participants assigned to receive lisinopril and chlorthalidone at years 1, 2, 4, and 6. This pattern was consistent for diabetic participants and when stratified by baseline GFR. In an RCT[162] (N=1513) comparing losartan (50 to 100 mg once daily) to placebo, both taken in addition to conventional antihypertensive treatment (calcium-channel antagonists, diuretics, alpha-blockers, beta-blockers, and centrally acting agents), for a mean of 3.4 years, a total of 327 patients in the losartan group vs 359 in the placebo group reached the primary end point (risk reduction - 16%, P=0.02). Losartan reduced the incidence of a doubling of the serum creatinine concentration (risk reduction, 25%; P=0.006) and end-stage renal disease (risk reduction, 28%; P=0.002) but had no effect on the rate of death. The reductions in the risk of end-stage renal disease and of end-stage renal disease or death changed little after correction for blood pressure (26%, P=0.007, and 19%, P=0.02, respectively). In the ONTARGET[164] study, 6982/17118 patients had diabetes, and no interaction of diabetes vs non diabetes was observed. There was no difference in mortality in the overall group between ramipril or telmisartan, but there was a higher mortality in the group randomised to the combination therapy (HR combination vs ramipril: HR 1.07, 95% CI 0.98-1.17).

**Renal outcomes**

For the composite renal outcome of dialysis or doubling of serum creatinine, the effects of telmisartan in the TRANSCEND trial[167] varied according to the baseline Urinary Albumin Creatinine Ratio (P=0.006 for interaction) and estimated glomerular filtration rate (P=0.022). Telmisartan increased the incidence of the composite renal outcome in patients with no microalbuminuria or an estimated GFR greater than 60 mL/min per 1.73 m². In contrast, telmisartan tended to reduce this outcome in those with microalbuminuria or an estimated GFR below 60 mL/min per 1.73 m². Treatment with RAAS inhibitors was associated with slower progression to ESRD[155, 157, 161-163] as defined by doubling of the serum creatinine concentration or renal replacement therapy, the hazard ratio ranging from 0.67 to 1.29 in the included studies. In the ONTARGET[164] study, 6982/17118 patients were patients with diabetes. There was no interaction of diabetes vs no diabetes. Whereas there was no difference between ramipril and telmisartan in the end points "acute dialysis", "chronic dialysis" or doubling of serum creatinine (HR 1.09, 95%CI: 0.89-1.34), the combination group had a higher risk vs the ramipril alone group (HR 1.24, 95%CI: 1.01-1.51). In a meta-analysis by Casas et al[168], a subgroup analysis for patients with diabetes (34 studies, 4772 patients; no further segregation for baseline renal function or albuminuria), the use of ACE-I or ARB was associated with a reduction in albuminuria (mean difference −12.21, 95% CI −21.68 to −2.74 mg/day), but had no impact on glomerular filtration rate (−1.19, 95% CI−2.69 to +0.31 mml/min).
The authors conclude that claims that ACE inhibitors and ARBs are renoprotective in diabetes seem to derive from small placebo-controlled trials and any true advantage over and above blood-pressure control is uncertain.

In a Cochrane review[166] of general diabetic patients, there was a significant reduction in the risk of ESRD with ACE-I compared to placebo/no treatment (10 studies, 6819 patients, RR 0.60, 95% CI 0.39 to 0.93) and with Angiotensin receptor blockers compared to placebo/no treatment (3 studies, 3251 patients, RR 0.78, 95% CI 0.67 to 0.91). There was some evidence of reduction of the risk of doubling of serum creatinine concentration with ACE-I compared to placebo/no treatment (9 studies, 6780 patients, RR 0.68, 95% CI 0.47 to 1.00) and with Angiotensin receptor antagonists compared to placebo/no treatment (3 studies, 3251 patients, RR 0.79, 95% CI 0.67 to 0.93). ACE-I and angiotensin receptor blockers significantly reduced the risk of progression from micro- to macro-albuminuria (17 studies, 2036 patients, RR 0.45, 95%CI 0.29 to 0.69 and 3 studies, 761 patients, RR 0.49, 95% CI 0.32 to 0.75 respectively). In this systematic review, no separate analysis was done for patients with diabetes and advanced CKD stage 3b or higher. However, the stage of nephropathy in enrolled populations (micro-albuminuria versus macro-albuminuria or mixed populations with micro or macro-albuminuria) did not significantly affect any of the reported outcomes.

No studies on the effects of aldosteron receptor antagonists in this subpopulation were retrieved.

- How did we translate the evidence into the statement?

The data seem to be consistent with an improved overall mortality and reduced cardiovascular events in diabetic patients treated with ACE-I. Therefore, the guideline development group believes that the use of these drugs can be justified in patients with a cardiac indication for RAAS blockade, as the risk of death is in diabetic patients with CKD stage 3b or higher (eGFR<45ml/min) higher as that of progression to ESRD.

For angiotensin receptor blockers, the protective effect on mortality and cardiovascular events is less clear, and, according to the TRANSCEND trial, switching to an angiotensin receptor blocker in patients intolerant for ACE-I, does not improve outcome. Recent data[169], not included in our data extraction as they appeared after our official search dates, indicate that brachial blood pressure decreased as well without any significant difference between placebo and irbesartan. Intermediate cardiovascular end points such as central aortic blood pressure, carotid–femoral pulse wave velocity, left ventricular mass index, N-terminal brain natriuretic prohormone, heart rate variability, and
plasma catecholamines were not significantly affected by irbesartan vs placebo treatment. Changes in systolic blood pressure during the study period significantly correlated with changes in both left ventricular mass and arterial stiffness. Thus, significant effects of irbesartan on intermediate cardiovascular end points beyond blood pressure reduction were absent in haemodialysis patients. Recent meta-analyses in the overall diabetes population[170] and in patients with hypertension[171] come to comparable conclusions.

The present data on the withdrawing of RAAS inhibitors on patients already taking them for a cardiac indication when their chronic kidney disease progresses to an eGFR<30ml/min/1.73m² are controversial, and no randomised trials on this intervention are available. However, observational data, be it in patients without diabetes, suggest that in patients with an eGFR<30ml/min, the risk for hyperkalemia is 6.8 (95% CI, 2.7-17.4) times higher as in patients with eGFR>50ml/min[172]. In an observational study of 52 patients (46% with diabetes), Ahmed et al [173] report an increase of eGFR from 16.38 ± 1 ml/min/1.73m² at inclusion to 26.6 ± 2.2 ml/min/ 1.73 m² (p = 0.0001) after 12 months.

The guideline development group judges that it thus makes sense to discuss the withdrawal of a RAAS inhibitor with patients whose eGFR progresses to below 15ml/min, in an attempt to delay the need for start of renal replacement therapy.

- What do other guidelines say?

The KH-CARI guideline on management of cardiovascular risk in CKD from 2013 suggests that angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) should be used in most people with CKD who require blood pressure lowering (particularly those with albuminuria), due to the volume of evidence showing benefits for cardiovascular as well as renal outcomes (2B), but that diuretics, calcium channel blockers and beta blockers may also be used to lower blood pressure in people with CKD requiring treatment (2B). KH-CARI further recommends that a combination of two or more of ACE-I, ARB and direct renin inhibitors should not be used to prevent cardiovascular or renal events in people with CKD, as the combination provides no additional proven benefit, while increasing the risk of adverse outcomes (1B)

- Suggestions for future research?

A randomised controlled trial on the impact of withdrawing or maintaining of RAAS inhibitors in patients already taking them for a cardiac indication when their chronic kidney disease progresses below different thresholds below eGFR<45ml/min/1.73m² on mortality, cardiovascular outcomes, and evolution to ESRD.
Chapter 3.3.
In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²) or on dialysis, should we prescribe Beta Blockers to prevent sudden cardiac death?

<table>
<thead>
<tr>
<th>Statements</th>
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<tbody>
<tr>
<td>3.3.1 We suggest starting a selective B-blocking agent as primary prevention in patients with diabetes and CKD stage 3b or higher and continue it in function of patient tolerance (2C).</td>
</tr>
<tr>
<td>3.3.2 We suggest to prescribe lipophilic rather than hydrophylic beta blockers in patients with diabetes and CKD stage 3b or higher (eGFR&lt;45ml/min) (2C).</td>
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</tbody>
</table>

Rationale
- **Why this question?**
  Sudden cardiac death is an important cause of mortality in patients with CKD stage 3b or higher and in patients with diabetes. Ventricular re-entrant circuits and fibrosis-ischaemia are likely to be part of this paradigm, together with electrolyte disturbances, and other explanations. It is appreciated that beta-blockers can have an important role in several cardiac situations eg ventricular rate control, and heart failure. The question is whether or not the routine prescription of these drugs, with their known side-effects, can provide a survival advantage in diabetic patients with CKD stage 3b or higher (eGFR<45ml/min).

- **What did we find?**
  We retrieved one systematic review[174] analysing the impact of different anti-hypertensive agents in patients with diabetes. No separate subgroup analysis of patients with CKD stage 3b or higher was provided however. According to this systematic review, addition of a beta-blocking agent consistently reduced mortality (HR 7.13, 95% CI: 1.37-41.39).
  Further, we retrieved two multi-centre international RCTs [175, 176], one post-hoc analysis[177] and 4 observational cohort studies[178-181] (2 prospective[178, 179]). Most of these were at high risk of selection bias and bias by indication.
  In the cardiac insufficiency bisoprolol study (CIBIS)[177], 2647 patients with congestive heart failure (ejection fraction<35%) were randomised to different doses of bisoprolol or placebo. Patients on bisoprolol had lower hospitalisation hazard (0.80, 95%CI 0.71-0.91), reduced all cause mortality (0.66, 95CI 0.55-0.81) and sudden death (0.56, 95%CI 0.39-0.80). In an older RCT beta-blockers as compared to enalapril in patients with congestive heart failure (ejection fraction <85%), had comparable progression to end stage renal disease[175].
• How did we translate the evidence into the statement? (which considerations were taken into account? -GRADE)

There is no direct evidence that there is no interaction from diabetes nor CKD stage 3b or higher (eGFR<45ml/min) on the impact of the use of B-blocking agents. We did not find any study reporting an increased harm or more side effects in the diabetic vs non diabetic population. Although the CIBIS study[176, 177] was focussing on patients with congestive heart failure, and did not report an interaction for patients with diabetes and CKD stage 3b or higher, the guideline development group judges that this condition is quite prevalent in our target population, and that therefore, the results are very likly to also apply in this population. Based on these considerations, the guideline development group judged that it was logical to apply the same recommendations in patients with diabetes and CKD stage 3b or higher (eGFR<45ml/min) as in patients with diabetes without CKD or in patients with CKD without diabetes., as is done in the European Society of Cardiology guideline[137]

• What do other guidelines say?

We did not retrieve other guidelines providing advice on this topic

• Suggestions for future research?

  • A randomised controlled trial on the impact of Beta Blockade in diabetic patients diabetes and CKD stage 3b or higher (eGFR<45ml/min) without heart failure.
Chapter 3.4.
In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²), should we aim at lower blood pressure targets than in the general population?

**Statements**

3.4.1 We suggest against applying lower blood pressure targets in patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²) as compared to the general population *(2C)*

3.4.2 We suggest that in patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²) but without proteinuria, all blood pressure lowering drugs can be equally used to lower blood pressure. *(2C)*

**advice for clinical practice:**
- blood pressure should be carefully titrated to a target <140mmHg systolic blood pressure, while monitoring tolerance and avoiding side effects
- keep in mind that patients with diabetes and CKD stage 3b or higher might suffer from autonomic dysfunction and are thus more prone to complications associated with sudden hypotension
- A too low diastolic blood pressure can jeopardize coronary perfusion

**Why this question?**
Recommended blood pressure targets in the general population have over the last years slightly increased to 140mmHg systolic. There is a general perception that in patients with diabetes and/or chronic kidney disease, we should aim at lower blood pressure targets. However, it is not established whether such lower targets in this subpopulation will result in reduced mortality, morbidity or slower progression of chronic kidney disease.

**What did we find?**
We have found one Cochrane review on this topic[182], dealing however with the diabetic population in general. This review searched for randomized controlled trials comparing people with diabetes randomized to lower (<130/85mmHg) or to standard (140-160/100mmHg) BP targets, and providing data on any of the following primary outcomes: total mortality, total serious adverse events, myocardial infarction, stroke, congestive heart failure and end-stage renal disease. Secondary outcomes were achieved mean systolic and diastolic BP, and withdrawals due to adverse effects.

This Cochrane review[182] retrieved five randomized trials[183-187], (7314 participants, mean follow-up of 4.5 years). Despite achieving a significantly lower BP (119.3/64.4 mmHg vs 133.5/70.5 mmHg, P < 0.0001), the only benefit in the ‘lower’ systolic blood pressure (SBP) group was a reduction in the incidence of stroke: risk ratio (RR) 0.58, 95% confidence interval (CI) 0.39 to 0.88, absolute risk reduction 1.1%. There was no effect on mortality (RR 1.05; CI 0.84 to 1.30, low quality
evidence), but there was a significant increase in the number of serious adverse events (RR 2.58, 95% CI 1.70 to 3.91, absolute risk increase 2.0%).

Four trials (total N= 2580)([183-187] specifically compared clinical outcomes associated with ‘lower’ versus ‘standard’ targets for diastolic blood pressure in people with diabetes. Despite a significantly lower achieved blood pressure (128/76 mmHg vs 135/83 mmHg, P < 0.0001), there was no reduction in total mortality in the group assigned to the ‘lower’ diastolic blood pressure target (RR 0.73, 95% CI 0.53 to 1.01), stroke (RR 0.67, 95% CI 0.42 to 1.05), myocardial infarction (RR 0.95, 95% CI 0.64 to 1.40) or congestive heart failure (RR 1.06, 95% CI 0.58 to 1.92), all low quality evidence due to high risk of selection bias. End-stage renal failure and total serious adverse events were not reported in any of the trials. A sensitivity analysis of trials comparing diastolic blood pressure targets < 80 mmHg (as suggested in clinical guidelines) versus < 90 mmHg showed similar results.

- **How did we translate the evidence into the statement?**
  The guideline development group judged that based on these data, there is insufficient evidence to support the notion that in patients with advanced renal impairment and diabetes, we should aim at lower blood pressure targets than in the general population. It was noted that the evidence was not specifically collected in our target group, as no separate analysis was made for the specific subgroup of patients with diabetes with vs without chronic kidney disease stage 3b or higher. However, the guideline development group judged that it is quite unlikely that the situation in this particular subgroup would be any different, in view of the fact that this patient group is more likely to suffer from side effects and less likely to benefit from a decrease in (cardio-vascular) mortality and morbidity.

- **What do other guidelines state?**
  The recent KDIGO guideline on management of hypertension advocates that adults with diabetes and CKD ND with a urine albumin excretion of < 30 mg per 24 hours whose office BP is consistently >140 mmHg systolic or >90 mmHg diastolic be treated with BP lowering drugs to maintain a BP that is consistently < 140 mmHg systolic and < 90 mmHg diastolic. (1B). When urine albumin excretion is > 30 mg per 24 hours, these targets are 130 mmHg systolic or 80 mmHg diastolic (2D). However, it is clear from the rationale that this recommendation is mainly focussed on patients with eGFR>45ml. The recommendation for elderly patients advocates that blood pressure treatment in elderly patients with CKD ND should be tailored 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)
The KH-CARI guideline on management of cardiovascular risk factors in CKD recommends that blood pressure targets in people with chronic kidney disease (CKD) should be determined on an individual basis taking into account a range of patient factors (1C) including baseline risk, albuminuria level, tolerability and starting blood pressure levels. They suggest that most people with CKD should be treated to similar targets as the general population, such that most blood pressure readings are below 140/90 (2D). KH-CARI suggests that most blood pressure readings should be below 130/80 in individuals with CKD and macro-albuminuria (2B). KH-CARI also suggests that angiotensin converting enzyme inhibitors or angiotensin receptor blockers should be used in most people with CKD who require blood pressure lowering (particularly those with albuminuria), due to the volume of evidence showing benefits for cardiovascular as well as renal outcomes (2B). Diuretics, calcium channel blockers and beta blockers may also be used to lower blood pressure in people with CKD requiring treatment (2B).

- Questions for further research
Chapter 3.5.
In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²) or on dialysis, should we prescribe lipid lowering therapy in primary prevention?

<table>
<thead>
<tr>
<th>Statements</th>
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<tbody>
<tr>
<td>3.5.1 We recommend to start a statin in diabetic patients with CKD stage 3b and 4 (1B)</td>
</tr>
<tr>
<td>3.5.2 We suggest a statin be considered in diabetic patients with CKD stage 5 (2C)</td>
</tr>
<tr>
<td>3.5.3 We recommend against starting a statin in diabetic patients on renal replacement therapy (1A)</td>
</tr>
<tr>
<td>3.5.4 There was no consensus in the guideline development group on whether statins should be stopped or not in patients with diabetes with CKD stage5D, this in view of the absence of convincing evidence for one or the other option</td>
</tr>
<tr>
<td>3.5.5 We suggest fibrates can replace statins in patients who do not tolerate statins (2B)</td>
</tr>
</tbody>
</table>

Advice for clinical practice
- Doses of lipid lowering agents should be adapted according to renal function (table 7)
- As the doses in table 7 should be considered maximal doses in patients with chronic kidney disease, repetitive measurement of lipid levels does not add diagnostic nor therapeutic value.
- for patients with CKD stage 5 or CKD stage 5D, patient preference and motivation to take another pill with risk of side effects and limited expected benefit should guide management

Rationale
- **Why this question?**
In diabetic patients with CKD stage 3b or higher (eGFR<45ml/min) the impact of lipid-lowering treatment on patient important outcomes is still not completely clear. Patients with CKD have a higher burden of cardiovascular disease as compared with the general population, and patients with CKD stage 3b or higher suffering from diabetes are considered to be at highest risk. However, the risk profile of diabetic patients with CKD stage 3b or higher appears to be different from other patient categories, with uraemia-specific risk factors and non-atherosclerotic cardiovascular disease playing a major role. Furthermore, due to a high medication load in this patient group, treatment related side effects are perceived to be more prevalent and intrusive as compared to the general population. We therefore aim to provide evidence about the effect of lipid-lowering treatment in diabetic patients with CKD stage 3b or higher.

- **What did we find?:**
We retrieved 3 recent systematic reviews analysing the effect of lipid lowering therapies in patients with chronic kidney disease. Upadhyay et al[188] retrieved 18 RCTs, five of which involved CKD populations, and 13 were CKD subgroup analyses from trials in the general population. They
concluded that lipid-lowering therapy with statins did not improve kidney outcomes but decreases the risk for cardiac mortality (pooled risk ratio from 6 trials, 0.82 [95%CI, 0.74 to 0.91]),
cardiovascular events (including revascularization) (pooled RR from 9 trials, 0.78 [CI, 0.71 to 0.86]),
and myocardial infarction (pooled RR from 9 trials, 0.74 [CI, 0.67 to 0.81]). The significant benefit of all-cause mortality was limited by a high degree of heterogeneity. No benefit was found for other cardiovascular outcomes. Rates of adverse events were not different between intervention and comparator groups. No separate analysis was provided for patients with CKD5 or on dialysis. Palmer et al[189] retrieved a total of eighty trials comprising 51 099 participants, as these authors, in contrast to Upadhyay et al[188], also included studies comparing statin with no treatment, or another statin. Treatment effects of statins varied with stage of CKD. Moderate- to high-quality evidence indicated that statins reduced all-cause mortality (relative risk [RR], 0.81 [95% CI, 0.74 to 0.88]), cardiovascular mortality (RR, 0.78 [CI, 0.68 to 0.89]), and cardiovascular events (RR, 0.76 [CI, 0.73 to 0.80]) in persons not receiving dialysis. Moderate- to high-quality evidence indicated that statins had little or no effect on all-cause mortality (RR, 0.96 [CI, 0.88 to 1.04]), cardiovascular mortality (RR, 0.94 [CI, 0.82 to 1.07]), or cardiovascular events (RR, 0.95 [CI, 0.87 to 1.03]) in persons receiving dialysis. Effects of statins in kidney transplant recipients were uncertain. Statins had little or no effect on cancer, myalgia, liver function, or withdrawal from treatment, although adverse events were evaluated systematically in fewer than half of the trials. The results of both these systematic reviews were heavily influenced by the data of the SHARP study[190].

Jun et al[191] searched for prospective randomized controlled trials assessing the effects of fibrate therapy compared with placebo in people with CKD, retrieving 10 studies including 16,869 participants. In patients with mild- to-moderate CKD (estimated glomerular filtration rate [eGFR]<60 ml/min/1.73 m2), fibrates improved some surrogate markers (total cholesterol [0.32 mmol/l, p<0.05] and triglyceride levels [0.56 mmol/l, p= 0.03] but not low-density lipoprotein cholesterol [0.01 mmol/l, p= 0.83]; increased high-density lipoprotein cholesterol [0.06 mmol/l, p< 0.001]). In people with diabetes, fibrates reduced the risk of albuminuria progression (relative risk [RR]: 0.86; 95% confidence interval [CI]: 0.76 to 0.98; p< 0.02). Serum creatinine was elevated by fibrate therapy (33µmol/l, p<0.001), and calculated GFR was reduced (2.67 ml/min/1.73 m2, p< 0.01) but there was no detectable effect on the risk of end-stage kidney disease (RR: 0.85; 95% CI: 0.49 to 1.49; p= 0.575).

In patients with eGFR of 30 to 59.9 ml/min/1.73 m2, fibrates reduced the risk of major cardiovascular events (RR: 0.70; 95% CI: 0.54 to 0.89; p < 0.004) and cardiovascular death (RR: 0.60; 95% CI: 0.38 to 0.96; p <0.03) but not all-cause mortality. There were no clear safety concerns specific to people with CKD but available data were limited.
• How did we translate the evidence into the statement? (which considerations were taken into account? -GRADE)

The guideline development group, after extended discussion, agreed to base the decision to treat or not on the estimated underlying risk for atherosclerotic cardiovascular disease (ASCVD). According to the AHA guideline for the general population, patients with diabetes represent a high risk group, having a 10 year risk for ASCVD of >10%. There is good evidence from epidemiologic studies that also CKD stage 3b or higher substantially increases the risk for atherosclerotic cardiovascular disease[132]. As a consequence, the guideline development group agrees that it is justified to accept that in patients with diabetes and CKD stage 3b or higher (eGFR<45ml/min), the 10 year risk for ASCVD largely exceeds 10%, and that accordingly they should be treated.

The results of SHARP[190] seem to support a benefit of treatment for patients in CKD stages 3-4 (number needed to treat during 5 years to avoid one composite atherosclerotic event ≈ 50). In the SHARP[190] trial, subgroup analyses of diabetic patients revealed similar results as compared to non-diabetic patients. For reasons of simplicity, all GFR stages except CKD 5 and CKD5d are combined in one recommendation as a consequence of the high risk classification of patients with diabetes. The AHA guidelines cite evidence for patients with diabetes aged 40 years or older. In the CKD population, most patients with diabetes are above 40 years of age so that no age restriction has been made here.

The 4D study[192] did not show a meaningful benefit in patients with diabetes undergoing dialysis (mean time on dialysis 8 months). There was a non-significant 8% risk reduction of the primary endpoint of CV death, non-fatal MI and stroke. This means that there is no general recommendation to initiate statins in dialysis dependent patients with diabetes.

A substantial number of patients became dialysis-dependent during the study period in the SHARP trial[190]. These patients were analyzed in the non-dialysis group showing a benefit of treatment. There are no data directly addressing the question of whether lipid-lowering treatment should be stopped after initiation of dialysis. SHARP data are by some interpreted as that starting lipid lowering before ESRD and continuing through ESRD is beneficial, while starting too late during ESRD associates with an uncertain benefit. There was no consensus on this topic within the guideline development group, except for making a statement that shared decision making to continue or stop lipid lowering treatment is mainly driven by the patient's condition and informed preference.

As the guideline development group decided to recommend a risk based treatment strategy, follow up of lipid levels once treatment has started is considered to be not useful, which is in line with judgements of other groups [193], especially as for most statins, a maximal dose should be considered in patients with CKD stage 3b or higher (eGFR<45ml/min) (see table). One initial measurement to identify and treat potential secondary causes of hyperlipidaemia is however still
What do the other guidelines say

No guideline specifically provides guidance for our target audience.

The KDIGO guideline on lipid management in chronic kidney disease recommends a statin in adults aged >50 years with eGFR <60 ml/min/1.73 m² but not treated with chronic dialysis or kidney transplantation (GFR categories G3a–G5) (1A), whereas in adults aged >50 years with CKD and eGFR>60 ml/min/1.73 m² (GFR categories G1–G2), they recommend treatment with a statin. (1B).

2.2: In adults aged 18–49 years with CKD but not treated with chronic dialysis or kidney transplantation, KDIGO suggests statin treatment in people with known coronary disease (myocardial infarction or coronary revascularization), diabetes mellitus, prior ischemic stroke, estimated 10-year incidence of coronary death or nonfatal myocardial infarction >10% (2A). In adults with dialysis-dependent CKD, KDIGO suggests against initiation of a statins (2A), but also to continue it in those already on a statin (2C). Of note, as KDIGO recommends that all patients with CKD stage 3b or higher (eGFR<45ml/min) should be started on a statin, in real life practice this would imply that all patients on renal replacement therapy will be on a statin. In fact, this is the only point of discordance between ERBP and KDIGO guidance, and within the ERBP guideline development group, there was no consensus on the topic. As ERBP, KDIGO states that in adults with CKD (including those treated with chronic dialysis or kidney transplantation), follow-up measurement of lipid levels is not required for the majority of patients (Not Graded)

Suggestions for future research

* should lipid lowering therapy be stopped in patients entering renal replacement therapy?
Chapter 3.6.
A. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²), should we recommend interventions aimed at increasing energy expenditure and physical activity?
B. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²), should we recommend interventions aimed at reducing energy intake?

Statements

3.6.1 We suggest that patients with diabetes and CKD stage 3b or higher (eGFR<45ml/min) perform additional physical exercise during at least 3 times 1/2 to 1 hour/week to reduce fat mass and improve Quality of Life (QoL) (2D).

3.6.2 We suggest there is no evidence of harm when promoting increased physical exercise (2C)

3.6.3 When promoting weight loss in diabetic patients with overweight, we recommend supervision of this process by a dietician and ensure that only fat mass is lost and malnutrition is avoided (1C)

Rationale

- Why this question?
Physical activity is promoted in patients with diabetes as a life style change measure complementary to diet and drugs, with the intention to improve metabolism and preserve cardiovascular functionality. Promoting physical activities requires specific programs and follow-up, which might have a substantial impact on resources. Therefore, in patients with diabetes and CKD stage 3b or higher (GFR<45ml/min), it is crucial to ascertain whether interventions focused at increasing energy expenditure may influence survival, morbidity and other major outcomes, such as physical performance, QoL and depression.

Dietary advice plays a central role in the management of diabetes. Dietary advices can impact on Quality of Life of patients, especially when combined for different targets, such as in patients with diabetes and chronic kidney disease. Organisation of dietary advice can have impact on utilisation of resources. Therefore, in patients with diabetes and chronic kidney disease stage 3b or higher (eGFR<45ml/min) it is important to verify whether structured dietary plans favourably influence survival, morbidity, and other outcomes such as weight control, proteinuria, adherence to treatment and insulin sensitivity, with respect to standard care without structured dietary advice, and this without jeopardizing overall nutritional status or quality of life.

- What did we find?
The results of this systematic review are published as a separate document[194] . In brief, we retained 11 studies[195-205], none of them specifically designed for our target population. Overall,
there were insufficient data to evaluate the effect on mortality of lifestyle interventions to promote negative energy balance. None of the studies reported a difference in the incidence of Major Adverse Cardiovascular Events. Reduction of energy intake does not alter creatinine clearance but reduces 24h proteinuria\[200, 204, 205\]. Combined exercise and diet interventions resulted in a slower decline of eGFR (-9.2 vs. -20.7 mL/min; p<0.001) over a two year observation period [201]. Aerobic and resistance exercise reduced HbA1c (-0.51 (-0.87 to -0.14); p=0.007 and -0.38 (-0.72 to -0.22); p=0.038, respectively) in some [195, 198] but not all studies[197, 202]. Exercise interventions improve the overall functional status[195, 197, 199] and the quality of life in this specific subgroup. Aerobic exercise reduces BMI (-0.74% (-1.29 to -0.18); p=0.009), body weight (-2.2 kg (-3.9 to -0.6); p=0.008) and body composition[198]. Resistance exercise reduced trunk fat mass (-0.7 ± 0.1 vs. +0.8 kg ±0.1kg; p=0.001-0.005)[195]. In none of the studies did the intervention cause an increase in adverse events[195, 198, 202].

- **How did we translate the evidence into the statement? (which considerations were taken into account? -GRADE)**

There is lack of evidence that energy control in diabetic CKD patients can improve hard patient centred outcomes such as mortality, major cardiovascular events or hospitalizations. There is, however, enough evidence that promoting energy expenditure or reducing energy intake (particularly by lifestyle interventions) might be useful for improving glycaemic control, BMI, body composition, quality of life and physical functioning. An improvement of all these factors might translate into better long-term outcomes, but future studies focusing on hard outcomes are needed. It is likely that the ‘dose’ of interventions to improve energy balance may have been inadequate in many of the studies, with relatively small increases in energy expenditure on exercise programmes, and relatively small decreases in calorie intake in patients given dietary advice: if it were possible to persuade patients with diabetes and CKD to take enough exercise, for instance, more weight loss, improved fitness, and better long-term outcomes would be expected. Since there is also no evidence that these programs may cause harm, it would be reasonable to recommend energy control in those patients who are likely to benefits the most, like obese patients. When introducing such measures in diabetic patients with CKD stage 3b or higher (eGFR<45ml/min), we should provide professional advice and guidance to prevent malnutrition in this frail population.

**What do the other guidelines say**
We did not retrieve a guideline providing guidance for this specific patient population. The diabetes guideline of NICE recommends provision of an individualised and ongoing nutritional advice from a healthcare professional with specific expertise and competencies in nutrition. The dietary advice
should be provided in a form sensitive to the individual's needs, culture and beliefs and should take into account willingness to change of patients, and the effects on their quality of life. NICE further recommends individualising recommendations for carbohydrate and alcohol intake, and meal patterns. Reducing the risk of hypoglycaemia should be a particular aim for a person using insulin or an insulin secretagogue. There is no specific recommendation on exercise therapy.

Suggestions for future research

- Large-scale studies of the effects of a combination of regular aerobic and/or resistance exercise and dietitian-supervised calorie restriction on the functional status, quality of life, and survival of obese patients with diabetes and CKD are required.
Chapter 3.7.
In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²), should antiplatelet therapy be recommended, regardless of their cardiovascular risk?

<table>
<thead>
<tr>
<th>Statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.7.1 We recommend against adding Glycoprotein IIb/IIIa inhibitors to standard care to reduce death, myocardial infarction, or need for coronary revascularization in diabetic persons with CKD stage 3b or higher (eGFR&lt;45ml/min) and acute coronary syndromes or high-risk coronary artery intervention. (1B)</td>
</tr>
<tr>
<td>3.7.2 We suggest only adding a thienopyridine or ticagrelor to standard care to reduce death, myocardial infarction, or need for coronary revascularization in patients with diabetes and CKD stage 3b or higher (eGFR&lt;45ml/min) and acute coronary syndromes or high-risk coronary artery intervention when there is no additional risk factor for bleeding. (2B)</td>
</tr>
<tr>
<td>3.7.3 We recommend starting aspirin as secondary prevention, unless there is a contra-indication or side-effects (1C)</td>
</tr>
<tr>
<td>3.7.4 We suggest starting aspirin as primary prevention only in patients without additional risk factors for bleeding (2C)</td>
</tr>
</tbody>
</table>

advice for clinical practice:
- Consider Clopidogrel as an alternative for aspirin in patients with clear intolerance or contra-indications for aspirin

Rationale
- **Why this question?**
  
  In patients with diabetes and CKD stage 3b or higher (especially those on dialysis) it is important to clarify if anti-platelet therapy should be prescribed in primary prevention. Some would argue that CKD patients have an enhanced cardiovascular risk, and should be placed on antiplatelet therapy in primary prevention based on that. On the other hand, CKD patients might suffer from uraemic coagulopathy, and can therefore be at higher risk for complications. In patients on haemodialysis in particular, it is still debated whether antiplatelet therapy may improve the major outcomes and survival of vascular access or whether it increases the risk of specific complications, such as bleeding or the need of transfusions.

- **What did we find?**
  
  We retrieved 303 records through database searching, 47 of which were assessed as full text articles for eligibility. Finally, 12 studies were included for data extraction and quality assessment. Only two RCT’s handled this question [206, 207]. In addition, we found one meta analysis including post hoc
analyses, one Cochrane Database of systemic reviews [208, 209], one prospective cohort study [210], one case control study[211], one quasi-randomized controlled trial in patients with diabetes and CKD 1 [212] and one case series study [213].

Palmer et al analysed the impact of antiplatelet agents in CKD patients with stable or no cardiovascular disease, finding uncertain effects on mortality[208]. In this systematic review, nine trials (all post hoc subgroup analyses for patients with chronic kidney disease, but not specific for patients with diabetes) involving 9969 persons who had acute coronary syndromes or were undergoing percutaneous coronary intervention and 31 trials involving 11 701 persons with stable or no cardiovascular disease were identified. Low-quality evidence was found that in persons with diabetes and CKD stage 3b or higher (eGFR<45ml/min) presenting with acute coronary syndromes (ACS), glycoprotein IIb/IIIa inhibitors or clopidogrel plus standard care compared with standard care alone had little or no effect on all-cause or cardiovascular mortality or on myocardial infarction but increased serious bleeding. Compared with placebo or no treatment in persons with stable or no cardiovascular disease, antiplatelet agents prevented myocardial infarction but had uncertain effects on mortality and increased minor bleeding according to generally low-quality evidence.

Dasgupta et al. (Charisma trial) reported increased risk of death (overall and cardiovascular) in patients with type 2 diabetes with diabetic nephropathy on dual antiplatelet therapy (clopidogrel plus aspirin) as compared to aspirin alone[206]. This increase in mortality was not caused by a significant increase in bleeding risks in patients with nephropathy receiving clopidogrel, thus suggesting an independent interaction.

The Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) trial was a prospective, randomized, open-label trial conducted throughout Japan that enrolled 2,539 type 2 diabetic patients without a history of atherosclerotic diseases. Patients were assigned to the aspirin group (81 mg/day or 100 mg/day) or the non-aspirin group and followed for a median of 4.37 years. In this subgroup analysis of JPAD, in Japanese type 2 patients with diabetes, low-dose aspirin therapy reduced the incidence of atherosclerotic events such as death from coronary or cerebro-vascular causes in diabetic patients with eGFR 60–89 mL/min/1.73 m², but not in those with eGFR < 60 mL/min/1.73 m²[207]. In concordance with the mortality results, the JPAD trial did not demonstrate a benefit for myocardial infarction or stroke in diabetic patients with eGFR < 60 mL/min/1.73 m²[207]. McCullough et al. demonstrated reduction for the in-hospital mortality rate in CKD patients with acute myocardial infarction treated with ASA and Beta-blockers as a secondary prevention[211]. However, in this study few details on diabetic nephropathy were provided.

Wang et al.[209] studied the benefits and harms of PGE1 for preventing the progression of diabetic kidney disease. Based on the six small RCTs conducted in China, PGE1 may have a positive effect on reducing urinary albumin excretion, micro-albuminuria and proteinuria in patients with diabetic
kidney disease. None of the included studies reported the incidence of ESRD, all-cause mortality or quality of life. These results should be interpreted with caution because of the poor methodological quality of the included studies and the small numbers of participants[209]. Pre-specified subgroup data from the PLATO (Platelet Inhibition and Patient Outcomes) trial indicates that ticagrelor, an oral purinergic receptor inhibitor cleared by extra-renal mechanisms, reduces mortality and major cardiovascular events better than clopidogrel among patients with eGFR<60ml/min/1.73m² and presenting with an acute coronary syndrome[214]. However, in previous studies analysing aspirin plus clopidogrel vs placebo, there was a trend for superior outcomes (all cause and cardiovascular mortality) in the group administered placebo. As such, the role of antiplatelet therapy in patients with CKD stage 3b or higher (eGFR<45ml/min) remains uncertain.

Higher bleeding rates were observed in CKD patients with double or standard antiplatelet therapy[206, 208, 210]. The UK-HARP-I[215] trial, evaluating the safety of aspirin 100mg daily vs placebo in chronic kidney disease patients, found no increased risk for major bleeding (4/225 vs 6/223, p=NS), but a 3 fold higher risk of minor bleeding (34/225 vs 12./223, p=0.001)). Evidence for efficacy and safety of aspirin in primary prevention is lacking or, at best, inconclusive, especially in the subpopulation of patients with diabetes and CKD stage 3b or higher (eGFR<45ml/min). We retrieved a systematic review[216], including three trials conducted specifically in patients with diabetes mellitus, and six other trials in which such patients represent a subgroup within a broader population. Aspirin was found to be associated with a non-significant 9% decrease in the risk of coronary events (RR 0.91; 95% CI 0.79–1.05) and a non-significant 15% reduction in the risk of stroke (RR 0.85; 95% CI 0.66–1.11). There was a great heterogeneity between the studies for the estimated 10 year coronary event rates (2.5% to 33.5%).

- **How did we translate the evidence into the statement? (Which considerations were taken into account? -GRADE)**

The important methodological pitfalls in the small studies on the use of antiplatelet therapy in patients with CKD stage 3b or higher (eGFR <45 mL/min/1.73m² or on dialysis) and diabetes, regardless of their cardiovascular risk hamper an evidence based conclusion.

Taking into account the published data, we consider that there is low quality evidence that adding Glycoprotein IIb/IIIa inhibitors, thienopyridine or ticagrelor as primary prevention to standard care, despite a positive effect on myocardial infarction, does not lead to a reduction of all cause mortality, cardiovascular death, stroke or need for coronary revascularization in persons with CKD stage 3b or higher (eGFR<45ml/min) and diabetes, but may result in an enhanced bleeding risk, which might
even be substantial for glycoprotein IIb/IIa inhibitors[217]. As such, the guideline development group judges that these latter agents do not have a place in primary prevention of patients with diabetes and CKD stage 3b or higher (eGFR<45ml/min) with or without or with stable cardiovascular disease. In the acute setting of a percutaneous intervention, there is a non significant trend for improved all cause mortality, cardiovascular mortality and need for coronary revascularisation, but there is substantial enhanced risk for bleeding in patients treated with platelet inhibiting agents, especially for gastro-intestinal bleeding[218]. When administered in the pre-operative phase before coronary artery bypass surgery, clopidogrel results in higher risk of bleeding, and even death[219]. Ticagrelor was shown to be superior to clopidogrel in ACS patients with chronic kidney disease (eGFR<60ml/min)[214], but in this specific subgroup, clopidogrel itself was non-significantly worse as compared to placebo (CREDO, CURE)[220, 221], so the implications of this observation are unclear in absence of a ticagrelor-placebo controlled trial.

Bleeding hazards and lack of clear efficacy in reducing cardiovascular morbidity and mortality need to be acknowledged when patients with CKD are being counselled about acute or long-term antiplatelet therapy[208].

The general recommendation to prescribe low dose aspirin for secondary prevention is well established. There is no plausible reason why the impact of low dose aspirin should be different in patients with diabetes and CKD stage 3b or higher (eGFR<45ml/min), unless there would be evidence for an enhanced bleeding risk. Based on the UK-HARP data, there is evidence that use of aspirin does not increase the rate of major bleeding, although there is an enhanced risk for minor bleeding. Based on this indirect evidence, and in absence of direct comparisons in our target population, the guideline development group suggests to start aspirin in secondary prevention, unless there is a contra-indication or side-effects.

- What do the other guidelines say

No guidelines focused specifically on this subpopulation of patients with diabetes and CKD stage 3b or higher (eGFR<45ml/min). However, the Canadian guidelines (2011) studied the use of antiplatelet therapies in patients with CKD in general, and recommend aspirin 75 to 162 mg daily for primary prevention of ischemic vascular events in patients with CKD stage 3b or higher (eGFR<45ml/min) and a low risk of bleeding. In addition antiplatelet therapy should be considered for secondary prevention in patients with CKD and manifest vascular disease for which its benefits are established. [222]. The American Diabetes Association guidelines from 2013 recommend to consider aspirin therapy (75–162 mg/day) as a primary prevention strategy only in those with type 1 or type 2 diabetes at increased cardiovascular risk (10-year risk > 10%). This includes most men aged > 50 years or women...
aged > 60 years who have at least one additional major risk factor (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria), and probably also most diabetic patients with CKD stage 3b or higher (eGFR<45ml/min)[223].

NICE recommends in its guideline on management of diabetes to offer low-dose aspirin, 75 mg daily, to a person with diabetes who is 50 years old or over if blood pressure is below 145/90 mmHg; to offer low-dose aspirin, 75 mg daily, to a person who is under 50 years old and has significant other cardiovascular risk factors (features of the metabolic syndrome, strong early family history of cardiovascular disease, smoking, hypertension, extant cardiovascular disease, microalbuminuria); to offer Clopidogrel instead of aspirin only in those with clear aspirin intolerance (except in the context of acute cardiovascular events and procedures).

- **Suggestions for future research**

  Randomized controlled trials to examine the benefits and harms of the use of antiplatelet agents as primary prevention in patients with diabetes and CKD stage 3b or higher (eGFR<45ml/min).
10. Tables
Table 1: Suggested outcomes and level of importance

**Critically important outcomes**

Survival/mortality
- Progression to end-stage kidney disease/Deterioration of residual renal function
- Hospital admissions: Highly important
- Qol/patient satisfaction
- Major morbid events:
  - Myocardial infarction
  - Stroke
  - Amputation
  - Loss of vision

**Highly important outcomes**

- Hypoglycemia
- Delayed wound healing
- Infection
- Visual disturbances
- Pain
- Functional status

**Moderately important outcomes (surrogate outcomes)**

- Hyperglycaemia
- Glycaemic control
  - Glycated haemoglobin
  - Point of care (measure)

**Question specific outcomes**
Table 2: Method of rating the quality of the evidence

<table>
<thead>
<tr>
<th>Step 1: Starting grade according to study design</th>
<th>Step 2: Lower if</th>
<th>Step 3: Higher if</th>
<th>Step 4: determine final grade for quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized trials = High Risk of Bias:</td>
<td></td>
<td>Large effect</td>
<td>High (four plus: 🌟🌟🌟🌟)</td>
</tr>
<tr>
<td>Observational Studies = Low Risk of Bias:</td>
<td>-1 Serious</td>
<td>+1 Large</td>
<td>Moderate (three plus: 🌟🌟🌟)</td>
</tr>
<tr>
<td>-2 Very Serious</td>
<td></td>
<td>+2 Very Large</td>
<td>Low (two plus: 🌟🌟)</td>
</tr>
<tr>
<td>Inconsistency:</td>
<td>-1 Serious</td>
<td>Dose response</td>
<td>Very Low (one plus: 🌟🌟🌟)</td>
</tr>
<tr>
<td>-2 Very Serious</td>
<td></td>
<td>+1 Evidence of a gradient</td>
<td></td>
</tr>
<tr>
<td>Indirectness:</td>
<td>-1 Serious</td>
<td>All plausible confounding</td>
<td></td>
</tr>
<tr>
<td>-2 Very Serious</td>
<td></td>
<td>+1 Would reduce a demonstrated effect</td>
<td></td>
</tr>
<tr>
<td>Imprecision:</td>
<td>-1 Serious</td>
<td>+1 Would suggest a spurious effect</td>
<td></td>
</tr>
<tr>
<td>-2 Very Serious</td>
<td></td>
<td>when results show no effect</td>
<td></td>
</tr>
<tr>
<td>Publication Bias:</td>
<td>-1 Likely</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-2 Very likely</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Balshem H et al. J Clin Epidemiol 2011; 46: 401-406.[224]

Table 3: Grade for the overall quality of evidence

<table>
<thead>
<tr>
<th>Grade</th>
<th>Quality Level</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>High</td>
<td>We are confident that the true effects lies close to that of the estimates of the effect</td>
</tr>
<tr>
<td>B</td>
<td>Moderate</td>
<td>The true effects are likely to be close to the estimates of the effects, but there is a possibility that they are substantially different</td>
</tr>
<tr>
<td>C</td>
<td>Low</td>
<td>The true effects might be substantially different from the estimates of effects</td>
</tr>
<tr>
<td>D</td>
<td>Very low</td>
<td>The estimates are very uncertain, and often will be far from the truth.</td>
</tr>
</tbody>
</table>

Adapted from Gyatt GH et al. BMJ 2008; 336: 924-926.[225]
### Table 4: Implications of strong and weak recommendations for stakeholders

<table>
<thead>
<tr>
<th>Grade</th>
<th>Patients</th>
<th>Clinicians</th>
<th>Policy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - strong 'We recommend'</td>
<td>Most people in your situation would want the recommended course of action, only a small proportion would not</td>
<td>Most patients should receive the recommended course of action</td>
<td>The recommendation can be adopted as policy in most situations</td>
</tr>
<tr>
<td>2 - weak 'We suggest'</td>
<td>Most people in your situation would want the recommended course of action, but many would not</td>
<td>You should recognise that different choices will be appropriate for different patients. You must help each patient to arrive at a management decision consistent with her or his values and preferences.</td>
<td>Policy making will require substantial debate and involvement of many stakeholders</td>
</tr>
</tbody>
</table>

Adapted from Gyatt GH et al. *BMJ* 2008; 336: 924-926. [226]

The additional category ‘Ungraded’ was used, typically, to provide guidance based on common sense rather than on a systematic literature search. Where applicable, these statements were provided as “advice for clinical practice”. Typical examples include recommendations regarding monitoring intervals, counselling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.
Table 5: observational studies on outcome after different modalities of transplantation in patients with type 1 diabetes

<table>
<thead>
<tr>
<th>Time period</th>
<th>Mean age</th>
<th>Subjects</th>
<th>1y patient survival</th>
<th>5y patient survival</th>
<th>7y patient survival</th>
<th>10y patient survival</th>
<th>1y kidney graft survival</th>
<th>5y kidney graft survival</th>
<th>7y kidney graft survival</th>
<th>10y kidney graft survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rayhill[65] 2000</td>
<td>1986-1996</td>
<td>39</td>
<td>805</td>
<td>99% haplo-identical LRDK, 96% SPK and 94% DKD</td>
<td>85% haplo-identical LRDK, 88% SPK and 72% DKD</td>
<td>94% haplo-identical LRDK</td>
<td>87% SPK, 86% DKD</td>
<td>72% haplo-identical LRDK</td>
<td>76% SPK, 64% DKD</td>
<td></td>
</tr>
<tr>
<td>Bunnapradist[2 27] 2003</td>
<td>1994-1997</td>
<td>41</td>
<td>6016</td>
<td>87% SPK and 76% DKD</td>
<td>77% SPK and 64% DKD</td>
<td>67% for SPK vs. 56% for LDK vs. 36% for DKD</td>
<td>70% for SPK vs. 72% for LDK vs. 60% for DKD</td>
<td>57% for SPK vs. 45% for LDK vs. 30% for DKD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lindahl[67] 2013</td>
<td>1983-2010</td>
<td>47</td>
<td>630</td>
<td>84% for SPK vs. 95% for LDK vs. 89% for DKD</td>
<td>85% for SPK vs. 79% for LDK vs. 63% for DKD</td>
<td>74% for SPK vs. 72% for LDK vs. 60% for DKD</td>
<td>90% for SPK vs. 89% for LDK vs. 77% for DKD</td>
<td>57% for SPK vs. 45% for LDK vs. 30% for DKD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mohan[68] 2003</td>
<td>1992-2002</td>
<td>47</td>
<td>101</td>
<td>96% for SPK vs. 93% KTA</td>
<td>89% for SPK vs. 57% KTA</td>
<td>93% for SPK vs. 94% KTA</td>
<td>76% for SPK vs. 58% KTA*</td>
<td>85.2% SPK vs. 70.0% KTA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>La Rocca[63] 2001</td>
<td>1984-1998</td>
<td>46</td>
<td>ESRD type 1 DM (N=351)</td>
<td>77.4% SPK vs. 56.0% KTA vs. 39.6% WL</td>
<td>80.5% SPK vs. 68.7% KTA vs. 50.1% WL</td>
<td>92.0% SPK vs. 94.8% KTA vs. 86.7% WL</td>
<td>90% SPK vs. 88% KTA vs. 81% WL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young[77] 2009</td>
<td>2000-2007</td>
<td>42</td>
<td>type 1 DM who received a kidney transplant (N=11362)</td>
<td>87% LDK and SPK vs. 75% DKD</td>
<td>88.6% SPK vs. 80.0% LDK vs. 73.9% SPK with pancreas loss y1 vs 64.8% DKD</td>
<td>92.0% SPK vs. 94.8% LDK vs. 90.3% DKD</td>
<td>72% SPK (functioning pancreas y1) vs. 63.6% LDK vs. 59.8% SPK with pancreas loss y1 vs 49.7% DKD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waki[92] 1995-2002</td>
<td>1995-2002</td>
<td>44</td>
<td>type 1 DM who received a kidney transplant (N=1088)</td>
<td>96.4% SPK vs. 95.2% KTA</td>
<td>89.6% SPK vs. 78.2% KTA</td>
<td>78.2% SPK vs. 65.5% KTA</td>
<td>85.2% SPK vs. 70.0% KTA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weiss [80] 1997-2005</td>
<td>1997-2005</td>
<td>40</td>
<td>type 1 DM on SPK waiting list (N=9630)</td>
<td>95.9% SPK vs. 97.2% LDK vs. 95.6% DKD</td>
<td>88.6% SPK vs. 80.0% LDK vs. 73.9% SPK with pancreas loss y1 vs 64.8% DKD</td>
<td>92.0% SPK vs. 94.8% LDK vs. 90.3% DKD</td>
<td>72% SPK (functioning pancreas y1) vs. 63.6% LDK vs. 59.8% SPK with pancreas loss y1 vs 49.7% DKD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ojo [78] 1988-1998</td>
<td>1988-1998</td>
<td>34</td>
<td>ESRD type 1 DM on SPK waiting list (N=13467)</td>
<td>95.9% SPK vs. 97.2% LDK vs. 95.6% DKD</td>
<td>88.6% SPK vs. 80.0% LDK vs. 73.9% SPK with pancreas loss y1 vs 64.8% DKD</td>
<td>92.0% SPK vs. 94.8% LDK vs. 90.3% DKD</td>
<td>72% SPK (functioning pancreas y1) vs. 63.6% LDK vs. 59.8% SPK with pancreas loss y1 vs 49.7% DKD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poommipannit [74] 2000-2007</td>
<td>2000-2007</td>
<td>28</td>
<td>type 1 DM on SPK waiting list (N=11966)</td>
<td>99.2% PALK vs. 95.6% SPK</td>
<td>91% PALK vs. 87% SPK</td>
<td>86% PALK vs. 77% SPK</td>
<td>92% PALK vs. 84% KTA-eligible PAK</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Kleinclaus [62] 1995-2003</td>
<td>1995-2003</td>
<td>45</td>
<td>Diabetes (type 1 or 2) LDK recipients (N=250)</td>
<td>98% PAK vs. 100% KTA-eligible PAK</td>
<td>89% PAK vs. 88% KTA-eligible PAK</td>
<td>71% PAK vs. 76% KTA-eligible PAK</td>
<td>82% PAK vs. 84% KTA-eligible PAK</td>
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<td></td>
</tr>
</tbody>
</table>


*it is unclear whether this is not a mistake in the original data, as 5 year graft KTA was reported to be 58%, whereas 5 year patient survival was reported to be 57%
Table 6: Comparison of the different glycaemic markers in patients with diabetes and CKD stage 3b or higher

<table>
<thead>
<tr>
<th>Marker</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>• Marker of longer-term glycaemic concentrations</td>
<td>• Falsely increased values with iron deficiency, vitamin B12 deficiency, decreased erythropoiesis,</td>
</tr>
<tr>
<td></td>
<td>• Excellent standardization of HbA1c assays,</td>
<td>alcoholism, chronic renal failure, decreased erythrocyte pH, increased erythrocyte lifespan,</td>
</tr>
<tr>
<td></td>
<td>• Universally available primary reference measurement system</td>
<td>splenectomy, hyperbilirubinemia, carbamylated hemoglobin, alcoholism, intake of large doses of</td>
</tr>
<tr>
<td></td>
<td>• Scientific evidence on association with outcomes from several trials</td>
<td>aspirin, chronic opiate use</td>
</tr>
<tr>
<td></td>
<td>• In comparison with blood glucose, less sensitivity to preanalytical variables, lower within</td>
<td>• Falsely decreased values have been reported after administration of erythropoietin, iron or</td>
</tr>
<tr>
<td></td>
<td>subject biological variability, little/no diurnal variations, little/no influence from common</td>
<td>vitamin B12; with reticulocytosis; chronic liver disease, ingestion of aspirin, vitamin C, vitamin E,</td>
</tr>
<tr>
<td></td>
<td>drugs which are known to influence glucose metabolism</td>
<td>certain hemoglobinopathies, increased erythrocyte pH, a decreased erythrocyte lifespan,</td>
</tr>
<tr>
<td></td>
<td>• Excellent separation of the HbA1c fraction from other hemoglobin adducts</td>
<td>hemoglobinopathies, splenomegaly, rheumatoid arthritis, drugs such as antiretrovirals, ribavirin</td>
</tr>
<tr>
<td></td>
<td>and with no interference from carbamylated hemoglobin due to technological advances in HbA1c</td>
<td>and dapsone, hypertriglyceridemia</td>
</tr>
<tr>
<td></td>
<td>measurement</td>
<td>• Variable changes have been seen in patients with HbF, hemoglobinopathies, methemoglobin,</td>
</tr>
<tr>
<td>Glycated albumin</td>
<td>• Measure of shorter-term glycaemic control (2-3 weeks)</td>
<td>genetic determinants</td>
</tr>
<tr>
<td></td>
<td>• Not influenced by gender, erythrocyte lifespan, erythropoietin therapy or serum albumin</td>
<td>• Values can be influenced by lipemia, hyperbilirubinemia, hemolysis, increased uric acid, uremia,</td>
</tr>
<tr>
<td></td>
<td>concentration</td>
<td>intake of high doses of aspirin, low serum protein concentrations/ nutritional status, age,</td>
</tr>
<tr>
<td></td>
<td>• Significant association with markers of vascular injury</td>
<td>albuminuria, cirrhosis, thyroid dysfunction and smoking</td>
</tr>
<tr>
<td>Fructosamine</td>
<td>• Correlates with average glucose levels in the previous 10-14 days</td>
<td>• Concentration is inversely influenced by body mass index, body fat mass and visceral adipose tissue</td>
</tr>
<tr>
<td></td>
<td>• Simple, automated analysis</td>
<td>• Different reference ranges depending on the applied method</td>
</tr>
<tr>
<td>1,5-anhydroglucitol</td>
<td>• Reflects day-to-day changes in glucose levels</td>
<td>• Limited data, especially on the impact of using it as a target</td>
</tr>
<tr>
<td></td>
<td>• Retained metabolic inertness, steady-state levels in all tissues and negligible influence of</td>
<td>• Expensive, time consuming, not widely available</td>
</tr>
<tr>
<td></td>
<td>sampling conditions such as collection time, body weight, age, sex and food intake of the subjects</td>
<td></td>
</tr>
<tr>
<td>Continuous glucose measurement</td>
<td>• Theoretically the most ideal marker for glycaemic control</td>
<td>• Poorer performance in identifying cases of undiagnosed diabetes in comparison with other</td>
</tr>
<tr>
<td></td>
<td>• Allows examination of short-term glycaemic changes around the time of</td>
<td>glycaemic markers</td>
</tr>
<tr>
<td></td>
<td>dialysis</td>
<td>• Influenced by traditional Chinese herbal drugs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Limitations for use in subjects with renal tubular acidosis, or advanced renal disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Not widely available, limited data on its clinical everyday value</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Table 7: Dose recommendations of statins in patients with CKD stage 3b or higher (eGFR<45ml/min)

<table>
<thead>
<tr>
<th>Statin</th>
<th>Maximum dose when eGFR &lt;45ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin</td>
<td>No data</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>80mg</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>20mg</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>10mg</td>
</tr>
<tr>
<td>Simvastatin/ezetimibe</td>
<td>20/10mg</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>40mg</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>40mg</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>2mg</td>
</tr>
</tbody>
</table>

(adapted from Tonelli and Wanner, Annals of Internal Medicine, 2014[193])
11. Figures

Figure 1: Grade System for Grading Recommendations

Adapted from Gyatt GH et al. BMJ 2008; 336: 924-926. [8]
Figure 2: decision flow chart for vascular access in patients with diabetes

1. **Patient eGFR <15ml/min?**
   - yes
   - no

2. **eGFR decline progressive?**
   - yes
   - no

3. **Patient selects HD as RRT modality?**
   - yes
   - no

4. **Projected life expectancy > 1 year?**
   - yes
   - no

5. **Vascular mapping:**
   - diameter of vene >2.5mm
   - diameter of artery >2.0 mm
   - positive fist squenches test?
     - yes
     - no

6. **Discuss options**
   - native fistula
   - graft
   - catheter
   - with
     - vascular surgeon
     - patient

7. **Create native vascular access**
Figure 3: Transplantation decision flow chart for patients with type 1 diabetes

Patient with type 1 diabetes suitable candidate for kidney transplantation

Living donor available?

- Yes: Pre-emptive living donor kidney
  - Pancreas after kidney?
    - No: Simultaneous pancreas kidney
    - Yes: Cadaveric kidney alone
  - Yes: Cardiac vascular comorbidity or increased peri-operative risk?

- No: Cardiovascular comorbidity or increased peri-operative risk?
  - No: Simultaneous pancreas kidney
  - Yes: Cadaveric kidney alone

Figure 4: Flowchart of management targets for HbA1C in patients with diabetes and CKD stage 3b or higher (eGFR < 45 ml/min)

Comprehensive risk analysis:

FRAILTY or ONE of the following:

- Risk for hypoglycaemia (see figure)
- Poor motivation and attitude of patient
- Decreased general life expectancy
- Cardiovascular disease
- Presence of micro-vascular complications

- Yes: ≤ 69 mmol/mol
- No

Lifestyle only or therapy with low hypoglycaemia risk

- Yes: ≤ 53 mmol/mol
- No

Diabetes duration > 10 years

- Yes: ≤ 64 mmol/mol
- No: ≤ 58 mmol/mol

The guideline group wants to promote the new units to express HbA1C (mmol/mol rather than %). Corresponding values of 69, 64, 58 and 53 mmol/l are 8.5, 8.0, 7.5 and 7% respectively.
Figure 5: Assessment of risk for hypoglycaemia

- Short acting SU derivates or SU derivates with inactive metabolites
- Meglitinides
- Insulin
- Long acting SU derivates with active metabolites
- Metformin
- Alpha glucosidase inhibitors
- DPP-IV inhibitors
- Incretin mimetics
- TZD’s
- SGLT-2 inhibitors

* Drug-drug interactions
* Hepatic failure
* CKD stage 5
* Gastroparesis

Hypoglycaemia risk
Figure 6: Dose recommendations in CKD

<table>
<thead>
<tr>
<th>Drug</th>
<th>CKD-1</th>
<th>CKD-2</th>
<th>CKD-3</th>
<th>CKD-4</th>
<th>CKD-5N</th>
<th>CKD-5D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>No adjustments</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Consider carefully/Awaiting further data</td>
</tr>
<tr>
<td>Chlorpropamide</td>
<td>No adjustments</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aceto-hexamide</td>
<td>To be avoided</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tolazamide</td>
<td>To be avoided</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>250mg, 1-3 times/day</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Glipizide</td>
<td>No adjustments</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gliclazide</td>
<td>Start at low doses and dose titration every 1-4 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glyburide</td>
<td>To be avoided</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gliclazide</td>
<td>Reduce dosage to 1 mg/day</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Glimepiride</td>
<td>No adjustments</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gliquidone</td>
<td>No adjustments</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repaglinide</td>
<td>No adjustments</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nateglinide</td>
<td>No adjustments</td>
<td>Start at 60 mg/day</td>
<td></td>
<td></td>
<td></td>
<td>To be avoided</td>
</tr>
<tr>
<td>Acarbose</td>
<td>No adjustments</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miglitol</td>
<td>No adjustments</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>No adjustments</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Sitagliptin</td>
<td>No adjustments</td>
<td>Reduce to 50 mg/day</td>
<td>Reduce to 25 mg/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>No adjustments</td>
<td></td>
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<td></td>
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<tr>
<td>Saxagliptin</td>
<td>No adjustments</td>
<td>Reduce to 50 mg/once daily</td>
<td></td>
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</tr>
<tr>
<td>Linagliptin</td>
<td>No adjustments</td>
<td>Reduce to 2,5 mg/once daily</td>
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<tr>
<td>Alogliptin</td>
<td>No adjustments</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Exenatide</td>
<td>No adjustments</td>
<td>Reduce dose to 5 mcg/once to twice daily</td>
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</tr>
<tr>
<td>Liraglutide</td>
<td>Limited experience available</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Lixisenatide</td>
<td>No adjustments</td>
<td></td>
<td>Careful use if GFR 80-50 mL/min</td>
<td></td>
<td></td>
<td>No experience available</td>
</tr>
<tr>
<td>Pramlintide</td>
<td>Limited experience available</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>Limited experience available</td>
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</tr>
<tr>
<td>Canagliflozin</td>
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<td>Careful monitoring</td>
<td></td>
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<tr>
<td>Empagliflozin</td>
<td>Limited experience available</td>
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Figure 7: impact of different classes of glycaemia lowering drugs on different outcomes

<table>
<thead>
<tr>
<th>Class</th>
<th>All cause mortality</th>
<th>Cardiovascular events</th>
<th>Risk of hypoglycaemia</th>
<th>Weight gain</th>
<th>HbA1C change</th>
<th>dose adaptation in CKD stage 3b or higher (eGFR&lt;45ml/min)</th>
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<td>Biguanides</td>
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<tr>
<td>Metformin</td>
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<td>Yes</td>
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<td>a-glucosidase inhibitors</td>
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</tr>
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<td>No</td>
<td>No</td>
<td>Avoid</td>
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<td>Yes</td>
<td>Yes</td>
<td>Avoid</td>
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<td>Incretin mimetics</td>
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<tr>
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<td>Avoid</td>
<td>Most likely not</td>
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<tr>
<td>Liraglutide</td>
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<td>Avoid</td>
<td>Avoid</td>
<td>Most likely not</td>
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<td>Avoid</td>
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<tr>
<td>Lixisenatide</td>
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<td>Avoid</td>
<td>Avoid</td>
<td>Most likely not</td>
<td>No data</td>
<td>Avoid</td>
</tr>
<tr>
<td>Pramlintide</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>Avoid</td>
</tr>
<tr>
<td>SGLT-2 inhibitors</td>
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</tr>
<tr>
<td>Dapagliflozin</td>
<td>Avoid; not effective</td>
<td>Avoid; not effective</td>
<td>No</td>
<td>Yes</td>
<td>No data</td>
<td>Avoid; not effective</td>
</tr>
<tr>
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<td>Avoid; not effective</td>
<td>No</td>
<td>Yes</td>
<td>No data</td>
<td>Avoid; not effective</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>Avoid; not effective</td>
<td>Avoid; not effective</td>
<td>No</td>
<td>Yes</td>
<td>No data</td>
<td>Avoid; not effective</td>
</tr>
</tbody>
</table>

(for full data extraction: see supplementary tables) and Arnouts et al[111]. dark green: evidence for beneficial effect; red: evidence for negative effect; yellow: not investigated or insufficient data; salmon: evidence for weak negative effect; aquamarin: evidence for neutral to weak positive effect; dark blue: evidence for lack of effect/neutral
12. Acknowledgements

We would like to express our sincerest gratitude to all internal reviewers for taking the time to critically read the drafts of this document and to provide us with their comments: We strongly believe it has contributed to the quality of the guideline and has helped maximizing its practical value.

Finally, we gratefully acknowledge the careful assessment of the draft guideline by external reviewers. The guideline development group considered all the valuable comments made and, where appropriate, we incorporated suggested changes in the final document. The following individuals provided an external review of the draft guideline:
Appendix 1

Guideline Development Group Area of Expertise

Guideline Development Group

**Henk Bilo** is consultant physician at the Isala Hospital in Zwolle and professor in internal medicine at the university of Groningen, the Netherlands. He is working both in secondary practice and in close cooperation with primary care groups with regard to diabetes care. He authored and co-authored over 250 articles and wrote contributions for over 35 books, mainly in the field of diabetes and nephrology. He participated in country wide initiatives to improve diabetes care.

**Luís Coentrão** finished his graduation from the Medical University of Porto in 2005. From 2006-2011 was Junior Assistant of Pharmacology and Therapeutic from the Medical University of Porto. Finished the Specialty of Nephrology in Hospital São João Centre, Porto, in 2012. During the specialty he dedicated his efforts to the Interventional Nephrology field. Presented his PhD thesis titled “Dialysis Access for Chronic Renal Replacement Therapy: Clinical and Economic Implications” to the Medical University of Porto in 2013. Since 2012 he is a fellow of the Intensive Care Medicine Department in Hospital São João Centre, Porto

**Cécile Couchoud** is nephrologist and has a PhD in epidemiology. She is working for the French end-stage renal disease registry since 2003 and plays a part in the Moroccan end-stage renal disease registry since 2005. Currently Dr. Couchoud is specializing in renal epidemiology. Her research interests include development of statistical tools for decision making in Public Health or Clinical Nephrology.

**Adrian Covic** is a Full Professor of Nephrology and Internal Medicine at the “Gr.T. Popa” University of Medicine and Pharmacy and the Director of the Nephrology Clinic and the Dialysis and Transplantation Center in Iasi, Romania. Prof. Covic published more than 200 original and review papers in peer-reviewed journals, 11 books and 22 chapters.

**Johan De Sutter** is a cardiologist and professor of at the Ghent University Belgium. He is author and co-author of more than 160 articles dealing with a wide variety of topics in cardiology (heart failure, valvular heart disease, non-invasive imaging, cardiovascular prevention). He is active within the European Society of Cardiology since several years and participated in different ESC guidelines (including atrial fibrillation, non-STEMI etc). He is current board member of the European Association of Cardiovascular Prevention and Rehabilitation and the actual programm committee chair of Europrevent, the largest CV prevention congress in Europe. He is also Associate Editor of the International Journal of Cardiovascular Imaging and member of the editorial board of different other journals. He is a Subject Editor for NDT, an Editor in Chief Nephrology for the International Journal of Urology and Nephrology, and editor / reviewer for several prestigous journals. Prof. Covic is the current president of Romanian Society of Nephrology and a board member of ERBP. His main areas of interest are: cardiovascular complications in renal disease, renal anaemia, CKD-MBD, peritoneal dialysis, and acute renal failure.

**Luigi Gnudi** obtained his MD with Honours from the University of Parma (Italy) in 1988. He subsequently joined the residency programme at the School of Diabetes and Endocrinology at the University of Padua-Italy (1989-1993). During 1993-1995, he worked as a postdoctoral fellow with
Prof Barbara B Kahn at Beth Israel Hospital, Harvard Medical School in Boston. In 1998 he obtained a PhD in Endocrinological Sciences from the University of Milan. He became a Fellow of both the Royal College of Physicians and the American Society of Nephrology in 2005. Dr Gnudi joined the Unit for Metabolic Medicine (within the Department of Diabetes, Endocrinology and Internal Medicine) in 1997 as Senior Lecturer and was promoted to Professor of Diabetes and Metabolic Medicine in 2011. He became Head of the Unit for Metabolic Medicine in 2010. Prof Gnudi is an Honorary Consultant Physician in Diabetes, Endocrinology and Metabolic Medicine at Guy's and St Thomas' Hospital NHS Foundation Trust.

David Goldsmith is a Consultant Nephrologist at Guy's and St Thomas' Hospitals (1998-present) and is Professor of Nephrology at G.T.Popu University of Medicine and Pharmacy, Iasi, Romania. He is a co-author of 4 books, 25 chapters, and around 350 PubMed published articles. His clinical and research interests focus on cardiovascular diseases, calcification syndromes and other metabolic derangements in chronic kidney disease.

James Heaf is a nephrology consultant at Herlev Hospital, University of Copenhagen, with special responsibility for peritoneal dialysis. He is the director of the Danish Nephrology Registry, and a member of the ERA-EDTA Registry committee. His MD thesis on the subject of aluminium osteodystrophy was published in 1992. He has published more than 130 papers on a number of nephrological subjects including mineral bone disease, peritoneal dialysis, epidemiology and uraemia progression. He is a reviewer for a several nephrology journals.

Olof Heimbürger is consultant nephrologist and director of peritoneal dialysis at the department of renal medicine, Karolinska University Hospital, Stockholm, Sweden and associate professor of nephrology at the Karolinska Institutet. He has more than 25 years of clinical experience in renal medicine and has published about 300 scientific papers and text-book chapter, mainly about peritoneal dialysis, nutrition, metabolism, inflammation, biomarkers, cardiovascular disease and genetics in patients with chronic kidney disease. Olof Heimbürger was secretary of the International Society of Peritoneal Dialysis 2006-2014 and is member of the ERBP advisory board. He is a regular reviewer of scientific papers on nephrology journals.

Kitty Jager is associate professor of medical informatics at the Academic Medical Center in Amsterdam, The Netherlands. She has authored and co-authored over 210 scientific papers on the epidemiology of kidney disease, quality of care in renal replacement therapy and related research methods. She is the director of the ERA-EDTA Registry and leads a number of other European renal registries and studies. Currently, she is Perspectives Editor for renal epidemiology for Nephrology Dialysis Transplantation and serves as an editor for a number of other journals. In addition, she is a reviewer for different nephrology journals.

Hakan Nacak started medical school in 2008 at the Leiden University Medical Center in The Netherlands. In 2012 he started his PhD-thesis about pre-dialysis care, specifically concerning uric acid and sodium management, and initiation of dialysis. In the same year he also started his training to become an epidemiologist. In 2012 Hakan joined the ERBP guideline working group and investigates optimal timing of dialysis initiation in patients with diabetes with CKD.

Maria José Soler is a consultant nephrologist at the Hospital del Mar, Barcelona, Spain. She is also associate professor of nephrology at the University of Pompeu Fabra of Barcelona, Spain. Since 2000, she has been working in the hospitalization unit and outpatient consultation within the chronic and acute kidney disease management. Her research interest has focused on diabetic nephropathy from the bench to the bedside. Dr. Soler completed a fellowship in Research and Nephrology at the Northwestern University of Chicago, USA, in 2005-2007. She has completed a doctoral thesis in 2007, on "Angiotensin converting enzyme 2 in diabetic kidney disease", and received extraordinary Ph.D.
Award in 2007. She is author or co-author of more than 200 congress communications and peer-reviewed journal articles, covering a wide variety of topics in nephrology (clinical and experimental diabetic nephropathy, haemodialysis, transplantation). Her basic research work has been consistently funded by the National Institute of Health.

Charles Tomson has been a consultant nephrologist in Bristol since 1993. He chaired the group that developed the first UK joint guidelines on CKD, published in 2005. He was Chair of the UK Renal Registry, 2006-2010, President of the Renal Association 2010-2012, and Chair of the Joint Committee on Renal Disease of the Renal Association and the Royal College of Physicians 2012-2014. He led on the chapter on CKD with diabetes mellitus in the 2012 KDIGO guideline on blood pressure in CKD. His clinical practice includes CKD, AKI, dialysis, transplantation, and metabolic stone disease.

Liesbeth Van Huffel graduated from the Ghent Medical University in 2009 and started her fellowship Endocrinology in 2013 with Professor Jean-Marc Kaufman. Along with her clinical training Dr. Van Huffel worked on several projects about the effect of exercise and diet on diabetic patients. She joined the ERBP fellows group for this project in September 2013. She is currently finishing her fellowship Endocrinology at the Ghent University.

Steven Van Laecke is Consultant Nephrologist at the Ghent University Hospital in Belgium and graduated in 2000. He has published clinical research especially concerning his main topics of interest, which are transplantation and chronic kidney disease. In 2012, he completed his PhD in Medical Science on the role of magnesium in transplantation. He is a regular reviewer of scientific papers in the field of transplantation and clinical nephrology.

Laurent Weekers is a chief of clinics in the Nephrology and Transplantation Unit at the Liege University Hospital, Belgium. He has trained both in Diabetology and Nephrology and has published several papers on the risk factors for diabetic nephropathy. He is one of the current Belgian representatives at Eurotransplant Kidney Transplant Advisory Committee.

Andrzej Wiecek, MD, PhD, FRCP (Edin.), FERA initially studied for his medical degree from 1974 to 1980 in Katowice, Poland. From 1985 to 1986 and in 1993 he held scientific scholarships in nephrology at the University of Heidelberg, Germany. Professor Wiecek has furthermore received a membership of the Polish Academy of Arts and Sciences (2011), Polish Academy of Science (2013). In 2011, he received a doctor honoris causa from the Semmelweis University in Budapest, Hungary and is a honorary member of the Romanian Society of Nephrology (2003). Professor Wiecek is the author or co-author of more than 600 scientific papers and more than 100 book chapters, as well as co-editor of 20 books on the field of hypertension and kidney diseases. During recent years Professor Wiecek has served in eminent positions such as: President of the Polish Society of Hypertension (2000 -2002); President of the Polish Society of Nephrology (2007 -2010) · Council member of the Polish Society of Transplantology (2003 -2005) · Council member of the ERA-EDTA (1999 – 2002 and 2006 – 2009) · Secretary - Treasurer of the ERA-EDTA (2011 -2014) · President of the ERA-EDTA (2014 -2017) · Member of numerous KDIGO expert groups and director boards.

ERBP Methods Support Team

Davide Bolignano is a specialist registrar in nephrology, working as full researcher at the Institute of Clinical Physiology of the National Council of Research in Reggio Calabria, Italy. In 2011, he joined the ERBP group as member of the methods support team. Dr. Bolignano is currently pursuing a PhD in renal pathophysiology at the Erasmus University of Rotterdam. In 2012 he trained in guideline.
development and systematic reviews methodology at the Cochrane Renal group in Sydney, Australia and in 2014 he obtained the Global Clinical Scholars Research Training Program in methods and conduct of clinical research certificate at the Harvard Medical School. Dr. Bolignano is currently author/co-author of more than 90 articles on various topics in nephrology and regular reviewer for different scientific journals.

Christiane Drechsler is a consultant nephrologist at the University of Würzburg in Germany. She has also been trained in clinical epidemiology at the Netherlands Institute of Health Sciences in Rotterdam, and the Department of Clinical Epidemiology in Leiden, the Netherlands. She graduated with a Master of Science in 2007 and with a PhD in clinical epidemiology in 2010. At the University Hospital Würzburg, she is doing clinical practice in nephrology as well as research activities. Her research work focuses on sudden cardiac death and the clinical epidemiology of cardiac and diabetic complications in chronic kidney disease. She has published a variety of scientific papers and is a regular reviewer of scientific papers in nephrology. She joined the methods support team of ERBP in 2014.

Maria Haller graduated from the Medical University Vienna in 2006 and started her renal fellowship in 2008 with Professor Rainer Oberbauer. Along with her clinical training Dr. Haller worked on renal research projects, such as a cost effectiveness analysis of renal replacement therapy and the molecular mechanisms of sirolimus induced phosphaturia at the University of Zurich. Additionally Maria obtained a Master's degree in Health Care Management at the Vienna University of Economics and Business in 2012. A description of her PhD plan and full CV can be viewed through this link. Maria joined the ERBP fellow group in June 2012.

Ionut Nistor is a Nephrologist at the Nephrology Department, "Gr. T. Popa" University of Medicine and Pharmacy, Iasi, Romania. He started a PhD in 2011, on the evidence for treatment of diabetic patients with developed CKD 3b/4/5. Ionut Nistor joined the European Renal Best Practice (ERBP) from August 2011 as an ERBP fellow in the Methods team. His research interests also include cardiovascular complication in CKD patients, dialysis and transplant patients. Ionut got trained in the skills of guideline-related literature searching and evidence grading from the Cochrane Renal Group. He worked as Honorary Research Fellow with the Cochrane Renal Group (based at the Centre for Kidney Research, The Children's Hospital at Westmead, Sydney, Australia).

Evi Nagler is a specialist registrar in Nephrology at the University of Ghent, Belgium, currently pursuing a PhD in clinical epidemiology. She was the first of four fellows to be enrolled in a fellowship program, awarded by European Renal Best Practice, to train in guideline development methodology. As member of the methods support team she is primarily responsible for providing methodological support to the guideline development working groups. In addition she is involved with process management and as such engaged in optimizing the tools and techniques used in the management of the guideline development process.

Sabine van der Veer worked as an IT project manager in the Academic Medical Center (Amsterdam, the Netherlands) after obtaining her degree in medical informatics at the University of Amsterdam. In 2007, she started a PhD project under the supervision of Kitty Jager, entitled Systematic quality improvement in healthcare: clinical performance measurement and registry-based feedback. Within this project she developed an instrument to measure dialysis patient experience, investigated implementation of best renal practice as a NephroQUEST research fellow at the UK Renal Registry (Bristol, UK), and conducted a cluster RCT among Dutch intensive care units to evaluate the effectiveness of clinical performance feedback. She defended her PhD thesis in June 2012. She joined the ERBP fellow group since February 2012. Her focus is on investigating and improving the dissemination and implementation of guidance on renal best practice in Europe; this includes documents produced by the ERBP as well as by other organisations.
Wim Van Biesen is professor of nephrology at the Ghent University Hospital, Belgium. 
He is author and co-author of more than 230 articles dealing with a wide variety of topics in 
nephrology (peritoneal dialysis, haemodialysis, chronic kidney disease management), intensive care 
nephrology. He is the actual chair of ERBP. He is also Subject Editor for dialysis for Nephrology, 
Dialysis and Transplantation and is member of the editorial board of different other journals. He is a 
regular reviewer of scientific papers for different journals on nephrology, intensive care and 
epidemiology.

Guideline development group Declaration of Interest

DR HENK BILO

1. Do you have, or have you had during the past 2 years, any formal association with a company or other 
interested party?
No

2. Do you have, or have you had during the past 2 years, any of the following types of association with a 
company or other interested party?
No

3. Do you have, or have you had during the past 2 years, any job, position, research grant, or other grant 
that involved a company or other interested party?
Research grant

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<td>2013-2014</td>
<td>Novo Nordisk</td>
<td>More than EUR 10,000</td>
<td>grant for research purposes, study approved by medical ethical committee</td>
</tr>
<tr>
<td></td>
<td>Research fund</td>
<td></td>
<td>Unrestricted</td>
</tr>
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</table>

4. Other potential conflicts of interest?
No

5. Is there anything else that might influence your judgement, or might be perceived to do so?
No

6. Member (current) of any kind of committee, board, WG, etc. of another scientific association with 
similar aims as ERA-EDTA
Yes, involved in standard committees of the Dutch primary care organisation, Dutch consultant physician 
organisation

DR. DAVIDE BOLIGNANO

1. Do you have, or have you had during the past 2 years, any formal association with a company or other 
interested party?
No
2. Do you have, or have you had during the past 2 years, any of the following types of association with a company or other interested party?

No

3. Do you have, or have you had during the past 2 years, any job, position, research grant, or other grant that involved a company or other interested party?

No

4. Other potential conflicts of interest?

No

5. Is there anything else that might influence your judgement, or might be perceived to do so?

No

6. Member (current) of any kind of committee, board, WG, etc. of another scientific association with similar aims as ERA-EDTA

Yes. ERA-EDTA Young Nephrologists Platform Board member

DR. LUIS COENTRAO

1. Do you have, or have you had during the past 2 years, any formal association with a company or other interested party?

No

2. Do you have, or have you had during the past 2 years, any of the following types of association with a company or other interested party?

No

3. Do you have, or have you had during the past 2 years, any job, position, research grant, or other grant that involved a company or other interested party?

No

4. Other potential conflicts of interest?

No

5. Is there anything else that might influence your judgement, or might be perceived to do so?

No

6. Member (current) of any kind of committee, board, WG, etc. of another scientific association with similar aims as ERA-EDTA

No

DR. CECILE COUCHOUD

1. Do you have, or have you had during the past 2 years, any formal association with a company or other interested party?

No

2. Do you have, or have you had during the past 2 years, any of the following types of association with a company or other interested party?

No

3. Do you have, or have you had during the past 2 years, any job, position, research grant, or other grant that involved a company or other interested party?
No

4. Other potential conflicts of interest?
No

5. Is there anything else that might influence your judgement, or might be perceived to do so?
No

6. Member (current) of any kind of committee, board, WG, etc. of another scientific association with similar aims as ERA-EDTA
Yes. KDIGO, French Society of Nephrology

PROF. ADRIAN COVIC

1. Do you have, or have you had during the past 2 years, any formal association with a company or other interested party?
No

2. Do you have, or have you had during the past 2 years, any of the following types of association with a company or other interested party?
No

3. Do you have, or have you had during the past 2 years, any job, position, research grant, or other grant that involved a company or other interested party?
No

4. Other potential conflicts of interest?
No

5. Is there anything else that might influence your judgement, or might be perceived to do so?
No

6. Member (current) of any kind of committee, board, WG, etc. of another scientific association with similar aims as ERA-EDTA
No

DR. CHRISTIANE DRECHSLER

1. Do you have, or have you had during the past 2 years, any formal association with a company or other interested party?
No

2. Do you have, or have you had during the past 2 years, any of the following types of association with a company or other interested party?
No

3. Do you have, or have you had during the past 2 years, any job, position, research grant, or other grant that involved a company or other interested party?
No

4. Other potential conflicts of interest?
No

5. Is there anything else that might influence your judgement, or might be perceived to do so?
No
6. Member (current) of any kind of committee, board, WG, etc. of another scientific association with similar aims as ERA-EDTA

Yes. ASN, German Society of Nephrology

**DR. LUIGI GNUDI**

1. Do you have, or have you had during the past 2 years, any formal association with a company or other interested party?

<table>
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3. Do you have, or have you had during the past 2 years, any job, position, research grant, or other grant that involved a company or other interested party?

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<th>Date</th>
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<td>Abbvie</td>
<td>Less than EUR 1,000</td>
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<td>Research grant</td>
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4. Other potential conflicts of interest?
No

5. Is there anything else that might influence your judgement, or might be perceived to do so?
No

6. Member (current) of any kind of committee, board, WG, etc. of another scientific association with similar aims as ERA-EDTA
No

**DR. DAVID GOLDSMITH**

1. Do you have, or have you had during the past 2 years, any formal association with a company or other
interested party?

<table>
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<tr>
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2. Do you have, or have you had during the past 2 years, any of the following types of association with a company or other interested party?

- **Giving expert/scientific advice**
  - Date: 2013-2014
  - Company or interest group: Sanofi, Keryx, Amgen, Abbott, Fresenius
  - Value: EUR 1,000-10,000
  - Payment made to: Personal account

- **Lecturing, chairing lectures or participation in symposia/panel discussions**
  - Date: 2013-2014
  - Company or interest group: Sanofi, Keryx, Amgen, Abbott, Fresenius
  - Value: Less than EUR 1,000
  - Payment made to: Personal account

- **Conference/meeting registration fees paid or reimbursed**
  - Date: 2013-2014
  - Company or interest group: Sanofi, Keryx, Amgen, Abbott, Fresenius
  - Value: EUR 1,000-10,000
  - Payment made to: Personal account

- **Travel or accommodation provided or reimbursed**
  - Date: 2013-2014
  - Company or interest group: Sanofi, Keryx, Amgen, Abbott, Fresenius
  - Value: EUR 1,000-10,000
  - Payment made to: Personal account

3. Do you have, or have you had during the past 2 years, any job, position, research grant, or other grant that involved a company or other interested party?

No

4. Other potential conflicts of interest?

No

5. Is there anything else that might influence your judgement, or might be perceived to do so?

No

6. Member (current) of any kind of committee, board, WG, etc. of another scientific association with similar aims as ERA-EDTA

Yes. Board of CKD-MBD WG

**DR. JAMES G. HEAF**

1. Do you have, or have you had during the past 2 years, any formal association with a company or other interested party?

No

2. Do you have, or have you had during the past 2 years, any of the following types of association with a company or other interested party?

No
3. Do you have, or have you had during the past 2 years, any job, position, research grant, or other grant that involved a company or other interested party?

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4. Other potential conflicts of interest?

No

5. Is there anything else that might influence your judgement, or might be perceived to do so?

No

6. Member (current) of any kind of committee, board, WG, etc. of another scientific association with similar aims as ERA-EDTA

Yes. ISPD, ASN

DR. OLOF HEIMBURGER

1. Do you have, or have you had during the past 2 years, any formal association with a company or other interested party?

   Consultant for company
   
<table>
<thead>
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<tbody>
<tr>
<td>Company or interest group</td>
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2. Do you have, or have you had during the past 2 years, any of the following types of association with a company or other interested party?

   Lecturing, chairing lectures or participation in symposia/panel discussions
   
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3. Do you have, or have you had during the past 2 years, any job, position, research grant, or other grant that involved a company or other interested party?

   Principal investigator
   
<table>
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<tr>
<th>Date</th>
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4. Other potential conflicts of interest?

Related to, or have close relationship with, someone in company or interest group

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<tr>
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<tr>
<td>Payment made to</td>
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<tr>
<td>Nature of interest</td>
<td>My brother is employed by Abbvie</td>
</tr>
</tbody>
</table>

5. Is there anything else that might influence your judgement, or might be perceived to do so?

No

6. Member (current) of any kind of committee, board, WG, etc. of another scientific association with similar aims as ERA-EDTA

Yes. Representative for Sweden in the UEMS Renal Section

DR. KITTY J JAGER

1. Do you have, or have you had during the past 2 years, any formal association with a company or other interested party?

No

2. Do you have, or have you had during the past 2 years, any of the following types of association with a company or other interested party?

No

3. Do you have, or have you had during the past 2 years, any job, position, research grant, or other grant that involved a company or other interested party?

No

4. Other potential conflicts of interest?

No

5. Is there anything else that might influence your judgement, or might be perceived to do so?

No

6. Member (current) of any kind of committee, board, WG, etc. of another scientific association with similar aims as ERA-EDTA

Yes. ESPN

MRS ANNA MARTI I MONROS

1. Do you have, or have you had during the past 2 years, any formal association with a company or other interested party?

Board of company

<table>
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<td>Fresenius Medical Care</td>
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<tr>
<td>Value</td>
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</tbody>
</table>
2. Do you have, or have you had during the past 2 years, any of the following types of association with a company or other interested party?

| Lecturing, chairing lectures or participation in symposia/panel discussions |  
| Company or interest group | Janse Cilag  
| Value | Less than EUR 1,000  
| Payment made to | Personal account  
| Date | 2011-2012  
| Company or interest group | Arbor Research  
| Value | EUR 1,000-10,000  
| Payment made to | Other, Conference Department  
| Conference/meeting registration fees paid or reimbursed |  
| Company or interest group | Fresenius Medical Care  
| Value | Less than EUR 1,000  
| Payment made to | Other, Conference Organization  
| Travel or accommodation provided or reimbursed |  
| Company or interest group | IZASA  
| Value | Less than EUR 1,000  
| Payment made to | Other, Conference Department  

3. Do you have, or have you had during the past 2 years, any job, position, research grant, or other grant that involved a company or other interested party?

| Other type of grant |  
| Company or interest group | EDTNA/ERCA DOPPS European Product Manager  
| Value | EUR 1,000-10,000  
| Payment made to | Personal account  
| Nature of interest | Coordinating data collection in DOPPS European countries  
| Nature of restriction | Unrestricted  

4. Other potential conflicts of interest?

No

5. Is there anything else that might influence your judgement, or might be perceived to do so?

No

6. Member (current) of any kind of committee, board, WG, etc. of another scientific association with similar aims as ERA-EDTA

DR HAKAN NACAK

1. Do you have, or have you had during the past 2 years, any formal association with a company or other interested party?

No

2. Do you have, or have you had during the past 2 years, any of the following types of association with a company or other interested party?

No

3. Do you have, or have you had during the past 2 years, any job, position, research grant, or other grant that involved a company or other interested party?

No
4. Other potential conflicts of interest?
No

5. Is there anything else that might influence your judgement, or might be perceived to do so?
No

6. Member (current) of any kind of committee, board, WG, etc. of another scientific association with similar aims as ERA-EDTA
No

DR. EVI NAGLER

1. Do you have, or have you had during the past 2 years, any formal association with a company or other interested party?
No

2. Do you have, or have you had during the past 2 years, any of the following types of association with a company or other interested party?
No

3. Do you have, or have you had during the past 2 years, any job, position, research grant, or other grant that involved a company or other interested party?

   Academic position funded by company or interested party
   
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<td>Payment made to</td>
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<td>Nature of interest</td>
<td>Research Fellow - Assisting ERBP in its Guideline Development Process</td>
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4. Other potential conflicts of interest?
No

5. Is there anything else that might influence your judgement, or might be perceived to do so?
No

6. Member (current) of any kind of committee, board, WG, etc. of another scientific association with similar aims as ERA-EDTA
No

DR. IONUT NISTOR

1. Do you have, or have you had during the past 2 years, any formal association with a company or other interested party?
No

2. Do you have, or have you had during the past 2 years, any of the following types of association with a company or other interested party?
No

3. Do you have, or have you had during the past 2 years, any job, position, research grant, or other grant that involved a company or other interested party?
No

4. Other potential conflicts of interest?
5. Is there anything else that might influence your judgement, or might be perceived to do so?  
No

6. Member (current) of any kind of committee, board, WG, etc. of another scientific association with similar aims as ERA-EDTA  
No

**DR MARIA JOSE SOLER ROMEO**

1. Do you have, or have you had during the past 2 years, any formal association with a company or other interested party?  
No

2. Do you have, or have you had during the past 2 years, any of the following types of association with a company or other interested party?

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3. Do you have, or have you had during the past 2 years, any job, position, research grant, or other grant that involved a company or other interested party?

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4. Other potential conflicts of interest?  
No

5. Is there anything else that might influence your judgement, or might be perceived to do so?  
No

6. Member (current) of any kind of committee, board, WG, etc. of another scientific association with similar aims as ERA-EDTA  
No

**DR. CHARLES R.V. TOMSON**

1. Do you have, or have you had during the past 2 years, any formal association with a company or other interested party?  
No

2. Do you have, or have you had during the past 2 years, any of the following types of association with a company or other interested party?  
No

3. Do you have, or have you had during the past 2 years, any job, position, research grant, or other grant
that involved a company or other interested party?
No

4. Other potential conflicts of interest?
No

5. Is there anything else that might influence your judgement, or might be perceived to do so?
No

6. Member (current) of any kind of committee, board, WG, etc. of another scientific association with similar aims as ERA-EDTA
Yes. NHS England/UK Renal Registry Acute Kidney Injury National Programme

DR. WIM VAN BIESEN

1. Do you have, or have you had during the past 2 years, any formal association with a company or other interested party?
No

2. Do you have, or have you had during the past 2 years, any of the following types of association with a company or other interested party?

Involvement in marketing or product development

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Lecturing, chairing lectures or participation in symposia/panel discussions

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3. Do you have, or have you had during the past 2 years, any job, position, research grant, or other grant that involved a company or other interested party?
No

4. Other potential conflicts of interest?
No

5. Is there anything else that might influence your judgement, or might be perceived to do so?
No

6. Member (current) of any kind of committee, board, WG, etc. of another scientific association with similar aims as ERA-EDTA
No

DR LIESBETH VAN HUFFEL

1. Do you have, or have you had during the past 2 years, any formal association with a company or other interested party?
No

2. Do you have, or have you had during the past 2 years, any of the following types of association with a company or other interested party?

Lecturing, chairing lectures or participation in symposia/panel discussions

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No

4. Other potential conflicts of interest?

No

5. Is there anything else that might influence your judgement, or might be perceived to do so?

No

6. Member (current) of any kind of committee, board, WG, etc. of another scientific association with similar aims as ERA-EDTA

No

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**DR. STEVEN VAN LAECKE**

1. Do you have, or have you had during the past 2 years, any formal association with a company or other interested party?

No

2. Do you have, or have you had during the past 2 years, any of the following types of association with a company or other interested party?

No

3. Do you have, or have you had during the past 2 years, any job, position, research grant, or other grant that involved a company or other interested party?

No

4. Other potential conflicts of interest?

No

5. Is there anything else that might influence your judgement, or might be perceived to do so?

No

6. Member (current) of any kind of committee, board, WG, etc. of another scientific association with similar aims as ERA-EDTA

No

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**DR. LAURENT WEEKERS**

1. Do you have, or have you had during the past 2 years, any formal association with a company or other interested party?

No

2. Do you have, or have you had during the past 2 years, any of the following types of association with a company or other interested party?

Giving expert/scientific advice

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No

4. Other potential conflicts of interest?

No

5. Is there anything else that might influence your judgement, or might be perceived to do so?

No

6. Member (current) of any kind of committee, board, WG, etc. of another scientific association with similar aims as ERA-EDTA

No

PROF. ANDRZEJ JAN WIECEK

1. Do you have, or have you had during the past 2 years, any formal association with a company or other interested party?

No

2. Do you have, or have you had during the past 2 years, any of the following types of association with a company or other interested party?

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**Research grant**

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4. Other potential conflicts of interest?

No

5. Is there anything else that might influence your judgement, or might be perceived to do so?

No

6. Member (current) of any kind of committee, board, WG, etc. of another scientific association with similar aims as ERA-EDTA

No
## Appendix 2 | Review Questions – PICOM Format

### Chapter 1.1.
**Should patients with diabetes and CKD stage 5 start with peritoneal dialysis or haemodialysis as a first modality?**

| Patients                                      | Patients with diabetes mellitus (comorbidity or diabetic nephropathy) and chronic kidney disease CKD stage 5  
|                                               | Children, adults, aged adults  
|                                               | Diabetes mellitus type 1 or type 2 |
| Intervention                                  | Peritoneal dialysis of any kind as first modality  
|                                               | 1. Continuous ambulatory peritoneal dialysis - CAPD  
|                                               | 2. Automated peritoneal dialysis - APD |
| Comparator                                    | Haemodialysis of any kind as first modality (on day 90)  
|                                               | 1. Conventional haemodialysis  
|                                               | 2. Hemofiltration  
|                                               | 3. Haemodiafiltration  
|                                               | 4. Daily haemodialysis |
| Outcome                                       | Core outcome measures  
|                                               | Critical outcomes  
|                                               | 1. Survival/mortality  
|                                               | 2. Progression to end-stage kidney disease  
|                                               | 3. Quality of life  
|                                               | 4. Major morbid events:  
|                                               | a. Myocardial infarction  
|                                               | b. Stroke  
|                                               | c. Amputation  
|                                               | d. Loss of vision  
|                                               | Highly important outcomes  
|                                               | 1. Hospital admissions  
|                                               | 2. Deterioration of residual renal function when already on dialysis  
|                                               | 3. Patient satisfaction  
|                                               | 4. Minor morbid events  
|                                               | a. Hypoglycemia  
|                                               | b. Delayed wound healing  
|                                               | c. Infection  
|                                               | d. Visual disturbances  
|                                               | e. Pain  
|                                               | f. Functional status  
|                                               | Moderately important outcomes  
|                                               | 1. Hyperglycemia  
|                                               | 2. Glycemic control  
|                                               | a. Glycated hemoglobin  
|                                               | b. Self-measurement |

Question specific outcome measures
Chapter 1.2.
Should patients with diabetes and CKD stage 5 start dialysis earlier, i.e. before becoming symptomatic, than patients without diabetes?

| Patients | Patients with diabetes mellitus (comorbidity or diabetic nephropathy) and chronic kidney disease CKD stage 5
|          | Adults, aged adults
|          | Diabetes mellitus type 1 or type 2
| Intervention | Start dialysis without clinical symptoms or biochemical alterations at a predefined fixed point of clearance
| Comparator | Start dialysis when symptomatic: hyperkalemia, fluid overload, metabolic acidosis, or deterioration of nutritional status
|            | 1. Continuous ambulatory peritoneal dialysis - CAPD
|            | 2. Automated peritoneal dialysis - APD
|            | 3. Conventional haemodialysis
|            | 4. Hemofiltration
|            | 5. Haemodiafiltration
|            | 6. Daily haemodialysis

| Outcome | Core outcome measures
|         | Question specific outcome measures
|         | 1. Need for temporary haemodialysis catheter: important

| Methodology | Systematic reviews
|            | Randomised controlled trials
|            | Cohort studies
|            | Registry studies

Chapter 1.3.
In patients with diabetes and CKD stage 5, should a native fistula, a graft or a tunnelled catheter be preferred as initial access?

| Patients | Patients with diabetes mellitus (comorbidity or diabetic nephropathy) and chronic kidney disease CKD stage 5
|          | Children, Adults, aged adults
|          | Diabetes mellitus type 1 or type 2
| Intervention | Tunnelled catheter any position
|              | 1. Jugular vein
|              | 2. Femoral vein
|              | 3. Subclavian vein
|              | Graft any position
|              | 1. Radial artery
|              | 2. Cubital artery
Chapter 1.4.

What is the benefit of renal transplantation for dialysis patients with diabetes and CKD stage 5?

A. Is there evidence for a selection bias in observational studies?

| Patients | Patients with diabetes mellitus (comorbidity or diabetic nephropathy) and renal failure on dialysis  
Children, Adults, aged adults  
Diabetes mellitus type 1 or type 2 |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Percentage of dialysis patients with diabetes mellitus registered on waiting list</td>
</tr>
<tr>
<td>Comparator</td>
<td>Percentage of other patients registered on the waiting list</td>
</tr>
<tr>
<td>Outcome</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>
| Methodology | Registry data  
Cross-sectional studies |

Chapter 1.4.

B. Is there a benefit of renal transplantation for dialysis patients with diabetes and CKD stage 5?

| Patients | Patients with diabetes mellitus (comorbidity or diabetic nephropathy) and renal failure on dialysis  
Children, Adults, aged adults  
Diabetes mellitus type 1 or type 2 |
|----------|--------------------------------------------------------------------------------------------------|
| Intervention | Kidney transplantation  
1. Cadaveric kidney transplantation alone  
2. Living-donor kidney transplantation alone  
3. Simultaneous cadaveric kidney-pancreas transplantation |
| Comparator | Dialysis of any kind in patients on the waiting list  
1. Continuous ambulatory peritoneal dialysis - CAPD  
2. Automated peritoneal dialysis - APD  
3. Conventional haemodialysis  
4. Hemofiltration  
5. Haemodiafiltration  
6. Daily haemodialysis |
| Outcome | Core outcome measures |
Chapter 2.1.
A. **In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²), should we aim to lower HbA1C by more tight glycaemic control**

<table>
<thead>
<tr>
<th><strong>Patients</strong></th>
<th>Patients with diabetes mellitus (comorbidity or diabetic nephropathy) and CKD stage 3b or higher (eGFR &lt; 45 mL/min/1.73m²) Children, adults, aged adults Diabetes mellitus type 1 or type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
<td>Intensive glycemic control: as measured by HbA1C</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>Conventional glycemic control - as measured by Hb1Ac</td>
</tr>
</tbody>
</table>
| **Outcome** | Core outcome measures  
Critical outcomes  
1. Survival/mortality  
2. Progression to end-stage kidney disease  
3. Quality of life  
4. Major morbid events:  
a. Myocardial infarction  
b. Stroke  
c. Amputation  
d. Loss of vision  
Highly important outcomes  
1. Hospital admissions  
2. Deterioration of residual renal function when already on dialysis  
3. Patient satisfaction  
4. Minor morbid events  
a. Hypoglycemia  
b. Delayed wound healing  
c. Infection  
d. Visual disturbances  
e. Pain  
f. Functional status  
Moderately important outcomes  
1. Hyperglycemia  
2. Glycemic control  
a. Glycated hemoglobin  
b. Self-measurement  
Question specific outcome measures  
1. Keto-acidosis: critically important |

Methodology  
Systematic reviews  
Randomised controlled trials  
Cohort studies
Registry studies

Chapter 2.1.
B. **Is an aggressive treatment strategy (in number of injections and controls and follow up) superior to a more relaxed treatment strategy in patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²) and using insulin?**

| Patients | Patients with diabetes mellitus (comorbidity or diabetic nephropathy) and chronic kidney disease CKD stage 5  
Adults, aged adults  
Diabetes mellitus type 1 or type 2 |
<table>
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<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Aggressive regimen either defined as more frequent injections, more frequent monitoring and adapted insulin</td>
</tr>
<tr>
<td>Comparator</td>
<td>Relaxed regimen with limited controls and insulin in one or maximum two injections</td>
</tr>
<tr>
<td>Outcome</td>
<td>Core outcome measures</td>
</tr>
</tbody>
</table>
| Methodology | Systematic reviews  
Randomised controlled trials  
Cohort studies  
Registry studies |

Chapter 2.2.
In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²) or on dialysis, are there better alternatives than HbA1c to estimate glycaemic control?

| Patients | Patients with diabetes mellitus (comorbidity or diabetic nephropathy) and CKD stage 3b or higher (eGFR < 45 mL/min/1.73m²)  
Children, Adults, aged adults  
Diabetes mellitus type 1 or type 2 |
| --- | --- |
| Intervention | Glycaemic control evaluated with:  
1. Glycated albumin  
2. Self-measurement point of care  
3. Continuous registration  
4. others methods |
| Comparator | Glycemic control evaluated with HbA1c as reference standard |
| Outcome | Core outcome measures |
| Methodology | Systematic reviews  
Randomised controlled trials  
Cohort studies  
Registry studies |

Chapter 2.3.
A. **Is any oral drug superior to another in terms of mortality/complications/glycaemic control in diabetic patients with CKD stage 3b or higher (eGFR <45 mL/min/1.73m²)?**

| Patients | Patients with diabetes mellitus and CKD stage 3b or higher (eGFR < 45mL/min/1.73m²)  
Children, adults, aged adults |
Diabetes mellitus type 1 or type 2

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sulfonylurea</td>
</tr>
<tr>
<td></td>
<td>Glitazones</td>
</tr>
<tr>
<td></td>
<td>Glitazones</td>
</tr>
<tr>
<td></td>
<td>DDP4 inhibitor</td>
</tr>
<tr>
<td></td>
<td>Acarbose</td>
</tr>
<tr>
<td>Comparator</td>
<td>Any other oral drug for reducing hyperglycaemia</td>
</tr>
<tr>
<td>Outcome</td>
<td>Core outcome measures</td>
</tr>
<tr>
<td>Question specific outcome measures</td>
<td></td>
</tr>
<tr>
<td>1. Weight gain: moderately important</td>
<td></td>
</tr>
</tbody>
</table>

Methodology

Systematic review
Randomised controlled trials
Cohort studies
Registry studies

Chapter 2.3.

B. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²), is maximal oral therapy better than starting/adding insulin in an earlier stage?

Patients
Patients with diabetes mellitus (comorbidity or diabetic nephropathy) and CKD stage 3b or higher (eGFR < 45mL/min/1.73m²)
Children, Adults, aged adults
Diabetes mellitus type 1 or type 2

Intervention
Start insulin as first line or as step up to maximum dose of one oral agent

Comparator
Maximal oral therapy (all oral options in all combinations at maximum allowed dosage)

Outcome
Core outcome measures

Question specific outcome measures

1. Weight gain: moderately important

Methodology
Systematic reviews
Randomised controlled trials
Cohort studies
Registry studies

Chapter 3.1.

In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²) and coronary artery disease, is PCI or CABG or conservative treatment to be preferred?

Patients
Patients with diabetes mellitus and CKD stage 3b or higher (eGFR <45 mL/min/1.73m² or on dialysis) with established cardiac ischemia/coronary artery disease
Children, adults, aged adults
Diabetes mellitus type 1 or type 2

Intervention
Coronary artery bypass graft (CABG)
Percutaneous coronary intervention (PCI)
### Chapter 3.2.

In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²) and with a cardiac indication (heart failure, ischemic heart disease, hypertension) should we prescribe inhibitors of the RAAS system or aldosterone-antagonists as cardiovascular prevention?

| Patients            | Patients with diabetes mellitus and CKD stage 3b or higher (eGFR <45 mL/min/1.73m² or on dialysis) with a cardiac indication (heart failure, ischemic heart disease, hypertension) for RAAS or aldosterone treatment
|                    | Children, adults, aged adults
|                    | Diabetes mellitus type 1 or type 2

| Intervention      | Inhibitor of the RAAS system
|                   | Aldosterone-antagonist
|                   | Any combination

| Comparator         | Placebo or no treatment

| Outcome            | Core outcome measures
|                    | Question specific outcome measures
|                    | 1. Sudden death: critically important

| Methodology        | Systematic review
|                    | Randomised controlled trials
|                    | Cohort studies
|                    | Registry studies

### Chapter 3.3

In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²), should we prescribe Beta Blockers to prevent sudden cardiac death?

| Patients            | Patients with diabetes mellitus and CKD stage 3b or higher (eGFR <45 mL/min/1.73m² or on dialysis)
|                    | Children, adults, aged adults
|                    | Diabetes mellitus type 1 or type 2

| Intervention      | Beta Blocker (any type)

| Comparator         | Placebo or no treatment

| Outcome            | Core outcome measures
|                    | Question specific outcome measures
|                    | 1. Sudden death: critically important

| Methodology        | Systematic review
|                    | Randomised controlled trials
|                    | Cohort studies
**Chapter 3.4.**
In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²), should we aim at lower blood pressure targets than in the general population?

A Cochrane review of sufficient quality was used to answer this question.

**Chapter 3.5.**
In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²), should we prescribe lipid lowering therapy in primary prevention?

<table>
<thead>
<tr>
<th>Patients</th>
<th>Lipid lowering therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with diabetes mellitus and CKD stage 3b or higher (eGFR &lt;45 mL/min/1.73m² or on dialysis)</td>
<td>Statin (all compounds)</td>
</tr>
<tr>
<td>Children, adults, aged adults</td>
<td>Fibrate (all compounds)</td>
</tr>
<tr>
<td>Diabetes mellitus type 1 or type 2</td>
<td>Any other class of agents</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Placebo or no treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any other class of agents</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Core outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Question specific outcome measures</td>
<td>1. Cancer: critically important</td>
</tr>
<tr>
<td></td>
<td>2. Rhabdomyolysis: highly important</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Methodology</th>
<th>Systematic review</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Randomised controlled trials</td>
</tr>
<tr>
<td></td>
<td>Cohort studies</td>
</tr>
<tr>
<td></td>
<td>Registry studies</td>
</tr>
</tbody>
</table>

**Chapter 3.6.**
A. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²), should we recommend interventions aimed at increasing energy expenditure and physical activity?

<table>
<thead>
<tr>
<th>Patients</th>
<th>Structured education/intervention aimed at increasing energy expenditure and/or physical activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with diabetes mellitus and CKD stage 3b or higher (eGFR &lt;45 mL/min/1.73m² or on dialysis)</td>
<td>1. Advice to exercise</td>
</tr>
<tr>
<td>Children, adults, aged adults</td>
<td>2. Structured education programmes including advice on exercise</td>
</tr>
<tr>
<td>Diabetes mellitus type 1 or type 2</td>
<td>3. Provision of a supervised exercise programme</td>
</tr>
<tr>
<td></td>
<td>4. Provision of exercise bikes (for instance during haemodialysis)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Standard care</th>
</tr>
</thead>
</table>
| Outcome | Core outcome measures  
| Question specific outcome measures  
1. Depression symptoms: critically important  
2. Exercise capacity: highly important  
3. Weight loss: moderately important  
4. Insulin sensitivity: moderately important  
5. Improved efficiency of haemodialysis  
6. Adherence to treatment strategy |

| Methodology | Systematic review  
| Randomised controlled trials  
| Cohort studies  
| Registry studies |

**Chapter 3.6.**

**B. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²), should we recommend interventions aimed at reducing energy intake?**

| Patients | Patients with diabetes mellitus and CKD stage 3b or higher (eGFR <45 mL/min/1.73m² or on dialysis)  
| Children, adults, aged adults  
| Diabetes mellitus type 1 or type 2 |

| Intervention | Structured education/intervention aimed at decreasing energy intake  
1. Dietary advice  
2. Structured dietary plans supervised by a dietician |

| Comparator | Standard care |

| Outcome | Core outcome measures  
| Question specific outcome measures  
1. Weight loss: moderately important  
2. Insulin sensitivity: moderately important  
3. Blood pressure: moderately important - surrogate outcome  
4. Proteinuria: moderately important - surrogate outcome  
5. Adherence to treatment strategy |

| Methodology | Systematic review  
| Randomised controlled trials  
| Cohort studies  
| Registry studies |

**Chapter 3.7.**

**In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²), should antiplatelet therapy be recommended, regardless of their cardiovascular risk?**

| Patients | Patients with diabetes mellitus and CKD stage 3b or higher (eGFR <45 mL/min/1.73m² or on dialysis)  
| Children, adults, aged adults  
| Diabetes mellitus type 1 or type 2 |

<p>| Intervention | Platelet aggregation inhibitors |</p>
<table>
<thead>
<tr>
<th>Comparator</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
<td>Core outcome measures</td>
</tr>
<tr>
<td></td>
<td>Question specific outcome measures</td>
</tr>
<tr>
<td></td>
<td>1. Need for blood transfusion</td>
</tr>
<tr>
<td></td>
<td>2. Bleeding</td>
</tr>
<tr>
<td>Methodology</td>
<td>Systematic review</td>
</tr>
<tr>
<td></td>
<td>Randomised controlled trials</td>
</tr>
<tr>
<td></td>
<td>Cohort studies</td>
</tr>
<tr>
<td></td>
<td>Registry studies</td>
</tr>
</tbody>
</table>
Appendix 3 | Search Strategies

Chapter 1.1.
Should patients with diabetes and CKD stage 5 start with peritoneal dialysis or haemodialysis as a first modality?

MEDLINE
1. Kidney Diseases/
2. exp Renal Replacement Therapy/
3. Renal Insufficiency/
4. exp Renal Insufficiency, Chronic/
5. dialysis.tw.
6. (haemodialysis or haemodialysis).tw.
7. (hemofiltration or haemofiltration).tw.
8. (haemodiafiltration or haemodiafiltration).tw.
9. (end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw.
10. (ESRF or ESKF or ESRD or ESKD).tw.
11. (chronic kidney or chronic renal).tw.
12. (CKF or CKD or CRF or CRD).tw.
13. (CAPD or CCPD or APD).tw.
14. (predialysis or pre-dialysis).tw.
15. or/1-14
16. exp diabetes mellitus/
17. exp Diabetes Mellitus, Type 1/
18. exp Diabetes Mellitus, Type 2/
19. Diabetic Nephropathies/
20. diabet$.tw.
21. (niddm or iddm).tw.
22. or/16-21
23. ((first or dialysis or choice or best) adj3 modality).tw.
24. ((first or dialysis or modality or starting or best) adj3 choice).tw.
25. ((dialysis or modality or best) adj3 start).tw.
26. ((begin or first or initiat$) adj3 dialysis).tw.
27. or/23-26
28. 15 and 22 and 27

**COCHRANE CENTRAL**

#1 dialysis:ti,ab,kw
#2 h*emofiltration:ti,ab,kw
#3 h*emodiafiltration:ti,ab,kw
#4 (end-stage renal or end-stage kidney or endstage renal or endstage kidney):ti,ab,kw
#5 (ESRF or ESKF or ESRD or ESKD):ti,ab,kw
#6 (chronic kidney or chronic renal):ti,ab,kw
#7 (CKF or CKD or CRF or CRD):ti,ab,kw
#8 (CAPD or CCPD or APD):ti,ab,kw
#9 (predialysis or pre-dialysis):ti,ab,kw
#10 MeSH descriptor Kidney Failure, Chronic, this term only
#11 MeSH descriptor Renal Replacement Therapy explode all trees
#12 MeSH descriptor Renal Insufficiency, Chronic explode all trees
#13 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)
#14 MeSH descriptor Diabetes Mellitus, this term only
#15 MeSH descriptor Diabetes Mellitus, Type 1 explode all trees
#16 MeSH descriptor Diabetes Mellitus, Type 2 explode all trees
#17 MeSH descriptor Diabetic Nephropathies explode all trees
#18 diabet*:ti,ab,kw
#19 (niddm or iddm):ab,ti,kw
#20 (#14 OR #15 OR #16 OR #17 OR #18 OR #19)
#21 (#13 AND #20)
#22 first modality:ti,ab,kw
#23 dialysis modality:ti,ab,kw
#24 choice modality:ti,ab,kw
#25 best modality:ti,ab,kw
#26 first choice:ti,ab,kw
#27 dialysis choice:ti,ab,kw
#28 modality choice:ti,ab,kw
#29 starting choice:ti,ab,kw
#30 best choice:ti,ab,kw
#31 dialysis begin:ti,ab,kw
#32 first dialysis:ti,ab,kw
Chapter 1.2.
Should patients with diabetes and CKD stage 5 start dialysis earlier, i.e. before becoming symptomatic, than patients without diabetes?

MEDLINE
1. Kidney Diseases/
2. exp Renal Replacement Therapy/
3. Renal Insufficiency/
4. exp Renal Insufficiency, Chronic/
5. dialysis.tw.
6. (haemodialysis or haemodialysis).tw.
7. (hemofiltration or haemofiltration).tw.
8. (haemodiafiltration or haemodiafiltration).tw.
9. (end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw.
10. (ESRF or ESKF or ESRD or ESKD).tw.
11. (chronic kidney or chronic renal).tw.
12. (CKF or CKD or CRF or CRD).tw.
13. (CAPD or CCPD or APD).tw.
14. (predialysis or pre-dialysis).tw.
15. or/1-14
16. exp diabetes mellitus/
17. exp Diabetes Mellitus, Type 1/
18. exp Diabetes Mellitus, Type 2/
19. Diabetic Nephropathies/
20. diabet$.tw.
21. (niddm or iddm).tw.
22. or/16-21
23. ((ideal or preemptive or pre-emptive or early) adj11 start).tw
24. ((ideal or preemptive or pre-emptive or early) adj11 initiation).tw
25. ((ideal or preemptive or pre-emptive or early) adj11 timing).tw
26. ((begin or first or initiat$ or start$) adj11 dialysis).tw.
27. (early-start or late-start).tw
Chapter 1.3.
In patients with Diabetes and CKD stage 5, should a native fistula, a graft or a tunnelled catheter be preferred as initial access?
MEDLINE
1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab,ti.
4. placebo$.ab,ti.
5. drug therapy.fs.
6. randomly.ab,ti.
7. trial$.ab,ti.
8. group$.ab,ti.
9. or/1-8
11. exp Technology Assessment, Biomedical/
12. exp Meta-analysis/
13. exp Meta-analysis as topic/
15. hta.tw,ot.
16. (meta analy$ or metaanaly$ or meta?analy$).tw,ot.
17. exp Cohort studies/
18. Incidence.tw.
19. exp mortality/
20. exp follow-up studies/
21. mo.fs.
22. prognosis.tw.
23. predict$.tw.
24. course.tw.
25. exp survival analysis/
26. or/10-25
27. (comment or editorial or historical-article).pt.
28. 26 not 27
29. 9 or 28
30. Arteriovenous Fistula/
31. Arteriovenous Shunt, Surgical/
32. Blood Vessel Prosthesis/
33. Blood Vessel Prosthesis Implantation/
34. (vascular access or venous access).tw.
35. (dialysis access or haemodialysis access or haemodialysis access).tw.
36. Catheterization, Central Venous/
37. fistula$:tw.
38. (graft or grafts).tw.
39. (shunt or shunts).tw.
40. prosthesis.tw.
41. tunne$.tw.
42. catheter$:tw.
43. central line$:tw.
44. (AVF or AVG or CVC).tw.
45. or/30-44
46. Kidney Failure/
47. exp Renal Insufficiency, Chronic/
48. (end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw.
49. (ESRF or ESKF or ESRD or ESKD).tw.
50. (chronic kidney or chronic renal).tw.
51. (CKF or CKD or CRF or CRD).tw.
52. predialysis.tw.
53. *Kidney Transplantation/ or exp *Peritoneal Dialysis/
54. exp diabetes mellitus/
55. exp Diabetes Mellitus, Type 1/
56. exp Diabetes Mellitus, Type 2/
57. Diabetic Nephropathies/
58. diabet$:tw.
59. (niddm or iddm).tw.
60. or/54-59
61. or/46-52
62. 61 not 53
63. 45 and 60 and 62

COCHRANE CENTRAL
#1 fistula*:ti,ab,kw
#2. (shunt or shunts):ti,ab,kw
#3. (graft or grafts*):ti,ab,kw
Chapter 1.4.

What is the benefit of renal transplantation for dialysis patients with diabetes and CKD stage 5?

A. is there evidence for a selection bias in observational studies?

MEDLINE

1. exp Registries/
2. exp Waiting Lists/
3. wait list*.tw.

MEDLINE
4. wait* list.tw.
5. waiting list*.tw.
6. waitlist*.tw.
7. 2 or 3 or 4 or 5 or 6
8. registry.tw.
9. registries.tw.
10. 1 or 8 or 9
11. kidney transplantation.mp. or exp Kidney Transplantation/
12. kidney transplant*.tw.
13. renal transplant*.tw.
14. 11 or 12 or 13
15. 7 and 10 and 14

Chapter 1.4.
B. What is the benefit of renal transplantation for dialysis patients with diabetes and CKD stage 5?

MEDLINE
1. Kidney Diseases/
2. exp Renal Replacement Therapy/
3. Renal Insufficiency/
4. exp Renal Insufficiency, Chronic/
5. dialysis.tw.
6. (haemodialysis or haemodialysis).tw.
7. (hemofiltration or haemofiltration).tw.
8. (haemodiafiltration or haemodiafiltration).tw.
9. (end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw.
10. (ESRF or ESKF or ESRD or ESKD).tw.
11. (chronic kidney or chronic renal).tw.
12. (CKF or CKD or CRF or CRD).tw.
13. (CAPD or CCPD or APD).tw.
14. (predialysis or pre-dialysis).tw.
15. or/1-14
16. exp diabetes mellitus/
17. exp Diabetes Mellitus, Type 1/
18. exp Diabetes Mellitus, Type 2/
19. diabet$.tw.
20. (niddm or iddm).tw.
21. or/16-20
22. 15 and 21
23. Diabetic Nephropathies/
24. diabet* nephropath*.tw.
25. (diabet* adj5 (kidney or renal)).tw.
26. or/23-25
27. 22 or 26
28. kidney transplantation/
29. kidney transplant$.tw.
30. renal transplant$.tw.
31. or/28-30
32. 27 and 31
33. limit 32 to human
34. (comment or editorial or historical-article).pt.
35. 33 not 34
36. randomized controlled trial.pt.
37. controlled clinical trial.pt.
38. randomized.ab.
39. placebo.ab.
40. clinical trials as topic.sh.
41. randomly.ab.
42. trial.ti.
43. or/36-42
44. exp animals/ not humans.sh.
45. 43 not 44
46. 35 and 45

COCHRANE CENTRAL
#1 dialysis:ti,ab,kw
#2 h*emofiltration:ti,ab,kw
#3 h*emodiafiltration:ti,ab,kw
Chapter 2.1.

C. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²), should we aim to lower HbA1C by more tight glycaemic control
9. (end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw.
10. (ESRF or ESKF or ESRD or ESKD).tw.
11. (chronic kidney or chronic renal).tw.
12. (CKF or CKD or CRF or CRD).tw.
13. (CAPD or CCPD or APD).tw.
14. (predialysis or pre-dialysis).tw.
15. or/1-14
16. Diabetes Mellitus/
17. exp Diabetes Mellitus, Type 1/
18. exp Diabetes Mellitus, Type 2/
19. Diabetic Nephropathies/
20. diabet$.tw.
21. (niddm or iddm).tw.
22. exp Blood Glucose/
23. exp Hyperglycemia/
24. exp Hemoglobin A, Glycosylated/
25. (blood glucos$ or hyperglyc?emi$ or h?emoglobin$ A).ab,ti.
26. (HbA1C or Hb A or HbA 1c or HbA or A1Cs).ab,ti,ot.
27. (glycosylated adj6 h?emoglobin$).ab,ti.
29. or/16-28
30. ((intensi$ or conventional$ or regular or tight or usual or routin$ or standard) adj3 (control$ or therap$ or treatment or intervention$ or management$)).ab,ti.
31. 30 and 29 and 15
32. randomized controlled trial.pt.
33. controlled clinical trial.pt.
34. randomi?ed.ab,ti.
35. placebo$.ab,ti.
36. drug therapy.fs.
37. randomly,ab,ti.
38. trial$.ab,ti.
39. group$.ab,ti.
40. or/32-39
41. Meta-analysis.pt.
42. exp Technology Assessment, Biomedical/
43. exp Meta-analysis/
44. exp Meta-analysis as topic/
45. hta.tw,ot.
46. (health technology adj6 assessment$).tw,ot.
47. (meta analy$ or metaanaly$ or meta?analy$).tw,ot.
48. ((review$ or search$) adj10 (literature$ or medical database$ or medline or pubmed or embase or cochrane or cinahl or psycinfo or psyclit or healthstar or biosis or current content$ or systemat$)).tw,ot.
49. or/41-48
50. (comment or editorial or historical-article).pt.
51. 49 not 50
52. 40 or 51
53. 31 and 52
54. (animals not (animals and humans)).sh.
55. 53 not 54

**COCHRANE CENTRAL search strategy**

#1  MeSH descriptor Blood Glucose, this term only
#2  MeSH descriptor Hyperglycemia explode all trees
#3  MeSH descriptor Hemoglobin A, Glycosylated, this term only
#4  (blood glucos*):ti,ab,kw or (hyperglyc?emi*):ti,ab,kw or (h?emoglobin* A):ti,ab,kw
#5  (HbA1C):ti,ab,kw or (Hb A):ti,ab,kw or (HbA 1c):ti,ab,kw or (HbA):ti,ab,kw or (A1Cs):ti,ab,kw
#6  (glycosylated near/6 h?emoglobin*):ti,ab,kw
#7  (glucos* near/3 management*):ti,ab,kw
#8  (#1 OR #2 OR #3 OR #4 OR #4 OR #5 OR #6 OR #7)
#9  MeSH descriptor Diabetes Mellitus explode all trees
#10 MeSH descriptor Diabetes Complications explode all trees
#11 (MODY):ti,ab,kw or (NIDDM ):ti,ab,kw or (T2DM ):ti,ab,kw
#12 (non insulin* depend*):ti,ab,kw or (noninsulin* depend*):ti,ab,kw or (noninsulin?depend* ):ti,ab,kw or (non insulin?depend):ti,ab,kw
#13 (insulin* depend*):ti,ab,kw or (insulin?depend* ):ti,ab,kw or (insulin?depend):ti,ab,kw
#14 ((typ* 2 or type-2 or typ* II or type-II) near/3 diabet*)
#15 ((typ* 1 or type-1 or typ* I or type-I) near/3 diabet*)
#16 (late near/3 onset):ab,ti,kw
#17 (matur* near/3 onset):ab,ti,kw
#18 (adult* near/3 onset):ab,ti,kw
#19 (slow near/3 onset):ab,ti,kw
#20 (stabl* near/3 onset):ab,ti,kw
#21 (#16 OR #17 OR #18 OR #19 OR #20)
#22 diabet*:ab,ti,kw
#23 (#21 AND #22)
#24 (#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #23)
#25 MeSH descriptor Diabetes Insipidus explode all trees
#26 (diabet* insipidus):ab,ti,kw
#27 (#25 OR #26)
#28 (#24 AND NOT #27)
#29 MeSH descriptor Renal Dialysis explode all trees
#30 MeSH descriptor Hemofiltration explode all trees
#31 (renal replacement therapy):kw,ab,ti
#32 MeSH descriptor Dialysis explode all trees
#33 kidney failure chronic
#34 kidney failure acute
#35 uremia
#36 (ultrafiltrat*):ti,ab,kw or (dialy*):ti,ab,kw
#37 peritoneal dialysis
#38 MeSH descriptor Peritoneal Dialysis explode all trees
#39 ESRD:ti,ab,kw
#40 ur?emi*:ti,ab,kw
#41 (kidney* near/2 disease*):ab,ti,kw
#42 (kidney* near/2 failure*):ab,ti,kw
#43 (kidney* near/2 insufficien*):ab,ti,kw
#44 (renal* near/2 disease*):ab,ti,kw
#45 (renal* near/2 failure*):ab,ti,kw
#46 (renal* near/2 sufficien*):ab,ti,kw
#47 (renal* near/2 insufficien*):ab,ti,kw
#48 (kidney* near/2 replac*):ab,ti,kw
#49 (kidney* near/2 artificial):ab,ti,kw
#50 (kidney* near/2 extracorporeal):ab,ti,kw
#51 (renal* near/2 replac*):ab,ti,kw
#52 (renal* near/2 artificial*):ab,ti,kw
#53 (renal* near/2 extracorporeal*):ab,ti,kw
#54 predialy*:ti,ab,kw
#55 pre-dialy*:ti,ab,kw
#56 (#29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55)
#57 (#8 OR #28)
#58 (#56 AND #57)
#59 (intensi* near/3 control*):ab,ti,kw
#60 (intensi* near/3 therap*):ab,ti,kw
#61 (intensi* near/3 treatment*):ab,ti,kw
#62 (intensi* near/3 intervention*):ab,ti,kw
#63 (intensi* near/3 management*):ab,ti,kw
#64 (conventional* near/3 control*):ab,ti,kw
#65 (conventional* near/3 therap*):ab,ti,kw
#66 (conventional* near/3 treatment*):ab,ti,kw
#67 (conventional* near/3 intervention*):ab,ti,kw
#68 (conventional* near/3 management*):ab,ti,kw
#69 (regular* near/3 control*):ab,ti,kw
#70 (regular* near/3 therap*):ab,ti,kw
#71 (regular* near/3 treatment*):ab,ti,kw
#72 (regular* near/3 intervention*):ab,ti,kw
#73 (regular* near/3 management*):ab,ti,kw
#74 (tight near/3 control*):ab,ti,kw
#75 (tight near/3 therap*):ab,ti,kw
#76 (tight near/3 treatment*):ab,ti,kw
#77 (tight near/3 intervention*):ab,ti,kw
#78 (tight near/3 management*):ab,ti,kw
#79 (usual near/3 control*):ab,ti,kw
#80 (usual near/3 therap*):ab,ti,kw
#81 (usual near/3 treatment*):ab,ti,kw
#82 (usual near/3 intervention*):ab,ti,kw
#83 (usual near/3 management*):ab,ti,kw
#84 (routin* near/3 control*):ab,ti,kw
#85 (routin* near/3 therap*):ab,ti,kw
#86 (routin* near/3 treatment*):ab,ti,kw
#87 (routin* near/3 intervention*):ab,ti,kw
#88 (routin* near/3 management*):ab,ti,kw
Chapter 2.1.

D. Is an aggressive treatment strategy (in number of injections and controls and follow up) superior to a more relaxed treatment strategy in patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²) and using insulin

MEDLINE search strategy

1. Kidney Diseases/
2. exp Renal Replacement Therapy/
3. Renal Insufficiency/
4. exp Renal Insufficiency, Chronic/
5. dialysis.tw.
6. (haemodialysis or haemodialysis).tw.
7. (hemofiltration or haemofiltration).tw.
8. (haemodiafiltration or haemodiafiltration).tw.
9. (end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw.
10. (ESRF or ESKF or ESRD or ESKD).tw.
11. (chronic kidney or chronic renal).tw.
12. (CKF or CKD or CRF or CRD).tw.
13. (CAPD or CCPD or APD).tw.
14. (predialysis or pre-dialysis).tw.
15. or/1-14
16. exp diabetes mellitus/
17. exp Diabetes Mellitus, Type 1/
18. exp Diabetes Mellitus, Type 2/
19. Diabetic Nephropathies/
20. diabet$.tw.
21. (niddm or iddm).tw.
22. or/16-21
23. ((intensi$ or conventional$ or regular or tight or usual or routin$ or standard or frequent$ or aggressive or relaxed$) adj3 glucos$ adj3 (control$ or therap$ or treatment or intervention$ or management$)).tw.
24. ((intensi$ or conventional$ or regular or tight or usual or routin$ or standard or frequent$ or aggressive or relaxed$) adj3 glyc?emi$ adj3 (control$ or therap$ or treatment or intervention$ or management$)).tw.
25. ((intensi$ or conventional$ or regular or tight or usual or routin$ or standard or frequent$ or aggressive or relaxed$) adj3 diabet$ adj3 (control$ or therap$ or treatment or intervention$ or management$)).tw.
27. (glucos$ adj3 management$).tw.
28. 23 or 24 or 25 or 26 or 27
29. 15 and 22 and 28
30. randomized controlled trial.pt.
31. controlled clinical trial.pt.
32. randomi?ed.ab,ti.
33. placebo$.ab,ti.
34. drug therapy.fs.
35. randomly.ab,ti.
36. trial$.ab,ti.
37. group$.ab,ti.
38. or/30-37
40. exp Technology Assessment, Biomedical/
41. exp Meta-analysis/
42. exp Meta-analysis as topic/
43. (health technology adj6 assessment$).tw,ot.
44. hta.tw,ot.
45. (meta analy$ or metaanaly$ or meta?ana$ly$).tw,ot.
46. exp Cohort studies/
47. Incidence.tw.
48. exp mortality/
49. exp follow-up studies/
50. mo.fs.
51. prognos$.tw.
52. predict$.tw.
COCHRANE CENTRAL search strategy

#1 dialysis:ti,ab,kw
#2 h*emofiltration:ti,ab,kw
#3 h*emodiafiltration:ti,ab,kw
#4 (end-stage renal or end-stage kidney or endstage renal or endstage kidney):ti,ab,kw
#5 (ESRF or ESKF or ESRD or ESKD):ti,ab,kw
#6 (chronic kidney or chronic renal):ti,ab,kw
#7 (CKF or CKD or CRF or CRD):ti,ab,kw
#8 (CAPD or CCPD or APD):ti,ab,kw
#9 (predialysis or pre-dialysis):ti,ab,kw
#10 MeSH descriptor: [Kidney Failure, Chronic] this term only
#11 MeSH descriptor: [Renal Replacement Therapy] explode all trees
#12 MeSH descriptor: [Renal Insufficiency, Chronic] explode all trees
#13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
#14 MeSH descriptor: [Diabetes Mellitus] this term only
#15 MeSH descriptor: [Diabetes Mellitus, Type 1] explode all trees
#16 MeSH descriptor: [Diabetes Mellitus, Type 2] explode all trees
#17 MeSH descriptor: [Diabetic Nephropathies] explode all trees
#18 diabet*:ti,ab,kw
#19 (niddm or iddm):ab,ti,kw
#20 (#14 or #15 or #16 or #17 or #18 or #19)
#21 #13 and #20
#22 (standard or frequent* or aggressive or relaxed*) near/3 glucos* near/3 (control* or therap* or treatment or intervention* or management*):ab,ti,kw
#23 (intensi* or conventional* or regular or tight or usual or routin* or standard or frequent* or aggressive or relaxed*) near/3 glucos* near/3 (control* or therap* or treatment or intervention* or management*):ab,ti,kw
#24 (intensi* or conventional* or regular or tight or usual or routin* or standard or frequent* or aggressive or relaxed*) near/3 glycemic* near/3 (control* or therap* or treatment or intervention* or management*):ab,ti,kw
Chapter 2.2.
In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²) are there better alternatives than HbA1c to estimate glycaemic control?

MEDLINE search strategy
1. Kidney Diseases/
2. exp Renal Replacement Therapy/
3. Renal Insufficiency/
4. exp Renal Insufficiency, Chronic/
5. dialysis.tw.
6. (haemodialysis or haemodialysis).tw.
7. (hemofiltration or haemofiltration).tw.
8. (haemodiafiltration or haemodiafiltration).tw.
9. (end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw.
10. (ESRF or ESKF or ESRD or ESKD).tw.
11. (chronic kidney or chronic renal).tw.
12. (CKF or CKD or CRF or CRD).tw.
13. (CAPD or CCPD or APD).tw.
14. (predialysis or pre-dialysis).tw.
15. or/1-14
16. exp diabetes mellitus/
17. exp Diabetes Mellitus, Type 1/
18. exp Diabetes Mellitus, Type 2/
19. Diabetic Nephropathies/
20. diabet$.tw.
21. (niddm or iddm).tw.
22. or/16-21
23. 15 and 22
24. fructosamine.tw.
25. exp Blood glucose self-monitoring/
26. self monitor$.ti,ab.
27. exp Hyperglycemia/di, pc [Diagnosis, Prevention & Control]
28. exp Hemoglobin A, Glycosylated/
29. exp Fructosamine/
30. exp Glycemic Index/
31. exp Hexosamines/
32. HbA1c?.tw.
33. (glycated adj h?emoglobin).tw.
34. (glycosylated adj h?emoglobin).tw.
35. (glycosylated adj2 albumin).tw.
36. exp Blood Glucose/an, du, me [Analysis, Diagnostic Use, Metabolism]
38. (glycated adj2 albumin).tw.
39. or/24-38
40. 23 and 39
41. (glucos$ adj3 control$).ab,ti.
42. (glyc?emic adj3 monitor$).tw.
43. (glyc?emic adj control$).tw.
44. 41 or 42 or 43
45. 40 and 44

COCHRANE CENTRAL search strategy
#1 dialysis:ti,ab,kw
#2 h*emofiltration:ti,ab,kw
#3 h*emodiafiltration:ti,ab,kw
#4 (end-stage renal or end-stage kidney or endstage renal or endstage kidney):ti,ab,kw
#5 (ESRF or ESKF or ESRD or ESKD):ti,ab,kw
#6 (chronic kidney or chronic renal):ti,ab,kw
#7 (CKF or CKD or CRF or CRD):ti,ab,kw
#8 (CAPD or CCPD or APD):ti,ab,kw
#9 (predialysis or pre-dialysis):ti,ab,kw
#10 MeSH descriptor Kidney Failure, Chronic, this term only
Chapter 2.3.
A. Is any oral drug superior to another in terms of mortality/complications/glycaemic control in diabetic patients with CKD stage 3b or higher (eGFR <45 mL/min/1.73m²)?
MEDLINE search strategy
1. Kidney Diseases/
2. exp Renal Replacement Therapy/
3. Renal Insufficiency/
4. exp Renal Insufficiency, Chronic/
5. dialysis.tw.
6. (haemodialysis or haemodialysis).tw.
7. (hemofiltration or haemofiltration).tw.
8. (haemodialfiltration or haemodiafiltration).tw.
9. (end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw.
10. (ESRF or ESKF or ESRD or ESKD).tw.
11. (chronic kidney or chronic renal).tw.
12. (CKF or CKD or CRF or CRD).tw.
13. (CAPD or CCPD or APD).tw.
14. (predialysis or pre-dialysis).tw.
15. or/1-14
16. exp diabetes mellitus/
17. exp Diabetes Mellitus, Type 1/
18. exp Diabetes Mellitus, Type 2/
19. Diabetic Nephropathies/
20. diabet$.tw.
21. (niddm or iddm).tw.
22. or/16-21
23. exp Hypoglycemic Agents/
24. (glucose lowering and (therap$ or agent$ or drug$)).tw.
25. (hypoglycemic and (agent$ or drug$ or therap$)).tw.
26. (antidiabet$ and (agent$ or drug$ or therap$)).tw.
27. metformin.tw.
28. Thiazolidinediones/
29. Rosiglitazone.tw.
30. Rivoglitazone.tw.
31. Pioglitazone.tw.
32. Troglitazone.tw.
33. glitazone$.tw.
34. exp Sulfonylurea Compounds/
35. (acarbose or miglitol or voglibose).tw.
36. Alogliptin.tw.
37. Linagliptin.tw.
38. (repaglinide or nateglinide or exenatide or pramlintide or benfluorex or liraglutide or mitiglinide).tw.
39. (sitagliptin or vildagliptin or saxagliptin).tw.
40. Dipeptidyl-Peptidase IV Inhibitors/
41. Glucagon-Like Peptide 1/
42. glucagon-like peptide-1.tw.
43. Incretin mimetic$.tw.
44. alpha-Glucosidases/
45. alpha-glucosidase inhibitor$.tw.
46. Sodium-Glucose Transporter 2/
47. Sodium glucose co-transporter 2 inhibitor$.tw.
48. ddp iv inhibitor$.tw.
49. exenatide.tw.
50. or/23-49
51. randomized controlled trial.pt.
52. controlled clinical trial.pt.
53. randomi?ed.ab,ti.
54. placebo$.ab,ti.
55. drug therapy.fs.
56. randomly.ab,ti.
57. trial$.ab,ti.
58. group$.ab,ti.
59. or/51-58
60. Meta-analysis.pt.
61. exp Technology Assessment, Biomedical/
62. exp Meta-analysis/
63. exp Meta-analysis as topic/
64. (health technology adj6 assessment$).tw,ot.
65. hta.tw,ot.
66. (meta analy$ or metaanaly$ or meta?analy$).tw,ot.
67. exp Cohort studies/
68. Incidence.tw.
69. exp mortality/
70. exp follow-up studies/
71. mo.fs.
72. prognos$.tw.
73. predict$.tw.
74. course.tw.
75. exp survival analysis/
76. or/60-75
77. (comment or editorial or historical-article).pt.
78. 76 not 77
79. 59 or 78
80. 15 and 22 and 50 and 79
81. animals/ not (humans/ and animals/)
82. 80 not 81

COCHRANE CENTRAL search strategy
#1 dialysis:ti,ab,kw
#2 h*emofiltration:ti,ab,kw
#3 h*emodiafiltration:ti,ab,kw
#4 (end-stage renal or end-stage kidney or endstage renal or endstage kidney):ti,ab,kw
#5 (ESRF or ESKF or ESRD or ESKD):ti,ab,kw
#6 (chronic kidney or chronic renal):ti,ab,kw
#7 (CKF or CKD or CRF or CRD):ti,ab,kw
#8 (CAPD or CCPD or APD):ti,ab,kw
#9 (predialysis or pre-dialysis):ti,ab,kw
#10 MeSH descriptor Kidney Failure, Chronic, this term only
#11 MeSH descriptor Renal Replacement Therapy explode all trees
#12 MeSH descriptor Renal Insufficiency, Chronic explode all trees
#13 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)
#14 MeSH descriptor Diabetes Mellitus, this term only
#15 MeSH descriptor Diabetes Mellitus, Type 1 explode all trees
#16 MeSH descriptor Diabetes Mellitus, Type 2 explode all trees
#17 MeSH descriptor Diabetic Nephropathies explode all trees
#18 diabet*:ti,ab,kw
#19 (niddm or iddm):ab,ti,kw
#20 (#14 OR #15 OR #16 OR #17 OR #18 OR #19)
Chapter 2.3.

A. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²), is maximal oral therapy better than starting/adding insulin in an earlier stage?

MEDLINE search strategy

1. Kidney Diseases/
2. exp Renal Replacement Therapy/
3. Renal Insufficiency/
4. exp Renal Insufficiency, Chronic/
5. dialysis.tw.
6. (haemodialysis or haemodialysis).tw.
7. (hemofiltration or haemofiltration).tw.
8. (haemodiafiltration or haemodiafiltration).tw.
9. (end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw.
10. (ESRF or ESKF or ESRD or ESKD).tw.
11. (chronic kidney or chronic renal).tw.
12. (CKF or CKD or CRF or CRD).tw.
13. (CAPD or CCPD or APD).tw.
14. (predialysis or pre-dialysis).tw.
15. or/1-14
16. exp diabetes mellitus/
17. exp Diabetes Mellitus, Type 1/
18. exp Diabetes Mellitus, Type 2/
19. Diabetic Nephropathies/
20. diabet$.tw.
21. (niddm or iddm).tw.
22. or/16-21
23. 15 and 22
24. exp Hypoglycemic Agents/
25. (glucose lowering and (therap$ or agent$ or drug$)).tw.
26. (hypoglycemic and (agent$ or drug$ or therap$)).tw.
27. (antidiabet$ and (agent$ or drug$ or the rap$)).tw.
28. metformin.tw.
29. Thiazolidinediones/
30. Rosiglitazone.tw.
31. Rivoglitazone.tw.
32. Pioglitazone.tw.
33. Troglitazone.tw.
34. glitazone$.tw.
35. exp Sulfonylurea Compounds/
36. (acarbose or miglitol or voglibose).tw.
37. Alogliptin.tw.
38. Linagliptin.tw.
39. (repaglinide or nateglinide or exenatide or pramlintide or benfluorex or liraglutide or mitiglinide).tw.
40. (sitagliptin or vildagliptin or saxagliptin).tw.
41. Dipeptidyl-Peptidase IV Inhibitors/
42. Glucagon-Like Peptide 1/
43. glucagon-like peptide-1.tw.
44. Incretin mimetic$.tw.
45. alpha-Glucosidases/
46. alpha-glucosidase inhibitor$.tw.
47. Sodium-Glucose Transporter 2/
48. Sodium glucose co-transporter 2 inhibitor$.tw.
49. ddp iv inhibitor$.tw.
50. exenatide.tw.
51. or/24-50
52. exp Insulins/
53. insulin$.tw.
54. or/52-53
55. 51 and 54
56. 55 and 23
57. randomized controlled trial.pt.
58. controlled clinical trial.pt.
59. randomized.ab.
60. placebo.ab.
61. clinical trials as topic/
62. randomly.ab.
63. trial.ti.
64. or/57-63
66. exp Technology Assessment, Biomedical/
67. exp Meta-analysis/
68. exp Meta-analysis as topic/
69. (health technology adj6 assessment$).tw,ot.
70. hta.tw,ot.
71. (meta analy$ or metaanaly$ or meta?analy$).tw,ot.
72. exp Cohort studies/
73. Incidence.tw.
74. exp mortality/
75. exp follow-up studies/
76. mo.fs.
77. prognos$.tw.
78. predict$.tw.
79. course.tw.
80. exp survival analysis/
81. or/65-80
82. (comment or editorial or historical-article).pt.
83. 81 not 82
84. 64 or 83
85. 56 and 84
86. animals/ not (humans/ and animals/)
87. 85 not 86

**COCHRANE CENTRAL search strategy**

#1 dialysis:ti,ab,kw
#2 h*emofiltration:ti,ab,kw
#3 h*emodiafiltration:ti,ab,kw
#4 (end-stage renal or end-stage kidney or endstage renal or endstage kidney):ti,ab,kw
#5 (ESRF or ESKF or ESRD or ESKD):ti,ab,kw
#6 (chronic kidney or chronic renal):ti,ab,kw
#7 (CKF or CKD or CRF or CRD):ti,ab,kw
#8 (CAPD or CCPD or APD):ti,ab,kw
#9 (predialysis or pre-dialysis):ti,ab,kw
#10 MeSH descriptor Kidney Failure, Chronic, this term only
#11 MeSH descriptor Renal Replacement Therapy explode all trees
#12 MeSH descriptor Renal Insufficiency, Chronic explode all trees
#13 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)
#14 MeSH descriptor Diabetes Mellitus, this term only
#15 MeSH descriptor Diabetes Mellitus, Type 1 explode all trees
#16 MeSH descriptor Diabetes Mellitus, Type 2 explode all trees
#17 MeSH descriptor Diabetic Nephropathies explode all trees
#18 diabet*:ti,ab,kw
#19 (niddm or iddm):ab,ti,kw
#20 (#14 OR #15 OR #16 OR #17 OR #18 OR #19)
#21 (#13 AND #20)
#22 MeSH descriptor Hypoglycemic Agents explode all trees
#23 MeSH descriptor Sulfonylurea Compounds explode all trees
#24 MeSH descriptor Dipeptidyl-Peptidase IV Inhibitors, this term only
#25 MeSH descriptor Glucagon-Like Peptide 1, this term only
#26 MeSH descriptor alpha-Glucosidases, this term only
#27 MeSH descriptor Sodium-Glucose Transporter 2, this term only
#28 (glucose lowering and (therap* or agent* or drug*)):ti,ab,kw in Clinical Trials
#29 (hypoglycemi* and (agent* or drug* or therap*)):ti,ab,kw in Clinical Trials
#30 (antidiabet* and (agent* or drug* or therap*)):ti,ab,kw in Clinical Trials
#31 (metformin):ti,ab,kw in Clinical Trials
#32 (Rosiglitazone):ti,ab,kw or (Rivoglitazone):ti,ab,kw or (Pioglitazone):ti,ab,kw or (Troglitazone):ti,ab,kw in Clinical Trials
#33 MeSH descriptor Thiazolidinediones, this term only
#34 (acarbose):ti,ab,kw or (miglitol):ti,ab,kw or (voglibose):ti,ab,kw in Clinical Trials
#35 (repaglinide or nateglinide or exenatide or pramlintide or benfluorex or liraglutide or mitiglinide):ti,ab,kw in Clinical Trials
#36 (sitagliptin or vildaglaptin or saxagliptin):ti,ab,kw
#37 (Linagliptin):ti,ab,kw or (Alogliptin):ti,ab,kw in Clinical Trials
#38 "glucagon-like peptide-1"*:ti,ab,kw in Clinical Trials
#39 (Incretin mimetic*):ti,ab,kw in Clinical Trials
#40 (alpha-glucosidase inhibitor*):ti,ab,kw in Clinical Trials
#41 (exenatide):ti,ab,kw in Clinical Trials
#42 (#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41)
#43 MeSH descriptor Insulins explode all trees
#44 insulin*:ti,ab,kw
#45 (#43 OR #44)
#46 (#42 AND #45)
#47 (#21 AND #46)

Chapter 3.1.
In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²) and coronary artery disease, is PCI or CABG or conservative treatment to be preferred?
MEDLINE search strategy

1. Kidney Diseases/
2. exp Renal Replacement Therapy/
3. Renal Insufficiency/
4. exp Renal Insufficiency, Chronic/
5. dialysis.tw.
6. (haemodialysis or haemodialysis).tw.
7. (hemofiltration or haemofiltration).tw.
8. (haemodiafiltration or haemodiafiltration).tw.
9. (end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw.
10. (ESRF or ESKF or ESRD or ESKD).tw.
11. (chronic kidney or chronic renal).tw.
12. (CKF or CKD or CRF or CRD).tw.
13. (CAPD or CCPD or APD).tw.
14. (predialysis or pre-dialysis).tw.
15. or/1-14
16. exp diabetes mellitus/
17. exp Diabetes Mellitus, Type 1/
18. exp Diabetes Mellitus, Type 2/
19. Diabetic Nephropathies/
20. diabet$.tw.
21. (niddm or iddm).tw.
22. or/16-21
23. exp coronary disease/
24. exp myocardial infarction/
25. exp angina pectoris/
26. coronary.tw.
27. angina.tw.
28. myocardial infarction.tw.
29. exp Myocardial Ischemia/
31. myocardial infarct$.tw.
32. heart infarct$.tw.
33. (cardiac adj5 ischemia).tw.
34. or/23-33
35. exp Coronary Artery Bypass/
36. coronary artery bypass$.tw.
37. CABG.tw.
38. exp Coronary Angiography/
39. exp Angioplasty, Balloon/
40. percutaneous coronary intervention$.tw.
41. pci.tw.
42. coronary angioplast$.tw.
43. exp stents/
44. stent$.tw.
45. (coronary adj4 bypass$).tw.
46. ptca.tw.
47. (balloon adj3 angioplast*).tw.
48. (coronary adj5 balloon dilation*).tw.
49. (coronary adj5 stent*).tw.
50. or/35-49
51. 15 and 22 and 34 and 50
52. randomized controlled trial.pt.
53. controlled clinical trial.pt.
54. randomi?ed.ab,ti.
55. placebo$.ab,ti.
56. drug therapy.fs.
57. randomly.ab,ti.
58. trial$.ab,ti.
59. group$.ab,ti.
60. or/52-59
62. exp Technology Assessment, Biomedical/
63. exp Meta-analysis/
64. exp Meta-analysis as topic/
65. (health technology adj6 assessment$).tw,ot.
66. hta.tw,ot.
67. (meta analy$ or metaanaly$ or meta?analy$).tw,ot.
68. exp Cohort studies/
69. Incidence.tw.
70. exp mortality/
71. exp follow-up studies/
72. mo.fs.
73. prognos$.tw.
74. predict$.tw.
75. course.tw.
76. exp survival analysis/
77. or/61-76
78. (comment or editorial or historical-article).pt.
79. 77 not 78
80. 60 or 79
81. 51 and 80
82. exp animal/ not humans/
83. 81 not 82

**COCHRANE CENTRAL search strategy**

#1 dialysis:ti,ab,kw
#2 h*emofiltration:ti,ab,kw
#3 h*emodiafiltration:ti,ab,kw
#4 (end-stage renal or end-stage kidney or endstage renal or endstage kidney):ti,ab,kw
#5 (ESRF or ESKF or ESRD or ESKD):ti,ab,kw
#6 (chronic kidney or chronic renal):ti,ab,kw
#7 (CKF or CKD or CRF or CRD):ti,ab,kw
#8 (CAPD or CCPD or APD):ti,ab,kw
#9 (predialysis or pre-dialysis):ti,ab,kw
#10 MeSH descriptor Kidney Failure, Chronic, this term only
#11 MeSH descriptor Renal Replacement Therapy explode all trees
#12 MeSH descriptor Renal Insufficiency, Chronic explode all trees
#13 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)
#14 MeSH descriptor Diabetes Mellitus, this term only
#15 MeSH descriptor Diabetes Mellitus, Type 1 explode all trees
#16 MeSH descriptor Diabetes Mellitus, Type 2 explode all trees
#17 MeSH descriptor Diabetic Nephropathies explode all trees
#18 diabet*:ti,ab,kw
Chapter 3.2.

In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²) and with a cardial indication (heart failure, ischemic heart disease, hypertension) should we prescribe inhibitors of the RAAS system or aldosteron-antagonists as cardiovascular prevention?

MEDLINE search strategy
1. Diabetes Mellitus/
2. exp Diabetes Mellitus, Type 1/
3. exp Diabetes Mellitus, Type 2/
4. Diabetic Nephropathies/
5. diabet$.tw.
6. (niddm or iddm).tw.
7. or/1-6
8. Kidney Diseases/
9. exp Renal Replacement Therapy/
10. Renal Insufficiency/
11. exp Renal Insufficiency, Chronic/
12. dialysis.tw.
13. (haemodialysis or haemodialysis).tw.
14. (hemofiltration or haemofiltration).tw.
15. (haemodiafiltration or haemodiafiltration).tw.
16. (end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw.
17. (ESRF or ESKF or ESRD or ESKD).tw.
18. (chronic kidney or chronic renal).tw.
19. (CKF or CKD or CRF or CRD).tw.
20. (CAPD or CCPD or APD).tw.
21. (predialysis or pre-dialysis).tw.
22. or/8-21
23. Coronary Disease/
24. Coronary Artery Disease/
25. Coronary Stenosis/
27. coronary stenos$.tw.
28. coronary atheroscleros$.tw.
29. coronary arterioscleros$.tw.
31. CAD.tw.
32. exp Myocardial Ischemia/
33. exp Myocardial Revascularization/
34. (isch?emi$ adj3 heart).tw.
35. angina.tw.
36. myocardial infarct$.tw.
37. heart infarct$.tw.
38. (cardiac adj5 ischemia).tw.
39. exp stents/
40. stent$.tw.
41. exp Coronary Artery Bypass/
42. (coronary adj4 bypass$).tw.
43. cabg.tw.
44. pci.tw.
45. heart failure.tw.
46. cardiac failure.tw.
47. exp Heart Failure/
48. or/23-47
49. exp Aldosterone Antagonists/
50. Canrenoate Potassium.tw.
51. Canrenone$.tw.
52. spirinolactone$.tw.
53. aldosterone antagonist$.tw.
54. aldactone$.tw.
55. practon$.tw.
56. sc-9420$.tw.
57. spiractin$.tw.
58. sc-14266$.tw.
59. soldactone$.tw.
60. aldadiene$.tw.
61. phanurane$.tw.
62. sc-9376.tw.
63. eplerenone$.tw.
64. or/49-63
65. exp angiotensin converting enzyme inhibitors/
66. captopril.tw.
67. enalapril.tw.
68. cilazapril.tw.
69. enalaprilat.tw.
70. fosinopril.tw.
71. lisinopril.tw.
72. perindopril.tw.
73. ramipril.tw.
74. saralasin.tw.
75. teprotide.tw.
76. exp losartan/
77. losartan.tw.
78. imidazole$.tw.
79. irbesartan.tw.
80. candesartan.tw.
81. eprosartan.tw.
82. valsartan.tw.
83. olmesartan.tw.
84. telmisartan.tw.
85. (ace adj2 inhibitor$).tw.
86. (angiotensin adj2 receptor antagonist$).tw.
87. or/65-86
88. 64 or 87
89. 7 and 22 and 48 and 88

COCHRANE CENTRAL search strategy
#1 dialysis:ti,ab,kw
#2 h*emofiltration:ti,ab,kw
#3 h*emodiafiltration:ti,ab,kw
#4 (end-stage renal or end-stage kidney or endstage renal or endstage kidney):ti,ab,kw
#5 (ESRF or ESKF or ESRD or ESKD):ti,ab,kw
#6 (chronic kidney or chronic renal):ti,ab,kw
#7 (CKF or CKD or CRF or CRD):ti,ab,kw
#8 (CAPD or CCPD or APD):ti,ab,kw
#9 (predialysis or pre-dialysis):ti,ab,kw
#10 MeSH descriptor: [Kidney Failure, Chronic] this term only
#11 MeSH descriptor: [Renal Replacement Therapy] explode all trees
#12 MeSH descriptor: [Renal Insufficiency, Chronic] explode all trees
#13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
#14 MeSH descriptor: [Diabetes Mellitus] this term only
#15 MeSH descriptor: [Diabetes Mellitus, Type 1] explode all trees
#16 MeSH descriptor: [Diabetes Mellitus, Type 2] explode all trees
#17 MeSH descriptor: [Diabetic Nephropathies] explode all trees
#18 diabet*:ti,ab,kw
#19 (niddm or iddm):ab,ti,kw
#20  (#14 or #15 or #16 or #17 or #18 or #19)
#21  #13 and #20
#22  MeSH descriptor: [Aldosterone Antagonists] explode all trees
#23  MeSH descriptor: [Angiotensin-Converting Enzyme Inhibitors] explode all trees
#24  Canrenoate Potassium:ti,ab,kw
#25  Canrenone*:ti,ab,kw
#26  spironolactone*:ti,ab,kw
#27  aldosterone antagonist*:ti,ab,kw
#28  aldactone*:ti,ab,kw
#29  practone*:ti,ab,kw
#30  sc-9420*:ti,ab,kw
#31  spiractin*:ti,ab,kw
#32  sc-14266*:ti,ab,kw
#33  soldactone*:ti,ab,kw
#34  aldadiene*:ti,ab,kw
#35  phanurane*:ti,ab,kw
#36  sc-9376*:ti,ab,kw
#37  eplerenone*:ti,ab,kw
#38  captopril:ti,ab,kw
#39  enalapril:ti,ab,kw
#40  cilazapril:ti,ab,kw
#41  enalaprilat:ti,ab,kw
#42  fosinopril:ti,ab,kw
#43  lisinopril:ti,ab,kw
#44  perindopril:ti,ab,kw
#45  ramipril:ti,ab,kw
#46  saralasin:ti,ab,kw
#47  teprotide:ti,ab,kw
#48  losartan:ti,ab,kw
#49  imidazole*:ti,ab,kw
#50  irbesartan:ti,ab,kw
#51  candesartan:ti,ab,kw
#52  eprosartan:ti,ab,kw
#53  valsartan:ti,ab,kw
#54  olmesartan:ti,ab,kw
Chapter 3.3
In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²) should we prescribe Beta Blockers to prevent sudden cardiac death

MEDLINE search strategy
1. Diabetes Mellitus/ 
2. exp Diabetes Mellitus, Type 1/ 
3. exp Diabetes Mellitus, Type 2/ 
4. Diabetic Nephropathies/ 
5. diabet$.tw. 
6. (niddm or iddm).tw. 
7. or/1-6 
8. Kidney Diseases/ 
9. exp Renal Replacement Therapy/ 
10. Renal Insufficiency/ 
11. exp Renal Insufficiency, Chronic/ 
12. dialysis.tw. 
13. (haemodialysis or haemodialysis).tw. 
14. (hemofiltration or haemofiltration).tw. 
15. (haemodiafiltration or haemodiafiltration).tw. 
16. (end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw. 
17. (ESRF or ESKF or ESRD or ESKD).tw. 
18. (chronic kidney or chronic renal).tw. 
19. (CKF or CKD or CRF or CRD).tw. 
20. (CAPD or CCPD or APD).tw. 
21. (predialysis or pre-dialysis).tw. 
22. or/8-21 
23. exp adrenergic beta-antagonists/ 
24. alprenolol.tw.
25. atenolol.tw.
26. metoprolol.tw.
27. nadolol.tw.
28. exprenolol.tw.
29. pindolol.tw.
30. propranolol.tw.
31. exp adrenergic alpha-antagonists/
32. labetalol.tw.
33. prazosin.tw.
34. beta block$.tw.
35. or/23-34
36. 7 and 22 and 35

COCHRANE CENTRAL search strategy

#1 dialysis:ti,ab,kw
#2 h*emofiltration:ti,ab,kw
#3 h*emodiafiltration:ti,ab,kw
#4 (end-stage renal or end-stage kidney or endstage renal or endstage kidney):ti,ab,kw
#5 (ESRF or ESKF or ESRD or ESKD):ti,ab,kw
#6 (chronic kidney or chronic renal):ti,ab,kw
#7 (CKF or CKD or CRF or CRD):ti,ab,kw
#8 (CAPD or CCPD or APD):ti,ab,kw
#9 (predialysis or pre-dialysis):ti,ab,kw
#10 MeSH descriptor: [Kidney Failure, Chronic] this term only
#11 MeSH descriptor: [Renal Replacement Therapy] explode all trees
#12 MeSH descriptor: [Renal Insufficiency, Chronic] explode all trees
#13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
#14 MeSH descriptor: [Diabetes Mellitus] this term only
#15 MeSH descriptor: [Diabetes Mellitus, Type 1] explode all trees
#16 MeSH descriptor: [Diabetes Mellitus, Type 2] explode all trees
#17 MeSH descriptor: [Diabetic Nephropathies] explode all trees
#18 diabet*:ti,ab,kw
#19 (niddm or iddm):ab,ti,kw
#20 (#14 or #15 or #16 or #17 or #18 or #19)
#21 #13 and #20
#22 MeSH descriptor: [Adrenergic beta-Antagonists] explode all trees
#23 MeSH descriptor: [Adrenergic alpha-Antagonists] explode all trees
#24 alprenolol:ti,ab,kw
#25 atenolol:ti,ab,kw
#26 metoprolol:ti,ab,kw
#27 nadolol:ti,ab,kw
#28 oxprenolol:ti,ab,kw
#29 pindolol:ti,ab,kw
#30 propranolol:ti,ab,kw
#31 labetalol:ti,ab,kw
#32 prazosin:ti,ab,kw
#33 beta block*:ti,ab,kw
#34 (#22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33)
#35 #21 and #34

**Chapter 3.4.**
**In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²) should we aim at lower blood pressure targets than in the general population?**

A Cochrane review of sufficient quality was used to answer this question

**Chapter 3.5.**
**In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²) should we prescribe lipid lowering therapy in primary prevention?**

**MEDLINE search strategy**
1. Kidney Diseases/
2. exp Renal Replacement Therapy/
3. Renal Insufficiency/
4. exp Renal Insufficiency, Chronic/
5. dialysis.tw.
6. (haemodialysis or haemodialysis).tw.
7. (hemofiltration or haemofiltration).tw.
8. (haemodiafiltration or haemodiafiltration).tw.
9. (end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw.
10. (ESRF or ESKF or ESRD or ESKD).tw.
11. (chronic kidney or chronic renal).tw.
12. (CKF or CKD or CRF or CRD).tw.
13. (CAPD or CCPD or APD).tw.
14. (predialysis or pre-dialysis).tw.
15. or/1-14
16. diabetes mellitus/
17. exp Diabetes Mellitus, Type 1/
18. exp Diabetes Mellitus, Type 2/
19. Diabetic Nephropathies/
20. diabet$.tw.
21. (niddm or iddm).tw.
22. or/16-21
23. exp Hypolipidemic Agents/
24. exp hyperlipidemias/
25. lipid-lower$.tw.
26. hypercholesterol$.tw.
27. antilipid$.tw.
28. hyperlipemia.tw.
29. hyperlipid$.tw.
30. dyslipemia.tw.
31. cholesterol-lower$.tw.
32. hydroxymethylglutaryl-coa reductase inhibitor*.tw.
33. HMG-CoA reductase inhibitor*.tw.
34. fibrate$.tw.
35. statin*.tw.
36. fluvastatin.tw.
37. simvastatin.tw.
38. pravastatin.tw.
39. lovastatin.tw.
40. meglutol.tw.
41. cerivastatin.tw.
42. atorvastatin.tw.
43. mevacor.tw.
44. pravachol.tw.
45. lescol.tw.
46. lipitor.tw.
47. cholestyramine.tw.
48. colestipol.tw.
49. gemfibrozil.tw.
50. fibrate.tw.
51. clofibrate.tw.
52. ezetimibe.tw.
53. nicotinic acid.tw.
54. or/23-53
55. 15 and 22 and 54
56. randomized controlled trial.pt.
57. controlled clinical trial.pt.
58. randomi?ed.ab,ti.
59. placebo$.ab,ti.
60. drug therapy.fs.
61. randomly.ab,ti.
62. trial$.ab,ti.
63. group$.ab,ti.
64. or/56-63
66. exp Technology Assessment, Biomedical/
67. exp Meta-analysis/
68. exp Meta-analysis as topic/
69. (health technology adj6 assessment$).tw,ot.
70. hta.tw,ot.
71. (meta analy$ or metaanaly$ or meta?analy$).tw,ot.
72. exp Cohort studies/
73. Incidence.tw.
74. exp mortality/
75. exp follow-up studies/
76. mo.fs.
77. prognos$.tw.
78. predict$.tw.
79. course.tw.
80. exp survival analysis/
81. or/65-80
82. (comment or editorial or historical-article).pt.
83. 81 not 82
84. 64 or 83
85. 55 and 84
86. exp animal/ not humans/
87. 85 not 86

COCHRANE CENTRAL search strategy

#1 dialysis:ti,ab,kw
#2 h*emofiltration:ti,ab,kw
#3 h*emodiafiltration:ti,ab,kw
#4 (end-stage renal or end-stage kidney or endstage renal or endstage kidney):ti,ab,kw
#5 (ESRF or ESKF or ESRD or ESKD):ti,ab,kw
#6 (chronic kidney or chronic renal):ti,ab,kw
#7 (CKF or CKD or CRF or CRD):ti,ab,kw
#8 (CAPD or CCPD or APD):ti,ab,kw
#9 (predialysis or pre-dialysis):ti,ab,kw
#10 MeSH descriptor Kidney Failure, Chronic, this term only
#11 MeSH descriptor Renal Replacement Therapy explode all trees
#12 MeSH descriptor Renal Insufficiency, Chronic explode all trees
#13 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)
#14 MeSH descriptor Diabetes Mellitus, this term only
#15 MeSH descriptor Diabetes Mellitus, Type 1 explode all trees
#16 MeSH descriptor Diabetes Mellitus, Type 2 explode all trees
#17 MeSH descriptor Diabetic Nephropathies explode all trees
#18 diabet*:ti,ab,kw
#19 (niddm or iddm):ab,ti,kw
#20 (#14 OR #15 OR #16 OR #17 OR #18 OR #19)
#21 (#13 AND #20)
#22 MeSH descriptor Hypolipidemic Agents explode all trees
#23 MeSH descriptor Hyperlipidemias explode all trees
#24 lipid-lower*:ti,ab,kw
Chapter 3.6.

A. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²) should we recommend interventions aimed at increasing energy expenditure and physical activity?

MEDLINE
1. Kidney Diseases/
2. exp Renal Replacement Therapy/
3. Renal Insufficiency/
4. exp Renal Insufficiency, Chronic/
5. dialysis.tw.
6. (haemodialysis or haemodialysis).tw.
7. (hemofiltration or haemofiltration).tw.
8. (haemodiafiltration or haemodiafiltration).tw.
9. (end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw.
10. (ESRF or ESKF or ESRD or ESKD).tw.
11. (chronic kidney or chronic renal).tw.
12. (CKF or CKD or CRF or CRD).tw.
13. (CAPD or CCPD or APD).tw.
14. (predialysis or pre-dialysis).tw.
15. or/1-14
16. exp diabetes mellitus/
17. exp Diabetes Mellitus, Type 1/
18. exp Diabetes Mellitus, Type 2/
19. Diabetic Nephropathies/
20. diabet$.tw.
21. (niddm or iddm).tw.
22. or/16-21
23. Physical Exertion/
24. exp Exercise Therapy/
25. exp Exercise Test/
26. exp Physical Fitness/
27. exercise.tw.
28. (resistance training or resistance program$).tw.
29. (physical fitness or physical rehabilitation).tw.
30. (strength$ and (muscle or program$ or training)).tw.
31. (Physical and (Education or Training)).tw.
32. or/23-31
33. 15 and 22 and 32
34. exp animal/ not humans/
35. 33 not 34

**COCHRANE CENTRAL**

#1 dialysis:ti,ab,kw
#2 h*emofiltration:ti,ab,kw
#3 h*emodiafiltration:ti,ab,kw
#4 (end-stage renal or end-stage kidney or endstage renal or endstage kidney):ti,ab,kw
#5 (ESRF or ESKF or ESRD or ESKD):ti,ab,kw
#6 (chronic kidney or chronic renal):ti,ab,kw
#7 (CKF or CKD or CRF or CRD):ti,ab,kw
Chapter 3.6.

B. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²) should we recommend interventions aimed at reducing energy intake?

MEDLINE
1. Kidney Diseases/
2. exp Renal Replacement Therapy/
3. Renal Insufficiency/
4. exp Renal Insufficiency, Chronic/
5. dialysis.tw.
6. (haemodialysis or haemodialysis).tw.
7. (hemofiltration or haemofiltration).tw.
8. (haemodiafiltration or haemodiafiltration).tw.
9. (end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw.
10. (ESRF or ESKF or ESRD or ESKD).tw.
11. (chronic kidney or chronic renal).tw.
12. (CKF or CKD or CRF or CRD).tw.
13. (CAPD or CCPD or APD).tw.
14. (predialysis or pre-dialysis).tw.
15. or/1-14
16. exp diabetes mellitus/
17. exp Diabetes Mellitus, Type 1/
18. exp Diabetes Mellitus, Type 2/
19. Diabetic Nephropathies/
20. diabet$.tw.
21. (niddm or iddm).tw.
22. or/16-21
23. energy intake/
24. exp Diet Therapy/
25. exp Feeding Behavior/
26. exp Diet/
27. nutrition*.tw.
28. (nutri$ or diet$ or food or eat$).tw.
29. or/23-28
30. 15 and 22
31. 29 and 30
32. limit 31 to human
33. randomized controlled trial.pt.
34. controlled clinical trial.pt.
35. randomized.ab.
36. placebo.ab.
37. clinical trials as topic/
38. randomly.ab.
39. trial.ti.
40. exp Cohort studies/
41. or/33-40

**COCHRANE CENTRAL**
#1 dialysis:ti,ab,kw
#2 h*emofiltration:ti,ab,kw
#3 h*emodiafiltration:ti,ab,kw
#4 (end-stage renal or end-stage kidney or endstage renal or endstage kidney):ti,ab,kw
#5 (ESRF or ESKF or ESRD or ESKD):ti,ab,kw
#6 (chronic kidney or chronic renal):ti,ab,kw
#7 (CKF or CKD or CRF or CRD):ti,ab,kw
#8 (CAPD or CCPD or APD):ti,ab,kw
#9 (predialysis or pre-dialysis):ti,ab,kw
#10 MeSH descriptor Kidney Failure, Chronic, this term only
#11 MeSH descriptor Renal Replacement Therapy explode all trees
#12 MeSH descriptor Renal Insufficiency, Chronic explode all trees
#13 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)
#14 MeSH descriptor Diabetes Mellitus, this term only
#15 MeSH descriptor Diabetes Mellitus, Type 1 explode all trees
#16 MeSH descriptor Diabetes Mellitus, Type 2 explode all trees
#17 MeSH descriptor Diabetic Nephropathies explode all trees
#18 diabet*:ti,ab,kw
#19 (niddm or iddm):ab,ti,kw
#20 (#14 OR #15 OR #16 OR #17 OR #18 OR #19)
#21 (#13 AND #20)
#22 energy intake:ti,ab,kw
#23 explode Diet Therapy
#24 explode diet
#25 explode Feeding Behavior
#26 nutrition*:ti,ab,kw
#27 (nutri$ or diet$ or food or eat$):ti,ab,kw
#28 (#22 OR #23 OR #24 OR #25 OR #26 OR #27)
#29 (#21 AND #28)
Chapter 3.7.

In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²) should antiplatelet therapy be recommended, regardless of their cardiovascular risk?

MEDLINE
1. exp Platelet Aggregation Inhibitors/
2. exp Phosphodiesterase Inhibitors/
3. Adenosine Diphosphate [Antagonists & Inhibitors]
4. Platelet Glycoprotein GPIIb-IIIa Complex [Antagonists & Inhibitors]
5. Sulfinpyrazone/
6. (antiplatelet agents$ or anti-platelet agent$).tw.
7. (antiplatelet therap$ or anti-platelet therap$).tw.
8. platelet aggregation inhibit$.tw.
9. phosphodiesterase inhibit$.tw.
10. thrombocyte aggregation inhibit$.tw.
11. (antithrombocytic agent$ or anti-thrombocytic agent$).tw.
12. (antithrombocytic therap$ or anti-thrombocytic therap$).tw.
13. alprostadil.tw.
14. aspirin.tw.
15. acetylsalicylic acid.tw.
16. (adenosine reuptake inhibit$ or adenosine re-uptake inhibit$).tw.
17. adenosine diphosphate receptor inhibit$.tw.
18. dipyridamole.tw.
19. disintegrins.tw.
20. epoprostenol.tw.
21. iloprost.tw.
22. ketanserin.tw.
23. milrinone.tw.
24. pentoxifylline.tw.
27. trapidil.tw.
28. ticlopidine.tw.
29. clopidogrel.tw.
30. (sulfinpyrazone or sulphinpyrazone).tw.
31. cilostazol.tw.
32. (P2Y12 adj2 antagonis$).tw.
33. prasugrel.tw.
34. ticagrelor.tw.
35. cangrelor.tw.
36. elinogrel.tw.
37. “glycoprotein IIb/IIIa inhibitors”.tw.
38. abciximab.tw.
39. eptifibatide.tw.
40. tirofiban.tw.
41. defibrotide.tw.
42. picotamide.tw.
43. beraprost.tw.
44. ticlid.tw.
45. aggrenox.tw.
46. ditrazole.tw.
47. or/1-46
48. exp Renal Dialysis/
49. (haemodialysis or haemodialysis).tw.
50. (hemofiltration or haemofiltration).tw.
51. (haemodiafiltration or haemodiafiltration).tw.
52. dialysis.tw.
53. (PD or CAPD or CCPD or APD).tw.
54. Renal Insufficiency/
55. Kidney Failure/
56. exp Renal Insufficiency, Chronic/
57. Kidney Diseases/
58. Uremia/
59. (end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw.
60. (ESRF or ESKF or ESRD or ESKD).tw.
61. (chronic kidney or chronic renal).tw.
62. (CKF or CKD or CRF or CRD).tw.
63. (predialysis or pre-dialysis).tw.
64. ur?emi$.tw.
65. or/48-64
66. and/47,65
67. exp diabetes mellitus/
68. exp Diabetes Mellitus, Type 1/
69. exp Diabetes Mellitus, Type 2/
70. Diabetic Nephropathies/
71. diabet$.tw.
72. (niddm or iddm).tw.
73. or/67-72
74. 73 and 66

COCHRANE CENTRAL
#1. MeSH descriptor Phosphodiesterase Inhibitors explode all trees
#2. MeSH descriptor Adenosine Diphosphate, this term only with qualifier: AI
#3. MeSH descriptor Platelet Glycoprotein GPIIb-IIIa Complex, this term only with qualifier: AI
#4. ((antiplatelet next agent*) or (anti-platelet next agent*)):ti,ab,kw
#5. ((antiplatelet therap*) or (anti-platelet therap*)):ti,ab,kw
#6. (platelet next aggregation next inhibit*):ti,ab,kw
#7. (phosphodiesterase next inhibit*):ti,ab,kw
#8. (thrombocyte next aggregation next inhibit*):ti,ab,kw
#9. ((antithrombocytic next agent*) or (anti-thrombocytic next agent*)):ti,ab,kw
#10. ((antithrombocytic next therap*) or (anti-thrombocytic next therap*)):ti,ab,kw
#11. alprostadil:ti,ab,kw
#12. aspirin:ti,ab,kw
#13. acetylsalicylic acid:ti,ab,kw
#14. ((adenosine next reuptake inhibit*) or (adenosine re-uptake inhibit*)):ti,ab,kw
#15. (adenosine next diphosphate next receptor next inhibit*):ti,ab,kw
#16. dipyridamole:ti,ab,kw
#17. disintegrins:ti,ab,kw
#18. epoprostenol:ti,ab,kw
#19. iloprost:ti,ab,kw
#20. ketanserin:ti,ab,kw
#21. milrinone:ti,ab,kw
#22. pentoxifylline:ti,ab,kw
#23. (S-nitrosoglutathione):ti,ab,kw
#24. S-nitrosothiols:ti,ab,kw
#25. trapidil:ti,ab,kw
#26. ticlopidine:ti,ab,kw
#27. clopidogrel:ti,ab,kw
#28. (sulfinpyrazone or sulphinpyrazone):ti,ab,kw
#29. cilostazol:ti,ab,kw
#30. (P2Y12 NEAR/2 antagonis*:):ti,ab,kw
#31. prasugrel:ti,ab,kw
#32. ticagrelor:ti,ab,kw
#33. cangrelor:ti,ab,kw
#34. elinogrel:ti,ab,kw
#35. “glycoprotein IIB/IIIa inhibitors”:ti,ab,kw
#36. abciximab:ti,ab,kw
#37. eptifibatide:ti,ab,kw
#38. tirofiban:ti,ab,kw
#39. defibrotide:ti,ab,kw
#40. picotamide:ti,ab,kw
#41. beraprost:ti,ab,kw
#42. ticlid:ti,ab,kw
#43. aggrenox:ti,ab,kw
#44. ditaazole:ti,ab,kw
#45. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44)
#46. dialysis:ti,ab,kw
#47. (haemodialysis or haemodialysis):ti,ab,kw
#48. (hemofiltration or haemofiltration):ti,ab,kw
#49. (haemodiafiltration or haemodiafiltration):ti,ab,kw
#50. (PD or CAPD or CCPD or APD):ti,ab,kw
#51. (renal next insufficiency):ti,ab,kw
#52. (kidney next failure):ti,ab,kw
#53. (kidney next disease*):ti,ab,kw
#54. ur*emi*:ti,ab,kw
#55. ((chronic next kidney) or (chronic next renal)):ti,ab,kw
#56. (CKF or CKD or CRF or CRD):ti,ab,kw
#57. predialysis:ti,ab,kw
#58. ((end-stage next renal) or (end-stage next kidney) or (endstage next renal) or (endstage next kidney)):ti,ab,kw
#59. (ESKD or ESRD or ESKF or ESRF):ti,ab,kw
#60. (#46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59)
#61. (#45 AND #60)
#62. MeSH descriptor Diabetes Mellitus, this term only
#63. MeSH descriptor Diabetes Mellitus, Type 1 explode all trees
#64. MeSH descriptor Diabetes Mellitus, Type 2 explode all trees
#65. MeSH descriptor Diabetic Nephropathies explode all trees
#66. diabet*:ti,ab,kw
#67. (niddm or iddm):ab,ti,kw
#68. (#62 OR #63 OR #64 OR #65 OR #66 OR #67)
#69. (#68 AND #61)
Appendix 4 | Selection of Study Flowcharts

Chapter 1.1.
Should patients with diabetes and CKD stage 5 start with peritoneal dialysis or hemodialysis as a first modality?

423 Citations identified by electronic database searching
• 127 Cochrane Central
• 296 MEDLINE

3 additional citations identified via other sources

425 potentially relevant citations identified for title and abstract review

350 Citations excluded on screening of title and abstracts using general criteria

76 potentially relevant citations identified for full-text review

51 Citations excluded based on full-text screening using inclusion criteria
• 19 inappropriate population
• 15 intervention/comparator not of interest
• 17 No primary data

25 Documents included in qualitative analyses
Chapter 1.2.
Should patients with diabetes and CKD stage 5 start dialysis earlier, i.e. before becoming symptomatic, than non-diabetics?
Chapter 1.3.
In patients with diabetes and CKD stage 5, should a native fistula, a graft or a tunnelled catheter be preferred as initial access?
Chapter 1.4.
What is the benefit of renal transplantation for dialysis patients with diabetes and CKD stage 5?
C. is there evidence for a selection bias in observational studies?
Chapter 1.4.

D. Is there a benefit of renal transplantation for patients with diabetes and CKD stage 5?

- **541 Citations** identified by electronic database searching
  - **138** Cochrane Central
  - **403** MEDLINE

- **28 additional citations** identified via other sources

- **569 potentially relevant citations** identified for title and abstract review

- **522 Citations excluded** on screening of title and abstracts using general criteria

- **47 potentially relevant citations** identified for full-text review

- **17 Citations excluded** based on full-text screening using inclusion criteria
  - **10** inappropriate population
  - **7** intervention/comparator not of interest

- **30 Documents included** in qualitative analyses
Chapter 2.1.

E. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²), should we aim to lower HbA1C by more tight glycaemic control

No flow chart available. Evidence extracted from the Cochrane Review written by Hemmingsen et al
Chapter 2.1.

F. Is an aggressive treatment strategy (in number of injections and controls and follow up) superior to a more relaxed treatment strategy in patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²) and using insulin

![Diagram showing the flow of citations and screening process.]

- 336 Citations identified by electronic database searching
  - 29 Cochrane Central
  - 307 MEDLINE

- 323 potentially relevant citations identified for title and abstract review after duplicates were removed

- 252 Citations excluded on screening of title and abstracts using general criteria

- 71 potentially relevant citations identified for full-text review

- 66 Citations excluded based on full-text screening using inclusion criteria
  - 23 inappropriate population
  - 13 intervention not of interest
  - 4 No primary data
  - 26 Review design

- 5 Documents included in qualitative analyses
Chapter 2.2.
In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²), are there better alternatives than HbA1c to estimate glycaemic control?

No Flow Chart available

All the included studies are listed in the narrative review from NDT:

Chapter 2.3.

B. Is any oral drug superior to another in terms of mortality/complications/glycaemic control in diabetic patients with CKD stage 3b or higher (eGFR <45 mL/min/1.73m²)?
Chapter 2.3.

A. Is any oral drug superior to another in terms of mortality/complications/glycaemic control in diabetic patients with CKD stage 3b or higher (eGFR <45 mL/min/1.73m²) ?

Review of systematic reviews

- Records identified through database searching: n=549
- Records after duplicates removal: n=545
- Records excluded based on title and abstract: n = 385 (total number):
  - 363 not about our intervention;
  - 22 not a systematic review.
-Potentially relevant records identified for full-text review: n=160
- Record excluded based on full-text review (n=117):
  - 23 not about our population;
  - 55 not about our intervention;
  - 36 not the right study design (not a systematic review).
- Records included: n=42
Chapter 2.3.

B. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²), is maximal oral therapy better than starting/adding insulin in an earlier stage?
Chapter 3.1.
In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²) and coronary artery disease, is PCI or CABG or conservative treatment to be preferred?

616 Citations identified by electronic database searching
  • 44 Cochrane Central
  • 572 MEDLINE

589 potentially relevant citations identified for title and abstract review after duplicates removed

533 Citations excluded on screening of title and abstracts using general criteria

56 potentially relevant citations identified for full-text review

49 Citations excluded based on full-text screening using inclusion criteria
  • 26 inappropriate population
  • 13 intervention not of interest
  • 2 No primary data
  • 8 Review design

7 Documents included in qualitative analyses
Chapter 3.2.
In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²) and with a cardial indication (heart failure, ischemic heart disease, hypertension) should we prescribe inhibitors of the RAAS system or aldosterone-antagonists as cardiovascular prevention?
Chapter 3.3.
In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²), should we prescribe Beta Blockers to prevent sudden cardiac death?
Chapter 3.4.
In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²), should we aim at lower blood pressure targets than in the general population?

A Cochrane review of sufficient quality was used to answer this question.
Chapter 3.5.
In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²), should we prescribe lipid lowering therapy in primary prevention?
Chapter 3.6.

C. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²), should we recommend interventions aimed at increasing energy expenditure and physical activity?

D. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²), should we recommend interventions aimed at reducing energy intake?
Chapter 3.7.
In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²), should antiplatelet therapy be recommended, regardless of their cardiovascular risk?
Appendix 5| Summary Tables

Chapter 1: Issues on modality selection in patients with diabetes and CKD stage 5
Chapter 1.1.
Should patients with diabetes and CKD stage 5 start with peritoneal dialysis or hemodialysis as a first modality?

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<tr>
<td>van de Luijtgaarden[234]</td>
<td>2011</td>
<td>3976</td>
<td>955</td>
<td>Death in diabetic men aged 45-59 years</td>
<td>0-3 years</td>
<td>Hazard Ratio</td>
<td>0.79</td>
<td>0.54</td>
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<tr>
<td>van de Luijtgaarden[234]</td>
<td>2011</td>
<td>3976</td>
<td>955</td>
<td>Death in diabetic men aged 60-69 years</td>
<td>0-3 years</td>
<td>Hazard Ratio</td>
<td>0.96</td>
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<td>3976</td>
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<td>Death in diabetic women aged 45-59 years</td>
<td>0-3 years</td>
<td>Hazard Ratio</td>
<td>0.80</td>
<td>0.47</td>
<td>1.38</td>
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<td>van de Luijtgaarden[234]</td>
<td>2011</td>
<td>3976</td>
<td>955</td>
<td>Death in diabetic men aged =&gt;70 years</td>
<td>0-3 years</td>
<td>Hazard Ratio</td>
<td>0.80</td>
<td>0.61</td>
<td>1.04</td>
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<tr>
<td>van de Luijtgaarden[234]</td>
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<td>3976</td>
<td>955</td>
<td>Death in diabetic men</td>
<td>0-3 years</td>
<td>Hazard Ratio</td>
<td>0.84</td>
<td>0.71</td>
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<tr>
<td>van de Luijtgaarden[234]</td>
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<td>3976</td>
<td>955</td>
<td>Death in diabetic women</td>
<td>0-3 years</td>
<td>Hazard Ratio</td>
<td>1.16</td>
<td>0.93</td>
<td>1.44</td>
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<tr>
<td>van de Luijtgaarden[234]</td>
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<td>3976</td>
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<td>Death in diabetic women aged 20-44 yrs</td>
<td>0-3 years</td>
<td>Hazard Ratio</td>
<td>0.76</td>
<td>0.33</td>
<td>1.76</td>
</tr>
<tr>
<td>van de Luijtgaarden[234]</td>
<td>2011</td>
<td>3976</td>
<td>955</td>
<td>Death in diabetic women aged 60-69 years</td>
<td>0-3 years</td>
<td>Hazard Ratio</td>
<td>0.95</td>
<td>0.60</td>
<td>1.49</td>
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<tr>
<td>van de Luijtgaarden[234]</td>
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<td>Death in diabetic women aged =&gt;70 years</td>
<td>0-3 years</td>
<td>Hazard Ratio</td>
<td>1.59</td>
<td>1.15</td>
<td>2.08</td>
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<tr>
<td>Venesh[235]</td>
<td>2004</td>
<td>352706</td>
<td>46234</td>
<td>Death in diabetic patients aged 18-44 years without comorbidity</td>
<td>0-3 years</td>
<td>Relative Risk</td>
<td>0.82</td>
<td>0.70</td>
<td>0.95</td>
</tr>
<tr>
<td>Venesh[235]</td>
<td>2004</td>
<td>352706</td>
<td>46234</td>
<td>Death in diabetic patients aged 45-64 years with comorbidity</td>
<td>0-3 years</td>
<td>Relative Risk</td>
<td>1.22</td>
<td>1.15</td>
<td>1.30</td>
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<tr>
<td>Venesh[235]</td>
<td>2004</td>
<td>352706</td>
<td>46234</td>
<td>Death in diabetic patients aged 18-44 years with comorbidity</td>
<td>0-3 years</td>
<td>Relative Risk</td>
<td>0.91</td>
<td>0.76</td>
<td>1.09</td>
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<tr>
<td>Venesh[235]</td>
<td>2004</td>
<td>352706</td>
<td>46234</td>
<td>Death in diabetic patients aged &gt;=65 years with comorbidity</td>
<td>0-3 years</td>
<td>Relative Risk</td>
<td>1.25</td>
<td>1.18</td>
<td>1.32</td>
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<tr>
<td>Venesh[235]</td>
<td>2004</td>
<td>352706</td>
<td>46234</td>
<td>Death in diabetic patients aged 45-64 years without comorbidity</td>
<td>0-3 years</td>
<td>Relative Risk</td>
<td>1.09</td>
<td>1.00</td>
<td>1.18</td>
</tr>
<tr>
<td>Venesh[235]</td>
<td>2004</td>
<td>352706</td>
<td>46234</td>
<td>Death in diabetic patients aged &gt;= 65 years with no comorbidity</td>
<td>0-3 years</td>
<td>Relative Risk</td>
<td>1.16</td>
<td>1.08</td>
<td>1.27</td>
</tr>
<tr>
<td>Jaar[236]</td>
<td>2005</td>
<td>433</td>
<td>140</td>
<td>Death in diabetic patients</td>
<td>0-2 years</td>
<td>Relative Risk</td>
<td>1.41</td>
<td>0.91</td>
<td>2.19</td>
</tr>
</tbody>
</table>

Late mortality (> 36 months)
<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Patients</th>
<th>Follow-up</th>
<th>Hazard Ratio</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weinhandl[16]</td>
<td>2010</td>
<td>3099</td>
<td>3086</td>
<td>Death in DM patients over 18 years, from day 90</td>
<td>36-48 months</td>
</tr>
<tr>
<td></td>
<td>2010</td>
<td>3099</td>
<td>3086</td>
<td>Death in DM patients over 18 years, from day 90</td>
<td>90-120 months</td>
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<tr>
<td></td>
<td>2010</td>
<td>3099</td>
<td>3086</td>
<td>Death in DM patients over 18 years</td>
<td>0-4 years</td>
</tr>
<tr>
<td></td>
<td>2010</td>
<td>3099</td>
<td>3086</td>
<td>Death in DM patients over 18 years, from day 90</td>
<td>0-4 years</td>
</tr>
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<td>Collins[228]</td>
<td>2002</td>
<td>26049</td>
<td>2805</td>
<td>Death rates per 1 000 patients years</td>
<td>18-24 months</td>
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<tr>
<td></td>
<td>2005</td>
<td>26049</td>
<td>2805</td>
<td>Death rates per 1 000 patients years</td>
<td>36-42 months</td>
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<td>2002</td>
<td>26049</td>
<td>2805</td>
<td>Death rates per 1 000 patients years</td>
<td>42-48 months</td>
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<td>Termorshuizen[14]</td>
<td>2003</td>
<td>111</td>
<td>70</td>
<td>Death in diabetic patients aged &gt; 60 yrs</td>
<td>24-48 months</td>
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<tr>
<td></td>
<td>2003</td>
<td>111</td>
<td>70</td>
<td>Death in diabetic patients aged &lt; 60 yrs</td>
<td>24-48 months</td>
</tr>
<tr>
<td>Heaf[237]</td>
<td>2002</td>
<td>724</td>
<td>479</td>
<td>Death in diabetic patients</td>
<td>0-10 years</td>
</tr>
<tr>
<td></td>
<td>2002</td>
<td>724</td>
<td>479</td>
<td>Death in diabetic patients &lt; 55 years</td>
<td>0-10 years</td>
</tr>
<tr>
<td></td>
<td>2002</td>
<td>724</td>
<td>479</td>
<td>Death in diabetic patients &gt; 55 years</td>
<td>0-10 years</td>
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<tr>
<td>Lee[233]</td>
<td>2009</td>
<td>497</td>
<td>79</td>
<td>Death in diabetic patients</td>
<td>0-15 years</td>
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<td>Mircescu[238]</td>
<td>2006</td>
<td>122</td>
<td>89</td>
<td>Adjusted death rates per 100 patients-years, patients without comorbid conditions aged 18-65</td>
<td>0-7 years</td>
</tr>
<tr>
<td></td>
<td>2006</td>
<td>122</td>
<td>89</td>
<td>Adjusted death rates per 100 patients-years, patients with comorbid conditions and aged &gt;65</td>
<td>0-7 years</td>
</tr>
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<td></td>
<td>2006</td>
<td>122</td>
<td>89</td>
<td>Adjusted death rates per 100 patients-years, patients with comorbid conditions and aged 18-65</td>
<td>0-7 years</td>
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<tr>
<td>Sanabria[239]</td>
<td>2008</td>
<td>157</td>
<td>220</td>
<td>Death in diabetic, &lt;65 years</td>
<td>0-4 years</td>
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<td></td>
<td>2008</td>
<td>157</td>
<td>220</td>
<td>Death in diabetic, =&gt;65 years</td>
<td>0-4 years</td>
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<tr>
<td>Fenton[15]</td>
<td>1997</td>
<td>1800</td>
<td>907</td>
<td>Death in diabetic patients &lt; 65 years</td>
<td>0-5 years</td>
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<tr>
<td></td>
<td>1997</td>
<td>1800</td>
<td>907</td>
<td>Death in diabetic patients &gt; 65 years</td>
<td>0-5 years</td>
</tr>
</tbody>
</table>

Hazard ratio or a relative risk higher than 1 (highlighted in red) indicates a higher mortality for PD patients. A HR lower than 1 (highlighted in green) indicates a higher mortality for HD patients.
### Chapter 1.2.

**Should patients with diabetes and CKD stage 5 start dialysis earlier, i.e. before becoming symptomatic, than patients without diabetes?**

<table>
<thead>
<tr>
<th>Study</th>
<th>Publication Year</th>
<th>Time Frame</th>
<th>Location</th>
<th>Design</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Patients’ characteristics</th>
<th>Intervention (n=)</th>
<th>Comparator (n=)</th>
<th>Duration</th>
<th>Outcome(s)</th>
<th>Results</th>
<th>Quality of evidence</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cooper et al.</td>
<td>2010</td>
<td>2000-2008</td>
<td>Australia/New Zealand</td>
<td>Randomized controlled trial (IDEAL study)</td>
<td>Patients were eligible for inclusion in the study if they had progressive chronic kidney disease (patients with a failing kidney transplant were eligible) and an estimated GFR between 10.0 and 15.0 ml per minute per 1.73 m²</td>
<td>- exclusion: &lt; 18 years of age, eGFR&lt; 10.0 ml/min, planned living donation within 12 months, cancer that was likely to affect mortality</td>
<td>- Age: 60.3 yrs</td>
<td>- Late start of dialysis group (eGFRCG between 5-7 ml) (n=424)</td>
<td>- Early start of dialysis group (eGFRCG between 10-14 ml) (n=404)</td>
<td>- FU until November 2009</td>
<td>- Mortality</td>
<td>-HR 1.04 (0.83-1.30) p=0.75. P for interaction for early or late start of dialysis with diabetes = 0.63.</td>
<td>High.</td>
<td>Randomized controlled trial with proper subgroup analysis for interaction in diabetics.</td>
</tr>
</tbody>
</table>

| Coronel et al. | 2009 | 1982-2004 | Europe | Retrospective cohort study | they had begun PD as the first renal replacement treatment, remained on the therapy for more than 2 months, and had sufficient parameters to measure the GFR by Modification of Diet in Renal Disease-7 (MDRD-7) [13], a currently validated method used to measure the GFR in diabetic CKD patients | - Age: 53 yrs | - eGFRMDRD ≤ 7.7 ml/min/1.73m² (n=56) | - eGFRMDRD > 7.7 ml/min/1.73m² (n=44) | - 60 months FU | - Mortality (on PD in diabetics, in DM1 and in DM2) | - Hospital admissions (admissions/year and days of hospitalizations) | - KM higher actuarial mortality in eGFR>7.7ml group. p=0.007 | - KM: similar mortality in eGFR>7.7 ml group with DM 1. P=0.2 | - KM higher actuarial mortality in eGFR>7.7ml in DM2 group. P=0.045 | - No difference in admissions per year between intervention and comparator group (i.e.1.3±1.0 vs. 1.5±1.2 admission/year p=NS) | Low. | No (adjusted) effect measures provided. Limited population size and only PD patients |
Retrospective cohort study 
-In principle all North American pts that start dialysis. The extent in which the ESRD Medical Evidence Form covers these pts is not mentioned. 
-Patients with missing GFR values, acquired HIV virus, or cancer were excluded from this analysis. 
-Age: 62 yrs 
-Gender: 53% male 
-DM (PRD): 46% 
-DM (Comorbid): 48% 
-eGFR at start: 8.4 ml/min/1.73m² 
-eGFR_{MDRD} 5-7.5 mL (n=99,940), 7.6-10 mL (n=74,656), >10 mL at start of dialysis (n=76,046) 
-eGFR_{MDRD} <5 mL (n=51,645) at start of dialysis 
-Until December 31, 2000 

- No difference in number of days of hospitalization between intervention and comparator group (23.1±29 vs 20±22 days/patient/year) 

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Lassalle et al. - 2010 - Europe - 2002-2006 
Retrospective cohort study 
-The REIN Registry includes all ESRD patients on renal replacement therapy, either dialysis or transplantation, treated in France 
-Patients with acute kidney failure are excluded; that is, those who recover all or some renal function within 45 days or who die before 45 days and are diagnosed with acute kidney failure by experts. 
-Age: 67 yrs 
-Gender: 62% male 
-DM (PRD): 21.2% 
-DM (Comorbid): 35.8% 
-eGFR at start: 8.8 ml/min/1.73m² 
-eGFR_{MDRD} 5-10 mL (n=6683), 10-15 mL (n=2517), 15-20 mL (n=633), >20 mL at start of dialysis (n=265) 
-eGFR_{MDRD} ≤ 5 mL (n=1587) 
-21.9 months 

-1/Mortality on dialysis (+ KM) 
-2/Access to transplantation 

1/HR=1.03 (1.03-1.04, p<0.05) 
2/HR=1.03 (1.03-1.04, p<0.05) 
3/HR=1.03 (1.03-1.03, p<0.05) 

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-1/Mortality on dialysis (+ KM) 
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1/HR=1.09 (1.05-1.14, p<0.05). Mortality decreased strongly with increasing MDRD eGFR (Figure 3, log rank P<0.0001). 
Two-year mortality decreased from 79 to 46% for the lowest versus the highest eGFR levels 
2/ Of the patients who began dialysis with eGFR p5, 6–10, 11–15, 16–20, and 420 mL/min per 1.73m², 21, 17, 8, 4, 

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2/ Of the patients who began dialysis with eGFR p5, 6–10, 11–15, 16–20, and 420 mL/min per 1.73m², 21, 17, 8, 4, 

Mediocre 
Observational study that extensively adjusts for potential confounders. Despite this fact there might be a risk of selection bias and (residual) confounding (by indication)
| Study                  | Year          | Region         | Study Design      | Characteristics                                                                 | Outcomes                                                                                       | HR (95% CI)                                                                                     | Conclusion                                                                                       |
|-----------------------|---------------|----------------|-------------------|--------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Tang et al.           | 2002-2004     | Asia           | Prospective cohort study | All patients with chronic renal failure and their close relatives were invited. | - Age: 58 yrs  
- Gender: 52% Male  
- DM2: 42%  
- eGFR at start in elective starters: 9.21 ml/min/1.73 m²  
- eGFR at start in initial refusers: 8.89 ml/min/1.73 m²  
- Initial refusers (n=82)  
- Elective starters (n=151)  
- 1 year (5 yrs for outcome 'need for blood transfusion')  
- 1/all cause mortality, crude HR  
- 2/all cause mortality on dialysis (adjusted for MD, age, sex, eGFR)  
- 3/Cardiovascular mortality  
- 4/Hospital admission (episodes/person/year)  
- 5/ Need for blood transfusion (episodes/person/year) | 1/ HR = 3.12 (1.34-9.88, p=0.011)  
2/ HR = 3.01 (1.32-9.40, p=0.01)  
3/ 2.6% vs 9.8% in initial refusers, p=0.014  
4/ 2.13 ± 1.13 vs. 3.14 ± 1.17 episodes/person-year in initial refusers, p = 0.05  
5/ 0.38 ± 0.07 vs. 0.8 ± 0.35 episodes/person-year in initial refusers, p = 0.033 | The two groups compared in this study might hamper from confounding, since the choice to electively start dialysis or initially refuse might be in relation with factors that influence mortality. These factors are almost certainly not adjusted for. |
| Traynor et al.        | 2002          | Europe         | Retrospective cohort study | Patients had to have started dialysis, first referral had to be with an eGFR>20 ml, the time between referral and start of dialysis had to be >180 days | - Age: 53 yrs  
- Gender: 67% male  
- DM2: 21.7%  
- Median eGFR at start: 10.4 (IQR: 9.1-11.9) in the early start group and 6.7 (IQR: 5.6-7.5) ml/min in the late start group.  
* Including diabetics  
- Late start eGFR<8.3 ml/min (n=116)  
- Early start eGFR≥8.3 ml/min (n=119)  
* Excluding diabetics  
- Late start eGFR<8.0 ml/min (n=87)  
- Early start eGFR≥8.0 ml/min (n=97)  
- 10 years from eGFR = 20 ml/min | Mortality/mortality on dialysis  
- HR = 1.11 (1.01-1.21, p = 0.024) | Low  
Estimates the effect of lead time bias, but does this in 235 patients for which eGFR = 20 ml/min could be estimated. Although specific results for subgroup of diabetics are lacking, that subgroup is supposedly very similar to the group without diabetics. |
| Wright et al.         | 2010          | North America  | Retrospective cohort study | Incident dialysis patients aged>18 years  
- Renal transplantation or renal function recover. | - Age: 64.7 yrs  
- Gender: 53.1%  
- DM (PRD): 46.7%  
- DM (Comorbid): 56.2%  
- dialysis started at eGFR<55 ml/min (n=113,510) and dialysis started at eGFR>15 ml/min (n=99,231) | Mortality/mortality at 60 months  
HR = 0.89 (0.88-0.90, p<0.06) vs eGFR | Mediocre  
Observational study that extensively adjusts for potential confounders. Despite this fact there might be a risk of selection bias and... |
Outliers in BMI, weight or height

- HD: 92.8%
- sCreat: 7.2 (3.5) mg/dl
- - dialysis started at eGFR >5 -10
- - 150 months

- Mid start of dialysis at eGFR 7.5-10.5 (n=2670) and early start at eGFR > 10.5 ml/min/1.73m² (n=2994)
- - Late start of dialysis at eGFR < 7.5 ml/min/1.73m² (n=2383)
- - 2.2 years (2.3, 2.2, and 1.9 years in the early, mid, and late start groups, respectively)

- 5 ml/min increase in eGFR MDRD at start of dialysis (n=2920)
- - 5585 patient-years of follow-up

- 5 ml/min increase in eGFR MDRD at start of dialysis (n=2920)

Mortality/ mortality HR = 1.18 (1.13 - 1.23) for every 5 ml/min increase in eGFR at start of dialysis

Prospective cohort study

- All incident chronic hemodialysis and peritoneal dialysis patients who initiated dialysis therapy in 1996 and early 1997
- Patients with previous renal replacement therapy, duplicate entries, missing USRDS identification numbers, or missing follow-up data and patients younger than 18 years, missing data for age, sex, race height, weight, blood urea nitrogen (BUN), serum creatinine, serum albumin, hematocrit, and serum bicarbonate were excluded.

- Age: 59
- Male: 53%
- Ethnicity: White: 64%
Black: 28%
- DM (PRD): 42%
- HD: 53%
- eGFR MDRD: 8.2±3.9
- Hematocrit: 30.8±5.4
- BUN: 87±31
- Bicarbonate: 22.0±4.6
- BMI: 26.3±5.8

Mortality/ mortality HR = 1.14 (1.06 - 1.14) for every 5 ml/min increase in eGFR at start of dialysis

Retrospective cohort study

- All adult (≥18 years) patients with a recorded serum creatinine value who started with hemodialysis as their first form of renal replacement therapy
- Age: Early group: 67.5(14.0), Late group: 63.7 (15.2)
- Male: Early: 67%, Late: 56.4%
- DM (PRD): Early: 40.6%, Late: 33.9%
- Early initiation of dialysis with eGFR MDRD < 10.5 ml/min/1.73m² (n=8441)
- - Late start of dialysis with eGFR MDRD ≤

Mortality/ mortality HRadj = 1.18 (1.13 - 1.23) for early initiation of dialysis compared with late initiation of dialysis.
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Type</th>
<th>Sample Characteristics</th>
<th>Follow-up</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harris et al.</td>
<td>2011-2008</td>
<td>Randomized controlled trial (IDEAL study)</td>
<td>Patients were eligible for inclusion in the study if they had progressive chronic kidney disease (patients with a failing kidney transplant were eligible) and an estimated GFR between 10.0 and 15.0 ml per minute per 1.73 m²</td>
<td>2.3 years of follow-up</td>
<td>- DM (Comorbid): Early: 52.7%, Late: 43.4%</td>
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<td>Patients could not be included in the study if they were younger than 18 years of age, had an estimated GFR of less than 10.0 ml per minute, had plans to receive a kidney transplant from a live donor within the next 12 months, had a recently diagnosed cancer that was likely to affect mortality, or were unable to provide written informed consent.</td>
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<td></td>
<td></td>
<td></td>
<td>Early: 60.0 ± 13.2, Late: 60.5 ± 12.1</td>
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<td></td>
<td></td>
<td></td>
<td>Male: early: 64%, late: 64%</td>
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<td></td>
<td></td>
<td></td>
<td>DM (PRD): early: 33.2%, late: 34.6%</td>
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<td>DM (Comorbid): early: 42%, late: 43.6%</td>
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<td></td>
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<td></td>
<td>Quality of Life - QALY</td>
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<td></td>
<td></td>
<td></td>
<td>Total cost of treatment - Difference in QoL between early- and late-start: -0.00 (-0.03;0.03)</td>
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<td></td>
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<td></td>
<td>QALY early: 1.97 (1.83-2.14) QALY late: 2.07 (1.92-2.23) Difference in QALY (adjusted for baseline AQoL): -0.09 (-0.12;0.31)</td>
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<td></td>
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<td></td>
<td>Early start group: $215,354 ($114,777-$311,713) vs. Late start group: $202,124 ($114,636-$288,704)</td>
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</tr>
<tr>
<td>Hwang et al.</td>
<td>2010</td>
<td>Retrospective cohort study</td>
<td>Incident hemodialysis patients between July 2001 and December 2004</td>
<td>4.15 years of follow-up</td>
<td>- eGFR MDRD: 4.7 (3.6-6.1) ml/min/1.73m² at start of dialysis or mortality &lt; 3 months (90 days)</td>
</tr>
<tr>
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<td>Patients with age &lt; 20 years, PD as primary treatment, incomplete ID digits, eGFR &gt; 15 mL/min/1.73m² at start of dialysis or mortality &lt; 3 months (90 days)</td>
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<td></td>
<td>Age: 61.5 ± 14.0</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Male: 47.7%</td>
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<td></td>
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<td>DM (PRD): 42.9%</td>
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<td></td>
<td>2nd quintile (eGFR (MDRD) 3.29-4.27 ml/min/1.73 m²) (n=4749), 3rd quintile (eGFR 4.28-5.20) (n=4727), 4th quintile (eGFR 5.21-6.51) (n=4708), 5th quintile (eGFR ≥ 6.52) (n=4698)</td>
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<td></td>
<td>1st quintile (eGFR &lt; 3.29) (n=4669)</td>
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<td></td>
<td>Mortality/mortality HRⱼₐₒₜ = 1.18 (1.01-1.37)</td>
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<td></td>
<td></td>
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<td>HRⱼₐₒₜ = 1.21 (1.04-1.41)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>HRⱼₐₒₜ = 1.66 (1.43-1.93)</td>
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<td></td>
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<td></td>
<td>HRⱼₐₒₜ = 2.44 (2.11-2.81)</td>
<td></td>
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</tr>
</tbody>
</table>

Hwang et al. 2010: Asia 2001-2004

High Randomized trial comparing early vs. late with respect to costs on dialysis. There is an absence of QoL and mortality advantage for early start of dialysis, whereas it costs more and patients are dialyzed for a longer period of time.

Harris et al. 2011-2008: Australia/New Zealand

High Randomized controlled trial (IDEAL study)
Chapter 1.3.

In patients with Diabetes and CKD stage 5, should a native fistula, a graft or a tunnelled catheter be preferred as initial access?

<table>
<thead>
<tr>
<th>Study</th>
<th>-Publication Year -Time Frame -Location</th>
<th>Design</th>
<th>-Inclusion criteria -Exclusion criteria</th>
<th>Patients’ characteristics</th>
<th>-Intervention (n=) -Comparator (n=) -Duration</th>
<th>Outcome(s)</th>
<th>Results</th>
<th>Quality of evidence</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan[44]</td>
<td>-2007 -1996 -North America</td>
<td>Retrospective cohort study</td>
<td>- HD patients age 65 years and older, included in the DMMS Wave 2 study, were eligible for inclusion into the study - Subjects were excluded if PD was the recorded modality, a temporary or tunneled catheter was used for HD at the time of the DMMS interview, and if the data necessary to conduct time to event analysis was missing.</td>
<td>- 43% Diabetes</td>
<td>- AVG placement - AVF placement - 25 months - n = 462</td>
<td>- Survival of the technique (patency rate) - Mortality</td>
<td>- OR 1.49 (0.76-2.89; p=0.224) - OR 1.34 (0.92-1.95; p=0.123)</td>
<td>Registry-based reporting of outcome. Incomplete adjustment for co-variates.</td>
<td>Number of events not stated. Number of analyzed participants in each study group not stated.</td>
</tr>
<tr>
<td>David[45]</td>
<td>-2010 -2003-2008 -Europe</td>
<td>Retrospective cohort study</td>
<td>- Incident HD patients referred to AVF placement - age 67±12 years - 26% Diabetes</td>
<td>- Proximal AVF placement (n=38) - Distal AVF placement (n=34) - 80 months</td>
<td>- Survival of the technique (primary patency rate)</td>
<td>- 55% - 30%</td>
<td>Generalizability uncertain. Incomplete adjustment for co-variates. Centre bias. No valid outcome measures.</td>
<td>No baseline characteristic.</td>
<td></td>
</tr>
<tr>
<td>Dhirgra[46]</td>
<td>-2001 -1993-1995 - North America</td>
<td>Retrospective cohort study</td>
<td>- Incident and prevalent HD patients. - Patients were excluded if they were less than 15 years of age at the study start</td>
<td>- age 59 years - male gender: 51% - 31% Diabetes</td>
<td>- HD patients with AVG (n=3129) and HD patients with CVC (n=875). - HD patients with AVF (n=1340) - 24 months</td>
<td>- All-cause mortality - Cardiovascular-related mortality - Infection-related mortality</td>
<td>- RR=1.54, 1.17-2.02; RR=1.41, 1.13-1.77, CVC vs. AVF and AVG vs. AVF, respectively - RR=1.47, 1.00-1.16; RR=1.35, 0.98-1.85, CVC vs. AVF and AVG vs. AVF,</td>
<td>Registry-based reporting of outcome. Large population from the Master List of Medicare Approved Dialysis Facilities.</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Location</td>
<td>Study Design</td>
<td>Patients</td>
<td>Follow-up</td>
<td>Main Findings</td>
<td>OR/RR</td>
<td>Number of Events</td>
<td>Generalizability</td>
</tr>
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<tr>
<td>Diehm[52]</td>
<td>2010</td>
<td>Europe</td>
<td>Retrospective cohort study</td>
<td>All patients with successful access placement in the vascular access centre</td>
<td>- 25% Diabetes (n=62)</td>
<td>- Diabetic patients (n=62)</td>
<td>- Survival of the technique (primary and secondary patency rates)</td>
<td>OR=0.60 (0.30-1.00)</td>
<td>- Generalizability uncertain. Center bias. No adjustment for covariates.</td>
</tr>
<tr>
<td>Field[47]</td>
<td>2008</td>
<td>Europe</td>
<td>Retrospective cohort study</td>
<td>Incident HD patients with AVF</td>
<td>- age: 61 years</td>
<td>- Diabetic patients (n=103)</td>
<td>- Survival of the technique (primary patency rate)</td>
<td>- 34% vs. 26% (p=0.110)</td>
<td>- Generalizability uncertain. Center bias. No adjustment for confounders. No valid outcome measures.</td>
</tr>
<tr>
<td>Hammes[48]</td>
<td>2008</td>
<td>North America</td>
<td>Retrospective cohort study</td>
<td>HD patients who underwent vascular access angiography and had at least 1 follow-up venogram done as clinically indicated</td>
<td>- 41% diabetes (n=27)</td>
<td>- Cephalic arch stenosis in diabetic patients with (n=27) ad without (n=25) cephalic arch lesion at baseline</td>
<td>- Survival of the technique (the number of weeks to the development of clinically significant stenosis).</td>
<td>Mean difference: 114 ±17 vs. 109 ±18</td>
<td>- Generalizability uncertain. Center bias. Small patient numbers. No adjustment for confounders. No valid outcome measures.</td>
</tr>
<tr>
<td>Konner[240]</td>
<td>2000</td>
<td>Europe</td>
<td>Retrospective cohort study</td>
<td>Incident HD patients undergoing AVF placement</td>
<td>- age: 59 years</td>
<td>- Diabetic patients (n=78)</td>
<td>- Survival of the technique (median time to first event)</td>
<td>- 42.3 vs. 45.8 months</td>
<td>- Generalizability uncertain. Center bias. Small patient numbers. No valid outcome measures.</td>
</tr>
<tr>
<td>Konner[49]</td>
<td>2002</td>
<td>Europe</td>
<td>Retrospective cohort study</td>
<td>ESKD patients with first AVF placement</td>
<td>- age: 60 years</td>
<td>- Diabetic patients with proximal perforating vein (n=86) and non-perforating vein (n=52) AVF</td>
<td>- Survival of the technique (primary and secondary patency rates)</td>
<td>- 80% vs. 80%. vs. 50%. vs. 90% vs. 80%.</td>
<td>- Generalizability uncertain. Center bias. Small patient numbers.</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Region</td>
<td>Study Design</td>
<td>Patient Description</td>
<td>Follow-up</td>
<td>Outcome Measures</td>
<td>Generalizability</td>
<td>Data Quality</td>
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<tr>
<td></td>
<td>1996-1995</td>
<td>North America</td>
<td></td>
<td>Forearm AVF (n=43)</td>
<td></td>
<td>63% vs. 42%</td>
<td></td>
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</tr>
<tr>
<td>Murphy[50]</td>
<td>2002-2000</td>
<td>Europe</td>
<td>Retrospective cohort study</td>
<td>Incident HD patients undergoing elbow AVF placement</td>
<td>12 months</td>
<td>Survival of the technique (cumulative patency rate)</td>
<td>Generalizability uncertain. Center bias. No valid outcome measures.</td>
<td>No reliable data within the diabetic group</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2002-2000</td>
<td>Europe</td>
<td></td>
<td></td>
<td></td>
<td>39% vs. 40% (p=N.S.)</td>
<td></td>
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<tr>
<td>Ravani[42]</td>
<td>2002-2001</td>
<td>North America</td>
<td>Prospective cohort study</td>
<td>Incident HD patients with vascular access placement by nephrologists</td>
<td>36 months</td>
<td>Survival of the technique (primary and cumulative patency rate)</td>
<td>Generalizability uncertain. Center bias.</td>
<td>No reliable data within the diabetic group</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2002-2001</td>
<td>North America</td>
<td></td>
<td></td>
<td></td>
<td>HR=1.85, p=0.01 - HR=2.38, p=0.04</td>
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<tr>
<td></td>
<td>2002-2000</td>
<td>North America</td>
<td></td>
<td>Diabetic patients with AVF (n=36)</td>
<td></td>
<td>15%, 42% (p&lt;0.0006), 33% (p=0.03), 37.5% (p=0.001), 100% (p=0.0005).</td>
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<tr>
<td>Yeager[53]</td>
<td>2002-2000</td>
<td>North America</td>
<td>Retrospective case-control study</td>
<td>HD patients</td>
<td>36 months</td>
<td>Survival rate</td>
<td>Generalizability uncertain. Center bias. No adjustment for confounders. Unbalance between the number of cases and controls.</td>
<td>No reliable data within the diabetic group.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2002-2000</td>
<td>North America</td>
<td></td>
<td>Male gender: 97% - 55% Diabetes</td>
<td></td>
<td>49% vs. 52% (p&gt;0.05)</td>
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</tr>
</tbody>
</table>

*AVF = Arteriovenous Fistula, HD = Hemodialysis, CVC = Central Venous Catheter*
What is the benefit of renal transplantation for dialysis patients with diabetes and CKD stage 5?

E. Is there evidence for a selection bias in observational studies?

<table>
<thead>
<tr>
<th>Study</th>
<th>Population/Source/Aim</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batbayal [61] 2012</td>
<td>Published guidelines from 2001 to 2011 from Australia, Japan, Malaysia, South Africa, United Kingdom, United States, Continental Europe, and Canada. This study aimed to compare the quality, the scope, and the consistency of national and international clinical practice guidelines on wait-listing of patients for kidney transplantation</td>
<td>Diabetes was not contraindicated unless associated with multiple organ failure or significant cardiovascular complications. Of the 10 guidelines discussing diabetes, 7 recommended simultaneous screening for cardiovascular disease. Almost all guidelines suggested simultaneous pancreas-kidney transplantation for patients with type 1 diabetes but did not recommend age thresholds</td>
</tr>
<tr>
<td>Bayat [241] 2008</td>
<td>NPHROCOLOR database(all ESRD patients living in Lorraine and placed on the waiting list N=809)</td>
<td>Diabetes was independent factor associated with non-registration in waiting list (OR 2.97; 95CI 1.67 – 5.28)</td>
</tr>
<tr>
<td>Dudley [242] 2009</td>
<td>Cross-sectional study of 12, 401 prevalent adult dialysis patients from 41 renal units across England and Wales. A total of 23.3% of patients were active on the transplant waiting list.</td>
<td>Patients with a primary renal diagnosis of diabetes mellitus were least likely to be on the active waiting list. (n=1963; OR 0.30; 0.25–0.36)</td>
</tr>
<tr>
<td>Goldfarb-Rumyantzev [243] 2011</td>
<td>Patients from the United States Renal Data System (January 1, 1990–September 1, 2007; n = 3407; 50.4% had diabetes) to study association between the Social Adaptability Index (SAI; based upon employment, marital status, education, income, and substance abuse) and outcomes (time to being placed on the waiting list and time to being transplanted once listed).</td>
<td>In patients with no history of diabetes (compared to history of diabetes) HR of being waitlisted is 1.19 (0.89–1.57)p=0.238; HR of being transplanted 0.81 (0.61–1.07) p=0.141</td>
</tr>
<tr>
<td>Machado [244] 2012</td>
<td>Non-concurrent cohort study of 835 patients on the waiting list for kidney transplant from 2000 to 2004 to analyze factors associated with access to kidney transplants from living and cadaver donors in Belo Horizonte, Brazil</td>
<td>144 patients in the waitlist (18,4%) had diabetes. 17 (9,9%) were transplanted vs. 127 (20,8%) not transplanted (p=0.001). Mean time (year)for receiving a transplant was 3,753 in diabetes vs 2,068 in non-diabetes (p=0.01). RR of being transplanted in patients with diabetes was 0,337 (0,137; 0,830) for KT from living and 0,830 (0,421; 1,637) from deceased donors.</td>
</tr>
<tr>
<td>McCullough [245] 2009</td>
<td>Kidney and Pancreas Transplantation in the United States, 1998–2007 (n=40 825 to 76 070) from the national Organ Procurement and Transplantation Network (OPTN) kidney or simultaneous pancreas–kidney (SPK) transplant</td>
<td>38% of the 58 617 patients with diabetes and ESRD who were under the age of 50 years were waitlisted and 13693 were transplanted with either a living or deceased donor kidney alone or an SPK transplant. 23% of the total younger diabetic ESRD population and 62% of the younger diabetic waitlisted cohort received a kidney transplant. Within this cohort, 3509 patients with diabetes were preemptively waitlisted; among that group, 2596 (74%) were eventually transplanted. Of the younger patients with diabetes who were preemptively waitlisted, 792 were also preemptively transplanted: 486 from a living donor and 306 from a deceased donor. An additional 1804 transplants occurred among these preemptively waitlisted candidates after they began dialysis: 447 from living donor and 1357 from deceased donor sources. In addition, during this period, 449 patients with diabetes under age 50 years were transplanted preemptively from a living donor without ever being waitlisted. Transplant rates were lower among non-preemptively waitlisted patients with diabetes under the age of 50 years, and the ratio of living to deceased donation among these patients was nearly the inverse of that seen among those who were preemptively transplanted. Some 18 537 patients with diabetes under the age of 50 years were waitlisted after beginning dialysis; of these, 10 648 (57%) received a kidney transplant: 3162 (30%) from a living kidney donor.</td>
</tr>
<tr>
<td>Patibandla [246] 2012</td>
<td>Data from the United States Renal Data System (01/01/2000–24/09/2007; n = 619 153)</td>
<td>In Cox models adjusted for a priori defined potential confounders, history of diabetes was associated with reduced transplant access (compared with non-diabetic population) – both for wait-listing/transplant without being listed (hazard ratio, HR = 0.80, p &lt; 0.001) and for transplant after being listed (HR = 0.72, p &lt; 0.001). In Cox models adjusted for BMI and comorbidity index along with the potential confounders, history of diabetes was associated with shorter time to waitlisting or transplantation without being listed (HR = 1.07, p &lt; 0.001), and there was no significant difference in time to transplantation after being listed (HR = 1.01, p = 0.42).</td>
</tr>
<tr>
<td>Patzer [247] 2009</td>
<td>Cohort study using data for incident, adult ESRD patients (1998 to 2002) from the ESRD Network (Georgia, North Carolina, and South Carolina) plus the United Network for Organ Sharing</td>
<td>Diabetes was associated with HR of waitlisting of 0.78 (0.72 to 0.85) P &lt; 0.0001</td>
</tr>
</tbody>
</table>
(UNOS) transplant registry through 2005 and the 2000 U.S. Census geographic data. 35,346 subjects, 12% were waitlisted, 45% had diabetes as the primary etiology of ESRD.

Diabetes was associated with a lower probability of activation on waiting list within two years of start of renal replacement treatment: OR 0.40 (0.36 to 0.45) <0.001

Segev [249] 2008 Prospective cohort of 132,353 patients who were registered for kidney transplantation in the United States between 1995 and 2006

In a fully adjusted model, diabetes was significantly associated with a lower probability of being bypassed for a kidney offer (IRR 0.94; 95% CI 0.90 to 0.98)

Patients had a non-significantly lower Relative rate of transplantation; RR 0.93 (p=0.52)

Chapter 1.4.

B. What is the benefit of renal transplantation for dialysis patients with diabetes and CKD stage 5?

<table>
<thead>
<tr>
<th>Study</th>
<th>Publication Year - Time Frame - Location</th>
<th>Design</th>
<th>Inclusion criteria - Exclusion criteria</th>
<th>Patients’ characteristics</th>
<th>Intervention (n=) - Comparator (n=) - Duration</th>
<th>Outcome(s)</th>
<th>Results</th>
<th>Quality of evidence</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott [252]</td>
<td>-2001 - 1994-1997 - North America</td>
<td>Retrospective cohort study</td>
<td>-Patients with ESRD due to diabetes having their first dialysis in or after 1992 being placed on the waiting list 1 July 1994-30 June 1997. -No diabetes as cause of ESRD wait-listing before 1992</td>
<td>-age 57.4±11.3 -gender: 59% male</td>
<td>-transplantation (n=5683) -remaining on the waiting list (n=5686) -1.93y</td>
<td>Congestive heart failure</td>
<td>HR 0.64 (0.54-0.77; p&lt;0.05)</td>
<td>Representativeness uncertain Registry-based reporting of outcome</td>
<td>Adjustment for covariates renders the association non-significant</td>
</tr>
</tbody>
</table>
| Abbott [253]   | -2002 - 1994-1997 - North America       | Retrospective cohort study | -Patients with ESRD due to diabetes having their first dialysis in or after 1992 being placed on the waiting list 1 July 1994-30 June 1997. -No diabetes as cause of ESRD wait-listing before 1992 | -age 57.4±11.3 -gender: 59% male | -transplantation (n=5683) -remaining on the waiting list (n=5686) -1.93y | -sepsis due to gram-negative organisms -bacterial septicemia -sepsis due to urinary tract infection | -HR 3.32 (2.61-4.23; p<0.05) -HR 1.20 (1.02-1.35; p<0.05) -HR 10.43 (6.72-16.17) | Generalizability uncertain Registry-based reporting of outcome Incomplete adjustment for covariates Possible selection bias | Selection bias: patients remaining waitlisted are possibly more highly immunized with intrinsically a higher infection risk post transplantation, which could alter the observed
outcome in accordance with longer follow-up time. No data on prophylaxis, induction, immunosuppressive regimen, bladder catheterization.

<p>| Adang [91] | 1996-1992-1994 -Europe | Prospective case-control study | All patients receiving SPK from June 1992-January 1994 | Transplantation (n=17) - SPK with early loss of pancreas after transplantation and preservation of kidney function (n=5) | Quality of life | Visual Analogue score, disease-specific questionnaire NHP-1; NPHS-2 ABS, family impact questionnaire all better in the intervention group | Very small patient numbers Possible selection bias No comparator group of type 1 patients with diabetes remaining on the waitlist No adjustment for covariates | High chance of type 1 error |
| Allen [82] | 1997-1987-1996 -Australia/New Zealand | Before-after study | Patients with insulin-dependent diabetes mellitus and ESRD receiving SPK without graft loss before 6 months posttransplantation in which pre- and posttransplantation conduction velocity was available. In addition, a group of SPK recipients with early pancreatic loss from graft thrombosis who maintained a functioning kidney allograft as well as one type I diabetic recipient who was on the SPK waiting list and elected to receive a cadaveric kidney transplant alone before being offered a SPK were also studied. | Age 38.5±7.9 -gender: 49% male -dialysis vintage: 25.2 ±7.6 | SPK with functioning pancreas graft&gt;6months (n=44) -SPK with non-functioning pancreas graft (n=9) | Recovery of total NCS after SPK Recovery of conduction velocity Recovery of nerve amplitude | Increased conduction velocity score of 22.2% at 6 months. Improvement in all parameters considered in functioning SPK | Generalizability uncertain Selection bias Center bias No adjustment for covariates | Mash-up of numerous comparisons, differences both adjusted and unadjusted with alternating comparators, differences in time points and very few long term assessments. High risk for type 1 error. |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Region</th>
<th>Study Design</th>
<th>Patients</th>
<th>Age</th>
<th>Gender</th>
<th>BMI</th>
<th>Diabetes Vintage</th>
<th>Follow-up</th>
<th>Intervention</th>
<th>Controls</th>
<th>Outcomes</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fiorina</td>
<td>2005</td>
<td>Europe</td>
<td>Before-after study</td>
<td>Type 1 diabetes patients with a functioning kidney graft received from a cadaveric donor</td>
<td>48.6</td>
<td>54% male</td>
<td>23 ±2 kg/m²</td>
<td>31 years</td>
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<td>Glycemic control</td>
<td>Lower need of insulin in the kidney-islet group</td>
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<tr>
<td>Gaber [85]</td>
<td>1995</td>
<td>North America</td>
<td>Before-after study</td>
<td>Type 1 diabetes patients transplanted with a single kidney, with pancreas-kidney or pancreas transplantation after kidney transplantation</td>
<td>40 ±7</td>
<td>54% male</td>
<td>23 ±2 kg/m²</td>
<td>24 ±8</td>
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<td></td>
<td>Combined pancreas-kidney transplantation pancreas after kidney</td>
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<tr>
<td>Giannarelli [83]</td>
<td>2005</td>
<td>Europe</td>
<td>Before-after study</td>
<td>-SPK patients with retinopathy</td>
<td>45</td>
<td>54% male</td>
<td>23 ±2 kg/m²</td>
<td>24 ±8</td>
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<td></td>
<td></td>
<td>SPK (48) non-transplanted type 1 diabetes patients (43)</td>
<td>Visual disturbances improvement and/or stabilization of diabetic retinopathy</td>
</tr>
<tr>
<td>Kleinclaus[62]</td>
<td>2009</td>
<td>Retrospective</td>
<td>Diabetic recipients of</td>
<td>Age: 45</td>
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<td>Progression to end-</td>
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<tr>
<td>Study</td>
<td>Year</td>
<td>Cohort Type</td>
<td>Population</td>
<td>Follow-up</td>
<td>Graft Survival</td>
<td>Patient Survival</td>
<td>Selection Bias</td>
<td>Data</td>
<td>Comment</td>
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<tr>
<td>La Rocca[63]</td>
<td>2001-1984-1998</td>
<td>Retrospective cohort study</td>
<td>Type 1 diabetic ESKD patients</td>
<td>-Type 1 diabetic patients (n=196)</td>
<td>-Age 45.6</td>
<td>Diabetes vintage 27.7 years</td>
<td>-SPK (n=43) vs. WL (n=23)</td>
<td>-7 year graft survival 85.2% vs. 70%</td>
<td>Generalizability uncertain (very high HbA1c)</td>
<td>No data exist on baseline comorbidity (CV disease). CV mortality is higher in the KTA-E group. Also, KTA-E patients have more frequently type 2 diabetes as cause of ESRD with possibly issues of obesity. No adjustment for comorbid status in the Cox model.</td>
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<tr>
<td>Sureshkumar[254]</td>
<td>2006-1988-2004</td>
<td>Retrospective case-control study</td>
<td>Type 1 diabetes patients with ESKD</td>
<td>-Type 1 diabetes patients with ESKD (n=43)</td>
<td>-Age 44 years</td>
<td>Male gender: 59%</td>
<td>SPK group had better satisfaction subscore compared with WL (1.8 ± 0.5 vs. 2.6 ± 0.6, p &lt; 0.001) and better impact subscore compared with WL (1.7 ± 0.6 vs. 2.3 ± 0.6, p &lt; 0.01)</td>
<td>Potential for selection bias/allocation bias. Informative censoring in the follow-up.</td>
<td>Longitudinal outcome data (quality of life) available only in a subset of patients with CKT/SPK. Some patients in the kidney transplantation groups were offered SPK transplantation but opted for</td>
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</table>
There were no significant differences on physical/mental composite scores of SF-36. QWB score was better in SPK group vs. WL group (0.62 ± 0.11 vs. 0.55 ± 0.04, p < 0.05).

| Young [77] | 2009 -2000-2007 -North America | Retrospective cohort study | Adult (age 20 to 59) type I patients with diabetes who received a solitary first-time kidney transplant -Dual organ transplants other than SPKTs | -age 41.9 years -male gender: 59% | -living donation kidney (n=3,309) transplantation -SPK (n=5,352) | -Progression to end-stage kidney disease -survival (mortality) | 7 year graft loss: HR 0.71 (0.61-0.83; p=0.001) 7 year survival: HR 0.78 (0.65-0.94; p=0.007) | Large sample size Adjustment for main demographics, somatometrics and biological data | Possible selection bias in the cadaveric graft population; more blacks and longer dialysis vintage. Maybe also lower socio-economic status (not controlled for) which affects outcome, partially through dyscompliance, drug fatigue,.. |
| Reddy [76] | 2003 -1987-1996 -North America | Retrospective cohort study | -type 1 diabetes who received a kidney transplant between 1987 and 1996 -Patients who received segmental pancreas grafts from living donors | -age 40.7 years -male gender: 59% | -SPK (n=4602) -LDK (n=3,991) -cadaveric kidney only (n=9,956) | -survival/mortality | -survival at 5y with survivors with renal allograft function at 1 year : respectively 89.8, 87.8 and 79.7%. -mortality beyond 18months posttransplantation in SPK vs. LDK transplantation: HR 0.86; p=0.02 -survival 5 years after | High potential for selection bias | The healthiest patients are allocated to SPK and receive the highest quality organs Center bias: SPK especially in the early era mostly in high-volume centers No confidence intervals provided |
| Study   | Year Range | Study Design                        | Eligible Patients                                                                                           | Age | Male Gender | BMI   | Duration of Dialysis | African American | SPK (n=544) Kidney Transplantation | SPK (n=544) Kidney Transplantation alone | Progression to End-Stage Kidney Disease (up to December 2004) | Survival (at one year): Mortality (up to December 2004) | Survival (at five year): Mortality (up to December 2004) |
|---------|------------|------------------------------------|------------------------------------------------------------------------------------------------------------|-----|-------------|-------|----------------------|-----------------|---------------------------------|------------------------------------------|----------------------------------------------------------|----------------------------------------------------------|
| Waki[92]| 1995-2002  | Retrospective cohort study         | Eligible patients were those who received their first SPK or kidney alone from January 1995 to December 2002. Survival <1 year post-transplantation | 44.4 | 59%         | 25.8  | 2.3 years            | 14%             | SPK (n=544) kidney transplantation alone (n=544) | HR 0.8 (0.49-1.31; p=0.38)                      | -80.0% SPK vs. 85.5% kidney transplantation alone. HR 0.77 (0.41-1.48; p=0.43) | 78.2% SPK vs. 78.2% kidney transplantation alone. |
| Ziaja[88]| 2009      | Prospective cohort study           | Eligible patients were those who received their first SPK or kidney alone from January 1995 to December 2002. Survival <1 year post-transplantation | 37   | 59%         | 25.8  | 2.3 years            | 14%             | SPK (n=21) patients with only a functional kidney graft period: those referred to KTA only, or refusing pancreas transplantation or in whom pancreas grafting was technically impossible (n=17) | HR 0.8 (0.49-1.31; p=0.38)                      | -80.0% SPK vs. 85.5% kidney transplantation alone. HR 0.77 (0.41-1.48; p=0.43) | 78.2% SPK vs. 78.2% kidney transplantation alone. |

High potential for selection bias. Incomplete adjustment Registry data: UNOS; generalizability uncertain.

Selection bias: patients with a functioning kidney graft alone include those with previous failure of pancreas graft or those refusing pancreas grafting which might affect outcome (quality of life). Also, selection bias in donor selection with younger age and shorter CIT in the
<table>
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<tr>
<th>Study</th>
<th>Year</th>
<th>Region</th>
<th>Study Design</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Follow-up Time</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wolfe[69]</td>
<td>1999</td>
<td>North America</td>
<td>Retrospective cohort study</td>
<td>Patients under the age of 70 years starting with treatment for end-stage renal disease. Patients 70 years or older.</td>
<td>Non-reporting of the cause of end-stage renal disease or the region they were from. Patients who received transplants without first undergoing dialysis.</td>
<td>Survival was analyzed as the time from initial placement on the waiting list to death, with data censored at the time of receipt of a first transplant from a living donor or on December 31, 1997 (patients with diabetes as cause of ESRD).</td>
<td>RR 0.27 (0.24-0.30; p&lt;0.001)</td>
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<tr>
<td>Weiss[80]</td>
<td>2009</td>
<td>North America</td>
<td>Retrospective cohort study</td>
<td>All patients on the SPK wait-list who were transplanted January 1997 through December 2005</td>
<td>Exclusion criteria included death or kidney graft loss before 12 months post-transplant or follow-up less than 12 months at the time of analysis.</td>
<td>AGE 39.9 years - Male gender: 59% - SPK with functional pancreas at year 1 (n=6,486) - SPK with pancreas loss the first year (n=371) - LDK (n=904) - DDK (n=520)</td>
<td>Progression to end-stage kidney disease during follow-up (DDK vs. SPK with functional pancreas) - Progression to end-stage kidney disease; survival free from renal graft loss 84 months after transplantation (SPK with functioning pancreas at 3 year as reference) - Survival free from graft loss DDK vs LDK - Graft loss during follow-up in LDK in comparison to SPK with functioning pancreas graft at one year as reference - Progression to end-stage kidney disease during follow-up SPK</td>
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</tbody>
</table>
with vs. without pancreas graft loss
-survival free from renal graft loss SPK vs LDK
-survival in LDK comparison to SPK with functioning pancreas one year after transplantation as reference
-survival the first year in DDK vs LDK
-survival the first year after transplantation SPK vs. LDK
-survival in SPK with pancreas graft loss comparison to SPK with functioning pancreas one year after transplantation as reference
-survival within 84 months post-transplantation vs. SPK with functioning pancreas as reference
-survival in DDK in comparison to SPK with functioning pancreas one year after transplantation as reference

(p=0.04)
-HR 2.66 (1.98-3.57; p<0.001)
-88.6% SPK with functioning graft vs. 73.9% SPK with pancreas graft loss vs. 80.0% LDK vs. 64.8% DDK.
-HR 2.05 (1.48-2.83; p<0.001).

- Retrospective cohort study
- The study population consisted of patients with ESRD due to type 1 DM who were 18 years or older at the time of the onset of ESRD and were enrolled on the transplant waiting list between October 1, 1988 and June 30, 1997.
- missing date of wait-list registration receiving living donation or never
- age 35.4 years
- male gender: 55%

- SPK (n=4718)
- LDK (n=671)
- DDK (n=4127)
- mortality DKD vs. remaining on waitlist
- survival the first 10 years after transplantation
- mortality the first 5 years after transplantation of LDK vs. remaining on waitlist
- mortality SPK the first 5 years after transplantation vs. remaining on the waiting list

- HR 0.75 (0.63-0.89; p<0.05)
- -67% SPK vs. 65% LDK vs. 43% DDK
- HR 0.45 (0.32-0.64; p<0.05)
- HR 0.40 (0.33-0.49; p<0.05)

Generalizability uncertain
Potential for selection bias incomplete adjustment
Potential misclassification bias (only patients who were likely to have developed DM before the age of 24 years were included in the non-SPK study groups).
<table>
<thead>
<tr>
<th>Ref</th>
<th>Year</th>
<th>Study Type</th>
<th>Study Description</th>
<th>Data Analysis</th>
<th>Potential for Selection Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morath[79]</td>
<td>2008</td>
<td>Retrospective cohort study</td>
<td>- Transplants reported to the CTS from 1984 to 2000 were analyzed. All patients who were reported to the study center with type 1 diabetes and ESRD and received either a first SPK transplant from a deceased donor or a kidney transplant alone, from either a deceased donor (DDK) or a living donor (LDK), were included. Transplanted between 1991-2000. - Patients with pancreas after kidney transplantation. Recipients who were older than 45 yr at the time of transplantation.</td>
<td>- Age 35.7 years - Male gender: 58%</td>
<td>- Progression to end-stage kidney disease 6-10y after transplantation (death censored) SPK vs. DDK - Progression to end-stage kidney disease (death-censored) from year 2 to 5 post-transplantation patients transplanted between 1991-2000 SPK vs. DDK - Progression to end-stage kidney disease 6-10y after transplantation (death censored) SPK vs. LDK - Progression to end-stage kidney disease (death-censored) from year 2 to 5 post-transplantation patients transplanted between 1991-2000 SPK vs. LDK</td>
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<td>Morath[79]</td>
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<td>Retrospective cohort study</td>
<td>- Transplants reported to the CTS from 1984 to 2000 were analyzed. All patients who were reported to the study center with type 1 diabetes and ESRD and received either a first SPK transplant from a deceased donor or a kidney transplant alone, from either a deceased donor (DDK) or a living donor (LDK), were included. Transplanted between 1991-2000. - Patients with pancreas after kidney transplantation. Recipients who were older than 45 yr at the time of transplantation.</td>
<td>- Age 35.7 years - Male gender: 58%</td>
<td>- Progression to end-stage kidney disease 6-10y after transplantation (death censored) SPK vs. DDK - Progression to end-stage kidney disease (death-censored) from year 2 to 5 post-transplantation patients transplanted between 1991-2000 SPK vs. DDK - Progression to end-stage kidney disease 6-10y after transplantation (death censored) SPK vs. LDK - Progression to end-stage kidney disease (death-censored) from year 2 to 5 post-transplantation patients transplanted between 1991-2000 SPK vs. LDK</td>
</tr>
</tbody>
</table>

Potential for selection bias: SPK recipients were more often categorized as "good risk recipients" (59.6%) as compared with LDK recipients (55.5%; P = 0.009) and DDK recipients (45.5%; P < 0.001). No adjustment for individual cardiovascular risk factors (e.g., hypertension, hyperlipidemia, and statin use; tobacco use; use of inhibitors of the renin angiotensin system).
<table>
<thead>
<tr>
<th>Study</th>
<th>Year Range</th>
<th>Study Design</th>
<th>Participants</th>
<th>Follow-Up</th>
<th>Outcomes</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poommipanit [74]</td>
<td>2010-2000-2008</td>
<td>Retrospective cohort study</td>
<td>Patients with type 1 diabetes according to diagnosis codes, aged 18 to 59 years, who were waitlisted for kidney-pancreas and received a primary kidney transplant between January 2000 and December 2007 with follow-up data available through August 2008.</td>
<td>Dual organ transplants other than kidney-pancreas transplants</td>
<td>-mortality 11-18y after transplantation SPK vs. LDK</td>
<td>High potential for selection bias, Incomplete adjustment, Univariate comparisons, No p-values</td>
</tr>
</tbody>
</table>
| Becker [66] | 2000-1966-1995 | Retrospective Cohort study | -type 1 diabetic patients who developed ESRD between the ages of 21 | | -0.5 observed/expected life span | Possibly outdated study, Very high rejection rates,
<table>
<thead>
<tr>
<th>Study</th>
<th>Year - Period</th>
<th>Study Design</th>
<th>Population</th>
<th>Methodology</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindahl[67]</td>
<td>2013 -1983-2010 -Europe</td>
<td>Retrospective cohort study</td>
<td>diabetic ESRD who received a first kidney or a combined transplant (SPK)</td>
<td>age: 47 years -male gender: 70.1%</td>
<td>-Renal graft rejection respectively vs SPK: 1.5%; DDK: 6.27%; LDK: 3.65% (P =0.008, SPK vs. other) -57.2%, 57.1% and 34.6% in DDL, LDK and SPK, respectively (all P=0.0003 Vs. SPK)</td>
<td>-Annual mortality rate -57.2%, 57.1% and 34.6% in DDL, LDK and SPK, respectively (all P=0.0003 Vs. SPK)</td>
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<tr>
<td>Mohan[68]</td>
<td>2003 -1992-2002 -Europe</td>
<td>Retrospective cohort study</td>
<td>patients with type 1 diabetes undergoing kidney alone or SPK transplantation -no SPK in patients&gt;50 years old</td>
<td>age 47 years old -male gender: 60%</td>
<td>-Renal graft survival -1, 3, 5 and 8 years graft survival was 93, 91, 76 and 46 per cent respectively in the SPK group, and 94, 76, 58 and 44 per cent after KTA (p=0.41)</td>
<td>-Patient survival -1, 3, 5- and 8-year actuarial patient survival -High potential of selection bias. Small patient sample Generalizability uncertain</td>
</tr>
<tr>
<td>Study (Ref)</td>
<td>Year - Range</td>
<td>Type of Study</td>
<td>Main Findings</td>
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<tr>
<td>Sorensen[72]</td>
<td>2006 - 1990-2005</td>
<td>Retrospective cohort study</td>
<td>Patients on the waitlist or receiving kidney transplant. Data pooled from the Danish National Register on Dialysis and Transplantation and from the Scandiatransplant database. - Age 42.6 (diabetes patients) - 13% with type 1 diabetes, 9% with type 2 diabetes - DM-1 (n=1105) - DM-2 (n=718) - Non DM (n=6598) - Renal graft survival - Patient survival - All-DM vs. non-DM HR: 1.14, (0.94-1.37) p=0.19 - DM-1 vs non-DM HR: 1.66 (1.53-1.81) p&lt;0.0001; DM-1 vs DM-2 HR:1.0 (0.87–1.14) p=0.96; All-DM vs. non-DM HR:1.55 (1.45–1.66) p&lt;0.0001 - Possible selection bias. Generalizability uncertain. Results adjusted for the most important confounders. Not adjusted for additional confounders. Patients analyzed on an ‘intention to treat’ basis. Patients were categorized as ‘transplanted’ patients, even if the kidney never functioned.</td>
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<tr>
<td>Keddis et al.[70]</td>
<td>2014 - 1996-2007</td>
<td>Retrospective cohort study</td>
<td>Patients receiving a kidney transplantation between 1996 and October 2007. - Patients with non-renal transplants - Age 52±13.8 years - Male gender: 58% - Race: Caucasian: 92% - Pre-transplant cardiovascular events: 26% - Living donation: 76% - Patients with diabetes receiving a kidney transplantation (n=413) - Patients without diabetes receiving a kidney transplantation (n=1275) - Five year mortality - Five year mortality in recipients transplanted after 2004 (2005-2007) - CV death during follow-up - CV death during 2003-2007 - HR 2.681 (1.951-3.685; p&lt;0.0001) - HR 1.455 (0.737-2.873; p=0.279) - HR=3.776 (2.155–6.18; P&lt;0.0001) - HR=2.265 (0.978–5.241; P=0.056)</td>
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<tr>
<td>Cosio et al.[71]</td>
<td>2008 - 1998-2006</td>
<td>Retrospective cohort study</td>
<td>Patients receiving a first kidney transplant from January 1998 to June 2006. - Recipients of pancreas or other transplants - Age: 53±14.4 years - Male gender: 57% - Obese: 32% - Race: Caucasian: 92% - Pre-transplant cardiovascular - Patients with diabetes receiving a kidney transplantation (n=212) - Patients without diabetes receiving a kidney - Death censored graft survival during follow-up - Post-transplantation cardiovascular events - Cardiovascular mortality - All-cause mortality - HR 1.19 (0.76–1.86; p = 0.442) - 53 (7.4%) in subjects without diabetes vs. 53 (25%) in subjects with</td>
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</table>

Potential for discrimination. No clear generalizability subgroups. Patients with diabetes were more likely to have undergone coronary intervention pre-transplantation. No clear discrimination between type 1 and type 2 diabetes.
<table>
<thead>
<tr>
<th>Rayhill et al.[65]</th>
<th>2000 - 1986-1996</th>
<th>North America</th>
<th>Retrospective cohort study</th>
<th>patients with diabetes receiving a kidney transplantation between 1986 and 1996</th>
<th>age: 39 years</th>
<th>duration IDDM 23 years</th>
<th>SPK (n=379)</th>
<th>LDK (n=130)</th>
<th>DKD (n=296)</th>
<th>one year renal allograft survival</th>
<th>five year renal allograft survival</th>
<th>one year patient survival</th>
<th>five year patient survival</th>
<th>in HLA identical LDK, haplo-identical LDK, SPK and DKD respectively 96, 94, 97 and 86%.</th>
<th>- in HLA identical LDK, haplo-identical LDK, SPK and DKD respectively 85, 72, 78 and 64%.</th>
<th>- in HLA identical LDK, haplo-identical LDK, SPK and DKD respectively 100, 99, 96 and 94%.</th>
<th>Generalizability uncertain</th>
<th>Single-center Univariate comparison (multivariate analysis only in the overall cohort) No exclusion criteria</th>
<th>Rejection rate the first year of up to 77% in SPK group (48% in the DKD group). Similar demographic composition of LDK and SPK groups Unknown prevalence of type 1 and type 2 diabetes</th>
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<tbody>
<tr>
<td>events: 23%</td>
<td>transplantation (n=721)</td>
<td>diabetes (p&lt;0.001) - 8 (1.1%) in subjects without diabetes vs. 25 (12%) in subjects with diabetes (p&lt;0.001) - 44 (6.1%) in subjects without diabetes vs. 41 (19.3%) in subjects with diabetes (p&lt;0.001)</td>
<td>selection bias</td>
<td>Univariate comparison</td>
<td>and type 2 diabetes</td>
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<tr>
<td>Study</td>
<td>Year range</td>
<td>Type of study</td>
<td>Participants</td>
<td>Methods</td>
<td>Findings</td>
<td>Generalizability</td>
<td>Notes</td>
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<tr>
<td>Norman et al. [81]</td>
<td>2000-2007</td>
<td>Retrospective cohort study</td>
<td>All primary SPK transplants performed in the United States between January 1, 2000, and December 31, 2007, who had maintained kidney graft function at 90 days post-transplantation and follow-up up to Feb 28th 2010. Age &lt;18 years and kidney graft loss the first 90 days.</td>
<td>- Age: 41.4±8.2 years - Male gender: 61.7% - Mean duration of diabetes: 26.6±8.1 years</td>
<td>- Kidney graft failure in those with vs. without pancreas graft loss at 3 years: HR 3.78 (1.95-7.35; P&lt;0.001) - 93 vs. 94% (p=0.266) - 90 vs. 91% (p=0.490) - 90.4 vs. 94.8% (p&lt;0.001) - 86.2 vs. 92.1% (p&lt;0.001)</td>
<td>Uncertain</td>
<td>Potential for selection bias, incomplete adjustment, missing data.</td>
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<tr>
<td>Bunnapradist et al. [227]</td>
<td>1994-1997</td>
<td>Retrospective cohort study</td>
<td>Type 1 diabetes patients receiving a kidney transplantation between 1994 with reporting in UNOS registry. Patients transplanted in centers which offer only one option for type 1 diabetes (SPK or DKT).</td>
<td>- Age: 40.8 years - Male gender: 58% - Black race: 12.8%</td>
<td>- Graft loss DKT vs. SPK: HR 0.98 (0.85-1.12; p=0.73) - HR 1.06 (0.88-1.28; p=0.53)</td>
<td>No living donation comparator group</td>
<td>Possible selection bias, uncertain generalizability, incomplete adjustment</td>
<td>Patients who received SPK were younger, less often sensitized, transplanted after shorter periods on dialysis, and less often black. Slightly outdated analysis.</td>
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</tbody>
</table>
Chapter 2: Issues related to glycaemic control in patients with diabetes and chronic CKD stage 3b or higher (eGFR<45ml/min)
Chapter 2.3:
A. Is any oral drug superior to another in terms of mortality/complications/glycaemic control in diabetic patients with CKD stage 3b or higher (eGFR <45 mL/min/1.73m²)?
B. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²), is maximal oral therapy better than starting/adding insulin in an earlier stage?

Chapter 2.3 supplementary data extraction table: General data on included systematic reviews on different glycaemia lowering drugs

<table>
<thead>
<tr>
<th>First Author Publication year</th>
<th>Setting</th>
<th>nr of studies overall</th>
<th>Specific for advanced CKD?</th>
<th>AMSTAR score</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety and Efficacy of Gliclazide as Treatment for Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Trials Landman [255] 2014</td>
<td>Patients: adults with type 2 diabetes Medication/intervention: studies comparing gliclazide (either short sustained release) Comparison: with other glucose lowering drugs; trials using placebo, diet, insulin or roziglitazones were excluded.</td>
<td>19 RCT</td>
<td>No</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Comparative Effectiveness and Safety of Medications for Type 2 Diabetes: An Update Including New Drugs and 2-Drug Combinations Bennet [122] 2011</td>
<td>Patients: T2DM Medication/intervention: metformin,second-generation sulfonylureas (SGSUs), TZDs, meglitindes,DPP-4 inhibitors and GLP-1 agonists Comparison: as monotherapy and in combination</td>
<td>140 RCT and 26 observational</td>
<td>NO</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Predictors of response to dipeptidyl peptidase-4 inhibitors: evidence from randomized clinical trials Monami [256] 2011</td>
<td>Patients: T2DM Medication/intervention: maximal dose DPP-4 inhibitors, other oral drugs (TZDs, metformin, sulfonylurea, α-glucosidase inhibitors) Comparison: DPP-4 inhibitors vs. other oral drugs or insulin or placebo as monotherapy</td>
<td>44</td>
<td>NO</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Comparison of different drugs as add-on treatments to metformin in type 2 diabetes: A meta-analysis Monami [257] 2008</td>
<td>Patients: T2DM with inadequate glycaemic control on metformin Medication/intervention: add-on to metformin: glibenclamide, glyburide, glipizide, gliclazide, chlorpropamide, tolbutamide, glimepiride, gliquidione, repaglinide, nateglinide, acarbose, miglitol, pioglitazone, rosiglitazone, troglitazone, exenatide, liraglutide, sitagliptin, vildagliptin, muraglitazar, pramlintide, insulin, glargine, lispro, aspart,glulisine and detemir Comparison: metformin plus placebo vs.metformin plus other drugs, or head to head comparisons</td>
<td>16</td>
<td>NO</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Meglitinide analogues for type 2 diabetes mellitus Black [258] 2009</td>
<td>Patients: T2DM Medications/interventions: meglitinide analogues, placebo, metformin, insulin Comparisons: meglitinide analogues to placebo, head-to-head, metformin or in combination with insulin.</td>
<td>15</td>
<td>NO</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Study Title</td>
<td>Authors (Year)</td>
<td>Patients:</td>
<td>Medication/intervention:</td>
<td>Comparison:</td>
<td></td>
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<tr>
<td>---------------------------------------------------------------------------</td>
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<tr>
<td>Estimating the effect of sulfonylurea on HbA1c in diabetes: a systematic</td>
<td>Hirst [259] 2013</td>
<td>T2DM</td>
<td>SU (glimepiride, tolbutamide, glipizide, glibenclamide)</td>
<td>fixed-dose sulfonylurea monotherapy or sulfonylurea added on to other glucose lowering treatments (metformin, insulin or TZD).</td>
<td></td>
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<tr>
<td>review and meta-analysis</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes mellitus</td>
<td>Richter [123] 2008</td>
<td>T2DM</td>
<td>sitagliptin, vildagliptin</td>
<td>sitagliptin or vildagliptin vs. placebo sitagliptin or vildagliptin vs. single hypoglycaemic agents sitagliptin or vildagliptin in combination with other hypoglycaemic agents vs. other combinations of hypoglycaemic agents sitagliptin or vildagliptin vs. intensive lifestyle interventions.</td>
<td></td>
</tr>
<tr>
<td>GLP-1 agpnists for type 2 diabetes mellitus</td>
<td>Shyangdang [260] 2013</td>
<td>T2DM</td>
<td>GLP-1 agonists (exenatide, liraglutide, lixisenatide, albiglutide)</td>
<td>placebo, TZDs, DPP-4 inhibitors, insulin glargine, SU, other GLP-1 agonist</td>
<td></td>
</tr>
<tr>
<td>Metformin added to insulin therapy for type 1 diabetes mellitus in</td>
<td>Abdelghaffar [261] 2009</td>
<td>patients with type 1 diabetes</td>
<td>metformin, insulin</td>
<td>metformin as add-on to insulin vs. insulin alone</td>
<td></td>
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<tr>
<td>adolescents</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Metformin monotherapy for type 2 diabetes mellitus Cochrane review</td>
<td>Saenz[262] 2013</td>
<td>patients on monotherapy</td>
<td>metformin, SU, meglitinide, α-glucosidase inhibitor, insulin</td>
<td>monotherapy vs. placebo or vs. alternative monotherapy or vs. diet/lifestyle intervention</td>
<td></td>
</tr>
<tr>
<td>Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes</td>
<td>Karagiannis [124] 2012</td>
<td>T2DM</td>
<td>DPP-4 inhibitors, metformin, sulfonylurea, pioglitazone, GLP-1 agonists, basal insulin</td>
<td>DPP-4 vs. metformin as monotherapy or with a sulfonylurea, pioglitazone, a GLP-1 agonist, or basal insulin combined with metformin</td>
<td></td>
</tr>
<tr>
<td>mellitus in the clinical setting: systematic review and meta-analysis</td>
<td></td>
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</tr>
</tbody>
</table>
## Comparative safety and effectiveness of metformin in patients with diabetes mellitus and heart failure: systematic review of observational studies involving 34,000 patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Medication/intervention</th>
<th>Comparison</th>
<th>Observations</th>
<th>Study Design</th>
<th>Comparison Notes</th>
</tr>
</thead>
</table>
| Eurich [263] 2013 | T2DM with heart failure | Metformin | • metformin as monotherapy  
• metformin in combination with other agents  
• other agents without metformin | 9  
observational +1 unpublished RCT | YES | 8 |
| Hemmingsen [264] 2013 | Sulphonylurea monotherapy for patients with type 2 diabetes mellitus | T2DM  
first-generation SU (FGSUs): acetohexamide, carbutamide, chlorpropamide, tolbutamide, tolazamide; SGSUs: glibencamide or glyburide, glibornuride, gliclazide, glipizide; third-generation SUs (TGSUs): gliclazide modified release, glimepiride, glipizide gastrointestinal therapeutic system, lifestyle interventions | SU monotherapy vs. placebo, no intervention or other glycaemia lowering interventions | 72 | NO | 11 |
| Hemmingsen[265] 2012 | Comparison of metformin and insulin vs. insulin alone for type 2 diabetes: systematic review of randomised clinical trials with meta-analyses and trial sequential analyses | T2DM  
metformin, insulin | to compare the benefit and harm of metformin and insulin vs. insulin alone | 23 | 9 |
| Van De Laar [266] 2005 | Alpha-glucosidase inhibitors for type 2 diabetes mellitus | T2DM  
α-glucosidase inhibitor vs. all other interventions | α-glucosidase inhibitor monotherapy vs. all other interventions | 41 | NO | 11 |
metformin vs. diet alone, vs. placebo, and vs. no treatment; metformin as an add-on therapy; metformin withdrawal | | 13 | NO | 3  
Unclear why study selection was conceived this way; mixed bag of different types of interventions. |
| Bolen [126] 2007 | Systematic Review: Comparative effectiveness and safety of oral medications for type 2 diabetes mellitus | T2DM  
SGSUs, biguanides, TZDs, meglitinides, and α-glucosidase inhibitors | all possible combinations, also with placebo | 216 | NO | 6 |
| Zhu [268] 2013 | Comparative efficacy of glimepiride and metformin in monotherapy of type 2 diabetes mellitus: meta-analysis of randomized controlled trials | T2DM  
metformin vs. glimepiride | | 15 | NO | 6 |
<table>
<thead>
<tr>
<th>Study Description</th>
<th>Reference</th>
<th>Patients</th>
<th>Medication/intervention</th>
<th>Comparisons</th>
<th>N</th>
<th>NO</th>
<th>Only Benefit or Higher Risk of Hypoglycaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early combination therapy for the treatment of type 2 diabetes mellitus: systematic review and meta-analysis</td>
<td>Phung [269] 2013</td>
<td>T2DM</td>
<td>metformin, other agents</td>
<td>metformin monotherapy vs. combination therapy including metformin</td>
<td>15</td>
<td>NO</td>
<td>7</td>
</tr>
<tr>
<td>Sulphonylureas and risk of cardiovascular disease: systematic review and meta-analysis</td>
<td>Phung [270] 2013</td>
<td>T2DM</td>
<td>SUs, other agents</td>
<td>clinical and observational studies that reported the association between SUs and CV disease events as compared to other glycaemia lowering drugs</td>
<td>33</td>
<td>NO</td>
<td>Also includes observational data, which might induce bias by indication; opposite effect for observational and RCTs; as SU has the same effect as placebo, the apparent negative effect compared to non placebo is probably due to a beneficial effect of metformin.</td>
</tr>
<tr>
<td>Efficacy and safety of dipeptidyl peptidase-4 inhibitors and metformin as initial combination therapy and as monotherapy in patients with type 2 diabetes mellitus: a meta-analysis</td>
<td>Wu [271] 2014</td>
<td>T2DM</td>
<td>DPP-4 inhibitors, metformin</td>
<td>DPP-4 inhibitors plus metformin as initial combination therapy or as monotherapy compared to metformin monotherapy</td>
<td>8</td>
<td>NO</td>
<td>5</td>
</tr>
<tr>
<td>Second-line therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy: a systematic review and mixed-treatment comparison meta-analysis</td>
<td>McIntosh [125] 2011</td>
<td>Adults and children with T2DM requiring a second-line anti-hyperglycemic agent because of inadequate control</td>
<td>HbA1c &gt; 6.5% (46 mmol/mol), fasting plasma glucose (FPG) &gt; 7 mmol/L or 2-hour postprandial glucose (PPG) &gt; 10 mmol/L on metformin monotherapy or because of intolerance to this therapy.</td>
<td>SU, meglitinides, TZDs, DPP-4 inhibitors, GLP-1 agonists, insulin and insulin analogues; α-glucosidase inhibitors and weight-loss agents (orlistat and sibutramine).</td>
<td>49</td>
<td>NO</td>
<td>11</td>
</tr>
<tr>
<td>Choice of therapy in patients with type 2 diabetes inadequately controlled with metformin and a sulphonylurea: a systematic review and mixed-treatment comparison meta-analysis</td>
<td>McIntosh [129] 2012</td>
<td>Patients with T2DM, inadequately controlled on metformin/sulfonylurea combination therapy</td>
<td>all available classes of anti-hyperglycaemic therapies</td>
<td>comparative safety and efficacy of all available classes of antihyperglycemic therapies as add-on to combination metformin+SU</td>
<td>33</td>
<td>NO</td>
<td>8</td>
</tr>
</tbody>
</table>

Overall, studies were of poor quality; no mortality data presented.
<table>
<thead>
<tr>
<th>Research Question</th>
<th>Authors</th>
<th>Year</th>
<th>Study Population</th>
<th>Medications/Interventions</th>
<th>Comparisons</th>
<th>Patients</th>
<th>NO</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect of Antihyperglycemic Agents Added to Metformin and a SU on Glycemic Control and Weight Gain in Type 2 Diabetes: A Network Meta-analysis</td>
<td>Gross [130]</td>
<td>2011</td>
<td>Patients: adults aged 18 years or older with T2DM and a HbA1c level greater than 7.0% (53 mmol/mol) who were already receiving a combination of metformin and SU.</td>
<td>Medication/interventions: any anti-hyperglycaemic drug</td>
<td>Comparisons: Studies evaluated the effects of adding a third antihyperglycemic drug as compared to placebo or head to head</td>
<td>18</td>
<td>NO</td>
<td>10</td>
</tr>
<tr>
<td>Effect of metformin on cardiovascular events and mortality: a meta-analysis of randomized clinical trials</td>
<td>Lamanna [272]</td>
<td>2011</td>
<td>Patients: T2DM</td>
<td>Medications/interventions: metformin, active glucose lowering therapies</td>
<td>Comparisons: all trials comparing metformin with placebo, active glucose lowering therapies, or no therapy, provided that their duration was ≥52 weeks and that concurrent therapies were not different in metformin and comparator arms.</td>
<td>35</td>
<td>NO</td>
<td>5</td>
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<tr>
<td>Effect of Noninsulin Antidiabetic Drugs Added to Metformin Therapy on Glycemic Control, Weight Gain, and Hypoglycemia in Type 2 Diabetes</td>
<td>Phung [127]</td>
<td>2010</td>
<td>Patients: patients with type 2 diabetes experiencing an inadequate response to maximized and stable (4 weeks at 1500 mg or maximally tolerated dose) metformin therapy</td>
<td>Medications/interventions: non-insulin glycaemia lowering drugs (TZDs, SUs, glinides, GLP-1 agonists, α-glucosidase inhibitors, and DPP-4 inhibitors), metformin</td>
<td>Comparisons: drugs added to metformin, head to head or vs. placebo</td>
<td>27</td>
<td>NO</td>
<td>8</td>
</tr>
<tr>
<td>Cardiovascular Outcomes in Trials of Oral Diabetes Medications</td>
<td>Selvin [273]</td>
<td>2008</td>
<td>Patients: T2DM: Medications/interventions: metformin, SGSUs, and TZDs. Studies including FGSUs or with α-glucosidase inhibitors were excluded. Comparisons: drugs either as monotherapy (vs. placebo or vs. other oral agent) or as dual therapy (all possible combinations).</td>
<td>40</td>
<td>NO</td>
<td>7</td>
<td></td>
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<tr>
<td>Effect of antidiabetic agents added to metformin on glycaemic control, hypoglycaemia and weight change in patients with type 2 diabetes: a network meta-analysis</td>
<td>Liu [128]</td>
<td>2012</td>
<td>Patients: T2DM who showed inadequate response to metformin monotherapy at randomisation (mean HbA1c ≥7.0% (53 mmol/mol)). Medications/interventions: SUs, glinides, TZDs, α-glucosidase inhibitors, DPP-4 inhibitors, GLP-1 agonists, basal insulin and biphasic insulin. Comparison: • glycaemia lowering agents with either a placebo or another class of glycaemia lowering agents in addition to metformin; for at least 12 weeks, but no more than 52 weeks; • trials were excluded if they stopped metformin use or changed the metformin dose after randomisation</td>
<td>39</td>
<td>NO</td>
<td>4</td>
<td></td>
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</tr>
<tr>
<td>Study Title</td>
<td>Patients: T2DM</td>
<td>Medications/Interventions</td>
<td>Comparison:</td>
<td>Studies</td>
<td>No. of studies</td>
<td>Authors' conclusion</td>
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<tr>
<td>Proportion of patients at HbA1c target &lt;7% with eight classes of antidiabetic drugs in type 2 diabetes: systematic review of 218 randomized controlled trials with 78 945 patients</td>
<td>Esposito [274] 2012</td>
<td>metformin, SUs, α-glucosidase inhibitors, TZDs, glinides, DPP-4 inhibitors, GLP-1 agonists and insulin analogues</td>
<td>Drugs could be either used as monotherapy in drug naive patients, or add-on medication</td>
<td>218</td>
<td>NO</td>
<td>High heterogeneity in studies; high heterogeneity between studies; main driver for Hb1AC change was baseline HbA1c.</td>
<td></td>
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</tr>
<tr>
<td>Efficacy and Safety of Incretin Therapy in Type 2 Diabetes</td>
<td>Amori [118] 2007</td>
<td>incretin therapy (GLP-1 agonists and DPP-4 inhibitors), placebo, other glycaemia lowering drugs;</td>
<td>monotherapy and add-on therapy were considered</td>
<td>29</td>
<td>NO</td>
<td>All but 3 trials had a 30-week or shorter duration; thus, long-term efficacy and safety could not be evaluated.</td>
<td></td>
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</tr>
<tr>
<td>Efficacy of GLP-1 Receptor Agonists and DPP-4 Inhibitors: Meta-Analysis and Systematic Review</td>
<td>Aroda [275] 2012</td>
<td>exenatide, exendin, liraglutide, taspoglutide, albiglutide, sitagliptin, alogliptin, vildagliptin, saxagliptin, lixisenatide, and albugon</td>
<td>monotherapy vs. placebo; one single vs. another glycaemia lowering agent; as single add-on vs. placebo or vs. other glycaemia lowering agent</td>
<td>80</td>
<td>NO</td>
<td>Strong heterogeneity between studies severely hampers conclusions.</td>
<td></td>
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</tr>
<tr>
<td>Glycaemic control and adverse events in patients with type 2 diabetes treated with metformin and sulphonylurea: a meta-analysis</td>
<td>Belsey [276] 2008</td>
<td>metformin+placebo vs. metformin plus SU. Other combinations of glycaemia lowering drugs and combination of metformin and SU</td>
<td>SU</td>
<td>6</td>
<td>NO</td>
<td>This meta-analysis only analysed SU in addition to metformin, not to other drugs.</td>
<td></td>
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</tr>
<tr>
<td>Comparative Effectiveness of DPP-4 inhibitors in Type 2 Diabetes: A Systematic Review and Mixed Treatment Comparison</td>
<td>Craddy [277] 2014</td>
<td>any pharmacological glycaemia lowering treatment; alogliptin, sitagliptin, saxagliptin, vildagliptin, and vildagliptin; dual therapy (plus metformin, SU, pioglitazone, or insulin), and triple therapy (plus metformin/SU).</td>
<td>metformin plus SU vs. placebo or vs. other glycaemia lowering agent</td>
<td>83</td>
<td>NO</td>
<td>Authors sponsored by Takeda to conduct this study.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GLP-1 agonists as add-on therapy to basal insulin in patients with type 2 diabetes: a systematic review</td>
<td>Berlie [120] 2012</td>
<td>non-pregnant adults with T2DM</td>
<td>GLP-1 agonists (exenatide, liraglutide, albiglutide, lixisenatide), basal insulin therapy</td>
<td>5</td>
<td>NO</td>
<td>No patient relevant outcomes assessed. Interpretation appears somewhat biased.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy of Various Antidiabetic Agents as Add-On Treatments to Metformin in Type 2 DiabetesMellitus: Systematic Review and Meta-Analysis</td>
<td>Poolsup [278] 2012</td>
<td>metformin alone</td>
<td>only long-acting insulin</td>
<td>8</td>
<td>NO</td>
<td>No patient relevant outcomes assessed. Interpretation appears somewhat biased.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the Combination of</td>
<td>Rao [279] 2012</td>
<td>T2DM</td>
<td></td>
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</tr>
</tbody>
</table>

Note: T2DM: Type 2 Diabetes; SUs: Sulfonylureas; TZDs: Thiazolidinediones; DPP-4: Dipeptidyl Peptidase-4; GLP-1: Glucagon-like Peptide-1; SU: Sulfonylureas; NPH: Neutral Protamine Hagedorn; Hb1AC: Hemoglobin A1C; RCTs: Randomized Controlled Trials.
<table>
<thead>
<tr>
<th>Study Title</th>
<th>Year</th>
<th>Patients</th>
<th>Medications/Interventions</th>
<th>Comparisons</th>
<th>N</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas and Metformin Associated With an Increased Risk of Cardiovascular Disease or All-Cause Mortality? A meta-analysis of observational studies</td>
<td>2008</td>
<td></td>
<td>Medications/interventions: acetoheaxamide, chlorpropamide, tolbutamide, tolamazine, glyburide, glipizide, biguanides, metformin, and glimepiride. <strong>Comparisons:</strong> observational studies that examined the association between combination therapy of SUs and metformin on risk of CVD or all-cause mortality</td>
<td></td>
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</tr>
<tr>
<td>The incidence of mild and severe hypoglycaemia in patients with type 2 diabetes mellitus treated with sulfonylureas: a systematic review and meta-analysis</td>
<td>2014</td>
<td></td>
<td>Patients: T2DM Medications/interventions: GLP-1 agonists (liraglutide, exenatide), DPP-4 inhibitors (sitagliptin, vildagliptin and saxagliptin), SUs, insulin glargine or pre-mixed insulin <strong>Comparisons:</strong> GLP-1 agonists or DPP-4 inhibitors with SUs, insulin glargine or pre-mixed insulin</td>
<td>25</td>
<td>No data on hypoglycaemia episodes in patients on GLP-1 agonists are provided.</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular safety and glycemic control of GLP-1 agonists for type 2 diabetes mellitus: A pairwise and network meta-analysis</td>
<td>2012</td>
<td></td>
<td>Patients: T2DM Medications/interventions: exenatide, liraglutide, albiglutide, tasapoglutide orlixisenatide <strong>Comparisons:</strong> exenatide, liraglutide, albiglutide, tasapoglutide orlixisenatide vs. active comparator or placebo</td>
<td>45</td>
<td>NO</td>
<td>4</td>
</tr>
<tr>
<td>Sodium–Glucose Cotransporter 2 Inhibitors for Type 2 Diabetes A Systematic Review and Meta-analysis</td>
<td>2013</td>
<td></td>
<td>Patients: T2DM Medications/Interventions: SGLT-2 inhibitors, other medication for T2DM <strong>Comparisons:</strong> RCTs comparing SGLT-2 with placebo or other medication for T2DM</td>
<td>55</td>
<td>9</td>
<td>Limitation: Most trials were rated as high risk of bias</td>
</tr>
<tr>
<td>GLP-1 agonists vs. insulin in inadequately controlled patients with type 2 diabetes mellitus: a meta-analysis of clinical trials</td>
<td>2011</td>
<td></td>
<td>Patients: non-pregnant adults at least 18 years of age, with T2DM for at least 3 months, suboptimally controlled with oral agents (e.g. metformin and/or SU) with HbA1c levels between 7 and 11% (53–97 mmol/mol) Medications/interventions: GLP-1 agonists, insulin, e.g. glarine or biphasic insulin aspart <strong>Comparisons:</strong> GLP-1 agonists (exenatide or liraglutide) with insulin</td>
<td>8</td>
<td>NO</td>
<td>9</td>
</tr>
<tr>
<td>The effects of sulfonylureas plus metformin on lipids, blood pressure, and adverse events in type 2 diabetes: a meta-analysis of randomized controlled trials</td>
<td>2013</td>
<td></td>
<td>Patients: T2DM Medications/interventions: metformin, glimepiride, glipizide, glibenclamide, gliclazide <strong>Comparisons:</strong> metformin vs. metformin+SU</td>
<td>20</td>
<td>NO</td>
<td>8</td>
</tr>
<tr>
<td>Longer term safety of dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes mellitus: systematic review and meta-analysis</td>
<td>2012</td>
<td></td>
<td>Patients: T2DM Medications/interventions: alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin <strong>Comparisons:</strong> DPP-4 Inhibitors compared to placebo, another gliptin or any other glycaemia lowering drug</td>
<td>67</td>
<td>8</td>
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</tbody>
</table>

Chapter 2.3 supplementary table: Systematic reviews presenting data on all-cause and cardiovascular mortality associated with different glycaemia
Safety and Efficacy of Gliclazide as Treatment for Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Trials

<table>
<thead>
<tr>
<th>Setting</th>
<th>All-cause mortality</th>
<th>Cardiovascular (CV) mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients:</strong> adults with type 2 diabetes</td>
<td>There were 12 deaths in 2500 gliclazide users and 8 deaths in the comparator group of 2569 patients, risk ratio gliclazide vs. others; 1.50 (95% CI: 0.62, 3.62)</td>
<td>There were 11 cases with cardiovascular events (different definitions) in 1480 gliclazide users and 20 cases in the comparator group of 1508 patients, risk ratio for gliclazide 0.95 (95% CI: 0.57, 1.61). There were 3 cardiovascular deaths in 1602 gliclazide users and 7 in 1619 comparator patients, risk ratio gliclazide 0.81 (95% CI: 0.26, 2.47) [8,14,20–28,31–34,36].</td>
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<tr>
<td><strong>Medication/Intervention:</strong> studies comparing gliclazide (either short sustained release)</td>
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<tr>
<td><strong>Comparison:</strong> with other glucose lowering drugs; trials using placebo, diet, insulin or roziglitazones were excluded.</td>
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Hemmingse [264] 2013

| **Patients:** T2DM                                                     | FGSU vs. placebo: RR 1.46, 95% confidence interval (CI) 0.87 to 2.45; vs. insulin: relative risk (RR) 1.18, CI (0.88 to 1.59); SGSU vs. metformin; (RR 0.98, CI 0.61 to 1.58), SGSU vs. insulin (RR 0.96, CI 0.79 to 1.18), SGSU vs. meglitinides (RR 1.44, CI 0.47 to 4.42), SGSU vs. incretin-based interventions (RR 1.39, CI 0.52 to 3.68). Mortality data for the SGSU vs. placebo were sparse. TGSUs could not be included in any meta-analysis of all-cause mortality, CV mortality, non-fatal macro- or microvascular outcomes due to lack of data. | FGSU vs. placebo: RR 2.63, CI 1.32 to 5.22; FGSU vs. insulin: RR 1.36, CI 0.68 to 2.71; SGSU vs. metformin and meglitinides showed no statistical significance for non-fatal myocardial infarction. SGSU vs. meglitinides did not show statistically significant differences for a composite of non-fatal macrovascular outcomes. SGSU vs. metformin showed statistical significance in favour of SGSU for a composite of non-fatal macrovascular outcomes (RR 0.67, CI 0.48 to 0.93). |
| **Comparison:** sulphonylurea monotherapy vs. placebo, no intervention or other glycaemia lowering interventions |                                                                      |                                              |

Hemmingse [265] 2012

| **Patients:** T2DM                                                     | Metformin and insulin vs. insulin alone did not significantly affect all-cause mortality (RR 1.30, CI 0.57 to 2.99) | Metformin and insulin vs. insulin alone: RR 1.70 (0.35 to 8.30). |
| **Comparison:** to compare the benefits and harms of metformin and insulin vs. insulin alone. |                                                                      |                                              |

Boussageon [267] 2012

| **Patients:** T2DM                                                     | RR = 0.99 ( CI: 0.75 to 1.31) | RR = 1.05 ( CI: 0.67 to 1.64). There was significant heterogeneity when including the UK Prospective Diabetes Study subgroups (I2 = 41% and 59%). |
| **Comparison:** metformin vs. diet alone, vs. placebo, and vs. no treatment; metformin as an add-on therapy; and metformin withdrawal |                                                                      |                                              |

Lamanna [272] 2011

| **Patients:** T2DM                                                     | It is likely that metformin monotherapy is associated with improved survival (RR: 0.801 CI 0.625–1.024, p= 0.076). However, concomitant use with SUs was associated with reduced survival (RR: 1.432 CI 1.068–1.918), p= 0.016 | CV events: overall effect of metformin (RR 0.94 (0.82–1.07), p= 0.34). A significant benefit was observed in trials vs. placebo/no therapy (RR 0.79 (0.64–0.98), p= 0.031), but not in active-comparator trials (RR 1.03 (0.72–1.77), p= 0.89). Meta-regression showed a significant correlation of the effect of metformin on CV events with trial duration and with minimum and maximum age for inclusion, meaning that the drug appeared to be more beneficial in longer trials enrolling younger patients. |
| **Comparisons:** All trials comparing metformin with placebo, active glucose lowering therapies, or no therapy, provided that their duration was ≥52 weeks and that concurrent therapies were not different in metformin and comparator arms. |                                                                      |                                              |
Selvin [273] 2008

Patients: T2DM
Comparisons: drugs either as monotherapy (vs. placebo or vs. other oral agent) or as dual therapy (all possible combinations).

Metformin compared with any other oral diabetes agent or placebo: no statistically significant difference in all-cause mortality.

Rao [279] 2008

Patients: T2DM
Comparisons: observational studies that examined the association between combination therapy of SUs and metformin on risk of CVD or all-cause mortality

Combination therapy of SUs and metformin vs. other: pooled RR 1.19 CI (0.88 – 1.62)

Phung [270] 2013

Patients: T2DM
Comparisons: clinical and observational studies that reported the association between SU and CV disease events compared to other glycaemia lowering drugs

CV death: overall RR for SU: 1.27, CI 1.18–1.34, 27 comparisons; SU vs. metformin RR: 1.26 (CI 1.17–1.35, 17 comparisons); SU vs. placebo: RR 1.31 (0.90–1.85); composite CV event overall RR for SU: 1.10, CI 1.04–1.16, 43 comparisons; SU vs. metformin 1.18 (CI 1.13–1.24, 16 comparisons); SU vs. placebo: RR 0.99 (0.85–1.16)

Sun [281] 2012

 Patients: T2DM on monotherapy
Comparisons: exenatide, liraglutide, albiglutide, taspoglutide orlistat vs active comparator (not further specified, so unclear what this means) or placebo

A low incidence of CVD was found: events for GLP-1s (0.69% (40/5826)) vs. placebo (1.19% (28/2350)); (OR 0.70, CI 0.40–1.22)

Saenz [262] 2005

Patients: T2DM on monotherapy
Comparisons: monotherapy vs. Placebo, vs. alternative monotherapy or vs. diet/lifestyle intervention

Obese patients allocated to intensive blood glucose control with metformin showed a greater benefit than chlorpropamide, glibenclamide, or insulin for all-cause mortality (P = 0.03). Obese participants assigned to intensive blood glucose control with metformin showed a greater benefit than overweight patients on conventional treatment (mainly diet) for all-cause mortality (P = 0.01).

Obese patients allocated to intensive blood glucose control with metformin showed a greater benefit than chlorpropamide, glibenclamide, or insulin for any diabetes-related outcomes (P = 0.009). Obese participants assigned to intensive blood glucose control with metformin showed a greater benefit than overweight patients on conventional treatment for any diabetes-related outcomes (P = 0.004), and myocardial infarction (P = 0.02).

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Chapter 2.3 supplemental table: Systematic reviews presenting data on hypoglycaemic risk, HbA1c change and body weight change associated with different glycaemia lowering drugs

<table>
<thead>
<tr>
<th>First Author</th>
<th>Protocol and drugs included</th>
<th>Hypoglycaemia risk</th>
<th>HbA1c Change*</th>
<th>Body weight change</th>
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</thead>
</table>

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Landman [255] 2014</td>
<td>Adults with type 2 diabetes</td>
<td>Monotherapy: Oral drugs or insulin or placebo as monotherapy</td>
<td>Comparison: with other glucose lowering drugs; trials using placebo, diet, insulin or rosiglitazones were excluded.</td>
<td>There was one severe hypoglycemic event in 2,387 glitazide users and one in the 2,430 patients in the comparator group. There were 25 non-severe hypoglycemic events (2.2%) in 1,152 glitazide users and 22 hypoglycemic events (1.8%) in 1,163 patients in the comparator group (p = 1.09)</td>
<td>Compared to other interventions, glitazide was more effective: 20.12% (95% CI: 20.23, 20.01). Compared to metformin monotherapy, the effect estimate of glitazide monotherapy was 0.26 (95% CI: 0.25, 0.11, p = 0.06).</td>
<td>The difference in weight was 0.47 kg (95% CI: 20.75, 1.70) in favor of the control group (p = 0.87%). When comparing glitazide to metformin the effect estimate was 1.37 kg (95% CI: 0.15, 2.60, p = 28%).</td>
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<tr>
<td>Bennet [122] 2009</td>
<td>Patients: T2DM</td>
<td>Monotherapy: Oral drugs or insulin or placebo as monotherapy</td>
<td>Comparison: as monotherapy and in combination</td>
<td>SUs had a higher risk for mild or moderate hypoglycaemia than metformin alone (RR 4.6, CI 3.2-6.5) and, in combination with metformin, an increased risk compared with metformin plus TZDs (RR 5.8, CI 4.3-7.7). The RR for meglitinide monotherapy and meglitinide plus metformin was 3.0 (CI 1.8-5.2) and compared to metformin monotherapy 2.7 (CI 1.0-7.7). Metformin plus DPP-4i had no higher risk for hypoglycaemia than metformin monotherapy (RR 0.9, CI 0.4 to 2.4)</td>
<td>Evidence supports metformin as a first-line agent to treat T2DM. Most 2-drug combinations similarly reduce hemoglobin A1C levels, but some increased risk for hypoglycaemia and other adverse events.</td>
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<tr>
<td>Poolsup [278] 2012</td>
<td>Patients: T2DM poorly treated on metformin alone</td>
<td>Monotherapy: Oral drugs or insulin or placebo as monotherapy</td>
<td>Comparison: as monotherapy and in combination</td>
<td>SUs had a higher risk for mild or moderate hypoglycaemia than metformin alone (RR 4.6, CI 3.2-6.5) and, in combination with metformin, an increased risk compared with metformin plus TZDs (RR 5.8, CI 4.3-7.7). The RR for meglitinide monotherapy and meglitinide plus metformin was 3.0 (CI 1.8-5.2) and compared to metformin monotherapy 2.7 (CI 1.0-7.7). Metformin plus DPP-4i had no higher risk for hypoglycaemia than metformin monotherapy (RR 0.9, CI 0.4 to 2.4)</td>
<td>T2Ds reduced as effectively as DPP-4 inhibitors. Hba1c value (pooled mean difference –0.03%; CI –0.16 to 0.10%)</td>
<td>TZDs and SU: no difference in reduction of Hba1c.</td>
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<tr>
<td>Monami [256] 2011</td>
<td>Patients: T2DM</td>
<td>Monotherapy: Oral drugs or insulin or placebo as monotherapy</td>
<td>Comparison: as monotherapy and in combination</td>
<td>DPP-4 inhibitors were associated with a lower risk of hypoglycaemia than SUs (RR 0.10, CI 0.07-0.13, p &lt; 0.01; 3 trials), whereas no significant difference was observed in comparisons with metformin (RR 0.71 CI 0.24-2.09, p = 0.53; 6 trials) or TZDs (RR 1.32, CI 0.30-5.83, p = 0.71; 4 trials)</td>
<td>DPP-4 inhibitors significantly reduced Hba1c at 24 weeks (0.6%, CI 0.5-0.7) when compared with placebo; no difference in Hba1c was observed in comparisons with TZDs and α-glucosidase inhibitors, whereas SUs and metformin produced a greater reduction of Hba1c.</td>
<td>In the 14 trials with available data, DPP-4 inhibitors produced a significant increase of BMI at 21–30 weeks (0.10 kg/m², CI 0.05-0.15, p &lt; 0.001). In active comparator studies, 21–30-week treatment with DPP-4 inhibitors was associated with a significantly lower BMI in comparison with TZDs (–0.10 kg/m², CI –0.21 to –0.01, p = 0.049), whereas no significant difference was observed with respect to metformin (0.05 kg/m², CI –0.02-0.13, p = 0.18).</td>
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</table>
| Monami [257] 2008 | **Patients:** T2DM with inadequate glycaemic control on metformin  
**Comparison:** metformin plus placebo vs. plus other drugs or head to head comparisons | **Reduction of HbA1c with SUs, TZDs, and α-glucosidase inhibitors, was 0.85% (CI 0.78-0.94), 0.42% (CI 0.40-0.44) and 0.61% (CI 0.55-0.67) respectively.** |
| --- | --- | --- |
| Black [258] 2009 | **Patients:** T2DM  
**Comparisons:** meglitinide analogues to placebo, head-to-head, metformin or in combination with insulin.  
Three studies found rates of symptomatic hypoglycaemia ranging from 17% to 44% in the treated groups. Two studies compared two different doses of repaglinide, and reported higher rates of symptomatic hypoglycaemia with 4.0 mg compared with 1.0 mg (35% vs. 27%, respectively) and 2.0 mg compared with 0.5 mg (17% vs. 11%, respectively). One study reported that three patients (1%) receiving repaglinide experienced major hypoglycaemic episodes requiring third party help. The four other studies reported no major hypoglycaemic episodes  
When compared to metformin monotherapy, both repaglinide and nateglinide produce a similar reduction in HbA1c than metformin. The combination of metformin with a meglitinide produced a clinically significant additional reduction in HbA1c when compared to metformin monotherapy. Metformin in combination with insulin was more effective in reducing HbA1c than repaglinide in combination with insulin. | For both repaglinide and nateglinide, in almost all studies where weight was reported, weight gains occurred. Where meglitinides were compared directly to metformin, those treated with metformin experienced the greater weight losses. |
| Hirst [259] 2013 | **Patients:** T2DM  
**Comparison:** fixed-dose SU monotherapy or SU added on to other glucose lowering treatments (metformin, insulin or TZD).  
SUs appear to be associated with an increased risk of hypoglycaemic events.  
SU monotherapy lowered HbA1c level more than previously reported (-1.51%, CI -1.78 to -1.25). SU added to another oral glycaemia lowering agent resulted in a mean HbA1c change of -1.62% (CI: -2.24 to -1.00) and to insulin -0.46% (CI -0.69 to -0.24). There is no evidence that increasing SU doses resulted in lower HbA1c. |  |
| Richter [123] 2008 | **Patients:** T2DM  
**Comparisons:**  
- sitagliptin or vildagliptin vs. placebo;  
- sitagliptin or vildagliptin vs. single hypoglycaemic agents;  
- sitagliptin or vildagliptin in combination with other hypoglycaemic agents vs. other combinations of hypoglycaemic agents;  
- sitagliptin or vildagliptin vs. intensive lifestyle interventions.  
No severe hypoglycaemia was reported in patients taking sitagliptin or vildagliptin.  
| Sitagliptin vs. placebo or another agent: 0.66 kg (CI 0.37-0.94);  
Vildagliptin vs. placebo: 0.76 kg (CI 0.19-1.32); vildagliptin vs. other single agent: 1.55 kg (CI 1.19-1.91) |
<table>
<thead>
<tr>
<th>Study Authors</th>
<th>Study Period</th>
<th>Study Design</th>
<th>Study Population</th>
<th>Comparisons</th>
<th>Summary of Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saenz [262]</td>
<td>2013</td>
<td>Clinical trial</td>
<td>Patients: T2DM on monotherapy</td>
<td>Comparisons: monotherapy vs. placebo or vs. alternative monotherapy or vs. diet/lifestyle intervention</td>
<td>Nine trials reported more hypoglycaemic events in the participants on SUs vs. metformin (34 vs. 126, ( p = 0.04 ))</td>
</tr>
<tr>
<td>Shyangdang [260]</td>
<td>2013</td>
<td>Randomised controlled trial</td>
<td>Patients: T2DM</td>
<td>Comparisons: Placebo, TZD, DPP-4 inhibitors, insulin glargine, SU, other GLP-1 agonist</td>
<td>Hypoglycaemia occurred more frequently in participants taking concomitant SU.</td>
</tr>
<tr>
<td>Abdelghaffar [261]</td>
<td>2009</td>
<td>Parallel group trial</td>
<td>Patients: patients with Type 1 diabetes</td>
<td>Comparisons: metformin as add-on to insulin vs. insulin alone</td>
<td>Severe hypoglycaemia occurred in two patients (13%) in the metformin group and one participant (7%) in the control group, while mild hypoglycaemia occurred more frequently in the metformin than in the placebo group after three months of therapy: mean 1.75 (0.8) vs. 0.9 (0.4) events/patient/week, respectively (( p = 0.03 )) (one study)</td>
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<tr>
<td>Patients: T2DM</td>
<td>Comparisons: DPP-4 inhibitors vs. metformin as monotherapy or with a SU, pioglitazone, a GLP-1 agonist, or basal insulin combined with metformin</td>
<td>Across all studies analysed, severe hypoglycaemia (defined as an episode that required the help of another person) occurred in six patients receiving a DPP-4 inhibitor (n=6615). In the control groups, one patient receiving metformin as monotherapy (n=1647), 51 receiving a SU (n=3873), one patient receiving a GLP-1 agonist (n=381), and none of the 445 patients receiving pioglitazone experienced at least one episode of severe hypoglycaemia. Compared with metformin as monotherapy, DPP-4 inhibitors were associated with a smaller decline in HbA1c (weighted mean difference 0.20%, CI 0.08 to 0.32). As a second line treatment, DPP-4 inhibitors were inferior to GLP-1 agonists (0.49%, CI 0.31 to 0.67) in reducing HbA1c and had no advantage over SUs in the attainment of the HbA1c goal (RR in favour of SUs 1.06, CI 0.98 to 1.14). DPP-4 inhibitors had a favourable weight profile compared with SUs (weighted mean difference −1.92, CI −2.34 to −1.49) but not compared with GLP-1 agonists (1.56, CI 0.94 to 2.18).</td>
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<tr>
<td>Van De Laar [266] 2009</td>
<td>Patients: T2DM</td>
<td>Comparisons: α-glucosidase inhibitor monotherapy vs. all other interventions</td>
<td>Acarbose vs. placebo: HbA1c -0.8% (CI -0.9 to -0.7), FPG -1.1 mmol/l (CI -1.4 to -0.9). The effect on HbA1c by acarbose was not dose-dependent.</td>
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<tr>
<td>Hemmingsen [286] 2013</td>
<td>Patients: T2DM</td>
<td>Comparisons: SU monotherapy vs. no intervention or other glycaemia lowering interventions</td>
<td>SGSU vs. meglitinides showed no statistical significance for the risk of severe hypoglycaemia. SGSU vs. metformin showed statistical significance in favour of metformin (RR 5.64, CI 1.22-26.0) for severe hypoglycaemia.</td>
<td></td>
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</tr>
<tr>
<td>Hemmingsen [265] 2012</td>
<td>Patients: T2DM</td>
<td>Comparison: to compare the benefits and harms of metformin and insulin vs. insulin alone</td>
<td>In a fixed effect model, but not in a random effects model, severe hypoglycaemia was significantly more frequent with metformin and insulin than with insulin alone (RR 2.83, CI 1.17-6.86). The achieved percentage of HbA1c decreased with metformin and insulin compared with insulin alone (mean difference −0.60%, CI −0.89 to −0.31, p &lt; 0.001, 20 trials; heterogeneity I²=82%, p=0.001). Trial sequential analyses showed sufficient evidence for a HbA1c reduction of 0.5% with metformin+insulin vs. insulin alone. Both body mass index and weight gain were significantly reduced by metformin and insulin compared with insulin alone (body mass index: mean difference −1.27, CI −2.07 to −0.47, p=0.002, 6 trials (heterogeneity I²=86%, p=0.001); weight gain: −1.68 kg, CI −2.22 to −1.13, p&lt;0.001, 13 trials (I²=36%, p=0.09). A trial sequential analysis showed sufficient evidence for a lower weight gain of 1 kg with metformin+insulin vs. insulin alone.</td>
<td></td>
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<tr>
<td>Year</td>
<td>Authors</td>
<td>Type of Study</td>
<td>Patients:</td>
<td>Comparisons:</td>
<td>Findings:</td>
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<tr>
<td>2007</td>
<td>Bolen [126]</td>
<td></td>
<td>T2DM</td>
<td>all possible combinations, also with placebo</td>
<td>RR (CI) pooled effect for hypoglycaemia: Met vs. Met + TZD: 0.00 (−0.01 to 0.01); SU vs. repag: 0.02 (−0.02 to 0.05); glyb vs. other SU: 0.03 (0.00 to 0.05); SU vs. Met: 0.04 (0.00 to 0.09); SU + TZD vs. SU: 0.08 (0.00 to 0.16); SU vs. TID: 0.09 (0.03 to 0.15); SU + Met vs. SU: 0.11 (0.07 to 0.14); SU + Met vs. Met: 0.14 (0.07 to 0.21)</td>
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<tr>
<td>2013</td>
<td>Zhu [268]</td>
<td></td>
<td>T2DM</td>
<td>metformin vs. glimepiride vs. placebo as monotherapy</td>
<td>Higher risk of hypoglycaemia with glimepiride</td>
</tr>
<tr>
<td>2013</td>
<td>Phung [270]</td>
<td></td>
<td>T2DM</td>
<td>clinical and observational studies that reported the association between SU and CVD events as compared to other glycaemia lowering drugs</td>
<td>Hypoglycaemia risk increased with combination therapy: RR 1.56 (CI 1.08-2.26). Drugs combined with metformin included TIDs, insulin secretagogues, DPP-4 inhibitors or SGLT-2 inhibitors. Compared to metformin alone, combination therapy with metformin resulted in reductions in HbA1c (−0.43%, CI −0.56 to −0.30), increases in attainment of HbA1c goal of less than 7% (53 mmol/mol) (RR 1.40, CI 1.33–1.48)</td>
</tr>
<tr>
<td>2010</td>
<td>Phung [127]</td>
<td></td>
<td>T2DM</td>
<td>experiencing an inadequate response to maximized and stable (4 weeks at 1500 mg or maximally tolerated dose) metformin therapy</td>
<td>The different classes of drugs were associated with similar HbA1c reductions (range 0.64-0.97%) compared with placebo. Although use of TIDs, SUs, and glinides were associated with weight gain (range, 1.77-2.08 kg), GLP-1 agonists, α-glucosidase inhibitors, and DPP-4 inhibitors were associated with weight loss or no weight change.</td>
</tr>
<tr>
<td>2011</td>
<td>McIntosh [125]</td>
<td></td>
<td>adults and children with T2DM requiring a second-line glycaemia lowering agent because of inadequate control (HbA1c &gt; 6.5% (46 mmol/mol), FPG &gt; 7 mmol/L or PPG &gt; 10 mmol/L) on metformin monotherapy or because of intolerance to this therapy.</td>
<td>Relative to metformin monotherapy, RR (CI) was significantly elevated with SUs 8.22 (4.5-16.63), meglitinides 8.59 (3.34-25.2), basal insulin 5.20 (1.48-21.46) and biphasic insulin 11.02 (3.48-40.43), but not with TIDs 1.10 (0.5-2.27), DPP-4 inhibitors 1.05 (0.56-2.23), α-glucosidase inhibitors 0.39 (0.01-6.67) or GLP-1 agonists 1.12 (0.33-3.90). An increase in body weight was observed with the majority of second-line therapies (1.8 to 3.0 kg), the exceptions being DPP-4 inhibitors, α-glucosidase inhibitors and GLP-1 agonists (0.6 to 1.8 kg).</td>
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<td>2012</td>
<td>McIntosh [129]</td>
<td></td>
<td>patients with T2DM, inadequately controlled on metformin/SU combination therapy</td>
<td>Treatment regimens containing insulin were associated with increased hypoglycaemia relative to comparators, but severe hypoglycaemia was rare across all treatments. RR (CI): basal insulin + Met + SU vs. Insulins (basal, biphasic, bolus), DPP-4 inhibitors, GLP-1 agonists and T2Ds (TZDs) all produced statistically significant reductions in HbA1c in combination with metformin and a SU (−0.89% to −1.17%), whereas Biphasic insulin, bolus insulin, and T2Ds were associated with weight gain (1.85–5.0 kg), whereas DPP-4 inhibitors and α-glucosidase inhibitors were weight-neutral, and GLP-1 agonists were associated with modest weight loss.</td>
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<tr>
<td>to combination metformin+SU</td>
<td>placebo + Met + SU: 2.03 (1.15–3.58); T2D + Met + SU vs. placebo + Met + SU: 5.62 (2.81–11.25); DPP-4 inhibitor + Met + SU vs. placebo + Met + SU: 2.07 (1.54–2.77); biphasic insulin + Met + SU vs. basal insulin + Met + SU: 4.01 (2.31–6.96); biphasic insulin + Met + SU vs. basal insulin + Met + SU: 2.12 (0.90–1.86); GLP-1 + Met + SU vs. basal insulin + Met + SU: 0.93 (0.62–1.39); bolus insulin + Met + SU vs. basal insulin + Met + SU 8.97 (4.34–18.56); biphasic insulin vs. basal insulin + Met + SU: 1.32 (0.86–2.03); GLP-1 + Met + SU vs. biphasic insulin + Met + SU: 0.33 (0.19–0.55); bolus insulin vs. biphasic insulin + Met + SU: 2.24 (0.99–5.05); biphasic insulin + Met vs. biphasic insulin + Met + SU 1.26 (0.76–2.09); biphasic insulin vs. GLP-1 + Met + SU: 3.87 (2.28–6.58); biphasic insulin vs. basal insulin + Met + SU: 1.50 (0.90–2.43); basal insulin + meglitinide vs. basal insulin + metformin: 0.92 (0.43–1.96); basal insulin vs. basal insulin + basal insulin: 1.14 (0.59–2.19); GLP-1 vs. basal insulin + Met: 0.94 (0.49–1.81);</td>
<td>meglitinides and α-glucosidase inhibitors did not.</td>
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</table>

**Gross [130] 2011**  
**Patients:** adults aged 18 years or older with T2DM and a HbA1c level greater than 7.0% (53 mmol/mol) who were already receiving a combination of metformin and a SU.  
**Comparisons:** Studies evaluated the effects of adding a third glycaemia lowering drug as compared to placebo or head to head.  
**Insulins caused twice the absolute number of severe hypoglycaemic episodes than noninsulin antihyperglycemic agents.**  
**Compared with placebo, drug classes did not differ in effect on HbA1c level (reduction ranging from 0.70% (credible interval (CrI) 1.33–0.08%) for acarbose to 1.08% (CrI 1.41–0.77%) for insulin).**  
**Compared with placebo, weight loss was seen with GLP-1 agonists (1.63 kg (CrI 2.71–0.60 kg)).**
<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Comparisons</th>
<th>Outcomes</th>
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</thead>
<tbody>
<tr>
<td>Phung [127] 2010</td>
<td>T2DM experiencing an inadequate response to maximized and stable (4 weeks at 1500 mg or maximally tolerated dose) metformin therapy</td>
<td>In mixed-treatment comparison meta-analysis, SU (RR, 4.57, CrI, 2.11-11.45) and glinide (RR, 7.50, CrI, 2.12-41.52) treatments were associated with increased risk of hypoglycaemia compared with placebo. TZDs (RR, 0.56, CrI, 0.19-1.69), α-glucosidase inhibitors (RR, 0.42; CrI, 0.01-9.00), DPP-4 inhibitors (RR, 0.63; CrI, 0.26-1.71), and GLP-1 analogs (RR, 0.89; CrI, 0.22-3.96) were not associated with increased risk of hypoglycaemia compared with placebo.</td>
<td></td>
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<tr>
<td>Esposito [274] 2012</td>
<td>T2DM</td>
<td>Drugs could be either used as monotherapy in drug naive patients, or add-on medication</td>
<td>Mean (SD) HbA1c decrease: insulin basal: −1.28 (0.36); biphasic −1.91 (0.64); prandial −1.08 (0.68); basal bolus −1.22 (0.58); GLP-1 agonists −1.12 (0.23); exenatide LAR −1.61 (0.16); DPP-4 inhibitors −0.74 (0.30); α-glucosidase inhibitor −0.72 (0.41); SUs −0.77 (0.29); glinides −0.64 (0.20); metformin −1.21 (0.48); Percentage attaining &lt;7% (53 mmol/mol) HbA1c (CI): insulin basal 38.9 (35.7–42.2); biphasic 34.4 (31.1–37.9); prandial 36.3 (26.3–47.7); basal bolus 50.2 (43.0–57.4); GLP-1 agonists 45.7 (42.2–49.2); exenatide LAR 63.2 (54.1–71.5); DPP-4 inhibitors 39.0 (35.7–42.3); α-glucosidase inhibitors 25.9 (18.5–34.9); SUs 48.2 (43.0–53.5); glinides 39.1 (29.3–49.9); metformin 42.0 (35.5–48.9)</td>
</tr>
<tr>
<td>Amori [118]</td>
<td>T2DM</td>
<td>Monotherapy and add-on therapy were considered</td>
<td>Glycemic efficacy: incretins lowered HbA1c compared with placebo: WMD −0.97% (CI −1.13% to −0.81%) for GLP-1 agonists and −0.74% (CI −0.85% to −0.62%) for DPP-4 inhibitor, and were non-inferior to other hypoglycaemic agents. GLP-1 agonists resulted in weight loss (1.4 kg and 4.8 kg vs. placebo and insulin, respectively) while DPP-4 inhibitors were weight neutral.</td>
</tr>
<tr>
<td>Study</td>
<td>Patients</td>
<td>Comparisons</td>
<td>Findings</td>
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<tr>
<td>Aroda [275]</td>
<td>Patients: T2DM who showed inadequate response to metformin monotherapy at randomisation (mean HbA1c ≥7.0% (53 mmol/mol)). Comparison: glycaemia lowering agents with either a placebo or another class of glycaemia lowering agents in addition to metformin; for at least 12 weeks, but no more than 52 weeks. Trials were excluded if they stopped metformin use or changed the metformin dose after randomisation.</td>
<td>The RR (CI) of hypoglycaemia with DPP-4 inhibitor treatment was 0.92 (0.74–1.15) compared to placebo, 0.20 (0.17–0.24) compared to SUs in the absence of SU or insulin co-therapy; when combined with SU or insulin, sitagliptin or linagliptin had a RR 1.86 (1.46–2.37) compared to placebo).</td>
<td>GLP-1 agonists resulted in greater decrease in HbA1c compared with SUs, glinides, TZDs, α-glucosidase inhibitors and DPP-4 inhibitors (−0.20% (CI −0.34 to −0.04%), −0.31% (CI −0.61 to −0.02%), −0.20% (CI −0.38 to −0.00), −0.36% (CI −0.64 to −0.07%), −0.32% (CI −0.47 to −0.17%), respectively) and was comparable with basal insulin and biphasic insulin. HbA1c decrease was greater for SUs compared with DPP-4 inhibitors (−0.12% (−0.23 to −0.03%), and for biphasic insulin compared with glinides (−0.36%, CI −0.82 to −0.11%).</td>
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<tr>
<td>Liu [128] 2012</td>
<td>Patients: T2DM who showed inadequate response to metformin monotherapy (mean HbA1c ≥7.0% (53 mmol/mol)).</td>
<td>Mean reductions of HbA1c (%) after adjustment for differences in baseline HbA1c by Bayesian analysis. Mean (CI): exenatide BID 1.08 (1.22–0.94); exenatide QW 1.54 (1.73–1.36); liraglutide once daily 1.22 (1.39–1.05); alogliptin 0.70 (0.90–0.50); linagliptin 0.60 (0.80–0.40); saxagliptin 0.71 (0.89–0.54); sitagliptin 0.70 (0.78–0.63); vildagliptin 0.98 (1.46–0.52).</td>
<td>Weight change: mean kg (CI): exenatide BID 1.94 (2.35–1.53); exenatide QW 2.41 (2.83–1.99); liraglutide once daily 1.66 (2.43–0.88); alogliptin 0.27 (0.87–0.34); saxagliptin 0.64 (1.11–0.16); sitagliptin 0.29 (0.61–0.03); vildagliptin 0.21 (0.84–0.42).</td>
</tr>
<tr>
<td>Belsey [276] 2008</td>
<td>Patients: T2DM inadequately controlled on metformin. Comparison: metformin plus SU. Other combinations of glycaemia lowering drugs and combination of metformin and SU.</td>
<td>The odds of experiencing a hypoglycaemic event was higher in SU-treated patients than in those on comparator treatments (RR 5.3, CI 1.7–16.3).</td>
<td>Based on random effects meta-analysis, the pooled estimate of change in HbA1c from baseline was 0.9% (CI 0.7–1.1) for change in FPG from baseline 1.8 mmol/l (CI 1.1–2.5).</td>
</tr>
<tr>
<td>Craddy [277] 2014</td>
<td>Patients: T2DM with inadequate glycemic control. Comparison: via meta-analysis DPP-4 inhibitors were compared as monotherapy, dual therapy (plus metformin, SU, pioglitazone, or insulin), and triple therapy (plus metformin/SU).</td>
<td>This systematic review demonstrated no differences between DPP-4 inhibitors in the proportions of patients experiencing a hypoglycaemic event.</td>
<td>No differences between DPP-4 inhibitors were seen in mean change from baseline in HbA1c. Patients on alogliptin plus metformin achieved HbA1c &lt;7% (53 mmol/mol) more frequently than those treated with saxagliptin plus metformin (odd ratio 6.41 (CI 3.15–11.98) vs. 2.17 (CI 1.56–2.95)).</td>
</tr>
<tr>
<td>Study</td>
<td>Patients</td>
<td>Comparisons</td>
<td>Hypoglycaemia with glucose ≤3.1 mmol/L or ≤2.8 mmol/L was experienced by 30.1% (CI 7.3–13.8%) and 5.9% (CI 2.5–13.4%) of patients with any SU treatment. Severe hypoglycaemia was experienced by 0.8% (CI 0.5–1.3%) of patients. Hypoglycaemia with glucose ≤3.1 mmol/L and severe hypoglycaemia occurred least frequently with gliclazide: in 1.4% (CI 0.8–2.4%) and 0.1% (CI 0–0.7%) of patients, respectively. Too few studies had insulin as comparator, so these data could not be meta-analysed. No data on hypoglycaemia episodes in patients on GLP-1 agonists are provided.</td>
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<tr>
<td>Schopman (280) 2014</td>
<td>Patients: T2DM</td>
<td>Comparisons: GLP-1 agonists or DPP-4 inhibitors with SUs, insulin glargine or pre-mixed insulin</td>
<td>Overall, hypoglycaemia was reported less in the GLP-1 group, (RR 0.45, CI 0.2–0.76, p &lt; 0.01), while there was no significant difference in occurrence of severe hypoglycaemia (0.65, CI 0.29–1.45, p= 0.29).</td>
</tr>
<tr>
<td>Vasilakou (282) 2013</td>
<td>Patients: patients with Type 2 diabetes</td>
<td>Comparisons: RCTs comparing SGLT2 with placebo or other medication for T2DM</td>
<td>The mean net change (CI) for weight loss for patients treated with GLP-1 agonists as compared with insulin was −4.40 kg (CI −5.23 to −3.56, p &lt; 0.01)</td>
</tr>
<tr>
<td>Wang (283) 2011</td>
<td>Patients: non-pregnant adults at least 18 years of age, with T2DM for at least 3 months, suboptimally controlled with oral agents (e.g. metformin and/or SU) with HbA1c levels between 7 and 11% (53–97 mmol/mol)</td>
<td>Comparisons: GLP-1 agonists (exenatide or liraglutide) with insulin</td>
<td>Overall, hypoglycaemia was reported less in the GLP-1 group, (RR 0.45, CI 0.2–0.76, p &lt; 0.01), while there was no significant difference in occurrence of severe hypoglycaemia (0.65, CI 0.29–1.45, p= 0.29).</td>
</tr>
</tbody>
</table>
| Study Authors | Study Year | Patients: T2DM | Comparisons: | Hypoglycaemia or Weight Loss
<table>
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<tbody>
<tr>
<td>Zhang [284]</td>
<td>2013</td>
<td>metformin vs. metformin+SU.</td>
<td>metformin vs. metformin+SU.</td>
<td>Hypoglycaemia was more frequent among patients treated with SUs plus metformin than metformin alone (RR = 6.79, CI 3.79–12.17)</td>
</tr>
<tr>
<td>Goossen [285]</td>
<td>2012</td>
<td>DPP-4 inhibitors compared to placebo, another gliptin or any other glycaemia lowering drug</td>
<td>DPP-4 inhibitors compared to placebo, another gliptin or any other glycaemia lowering drug</td>
<td>The RR of hypoglycaemia for DPP-4 inhibitor was 0.92 (CI 0.74, 1.15) compared to placebo, and 0.20 (CI 0.17-0.24) compared to SUs in the absence of SU or insulin co-therapy. It was significantly elevated for combination therapy of SU or insulin with sitagliptin or linagliptin (RR 1.86, CI 1.46-2.37 compared to placebo).</td>
</tr>
<tr>
<td>Wu [271]</td>
<td>2014</td>
<td>DPP-4 inhibitors plus metformin as initial combination therapy or as monotherapy compared to metformin monotherapy</td>
<td>DPP-4 inhibitors plus metformin as initial combination therapy or as monotherapy compared to metformin monotherapy</td>
<td>Compared with metformin monotherapy, DPP-4 inhibitor monotherapy was associated with lower reduction in HbA1c level (WMD=0.28%, CI 0.17-0.40, p&lt;0.00001). Compared with metformin monotherapy, DPP-4 inhibitors plus metformin as initial combination therapy was associated with greater reduction in HbA1c level (WMD =−0.49 CI −0.57 to −0.40, p&lt;0.00001). Compared with metformin monotherapy, DPP-4 inhibitor monotherapy was associated with lower weight loss (WMD=0.44, CI 0.22-0.67, p=0.0001).</td>
</tr>
</tbody>
</table>
### Chapter 2.3 supplementary data extraction table: systematic review of case reports on metformin associated lactic acidosis

<table>
<thead>
<tr>
<th>Author &amp; year</th>
<th>No. of reported cases</th>
<th>Manifestations</th>
<th>Cause of metformin overload</th>
<th>Dose/serum level of metformin (mcg/ml)</th>
<th>Relevant Comorbidities and medication</th>
<th>Renal function</th>
<th>Cause of AKI (if applicable)</th>
<th>Casual relationship?</th>
<th>Lactate level (mmol/l)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perrone[287], 2011</td>
<td>Case 1: 40 years, F</td>
<td>Case 1: unremarkable except mild lethargy, BP = 126/49 mmHg, HR = 79 b/min. Within 8 h of her arrival, the patient vomited multiple times and had become more lethargic. Case 2: Kussmaul respiration, dry mucous membranes, diffuse rhonchi, mild abdominal tenderness. Oral temperature 36.2°C, BP = 151/85 mmHg, HR 100 beats/min, 32 breaths/min. Case 3: complaint of dyspnea</td>
<td>Case 1: suicide attempt</td>
<td>Case 1: serum level=150 Case 2: SL=27.4 Case 3: NS</td>
<td>Case 1: overdose of sertraline, risperdone, hydrochlorothiazide and metformin/glyburide Case 2: Case 2: amiodarone, valsartan, clonidine, gabapentin, atorvastatin,amlodipine,furosemide,omeprazole,metformin/glyburide multiple conditions Case 3: HTN</td>
<td></td>
<td>Case 1: NS Case 2: ESRD Case 3: ESRD</td>
<td></td>
<td>Case 1: death Case 2: survived Case 3: death</td>
<td></td>
</tr>
<tr>
<td>Aperis[288], 2011</td>
<td>1, 74 years, M</td>
<td>Zoster-like abdominal pain, tachypnea,</td>
<td>UTR</td>
<td>NS</td>
<td>HIV infection, CAD Tenofovir, Emtricitabine, Efavirenz</td>
<td>AKI</td>
<td></td>
<td>Probably, Metformin = antiretroviral treatment</td>
<td>NS, just LA</td>
<td>survived</td>
</tr>
<tr>
<td>Authors</td>
<td>Year</td>
<td>Age</td>
<td>Gender</td>
<td>Symptoms/Findings</td>
<td>Diagnosis/Interpretation</td>
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<tr>
<td>Gamst[289], 2010</td>
<td>1</td>
<td>61</td>
<td>M</td>
<td>nausea and vomiting, hypotension, tachycardia, dehydration and oliguria</td>
<td>NS, obesity NS, Maybe, MALA should be suspected in therapy-resistant LA NS, just severe LA after resuscitation death</td>
<td></td>
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<tr>
<td>Dell’Aglio[290], 2010</td>
<td>1</td>
<td>40</td>
<td>F</td>
<td>At arrival: awake; soon hypotensive (91/54 mm Hg) and somnolent</td>
<td>Suicide attempt 75–100 g ingested metformin; SL=160 AKI (Crea rose from 1.5 mg/dl to 2.0 mg/dl, 2.3 mg/dl at discharge) Metformin-induced hypoperfusion Most likely 40 survived</td>
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<tr>
<td>Arroyo[291], 2010</td>
<td>1</td>
<td>49</td>
<td>F</td>
<td>presented 1 hour after ingestion, awake and alert</td>
<td>Suicide attempt 30g of ingested metformin; SL=380 HTN Hydrochlorothiazide 12, 5 mg + Lisinopril 20 mg–20 combination tablets AKI Crea=1.2 mg/dl Interfering RAAS system medication Possibly 9.6 death</td>
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<tr>
<td>Mizzi[292], 2009</td>
<td>1</td>
<td>53</td>
<td>M</td>
<td>Cardiac arrest</td>
<td>metformin 850 mg TID multiple coronary stenting, hypertension, atrial fibrillation AKI (serum crea = 3 mg/dl 30 days before and 13 mg/dl at admission) NS ? 30 death</td>
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<tr>
<td>Jung[293], 2009</td>
<td>1</td>
<td>51</td>
<td>M</td>
<td>progressive dysarthria and the new onset of gait disturbance and myoclonus</td>
<td>UTR 850 mgx2/day for the last 3 months chronic lung disease Insulin, amlodipine 10mg/day, aspirin 100 mg/day, ESRD - Most likely Not reported Improvement of encephalopathy after metformin was stopped</td>
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<tr>
<td>Van der Linden[294], 2007</td>
<td>1</td>
<td>85</td>
<td>F</td>
<td>NS Multiple conditions</td>
<td>Normal crea, but eGFR=23 ml/min/1.73 m² ? (Probably not) Not reported Death from post-op complications (initially, bowel ischemia was suspected)</td>
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<tr>
<td>Di Grande[295], 2008</td>
<td>I</td>
<td>NS</td>
<td>NS</td>
<td>Malaise and severe weakness tachypnea (Kussmaul's respiration), agitated</td>
<td>AKI (crea=9.75 mg/dl) history of dehydration due to diarrhea Maybe 15 survived</td>
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<tr>
<td>Ortega[296], 2007</td>
<td>Case 1: F, 58 years</td>
<td>Case 1: Pain in the popliteal space, vomiting for 48 hours. Case 2: abdominal pain, nausea, vomiting, anuria, dyspnea and chest pain. Case 3: abdominal pain and vomiting for 5 days + sudden severe dizziness and anuria – acute pancreatitis Case 4: general malaise, anuria, dyspnea, 3 episodes of diarrhea 2 days before Case 5: abdominal pain, vomiting and diarrhea for 3 days</td>
<td>Case 1: UTR Case 2: UTR Case 3: UTR Case 4: UTR Case 5: UTR Case 6: UTR</td>
<td>Case 1: 850 mg/12 h Case 2: 850 mg/12 h Case 3: 850 mg/8 h Case 4: 850 mg/8 h Case 5: NS Case 6: 850 mg/12 h</td>
<td>Case 1: HTN, dyslipidemia, hyperuricemia, CHF, depression + deep venous thrombosis; Insulin, enoxaparin, torsemid, enalapril, allopurinol, mirtazapin, digoxin Case 2: acute MI 13 days before and coronaryography + PTCA 5 days before diltiazem, aspirin, enoxaparin trimetazidine, nitroglycerine and torasemis between MI and PTCA intervention; aspirin, ramipril, clopidogrel, diltiazem and glibenclamide. Case 3: glibenclamide Case 4: hypertension, chronic bronchitis, dyslipidemia, acute urinary retention 3 weeks before metastatized prostate cancer gliclazide, nebivolol, tamsulosin, metamizol, acetaminophen. Case 5: hypertension, hypothyroidism, captopril, levothyroxine and for 15 days: diclofenac, naproxen, rofecoxib Case 6: HTN rbesartan, amlodipine</td>
<td>Case 1: AKI (oligo anuria, crea = 9.4 mg/dl) Case 2: AKI (anuria, crea = 11.6 mg/dl) Case 3: AKI (anuria, crea = 7 decreasing during hospitalization) Case 4: AKI (crea = 10.3 mg/dl at admission normalized at discharge) Case 5: AKI (crea = 8.6 mg/dl at admission and 1.2 mg/dl at discharge) Case 6: AKI (crea = 10 mg/dl at admission and 2.2 mg/dl in 12 hours after admission)</td>
<td>Case 1: NS, but probably due to unadjusted metformin dosage in accordance to the “polypharmacy” status of the patient. Case 2: CIN Case 3: NS, but probably due to continuation of metformin and glibenclamide in conditions of abdominal compartment syndrome and release of pancreatic amylase leading to decreased renal perfusion pressure. Case 4: continuation of habitual treatment in condition of anuria (acute urine</td>
<td>Case 1: AKI (oligo anuria, crea = 9.4 mg/dl) Case 2: AKI (anuria, crea = 11.6 mg/dl) Case 3: AKI (anuria, crea = 7 decreasing during hospitalization) Case 4: AKI (crea = 10.3 mg/dl at admission normalized at discharge) Case 5: AKI (crea = 8.6 mg/dl at admission and 1.2 mg/dl at discharge) Case 6: AKI (crea = 10 mg/dl at admission and 2.2 mg/dl in 12 hours after admission)</td>
<td>Case 1: NS, but probably due to unadjusted metformin dosage in accordance to the “polypharmacy” status of the patient. Case 2: CIN Case 3: NS, but probably due to continuation of metformin and glibenclamide in conditions of abdominal compartment syndrome and release of pancreatic amylase leading to decreased renal perfusion pressure. Case 4: continuation of habitual treatment in condition of anuria (acute urine</td>
<td>Case 1: not reported Case 2: not reported Case 3: not reported Case 4: not reported Case 5: not reported Case 6: not reported</td>
</tr>
<tr>
<td>Name</td>
<td>Year</td>
<td>Age, Gender</td>
<td>Symptoms, Treatments</td>
<td>Outcome</td>
<td>Other Notes</td>
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<tr>
<td>Gudmundsdottir[297], 2006</td>
<td>5</td>
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<td>Case 6: severe diarrhea and vomiting for one week (acute pancreatitis)</td>
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<td>Case 5: NSAIDs therapy Case 6: acute pancreatitis retention)</td>
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<tr>
<td>Alivanis[298], 2006</td>
<td>1, 70 years, M</td>
<td></td>
<td>Malaise, respiratory distress, myalgia, desorientatio n, abdominal discomfort, increasing somnolence.</td>
<td>Between 14 and 23</td>
<td>Survived</td>
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<tr>
<td>Von Mach[299], 2004</td>
<td>1, 64 years, F (+ a retrospective analysis of other 14 cases)</td>
<td></td>
<td>Cardiac arrest NS</td>
<td>?</td>
<td>Complete recovery</td>
<td></td>
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<tr>
<td>Pertek[300], 2003</td>
<td>1, 65 years, F</td>
<td></td>
<td>Acute abdominal pain, 48 h of anuria, vomiting, tachypnea</td>
<td>12.4</td>
<td>Survived</td>
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<tr>
<td>Berner[301], 2002</td>
<td>1, 83 years</td>
<td></td>
<td>Impaired consciousness, Kussmaul breathing, hypothermia 32.1 C, hemodynamic instability</td>
<td>Most likely 24.4</td>
<td>Survived</td>
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<tr>
<td>Barrueto[302], 2002</td>
<td>1, 58 years, Lethargy, hypotension, Suicide attempt</td>
<td></td>
<td>Metformin 20 g ingested; HTN, bipolar disease, CKD20 tablets of 240 mg/tablet of</td>
<td>22.8</td>
<td>Death</td>
<td></td>
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<td></td>
<td>CKD (baseline crea = 1.7)</td>
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<tr>
<td>Study</td>
<td>Gender</td>
<td>Age</td>
<td>Presenting Symptoms</td>
<td>Labs</td>
<td>Diagnoses</td>
<td>Medical Management</td>
<td>Outcome</td>
<td>Comments</td>
<td></td>
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<tr>
<td>Reeker[303], 2000</td>
<td>M</td>
<td>62y</td>
<td>Bradycardia</td>
<td>SL=110</td>
<td>Diltiazem</td>
<td>Mg/dl, with an increase to 2.5 mg/dl within 5 hours</td>
<td>-</td>
<td>Probably 45.3 survived</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Houwerzijl[304], 2000</td>
<td>F</td>
<td>52y</td>
<td>Unconsciousness, abdominal complaints and dyspnea</td>
<td>NS</td>
<td>Chronic alcoholism, liver function disorders</td>
<td>NS</td>
<td>? metformin consumption in association with acute alcohol intoxication</td>
<td>NS</td>
<td>death</td>
<td></td>
</tr>
<tr>
<td>Doorenbos[305], 2001</td>
<td>F</td>
<td>66y</td>
<td>Somnolent, BP = 105±80 mmHg, HR = 100 bpm, abdominal pain</td>
<td>850 mg x 3/day for the past 7 months; SL=19.4 mg/l</td>
<td>HTN, CKD (baseline creat=236 micromol/l) Insulin, ACE-I</td>
<td>AKI (crea =640 micromole/l) Dehydration due to extreme vomiting</td>
<td>Most likely</td>
<td>13.5 survived</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jain[40], 2001</td>
<td>M</td>
<td>47y</td>
<td>Severe headache and transient loss of consciousness on the previous day</td>
<td>500 mg x 2/day for the past 3 years</td>
<td>Acute subarachnoid hemorrhage Glyburide 5mg/day</td>
<td>AKI Crea = 0.25 mmol L⁻¹ CIN</td>
<td>Maybe (MALA was an exclusion diagnosis)</td>
<td>7.3</td>
<td>death</td>
<td></td>
</tr>
<tr>
<td>Kruse[306], 2001</td>
<td>F</td>
<td>76y</td>
<td>Nausea, anorexia, vague abdominal pain, and malaise</td>
<td>850 mg x 2/day for the past 3 years; SL=31.5</td>
<td>HTN, CKD (baseline creat=2.6 mg/dl), coronary artery bypass surgery after myocardial infarction, Helicobacter pylori infection Diltiazem, clonidine, oral nitroglycerine, lansoprazole, amoxicillin, clarithromycin</td>
<td>AKI (crea=7 mg/dl) dehydration related to preparation for the endoscopic procedure done a week</td>
<td>Probably</td>
<td>16.6 survived</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient Name</td>
<td>Gender</td>
<td>Age</td>
<td>Diagnosis</td>
<td>Medications</td>
<td>Kidney Function</td>
<td>Cause of AKI</td>
<td>Outcome</td>
<td>Follow-up</td>
<td></td>
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<tr>
<td>Schmidt[307], 2005</td>
<td>F</td>
<td>75 years</td>
<td>Gallstone disease, HTN, acute abscess formation from perforated gall bladder</td>
<td>Oral diclofenac 500 mg x 3/day for 5 days + rectal diclofenac</td>
<td>Previous normal renal function; AKI (crea=980 micromol/l)</td>
<td>Renal function-interfering medication; mixed metabolic acidosis</td>
<td>Survived</td>
<td>10 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schmidt[308], 1997</td>
<td>F</td>
<td>62 years</td>
<td>Gallstone disease, HTN, acute abscess formation from perforated gall bladder</td>
<td>Oral diclofenac 500 mg x 3/day for 5 days + rectal diclofenac</td>
<td>Previous normal renal function; AKI (crea=980 micromol/l)</td>
<td>Renal function-interfering medication; mixed metabolic acidosis</td>
<td>Survived</td>
<td>10 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shenoy[309], 2006</td>
<td>M</td>
<td>48 years</td>
<td>Gallstone disease, HTN, acute abscess formation from perforated gall bladder</td>
<td>Oral diclofenac 500 mg x 3/day for 5 days + rectal diclofenac</td>
<td>Previous normal renal function; AKI (crea=980 micromol/l)</td>
<td>Renal function-interfering medication; mixed metabolic acidosis</td>
<td>Survived</td>
<td>10 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yang[310], 2009</td>
<td>F</td>
<td>43 years</td>
<td>Gallstone disease, HTN, acute abscess formation from perforated gall bladder</td>
<td>Oral diclofenac 500 mg x 3/day for 5 days + rectal diclofenac</td>
<td>Previous normal renal function; AKI (crea=980 micromol/l)</td>
<td>Renal function-interfering medication; mixed metabolic acidosis</td>
<td>Survived</td>
<td>10 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Althof[311], 1978</td>
<td></td>
<td>9</td>
<td>Gallstone disease, HTN, acute abscess formation from perforated gall bladder</td>
<td>Oral diclofenac 500 mg x 3/day for 5 days + rectal diclofenac</td>
<td>Previous normal renal function; AKI (crea=980 micromol/l)</td>
<td>Renal function-interfering medication; mixed metabolic acidosis</td>
<td>Survived</td>
<td>10 days</td>
<td></td>
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</tr>
<tr>
<td>Bjarnason[312], 1974</td>
<td></td>
<td>74</td>
<td>Gallstone disease, HTN, acute abscess formation from perforated gall bladder</td>
<td>Oral diclofenac 500 mg x 3/day for 5 days + rectal diclofenac</td>
<td>Previous normal renal function; AKI (crea=980 micromol/l)</td>
<td>Renal function-interfering medication; mixed metabolic acidosis</td>
<td>Survived</td>
<td>10 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year</td>
<td>Duration</td>
<td>Gender</td>
<td>Symptoms</td>
<td>Treatment</td>
<td>Complications</td>
<td>Outcome</td>
<td></td>
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<tr>
<td>2006</td>
<td>5 years, M</td>
<td></td>
<td></td>
<td></td>
<td>media induced nephrotoxicity</td>
<td>?</td>
<td></td>
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<tr>
<td>Brouwers [313], 2009</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>?</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Chang [314], 2002</td>
<td>5</td>
<td></td>
<td>2 suicide attempts</td>
<td></td>
<td>Case 1-4: normal renal function</td>
<td>?</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Chu [315], 2003</td>
<td>1, 75 years, F</td>
<td></td>
<td>vomiting, diarrhea, hypothermia, hypotension and transitory sudden blindness</td>
<td>HTN and diabetic foot for 2 years, amiodipine, furosemide, gliclazide, spironolactone, pentoxifylline, magnesium oxide</td>
<td>AKI (baseline crea =1.2 mg/dl to 7.7 mg/dl at admission and 1.3 mg/dl at discharge)</td>
<td>MALA</td>
<td>Probably</td>
<td>12.6</td>
<td>survived</td>
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</tr>
<tr>
<td>De Pont [316], 2007</td>
<td>1, 39 years, F</td>
<td></td>
<td>Suicide attempt</td>
<td></td>
<td></td>
<td>?</td>
<td>death</td>
<td></td>
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<tr>
<td>De Palo [317], 2005</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>?</td>
<td></td>
<td></td>
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<tr>
<td>El-Hennawy [318], 2007</td>
<td>1</td>
<td></td>
<td>a 9-day history of weakness, nausea, dizziness, and difficulty moving</td>
<td></td>
<td>AKI</td>
<td>Dehydration due to diarrhea + poor oral intake</td>
<td></td>
<td></td>
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<tr>
<td>Gan [319], 1992</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>ESRD</td>
<td>10.9</td>
<td>survived</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hermann [320], 1981</td>
<td>1</td>
<td></td>
<td>HF Digitalis intoxication</td>
<td>Impaired renal function</td>
<td></td>
<td>death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jurovich [321], 1997</td>
<td>1, 67 years, M</td>
<td></td>
<td></td>
<td></td>
<td>AKI</td>
<td></td>
<td></td>
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<tr>
<td>Lalau [322], Westel 1987</td>
<td>Case 1: 70 years, F</td>
<td></td>
<td>collapse and coma</td>
<td>Case 1: serum crea = 600 micromoll/l at admission</td>
<td></td>
<td>Case 1: survived</td>
<td></td>
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<tr>
<td></td>
<td>Case 2: 48 years, M</td>
<td></td>
<td>scrotal abscess</td>
<td>Case 2: AKI - dehydration (vomiting + diarrhea)</td>
<td>Case 1: yes</td>
<td>Case 1: 18.4</td>
<td>Case 2: survived</td>
<td></td>
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<td></td>
<td>Case 4: NS</td>
<td></td>
<td>Case 4: NS</td>
<td>Case 3: AKI</td>
<td>Case 3: yes</td>
<td>Case 3: 12.7</td>
<td>Case 4: survived</td>
<td></td>
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<tr>
<td></td>
<td>Case 5: UTR</td>
<td></td>
<td>Case 5: NS</td>
<td>Case 4: AKI</td>
<td>Case 4: yes</td>
<td>Case 4: 14.2</td>
<td>Case 5: survived</td>
<td></td>
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<tr>
<td></td>
<td>Case 6: UTR</td>
<td></td>
<td>Case 6: NS</td>
<td>Case 5: NS</td>
<td>Case 5: yes</td>
<td>Case 5: 16.3</td>
<td></td>
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</tr>
<tr>
<td>Case</td>
<td>Age</td>
<td>Sex</td>
<td>Diagnosis</td>
<td>Treatment</td>
<td>Admission Crea</td>
<td>Discharge Crea</td>
<td>Outcome</td>
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<tr>
<td>Case 1:</td>
<td>76 years, F</td>
<td></td>
<td>General malaise, APACHE II score = 35</td>
<td></td>
<td>79 μmol/l</td>
<td>254 μmol/l</td>
<td>survived</td>
<td></td>
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<tr>
<td>Case 2:</td>
<td>73 years, M</td>
<td></td>
<td>Vomiting, confusion, APACHE II score = 33</td>
<td></td>
<td>166 μmol/l</td>
<td>209 μmol/l</td>
<td>survived</td>
<td></td>
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<tr>
<td>Case 3:</td>
<td>63 years, F</td>
<td></td>
<td>Diarrhoea, vomiting, cardiac arrest, APACHE II score = 44</td>
<td></td>
<td>76 μmol/l</td>
<td>113 μmol/l</td>
<td>died</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Case 4:</td>
<td>77 years, F</td>
<td></td>
<td>Diarrhoea, vomiting, malaise</td>
<td></td>
<td>79 μmol/l</td>
<td>254 μmol/l</td>
<td>survived</td>
<td></td>
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<tr>
<td>Case 5:</td>
<td>61 years, M</td>
<td></td>
<td>Vigil coma + AKI (renal + ureteral lithiasis on unique kidney)</td>
<td></td>
<td>846 μmol/l</td>
<td>210 μmol/l</td>
<td>survived</td>
<td></td>
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<tr>
<td>Case 6:</td>
<td>83 years, M</td>
<td></td>
<td></td>
<td></td>
<td>&gt; 2000 μmol/l</td>
<td>110 μmol/l</td>
<td>survived</td>
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<tr>
<td>Case 7:</td>
<td>55 years, M</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>survived</td>
<td></td>
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<tr>
<td>Case 8:</td>
<td>85 years, F</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>survived</td>
<td></td>
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<tr>
<td>Case 9:</td>
<td>79 years, F</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>survived</td>
<td></td>
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<tr>
<td>Case 10:</td>
<td>72 years, F</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>survived</td>
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</tbody>
</table>

**Notes:**
- Case 1: ARBs
- Case 2: NSAID
- Case 3: IV contrast 5 days before admission
- Case 4: ARBs
- Case 5: ARBs
- Case 6: ACEIs, NSAIDs
- Case 7: NSAID
- Case 8: ARBs
- Case 9: NSAIDs
- Case 10: NSAID

**Diagnosis:**
- Renal insufficiency
- AKI

**Other Information:**
- Seven had a clear history of diarrhoea and/or vomiting, while two had vague malaise, and one was hypothermic and unconscious.
- APACHE II score was recorded for all cases.
- Hypovolemia induced by vomiting or diarrhoea + continuation of renal function-interfering medication.
| Case 8: 70 years, F | APACHE II score = 33  
Case 5: Diarrhoea, lethargy, APACHE II score = 21  
Case 6: Vomiting, abdominal pain, APACHE II score = 32  
Case 7: Unconscious, hypothermia, APACHE II score = 29  
Case 8: Lethargy, drowsiness, APACHE II score = 24  
Case 9: Vomiting, collapse, APACHE II score = 30  
Case 10: Diarrhoea, vomiting, APACHE II score = 27 | crea = 316 μmol/l  
Case 6: admission crea = 151 μmol/l; discharge crea = 139 μmol/l  
Case 7: admission crea = 91 μmol/l; discharge crea = 76 μmol/l  
Case 8: admission crea = 74 μmol/l; discharge crea = 154 μmol/l  
Case 9: admission crea = 87 μmol/l; discharge crea = 144 μmol/l  
Case 10: admission crea = 77 μmol/l; discharge crea = 55 μmol/l |
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</thead>
<tbody>
<tr>
<td>Case 9: 57 years, M</td>
<td>Case 10: 58 years, F</td>
<td></td>
</tr>
</tbody>
</table>
| Case 1: 48 years, M  
Case 2: the same with case 2 (Lalau, 1987) | Case 1: UTR  
Case 1: vomiting, urinary infection, fever, haematemesis | Case 1: NS  
Case 1: serum crea = 130 micromoll/l  
Case 1: moderate AKI at admission (infection + dehydration)  
Case 1: yes  
Case 1: 1700 mg/day  
Case 1: survived  
Case 1: 18.42 |

F= female; M=male; NS= not stated; LA=lactic acidosis; MALA = metfMALA= Metformin-associated lactic acidosis; LA=lactic acidosis, BP=blood pressure; HR=hear rate; CAD=coronary artery disease; CHF=chronic heart failure; HTN=hypertension; CHD=coronary heart disease; TID=total ingested dose; CKD=chronic kidney disease; ESRD=end-stage renal disease; PD=peritoneal dialysis; AKI=acute kidney injury; UTR= Usual Treatment Regimen; CIN: contrast induced nephropathy; therapeutic metformin serum
level = 1-2 microgr/ml. Studies in italic are published in non-English language.
Chapter 3: Issues related to management of cardiovascular risk in patients with diabetes and CKD stage 3b or higher (eGFR<45ml/min)
Chapter 3.1: In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²) and coronary artery disease, is PCI or CABG or conservative treatment to be preferred?

<table>
<thead>
<tr>
<th>Study</th>
<th>Title</th>
<th>Design</th>
<th>Summary conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aoki [325] 2002</td>
<td>Coronary revascularization improves long-term prognosis in diabetic and non-diabetic end-stage renal disease</td>
<td>Cohort study, 121 patients, CABG vs PCI, Diabetes vs non-diabetes</td>
<td>Complete revascularization improves long-term survival in both diabetic and non-diabetic patients</td>
</tr>
<tr>
<td>Ferguson[326] 1999</td>
<td>Outcome After Myocardial Revascularization and Renal Transplantation</td>
<td>Cohort study, 83 transplant patients, CABG vs PCI</td>
<td>PTCA and CABG posed little risk for renal allograft loss</td>
</tr>
<tr>
<td>Sedlis[327] 2009</td>
<td>Optimal medical therapy with or without percutaneous coronary intervention for patients with stable coronary artery disease and chronic kidney disease</td>
<td>Post hoc analysis of the COURAGE study; 2,287 patients, stable CAD patients with and without CKD randomized to percutaneous coronary intervention (PCI) and optimal medical therapy (OMT) or OMT alone</td>
<td>PCI did not reduce the risk of death or myocardial infarction when added to OMT for patients with CKD, it also was not associated with worse outcomes in this high-risk group.</td>
</tr>
<tr>
<td>Hachinohe[328] 2011</td>
<td>Management of non-ST-segment elevation acute myocardial infarction in patients with chronic kidney disease (from the Korea Acute Myocardial Infarction Registry)</td>
<td>Registry Korean Study: 5,185 patients in total, early invasive (EI), deferred invasive (DI), and conservative strategies in patients with acute non-ST-segment elevation myocardial infarction (NSTEMI) and chronic kidney disease (CKD).</td>
<td>At 1-year follow-up, mortality rates in the conservative group were significantly higher than in the invasive groups except for the severe CKD group. The benefit of the EI over the DI strategy, although there were no significant differences between the 2 groups, tended to decrease as renal function decreased</td>
</tr>
<tr>
<td>Herzog[150] 2002</td>
<td>Comparative survival of dialysis patients in the United States after coronary angioplasty, coronary artery stenting, and coronary artery bypass surgery and impact of diabetes</td>
<td>Registry data to compare the long-term survival of dialysis patients in the United States after PTCA, coronary stenting, or CABG</td>
<td>Dialysis patients in the United States had better long-term survival after CABG surgery than after percutaneous coronary intervention. Stent outcomes were relatively worse in diabetic patients (CABG 19% survival advantage vs PTCA only)</td>
</tr>
<tr>
<td>Chang[151] 2012</td>
<td>Multivessel Coronary Artery Bypass Grafting Versus Percutaneous Coronary Intervention in ESRD</td>
<td>CABG vs PCI; US Registry data; cohort of 21,981 patients on maintenance dialysis;</td>
<td>CABG compared with PCI associated with significantly lower risks for both death (HR=0.87, 95% CI=0.84–0.90) and the composite of death or myocardial infarction (HR=0.88, 95% CI=0.86–0.91). We found no evidence that age, race, diabetes, duration of ESRD, MI on index presentation, dialysis modality, stent era, or index year significantly modified the association of CABG and PCI on death</td>
</tr>
<tr>
<td>Farkouh[329] 2012</td>
<td>Strategies for Multivessel Revascularization in Patients with Diabetes</td>
<td>Randomized trial, patients with diabetes and multivessel coronary artery disease to undergo either PCI with drug-eluting stents or CABG, 1900 patients</td>
<td>For patients with diabetes and advanced coronary artery disease, CABG was superior to PCI in that it significantly reduced rates of death and myocardial infarction, with a higher rate of stroke. Subgroup analysis of 129 patients, no difference between CABG vs PCI</td>
</tr>
</tbody>
</table>
Chapter 3.2.

In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²) and with a cardial indication (heart failure, ischemic heart disease, hypertension) should we prescribe inhibitors of the RAAS system or aldosteron-antagonists as cardiovascular prevention?

Baseline data of included studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>Intervention</th>
<th>Control group</th>
<th>Study duration (weeks)</th>
<th>Total no of patients</th>
<th>Mean age (years)</th>
<th>Men (%)</th>
<th>Baseline renal function – intervention group</th>
<th>Type of DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fogari et al[330], 1999</td>
<td>Ramipril</td>
<td>Nitrendipine</td>
<td>96</td>
<td>107</td>
<td>58 ± 1</td>
<td>100</td>
<td>Serum creatinine (mg/dl): 2.0 ± 0.4; CrCl (ml/min/1.73 m²): 44.4 ± 8; UAE (g/24 h): 0.79 ± 0.04</td>
<td>- *</td>
</tr>
<tr>
<td>Lewis et al.[155], 2001 (IDNT)</td>
<td>Irbesartan</td>
<td>Placebo; Amlodipine</td>
<td>124.8</td>
<td>1715</td>
<td>59.3 ± 7.1</td>
<td>66.4</td>
<td>Serum creatinine (mg/dl): 1.67 ± 5.4; UPE (g/24 h): 2.9 (iqr 1.6 to 5.4)</td>
<td>- *</td>
</tr>
<tr>
<td>Brenner et al[162], 2001 (RENAAL)</td>
<td>Losartan</td>
<td>Placebo</td>
<td>163.2</td>
<td>1513</td>
<td>60 ± 7</td>
<td>63.1</td>
<td>Serum creatinine (mg/dl): 1.9 ± 0.5</td>
<td>- *</td>
</tr>
<tr>
<td>Suzuki et al[331], 2002</td>
<td>Benazepril</td>
<td>Placebo</td>
<td>48</td>
<td>72</td>
<td>NS</td>
<td>38.8</td>
<td>UPE (g/24 h): 1.2 ± 0.6</td>
<td>- *</td>
</tr>
<tr>
<td>Tong et al.[160], 2006</td>
<td>Fosinopril</td>
<td>Placebo</td>
<td>73.7</td>
<td>38</td>
<td>65 ± 6</td>
<td>65.7</td>
<td>Serum creatinine (mg/dl): 2.07 ± 0.53; CrCl (ml/min/1.73 m²): 34.8 ± 9.8; UAE (g/24 h): 1.52 (iqr 0.19 to 4.6)</td>
<td>- *</td>
</tr>
<tr>
<td>Guo et al[332], 2009</td>
<td>Losartan</td>
<td>Amlodipine</td>
<td>24</td>
<td>41</td>
<td>59.2 ± 7.0</td>
<td>43.9</td>
<td>eGFR (ml/min/1.73 m²): 53.65 ± 7.70; UPE (g/24 h): 1.80 (iqr 0.8 to 3.6)</td>
<td>- *</td>
</tr>
<tr>
<td>Heerspink et al[333], 2010 (ADVANCE)</td>
<td>Perindopril-Indapamide</td>
<td>Placebo</td>
<td>206.4</td>
<td>2033</td>
<td>68.3 ± 6.4</td>
<td>42.5</td>
<td>NS</td>
<td>- *</td>
</tr>
<tr>
<td>Shahinfar et al[334], 2002 (RENAAL)</td>
<td>Losartan</td>
<td>Placebo</td>
<td>163.2</td>
<td>1513</td>
<td>60 ± 7</td>
<td>63.1</td>
<td>Serum creatinine (mg/dl): 1.9 ± 0.5</td>
<td>- *</td>
</tr>
<tr>
<td>Berl et al.[335], 2003 (IDNT)</td>
<td>Irbesartan</td>
<td>Placebo; Amlodipine</td>
<td>124.8</td>
<td>1715</td>
<td>59.3 ± 7.1</td>
<td>66.4</td>
<td>Serum creatinine (mg/dl): 1.67 ± 5.4; UPE (g/24 h): 2.9 (iqr 1.6 to 5.4)</td>
<td>- *</td>
</tr>
<tr>
<td>Rahman et al.[158], 2005 (ALLHAT)</td>
<td>Lisinopril</td>
<td>Chlortalidone; Amlodipine</td>
<td>288</td>
<td>1888</td>
<td>70.6 ± 7.9</td>
<td>NS</td>
<td>eGFR (ml/min/1.73 m²): 49.2 ± 9.0</td>
<td>- *</td>
</tr>
<tr>
<td>Saruta et al.[336], 2009 (CASE-J)</td>
<td>Candesartan</td>
<td>Amlodipine</td>
<td>153.6</td>
<td>2390</td>
<td>65.6 ± 10.3</td>
<td>51.7</td>
<td>NS</td>
<td>- *</td>
</tr>
<tr>
<td>Outcome</td>
<td>Trials reporting &gt; 1 event/total no of trials included</td>
<td>No of patients included</td>
<td>Median treatment duration (weeks)</td>
<td>Relative effect</td>
<td>95% CI</td>
<td>Quality of evidence*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>--------------------------------------------------------</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1. All-cause mortality (overall)</td>
<td>3/4</td>
<td>5309</td>
<td>135.6</td>
<td>0.97</td>
<td>0.85 to 1.10</td>
<td>moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. CV mortality (only patients with diabetes)</td>
<td>2/2</td>
<td>3748</td>
<td>165.6</td>
<td>1.03</td>
<td>0.75 to 1.41</td>
<td>low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Non-fatal CV events (overall)</td>
<td>3/3</td>
<td>138</td>
<td>161.6</td>
<td>0.90</td>
<td>0.81 to 1.00</td>
<td>low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Need for RRT/doubling of serum creatinine (overall)</td>
<td>3/5</td>
<td>5202</td>
<td>139.5</td>
<td>0.81</td>
<td>0.70 to 0.92</td>
<td>moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. eGFR/CrCl (ml/min/1.73 m2)—end of treatment (overall)</td>
<td>4/4</td>
<td>2074</td>
<td>120.4</td>
<td>-0.09</td>
<td>-2.75 to 2.57</td>
<td>very low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Total no of reported adverse events (overall)</td>
<td>2/2</td>
<td>1822</td>
<td>110.4</td>
<td>1.05</td>
<td>0.89 to 1.25</td>
<td>low</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Chapter 3.3

In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²), should we prescribe Beta Blockers to prevent sudden cardiac death

<table>
<thead>
<tr>
<th>Study</th>
<th>-Publication Year -Time Frame -Location</th>
<th>Design</th>
<th>-Inclusion criteria -Exclusion criteria</th>
<th>Patients’ characteristics</th>
<th>-Intervention (n=) -Comparator (n=) -Duration</th>
<th>Outcome(s)</th>
<th>Results</th>
<th>Quality of evidence</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castagno[176]</td>
<td>-2010 -NR -Global</td>
<td>Randomised controlled trial</td>
<td>- Aged 18-80 years with a left-ventricular ejection fraction of 35% or less. Symptoms had to include dyspnoea on exertion, orthopnoea, or paroxysmal nocturnal dyspnoea, with or without oedema, and fatigue, corresponding to class III or IV of the New York Heart Association. -uncontrolled hypertension, myocardial infarction or unstable angina pectoris in the previous 3 months, percutaneous transluminal coronary angioplasty or coronary-artery bypass graft in the previous 6 months, previous or scheduled heart transplant, atrioventricular block greater than first degree without a chronically implanted pacemaker, resting heart rate of less than 60 beats per min, systolic blood pressure at rest of less than 100 mm Hg, renal failure (serum creatinine &gt;300 µmol/L), reversible</td>
<td>-Age: 61 -Diabetes: 49.5% -Gender: 80% male -Mean diabetes vintage: 13 years -Kidney function (eGFR): 64.5 mL/min</td>
<td>-Bisoprolol 1.25mg, 2.5mg, 3.75mg, 5.0mg, 7.5mg, and 10.0 mg/d (n=1327) -Standard care plus placebo (n=1320) -1.3 years</td>
<td>-all cause hospital admission -myocardial infarction -all cause mortality -sudden death</td>
<td>-HR 0.8 (0.71-0.91, p=0.0006) -HR 0.85 (0.31-2.34, p=0.75) -HR 0.66 (0.54-0.81, p=0.0001) -HR 0.56 (0.39-0.80, p=0.0011)</td>
<td>Low risk of bias RCT</td>
<td>Patients with baseline renal function slightly better than guideline inclusion criteria</td>
</tr>
<tr>
<td>Reference</td>
<td>Year</td>
<td>Location</td>
<td>Study Design</td>
<td>Participants</td>
<td>Outcomes</td>
<td>Notes</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>El-Menyar[178]</td>
<td>2010</td>
<td>Middle-East</td>
<td>Prospective cohort study</td>
<td>Consecutive patients with acute coronary syndrome (ACS) were recruited</td>
<td>Use of β-blockers decreased as renal function worsened, particularly in patients with STEMI (mild CRI, 64%; moderate CRI, 51%; severe CRI, 43%)</td>
<td>Data collected from an observational study and presented in a descriptive way. The study was unable to determine whether the patient had acute renal dysfunction, Chronic, or a combination of both.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erdmann[177]</td>
<td>2001</td>
<td>Europe</td>
<td>Post-hoc analyses of the CIBIS II trial (Randomised controlled trial)</td>
<td>Symptomatic ambulatory patients in NYHA class III or IV, with an ejection fraction of ~35%, stable on standard treatment with ACE-inhibitors and diuretics.</td>
<td>- Bisoprolol 1.25mg, 2.5mg, 3.75mg, 5.0mg, 7.5mg, and 10.0 mg/d (n=1327) - Standard care plus placebo (n=1320) - 1.3 years</td>
<td>- All cause mortality (subgroup analysis on diabetes patients) - RR 0.81 (95% CI 0.51-1.28) - Funding source bias: &quot; sponsored by E Merck, Darmstadt&quot; - Post hoc and subgroup analysis for data available on patients with diabetes and advanced kidney disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gansevoort[337]</td>
<td>1995</td>
<td>Europe</td>
<td>Systematic review</td>
<td>Antiproteinuric effect of blood-pressure-lowering agents: a meta-analysis of comparative trials</td>
<td>- Included were 41 studies, comprising 1124 patients, of which 558 had non-diabetic renal disease. - 10 studies were on Beta blockers with 162 patients included</td>
<td>- Efficacy to lower proteinuria - MD -39.9% (-42.8% to -36.8%) - No separate subgroup analysis of patients with advanced chronic kidney disease provided</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knight[175]</td>
<td>1999</td>
<td></td>
<td>Randomised</td>
<td>- An ejection fraction of</td>
<td>- Progression to end-stage RR 0.70 (0.57-</td>
<td>Funding source</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Pun          | 2007  | Retrospective case-control study | - Global 1986-1989 controlled trial | -<35%. 
- Exclusion criteria included myocardial infarction within 30 days, arrhythmia-related syncope, major cardiac surgery, unstable angina, uncontrollable hypertension, advanced pulmonary disease, major neurologic disease or cerebrovascular disease, suspected renal artery stenosis, renal failure, other life-threatening disease, and likely noncompliance (eg, alcoholism, drug addiction). 
- Diabetes: 19% 
- Gender: 86% male  
- Kidney function (serum creatinine): 1.3 mg/dL. 
- Inhibitors, enalapril n=3269 
 Comparator-Placebo, n=3246  
 Co-intervention Betablockers, 17% from the placebo group and 18% from the intervention group had beta-blockers therapy - 974 days  
 Kidney disease  
 Odds Ratio of death at 6 months according to prescribed medication dosage (low, medium, high) vs not prescribed 
 - OR 0.34 (0.18 to 0.66)  
 - OR 0.25 (0.13 to 0.48)  
 - OR 0.15 (0.07 to 0.29) 
 No analysis available on diabetes patients, bias by indication  
 significantly higher proportion of nonsurvivors had indwelling catheters at the time of the event compared with 6-mo survivors | 0.85 in both groups when adjusted for the use of beta-blockers | Bias |
| Tonelli [179] | Prospective cohort study | Age: 60.8 (15.7) years | All patients seen for routine follow-up of chronic kidney disease during the 4-week study period in 1999 were eligible - dialysis dependence or calculated creatinine clearance (Cockcroft-Gault) more than 75 mL/min |
| -2001 - North America 1999 | -Diabetes: 37.5% - Gender: 61.8% male - Kidney function - mean creatinine clearance was 30.3 (18) mL/min | This study catalogued the percentage of patients with and without DM and at various CKD stages (CrCl) who were exposed to CV protective medicine such as statins, ACE and aspirin |
| | | Adherence to treatment strategy (Adrenergic blockers, acetylsalicylic acid (ASA), angiotensin-converting enzyme (ACE) inhibitors, and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins)) | History of diabetes mellitus was not significantly associated with the use of any of these medications |
| | | Old retrospective study; Bias by indication |
Chapter 3.5.

In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²), should we prescribe lipid lowering therapy in primary prevention?

<table>
<thead>
<tr>
<th>Study</th>
<th>Publication Year - Time Frame - Location</th>
<th>Design</th>
<th>-Inclusion criteria -Exclusion criteria</th>
<th>Patients’ characteristics</th>
<th>Intervention (n=) -Comparator (n=) -Duration</th>
<th>Outcome(s)</th>
<th>Results</th>
<th>Quality of evidence</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wanner[192]</td>
<td>2005 -1998-2004 -Europe</td>
<td>Randomised controlled trial</td>
<td>-Subjects with type 2 diabetes mellitus 18 to 80 years of age who had been receiving maintenance hemodialysis for less than two years -levels of fasting LDL cholesterol of less than 80 mg per deciliter (2.1 mmol per liter) or more than 190 mg per deciliter (4.9 mmol per liter), triglyceride levels greater than 1000 mg per deciliter (11.3 mmol per liter); liver function values more than three times the upper limit of normal or equal to those in patients with symptomatic hepatobiliary cholestatic disease; systemic disease unrelated to end-stage renal disease; vascular intervention, congestive heart failure, or</td>
<td>-Age 65.7±8.3 gender: 53% DM2: 100% HD: 100% 17.5±8.7 years with diabetes, 8.2±6.9 months on dialysis</td>
<td>- atorvastatin 20 mg daily -on intervention n=619 -control group n=636</td>
<td>-All cause mortality -Composite outcome/mortality -Sudden death -Stroke -Myocardial infarction</td>
<td>-RR 0.93 (0.79-1.08; p=0.33) -RR 0.92 (0.77-1.10; p=0.37) -RR 1.33 (0.90-1.97; p=0.15) -RR 1.33 (0.90-1.97; p=0.15) -RR 0.88 (0.64-1.21; P=0.42)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
myocardial infarction within the three months preceding the period of enrollment; unsuccessful kidney transplantation; and hypertension resistant to therapy

Upadhyay[188]
-2012
-2000-2011
-Global

Systematic review
-Systematic reviews of randomized, controlled trials (RCTs) in any language with included data about adults and children with CKD of any stage, including patients receiving dialysis and kidney transplantation patients
- Trials involving dietary supplements, phosphate binders, apheresis, stanols, or sterols. The minimum follow-up was 6 months. Studies had to include 100 or more participants with CKD per group for adults and 25 or more per group for children.

-Age 50 to 66 years
- Mean baseline LDL cholesterol level in intervention groups ranged from 2.59 mmol/L (100 mg/dL) to 4.09 mmol/L (158 mg/dL). Follow-up ranged from 6 months to 5 years, and most participants in each trial were men.
- Intervention: 1 or more lipid-lowering agents (statins, ezetimibe, niacin, colesteipol, or cholestyramine) or lifestyle-modification strategies (weight loss, special diet, or exercise)
- Comparator: no treatment (or placebo) or other lipid-lowering agents

-Myocardial infarction
-Stroke
-Survival/CV mortality
-Survival/mortality

RR 0.76 (0.63-0.91)
RR 1.16 (0.75-1.78)
RR 0.78 (0.68-0.89)
RR 0.93 (0.86-1.01)

Limitations:
- Results were obtained from subgroup analysis
- Literature search was limited to MEDLINE, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews

Tonelli[338]
-2005
-North America

Posthoc analysis of RCTs
-Overall analysis of the West of
-Age 64.2 +/- 7.0 years
- Intervention pravastatin 40 mg daily, n=290
- Myocardial infarction
- Stroke
- Survival/CV mortality
- Survival/mortality

HR 0.84 (0.63-1.18)
HR 1.12 (0.63-1.97)

Limitations:
- Subgroup analysis
<table>
<thead>
<tr>
<th>Ting[339]</th>
<th>2012</th>
<th>Australia/New Zealand</th>
<th>1998-2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scotland Coronary Prevention Study (WOSCOPS), Cholesterol and Recurrent Events (CARE), and Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) studies. The maximum baseline serum creatinine values for patient in WOSCOPS, CARE, and LIPID were 1.7, 2.5, and 4.5 mg/dl, respectively; patients with creatinine values above these levels were ineligible.</td>
<td>Male gender 78% -DM2: 100% -MDRD eGFR: 57.9 +/- 12.7 ml/min</td>
<td>Control: placebo, n=281 -Intervention Duration: ~5 years</td>
<td>Survival/mortality-any cause -Survival/mortality: composite outcome: Coronary heart disease death, nonfatal MI, CABG, or PTCA</td>
</tr>
<tr>
<td>Ting[339]</td>
<td>2012</td>
<td>Randomised controlled trial</td>
<td>1998-2010</td>
</tr>
<tr>
<td>-Type 2 diabetes mellitus with onset after the age of 35 years 2. Men and women aged 50-75 years of age 3. Average total cholesterol 3.0-6.5 mmol/L 4. Triglycerides/high-density cholesterol ratio of 4.0 or higher, or triglycerides over 1.0 mmol/L 5. Plasma creatinine &gt;130 mmol/L, liver or symptomatic gallbladder disease, or a cardiovascular event.</td>
<td>Age 66.51 (5.92) years - Male gender 56% -DM2: 100% - Diabetes vintage 6.02 (5.55-6.54) years - Kidney Function 30-59 ml/min/1.73 m2 eGFR</td>
<td>Intervention fenofibrate 200 mg daily, n=295 -Co-Intervention: diet -Intervention Duration: ~5 years</td>
<td>Myocardial infarction -Major CV events -Progression to end-stage kidney disease -Stroke -CV mortality -Survival/all-cause mortality</td>
</tr>
<tr>
<td></td>
<td>-HR 0.98 (0.69-1.39) -HR 0.75 (0.57-0.98)</td>
<td>and post hoc analysis not specifically designed at the beginning of the studies. ~70% of the included patients were male.</td>
<td>Limitations: imbalance baseline patients characteristics, Reasons for lost to follow-up not provided</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Design</td>
<td>Population</td>
</tr>
<tr>
<td>-------</td>
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<td>------------</td>
</tr>
<tr>
<td>Palmer[189]</td>
<td>2012</td>
<td>Systematic review</td>
<td>Adults with CKD (any stage)</td>
</tr>
<tr>
<td>Jun[191]</td>
<td>2012</td>
<td>Systematic review</td>
<td>Randomized controlled trials assessing the effects of fibrate therapy compared with placebo in people with CKD or on kidney-related outcomes. No exclusion criteria.</td>
</tr>
<tr>
<td>Holdaas[340]</td>
<td>2011</td>
<td>Randomised controlled trial</td>
<td>Diabetes subjects with end-stage renal failure aged 50-80 years, who have received regular haemodialysis treatment for at least 3 months. No underlying condition that is expected to limit survival to less than 1 year and is also unrelated to</td>
</tr>
</tbody>
</table>
end-stage renal disease (ESRD), not have received a statin therapy within the past 6 months.

Colhoun[341]
-2009
-Global
-1997-2001
Randomised controlled trial
- Patients with type 2 diabetes, no previous CVD and at least 1 of the following risk factors: history of hypertension, retinopathy (ie, any retinopathy, maculopathy, or prior photocoagulation), microalbuminuria or macroalbuminuria, or current smoking.
- Excluded if had history of myocardial infarction, angina, coronary vascular surgery, cerebrovascular accident, or severe peripheral vascular disease (defined as warranting surgery), if they had a plasma creatinine concentration greater than 1.7 mg/dL or glycated hemoglobin level greater than 12%.

<table>
<thead>
<tr>
<th>Age 65.0+/-6.7 years</th>
<th>Male 48%</th>
<th>DM2 100%</th>
<th>Kidney Function: creatinine 1.28 (1.10-1.37) mg/dL, eGFR 53.5 +/- 5.3 mL/min</th>
<th>Intervention atorvastatin 10 mg daily, n=1428</th>
<th>Control: placebo, n=1410</th>
<th>Co-Intervention: Renin-angiotensin system drug</th>
<th>Intervention duration: Mean 3.77 years (median, 4.0 years)</th>
<th>Myocardial infarction-Stroke-Survival/mortality (Major cardiovascular disease)-Survival/all-cause mortality</th>
<th>HR 0.66 (0.36-1.2, p=0.2)</th>
<th>HR 0.39 (0.15-1.01, p=0.04)</th>
<th>HR 0.58 (0.36-0.96, p=0.03)</th>
<th>HR 0.89 (0.53-1.5, p=0.7)</th>
<th>Limitation: funding source bias, adverse events reported inconsistently</th>
</tr>
</thead>
</table>
| Baigent[190]
-2011
-Global
Randomised controlled trial
- History of CKD: pre-dialysis or on dialysis, aged
- Age 62 (12) years | Male 63% | Intervention simvastatin 20 mg plus ezetimibe 10 mg daily, n=4650 | Major atherosclerotic events: defined as the combination of non-fatal | RR 0.78 (0.64-0.94) | Limitation: primary outcome changed during |
- greater than or equal to 40 years.
- history of myocardial infarction or coronary revascularization procedure; renal transplant, less than 2 months since presentation as an acute uraemic emergency, history of chronic liver disease, or abnormal liver function.
- Evidence of active inflammatory muscle disease, previous adverse reaction to a statin or to ezetimibe.
- Concurrent treatment with a contraindicated drug.
- Child-bearing potential, Known to be poorly compliant with clinic visits or prescribed medication, history of cancer other than non-melanoma skin cancer; or recent history of alcohol or substance misuse.

| DM2 23% | Kidney Function: MDRD-estimated GFR (mL/min per 1.73 m²): 26.6 (12.9), On dialysis ~33%, Haemodialysis ~27%, Peritoneal dialysis ~6%, Not on dialysis ~67%.
| Control: placebo, n=4620 | Intervention duration: 4.0 years |
| myocardial infarction, coronary death, ischemic stroke, or any revascularization procedure (i.e. exclusion of non-coronary cardiac deaths and strokes confirmed to be hemorrhagic) | the study, composite outcome |
Chapter 3.6: In patients with diabetes and CKD stage 3b or higher should we recommend interventions to increase energy expenditure and reduce energy intake

<table>
<thead>
<tr>
<th>Authors</th>
<th>- Publication Year -</th>
<th>- Time frame -</th>
<th>Design</th>
<th>- Inclusion criteria -</th>
<th>- Exclusion criteria -</th>
<th>Patients' characteristics</th>
<th>- Intervention (n=) -</th>
<th>- Comparator (n=) -</th>
<th>- Duration -</th>
<th>Outcome(s)</th>
<th>Results</th>
<th>Quality of evidence</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tawney et al.[199]</td>
<td>2000 North America</td>
<td>RCT</td>
<td>- Hemodialysis patients -</td>
<td>- Sufficient mobility to transfer independently around a room, screened by nephrologists to ensure they were medically stable at the start, excessive fluid gain, severe valvular disease, uncontrolled angina, severe joint pain, dizziness, dyspnoea, uncompensated congestive heart failure, inadequately managed diabetes, uncontrolled hypertension, hyperkalemia, screened by physician trained in physical medicine and rehabilitation to identify safety concerns as poor balance</td>
<td>- Age: 58.1 ±14 - Diabetes: 49.5% - Gender: 40% male - Mean dialysis vintage: 31 months</td>
<td>- Individual counselling to exercise 30min each day (household activities) (n=51) - Standard care (n=48)</td>
<td>- 6 months</td>
<td>QoL Mental component</td>
<td>QoL Physical component</td>
<td>Physical functioning score</td>
<td>Patient satisfaction</td>
<td>Mean Score on KDQoL-SF (SD)</td>
<td>I: 47.3 (12.9) C: 49.9 (10.5)</td>
</tr>
<tr>
<td>Castaneda et al.[195]</td>
<td>2002 North America</td>
<td>RCT</td>
<td>- &gt;55 years and type 2 diabetes of at least 3 years' duration - myocardial infarction (within past 6 months), any unstable chronic condition (including dementia, alcoholism, dialysis, retinal hemorrhage or detachment), current participation in resistance training</td>
<td>- Mean age: 66 - Diabetes type 2: 100% - Mean HbA1c: 8.6% - Mean BMI: 31kg/m² - 59.6% affected by CV disease</td>
<td>- Progressive resistance training, 45min 3 times/week (n=31) - Standard care: two-weekly telephone calls, control visit every 3 months (n=31)</td>
<td>- 16 weeks</td>
<td>SBP (mmHg)</td>
<td>DBP (mmHg)</td>
<td>HbA1c (%)</td>
<td>FBG (mmol/L)</td>
<td>Body weight (kg)</td>
<td>Functional status (on physical activity score questionnaires)</td>
<td>Mean (SE)</td>
</tr>
<tr>
<td>Morales et al. [200]</td>
<td>-2003 -Europe</td>
<td>RCT</td>
<td>-Chronic proteinuric nephropathy of diabetic or non-diabetic cause, BMI &gt;27 kg/m², serum creatinine level less than 2 mg/dL. -Unstable clinical condition, rapid loss of renal function, nephrotic syndrome requiring diuretic therapy, immunosuppressive treatment, hypertension requiring more than 2 drugs</td>
<td>-Mean age: 56 -Diabetes: 47% type 2 -Gender: 60% male -Mean serum creatinine: 1.5 mg/dL</td>
<td>-Energy reduction of 500 kcal/day, protein content adjusted to 1 to 1.2 g/kg/d (n=20) -Standard medical care (n=10) -5 months</td>
<td>SBP (mmHg)</td>
<td>DBP (mmHg)</td>
<td>Serum creatinine (mg/dL)</td>
<td>Creatinine clearance (Cockcroft-Gault formula)</td>
<td>Proteinuria (g/24h)</td>
<td>Weight (kg)</td>
<td>BMI (kg/m²)</td>
<td>Hospital admissions intervention group (%)</td>
</tr>
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<tr>
<td>Sigal et al. [198]</td>
<td>-2007 -1999-2005 -North America</td>
<td>RCT</td>
<td>-Type 2 diabetes - baseline HbA1c between 6.6% and 9.9% -Current insulin therapy, participation in exercise 2 or more times weekly for 20 minutes or longer per session or in any resistance training during the previous 6 months, changes during the previous 2 months in oral hypoglycemic, antihypertensive or lipid-lowering agents or body weight (&gt; or = 5%), serum creatinine level of 200 micromol/L or greater (&gt; or = 2.26 mg/dL), proteinuria greater than 1g/day, blood pressure greater than 160/95 mmHg, restrictions in physical activity because of disease, presence of other medical condition that made participation inadvisable</td>
<td>-Mean age: 54 -100% type 2 diabetes -Gender: 64% male -Mean HbA1c: 7.68%</td>
<td>-Intervention 1: 15 to 20 min per session at 60% of HFmax to 45 min per session at 75% of the HFmax 3 times/week (n=60)</td>
<td>SBP (mmHg)</td>
<td>DBP (mmHg)</td>
<td>HbA1c (%)</td>
<td>Body weight (kg)</td>
<td>BMI (kg/m²)</td>
<td>Hospital admissions intervention group (%)</td>
<td>Hypoglycemia intervention group (%)</td>
<td>1(-3.6 to 5.7) p=0.66</td>
</tr>
</tbody>
</table>
7 different exercises on weight machines each session, progressive resistance training, 3 times/week (n=64)

<table>
<thead>
<tr>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
<th>HbA1c (%)</th>
<th>Body weight (kg)</th>
<th>BMI (kg/m²)</th>
<th>Hospital admissions intervention group (%)</th>
<th>Hypoglycemia intervention group (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.9(-5.4 to 3.7)</td>
<td>-1.4(-4.6 to 1.7)</td>
<td>0.37</td>
<td>-0.38(-0.72 to -0.22)</td>
<td>0.038</td>
<td>-0.7(-2.4 to 0.9)</td>
<td>0.36</td>
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<tr>
<td>-0.26(-0.80 to 0.28)</td>
<td>0.35</td>
<td>6</td>
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</table>

- Intervention 3: Combination of aerobic and resistance exercise intervention (n=64)
  - Control: standard medical care (n=63) - 22 weeks

<table>
<thead>
<tr>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
<th>HbA1c (%)</th>
<th>Body weight (kg)</th>
<th>BMI (kg/m²)</th>
<th>Compared with AE</th>
<th>Compared with RE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.3 (-3.4 to 1.7)</td>
<td>1.7 (-1.5 to 5.0)</td>
<td>-0.46 (-0.83 to -0.09)</td>
<td>0.014</td>
<td>0.0 (-1.6 to 1.7)</td>
<td>0.98 (0.03 to 0.53)</td>
<td>0.93</td>
</tr>
<tr>
<td>3.2 (-1.4 to 7.8)</td>
<td>1.7 (-1.5 to 4.9)</td>
<td>-0.59 (-0.95 to -0.23)</td>
<td>0.001</td>
<td>-1.5 (-3.1 to 0.1)</td>
<td>0.075 (-0.50 to 0.04)</td>
<td>0.069</td>
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</tbody>
</table>
### Leehey et al.[197] - 2009 - North America

RCT

- Obese type 2 diabetes patients, CKD stage 2-4 with proteinuria. Treatment with ACE-i or ARB, aspirin and statin if LDL>100
- CKD stages other than 2-4. Hypertrophy/osteoporosis. Symptomatic neuropathy/retinopathy. Positive stress test due to coronary arterial disease. Symptomatic cardiovascular disease. Congestive Heart Failure (NYHA III or IV). COPD (FEV1 < 50% and/or requires oxygen support during exercise).
- Complaints of angina during stress test. Cerebrovascular disease/cognitive impairment. Renal transplant. Inability to walk on the treadmill. Any unforeseen illness of disability that would preclude exercise testing or training. Participation in a formal exercise program within the previous 12 weeks

<table>
<thead>
<tr>
<th>Hospital admissions intervention group (%)</th>
<th>Hypoglycemia intervention group (%)</th>
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<tbody>
<tr>
<td>0</td>
<td>3</td>
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</tbody>
</table>

**Mean (SD)**

- Mean age: 66
- Mean (SD): I: 113 (16) C: 136 (5)
- Gender: 100%
- Male
- Mean (SD): I: 65 (10) C: 77 (8)
- Mean (SD): I: 51 (26) C: 64 (10)
- Mean (SD): I: 8.3 (2.4) C: 8.1 (3.7)
- Mean (SD): I: 10.2 (2.8) C: 6.6 (2.1)
- Mean (SD): I: 115 (23) C: 136 (20)
- Mean (SD): I: 821 (1010) C: 490 (237)

### Chen et al.[196] - 2010 - Asia

Quasi-randomized controlled trial

- Stable CKD patients not on dialysis, selected by researcher
- Criteria for selection by researcher were not mentioned

<table>
<thead>
<tr>
<th>Mean blood glucose (mg/dL)</th>
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<tr>
<td>Mean (SD)</td>
</tr>
<tr>
<td>I: 114.81 (30.28) C: 110.31 (25.58)</td>
</tr>
</tbody>
</table>

- Selection bias, patients were selected before randomisation
- Pre-test blood glucose values were used as the covariate
<table>
<thead>
<tr>
<th>Study (Ref.)</th>
<th>Year Range</th>
<th>Region</th>
<th>Study Design</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Intervention</th>
<th>Main Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>MacLaughlin et al.[201]</td>
<td>2010 -2004-2007 -Europe</td>
<td>Nonrandomized controlled trial</td>
<td>CKD patients with BMI&gt;30 or BMI&gt;28 kg/m² with comorbidities (diabetes, hypertension, dyslipidemia), all eligible for kidney transplant, age between 18 and 65.</td>
<td>-no exclusion criteria mentioned</td>
<td>-Individual diet and exercise plan, at least 3 times/week, with increasing time and intensity, Orlistat 3 times 120 mg/d (n=32) -Standard care (n=20) -24 months</td>
<td>SBP (mmHg) DBP (mmHg) Decrease in eGFR (MDRD formula) from baseline (mL/min) (only CKD 3-4) Body weight (kg) Accepted on kidney transplant list (%) Number of transplants</td>
<td>Mean (SD)</td>
<td>-Selection bias: all patients were eligible for transplant, only motivated patients included</td>
</tr>
<tr>
<td>Matsuoka et al.[203]</td>
<td>1991 -Asia</td>
<td>Retrospective cohort study</td>
<td>Diabetes mellitus patients with diabetic nephropathy</td>
<td>-No exclusion criteria mentioned</td>
<td>-100% diabetes mellitus patients, type not mentioned, all had diabetic nephropathy but severity was not mentioned. -Restricted daily physical activity (n=10)</td>
<td>SBP (mmHg) DBP (mmHg) Onset of nephrotic stage to dialysis (months) Maximum proteinuria to dialysis (months) Karnofsky Score</td>
<td>Mean (SD)</td>
<td>-Retrospective study, dose, intensity and duration of intervention was not quantified</td>
</tr>
<tr>
<td>Cappy et al.[202]</td>
<td>1999 -1997-1998 -North America</td>
<td>Before-after study</td>
<td>Hemodialysis patients with stable general and cardiovascular conditions</td>
<td>-Any unstable medical condition</td>
<td>-Age: 53.9 ±15 -Diabetes: 50%, type not specified -Gender: 62% male</td>
<td>Training program consisting in a progressive, self-paced aerobic exercise: 20 to 40 min, 3 times/week (n=4) -12 months</td>
<td>SBP predialysis DBP predialysis Serum creatinine Serum glucose level</td>
<td>Mean % of change</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Study Type</td>
<td>Participants Description</td>
<td>Baseline Characteristics</td>
<td>Intervention</td>
<td>Changes</td>
<td>Long-Term Benefits</td>
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</table>
| Solerte et al.[204] | 1989 | Prospective cohort study | - Obese type 1 or 2 diabetic patients with CKD                                               | - 100% diabetes patients, type not specified  
  - BMI: 33± 1.6 kg/m²  
  - eGFR 66±13 mL/min  
  - Hypocaloric diet (1410 kcal/day) (n=24)  
  - 52 weeks                                                                 | MAP (mmHg)  
  Creatinine clearance (mL/min)  
  Proteinuria (g/24h)  
  BMI (kg/m²)                                                                 | Difference in change from baseline  
  -9.7 (p<0.05)  
  12 (p=0.01)  
  -0.66 (p=0.01)  
  -7.3 (p<0.001) | Creatinine clearance change probably explained by less protein intake and muscle loss | Small group Diet also improved total cholesterol, LDL and HDL cholesterol and triglycerides |
| Saiki et al.[205] | 2005 | Prospective cohort study | - Overweight type 1 or 2 diabetic patients with diabetic retinopathy, proteinuria (urinary albumin excretion >300mg/day) and serum creatinine level less than 3 mg/dL  
  - Unstable diabetic retinopathy, pleural effusion, severe leg edema  
  - Age: 53.6±8.4  
  - BMI 30.4±5.3 kg/m²  
  - 100% diabetes, HbA1c 7.11 ± 1.42  
  - eGFR 40.6±17.9 mL/min  
  - Proteinuria 3.27±2.63 g/24h  
  - 740-970 kcal per day diet (n=22)  
  - 4 weeks                                                                 | MAP (mmHg)  
  Creatinine clearance (mL/min)  
  Proteinuria (g/24h)  
  HbA1c (%)  
  BMI (kg/m²)                                                                 | Difference in change from baseline  
  -7.4 (p<0.05)  
  5.0 (NS)  
  -1.77 (p<0.0001)  
  -0.43 (p<0.05)  
  -2.2 (p<0.0001) | Changes in creatinine and proteinuria were significantly related to those on BMI (r=0.62 and 0.49 respectively). | Short intervention, very restricted diet. |
Chapter 3.7.

In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m²), should antiplatelet therapy be recommended, regardless of their cardiovascular risk?

<table>
<thead>
<tr>
<th>Study</th>
<th>-Publication Year</th>
<th>-Time Frame</th>
<th>-Location</th>
<th>Design</th>
<th>-Inclusion criteria</th>
<th>Patients' characteristics</th>
<th>-Intervention (n=)</th>
<th>-Comparator (n=)</th>
<th>-Duration</th>
<th>Outcome(s)</th>
<th>Results</th>
<th>Quality of evidence</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiolillo et al.[342]</td>
<td>2010</td>
<td>2003-2007</td>
<td>Europe</td>
<td>Case series</td>
<td>-Type 2 DM patients with stable CAD. Angiographically documented CAD, because they had all previously undergone PCI. -Known allergies to aspirin or clopidogrel; type 2 DM without pharmacological treatment; gestational diabetes; dialysis; blood dyscrasia; active bleeding or bleeding diathesis; gastrointestinal bleed within last 6 months; hemodynamic instability; acute coronary or cerebrovascular event within 3 months; any malignancy; concomitant use of other antithrombotic drugs (oral anticoagulants, dipyridamole, cilostazol, ticlopidine) or nonsteroid anti-inflammatory drugs; recent treatment with a glycoprotein IIb/IIIa antagonist; platelet count &lt;100/ 106/l; hematocrit &lt;25%; and liver disease (bilirubin level 2 mg/dl).</td>
<td>-Age: 72+-8 -DM2: 100% -Gender: 54% Male -eGFR&lt; 60 ml/min -HbA1C: 7+-1.4</td>
<td>Aspirin 100 mg/day (n=84)</td>
<td>-Platelet aggregation</td>
<td>-at least 3 months</td>
<td>-Improved platelet aggregation after Aspirin treatment</td>
<td>Possible indication bias. Uncontrolled study.</td>
<td>DM patients with moderate/severe CKD had significantly higher ADP-induced (60+-13% vs. 52+-15%, p&lt; 0.001) and collagen-induced (49+-20% vs. 41+-20%, p 0.004) platelet aggregation compared with those without.</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Study Design</td>
<td>Patients</td>
<td>Age</td>
<td>Gender</td>
<td>Diabetes</td>
<td>Antiplatelet Therapy</td>
<td>Bleeding Episodes</td>
<td>Exposed Cohort</td>
<td>Results</td>
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<tr>
<td>Daimon et al. [343]</td>
<td>2011</td>
<td>Prospective cohort study</td>
<td>HD patients</td>
<td>66.7</td>
<td>71% Male</td>
<td>45% Diabetes</td>
<td>Aspirin, Ticlopidine, Clopidogrel, Cilostazol, Sarpogrelate hydrochloride or Warfarin (n=21)</td>
<td>13 episodes in patients on antiplatelet therapy vs 3 in those non on antiplatelet therapy (p&lt;0.05)</td>
<td>Single center</td>
<td>Poorly reliable: no effect measure provided, unadjusted analyses</td>
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<tr>
<td>Dasgupta et al. [344]</td>
<td>2009</td>
<td>RCT</td>
<td>Patients</td>
<td>63 yrs</td>
<td>Male</td>
<td>DM2: 100%</td>
<td>Diuretics (48.2%), Nitrates (23.2%), Calcium antagonists (36.7%), Beta blockers (55%), Angiotensin II receptor blockers (25.5%), Angiotensin converting enzyme inhibitors (58.6%), Statins (76.8%), Insulin (17.4%), Oral hypoglycemic agents (42.3%)</td>
<td>Clotidogrel (75 mg once daily) plus low-dose aspirin (75 to 162 mg once daily) (n=1006)</td>
<td>HR 1.8 (0.90-3.30; p=0.075)</td>
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<tr>
<td></td>
<td>2002-2005</td>
<td>Global (32 centres)</td>
<td>Patients</td>
<td>65%</td>
<td>Male</td>
<td>DM2: 100%</td>
<td>Diuretics (48.2%), Nitrates (23.2%), Calcium antagonists (36.7%), Beta blockers (55%), Angiotensin II receptor blockers (25.5%), Angiotensin converting enzyme inhibitors (58.6%), Statins (76.8%), Insulin (17.4%), Oral hypoglycemic agents (42.3%)</td>
<td>Clotidogrel (75 mg once daily) plus low-dose aspirin (75 to 162 mg once daily) (n=1006)</td>
<td>HR 1.2 (0.70-2.00; p=0.543)</td>
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</table>

Results poorly reliable: no effect measure provided, unadjusted analyses.
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Design</th>
<th>Case-Control Study</th>
<th>Case Definition and Inclusion Criteria</th>
<th>Follow-Up</th>
<th>Allocation</th>
<th>Blinding</th>
<th>Methodology</th>
<th>Primary Outcomes</th>
<th>Secondary Outcomes</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nakamura et al.[346]</td>
<td>2005</td>
<td>Quasi-RCT</td>
<td></td>
<td>Patients with diabetic nephropathy (microalbuminuria 20-200 mcg/min) and non-silent cerebral infarction</td>
<td>MD 180±48</td>
<td>Blinding unclear.</td>
<td>Concealment and blinding unclear.</td>
<td>Controlled by the population.</td>
<td>Case definition and case representatives adequate. Controls adequately selected from the same population. Controlled by the most important confounders</td>
<td>No data on ASA intolerance or allergy, no doses reported.</td>
<td></td>
</tr>
<tr>
<td>McCullough et al.[345]</td>
<td>2002</td>
<td>Prospective</td>
<td></td>
<td>ST-segment elevation AMI, defined as characteristic chest pain and ST-segment elevation of 1 mm in 2 contiguous leads on the initial electrocardiogram with a consistent rise and fall of the creatinine phosphokinase myocardial band (CK-MB). Patients with a new left bundle branch block were included when a history consistent with ischemic chest pain and a positive CK-MB were present. -Chest pain of undetermined origin, unstable angina, non-q-wave myocardial infarction, and heart failure with and without ischemic contribution, all diagnoses outside of ST-segment elevation AMI. Coma, arrhythmias, and gastrointestinal bleeding.</td>
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<tr>
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<td>case-control study</td>
<td></td>
<td>Age: 63.4 yrs - Gender: 73% male - Various renal impairment - The combination of ASA+BB was used in 63.9%, 55.8%, 48.2%, and 35.5% of patients with corrected creatinine clearance values of 81.5, 81.5 to 63.1, 63.1 to 46.2, and &gt;46.2 mL/min/72 kg (p&lt;0.0001). ASA+BB used in 40.4% of patients undergoing dialysis.</td>
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<td>Acetylsalicylic acid (n=262) - Beta-blockers (n=328) - Acetylsalicylic acid plus beta-blockers (n=902) - no Acetylsalicylic acid or beta-blockers (n=232)</td>
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<td>Episodes of (in no ASA or BB, ASA alone, BB alone, ASA +BB): - Hematoma - Gastrointestinal bleeding - Shock - Sustained hypotension - Asystole - Ventricular fibrillation - Stroke - In hospital death - Pulmonary edema</td>
<td>P= none vs both controls</td>
<td>P= NS</td>
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<td>-5.4, 0.10 (p=NS) -1.1, 0.3 (p=0.82) -58.42, 15, 30 (p&lt;0.001) - 101.95, 83.173 (p&lt;0.001) - 21.16, 11.12 (p&lt;0.001) - 28.18, 22, .41 (p&lt;0.001) - 0.1, 0.1 (p&lt;0.001) -50, 51, 11.27 (p&lt;0.001) -107, 81, 79, 148 (p&lt;0.001)</td>
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<td>Associations were: - Acetylsalicylic acid (n=262) - Beta-blockers (n=328) - Acetylsalicylic acid plus beta-blockers (n=902) - no Acetylsalicylic acid or beta-blockers (n=232)</td>
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<td>- Age: 55.5 yrs - Gender: 70% male - DM2: 100% - Diabetes vintage: 12 yrs (mean) - eGFR: 79.55 umol/l - HbA1c: 7.8% - Dilazeq dihydrochloride plus standard therapy (including ACEI, ARB, Calcium antagonists, Beta-blockers, Alpha-blockers), 300 mg/day (n=15) - Standard therapy (including ACEI),</td>
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<td>-Microalbuminuria - Silent cerebral infarction</td>
<td>-MD 180±48 vs 64±22 mcg/min (p&lt;0.01) - Incidence 33.3% vs.6.7% (p&lt;0.01)</td>
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<td>None vs both</td>
<td>Not adjusted for the most important confounders. Not controlled for additional confounders.</td>
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</tbody>
</table>
### Palmer et al. [347]  
**-Study Design:** Systematic review of RCTs or quasi-RCTs  
**-Study Period:** 1980-2011  
**-Objectives:** Any study of adults CKD patients comparing antiplatelet agents with placebo, standard care, or no treatment trials with follow-up longer than 1 year  
**-Follow-up:** Shorter than 2 months. Pediatric trials  
**-Number of Trials:** 31 trials (20942 patients) included  
**-Inclusion Criteria:**  
- eGFR < 60 mL/min  
- Antiplatelet therapy (aspirin, dipyridamole, clopidogrel, sulfipyrazone, ticlopidine, or picotamide)  
- Placebo  
**-Main Outcomes:**  
- Minor bleeding in persons at risk for or with stable cardiovascular disease (8 RCTs, 7202 pts)  
- Major bleeding in persons at risk for or with stable cardiovascular disease (18 RCTs, 10230 pts)  
- Major bleeding after acute coronary syndrome or percutaneous coronary intervention (9 RCTs, 5776 pts)  
- Minor bleeding after acute coronary syndrome or percutaneous coronary intervention (9 RCTs, 5776 pts)  
- Fatal or nonfatal myocardial infarction in patients after acute coronary syndrome or percutaneous coronary intervention (7 RCTs, 5261 pts)  
- Fatal or nonfatal myocardial infarction in persons at risk for or with stable cardiovascular disease (10 RCTs, 9233 pts)  
**-Results:**  
- **RR 1.70 (0.44-2.02; p=0.69)**  
- **RR 1.29 (0.69-2.42; p=0.98)**  
- **RR 1.40 (1.05-1.86; p=0.09)**  
- **RR 1.47 (1.25-1.72; p=0.001)**  
- **RR 0.89 (0.76-1.05; p=0.41)**  
- **RR 0.66 (0.51-1.87; p=0.87)**  
**-Conclusion:** Scientific quality of studies assessed. Methods to combine findings correct. Likelihood of publication bias provided.  
**-Limitations:** Methods for random sequence generation, allocation concealment, blinding of outcome assessors, completeness to follow-up, or the risk for selective reporting or other biases were mostly unclear or inadequate.
- Coronary revascularization in patients after acute coronary syndrome or percutaneous coronary intervention (7 RCTs, 5265 pts)  
  - RR 0.93 (0.84-1.04; p=0.84)

- Fatal or nonfatal in persons with CKD at risk for or with stable cardiovascular disease (10 RCTs, 9133 pts)  
  - RR 0.66 (0.16-2.78; p=0.22)

- Hemorrhagic stroke in patients after acute coronary syndrome or percutaneous coronary intervention (5 RCTs, 4035 pts)  
  - RR 1.08 (0.47-2.49; p=0.45)

- All-cause mortality in persons at risk for or with stable cardiovascular disease (21 RCTs, 10632 pts)  
  - RR 0.87 (0.61-1.24; p=0.68)

- All-cause mortality in patients after acute coronary syndrome or percutaneous coronary intervention (8 RCTs, 5260 pts)  
  - RR 0.89 (0.75-1.05; p=0.48)

- Death due to cardiovascular causes in patients after acute coronary syndrome or percutaneous coronary intervention (2 RCTs, 411 pts)  
  - RR 0.96 (0.79-1.16; p=0.46)

- Death due to cardiovascular causes in persons with CKD at risk for or with stable cardiovascular disease (7 RCTs, 5265 pts)  
  - RR 0.91 (0.60-1.36; p=0.21)
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Design</th>
<th>Randomisation</th>
<th>Allocation concealment</th>
<th>Blinding</th>
<th>Subjects</th>
<th>Inclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saito et al. [207]</td>
<td>2011</td>
<td>RCT</td>
<td>-2002-2008</td>
<td>-Asia (163 centres)</td>
<td></td>
<td></td>
<td>Diagnosis of type 2 diabetes mellitus. Age between 30 and 85 years. Ability to provide informed consent. Use of antiplatelet or antithrombotic therapy (aspirin, ticlopidine, cilostazol, dipyridamole, warfarin, and argatroban). History of severe gastric or duodenal ulcer. Severe liver dysfunction. Severe renal dysfunction. Allergy to aspirin</td>
</tr>
<tr>
<td>Wang et al. [348]</td>
<td>2010</td>
<td>Systematic review of RCTs or quasi-RCTs</td>
<td>-6 trials (271 patients) included</td>
<td>-PGE1 + routine treatment</td>
<td></td>
<td></td>
<td>Any type 1 or type 2 diabetic patient with abnormal urinary albumin excretion rate. ESKD, other renal diseases, gestational diabetes</td>
</tr>
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</table>

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<tr>
<th>Outcome Measures</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in serum creatinine</td>
<td>-MD -7.59 (-15.61 to -0.44; p=NS)</td>
<td></td>
</tr>
<tr>
<td>Change in urinary albumin excretion</td>
<td>-MD -48.28 (-75.29 to -21.28; p&lt;0.05)</td>
<td></td>
</tr>
<tr>
<td>Change in proteinuria</td>
<td>-MD -300.00 (-518.34 to -81.66; p=NS)</td>
<td></td>
</tr>
</tbody>
</table>

List of included and excluded studies provided. Characteristics of included studies given. Scientific quality of studies assessed. Methods to combine findings correct. Likelihood of publication bias not provided. Only six reports found. All six studies stated that participants had been randomised, but no studies described the method of randomisation in detail. Blinding was not mentioned in any of the included studies. No studies reported a sample size calculation.
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Appendix 6 | External Review
13. References of general document

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