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Clinical Practice Guideline

Clinical Practice Guideline on management of patients with diabetes and chronic kidney disease stage 3b or higher (eGFR <45 mL/min)

1. ABBREVIATIONS AND ACRONYMS

CKD	Chronic kidney disease
ACE-I	ACE inhibitor
ERA-EDTA	European Renal Association – European Dialysis and Transplant Association
ERBP	European Renal Best Practice
MD	Mean difference
OR	Odds ratio
RR	Relative risk
95% CI	95% Confidence interval

2. FOREWORD

Diabetes mellitus is becoming increasingly prevalent and is considered a rapidly growing concern for healthcare systems. Besides the cardiovascular complications, diabetes mellitus is associated with chronic kidney disease (CKD). CKD in patients with diabetes can be caused by true diabetic nephropathy, but can also be caused indirectly by diabetes, e.g. due to polyneuropathic bladder dysfunction, increased incidence of relapsing urinary tract infections or macrovascular angiopathy. However, many patients who develop CKD due to a cause other than diabetes will develop or may already have diabetes mellitus. Finally, many drugs that are used for management of CKDs, e.g. corticosteroids or calcineurin inhibitors, can cause diabetes.

Despite the strong interplay between diabetes and CKD, the management of patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min) remains problematic. Many guidance-providing documents have been produced on the management of patients with diabetes to prevent or delay the progression to CKD, mostly defined as the presence of micro- and macro-albuminuria. However, none of these documents specifically deal with the management of patients with CKD stage 3b or higher (eGFR <45 mL/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 <45 mL/min), or both. This limits the evidence base to these approaches.

In addition, due to some new developments in this area, the advisory board of ERBP decided that a guideline on the management of patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/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 healthcare 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 that the document focused on patient-important outcomes and had utility for clinicians involved in everyday practice.

We hope you will enjoy reading this guideline and that you will find it useful in your everyday management of patients with diabetes and CKD stage 3b or higher.

The guideline development group

3. COMPOSITION OF THE GUIDELINE DEVELOPMENT GROUP

After approval of the project concept by the ERBP advisory board, a working group convened in May 2011 who 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 current members of the guideline development group, additional external experts would be approached for their expertise in specific areas.

Guideline development group

See Supplementary data Appendix 1 for more complete biographics and declarations of interest.

Henk Bilo
Consultant physician, Department of Internal Medicine, Isala Clinics, Zwolle, the Netherlands University Medical Center, Groningen, the Netherlands

Luis Coentrão
Consultant nephrologist, Nephrology and Infectious Diseases Research and Development Group, INEB-(I3S), University of Porto, Porto, Portugal

Cécile Couchoud
Epidemiologist, REIN registry, Agence de la biomédecine, Saint-Denis La Plaine, France

Adrian Covic
Consultant nephrologist, Clinic of Nephrology, C. I. Parhon University Hospital, Gr T. Popa, University of Medicine and Pharmacy, Iasi, Romania

Johan De Sutter
Consultant cardiologist, Maria Middelares Ziekenhuis, Ghent, Belgium

Christiane Drechsler
Consultant nephrologist, Division of Nephrology, University of Würzburg, Würzburg, Germany
Member of the ERBP Methods Support Team

Luigi Gnudi
Consultant endocrinologist, Unit for Metabolic Medicine, Department of Diabetes and Endocrinology, Cardiovascular Division, Guy's and St. Thomas Hospital, King's College London, London SE1 9NH, United Kingdom

David Goldsmith
Consultant nephrologist, Renal and Transplantation Department, Guy's Hospital, London, UK

James Heaf
Consultant nephrologist, Department of Nephrology B, Herlev Hospital, University of Copenhagen, Copenhagen, Denmark

Olof Heimburger
Consultant nephrologist, Division of Renal Medicine, Department of Clinical Science, Karolinska Institutet, Huddinge University Hospital, Stockholm, Sweden

Kitty J. Jager
Epidemiologist, director of the ERA-EDTA registry, Department of Medical Informatics, Amsterdam Medical Center, Amsterdam, the Netherlands

Hakan Nacak
PhD-student, Department of Clinical Epidemiology, University Medical Centre, Leiden, the Netherlands

Maria José Soler
Consultant nephrologist, Department of Nephrology, Hospital del Mar, Barcelona, Spain, Institut Hospital del Mar of Medical Research (IMIM), Barcelona, Spain

Liesbeth Van Huffel
Resident endocrinologist, Endocrinology Division, Ghent University Hospital, Ghent, Belgium.

Charlie Tomson
Consultant nephrologist, Newcastle upon Tyne Foundation Trust, Newcastle upon Tyne, United Kingdom

Steven Van Laecke
Consultant nephrologist, Renal Division, Ghent University Hospital, Ghent, Belgium

Laurent Weekers
Consultant nephrologist, Service of Nephrology, Dialysis and Transplantation, Centre Hospitalier Universitaire, Liège, Belgium

Andrzej Wieçek
Consultant nephrologist, Department of Nephrology, Endocrinology, and Metabolic Diseases, Medical University of Silesia, Katowice, Poland

ERBP methods support team

Davide Bolignano
Clinical researcher, Institute of Clinical Physiology, National Council of Research, Reggio Calabria-Italy

Maria Haller
Specialist registrar nephrology, KH Elisabethinen Linz, Linz, Austria

Evi Nagler
Consultant nephrologist, Renal Division, Ghent University Hospital, Ghent, Belgium

Ionut Nistor
Consultant nephrologist, Gr. T. Popa University of Medicine and Pharmacy, Iasi, Romania

Sabine van der Veer
Implementation specialist, Centre for Health Informatics, University of Manchester, Manchester, United Kingdom

Wim Van Biesen (chair of the guideline development group)
Chair of ERBP
Consultant nephrologist, Renal Division, Ghent University Hospital, Ghent, Belgium

4. CONFLICT OF INTEREST

4.1. Conflict of interest policy

We required all members of the guideline development group to complete a detailed 'declaration of interest statement' including all current and future conflicts of interest as well as past conflicts of interest restricted to 2 years before joining the guideline development group. ERBP felt that excluding all

individuals with some degree of potential conflict of interest would prevent the assembly of a guideline development group. We therefore 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 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 Supplementary data (Appendix 1).

5. PURPOSE AND SCOPE OF THIS GUIDELINE

5.1. Why was this guideline produced?

This clinical practice guideline was designed to facilitate informed decision-making on the management of adult individuals with diabetes mellitus and CKD stage 3b or higher (eGFR <45 mL/min). It was not intended to define a standard of care, and should not be construed as such. It should not be interpreted as a prescription for an exclusive course of management.

5.2. Who is this guideline for?

This guideline intends to support clinical decision making by any health care professional caring for patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/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 also aims to inform about the development of standards of care by policy-makers.

5.3. What is this guideline about?

The intended scope of the guideline was determined at the 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 and CKD stage 3b or higher (eGFR <45 mL/min) 3b–5. An electronic survey was taken among all members of European Renal Association-European Dialysis and Transplant Association to prioritize these questions.

5.3.1. Population. The guideline covers adults with diabetes mellitus and CKD stage 3b or higher (eGFR <45 mL/min), as defined by the recent KDIGO classification [1]. The guideline does not cover interventions in patients with diabetes and CKD stages 1–2 to prevent or delay development of micro- or macro-albuminuria.

5.3.2. Conditions. The guideline specifically covers the management of patients with diabetes mellitus and CKD stage 3b or higher (eGFR <45 mL/min), with a focus on three major areas: (i) selection of renal replacement modality; (ii) management of glycaemic control; (iii) management and prevention of cardiovascular comorbidity.

5.3.3. Healthcare setting. This guideline targets the management of patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min) in primary, secondary and tertiary healthcare settings.

5.3.4. Clinical management. The guideline intends to provide an evidence-based rationale for the day-to-day management of patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min), and to develop pathways of care by systematically compiling available evidence in this area. It provides an evidence-based rationale on why management of patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min) should or should not be different from patients with diabetes but without CKD stage 3b or higher (eGFR <45 mL/min), or from patients with CKD stage 3b or higher (eGFR <45 mL/min) but without diabetes. In line with the mission statement of ERBP, the guideline document intends to inform all involved stakeholders and to stimulate shared decision-making [2].

6. METHODS FOR GUIDELINE DEVELOPMENT

6.1. Establishment of the guideline development group

As defined by our guideline development methodology [3], the ERBP advisory board installed a steering group, which, after selection of the topics, selected further members for the guideline development group. Members of the steering group and the guideline development group were selected based on their clinical and research expertise and 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, including 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 process.

6.2. Development of clinical questions

With the final guideline scope as point of departure, the guideline devleopment group identified specific research questions for which a systematic review would be conducted. All questions addressed issues related to one of the following three areas:

1. Renal replacement modality selection in patients with diabetes with end-stage renal disease (CKD stage 5).
2. Glycaemic control in patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min).

3. Management of cardiovascular risk in patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/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 detailed specification of the patient group (P), intervention (I), comparator (C) and outcomes (O) for intervention questions and the patient group, index tests, reference standard and target conditions for questions of diagnostic test accuracy [4]. 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. They ranked the outcomes as critical, highly important or moderately important according to the relative importance of that outcome in the decision-making process (Table 1).

6.5. Target population perspectives

An effort was made to capture the target population perspectives by adopting different strategies.

ERBP 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.

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
Hypoglycaemia
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
As mentioned in the specific PICO questions

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 in Appendix 3.

Reference lists from the included publications were screened to identify additional papers. The methods support team also searched guideline databases and organizations 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 diagnostic questions, we included all studies that compared any of the pre-defined clinical or biochemical tests with a golden standard reference test. For intervention questions, we included all studies in which one of the pre-defined interventions was evaluated in humans. We excluded case series that reported on benefit if the number of participants was ≤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 organize the initial step of screening and selection of papers. The title and abstract of all papers retrieved by the original search were made available to those responsible for screening 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 independently screened all titles and abstracts and discarded the clearly irrelevant ones and those that did not meet the inclusion criteria. Any discrepancies at this stage were resolved by consensus.

In a second round, full texts of potentially relevant studies were retrieved and independently examined for eligibility and final inclusion in the data extraction step. 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 independently extracted all data. We produced tables displaying the data extraction of both reviewers. Any discrepancies were resolved by consensus, and if no consensus could be reached, disagreements were resolved by a third independent referee. From these data extraction tables, we produced merged consensus evidence tables for informing the recommendations. The evidence tables are available in Appendix 6.

Table 2. Method of rating the quality of the evidence. Adapted from Balshem *et al.* [222]

Step 1: Starting grade according to study design	Step 2: Lower if	Step 3: Higher if	Step 4: Determine final grade for quality of evidence
Randomized trials = high Observational studies = low	*Risk of bias* − 1 Serious − 2 Very serious *Inconsistency* − 1 Serious − 2 Very serious *Indirectness* − 1 Serious − 2 Very serious *Imprecision* − 1 Serious − 2 Very serious *Publication Bias* − 1 Likely − 2 Very likely	*Large effect* + 1 Large + 2 Very large *Dose–response* + 1 Evidence of a gradient *All plausible confounding* + 1 Would reduce a demonstrated effect + 1 Would suggest a spurious effect when results show no effect	High (four plus: ⊕⊕⊕⊕) Moderate (three plus: ⊕⊕⊕◯) Low (two plus: ⊕⊕◯◯) Very Low (one plus: ⊕◯◯◯)

Risk of bias of the included studies was evaluated using validated checklists, as recommended by the Cochrane Collaboration. These were AMSTAR for Systematic Reviews [5], the Cochrane Risk of Bias tool for randomized controlled trials (RCTs) [6], the Newcastle Ottawa scale for cohort and case–control studies [7] and QUADAS for diagnostic test accuracy studies [8]. Data were compiled centrally by the ERBP methods support team.

6.6.4. Evidence profiles. For research questions regarding therapeutic interventions, the methods support team constructed evidence profiles 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 unpooled—outcome data, an absolute measure of intervention effect when appropriate, and the summary of quality of evidence for each outcome. Evidence profiles were reviewed and approved with the rest of the guideline development group. Evidence profiles were constructed only for research questions addressed by at least two RCTs. If the body of evidence for a particular comparison of interest consisted of only one RCT 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

The guideline development group rated the overall quality of the evidence for each intervention separately addressing each outcome (see Table 3). 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 RCTs and as low if it originated from observational studies. We subsequently downgraded the quality of the evidence one or two levels if results from individual studies were at a high or very high 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 was suspected.

Table 3. Grade for the overall quality of evidence. Adapted from Guyatt *et al.* [223]

Grade	Quality Level	Definition
A	High	We are confident that the true effects lie close to those of the estimates of the effect.
B	Moderate	The true effects are likely to be close to the estimates of the effects, but there is a possibility that they are substantially different.
C	Low	The true effects might be substantially different from the estimates of effects.
D	Very low	The estimates are very uncertain and will often be far from the truth.

The quality of evidence arising from observational studies was upgraded if 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 (Table 2). Uncontrolled case series and case reports automatically received downgrading from a 'low' to 'very low' level of evidence for risk of bias, so that no other reasons for downgrading were marked.

6.8. Formulating and grading statements

6.8.1. Statements. After the evidence tables and profiles had been prepared, revised and approved, the guideline development group formulated and graded the statements during two full-day plenary meetings.

Recommendations can be for or against a certain strategy. The guideline development group drafted the statements based on their interpretation of the available evidence. 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 where applicable. In accordance to GRADE [9], we classified the strength of the statements as strong (coded 1) or weak (coded 2) (Table 4, Figure 1).

Table 4. Implications of strong and weak recommendations for stakeholders. Adapted from Guyatt *et al.* [224]

Grade	Implications		
	Patients	Clinicians	Policy
1: Strong, 'We recommend'	Most people in your situation would want the recommended course of action, only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be adopted a as policy in most situations.
2: Weak, 'We suggest'	Most people in your situation would want the recommended course of action, but many would not.	You should recognize 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.	Policy-making will require substantial debate and involvement of many stakeholders.

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.

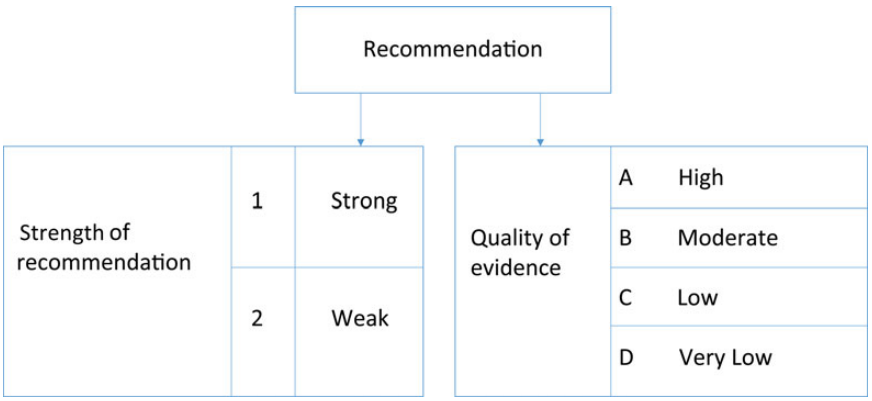

FIGURE 1: Grade system for grading recommendations. Adapted from Guyatt *et al.* [9].

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 and the variability in values and preferences. We did not conduct formal decision or cost analysis.

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. The ungraded statements were generally written as simple declarative statements but were not intended 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 [10, 11]. 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*. This advice is not graded, elaborates on one or more statements and is intended only to facilitate practical implementation.

6.9. Writing the rationale

We collated recommendations and ungraded statements for each clinical question in separate chapters structured according to a specific format. Each question resulted in one or more specific boxed statements. All statements were accompanied by their GRADE classification as levels 1 or 2 (strength of recommendations) and A, B, C or D (quality of the supporting evidence) (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 was translated into 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 textfields. 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 whether the statement needed to be adapted, 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 the American Society of Nephrology (ASN), with the request to have the guideline evaluated by two of their members.

In addition, all members of the ERA-EDTA received an online questionnaire in Survey Monkey format to evaluate the guideline using the AGREE-II framework. In addition, a free text field was provided to allow for additional comments (see Appendix 6).

All comments and suggestions were discussed with the guideline development group by e-mail, as well as 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

The guideline will be updated every 5 years or earlier following publication of new evidence that may require additional statements or changes to existing statements.

At least every 5 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 5-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 updated version of the guideline will be produced using the same procedures as for the initial guideline.

6.12. Funding

ERBP sponsored the entire production of this guideline, according to the statutes of ERA-EDTA and the bylaws of ERBP [3].

Activities of ERBP and its methods support team are supervised by an advisory board [3] (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 ERBP chair. 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 giving priority to the patient's general status and preference in selecting renal replacement therapy as there is an absence of evidence of superiority of one modality over another in patients with diabetes and CKD stage 5 (1C).

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

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

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

Advice for clinical practice

Make sure that all the different renal replacement therapy modalities (peritoneal dialysis (PD), in-centre HD, satellite HD, home HD, 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 <45 mL/min), the modality of renal replacement therapy (different modalities of HD or PD, or transplantation etc.) that is 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 [12]. This systematic review included 25 from the initial 426 records retrieved through database searching. All studies but one [13] 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 were 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 (e.g. HD versus HDF or manual versus 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

significant 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 (QoL), 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 (Supplemantary 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 [14], or only in patients under 60 years of age during the first 2 years [15], patients under 65 years [16] or during the first year [17]. In patients aged over 44, Yeates *et al.* showed a higher risk of death in patients with diabetes on PD [18]. Stack *et al.* [19] reported the 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 with 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 (hospitalization or access-related infections) being observed in PD patients with diabetes (1.28 versus 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) [20].

A systematic review (26 studies) on the impact of dialysis modality (centre HD and PD) on QoL [21] 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 QoL as assessed by the SF-36 score [22] 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 per cent of patients with diabetes. A third systematic review (27 articles) based on utility measures to assess preference-based QoL (HD, PD and TX) [23] concluded that there was no statistically significant difference in utilities between HD and PD patients. Mean QoL tended to be higher among PD patients. A fourth systematic review (190 articles) based on utility -based QoL (HD, PD,TX, CKD, conservative treatment) [24] 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 versus HDF, showing no interaction for presence of diabetes [25].

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

*We recommend giving priority to the patient's condition and preference in selecting renal replacement therapy as there is an absence of evidence of superiority of one modality over another in patients with diabetes and CKD stage 5 **(1C)**.*

*We recommend providing patients with unbiased information about the different available treatment options **(1A)**.*

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 that 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 of the 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 to start HD*, we suggest prefering high flux over low flux when this is available **(2C)**.*

*We suggest diabetes has no influence on the choice between HD or HDF **(2B)**.*

In patients opting for HD, 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 versus low-flux membranes [26]. In a recent meta-analysis of HDF versus HD, no interaction for diabetes and HDF versus HD was observed [25]. Consequently, the choice for HD versus 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 versus HD in different subgroups, such as elderly patients with diabetes, while 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 the exploration of different patient trajectories rather than HD versus 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 initiating dialysis in patients with diabetes on the same criteria as in patients without diabetes (**1A**).

Advice for clinical practice

1. Distinguish complaints due to long-standing diabetes (polyneuropathy, gastroparesis versus nausea on uraemia etc.) from uraemic complaints might be cumbersome in clinical practice.
2. In patients opting for HD, take into account and discuss with the patient the following factors to determine the decision on and optimal timing of vascular access creation:
   (a) speed of deterioration of renal function
   (b) pojected probability that a functioning vascular access will be achieved
   (c) 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 when compared with waiting to start renal replacement until patients do have uraemic complaints (as is recommended for patients without diabetes [27, 28]).

- What did we find?

  We found 12 papers reporting 11 studies on the association between some form of early versus late start of dialysis and survival/mortality on dialysis. One study was an RCT, three studies were prospective cohorts and the remaining studies were retrospective cohorts. The RCT was the IDEAL study by Cooper *et al.* [29], which was performed in 828 patients in Australia and New Zealand. Although initially patients randomized to late start were to start dialysis between 5 and 7 mL/min/1.73 m^2 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/1.73 m^2; in reality, $eGFR_{CG}$ at start of dialysis was 9.8 and 12.0 mL/min/1.73 m^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/1.73 m^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 6 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.* [30] 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.* [31] performed a prospective cohort study in 233 Asian patients. The comparison was between patients who accepted PD and were immediately started and patients who 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.* [32] 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 separate results for patients with diabetes were not presented. In only 25% of the patients with diabetes was dialysis unplanned versus 49% in patients without diabetes, indicating that the comparison of planned versus unplanned dialysis is perhaps different in patients with versus without diabetes. Finally, probably planned versus unplanned start of dialysis cannot be considered the same as early versus late start of dialysis.

  Coronel *et al.* [33] compared survival in 100 patients with diabetes that started PD either below or equal and higher to 7.7 mL/min/1.73 m^2, finding that starting early (i.e. ≥7.7 mL/min/1.73 m^2) was significantly associated with better survival at 3 years (61% versus 39%). However, this is an observational retrospective study, and patients who started at an eGFR below 7.7 mL/min/1.73 m^2 were not comparable with patients who start at higher levels. Kazmi *et al.* [34] studied the effect of comorbidity on the association between eGFR at start of dialysis and survival on dialysis in more than 300 000 people in the USA. 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.* [35] analysed more than 11 000 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.* [36] studied the effect of lead-time bias in 235 European patients by calculating when these patients reached eGFR = 20 mL/min/1.73 m^2 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.* [37] also studied the effect of early and late start of dialysis on survival on dialysis in almost 900 000 patients in the USA. 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. Beddhu *et al.* [38] also investigated timing of start of dialysis, modelled as renal function at the start of dialysis in a continuous fashion, in incident haemodialysis and PD 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.* [39] demonstrated that there was a dose–response relationship 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_{Adj} = 1.18 (95% CI 1.01–1.37)], Q3: HR_{Adj} = 1.21 (95% CI 1.04–1.41), Q4: HR_{Adj} = 1.66 (95% CI 1.43–1.93), and Q5: HR_{Adj} = 2.44 (95% CI 2.11–2.81). Clark *et al.* [40] found that 8441 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 with late start of dialysis [eGFR (MDRD) ≤10.5 mL/min] in 17 469 incident HD patients. Jain *et al.* [41] did not detect a survival difference between patients starting dialysis early (n = 2994) [eGFR (MDRD) >10.5 mL/min] [HR = 1.08 (95% CI 0.96–1.23)] mid-start of dialysis (n = 2670) [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 the 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 of 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 RCT, there appears to be no evidence to support the hypothesis that in patients with diabetes, start of dialysis based on pre-defined levels of eGFR before they become symptomatic versus when they become symptomatic is of any benefit in terms of mortality or QoL. As such, the same recommendations as made previously by ERBP [27] for the general CKD 5 population can be maintained for CKD 5 patients with diabetes.

In patients with diabetes, it might be cumbersome to distinguish whether polyneuropathy, nausea, concentration disturbances or 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 in making this distinction. Therefore, it can be that, in reality, patients with diabetes start at somewhat higher eGFR levels compared with patients without diabetes. Although this was already mentioned in the original guidance published by ERBP [27] 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 reassessment in the current guidance production process makes it clear that there is no reason to start patients with diabetes at higher levels of eGFR *just because* they *have diabetes*, rather 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 discuss in a timely manner, in patients opting for HD, 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. In addition, 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, graft or tunnelled catheter be preferred as initial access?

Statements

1.3.1 We recommend that reasonable effort be made to avoid tunnelled catheters as primary access in patients with diabetes starting HD as renal replacement therapy **(1C).**

1.3.2 We recommend that the advantages, disadvantages and risks of each type of access be discussed with the patient.

Advice for clinical practice

- When deciding whether or not to create a native vascular access, the following points should be considered:
  - expected life expectancy of the patient
  - expected QoL 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 HD patients with a native vascular access have a better outcome when compared with 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 a vascular access, and especially at the more distal parts of the arm, can be cumbersome in view of the 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 [42]. 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 the further exclusion of 36 articles. Finally, 13 studies were included in the data extraction table: 2 prospective cohort studies, but which dated from an older era [43, 44], 10 retrospective cohort studies [45–53] and 1 case–control study [54]. 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 [55], starting from the hypothesis that if any difference at all exists in 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, >65-year-old HD patients (total $n = 764\,200$ patients with diabetes), Chan *et al.* [45] reported a similar mortality rate and vascular access patency among patients with AVF versus AVG. Dhingra *et al.*

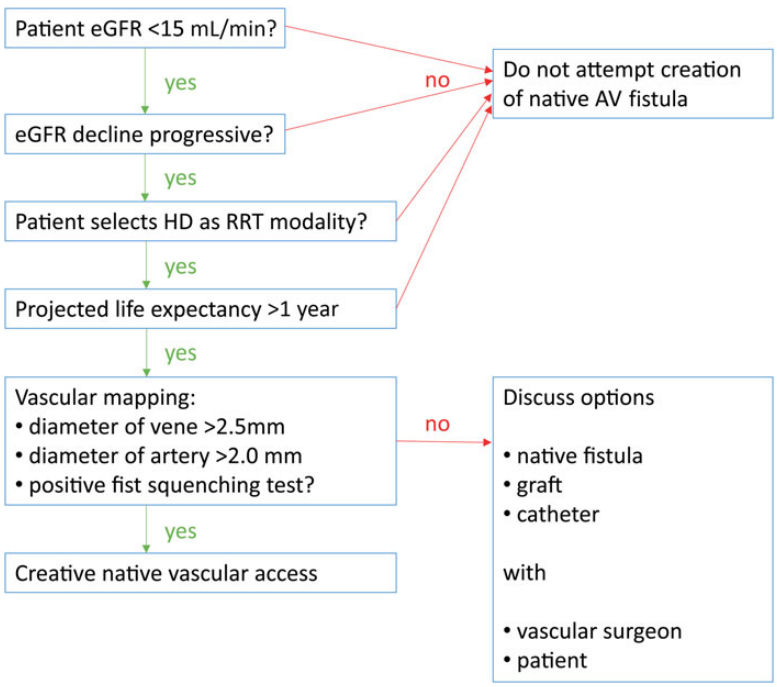

FIGURE 2: Decision flow chart for vascular access in patients with diabetes.

[47] 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 were higher in CVC versus AVF, and all-cause and infection mortality were higher in AVG versus AVF. In a prospective single-centre cohort study including incident and prevalent HD patients (total $n = 21863$ with diabetes), Saxena *et al.* [44] reported a lower rate of vascular access-related sepsis among patients with AVF compared with those with AVG or dialysis catheter; patients with femoral catheters presented a higher sepsis-related mortality in comparison with 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 $n = 29\,368$ with diabetes), Murphy *et al.* [51] reported apparently similar results for age and better results in males versus females, but no statistical significance was reported. Field *et al.* [48] 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 [43], similar cumulative patency rates between distal *versus* proximal AVF were observed. Konner *et al.* [50] reported in their retrospective single-centre cohort study [total $n = 247$ 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 versus 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.* [49] reported in a retrospective single-centre cohort study (total $n = 127$, 52 with diabetes) that patients with versus without diabetes had a 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.* [53] 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.* [54] report the risk factors associated with finger gangrene after placement of an AV fistula in a case-control single-centre study [total $n = 222$ patients, 121 with diabetes (54%)]: diabetes, peripheral and coronary artery disease (CAD) and age under 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 [56] to support technical details of vascular access creation.

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

> *We recommend reasonable effort be made to avoid tunnelled catheters as primary access in patients with diabetes starting* HD *as renal replacement therapy* ***(1C).***

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 has been a general consensus that efforts should be made to reduce these high rates as, according to various large observational studies [55], there is 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 [57–59]. 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 having a functioning fistula.

> *We recommend that the advantages, disadvantages and risks of each type of access be discussed with the patient.*

Although the evidence is scanty, creation of vascular access is more cumbersome and results more often in non-maturation in patients with versus without diabetes, and this particularly in women and the elderly. Factors predicting non-maturation in the general dialysis population, such as a diameter of the feeding artery <2 mm and/or of the draining vein <2.5 mm, or absence of flow increase with fist exercise, should certainly raise concern as to the probability that a functioning access can be created in such a patient [56]. In addition, life expectancy in some patients is low, and protracted and persisting efforts to create a vascular access might cause a substantial decrease in QoL, 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 using a native fistula as preferred access, when feasible. Three of them recommend trying to place a graft rather than a tunnelled catheter in case a native fistula is deemed impossible. In their respective discussions, they all highlight that the creation of a native vascular access might be more problematic in patients with versus 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, RCTs should be designed to explore potential hypotheses.

Chapter 1.4 Is there a benefit to undergoing renal transplantation for patients with diabetes and CKD stage 5?

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

Statements only for patients with type 1 diabetes and CKD stage 5

1.4.2 We suggest living donation kidney transplantation or simultaneous pancreas kidney transplantation to improve survival of suitable patients (**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 and CKD stage 5

1.4.5 We recommend against pancreas or simultaneous kidney pancreas transplantation (**1D**).

1.4.6 We recommend diabetes in itself should not be considered a contraindication to kidney transplantation in patients who otherwise comply with inclusion and exclusion criteria for transplantation (**1C**).

Advice for clinical practice

- Successful simultaneous pancreas–kidney transplantation improves QoL, neuropathy, glycaemic control and diabetic retinopathy in type 1 diabetes.
- Perioperative comorbidity of simultaneous pancreas kidney transplantation can be substantial.
- We refer to the ERBP guideline [60] on kidney transplant donor and recipient evaluation and peri-operative management for assessing 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 as to what extent only the most optimal patients with diabetes are accepted for transplantation is important for correct interpretation of the observational data. This information, together with information on the outcome of transplantation, can help us to formulate advice on 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 <45 mL/min) mostly have complex comorbidity. In the post-transplantation period, immunosuppressive medication can deteriorate glycaemic control and worsen already existing vascular comorbidity. On the other hand, survival and QoL when remaining on dialysis might also be far from optimal. Therefore, we need to ascertain whether patients with diabetes could 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 for evaluating the potential selection bias for patients for transplantation (see Supplementary data extraction tables). Most studies were consistent with the hypothesis that compared with CKD patients without diabetes, those with diabetes are less likely to be waitlisted. Most guidelines recommend more extensive screening in patients with diabetes [60–62].

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

We found 21 papers reporting observational data. Eight additional studies were identified by hand searching the reference lists of previously identified papers. The majority of the studies suffered from methodological limitations and were at high risk of different forms of bias. The studies reporting on hard endpoints such as mortality or graft outcome were mostly large registry-based patient populations. Some reported data from a single centre [63–69] with a high potential of centre bias, limiting generalizability. Also, not all studies distinguished type 1 from type 2 diabetes in their evaluation of outcome of transplantation versus remaining on dialysis [70] or in the outcome of a pancreas graft [63]. Most importantly, most studies suffered 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.

Some studies stratified their analysis according to diabetes status [71–73], whereby the adjusted mortality risk is higher

Table 5. Observational studies on outcome after different modalities of transplantation in patients with type 1 diabetes

	Time period	Mean age	Subjects	1-year patient survival	5-year patient survival	7-year patient survival	10-year patient survival	1-year kidney graft survival	5-year kidney graft survival	7-year kidney graft survival	10-year kidney graft survival
Rayhill *et al.* [66] 2000	1986–1996	39	805	99% haplo-identical LRDK, 96% SPK and 94% DKD	85% haplo-idential LRDK, 88% SPK and 72% DKD			94% haplo-idential LRD 87% SPK, 86% DKD	72% haplo-identical LRD 78% SPK 64% DKD		
Bunnapradist *et al.* [225] 2003	1994–1997	41	6016		87% SPK and 76% DKD				73% SPK and 64% DKD		
Lindahl *et al.* [68] 2013	1983–2010	47	630	94% for SPK versus 95% for LDK versus 89% for DKD	85% for SPK versus 79% for LDK versus 63% for DKD		67% for SPK versus 56% for LDK versus 36% for DKD	90% for SPK versus 92% for LDK versus 85% for DKD	75% for SPK versus 72% for LDK versus 60% for DKD		57% for SPK versus 45% for LDK versus 30% for DKD
Mohan *et al.* [69] 2003	1992–2002	47	101	96% for SPK versus 93% KTA	89% for SPK versus 57% KTA			93% for SPK versus 94% KTA	76% for SPK versus 58% KTA[a]		
La Rocca *et al.* [64] 2001	1984–1998	46	ESRD type 1 DM ($n = 351$)			77.4% SPK versus 56.0% KTA versus 39.6% WL				85.2% SPK versus 70.0% KTA.	
Young *et al.* [78] 2009	2000–2007	42	type 1 DM who received a kidney transplant ($n = 11\,362$)		87% LDK and SPK versus 75% DDK				78% LDK versus 76% SPK versus 66% DDK		
Waki *et al.* [90] 2012	1995–2002	44	type 1 DM who received a kidney transplant ($n = 1088$)	96.4% SPK versus 95.2% KTA	89.6% SPK versus 78.2% KTA				78.2% SPK versus 65.5% KTA		
Weiss *et al.* [81] 2009	1997–2005	40	type 1 DM on SPK waiting list ($n = 9630$)	95.9% SPK versus 97.2% LDK versus 95.6% DDK		88.6% SPK versus 80.0% LDK versus 73.9% SPK with pancreas loss y1 versus 64.8% DDK		92.0% SPK versus 94.8% LDK versus 90.3% DDK		72% SPK (functioning pancreas y1) versus 63.6% LDK versus 59.8% SPK with pancreas loss y1 versus 49.7% DDK	
Ojo *et al.* [79] 2001	1988–1998	34	ESRD type 1 DM on SPK waiting list ($n = 13467$)				67% SPK versus 65% LDK versus 46% DKD				
Poommipanit *et al.* [75] 2010	2000–2007	28	type 1 DM on SPK waiting list ($n = 11966$)	99.2% PALK versus 95.6% SPK	91% PALK versus 87% SPK				86% PALK versus 77% SPK		
Kleinclauss *et al.* [63] 2009	1995–2003	45	diabetes (type 1 or 2) LDK recipients ($n = 250$)	98% PAK versus 100% KTA-eligible PAK	89% PAK versus 88% KTA-eligible PAK		71% PAK versus 76% KTA-eligible PAK		82% PAK versus 84% KTA-eligible PAK		67% PAK versus 62% KTA-eligible PAK

DKD, deceased kidney donor, KTA, kidney transplant alone; L(R)DK, living (related) kidney donor; SPK, simultaneous kidney pancreas transplant; WL, waitlisted patients; PA(L)K, pancreas after kidney (from living donor).
[a]It is unclear whether this is perhaps a mistake in the original data, as 5-year graft KTA was reported to be 58%, whereas 5-year patient surival was reported to be 57%.

in patients with versus without diabetes [73, 74]. Patient survival is better in CKD stage 5 patients with diabetes who actually had a transplant versus those remaining on the waiting list [70, 73].

The studies dealing with the different options for type 1 diabetes are summarized in Table 5. The table intends to help physicians to discuss the different options and their pros/cons with the patient to support shared decision-making. Patients receiving a pancreas after kidney transplantation had better graft survival compared with those who were eligible but did not receive a pancreas graft or only after 5 years or more). Other analyses have demonstrated superior outcomes of pancreas transplantation after living donor kidney versus simultaneous pancreas and kidney [75]. The survival benefit of simultaneous pancreas–kidney compared with kidney transplantation alone in patients with type 1 diabetes appeared inconsistent and also depended on the modality of kidney transplantation (cadaveric versus living donor kidney), the time point of assessment and the adjustment for confounders. Changes in patient selection criteria, donor criteria and surgical and immunosuppressive treatment can also explain changes in outcome according to time period [68]. Early survival benefit in simultaneous pancreas kidney versus kidney transplant alone often is not observed with even increases in early post-transplantation mortality [76]. Long-term outcome is in most, but not all, studies better with simultaneous pancreas-kidney than with kidney transplantation alone [65, 67–69, 76]. In an older UNOS analysis, simultaneous pancreas–kidney recipients had a higher mortality than living donor kidney recipients through the first 18 months post-transplantation, but they had a lower relative hazard thereafter [77]. In the univariate survival analysis, no difference in outcome for patient and graft [78] was observed between patients receiving a simultaneous pancreas–kidney versus 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 versus solitary renal transplantation in other studies [79, 80]. Pancreas graft failure in the first year seems to attenuate or even abolish the beneficial long-term effects of SPK versus kidney transplantation alone [81] as it decreases both graft and patient survival [82], and also having preserved kidney graft function at year 1 seems to be an important modulating factor [77].

Analyses of QoL or intermediate endpoints such as neuropathy [83], retinopathy [84] or cardiovascular surrogate markers [85–87] without exception included small patient numbers and/or lacked adjustment for confounders. They compare different patient populations (for instance, simultaneous pancreas–kidney transplantation with failed versus functioning pancreas graft) [88, 89] with—in the QoL studies—numerous, and not always consistent, uses of valid assessments of physical state, cognitive functioning and mental health. Comparing QoL of patients receiving simultaneous pancreas–kidney transplantation with that of patients losing or refusing their pancreatic graft [89] might overestimate the differences in perceived QoL between the groups.

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

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 5) ***(1D).***

Only observational data are available to support guidance in this area.

Statements only for patients with type 1 diabetes:

*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**).*

*We suggest against islet transplantation after kidney transplantation with the aim to improve survival (**2C**).*

*We suggest pancreas grafting to improve survival after kidney transplantation (**2C**).*

The same risk of selection bias might be present in the studies on simultaneous pancreas–kidney transplantation for patients with type 1 diabetes. Simultaneous pancreas–kidney transplantation is mostly performed at high-volume centres, which most likely hampers generalizability of outcomes. The healthiest patients are also likely to be allocated to simultaneous pancreas–kidney transplantation, receive the highest quality organs [90] and more often receive a pre-emptive transplant [67].

Figure 3 provides a potential decision flow chart for transplantation modality selection in patients with type 1 diabetes. If 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.

Statements only for patients with type 2 diabetes:

*We recommend against pancreas or simultaneous kidney-pancreas transplantation (**1D**).*

*We recommend diabetes per se should not be considered a contraindication to kidney transplantation in patients who otherwise comply with inclusion and exclusion criteria for transplantation (**1C**).*

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

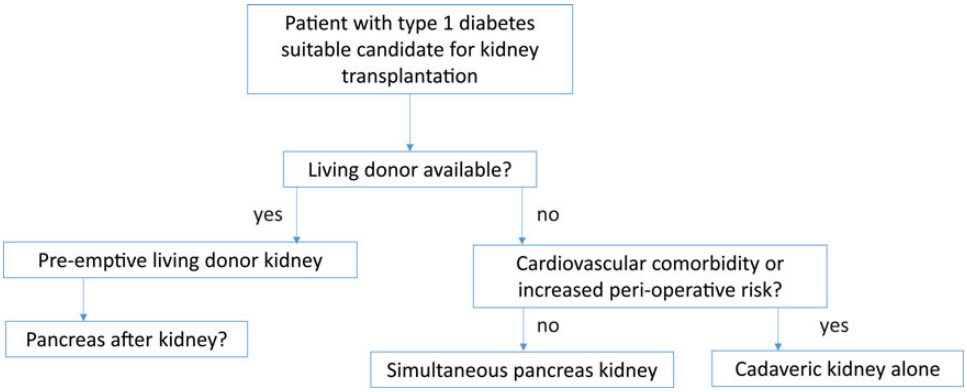

FIGURE 3: Transplantation decision flow chart for patients with type 1 diabetes.

for cardiovascular disease [60], in patients with diabetes. As a result, it should be taken into account that, for patients with diabetes, the outcomes observed after transplantation are only valid for those without substantial comorbidity, i.e who passed our current pre-transplant screening procedures [60]. For this group of patients with type 2 diabetes, the presence of diabetes does not appear to be an additional risk factor per se; as a consequence, the guideline development group judges that diabetes in itself should not be a contraindication for transplantation, provided that the patient complies with current pre-transplant screening recommendations.

What do the other guidelines say?

We did not find any guidelines providing guidance on this topic.

Suggestions for future research

1. Prospective multicentre observational studies comparing hard endpoints between living donor kidney transplantation and simultaneous pancreas–kidney transplantation in patients with type 1 diabetes, appropriately adjusted for comorbidity.
2. Prospective, adequately powered multicentre studies to assess the effect of transplantation compared with 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 <45 mL/min)

Chapter 2.1

A. Should we aim to lower HbA1C by tighter 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?

Statements

2.1.1 We recommend against tighter glycaemic control if this results in severe hypoglycaemic episodes (**1B**).

2.1.2 We recommend vigilant attempts to tighten glycaemic control with the intention to lower HbA1C when values are >8.5% (69 mmol/mol) (**1C**).

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**).

2.1.4 We recommend intense self-monitoring only to avoid hypoglycaemia in patients at high risk for hypoglycaemia (**2D**).

Advice for clinical practice

- Severity of hypoglycaemic episodes are defined as 'mild' when it can be treated by the patient himself and as 'severe' when assistance is required.
- The most important concern is to avoid episodes of hypoglycaemia.
- Empower patients at moderate and high 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

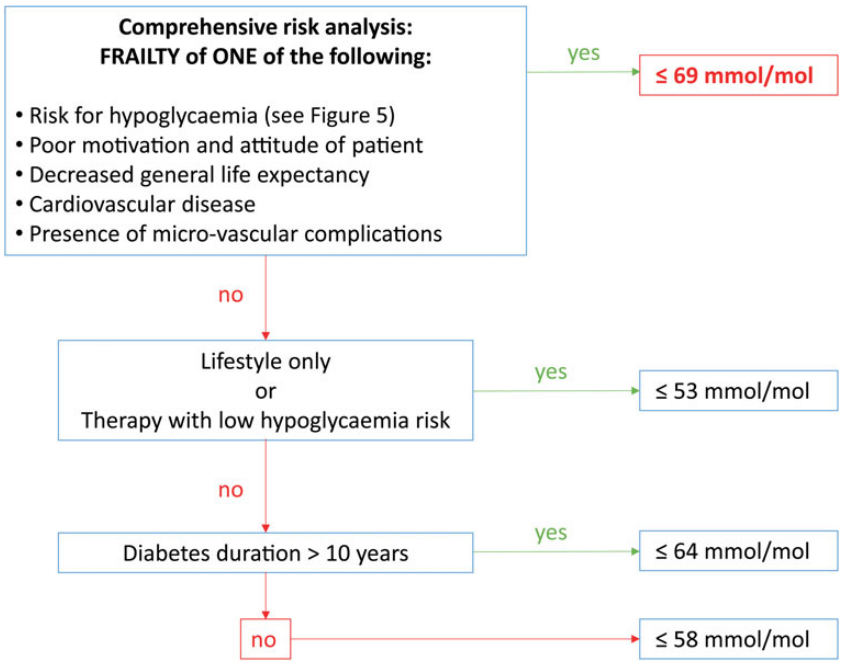

FIGURE 4: Flowchart of management targets for HbA1C in patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min).

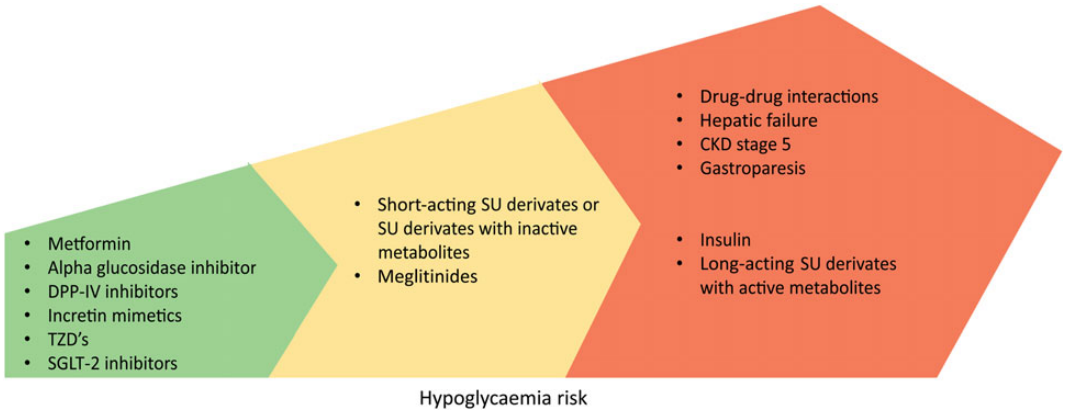

FIGURE 5: Assessment of risk for hypoglycaemia.

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 programmes helps to decrease diabetes-specific complications in this specific patient population. These programmes are labour intensive and expensive and thus have an important impact on health care resources.

- What did we find?

We found one recent systematic review in dialysis patients [91] on the association between HbA1C and outcome that included 10 studies (83 684 participants) (9 observational studies and 1 secondary analysis of a randomized trial). After adjustment for confounders, patients with baseline HbA1c levels >69 mmol/mol (8.5%) versus 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 >69 mmol/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 <36 mmol/mol (5.4%) were also associated with increased mortality risk (HR 1.29; 95% CI 1.23–1.35).

A recent randomized trial demonstrated that adding saxagliptin to the existing treatment, resulted in a decrease of HbA1C and a higher percentage of patients reaching an HbA1C <7%, but not in an improvement in cardiovascular outcomes [92].

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

stage 3b or higher (eGFR <45 mL/min).

A high-quality systematic review demonstrated lack of benefit of tighter glycaemic control as assessed by an HbA1C <7 (53 mmol/mol) or 7.5% (59 mmol/mol) [93], whereas there was a clear risk for enhanced hypoglycaemia episodes when glycaemic control is tightened [93].

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 [97]. Although there was an improvement in HbA1C levels in the self-monitoring group (−2.7 mmol/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: (i) evaluate the available evidence in the general population with diabetes; (ii) evaluate which considerations made our target population special in this regard, and would have an impact on translation of the data from the general diabetes population.

*We recommend against tighter glycaemic control if this results in or increases the risk for severe hypoglycaemic episodes (**1B**).*

*We recommend vigilant attempts to tighten glycaemic control with the intention to lower HbA1C when values are >8.5% (69 mmol/mol) (**1C**).*

*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**).*

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 <45 mL/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).

*We recommend intense self-monitoring only to avoid hypoglycaemia in patients at high risk for hypoglycaemia (**2D**).*

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 CKD stage 3b or higher (eGFR <45 mL/min).

  In their 2012 position statement [94], the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) also promote taking 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 CKD, KDOQI [95] recommends a target 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 aiming for an HbA1c target of <7.0% in patients at risk of hypoglycaemia, and suggest that the target of HbA1c can be extended above 7.0% in individuals with comorbidities or limited life expectancy and risk of hypoglycaemia. In their rationale, they explain that the risk for hypoglycaemia outweighs the potential benefits of reduced microvascular complications in patients with advanced stages of CKD.

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 versus standard control (HbA1c <53 mmol/mol versus <69 mmol/mol), specifically in patients with diabetes and CKD stage 3b–5 using drugs with very low risk to induce hypoglycaemia, is warranted.

Chapter 2.2. Are there better alternatives than HbA1c to estimate glycaemic control in patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2)?

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 <45 mL/min/1.73 m^2) (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 versus without CKD stage 3b or higher (eGFR <45 mL/min), and this both for the absolute value as well 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 CKD stage 3b or higher (eGFR <45 mL/min) has been questioned. As a different association between glycaemic control and morbidity/mortality might be observed in patients with and without CKD stage 3b or higher (eGFR <45 mL/min), we wanted to summarize the current knowledge and evidence of the use of HbA1C and of alternative glycaemic markers [glycated albumin, fructosamine, 1,5-anhydroglucitol (1,5-AG) and continuous glucose monitoring] in this specific patient population.
- What did we find?

  The guideline development group conducted a narrative review [96] to explore different methods to assess longer term glycaemic control, and their accuracy in patients with CKD stage 3b or higher (eGFR <45 mL/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 the superiority of other glycaemic markers (glycated albumin, fructosamine, 1,5-AG and continuous glucose monitoring) at this time, the guideline development group judges that HbA1c should remain the reference standard for glycaemic monitoring in patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min).

  In the future, continuous subcutaneous glucose monitoring seems to be a promising method to correctly evaluate glycaemic control in patients with diabetes undergoing HD 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 CKD stage 3b or higher (eGFR <45 mL/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 CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2)?

B. In patients with diabetes type 2 and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2), is maximal oral therapy better than starting/adding insulin at 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 adding on a drug with a low risk for hypoglycaemia (fig 5, 6 and 7) as 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 in situations with an increased risk for AKI (1C).

Advice for clinical practice

- Consider instructing 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 Figures 5 and 7.
- In patients with diabetes type 2 and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2) who are on metformin, the

Table 6. Comparison of the different glycaemic markers in patients with diabetes and CKD stage 3b or higher

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

		CKD-1	CKD-2	CKD-3	CKD-4	CKD-5ND	CKD-5D
	Metformin	No adjustments		1,5g-850 mg/day*	500 mg/day**	Consider carefully/Awaiting further data	
Sulfonylureas	Chlorpropamide	No adjustments		100-125 mg/day	To be avoided		
	Acetohexamide	To be avoided					
	Tolazamide	To be avoided					
	Tolbutamide	250mg, 1-3 times/day				To be avoided	
	Glipizide	No adjustments					
	Glicazide	Start at low doses and dose titration every 1-4 weeks					
	Glyburide	To be avoided					
	Glimepiride	Recude dosage to 1 mg/day				To be avoided	
	Gliquidone	No adjustments					
Meglitinides	Repaglinide	No adjustments				Limited experience available	
	Nateglinide	No adjustments				Start at 60 mg/day	To be avoided
α-gluc inhibitors	Acarbose	No adjustments			use lowest dose and <50mg		
	Miglitol	Limited experience available					
	Pioglitazone	No adjustments					
DPP-IV inhibitors	Sitagliptin	No adjustments		Reduce to 50 mg/day	Reduce to 25 mg/day		
	Vildagliptin	No adjustments		Reduce to 50 mg/once daily			
	Saxagliptin	No adjustments		Reduce to 2,5 mg/once daily			
	Linagliptin	No adjustments					
	Alogliptin	No adjustments		Reduce to 12,5 mg/daily			
Incretin Mimetics	Exenatide	No adjustments	Reduce dose to 5 mcg/once to twice daily		To be avoided		
	Liraglutide	Limited experience available					
	Lixisenatide	No adjustments	Careful use if GFR 80-50 mL/min				No experience available
	Pramlintide	Limited experience available					
SGLT-2 inhibitors	Dapagliflozin	Limited experience available					
	Canagliflozin	Reduced efficacy		Careful monitoring		To be avoided	
	Empagliflozin	Limited experience available					

FIGURE 6: Dose recommendations in CKD.

		All-cause mortality	Cardiovascular events	Risk of hypoglycaemia	Weight gain	HbA1C change	dose adaptation in advanced CKD
Biguanides	Metformin						Yes
Sulfonylureas	Ckoorpropamide						Avoid
	Acetohexamide						Avoid
	Tolazamide						Avoid
	Tolbutamide						Avoid
	Glipizide						no
	Glicazide						Yes
	Glyburide						Avoid
	Glimepiride						Avoid
	Gliquidone						no
Meglitinides	Repaglinide						Yes
	Nateglinide						Yes
a-glucosidase inhibitors	Acarbose						No
	Miglitol						no data
DPP-IV inhibitors	Sitagliptin						Yes
	Vildagliptin						Yes
	Saxagliptin						Yes
	Linagliptin						No
	Alogliptin						Yes
Incretin mimetics	Exenatide						Avoid
	Liraglutide						most likely not
	Lixisenatide						Yes
	Pramlintide						no data
SGLT-2 inhibitors	Dapagliflozin						avoid;not effective
	Canagliflozin						avoid;not effective
	Empagliflozin						avoid;not effective

FIGURE 7: Impact of different classes of glycaemia-lowering drugs on different outcomes. (For full data extraction: see Supplementary tables) and Arnouts *et al.* [110]. Dark green denotes evidence for beneficial effect; red indicates evidence for negative effect; yellow represents not investigated or insufficient data; salmon denotes evidence for weak negative effect; aquamarin represents evidence for neutral to weak positive effect; dark blue indicates evidence for lack of effect/neutral.

decision to withhold the drug 48 h 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 versus intra-arterial), and presence of other coexisting 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 good glycaemic control is postulated to be one of the cornerstones for preventing and delaying progression of microvascular and macrovascular complications in patients with both diabetes and CKD. 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 put them in 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 than starting/adding insulin and whether specific types of drugs should be preferred over others.

- What did we find?

  We did not retrieve any RCTs 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 <45 mL/min/1.73 m^2). Some drugs need dose adaptation when administered in patients with renal insufficiency (see Table 6). The different classes of glycaemia-lowering drugs and their main mechanisms of action are listed in Table 7.

  One study [97] showed a high rate of hypoglycaemia when using insulin when compared with glyburide in patients with CKD, but apparently, the reported risk was lower than in patients with normal kidney function. Another study showed a high rate of hypoglycaemia in patients with CKD treated with sulphonylureas [98].

  Three studies analysing the effects of DPP4 inhibitors in patients with CKD (one sitagliptin [99], one vildagliptin [100], two saxagliptin [101, 102]) were retrieved. Most of these studies only analysed surrogate endpoints, mostly reduction of HbA1C levels. None of these studies reported on higher incidence of side effects when compared with non-CKD patients. Only one study was performed in ESRD patients (saxagliptin), demonstrating no effect on all-cause or cardiovascular comorbidity [92]. There was however a trend for an increased risk for the prespecified secondary outcomes of need for hospitalization for congestive heart failure (3.5 versus 2.8% in saxagliptin versus placebo group, hazard ratio 1.27, 95% CI 1.07–1.51). One study [103] evaluated the effect of liraglutide in CKD, reporting an increased frequency of nausea. Another study [104] demonstrated that risk of hypoglycaemia was lower with meglitinides when compared with insulin in patients on HD. One study [105] demonstrated that the 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 <45 mL/min/1.73 m^2 11 manuscripts reporting on 10 studies: 3 RCTs, 5 prospective observational and 2 retrospective observational cohorts. The study by Lukashevic [100] is a double-blind randomized study on vildagliptin versus placebo added to already existing glycaemia-lowering treatment. In patients with diabetes and CKD stage 3 (vildagliptin 165/placebo 129) or CKD stage 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 $-0.4 \pm 0.2\%$ ($P = 0.005$) in CKD stage 3 (baseline = 7.8%) and $-0.7 \pm 0.2\%$ ($P < 0.0001$) in CKD stage 5 (baseline = 7.6%). In patients with CKD stage 3, similar proportions of patients experienced any adverse event (AE) (84 versus 85%), any serious adverse event (SAE) (21 versus 19%), any AE leading to discontinuation (5% versus 6%) and death (1% versus 0%) with vildagliptin and placebo, respectively. This was also true for patients with CKD stage 5: AEs (85% versus 88%), SAEs (25% versus 25%), AEs leading to discontinuation (10% versus 6%) and death (3% versus 2%). Of note, the first authors of these papers are employees of the pharmaceutical company producing the drug.

  Nowicki *et al.* [101] present one randomized double-blind 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 creatinine clearance <50 mL/min. The study by McGill [106] 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-analyses comparing different combinations of oral glycaemia-lowering drugs or insulin and providing data on all-cause mortality, cardiovascular events, risk for hypoglycaemia, 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 that they included patients with CKD stage 3b or higher. In none of the others was interaction of CKD versus no CKD on the reported outcomes taken into account.

Table 7. Oral glycaemia-lowering drugs: mechanisms of action

Drug class	Mechanisms of action	Examples (alphabetical order)
Biguanides	- Decrease hepatic glucose production - Increase insulin sensitivity - Increase insulin-mediated utilization of glucose in peripheral tissues - Decrease glucose intestinal absorption	Metformin
Sulfonylureas	- Stimulate insulin secretion from the pancreas - Closes K-ATP channels on β-cell plasma membranes	Acetohexamide, chlorpropamide, glibenclamide, gliclazide, glyburide, glimeperide, glipizide, gliquidone
Meglitinides	- Stimulate pancreatic insulin secretion by closing K-ATP channels on β-cell plasma membranes	Nateglinide, repaglinide
Alfa glucosidase inhibitors	- Block the action of the α-glucosidase with reduced hydrolysis of complex saccharides - Reversible inhibition of the pancreatic enzyme α-amylase	Acarbose, miglitol
Glitazones	- Reduce insulin resistance - Increase glucose uptake in muscles and adipose tissue - Decrease hepatic glucose production	Pioglitazone
DPP-IV inhibitors	- Inhibit DPP-4, which inactivates endogenous incretins	Alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin,
Incretin mimetics	- Promote glucose dependent insulin secretion by pancreatic β cells - Suppress glucagon secretion - Slow gastric emptying	Eexenatide, liraglutide, lixisenatide
Amylin analogues	- Regulate glucose levels in response to food intake - Control gastric emptying and postprandial glucagon secretion - Reduce food intake by increasing satiety	Pramlinitide
SLT-2 inhibitors	- Block the sodiumglucose transport protein subtype 2, thus increasing renal loss of glucose	Canagliflozin, dapagliflozin, empagliflozin

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, DPP-IV inhibitors and the SGLT2 inhibitors. Metformin, acarbose, exenatide, liraglutide, lixisenatide, pramlinitide 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 [107]. Although this Cochrane review was not restricted to patients with CKD stage 3b or higher, it also did 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 cases, overdosing of metformin was present, although there was no consistent association between metformin levels and metabolic acidosis or lactate levels. 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 (GFR) 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 <45 mL/1.73 m^2 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 into our target population of patients with diabetes type 2 and CKD stage 3b or higher (eGFR <45 mL/1.73 m^2 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 the pharmacokinetic data of glycaemia-lowering drugs was done (Supplementary data tables). 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 versus without eGFR <45 mL/1.73 m^2 min. Based on interpretation of the available evidence, the guideline development group judged that particularly 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, as visualized and summarized in Figures 5 and 7.

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).***

There is little doubt in general guidelines on management of type 2 diabetes that metformin should be the first-line glycaemia-lowering drug [94, 108] because of its beneficial impact on all-cause and cardiovascular mortality. In addition, metformin carries 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 up to a clearance of 30 mL/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 into metformin therapy [109]. In any case, metformin dose should be adapted to renal function [110]. The guideline development group acknowledged that, despite its proven value, the use of metformin in patients with CKD remains controversial. Even below the threshold of 30 mL/min, the guideline development group considers the cost–benefit of metformin to be positive, but as less data are available [111, 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 an eGFR <30 mL/min/1.73 m^2 [108]. In another systematic review, Kajbaf *et al.* [112] 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 logical recommendation to adapt the dose of metformin according to renal function, as is done for other drugs excreted by the kidneys, only appeared in eight guidance documents.

The guideline development group explicitly wanted to highlight this important change in paradigm to adapt the dose to renal function rather than to stop metformin.

With regard to 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 may be publicly available, and that, by lack of access to all information, an incorrect statement would be made.

*We recommend adding on a drug with a low risk for hypoglycaemia (Figs. 5, 6 and 7) as additional agent when improvement of glycaemic control is deemed appropriate according to Figure 4 (**1B**).*

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 <45 mL/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 these drugs are commonly cheaper than other glycaemia-lowering drugs. However, one should take into account that a reduction of the glycaemia-lowering effect of sulphonylurea over time is common, due to islet cell exhaustion. Many of these drugs require progressive dose reduction with progression of CKD, and some are contraindicated in CKD stage 5, as depicted in Figure 6 [110]. Glipizide, repaglinide, and gliquidone, however, do not require specific dose reduction. In dialysis patients, the glitinides 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 [113]. 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 [114]. 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, is not eliminated through a kidney-mediated pathway and only a small fraction of its metabolites are recovered in urine [115]. From a pharmacokinetic or pharmacodynamic perspective, the drug should thus be considered as safe in patients with renal insufficiency, even at advanced stages. Exenatide is cleared by proteolytic activity after glomerular filtration, and its clearance is therefore strongly diminished in patients with impaired renal function. As a consequence, its use is not recommended in CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2) [110]. Pancreatitis is a rare complication of GLP-1 agonists [116].

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 [113]. A recent large RCT demonstrated no improvement in cardiovascular outcomes in patients receiving saxagliptin versus placebo as add-on therapy, and with an increased risk for hospitalization for congestive heart failure [92]. As a consequence, the guideline group judges that adding a DPP4-I to metformin seems to be safe in terms of hypoglycaemia risk, and does not result in an increase of weight [117–119], but on the other hand, the expected benefit in terms of hard endpoints is low. Sitagliptin, vildagliptin, alogliptin and saxagliptin all require dose reduction in CKD, whereas linagliptin does not [110]. 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 <45 mL/min/1.73 m^2), as the two components have different dose adaptation requirements.

Although gastrointestinal tolerance might be problematic, adding an α-glucosidase inhibitor as second-line therapy to metformin might be considered, as the risk of hypoglycaemia is very low [120, 121], and they result in a modest weight decrease [122, 123]. However, also here, data on patient-relevant outcomes such as all-cause mortality or cardiovascular effects are largely lacking.

Triple therapy further increases the risk for hypoglycaemia [124], especially when insulin rather than another oral glycaemia-lowering agent was added as a third agent [125]. 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 α-glucosidase inhibitors were weight-neutral, and GLP-1 analogues were associated with modest weight loss [124, 125].

*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**).*

As it is unclear whether metformin per se is associated with an enhanced risk for lactic acidosis [108, 109], the guideline development group judges that using metformin in doses adapted to GFR in stable CKD is safer than switching to other glycaemia-lowering drugs such as insulin, which might increase the risk of hypoglycaemia.

However, there is indirect evidence that a rapid drop of GFR 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 diarrhoea, or dehydration 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 providing a patient information card/leaflet that should be handed over to patients with CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2) on metformin.

- What do the other guidelines say?

No other guidelines provide specific recommendations on this topic for our patient population.

Suggestions for future research

1. Ideally, glycaemia-lowering drugs should be investigated and compared for their effects on hard endpoints, e.g. cardiovascular disease, death, micro- and macrovascular complications, QoL and risk for severe hypoglycaemia, and this in patients with diabetes and CKD stage 3b–5.
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 clarify 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/1.73 m^2) or on dialysis and with CAD, is percutaneous coronary intervention (PCI), 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 diabetes and CKD stage 3b–5 who have stable CAD, unless there are large areas of ischaemia or significant left main or proximal LAD lesions (1C).

3.1.3 We recommend that when a decision is taken to consider revascularization, CABG is preferred over PCI in patients with multivessel or complex (SYNTAX score >22) CAD (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 than 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 infarcton (STEMI)**, primary PCI is recommended over fibrinolysis if it can be performed within the recommended time limits.

* For patients presenting with *non-STEMI (NSTEMI)*

- CABG results in improved outcomes (mortality, MACE) when compared with 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?

  CKD and diabetes are two of the most important risk factors for poor outcomes in patients with 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 CAD. PCI or CABG may improve the major outcomes and survival but also increase the risk of specific complications, such as bleeding and 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 population.

- What did we find?

  Both diabetes and CKD are associated with a poorer prognosis in patients with acute and stable CAD [126–129]. In large registry cohorts, these conditions are also associated with less and delayed diagnostic and therapeutic interventions [130].

  In general, three different clinical scenarios can be considered for patients with diabetes and CKD stage 3b–5 who have CAD: patients with stable CAD, patients with STEMI and patients with NSTEMI.

  The guidelines of the European Society of Cardiology (ESC) describe extensively the different treatment options in general for patients with stable CAD, STEMI and NSTEMI [131]. Specific ESC guidelines have also been developed for patients with diabetes [132] 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 diabetes and CKD stage 3b or higher, 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 (Supplementary data table in Chapter 3.1).

Patients with stable CAD. The ESC guideline on management of cardiovascular disease in patients with diabetes [132] 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 [133]. In this trial, however, patients with a creatinine level >2 mg/dL (>177 μmol/L) were excluded as well as patients who required immediate revascularization or had left main CAD 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, the ESC guidelines recommended CABG to 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 [133], SYNTAX [134], FREEDOM [135] trial and recent larger registries and meta-analyses [136–139]). PCI for symptom control may be considered as an alternative to CABG in patients with diabetes and less complex multi-vessel CAD (Syntax score ≤22) in need of revascularization.

In a *post hoc* analysis of the COURAGE study [140] with 2287 patients with stable CAD, patients with and without CKD were randomized to PCI and optimal medical therapy (OMT) or OMT alone. After adjustment for differences, the study showed that PCI did not reduce the risk of death or myocardial infarction when added to OMT [141]. Available data from registries suggest a trend towards better long-term survival with CABG when compared with PCI in patients with CKD stage 3b or higher. In patients with CKD stage 3b or higher, but not yet dialysis-dependent, CABG is associated with a higher procedural mortality and a greater likelihood of need for dialysis after revascularization.

Patients with STEMI

In patients with diabetes who present with STEMI, primary PCI is recommended over fibrinolysis, if available, and should be performed within recommended time limits [142]. As a consequence of the higher absolute risk, the number needed to treat (NNT) to save one life 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 [143] showed no benefit of revascularization of an occluded infarct-related artery 3–28 days after myocardial infarction. In patients with milder degrees of CKD, results from registries suggest that primary PCI is associated with a better outcome, but this finding is uncertain for those with CKD stage 3b–5 or on dialysis.

Patients with NSTEMI. Patients with diabetes have a high risk for mortality and an unfavourable course, and as such require aggressive pharmacological as well as early invasive (EI) management when presenting with NSTEMI. In the 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 diabetes patients who have stable CAD, and it is unclear whether these data can be extrapolated to patients with NSTEMI. Patients with NSTEMI and CKD stage 3b–5 should receive the same first-line antithrombotic treatment as patients without CKD stage 3b–5, unless they have main stem lesions and or/advanced multi-vessel disease on coronarography. Appropriate dose adjustments according to the severity of renal dysfunction should be made. It is unclear, however, whether an invasive strategy has an impact on clinical endpoints in these patients, as most trials of revascularization in NSTEMI excluded patients with more advanced stages of CKD. In general, ESC guidelines on NSTEMI state that CABG or PCI is recommended in

patients with CKD amenable to revascularization after careful assessment of the risk-benefit ratio in relation to the severity of renal dysfunction. Data from registries and observational studies suggest that an EI therapy is associated with a better outcome in earlier stages of CKD, but the benefit decreases with worsening renal function and is uncertain in those with CKD stage 3b–5 or on dialysis. Data from the Korean Registry Study [144] with 5185 patients in total, compared EI, deferred invasive (DI) and conservative strategies in patients with acute NSTEMI and 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 tended to decrease as renal function decreased. Data presented by the USRDS registry in a 2002 [145] report showed that in diabetic ESRD, there was no significant difference in all-cause death risk for stent intervention (RR 0.99; 95% CI 0.91–1.08) but a 19% reduction for CABG surgery (RR 0.81; 95% CI 0.75–0.88) compared with PTCA. In patients with diabetes and on dialysis, there was also no significant reduction in cardiac death risk for stent intervention (RR 0.99; 95% CI 0.89–1.11) compared with PTCA alone. In contrast, the risk for cardiac death in patients with diabetes undergoing dialysis was 27% lower after CABG surgery (RR 0.73; 95% CI 0.66–0.81) compared with PTCA.

More recently, a 2012 USRDS report [146] showed that in dialysis patients, CABG when compared with PCI is associated with significantly lower risks of both death (HR 0.87; 95% CI 0.84–0.90) and the composite of death and 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 [135] results, a randomized trial that enrolled 1900 patients with diabetes and multi-vessel CAD to undergo either PCI with drug-eluting stents or CABG. For patients with diabetes and advanced CAD, CABG was superior to PCI in that it significantly reduced rates of death and myocardial infarction but was associated with a higher rate of stroke. A subgroup analysis of 129 patients with CKD showed that CABG when compared with PCI resulted in a non-significant reduction of the primary composite outcome of mortality, non-fatal MI or non-fatal stroke. However, the greater benefit of CABG versus PCI was consistent across all prespecified subgroups.

A very recent meta-analysis including patients with diabetes in general demonstrated a beneficial effect for CABG over PCI [147].

What do the other guidelines say?

Guidance in this section is largely based on the ESC guidelines. The KH-CARI guideline on management of cardiovascular risk in CKD recommends that, in patients with CKD, end-stage renal failure and after kidney transplantation, guidelines for revascularization of the general population should be adhered to (1D).

None of the other nephrology guidelines provide guidance in this area.

Suggestions for future research. A RCT of conservative versus PCI versus CABG in patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min) who present either with stable CAD or non-STEMI to investigate hard outcomes such as mortality, ESRD, QoL.

Chapter 3.2

In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2) or on dialysis and with a cardiac indication (heart failure, ischaemic 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/1.73 m^2 or on dialysis) and diabetes who have a cardiovascular indication (heart failure, ischaemic 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 (ARB) in adults with CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2 or on dialysis) and diabetes who have a cardiovascular indication (heart failure, ischaemic heart disease) but intolerance for ACE-I (2B).

3.2.3 We recommend not combining different classes of renin angiotensin-blocking agents (ACE-I, ARBs 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 stopping the RAAS inhibitor with the aim to delay the need to start renal replacement therapy can be discussed with the patient.

Rationale

- Why this question?

  In patients with CKD stage 3–5, death is a more likely 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 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 an 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 endpoints and mortality. We found nine RCTs and two *post hoc* analyses examining the outcomes after using inhibitors of the RAAS system or aldosteron receptor antagonists as cardiovascular prevention in patients with CKD (eGFR <60 mL/min/1.73 m^2 or on dialysis) and diabetes and with a cardiovascular indication (heart failure, ischaemic heart disease, vascular disease) [148–159]. Unfortunately, none of these studies data were presented by categories of patients according to staging of CKD, making it impossible to make a statement specifically about inhibitors of the RAAS system or aldosteron receptor antagonists in the eGFR <45 mL/min/1.73 m^2 or on dialysis category. Results varied widely between studies (see Supplementary data). For the major endpoint of mortality, the overall analysis shows no difference between intervention and controls, with a hazard ratio ranging from 0.64 to 1.05 (four studies in favour of RAAS inhibition, three 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 versus 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 [160] including atherosclerotic normotensive (systolic RR <130 mmHg) patients. Only patients treated with maximally tolerated doses of ACE-I versus placebo, had a 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 ARBs (RR 0.99, 95% CI 0.85–1.17) in a Cochrane review [161].

The TRANSCEND [162] (Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease, $n = 5927$ patients) compared telmisartan with placebo in patients at high vascular risk and intolerant for ACE inhibitors (ACE-Is). Telmisartan had no effect on the primary cardiovascular outcome (15.7% versus 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% versus 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) [153] ($n = 33\,357$), treatment with a calcium channel blocker, ACE-I or a diuretic was compared in high-risk hypertensive patients with a reduced GFR for a composite endpoint including ESRD, 50% or greater decline in GFR, or death from any cause. The RRs for patients taking amlodipine compared with those taking chlorthalidone for this endpoint 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 a GFR of <60 mL/min per 1.73 m^2 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 participants with diabetes and when stratified by baseline GFR. In an RCT [157] ($n = 1513$) 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 versus 359 in the placebo group reached the primary endpoint (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 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 [159] study, of 17 118 patients, 6982 had diabetes, and no interaction of diabetes versus 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 randomized to the combination therapy (HR combination versus 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 [162] varied according to the baseline urinary lbumin creatinine ratio (P = 0.006 for interaction) and estimated GFR (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 m^2. In contrast, telmisartan tended to reduce this outcome in those with microalbuminuria or an estimated GFR <60 mL/min/1.73 m^2. Treatment with RAAS inhibitors was associated with slower progression to ESRD [150, 152, 156–158] 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 [159] study, of 17 118 patients, 6982 were patients with diabetes. There was no interaction of diabetes versus no diabetes. Whereas there was no difference between ramipril and telmisartan in the endpoints 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 versus the ramipril alone group (HR 1.24; 95% CI 1.01–1.51). In a meta-analysis by Casas *et al.* [163], 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 GFR (–1.19, 95% CI –2.69 to +0.31 μL/min). The authors conclude that claims that ACE-Is 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 [161] of general patients with diabetes, there was a significant reduction in the risk of ESRD with ACE-I compared with placebo/no treatment (10 studies, 6819 patients, RR 0.60, 95% CI 0.39–0.93) and with ARBs compared with placebo/no treatment (3 studies, 3251 patients, RR 0.78, 95% CI 0.67 to 0.91). There was some evidence of a reduction of the risk of doubling of serum creatinine concentration with ACE-I compared with placebo/no treatment (9 studies, 6780 patients, RR 0.68, 95% CI 0.47–1.00) and with angiotensin-receptor antagonists compared with placebo/no treatment (3 studies, 3251 patients, RR 0.79, 95% CI 0.67 to 0.93). ACE-Is and ARBs significantly reduced the risk of progression from micro- to macroalbuminuria (17 studies, 2036 patients, RR 0.45, 95% CI 0.29–0.69 and 3 studies, 761 patients, RR 0.49, 95% CI 0.32–0.75, 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 (microalbuminuria versus macroalbuminuria or mixed populations with micro- or macroalbuminuria) did not significantly affect any of the reported outcomes.

The ONTARGET trial, described in the preceding section, evaluated ramipril, telmisartan and combination therapy in over 25 000 patients at high risk for cardiovascular events. Combined therapy compared with ramipril alone was associated with significant increases in hypotensive symptoms (4.8% versus 1.7%), syncope (0.3% versus 0.2%) and renal dysfunction (1.1% versus 0.7%) [159]. There was also a significant increase in hyperkalaemia, defined as a serum potassium above 5.5 mEq/L (5.7% versus 3.3%) and an almost significant increase in overall mortality (12.5% versus 11.8% with ramipril alone, risk ratio 1.07, 95% CI 0.98–1.16).

An increased incidence of adverse events with combination therapy was also demonstrated in a meta-analysis of four randomized trials that compared 17 337 patients with chronic heart failure who received either an ACE-I alone or the combination of an ACE-I and an ARB [164].

Compared with patients who received an ACE-I alone, those treated with both agents had significantly higher rates of the following complications: increased medication discontinuation due to adverse effects (15% versus 11%); worsening renal function, defined as an increase in creatinine of 0.5 mg/dL (44.2 μmol/L) or more over baseline (3.3% versus 1.5%); hyperkalaemia (3.5% versus 0.7%) and symptomatic hypotension (2.4% versus 1.5%).

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

- How did we translate the evidence into the statement?

We recommend that adults with CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2 or on dialysis) and diabetes who have a cardiovascular indication (heart failure, ischaemic heart disease) be treated with an ACE-I at maximally tolerated dose ***(1B)****.*

The data seem to be consistent with an improved overall mortality and reduced cardiovascular events in patients with diabetes treated with ACE-Is. 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 patients with diabetes with CKD stage 3b or higher (eGFR <45 mL/min), higher than that of progression to ESRD.

We suggest there is insufficient evidence to justify the start of an ARB in adults with CKD stage 3b or higher (eGFR <45 mL/min/*1.73* m^2 *or on dialysis) and diabetes who have a cardiovascular indication (heart failure, ischaemic heart disease) but intolerance for ACE-I* ***(2B)****.*

For ARBs, the protective effect on mortality and cardiovascular events is less clear, and, according to the TRANSCEND trial, switching to an ARB in patients intolerant for ACE-Is, does not improve outcome. Recent data [165], 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 endpoints 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 versus placebo treatment. Changes in systolic blood pressure (SBP) during the study period significantly correlated with changes in both left ventricular mass and arterial stiffness. Thus, significant effects of irbesartan on intermediate cardiovascular endpoints beyond blood pressure reduction were absent in HD patients.

Recent meta-analyses in the overall diabetes population [166] and in patients with hypertension [167] come to comparable conclusions.

The present data on withdrawing RAAS inhibitors in patients already taking them for a cardiac indication when their CKD progresses to an eGFR <30 mL/min/1.73 m^2 are controversial, and no randomized trials on this intervention are available. However, observational data, even in patients without diabetes, suggest that in patients with an eGFR <30 mL/min, the risk for hyperkalaemia is 6.8 (95% CI 2.7–17.4) times higher than in patients with an eGFR >50 mL/min [168]. In an observational study of 52 patients (46% with diabetes), Ahmed *et al.* [169] report an increase in eGFR from 16.38 ± 1 mL/min/1.73 m^2 at inclusion to 26.6 ± 2.2 mL/min/1.73 m^2 (P = 0.0001) after 12 months.

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

We recommend not combining different classes of renin angiotensin blocking agents (ACE-I, ARBs *or direct renin inhibitors)* ***(1A)****.*

This statement is mainly based on a large RCT demonstrating no beneficial effect, and increased side effects in patients randomized to a combination therapy of ramipril and telmisartan[159]. In this study, an interaction analysis was performed for presence of diabetes, showing no arguments that the interpretation of the results should be different in patients with diabetes.

- What do other guidelines say?

  The KH-CARI guideline on management of cardiovascular risk in CKD from 2013 suggests that ACEi or ARBs 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 *renin angiotensin-blocking agents,* ACE-Is, ARBs or 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?

  An RCT on the impact of withdrawing or maintaining of RAAS inhibitors in patients already taking them for a cardiac indication when their CKD progresses below different thresholds below eGFR <45 mL/min/1.73 m^2 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/1.73 m^2) or on dialysis, should we prescribe beta blockers to prevent sudden cardiac death?

Statements

3.3.1 We suggest starting a selective beta-blocking agent as primary prevention in patients with diabetes and CKD stage 3b or higher and then continuing it when tolerated **(2C)**.

3.3.2 We suggest prescribing lipophilic rather than hydrophylic beta-blocking agents in patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min) **(2C).**

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, e.g. 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 patients with diabetes with CKD stage 3b or higher (eGFR <45 mL/min).

- What did we find?

  We retrieved one systematic review [170] 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 versus non-addition consistently improved survival (HR 7.13; 95% CI 1.37–41.39).

  Furthermore, we retrieved two multi-centred international RCTs [171, 172], one *post hoc* analysis [173] and four observational cohort studies [174–177] (two prospective [174, 175]). Most of these were at high risk of selection bias and bias by indication.

  In the Cardiac Insufficiency Bisoprolol Study (CIBIS) [173], 2647 patients with congestive heart failure (ejection fraction <35%) were randomized to different doses of bisoprolol or placebo. Patients on bisoprolol had a lower risk for hospitalization (0.80; 95% CI 0.71–0.91), reduced all-cause mortality (0.66; 95% CI 0.55–0.81) and sudden death (0.56; 95% CI 0.39–0.80). In an older RCT, use of beta-blocking agents when compared with enalapril in patients with congestive heart failure (ejection fraction <85%), resulted in comparable progression with end-stage renal disease [171].

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

  There is no direct evidence that there is an interaction from diabetes or CKD stage 3b or higher (eGFR <45 mL/min) on the impact of the use of beta-blocking agents. We did not find any study reporting an increased harm or more side effects in patients with versus without diabetes. Although the CIBIS study [172, 173] was focused 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 congestive heart failure is quite prevalent in our target population, and that therefore, the results are very likely to also apply in our 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 <45 mL/min) as in patients with diabetes without CKD or in patients with CKD without diabetes [132].

What do other guidelines say?

We did not retrieve other guidelines providing advice on this topic for our target population.

Suggestions for future research. An RCT on the impact of beta-blocking agents on hard outcomes in patients with

diabetes and CKD stage 3b or higher (eGFR <45 mL/min) without heart failure.

Chapter 3.4

In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2), 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/1.73 m^2) than in the general population **(2C).**

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

Advice for clinical practice

- Blood pressure should be carefully titrated to a target <140 mmHg SBP, while monitoring tolerance and avoiding side effects.
- 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 diastolic blood pressure that is too low can jeopardize coronary perfusion.
- Why this question?

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

  We found one Cochrane review [178], focusing, however, on the diabetes population in general. This review searched for RCTs comparing people with diabetes randomized to lower (<130/85 mmHg) or to standard (140–160/100 mmHg) BP targets and providing data on the following primary outcomes: total mortality, total serious adverse events, myocardial infarction, stroke, congestive heart failure and end-stage renal disease. As secondary outcomes, achieved mean systolic and diastolic BP and withdrawals due to adverse effects were registered.

  This Cochrane review [178] identified five randomized trials [179–183] (7314 participants, mean follow-up 4.5 years). Despite achieving a significantly lower BP (119.3/64.4 mmHg versus 133.5/70.5 mmHg, P <0.0001), the only benefit in the 'lower' SBP group was a reduction in the incidence of stroke: relative risk (RR) 0.58, 95% CI 0.39 to 0.88, absolute risk reduction 1.1%. There was no effect on mortality (RR 1.05; CI 0.84–1.30, low-quality evidence), but there was an increase in the number of serious adverse events (RR 2.58; 95% CI 1.70–3.91, absolute risk increase 2.0%).

  Four trials (total $n = 2580$) [179–183] specifically compared clinical outcomes associated with 'lower' versus 'standard' targets for diastolic blood pressure in people with diabetes. Despite a lower achieved blood pressure in the group assigned to the 'lower' diastolic blood pressure target (128/76 versus 135/83 mmHg, P <0.0001), there was no reduction in total mortality (RR 0.73; 95% CI 0.53–1.01), stroke (RR 0.67; 95% CI 0.42–1.05), myocardial infarction (RR 0.95; 95% CI 0.64–1.40) or congestive heart failure (RR 1.06; 95% CI 0.58–1.92) (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 diabetes and CKD stage 3b or higher (eGFR <45 mL/min), we should aim at lower blood pressure targets than in the general population. The guideline development group acknowledges that the evidence was not specifically collected in our target group, as no separate analysis was performed for the specific subgroup of patients with diabetes with versus without CKD stage 3b or higher. However, the guideline development group judged that it is quite unlikely that the findings 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 (cardiovascular) mortality and morbidity.
- What do other guidelines state?

  The recent KDIGO guideline on management of hypertension advocates that adults with diabetes and CKD not on dialysis and with a urine albumin excretion of <30 mg per 24 h whose office blood pressure is consistently >140 mmHg systolic or >90 mmHg diastolic be treated with blood pressure-lowering drugs to maintain a blood pressure that is consistently <140 mmHg systolic and <0 mmHg diastolic (1B). If urine albumin excretion is >30 mg per 24 h, these targets are 130 mmHg systolic or 80 mmHg diastolic (2D). However, it is clear from the rationale that this recommendation is mainly focused on patients with an eGFR >45 mL. The recommendation for elderly patients advocates that blood pressure treatment in elderly patients with CKD not on dialysis should be tailored by carefully considering age, comorbidities 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 KHA-CARI guideline on management of cardiovascular risk factors in CKD recommends that blood pressure targets in people with 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 <140/90 (2D). KHA-CARI suggests that most blood pressure readings should be <130/80 in individuals with CKD and macroalbuminuria (2B). KH-CARI also suggests that ACE-Is or ARBs 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-blocking agents may also be used to lower blood pressure in people with CKD requiring treatment (2B).

Chapter 3.5

In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2) or on dialysis, should we prescribe lipid-lowering therapy in primary prevention?

Statements

- 3.5.1 We recommend starting a statin in patients with diabetes and CKD stage 3b and 4 (1B).
- 3.5.2 We suggest a statin be considered in patients with diabetes and CKD stage 5 (2C).
- 3.5.3 We recommend against starting a statin in patients with diabetes and CKD stage 5D (1A).
- 3.5.4 There was no consensus in the guideline development group on whether or not statins should be stopped in patients with diabetes with CKD stage 5D.
- 3.5.5 We suggest fibrates can replace statins in patients with CKD stage 3b who do not tolerate statins (2B).

Advice for clinical practice

- Doses of lipid-lowering agents should be adapted according to renal function (Table 8).
- As the doses in Table 8 should be considered maximal doses in patients with CKD, repetitive measurement of lipid levels does not add diagnostic or therapeutic value.
- For patients with CKD stage 5 or CKD stage 5D, patient preference and motivation to take another pill with its risk of side effects and limited expected benefit should guide management.

Table 8. Dose recommendations of statins in patients with CKD stage 3b or higher (eGFR <45 mL/min). Adapted from Tonelli and Wanner [189].

Statin	Maximum dose when eGFR <45 mL/min
Lovastatin	No data
Fluvostatin	80 mg
Atorvastatin	20 mg
Rosuvastatin	10 mg
Simvastatin/ezetimibe	20/10 mg
Pravastatin	40 mg
Simvastatin	40 mg
Pitavastatin	2 mg

Rationale

- Why this question?

  In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/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 patients with diabetes with CKD stage 3b or higher appears to be different from other patient populations, with uraemia-specific risk factors and non-atherosclerotic cardiovascular disease (non-ASCVD) 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 more serious when compared with the general population. We therefore aim to provide evidence about the effect of lipid-lowering treatment in patients with diabetes with CKD stage 3b or higher.

- What did we find?

  We retrieved three recent systematic reviews analysing the effect of lipid-lowering therapies in patients with CKD. Upadhyay *et al.* [184] retrieved 18 RCTs, 5 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 (RR) from six trials, 0.82 (95% CI 0.74–0.91)], cardiovascular events (including revascularization) [pooled RR from 9 trials, 0.78 (95% CI 0.71– 0.86)] and myocardial infarction [pooled RR from 9 trials, 0.74 (CI, 0.67–0.81)]. Although there was a significant benefit for all-cause mortality (RR0.91, 95% CI 0.83–0.99), the upper limit of the confidence interval was close to 1 and there was significant heterogeneity across the studies. 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 CKD stage 5 or on dialysis. Palmer *et al.* [185] retrieved a total of eighty trials comprising 51 099 participants. These authors, in contrast to Upadhyay *et al.* [184], also included studies comparing statin therapy with no treatment. Treatment effects of statins varied with stages of CKD. Moderate-to-high-quality evidence indicated that

statins reduced all-cause mortality (RR 0.81; 95% CI, 0.74–0.88), cardiovascular mortality (RR 0.78; 95% CI 0.68–0.89]), and cardiovascular events (RR 0.76; CI 0.73–0.80) in persons not receiving dialysis. In contrast, in patients on dialysis, moderate- to high-quality evidence indicated that statins had little or no effect on all-cause mortality (RR 0.96; 95% CI 0.88–1.04), cardiovascular mortality (RR 0.94; 95% CI 0.82–1.07) or cardiovascular events (RR 0.95; 95% CI 0.87–1.03). Effects of statins in kidney transplant recipients were uncertain. Concerning adverse events, statins had little or no effect on cancer, myalgia, liver function or withdrawal from treatment. However, adverse events were evaluated systematically in fewer than half of the trials. The results of both of these systematic reviews were heavily influenced by the data of the SHARP study [186].

Jun *et al.* [187] searched for prospective RCTs assessing the effects of fibrate therapy compared with placebo in people with CKD. This systematic review retrieved 10 studies including 16 869 participants. In patients with mild-to-moderate CKD [estimated GFR (eGFR) [<60 mL/min/1.73 m^2], fibrates improved surrogate markers, including total cholesterol [reduction of 0.32 mmol/L, P <0.05, triglyceride levels (reduction of 0.56 mmol/L, P = 0.03)] and high-density lipoprotein cholesterol (increase of 0.06 mmol/L, P <0.001) but not low-density lipoprotein cholesterol (reduction of 0.01 mmol/L, P = 0.83). In patients with type 2 diabetes, fibrates reduced the risk of albuminuria progression (RR 0.86; 95% CI 0.76– 0.98). Serum creatinine was elevated by fibrate therapy (increase of 33 µmol/L, P <0.001), and estimated GFR was reduced (2.67 mL/min/1.73 m^2, P <0.01). There was no detectable effect on the risk of end-stage kidney disease (RR 0.85; 95% CI 0.49–1.49). In patients with an eGFR of 30–59.9 mL/min/1.73 m^2, fibrates reduced the risk of major cardiovascular events (RR 0.70; 95% CI 0.54–0.89) and cardiovascular death (RR 0.60; 95% CI 0.38– 0.96) but not all-cause mortality. There were no clear safety concerns specific to people with CKD stage 3b. Data on effects and safety in CKD stage 4 and 5 are lacking.

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

*We recommend starting a statin in patients with diabetes and CKD stage 3b and 4 (**1B**).*

The guideline development group, after extended discussion, agreed to base the decision to treat or not to treat on the estimated underlying risk for 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 epidemiological studies that also CKD stage 3b or higher substantially increases the risk for ASCVD [127]. As a consequence, the guideline development group agrees that it is justified to accept that in patients with diabetes and CKD stage 3b and 4, the 10-year risk for ASCVD largely exceeds 10%, and that accordingly they should be treated.

The results of SHARP [186] seem to support a benefit of treatment for patients in CKD stages 3–4 (number NNT during 5 years to avoid one composite atherosclerotic event ≈50). In the SHARP trial [191], subgroup analyses of patients with diabetes revealed similar results when compared with patients without diabetes. 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.

*We suggest a statin be considered in patients with diabetes and CKD stage 5 (**2C**).*

In most *post hoc* analyses of RCTs, patients with CKD stage 5 not on dialysis were analysed as part of a larger group of non-dialysis-dependent patients including those with earlier stages of CKD. In general, these analyses suggested a benefit of statins in non-dialysis-dependent CKD. The SHARP study included 1221 patients with CKD stage 5 not undergoing dialysis. In these patients, lipid-lowering treatment resulted in a non-significant 8% risk reduction of the primary endpoint of major vascular events.

*We recommend against starting a statin in patients with diabetes in CKD stage 5D (**1A**).*

The 4D Study [188] 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. Therefore, the guideline group judged that there is no general recommendation to initiate statins in dialysis-dependent patients with diabetes.

There was no consensus in the guideline development group on whether or not statins should be stopped in patients with diabetes with CKD stage 5D.

A substantial number of patients became dialysis dependent during the study period in the SHARP trial [186]. There are no data directly addressing the question of whether lipid-lowering treatment should be stopped after initiation of dialysis. The SHARP data are interpreted by some as meaning that starting lipid lowering before ESRD and continuing through ESRD is beneficial, while starting too late during ESRD is associated 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.

*We suggest that fibrates can replace statins in patients with CKD stage 3b who do not tolerate statins (**2B**).*

Fibrates were investigated mainly in patients with earlier stages of CKD up to and including CKD stage 3b. These studies show a benefit by reducing cardiovascular events. No recommendation can be made for patients with diabetes and CKD stages 4 or higher, as data for this population are lacking.

As the guideline development group decided to recommend a risk-based treatment strategy, follow-up evaluation of lipid levels once treatment has started is not considered to be useful. This is in line with judgements of other groups [189], especially as, for most statins, a maximal dose should be considered in patients with CKD stage 3b or higher (eGFR <45 mL/min) (see Table 8). One initial measurement to identify and treat potential secondary causes of hyperlipidaemia is, however, still recommended.

What do the other guidelines say?

No guideline specifically provides guidance for our target audience of patients with diabetes and CKD stage 3b–5.

The KDIGO guideline on lipid management in CKD recommends treatment with a statin in adults aged >50 years with an eGFR <60 mL/min/1.73 m^2 but not treated with chronic dialysis or kidney transplantation (GFR categories G3a–G5) *(1A)*. In adults aged >50 years with CKD and eGFR >60 mL/min/1.73 m^2 (GFR categories G1–G2), they recommend treatment with a statin, but with a lower level of evidence *(1B)*. 2.2: In adults aged 18–49 years with CKD but not treated with chronic dialysis or kidney transplantation, KDIGO recommends statin treatment in people with known coronary disease (myocardial infarction or coronary revascularization), diabetes mellitus, prior ischaemic stroke, or an estimated 10-year incidence of coronary death or nonfatal myocardial infarction >10% (2A). In adults with dialysis-dependent CKD, KDIGO advises against initiation of a statin (2A), but also recommends continuing it in those already on a statin (2C). Of note, as KDIGO recommends that all patients with CKD stage 3b–5 should be started on a statin, in real-life practice this would imply that all patients on renal replacement therapy would be on a statin. In fact, this is a point of discordance between ERBP and KDIGO guidance. Within the ERBP guideline development group, there was no consensus on the topic of whether or not to stop statin treatment when starting dialysis. 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/1.73 m^2), 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/1.73 m^2), 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 <45 mL/min) perform additional physical exercise at least three times 1/2 to 1 hour/week to reduce fat mass and improve QoL **(2D)**.

3.6.2 We suggest that there is no evidence of harm when promoting an individualized regimen of increased physical exercise **(2C).**

3.6.3 When promoting weight loss in patients with diabetes and with overweight, we recommend supervision of this process by a dietician and to 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 programmes and follow-up, which might have a substantial impact on resources. Therefore, in patients with diabetes and CKD stage 3b or higher (GFR <45 mL/min), it is crucial to ascertain whether interventions focused on 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 advice can have an impact on the QoL of patients, especially when combined for different targets, such as in patients with diabetes and CKD. Organisation of dietary advice can have an impact on utilization of resources. Therefore, in patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/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 QoL.

- What did we find?

The results of this systematic review are published as a separate document [190]. In brief, we retained 11 studies

[191–201], none of which was 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 24-h proteinuria [196, 200, 201]. Combined exercise and diet interventions resulted in a slower decline of eGFR (−9.2 versus −20.7 mL/min; P <0.001) over a 2-year observation period [197]. 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 [191, 194] but not all studies [193, 198]. Exercise interventions improve the overall functional status [191, 193, 195] and the QoL 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 [194]. Resistance exercise reduced trunk fat mass (−0.7 ± 0.1 versus +0.8 kg ±0.1 kg; P = 0.001–0.005) [191]. In none of the studies did the intervention cause an increase in adverse events [191, 194, 198].

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

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

There is lack of evidence that energy control in patients with diabetes and CKD can improve patient-centred hard 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, QoL 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 do enough exercise, for instance, more weight loss, improved fitness and better long-term outcomes would be expected.

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

Since there is also no evidence that these programmes may cause harm, it would be reasonable to recommend energy control in those patients who are likely to benefit the most, such as obese patients.

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

When introducing such measures in patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/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 individualized 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 the individual patient's willingness to change and the effects on their QoL. NICE further recommends individualizing 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, QoL, 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/1.73 m^2), should antiplatelet therapy be recommended, regardless of the cardiovascular risk?

Statements

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 patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min) and acute coronary syndromes (ACSs) or high-risk coronary artery intervention **(1B).**

3.7.2 We suggest not 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 <45 mL/min) and ACSs or high-risk coronary artery intervention unless there is no additional risk factor for bleeding **(2B).**

3.7.3 We recommend starting aspirin as secondary prevention, unless there is a contraindication, side effects or intolerance **(1C).**

3.7.4 We suggest starting aspirin as primary prevention only in patients without additional risk factors for major bleeding **(2C).**

Advice for clinical practice. Consider clopidogrel as an alternative for aspirin in patients with clear intolerance or contraindications 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 whether antiplatelet therapy should be prescribed in primary prevention. Some would argue that CKD patients have an enhanced cardiovascular risk, and based on that, should be placed on antiplatelet therapy in primary prevention. On the other hand, CKD patients might suffer from uraemic coagulopathy and may therefore be at a higher risk for major bleeding. In particular, in patients on HD, it is still debated whether antiplatelet therapy may improve the major outcomes and survival of vascular access or whether it may increase the risk of specific complications, such as bleeding or the need for 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 RCTs specifically handled this question [202, 203]. In addition, we found one meta-analysis including *post hoc* analyses, one systematic review by the Cochrane Collaboration [204, 205], one prospective cohort study [206], one case–control study [207], one quasi-RCT in patients with diabetes and CKD 1–2 [208] and one case series study [209].

  Palmer *et al.* [204] analysed the impact of antiplatelet agents in CKD patients with stable or no cardiovascular disease and found uncertain effects on mortality. In this systematic review, nine trials (all *post hoc* subgroup analyses for patients with CKD, but not specific for patients with diabetes) involving 9969 persons, who had ACSs or were undergoing PCI, and 31 trials involving 11 701 persons with stable or no cardiovascular disease, were identified. Low-quality evidence was found indicating that in persons with diabetes and CKD stage 3b or higher (eGFR <45 mL/min) presenting with ACSs, 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 an increased risk of death (overall and cardiovascular) in patients with type 2 diabetes with diabetic nephropathy on dual antiplatelet therapy (clopidogrel plus aspirin) when compared with aspirin alone [202]. This increase in mortality was not caused by a significant increase in bleeding risk, thus suggesting an independent effect.

  The Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial was a prospective, randomized, open-label trial conducted throughout Japan that enrolled 2539 type 2 diabetes patients without a history of atherosclerotic disease. Patients were assigned to aspirin versus placebo group (81 mg/day or 100 mg/day) and followed for a median of 4.37 years. In this subgroup analysis of JPAD, in Japanese patients with type 2 diabetes, low-dose aspirin therapy reduced the incidence of atherosclerotic events such as death from coronary or cerebrovascular causes in patients with a eGFR 60–89 mL/min/1.73 m^2, but not in those with eGFR <60 mL/min/1.73 m^2 [208]. In concordance with the mortality results, the JPAD trial did not demonstrate a benefit for myocardial infarction or stroke in patients with diabetes and eGFR <60 mL/min/1.73 m^2 [208]. McCullough *et al.* demonstrated a reduction of the in-hospital mortality rate in CKD patients with acute myocardial infarction treated with aspirin and beta-blocking agents as a secondary prevention [207]. However, in this study, few details on the subpopulation with diabetes were provided.

  Wang *et al.* [205] 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, microalbuminuria and proteinuria in patients with diabetic kidney disease. None of the included studies reported the incidence of ESRD, all-cause mortality or QoL. These results should be interpreted with caution because of the poor methodological quality of the included studies and the small numbers of participants [205].

  Prespecified subgroup data from the PLATO (Platelet Inhibition and Patient Outcomes) trial indicate that ticagrelor, an oral purinergic receptor inhibitor cleared by extra-renal mechanisms, reduces mortality and major cardiovascular events better than clopidogrel among patients with an eGFR <60 mL/min/1.73 m^2 and presenting with an ACS [212]. However, in previous studies analysing aspirin plus clopidogrel versus placebo, there was a trend for superior outcomes (all-cause and cardiovascular mortality) in the group receiving placebo. As such, the role of antiplatelet therapy in patients with CKD stage 3b or higher (eGFR <45 mL/min) remains uncertain.

  Higher bleeding rates were observed in CKD patients with double or standard antiplatelet therapy [220, 204, 206]. The UK-HARP-I [213] trial, evaluating the safety of aspirin 100 mg daily versus placebo in CKD patients, found no increased risk for major bleeding (4/225 versus 6/223, P = NS), but a 3-fold higher risk of minor bleeding (34/225 versus 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 <45 mL/min). We retrieved a systematic review [214], 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 significant 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/1.73 m^2) and diabetes, regardless of their cardiovascular risk hamper an evidence-based conclusion.

We recommend against adding glycoprotein IIb/IIIa inhibitors to standard care to reduce death, myocardial infarction or need for coronary revascularization in patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min) and acute coronary syndromes or high-risk coronary artery intervention ***(1B).***

Taking into account the published data, we consider that there is only low-quality evidence to support adding glycoprotein IIb/IIIa inhibitors, thienopyridine or ticagrelor, to standard care. Indeed, despite a positive effect on myocardial infarction, the addition 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 <45 mL/min) and diabetes, but may result in an enhanced bleeding risk, which might even be substantial for glycoprotein IIb/IIIa inhibitors [215]. As such, the guideline development group judges that these latter agents do not have a place in patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min) with or without stable cardiovascular disease.

We suggest not 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 <45 mL/min) and ACSs *or high-risk coronary artery intervention unless there is no additional risk factor for bleeding* ***(2B).***

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 gastrointestinal bleeding [216]. When administered in the pre-operative phase before coronary artery bypass surgery, clopidogrel results in a higher risk of bleeding, and even a higher risk of death [217]. Ticagrelor was shown to be superior to clopidogrel in ACS patients with CKD (eGFR <60 mL/min) [212], but in this specific subgroup, clopidogrel itself was non-significantly worse when compared with placebo (CREDO, CURE) [218, 219]. The implications for the use of ticagrelor from these observations are unclear in the 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 [204].

We recommend starting aspirin as secondary prevention, unless there is a contraindication or side effects ***(1C).***

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 <45 mL/min), unless there would be evidence for an enhanced bleeding risk. Based on the UK-HARP data, there is evidence that the 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 the absence of direct comparisons in our target population, the guideline development group suggests starting aspirin as secondary prevention, unless there is a contraindication or side effects.

We suggest starting aspirin as primary prevention only in patients without additional risk factors for bleeding ***(2C).***

Data on the use of aspirin in primary prevention in our target population of patients with diabetes and CKD stage 3b–5 are scarce and show a non-significant trend for reduced incidence of coronary events and stroke. It was argued by some members of the guideline development group that CKD stage 3b–5 should be considered as a high cardiovascular risk, which justifies accepting this population as secondary prevention. In view of the evidence for a potential benefit for relevant outcomes, the high risk and the low economic cost of aspirin, the guideline group concluded that, in patients with diabetes and CKD stage 3b–5, use of aspirin can be considered unless there is a risk factor for bleeding or intolerance.

- What do the other guidelines say?

No guidelines focused specifically on this subpopulation of patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min). However, the Canadian guidelines (2011) studied the use of antiplatelet therapies in patients with CKD in general, and recommend aspirin, 75–162 mg daily, for primary prevention of ischaemic vascular events in patients with CKD stage 3b or higher (eGFR <45 mL/

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 [220]. The American Diabetes Association guidelines from 2013 recommend considering 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, dyslipidaemia, or albuminuria), and probably also most patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min) [221].

NICE recommends in its guideline on the management of diabetes to offer the following: 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; low-dose aspirin, 75 mg daily, to a person who is under 50 years of age and has other significant cardiovascular risk factors (features of the metabolic syndrome, strong early family history ofcardiovascular disease, smoking, hypertension, extant cardiovascular disease, microalbuminuria); 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. RCTs to examine the benefits and harms of using antiplatelet agents as primary prevention in patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min).

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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APPENDIX 1
GUIDELINE DEVELOPMENT GROUP AREA OF EXPERTISE

Guideline development group

Henk Bilo is a 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 has authored or co-authored over 250 articles and has written contributions for over 35 books, mainly in the field of diabetes and nephrology. He has participated in country-wide initiatives to improve diabetes care.

Luís Coentrão graduated from the Medical University of Porto in 2005. From 2006 to 2011, he was a Junior Assistant of Pharmacology and Therapeutics from the Medical University of Porto. He completed his specialty in nephrology in Hospital São João Centre, Porto, in 2012. Since then, he has dedicated his efforts to the field of interventional nephrology and presented his PhD thesis entitled 'Dialysis Access for Chronic Renal Replacement Therapy: Clinical and Economic Implications' to the Medical University of Porto in 2013. Since 2012 he has been a fellow of the Intensive Care Medicine Department in Hospital São João Centre, Porto.

Cécile Couchoud is a nephrologist and has a PhD in epidemiology. She has been working for the French end-stage renal disease registry since 2003 and has played a role in the Moroccan end-stage renal disease registry since 2005. Currently Dr Couchoud is specializing in renal epidemiology. Her research interests include the development of statistical tools for decision-making in public health and 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 Centre in Iasi, Romania. Prof. Covic has published more than 200 original and review papers in peer-reviewed journals as well as 11 books and 22 chapters. Prof. Covic is also the current president of the 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, PD and acute renal failure.

Johan De Sutter is a cardiologist and professor 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 has been active within the European Society of Cardiology for several years and has participated in various ESC guidelines (including atrial fibrillation, NSTEMI etc.). He is currently a board member of the European Association of Cardiovascular Prevention and Rehabiliation and the current programme 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 several 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 prestigious journals.

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). Between 1993 and 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 Professor of Nephrology at G.T. Popa University of Medicine and Pharmacy, Iasi, Romania. He is 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 CKD.

James Heaf is a nephrology consultant at Herlev Hospital, University of Copenhagen, with special responsibility for PD. 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, PD, epidemiology and uraemia progression. He is a reviewer for several nephrology journals.

Olof Heimbürger is consultant nephrologist and Director of PD 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 textbook chapters, mainly about peritoneal dialysis, nutrition, metabolism, inflammation, biomarkers, cardiovascular disease and genetics in patients with CKD. Olof Heimbürger was the Secretary of the International Society of Peritoneal Dialysis 2006–2014 and is a member of the ERBP advisory board. He is a regular reviewer of scientific papers for various journals on nephrology.

Kitty Jager is an Associate Professor of Medical Informatics at the Academic Medical Centre 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 a 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 various nephrology journals.

Hakan Nacak started medical school in 2008 at the Leiden University Medical Centre 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, he joined the ERBP guideline working group and is investigating optimal timing of dialysis initiation in patients with diabetes with CKD.

María José Soler is a consultant nephrologist at the Hospital del Mar, Barcelona, Spain. She is also an 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 completed a doctoral thesis in 2007, on 'Angiotensin-converting enzyme 2 in diabetic kidney disease', and received an extraordinary PhD 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, HD, 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 and now works at Newcastle upon Tyne. 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 in endocrinology in 2013 with Professor Jean-Marc Kaufman. Along with her clinical training, Dr Van Huffel has worked on several projects about the effect of exercise and diet in patients with diabetes. She joined the ERBP fellows group for this project in September 2013. She is currently finishing her fellowship endocrinology at the the Ghent University.

Steven Van Laecke is a 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 CKD. 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 Wieçek, 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 Wieçek 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 an honorary member of the Romanian Society of Nephrology (2003). Professor Wieçek 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 in the field of hypertension and kidney diseases.

During recent years, Professor Wieçek 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) and 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 a 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 a regular reviewer for several 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 CKD. 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.

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 patients with diabetes who developed CKD 3b/4/5. Dr Nistor joined the European Renal Best Practice (ERBP) group from August 2011 as an ERBP fellow in the methods team. His research interests also include cardiovascular complications in CKD patients, dialysis and transplant patients. Dr Nistor was 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 programme, 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 Centre (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 Professor 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 in 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 250 articles dealing with a wide variety of topics in nephrology (PD, HD, CKD management) and intensive care nephrology. He is the current chair of ERBP. He is also theme editor for dialysis for *Nephrology Dialysis Transplantation* and is a member of the editorial board of various 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 grants

Date	2013–2014
Company or interest group	Novo Nordisk
Value	More than EUR 10 000
Payment made to	Research fund
Nature of interest	Grant for research purposes, study approved by medical ethical committee
Nature of restriction	Unrestricted
Date	2013– 2014
Company or interest group	Sanofi Aventis
Value	More than EUR 10 000
Payment made to	Research fund
Nature of interest	Grant for research purposes, study approved by medical ethical committee
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

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

PROF. 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?

Consultant for company

Date	2014–2014
Company or interest group	Glaxosmithkline
Value	EUR 1000–10 000
Payment made to	Personal account

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

Date	2013–2014
Company or interest group	Janssen
Value	EUR 1000–10 000
Payment made to	Personal account

Date	2013–2014
Company or interest group	Boehringer-Lilly
Value	EUR 1000–10 000
Payment made to	Personal account
Date	2014–2014
Company or interest group	Sanofi
Value	Less than EUR 1000
Payment made to	Personal account
Date	2013–2014
Company or interest group	Astrazeneca
Value	EUR 1000–10 000
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?

Principal investigator

Date	2013–2014
Company or interest group	Abbvie
Value	Less than EUR 1000
Payment made to	Personal account
Nature of interest	Portion of funds paid into my salary for work conducted
Nature of restriction	Unrestricted

Research grant

Date	2013–2014
Company or interest group	AstraZeneca
Value	More than EUR 10 000
Payment made to	Research fund
Nature of interest	Research fund
Nature of restriction	Restricted: Specific research project

Other type of grant

Date	2014–2014
Company or interest group	Janssen
Value	More than EUR 10 000
Payment made to	Hospital/institution
Nature of interest	EDNSG 2014 meeting support
Nature of restriction	Restricted: EDNSG 2014 meeting support
Date	2014–2014
Company or interest group	AstraZeneca
Value	More than EUR 10 000
Payment made to	Hospital/institution
Nature of interest	EDNSG 2014 meeting support
Nature of restriction	Restricted: EDNSG 2014 meeting support
Date	2014- 2014
Company or interest group	Abbvie
Value	More than EUR 10 000
Payment made to	Hospital/institution
Nature of interest	EDNSG 2014 meeting support
Nature of restriction	Restricted: EDNSG 2014 meeting support
Date	2014–2014
Company or interest group	Boehringer-Lilly
Value	More than EUR 10 000
Payment made to	Hospital/institution
Nature of interest	EDNSG 2014 meeting support
Nature of restriction	Restricted: EDNSG 2014 meeting support
Date	2014–2014
Company or interest group	Sanofi
Value	More than EUR 10 000
Payment made to	Hospital/institution
Nature of interest	EDNSG 2014 meeting support
Nature of restriction	Restricted: EDNSG 2014 meeting support
Date	2014–2014
Company or interest group	Novo-Nordisk
Value	More than EUR 10 000
Payment made to	Hospital/institution
Nature of interest	EDNSG 2014 meeting support
Nature of restriction	Restricted: EDNSG 2014 meeting support
Date	2014–2014
Company or interest group	Takeda
Value	More than EUR 10 000
Payment made to	Hospital/institution
Nature of interest	EDNSG 2014 meeting support
Nature of restriction	Restricted: EDNSG 2014 meeting support
Date	2014–2014
Company or interest group	Chemocentrix
Value	EUR 1000–10 000
Payment made to	Personal account
Nature of interest	EDNSG 2014 meeting support
Nature of restriction	Restricted: EDNSG 2014 meeting support

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. 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?

Consultant for company

Date	2013–2014
Company or interest group	Sanofi, Keryx, Amgen, Abbott, Fresenius
Value	EUR 1000–10 000
Payment made to	Personal account

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 1000–10 000
Payment made to	Personal account
Date	2013–2014
Company or interest group	Sanofi, Keryx, Amgen, Abbott, Fresenius
Value	Less than EUR 1000
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	EUR 1000–10 000
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 1000–10 000
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 1000–10 000
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?

Other position in clinical trial

Date	2013–2014
Company or interest group	Fresenius
Value	EUR 1000–10 000
Payment made to	Research fund
Nature of interest	Participant in Clinical Trial
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

Yes. ISPD, ASN

PROF. 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

Date	2013–2014
Company or interest group	Medivir
Value	Less than EUR 1000
Payment made to	Personal account

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

Date	2013–2014
Company or interest group	Baxter Healthcare
Value	EUR 1000–10 000
Payment made to	Personal account
Date	2013–2014
Company or interest group	Fresenius Medical Care
Value	EUR 1000–10 000
Payment made to	Personal account
Date	2013–2014
Company or interest group	Bayer Healtcare
Value	EUR 1000–10 000
Payment made to	Personal account

Travel or accommodation provided or reimbursed

Date	2013–2013
Company or interest group	Sandoz
Value	Less than EUR 1000
Payment made to	Hospital/institution

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

Date	2014–2014
Company or interest group	AstraZeneca
Value	Less than EUR 1000
Payment made to	Hospital/institution
Nature of interest	Principal Investigator in clinical trial
Nature of restriction	Restricted: restricted to this trial

4. Other potential conflicts of interest?

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

Date	2013–2014
Company or interest group	Abbvie
Value	Less than EUR 1000
Payment made to	Other, No payment
Nature of interest	My brother is emplyed by Abbvie

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

PROF. 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

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

Date	2013–2014
Company or interest group	European Renal Best Practice - Official Guideline Writng Body of ERA-EDTA
Value	More than EUR 10 000
Payment made to	Hospital/institution
Nature of interest	Research Fellow - Assisting ERBP in its Guideline Development Process
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

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?

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 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?

Other type of involvement

Date	2013–2014
Company or interest group	Abbvie
Value	EUR 1000–10 000
Payment made to	Personal account
Nature of interest	Nephrology chapter books

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

Date	2013–2014
Company or interest group	Abbvie
Value	More than EUR 10 000
Payment made to	Research fund
Nature of interest	Diabetic research mechanisms
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

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

PROF. 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

Date	2013–2014
Company or interest group	Fresenius
Value	Less than EUR 1000
Payment made to	Personal account

Lecturing, chairing lectures or participation in symposia/ panel discussions

Date	2013–2014
Company or interest group	Fresenius, Baxter, Gambro
Value	Less than EUR 1000
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

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

Date	2014–2014
Company or interest group	Roche Diagnostics Belgium
Value	Less than EUR 1000
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

No

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

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

Date	2013–2013
Company or interest group	Alexion
Value	EUR 1000–10 000
Payment made to	Personal account

Conference/meeting registration fees paid or reimbursed

Date	2013–2014
Company or interest group	Astellas, Novartis
Value	EUR 1000–10 000
Payment made to	Hospital/institution

Travel or accommodation provided or reimbursed

Date	2013–2014
Company or interest group	Astellas, Sandoz
Value	EUR 1000–10 000
Payment made to	Hospital/institution

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

PROF. ANDRZEJ JAN WIEÇEK

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

Date	2013–2014
Company or interest group	Boehringer Ingelheim
Value	EUR 1000–10 000
Payment made to	Personal account
Date	2013–2014
Company or interest group	Vifor
Value	Less than EUR 1000
Payment made to	Personal account

Lecturing, chairing lectures or participation in symposia/panel discussions

Date	2013–2014
Company or interest group	Amgen,
Value	Less than EUR 1000
Payment made to	Personal account
Date	2013–2014
Company or interest group	Fresenius
Value	Less than EUR 1000
Payment made to	Personal account
Date	2013–2014
Company or interest group	Vifor
Value	Less than EUR 1000
Payment made to	Personal account

Conference/meeting registration fees paid or reimbursed

Date	2013–2014
Company or interest group	Amgen, Roche, Fresenius,
Value	EUR 1000–10 000
Payment made to	Other, Event orgianizer account

Travel or accommodation provided or reimbursed

Date	2013–2014
Company or interest group	Amgen, Roche, Fresenius, Astellas, Apotex,
Value	EUR 1000–10 000
Payment made to	Other, Event orgianizer account or 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?

Research grant

Date	2013–2014
Company or interest group	National Centre of Science
Value	More than EUR 10 000
Payment made to	Hospital/institution
Nature of interest	Research grant
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

No

APPENDIX 2. REVIEW QUESTIONS: PICOM FORMAT

Chapter 1.1. Should patients with diabetes and CKD stage 5 start with PD or HD 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	PD of any kind as first modality (1) Continuous ambulatory PD: CAPD (2) Automated PD: APD
Comparator	HD of any kind as first modality (on Day 90) (1) Conventional HD (2) Haemofiltration (3) Haemodiafiltration (4) Daily HD
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) Hypoglycaemia (b) Delayed wound healing (c) Infection (d) Visual disturbances (e) Pain (f) Functional status Moderately important outcomes (1) Hyperglycaemia (2) Glycaemic control (a) Glycated haemoglobin (b) Self-measurement Question-specific outcome measures (1) Access to transplantation (2) Survival of the technique
Methodology	Systematic reviews RCTs Longitudinal studies Registry studies

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: hyperkalaemia, fluid overload, metabolic acidosis, or deterioration of nutritional status (1) Continuous ambulatory PD: CAPD (2) Automated PD: APD (3) Conventional HD (4) Haemofiltration (5) Haemodiafiltration (6) Daily HD
Outcome	Core outcome measures Question-specific outcome measures 1. Need for temporary HD catheter: important
Methodology	Systematic reviews RCTs 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 (3) Humeral artery
Comparator	Native fistula any position (1) Radial artery (2) Cubital artery (3) Humeral artery
Outcome	Core outcome measures Question-specific outcome measures (1) Need for temporary catheter: highly important outcome (2) Infections of the vascular access: highly important outcome
Methodology	Systematic reviews RCTs Cohort studies Registry studies

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
Intervention	Percentage of dialysis patients with diabetes mellitus registered on waiting list
Comparator	Percentage of other patients registered on the waiting list
Outcome	Not applicable
Methodology	Registry data Cross-sectional studies

Chapter 1.4. A.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 PD – CAPD (2) Automated PD – APD (3) Conventional HD (4) Haemofiltration (5) Haemodiafiltration (6) Daily HD
Outcome	Core outcome measures
Methodology	Systematic reviews RCTs Cohort studies Registry studies

Chapter 2.1. A. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2), should we aim to lower HbA1C by tighter glycaemic control?

Patients	Patients with diabetes mellitus (comorbidity or diabetic nephropathy) and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2) Children, adults, aged adults Diabetes mellitus type 1 or type 2
Intervention	Intensive glycaemic control: as measured by HbA1C
Comparator	Conventional glycaemic control - as measured by Hb1Ac
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) Hypoglycaemia (b) Delayed wound healing (c) Infection (d) Visual disturbances (e) Pain (f) Functional status Moderately important outcomes (1) Hyperglycaemia (2) Glycaemic control (a) Glycated haemoglobin (b) Self-measurement Question-specific outcome measures (1) Keto-acidosis: critically important
Methodology	Systematic reviews RCTs 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/1.73 m^2) 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
Intervention	Aggressive regimen either defined as more frequent injections, more frequent monitoring or adapted insulin
Comparator	Relaxed regimen with limited controls and insulin in one or maximum two injections
Outcome	Core outcome measures
Methodology	Systematic reviews RCTs Cohort studies Registry studies

Chapter 2.2. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2) 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/1.73 m^2) 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	Glycaemic control evaluated with HbA1c as reference standard
Outcome	Core outcome measures
Methodology	Systematic reviews RCTs 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/1.73 m^2)?

	Patients with diabetes mellitus and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2) Children, adults, aged adults Diabetes mellitus type 1 or type 2
Intervention	Metformin Sulfonylurea Gliptins DDP4 inhibitor Glitazones Acarbose Any other oral drug for reducing hyperglycaemia
Comparator	Any oral hypoglycaemic drug
Outcome	Core outcome measures Question-specific outcome measures (1) Weight gain: moderately important
Methodology	Systematic review RCTs Cohort studies Registry studies

Chapter 2.3. B. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2), 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 <45 mL/min/1.73 m^2) Children, adults, aged adults Diabetes mellitus type 1 or type 2
Intervention	Start insuline 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 RCTs Cohort studies Registry studies

Chapter 3.1. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2) and CAD, 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/1.73 m^2 or on dialysis) with established cardiac ischaemia/CAD Children, adults, aged adults Diabetes mellitus type 1 or type 2
Intervention	Coronary artery bypass grafting (CABG) PCI
Comparator	Medical treatment/management
Outcome	Core outcome measures Question-specific outcome measures (1) Symptom control: dyspnoea, chest pain: highly important
Methodology	Systematic review RCTs Cohort studies Registry studies

Chapter 3.2. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2) and with a cardial indication (heart failure, ischaemic heart disease, hypertension), should we prescribe inhibitors of the RAAS system or aldosteron-antagonists as cardiovascular prevention?

Patients	Patients with diabetes mellitus and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2 or on dialysis) with a cardial indication (heart failure, ischaemic 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 Aldosteron antagonist Any combination
Comparator	Placebo or no treatment
Outcome	Core outcome measures Question-specific outcome measures (1) Sudden death: critically important
Methodology	Systematic review RCTs Cohort studies Registry studies

Chapter 3.3 In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2), 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/1.73 m^2 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 RCTs Cohort studies Registry studies

Chapter 3.4. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2), 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/1.73 m^2), should we prescribe lipid-lowering therapy in primary prevention?

Patients	Patients with diabetes mellitus and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2 or on dialysis) Children, adults, aged adults Diabetes mellitus type 1 or type 2
Intervention	Lipid-lowering therapy (a) Statin (all compounds) (b) Fibrate (all compounds) (c) Any other class of agents
Comparator	Placebo or no treatment Any other class of agents Other strategies
Outcome	Core outcome measures Question-specific outcome measures (1) Cancer: critically important (2) Rhabdomyolysis: highly important
Methodology	Systematic review RCTs Cohort studies Registry studies

Chapter 3.6. A. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2), should we recommend interventions aimed at increasing energy expenditure and physical activity?

Patients	Patients with diabetes mellitus and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2 or on dialysis) Children, adults, aged adults Diabetes mellitus type 1 or type 2
Intervention	Structured education/intervention aimed at increasing energy expenditure and/or physical activity (1) Advise to exercise (2) Structured education programmes including advice on exercise (3) Provision of a supervised exercise programme (4) Provision of exercise bikes (for instance during HD)
Comparator	Standard care
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 HD (6) Adherence to treatment strategy
Methodology	Systematic review RCTs Cohort studies Registry studies

Chapter 3.6. B. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2), should we recommend interventions aimed at reducing energy intake?

Patients	Patients with diabetes mellitus and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2 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 RCTs Cohort studies Registry studies

Chapter 3.7. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2), should antiplatelet therapy be recommended, regardless of its cardiovascular risk?

Patients	Patients with diabetes mellitus and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2 or on dialysis) Children, adults, aged adults Diabetes mellitus type 1 or type 2
Intervention	Platelet aggregation inhibitors Aspirin Dipyridamole Glycoprotein IIb/IIIa inhibitors
Comparator	Placebo
Outcome	Core outcome measures Question specific outcome measures (1) Need for blood transfusion (2) Bleeding
Methodology	Systematic review RCTs Cohort studies Registry studies

APPENDIX 3. SEARCH STRATEGIES

Chapter 1.1. Should patients with diabetes and CKD stage 5 start with PD or HD 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
#33 initiat* dialysis: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)
#35 (#21 AND #34)

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
28. ((ideal or preemptive or pre-emptive or early) adj11 dialysis).tw
29. or/23-27
30. 15 and 22 and 28
31. limit 30 to human
32. (comment or editorial or historical-article).pt.
33. 31 not 32

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 (preemptive or emptive or first or start* or initiat* or begin):ti,ab,kw
#23 (#22 AND #1)
#24 (#21 AND #23)

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. randomi?ed.ab,ti.
4. placebo$.ab,ti.
5. drug therapy.fs.
6. randomly.ab,ti.
7. trial$.ab,ti.
8. group$.ab,ti.
9. or/1-8
10. Meta-analysis.pt.
11. exp Technology Assessment, Biomedical/
12. exp Meta-analysis/
13. exp Meta-analysis as topic/
14. (health technology adj6 assessment$).tw,ot.
15. hta.tw,ot.
16. (meta analy$ or metaanaly$ or meta?analy$).tw,ot.
17. exp Cohort studies/
18. Incidence.tw.
19. exp mortality/
20. exp follow-up studies/
21. mo.fs.
22. prognos$.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

#4. "blood vessel prosthesis":kw
#5. catheter*:ti,ab,kw
#6. central next line*:ti,ab,kw
#7. (AVF or AVG or CVC):ti,ab,kw
#8. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
#9. dialysis:ti,ab,kw
#10. (haemodialysis or haemodialysis):ti,ab,kw
#11. (haemodiafiltration or haemodiafiltration):ti,ab,kw
#12. (hemofiltration or haemofiltration):ti,ab,kw
#13. "chronic kidney":ti,ab,kw
#14. "chronic renal":ti,ab,kw
#15. "kidney failure":ti,ab,kw
#16. ("end-stage kidney" or "end stage kidney" or "end-stage renal" or "end stage renal" or "endstage kidney" or "endstage renal"):ti,ab,kw
#17. (CKF or CKD or CRF or CRD):ti,ab,kw
#18. (ESKF or ESKD or ESRF or ESRD):ti,ab,kw
#19. ("pre-dialysis" or predialysis):ti,ab,kw
#20. (#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19)
#21. MeSH descriptor Diabetes Mellitus, this term only
#22. MeSH descriptor Diabetes Mellitus, Type 1 explode all trees
#23. MeSH descriptor Diabetes Mellitus, Type 2 explode all trees
#24. MeSH descriptor Diabetic Nephropathies explode all trees
#25. diabet*:ti,ab,kw
#26. (niddm or iddm):ab,ti,kw
#27. (#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27)
#28. (#8 AND #20 AND #28)

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.
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
#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 kidney transplantation/
#22 kidney transplant*.tw.
#23 renal transplant*.tw.
#24 (#21 OR #22 OR #23)
#25 (#13 AND #20 AND #24)

Chapter 2.1

C. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2), should we aim to lower HbA1C by more tight 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. 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$).ab,ti.
28. (glucos$ adj3 management$).ab,ti.
29. or/16-28
30. ((intensi$ 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
#89 (standard near/3 control*):ab,ti,kw
#90 (standard near/3 therap*):ab,ti,kw
#91 (standard near/3 treatment*):ab,ti,kw
#92 (standard near/3 intervention*):ab,ti,kw
#93 (standard near/3 management*):ab,ti,kw
#94 (#59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93)
#95 (#58 AND #94)

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/1.73 m^2) 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$)).tw.
26. (glucos$ adj3 control$).tw.
27. (glucos$ 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
39. Meta-analysis.pt.
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?analy$).tw,ot.
46. exp Cohort studies/
47. Incidence.tw.
48. exp mortality/
49. exp follow-up studies/
50. mo.fs.
51. prognos$.tw.
52. predict$.tw.
53. course.tw.
54. exp survival analysis/
55. or/39-54
56. (comment or editorial or historical-article).pt.
57. 55 not 56
58. 38 or 57
59. 29 and 58

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 aggresive 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 aggresive 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 aggresive or relaxed*) near/3 glycemic* near/3 (control* or therap* or treatment or intervention* or management*):ab,ti,kw
#25 (intensi* or conventional* or regular or tight or usual or routin* or standard or frequent* or aggresive or relaxed*) near/3 glycaemic* near/3 (control* or therap* or treatment or intervention* or management*):ab,ti,kw
#26 (intensi* or conventional* or regular or tight or usual or routin* or standard or frequent* or aggresive or relaxed*) near/3 diabet* near/3 (control* or therap* or treatment or intervention* or management*):ab,ti,kw
#27 (glucos* near/3 control*):ab,ti
#28 (glucos* near/3 management*):ti,ab
#29 #22 or #23 or #24 or #25 or #26 or #27 or #28
#30 #21 and #29

Chapter 2.2. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2), 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. HbA?1c?.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]
37. (h?emoglobin adj A1c).tw.
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
#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 Hemoglobin A, Glycosylated explode all trees
#23 HbA*1c*:ti,ab,kw
#24 (h*emoglobin NEAR A1c):ti,ab,kw
#25 (glycated NEAR h*emoglobin):ti,ab,kw
#26 (glycosylated NEAR h*emoglobin):ti,ab,kw
#27 (glycated NEAR albumin):ti,ab,kw
#28 (glycosylated NEAR albumin):ti,ab,kw
#29 MeSH descriptor Hexosamines explode all trees
#30 fructosamine:ti,ab,kw
#31 MeSH descriptor Blood Glucose Self-Monitoring explode all trees
#32 (self monitor*):ti,ab,kw
#33 MeSH descriptor Hyperglycemia, this term only
#34 MeSH descriptor Blood Glucose explode all trees
#35 (#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)
#36 (#21 AND #35)

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/1.73 m^2)?

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$.tw.
21. (niddm or iddm).tw.
22. or/16-21
23. exp Hypoglycemic Agents/
24. (glucose lowering and (therap$ 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)
#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 (insulin*):ti,ab,kw in Clinical Trials
#32 (metformin):ti,ab,kw in Clinical Trials
#33 (Rosiglitazone):ti,ab,kw or (Rivoglitazone):ti,ab,kw or (Pioglitazone):ti,ab,kw or (Troglitazone):ti,ab,kw in Clinical Trials

#34 MeSH descriptor Thiazolidinediones, this term only
#35 (acarbose):ti,ab,kw or (miglitol):ti,ab,kw or (voglibose):ti,ab,kw in Clinical Trials
#36 (repaglinide or nateglinide or exenatide or pramlintide or benfluorex or liraglutide or mitiglinide):ti,ab,kw in Clinical Trials
#37 (sitagliptin or vildagliptin or saxagliptin):ti,ab,kw
#38 (Linagliptin):ti,ab,kw or (Alogliptin):ti,ab,kw in Clinical Trials
#39 "glucagon-like peptide-1":ti,ab,kw in Clinical Trials
#40 (Incretin mimetic*):ti,ab,kw in Clinical Trials
#41 (alpha-glucosidase inhibitor*):ti,ab,kw in Clinical Trials
#42 (exenatide):ti,ab,kw in Clinical Trials
#43 (#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)
#44 (#21 AND #43)

Chapter 2.3. B. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2), 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 therap$)).tw.
28. metformin.tw.
29. Thiazolidinediones/
30. Rosiglitazone.tw.
31. Rivoglitazone.tw.
32. Pioglitazone.tw.
33. Troglitazone.tw.
34. glitazone$.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$.tw.
54. or/52-53
55. 51 and 54
56. 55 and 23
57. randomized controlled trial.pt.
58. controlled clinical trial.pt.
59. randomized.ab.
60. placebo.ab.
61. clinical trials as topic/
62. randomly.ab.
63. trial.ti.
64. or/57-63
65. Meta-analysis.pt.
66. exp Technology Assessment, Biomedical/
67. exp Meta-analysis/
68. exp Meta-analysis as topic/
69. (health technology adj6 assessment$).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 vildagliptin 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/1.73 m^2) and CAD, 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$.tw.
21. (niddm or iddm).tw.
22. or/16-21
23. exp coronary disease/
24. exp myocardial infarction/
25. exp angina pectoris/
26. coronary.tw.
27. angina.tw.
28. myocardial infarction.tw.
29. exp Myocardial Ischemia/
30. (isch?emi$ adj3 heart).tw.
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
61. Meta-analysis.pt.
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
#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 Coronary Disease, this term only
#23 MeSH descriptor Myocardial Infarction, this term only
#24 MeSH descriptor Angina Pectoris explode all trees
#25 coronary:ti,ab,kw
#26 angina:ti,ab,kw
#27 MeSH descriptor Myocardial Ischemia explode all trees
#28 (#22 OR #23 OR #24 OR #25 OR #26 OR #27)
#29 MeSH descriptor Coronary Artery Bypass explode all trees
#30 MeSH descriptor Angioplasty explode all trees
#31 MeSH descriptor Stents explode all trees
#32 CABG:ti,ab,kw
#33 pci:ti,ab,kw
#34 ptca:ti,ab,kw
#35 stent*:ti,ab,kw
#36 (coronary near bypass*):ti,ab,kw
#37 (myocard* near revasculari*):ti,ab,kw
#38 (heart near revasculari*):ti,ab,kw
#39 MeSH descriptor Coronary Angiography explode all trees
#40 MeSH descriptor Angioplasty, Balloon, Coronary, this term only
#41 (#29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40)
#42 (#21 AND #41)

Chapter 3.2. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2) and with a cardial indication (heart failure, ischaemic 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/
26. (coronary arter$ and stenos$).tw.
27. coronary stenos$.tw.
28. coronary atheroscleros$.tw.
29. coronary arterioscleros$.tw.
30. (coronary adj5 disease).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 practon*: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
#55 telmisartan:ti,ab,kw
#56 (ace near inhibitor*):ti,ab,kw
#57 (angiotensin near receptor antagonist*):ti,ab,kw
#58 (#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 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57)
#59 #21 and #58

Chapter 3.3. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2), 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$.tw.
6. (niddm or iddm).tw.
7. or/1-6
8. Kidney Diseases/
9. exp Renal Replacement Therapy/
10. Renal Insufficiency/
11. exp Renal Insufficiency, Chronic/
12. dialysis.tw.
13. (haemodialysis or haemodialysis).tw.
14. (hemofiltration or haemofiltration).tw.
15. (haemodiafiltration or haemodiafiltration).tw.
16. (end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw.
17. (ESRF or ESKF or ESRD or ESKD).tw.
18. (chronic kidney or chronic renal).tw.
19. (CKF or CKD or CRF or CRD).tw.
20. (CAPD or CCPD or APD).tw.
21. (predialysis or pre-dialysis).tw.
22. or/8-21
23. exp adrenergic beta-antagonists/
24. alprenolol.tw.
25. atenolol.tw.
26. metoprolol.tw.
27. nadolol.tw.
28. oxprenolol.tw.
29. pindolol.tw.
30. propranolol.tw.
31. exp adrenergic alpha-antagonists/
32. labetalol.tw.
33. prazosin.tw.
34. beta block$.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/1.73 m^2), 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/1.73 m^2), 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. hyperlip?emia.tw.
29. hyperlipid$.tw.
30. dyslip?emia.tw.
31. cholesterol-lower$.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
65. Meta-analysis.pt.
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
#25 antilipid*:ti,ab,kw
#26 dyslip*emia:ti,ab,kw
#27 cholesterol-lower*:ti,ab,kw
#28 HMG-CoA reductase inhibitor*:ti,ab,kw
#29 *statin*:ti,ab,kw
#30 *fibrate*:ti,ab,kw
#31 mevacor:ti,ab,kw
#32 pravachol:ti,ab,kw
#33 lescol:ti,ab,kw
#34 lipitor:ti,ab,kw
#35 cholestyramine:ti,ab,kw
#36 colestipol:ti,ab,kw
#37 gemfibrozil:ti,ab,kw
#38 clofibrate:ti,ab,kw
#39 ezetimibe:ti,ab,kw
#40 nicotinic acid:ti,ab,kw
#41 (#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)
#42 (#21 AND #41)

Chapter 3.6. A. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2), 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
#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 Exertion explode all trees
#23 exercise:ti,ab,kw
#24 (Physical and (Education or Training))
#25 (physical next (training or activity or fitness or rehabilitation)):ti,ab,kw
#26 (resistance next (training or program*)):ti,ab,kw
#27 (strength* and (muscle* or program* or training)):ti,ab,kw
#28 kinesiotherapy:ti,ab,kw
#29 (#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28)
#30 (#21 AND #29)

Chapter 3.6. B. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2), 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/1.73 m^2), should antiplatelet therapy be recommended, regardless of their cardiovascular risk?

MEDLINE

1. exp Platelet Aggregation Inhibitors/
2. exp Phosphodiesterase Inhibitors/
3. Adenosine Diphosphate/ai [Antagonists & Inhibitors]
4. Platelet Glycoprotein GPIIb-IIIa Complex/ai [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.
25. S-nitrosoglutathione.tw.
26. S-nitrosothioles.tw.
27. trapidil.tw.
28. ticlopidine.tw.
29. clopidogrel.tw.
30. (sulfinpyrazone or sulphinpyrazone).tw.
31. cilostazol.tw.
32. (P2Y12 adj2 antagonis$).tw.
33. prasugrel.tw.
34. ticagrelor.tw.
35. cangrelor.tw.
36. elinogrel.tw.
37. "glycoprotein IIB/IIIA inhibitors".tw.
38. abciximab.tw.
39. eptifibatide.tw.
40. tirofiban.tw.
41. defibrotide.tw.
42. picotamide.tw.
43. beraprost.tw.
44. ticlid.tw.
45. aggrenox.tw.
46. ditazole.tw.
47. or/1-46
48. exp Renal Dialysis/
49. (haemodialysis or haemodialysis).tw.
50. (hemofiltration or haemofiltration).tw.
51. (haemodiafiltration or haemodiafiltration).tw.
52. dialysis.tw.
53. (PD or CAPD or CCPD or APD).tw.
54. Renal Insufficiency/
55. Kidney Failure/
56. exp Renal Insufficiency, Chronic/
57. Kidney Diseases/
58. Uremia/
59. (end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw.
60. (ESRF or ESKF or ESRD or ESKD).tw.
61. (chronic kidney or chronic renal).tw.
62. (CKF or CKD or CRF or CRD).tw.
63. (predialysis or pre-dialysis).tw.
64. ur?emi$.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

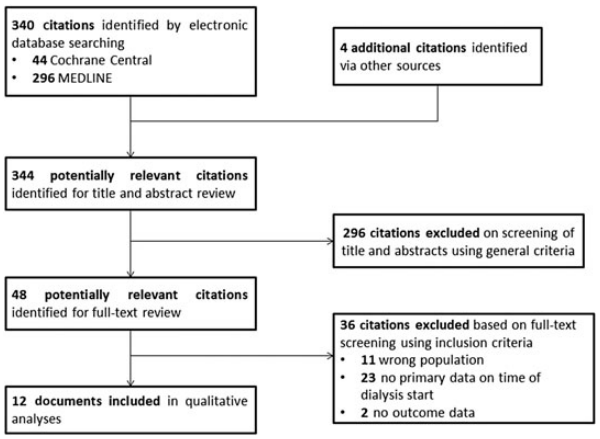
#1. MeSH descriptor Phosphodiesterase Inhibitors explode all trees
#2. MeSH descriptor Adenosine Diphosphate, this term only with qualifier: AI
#3. MeSH descriptor Platelet Glycoprotein GPIIb-IIIa Complex, this term only with qualifier: AI
#4. ((antiplatelet next agent*) or (anti-platelet next agent*)):ti,ab,kw
#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 reuptake 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. ditazole: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)

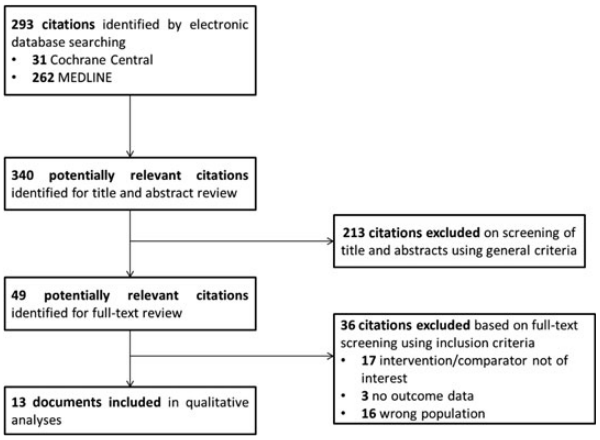
APPENDIX 4. SELECTION OF STUDY FLOW CHARTS

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

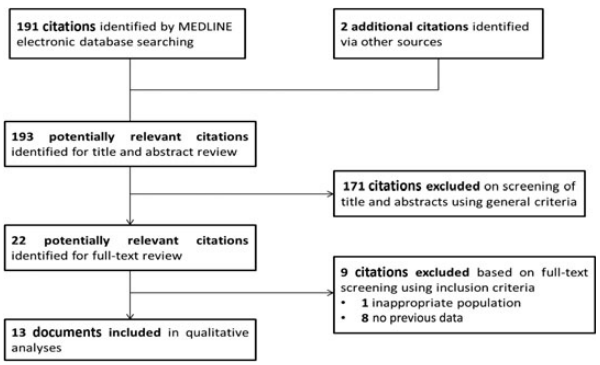
Chapter 1.2. Should patients with diabetes and CKD stage 5 start dialysis earlier, i.e. before becoming symptomatic, than those without?



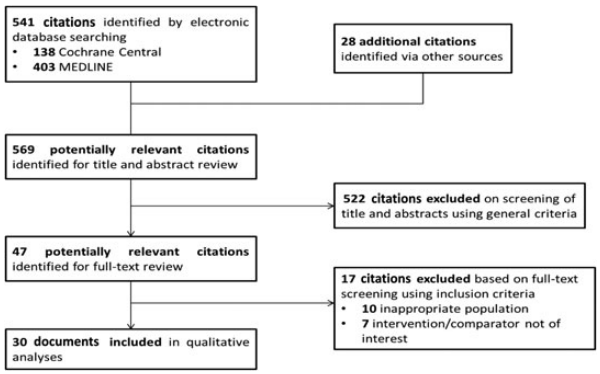
Chapter 1.3. In patients with diabetes and CKD stage 5, should a native fistula, a graft or a tunnelled catheter be preferred as initial access?



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?



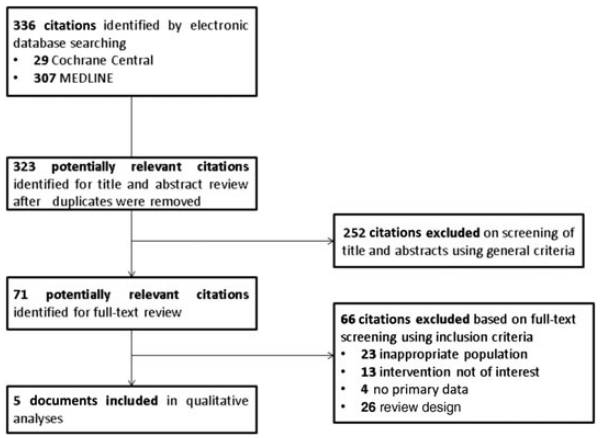
Chapter 1.4. C. Is there a benefit of renal transplantation for patients with diabetes and CKD stage 5?



Chapter 2.1. E. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2), should we aim to lower HbA1C by tighter glycaemic control?

No flowchart available. Evidence extracted from the Cochrane Review written by Hemmingsen *et al.* [93].

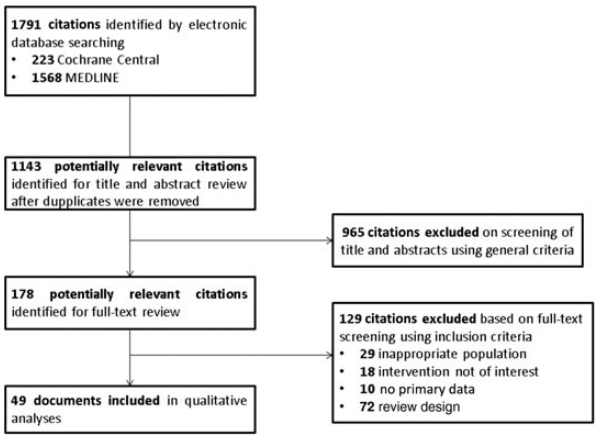
Chapter 2.1. F. Is an aggressive treatment strategy (in number of injections and controls and follow up) superior to a more relaxed treatment strategy in patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2) and using insulin?



Chapter 2.2. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2), are there better alternatives than HbA1c to estimate glycaemic control?

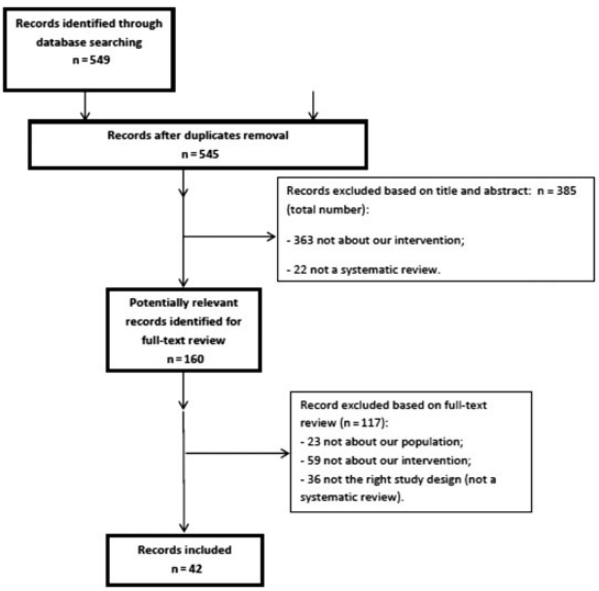
No flowchart available. All the included studies are listed in the narrative review from NDT: Are there better alternatives than haemoglobin A1c to estimate glycaemic control in the chronic kidney disease population? *Nephrol Dial Transplant* 2014; doi:10.1093/ndt/gfu006

Chapter 2.3. B. Is any oral drug superior to another in terms of mortality/complications/glycaemic control in patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2)?

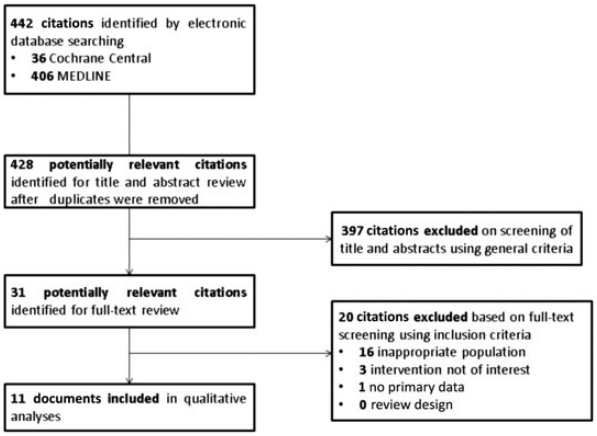


Chapter 2.3. A. Is any oral drug superior to another in terms of mortality/complications/glycaemic control in patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2)?

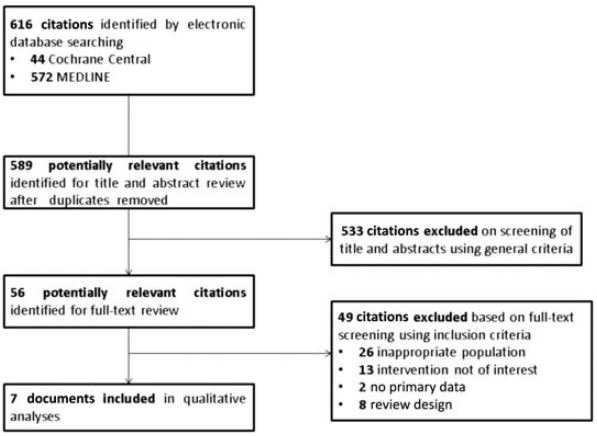
Review of systematic reviews



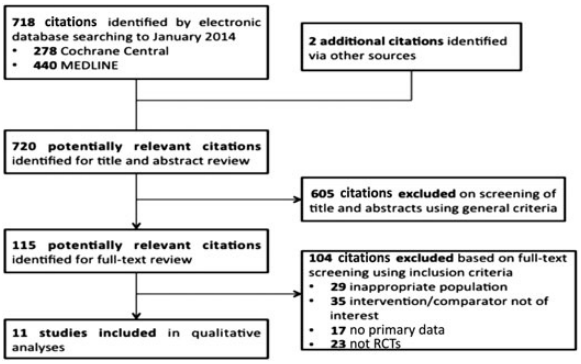
Chapter 2.3. B. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2), is maximal oral therapy better than starting/adding insulin in an earlier stage?



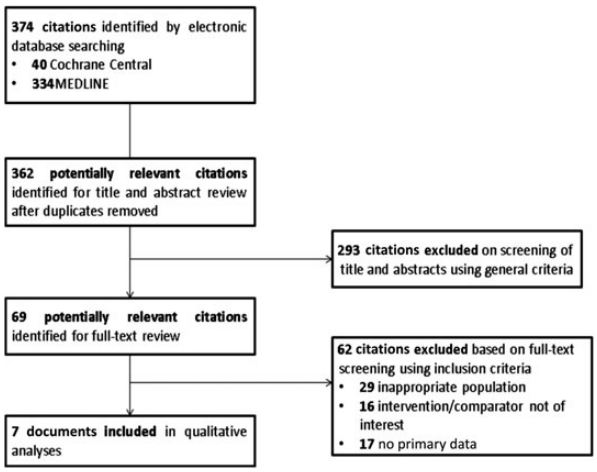
Chapter 3.1. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2) and CAD, is PCI or CABG or conservative treatment to be preferred?



Chapter 3.2. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2) and with a cardial indication (heart failure, ischaemic heart disease, hypertension), should we prescribe inhibitors of the RAAS system or aldosteron antagonists as cardiovascular prevention?



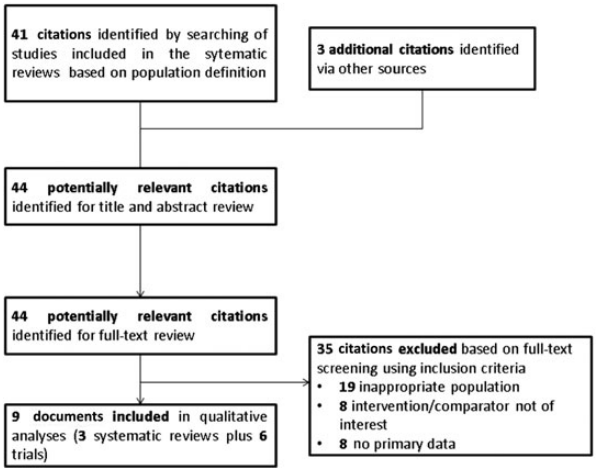
Chapter 3.3. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2), should we prescribe beta blockers to prevent sudden cardiac death?



Chapter 3.4. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2), 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.

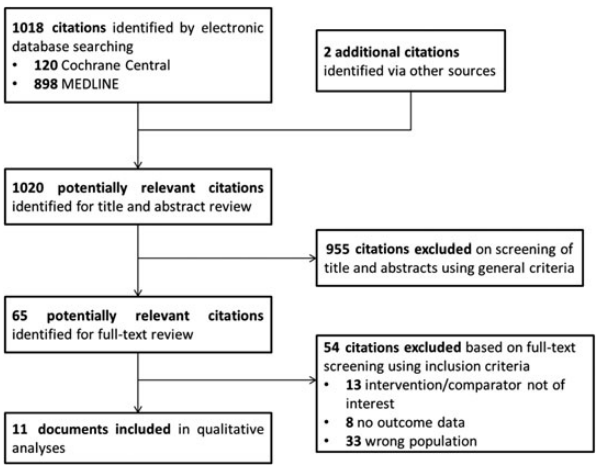
Chapter 3.5. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2), should we prescribe lipid-lowering therapy in primary prevention?



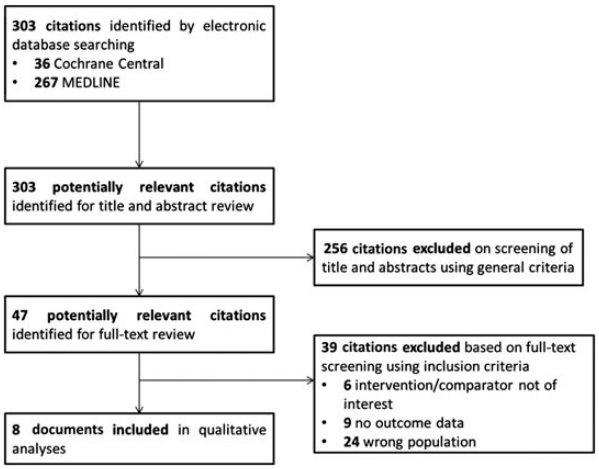
Chapter 3.6

C. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2), 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/1.73 m^2), 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/1.73 m^2), should antiplatelet therapy be recommended, regardless of the cardiovascular risk?



APPENDIX 5. SUMMARY TABLES

Chapter 1. Issues on modality selection in patients with diabetes and CKD stage 5

Author	Publication Year	N HD	N PD	Outcome	Observation time	Effect Measure	Value Effect Measure	Lower Bound Confidence Interval	Upper Bound Confidence Interval
				Early mortality (<12 months)					
Collins [226]	2002	26049	2805	Death rates per 1000 patient years	0–6 months	Relative risk	2.17	1.43	3.33
Collins [226]	2002	26049	2805	Death rates per 1000 patient years	6–12 months	Relative risk	1.22	1.11	1.33
Ganesh [227]	2003	12905	1844	Death in patients with CAD	0–6 months	Relative risk	1.03	0.9	1.18
Ganesh [227]	2003	28392	4651	Death in patients without CAD	0–6 months	Relative risk	1.04	0.92	1.17
Ganesh [227]	2003	28392	4651	Death in patients without CAD	6–12 months	Relative risk	1.37	1.18	1.58
Ganesh [227]	2003	12905	1844	Death in patients with CAD	6–12 monts	Relative risk	1.32	1.16	1.49
Liem [228]	2007	1615	928	Death in DM patients aged 40 years	3–6 months	Hazard ratio	0.40	0.23	0.68
Liem [228]	2007	1615	928	Death in DM patients aged 50 years	3–6 months	Hazard ratio	0.53	0.34	0.83
Liem [228]	2007	1615	928	Death in DM patients aged 60 years	3–6 months	Hazard ratio	0.71	0.48	1.04
Liem [228]	2007	1615	928	Death in DM patients aged 70 years	3–6 months	Hazard ratio	0.95	0.64	1.39
Stack [19]	2003	41316	6464	Death in diabetic patients with congestive heart failure	0–6 months	Relative risk	1.14	1.01	1.28
Stack [19]	2003	41316	6464	Death in diabetic patients withoutcongestive heart failure	0–6 months	Relative risk	0.93	0.82	1.07
Stack [19]	2003	41316	6464	Death in diabetic patients with congestive heart failure	6–12 months	Relative risk	1.37	1.20	1.57
Stack [19]	2003	41316	6464	Death in diabetic patients without congestive heart failure	6–12 months	Relative risk	1.31	1.16	1.49
Winkelmayer [229]	2002	951	274	Death in diabetic patients > 65 years	0–3 months	Relative risk	NS		
Winkelmayer [229]	2002	951	274	Death in diabetic patients >65 years	3–6 months	Relative risk	NS		
Winkelmayer [229]	2002	951	274	Death in diabetic patients >65 years	6–9 months	Relative risk	>1		
Winkelmayer [229]	2002	951	274	Death in diabetic patients >65 years	9–12 months	Relative risk	>1		
Weinhandl [17]	2010	3099	3086	Death in DM patients over 18 years	0–12 months	Hazard ratio	<1		
				Medium term mortality 12–36 months					
Liem [228]	2007	1615	928	Death in DM patients aged 40 years	6–15 months	Hazard ratio	0.59	0.44	0.81
Liem [228]	2007	1615	928	Death in DM patients aged 50 years	6–15 months	Hazard ratio	0.72	0.56	0.83
Liem [228]	2007	1615	928	Death in DM patients aged 60 years	6–15 months	Hazard ratio	0.87	0.71	1.09
Liem [228]	2007	1615	928	Death in DM patients aged 70 years	6–15 months	Hazard ratio	1.07	0.85	1.33
Liem [228]	2007	1615	928	Death in DM patients aged 40 years	>15 months	Hazard ratio	1.06	0.88	1.26
Liem [228]	2007	1615	928	Death in DM patients aged 50 years	>15 months	Hazard ratio	1.17	1.00	1.35
Liem [228]	2007	1615	928	Death in DM patients aged 60 years	>15 months	Hazard ratio	1.29	1.12	1.48
Liem [228]	2007	1615	928	Death in DM patients aged 70 years	>15 months	Hazard ratio	1.42	1.23	1.65
Termorshuizen [15]	2003	111	70	Death in diabetic patients aged > 60 years	3–24 months	Hazard ratio	0.78	0.40	1.54
Termorshuizen [15]	2003	111	70	Death in diabetic patients aged <60 years	3–24 months	Hazard ratio	0.16	0.04	0.70
Stack [19]	2003	41316	6464	Death in diabetic patients with congestive heart failure	12–18 months	Relative risk	1.5	1.29	1.75
Stack [19]	2003	41316	6464	Death in diabetic patients without congestive heart failure	12–18 months	Relative risk	1.39	1.21	1.61
Stack [19]	2003	41316	6464	Death in diabetic patients with congestive heart failure	18–24 months	Relative risk	1.39	1.12	1.72
Stack [19]	2003	41316	6464	Death in diabetic patients without congestive heart failure	18–24 months	Relative risk	1.32	1.09	1.6
Stack [19]	2003	41316	6464	Death in diabetic patients with congestive heart failure	0–2 years	Relative risk	1.30	1.20	1.41
Stack [19]	2003	41316	6464	Death in diabetic patients without congestive heart failure	0–2 years	Relative risk	1.11	1.02	1.21
Weinhandl [17]	2010	3099	3086	Death in DM patients over 18 years	12–24 months	Hazard ratio	NS		
Weinhandl [17]	2010	3099	3086	Death in DM patients over 18 years, from day 90	12–24 months	Hazard ratio	>1		
Weinhandl [17]	2010	3099	3086	Death in DM patients over 18 years	24–36 months	Hazard ratio	NS		
Weinhandl [17]	2010	3099	3086	Death in DM patients over 18 years, from day 90s	24–36 months	Hazard ratio	>1		
Collins [226]	2002	26049	2805	Death rates per 1000 patient years	12–18 months	Relative risk	1.56	1.41	1.72
Collins [226]	2003	26049	2805	Death rates per 1000 patient years	24–30 months	Relative risk	1.75	2.08	1.44

Continued

Chapter 1.1. Continued

Author	Publication Year	N HD	N PD	Outcome	Observation time	Effect Measure	Value Effect Measure	Lower Bound Confidence Interval	Upper Bound Confidence Interval
Collins [226]	2004	26049	2805	Death rates per 1000 patient years	30–36 months	Relative risk	1.79	2.22	1.41
Couchoud [230]	2007	991	191	Death in patients aged 75 years and over	0–2 years	Hazard ratio	1.00	0.80	1.30
Ganesh [227]	2003	28392	4651	Death in patients without CAD	12–18 months	Relative risk	1.57	1.34	1.85
Ganesh [227]	2003	12905	1844	Death in patients with CAD	12–18 months	Relative risk	1.35	1.17	1.54
Ganesh [227]	2003	12905	1844	Death in patients with CAD	0–2 years	Relative risk	1.23	1.12	1.34
Ganesh [227]	2003	28392	4651	Death in diabetic patients without CAD	0–2 years	Relative risk	1.17	1.08	1.26
Ganesh [227]	2003	28392	4651	Death in patients without CAD	18–24 months	Relative risk	1.39	1.11	1.75
Ganesh [227]	2003	12905	1844	Death in patients with CAD	18–24 months	Relative risk	1.31	1.09	1.57
Lee [231]	2009	437	79	Death in diabetic patients	0–2 years	Hazard ratio	0.93	0.41	2.12
van de Luijtgaarden [232]	2011	3976	955	Death in diabetic men aged 20–44 years	0–3 years	Hazard ratio	0.86	0.45	1.68
van de Luijtgaarden [232]	2011	3976	955	Death in diabetic men aged 45–59 years	0–3 years	Hazard ratio	0.79	0.54	1.15
van de Luijtgaarden [232]	2011	3976	955	Death in diabetic men aged 60–69 years	0–3 years	Hazard ratio	0.96	0.69	1.34
van de Luijtgaarden [232]	2011	3976	955	Death in diabetic women aged 45–59 years	0–3 years	Hazard ratio	0.80	0.47	1.38
van de Luijtgaarden [232]	2011	3976	955	Death in diabetic men aged ≥70 years	0–3 years	Hazard ratio	0.80	0.61	1.04
van de Luijtgaarden [232]	2011	3976	955	Death in diabetic men	0–3 years	Hazard ratio	0.84	0.71	1.00
van de Luijtgaarden [232]	2011	3976	955	Death in diabetic women	0–3 years	Hazard ratio	1.16	0.93	1.44
van de Luijtgaarden [232]	2011	3976	955	Death in diabetic women aged 20–44 years	0–3 years	Hazard ratio	0.76	0.33	1.76
van de Luijtgaarden [232]	2011	3976	955	Death in diabetic women aged 60–69 years	0–3 years	Hazard ratio	0.95	0.60	1.49
van de Luijtgaarden [232]	2011	3976	955	Death in diabetic women aged ≥70 years	0–3 years	Hazard ratio	1.55	1.15	2.08
Vonesh [233]	2004	352706	46234	Death in diabetic patients aged 18–44 years without comorbidity	0–3 years	Relative risk	0.82	0.70	0.95
Vonesh [233]	2004	352706	46234	Death in diabetic patients aged 45–64 years with comorbidity	0–3 years	Relative risk	1.22	1.15	1.30
Vonesh [233]	2004	352706	46234	Death in diabetic patients aged 18–44 years with comorbidity	0–3 years	Relative risk	0.91	0.76	1.09
Vonesh [233]	2004	352706	46234	Death in diabetic patients aged ≥65 years with comorbidity	0–3 years	Relative risk	1.25	1.18	1.32
Vonesh [233]	2004	352706	46234	Death in diabetic patients aged 45–64 years without comorbidity	0–3 years	Relative risk	1.09	1.00	1.18
Vonesh [233]	2004	352706	46234	Death in diabetic patients aged ≥ 65 years with no comorbidity	0–3 years	Relative risk	1.16	1.08	1.27
Jaar [234]	2005	433	140	Death in diabetic patients	0–2 years	Relative risk	1.41	0.91	2.19
				Late mortality (>36 months)					
Weinhandl [17]	2010	3099	3086	Death in DM patients over 18 years, from day 90	36–48 months	Hazard ratio	NS		
Weinhandl [17]	2010	3099	3086	Death in DM patients over 18 years, from day 90	36–48 months	Hazard ratio	NS		
Weinhandl [17]	2010	3099	3086	Death in DM patients over 18 years, from day 90	90–120 months	Hazard ratio	NS		
Weinhandl [17]	2010	3099	3086	Death in DM patients over 18 years	0–4 years	Hazard ratio	NS		
Weinhandl [17]	2010	3099	3086	Death in DM patients over 18 years, from day 90	0–4 years	Hazard ratio	>1		
Collins [226]	2002	26049	2805	Death rates per 1000 patient years	18–24 months	Relative risk	1.64	1.45	1.85
Collins [226]	2005	26049	2805	Death rates per 1000 patient years	36–42 months	Relative risk	1.56	2.17	1.11
Collins [226]	2002	26049	2805	Death rates per 1000 patient years	42–48 months	Relative risk	2.17	1.43	3.33

Termorshuizen [15]	2003	111	70	Death in diabetic patients aged > 60 years	24–48 months	Hazard ratio	1.52	0.67	3.33
Termorshuizen [15]	2003	111	70	Death in diabetic patients aged <60 years	24–48 months	Hazard ratio	2.44	0.76	7.69
Heaf [235]	2002	724	479	Death in diabetic patients	0–10 years	Relative risk	0.93	0.76	1.14
Heaf [235]	2002	724	479	Death in diabetic patients <55 years	0–10 years	Relative risk	0.91	0.7	1.19
Heaf [235]	2002	724	479	Death in diabetic patients >55 years	0–10 years	Relative risk	1.04	0.75	1.43
Lee [231]	2009	437	79	Death in diabetic patients	0–15 years	Hazard ratio	1.39	0.78	2.50
Mircescu [236]	2006	122	93	Adjusted death rates per 100 patient years, patients without comorbid conditions aged 18–65	0–7 years	Relative risk	0.57	0.23	1.40
Mircescu [236]	2006	122	93	Adjusted death rates per 100 patient years, patients with comorbid conditions and aged >65	0–7 years	Relative risk	0.80	0.28	2.33
Mircescu [236]	2006	122	93	Adjusted death rates per 100 patient years, patients with comorbid conditions and aged 18–65	0–7 years	Relative risk	1.04	0.62	1.75
Sanabria [237]	2008	157	220	Death in diabetic, <65 years	0–4 years	Hazard ratio	NS		
Sanabria [237]	2008	157	220	Death in diabetic, ≥65 years	0–4 years	Hazard ratio	NS		
Fenton [16]	1997	1800	907	Death in diabetic patients <65 years	0–5 years	Hazard ratio	0.92	0.77	1.09
Fenton [16]	1997	1800	907	Death in diabetic patients > 65 years	0–5 years	Hazard ratio	1.1	0.89	1.36

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

Study	-Publication year -Time frame -Location	Design	-Inclusion criteria -Exclusion criteria	Patient characteristics	-Intervention (n) -Comparator (n) -Duration	Outcome(s)	Results	Quality of evidence	Notes
Cooper *et al.* [29]	-2010 -2000–2008 -Australia/ New Zealand	Randomized controlled trial (IDEAL study)	-Patients were eligible for inclusion in the study if they had progressive CKD (patients with a failing kidney transplant were eligible) and an estimated GFR between 10.0 and 15.0 mL per minute per 1.73 m^2 -Exclusion: <18 years of age, eGFR <10.0 mL/min, planned living donation within 12 months, cancer that was likely to affect mortality	-Age: 60.3 years -Gender: 65% male -DM (as PRD): 34% -eGFR at start: 9.9 mL/min/1.73 m^2	-Late start of dialysis group ($eGFR_{CG}$ between 5–7 mL) (n = 424) -Early start of dialysis group ($eGFR_{CG}$ between 10–14 mL) (n = 404) -FU until November 2009	-Mortality	-HR 1.04 (0.83–1.30) P = 0.75. P for interaction for early or late start of dialysis with diabetes = 0.63	High	RCT with proper subgroup analysis for interaction in diabetics
Coronel *et al.* [33]	-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 years -Gender: 65% male -DM = 100% -DM1 = 54% -PD = 100% -Median eGFR at start: 7.7 mL/min/1.73 m^2	-$eGFR_{MDRD\text{-}7}$ ≤7.7 mL/min/1.73 m^2 (n = 56) -$eGFR_{MDRD\text{-}7}$ >7.7 mL/min/1.73 m^2 (n = 44) -60 months FU	-Mortality (on PD in diabetics, in DM1 and in DM2) -Hospital admissions (admissions/year and days of hospitaliz-ations)	-KM higher actuarial mortality in eGFR >7.7 mL 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 >7.7 mL in DM2 group P = 0.045 -No difference in admissions per year between intervention and comparator group (i.e. 1.3 ± 1.0 versus 1.5 ± 1.2 admission/year P = NS) -No difference in number of days of hospitalization between intervention and comparator group (23.1 ± 29 versus 20 ± 22 days/ patient/year)	Low	No (adjusted) effect measures provided. Limited population size and only PD patients
Kazmi *et al.* [34]	-2005 -North America -1996–1999	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 years -Gender: 53% male -DM (PRD): 46% -DM (Comorbid): 48% -eGFR at start: 8.4 mL/min/1.73 m^2	-$eGFR_{MDRD}$ 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 31 December 2000	-Mortality/mortality on dialysis in 1) whole population (fully adjusted) 2) in a low-risk population of patients w/o DM, HF, atherosclerosis (fully adjusted) 3) an older population (fully adjusted)	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)	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)
Lassalle *et al.* [35]	-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 years -Gender: 62% male -DM (PRD) : 21.2% -DM (Comorbid): 35.8% -eGFR at start: 8.8 mL/min/1.73 m^2	-$eGFR_{MDRD}$ 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/ Mortality on dialysis (+ KM) 2) Access to transplant-ation	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 1.73 m^2, 21, 17, 8, 4, and 6%, respectively, received kidney transplants	Low	Observational study that extensively adjusts for potential confounders. Despite this fact there might be a risk of selection bias and (residual) confounding (by indication)

Tang *et al.* [31]	-2007 -2002–2004 -Asia	Prospective cohort study	-All patients with chronic renal failure and their close relatives were invited	-Age: 58 years -Gender: 52% Male -DM2: 42% -eGFR at start in electiver starters: 9.21 mL/min/1.73 m^2 -eGFR at start in initial refusers: 8.89 mL/min/ 1.73 m^2	-Initial refusers (n = 82) -Elective starters (n = 151) -1 year (5 years 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% versus 9.8% in initial refusers, P = 0.014 4) 2.13 ± 1.13 versus 3.14 ± 1.17 episodes/person-year in initial refusers, P = 0.05 5) 0.38 ± 0.07 versus 0.8 ± 0.35 episodes/person-year in initial refusers, P = 0.033	Very low	The two groups compared in this study might be hampered 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.* [36]	-2002 -Europe -1987–2000	Retrospective cohort study	-Patients had to have to 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 years -Gender: 67% male -DM2: 21.7% -Median $eGFR_{CR}$ 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 $eGFR_{CG}$ < 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 a subgroup of diabetics are lacking, that subgroup is supposedly very similar to the group without diabetics
Wright *et al.* [37]	-2010 -North America -1995–2006	Retrospective cohort study	-Incident dialysis patients aged >18 years -Renal transplantation or renal function recover. Outliers in BMI, weight or height	-Age: 64.7 years -Gender: 53.1% -DM (PRD): 46.7% -DM (Comorbid): 56.2% -HD: 92.8% -sCreat: 7.2 (3.5) mg/ dL	-Dialysis started at $eGFR_{MDRD}$ ≤ 5 mL/min (n = 113 510) and dialysis started at eGFR >15 mL/min (n = 99 231) -Dialysis started at eGFR >5–10 -150 months	-Mortality/mortality at 60 months	-HR = 0.89 (0.88–0.90, P <0.06) versus eGFR	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)
Jain *et al.* [41]	-2014 -North America -2001–2009	Retrospective cohort study	-All incident PD patients (aged >18 years at dialysis therapy initiation) who had a recorded value for serum creatinine at dialysis therapy initiation and who received PD as their first form of renal replacement therapy between 1 January 2001, and 31 December 2009	-Age: 60.9 -Male: 57.3% -DM (PRD): 36.2% -DM (comorbid): 42.9%	-Mid start of dialysis at eGFR 7.5–10.5 (n = 2670) and early start at eGFR > 10.5 mL/min/ 1.73 m^2 (n = 2994) -Late start of dialysis at eGFR 7.5 mL/min/1.73 m^2 (n = 2383) -2.2 years (2.3, 2.2, and 1.9 years in the early, mid, and late start groups, respectively)	-Mortality/mortality at 5 years	-HR = 1.16 (0.82–1.63) for early versus late. -HR = 0.99 (0.70–1.39) for mid versus late	Mediocre	Observational study in incident PD patients that extensively adjusts for potential confounders. Despite this fact, bias and residual confounding might still play a role
Beddhu *et al.* [38]	-2003 -North America -1996–1997	Prospective cohort study	-Incident chronic HD and PD 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	-Age: 59 -Male: 53% -Ethnicity White: 64% Black: 28% -DM (PRD): 42% -HD: 53% -$eGFR_{MDRD}$: 8.2 ± 3.9 -Haematocrit: 30.8 ± 5.4	-a 5 mL/min increase in $eGFR_{MDRD}$ at start of dialysis (n = 2920) -5585 patient-years of follow-up	-Mortality/mortality	-HR_{adj} = 1.14 (1.06 - 1.14) for every 5 mL/min increase in eGFR at start of dialysis	Low	A random sample in a prospective U.S. dialysis population which adjusts for confounders using propensity scores. Howevere, propensity scores cannot control different sources of bias

Continued

Chapter 1.2. Continued

Study	-Publication year -Time frame -Location	Design	-Inclusion criteria -Exclusion criteria	Patient characteristics	-Intervention (n) -Comparator (n) -Duration	Outcome(s)	Results	Quality of evidence	Notes
			height, weight, blood urea nitrogen (BUN), serum creatinine, serum albumin, haematocrit, and serum bicarbonate were excluded.	-BUN: 87 ± 31 -Bicarbonate: 22.0 ± 4.6 -BMI: 26.3 ± 5.8					
Clark *et al.* [40]	-2011 -North America -2001–2007	Retrospective cohort study	-All adult (≥18 years) patients with a recorded serum creatinine value who started with HD 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% -DM (Comorbid): Early: 52.7%, Late: 43.4%	-Early initiation of dialysis with $eGFR_{MDRD} < 10.5$ mL/min/1.73 m^2 ($n = 8441$) -Late start of dialysis with $eGFR_{MDRD} \leq 10.5$ mL/min/1.73 m^2 ($n = 17\,469$) -2.3 years of follow-up	-Mortality/mortality	-$HR_{Adj} = 1.18$ (1.13–1.23) for early initiation of dialysis compared with late initiation of dialysis	Mediocre	Retrospective cohort study in Canadian registry data with substantial adjustment for confounding although never sufficient to be absolutely sure benefits of late start are not a reflection of other factors
Harris *et al.* [210]	-2011 -2002–2008 -Australia/ New Zealand	RCT (IDEAL study)	-Patients were eligible for inclusion in the study if they had progressive CKD (patients with a failing kidney transplant were eligible) and an estimated GFR between 10.0 and 15.0 mL per minute per 1.73 m^2 -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	-Age: Early starters: 60.0 ± 13.2, Late starters: 60.5 ± 12.1 -Male: early: 64%, late: 64%. -DM (PRD): early: 33.2%, Late: 34.6% -DM (Comorbid): early: 42%, late: 43.6%	-Late start of dialysis group ($eGFR_{CG}$ between 5–7 mL) ($n = 335$). -Early start of dialysis group ($eGFR_{CG}$ between 10–14 mL) ($n = 307$) -Time to dialysis in early: 1.90 months, late: 7.30 months -4.15 years of follow-up	-QoL -QALY -Total cost of treatment	-Difference in QoL between early- and late-start: −0.00 (−0.03; 0.03) -QALY early: 1.97 (1.81–2.14) QALY late: 2.07 (1.92–2.21) Difference in QALY (adjusted for baseline AQoL): −0.09 (−0.12; 0.31) -Early start group: $215 354 ($114 777–$311 713) versus Late start group: $202 124 ($114 636-$288 704)	High	Randomized trial comparing early versus late with respect to costs on dialysis. There is an absence of QoL and mortality advantage for early start of dialysis, whereas it costs more and patients are dialysed for a longer period of time
Hwang *et al.* [39]	-2010 -Asia 2001–2004	Retrospective cohort study	-Incident HD patients between July 2001 and December 2004 -Patients with age <20 years, PD as primary treatment, incomplete ID digits, eGFR >15 mL/min/1.73 m^2 at start of dialysis or mortality <3 months (90 days)	-Age: 61.5 ± 14.0 -Male: 47.7% -DM (PRD): 42.9% -$eGFR_{MDRD}$: 4.7 (3.6–6.1) mL/min/1.73 m^2	-2nd quintile (eGFR (MDRD) 3.29–4.27 mL/min) ($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$) -1st quintile (eGFR <3.29) ($n = 4669$) -Follow-up: 22 291 patient years in 23 551 patients	Mortality/mortality	$HR_{Adj;Q2}$ versus $_{Q1}$: 1.18 (1.01–1.37) $HR_{Adj;Q3}$ versus $_{Q1}$: 1.21 (1.04–1.41) $HR_{Adj;Q4}$ versus $_{Q1}$: 1.66 (1.43–1.93) $HR_{Adj;Q5}$ versus $_{Q1}$: 2.44 (2.11–2.81)	Mediocre	Large observational study in incident Taiwanese HD patients with adjustment for confounding

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?

Study	-Publication year -Time frame -Location	Design	-Inclusion criteria -Exclusion criteria	Patient characteristics	-Intervention (*n*) -Comparator (*n*) -Duration	Outcome(s)	Results	Quality of evidence	Notes
Chan *et al.* [45]	-2007 -1996– -North America	Retrospective cohort study	-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 tunnelled 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	-43% diabetes	-AVG placement -AVF placement -25 months -*n* = 462	-Survival of the technique (patency rate) -Mortality	-OR 1.49 (0.76–2.89; P = 0.224) -OR 1.34 (0.92–1.95; *P* = 0.123)	Registry-based reporting of outcome Incomplete adjustment for co-variates	Number of events not stated. Number of analysed participants in each study group not stated
David *et al.* [46]	-2010 -2003–2008 -Europe	Retrospective cohort study	-Incident HD patients referred to AVF placement	-Age 67 ± 12 years -26% diabetes	-Proximal AVF placement (*n* = 38) -Distal AVF placement (*n* = 34) -80 months	-Survival of the technique (primary patency rate)	-55% -30%	Generalizability uncertain. Incomplete adjustment for co-variates Centre bias No valid outcome measures	No baseline characteris-tics
Dhingra *et al.* [47]	-2001 -1993–1995 -North America	Retrospective cohort study	-Incident and prevalent HD patiens. -Patients were excluded if they were less than 15 years of age at the study start date had a functioning kidney transplant, were in training for any self-care treatment, or were receiving PD or home HD at the study start date	-Age 59 years -Male gender: 51% -31% diabetes	-HD patients with AVG (*n* = 3129) and HD patients with CVC (*n* = 875). -HD patients with AVF (*n* = 1340) -24 months	-All-cause mortality -Cardiovascular-related mortality -Infection-related mortality	-RR = 1.54, 1.17–2.02; RR = 1.41, 1.13–1.77, CVC versus AVF and AVG versus AVF, respectively -RR = 1.47, 1.00–1.16; RR = 1.35, 0.98–1.85, CVC versus AVF and AVG versus AVF, respectively -RR = 2.30, 0.96–5.52; RR = 2.47, 1.16–5.25, CVC versus AVF and AVG versus AVF, respectively	Registry-based reporting of outcome	Large population from the Master List of Medicare Approved Dialysis Facilities
Diehm *et al.* [53]	-2010 -Europe	Retrospective cohort study	-All patients with successful access placement in the vascular access centre	-25% Diabetes	-Diabetic patients (*n* = 62) -Nondiabetic patients (*n* = 182) -24 months	-Survival of the technique (primary and secondary patency rates)	-OR = 0.60 (0.30–1.00) -OR = 0.40 (0.20–0.70)	Generalizability uncertain Selection bias Center bias No adjustment for covariates	Number of events not stated No reliable data within the diabetic group
Field *et al.* [48]	-2008 -2003–2007 -Europe	Retrospective cohort study	-Incident HD patients with AVF	-Age: 61 years -Male gender: 54% -36% diabetes	-Diabetic patients (*n* = 103) -Nondiabetic patients (*n* = 186) -48 months	-Survival of the technique (primary patency rate)	-34% versus 26% (P = 0.110)	Generalizability uncertain Centre bias No adjustment for confounders No valid outcome measures	Number of events not stated No reliable data within the diabetic group
Hammes *et al.* [49]	-2008 -2000–2007 -North America	Retrospective cohort study	-HD patients who underwent vascular access angiography and had at least 1 follow-up venogram done as clinically indicated	-41% diabetes	-Cephalic arch stenosis in diabetic patients with (*n* = 27) and without (*n* = 25) cephalic arch lesion	-Survival of the technique (the number of weeks to the development of clinically	-Mean difference: 114 ± 17 versus 109 ± 18	Generalizability uncertain Centrer bias Small patient	No baseline characteristics

Continued

Chapter 1.3. Continued

Study	-Publication year -Time frame -Location	Design	-Inclusion criteria -Exclusion criteria	Patient characteristics	-Intervention (*n*) -Comparator (*n*) -Duration	Outcome(s)	Results	Quality of evidence	Notes
					at baseline -78 months	significant stenosis)		numbers. No adjustment for confounders No valid outcome measures	
Konner *et al.* [238]	-2000 -1993–1998 -Europe	Retrospective cohort study	-Incident HD patients undergoing AVF placement	-Age: 59 years -Gender: -22% diabetes	-Diabetic patients ($n = 78$) -Nondiabetic patients ($n = 269$) -72 months	-Survival of the technique (median time to first event)	-42.3 versus 45.8 months	Generalizability uncertain Centre bias. Small patient numbers No valid outcome measures	No reliable data within the diabetic group
Konner *et al.* [50]	-2002 -1993–1998 -Europe	Retrospective cohort study	-ESKD patients with first AVF placement -ESKD with contraindications to AVF placement	-Age: 60 years -Male gender: 59% -24% diabetes	-Diabetic patients with proximal perforating vein ($n = 86$) and non-perforating vein ($n = 52$) AVF -Diabetic ESRD patients with forearm AVF ($n = 43$) -24 months	-Survival of the technique (primary and secondary patency rates)	-80% versus 80% versus 50% -90% versus 80% versus 80%	Generalizability uncertain Centre bias Small patient numbers No valid outcome measures	Descriptive outcome measures
Leapman *et al.* [52]	-1996 -1989–1995 -North America	Retrospective cohort study	-Incident HD patients undergoing wrist AVF placement	-Age 50 ± 16 years -Male gender: 66% -34% diabetes	-Diabetic patients ($n = 51$) -Nondiabetic patients ($n = 109$) -60 months	-Survival of the technique (cumulative patency rate)	-63% versus 42%	Generalizability uncertain Centre bias No valid outcome measures	No reliable data within the diabetic group
Murphy *et al.* [51]	-2002 -1993–2000 -Europe	Retrospective cohort study	-Incident HD patients undergoing elbow AVF placement	-Age 60 years -Male gender: 65% -29% diabetes	-Diabetic patients -Nondiabetic patients -$n = 232$ -12 months	-Survival of the technique (cumulative patency rate)	-39% versus 40% (P = N.S.)	Generalizability uncertain Centre bias No adjustment for confounders	No reliable data within the diabetic group
Ravani *et al.* [43]	-2002 -1995–2001 -North America	Prospective cohort study	-Incident HD patients with vascular access placement by nephrologists -Previous history of HD and kidney transplantation and an incomplete follow-up or exit from the system to see other caregivers	-22% diabetes	-Diabetic patients -Nondiabetic patients -$n = 232$ -36 months	-Survival of the technique (primary and cumulative patency rate)	-HR = 1.85, P = 0.01 -HR = 2.38, P = 0.04	Generalizability uncertain Centre bias	No reliable data within the diabetic group
Saxena *et al.* [44]	-2002 -1996–2000 -North America	Prospective cohort study	-HD patients		Diabetic patients with AVF ($n = 36$) -Diabetic patients with AVG ($n = 9$), tunnelled CVC ($n = 5$), subclavian CVC ($n = 9$) and femoral CVC ($n = 4$) -48 months	-Vascular access infection-related mortality	-15%, 42% (P <0.0006), 33% (P <0.03), 37.5% (P <0.001), 100% (P <0.0005)	Generalizability uncertain Centre bias No adjustment for confounders Small number of patients	
Yeager *et al.* [54]	-2002 -1991–2000 -North America	Retrospective case-control study	-HD patients	-Male gender: 97% -55% Diabetes	-Patients without finger gangrene ($n = 23$) -Patients with finger gangrene ($n = 199$) -36 months	-Survival rate	-49% versus 52% (P > 0.05)	Generalizability uncertain Centre bias No adjustment for confounders Unbalance between the number of cases and controls	No reliable data within the diabetic group

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?

Study	Population/Source/Aim	Findings
Batabyal *et al.* [62] 2012	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 waitlisting of patients for kidney transplantation.	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.
Bayat *et al.* [239] 2008	NEPHROLOR database (all ESRD patients living in Lorraine and placed on the waiting list), $n = 809$.	Diabetes was an independent factor associated with non-registration on waiting list (OR 2.97; 95CI 1.67–5.28).
Dudley *et al.* [240] 2009	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.	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).
Goldfarb-Rumyantzev *et al.* [241] 2011	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).	In patients with no history of diabetes (compared with 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.
Machado *et al.* [242] 2012	Non-concurrent cohort study of 835 patients on the waiting list for kidney transplants from 2000 to 2004 to analyse factors associated with access to kidney transplants from living and cadaver donors in Belo Horizonte, Brazil.	144 patients on the waiting list (18.4%) had diabetes and 17 (9.9%) were transplanted versus 127 (20.8%) not transplanted (P = 0.001). Mean time (year) for receiving a transplant was 3753 in diabetes versus 2068 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.
McCullough *et al.* [243] 2009	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.	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 pre-emptively waitlisted; among that group, 2596 (74%) were eventually transplanted. Of the younger patients with diabetes who were pre-emptively waitlisted, 792 were also pre-emptively transplanted: 486 from a living donor and 306 from a deceased donor. An additional 1804 transplants occurred among these pre-emptively 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 pre-emptively from a living donor without ever being waitlisted. Transplant rates were lower among non-pre-emptively 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 pre-emptively 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.
Patibandla *et al.* [244] 2012	Data from the United States Renal Data System (01/01/2000–24/09/2007; $n = 619\,151$).	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 waitlisting/transplant without being listed (hazard ratio, HR = 0.80, P <0.001) and for transplant after being listed (HR = 0.72, P <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 <0.001), and there was no significant difference in time to transplantation after being listed (HR = 1.01, P = 0.42).

Continued

Chapter 1.4. Continued

Study	Population/Source/Aim	Findings
Patzer *et al.* [245] 2009	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 (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 aetiology of ESRD.	Diabetes was associated with HR of waitlisting of 0.78 (0.72 to 0.85) P <0.0001.
Ravanan *et al.* [246] 2010	16 202 incident renal replacement treatment patients (1757 patients with diabetes) from 65 renal centres submitting data to the UK Renal Registry between 1 January 2003 and 31 December 2005, followed until 31 December 2008.	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 *et al.* [247] 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 0.90–0.98).
Oniscu *et al.* [248] 2003	4523 adults (226 patients with diabetes) starting renal replacement therapy in Scotland between 1 January 1989 and 31 December 1999.	Patients were less likely to be placed on the list if they had diabetes; RR 0.81 (0.64 to 1.01) P = 0.06.
Satayathum *et al.* [249] 2005	5267 randomly selected DOPPS I patients (35.9 % patients with diabetes) in dialysis units in the United States, Europe, and Japan who received chronic HD therapy for at least 90 days in 2000.	Patients with diabetes 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?

Study	-Publication Year -Time Frame -Location	Design	-Inclusion criteria -Exclusion criteria	Patient characteristics	-Intervention (*n*) -Comparator (*n*) -Duration	Outcome(s)	Results	Quality of evidence	Notes
Abbott *et al.* [250]	-2001 -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 waitlisting before 1992.	-Age 57.4 ± 11.3 -Gender: 59% male	-Transplantation (*n* = 5683) -Remaining on the waiting list (*n* = 5686) -1.93 years	-Congestive heart failure	-HR 0.64 (0.54–0.77; P <0.05)	Representative-Dea ness uncertain Registry-based reporting of outcome	Adjustment for covariates renders the association non-significant
Abbott *et al.* [251]	-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 waitlisting before 1992	-Age 57.4 ± 11.3 -Gender: 59% male	-Transplantation (*n* = 5683) -Remaining on the waiting list (*n* = 5686) -1.93 years	-Sepsis due to Gram-negative organisms -Bacterial septicaemia -Sepsis due to urinary tract infection	-HR 3.32 (2.61–4.23; P <0.05) -HR 1.20 (1.02–1.55; 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, immunosup-pressive regimen, bladder catheterization
Adang *et al.* [88]	-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)	-QoL	-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 waiting list No adjustment for covariates	High chance of type 1 error
Allen *et al.* [83]	-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 post-transplantation 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 an SPK were also studied.	-Age 38.5 ± 7.9 -Gender: 49% male -Dialysis vintage: 25.2 ± 7.6	-SPK with functioning pancreas graft >6 months (*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 Centre 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

Continued

Chapter 1.4.B. Continued

Study	-Publication Year -Time Frame -Location	Design	-Inclusion criteria -Exclusion criteria	Patient characteristics	-Intervention (*n*) -Comparator (*n*) -Duration	Outcome(s)	Results	Quality of evidence	Notes
			-Death with a functioning transplant, or kidney and pancreas failure, within 6 months of transplantation						
Fiorina *et al.* [85]	-2005 -Europe	Before-after study	-Type 1 diabetes patients with a functional kidney graft received from a cadaveric donor. -Exclusion criteria for the intervention group (islet transplant) were: 1) severe hepatic dysfunction, 2) major stroke with neurological inability, 3) major amputation, 4) severe dilated cardiomyopathy, or 5) severe CAD/myocardial infarction during follow-up.	-Age 48.6 -Gender: 54% male -Diabetes vintage: 31years	-Renal transplantation followed by islet transplantation (=17). -Renal transplantation not followed by islet transplantation (*n* = 25)	-Glycaemic control -Cardiovascular status (change in surrogate markers of cardiac function: ejection fraction, IMT, QT dispersion, NaK-ATPase activity, BNP and ANP)	-Lower need of insulin in the kidney-islet group -Cardiovascular parameters improved in the kidney-islet group, but not in the kidney-only group	High potential for selection bias. Small patient numbers No adjustment for confounders No valid outcome measures (surrogates for clinical relevant endpoints). Multi-comparisons without appropriate statistical approach and with high risk of type 1 error due to cherry picking	Comparison of cardiovascular outcome in two groups while the exclusion criterion to be allocated to the intervention group (=islet) is partially cardiovascular
Gaber *et al.* [86]	-1995 -North-America	Before-after study	-Type 1 diabetes patients transplanted with a single kidney, with pancreas–kidney or pancreas transplantation after kidney transplantation		-Combined pancreas–kidney transplantation pancreas after kidney (22) -Kidney transplantation alone (11)	-Cardiovascular status: (echocardiographic measures)	-Sustained improvement of echocardiographic measures in pancreas versus kidney alone group	High potential for selection bias Small patient numbers No adjustment for confounders	Multi-comparison with risk of type 1 error No baseline characteristics
Giannarelli *et al.* [84]	-2005 -Europe	Before-after study	-SPK patients with retinopathy	-Age: 40 ± 7 -Gender: 54% male -BMI: 23 ± 2 kg/m^2 -Diabetes vintage: 24 ± 8	-SPK (48) -Non-transplanted type 1 diabetes patients (43)	-Visual disturbances -Improvement and/or stabilisation of diabetic retinopathy	-RR 1.83 (1.38–2.61; P <0.05)	High potential for selection bias Small patient numbers No adjustment for confounders	No baseline characteristics of comparator non-transplanted type 1 diabetes patients Comparator group ill-defined with potential of selection bias No mentioning the assessment after graft loss in the SPK group
Kleinclauss *et al.* [63]	-2009 -1995–2003 -North-America	Retrospective cohort study	-Diabetic recipients of living donor (LD) kidney transplants	-Age: 45 Gender: 54% male -Diabetes type 1: 80%	-PAK (*n* = 175) -No subsequent pancreas transplant although deemed eligible (KTA-E), but did not receive it for personal or financial reasons (*n* = 75) -120 months of follow-up	-Progression to end-stage kidney disease (dialysis) -Survival	-RR 1.2 (0.8–1.9; P = 0.41). -RR 1.03 (0.51–2.09; P = 0.93)	High potential for selection bias Small patient numbers No adjustment for confounders	Single-centre data 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 possibly with issues of obesity. No adjustment for comorbid status in the Cox model
La Rocca *et al.* [64]	-2001 -1984–1998 -Europe	Retrospective cohort study	-Type 1 diabetic ESKD patients -Previous strokes, major amputations and severe dilated cardiomyopathy	-Age 45.6 -Diabetes vintage 27.7 years	-SPK (*n* = 196) -Remaining on the waiting list (*n* = 130)	-Progression to end-stage kidney disease (dialysis) -Survival	-7 year graft survival 85.2% (SPK) versus 70% kidney alone -7 year patient survival 77.4% versus 39.6% kidney transplant alone (P = 0.01)	Generalizability uncertain (very high HbA1c) Potential for selection bias (for instance more smokers in the waitlisted group) Univariate differences Small patient numbers Follow-up incomplete	Patients remaining on the waiting list for immunological reasons such as low HLA matching and/or antibodies. This might confer a higher comorbid state

Sureshkumar *et al.* [252]	-2006 -1988–2004 -North America	Retrospective case-control study	-Type 1 diabetes patients with ESKD minimum follow-up of 3 months after transplantation	-Age 44 years -Male gender: 59%	-SPK ($n = 43$) -Type 1 diabetes patients with ESKD waitlisted for transplantation ($n = 23$)	-QoL: Diabetes QoL (DQoL), Short Form-36 (SF-36) and Quality of Well-Being (QWB) questionnaires were utilized (overall 15 compounds were being tested)	S-PK group had better satisfaction subscore compared with WL (1.8 ± 0.5 versus 2.6 ± 0.6, P <0.001) and better impact subscore compared with WL (1.7 ± 0.6 versus 2.3 ± 0.6, P <0.01) groups. There were no significant differences on physical/mental composite scores of SF-36. QWB score was better in SPK group versus WL group (0.62 ± 0.11 versus 0.55 ± 0.04, P <0.05). group	Potential for selection bias/allocation bias Informative censoring in the follow-up Univariate differences Multi-comparison; high chance of type 1 error Small patient numbers	Longitudinal outcome data (QoL) available only in a subset of patients with CKT/SPK Some patients in the kidney transplantation groups were offered SPK Transplantation but opted for kidney-alone transplantation (either cadaver or living). So differences in QoL in groups might reveal disparities in personality traits
Young *et al.* [78]	-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 ($n = 3309$) transplantation -SPK ($n = 5352$)	-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 *et al.* [77]	-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 ($n = 3991$) -Cadaveric kidney only ($n = 9956$)	-Survival/mortality	-Survival at 5y with survivors with renal allograft function at 1 year: respectively 89.8, 87.8 and 79.7% -Mortality beyond 18 months posttransplant-ation in SPK versus LDK transplantation: HR 0.86; P = 0.02 -Survival 5 years after transplantation: 81%, 84% and 71% respectively; SPK versus LDK transplantation HR 0.92; P = 0.04 -Mortality 18 months post-transplantation in SPK versus LDK: HR 2.2; P <0.001	High potential for selection bias	The healthiest patients are allocated to SPK and receive the highest quality organs-Centre bias: SPK especially in the early era mostly in high-volume centres No confidence intervals provided
Waki *et al.* [90]	-2006 -1995–2002 -North America	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	-Age 44.4 years -Male gender: 59% -BMI: 25.8 kg/m^2 -Duration of dialysis: 2.3 years -African American: 14%	-SPK ($n = 544$) -Kidney transplantation alone ($n = 544$)	-Progression to end-stage kidney disease (up to december 2004) -Survival free from graft loss (5y) -Survival (at one year): -Mortality (up to december 2004) -Survival (at five year)	-HR 0.8 (0.49–1.31; P = 0.38) -78.2% SPK versus 65.5% kidney transplantation alone -96.4% SPK versus 95.2% kidney transplantation alone -HR 0.77 (0.4–1.48; P = 0.43) -89.6% SPK versus 78.2% kidney transplantation alone	High potential for selection bias Incomplete adjustment. Registry data UNOS; generalizability uncertain	-

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Chapter 1.4.B. Continued

Study	-Publication Year -Time Frame -Location	Design	-Inclusion criteria -Exclusion criteria	Patient characteristics	-Intervention (*n*) -Comparator (*n*) -Duration	Outcome(s)	Results	Quality of evidence	Notes
Ziaja *et al.* [89]	-2009 -Europe	Prospective cohort study	-Type 1 diabetes receiving kidney transplantation alone with or without failure of the pancreas graft after transplantation and/or receiving SPK -Type 2 diabetes mellitus organs from living donation	-Age 37 years	-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)	-QoL.	-Benefit in SPK group for -Physical functioning (P = 0.03). -Overall health (P = 0.001). -Pain (P = 0.005). -Effects of kidney disease (P = 0.001) -Symptoms/problem list (P = 0.04). -Cognitive function (P = 0.03)	High potential of selection bias Small patient sample Generalizability uncertain No adjustment	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 (QoL). Also, selection bias in donor selection with younger age and shorter CIT in the SPK group Functioning kidney grafts in the kidney graft only group does not specify the degree of renal impairment which is possibly more pronounced than in the SPK group
Wolfe *et al.* [70]	-1999 -1991–1996 -North America	Retrospective cohort study	-Patients under the age of 70 years starting with treatment for end-stage renal disease -Patients >70 years. Non-reporting of the cause of end-stage renal disease or the region they were from. Patients who received transplants without first undergoing dialysis		-Transplantation of patients with diabetes as cause of ESRD (*n* = 7262) -Patients with diabetes as cause of ESRD remaining on the waiting list (*n* = 7926)	-Survival was analysed 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 31 December 1997 (patients with diabetes as cause of ESRD)	-RR 0.27 (0.24–0.30; P <0.001)	Incomplete adjustment Registry data	Misclassification bias excluding diabetic patients on the waiting list No separation type 1/type 2 diabetes
Weiss *et al.* [81]	-2009 -1997–2005 -North America	Retrospective cohort study	-All patients on the SPK waiting list who were transplanted January 1997 through December 2005 -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	-Age 39.9 years -Male gender: 59%	-SPK with functional pancreas at year 1 (*n* = 6486) -SPK with pancreas loss the first year (*n* = 371) -LDK (*n* = 904) -DDK (*n* = 520)	-Progression to end-stage kidney disease during follow-up (DDK versus 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 1year as reference). -Survival free from graft loss DDK versus 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 with versus without pancreas graft loss. -Survival free from renal graft loss SPK versus LDK. -Survival in LDK comparison	-HR 1.63 (1.28–2.06; P <0.001) -72% SPK, 59.8% SPK with pancreas loss, 62.6% LDK and 497% DDK -94.8% LDK versus 90.3% DDK. -HR 1.51 (1.22–1.88; P <0.001) -HR 1.64 (1.31–2.05; P <0.001) -92% SPK versus 94.8% LDK (P = 0.001) -HR 1.98 (1.47–2.67; P <0.001) -95.6% (DDK) versus 97.2% (LDK) (P = 0.01) -95.9% (SPK) versus 97.2% (LDK) (P = 0.04) -HR 2.66 (1.98–3.57; P <0.001) -88.6% SPK with functioning graft versus 73.9% SPK with pancreas graft loss versus	Generalizability uncertain High probability of selection bias Incomplete adjustment	Registry data (SRTR)

						to SPK with functioning pancreas one year after transplantation as reference. -Survival the first year in DDK versus LDK. -Survival the first year after transplantation SPK versus 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 versus SPK with functioning pancreas as reference -Survival in DDK in comparison to SPK with functioning pancreas one year after transplantation as reference	80.0% LDK versus 64.8% DDK -HR 2.05 (1.48–2.83; P <0.001)		
Ojo *et al.* [79]	-2001 -1988–1998 -North America	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 1 October 1988 and 30 June 1997 -Missing date of wait-list registration receiving living donation or never waitlisted	-Age 35.4 years -Male gender: 55%	-SPK ($n = 4718$) -LDK ($n = 671$) -DDK ($n = 4127$)	-Mortality DKD versus remaining on waitlist -Survival the first 10 years after transplantation -Mortality the first 5 years after transplantation of LDK versus remaining on wait ing list -Mortality SPK the first 5 years after transplantation versus remaining on the waiting list.	-HR 0.75 (0.63–0.89; P <0.05) -67% SPK versus 65% LDK versus 43% DKD -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)
Morath *et al.* [80]	-2008 -1984–2000 -Europe	Retrospective cohort study	-Transplants reported to the CTS from 1984 to 2000 were analysed. All patients who were reported to the study centre 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	-Age 35.7 years -Male gender: 58%	-SPK ($n = 3525$) -LDK ($n = 2190$) -DDK ($n = 5705$)	-Progression to end-stage kidney disease 6–10 years after transplantation (death censored) SPK versus DDK -Progression to end-stage kidney disease (death-censored) from year 2 to 5 post-transplantation patients transplanted between 1991–2000 SPK versus DDK -Progression to end-stage kidney disease 6–10 years after transplantation (death censored) SPK versus LDK -Progression to end-stage kidney disease (death-censored) from year 2 to 5 post-transplantation patients	-HR 1 (0.79–1.26; P = 0.931) -HR 0.96 (0.79–1.17; P = 0.711) -HR 1.31 (0.94–1.83; P = 0.111) -HR 1.32 (1–1.74; P = 0.052) -HR 0.89 (0.63–1.27; P = 0.533) -HR 0.52 (0.37–0.73; P <0.001) -HR 0.64 (0.51–0.82; P <0.001) -HR 1.31 (0.96–1.79) HR 0.82 (0.66–1.01; P = 0.064) -HR = 0.55 (0.36–0.83; P = 0.005)	Potential for selection bias Incomplete adjustment	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, hyperlipidaemia, and statin use; tobacco use; use of inhibitors of the renin angiotensin system)

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Chapter 1.4.B. Continued

Study	-Publication Year -Time Frame -Location	Design	-Inclusion criteria -Exclusion criteria	Patient characteristics	-Intervention (*n*) -Comparator (*n*) -Duration	Outcome(s)	Results	Quality of evidence	Notes
					transplanted between 1991–2000 SPK versus LDK -Mortality 6–10 years after transplantation (with the transplantation between 1991 and 2000) SPK versus LDK -Mortality 11–18 years after transplantation SPK versus DDK -Mortality 6–10 years after transplantation -Transplantation between 1991 and 2000 SPK versus DDK -Mortality 2–5 years after transplantation with transplantation between 1991–2000 SPK versus LDK -Mortality 2–5 years after transplantation with transplantation between 1991 and 2000 SPK versus LDK -Mortality 11 and 18 years after transplantation SPK versus LDK				
Poommipanit *et al.* [75]	-2010 -2000–2008 -North America	Retrospective cohort study	-Patients with type I 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 -Dual organ transplants other than kidney-pancreas transplants	-Age 28.2 years -Male gender: 59%	-PALK (*n* = 807) -SPK (*n* = 5580)	-Progression to end-stage kidney disease, graft failure of the kidney in PALK versus SPK -Progression to end-stage kidney disease within 5 years post-transplantation -Mortality during the study period PALK versus SPK -Survival the first year post-transplantation	-HR 0.48 (0.39–0.60; P <0.01) -77% SPK versus 86% PALK -HR 0.52 (0.39–0.70; P <0.01) -99.24% PALK versus 95.55% SPK	High potential for selection bias Incomplete adjustment Univariate comparisons No P-values	Less comorbidity in the SPK group with incomplete correction for comorbid status	
Gross *et al.* [253]	-1992 -1980–1991 -North America	Prospective case-control study	-Functioning pancreas graft more than one year post-transplantation. -Pancreas graft not for type 1 diabetes and both pancreas and kidney graft failure (*n* = 2).	-Age 36.8 years -Male gender: 35%	-Successful pancreas Transplant (*n* = 65) -Failed pancreas Transplant (*n* = 64)	-Positive health perceptions -Pain -Ability to function socially -Ability to perform routine activities (Karnofsky)	-51.9 successful versus 28.9 failed pancreas -33.9 successful transplant versus 45.3 failed transplant -84.9 successful transplant versus 71.3 failed transplant -2.92 successful versus 3.63 failed transplant	Small patient numbers. Generalizability uncertain High potential for selection bias	Possibly outdated study	
Zehrer *et al.* [254]	-1993 -1990–1990 -North America	Retrospective case-control study	-Functioning pancreas transplant for type 1 diabetes mellitus at least one year post-transplantation in August 1990 -Non-diabetic pancreas transplants	-Age 36.5 years -Male gender: 32%	-Functioning pancreas (*n* = 62) -Non-functioning pancreas (*n* = 67)	-Overall life satisfaction -DQoL Diabetes Management Subscale -Health satisfaction -Karnofsky index score -DQoL Satisfaction Measure	-P <0.01 versus control group on all measures	High potential for selection bias Univariate comparisons	Possibly outdated study Significant heterogeneity study population	

Becker *et al.* [67]	-2000 -1966–1995 -North America	Retrospective Cohort study	-Type 1 diabetic patients who developed ESRD between the ages of 21 and 40 and received an initial kidney or SPK transplantation	-80% Caucasian -Male gender: 59.5%	-DDK ($n = 147$) -LDK ($n = 160$) -SPK ($n = 335$)	-0.5 observed/expected life span -Annual mortality rate -Renal graft rejection	-70% of DDK and 39% of LDK P = 0.002 and 0.003 respectively versus SPK) achieved the life-span endpoint -SPK: 1.5%; DDK: 6.27%; LDK: 3.65% (P = 0.008, SPK versus other) -57.2%, 57.1% and 34.6% in DDL, LDK and SPK, respectively (all P = 0.0003 versus SPK)	High potential for selection bias Incomplete adjustment	Possibly outdated study Very high rejection rates, possibly affecting the overall generalizability
Lindahl *et al.* [68]	-2013 -1983–2010 -Europe	Retrospective cohort study	-Diabetic ESRD who received a first kidney or a combined transplant (SPK)	-Age: 47 years -Male gender: 70.1%	-SPK ($n = 222$) -LDK ($n = 171$) -DDK ($n = 237$)	-Renal graft loss -Patient survival	-SPK versus LDK HR 0.99 (0.73, 1.37) P = 0.99; DDK versus LDK HR 1.45 (1.08, 1.96) P = 0.014 -SPK versus LDK HR 0.84 (0.60, 1.18) P = 0.32; DDK versus LDK HR 1.41 (1.04, 1.93) P = 0.029	Possible selection bias Adjustment for main demographics, somatometrics and biological data	Data adjusted for transplant type, recipient factors. and donor age
Mohan *et al.* [69]	-2003 -1992–2002 -Europe	Retrospective cohort study	-Patients with type 1 diabetes undergoing kidney alone or SPK transplantation -No SPK in patients >50 years old	-Age 47 years old -Male gender: 60%	-KTA ($n = 51$) -SPK ($n = 50$)	-Renal graft survival -Patient 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) -1, 3, 5- and 8-year actuarial patient survival rates were 96, 93, 89 and 77 per cent respectively in the SPK group versus with 93, 75, 57 and 47 % in the KTA group (P = 0.01 and P = 0.018 at 5 and 8 years respectively)	High potential of selection bias Small patient sample Generalizability uncertain No adjustment	Not mentioned if KTA received cadaveric or living donor
Sorensen *et al.* [73]	-2006 -1990–2005 -Europe	Retrospective cohort study	-Patients on the waiting list 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 versus non-DM HR:1.14, (0.94–1.37) P = 0.19) -DM-1 versus non-DM HR:1.66 (1.53–1.81) P <0.0001; DM-1 versus DM-2 HR:1.0 (0.87–1.14) P = 0.96; All-DM versus non-DM HR:1.55 (1.45–1.66) P <0.0001	-Possible selection bias. Generalizability uncertain. Results adjusted for the most important confounders. Not adjusted for additional confounders	Patients analysed on an 'intention to treat' basis. Patients were categorized as 'transplanted' patients, even if the kidney never functioned
Keddis *et al.* [71]	-2014 -1996–2007 -North America	Retrospective cohort study	-Patients receiving a kidney transplantation between 1996 and October 2007 -Patients with non-renal transplants	-Age 52.3 ± 13.8 years -Male gender: 58% -Race:	-Patients with diabetes receiving a kidney transplantation ($n = 413$) -Patients without diabetes receiving a	-Five-year mortality -Five-year mortality in recipients transplanted after 2004 (2005–2007)	-HR 2.681 (1.951–3.685; P <0.0001) -HR 1.455 (0.737–2.873; P = 0.279) -HR = 3.776	Single-centre data Small patient numbers (especially in subgroups) Generalizability	Patients with diabetes were more likely to have undergone coronary intervention pre-transplantation

Continued

Chapter 1.4.B. Continued

Study	-Publication Year -Time Frame -Location	Design	-Inclusion criteria -Exclusion criteria	Patient characteristics	-Intervention (*n*) -Comparator (*n*) -Duration	Outcome(s)	Results	Quality of evidence	Notes
			Caucasian: 92% -Pre-transplant cardiovascular events: 26% -Living donation: 76%	kidney transplantation (*n* = 1275)	-CV death during follow-up -CV death during 2003-2007	(2.155–6.618; P <0.0001) -HR = 2.265 (0.978–5.241; P = 0.056)	uncertain Potential for selection bias		No clear discrimination between type 1 and type 2 diabetes
Cosio *et al.* [72]	-2008 -1998–2006 -North America	Retrospective cohort study	-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 events: 23%	-Patients with diabetes receiving a kidney transplantation (*n* = 212) -Patients without diabetes receiving a kidney transplantation (*n* = 721)	-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 versus 53 (25%) in subjects with diabetes P <0.001) -8 (1.1%) in subjects without diabetes versus 25 (12%) in subjects with diabetes (P <0.001) -44 (6.1%) in subjects without diabetes versus 41 (19.3%) in subjects with diabetes (P <0.001)	Single-centre data Small patient numbers (especially in subgroups) Generalizability uncertain Potential for selection bias Univariate comparison	Patients with diabetes were significantly older and heavier No clear discrimination between type 1 and type 2 diabetes
Rayhill *et al.* [66]	-2000 -1986–1996 -North America	Retrospective cohort study	-Patients with diabetes receiving a kidney transplantation between 1986 and 1996	-Age: 39 years -Duration IDDM 23 years	-SPK (*n* = 379) -LDK (*n* = 130) -DKD (*n* = 296)	-One-year renal allograft survival -Five-year renal allograft survival -One-year patient survival -Five-year patient survival	-In HLA identical LDK, haplo-identical LDK, SPK and DKD respectively 96, 94, 97 and 86%. -In HLA identical LDK, haplo-identical LDK, SPK and DKD respectively 85, 72, 78 and 64%. -In HLA identical LDK, haplo-identical LDK, SPK and DKD respectively 100, 99, 96 and 94%. -In HLA identical LDK, haplo-identical LDK, SPK and DKD respectively 94, 85, 88 and 72%	Generalizability uncertain Single-centre Univariate comparison (multivariate analysis only in the overall cohort) No exclusion criteria	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
Norman *et al.* [82]	-2011 -2000–2007 -North America	Retrospective cohort study	-All primary SPK transplants performed in the United States between 1 January 2000, and 31 December 2007, who had maintained kidney graft function at 90 days post-transplantation and follow-up up to Feb 1th 2010 -Age <18 years and kidney graft loss the first 90 days	-Age 41.4 ± 8.2 years -Male gender: 61.7% -Mean duration of diabetes: 26.6 ± 8.1 years	-SPK without pancreas graft the first 90 days (*n* = 5812) -SPK with pancreas graft loss the first 90 days (*n* = 470)	-Kidney graft failure in those with versus without pancreas graft loss -Graft survival with versus without pancreas graft loss at 3 year -Graft survival with versus without pancreas graft loss at 5 year -Patient survival with versus without pancreas graft loss at 3 year -Patient survival with versus without pancreas graft loss at 5 year	-HR 3.78 (1.95–7.35; P <0.001) -93 versus 94% (P = 0.266) -90 versus 91% (P = 0.490) -90.4 versus 94.8% (P <0.001) -86.2 versus 92.1% (P <0.001) -HR 2.18 (1.67–2.85; P <0.001)	Generalizability uncertain Registry data (SRTR) Potential for selection bias Incomplete adjustment	Missing data

						-Mortality in patient with versus without pancreas graft loss during the study period			
Bunnapradist *et al.* [225]	-2003 -1994–1997 -North America	Retrospective cohort study	-Type 1 diabetes patients receiving a kidney transplantation between 1994 with reporting in UNOS registry -Patients transplanted in centres which offer only one option for type 1 diabetes (SPK or DKT)	-Age: 40.8 years -Male gender: 58% -Black race: 12.8%	-SPK ($n = 3642$) -DKT ($n = 2374$)	-Graft loss DKT versus SPK: -Mortality DKT versus SPK	-HR 0.98 (0.85–1.12; P = 0.73) -HR 1.06 (0.88–1.28; P = 0.53)	Possible selection bias No living donation comparator group Generalizability uncertain Incomplete adjustment	Patients who received SPK were younger, less often sensitized, transplanted after shorter periods on dialysis, and less often black Slightly outdated analysis

CHAPTER 2: ISSUES RELATED TO GLYCAEMIC CONTROL IN PATIENTS WITH DIABETES AND CHRONIC CKD STAGE 3B OR HIGHER (eGFR <45 mL/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/1.73 m^2)?

B. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2), is maximal oral therapy better than starting/adding insulin in an earlier stage?

Chapter 2.3. General data on included systematic reviews on different glycaemia-lowering drugs

	First Author Publication year	Setting	No of studies overall	Specific for advanced CKD?	AMSTAR score	Comments
Safety and Efficacy of Gliclazide as Treatment for Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Trials	Landman *et al.* [255] 2014	**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.	19 RCTs	No	10	
Comparative Effectiveness and Safety of Medications for Type 2 Diabetes: An Update Including New Drugs and 2-Drug Combinations	Bennet *et al.* [117] 2011	**Patients**: T2DM **Medication/intervention**: metformin, second-generation sulfonylureas (SGSUs), TZDs, meglitinides,DPP-4 inhibitors and GLP-1 agonists **Comparison**: as monotherapy and in combination	140 RCTs and 26 observational	NO	5	
Predictors of response to dipeptidyl peptidase-4 inhibitors: evidence from randomized clinical trials	Monami *et al.* [256] 2011	**Patients**: T2DM **Medication/intervention**: maximal dose DPP-4 inhibitors, other oral drugs (TZDs, metformin, sulfonylurea, α-glucosidase inhibitors) **Comparatison**: DPP-4 inhibitors vs. other oral drugs or insulin or placebo as monotherapy	44	NO	5	
Comparison of different drugs as add-on treatments to metformin in type 2 diabetes: A meta-analysis	Monami *et al.* [257] 2008	**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, vidagliptin, muraglitazar, pramlintide, insulin, glargine, lispro, aspart,glulisine and detemir **Comparison:** metformin plus placebo vs.metformin plus other drugs, or head-to-head comparisons	16	NO	4	
Meglitinide analogues for type 2 diabetes mellitus	Black *et al.* [258] 2009	**Patients:** T2DM **Medications/interventions:** meglitinide analogues, placebo, metformin, insulin **Comparisons:**. meglitinide analogues to placebo, head-to-head, metformin or in combination with insulin	15	NO	11	
Estimating the effect of sulfonylurea on HbA1c in diabetes: a systematic review and meta-analysis	Hirst *et al.* [259] 2013	**Patients**: T2DM **Medication/intervention:** SU (glimepiride, tolbutamide, glipizide, glibenclamide) **Comparison:** fixed-dose sulfonylurea monotherapy or sulfonylurea added on to other glucose lowering treatments (metformin, insulin or TZD)	31	NO	6	
Dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes mellitus	Richter *et al.* [118] 2008	**Patients**: T2DM **Medication/intervention**: sitagliptin, vildagliptin **Comparisons**: • sitagliptin or vildagliptin vs. placebo	25	NO	10	

Continued

Chapter 2.3. Continued

	First Author Publication year	Setting	No of studies overall	Specific for advanced CKD?	AMSTAR score	Comments
		• 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				
GLP-1 agpnists for type 2 diabetes mellitus	Shyangdan Deepson *et al.* [260] 2013	**Patients**: T2DM **Medication/interventions**: GLP-1 agonists (exenatide, liraglutide, lixisenatide, albiglutide) **Comparisons:** placebo, TZDs, DPP-4 inhibitors, insulin glargine, SU, other GLP-1 agonist	17	NO	10	None of the studies was long enough to assess long-term positive or negative effects.
Metformin added to insulin therapy for type 1 diabetes mellitus in adolescents	Abdelghaffar *et al.* [261] 2009	**Patients**: patients with type 1 diabetes **Medications/interventions**: metformin, insulin **Comparisons:** metformin as add-on to insulin vs. insulin alone	2	NO	11	Only side effets of metformin were registered.
Metformin monotherapy for type 2 diabetes mellitus Cochrane review	Saenz *et al.* [262] 2013	**Patients**: T2DM on monotherapy **Medication/intervention**: metformin, SU, meglitinide, α-glucosidase inhibitor, insulin **Comparisons:** monotherapy vs. placebo or vs. alternative monotherapy or vs. diet/lifestyle intervention	29	NO: renal failure was explicit exclusion criterium	11	This Cochrane analysis excluded patients with impaired renal function; however, based on the reasons for exclusion, no such studies were apparently found. Studies where metformin was combined with other medication were excluded.
Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis	Karagiannis *et al.* [119] 2012	**Patients:** T2DM **Medications/intervention**: DPP-4 inhibitors, metformin, sulfonylurea, pioglitazone, GLP-1 agonists. agonist, basal insulin **Comparisons**: • DPP-4 vs. metformin as monotherapy • or with a sulfonylurea, pioglitazone, a GLP-1 agonist, or basal insulin combined with metformin	19	NO	10	
Comparative safety and effectiveness of metformin in patients with diabetes mellitus and heart failure: systematic review of observational studies involving 34 000 patients	Eurich *et al.* [263] 2013	**Patients**: T2DM with heart failure **Medication/intervention**: Metformin **Comparison**: • metformin as monotherapy • metformin in combination with other agents • other agents without metformin	9 observa-tional +1 unpublished RCT	YES	8	
Sulphonylurea monotherapy for patients with type 2 diabetes mellitus	Hemmingsen *et al.* [264] 2013	**Patients:** T2DM **Medication/intervention**: first-generation SU (FGSUs): acetohexamide, carbutamide, chlorpropamide, tolbutamide, tolazamide; SGSUs: glibenclamide or glyburide, glibornuride, gliclazide, glipizide; third-generation SUs (TGSUs): gliclazide modified release , glimepiride, glipizide gastrointestinal therapeutic system, lifestyle	72	NO	11	

		interventions **Comparison**: SU monotherapy vs. placebo, no intervention or other glycaemia-lowering interventions				
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	Hemmingsen *et al.* [265] 2012	**Patients**: T2DM **Medications/interventions:** metformin, insulin **Comparison**: to compare the benefit and harm of metformin and insulin vs. insulin alone	23		9	
Alpha-glucosidase inhibitors for type 2 diabetes mellitus	Van De Laar *et al.* [266] 2005	**Patients**: T2DM **Medications/interventions**: α-glucosidase inhibitor; all other interventions **Comparisons**: α-glucosidase inhibitor monotherapy vs. all other interventions	41	NO	11	
Reappraisal of metformin efficacy in the treatment of type 2 diabetes: A meta-analysis of randomised controlled trials	Boussageon *et al.* [267] 2012	**Patients**: T2DM **Medication/interventions**: metformin, diet **Comparisons:** 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.
Systematic review: Comparative effectiveness and safety of oral medications for type 2 diabetes mellitus	Bolen *et al.* [121] 2007	**Patients**: T2DM **Medications/interventions**: SGSUs, biguanides, TZDs, meglitinides, and α-glucosidase inhibitors **Comparisons**: all possible combinations, also with placebo	216	NO	6	
Comparative efficacy of glimepiride and metformin in monotherapy of type 2 diabetes mellitus: meta-analysis of randomized controlled trials	Zhu *et al.* [268] 2013	**Patients**: T2DM **Medications/interventions:** metformin, glimiperide **Comparisons:** metformin vs. glimipiride vs. placebo as monotherapy	15	NO	6	
Early combination therapy for the treatment of type 2 diabetes mellitus: systematic review and meta-analysis	Phung *et al.* [269] 2013	**Patients**: T2DM **Medication/intervention**: metformin, other agents **Comparisons**: metformin monotherapy vs. combination therapy including metformin	15	NO	7	Only benefit for surrogate endpoints; higher risk of hypoglycaemia.
Sulphonylureas and risk of cardiovascular disease: systematic review and meta-analysis	Phung *et al.* [270] 2013	**Patients**: T2DM **Medication/interventions**: SUs, other agents **Comparisons:** clinical and observational studies that reported the association between SUs and CV disease events as compared to other glycaemia-lowering drugs	33	NO		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.
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	Wu *et al.* [271] 2014	**Patients**: T2DM **Medication/intervention**: DPP-4 inhibitors, metformin **Comparisons**: DPP-4 inhibitors plus metformin as initial combination therapy or as monotherapy compared to metformin monotherapy	8	NO	5	CV mortality and hypoglycaemia not interpretable as very low event rates (24 and 77 respectively).
Second-line therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy: a systematic review and mixed-treatment comparison meta-analysis	McIntosh *et al.* [120] 2011	**Patients**: adults and children with T2DM requiring a second-line antihyperglycaemic agent because of inadequate control (HbA1c > 6.5% (46 mmol/mol), fasting plasma glucose (FPG)> 7 mmol/L or 2-hour postprandial glucose (PPG) > 10 mmol/L) on	49	NO	11	

Continued

Chapter 2.3. Continued

	First Author Publication year	Setting	No of studies overall	Specific for advanced CKD?	AMSTAR score	Comments
		metformin monotherapy or because of intolerance to this therap. **Medication/intervention**: SUs, meglitinides, TZDs, DPP-4 inhibitors, GLP-1 agonists, insulin and insulin analogues, α-glucosidase inhibitors and weight-loss agents (orlistat and sibutramine) **Comparisons**: drugs were added to metformin or replaced metformin.				
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	McIntosh *et al.* [124] 2012	**Patients:** patients with T2DM, inadequately controlled on metformin/sulfonulurea combination therapy **Medications/interventions:** all available classes of anti-hyperglycaemic therapies **Comparison:** comparative safety and efficacy of all available classes of antihyperglycaemic therapies as add-on to combination metformin+SU	33	NO	8	Overall, studies were of poor quality; no mortality data presented.
Effect of Antihyperglycemic Agents Added to Metformin and a SU on Glycemic Control and Weight Gain in Type 2 Diabetes: A Network Meta-analysis	Gross *et al.* [125] 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 SU. **Medication/interventions**: any anti-hyperglycaemic drug **Comparisons**: Studies evaluated the effects of adding a third antihyperglycaemic drug as compared to placebo or head to head	18	NO	10	
Effect of metformin on cardiovascular events and mortality: a meta-analysis of randomized clinical trials	Lamanna *et al.* [272] 2011	**Patients**: T2DM **Medications/interventions**: metformin, active glucose-lowering therapies **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	35	NO	5	
Effect of Noninsulin Antidiabetic Drugs Added to Metformin Therapy on Glycemic Control, Weight Gain, and Hypoglycemia in Type 2 Diabetes	Phung *et al.* [122] 2010	**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 **Medications/interventions**: non-insulin glycaemia-lowering drugs (TZDs, SUs, glinides, GLP-1 agonists, α-glucosidase inhibitors, and DPP-4 inhibitors), metformin **Comparisons**: drugs added to metformin, head to head or vs. placebo	27	NO	8	
Cardiovascular Outcomes in Trials of Oral Diabetes Medications	Selvin *et al.* [273] 2008	**Patients**: T2DM: **Medications/interventions**: metformin, SGSUs, and TZDs. Studies including FGSUs or with	40	NO	7	

		α-glucosidase inhibitors were excluded. **Comparisons:** drugs either as monotherapy (vs. placebo or vs. other oral agent) or as dual therapy (all possible combinations)				
Effect of antidiabetic agents added to metformin on glycaemic control, hypoglycaemia and weight change in patients with type 2 diabetes: a network meta-analysis	Liu *et al.* [123] 2012	**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	39	NO	4	
Proportion of patients at HbA1c target <7% with eight classes of antidiabetic drugs in type 2 diabetes: systematic review of 218 randomized controlled trials with 78 945 patients	Esposito *et al.* [274] 2012	**Patients:** T2DM **Medications/interventions**: metformin, SUs, α-glucosidase inhibitors, TZDs, glinides, DPP-4 inhibitors, GLP-1 agonists and insulin analogues **Comparisons**: Drugs could be either used as monotherapy in drug naive patients, or add-on medication	218	NO	8	Signifcant heterogeneity in studies; high heterogeniety between studies; main driver for Hb1AC change was baseline HbA1c.
Efficacy and Safety of Incretin Therapy in Type 2 Diabetes	Amori *et al.* [113] 2007	**Patients**: T2DM **Medications/interventions**: incretin therapy (GLP-1 agonists and DPP-4 inhibitors), placebo, other glycaemia-lowering drugs; **Comparison:** monotherapy and add-on therapy were considered	29	NO	7	All but 3 trials had a 30-week or shorter duration; thus, long-term efficacy and safety could not be evaluated.
Efficacy of GLP-1 Receptor Agonists and DPP-4 Inhibitors: Meta-Analysis and Systematic Review	Aroda *et al.* [275] 2012	**Patients**: T2DM **Medications/interventions**: exenatide, exendin, liraglutide, taspoglutide, albiglutide, sitagliptin, alogliptin, linagliptin, vildagliptin, saxagliptin, lixisenatide, and albugon **Comparisons:** • monotherapy vs. placebo • one single vs. another glycaemia-lowering agent • as single add-on vs. placebo or vs. other glycaemia-lowering agent	80	NO	9	Significant heterogeneity between studies severely hampers conclusions.
Glycaemic control and adverse events in patients with type 2 diabetes treated with metformin and sulphonylurea: a meta-analysis	Belsey *et al.* [276] 2008	**Patients**: T2DM inadequately controlled on metformin. **Medications/interventions**: SU **Comparisons:** metformin+placebo vs. metformin plus SU. Other combinations of glycaemia lowering drugs and combination of metformin and SU	6		7	This meta-analysis only analysed SU in addition to metformin, not to other drugs.
			83	NO	9	

Continued

Chapter 2.3. Continued

	First Author Publication year	Setting	No of studies overall	Specific for advanced CKD?	AMSTAR score	Comments
Comparative Effectiveness of DPP-4 inhibitors in Type 2 Diabetes: A Systematic Review and Mixed Treatment Comparison	Craddy *et al.* [277] 2014	**Patients**: T2DM with inadequate glycemic control **Medications/interventions:** any pharmacological glycaemia-lowering treatment; alogliptin, linagliptin, saxagliptin, sitagliptin, and vildagliptin) **Comparisons**: a meta-analysis of DPP-4 inhibitors compared as monotherapy, dual therapy (plus metformin, SU, pioglitazone, or insulin), and triple therapy (plus metformin/SU).				Authors sponsored by Takeda to conduct this study.
GLP-1 agonists as add-on therapy to basal insulin in patients with type 2 diabetes: a systematic review	Berlie *et al.* [115] 2012	**Patients:** non-pregnant adults with T2DM **Medications/interventions**: GLP-1 agonists (exenatide, liraglutide, albiglutide, lixisenatide), basal insulin therapy **Comparisons:** basal insulin therapy combined with GLP-1 agonists or placebo	5	NO		
Efficacy of Various Antidiabetic Agents as Add-On Treatments to Metformin in Type 2 DiabetesMellitus: Systematic Review and Meta-Analysis	Poolsup *et al.* [278] 2012	**Patients**: T2DM with inadequate control on metformin alone **Medication/intervention**: SUs, TZDs, DPP-4 inhibitors, insulin, insulin NPH, and long-acting insulin **Comparison**: RCTs of combination therapy of metformin with various glycaemia lowering agents.	8	NO	7	No patient-relevant outcomes assessed. Interpretation appears somewhat biased.
Is the Combination of Sulfonylureas and Metformin Associated With an Increased Risk of Cardiovascular Disease or All-Cause Mortality? A meta-analysis of observational studies	Rao *et al.* [279] 2008	**Patients:** T2DM **Medications/interventions:** acetohexamide, chlorpropamide, tolbutamide, tolazamide, glyburide, glipizide, biguanides, metformin, and glimepiride. **Comparisons:** observational studies that examined the association between combination therapy of SUs and metformin on risk of CVD or all-cause mortality	9		7	
The incidence of mild and severe hypoglycaemia in patients with type 2 diabetes mellitus treated with sulfonylureas: a systematic review and meta-analysis	Schopman *et al.* [280] 2014	**Patients**: T2DM **Medications/interventions**: GLP-1 agonists (liraglutide, exenatide), DPP-4 inhibitors (sitagliptin, vildagliptin and saxagliptin), SUs, insulin glargine or pre-mixed insulin **Comparisons:** GLP-1 agonists or DPP-4 inhibitors with SUs, insulin glargine or pre-mixed insulin	25		6	No data on hypoglycaemia episodes in patients on GLP-1 agonists are provided.
Cardiovascular safety and glycemic control of GLP-1 agonists for type 2 diabetes mellitus: A pairwise and network meta-analysis	Sun *et al.* [104] 2012	**Patients**: T2DM **Medications/interventions**: exenatide, liraglutide, albiglutide, taspoglutide orlixisenatide **Comparisons:** exenatide, liraglutide, albiglutide, taspoglutide orlixisenatide vs. active comparator or placebo	45	NO	4	
Sodium–Glucose Cotransporter 2 Inhibitors for Type 2 Diabetes A Systematic Review and Meta-analysis	Vasilakou *et al.* [281] 2013	**Patients**: T2DM **Medications/Interventions:** SGLT-2 inhibitors, other medication for T2DM	55		9	Limitation: Most trials were rated as high risk of bias.

		Comparisons: RCTs comparing SGLT-2 with placebo or other medication for T2DM			
GLP-1 agonists vs. insulin in inadequately controlled patients with type 2 diabetes mellitus: a meta-analysis of clinical trials	Wang *et al.* [282] 2011	**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. glargine or biphasic insulin aspart **Comparisons:** GLP-1 agonists (exenatide or liraglutide) with insulin	8	NO	9
The effects of sulfonylureas plus metformin on lipids, blood pressure, and adverse events in type 2 diabetes: a meta-analysis of randomized controlled trials	Zhang *et al.* [283] 2013	**Patients:** T2DM **Medications/interventions:** metformin, glimepiride, glipizide, glibenclamide, gliclazide **Comparisons:** metformin vs. metformin+SU	20	NO	8
Longer term safety of dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes mellitus: systematic review and meta-analysis	Goossen *et al.* [284] 2012	**Patients:** T2DM **Medications/interventions:** alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin **Comparisons**: DPP-4 inhibitors compared to placebo, another gliptin or any other glycaemia-lowering drug	67		8

Chapter 2.3. Systematic reviews presenting data on all-cause and cardiovascular mortality associated with different glycaemia-lowering drugs

	Setting	All-cause mortality	Cardiovascular (CV) mortality
Landman *et al.* [255] 2014	**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	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).	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].
Hemmingsen *et al.* [264] 2013	**Patients:** T2DM **Comparison**: sulphonylurea monotherapy vs. placebo, no intervention or other glycaemia- lowering interventions	FGSU vs. placebo: RR 1.46, 95% confidence inteval (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).
Hemmingsen *et al.* [265] 2012	**Patients**: T2DM **Comparison**: to compare the benefits and harms of metformin and insulin vs. insulin alone	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).
Boussageon *et al.* [267] 2012	**Patients**: T2DM **Comparisons:** metformin vs. diet alone, vs. placebo, and vs. no treatment; metformin as an add-on therapy; and metformin withdrawal	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%).
Lamanna *et al.* [272] 2011	**Patients**: T2DM **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	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.
Selvin *et al.* [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 *et al.* [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).	Combination therapy of SUs and metformin vs. other: pooled RR 1.43 (1.10 –1.85) for a composite end point of CVD hospitalizations or mortality (fatal or nonfatal events).
Phung *et al.* [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 (0.90–1.93); 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 *et al.* [104] 2012	**Patients**:T2DM **Comparisons:** exenatide, liraglutide, albiglutide, taspoglutide		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).

	orlixisenatide vs active comparator (not further specified, so unclear what this means) or placebo		
Saenz *et al.* [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).

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

First Author	Protocol and drugs included	Hypoglycaemia risk	HbA1c change*	Body weight change
Landman *et al.* [255] 2014	**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.	There was one severe hypoglycaemic event in 2,387 gliclazide users and one in the 2,430 patients in the comparator group. There were 25 non-severe hypoglycemic events (2.2%) in 1,152 gliclazide users and 22 hypoglycaemic events (1.8%) in 1,163 patients in the comparator group (rr 1.09 (95% CI:0.20, 5.78) after 13 to 104 weeks follow-up.	Compared to all other interventions, gliclazide was more effective: 20.12% (95%CI: 20.23, 20.01). Compared to metformin monotherapy, the effect estimate of gliclazide monotherapy was 0.26 (95%CI: 20.59, 1.11, I2 0%).	The difference in weight was 0.47 kg (95% CI 20.75, 1.70) in favor of the control group (I2 87%). When comparing gliclazide to metformin the effect estimate was 1.37 kg (95%CI 0.15, 2.60, I2 28%).
Bennett *et al.* [117] 2009	**Patients**: T2DM **Comparison**: as monotherapy and in combination	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 DDP4-i had no higher risk for hypoglycaemia than metformin monotherapy (RR 0.9, CI 0.4 to 2.4).	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. Mean Difference in HbA1c Level (CI), Met vs. SU: 0.07 (–0.12 to 0.26); SU vs. Meg: 0.07 (–0.15 to 0.29); Met vs. TZD: –0.07 (–0.18 to 0.04); TZD vs. SU: –0.10 (–0.22 to 0.01); Met vs. DPP-4 inhibitor: –0.37 (–0.54 to –0.20); Met vs. Met + SU: 1.00 (0.75 to 1.25); Met vs. Met + DPP-4 inhibitor: 0.69 (0.56 to 0.82); Met vs. Met+TZD: 0.66 (0.45 to 0.86); Met+basal vs. Met+premixed: 0.30 (–0.26 to 0.86) Met+TZD vs. Met+SU:–0.06 (–0.17 to 0.06); Met+SU vs. TZD+SU–0.09 (–0.19 to 0.01).	Metformin decreased weight compared with TZDs and SUs. SUs and meglitinides increased weight similarly, SUs increased weight less than TZDs, and GLP-1 agonists decreased weight compared with SUs. Combinations of metformin plus a TZD or metformin plus a SU increased weight more than metformin monotherapy. The combination of metformin plus a DPP-4 inhibitor compared with metformin alone affected weight similarly. Weight gain was slightly less with metformin plus SU than with either metformin plus a TZD or a TZD plus a SU. Reduction in weight was greater with metformin plus a GLP-1 agonist than with most standard combinations, although few studies used the same comparators and therefore the strength of evidence was low. Weight change in kg (CI): SU vs. GLP-1: 2.5 (1.2 to 3.8); TZD vs. SU: 1.2 (0.6 to 1.9); SU vs. Meg: 0.0 (–1.0 to 1.0); Met vs. DPP-4 inhibitor: –1.4 (–1.8 to –1.0); Met vs. TZD: –2.6 (–4.1 to –1.2); Met vs. SU: –2.7 (–3.5 to –1.9); Met vs. Met+DPP-4 inhibitor: –0.2 (–0.7 to 0.2); Met vs. Met + TZD: –2.2 (–2.6 to –1.9); Met vs. Met + SU: –2.3 (–3.3 to –1.2); Met + TZD vs. Met + SU: 0.9 (0.4 to 1.3); Met + basal vs. Met + premixed: –1.8 (–7.8 to 4.2);Met + SU vs. TZD + SU:–3.2 (–5.2 to –1.1).
Poolsup *et al.* [278] 2012	**Patients:** T2DM poorly treated on metformin alone **Comparison**: RCTs of combination therapy of metformin with various glycaemia-lowering agents		TZDs reduced as effectively as DPP-4 inhibitors. HbA1c value (pooled mean difference −0.03%, CI −0.16 to 0.10%). TZDs vs. SU: no difference in reduction of HbA1c.	
Monami *et al.* [256] 2011	**Patients**: T2DM **Comparatison**: DPP-4 inhibitors vs other oral drugs or insulin or placebo as monotherapy	DPP-4 inhibitors were associated with a lower risk of hypoglycaemia than SUs (RR 0.10, CI 0.07–0.13, p < 0.01; 3 trials), whereas no significant difference was observed in comparisons with metformin (RR	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	In the 14 trials with available data, DPP-4 inhibitors produced a significant increase of BMI at 21–30 weeks (0.10 kg/m^2, CI 0.05–0.15, P <0.001). In active

		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).	TZDs and α-glucosidase inhibitors, whereas SUs and metformin produced a greater reduction of HbA1c.	comparator studies, 21–30-week treatment with DPP-4 inhibitors was associated with a significantly lower BMI in comparison with TZDs (−0.10 kg/m^2, CI −0.21 to −0.01, P = 0.049), whereas no significant difference was observed with respect to metformin (0.05 kg/m^2, CI −0.02–0.13, P = 0.18).
Monami *et al.* [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 *et al.* [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 *et al.* [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 *et al.* [118] 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); Vildagliptn vs. placebo: 0.76 kg (CI 0.19–1.32); vildagliptin vs. other single agent: 1.55 kg (CI 1.19–1.91)
Saenz *et al.* [262] 2005	**Patients**: T2DM on monotherapy **Comparisons:** monotherapy vs. placebo or vs. alternative monotherapy or vs. diet/ lifestyle intervention	Nine trials reported more hypoglycaemic events in the participants on SUs vs. metformin (34 vs. 126, P = 0.04)	Metformin showed a significant reduction in the levels of HbA1c (standardised mean difference (SMD) -0.86%, CI -1.05 to -0.66) vs. placebo; When comparing with SUs, metformin showed more benefit for HbA1c (SMD -0.14, CI -0.28 to -0.01).	.
Shyangdan Deepson *et al.*	**Patients**: T2DM **Comparisons: p**lacebo, TZD, DPP-4	Hypoglycaemia occurred more frequently in participants taking concomitant SU.	Compared to placebo, all GLP-1 agonists lowered HbA1c levels by about 1%. Exenatide	Both exenatide and liraglutide led to greater weight loss than most active comparators,

Continued

Chapter 2.3. Continued

First Author	Protocol and drugs included	Hypoglycaemia risk	HbA1c change*	Body weight change
[260] 2013	inhibitors, insulin glargine, SU, other GLP-1 agonist		2 mg once weekly and liraglutide 1.8 mg reduced it by 0.20% and 0.24% respectively more than insulin glargine. Exenatide 2 mg once weekly reduced HbA1c more than exenatide 10 μg twice daily, sitagliptin and pioglitazone. Liraglutide 1.8 mg reduced HbA1c by 0.33% (4 mmol/mol) more than exenatide 10 μg twice daily. Liraglutide led to similar improvements in HbA1c compared to SUs but reduced it more than sitagliptin and rosiglitazone.	including in participants not experiencing nausea
Abdelghaffar *et al.* [261] 2009	**Patients**: patients with Type 1 diabetes **Comparisons:** metformin as add-on to insulin vs. insulin alone	Severe hypoglycaemia occurred in two patients (13%) in the metformin group and one participant (7%) in the controlgroup, 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)	Metformin treatment lowered HbA1c in adolescents with type 1 diabetes and poor metabolic control.	Improvements in body composition were not documented in either study.
Karagiannis *et al.* [119] 2012	**Patients:** T2DM **Comparisons**: DPP-4 inhibitors vs. metformin as monotherapy or with a SU, pioglitazone, a GLP-1 agonist, or basal insulin combined with metformin	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).
Van De Laar *et al.* [266] 2009	**Patients**: T2DM **Comparisons**: α-glucosidase inhibitor monotherapy vs. all other interventions		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.	
Hemmingsen *et al.* [285] 2013	**Patients:** T2DM **Comparison**: SU monotherapy vs. placebo, no intervention or other glycameia-lowering interventions	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.		
Hemmingsen *et al.* [265] 2012	**Patients**: T2DM **Comparison**: to compare the benefits and harms of metformin and insulin vs. insulin alone	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<0.001, 20 trials; Significant 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 (Significant heterogeneity I2=86%, P<0.001); weight gain: −1.68 kg, CI −2.22 to −1.13, P<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.

Bolen *et al.* [121] 2007	**Patients**: T2DM **Comparisons**: all possible combinations, also with placebo	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. TZD: 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)	Glyb vs. other SU:–0.03 (–0.13 to 0.07); TZD vs. SU: –0.05 (–0.13 to 0.02); TZD vs. Met: –0.04 (–0.23 to 0.15); repag vs. SU: –0.06 (–0.30 to 0.18); SU vs. Met: –0.09 (–0.30 to 0.10); SU vs. acarbose: –0.38 (–0.77 to 0.02); Met + TZD vs. Met: –0.62 (–1.0 to –0.23); SU + TZD vs. SU: –1.0 (–1.30 to –0.69); Met + SU vs. Met: –1.0 (–1.34 to –0.76); Met + SU vs. SU: –1.0 (–1.34 to –0.67)	SU vs. Met: 3.5 (3.0 to 4.0) Met + SU vs. Met: 2.4 (1.1 to 3.6) SU vs. Met: 1.9 (1.4 to 2.4) TZD vs. Met: 1.9 (0.5 to 3.3) SU vs. acarbose: 1.9 (0.2 to 4.0) TZD vs. SU: 1.1 (–0.9 to 3.1) SU vs. Met + SU: 0.05 (–0.5 to 0.6) SU vs. repag: 0.03 (–1.0 to 1.0)
Zhu *et al.* [268] 2013	**Patients**: T2DM **Comparisons:** metformin vs. glimipiride vs. placebo as monotherapy	Higher risk of hypoglycaemia with glimipiride		
Phung *et al.* [270] 2013	**Patients**: T2DM **Comparisons:** clinical and observational studies that reported the association between SU and CVD events as compared to other glycaemia-lowering drugs	Hypoglycaemia risk increased with combination therapy: RR 1.56 (CI 1.08–2.26). Drugs combined with metformin included TZDs, 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)	
Phung *et al.* [122] 2010	**Patients:** T2DM experiencing an inadequate response to maximized and stable (4 weeks at 1500 mg or maximally tolerated dose) metformin therapy **Comparisons**: drugs added to metformin, head to head or vs. placebo		The different classes of drugs were associated with similar HbA1c reductions (range 0.64%-0.97%) compared with placebo.	Although use of TZDs, 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.
McIntosh *et al.* [120] 2011	**Patients**: adults and children with T2DM requiring a second-line glycaemia-lowering agent because of inadequate control (HbA1c > 6.5% (46 mmol/mol), FPG > 7 mmol/L or PPG > 10 mmol/L) on metformin monotherapy or because of intolerance to this therapy **Comparisons**: drugs were associated to metformin or replaced metformin	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 TZDs 1.10 (0.5–2.27), DPP-4 inhibitors 1.05 (0.56–2.21), 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).
McIntosh *et al.* [124] 2012	**Patients:** patients with T2DM, inadequately controlled on metformin/SU combination therapy **Comparison:** comparative safety and efficacy of all available classes of glycaemia-lowering therapies as add-on to combination metformin+SU	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. placebo + Met + SU: 2.03 (1.15–3.58); TZD + Met + SU vs. placebo + Met + SU: 5.62 (2.81–11.25); DPP-4 inhibitor + Met + SU vs. placebo + Met + SU 21.94 (2.88–167); GLP-1 + 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: 1.29 (0.90–1.86); TZD + Met + SU vs. basal insulin + Met + SU 0.40 (0.21–0.75); GLP-1 + Met + SU vs. basal insulin + Met + SU: 0.93	Insulins (basal, biphasic, bolus), DPP-4 inhibitors, GLP-1 agonists and TZDs (TZDs) all produced statistically significant reductions in HbA1c in combination with metformin and a SU (–0.89% to –1.17%), whereas meglitinides and α-glucosidase inhibitors did not.	Biphasic insulin, bolus insulin, and TZDs 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.

Continued

Chapter 2.3. Continued

First Author	Protocol and drugs included	Hypoglycaemia risk	HbA1c change*	Body weight change
		(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 + Met + SU 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 + Met vs. GLP-1 + Met + SU: 3.87 (2.28–6.58); biphasic insulin + Met vs. basal insulin + Met: 1.32 (0.40–4.33); basal insulin + meglitinide + Met vs. basal insulin + Met: 0.57 (0.15–2.23); basal insulin + meglitinide + Met vs. biphasic insulin + Met: 0.43 (0.11–1.66); basal insulin vs. basal insulin + Met: 1.08 (0.01–218.9); biphasic insulin vs. basal insulin + Met: 1.12 (0.01–115.9); biphasic insulin vs. basal insulin: 1.04 (0.09–12.34).		
Gross *et al.* [125] 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]).
Phung *et al.* [122] 2010	**Patients:** T2DM experiencing an inadequate response to maximized and stable (4 weeks at 1500 mg or maximally tolerated dose) metformin therapy **Comparisons**: drugs added to metformin, head to head or vs. placebo	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 analogues (RR, 0.89; CrI, 0.22–3.96) were not associated with increased risk of hypoglycaemia compared with placebo.		
Esposito *et al.* [274] 2012	**Patients:** T2DM **Comparisons**: drugs could be either used as monotherapy in drug naive patients, or add-on medication		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 <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)	
Amori *et al.* [113] 2007	**Patients**: T2DM **Comparison:** Monotherapy and add-on therapy were considered		Glycaemic 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.
Aroda *et al.* [275] 2012	**Patients:** **Comparisons:** • monotherapy vs. placebo • one single vs. another glycaemia- lowering agent as single add-on vs. placebo or vs. other glycaemia-lowering agent		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)).	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).
Liu *et al.* [123] 2012	**Patients:** T2DM who showed inadequate response to metformin monotherapy at randomisation [mean HbA1c ≥7.0% (53 mmol/mol)]. **Comparison:** glycameia-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	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).	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%).	Weight increase was seen with SUs, glinides, TZDs, basal insulin and biphasic insulin, and weight loss was seen with α-glucosidase inhibitors and GLP-1 agonists.
Belsey *et al.* [276] 2008	**Patients**: T2DM inadequately controlled on metformin **Comparisons:** metformin+placebo vs. metformin plus SU. Other combinations of glycaemia-lowering drugs and combination of metformin and SU	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).	Based on random effects meta-analysis, the pooled estimate of change in HbA1c from baseline was 0.9% (CI 0.7–1.1) and for change in FPG from baseline 1.8 mmol/l (CI 1.1–2.5).	Mean weight change ranged from +2.5 to -0.1 kg, depending on the comparator treatment.
Craddy *et al.* [277] 2014	**Patients**: T2DM with inadequate glycemic control **Comparisons**: via meta-analysis DPP-4 inhibitors were compared as monotherapy, dual therapy (plus metformin, SU, pioglitazone, or insulin), and triple therapy (plus metformin/SU) **Patients**: T2DM **Comparisons:** GLP-1 agonists or DPP-4	This systematic review demonstrated no differences between DPP-4 inhibitors in the proportions of patients experiencing a hypoglycaemic event. Hypoglycaemia with glucose ≤3.1 mmol/L or ≤2.8 mmol/L was experienced by 10.1% (CI 7.3–13.8%) and 5.9% (CI	No differences between DPP-4 inhibitors were seen in mean change from baseline in HbA1c. Patients on alogliptin plus metformin achieved HbA1c <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)).	No differences between DPP-4 inhibitors in body weight,

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Chapter 2.3. Continued

First Author	Protocol and drugs included	Hypoglycaemia risk	HbA1c change*	Body weight change
	inhibitors with SUs, insulin glargine or pre-mixed insulin)	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.		
Schopman *et al.* [280] 2014		No data on hypoglycaemia episodes in patients on GLP-1 agonists are provided.		
Vasilakou *et al.* [281] 2013	**Patients**: patients with Type 2 diabetes **Comparisons:** RCTs comparing SGLT2 with placebo or other medication for T2DM	The RR for any hypoglycaemia with SGLT-2 inhibitors was 1.28 (CI 0.99–1.65) compared with placebo and 0.44 (CI 0.35–0.54 compared with other glycaemia-lowering medications. However, exclusion of one SU-controlled study in a *post hoc* sensitivity analysis resulted in similar hypoglycaemic risk compared with other glycaemia-lowering agents and removed heterogeneity (OR, 1.01, CI 0.77–1.32). Across all studies analyzed, severe hypoglycaemia (defined as an episode requiring assistance from another person) was rare in all treatment groups and was seen primarily in participants already receiving a SU.	SGLT-2 inhibitors had a favourable effect on HbA1c: mean difference vs. placebo 0.66% (CI 0.73–0.58%); mean difference vs. active comparators 0.06% (CI 0.18–0.05%).	Compared with other agents, SGLT-2 inhibitors reduced body weight (mean difference 1.80 kg [CI 3.50–0.11 kg])
Wang *et al.* [282] 2011	**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) **Comparisons:** GLP-1 agonists (exenatide or liraglutide) with insulin	Overall, hypoglycaemia was reported less in the GLP-1 group, (RR 0.45, CI 0.2–0.76, P < 0.01), while there was no significant difference in occurrence of severe hypoglycaemia (0.65, CI 0.29–1.45, P= 0.29).	The mean net change (CI) for HbA1c, weight loss and FPG for patients treated with GLP-1 agonists as compared with insulin was −0.14%, (CI −0.27 to −0.02, P= 0.03); −4.40 kg, (CI −5.23 to −3.56, P < 0.01) and 1.18 mmol/l (CI 0.43–1.93, p <0.01) respectively.	The mean net change 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 < 0.01)
Zhang *et al.* [283] 2013	**Patients:** T2DM **Comparisons:** metformin vs. metformin+SU	Hypoglycaemia was more frequent among patients treated with SUs plus metformin than metformin alone (RR = 6.79, CI 3.79–12.17		
Goossen *et al.* [284] 2012	**Patients:** T2DM **Comparisons**: DPP-4 inhibitors compared to placebo, another gliptin or any other glycaemia-lowering drug	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).		
Wu *et al.* [271] 2014	**Patients**: T2DM **Comparisons**: DPP-4 inhibitors plus metformin as initial combination therapy or as monotherapy compared to metformin monotherapy		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<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<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).

Author & year	No. of reported cases	Manifestations	Cause of metformin overload	Dose/serum level of metformin (mcg/mL)	Relevant comorbidities and medication Other medication	Renal function	Cause of AKI (if applicable)	Casual relationship?	Lactate level (mmol/l)	Outcome
Perrone *et al.* [286] 2011	Case 1: 40 years, F Case 2: 69 years, F Case 3: 57 years, F	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 mm Hg, HR 100 beats/min, 32 breaths/min. Case 3: complaint of dyspnea	Case 1: Suicide attempt Case 2: UTR Case 3: UTR started 3 days before	Case 1: serum level=150 Case 2:SL=27.4 Case 3: NS	Case 1: overdose of sertraline, risperidone, hydrochlorthiazide and metformin/ glyburide Case 2: amiodarone, valsartan, clonidine, gabapentin, atorvastatin,amlodipine, furosemide,omeprazole,metformin/ glyburide multiple conditions Case 3: HTN	Case 1: NS Case 2: ESRD Case 3: ESRD	-	Most likely	Case 1: 21 Case 2:18.9 Case 3: 16	Case 1: death Case 2: survived Case 3: death
Aperis et al. [287] 2011	*1, 74 years, M*	*Zoster-like abdominal pain, tachypnea, nausea and vomiting, hypotension, tachycardia, dehydration and oliguria*	*UTR*	*NS*	*HIV infection, CAD Tenofovir, Emtricitabine, Efavirenz*	*AKI*		*Probably, Metformin ≈ antiretroviral treatment*	*NS, just LA*	*Survived*
Gamst *et al.* [288] 2010	*1, 61 years, M*			*NS*	*Obesity*	*NS*		*Maybe, MALA should be suspected in therapy-resistant LA*	*NS, just severe LA after resuscitation*	*Death*
Dell'Aglio *et al.* [289] 2010	1, 40 years, F	At arrival: awake; soon hypotensive (91/54 mm Hg) and somnolent	Suicide attempt	75–100 g ingested metformin; SL=160	NS	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
Arroyo *et al.* [290] 2010	*1, 49 years, F*	*Presented 1 hour after ingestion, awake and alert*	*Suicide attempt*	*30 g of ingested metformin; SL=380*	*HTN Hydrochlorthiazide 12, 5 mg + Lisinopril 20 mg– 20 combination tablets*	*AKI Crea=1.2 mgLdL*	*Interfering RAAS system medication*	*Possibly*	*9.6*	*Death*
Mizzi *et al.* [291] 2009	1, 53 years, M	Cardiac arrest	NS	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
Jung *et al.* [292] 2009	1, 51 years, M	Progressive dysarthria and the new onset of gait disturbance and myoclonus	UTR	850 mgx2/day for the last 3 months	Chronic lung disease insulin, amlodipine 10 mg/day, aspirin 100 mg/day,	ESRD	-	Most likely	Not reported	Improvement of encephalopathy after metformin was stopped

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Chapter 2.3. Continued

Author & year	No. of reported cases	Manifestations	Cause of metformin overload	Dose/serum level of metformin (mcg/mL)	Relevant comorbidities and medication Other medication	Renal function	Cause of AKI (if applicable)	Casual relationship?	Lactate level (mmol/l)	Outcome
Van der Linden *et al.* [293] 2007	*1, 85 years, F*			*NS*	*Multiple conditions*	*Normal crea, but eGFR=23 mL/min/1,73 m^2*		*? (Probably not)*	*Not reported*	*Death from post-op complications (initially, bowel ischaemia was suspected)*
Di Grande *et al.* [294] 2008	*1, NS*	*Malaise and severe weakness tachypnea (Kussmaul's respiration), agitated and confused, Glasgow Coma Scale score of 13/15, HR = 75 b/min and BP = 110/80 mmHg*	*?*	*NS*	*NS*	*AKI (crea=9.75 mg/dL)*	*History of dehydration due to diarrhoea*	*Maybe*	*15*	*survived*
Ortega *et al.* [295] 2007	Case 1: F, 58 years Case 2: M, 68 years Case 3: F, 74 years Case 4: M, 77 years Case 5: F, 61 years Case 6: transferred from another hospital for AKI	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 diarrhoea 2 days before Case 5: abdominal pain, vomiting and diarrhoea for 3 days Case 6: severe diarrhoea and vomiting for one week (acute pancreatitis)	Case 1: UTR Case 2: UTR Case 3: UTR Case 4: UTR Case 5: UTR Case 6: UTR	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	Case 1:, HTN, dyslipidaemia, hyperuricaemia, CHF, depression + deep venous thrombosis; insulin, enoxaparin, torasemid, enalapril, allopurinol, mirtazapin,digoxin Case 2: acute MI 13 days before and coronarography + 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, dyslipidaemia, acute urinary retention 3 weeks before metastazised prostate cancer gliclazide, nebivolol, tamsulosin, metamizol, acetaminophen. Case 5: hypertension, hypothyroidism, captopril, levothyroxine and for 15 days: diclofenac, naproxen, rofecoxib Case 6: HTN irbesartan, amlodipine	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)	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 retention) Case 5: NSAIDs therapy Case 6: acute pancreatitis	Case 1: probably Case 2: most likely Case 3: most likely Case 4: most likely Case 5: most likely Case 6: most likely	Case 1: not reported Case 2: not reported Case 3: 17.64 Case 4: 14.31 Case 5: 11.65 Case 6: 14.98	Case 1: death (most surely not related to metformin treatment) Case 2: death (cardiac reason) Case 3: survived Case 4: survived Case 5: survived Case 6: survived
Gudmundsdottir *et al.* [296] 2006	*5*			*NS*	*HTN RAAS blockers*	*AKI*	*Dehydration + ACEIs/ARBs treatment not discontinued*	*Probably*	*Between 14 and 23*	*Survived*
Alivanis *et al.* [297] 2006	1, 70 years, M	Malaise, respiratory distress, myalgia, desorientation, abdominal discomfort, increasing somnolence.	UTR	850 mg TID metformin	CHD, CHF NYHA III, CKD (creat clear. =49.8) Isosorbide mononitrate + furosemide + quinapril (+ 2 weeks of diclofenac	Pre-existing CKD + AKI (crea clear. = 10.1)	NSAIDs therapy	LA ≈ HF ≈ Previous use of diclofenac	7.8	Survived

Von Mach *et al.* [298] 2004	*1, 64 years, F (+ a retrospective analysis of other 14 cases)*	*Cardiac arrest*		*NS*	*NS*	*?*		*?*	*17.5*	*Complete recovery*
Pertek *et al.* [299] 2003	1, 65 years, F	Acute abdominal pain, 48 h of anuria, vomiting, tachypnea	UTR	850 mg×3/day	HTN, chronic anemia, gout Miglitol + glicazide; Diuretics + NSAI + colchicine (26 g in 10 days) + B12 intravenous	AKI (baseline crea = 109 µmol/ L^{-1} crea. =643 µmol/ L^{-1})	Hypovolaemia due to diarrhoea and vomiting after colchicine treatment	Probably	12.4	Survived
Berner *et al.* [300] 2002	*1, 83 years*	*impaired consciousness Kussmaul breathing, hypothermia 32.1 C, hemodynamic instability*	*?*	*NS, just high metformin SL*	*Mild CKD*	*Previously mild CKD + AKI (crea=10.6 mg/dL)*	*?*	*Most likely*	*24.4*	*Survived*
Barrueto *et al.* [301] 2002	1, 58 years, M	Lethargy, hypotension, bradycardia	Suicide attempt	Metformin 20 g ingested; SL=110	HTN, bipolar disease, CKD20 tablets of 240 mg/tablet of diltiazem	CKD (baseline crea = 1.7 mg/ dL, with an increase to 2.5 mg/dL within 5 hours)	-	Probably	22.8	Death
Reeker *et al.* [302] 2000	*1, 62 years. F*	*Found unconscious on her bed. resuscitated several times in the ambulance; fixed dilated pupils, haemodynamically unstable; hypothermia 28 C*	*UTR*	*NS*	*CHD, HF, mild CKD*	*Mild-moderate CKD (creat=1.5 mg/dL)*	-	*Probably*	*45.3*	*Survived*
Houwerzijl *et al.* [303] 2000	*1, 52 years, F*	*Haematemesis, abdominal complaints and dyspnea*		*NS*	*Chronic alcoholism, liver function disorders*	*NS*		*? Metformin consumption in association with acute alcohol intoxication*	*NS*	*Death*
Doorenbos *et al.* [304] 2001	1, 66 years, F	Somnolent, BP = 105 ±80 mmHg, HR = 100 bpm, abdominal pain	UTR	850 mg×3/day for the past 7 months; SL=19.4 mg/l!	HTN, CKD (baseline creat=236 micromol/l Insulin , ACE-I)	AKI (crea =640 micromole/l)	Dehydration due to extreme vomiting	Most likely	13.5	Ssurvived
Jain *et al.* [41] 2001	47 years, M	A 2-day history of severe headache and transient loss of consciousness on the previous day	UTR	500 mg×2/day for the past 3 years	Acute subarachnoid haemorrhage Glyburide 5 mg/day	AKI Crea = 0.25 mmol L^{-1}	CIN	Maybe (MALA was an exclusion diagnosis)	7.3	Death
Kruse *et al.* [305] 2001	76 years, F	Nausea, anorexia, vague abdominal pain, and malaise	UTR	850 mg×2/day for the past 3 years; SL=31.5	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 ,	AKI (crea=7 mg/dl)	Dehydration related to preparation for the endoscopic procedure done a week prior to admission	Probably	16.6	Survived

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Chapter 2.3. Continued

Author & year	No. of reported cases	Manifestations	Cause of metformin overload	Dose/serum level of metformin (mcg/mL)	Relevant comorbidities and medication Other medication	Renal function	Cause of AKI (if applicable)	Casual relationship?	Lactate level (mmol/l)	Outcome
Schmidt *et al.* [306] 2005	1, 75 years, F	A 7-day history of increasing upper abdominal pain, nausea, anorexia and mental confusion, and 2 days of anuria.	UTR	1 g×3/day	Gall-stone disease, HTN, acute abscess formation from perforated gall bladder, oral diclofenac 500 mg×3/day for 5 days + rectal diclofenac	Previous normal renal function; AKI (crea=980 micromol/l)	Renal function-interfering medication	? Mixed metabolic acidosis	10	Survived
Schmidt *et al.* [307] 1997	1, 62 years, F	A 4-day history of nausea, diarrhoea and poor concentration	UTR	500 mg×2/day started 1 months earlier	HTN, CAD, PTCA Paroxetine, diltiazem, enalapril, amitriptyline, cisapride, calcitriol, iron sulfate[2], calcium carbonate	ESRD (PD)	-	Most likely	20.4	Survived
Shenoy *et al.* [308] 2006	1, 48 years, M	Severe nausea, vomiting, diarrhoea, and vague abdominal pain that started the day prior to his presentation	UTR	5oo mg×3/day for the past 8 years	Chronic alcohol intake	Baseline crea between 0.9 and 1.2 mg/dl; AKI (crea=2.9 mg/dl)	Hypovolaemia + alcoholism	Probably, LA in setting of AKI (vomiting and severe diarrhoea)	25.0	Survived
Yang *et al.* [309] 2009	1, 43 years, F	Poor appetite and olig-uria for 3 days. lethargy. On arrival, E1V1M1 on (GCS), BP = 115/59 mmHg, HR = 132 b/ min, respiration rate = 18 breaths/ minute, T° 30°C.	Suicide attempt	500 mg×2/day for the past 10 years; now: unknown ingested dose of metformin;		Unknown baseline renal function. AKI (crea=8.1 mg/dL)	Metformin-induced hypoperfusion, probably	Most likely	Initially 5.0 and increasing up to 39.3 within first 20 hours	Survived
Althoff *et al.* [310] 1978	*9*									
Bjarnason *et al.* [311] 2006	*1, 74 years, M*					*AKI*	*Contrast-media induced nephrotoxicity*			
Brouwers *et al.* [312] 2009	*1*					*?*				
Chang *et al.* [313] 2002	*5*		*2 sucide attempts*			*Case 1–4: normal renal function Case 5: ESRD*				
Chu *et al.* [314] 2003	1, 75 years, F	Vomiting, diarrhoea, hypothermia, hypotension and transitory sudden blindness	NTR	1000 mg×2/day for the past years and 1000 mg×3/day for the last 6 days	HTN and diabetic foot for 2 years amlodipine, furosemide, gliclazide, spironolactone, pentoxifylline, magnesium oxide	AKI (baseline crea =1.2 mg/dL to 7.7 mg/dL at admission and 1.3 mg/dL at discharge)	MALA	Probably	12.6	Survived
Depont *et al.* [315] 2007	*1, 39 years, F*		*Suicide attempt*			*?*				*Death*
De Palo *et al.* [316] 2005	*4*					*?*				
El-Hennawy *et al.* [317] 2007	*1*					*AKI*	*Dehydration due to diarrhoea + poor oral intake*			
Gan *et al.* [318] 1992	*1*					*ESRD*			*10.9*	*Survived*
Hermann *et al.* [319] 1981	*1*				*HF Digitalis intoxication*	*Impaired renal function*				*Death*
Jurovich *et al.* [320] 1997	*1, 67 years, M*	*A 9-day history of weakness, nausea,*				*AKI*				*Survived*

		dizziness, and difficulty moving								
Lalau *et al.* [321] 1987	Case 1: 70 years, F Case 2: 48 years, M Case 3: 62 years, F Case 4: 80 years, F Case 5: 61 years, M	Case 1: collapse and coma Case 2: scrotal abscess Case 3: septic shock Case 4:NS Case 5: Vigil coma + AKI (renal + uereteral lithiasis on unique kidney)	Case 1: UTR Case 2: UTR Case 3: UTR Case 1: UTR Case 4: NTR Case 5: UTR	Case 1: 1700mg/day Case 2: 5100 mg/ day + glibornuride Case 3: 3400 mg/ day + glibenclamide Case 4: 2550 mg/ day + gliclazide Case 5: 1700mg/day	Case 1: NS Case 2: NS Case 3: NS Case 4: NS Case 5: NS	Case 1: serum crea = 600 micromoll/L at admission Case 2: serum crea = 750 micromoll/L at admission and 100 micromoll/L at discharge Case 3: serum crea = 386 micromoll/L at admission and 100 micromoll/L at discharge Case 4: serum crea = 846 micromoll/L at admission and 210 micromoll/L at discharge Case 5: serum crea > 2000 micromoll/L at admission 110 micromoll/L at discharge	Case 1: AKI - dehydration (vomiting + diarrhoea) Case 2: AKI - CIN Case 3: AKI septic shock Case 4: AKI CIN Case 5: AKI at admission	Case 1: yes Case 2: yes Case 3: yes Case 4: yes Case 5: yes	Case 1: 18.4 Case 2: 20.2 Case 3: 12.7 Case 4: 14 Case 5: 7.85	Case 1: survived Case 2: survived Case 3: survived Case 4: survived Case 5: survived
Løvås *et al.* [211] 2000	*1, 72 years, F*					*AKI*				*Survived*
Mirouze *et al.* [341] 1976	*2*					*Renal insufficiency AKI*				
Moerer *et al.* [342] 2004 – Nyirenda *et al.* [343] 2006	*1, 79 years, F* Case 1: 76 years, F Case 2: 73 years, M Case 3: 63 years, F Case 4: 77 years, F Case 5: 73 years, F Case 6: 83 years, M Case 7: 55 years, M Case 8: 70 years, F Case 9: 57 years, M Case 10: 58 years, F	Case 1: General malaise, APACHE II score = 35 Case 2: Vomiting, confusion, APACHE II score = 33 Case 3: Diarrhoea, vomiting, cardiac arrest, APACHE II score = 44 Case 4: Diarrhoea, vomiting, malaise, APACHE II score = 33 Case 5: Diarrhoea, lethargy, APACHE II score = 21 Case 6: Vomiting, abdominal pain, APACHE II score = 32	UTR	850 mg×2/day or 1 g x2 .day	6/10 HTN and/or CHD; 1/10 intravenous contrast X- ray procedure <5 days; Seven had a clear history of diarrhoea and/ or vomiting, while two had vague malaise, and one was hypothermic and unconscious. Case 1: ARBs Case 2: NSAID Case 3: - Case 4: IV contrast 5 days before Case 5: ARBs Case 6: - Case 7: - Case 8: ACEIs, NSAIDs Case 9: - Case 10: NSAID	*AKI* Case 1: admission crea = 79 µmol /L; discharge crea = 254 µmol /L Case 2: admission crea = 166 µmol /L; discharge crea = 209 µmol /L Case 3: admission crea= 76 µmol /L; Case 4: admission crea = 58 µmol /L; discharge crea = 113 µmol / l	All of the cases had either hypovolaemia induced by vomiting or diarrhoea + continuation of renal function-interfering medication		Case 1: 36 Case 2: 30.1 Case 3: 60.4 Case 4: 8.3 Case 5: 46.2 Case 6: 28.9 Case 7:12.2 Case 8: 38.3 Case 9: 43.9 Case 10: 27.4	*Survived* Case 1: survived Case 2: survived Case 3: died Case 4: survived Case 5: survived Case 6: survived Case 7: survived Case 8: survived Case 9: survived Case 10: survived

Continued

Chapter 2.3. Continued

Author & year	No. of reported cases	Manifestations	Cause of metformin overload	Dose/serum level of metformin (mcg/mL)	Relevant comorbidities and medication Other medication	Renal function	Cause of AKI (if applicable)	Casual relationship?	Lactate level (mmol/l)	Outcome
		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				Case 5: admission crea = NS; discharge 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				
Offerhaus *et al.* [322] 2007	*1, 85 years, F*					*?*				
Lalau *et al.* [323] 1984	Case 1: 48 years, M Case 2: the same with case 2 (Lalau, 1987)	Case 1: Vomiting, urinary infection, fever, haematemesis	Case 1: UTR	Case 1: 1700mg/day	Case 1: NS	Case 1: serum crea = 130 micromoll/L	Case 1: moderate AKI at admission (infection + dehydration)	Case 1: yes	Case 1: 18.42	Case 1: survived

F, female; M=male; NS, not stated; LA=lactic acidosis; MALA, metformin-associated lactic acidosis; LA,= lactic acidosis; BP , blood pressure; HR,= heart 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 bold are published in non-English language.

Chapter 3.1. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2) and CAD, is PCI or CABG or conservative treatment to be preferred?

Study	Title	Design	Summary conclusion
Aoki *et al.* [324] 2002	Coronary revascularization improves long-term prognosis in diabetic and nondiabetic end-stage renal disease	Cohort study, 121 patients, CABG versus PCI, Diabetes versus nondiabetes	Complete revascularization improves long-term survival in both diabetic and nondiabetic patients.
Ferguson *et al.* [325] 1999	Outcome After Myocardial Revascularization and Renal Transplantation	Cohort study, 83 transplant patients, CABG versus PCI	PTCA and CABG posed little risk for renal allograft loss.
Sedlis *et al.* [326] 2009	OMT with or without PCI for patients with stable CAD and CKD	*Post hoc* analysis of the COURAGE study; 2287 patients, stable CAD patients with and without CKD randomized to PCI and OMT or OMT alone	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.
Hachinohe *et al.* [144] 2011	Management of non-ST segment elevation acute myocardial infarction in patients with CKD (from the Korea Acute Myocardial Infarction Registry)	Registry Korean Study: 5185 patients in total, EI, DI, and conservative strategies in patients with acute NSTEMI and 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 EI over the DI strategy, although there were no significant differences between the two groups, tended to decrease as renal function decreased.
Herzog *et al.* [145] 2002	Comparative survival of dialysis patients in the United States after coronary angioplasty, coronary artery stenting, and coronary artery bypass surgery and impact of diabetes	Registry data to compare the long-term survival of dialysis patients in the United States after PTCA, coronary stenting, or CABG	Dialysis patients in the United States had better long-term survival after CABG surgery than after PCI. Stent outcomes were relatively worse in diabetic patients (CABG 19% survival advantage versus PTCA only).
Chang *et al.* [146] 2012	Multivessel CABG versus PCI in ESRD	CABG versus PCI; US Registry data; cohort of 21 981 patients on maintenance dialysis	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.
Farkouh *et al.* [327] 2012	Strategies for Multivessel Revascularization in Patients with Diabetes	Randomized trial, patients with diabetes and multivessel coronary artery disease to undergo either PCI with drug-eluting stents or CABG, 1900 patients	For patients with diabetes and advanced CAD, 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 versus PCI.

Chapter 3.2. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2) and with a cardial indication (heart failure, ischaemic heart disease, hypertension), should we prescribe inhibitors of the RAAS system or aldosteron-antagonists as cardiovascular prevention? Baseline data of included studies

Trial	Intervention	Control group	Study duration (weeks)	Total no of patients	Mean age (years)	Men (%)	Baseline renal function – intervention group	Type of DM	
								Type 1	Type 2
Fogari *et al.* [328] 1999	Ramiprill	Nitrendipine	96	107	58 ± 1	100	*Serum creatinine* (mg/dL): 2.0 ± 0.4; *CrCl* (mL/min/1.73 m^2): 44.4 ± 8; *UAE* (g/24 h): 0.79 ± 0.04	-	•
Lewis *et al.* [150] 2001 (IDNT)	Irbesartan	Placebo; Amlodipine	124.8	1715	59.3 ± 7.1	66.4	*Serum creatinine* (mg/dL): 1.67 ± 5.4; *UPE* (g/24 h): 2.9 (iqr 1.6 to 5.4)	-	•
Brenner *et al.* [157] 2001 (RENAAL)	Losartan	Placebo	163.2	1513	60 ± 7	63.1	*Serum creatinine* (mg/dL): 1.9 ± 0.5	-	•
Suzuki *et al.* [329] 2002	Benazepril	Placebo	48	72	NS	38.8	*UPE* (g/24 h): 1.2 ± 0.6	-	•
Tong *et al.* [155] 2006	Fosinopril	Placebo	73.7	38	65 ± 6	65.7	*Serum creatinine* (mg/dL): 2.07 ± 0.53; *CrCl* (mL/min/1.73 m^2): 34.8 ± 9.8; *UAE* (g/24 h): 1.52 (iqr 0.19 to 4.6)	-	•
Guo *et al.* [330] 2009	Losartan	Amlodipine	24	41	59.2 ± 7.0	43.9	*eGFR* (mL/min/1.73 m^2): 53.65 ± 7.70; *UPE* (g/24 h): 1.80 (iqr 0.8 to 3.6)	-	•
Heerspink *et al.* [331] 2010 (ADVANCE)	Perindopril-Indapamide	Placebo	206.4	2033	68.3 ± 6.4	42.5	NS	-	•
Shahinfar *et al.* [332] 2002 (RENAAL)	Losartan	Placebo	163.2	1513	60 ± 7	63.1	*Serum creatinine* (mg/dL): 1.9 ± 0.5	-	•
Berl *et al.* [333] 2003 (IDNT)	Irbesartan	Placebo; Amlodipine	124.8	1715	59.3 ± 7.1	66.4	*Serum creatinine* (mg/dL): 1.67 ± 5.4; *UPE* (g/24 h): 2.9 (iqr 1.6 to 5.4)	-	•
Rahman *et al.* [153] 2005 (ALLHAT)	Lisinopril	Chlorthalidone; Amlodipine	288	1888	70.6 ± 7.9	NS	*eGFR* (mL/min/1.73 m^2): 49.2 ± 9.0	-	•
Saruta *et al.* [334] 2009 (CASE-J)	Candesartan	Amlodipine	153.6	2390	65.6 ± 10.3	51.7	NS	-	•

Summary of findings table

Outcome	Trials reporting >1 event/total no of trials included	No of patients included	Median treatment duration (weeks)	Relative effect	95% CI	Quality of evidence*
1. All-cause mortality (overall)	3/4	5309	135.6	0.97	0.85 to 1.10	moderate
2. CV mortality (only patients with diabetes)	2/2	3748	165.6	1.03	0.75 to 1.41	low
3. Non-fatal CV events (overall)	3/3	138	161.6	0.90	0.81 to 1.00	low
4. Need for RRT/doubling of serum creatinine (overall)	3/5	5202	139.5	0.81	0.70 to 0.92	moderate
5. eGFR/CrCl (mL/min/1.73 m^2) –end of treatment (overall)	4/4	2074	120.4	−0.09	−2.75 to 2.57	very low
6. Total no of reported adverse events (overall)	2/2	1822	110.4	1.05	0.89 to 1.25	low

Chapter 3.3. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2), should we prescribe beta blockers to prevent sudden cardiac death?

Study	-Publication year -Time frame -Location	Design	-Inclusion criteria -Exclusion criteria	Patient characteristics	-Intervention (*n*) -Comparator (*n*) -Duration	Outcome(s)	Results	Quality of evidence	Notes
Castagno *et al.* [172]	-2010 -NR -Global	RCT	-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, SBP at rest of less than 100 mm Hg, renal failure (serum creatinine >300 μmol/L), reversible obstructive lung disease	-Age: 61 -Diabetes: 49.5% -Gender: 80% male -Mean diabetes vintage: 11 years -Kidney function (eGFR): 64.5 mL/min	-Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5.0 mg, 7.5 mg, and 10.0 mg/day (*n* = 1327) -Standard care plus placebo (*n* = 1320) -1.3 years	-All-cause hospital admission -Myocardial infarction -All-cause mortality -sudden death	-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)	Low risk of bias RCT	Patients with baseline renal function slightly better than guideline inclusion criteria
El-Menyar *et al.* [174]	-2010 -Middle-East -2007	-Prospective cohort study	-Consecutive patients with ACS were recruited -NR	-Age: 61+ to 11 y -Diabetes: 50% -Gender: 64% male -Mean diabetes vintage: 11 years -Kidney function (eGFR): 30–59 mL/min -STEMI: 37%	-Registry data on 6518 consecutive patients with ACS, prognostic value of renal function and medication use at discharge -1304 patients with eGFR 30–59 mL/min	-Use of beta blockers	-Use of beta blockers decreased as renal function worsened, particularly in patients with STEMI (mild CRI, 64%; moderate CRI, 51%; severe CRI, 43%)	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

Erdmann *et al.* [173]	-2001 -Europe -NR	*Post hoc* analyses of the CIBIS II trial (RCT)	-Symptomatic ambulatory patients in NYHA class III or IV, with an ejection fraction of ∼35%., stable on standard treatment with ACE-inhibitors and diuretics -NR	-Age: 61 -Gender: 80% male -Renal function: 33% with creatinine clearance <60 mL/min	-Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5.0 mg, 7.5 mg, and 10.0 mg/day ($n = 1327$) -Standard care plus placebo ($n = 1320$) -1.3 years	-All-cause mortality (subgroup analysis on diabetes patients)	-RR 0.81 (95% CI 0.51–1.28)	Funding source bias: "sponsored by E Merck, Darmstadt" *-Post hoc* and subgroup analysis for data available on patients with diabetes and advanced kidney disease	
Gansevoort *et al.* [335]	-1995 -Europe -till 1994	Systematic review	-Antiproteinuric effect of blood pressure-lowering agents: a meta-analysis of comparative trials -Excluded were reviews, case reports, abstracts, retrospective studies, studies in duration less than 1 week, studies reporting on follow-up of patients described in previous publications, and studies performed in patients with heart failure, renal transplantation or renovascular hypertension	-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	-Intervention: -ACE-Is -Comparator-beta blockers	-Efficacy to lower proteinuria	-MD -39.9% (−42.8% to −36.8%)	No separate subgroup analysis of patients with advanced CKD provided	Mean values of kidney function 82.9 mL/min eGFR.
Knight *et al.* [171]	-1999 -Global -1986–1989	RCT	-An ejection fraction of <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 non-compliance (eg, alcoholism, drug addiction)	-Age: 59 years -Diabetes: 19% -Gender: 86% male -Kidney function (serum creatinine): 1.3 mg/dL	-Intervention: -ACE-Is, enalapril $n = 3269$ -Comparator-placebo, $n = 3246$ **Co-intervention** Beta blockers, 17% from the placebo group and 18% from the intervention group had beta blockers therapy -974 days	-Progression to end-stage kidney disease	-RR 0.70 (0.57–0.85) in both groups when adjusted for the use of beta blockers	Funding source bias	

Continued

Chapter 3.3. Continued

Study	-Publication year -Time frame -Location	Design	-Inclusion criteria -Exclusion criteria	Patient characteristics	-Intervention (*n*) -Comparator (*n*) -Duration	Outcome(s)	Results	Quality of evidence	Notes
Pun *et al.* [176]	-2007 -North America -NR	Retrospective case-control study	-Events were included when any of the following key events were described in the database: deployment of an automated external defibrillator (AED), initiation of cardiopulmonary resuscitation, documentation of sudden pulselessness, lack of respiratory difficulties before the event, or a determination of CA after emergency medical services personnel arrived on the scene -Patients with missing outcome data (*n* = 15), as well as patients with documented "do not resuscitate" orders (*n* = 53)	-Age: 68 (13.5) y -Diabetes: 41% -Gender: 49% male -Kidney function (serum creatinine): 6.9 mg/dL -Years on dialysis: 2.3	-Intervention: beta blockers, *n* = 302 -Comparator: beta blockers not prescribed. *n* = 373 -6 months	-Odds ratio of death at 6 months according to prescribed medication dosage (low, medium, high) versus 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
Tonelli *et al.* [175]	-2001 -North America -1999	Prospective cohort study	-All patients seen for routine follow-up of CKD during the 4-week study period in 1999 were eligible -Dialysis dependence or calculated creatinine clearance (Cockcroft-Gault) more than 75 mL/min	-Age: 60.8 (15.7) years -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), ACE-Is, 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/1.73 m^2), should we prescribe lipid lowering-therapy in primary prevention?

Study	-Publication year -Time frame -Location	Design	-Inclusion criteria -Exclusion criteria	Patient characteristics	-Intervention (*n*) -Comparator (*n*) -Duration	Outcome(s)	Results	Quality of evidence	Notes
Wanner *et al.* [188]	-2005 -1998–2004 -Europe	RCT	-Subjects with type 2 diabetes mellitus 18 to 80 years of age who had been receiving maintenance HD for less than two years -Levels of fasting LDL cholesterol of less than 80 mg per decilitre (2.1 mmol per litre) or more than 190 mg per decilitre (4.9 mmol per litre), triglyceride levels greater than 1000 mg per decilitre (11.3 mmol per litre); 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 myocardial infarction within the three months preceding the period of enrolment; unsuccessful kidney transplantation; and hypertension resistant to therapy	-Age 65.7 ± 8.3 gender: 53% -DM2: 100% -HD: 100% 17.5 ± 8.7 years with diabetus, 8.2 ± 6.9 months on dialysis	-Atorvastatin 20 mg daily -4 years -On intervention *n* = 619 -Control group *n* = 636	-All-cause mortality -Composite outcome/ mortality -Sudden death -Stroke -Myocardial infarction	-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)		
Upadhyay *et al.* [184]	-2012 -2000–2011 -Global	Systematic review	-Systematic reviews of RCTs (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	-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, colestipol, 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

Continued

Chapter 3.5. Continued

Study	-Publication year -Time frame -Location	Design	-Inclusion criteria -Exclusion criteria	Patient characteristics	-Intervention (*n*) -Comparator (*n*) -Duration	Outcome(s)	Results	Quality of evidence	Notes
			or more participants with CKD per group for adults and 25 or more per group for children						
Tonelli *et al.* [336]	-2005 -North America	*Post hoc* analysis of RCTs	-Overall analysis of the West of 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	-Age 64.2 ± 7.0 years -Male gender 78% -DM2: 100% -MDRD eGFR: 57.9 ± 12.7 mL/min	-Intervention pravastatin 40 mg daily, *n* = 290 -Control: placebo, *n* = 281 -Intervention duration: ~5 years	-Myocardial infarction -Stroke -Survival/mortality-any cause -Survival/mortality: composite outcome: Coronary heart disease death,nonfatal MI, CABG, or PTCA	-HR 0.84 (0.6–1.18) -HR 1.12 (0.63–1.97) -HR 0.98 (0.69–1.39) -HR 0.75 (0.57–0.98)	Limitations: Subgroup analysis and *post hoc* analysis not specifically designed at the beginning of the studies; ~70% of the included patients were male	
Ting *et al.* [337]	-2012 -Australia/ New Zealand -1998–2010	RCT	-Type 2 diabetes mellitus with onset after the age of 35 years; men and women aged 50–75 years of age: average total cholesterol 3.0–6.5 mmol/L; triglycerides/ high-density cholesterol ratio of 4.0 or higher, or triglycerides over 1.0 mmol/L; -Plasma creatinine >130 mmol/L, liver or symptomatic gallbladder disease, or a cardiovascular event within 3 months before recruitment	-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 m^2 eGFR	-Intervention fenofibrate 200 mg daily, *n* = 295 -Control: placebo, *n* = 224 -Co-intervention: diet -Intervention duration: ~5 years	-Myocardial infarction -Major CV events -Progression to end-stage kidney disease -Stroke -CV mortality -Survival/all-cause mortality	-HR 0.67 (0.38–1.18; P = 0.17) -RR 1.39 (1.01–1.91, P = 0.04) -RR 0.94 (0.3–2.92, P = 0.92) -HR 0.85 (0.47–1.55, P = 0.60) RR 1.9 (1.07–3.38, P = 0.03) RR 1.26 (0.85–1.86, P = 0.25)	Limitations: imbalance baseline patients characteristics Reasons for lost to follow-up not provided	
Palmer *et al.* [185]	-2012 -Global -1955–2012	Systematic review	-Randomized trials that compared statins with placebo, no treatment, standard care, or another statin and reported data for adults with CKD (any stage) -Studies with less than 8 weeks of follow-up	48 comparisons included 39 820 persons not receiving dialysis. 21 comparisons included 7982 persons receiving dialysis; 17 comparisons included 3297 kidney transplant recipients	-Intervention: statins, most trials (60 comparisons [70%]) evaluated statin doses equivalent to simvastatin, 20 mg, or less -Control: placebo or no treatment -Median follow-up was 6	-Myocardial infarction -Stroke -Survival/all-cause mortality -Survival/CV mortality	-RR 0.76 (0.68–0.86, P = 0.03) -RR 0.86 (0.62–1.2, P = 0.07) -RR 0.89 (0.82–0.97,	Limitations: not limited to diabetes population only.	

					months (range, 2 months to 5.5 years) -Total number of included patients 51099		P = 0.009) -RR 0.86 (0.78–0.95, P = 0.08)	
Jun *et al.* [187]	-2012 -Global -1950–2012	Systematic review	-RCTs assessing the effects of fibrate therapy compared with placebo in people with CKD or on kidney-related outcomes -No exclusion criteria	-Age between 51 and 67 years -DM2 40% -Male gender ranging from 63% to 100%	-Intervention: fibrate: bezafibrate, gemfibrozil, fenofibrate; two trials assessed the effects of gemfibrozil, 2 assessed bezafibrate, and 4 assessed fenofibrate -Control: placebo or dietary counselling -10 studies included with 16869 patients	-Major cardiovascular events -Renal function (progression to RRT) -Cardiovascular death -All-cause mortality	-RR 0.70 (95% CI 0.54–0.89; P = 0.004) -RR 0.85 (95% CI 0.49–1.49; P = 0.575) -RR 0.60 (95% CI 0.38–0.96; P = 0.03) -RR 0.86 (95% CI 0.62–1.18; P = 0.355)	Limitations: no protocol available, Insufficient data to allow separate analysis of effects in people with and without diabetes.	Results available based on subgroup analysis in patients with eGFR 30–59.9 mL/min/1.73 m^2
Holdaas *et al.* [338]	-2011 -Global -2003–2008	RCT	-Diabetes subjects with end-stage renal failure aged 50–80 years, who have received regular HD 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 end-stage renal disease (ESRD), not have received a statin therapy within the past 6 months	-Age 65 (8.2) years -DM2 100% -Male gender 65% -100% on HD -Dialysis vintage 2.4 (2.0) years -44 % were on ACE-Is and 37% on beta blockers	-Intervention rosuvastatin 10 mg daily, *n* = 388 -Control: placebo, *n* = 343 -Intervention duration: ∼5.6 years	-Access to transplantation -Any adverse events -Myocardial infarction (fatal or nonfatal) -Stroke -Survival/mortality	-RR 1.33 (0.79–2.23, P = 0.29) -RR 0.89 (0.7–1.14, P = 0.09) -HR 0.68 (0.51–0.9, P = 0.008) -RR 1.68 (1.00–2.83, P = 0.05) -RR 0.91 (0.81–1.03, P = 0.12)	Limitation: no clear definition of the criteria for transplantation, unclear how were the adverse events included in the final analysis. not reported as number of events per patient, per year	
Colhoun *et al.* [339]	-2009 -Global -1997–2001	RCT	-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	-Age 65.0 ± 6.7 years -Male 48% -DM2 100% -Kidney function: creatinine 1.28 (1.10–1.37) mg/dL, eGFR 53.5 ± 5.3 mL/min	-Intervention atorvastatin 10 mg daily, *n* = 1428 -Control: placebo, *n* = 1410 -Co-intervention: renin-angiotensin system drug -Intervention duration: mean 3.77 years (median, 4.0 years)	-Myocardial infarction -Stroke -Survival/mortality (major cardiovascular disease) -Survival/all-cause mortality	-HR 0.66 (0.36–1.2, P = 0.2) -HR 0.39 (0.15–1.01, P = 0.04) -HR 0.58 (0.36–0.96, P = 0.03) -HR 0.89 (0.53–1.5, P = 0.7)	Limitation: funding source bias, adverse events reported inconsistently	

Continued

Chapter 3.5. Continued

Study	-Publication year -Time frame -Location	Design	-Inclusion criteria -Exclusion criteria	Patient characteristics	-Intervention (*n*) -Comparator (*n*) -Duration	Outcome(s)	Results	Quality of evidence	Notes
			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 haemoglobin level greater than 12%						
Baigent *et al.* [186]	-2011 -Global	RCT	-History of CKD: pre-dialysis or on dialysis, aged 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.	-Age 62 (12) years -Male 63% -DM2 23% -Kidney function: MDRD-estimated GFR (mL/min per 1·73 m^2): 26·6 (12·9), On dialysis ∼33%, HD ∼27%, PD ∼6%, not on dialysis ∼67%	-Intervention simvastatin 20 mg plus ezetimibe 10 mg daily, *n* = 4650 -Control: placebo, *n* = 4620 -Intervention duration: 4.0 years	-Major atherosclerotic events: defined as the combination of non-fatal myocardial infarction, coronary death, ischaemic stroke, or any revascularization procedure (i.e. exclusion of non-coronary cardiac deaths and strokes confirmed to be haemorrhagic)	-RR 0.78 (0.64–0.94)	Limitation: primary outcome changed during 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?

Authors	-Publication year -Time frame -Location	Design	-Inclusion criteria -Exclusion criteria	Patient characteristics	-Intervention (*n*) -Comparator (*n*) -Duration	Outcome(s)	Results	Quality of evidence	Notes
Tawney *et al.* [195]	-2000 -North America	RCT	-HD patients -Sufficient mobility to move 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, hyperkalaemia, screened by physician trained in physical medicine and rehabilitation to idenify safety concerns as poor balance	-Age: 58.1 ± 14 -Diabetes: 49.5% -Gender: 40% male -Mean dialysis vintage: 31 months	-Individual counselling to exercise 30 min each day (household activities) (*n* = 51) -Standard care (*n* = 48) -6 months	QoL Mental component QoL Physical component Physical functioning score Patient satisfaction	*Mean Score on KDQoL-SF (SD)* I: 47.3 (12.9) C: 49.9 (10.5) I: 38.3 (10.5) C: 35.8 (8.8) I: 62.3 (26.7) C: 48.5 (25.9) (P = 0.04 after adjusting matching variables and adequacy of dialysis) I: 61 (20.3) C: 67.4 (21.2)	Low level of baseline participation Dropouts were excluded from analysis	Mixed group of diabetes and non-diabetes
Castaneda *et al.* [191]	-2002 -North America	RCT	->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 haemorraghe or detachment), current participation in resistance training	-Mean age: 66 -Diabetes type 2: 100% -Mean HbA1c: 8.6% -Mean BMI: 31kg/m^6 59.6% affected by CV disease	-Progressive resistance training, 45 min 3 times/week (*n* = 31) -Standard care: two-weekly telephone calls, control visit every 3 months (*n* = 31) -16 weeks	SBP (mmHg) DBP (mmHg) HbA1c (%) FBG (mmol/L) Body weight (kg) Functional status (on physical activity score questionnaires)	*Mean (SE)* I: 135.5 (3.3) C: 150.4 (3.9) P = 0.05 I: 69.2 (1.2) C: 70.8 (1.4) P = 0.52 I: 7.6 (0.2) C: 8.3 (0.5) P = 0.01 I: 7.9 (0.4) C: 8.9 (0.7) P = 0.34 I: 79.5 (3.3) C: 79.4 (2.9) P = 0.89 I: 28.3 (0.9) C: 7.2 (2.8) P = 0.01	Possible allocation bias: higher percentage on insulin in control group	Small groups and medication change during study
Morales *et al.* [196]	-2003 -Europe	RCT	-Chronic proteinuric nephropathy of diabetic or non-diabetic cause, BMI >27 kg/m^2, serum creatinine level less than 2 mg/dL -Unstable clinical condition, rapid loss of renal function, nephrotic syndrome requiring diuretic therapy, imunosuppressive treatment, hypertenstion requiring more than 2 drugs	-Mean age: 56 -Diabetes: 47% type 2 -Gender: 60% male -Mean serum creatinine: 1.5 mg/dL	-Energy reduction of 500 kcal/day, protein content adjusted to 1 to 1.2 g/kg/day (*n* = 20) -Standard medical care (*n* = 10) -5 months	SBP (mmHg) DBP (mmHg) Serum creatinine (mg/dL) Creatinine clearance (Cockroft-Gault formula) Proteinuria (g/24h) Weight (kg) BMI (kg/m^2)	*Mean (SD)* I: 138.5 (14.1) C: 140.4 (18.3) I: 76.6 (8.8) C: 88.5 (11.1) I: 1.5 (0.8) C: 1.8 (0.6) P <0.05 I: 67 (34.1) C: 56 (19.9) P <0.05 I: 1.9 (1.4) C: 3.5 (2.1) P <0.05	Sequence generation and allocation concealment unclear	Small groups, combination of diabetes and non-diabetes.

Continued

Chapter 3.6. Continued

Authors	-Publication year -Time frame -Location	Design	-Inclusion criteria -Exclusion criteria	Patient characteristics	-Intervention (*n*) -Comparator (*n*) -Duration	Outcome(s)	Results	Quality of evidence	Notes
							I: 83.9 (10.9) C: 98 (16.4) P <0.05 I: 31.6 (3.2) C: 35 (5.8) P <0.05		
Sigal *et al.* [194]	-2007 -1999–2005 -North America	RCT	-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 hypoglycaemic, antihypertensive or lipid-lowering agents or body weight (> or = 5%), serum creatinine level of 200 μmol/L or greater (> or = 2.26 mg/dL), proteinuria greater than 1 g/day, blood pressure greater than 160/95 mmHg, restrictions in physical activity because of disease, presence of other medical condition that made participation inadvisable	-Mean age: 54 -100% type 2 diabetes -Gender: 64% male -Mean HbA1c: 7.68%	-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)	SBP (mmHg) DBP (mmHg) HbA1c (%) Body weight (kg) BMI (kg/m^2) Hospital admissions intervention group (%) Hypoglycaemia intervention group (%)	*Difference in change from baseline to 6 months (95% CI)* 1(−3.6 to 5.7) P = 0.66 −1.5(−4.7 to 1.7) P = 0.36–0.51 (−0.87 to −0.14) P = 0.007–2.2 (−3.9 to −0.6) P = 0.008 − 0.74 (−1.29 to −0.18) P = 0.009 3 7	Selection bias: only patients with few comorbidities and better functional status were selected	Hospitalizations were elective and not related to intervention; hypoglycaemias were not severe
					-7 different exercises on weight machines each session, progressive resistance training, 3 times/week (*n* = 64)	SBP (mmHg) DBP (mmHg) HbA1c (%) Body weight (kg) BMI (kg/m^2) Hospital admissions intervention group (%) Hypoglycaemia intervention group (%)	-0.9 (−5.4 to 3.7) P = 0.71 -1.4 (−4.6 to 1.7) P = 0.37 -0.38 (−0.72 to −0.22) P = 0.038 -0.7 (−2.4 to 0.9) P = 0.36 -0.26 (−0.80 to 0.28) P = 0.35 0 6		
					-Intervention 3: combination of aerobic and resistance exercise intervention (*n* = 64) -Control: standard medical care (*n* = 63) -22 weeks		**Compared with AE** **Mean difference (95% CI)**	**Compared with RE**	

						SBP (mmHg) DBP (mmHg) HbA1c (%) Body weight (kg) BMI (kg/m^2) Hospital admissions intervention group (%) Hypoglycaemia intervention group (%)	1.3 (−3.4 to 1.7) P = 0.59 1.7 (−1.5 to 5.0) P = 0.30 − 0.46 (−0.83 to −0.09) P = 0.014 0.0 (−1.6 to 1.7) P = 0.98 0.03 (−0.58 to 0.53) P = 0.93 0 3	3.2 (−1.4 to 7.8) P = 0.168 1.7 (−1.5 to 4.9) P = 0.30 − 0.59 (−0.95 to −0.23) P = 0.001 − 1.5 (−3.1 to 0.1) P = 0.075 − 0.50 (−1.05 to 0.04) P = 0.069	
Leehey *et al.* [193]	-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. Hyperparathyroidism/ osteoporosis. Symptomatic neuropathy/retinopathy. Positive stress test due to coronary arterial disease. Symptomatic cardiovasc disease. Congestive Heart Failure (NYHA III or IV). COPD (FEV1 <50% and/or requires suppl oxigen 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	-Mean age: 66 -100% type 2 diabetes -Gender: 100% male	-Aerobic walking exercise, increasing intensity, 30 á 40 min 3 times/week (n = 7) -Standard care (n = 4) -24 weeks	SBP (mmHg) DBP (mmHg) Creatinine clearance (mL/min) HbA1c (%) Mean duration exercise (min) Weight change Proteinuria (mg/ 24h)	**Mean (SD)** I: 113 (16) C: 136 (5) I: 65 (10) C: 77 (8) I: 51 (26) C: 64 (10) I: 8.3 (2.4) C: 8.1 (3.7) I: 10.2 (2.8) C: 6.6 (2.1) I: 115 (23) C: 136 (20) I: 821 (1010) C: 490 (237)	Significant baseline differences between groups	Small group of patients
Chen *et al.* [192]	-2010 -Asia	Quasi-RCT	-Stable CKD patients not on dialysis, selected by researcher		-Exercise advice: 30 min per session, 3 to			Selection bias, patients were

Continued

Chapter 3.6. Continued

Authors	-Publication year -Time frame -Location	Design	-Inclusion criteria -Exclusion criteria	Patient characteristics	-Intervention (*n*) -Comparator (*n*) -Duration	Outcome(s)	Results	Quality of evidence	Notes
			-Criteria for selection by researcher were not mentioned	-Mean age: 78 -Diabetes: 41.5% -Gender: 78% male	5 times/week, group sessions and individual guidance over telephone ($n = 45$) -General health education ($n = 49$) -5 months	Mean blood glucose (mg/dL)	*Mean (SD)* I: 114.81 (30.28) C: 110.31 (25.58)	selected before randomisation	Pre-test blood glucose values were used as the covariate
MacLaughlin *et al.* [197]	-2010 -2004–2007 -Europe	Non-RCT	-CKD patients with BMI > 30 or BMI > 28 kg/m^2 with comorbidities (diabetes, hypertension, dyslipidaemia), all eligible for kidney transplant, age between 18 and 65. -No exclusion criteria mentioned	-Mean age: 49 -Diabetes: 31% (all type 2) -Gender: 61% male	-Individual diet and exercise plan, at least 3 times/week, with increasing time and intensity, Orlistat 3 times 120 mg/day ($n = 32$) -Standard care ($n = 20$) -24 months	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	*Mean (SD)* I: 139 C: 139 (SD not reported) I: 79 C: 84 (SD not reported) I: −9.2 C: −20.7 (SD not reported) P <0.001 I: 96 C: 101 (SD not reported) P <0.001 I: 35 C: 6 I: 3 C: 1	Selection bias: all patients were elegible for transplant, only motivated patients included	Small groups
Matsuoka *et al.* [199]	-1991 -Asia	Retrospective cohort study	-Diabetes mellitus patients with diabetic nephropathy -No exclusion criteria mentioned	-100% diabetes mellitus patients, type not mentioned, all had diabetic nephropathy but severity was not mentioned.	-Maintained daily physical activity ($n = 13$) -Restricted daily physical activity ($n = 10$)	SBP (mmHg) DBP (mmHg) Onset of nephrotic stage to dialysis (months) Maximum proteinuria to dialysis (months) Karnofsky Score	*Mean (SD)* I: 158 (27) C: 160 (11) I: 86 (9) C: 85 (7) I: 27.7 (13.9) C: 27.4 (14.7) I: 6.0 (3.8) C: 8.6 (4.4) I: 82.7 (4.6) C: 77.1 (4.9) P <0.05	Retrospective study, dose, intensity and duration of intervention was not quantified	Small groups
Cappy *et al.* [198]	-1999 -1997–1998 -North America	Before-after study	-HD patients with stable general and cardiovascular conditions -Any unstable medical condition	-Age: 53.9 ± 15 -Diabetes: 50%, type not specified -Gender: 62% male	Training programme consisting in a progressive, self-paced aerobic exercise, 20 to 40 min, 3 times/week ($n = 4$) -12 months	SBP predialysis DBP predialysis Serum creatinine Serum glucose level	*Mean % of change* -4% -1% 0% -16%	Many dropouts, results not included in analysis.	Small group
Solerte *et al.* [200]	-1989 -Europe	Prospective cohort study	-Obese type 1 or 2 diabetic patients with CKD	-100% diabetes patients, type not specified	-Hypocaloric diet (1410 kcal/day)	MAP (mmHg) Creatinine clearance	*Difference in change from baseline*	Creatinine clearance change probably explained by less	Small group Diet also improved total cholesterol, LDL

			-BMI: 33 ± 1.6 kg/m^2 -eGFR 66 ± 13 mL/min	(n = 24) -52 weeks	(mL/min) Proteinuria (g/24h) BMI (kg/m^2)	-9.7 (P <0.05) 12 (P = 0.01) -0.66 (P = 0.01) -7.3 (P <0.001)	protein intake and muscle loss	and HDL cholesterol and triglycerides
Saiki *et al.* [201]	-2005	Prospective cohort study	-Overweight type 1 or 2 diabetic patients with diabetic retinopathy, proteinuria (urinary albumin excretion >300 mg/day) and serum creatinine level less than 3 mg/dL -Unstable diabetic retinopathy, pleural effusion, severe leg oedema	-Age: 53.6 ± 8.4 -BMI 30.4 ± 5.3 kg/m^2 -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/m^2)	*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/1.73 m^2), should antiplatelet therapy be recommended, regardless of their cardiovascular risk?

Study	-Publication year -Time frame -Location	Design	-Inclusion criteria -Exclusion criteria	Patient characteristics	-Intervention (*n*) -Comparator (*n*) -Duration	Outcome(s)	Results	Quality of evidence	Notes
Angiolillo *et al.* [209]	-2010 -2003–2007 -Europe	Case series	-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; haemodynamic instability; acute coronary or cerebrovascular event within 3 months; any malignancy; concomitant use of other antithrombotic drugs (oral anticoagulants, dypiridamole, cilostazol, ticlopidine) or nonsteroid anti-inflammatory drugs; recent treatment with a glycoprotein IIb/IIIa antagonist; platelet count <100/ 106/l; haematocrit <25%; and liver disease (bilirubin level 2 mg/dL)	-Age: 72 ± 8 -DM2: 100% -Gender: 54% Male -eGFR< 60 mL/min -HbA1C: 7 ± 1.4	-Aspirin 100 mg/day (*n* = 84) -at least 3 months	-Platelet aggregation	-Improved platelet aggregation after aspirin treatment	Possible indication bias. Uncontrolled study	DM patients with moderate/severe CKD had significantly higher ADP-induced (60 ± 13% versus 52 ± 15%, P <0.001) and collagen-induced (49 ± 20% versus 41 ± 20%, P = 0.004) platelet aggregation compared with those without
Daimon *et al.* [340]	-2011 -Asia	Prospective cohort study	-HD patients	-Dialysis patients -Age: 66.7 -Gender: 71% Male -45% diabetes	-Diabetic patients on antiplatelet therapy (aspirin, ticlopidine, clopidogrel, cilostazol, sarpogrelate hydrochloride or warfarin) (*n* = 21) -Diabetic patients not receiving antiplatelet	-Bleeding episodes	-13 episodes in patients on antiplatelet therapy versus 3 in those not on antiplatelet therapy (P <0.05)	Exposed cohort poorly representative (single centre) Not adjusted for the most important confounders (only stratification by diabetes) Primary outcomes addressed	Results poorly reliable: no effect measure provided. Unadjusted analyses

Chapter 3.7. Continued

Study	-Publication year -Time frame -Location	Design	-Inclusion criteria -Exclusion criteria	Patient characteristics	-Intervention (*n*) -Comparator (*n*) -Duration	Outcome(s)	Results	Quality of evidence	Notes
					therapy (*n* = 29)			Completeness/ adequacy of follow-up unclear	
Dasgupta *et al.* [202]	-2009 -2002–2005 -Global (32 centres)	RCT	-45 years of age or older and had one of the following conditions: -multiple atherothrombotic -risk factors: documented coronary disease, documented cerebrovascular disease, or documented symptomatic peripheral arterial disease –Taking oral antithrombotic medications or nonsteroidal antiinflammatory drugs on a long-term basis (although cyclooxygenase-2 inhibitors were permitted). -Established indications for clopidogrel therapy (such as a recent ACS) -Patients who were scheduled to undergo a revascularization and require clopidogrel after revascularization	-Age: 63 years -Gender: 65% male -DM2: 100% -Co-medications were: diuretics (48.2%) nitrates (23.2%) calcium antagonists (36.7%) beta blockers (55%) angiotensin II receptor blockers (25.5%) ACE-Is (58.6%) statins (76.8%) Insulin (17.4%) oral hypoglycaemic agents (42.3%)	-Clopidogrel (75 mg once daily) plus low-dose aspirin (75 to 162 mg once daily) (*n* = 1006) -Placebo +low-dose aspirin (75 to 162 mg once daily) (*n* = 1006) -30 months	-Severe bleeding -Moderate bleeding -Hospitalization -Overall CV death/MI/ stroke/hospitalization -Non-fatal MI -Non-fatal stroke -Overall CV death/MI/ stroke -Overall death -Overall CV death	-HR 1.8 (0.90–3.30; P = 0.075) -HR 1.2(0.70–2.00; P = 0.543) -HR 0.9 (0.70–1.20; P = 0.634) -HR 1.0(0.80–1.30; P = 0.784) -HR 0.8(0.40–1.30; P = 0.347) -HR 0.9(0.50–1.70; P = 0.766) -HR 1.1(0.80–1.60; P = 0.405) -HR 1.6 (1.10–2.40; P = 0.008) -HR 1.7 (1.10–2.60; P = 0.023)	Random sequence adequately generated and allocation adequately conceived. Participants and personnel blinded to treatment. Unknown whether outcome assessors were blinded. All established outcomes measures	*Post hoc* analysis of the CHARISMA RCT in pts with diabetic nephropathy
McCullough *et al.* [207]	-2002 -1990–1998 -North America	Prospective case-control study	-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	-Age:63.4 years -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	-Acetylsalicylic acid (*n* = 262) -Beta blockers (*n* = 328) -Acetylsalicylic acid plus beta blockers (*n* = 902) -No acetylsalicylic acid or beta blockers (*n* = 232)	Episodes of (in no ASA or BB, ASA alone, BB alone, ASA +BB): -Haematoma -Gastrointestinal bleeding -Shock -Sustained hypotension -Asystole -Ventricular fibrillation	P = none versus both -0,4,0,10 (P = NS) -1,1,0,3 (P = 0.82) -58,42,15, 30 (P <0.001) -101,95,83,173 (P <0.001) -21,16,11, 12	Case definition and case representatives adequate. Controls adequately selected from the same population. Controlled by the most important confounders	No data on ASA intolerance or allergy, no doses reported

Continued

			band (CK-MB). Patients with a new left bundle branch block were included when a history consistent with ischaemic 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 ischaemic contribution, all diagnoses outside of ST-segment elevation AMI. Coma, arrhythmias, and gastrointestinal bleeding.	values of 81.5, 81.5 to 63.1, 63.1 to 46.2, and >46.2 mL/min/72 kg (P <0.0001). ASA + BB used in 40.4% of patients undergoing dialysis		-Stroke -In-hospital death -Pulmonary oedema	P <0.001) -28,18,22,41 (P <0.001) -0,1,0,1 (P <0.001) -50,51,11,27 (P <0.001) -107,81,79,148 (P <0.001)		
Nakamura *et al.* [208]	-2005 -Asia	Quasi-RCT	-Patients with diabetic nephropathy (microalbuminuria (20–200 μg/min)) and non-silent cerebral infarction	-Age: 55.5 years -Gender: 70% male -DM2: 100% -Diabetes vintage: 12 years (mean) -sCr: 79.55 μmol/L -HbA1c: 7.8%	-Dilazep dihydrochloride plus standard therapy (including ACEi, ARB, calcium antagonists, beta blockers, alpha blockers), 300 mg/day ($n = 15$) -Standard therapy (including ACEi, ARB, calcium antagonists, beta blockers, alpha blockers) ($n = 15$) -24 months	-Microalbuminuria -Silent cerebral infarction	-MD 180 ± 48 versus 64 ± 22 μg/min (P <0.01) -Incidence 33.3% versus 6.7% (P <0.01)	Quasi RCT. Allocation concealment and blinding unclear. Primary outcomes adequately assessed. Unclear if follow-up was completed for all subjects. All expected outcomes measured in all subjects	Not adjusted for the most important confounders. Not controlled for additional confounders
Palmer *et al.* [204]	-2012 -1980–2011	Systematic review of RCTs or quasi-RCTs	-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. Paediatric trials	-31 trials (20942 patients) included -eGFR <60 mL/min	-Antiplatelet therapy (aspirin, dipyridamole, clopidogrel, sulfinpyrazone, ticlopidine, or picotamide) -placebo	-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 ACS or PCI (9 RCTs,	-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)	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 provided	In all studies analysed, 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

Chapter 3.7. Continued

Study	-Publication year -Time frame -Location	Design	-Inclusion criteria -Exclusion criteria	Patient characteristics	-Intervention (*n*) -Comparator (*n*) -Duration	Outcome(s)	Results	Quality of evidence	Notes
					5776 pts) -Minor bleeding after ACS or PCI (9 RCTs, 5776 pts) -Fatal or nonfatal Myocardial infarction in patients after ACS or PCI (7 RCTs, 5261 pts) -Fatal or nonfatal myocardial infarction in persons at risk for or with stable cardiovascular disease (10 RCTs, 9233 pts) -Coronary revascularization in patients after ACS or PCI (7 RCTs, 5265 pts) -Fatal or nonfatal in persons with CKD at risk for or with stable cardiovascular disease (10 RCTs, 9133 pts) -Haemorrhagic stroke in patients after ACS or PCI (5 RCTs, 4035 pts) -All-cause mortality in persons at risk for or with stable cardiovascular disease (21 RCTs, 10632 pts) -All-cause mortality in patients after ACS or PCI (8 RCTs, 5260 pts) -Death due to cardiovascular causes in patients after ACS or PCI (2 RCTs, 411 pts) -Death due to cardiovascular causes in persons with CKD at risk for or with stable cardiovascular disease	-RR 0.93 (0.84-1.04; P = 0.84) -RR 0.66 (0.16-2.78; P = 0.22) -RR 1.08 (0.47-2.49; P = 0.45) -RR 0.87 (0.61-1.24; P = 0.68) -RR 0.89 (0.75-1.05; P = 0.48) -RR 0.96 (0.79-1.16; P = 0.46) -RR 0.91 (0.60-1.36; P = 0.21)			

						(16 RCTs, 8706 pts)			
Saito *et al.* [203]	-2011 -2002–2008 -Asia (163 centres)	RCT	-Diagnosis of type 2 diabetes mellitus. Age between 30 and 85 years. Ability to provide informed consent -History of heart disease. Use of antiplatelet or antithrombotic therapy (aspirin, ticlopidine, cilostazol, dipyridamole, trapidil, warfarin, and argatroban). History of severe gastric or duodenal ulcer. Severe liver dysfunction. Severe renal dysfunction. Allergy to aspirin	-Age:65 years -Gender: 55% Male -Mean DM2 vintage: 7 years -Insulin use: 12% -HbA1c:7.05% -eGFR 60–89 mL/min/1.73 m^2 Aspirin 661, nonaspirin 712; eGFR <60 mL/min/1.73 m^2 Aspirin 342, nonaspirin 290	-Aspirin, 81 mg or 100 mg/daily (n = 1251) -Standard therapy (n = 1272) -4.37 years	-Atherosclerotic events of fatal and nonfatal ischaemic heart disease, stroke, and peripheral arterial disease in pts with eGFR 60–89 mL/min/1.73 m^2 -Atherosclerotic events of fatal and nonfatal ischaemic heart disease, stroke, and peripheral arterial disease in pts with eGFR <60 mL/min/1.73 m^2	-HR 0.57(0.36–0.88; P = 0.011) -HR 1.3(0.76–2.42; P = 0.32)	Random sequence generation and allocation concealment unclear Participants, personnel not blinded Outcome assessors blinded. Primary outcomes adequately assessed. 7% lost to follow-up. ITT analysis. All expected outcomes measured in all subjects	Unblinded, not-placebo controlled study
Wang *et al.* [205]	-2010	Systematic review of RCTs or quasi-RCTs	-Any type 1 or type 2 diabetic patient with abnormal urinary albumin excretion rate -ESKD, other renal diseases, gestational diabetes	-6 trials (271 patients) included	-PGE1 + routine treatment -No treatment, placebo or other drugs (ACEi, ARB, CCB, Chinese herbal medicines)	-Change in serum creatinine -Change in urinary albumin excretion -Change in proteinuria	-MD-7.59 (−15.61 to −0.44; P = NS) -MD −48.28 (−75.29 to −21.28; P <0.05) -MD-300.00 (−518.34 to −81.66; P = NS)	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 randomized, 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