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Clinical Practice Guideline

Clinical Practice Guideline on management of older patients with chronic kidney disease stage 3b or higher (eGFR <45 mL/min/1.73 m^2)

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1. ABBREVIATIONS AND ACRONYMS

AKI	Acute kidney injury
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CM	Conservative management
eGFR	Estimated glomerular filtration rate
ERA-EDTA	European Renal Association – European Dialysis and Transplant Association
ERBP	European Renal Best Practice
ESKD	End-stage kidney disease
HD	Hemodialysis
HR	Hazard ratio
KFRE	Kidney Failure Risk Equation
MD	Mean Difference
MDRD	Modification of Diet in Renal Disease
OR	Odds Ratio
PD	Peritoneal dialysis
QoL	Quality of life
RCT	Randomized controlled trial
REIN	Renal Epidemiology and Information Network
RR	Relative Risk
RRT	Renal replacement therapy
SGA	Subjective global assessment
95% CI	95% Confidence Interval

2. FOREWORD

The mean age of the general population is increasing, resulting in a higher prevalence of older patients. The health management of this specific subpopulation poses serious questions, which are not limited to clinical issues, but also involve ethical and social issues.

Despite the growing number of frail and older patients with eGFR <45 mL/min/1.73 m^2, most studies still exclude this population, so providing guidance on the management of these patients with CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2) remains problematic. There is a paucity of well-designed, prospective studies in this population. This limits the evidence base for these approaches.

The advisory board of ERBP decided during its meeting in Istanbul 2013 that a guideline on the management of older patients with CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2) was needed and timely. There was a clear need to support patients, their families and the healthcare professionals with evidence-based guidance on how to approach this specific population. There was 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 within an ethical and societal perspective.

In addition to a rigorous approach to methodology and evaluation, we were keen to ensure that the document focussed on patient-centered outcomes and had utility for clinicians involved in everyday practice.

We hope you enjoy reading this guideline and that you will find it useful in your everyday management of older patients with CKD stage 3b or higher. Most of all, we hope that this guideline will contribute to improved outcomes for these patients.

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 2013 and decided on

the composition of the guideline development group, taking into account the clinical and research expertise of each proposed candidate. It was decided that, next to the actual members of the guideline development group, additional external experts would be approached for their expertise in specific areas.

Next to setting up a guideline development group, it was decided to perform a formal scoping procedure [1] to define the topics of interest to be covered within the guideline. For this aim, a separate expert group was assembled.

Expert panel scoping procedure

	Name	Specialism	Country	Role	GDG member
1	Pascale Bernaert	Geriatrics	Belgium	Expert	No
2	Wim van Biesen	Nephrology/ methods team	Belgium	Facilitator	No
3	Davide Bolignano	Nephrology	Italy	Expert	No
4	Edwina Brown	Nephrology	UK	Expert	Yes
5	Adrian Covic	Nephrology	Romania	Expert	Yes
6	Ken Farrington	Nephrology	UK—Stevenage	Expert	Yes
7	Jeroen Kooman	Nephrology	The Netherlands	Expert	Yes
8	Juan Florencio Macias	Geriatrics	Spain	Expert	Yes
9	Andrew Mooney	Nephrology	UK—Leeds	Expert	Yes
10	Barbara van Munster	Geriatrics	The Netherlands	Expert	No
11	Ionut Nistor	Nephrology/ methods team	Romania	Expert	Yes
12	Nele van den Noortgate	Geriatrics	Belgium	Expert	Yes
13	Sabine van der Veer	Methods team	The Netherlands	Administrator	Yes
14	Gerhard Wirnsberger	Geriatrics	Austria	Expert	No
15	Kitty Jager	Epidemiologist	The Netherlands	Expert	No
16	Eva Topinkova	Geriatrics	Czech Republic	Expert	No
17	Stefaan VandeCasteele	Nephrology	Belgium	Expert	No

GDG, guideline development group

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4. CONFLICT OF INTEREST

4.1. Conflict of interest policy

We required all participants in 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 the 2 years before joining the guideline development group. ERBP felt that excluding all individuals with some degree of potential conflict of interest would make assembling a guideline development group impossible. 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 insisted on transparency. All members of the guideline development group were allowed to participate in discussions and had equal weight in formulation of the statements. All were allowed equal involvement in data extraction and writing the rationales.

4.2. Guideline development group declaration of interest

The updated declaration of interest forms are available from http://www.european-renal-best-practice.org/content/guideline-development-group-management-older-patients-ckd and are updated on a regular basis.

None of the guideline development group members declared having a conflict of interest with the topic of the current guideline. The details of their declaration of interest at the moment of the guideline production can be found in Appendix 1.

5. PURPOSE AND SCOPE OF THIS GUIDELINE

5.1. Why was this guideline produced?

This clinical practice guideline was designed to assist shared decision-making on the management of older individuals (>65 years of age) with CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2). It was not intended to define a standard of care and should not be construed as one. It should not be interpreted as prescribing an exclusive course of management.

5.2. Who is this guideline for?

This guideline intends to support clinical decision-making by any healthcare professional caring for older patients (>65 years of age) with CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2), 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 the development of standards of care by policy-makers. Finally, the guideline also intends to provide tools for shared decision-making with patients and their families.

5.3. What is this guideline about?

The intended scope of this guideline was determined by a rigorous scoping procedure [1] by a steering group assembled for this purpose by the ERBP advisory board. In short, after a systematic review, an electronic survey was done among all members of ERA-EDTA and the members of the European Union of Geriatric Medicine Societies (EUGMS) to prioritize potential questions. On the basis of the results of the scoping procedure, the steering group defined a set of healthcare questions related to the management of older (>65 years of age) patients with CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2) during a scoping meeting in Brussels.

5.3.1. Population. The guideline covers older patients with CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2), as defined by the recent Kidney Disease: Improving Global Outcomes (KDIGO) classification [2]. It was widely discussed within the guideline development group what exactly the definition of 'older' should be. As the definitions of 'frail', 'comorbid' and 'decreased functionality' were unclear at the outset, and screening for these conditions was within the scope of the guideline, it was decided to use the age-based criterion of >65 years of age.

5.3.2. Conditions. The guideline specifically covers management of older (>65 years of age) patients with CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2), with a focus on six major areas: (1) estimation of GFR for classification and drug dose adaptation; (2) prognosticating rate of progression to end-stage renal disease; (3) prognosticating risk of death in the medium term; (4) assessment of functional status and strategies to improve it; (5) assessment of nutritional status and strategies to improve it; (vi) appraisal of benefits and drawbacks of RRT versus conservative care.

5.3.3. Healthcare setting. This guideline targets management of older (>65 years of age) patients with CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2) 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 older (>65 years of age) patients with CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2) and to develop pathways of care by systematically compiling available evidence in this area. It provides an evidence-based rationale on why management of older (>65 years of age) patients with CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2) should or should not be different from older (>65 years of age) patients without CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2), or from patients with CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2) but with age <65 years of age. In line with the mission statement of ERBP, the guideline document intends to inform all involved stakeholders and to stimulate shared decision-making [3].

6. METHODS FOR GUIDELINE DEVELOPMENT

6.1. Establishment of the guideline development group

As defined by our guideline development methodology [4], the ERBP advisory board installed a steering group, which, after selection of the topics based on the systematic scoping procedure, selected further members of the guideline development group. Members of the steering group and of 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 clinical geriatric medicine, general internal medicine, nutrition 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

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

(1) estimation of GFR for classification and dose adaptation;
(2) prognosticating rate of progression to end-stage renal disease;
(3) prognosticating risk of death in medium term periods;

(4) assessment of functional status and strategies to improve it;

(5) assessment of nutritional status and strategies to improve it;

(6) appraisal of benefits and drawbacks of RRT versus conservative care

Area (1) was intended to cover diagnosis of CKD stage 3b or higher in older (>65 years of age) patients. In addition, it was intended to provide guidance on which the method to estimate GFR was most adequate to be used for drug dose adaptation.

Areas (2) and (3) were intended to discriminate between older (>65 years of age) patients with CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2) who would versus would not rather reach the end point of end-stage renal disease than that of mortality. This is important in order to focus the shared decision-making process, and planning eventual RRT, both on the individual and on the center and society level. This information can provide a focus for shared decision-making for the individual and can also inform planning service provision at local and national levels.

Areas (4) and (5) intended to provide recommendations on screening tools to identify older (>65 years of age) patients with CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2) with or at risk of impairment of physical function [area (4)] and/or malnutrition [area (5)]. Screening tools were intended to be easy to perform, so that they can easily be used on an ongoing basis in the everyday evaluation of these specific patient groups. It was outside the scope to identify or evaluate more extended tools for more in-depth or mechanistic evaluation of physical function or nutritional status. Areas (4) and (5) further intended to evaluate which strategies potentially improve physical function [area (4)] and/or nutritional status [area (5)].

Area (6) intended to provide evidence to guide decision-making on benefits and drawbacks of RRT versus conservative care in older (>65 years) patients with CKD stage 5.

6.2.2. Pro–con debates. Besides these six predefined areas where a systematic review of the evidence was proposed, there also emerged different clinical questions where it was considered unlikely that a systematic review could provide substantial guidance. For these areas, it was decided to use a narrative approach to list arguments pro or con a certain management strategy in older (>65 years) patients with CKD stage 3b or higher. Within these pro–con debates, we intended to cover the following areas:

(1) Glycemic control in frail older patients with advanced kidney disease *point of debate:*

- should we try to achieve the same HbA1C values in this specific population of frail older patients with advanced CKD (eGFR <45 mL/min/1.73 m^2) as in other patients, or should we settle for less strict glycemic control?
- should we use in frail older patients with advanced kidney disease an elaborate monitoring regimen (multiple injections, multiple self-control, etc.)?

(2) Hypertension control in frail older patients with advanced kidney disease *point of debate:*

- should we in frail older patients with advanced kidney disease strive to blood pressure goals as in the general population?
- should we use RAAS inhibitors in this patient group?

(3) Kt/V as an adequacy parameter in frail older patients *point of debate:*

- should we use Kt/V as an adequacy parameter in frail older patients on dialysis?
- if yes: which targets should be used?
- if no: which other parameters should be used as quality indicators?

(4) Use of alternative dialysis regimens (prolonged slow dialysis, daily dialysis, nocturnal dialysis) in frail older patients *point of debate:*

- should we use prolonged slow dialysis/daily dialysis/nocturnal dialysis in frail older patient?

(5) HD versus PD and home versus center-based) *point of debate:*

- are there reasons to prefer HD or PD as treatment in frail older patients?
- list arguments pro PD/con HD and pro HD/con PD

(6) Criteria for and appropriateness of transplantation in older patients with end-stage renal failure *point of debate:*

- should the criteria to accept older patients (>70 years of age) on the waiting list for transplantation be similar to those of younger patients?
- if not: which criteria should be added
- should transplantation in the >70 year of age group be advocated/promoted?

Some of these pro–con debates have already been published; others will be published later as separate documents in the near future [5–7].

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), the intervention (I), the comparator (C) and the outcomes (O) for intervention questions and the patient group, index tests, reference standard and target condition for questions of diagnostic test accuracy [8]. For each question, the guideline development group agreed upon explicit review question criteria including study design features. (See Appendix 2 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

Efforts were made to capture the target population's 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. The flowchart was reviewed by patient groups in two renal centers and their comments were taken into account in producing the final version.

A draft version of the guideline was presented at the annual ERA-EDTA meeting in Vienna 2016. Attending participants could write down their comments and suggestions on the guideline through an electronic account.

6.6. Searching for evidence

6.6.1. Sources. The ERBP methods support team searched The Cochrane Database of Systematic Reviews (May 2016), DARE (May 2016), CENTRAL (May 2016) and Medline (1946 to May, week 4, 2016) 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.

Table 1. Suggested outcomes and level of importance

Critically important outcomes
Survival/mortality
QoL/patient satisfaction
Progression to ESKD/deterioration of residual renal function
Functional status
Highly important outcomes
Hospital admissions
Major morbid events
Myocardial infarction
Stroke
Amputation
Loss of vision
Infection
Pain
Moderately important outcomes (surrogate outcomes)
None
Question specific outcomes
For 1.1:
Bias [median difference between eGFR and measured GFR]
Precision (SD of Bias)
Accuracy (root mean square error of eGFR–mGFR difference)
Correlation (Concordance correlation coefficient)
For 1.2: *c*-statistic of predicted and observed ESKD/dialysis need, discrimination, calibration
For 1.3: *c*-statistic of predicted and observed mortality, discrimination, calibration, goodness of fit
For 1.4: Inter-rater agreement, sensitivity/specificity, positive predictive value (PPV)/negative predictive value (NPV)
For 1.5: Inter-rater agreement, sensitivity/specificity, PPV/NPV
For 1.6: Health economic assessment

Reference lists from 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 Geriatric medicine for guidelines to screen the reference lists.

6.6.2. Selection. For diagnostic questions, we included all studies that compared any of the predefined clinical or biochemical tests with a gold standard reference test. For intervention questions, we included all studies in which one of the predefined interventions was evaluated in humans. We excluded case series that reported on benefit if the number of participants was five or less, 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 through this system to those responsible for screening. 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 any that were clearly irrelevant 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 arbitration.

The flow of the paper selection is presented for each question in Appendix 4.

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 Excel table. 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 an independent referee. From these data extraction tables, we produced merged consensus evidence tables for informing the recommendations. The evidence tables are available in Appendix 5.

Risk of bias of the included studies was evaluated using validated checklists, as recommended by the Cochrane Collaboration. These were AMSTAR for systematic reviews [9], the Cochrane Risk of Bias tool for RCTs [10], the Newcastle Ottawa scale for cohort and case–control studies [11] and QUADAS for diagnostic test accuracy studies [12]. 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 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. 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 '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 a full-day plenary meeting.

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 when applicable. In accordance with GRADE [13], we classified the strength of the statements as strong (coded 1) or weak (coded 2) (Tables 3 and 4, Figure 1).

Judgments around four key factors determined the strength of a recommendation: the balance between desirable and undesirable consequences of alternative therapeutic or diagnostic strategies, the quality of the evidence, the variability in values and preferences. We did not conduct formal decision or cost analysis.

Table 2. The method of rating the quality of the evidence. Adapted from Balshem *et al.* [184].

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: ⊕◯◯◯)

Table 3. Grade for the overall quality of evidence. Adapted from Guyatt *et al.* [185].

Grade	Quality level	Definition
A	High	We are confident that the true effects lies close to that 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 often will be far from the truth

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 [14]. 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 only intended to facilitate practical implementation.

Table 4. Implications of strong and weak recommendations for stakeholders. Adapted from Guyatt *et al.* [186].

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, counseling 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.

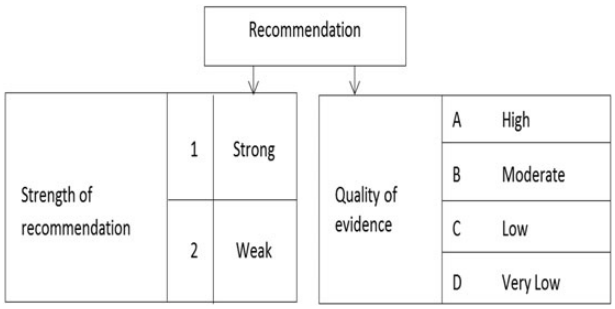

FIGURE 1: Grade system for grading recommendations. Adapted from Guyatt *et al.* [13].

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 level 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 in the recommendations made in 'how did we translate the evidence into the statement'.

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

6.10. Internal and external review

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

6.10.2. External review. All members of the ERA-EDTA had the option to provide comments through a Survey Monkey questionnaire.

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 1-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 [15]. Activities of ERBP and its methods support team are supervised by an advisory board [15] (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. RATIONALES

General approach to older patients with advanced CKD (eGFR <45 mL/min/1.73 m^2): a proposal for a management pathway (Figure 2)

Diagnosis of eGFR <45 mL/min/1.73 m^2 should be confirmed on different occasions, using an estimation equation, taking into account potential sources of bias, such as underlying sarcopenia and/or malnutrition (discussed in question 1). The guideline group wishes to stress that not all older patients with an eGFR <45 mL/min/1.73 m^2 should be labeled as having a kidney disease, as for some patients this might be just reflect physiologic aging. However, even for these patients, awareness of their eGFR is of importance to adjust dosing of medication.

It is important to identify those patients who will versus will not benefit from closer nephrologic follow-up. This decision is based on two factors: risk prediction for survival and risk prediction for progression of renal insufficiency. The guideline development group judges the Bansal score to be acceptable to be used for risk prediction of mortality in older patients (discussed in question 3). For patients with a high predicted risk, focus should be on advanced care planning. Nephroprotective measures should be installed, as far as they do not interfere with QoL. As explained in question 3, development and validation of the Bansal score was done in cohorts with low numbers of frail patients. Therefore, a low predicted risk for mortality can be misleading in frail patients. In these patients, an additional assessment of frailty should be performed, using a well-validated tool. If the frailty risk is high, the patient should still be regarded as high mortality risk, regardless of the Bansal score, and be managed accordingly.

The guideline development group judges that the KRFE score provides reasonable predictions of the risk for progression of kidney failure (discussed in question 2). Patients with a low predicted risk of progression should be informed that their kidney function will remain most likely rather stable, provided they follow the advice regarding nephroprotection. For these patients, the guideline development group judges that there is no need for a more extended planning or explanation on renal replacement therapies or CM.

For patients with a high predicted risk for progression and with a limited predicted risk for mortality, a shared decision approach should be undertaken (discussed in question 6). Patient expectations and values should be elicited and taken into account when weighing advantages and disadvantages of the different options for renal replacement. The REIN score provides a reasonable estimate of short-term mortality risk should dialysis be commenced. CM should be proposed as one of the potential options.

Older patients with advanced CKD (eGFR <45 mL/min/1.73 m^2) should be screened on a regular basis for functional impairment (discussed in question 4) and malnutrition (discussed in question 5). This assessment should be performed with the intention to identify those patients who will potentially benefit from a more in-depth examination by a geriatrician or a multidisciplinary team.

Q1. What parameter should be used in older patients (a) to estimate kidney function and (b) for dose adaptation purposes?

1.1 We recommend using estimating equations that correct for differences in creatinine generation rather than plain serum creatinine measurements to assess kidney function in older patients (1A).

1.2 We recommend that there is insufficient evidence to prefer one estimating equation over another since all perform equally and substantial misclassification can occur with any of these equations when used in older patients with differing body composition (1B).

1.3 We recommend formal measurement of kidney function if more accurate and precise estimation of GFR is required (1B). We suggest the use of CKD-EPI$_{Cr\text{-}Cyst}$ may be an acceptable alternative (2C).

1.4 We recommend taking account of kidney function when prescribing drugs whose active forms or metabolites are renally cleared (1A).

1.5 We suggest that for drugs with a narrow toxic/therapeutic range, regular measurement of serum concentrations can provide useful information. Differences in protein binding in relation to uremia may necessitate use of different target levels of total drug concentration. (2C).

Advice for clinical practice

(1) Kidney function can vary over time and should be monitored serially using the same equation.

(2) Estimating equations cannot be reliably used in patients with acute changes in kidney function.

(3) Use of different equations, even if well established, can result in different classifications of CKD stage for the same creatinine value from the same patient.

(4) Serum levels of drugs depend on absolute rather than body size corrected clearance.

(5) Formulae other than Cockcroft and Gault require correction for body surface area (BSA) to obtain absolute values. To achieve the required dose, the recommended dose should be multiplied by BSA and divided by 1.73.

Why this question?

Methods to accurately assess true GFR (Cr-EDTA, inulin clearance or Tc-DPTA) are impractical for use in routine clinical practice. Various formulae, based on creatinine and/or cystatin, are in widespread use but there is no consensus about which formula should be used in older patients with advanced CKD. As aging is associated with declining GFR, but also with reduced creatinine generation due to loss of muscle

mass and reduced food intake, recommendations for the general population cannot be transferred to this subgroup. In addition, older patients with advanced CKD mostly also have a high consumption of drugs. Hence CKD management, referral practices and accurate dosing of renally excreted drugs, may be compromised if renal function is not correctly estimated.

What did we find?

We found 30 studies, including 27 observational, noncomparative, cross-sectional studies, 2 observational comparative studies with prospective cohorts and 1 retrospective observational comparative study addressing our question.

Two studies looked at the importance of the creatinine assay methodology on the interpretation of estimated GFR [16, 17]. The method used was found to influence the bias and accuracy of estimating equations but not the precision (as explained below). Of the 30 studies included, 11 used an enzymatic assay, 12 the Jaffe method, 5 used a combination, while 3 did not specify. Whether different cystatin assays have similar discrepancies in bias, accuracy and precision has not been reviewed so far in the population of older patients with advanced CKD (eGFR <45 mL/min/1.73 m^2).

Five studies [18–22] related estimated GFR to clinical outcome in older patients, four of which studied survival in populations defined according to GFR estimated by different equations. Cystatin-based formulae were assessed in four studies [18, 20, 21, 23]. All demonstrated better correlation with survival using cystatin-based formulae compared with those that were purely creatinine based.

Twenty-three studies [24–44] looked at the *bias* (the difference between the mean of the measurements and the reference value), *precision* (the range of the difference) and *accuracy* (the closeness of a measurement to the true GFR) of different GFR estimating equations in relation to measured GFR. Forty-six different GFR estimating equations were studied, including those based purely on creatinine, purely on cystatin and those based on both (Cr-Cyst). Direct comparisons were confounded by the use of different creatinine assays, use of six different gold standards and use of different methodologies to describe bias, accuracy and precision, giving rise to an underlying theme of multiple conflicts in the interpretation of results.

Thirteen studies [25, 28–30, 32, 33, 35–37, 39, 41, 42, 44] included a bias comparison between the commonly used MDRD and CKD-EPI formulae against a gold standard. Nine demonstrated that CKD-EPI_{Cr} had less bias than MDRD, three found to the contrary and one found equivalent bias. In 10 studies, bias was positive, indicating that both MDRD and CKD-EPI overestimated GFR in older patient populations, whilst in another study [32] bias was negative for both and in another [44] negative for CKD-EPI but positive for MDRD.

There were also conflicts in the interpretation of results from equations including cystatin. CKD-$EPI_{Cr\text{-}Cyst}$ was used in five studies [28, 29, 32, 42, 44] deploying a variety of creatinine assays and gold standard methods of GFR estimation. The results were conflicting and provide no basis to suggest that using CKD-$EPI_{Cr\text{-}Cyst}$ improves bias with respect to CKD-EPI_{Cr}. The same was not true with respect to accuracy and precision. Each of these studies including a CKD-EPI_{Cr} and CKD-$EPI_{Cr\text{-}Cyst}$ among the comparator equations demonstrated an improvement in precision and accuracy for CKD-$EPI_{Cr\text{-}Cyst}$ over CKD-EPI_{Cr}, though this should be interpreted cautiously given the variety of creatinine assays and gold standard methods used.

For drug dosing, the equation that matches the one used during drug development and/or the drug insert should take precedence, though adequate information is often not sufficiently available. Cockcroft-Gault creatinine clearance estimates are the most frequently used in the assessment of kidney function during drug development and may be even most accurate in older patients [30, 40]. A high prevalence of dose calculation errors of 10 commonly prescribed drugs has been described for both MDRD (28.6%) and CKD-EPI (22.9%) when substituted for manufacturer-recommended Cockcroft-Gault creatinine clearance estimates during dose calculation in older patients.

How did we translate the evidence into the statement?

> *We recommend using estimating equations that correct for differences in creatinine generation rather than plain serum creatinine measurements to assess kidney function in older patients (1A).*

Older patients might have a different (lower) creatinine generation, based on lower muscle mass, less physical activity and reduced food intake. All these might impact on the relationship between serum creatinine and GFR. The deviations are difficult to predict, as they are more dependent on anthropometry, nutritional status and frailty rather than calendar age.

As such, serum creatinine alone might be insufficient to have a correct estimation of GFR in an older person.

> *We recommend that there is insufficient evidence to prefer one estimating equation over another since all perform equally and substantial misclassification can occur with any of these equations when used in older patients with differing body composition.*

Evidence suggests that there is no formula that performs consistently better than others. Relative performance is influenced by methodology to measure creatinine and case-mix of the older patient cohort (frail versus non-frail older patients, stage of CKD, age). Substantial reclassification in CKD stages has been demonstrated when one versus another formula is used, but no formula consistently outperforms the others.

> *We recommend formal measurement of kidney function if more accurate and precise estimation of GFR is required. We suggest the use of CKD-$EPI_{Cr\text{-}Cyst}$ may be an acceptable alternative.*

If exact knowledge of kidney function is essential, the guideline group judges that it is best to perform a formal measure of

kidney function, as none of the available formulae provides results that are accurate enough. However, formal measurement of kidney function might be laborious and/or expensive. In these patients, using the CKD-EPI$_{Cr\text{-}Cyst}$ might be considered, as this increases the performance of the estimation.

We recommend taking account of kidney function when prescribing drugs whose active forms or metabolites are renally cleared.

We suggest that for drugs with a narrow toxic/therapeutic range, regular measurement of serum concentrations can provide useful information. Differences in protein binding in relation to uremia may necessitate the use of different target levels of total drug concentration.

Dosing of medication should be adapted to renal function for all medications that are cleared themselves, or which have active metabolites that are cleared by the kidneys. Uremia might affect on protein binding, and also, older patients may suffer from malnutrition and hypo albuminemia. As such, the serum concentrations of free drugs, the active form, might be higher than expected from the measured total concentration. In these circumstances, lower concentrations of total drug should be aimed for.

What do other guidelines state?

No other guidelines provide guidance for this specific patient population.

Suggestions for future research

Pharmacokinetic and pharmacokinetic studies on dosing of most relevant drugs in frail older patients

Q2. What is the most reliable risk model score to predict progression of CKD in older patients with advanced CKD (eGFR <45 mL/min/1.73 m^2)?

2.1 We recommend that the 4-variable KFRE performs sufficiently well for use in older patients with advanced CKD and eGFR <45 mL/min/1.73 m^2 (1B).

Why this question?

Answers to this question will guide clinicians on how to estimate the risk of progression of CKD to ESKD in older patients. The prevalence of CKD increases with age, though only a minority progress to ESKD. A robust method for identifying those at high risk of progression would allow focussed renoprotective therapy and timely preparation for RRT if appropriate. Those at low risk of progression to ESKD could be spared unnecessary interventions. Risk prediction is challenging since GFR decline may not be linear, and rapid decline may occur unpredictably associated with AKI, especially in older people who are at greater risk of AKI because of the high prevalence frailty and other long-term conditions. The competing risk of death is also an issue. In those over 65 years of age, the risk of ESKD may exceed only that of death in those with GFR <15 mL/min/1.73 m^2. Older people are often excluded from studies on which risk prediction scores are based. Hence it is unclear whether current risk prediction scores perform adequately in older people.

What did we find?

We identified three prospective [45–47] and five retrospective [48–52] cohort studies that aimed to identify risk factors and/or develop a risk prediction score for progression to ESKD in predominantly older people. All the prospective studies and two retrospective studies [49, 52] were excluded from further consideration because they did not attempt to develop a risk prediction score that was clinically applicable. Two retrospective studies developed prediction equations that performed well but cannot be recommended for clinical application because of limitations including risk of bias, missing data and lack of adequate external validation [48, 51].

A further retrospective study analyzed data from Canadian adults with eGFR 10–59 mL/min/1.73 m^2 to develop an equation (KFRE) to predict the risk of ESKD at 2 and 5 years [50]. The 8-variable KFRE (age, gender, eGFR, albuminuria, serum calcium, serum phosphate, serum bicarbonate and serum albumin) achieved excellent discrimination in development (*c*-statistic = 0.917) and validation cohorts (*c*-statistic = 0.841). A 4-variable KFRE (age, gender, eGFR and albuminuria) performed similarly (*c*-statistic = 0.91 and 0.84 in development and validation cohorts, respectively) [53]. The 8- and 4-variable KFRE performed equally well in subgroups younger than 65 years and in older patients. External validation was carried out in a Dutch cohort with stage 3–5 CKD. The 8- and 4-variable KFREs both performed well, predicting 5-year risk with good discrimination (*c*-statistic 0.89 and 0.88, respectively) and calibration (difference between predicted and observed risk 4.0 and 7.1%, respectively). Further validation took place in a dataset that included 721 357 individuals with CKD stages 3–5 from 31 cohort studies in North America, Asia, Europe and Australasia (CKD Prognosis Consortium). The 4-variable KFRE achieved excellent discrimination (pooled *c*-statistic 0.90 at 2 years and 0.88 at 5 years). Within individual cohorts, discrimination was also excellent, with *c*-statistic >0.80 in all but two cohorts. The 8-variable KFRE performed similarly. Discrimination was similar in subgroups younger than 65 years and in older patients for both 4- and 8-variable KFREs. Calibration was good in North American cohorts, but the KFREs overestimated risk in some non-North American cohorts. Addition of a calibration factor improved calibration in 12/15 and 10/13 non-North American cohorts at 2 and 5 years, respectively [54]. At the instigation of the ERBP guideline development group, further analyses were performed in people aged >65 years with eGFR of <45 mL/min/1.73 m^2 from pooled European cohort studies. Both KFREs achieved excellent discrimination (4-variable KFRE: *c*-statistic 0.87 and 0.86 at 2 and 5 years, respectively; 8-variable KFRE: *c*-statistic 0.88 and 0.86 at 2 and 5 years, respectively). Calibration was slightly better with the 8-variable KFRE and improved for both KFREs on addition of the calibration factor for non-North American populations (CKD-PC unpublished data).

How did we translate the evidence into the statement?

We recommend that the 4-variable KFRE performs sufficiently well for use in older patients with advanced CKD and eGFR <45 mL/min/1.73 m^2 (1B).

The KFREs developed by Tangri *et al.* [50] performed well and have been well validated, though they require the application of a correction factor in non-North American populations. Subgroup analyses have shown that they perform equally well in younger and older people. They require only basic demographic and laboratory data, enabling a risk estimate to be generated automatically by laboratory computer systems. The 8-variable score performed only marginally better than the 4-variable score. We therefore recommend the 4-variable KFRE for clinical use.

What do other guidelines state?

The 2012 KDIGO Clinical Practice Guideline for the Evaluation and Management of CKD recommends 'timely referral for planning renal replacement therapy (RRT) in people with progressive CKD in whom the risk of kidney failure within 1 year is 10–20% or higher, as determined by validated risk prediction tools (1B), but does not recommend a specific risk prediction tool nor does the guideline refer specifically to older people with advanced CKD [55].

Recommendations for future research

(1) Validation of the KFRE in a prospective study of people aged 65 years or older with a GFR of <45 mL/min/1.73 m^2.

(2) Development of equations to predict the risk of progression to ESKD over 12 months in people aged 65 years or older with a GFR of <45 mL/min/1.73 m^2. Such a risk prediction equation would be valuable to inform the timing of referral for fistula formation in older people opting to have HD.

(3) Development of equations to predict the risk of death versus ESKD in people aged 65 years or older with a GFR of <45 mL/min/1.73 m^2. Such equations would be extremely valuable in identifying people who are more likely to die than reach ESKD, who could be spared the stress of unnecessary preparation for RRT.

Q3: What is the most reliable risk prediction model to predict mortality in older and/or frail patients with advanced CKD (eGFR <45 mL/min/1.73 m^2)

3.1 We suggest using the Bansal score to predict individual 5 year risk of death before ESKD in non-frail older patients with CKD stage 3–5 (2B).

3.2 We suggest that in patients at low risk in the Bansal score, a score including the assessment of frailty as stated in question 4a be performed (2B).

3.3 We suggest that the REIN score be used to predict the risk for mortality in older patients with CKD stage 5 (2B).

Why this question?

Counseling older people with advanced CKD on treatment options requires reliable estimates of an individuals' absolute probability of death within a given time frame, both with and without starting dialysis. Correctly identifying those people likely to die within the next few months, regardless of whether RRT is started, may avoid the added burden of dialysis. Conversely, correctly identifying those likely to live longer may inform shared decisions balancing quality versus quantity of life. Very few of the available risk prediction models have been targeted to older people with advanced CKD and fewer still have been tested in populations outside the ones used to develop them. Hence it unclear whether existing models reliably help estimate the risk of death in older people with advanced CKD.

What did we find?

An initial search for systematic reviews revealed two high-quality publications, one including models predicting death in older patients and one predicting death in people with CKD [56]. To avoid duplication of effort, we built on these reviews, including the studies that mostly had included participants aged 65 years and above.

Two reviewers assessed the quality of methodology guided by the CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling (CHARMS) [57].

In addition, we specifically assessed to what extent the development and validation cohorts matched our target population: older people with eGFR <45 mL/min/1.73 m^2 with or without frailty.

The search revealed 3042 citations. After consecutive exclusion based on title, abstract and full text, we identified 23 studies, including 31 risk prediction models. Fifteen models targeted older patients in general [58–70], 4 targeted older patients with CKD stage 3–5 [52, 71, 72] and 12 models targeted older patients with ESKD [73–78]. Most models were developed and validated in the USA. Only three models were developed or validated in Western Europe. Models consisted of 2–15 predictors. The most commonly included final predictors of death were age, sex, variables representing functional status and comorbid conditions such as heart failure, malignancy and diabetes. The prediction time horizon ranged from 3 months up to 5 years, with models in people with ESKD focussing on predicting death up to 1 year. Mortality rates varied from 10 to 12% within 3 months and 18–54% within 5 years. Although most models included parameters of frailty, only one model was specifically developed within a frail older patient group [58].

Model development and validation quality varied substantially, and no model was entirely free from potential sources of bias. Only 16 of 31 models were internally validated. For only five models, investigators attempted to validate performance measures in a dataset that differed from the one used to develop the model (external validation): three models in older patients, one model in CKD stage 3–5 and one model in ESKD. External validation was mostly carried out by the same investigators who had developed the model, and in patients who were geographically distinct but otherwise similar to the ones

included in the development cohort (e.g. all Medicare beneficiaries). One model was independently validated by investigators who were not involved in the model development (REIN index) but modification of individual predictors introduced a high risk of bias [73].

At least one comorbid condition was included as a final predictor by 27 models. The presence of comorbidities was mostly based on administrative data whereby different definitions (or International Classification of Diseases codes) of the same comorbidity were used. In four studies, the presence of comorbidities was based on self-report. Both methods can induce misclassification and may substantially reduce predictive performance, especially upon generalization to patient groups external to the ones used for model development. In general, model performance was moderate at best. Eight models had a *c*-statistic of <0.7, only one model achieved a *c*-statistic of >0.8 [64], and CIs were generally lacking. Missing data were not reported in 7 of 23 studies and if reported, incorrect handling of missing data induced a high risk of bias in three studies.

How did we translate the evidence into the statements

Very few of the available predictive models have specifically been targeted to older patients with advanced CKD (eGFR <45 mL/min/1.73 m^2). Even fewer have been tested in populations outside the ones used to develop the models. It is therefore unclear whether existing models for predicting death in older people may reliably help to estimate the risk of death in those with advanced CKD.

For the model to be useful in routine clinical practice, it should include simple, readily available variables and allow easy calculation of an individual's mortality risk using a calculator or smartphone.

We suggest using the Bansal score to predict individual 5 year risk of death before ESKD in non-frail older patients with CKD stage 3–5 (2B).

The Bansal risk prediction model predicts the absolute probability of death within 5 years for older people with CKD stage 3–5 not yet treated with dialysis, provides measures of predictive performance and has been externally validated [71]. The investigators used data from the cardiovascular health study to develop the model [79]. The development cohort consisted of 5888 community-dwelling Americans on Medicare, with an average age of 80 years. The final risk prediction model included nine readily available demographic, clinical and biochemical predictors: age, sex, ethnicity, eGFR, urinary albumin-to-creatinine ratio, diabetes, smoking, history of heart failure and stroke. External validation of the model was carried out using a cohort of 789 community-dwelling Medicare beneficiaries aged 70–79 years old who were fully independent for activities of daily living. There was no evidence of poor calibration, and model discrimination was moderate in both the development (0.72; 95% CI: 0.68–0.74) and validation cohort (0.69; 95% CI: 0.64–0.74). The major limitation is that comorbidities were measured by self-report, which could result in misclassification and reduce predictive performance when variables are clinically assessed by health care practitioners. The guideline development group agreed that this prediction model had the best credentials to be recommended as a prediction tool for mortality in patients with advanced CKD (eGFR <45 mL/min/1.73 m^2).

We recommend not using currently available risk prediction models to predict individual risk of death in frail older patients with or without CKD (1B).

We suggest that in patients at low risk in the Bansal score, a score including assessment of frailty be performed (2B).

The Bansal score was validated in 789 community-dwelling Medicare beneficiaries aged 70–79 years of age. These patients were reported to be fully independent for activities of daily living. As such, this cohort may not be representative of cohorts including frail patients. Frailty is a prevalent condition in patients with advanced CKD (eGFR <45 mL/min/1.73 m^2) [80]. Since external validation in a cohort with a substantial portion of frail older patients is lacking, it is difficult to recommend the Bansal score [71] as the sole means to predict mortality in this population. However, it has been suggested that frailty is an additional risk factor for mortality, on top of and independent of other traditional risk factors [81]. As such, a high predicted mortality with the Bansal score will deliver a reliable result even in a frail patient. In contrast, when the Bansal score predicts a low mortality, mortality should be predicted based on a reliable frailty score rather than by traditional risk factors.

We recommend the REIN score be used to predict the risk for mortality in older patients with CKD stage 5 (1B).

We found one risk prediction model estimating the risk of death at 3 months in older people with ESKD who actually started with dialysis [75]. Data from the REIN registry were used to develop the model. The development cohort consisted of 12 500 French incident dialysis patients who were at least 75 years old, with one in five >85 years. Comorbidity was high; one-third of the development cohort had heart failure and a quarter had peripheral vascular disease. The risk prediction model included nine demographic, clinical and biochemical predictors: age, sex, history of congestive heart failure, peripheral vascular disease, dysrhythmia, cancer, severe behavioral disorder, mobility and baseline serum albumin concentration. The score was internally validated in 11 848 different dialysis patients of the same REIN registry. The rate of death in the validation cohort increased with the score, indicating good calibration. Model discrimination was moderate with a *c*-statistic in the internal validation cohort of 0.75 (95% CI: 0.74–0.76). The model was externally validated in an American cohort [73] and a Flemish cohort [53], although in both studies, the investigators slightly modified the score.

We found a second risk prediction model estimating risk of death at 6 months in older people with ESKD started with dialysis [74]. Data from 2500 French incident dialysis patients of the same REIN registry were used to develop the model. Participants were on average 81 years old, 38% had heart failure and 35% had peripheral vascular disease. The model was internally validated in 1642 incident dialysis patients, showing no evidence of poor calibration (P-value of Hosmer–Lemeshow test of 0.93) and moderate discrimination with a *c*-statistic of 0.7. The quality of model development was considered high for both REIN scores, although the comorbid conditions included in the scores need further specification to improve inter-rater reliability. Both REIN scores include readily available and easily assessed variables and provide individual risk prediction that can be used during shared decision-making. Discrimination of the 3-month mortality score seemed slightly better (*c*-statistic of 0.75 versus 0.7), but calibration was not reported. However, the probability of early death increased with the score ($P < 0.001$), a finding indicating good calibration.

Since externally validated high-quality risk prediction models in frail older patients with CKD/ESKD are scant, we assessed whether risk prediction models in older patients without information on kidney function could be extrapolated to those with CKD. We found one externally validated risk prediction model predicting the absolute probability of death within 4 years in community-dwelling older people (mean age 67 years) with or without CKD [64] (development and the validation cohort, respectively, 14 661 and 8009 community-dwelling Americans). Comorbidity rates in the development and validation cohorts were <20%, except for hypertension at >35%. The model included two demographic (age and sex), six clinical [body mass index (BMI), diabetes, cancer, lung disease, heart failure and smoking status] and four functional measures (walking, pushing/pulling and managing finances). There was no evidence of poor calibration. Discrimination in the development as well as the validation cohort was rather good with a *c*-statistic of, respectively, 0.84 and 0.82. The model was developed and validated in a relatively healthy population, probably related to the age criterion for inclusion (>50 years). As for the Bansal score [71], the performance of the Lee score [64] remains untested in the frail older patients.

What do other guidelines state?

To the best of our knowledge, there are no guidelines organizations that have produced statements specifically related to risk prediction models predicting progression of CKD or death in older patients. The American Geriatric Society states that 'uncertainty exists regarding the use of existing prognostic measures in clinical practice, particularly in persons with multimorbidity' [82].

Recommendations for future research

Reliable, externally validated risk prediction models for progression of CKD to ESKD or mortality in frail older patients with or without CKD are scant. Rather than developing new models, we emphasize the importance of external validation by different investigators of those models in both frail and non-frail older patients to test their performance and applicability.

Q4a: What is the best alternative method to assess functional decline in older and/or frail patients with advanced CKD

4a.1	We recommend a simple score be used on a regular basis to assess functional status in older patients with CKD stage 3b–5d) with the intention to identify those who would benefit from a more in-depth geriatric assessment and rehabilitation (1C).
4a.2	We recommend most simple scores, including self-report scales and field tests ([sit-to-stand (STS), gait speed or 6-min walk test] have comparable and sufficient discriminating power to identify patients with decreased functional status (1C).

Advice for clinical practice

— On a regular basis implies:
  - for dialysis patients 6–8 weekly;
  - for ambulatory patients at least at every visit.

— Frailty scores are interlinked with functional status and can provide additional information during assessment and shared decision-making on the planning of patients.

Why this question?

CKD is an independent risk factor for functional impairment and frailty [83–86]. Functional decline is associated with adverse outcomes, including mortality and hospitalization [87]. Furthermore, there is evidence from observational studies that interventions can prevent functional decline in patients with CKD [88].

Several tools have been developed to assess the various domains of physical function in patients with CKD [83], which have been categorized into laboratory-based measures of physiologic impairment, measures of mobility and performance capacity that are either self-reported or field tests and measures of physical activity. There is, however, no consensus on the most appropriate tool for assessing physical function in older patients with advanced CKD. In addition to having a good discriminating power, a score should also be easy to use, convenient to allow regular application in routine clinical practice, and be able of captureing changes in functional status over time.

What did we find?

We found 16 observational comparative studies with prospective cohorts [89–104], one secondary analysis of a randomized control trial [105] and one systematic review [106] addressing the question. Cross-sectional studies were excluded as they do not provide estimates of risk prediction. Thirteen studies reported on self-reported scales of mobility and physical performance, eight reported on 'field' tests of physical performance, three on physical activity and physiological measures of physical function. Two studies compared measures of physical function to the reference standard (SF 36 physical function subscale) and four studies provided reliability estimates on measures of physical function. Finally, eight studies related to the impact of measures of physical function on mortality, four on hospitalization and one on the likelihood of continued employment.

We retrieved three observational studies relating SF36 to SF12 and to mortality [84, 107, 108]. These three studies consistently found a very good association between SF36 and SF12, both for the physical component score (PCS) as for the mental component score (MCS). There was a strong association between the PCS of both the SF36 and SF12 and mortality, but far less for the MCS.

Comparison of assessment methods to the reference standard. The SF36 PCS, a self-reported measure of physical function, was used as the reference standard. Altintepe *et al.* [109] in a study of 125 older dialysis patients and 61 age-matched controls found that the Rivermead mobility index, a self-reported assessment of mobility, correlated strongly with the SF36 PF ($r = 0.794$, $P = 0.0001$). Kutner *et al.* [101] assessed gait speed (field test) in 752 prevalent HD patients in the USA. Lower gait speed at baseline was associated with lower SF36 PCS scores after 12 months (estimated change = −8.20 (95% CI: −13.57 to −2.82). These studies suggest that both self-reported and field measures of mobility and physical performance are comparable to the reference standard. These studies were, however, small in size. The findings from these studies may therefore not be generalizable. In addition, the cohort described by Kutner *et al.* [101] was not exclusively drawn from the older population (age range = 20–92 years) and selection criteria for frailty were unclear. Painter and Roshanravan. [87] assessed the role of exercise on functional status as assessed by gait speed, STS test and 6-min walk, in a cohort of 286 HD patients. There was a significant increase in the functional scores in the intervention group, in tandem with changes in SF36 physical scales. There were no direct comparisons between the functional and SF36 scores, in this study. None of the studies compared physiologic measures of physical function or physical activity with the reference standard.

Which measures of physical function are reliable in older/frail patients with advanced CKD?. Four studies reported on the reliability of measures of functional status in older CKD patients. In a cohort of 39 HD patients (mean age 60.3 ± 15.8 years), Segura-Orti and Martinez-Olmos. [103] reported good test–retest reliability for field tests of mobility including the STS, 6-min walk and the one leg heel rise tests as well as the more physiologic measure of handgrip strength. Saito and Jassal. [99] found that the STS test showed good inter-rater as well as test–retest reliability in a small cohort of older dialysis patients. It was also shown to correlate strongly ($r = 0.875$, $P = 0.000$) with the gold standard functional independence measure, which assesses dependence with activities of daily living. Kutsuna *et al.* [95] developed a questionnaire evaluating disability in the activities of daily living in the upper extremities of HD patients (QDUE-HD). QDUE-HD was found to have good reliability and correlated significantly with hand grip strength. This tool is, however, limited in ability to assess the functional status as it assesses the upper extremities only.

Farrokhi and Jassal. [91] used an abbreviated four-item scale as a self-reported measure of physical performance in older dialysis patients. It was shown to have good internal consistency and 78% agreement with the Barthel index.

The ability of functional assessment methods to predict clinical outcomes in older patients with advanced CKD. Seven studies provided information on the relationship between functional status and mortality. Five of them found that functional status as assessed by self-reported measures was associated with mortality [91, 94, 97, 101, 104]. Three studies found that functional status as assessed by 'field' tests, including gait speed and the 6-min walk test, was associated with mortality [97, 101, 105]. Lopes *et al.* [102] reported an association between lower aerobic activity, as measured by the rapid assessment of physical activity (RAPA) questionnaire and mortality.

Three studies reported on the association between functional status and hospitalization. In two of the studies [101, 105], functional status was assessed by field tests. The other study evaluated functional status using self-reported measures [104]. Conversely, Lo *et al.* [100] reported a decline in functional status after hospitalization, as measured by basic activities of daily living, Lawton Brody Instrumental Activities of Daily Living score, timed up-and-go and handgrip tests.

Kutner *et al.* [93] used the human activity profile to assess the functional status in a cohort of 585 dialysis patients. Higher scores (reflecting higher physical activity and energy expenditure) were associated with an increased likelihood of continued employment.

Roshanravan *et al.* [85, 86] assessed the association between frailty and mortality in large cohorts of patients with CKD stages 1–4, finding increasing frailty with increasing CKD stage, and increasing mortality with increasing frailty. However, only a small portion of this cohort fitted to our target population of older patients with advanced CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2), so these studies were not included in the data extraction.

Examples of functional assessment tools (adapted from Painter and Marcus [83])

Measures of physical function	Examples
Measures of physiological impairment	Oxygen uptake Exercise tests Muscle function—strength, endurance
Measures of mobility and performance capacity	Field tests – 6-min walk – gait speed – timed up and go – Repeated chair stands (STS) Self-reported tests – Katz activities of daily living (ADL) – Lawton ADL – SF36 PF scale
Measures of physical activity	Self-report Accelerometry Step counters

How did we translate the evidence into the statement?

There are many assessment tools for physical function due to its multidimensional nature. The current studies addressing the question are limited by their observational nature. In addition, not many studies have looked at the reliability and validity of these tools exclusively in older patients with CKD. In general,

the quality of the underlying evidence base is thus low. However, the available data are consistent within our target population, and also with data from other populations (non-older patients and/or patients without CKD stage 3b or higher).

We recommend a simple score be used on a regular basis to assess functional status in older patients with CKD stage 3b–5d) with the intention to identify those who would benefit from a more in-depth geriatric assessment and rehabilitation program.

All studies consistently indicate that there is a high prevalence of frailty and low functional status in older patients with advanced CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2). All studies consistently indicate that there is an association of low functional status or frailty with mortality.

There is evidence that an individualized management approach can improve frailty, and potentially mortality, QoL or other patient-relevant outcomes. Screening for the presence or development of frailty or functional deterioration is worthwhile to identify patients at risk who should be further evaluated by an experienced physician and/or multi-disciplinary team.

We recommend that most simple scores, including self-reporting scales and field tests (STS, gait speed or 6-min walk test) have similar and sufficient discriminate power to detect patients with decreased functional status.

The evidence indicates that all simple scores and tests perform reasonably well. There is no evidence that a specific functional assessment tool stands out and should be specifically recommended for this particular cohort. Self-reported measures of physical performance have the advantage of being simple and easy to use. There is evidence that they are reliable with good internal consistency and are predictive of adverse outcomes including mortality and hospitalization. It is unclear, however, how sensitive these tools are to changes over time.

Field tests of mobility and physical performance such as STS, gait speed and 6-min walk tests have been validated in cohorts that include older CKD patients. They have been shown to have good test–retest and inter-rater reliability, while also being predictive of adverse outcomes. They have also been shown to respond to interventions aimed at improving the functional status. Low physical activity as assessed by RAPA is associated with mortality in dialysis patients, but there are no data on reliability. Physiologic measures such as grip strength and VO_2 max are difficult to incorporate in clinical practice and, therefore, likely to have a limited role in the assessment of physical function, especially in older or frail patients. It is, therefore, suggested that functional decline in older patients with CKD can feasibly be assessed using a combination of self-reporting and field tests.

What do other guidelines state?

There are no guidelines for functional assessment in this specific patient population.

Recommendations for future research

Validate field tests and self-reported physical performance in larger cohorts from different nationalities, ethnicities, cultural and financial background.

Q4b: Are interventions aimed at increasing functional status in older patients with renal failure (eGFR <45 mL/min/1.73 m^2 or on dialysis) of benefit?

4b.1 We recommend that exercise has a positive impact on the functional status of older patients with CKD stage 3b or higher (1C).

4b.2 We suggest that exercise training be offered in a structured and individualized manner to avoid adverse events (2C).

Advice for clinical practice

- 'Individualized' means that the prescription is tailored to the needs and capacities of the patient. This can ideally be achieved by involving a clinical physiotherapist to prescribe an ideal mix of strength and endurance exercises on a regular basis and within the physical limits of the patient.
- Combined strength and endurance exercise should be provided on a regular basis.
- In patients on HD, exercise training can be undertaken during the dialysis session.
- Regular follow-up is important in order to optimize adherence and adjust the exercise intensity.
- The evidence on the positive outcome of exercise tends to originate from programs benefitting from intensive involvement of motivated physiotherapy teams.
- There is little evidence that augmented dialysis improves the functional status in the absence of multidisciplinary physiotherapy and nutritional interventions.
- Why this question?

There is a high prevalence of frailty in the older population with advanced CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2). In frail patients with CKD the risk of death is three times higher among patients with weight loss and two times higher among those with physical inactivity.

In patients with CKD, there are data supporting that higher levels of physical activity are associated with lower risk of death and maintained or improved functional status [88].

Owing to the aging of the CKD population and the associated increase of frailty in this group, it is important to formulate guidelines on how to maintain or improve the functional status in an older patient CKD population. This question will explore existing evidence regarding interventions that effectively improve the functional status in frail older people with advanced CKD stages 3B or higher (eGFR <45 mL/min/1.73 m^2) including those on maintenance dialysis.

What did we find?

We retained 8 publications [95, 110–116] from a total of 516 articles retrieved by our search and based on personal

awareness of specific publications. In the final selection stage, we excluded studies in which patients' mean age was <60 years. In five studies, patients' mean age was between 60 and 70 years of age, in two studies between 70 and 80 years and in one study over 80, which was a paper reporting results from an older patient subgroup of a larger study. Six of the studies were in patients on HD, one study was in patients either on HD or on PD and one in patients with CKD stage 4–5. One study was an RCT [111], and the others were observational. There were two long-term studies with observation periods of 2 [111] and 5 [110] years, respectively. Three studies had observation periods of 6 months, two of 12 weeks and one of 6 weeks. We also retrieved one Cochrane review [117] and one systematic review [88] that analyzed the effects of exercise in adult patients with chronic disease in general, but not specifically focussed on our population of older patients with CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2).

Type of interventions. In six studies, the exercise training prescribed was a combination of resistance exercises and endurance training such as cycling on a bicycle ergometer or walking, while in two studies the intervention was purely muscle training. In four studies, the exercise training was intradialytic, performed within the first 2 h of hemodialysis, in three of the studies it was performed before the HD session and in one of these studies the patients were also recommended to walk on non-dialysis days. In the non-dialysis CKD stage 4–5 patients it was performed at the hospital gym. In three studies, the exercise training was performed three times per week and in the remaining five studies twice a week. All exercise regimes were carefully designed and monitored, often using the rate of perceived exertion to maintain an adequate level of intensity never exceeding moderate exertion.

Type of outcomes reported. Generally, there was a diverse collection of outcomes, although most studies report some measure of endurance and muscle strength, usually quadriceps and/or handgrip strength. Apart from testing actual physical function, five studies also had a questionnaire for self-reported physical function and health-related QoL. The following outcomes were reported in one or more studies. *Overall endurance*: W_{max} bicycle ergometer until exhaustion; walking distance in meters during 6-min walk test; WALK test, consisting of: walking speed in seconds of a 50 m walk, climbing speed in seconds of 22 steps, descent speed in seconds of 22 steps and finally walking speed in seconds of 50 m; gait speed in seconds during a 4-m walk—part of the Short Physical Performance Battery (SPPB). *Muscular endurance and fatigue*: STS 60 (number of STS transfers performed in 60 s); STS10 (time to perform 10 transfers from STS); timed up and go; five chair stands (part of SPPB). *Neuromuscular exercise function/strength*: abdomen and back; maximal strength in the quadriceps muscle; maximal static and dynamic endurance in quadriceps muscle as well as maximal strength; range of motion in the upper extremities; biceps strength; triceps strength; handgrip strength; palmar pinch and key pinch; standing in tandem and on one leg as part of the SPPB; sit and reach test; self-reported physical function and/or health-related QoL: SF 36; sickness impact profile; walking impairment questionnaire; own questionnaire.

There were no studies assessing the impact of exercise on mortality or major comorbidity. It was often not reported whether changes were sustained after cessation of the program.

How did we translate the evidence into the statement?

Quantity and quality of evidence. The majority of studies had small numbers of patients. Altogether just over 150 patients started exercise training. There was a good spread between short-term and long-term follow-up. All but one of the studies were in patients on HD, only one study was in patients with CKD stage 4–5. In the one randomized control study, the number of patients eventually randomized comprised 20% of the patients originally assessed, so although the actual randomization process was adequate, there is a risk of selection bias among the patients who were randomized. In the six controlled studies allocation of exercise training was pragmatic. It was allocated according to dialysis shift in two studies, according to patient preference in three studies, and in one the allocation process was not described. In all these studies there is a risk of selection bias. All investigators provided inclusion and exclusion criteria and baseline data showing no significant differences between index and control groups, respectively. All studies clearly describe the intervention and the outcomes.

Consistency of evidence. Although the studies are small, there is a consistency in reporting beneficial effects of exercise training in HD patients and the ability of these patients to maintain their physical function over time. In the one study in patients with CKD stage 4–5 there were two exercising groups and two control groups: one uremic group and one age-matched healthy group. Both the uremic and healthy exercise groups showed similar beneficial effects of exercise training with similar effects on outcomes. None of the studies reported any adverse events or negative effects, which supports the safety and feasibility of exercise training in the patients studied, though all patients had been carefully screened by a physician before participation. Older patients with CKD were able to respond with an increased physical function to exercise training. In the general CKD population, exercise was also associated with improvement in physical fitness, walking capacity, cardiovascular dimensions (e.g. blood pressure and heart rate), health-related QoL and also some nutritional parameters in adults with CKD [88, 117].

Effect size and relevance of available outcomes. The primary goal of the studies was to measure the effects of a prescribed exercise-training program. All studies used several different relevant outcome measures to achieve this. There is, however, a relatively large spread in outcomes measured.

> We recommend that exercise has a positive impact on the functional status of older patients with CKD stage 3b or higher.

Available evidence supports that in CKD patients who actually perform exercise, there is a positive impact on their physical, functional and psychological wellbeing. However, studies are small and have a high risk for selection bias. It is also unclear

how far improvement in the functional status was, such that it allowed or restored the ability to live independently. We did not retrieve any study reporting adverse events related to the exercise. In the general CKD population, exercising is also associated with improved outcomes. In older patients with advanced CKD stage 3b–5 (eGFR <45 mL/min/1.73 m^2), who are motivated to do so, exercising adapted to their physical capacity can be of benefit, and seems to be safe.

We suggest that exercise training be offered in a structured and individualized manner to avoid adverse events.

It is important to notice that in all studies, the exercise program was followed up closely by a team, including a physiotherapist. Most studies adapted the intensity of the exercise to the individual capacity of the patient. It cannot be excluded that both the positive impact and the absence of adverse events are due to this multi-disciplinary approach. Therefore, the guideline development group suggests that exercise programs are supervised by a physiotherapist as a part of structured multidisciplinary program.

What do other guidelines state?

The KDIGO CKD Work Group [55] guideline states in chapter 3: 1–150.3.1.21: *We recommend that people with CKD be encouraged to undertake physical activity compatible with cardiovascular health and tolerance (aiming for at least 30 minutes 5 times per week), achieve a healthy weight (BMI 20 to 25, according to country specific demographics), and stop smoking. (1D)*

Recommendations for future research

(1) There is a need to determine which clinical tests are simple and efficient measures of physical functioning to better and more accurately assess the effects of exercise training.

(2) There is a need for better definitions of different aspects of functional status, such as ability to live independently.

(3) There is a need for RCTs or well-performed prospective observational studies comparing the effects of different exercise training regimes. A number of RCTs on exercise on dialysis, though not restricted to older patients, are currently underway.

(4) The long-term effects of exercise training need to be studied with special focus on the ability of patients to sustain exercise training over time and whether this also results in a persisting improvement of physical function over time.

Q5a: Which is the best alternative to evaluate nutritional status in older patients with advanced CKD 3b or higher (eGFR <45 mL/min/1.73 m^2) or on dialysis?

5a.1 We recommend the SGA as the gold standard to assess nutritional status of older patients with CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2) (1C).

5a.2 We suggest that in older patients on HD, a score including serum albumin, BMI, serum creatinine/BSA and normalized protein nitrogen appearance nPNA) may be used to assess nutritional status (2D).

Why this question?

There are important nutritional deficiencies in patients with advanced CKD stage 3b (eGFR <45 mL/min/1.73 m^2) in response to metabolic defects, chronic inflammation, loss of appetite, repeated surgical interventions or episodes of infection [118]. This may lead to a state called protein-energy wasting, which is reported in 20–60% of patients just before the start of RRT [119]. Further impairments occur during the dialysis stage (5d). Nutritional status is a strong predictor of survival in patients starting or receiving chronic dialysis [120]. Older patients, in particular, have a high risk for wasting since they have a reduced appetite, including aversion for protein, often accompanying multiple comorbidities (diabetes, vascular disease, strokes and cancer) and are prone to social isolation and depression. Since the mean age at dialysis initiation continues to increase (~70 years in Western Europe [121]), it seems of importance to identify reliable tools to assess nutritional status and diagnose protein-energy wasting. Such tools should be easy to use in a routine clinical basis, so that patients at risk can be identified for further assessment and management.

To address this question, we searched for evidence to underpin the hypothesis that in patients with advanced CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2), subjective global assessment SGA can be accepted as the gold standard to assess nutritional status, implying that (i) it is associated with mortality and morbidity and/or other more elaborate nutritional scores and (ii) changes in SGA reflect changes in nutritional status.

Next, we searched for other more easily applied scores that associate with SGA and that can be used on a regular basis for screening.

What did we find?

We identified 1028 articles and finally selected 14 papers. The reasons for rejecting papers were: lack of gold standard as a comparator, and inadequate or insufficient nutritional information.

SGA was measured in 14 studies and compared with malnutrition inflammation score (MIS) [122–126], geriatric nutritional risk index (GNRI) [125], malnutrition screening tool [127], anthropometry [126, 128–134], handgrip strength [134], total body nitrogen [135], total body potassium [126], dual X-ray absorptiometry [134], bioimpedance [123, 129, 131, 132], serum albumin [126, 128, 130, 131, 133] and other biochemical factors [129, 130, 134].

Data were obtained from patients treated by HD (n = 1075), PD (n = 660) and those not yet on dialysis (n = 220). The mean age of patients ranged between 51 [123] and 70 years [126], and most studies included sufficient numbers of aged patients.

In nearly all studies, SGA was found to be a reliable tool to assess nutritional status. When analyzed cross-sectionally, SGA had a good agreement with protein-energy wasting [123, 124], total body nitrogen [135], serum albumin [128, 129, 132, 134], anthropometry [128, 129, 132] and with bio-impedance [123, 131]. Two

studies did not find clear correlations between SGA and other nutritional markers but were of small size ($n = 48$ [130] and $n = 56$ [126]). One study concluded that SGA had no additional value over a composite of BMI, serum albumin and weight loss pooled together [133].

When reported longitudinally, SGA was more able to correctly identify the change in the nutritional status than GNRI [125].

One study [120] evaluated a new protein-energy wasting (PEW) score based on the nomenclature proposed by the International Society of Renal Nutrition and Metabolism in 2008 [136]. This score, graded from 0 (worse) to 4 (best), was derived from four nutrition parameters: serum albumin, BMI, a normalized serum creatinine value and protein intake as assessed by nPNA. The score was applied to 1443 patients from the ARNOS prospective dialysis cohort. A distinct reduction in survival (5–7%; $P < 0.01$) was observed for each unit decrement in the score grade. More importantly, the 6-month variation in this PEW score also strongly predicted patients' survival ($P < 0.01$).

A number of studies reported an increasing incidence of PEW with age, suggesting that dietary surveillance should be carried out more rigorously in older patients.

The quality of studies was judged adequate (two), intermediate (four) or poor (eight), resulting in an overall limited quality of evidence.

How did we translate the evidence into statements?

We recommend the SGA as the gold standard to assess nutritional status of older patients with CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2) (1C).

Most of the retrieved studies demonstrate that SGA provides an acceptable estimate of nutritional status, is related to patient relevant outcomes (mortality and morbidity) and is sensitive enough to capture changes in nutritional status reliably. SGA is relatively easy to perform within an acceptable time frame and can thus be used on a recurrent basis. Therefore, the guideline development group suggests the use of SGA as a gold standard for routine assessment of nutritional status.

We suggest that in older patients on HD, a score including serum albumin, BMI, serum creatinine normalized to BSA and nPNA may be used to assess nutritional status (2C).

Specifically for older patients on dialysis, this score has the advantage that all the individual components can be derived from easily available laboratory or anthropometric measures, making it suitable for automatization. The score has an acceptable predictive value for mortality, and an improvement is associated with an improvement in the outcome. External validation is still lacking however.

What do other guidelines say?

No other guidelines provide guidance for this specific patient group.

Recommendations for future research

The International Society for Renal Nutrition and Metabolism released a protein energy wasting nomenclature in 2008 [136]. Four groups of parameters were identified (biochemistry, body composition, muscle mass and nutrient intake). However, these targets were not identified from older cohorts of patients. Research should address whether these parameters apply to older CKD patients as well. External validation of the ISNRNM (DF) score in HD patients should be performed.

Q5b: Which interventions are effective in improving nutritional status in older/frail patients with advanced CKD (eGFR <45 mL/min/1.73 m^2) or on dialysis?

5b.1 We suggest a trial of structured dietary advice and support with the aim of improving nutritional status (2C).

Advice for clinical practice

- Preserving nutritional status should prevail over any other dietary restriction
- There is insufficient evidence to prefer intravenous (intradialytic) nutritional support over oral nutritional support
- Correcting metabolic acidosis by oral supplementation is safe and cheap.

Why this question?

Complications involving malnutrition or protein-energy status are relatively common in CKD patients and contribute to morbidity and mortality [118]. Clinical assessment and management of malnutrition are unmet needs in this population. The prevalence of malnutrition may differ according its definition, either based on serum albumin (ranging 20–45%), clinical (SGA and BMI) or instrumental [bio-impedance assessment (BIA) and dual energy X-ray absorptiometry (DEXA)] evaluation (ranging 18–20%) [119]. Improvements in nutritional status were reported to improve clinical outcome, but, although a great variety of nutritional, pharmacological and dialytic interventions have been suggested, hard evidence from well-controlled and sufficiently powered randomized studies is largely lacking. Patients with advanced CKD (eGFR <45 mL/min/1.73 m^2) are often placed on restrictive diets (protein, potassium, phosphate, fat, etc.). These dietary restrictions come for older patients on top of many other factors potentially decreasing adequate nutritional intake, such as acute or chronic diseases, dental problems, polypharmacy, cognitive problems, impaired ability to prepare meals, depression, social deprivation, lack of dexterity in preparing and eating meals. As a consequence, there is uncertainty and disagreement on optimal nutritional care for the older patient with advanced CKD. There is thus a need for a step-by-step plan to correct malnutrition in older/frail patients with advanced CKD (eGFR <45 mL/min/1.73 m^2) based on available evidence.

What did we find?

In the screening stage, 1028 abstracts were evaluated; only 94 (9.1%) were selected for the assessment stage and 26 were finally useful for quality assessment and data extraction. One study

was excluded because it was only a study protocol [137]. Among the remaining studies, only eight were RCTs [138–145], the others being prospective interventional, non-randomized, cross-sectional or retrospective cohort studies.

The included studies showed no consensus about the definition of nutritional status or about which nutritional parameters need to be addressed or are relevant in this population. As a consequence, many different outcomes are reported as clinical end points, many of them surrogate biochemical markers, such as serum albumin, or composite markers such as SGA.

In the reported papers, two kinds of interventions were tested to potentially improve nutritional status:

(1) oral or intravenous nutritional supplements

(2) pharmacological interventions

Nutritional supplements: oral. Oral nutritional supplements were used in many of the reviewed studies [139, 140, 142–150]. Patient selection was based on low serum albumin [139, 143, 146–148], SGA results alone [142] or low albumin and SGA [150] or both SGA and HD prognostic nutrition index (HD-PNI) [149].

The nature of oral supplement used differed between studies: oral amino acid supplementation, 4 g twice a day for 6 months [139]; 200-kcal packets of a nonprotein calorie supplement containing 30 g maltodextrin and 8 g oil creamer, one packet daily at breakfast, for 24 weeks [145]; branched-chain amino acids, 12 g/day for 6 months [146]; a mixture of protein (16.6 g), carbohydrate (52.8 g) and fat (22.7 g), with a total of 475 calories in each dialysis session, for 6 months [147]; two mixtures administered at each dialysis session for 4 weeks, one containing 355 calories and 14.8 g protein per can, including maltodextrin, medium-chain triglycerides, borage oil, and refined and deodorized fish oil, the second protein (16.6 g), carbohydrate (52.8 g.) and fat (22.7 g.), with a total of 475 calories [148]; a comparison of two kinds of supplementation, a mixture of protein (16.6 g), carbohydrate (52.8 g) and fat (22.7 g), with a total of 475 calories versus extra calorie supply of 67.2 kcal and 16.8 g of protein daily [142]; a comparison of an high protein diet (1.4 g natural protein/kg target weight/day and 35 kcal/kg target weight/day); a calcium caseinate (0.7 g calcium caseinate plus 0.7 g natural protein diet/kg target weight/day and 35 kcal/kg target weight/day [143]; 500 kcal and 18.75 g of protein, as well as carbohydrates, lipids, minerals, trace elements and vitamins, daily for 3 months [150]; a fat supplementation based on 5.1 g of saturated fatty acids, 26.5 g of monounsaturated fatty acids, 15.5 g of polyunsaturated fatty acids (PUFA), of which 3.0 g were marine n-3 PUFAs and 1.8 MJ (430 kcal) per day [144]; and oral bicarbonate supplementation [140, 151].

In almost all papers a statistically significant improvement in surrogate nutritional parameters was reported, mainly increased serum albumin [139, 143, 146, 148], albumin and SGA [147], albumin but not SGA [150], or nutritional index [149]. Correcting metabolic acidosis by oral administration of bicarbonate appeared safe and improved serum albumin [151] and SGA [140].

Intradialytic parenteral nutrition (IDPN). The feasibility and clinical effectiveness of IDPN were evaluated in five studies [141, 152–155]. As for oral supplementation, also for IDPN different kinds of infusions and administration regimes were used: in a long-term study, lasting 9 months, a total supply of 1 L contained 35 g of amino acids, 50 g of lipids and 125 g of glucose, corresponding to an administration of 1140 kcal during each HD session [152]; a lower IV volume of 600 mL containing 200 mL of dextrose 50%, 200 mL of essential amino acids and 200 mL of lipid emulsion providing 800 kcal and 14.1 g of protein in each dialysis [154]; amino acid supplementation with intradialytic administration of 500 mL of 10% solution [153]; and amino acids (12 g/h), a glucose 15% solution (37.5 g/h) and a fat emulsion (12.5 g/h) [155].

All these studies reported improvement in serum albumin [153, 154], prealbumin [152], albumin and SGA [153]; we found only one RCT of acceptable quality comparing oral nutritional supplements with or without 1 year of IDPN [141]. Both groups demonstrated improvement in BMI and the nutritional parameters serum albumin and prealbumin. The latter independently predicted a 54% decrease in 2-year mortality, as well as reduced hospitalizations and improved Karnofsky score. However, no definite advantage of adding IDPN to oral nutritional supplementation was found. This is so far the first and only report showing that an improvement in prealbumin during nutritional therapy is associated with a decrease in morbidity and mortality in malnourished HD patients.

Pharmacological interventions. We found only low-quality, largely anecdotal studies on the effects of pharmacologic interventions on nutritional status, such as recombinant growth hormone (rhGH) [138, 156] or nandrolone decanoate [157].

rhGH was investigated in two small groups (eight and six patients, respectively) [138, 156]. Five milligrams of rhGH was administered subcutaneously at the end of each dialysis session for 6 weeks [156] showing an increase in muscle protein synthesis and by a decrease in the negative muscle protein balance. In another study, 0.2 IU/kg/day of rhGH was used [138] showing an anabolic reaction and weight gain.

Nandrolone decanoate was administered in CKD patients intramuscularly at the dose of 100 mg/week for a duration of 3 months, resulting in an anabolic effect on lean body mass without significant changes in dietary protein intake, serum lipid levels, hematocrit and renal function; however, serum albumin decreased [157]. All these experiences need to be considered as pilot studies and require to be confirmed in larger populations studied over longer and more relevant time periods.

Dietetic care. Although it appears logical to accept that care by a dietician may improve nutritional status throughout the course of CKD, we retrieved only one paper on the role of follow-up by a dietician [158]. There was an association between predialysis follow-up by a dietician and higher albumin and lower total cholesterol levels at dialysis therapy initiation. The results suggest an independent association between longer than 12 months predialysis care by a dietician and improved survival during the first year on dialysis therapy.

Mortality. We did not find papers addressing the impact of nutritional intervention on the hard outcome of mortality. We found one paper where an improvement in prealbumin

as a consequence of the intervention was associated with an improved survival, but this paper did not analyze improvement in mortality as an intention to treat by the intervention itself.

How did we translate the evidence into the statement?

Malnutrition and protein energy wasting are prevalent in older patients with advanced CKD (eGFR <45 mL/min/1.73 m^2) and are associated with mortality [118–120].

Avoiding malnutrition by a careful assessment and management of potential underlying causes is therefore warranted.

It is, however, unclear which interventions are most effective. Quantity and quality of evidence in this field are quite poor. There is only a limited number of RCTs, most papers deal with only single-center observations with low patient numbers and short follow-up. Only surrogate outcome parameters have been reported. It is difficult to synthesize the evidence because of different inclusion criteria and different outcomes being used. Moreover, there is no consensus about the definition of nutritional status or which nutritional parameters need to be addressed or are relevant in this population, so it is difficult to assess suitability and effect of interventions. Furthermore, there is a link between malnutrition and inflammation/protein-energy wasting, making it in most cases difficult to discriminate cause and effect.

What do other guidelines state?

There are no guidelines for this specific patient group.

Recommendations for future research

(1) Assessment of the impact of correction of metabolic acidosis by oral supplementation of $NaHCO_3$ on mortality, morbidity and general functional status of older patients with advanced CKD (eGFR <45 mL/min/1.73 m^2).

(2) Assessment of the impact of oral supplementation of calories and/or protein on mortality, morbidity and functional status in older patients with advanced CKD (eGFR <45 mL/min/1.73 m^2).

(3) Assess whether interventions have the same effect size in malnourished patients (to restore nutritional status) as in non-malnourished patients (to prevent *de novo* malnourishment).

Q6: What is the benefit of dialysis in frail and older patients?

6.1	We recommend the use of validated tools as explained in Q2 and Q3 to project likely outcomes and help decide the appropriateness of discussing options for RRT (see Figure 2).
6.2	We recommend that the option for CM be discussed during the shared decision-making process on different management options for ESKD (1D).
6.3	We recommend that the REIN score can be useful to stratify mortality risk of patients intending to start RRT (1C).

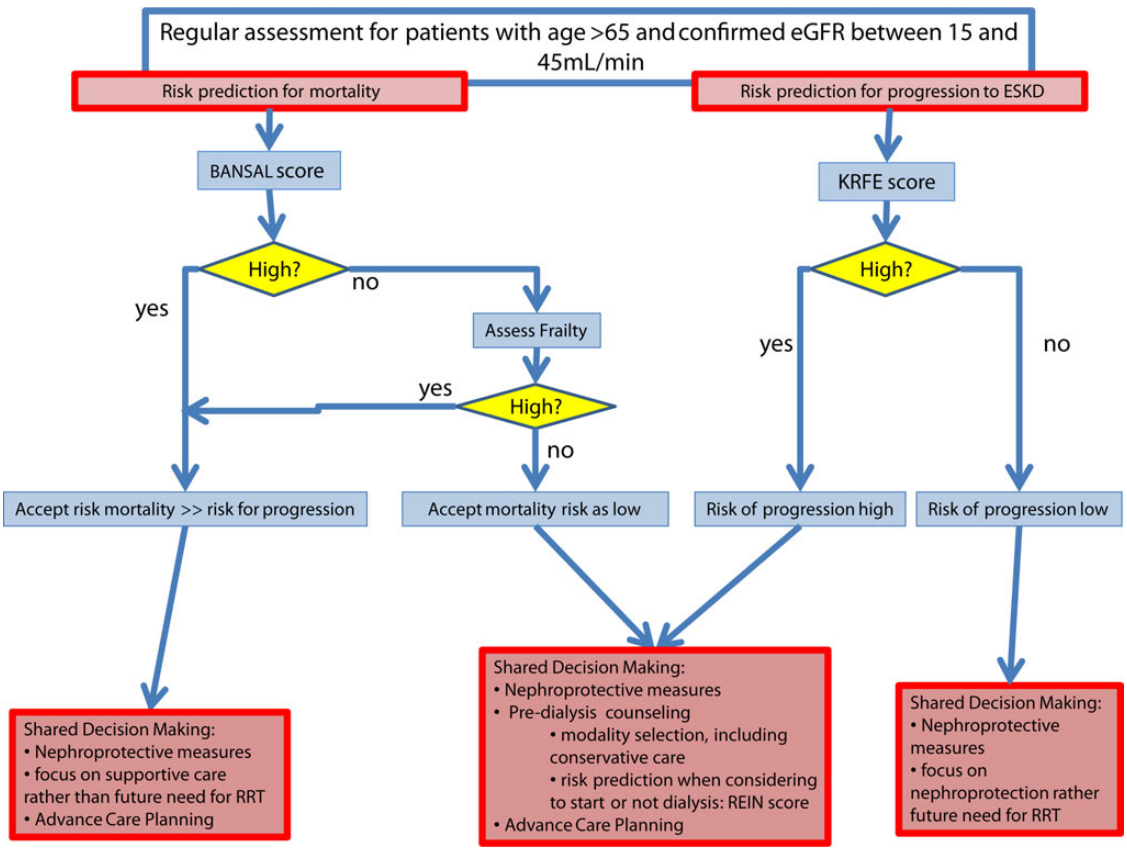

FIGURE 2: Decision flow chart when managing older patients with CKD stage 3b (eGFR <45 mL/min/1.73 m^2).

Advice for clinical practice

(1) Evidence on this topic derives from observational studies only.

(2) Patients can have difficulties in correctly understanding probabilities, life expectancies, QoL impact and the experience of being on dialysis. Using patient-friendly tools [159] to visualize the concepts and messages can improve patient understanding of the implications of different treatment options.

(3) Multidisciplinary assessment of older patients with stage 5 CKD should include cognitive function, frailty, comorbidities, and nutritional, functional and psychosocial factors.

Why this question?

Over the last few decades, the number of older people with ESKD has increased dramatically. Alongside this, the number of older patients receiving dialysis treatment has also increased [121]. Mortality rates are high among all dialysis patients, and with increasing age, mortality rates increase even more steeply. A substantial part of that mortality is due to dialysis withdrawal [160], and increase of withdrawal rates parallels the increase of dialysis incidence in older patients. Undertaking dialysis affects QoL, and providing some symptom relief comes at the cost of significant burdens for the patient, and their families and carers.

Decisions about whether to receive dialysis or not should take place some considerable time before dialysis is necessary (Figure 2). As discussed in previous sections, it has become difficult to know at what stage the mortality risk of undertaking dialysis outweighs the risk of mortality without dialysis. Decisions about whether any potential additional longevity is justified by the rigours of the treatment are even more difficult to quantify.

Thus the decision about the appropriateness of offering dialysis to patients with frailty, advanced age and comorbidity has been studied and wide discrepancy in clinician, patient and carer choices has been demonstrated. Therefore, this question was asked as part of this guideline to try to support clinicians faced with this common, complex and challenging clinical decision.

What did we find?

We did not find any RCTs comparing dialysis and nondialysis treatment of renal failure in older patients; therefore, evidence on this topic derives from observational studies only. We found plenty of descriptive cohort studies of older patients starting dialysis. These were not included in our analysis as such data are readily available in registry reports and they do not add knowledge on the fate of similar patients who did not start dialysis. We found 14 cohort studies comparing outcomes in patients undertaking dialysis versus CM and 6 cohort studies of outcomes in advanced kidney disease treated with CM with no comparator [161–180]. There have also been two systematic reviews on the subject [181, 182].

All the studies were of variable size and quality, with populations defined by different criteria, measuring different outcomes over different time periods in different eras. There is no consistent definition of the concept of CM. The majority of studies defined patients according to age; in only one study was a measurement of frailty undertaken. Mortality rates were reported in almost all the studies. The effect of comorbidity and functional status on survival was also commonly reported. Other outcomes such as QoL were frequently reported. The criteria by which patients were allocated to dialysis or CM were not always clear or reported. However, if reported, the switching of patients from conservative to active treatment was rare (0–4.7%) [161, 162, 164–166, 169, 172, 173, 178], and switches from active treatment to CM were more common (5.5–11%) [161, 169, 170, 178]. Other outcomes such as access to palliative care, use of invasive treatments and health economic studies were seldom reported.

Overall, we found that patients on conservative pathways were generally older, with high degree of comorbidity, reduced functional status and an increased prevalence of dementia compared with other groups.

Mortality/survival. This was reported in all studies analyzed except one [171]. The duration of follow-up of cohorts varied from a maximum of 144 [170] to 12 months [177]. In all studies with comparative groups, choosing to receive dialysis was associated with longer survival [161–163, 165, 166, 168–170, 172–178]. However, in every report, the allocation to the RRT group was prone to confounders. For example in many cohorts, the CM patients were older and increasing comorbidity was usually, but not always [178], more prevalent among the CM group. This high comorbidity appeared to underlie the reason for allocation to CM treatment in some studies [176]. In all other series, the reasons for allocation to receive RRT or CM were unclear. Hence it is likely that allocation to receive RRT or CM in most studies was biased by indication. For this reason, it is very difficult to quantify the extent of increased survival afforded by choosing RRT. Assessment of this hard outcome measure (mortality) is further complicated by the difficulty in knowing when dialysis would have been started in those who elected not to receive it. This lead-time bias was adjusted for using different methodologies in a number of studies. Most groups adjusted for this by measuring survival from fixed levels of renal function defined by biochemical parameters such as eGFR or creatinine clearance. However, this remains an important confounder, as creatinine is inversely related to outcome in frail patients. It should also be remembered that, in patients choosing dialysis, mortality rates of up to 15–20% were reported, even before the start of this treatment [169, 178]. Therefore, for the reasons outlined above, it can only be stated that in selected older frail patients with advanced kidney disease, there is an extension of longevity associated with choosing to receive dialysis, and this seems to be in the order of 1–2 years.

Comorbidity. The most common methodologies for measuring comorbidity were the Davies/Stoke score and the Charlson comorbidity index (CCI), whereas others used their own scores or sums of original morbidities. However, in all studies

where it was measured, the effect of extended longevity reduced with increasing comorbidity [169, 175, 178]. In two of these three studies, for patients with a CCI of 6 or 8, there was no association with survival advantage when choosing dialysis [169, 175]. In the third study [178], survival was significantly reduced among patients with high comorbidity opting for RRT, although it remained significantly better than for those choosing CM.

Functional status. Eight studies measured functional status [165, 166, 168–170, 173, 175, 176], mostly by Karnofsky score or WHO criteria. In all studies in which this was reported there was an association of reduced functional status with the choice of CM and of reduced longevity. Only one study measured frailty by the Fried phenotype model [173] wherein frailty was more prevalent among those choosing CM, but interestingly progressed over the 42-month study period in both CM- and RRT-choosing groups, with increasing numbers of nonfrail becoming prefrail, and prefrail becoming frail.

QoL and related measures. Among those studies that measured it, QoL data showed little measurable difference between CM and dialysis groups, although a dip in QoL was observed among those choosing dialysis when this treatment was initiated. Symptom burden, psychological health and physical health were studied less, but no discernable differences between CM or active treatment groups were apparent among those studies that reported results in this domain. QoL appears to be well maintained until the last couple of months of life in CM patients [171]. There were significant rates of anxiety and depression among both CM- and RRT-choosing patients, with slightly higher rates among those choosing CM [165, 166, 172, 173]. Disease burden, treatment burden and views on care by patient or carer were not reported in any study.

Hospitalization rates and preferred place of care. Rates of hospitalization for the two groups were not consistent between studies, but in three studies, admission rates were higher for those choosing dialysis [162, 166, 169] and one showed higher rates among CM patients [173, 175] and one no overall difference. One study reported increased likelihood of highly invasive treatments during hospital admission among patients choosing RRT [175].

Preferred place of care and place of death were rarely recorded; disadvantages in this regard were reported to be associated with choosing dialysis and benefits to choosing CM [162, 169, 176].

Other factors. Other important factors that are known to impact on survival/mortality in multiple health domains such as the effects of marital status, social support, educational status and social deprivation were rarely studied [164, 174, 175]. There was a tendency for patients choosing CM to have less family support. In these relatively small studies, there appeared to be no differences in education level among groups choosing CM or RRT.

Health economics. There was only one study with a rudimentary analysis of health economics, wherein each hospital admission was three times as costly for dialysis patients when compared with CM patients [177]; otherwise, no evaluation was undertaken in any study.

How did we translate the evidence in to statement?

We recommend the use of validated tools as explained in Q2 and Q3 to project likely outcomes and help decide the appropriateness of discussing options for RRT (see Figure 2).

In many patients with advanced kidney failure progression is slow and the likelihood is low of their reaching end-stage renal failure before death from other causes. In others their prognosis is poor as a result of multimorbidity. Discussions about RRT in either of these settings may be inappropriate, compromise optimal management and cause patients and their families unnecessary stress. There are validated tools that may help predict risks of progression of kidney failure and mortality risks, which have been discussed in questions 2 and 3, respectively.

We recommend that the option for CM be discussed during the shared decision-making process on different management options for ESKD (Figure 2).

Sufficient data exist to indicate that CM is a viable treatment option for older patients and/or comorbid and/or poor functional status that may not adversely affect survival or QoL. Choosing CM over dialysis might avoid unwanted outcomes such as hospital admissions and improve outcomes such as access to palliative care and receiving care in a preferred place.

We recommend the REIN score to stratify mortality risk of patients intending to start RRT.

The REIN score has been validated externally as having a good calibration and discrimination for risk prediction for mortality in patients starting dialysis. There are no randomized studies in this field, and assuming that mortality in this patient group is equal with or without dialysis, it is reasonable to use the REIN score to inform patients on their short-term mortality risk. The validation study [159] offers a visual tool to help patients understand this risk.

What do other guidelines say?

There are no other guidelines on this specific topic. Available guidelines discuss when to start dialysis rather than whether to start dialysis [183].

Recommendations for future research

Multiple gaps in the evidence base remain:

(1) the assessment of frailty as distinct from age, comorbidity and poor functional status;

(2) the effect of socioeconomic class, education, marital status etc. on outcomes;

(3) the method by which patients should be supported in treatment decisions/directed toward treatment choices;

(4) more data are required to estimate the effect of choosing CM versus dialysis on access to associated social and medical support, and service models to consistently allow equity of access to care;

(5) the views of patients and carers on CM are currently largely unknown.

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REFERENCES

1. van der Veer SN, van Biesen W, Bernaert P *et al.* Priority topics for European multidisciplinary guidelines on the management of chronic kidney disease in older adults. *Int Urol Nephrol* 2016; 48: 859–869
2. Levey AS, Eckardt KU, Tsukamoto Y *et al.* Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2005; 67: 2089–2100
3. Van Biesen W, van der Veer SN, Jager KJ *et al.* What guidelines should or should not be: implications for guideline production. *Nephrol Dial Transplant* 2013; 28: 1980–1984
4. Nagler EV, Webster AC, Bolignano D *et al.* European Renal Best Practice (ERBP) Guideline development methodology: towards the best possible guidelines. *Nephrol Dial Transplant* 2014; 29: 731–738
5. Segall L, Nistor I, Van Biesen W *et al.* Dialysis modality choice in elderly patients with end-stage renal disease: a narrative review of the available evidence. *Nephrol Dial Transplant* 2015 Dec 2015. pii: gfv411 [Epub ahead of print]
6. Chazot C, Farrington K, Nistor I *et al.* Pro and con arguments in using alternative dialysis regimens in the frail and elderly patients. *Int Urol Nephrol* 2015; 47: 1809–1816
7. Segall L. Criteria for and appropriateness of renal transplantation in elderly patients with end-stage renal disease: a literature review and position statement on behalf of the European Renal Association-European Dialysis and Transplant Association Descartes Working Group and European Renal Best Practice. *Transplantation* 2016; 100: e55–e65
8. Cross NB, Craig JC, Webster AC. Asking the right question and finding the right answers. *Nephrology* 2010; 15: 8–11
9. Shea BJ, Grimshaw JM, Wells GA *et al.* Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol* 2007; 7: 10
10. Higgins JPT, Altman DG, Sterne JAC. Chapter 8: assessing risk of bias in included studies. In: Higgins JPT, Green S (eds) *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org
11. Wells GA, Shea BJ, O'Connell D *et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses*. www.ohri.ca/programs/clinical_epidemiology/oxford.asp (7 October 2016, date last accessed)
12. Whiting PF, Rutjes AWS, Westwood ME *et al.* QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011; 155: 529–536
13. Guyatt GH, Oxman AD, Vist GE *et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; 336: 924–926
14. van der Veer STC, Jager K, Van Biesen W. Bridging the gap between what we know and what we do in renal medicine: improving the implementability of the European Renal Best Practice guidelines. *Nephrol Dial Transplant* 2014; 29: 951–957
15. Nagler EV, Webster AC, Bolignano D *et al.* European Renal Best Practice (ERBP) guideline development methodology: towards the best possible guidelines. *Nephrol Dial Transplant* 2014; 29: 731–738
16. Verhave JC, Fesler P, Ribstein J *et al.* Estimation of renal function in subjects with normal serum creatinine levels: influence of age and body mass index. *Am J Kidney Dis* 2005; 46: 233–241
17. Lamb EJ, Wood J, Stowe HJ *et al.* Susceptibility of glomerular filtration rate estimations to variations in creatinine methodology: a study in older patients. *Ann Clin Biochem* 2005; 42 (Pt 1): 11–18
18. Peralta CA, Lee A, Odden MC *et al.* Association between chronic kidney disease detected using creatinine and cystatin C and death and cardiovascular events in elderly Mexican Americans: the Sacramento Area Latino Study on Aging. *J Am Geriatr Soc* 2013; 61: 90–95
19. Pizzarelli F, Lauretani F, Bandinelli S *et al.* Predictivity of survival according to different equations for estimating renal function in community-dwelling elderly subjects. *Nephrol Dial Transplant* 2009; 24: 1197–1205
20. Van Pottelbergh G, Vaes B, Adriaensen W *et al.* The glomerular filtration rate estimated by new and old equations as a predictor of important outcomes in elderly patients. *BMC Med* 2014; 12: 27
21. Terpos E, Christoulas D, Kastritis E *et al.* The Chronic Kidney Disease Epidemiology Collaboration cystatin C (CKD-EPI-CysC) equation has an independent prognostic value for overall survival in newly diagnosed patients with symptomatic multiple myeloma; is it time to change from MDRD to CKD-EPI-CysC equations? *Eur J Haematol* 2013; 91: 347–355
22. Rule AD, Bailey KR, Schwartz GL *et al.* For estimating creatinine clearance measuring muscle mass gives better results than those based on demographics. *Kidney Int* 2009; 75: 1071–1078
23. Fontsere N, Esteve V, Saurina A *et al.* The search for a new marker of renal function in older patients with chronic kidney disease stages 3-4: usefulness of cystatin C-based equations. *Nephron Clin Pract* 2009; 112: c164–c170
24. Fontsere N, Bonal J, Navarro M *et al.* A comparison of prediction equations for estimating glomerular filtration rate in adult patients with chronic kidney disease stages 4-5. Effect of nutritional status and age. *Nephron Clin Pract* 2006; 104: c160–c168
25. Koppe L, Klich A, Dubourg L *et al.* Performance of creatinine-based equations compared in older patients. *J Nephrol* 2013; 26: 716–723
26. Liu X, Ma H, Huang H *et al.* Is the Chronic Kidney Disease Epidemiology Collaboration creatinine-cystatin C equation useful for glomerular filtration rate estimation in the elderly? *Clin Interv Aging* 2013; 8: 1387–1391
27. Rimon E, Kagansky N, Cojocaru L *et al.* Can creatinine clearance be accurately predicted by formulae in octogenarian in-patients? *Q J Med* 2004; 97: 281–287
28. Lopes MB, Araujo LQ, Passos MT *et al.* Estimation of glomerular filtration rate from serum creatinine and cystatin C in octogenarians and nonagenarians. *BMC Nephrol* 2013; 14: 265
29. Kilbride HS, Stevens PE, Eaglestone G *et al.* Accuracy of the MDRD (Modification of Diet in Renal Disease) study and CKD-EPI (CKD Epidemiology Collaboration) equations for estimation of GFR in the elderly. *Am J Kidney Dis* 2013; 61: 57–66
30. Dowling TC, Wang ES, Ferrucci L *et al.* Glomerular filtration rate equations overestimate creatinine clearance in older individuals enrolled in the Baltimore Longitudinal Study on Aging: impact on renal drug dosing. *Pharmacotherapy* 2013; 33: 912–921
31. Xun L, Cheng W, Hua T *et al.* Assessing glomerular filtration rate (GFR) in elderly Chinese patients with chronic kidney disease (CKD): a comparison of various predictive equations. *Arch Gerontol Geriatr* 2010; 51: 13–20

32. Zhu Y, Ye X, Zhu B *et al.* Comparisons between the 2012 new CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equations and other four approved equations. *PLoS One* 2014; 9: e84688
33. Levey AS, Stevens LA, Schmid CH *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; 150: 604–612
34. Giannelli SV, Patel KV, Windham BG *et al.* Magnitude of underascertainment of impaired kidney function in older adults with normal serum creatinine. *J Am Geriatr Soc* 2007; 55: 816–823
35. Nyman U, Grubb A, Sterner G *et al.* The CKD-EPI and MDRD equations to estimate GFR. Validation in the Swedish Lund-Malmo Study cohort. *Scand J Clin Lab Invest* 2011; 71: 129–138
36. Pei X, Bao L, Xu Z *et al.* Diagnostic value of cystatin C and glomerular filtration rate formulae in Chinese nonelderly and elderly populations. *J Nephrol* 2013; 26: 476–484
37. Schaeffner ES, Ebert N, Delanaye P *et al.* Two novel equations to estimate kidney function in persons aged 70 years or older. *Ann Intern Med* 2012; 157: 471–481
38. Fehrman-Ekholm I, Skeppholm L. Renal function in the elderly (>70 years old) measured by means of iohexol clearance, serum creatinine, serum urea and estimated clearance. *Scand J Urol Nephrol* 2004; 38: 73–77
39. Evans M, van Stralen KJ, Schon S *et al.* Glomerular filtration rate-estimating equations for patients with advanced chronic kidney disease. *Nephrol Dial Transplant* 2013; 28: 2518–2526
40. Pequignot R, Belmin J, Chauvelier S *et al.* Renal function in older hospital patients is more accurately estimated using the Cockcroft-Gault formula than the modification diet in renal disease formula. *J Am Geriatr Soc* 2009; 57: 1638–1643
41. Bjork J, Jones I, Nyman U *et al.* Validation of the Lund-Malmo, Chronic Kidney Disease Epidemiology (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) equations to estimate glomerular filtration rate in a large Swedish clinical population. *Scand J Urol Nephrol* 2012; 46: 212–222
42. Liu X, Xu H, Zheng Z *et al.* Estimating glomerular filtration rates in elderly Chinese patients with chronic kidney disease: performance of six modified formulae developed in Asian populations. *Clin Interv Aging* 2013; 8: 899–904
43. Marx GM, Blake GM, Galani E *et al.* Evaluation of the Cockroft-Gault, Jelliffe and Wright formulae in estimating renal function in elderly cancer patients. *Ann Oncol* 2004; 15: 291–295
44. Bevc S, Hojs R, Ekart R *et al.* Simple cystatin C formula compared to sophisticated CKD-EPI formulas for estimation of glomerular filtration rate in the elderly. *Ther Apher Dial* 2011; 15: 261–268
45. Dalrymple LS, Katz R, Kestenbaum B *et al.* Chronic kidney disease and the risk of end-stage renal disease versus death. *J Gen Intern Med* 2011; 26: 379–385
46. De Nicola L, Minutolo R, Chiodini P *et al.* The effect of increasing age on the prognosis of non-dialysis patients with chronic kidney disease receiving stable nephrology care. *Kidney Int* 2012; 82: 482–488
47. Faller B, Beuscart JB, Frimat L. Competing-risk analysis of death and dialysis initiation among elderly (>/=80 years) newly referred to nephrologists: a French prospective study. *BMC Nephrol* 2013; 14: 103
48. Drawz PE, Goswami P, Azem R *et al.* A simple tool to predict end-stage renal disease within 1 year in elderly adults with advanced chronic kidney disease. *J Am Geriatr Soc* 2013; 61: 762–768
49. Obi Y, Kimura T, Nagasawa Y *et al.* Impact of age and overt proteinuria on outcomes of stage 3 to 5 chronic kidney disease in a referred cohort. *Clin J Am Soc Nephrol* 2010; 5: 1558–1565
50. Tangri N, Stevens LA, Griffith J *et al.* A predictive model for progression of chronic kidney disease to kidney failure. *J Am Med Assoc* 2011; 305: 1553–1559
51. Johnson ES, Thorp ML, Platt RW *et al.* Predicting the risk of dialysis and transplant among patients with CKD: a retrospective cohort study. *Am J Kidney Dis* 2008; 52: 653–660
52. Johnson ES, Thorp ML, Yang X *et al.* Predicting renal replacement therapy and mortality in CKD. *Am J Kidney Dis* 2007; 50: 559–565
53. Peeters MJ, van Zuilen AD, van den Brand JA *et al.* Validation of the kidney failure risk equation in European CKD patients. *Nephrol Dial Transplant* 2013; 28: 1773–1779
54. Tangri N, Grams ME, Levey AS *et al.* Multinational assessment of accuracy of equations for predicting risk of kidney failure: a meta-analysis. *J Am Med Assoc* 2016; 315: 164–174
55. KDIGO. 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int* 2013; Suppl 3: 1–150
56. Tangri N, Kitsios GD, Inker LA *et al.* Risk prediction models for patients with chronic kidney disease: a systematic review. *Ann Intern Med* 2013; 158: 596–603
57. Moons KG, de Groot JA, Bouwmeester W *et al.* Critical appraisal and data extraction for systematic reviews of prediction modelling studies: the CHARMS checklist. *PLoS Med* 2014; 11: e1001744
58. Carey EC, Covinsky KE, Lui LY *et al.* Prediction of mortality in community-living frail elderly people with long-term care needs. *J Am Geriatr Soc* 2008; 56: 68–75
59. Carey EC, Walter LC, Lindquist K *et al.* Development and validation of a functional morbidity index to predict mortality in community-dwelling elders. *J Gen Intern Med* 2004; 19: 1027–1033
60. Gagne JJ, Glynn RJ, Avorn J *et al.* A combined comorbidity score predicted mortality in elderly patients better than existing scores. *J Clin Epidemiol* 2011; 64: 749–759
61. Han PK, Lee M, Reeve BB *et al.* Development of a prognostic model for six-month mortality in older adults with declining health. *J Pain Symptom Manage* 2012; 43: 527–539
62. Inouye SK, Bogardus ST Jr, Vitagliano G *et al.* Burden of illness score for elderly persons: risk adjustment incorporating the cumulative impact of diseases, physiologic abnormalities, and functional impairments. *Med Care* 2003; 41: 70–83
63. Lee JS, Chau PP, Hui E *et al.* Survival prediction in nursing home residents using the minimum data set subscales: ADL self-performance hierarchy, cognitive performance and the changes in health, end-stage disease and symptoms and signs scales. *Eur J Public Health* 2009; 19: 308–312
64. Lee SJ, Lindquist K, Segal MR *et al.* Development and validation of a prognostic index for 4-year mortality in older adults. *J Am Med Assoc* 2006; 295: 801–808
65. Levine SK, Sachs GA, Jin L *et al.* A prognostic model for 1-year mortality in older adults after hospital discharge. *Am J Med* 2007; 120: 455–460
66. Mazzaglia G, Roti L, Corsini G *et al.* Screening of older community-dwelling people at risk for death and hospitalization: the Assistenza Socio-Sanitaria in Italia project. *J Am Geriatr Soc* 2007; 55: 1955–1960
67. Porock D, Oliver DP, Zweig S *et al.* Predicting death in the nursing home: development and validation of the 6-month minimum data set mortality risk index. *J Gerontol A Biol Sci Med Sci* 2005; 60: 491–498
68. Schonberg MA, Davis RB, McCarthy EP *et al.* Index to predict 5-year mortality of community-dwelling adults aged 65 and older using data from the National Health Interview Survey. *J Gen Intern Med* 2009; 24: 1115–1122
69. Sharifi F, Ghaderpanahi M, Fakhrzadeh H *et al.* Older people's mortality index: development of a practical model for prediction of mortality in nursing homes (Kahrizak Elderly Study). *Geriatr Gerontol Int* 2012; 12: 36–45
70. Walter LC, Brand RJ, Counsell SR *et al.* Development and validation of a prognostic index for 1-year mortality in older adults after hospitalization. *J Am Med Assoc* 2001; 285: 2987–2994
71. Bansal N, Katz R, De Boer IH *et al.* Development and validation of a model to predict 5-year risk of death without ESRD among older adults with CKD. *Clin J Am Soc Nephrol* 2015; 10: 363–371
72. Weiss JW, Platt RW, Thorp ML *et al.* Predicting mortality in older adults with kidney disease: a pragmatic prediction model. *J Am Geriatr Soc* 2015; 63: 508–515
73. Cheung KL, Montez-Rath ME, Chertow GM *et al.* Prognostic stratification in older adults commencing dialysis. *J Gerontol A Biol Sci Med Sci* 2014; 69: 1033–1039
74. Couchoud C, Labeeuw M, Moranne O *et al.* A clinical score to predict 6-month prognosis in elderly patients starting dialysis for end-stage renal disease. *Nephrol Dial Transplant* 2009; 24: 1553–1561
75. Couchoud CG, Beuscart JB, Aldigier JC *et al.* Development of a risk stratification algorithm to improve patient-centered care and decision making for incident elderly patients with end-stage renal disease. *Kidney Int* 2015; 88: 1178–1186

76. Liu J, Huang Z, Gilbertson DT *et al.* An improved comorbidity index for outcome analyses among dialysis patients. *Kidney Int* 2010; 77: 141–151
77. Thamer M, Kaufman JS, Zhang Y *et al.* Predicting early death among elderly dialysis patients: development and validation of a risk score to assist shared decision making for dialysis initiation. *Am J Kidney Dis* 2015; 66: 1024–1032
78. van Diepen M, Schroijen MA, Dekkers OM *et al.* Predicting mortality in patients with diabetes starting dialysis. *PLoS One* 2014; 9: e89744
79. Fried LP, Borhani NO, Enright P *et al.* The Cardiovascular Health Study: design and rationale. *Ann Epidemiol* 1991; 1: 263–276
80. McAdams-DeMarco MA, Law A, Salter ML *et al.* Frailty as a novel predictor of mortality and hospitalization in individuals of all ages undergoing hemodialysis. *J Am Geriatr Soc* 2013; 61: 896–901
81. Rockwood K, Song X, MacKnight C *et al.* A global clinical measure of fitness and frailty in elderly people. *Can Med Assoc J* 2005; 173: 489–495
82. Guiding principles for the care of older adults with multimorbidity: an approach for clinicians: American Geriatrics Society Expert Panel on the Care of Older Adults with Multimorbidity. *J Am Geriatr Soc* 2012; 60: E1–E25
83. Painter P, Marcus RL. Assessing physical function and physical activity in patients with CKD. *Clin J Am Soc Nephrol* 2013; 8: 861–872
84. Dalrymple LS, Katz R, Rifkin DE *et al.* Kidney function and prevalent and incident frailty. *Clin J Am Soc Nephrol* 2013; 8: 2091–2099
85. Roshanravan B, Khatri M, Robinson-Cohen C *et al.* A prospective study of frailty in nephrology-referred patients with CKD. *Am J Kidney Dis* 2012; 60: 912–921
86. Roshanravan B, Robinson-Cohen C, Patel KV *et al.* Association between physical performance and all-cause mortality in CKD. *J Am Soc Nephrol* 2013; 24: 822–830
87. Painter P, Roshanravan B. The association of physical activity and physical function with clinical outcomes in adults with chronic kidney disease. *Curr Opin Nephrol Hypertens* 2013; 22: 615–623
88. Heiwe S, Jacobson SH. Exercise training in adults with CKD: a systematic review and meta-analysis. *Am J Kidney Dis* 2014; 64: 383–393
89. Kutner NG, Lin LS, Fielding B *et al.* Continued survival of older hemodialysis patients: investigation of psychosocial predictors. *Am J Kidney Dis* 1994; 24: 42–49
90. McClellan WM, Abramson J, Newsome B *et al.* Physical and psychological burden of chronic kidney disease among older adults. *Am J Nephrol* 2010; 31: 309–317
91. Farrokhi F, Jassal SV. Routine use of an abbreviated 4-item scale to assess dependence in essential activities of daily living amongst elderly hemodialysis patients: a validation study. *Int Urol Nephrol* 2013; 45: 259–264
92. Bowling CB, Muntner P, Sawyer P *et al.* Community mobility among older adults with reduced kidney function: a study of life-space. *Am J Kidney Dis* 2014; 63: 429–436
93. Kutner NG, Zhang R, Allman RM *et al.* Correlates of ADL difficulty in a large hemodialysis cohort. *Hemodial Int* 2014; 18: 70–77
94. Anderson JE, Kraus J, Sturgeon D. Incidence, prevalence, and outcomes of end-stage renal disease patients placed in nursing homes. *Am J Kidney Dis* 1993; 21: 619–627
95. Kutsuna T, Matsunaga A, Takagi Y *et al.* Development of a novel questionnaire evaluating disability in activities of daily living in the upper extremities of patients undergoing maintenance hemodialysis. *Ther Apher Dial* 2011; 15: 185–194
96. Kutner NG, Zhang R, Huang Y *et al.* Depressed mood, usual activity level, and continued employment after starting dialysis. *Clin J Am Soc Nephrol* 2010; 5: 2040–2045
97. Hsieh RL, Huang HY, Chen SC *et al.* Changes in physical functional performance and quality of life in hemodialysis patients in Taiwan: a preliminary study. *J Nephrol* 2010; 23: 41–48
98. Painter P, Carlson L, Carey S *et al.* Physical functioning and health-related quality-of-life changes with exercise training in hemodialysis patients. *Am J Kidney Dis* 2000; 35: 482–492
99. Saito GK, Jassal SV. The 'Sit-to-Scale' score—pilot study to develop an easily applied score to follow functional status in elderly dialysis patients. *Nephrol Dial Transplant* 2007; 22: 3318–3321
100. Lo D, Chiu E, Jassal SV. A prospective pilot study to measure changes in functional status associated with hospitalization in elderly dialysis-dependent patients. *Am J Kidney Dis* 2008; 52: 956–961
101. Kutner NG, Zhang R, Huang Y *et al.* Gait speed and mortality, hospitalization, and functional status change among hemodialysis patients: a US renal data system special study. *Am J Kidney Dis* 2015; 66: 297–304
102. Lopes AA, Lantz B, Morgenstern H *et al.* Associations of self-reported physical activity types and levels with quality of life, depression symptoms, and mortality in hemodialysis patients: the DOPPS. *Clin J Am Soc Nephrol* 2014; 9: 1702–1712
103. Segura-Orti E, Martinez-Olmos FJ. Test-retest reliability and minimal detectable change scores for sit-to-stand-to-sit tests, the six-minute walk test, the one-leg heel-rise test, and handgrip strength in people undergoing hemodialysis. *Phys Ther* 2011; 91: 1244–1252
104. DeOreo PB. Hemodialysis patient-assessed functional health status predicts continued survival, hospitalization, and dialysis-attendance compliance. *Am J Kidney Dis* 1997; 30: 204–212
105. Torino C, Manfredini F, Bolignano D *et al.* Physical performance and clinical outcomes in dialysis patients: a secondary analysis of the EXCITE trial. *Kidney Blood Press Res* 2014; 39: 205–211
106. Walker SR, Gill K, Macdonald K *et al.* Association of frailty and physical function in patients with non-dialysis CKD: a systematic review. *BMC Nephrol* 2013; 14: 228
107. Osthus TB, Preljevic VT, Sandvik L *et al.* Mortality and health-related quality of life in prevalent dialysis patients: comparison between 12-items and 36-items short-form health survey. *Health Qual Life Outcomes* 2012; 10: 46
108. Lacson E Jr, Xu J, Lin SF *et al.* A comparison of SF-36 and SF-12 composite scores and subsequent hospitalization and mortality risks in long-term dialysis patients. *Clin J Am Soc Nephrol* 2010; 5: 252–260
109. Altintepe L, Levendoglu F, Okudan N *et al.* Physical disability, psychological status, and health-related quality of life in older hemodialysis patients and age-matched controls. *Hemodial Int* 2006; 10: 260–266
110. Anding K, Bar T, Trojniak-Hennig J *et al.* A structured exercise programme during haemodialysis for patients with chronic kidney disease: clinical benefit and long-term adherence. *BMJ Open* 2015; 5: e008709
111. Chen JL, Godfrey S, Ng TT *et al.* Effect of intra-dialytic, low-intensity strength training on functional capacity in adult haemodialysis patients: a randomized pilot trial. *Nephrol Dial Transplant* 2010; 25: 1936–1943
112. Heiwe S, Tollback A, Clyne N. Twelve weeks of exercise training increases muscle function and walking capacity in elderly predialysis patients and healthy subjects. *Nephron* 2001; 88: 48–56
113. Mercer TH, Crawford C, Gleeson NP *et al.* Low-volume exercise rehabilitation improves functional capacity and self-reported functional status of dialysis patients. *Am J Phys Med Rehabil* 2002; 81: 162–167
114. Ota S, Takahashi K, Taniai K *et al.* Bone metabolism and daily physical activity in women undergoing hemodialysis. *Nihon Jinzo Gakkai Shi* 1997; 39: 441–446
115. Esteve Simo V, Junque Jimenez A, Moreno Guzman F *et al.* Benefits of a low intensity exercise programme during haemodialysis sessions in elderly patients. *Nefrologia* 2015; 35: 385–394
116. Esteve Simo V, Junque A, Fulquet M *et al.* Complete low-intensity endurance training programme in haemodialysis patients: improving the care of renal patients. *Nephron Clin Pract* 2014; 128: 387–393
117. Heiwe S, Jacobson SH. Exercise training for adults with chronic kidney disease. *Cochrane Database Syst Rev* 2011; 10: CD003236
118. Johansson L, Fouque D, Bellizzi V *et al.* As we grow old: nutritional considerations for older patients on dialysis. *Nephrol Dial Transplant* 2016; doi: 10.1093/ndt/gfw201.
119. Ikizler TA, Cano NJ, Franch H *et al.* Prevention and treatment of protein energy wasting in chronic kidney disease patients: a consensus statement by the International Society of Renal Nutrition and Metabolism. *Kidney Int* 2013; 84: 1096–1107
120. Moreau-Gaudry X, Jean G, Genet L *et al.* A simple protein-energy wasting score predicts survival in maintenance hemodialysis patients. *J Ren Nutr* 2014; 24: 395–400
121. Noordzij M, Kramer A, Abad Diez JM *et al.* Renal replacement therapy in Europe: a summary of the 2011 ERA-EDTA registry annual report. *Clin Kidney J* 2014; 7: 227–238

122. Cheng TH, Lam DH, Ting SK *et al.* Serial monitoring of nutritional status in Chinese peritoneal dialysis patients by subjective global assessment and comprehensive malnutrition inflammation score. *Nephrology (Carlton)* 2009; 14: 143–147
123. Hou Y, Li X, Hong D *et al.* Comparison of different assessments for evaluating malnutrition in Chinese patients with end-stage renal disease with maintenance hemodialysis. *Nutr Res* 2012; 32: 266–271
124. Chan JY, Che KI, Lam KM *et al.* Comprehensive malnutrition inflammation score as a marker of nutritional status in Chinese peritoneal dialysis patients. *Nephrology (Carlton)* 2007; 12: 130–134
125. Szeto CC, Kwan BC, Chow KM *et al.* Geriatric nutritional risk index as a screening tool for malnutrition in patients on chronic peritoneal dialysis. *J Ren Nutr* 2010; 20: 29–37
126. Campbell KL, Ash S, Bauer JD *et al.* Evaluation of nutrition assessment tools compared with body cell mass for the assessment of malnutrition in chronic kidney disease. *J Ren Nutr* 2007; 17: 189–195
127. Lawson JA, Lazarus R, Kelly JJ. Prevalence and prognostic significance of malnutrition in chronic renal insufficiency. *J Ren Nutr* 2001; 11: 16–22
128. Desbrow B, Bauer J, Blum C *et al.* Assessment of nutritional status in hemodialysis patients using patient-generated subjective global assessment. *J Ren Nutr* 2005; 15: 211–216
129. Kalantar-Zadeh K, Kleiner M, Dunne E *et al.* A modified quantitative subjective global assessment of nutrition for dialysis patients. *Nephrol Dial Transplant* 1999; 14: 1732–1738
130. Piratelli CM, Telarolli Junior R. Nutritional evaluation of stage 5 chronic kidney disease patients on dialysis. *Sao Paulo Med J* 2012; 130: 392–397
131. Maggiore Q, Nigrelli S, Ciccarelli C *et al.* Nutritional and prognostic correlates of bioimpedance indexes in hemodialysis patients. *Kidney Int* 1996; 50: 2103–2108
132. Enia G, Sicuso C, Alati G *et al.* Subjective global assessment of nutrition in dialysis patients. *Nephrol Dial Transplant* 1993; 8: 1094–1098
133. Gurreebun F, Hartley GH, Brown AL *et al.* Nutritional screening in patients on hemodialysis: is subjective global assessment an appropriate tool? *J Ren Nutr* 2007; 17: 114–117
134. Gama-Axelsson T, Heimburger O, Stenvinkel P *et al.* Serum albumin as predictor of nutritional status in patients with ESRD. *Clin J Am Soc Nephrol* 2012; 7: 1446–1453
135. Cooper BA, Bartlett LH, Aslani A *et al.* Validity of subjective global assessment as a nutritional marker in end-stage renal disease. *Am J Kidney Dis* 2002; 40: 126–132
136. Fouque D, Kalantar-Zadeh K, Kopple J *et al.* A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. *Kidney Int* 2008; 73: 391–398
137. Magnard J, Deschamps T, Cornu C *et al.* Effects of a six-month intradialytic physical ACTIvity program and adequate NUTritional support on protein-energy wasting, physical functioning and quality of life in chronic hemodialysis patients: ACTINUT study protocol for a randomised controlled trial. *BMC Nephrol* 2013; 14: 259
138. Iglesias P, Diez JJ, Fernandez-Reyes MJ *et al.* Recombinant human growth hormone therapy in malnourished dialysis patients: a randomized controlled study. *Am J Kidney Dis* 1998; 32: 454–463
139. Bolasco P, Caria S, Cupisti A *et al.* A novel amino acids oral supplementation in hemodialysis patients: a pilot study. *Ren Fail* 2011; 33: 1–5
140. Szeto CC, Wong TY, Chow KM *et al.* Oral sodium bicarbonate for the treatment of metabolic acidosis in peritoneal dialysis patients: a randomized placebo-control trial. *J Am Soc Nephrol* 2003; 14: 2119–2126
141. Cano NJ, Fouque D, Roth H *et al.* Intradialytic parenteral nutrition does not improve survival in malnourished hemodialysis patients: a 2-year multicenter, prospective, randomized study. *J Am Soc Nephrol* 2007; 18: 2583–2591
142. Hung SC, Tung TY, Yang CS *et al.* High-calorie supplementation increases serum leptin levels and improves response to rHuEPO in long-term hemodialysis patients. *Am J Kidney Dis* 2005; 45: 1073–1083
143. Aguirre Galindo BA, Prieto Fierro JG, Cano P *et al.* Effect of polymeric diets in patients on continuous ambulatory peritoneal dialysis. *Perit Dial Int* 2003; 23: 434–439
144. Ewers B, Riserus U, Marckmann P. Effects of unsaturated fat dietary supplements on blood lipids, and on markers of malnutrition and inflammation in hemodialysis patients. *J Ren Nutr* 2009; 19: 401–411
145. Wu HL, Sung JM, Kao MD *et al.* Nonprotein calorie supplement improves adherence to low-protein diet and exerts beneficial responses on renal function in chronic kidney disease. *J Ren Nutr* 2013; 23: 271–276
146. Hiroshige K, Sonta T, Suda T *et al.* Oral supplementation of branched-chain amino acid improves nutritional status in elderly patients on chronic haemodialysis. *Nephrol Dial Transplant* 2001; 16: 1856–1862
147. Caglar K, Fedje L, Dimmitt R *et al.* Therapeutic effects of oral nutritional supplementation during hemodialysis. *Kidney Int* 2002; 62: 1054–1059
148. Kalantar-Zadeh K, Braglia A, Chow J *et al.* An anti-inflammatory and antioxidant nutritional supplement for hypoalbuminemic hemodialysis patients: a pilot/feasibility study. *J Ren Nutr* 2005; 15: 318–331
149. Steiber AL, Handu DJ, Cataline DR *et al.* The impact of nutrition intervention on a reliable morbidity and mortality indicator: the hemodialysis-prognostic nutrition index. *J Ren Nutr* 2003; 13: 186–190
150. Malgorzewicz S, Rutkowski P, Jankowska M *et al.* Effects of renal-specific oral supplementation in malnourished hemodialysis patients. *J Ren Nutr* 2011; 21: 347–353
151. Verove C, Maisonneuve N, El Azouzi A *et al.* Effect of the correction of metabolic acidosis on nutritional status in elderly patients with chronic renal failure. *J Ren Nutr* 2002; 12: 224–228
152. Mortelmans AK, Duym P, Vandenbroucke J *et al.* Intradialytic parenteral nutrition in malnourished hemodialysis patients: a prospective long-term study. *JPEN J Parenter Enteral Nutr* 1999; 23: 90–95
153. Czekalski S, Hozejowski R. Intradialytic amino acids supplementation in hemodialysis patients with malnutrition: results of a multicenter cohort study. *J Ren Nutr* 2004; 14: 82–88
154. Hiroshige K, Iwamoto M, Kabashima N *et al.* Prolonged use of intradialysis parenteral nutrition in elderly malnourished chronic haemodialysis patients. *Nephrol Dial Transplant* 1998; 13: 2081–2087
155. Berneis K, Iseli-Schaub J, Garbani E *et al.* Effects of intradialytic parenteral nutrition in chronic haemodialysis patients with malnutrition: a pilot study. *Wien Klin Wochenschr* 1999; 111: 876–881
156. Garibotto G, Barreca A, Russo R *et al.* Effects of recombinant human growth hormone on muscle protein turnover in malnourished hemodialysis patients. *J Clin Invest* 1997; 99: 97–105
157. Eiam-Ong S, Buranaosot S, Wathanavaha A *et al.* Nutritional effect of nandrolone decanoate in predialysis patients with chronic kidney disease. *J Ren Nutr* 2007; 17: 173–178
158. Slinin Y, Guo H, Gilbertson DT *et al.* Prehemodialysis care by dietitians and first-year mortality after initiation of hemodialysis. *Am J Kidney Dis* 2011; 58: 583–590
159. Peeters P, Van Biesen W, Veys N *et al.* External Validation of a risk stratification model to assist shared decision making for patients starting renal replacement therapy. *BMC Nephrol* 2016; 17: 41
160. van Biesen W, van de Luijtgaarden MW, Brown EA *et al.* Nephrologists' perceptions regarding dialysis withdrawal and palliative care in Europe: lessons from a European Renal Best Practice survey. *Nephrol Dial Transplant* 2015; 30: 1951–1958
161. Brown MA, Collett GK, Josland EA *et al.* CKD in elderly patients managed without dialysis: survival, symptoms, and quality of life. *Clin J Am Soc Nephrol* 2015; 10: 260–268
162. Carson RC, Juszczak M, Davenport A *et al.* Is maximum conservative management an equivalent treatment option to dialysis for elderly patients with significant comorbid disease? *Clin J Am Soc Nephrol* 2009; 4: 1611–1619
163. Chandna SM, Da Silva-Gane M, Marshall C *et al.* Survival of elderly patients with stage 5 CKD: comparison of conservative management and renal replacement therapy. *Nephrol Dial Transplant* 2011; 26: 1608–1614
164. Chan CH, Noble H, Lo SH *et al.* Palliative care for patients with end-stage renal disease: experiences from Hong Kong. *Int J Palliat Nurs* 2007; 13: 310–314
165. Da Silva-Gane M, Farrington K. Supportive care in advanced kidney disease: patient attitudes and expectations. *J Ren Care* 2014; 40 (Suppl 1): 30–35
166. De Biase V, Tobaldini O, Boaretti C *et al.* Prolonged conservative treatment for frail elderly patients with end-stage renal disease: the Verona experience. *Nephrol Dial Transplant* 2008; 23: 1313–1317
167. Ellam T, El-Kossi M, Prasanth KC *et al.* Conservatively managed patients with stage 5 chronic kidney disease—outcomes from a single center experience. *Q J Med* 2009; 102: 547–554

168. Gracia-Garcia S, Montanes-Bermudez R, Morales-Garcia LJ *et al.* Current use of equations for estimating glomerular filtration rate in Spanish laboratories. *Nefrologia* 2012; 32: 508–516
169. Hussain JA, Mooney A, Russon L. Comparison of survival analysis and palliative care involvement in patients aged over 70 years choosing conservative management or renal replacement therapy in advanced chronic kidney disease. *Palliat Med* 2013; 27: 829–839
170. Joly D, Anglicheau D, Alberti C *et al.* Octogenarians reaching end-stage renal disease: cohort study of decision-making and clinical outcomes. *J Am Soc Nephrol* 2003; 14: 1012–1021
171. Murtagh FE, Addington-Hall J, Edmonds P *et al.* Symptoms in the month before death for stage 5 chronic kidney disease patients managed without dialysis. *J Pain Symptom Manage* 2010; 40: 342–352
172. Murtagh FE, Marsh JE, Donohoe P *et al.* Dialysis or not? A comparative survival study of patients over 75 years with chronic kidney disease stage 5. *Nephrol Dial Transplant* 2007; 22: 1955–1962
173. Rodriguez Villarreal I, Ortega O, Hinostroza J *et al.* Geriatric assessment for therapeutic decision-making regarding renal replacement in elderly patients with advanced chronic kidney disease. *Nephron Clin Pract* 2014; 128: 73–78
174. Seow YY, Cheung YB, Qu LM *et al.* Trajectory of quality of life for poor prognosis stage 5D chronic kidney disease with and without dialysis. *Am J Nephrol* 2013; 37: 231–238
175. Shum CK, Tam KF, Chak WL *et al.* Outcomes in older adults with stage 5 chronic kidney disease: comparison of peritoneal dialysis and conservative management. *J Gerontol A Biol Sci Med Sci* 2014; 69: 308–314
176. Smith C, Da Silva-Gane M, Chandna S *et al.* Choosing not to dialyse: evaluation of planned non-dialytic management in a cohort of patients with end-stage renal failure. *Nephron Clin Pract* 2003; 95: c40–46
177. Teo BW, Ma V, Xu H *et al.* Profile of hospitalisation and death in the first year after diagnosis of end-stage renal disease in a multi-ethnic Asian population. *Ann Acad Med Singapore* 2010; 39: 79–87
178. Verberne WR, Geers AB, Jellema WT *et al.* Comparative survival among older adults with advanced kidney disease managed conservatively versus with dialysis. *Clin J Am Soc Nephrol* 2016; 11: 633–640
179. Wong CF, McCarthy M, Howse ML *et al.* Factors affecting survival in advanced chronic kidney disease patients who choose not to receive dialysis. *Ren Fail* 2007; 29: 653–659
180. Echevers YM, Gaibor NGT, Pérez NN *et al.* Supervivencia de pacientes de edad avanzada (≥70 años)con enfermedad crónica estadios 4-5: diálisis vs tratamientoconservador. *Nefrologia* 2016; 36: 283–291
181. O'Connor NR, Kumar P. Conservative management of end-stage renal disease without dialysis: a systematic review. *J Palliat Med* 2012; 15: 228–235
182. Foote C, Kotwal S, Gallagher M *et al.* Survival outcomes of supportive care versus dialysis therapies for elderly patients with end-stage kidney disease: a systematic review and meta-analysis. *Nephrology (Carlton)* 2016; 21: 241–253
183. Tattersall J, Dekker F, Heimburger O *et al.* When to start dialysis: updated guidance following publication of the Initiating Dialysis Early and Late (IDEAL) study. *Nephrol Dial Transplant* 2011; 26: 2082–2086
184. Balshem H, Helfand M, Schunemann HJ *et al.* GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* 2011; 64: 401–406
185. Guyatt GH, Oxman AD, Vist GE *et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; 336: 924–926
186. Guyatt GH, Oxman AD, Kunz R *et al.* Going from evidence to recommendations. *BMJ* 2008; 336: 1049–1051
187. Chauvelier S, Pequignot R, Amzal A *et al.* Comparison between the three most popular formulae to estimate renal function, in subjects 75 years of age or older. *Drugs Aging* 2012; 29: 885–890
188. Couchoud CG, Beuscart JR, Aldigier JC *et al.* Development of a risk stratification algorithm to improve patient-centered care and decision making for incident elderly patients with end-stage renal disease. *Kidney Int* 2015; 88: 1178–1186
189. Da Silva-Gane M, Wellsted D, Greenshields H *et al.* Quality of life and survival in patients with advanced kidney failure managed conservatively or by dialysis. *Clin J Am Soc Nephrol* 2012; 7: 2002–2009

APPENDIX 1. GUIDELINE DEVELOPMENT GROUP AREA OF EXPERTISE

Guideline development group

Filippo Aucella qualified in medicine in 1984, and gained board certification in nephrology in 1988 and in internal medicine in 1994; he has been a consultant nephrologist at the Research Hospital 'Casa Sollievo della Sofferenza' since 1988. From 2005 until 2008, he was head of the Dialysis Unit at Lastaria Hospital, Foggia; since 2009 he has been the Director of the Nephrology and Dialysis Unit at the Research Hospital 'Casa Sollievo della Sofferenza', San Giovanni Rotondo, Italy. His main interests are HD, hepatitis C virus infection, geriatric nephrology and physical activity. He is involved as consultant in the regional health system for nephrology. He has published 116 papers indexed in PubMed, 5 chapters in Nephrology and 4 supplements (*Journal of Nephrology*, *Kidney & Blood Pressure Research* and *Italian Journal of Nephrology*) as Guest Editor.

Naomi Clyne has been a Consultant Nephrologist since 1994, first at Karolinska University Hospital and then at Skåne University Hospital. She completed her nephrology training in 1987 at Karolinska University Hospital. She became an associate Professor at the Karolinska Institute in 1996. She has held a number of managerial clinical appointments and was previously head of the Department of Nephrology in Lund, Skåne University Hospital. In 2001 she was co-founder of EURORECKD (European Association for Rehabilitation in Chronic Kidney Disease), which is endorsed by the ERA-EDTA. She is currently chair of the association. Her main research interests lie in the effects of CKD on various aspects of physical function and the effects of exercise training in patients with CKD. Her main clinical interests lie in the treatment of patients with CKD stages 4–5, end-stage renal failure and AKI. She was the chief editor for a Swedish textbook on nephrology published in 2015.

Adrian Covic is a Full Professor of Nephrology and Internal Medicine at the 'Gr. T. Popa' University of Medicine and Pharmacy and the Director of the Nephrology Clinic and the Dialysis and Transplantation Center in Iasi, Romania. Professor Covic has published more than 200 original and review papers in peer-reviewed journals, 11 books and 22 chapters.

Leen De Vos is a Registrar Nephrologist at the Renal Department of the Ghent University Hospital.

Ken Farrington has been a Consultant Nephrologist at the Lister Hospital since 1991. After training in chemistry, he went on to qualify in medicine in Cardiff, and complete his Nephrology training at the Royal Free. With colleagues he has played a significant role in the establishment and development of renal services in Herts and Beds. He is Treasurer of the British Renal Society. He has also held a number of clinical management roles within the Trust including Trust Medical Director and Director of R&D. He is head of the Centre for Clinical and Health Services Research at the University of Hertfordshire. His main research interests lie in metabolic aspects of CKD, HD, and conservative and supportive management in ESKD. He has published widely in these areas.

Andrew Findlay has been a Consultant Nephrologist at the Lister Hospital since 2015. He qualified in medicine in the University of Birmingham and completed his nephrology training at the Royal London Hospital. His main interests lie in AKI, HD and conservative kidney management.

Denis Fouque is a Professor of Nephrology at the University Claude Bernard Lyon 1 and Associate Chief of the Division of Nephrology, Centre Hospitalier Lyon Sud, France. He trained for his PhD at UCLA, Los Angeles. He has authored more than 270 articles and editorials dealing with nutrition, insulin and phosphocalcic metabolism and evidence-based nephrology. He has authored more than 20 book chapters on progression of kidney disease, nutrition, metabolism, including the nutrition chapter of the Brenner's *The Kidney*. He was the founding editor of the Cochrane Renal group and is the actual vice-chair of ERBP. He is the editor-in-chief elect of *Nephrology Dialysis Transplantation*.

Tomasz Grodzicki has been a Professor of Geriatrics since 2001. He qualified in medicine in Cracow and completed his training in internal medicine and geriatrics at the University Hospital in Cracow and Hammersmith Hospital in London. He graduated from the European Academy for Medicine of Ageing. He played a major role in developing geriatric services in Poland, serving for 14 years as Advisor to the Ministry of Health. He has also held a number of roles within the Jagiellonian University including Dean of Medical Faculty 2008–2016. He is also head of the Department of Internal Medicine and Geriatrics at the University Hospital in Cracow and member of the Academic Board of the EUGMS. His main interests lie in cardiovascular problems in older patients, multimorbidity and polypharmacy.

Osasuyi Iyasere is a Specialist Registrar in Nephrology at the John Walls Rrenal Unit, Leicester General Hospital. Until June 2016, he was also clinical research fellow at the Imperial College Renal and Transplant Center, Hammersmith Hospital, where he has been actively involved in the multicenter FEPOD study. His clinical and research interests include the impact of dialysis on cognitive function and patient-reported outcomes, particularly in older people. He has recently submitted his thesis for the award of MD(Res) and is the author of several peer-reviewed publications.

Kitty J. Jager is an Associate Professor of Medical Informatics at the Academic Medical Center in Amsterdam, the Netherlands. She has authored and coauthored over 210 scientific papers on the epidemiology of kidney disease, quality of care in RRT and related research methods. She is the director of the ERA-EDTA Registry and leads a number of other European renal registries and studies. Currently, she is Perspectives Editor for renal epidemiology for *Nephrology Dialysis Transplantation* and serves as an editor for a number of other journals. In addition, she is a reviewer for several different nephrology journals.

Hanneke Joosten completed her nephrology training in 2014 at the University Medical Centre Groningen, the Netherlands and did a honorary clinical fellowship in geriatric nephrology with Professor Dr E. Brown at the Hammersmith Hospital in London. She was subsequently trained in geriatric medicine and her clinical focus as a consultant lies in geriatric nephrology. Her PhD focussed on overlapping risk factors for renal and cognitive decline. She has recently started as a Consultant at the Department of Internal Medicine at the Maastricht University Medical Centre (MUMC+). Her main clinical interests lie in decision-making of RRT in older patients with ESRD and in palliative care in older patients with CKM and RRT. She was member of the Dutch guideline committee 'Palliative care in older patients with ESRD'. Her main research interests lie in the effects of CKD and cardiovascular risk profile on various aspects of frailty, like cognitive dysfunction and falls.

Juan Florencio Macias Núñez has been the Chief of the Renal Unit and Professor of Nephrology and Geriatrics at the University of Salamanca (US); head of the Experimental Research and Animal Care Unit at the Faculty of Medicine (USA); senior Registrar at the Renal Unit (Professor J.S. Cameron), Guy's Hospital, UK; visiting scientist, Department of Physiology and Biophysics (Professor F.G. Knox) and Renal Biochemistry (Professor Thomas Douza), Mayo Clinic, USA. He started the Renal Transplant Unit for aged patients at the University Hospital of Salamanca (Spain). His main field of interest lie in dissecting the differences between the physiological renal aging process and CKD in the aged with publications in this field since 1978. He qualified in medicine in the US, Spain for his PhD in medicine and in surgery in the US. Specialist in Nephrology, Dozor Professor of Geriatric Medicine, Ben-Gurion University of the Negev, Israel, Programmatic Director and Coordinator, Faculty of Medicine, Maimonides University, Buenos Aires (Argentina). Associate Member: The Interdepartmental Division of Geriatrics (Professor Rory H. Fischer), Faculty of Medicine, University of Toronto, Canada.

Andrew Mooney qualified from Nottingham University Medical School in 1988, trained at the Hammersmith Hospital in London, and was a MRC Training Fellow and Wellcome Clinician Scientist before becoming a Consultant Nephrologist at St James's University Hospital in Leeds in 1999. He has a full-time NHS contract though he continues a Kidney Research UK and Yorkshire Kidney Research Fund (YKRF)—funded laboratory research program investigating renal scarring, and Kidney Research UK, FIMDM, ERA/EDTA, ESRC and YKRF-funded research program studying clinical aspects of progressive CKD. He was appointed Honorary Clinical Associate Professor at the University of Leeds in 2013. As well as his work for the ERBP group, he has co-written guidelines on Planning, Initiating and Withdrawal of Renal Replacement Therapy for the UK Renal Association. He is currently Lead Clinician for the NICE guideline on Renal Replacement Therapy.

Dorothea Nitsch is a Clinical Senior Lecturer in Epidemiology at the London School of Hygiene and Tropical Medicine. She also holds an honorary consultant contract with the Royal Free NHS Trust in London since 2011. She qualified in medicine in Basel (Switzerland) in 1997, and completed her training in internal medicine and nephrology in various hospitals in Switzerland. Since being in the UK she has closely collaborated with the UK Renal Registry and is currently the Chair of its Research Methods Study Group. She also leads the analytic team of the National CKD Audit in the UK primary care. Her research focuses on the burden and outcomes of patients with CKD and on dialysis, and she has published more than 80 papers in this area.

Marijke Stryckers is a specialist registrar at the Ghent University Hospital.

Maarten Taal is a Professor of Medicine at the University of Nottingham and Honorary Consultant Nephrologist at Royal Derby Hospital, UK. He has a career-long interest in CKD and risk prediction. He is a coeditor of Brenner and Rector's *The Kidney* and section editor for *Current Opinion in Nephrology and Hypertension*. He has previously coauthored the Renal Association guidelines on the diagnosis and management of CKD. He is the current President of the British Renal Society.

James Tattersall has been working in dialysis units since 1984. He has publications in clinical biochemistry, dialysis technology, disaster management, when to start dialysis, and informatics and dialysis technology. He is a member of the European Renal Best Practice Advisory Board, which is involved in the development of renal guidelines. He is currently working in the dialysis and transplant clinics in Leeds and on the development of software to assist renal care.

Dieneke van Asselt is a Geriatrician and Medical Trainer at the Department of Geriatric Medicine of the Radboud University Medical Center in Nijmegen, the Netherlands. She was the chair of the working group which wrote the guideline 'Undernutrition in Geriatric Patients' published by the Dutch Geriatrics Society in 2013.

Nele Van Den Noortgate is the head of the Geriatric Department at the University Hospital Ghent and a senior lecturer in geriatric medicine at the University Ghent. She is interested in the diagnosis and treatment of older persons with acute and CKDs and obtained her PhD in 2003 with a dissertation on kidney function in the older person. She is also a trained physician in Palliative Care Medicine, a member of the VUB-UGent Research Group on End-of-life Care and leading a multidisciplinary research team focussing on end-of-life care in the older hospitalized population, which focusses on nontreatment decisions and advance care planning. She is general secretary of the Belgian Society for Gerontology and Geriatrics. At the European level, she is president of the European Academy for Medicine of Ageing, secretary of the Palliative Care Interest Group of the European Union of Geriatric Medicine Society (EUGMS) and member of the EAPC-EUGMS-Maruzza foundation task force.

ERBP methods support team

Davide Bolignano is a Specialist Registrar in nephrology, working as a 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/coauthor of more than 90 articles on various topics in nephrology and regular reviewer for different scientific journals.

Christiane Drechsler is a Consultant Nephrologist at the University of Würzburg in Germany. She has also been trained in clinical epidemiology at the Netherlands Institute of Health Sciences in Rotterdam, and the Department of Clinical Epidemiology in Leiden, the Netherlands. She graduated with a Master of Science in 2007 and with a PhD in clinical epidemiology in 2010. At the University Hospital Würzburg, she is doing clinical practice in nephrology as well as research activities. Her research work focuses on sudden cardiac death and the clinical epidemiology of cardiac and diabetic complications in 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 has worked on renal research projects, such as a cost-effectiveness analysis of RRT and the molecular mechanisms of sirolimus-induced phosphaturia at the University of Zurich. Additionally, she obtained a Master's degree in Health Care Management at the Vienna University of Economics and Business in 2012. A description of her PhD plan and full CV can be viewed at http://www.meduniwien.ac.at/hp/fileadmin/phd-mibcs/pdf/Studenten/Studenten_Info_Haller.pdf. Dr Haller joined the ERBP fellow group in June 2012.

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

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

Sabine van der Veer worked as an IT project manager in the Academic Medical Center (Amsterdam, the Netherlands) after obtaining her degree in medical informatics at the University of Amsterdam. In 2007, she started a PhD project under the supervision of Kitty Jager, entitled 'Systematic quality improvement in healthcare: clinical performance measurement and registry-based feedback'. Within this project she developed an instrument to measure dialysis patient experience, investigated implementation of best renal practice as a NephroQUEST research fellow at the UK Renal Registry (Bristol, UK), and conducted a cluster RCT among Dutch intensive care units to evaluate the effectiveness of clinical performance feedback. She defended her PhD thesis in June 2012.

She joined the ERBP fellow group 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 organizations.

Wim Van Biesen is a Professor of Nephrology at the Ghent University Hospital, Belgium. He is author and coauthor of more than 230 articles dealing with a wide variety of topics in nephrology (PD, HD, CKD management) and intensive care nephrology. He is the actual chair of ERBP. He is also the subject editor for dialysis for *Nephrology Dialysis Transplantation* and is a member of the editorial board of different other journals. He is a regular reviewer of scientific papers for different journals on nephrology, intensive care and epidemiology.

Guideline development group declaration of interest

FILIPPO AUCELLA

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 judgment, 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
Italian Society of Nephrology

NAOMI CLYNE

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?
None

5. Is there anything else that might influence your judgment, 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

LEEN DE VOS

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 judgment, 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

KEN FARRINGTON

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 judgment, 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
Member of Renal Association; Treasurer of British Renal Association

ANDREW FINDLAY

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 judgment, 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

DENIS FOUQUE

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

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?
Lecture fees from Fresenius Medical care, Fresenius Kabi, Sanofi, Amgen, Vifor

5. Is there anything else that might influence your judgment, 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

TOMASZ GRODZICKI

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 judgment, 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

OSASUYI IYASERE

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?
Yes. Research grant from Baxter Healthcare and DunHill Medical Trust

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?
Yes. Research grant from Baxter Healthcare and DunHill Medical Trust

4. Other potential conflicts of interest?
No

5. Is there anything else that might influence your judgment, 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

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 judgment, 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

HANNEKE JOOSTEN

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 judgment, 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

JUAN FLORENCIO MACIAS

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 judgment, 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

ANDREW MOONEY

1. Do you have, or have you had during the past 2 years, any formal association with a company or other interested party?
In the last 2 years I have received travel and accommodation expenses and speaker fees from Baxter on two occasions

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 interests?
No

5. Is there anything else that might influence your judgment, 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
Current member of UK Renal Association and member of guideline–writing team. Currently Lead Clinician for National Institute of Health and Care Excellence (NICE) Guideline on Renal Replacement Therapy: Management of RRT including transplant and conservative care

DOROTHEA NITSCH

1. Do you have, or have you had during the past 2 years, any formal association with a company or other interested party?
Yes. I am collaborating with Informatics Systems which provides a quality improvement tool in Primary Care as part of the National CKD Audit, which is tendered by HQIP (Health Quality Improvement Partnership) and funded by the UK Department of Health. The IP of the product lies with HQIP

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?
See above

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?
See above

4. Other potential conflicts of interest?
None

5. Is there anything else that might influence your judgment, or might be perceived to do so?
No, not aware of any

6. Member (current) of any kind of committee, board, WG, etc. of another scientific association with similar aims as ERA-EDTA
I am a member of the UK Renal Association Renal Research Committee. I also am an educational ambassador for the ISN.

MARIJKE STRYCKERS

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 judgment, 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

MAARTEN TAAL

1. Do you have, or have you had during the past 2 years, any formal association with a company or other interested party?
Yes. As a coeditor of Brenner and Rector's *The Kidney* I have a contract with the publishers, Elsevier

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?
Yes. I have received grant funding from Fresenius Medical Care and Baxter

4. Other potential conflicts of interest?
No

5. Is there anything else that might influence your judgment, 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. President of the British Renal Society. Member of the Renal Association, International Society of Nephrology and American Society of Nephrology

JAMES TATTERSALL

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 judgment, 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

DIENEKE VAN ASSELT

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 judgment, 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

VAN DEN NOORTGATE NELE.

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 judgment, 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

Table A1. Q1. What eGFR estimating equation should be used in older patients and advanced CKD patients for dose adaptation purpose?

Patients	Older and/or frail patients with CKD (eGFR <45 mL/min/1.73 m^2) Adults, aged adults
Target conditions	Assessment of GFR (Staging of CKD) Assessment of GFR to adapt dosing of medication Estimating GFR
Index test/ comparator	GFR estimating equations: 1. Cockcroft-Gault 2. 2006 MDRD study 3. 2009 CKD-EPI 4. $eGFR_{Cr\text{-}Cyst}$ by 2012 CKD-EPI
Reference standard	Iohexol measurements Inulin Urinary clearance of iothalamate
Objectives	To estimate the accuracy of GFR estimating equations applied to older patients with advanced CKD for dose adaptation
Methodology	Systematic reviews RCTs Longitudinal studies Registry studies

Table A2. Q2. Prognostic scores: what is the most reliable risk model score to predict CKD and its progression in older and/or frail patients with advanced CKD (eGFR <45 mL/min/1.73 m^2)

Patients	Older patients and/or frail with CKD (eGFR <45 mL/min/1.73 m^2)
Intervention	Risk models developed to predict the progression of CKD in those with CKD (eGFR <45 mL/min/1.73 m^2)
Comparator	Risk models scores of any kind
Outcome	Need for RRT or eGFR <15 mL/min/1.73 m^2 Question-specific outcome measures
Methodology	Systematic review Cross-sectional studies Longitudinal (cohort) studies Registry studies

Table A3. Q3. Prognostic scores: what is the most reliable risk model score to predict mortality in older and/or frail patients with advances CKD (eGFR <45 mL/min/1.73 m^2)

Patients	Patients older and/or frail with CKD (eGFR <45 mL/min/1.73 m^2)
Intervention	Risk models scores developed to predict mortality Planned subgroup analysis: risk models developed to predict mortality in ESKD patients (HD, PD, etc.)
Comparator	Risk models scores of any kind
Outcome	All-cause mortality rates (number of events, HR, RR, etc.) Question-specific outcome measures
Methodology	Systematic review Cross-sectional studies Longitudinal (cohort) studies Registry studies
Extra	Planned subgroup analysis: risk models developed to predict mortality in ESKD patients (HD, PD, etc.)

Table A4. Q4a. In patients with renal failure (eGFR <45 mL/min/1.73 m^2) or on dialysis, older and/or frail, which is the best alternative to estimate functional status?

Patients	Patients with renal failure (eGFR <45 mL/min/1.73 m^2) Adults, aged adults
Intervention	Functional status evaluated with: 1. Activities of daily living (ADL) 2. SF36 scale modified 3. Minimum dataset (MDS) 4. Others to be detailed (timed GUG test?)
Comparator	Reference standard SF36 scale
Outcome	Core outcome measures: mortality, rehabilitation
Methodology	Systematic review RCTs Cohort studies Registry studies *Include all studies with at least one participant with eGFR <45 mL/min/1.73 m^2*

Table A5. Q4b. Interventions aimed at increasing functional status in patients with renal failure (eGFR <45 mL/min/1.73 m^2 or on dialysis) and/or frail and older are of benefit?

Patients	Patients with renal failure (eGFR <45 mL/min/1.73 m^2 or on dialysis) and older and/or frail adults, aged adults
Intervention	Structured education/intervention aimed at increasing functional status 1. Advice to exercise 2. Structured education programs including advice on exercise 3. Provision of a supervised exercise program 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. Fractures: moderately important 5. Improved efficiency of HD (exercise during dialysis)
Methodology	Systematic review RCTs Cohort studies Registry studies

Table A6. Q5a. In patients with renal failure (eGFR <45 mL/min/1.73 m^2) or on dialysis, older and/or frail, which is the best alternative to evaluate nutritional status?

Patients	Patients with renal failure (eGFR <45 mL/min/1.73 m^2) Adults, aged adults
Intervention	Nutritional status evaluated with: 1. The Mini Nutritional Assessment (MNA) 2. The MNA-SF (MNA short form) 3. Nutritional risk screening (NRS) 4. Others to be detailed
Comparator	Reference standard–SGA
Outcome	Core outcome measures
Methodology	Systematic review RCTs Cohort studies Registry studies *Include all studies with at least one participant with eGFR <45 mL/min/1.73 m^2*

Table A7. Q5b. Interventions aimed at improving nutritional status in patients with renal failure (eGFR <45 mL/min/1.73 m^2 or on dialysis), older and/or frail are of any benefit?

Patients	Older patients and/or frail with renal failure (eGFR <45 mL/min/1.73 m^2 or on dialysis) Adults, aged adults
Intervention	Structured education/intervention aimed at increasing energy intake/improving nutritional status: 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
Methodology	Systematic review RCTs Cohort studies Registry studies *Include all studies with at least one participant with eGFR <45 mL/min/1.73 m^2*

Table A8. Q6. Access to renal replacement: what is the benefit of renal replacement therapy for older and or frail patients?

Patients	Patients older and/or frail and with renal failure stage 5 CKD with RRT indications Frail, aged adults
Intervention	Renal replacement therapy 1. HD [conventional HD, daily HD, hemodiafiltration, home HD, etc.] 2. PD (continuous ambulatory PD, automated PD, etc.) 3. Kidney transplantation (living donor, cadaveric-donor etc.)
Comparator	Conservative care of any kind in patients with dialysis indications (CM of ESKD)
Outcome	Core outcome measures
Methodology	Systematic reviews RCTs Cohort studies Registry studies

APPENDIX 3. SEARCH STRATEGIES

Q1. What eGFR estimating equation should be used in older and advanced CKD patients for dose adaptation purpose?

MEDLINE search strategy

1. Kidney Diseases/
2. exp Renal Replacement Therapy/
3. Renal Insufficiency/
4. exp Renal Insufficiency, Chronic/
5. dialysis.tw.
6. (hemodialysis or haemodialysis).tw.
7. (hemofiltration or haemofiltration).tw.
8. (hemodiafiltration 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. Elderly.tw.
17. community-dwelling.tw.
18. geriatric.tw.
19. mini-mental state.tw.
20. alzheimer*.tw.
21. mmse.tw.
22. caregivers.tw.
23. falls.tw.
24. Adl.tw.
25. Frailty.tw.
26. Gds.tw.
27. Ageing.tw.
28. hip fractures.tw.
29. elders.tw.
30. Frail*.tw.
31. Mci.tw.
32. Demented.tw.
33. Psychogeriatrics.tw.
34. cognitive impairment.tw.
35. postmenopausal women.tw.
36. dementia.tw.
37. aging.tw.
38. older.tw.
39. or/16-38
40. 15 and 39
41. exp Kidney Function Tests/
42. glomerular filtration rate.tw.
43. gfr.af.
44. serum creatin$.tw.
45. creatin$.tw.
46. cystat$.tw.
47. mdrd.tw.
48. (ckd adj2 epi).tw.
49. ckd-epi.tw.
50. 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49
51. 40 and 50
52. limit 51 to (english language and humans)

COCHRANE CENTRAL search strategy

ID Search

#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 Aged, 80 and over
#15 Frail Elderly
#16 #14 or #15
#17 #13 and #16

Q2. Prognostic scores: What is the most reliable Risk model score to predict CKD and its progression in older and/or frail patients with advanced CKD (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. (hemodialysis or haemodialysis).tw.
7. (hemofiltration or haemofiltration).tw.
8. (hemodiafiltration 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. Elderly.tw.
17. community-dwelling.tw.
18. geriatric.tw.
19. mini-mental state.tw.
20. alzheimer*.tw.
21. mmse.tw.
22. caregivers.tw.
23. falls.tw.
24. Adl.tw.
25. Frailty.tw.
26. Gds.tw.
27. Ageing.tw.
28. hip fractures.tw.
29. elders.tw.
30. Frail*.tw.
31. Mci.tw.
32. Demented.tw.
33. Psychogeriatrics.tw.
34. cognitive impairment.tw.
35. postmenopausal women.tw.
36. dementia.tw.
37. aging.tw.
38. older.tw.
39. exp aged/
40. or/16-39
41. 15 and 40
42. predict*.tw.
43. scor*.tw.
44. observ*.tw.
45. observer variation.tw.
46. predictive value of tests.tw.
47. 42 or 43 or 44 or 45 or 46
48. 41 and 47

Q3. Prognostic scores: What is the most reliable risk model score to predict mortality in older and/or frail patients with advances CKD (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. (hemodialysis or haemodialysis).tw.
7. (hemofiltration or haemofiltration).tw.
8. (hemodiafiltration 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. Elderly.tw.
17. community-dwelling.tw.
18. geriatric.tw.
19. mini-mental state.tw.
20. alzheimer*.tw.
21. mmse.tw.
22. caregivers.tw.
23. falls.tw.
24. Adl.tw.
25. Frailty.tw.
26. Gds.tw.
27. Ageing.tw.
28. hip fractures.tw.
29. elders.tw.
30. Frail*.tw.
31. Mci.tw.
32. Demented.tw.
33. Psychogeriatrics.tw.
34. cognitive impairment.tw.
35. postmenopausal women.tw.
36. dementia.tw.
37. aging.tw.
38. older.tw.
39. or/16-38
40. 15 and 39
41. Validat$.mp. or Predict$.ti. or Rule$.mp. or (Predict$ and (Outcome$ or Risk$ or Model$)).mp. or ((History or Variable$ or Criteria or Scor$ or Characteristic$ or Finding$ or Factor$) and (Predict$ or Model$ or Decision$ or Identif$ or Prognos$)).mp. or (Decision$.mp. and ((Model$ or Clinical $).mp. or Logistic Models/)) or (Prognostic and (History or Variable$ or Criteria or Scor$ or Characteristic$ or Finding$ or Factor$ or Model$)).tw. [mp=title, abstract, original title, name of substance word, subject heading word, keyword

heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
42. 40 and 41
43. limit 42 to (english language and humans)

Q4a. In patients with renal failure (eGFR <45 mL/min/1.73 m^2) or on dialysis, older and/or frail, which is the best alternative to estimate functional status?

Q4b. Interventions aimed at increasing functional status in patients with renal failure (eGFR <45 mL/min/1.73 m^2 or on dialysis) and/or frail and older are of benefit?

MEDLINE search strategy

1. Kidney Diseases/
2. exp Renal Replacement Therapy/
3. Renal Insufficiency/
4. exp Renal Insufficiency, Chronic/
5. dialysis.tw.
6. (hemodialysis or haemodialysis).tw.
7. (hemofiltration or haemofiltration).tw.
8. (hemodiafiltration 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. Elderly.tw.
17. community-dwelling.tw.
18. geriatric.tw.
19. mini-mental state.tw.
20. alzheimer*.tw.
21. mmse.tw.
22. caregivers.tw.
23. falls.tw.
24. Adl.tw.
25. Frailty.tw.
26. Gds.tw.
27. Ageing.tw.
28. hip fractures.tw.
29. elders.tw.
30. Frail*.tw.
31. Mci.tw.
32. Demented.tw.
33. Psychogeriatrics.tw.
34. cognitive impairment.tw.
35. postmenopausal women.tw.
36. dementia.tw.
37. aging.tw.
38. older.tw.
39. exp aged/
40. or/16-39
41. 15 and 40
42. exp "Activities of Daily Living"/
43. functional decline.tw.
44. functional status decline.tw.
45. functional status decline.tw.
46. ADL decline.tw.
47. decreased physical function.tw.
48. exp mobility limitation/
49. 42 or 43 or 44 or 45 or 46 or 47
50. 41 and 49

COCHRANE CENTRAL search strategy

ID Search
#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 Aged, 80 and over
#15 Frail Elderly
#16 #14 or #15
#17 #13 and #16

Q5a. In patients with renal failure (eGFR <45 mL/min/1.73 m^2) or on dialysis, older and/or frail, which is the best alternative to evaluate nutritional status?

Q5b. Interventions aimed at improving nutritional status in patients with renal failure (eGFR <45 mL/min/1.73 m^2 or on dialysis), older and/or frail are of any benefit?

MEDLINE search strategy

1. Kidney Diseases/
2. exp Renal Replacement Therapy/
3. Renal Insufficiency/
4. exp Renal Insufficiency, Chronic/
5. dialysis.tw.
6. (hemodialysis or haemodialysis).tw.
7. (hemofiltration or haemofiltration).tw.
8. (hemodiafiltration 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. Elderly.tw.
17. geriatric.tw.
18. caregivers.tw.
19. Frailty.tw.
20. Ageing.tw.

21. elders.tw.
22. Frail*.tw.
23. Psychogeriatrics.tw.
24. cognitive impairment.tw.
25. aging.tw.
26. older.tw.
27. exp aged/
28. predict*.tw.
29. scor*.tw.
30. observ*.tw.
31. observer variation.tw.
32. predictive value of tests.tw.
33. 28 or 29 or 30 or 31 or 32
34. exp nutrition assessment/
35. exp Nutritional Status/
36. exp Protein-Energy Malnutrition/
37. exp Nutrition Disorders/
38. 34 or 36 or 37
39. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
40. 34 or 35 or 36 or 37
41. 15 and 33 and 39 and 40
42. limit 41 to (english language and humans)

COCHRANE CENTRAL search strategy

ID Search
#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 Aged, 80 and over
#15 Frail Elderly
#16 #14 or #15
#17 #13 and #16

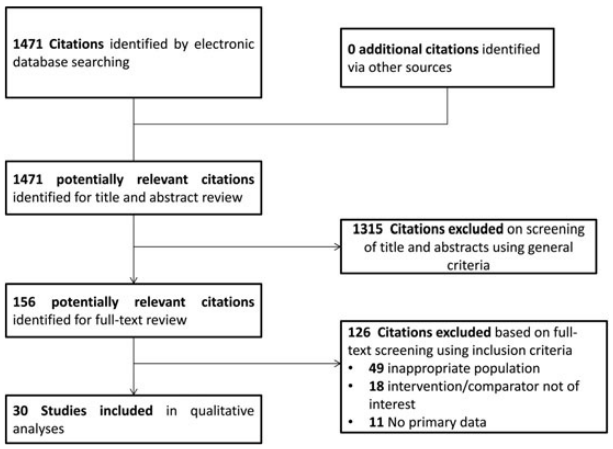
Q6. Access to renal replacement: what is the benefit of renal replacement therapy for older and or frail patients?

MEDLINE search strategy

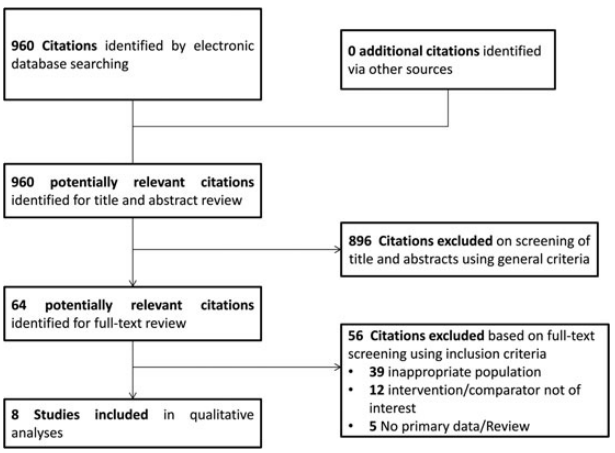
1. exp Renal Replacement Therapy/
2. exp Renal Insufficiency, Chronic/
3. dialysis.tw.
4. (hemodialysis or haemodialysis).tw.
5. (hemofiltration or haemofiltration).tw.
6. (hemodiafiltration or haemodiafiltration).tw.
7. (end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw.
8. (ESRF or ESKF or ESRD or ESKD).tw.
9. (CAPD or CCPD or APD).tw.
10. Elderly.tw.
11. geriatric.tw.
12. Frailty.tw.
13. Ageing.tw.
14. elders.tw.
15. Frail*.tw.
16. Psychogeriatrics.tw.
17. aging.tw.
18. older.tw.
19. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
21. 19 and 20
22. limit 21 to (abstracts and english language and humans and yr="1994 -Current")

APPENDIX 4. SELECTION OF STUDY FLOWCHARTS

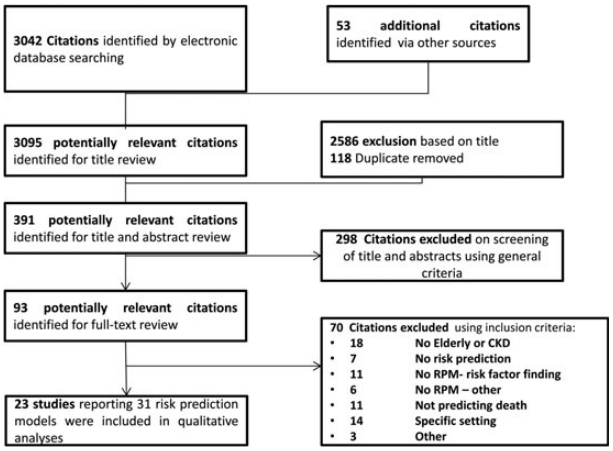
Question 1



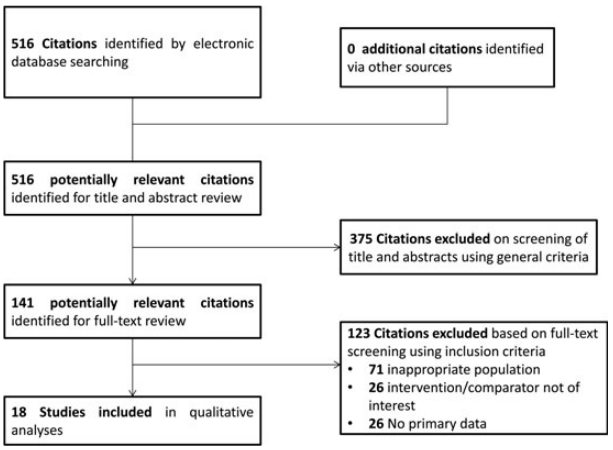
Question 2



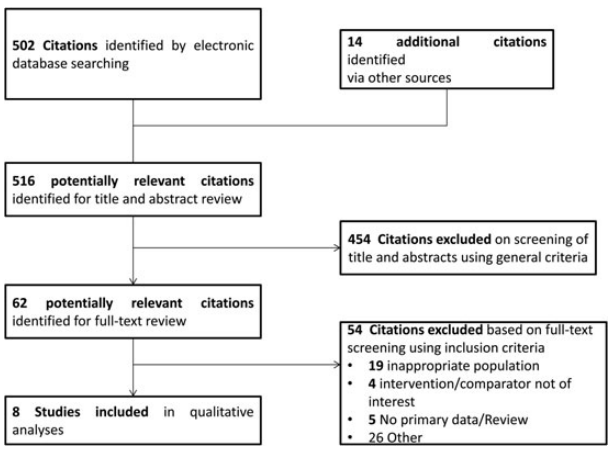
Question 3



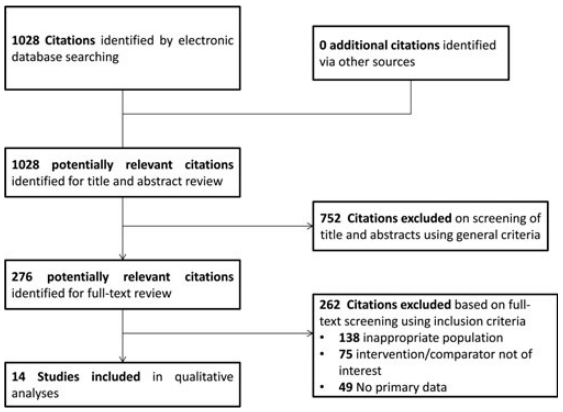
Question 4a



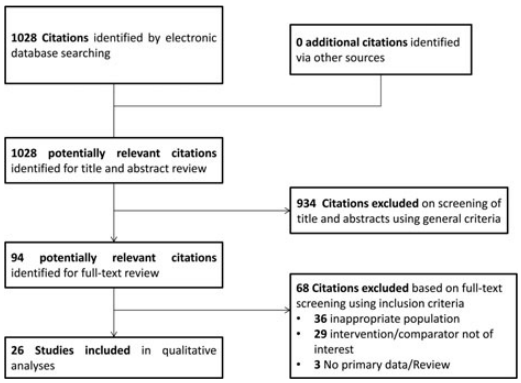
Question 4b



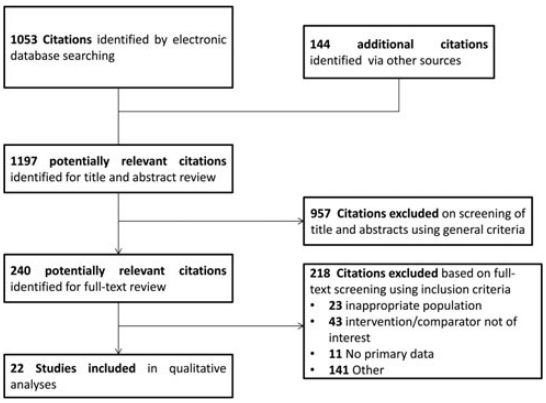
Question 5a



Question 5b



Question 6



APPENDIX 5. SUMMARY TABLES

Q1. What parameter should be used in older patients to estimate kidney function and/or for dose adaptation purposes?

Table A9

Q2. Prognostic scores: what is the most reliable risk prediction score to predict progression of CKD in older patients with advanced CKD (eGFR <45 mL/min/1.73 m^2)?

Table A10

Q3. What is the most reliable risk prediction model to predict mortality in older and/or frail patients with advanced CKD (eGFR <45 mL/min/1.73 m^2)

3.1 Descriptive data from included studies

Table A11

3.2 Performance characteristics of included studies

Table A12

Q4a. What is the best method to assess functional decline in older and/or frail patients with advanced CKD

Table A13

Q4b. Are interventions aimed at increasing functional status in patients with renal failure (eGFR <45 mL/min/1.73 m^2 or on dialysis) and/or the frail and older of benefit?

Table A14

Q5a. Which is the best alternative to evaluate nutritional status in older patients with CKD stage 3b or higher or on dialysis with advanced CKD (eGFR <45 mL/min/1.73 m^2).

Table A15

Q6. What is the benefit of renal replacement therapy for older patients with CKD stage 5?

Table A16

Table A9. Q1. What parameter should be used in older patients to estimate kidney function and/or for dose adaptation purposes?

Study Year Location	Inclusion criteria Exclusion criteria	Patients' characteristics	Intervention (*n*) Comparator(*n*) Duration	Outcome(s)	Results *P > 0.05	Quality of evidence
Koppe *et al.* [25] 2013 France	Caucasian patients over 70 with established or suspected renal impairment referred for inulin clearance Cr assay methodology: enzymatic method (Roche)	*N* = 224 Age 75.3 ± 4.1 Diabetes 21.9% mGFR 41.3 mL/min/1.73 m^2	Reference (mGFR): inulin clearance, Comparator eGFR equations: BIS-1; CKD-EPI; MDRD (*n* = 224)	For each comparator: Bias (median difference between eGFR and mGFR) Precision (SD of bias) Accuracy (root mean square error of eGFR–mGFR difference) Correlation (concordance correlation co efficient)	Bias (median): BIS-1 = 4.1; CKD EPI = 5.4; MDRD = 5.8 Precision (SD): BIS-1 = 9.21; CKD EPI = 10.83; MDRD = 12.78 Accuracy: BIS-1 = 10.17; CKD EPI = 12.77; MDRD = 14.9 Correlation: BIS-1 = 0.82 (0.77–0.86); CKD EPI = 0.79 (0.74–0.83); MDRD = 0.74 (0.68–0.79) BIS-1 equation most reliable creatinine-based equation in Caucasian patients over 70 versus MDRD and CKD EPI	Low risk of bias
Liu *et al.* [26] 2013 China	Inclusion: participants >60 years Exclusion: AKI, edema, skeletal muscle atrophy, pleural effusion or ascites, malnutrition, amputation, heart failure, ketoacidosis, cimetidine/trimethoprim, dialysis Cr assay methodology: enzymatic method (Roche)	*N* = 431 Age 69.9 ± 6.8 Diabetes 61% mGFR 53.4 ± 26.9 mL/min/1.73 m^2	Reference mGFR: 99mTc-DTPA Comparator eGFR equations: CG; MDRD; CKD-EPI_{CR}; CKD-$EPI_{Cr\text{-}Cyst}$	For each comparator: Bias (median difference between eGFR and mGFR) Precision (IQR of Bias) Accuracy (percentage of eGFR not deviating >30% from the mGFR)	Bias (median): CG = 2.5; MDRD = 0.4; CKD-EPI_{CR} = 0.5; CKD-$EPI_{Cr\text{-}Cyst}$= 5.7 Precision (IQR): CG = 23.6; MDRD = 23.6; CKD-EPI_{CR} = 23; CKD-$EPI_{Cr\text{-}Cyst}$= 19.5 Accuracy (%): CG = 57.7; MDRD = 57.5; CKD-EPI_{CR} = 55.5; CKD-$EPI_{Cr\text{-}Cyst}$= 59.9 Compared with Cr-based equations, CKD-EPI $_{Cr\text{-}Cyst}$ equation has more bias but better precision and accuracy in an elderly Chinese population	Moderate risk of information/detection and selection bias
Rimon *et al.* [27] 2004 Israel	Inclusion: >80 years old admitted to acute geriatric inpatient ward over 1 year + had urethral catheters for 48 h prior to enrollment Exclusion: terminally ill and sCr >2.5 mg/dL Cr Assay methodology: Kinetic Jaffee alkaline picrate assay	*N* = 154 Age 86.7 ± 5. 3 DM 22.7% mGFR (CrCl)	Reference mGFR: CrCl by 24 h urine Comparator GFR equations: CG; MDRD; Jelliffe	For each comparator: Bias (mean difference between eGFR and mGFR) Precision (SD of bias)	Bias (mean): CG = −0.51; MDRD = −0.008; Jelliffe = −0.47 Precision (SD): CG = 0.48; MDRD = 0.5; Jelliffe = 0.5	Moderate risk of information/detection bias
Lopes *et al.* [28] 2013 Brazil	Inclusion: >80 years inpatients Exclusion: institutionalized, unable to consent, acute infectious disease, cognitive impairment, heart failure, cirrhosis, dialysis, chronic pulmonary	*N* = 95 Age 85.3 ± 4.3 DM 23%; mGFR (iohexol) 55 ± 15 mL/min/1.73 m^2	Reference mGFR: iohexol clearance Comparator eGFR equations: MDRD; CKD-EPI_{Cr};	For each comparator: Bias (mean difference between eGFR and mGFR) Precision (SD of bias) Accuracy (percentage of eGFR	Bias (mean): MDRD = 4.6; CKD-EPI_{Cr}= 1.7; CKD-EPI_{Cyst}= −7.4; CKD-$EPI_{Cr.Cyst}$= −4.0; BIS_{Cr}= −6.6; $BIS_{Cr\text{-}Cyst}$= −8.3 Precision (SD):	Low risk of bias

Continued

Table A9. Q1. Continued

Study Year Location	Inclusion criteria Exclusion criteria	Patients' characteristics	Intervention (*n*) Comparator(*n*) Duration	Outcome(s)	Results *P > 0.05	Quality of evidence
	disease, immunosuppressive therapy within 6 months, previous chemotherapy for cancer, HIV infection, allergy to iodine. Cr assay methodology: Jaffe: colorimetric analysis		CKD-EPI$_{Cyst}$; CKD-EPI$_{Cr\text{-}Cyst}$; BIS$_{Cr}$; BIS$_{Cr\text{-}Cyst}$	not deviating >30% from the mGFR)	MDRD = 14.4; CKD-EPI$_{Cr}$= 13.3; CKD-EPI$_{Cyst}$= 14.5; CKD-EPI$_{Cr\text{-}Cyst}$= 11.7; BIS$_{Cr}$= 11.4; BIS$_{Cr\text{-}Cyst}$= 11.0 Accuracy (%): MDRD = 70.5; CKD-EPI$_{Cr}$= 74.7; CKD-EPI$_{Cyst}$= 65.3; CKD-EPI$_{Cr\text{-}Cyst}$= 85.3; BIS$_{Cr}$= 80; BIS$_{Cr\text{-}Cyst}$= 83.2	
Kilbride *et al.* [29] 2013 UK	Inclusion: >74 years Exclusion: reaction to iodinated contrast media, malignancy, life expectancy <3 months, inability to consent due to cognitive impairment, recent AKI, dialysis treatment Cr assay methodology: modified stable isotope-dilution electrospray tandem mass spectrometric	*N* = 394 Age 80 (74–97) DM 19% mGFR 53.4 (7.2–100.9)	Reference mGFR: iohexol clearance Comparator eGFR equations: MDRD; CKD-EPI$_{Cr}$; CKD-EPI$_{Cys}$; CKD-EPI$_{Cr\text{-}Cyst}$	For each comparator: Bias (median difference between eGFR and mGFR) Precision (IQR of bias) Accuracy (root mean square error of eGFR – mGFR difference) Accuracy (percentage of eGFR not deviating >30% from the mGFR)	Bias (median): MDRD = 3.5; CKD-EPI$_{Cr}$= 1.7; CKD-EPI$_{Cys}$= −1.2; CKD-EPI$_{Cr\text{-}Cyst}$= 0.8 Precision (IQR): MDRD = 13.7; CKD-EPI$_{Cr}$= 13.1; CKD-EPI$_{Cys}$= 14.2; CKD-EPI$_{Cr\text{-}Cyst}$= 12.7 Accuracy (RMSE): MDRD = 13.4; CKD-EPI$_{Cr}$= 10.9; CKD-EPI$_{Cys}$= 10.5; CKD-EPI$_{Cr\text{-}Cyst}$= 9.8 Accuracy (30%): MDRD = 81; CKD-EPI$_{Cr}$= 83; CKD-EPI$_{Cys}$= 86; CKD-EPI$_{Cr\text{-}Cyst}$= 86; CKD-EPI (all) performed better than MDRD	Low risk of bias
Chauvelier *et al.* [187] 2012 France	Inclusion: geriatric inpatients >75 years, bladder catheter for 48 h, and stable hemodynamic state Exclusion: unclear Cr assay methodology: Jasse's method	*N* = 157 Age 86.5 ± 6.1 DM no data Median mGFR 44 mL/min/1.73 m^2 (IQR 31.2–64.5)	Reference mGFR: CrCl by urine collection. Comparator eGFR equations: CG; MDRD4; MDRD6	For each comparator: Bias (median difference between eGFR and mGFR) Precision (SD of bias) Accuracy (percentage of eGFR not deviating >30% from the mGFR)	Bias (median): CG = −4.4; MDRD4 = 20.3; MDRD6 = 2.5 Precision (SD): CG = 23.1; MDRD4 = 27.4; MDRD6 = 23.5 Accuracy (%): CG = 63; MDRD4 = 37; MDRD6 = 59 In elderly hospitalized patients, CG and MDRD6 gave better predictions for measured CrCl than MDRD4, with no significant difference between them	Low risk of bias No gold standard mGFR
Fontsere *et al.* [24] 2006 Spain	Inclusion: Caucasian patients with stage 4 + 5 CKD, outpatients, no active co-morbidities, ambulatory and had regular review. Cr assay methodology: Jaffé alkaline pictrate	*N* = 87 Age 63.6 ± 12.1 DM no data mGFR = 22.2 ± 6.9	Reference mGFR: ^{51}Cr-EDTA Comparator eGFR equations: MDRD; sMDRD; CG; CrCl Mean Cr-Ur	For each comparator: Bias (mean difference between eGFR and mGFR) Precision + accuracy: Lin's concordance coefficient	Bias (mean): MDRD = −4.7; sMDRD = −3.8; CG = −1.1; CrCl = −0.03 Mean Cr-Ur = −5.4 Precision/accuracy: Lin's concordance coefficient MDRD = 0.47; sMDRD = 0.5; CG = 0.52; CrCl = 0.31 Mean Cr-Ur = 0.32	Moderate risk of selection bias

					In elderly subgroup analysis (age > 64 years) CG and sMDRD were most accurate. In poor nutritional status (Cr production) all formulae underestimated mGFR	
Dowling *et al.* [30] 2013 USA	Inclusion: subjects enrolled from Baltimore longitudinal study on aging, age >70 and mCrCl of <70 mL/min. Exclusion: overt signs of renal failure or on dialysis. Cr assay methodology: enzymatic method	*N* = 269 Age 80.7 ± 6 mGFR 52.8 ± 12.6	Reference mGFR: CrCl by 24 h urine collection. Comparator eGFR equations: MDRD; CG; CKD-EPI	For each comparator: Bias (mean difference between eGFR and mGFR) Precision (SD of bias) % discordance with 10 commonly prescribed drugs relative to CG	Bias (mean): MDRD = 12.8; CG = −3.2; CKD-EPI = 7.1 Precision (SD): MDRD = 17.5; CG = 14.2; CKD-EPI = 15.1 % Discordance median (range) MDRD = 28.6 (2.2–44.6); CKD-EPI = 22.9 (2.2–36.4) MDRD and CKD-EPI overestimated mGFR and should not be used in older individuals to alter drug doses	Low risk of bias
Xun *et al.* [31] 2010 China	Inclusion: patients with CKD >60 years Exclusion: AKI, edema, muscle atrophy, pleural effusion or ascites, malnutrition, amputation, heart failure, ketoacidosis, on dialysis, cimetidine therapy Cr assay methodology: enzymatic (Roche)	*N* = 103 Unclear mean age Unclear mean mGFR Unclear DM %	Reference mGFR: 99mTcDPTA renal dynamic imaging Comparator eGFR equations: CG; SC-reciprocal; Gate; Hull; Jelliffe 1973 and 1971; Mawer; Bjomsson; MDRD1; abbreviated MDRD	For each comparator: Bias (median difference between eGFR and mGFR) Precision (IQR of bias) Accuracy (percentage of eGFR not deviating >30% from the mGFR)	Bias (median): CG = −5.73; SC-recip = 17.49; Gate = 1.94; Hull = −4.42; Jelliffe 1973 = −5.52; Jelliffe 1971 = 5.02; Mawer = −8.83; Bjomsson = −40.85; MDRD1 = 1.69; AbMDRD = 1.81 Precision (IQR): CG = 12.57; SC-recip = 25.85; Gate = 20.81; Hull = 14.82; Jelliffe 1973 = 13.71; Jelliffe 1971 = 20.1; Mawer = 14.97; Bjomsson = 65.49; MDRD1 = 20.18; AbMDRD = 19.85 Accuracy (%): CG = 59.2; SC-recip = 35; Gate = 53.4; Hull = 56.3; Jelliffe 1973 = 64.1; Jelliffe 1971 = 44.7; Mawer = 48.5; Bjomsson = 10.7; MDRD1 = 60.2; AbMDRD = 54.4 GFR-estimation equations show great bias in elderly Chinese CKD patients	Low risk of bias
Zhu *et al.* [32] 2014 China	Inclusion: patients >19 years old Exclusion: severe heart failure, acute renal failure, pleural or abdominal effusion, serious edema or malnutrition, skeletal muscle atrophy, amputation, ketoacidosis were excluded; patients who were taking trimethoprim or cimetidine or ACEI therapy	*N* = 788 Age 54 (IQR 41–65) mGFR 76.35 (59.03–92.50) DM 10.66%	Reference mGFR: 99mTcDPTA renal dynamic imaging. Comparator eGFR equations: $CKD\text{-}EPI_{2012Cyst}$; $CKD\text{-}EPI_{2012Cr\text{-}Cyst}$; $CKD\text{-}EPI_{2009Scr}$; C-MDRD; MacIssac; Ma	For each comparator: Bias (median difference between eGFR and mGFR) Precision (IQR of bias) Accuracy (root mean square error of eGFR – mGFR difference) Accuracy (percentage of eGFR not deviating >30% from the mGFR)	Results (age >60 subgroup) Bias: $CKD\text{-}EPI_{2012Cyst}$= −14.16; $CKD\text{-}EPI_{2012Cr\text{-}Cyst}$= −9.46; $CKD\text{-}EPI_{2009Scr}$= −2.66; C-MDRD = 3.01; MacIssac = −4.64; Ma = 0.54 Precision (IQR):$CKD\text{-}EPI_{2012Cyst}$= 19.48; $CKD\text{-}EPI_{2012Cr\text{-}Cyst}$= 16.46; $CKD\text{-}EPI_{2009Scr}$= 18.01; C-MDRD = 23.96; MacIssac = 19.42; Ma = 18.19 Accuracy (RMSE) $CKD\text{-}EPI_{2012Cyst}$= 19.31;	Moderate risk information/detection bias

Continued

Table A9. Q1. Continued

Study Year Location	Inclusion criteria Exclusion criteria	Patients' characteristics	Intervention (*n*) Comparator(*n*) Duration	Outcome(s)	Results *P > 0.05	Quality of evidence
					CKD-EPI$_{2012Cr\text{-}Cyst}$= 15.60; CKD-EPI$_{2009SCr}$= 14.66; C-MDRD = 19.70; MacIssac = 14.28; Ma = 15.81 Accuracy (%) CKD-EPI$_{2012Cyst}$= 76.04; CKD-EPI$_{2012Cr\text{-}Cyst}$= 68.40; CKD-EPI$_{2009Scr}$= 76.04; C-MDRD = 68.06; MacIssac = 79.51; Ma = 76.39	
Levey *et al.* [33] 2009 International	Inclusion: study populations with a measured GFR using exogenous filtration marker, ability to calibrate serum Cr assay No published exclusion criteria		Reference mGFR: iothalamate. Comparator eGFR; CKD-EPI; MDRD	Measurement of bias, accuracy and precision against a reference measured eGFR and comparison of MDRD and CKD-EPI	CKD-EPI has less bias, improved accuracy and precision than MDRD	Limited number of elderly people included
Giannelli *et al.* [34] 2007	Inclusion: participants in the InCHIANTI study with normal range serum Cr. Exclusion: urine collection of <22 h and missing values for BMI and serum creatinine or Cr outside normal range	*N* = 660 Age, male 73.9 ± 6.5, female 74.4 ± 6.6 years No mGFR	Reference mGFR: CG; Cr Cl (24 h urine)	To estimate the magnitude of renal function misclassification in a community-dwelling elderly population with normal serum creatinine values	Serum Cr normal ranges will miss GFR <60 which increases with age and reduction in body mass	Moderate risk of information/detection bias No gold standard mGFR
Nyman *et al.* [35] 2011 Sweden	Inclusion: enrollment in Lund-Malmo study; aged 18 and over referred for determination of GFR	*N* = 850 subjects Age 60 (26–85) mGFR 55 (9–121)	Reference mGFR: iohexol clearance Comparator eGFR equations CKD-EPI; MDRD	For each comparator: bias (median difference between eGFR and mGFR) Precision (IQR of bias) Accuracy (percentage of eGFR not deviating >30% from the mGFR)	(Elderly subgroup—no exact data by elderly subgroup analysis) Bias (age 70 – 79, *n* = 167): CKD-EPI = 6.3; MDRD = 7.6; Bias (age 80+, *n* = 64): CKD-EPI = 7.6; MDRD = 17.7 Accuracy (%, age 70–79): CKD-EPI = 81.4; MDRD = 82 Accuracy (%, age 80+): CKD-EPI = 82.8; MDRD = 71.9	Low risk of bias
Pei *et al.* [36] 2013 China	Inclusion: Exclusion: heart failure, acute renal failure, pleural abdominal effusion, serious edema or malnutrition, skeletal muscle atrophy, amputation or ketoacidosis, glucocorticoid therapy	*N* = 534 (elderly subgroup) Age 54 ± 15.79 mGFR 72.71 ± 24.97 DM: no data	Reference mGFR: 99mTc-DTPA Comparator eGFR Cr based: CG; MDRD; CKD-EPI Cystatin-C based: Tan; Grubb; Macissac; Hoek; Hojs Cr and Cystatin C based Ma	For each comparator: bias (mean difference between eGFR and mGFR) Accuracy (percentage of eGFR not deviating >30% from the mGFR)	Elderly subgroup analysis (CKD 4/5) Bias: CG = 2.42; MDRD = 1.64; CKD-EPI = 3.5; Tan = 1.53; Grubb = 8.94; Macissac = −1.01; Hoek = 1.11; Hojs = −1.14; a = 1.66 Accuracy (%): CG = 52.62; MDRD = 42.11; CKD-EPI = 42.11; Tan = 36.84; Grubb = 21.05; Macissac = 26.32; Hoek = 36.84; Hojs = 36.84; Ma = 52.63 CG most accurate for CKD stage 4 + 5 in elderly, in CKD 2 + 3 MaciIssac most accurate and CKD 1 Hojs and Ma equations	Moderate risk selection bias Low risk of bias

Schaeffner *et al.* [37] 2012 Germany	Inclusion: taken from Berlin initiative cohort. Exclusion: under 70 years, having different health insurance, dialysis or transplant	*N* = 570 Age 78.5 mGFR 60.3 (15.5–116.7) DM 24%	Reference mGFR: iohexol clearance Comparator eGFR equations: BIS 1; BIS 2; MDRD; CKD-EPI; CysC2; CysC3	For each comparator: Bias (mean difference between eGFR and mGFR) Precision (SD of bias) Accuracy (percentage of eGFR not deviating >30% from the mGFR)	(Results from validation sample *n* = 285) Bias (mean): BIS 1 = 0.11; BIS 2 = 0.09; MDRD = 11.21; CKD-EPI = 8.94; CysC2 = 3.22; CysC3 = 9.32 Precision (SD): BIS 1 = 9.2; BIS 2 = 8.06; MDRD = 11.38; CKD-EPI = 10.12; CysC2 = 10.71; CysC3 = 9.84 Accuracy (%): BIS 1 = 95.1; BIS 2 = 96.1; MDRD = 70.9; CKD-EPI = 77.9; CysC2 = 89.1; CysC3 = 81.4 BIS 1 or BIS 2 equations should be used to evaluate GFR in the elderly with renal impairment	
Fehrman-Ekholm *et al.* [38] 2004	Inclusion: >70 years old and above. Exclusion criteria: no data	*N* = 52 Age 82.3 (71–110) mGFR 67.7 ± 10.8	Reference mGFR: iohexol clearance Comparator eGFR equations: CG; Walser; Levey	For each comparator Bias (median difference between eGFR and mGFR) Precision (95% range of bias) Accuracy (percentage of eGFR not deviating > 30% from the mGFR)	Correlation (R^2) CG = 0.52; Walser = 0.42; Levey = ?? Levey equation gives most accurate prediction of Cr clearance. Elderly decline renal function by 1 mL/min/year	No measurement of bias, precision or accuracy Limited patients with advanced CKD
Evans *et al.* [39] 2013 Sweden	Inclusion: referred to the Swedish CKD registry with eGFR <30 mL/min/1.73 m^2 Exclusion: no data	*N* = 2198 Age 67.3 (19.4–94) Median mGFR: 16 mL/min/1.73 m^2	Reference mGFR: iohexol clearance Comparator eGFR equations: Lund-Malmo; CKD-EPI; MDRD; MAYO; CG	For each comparator: Bias (median difference between eGFR and mGFR) Precision (95% range of bias) Accuracy (percentage of eGFR not deviating >30% from the mGFR)	Bias (median): Lund-Malmo = 0.7; CKD-EPI = 1.2; MDRD = 1.6; MAYO = 1.7; CG = 4.6 Precision (95% range): Lund-Malmo = (0.5–0.9); CKD-EPI = (0.9–1.5); MDRD = (1.4–1.9); MAYO = (1.4–2.0); CG = (4.3–4.8); Accuracy (%): Lund-Malmo = 75.6; CKD-EPI = 66.8; MDRD = 65.2; MAYO = 67.5; CG = 53.6 All equations inaccurate in elderly and those with diabetic nephropathy	Low risk of bias
Pequignot *et al.* [40] 2009 France	Inclusion: inpatients in geriatric ward >65 with indwelling catheter for >48 h Exclusion: AKI, heart failure, dehydration	*N* = 121 Age 86.1 ± 6.7 mGFR 48.3 mL/min/1.73 m^2 (IQR 31–52.6)	Reference mGFR: CrCl by urine collection Comparator eGFR equations: CG; MDRD	For each comparator: Bias (mean difference between eGFR and mGFR) Precision (SD of bias) Accuracy (percentage of eGFR not deviating >30% from the mGFR)	Bias (mean): CG = −3.5; MDRD = 20.1; Precision (SD): CG = 22.5; MDRD = 28.2 Accuracy (%): CG = 66.1; MDRD = 35.5 In hospitalized very elderly patients CG gives better accuracy than MDRD	Moderate risk of selection bias Concern over malnutrition affecting results. Lack of gold standard for mGFR
Bjork *et al.* [41] 2012 Sweden	Inclusion: non-transplant patients >16 years old referred for determination of GFR	*N* = 1397 Age 61 (19–83) mGFR 41 (12–116)	Reference mGFR: iohexol clearance Comparator eGFR equations: revised Lund-Malmo; MDRD; CKD-EPI	For each comparator: Bias (median difference between eGFR and mGFR) Precision (IQR of bias) Accuracy (percentage of eGFR	Bias (median): r Lund-Malmo = −2.1; MDRD = −0.8; CKD-EPI = 0.8 Precision (IQR): r Lund-Malmo = 11.9; MDRD = 12.3; CKD-EPI = 11.7 Accuracy (%) : r Lund-Malmo = 83.5;	Low-risk differences in Cr methodology make the generalizability of these results difficult

Continued

Table A9. Q1. Continued

Study Year Location	Inclusion criteria Exclusion criteria	Patients' characteristics	Intervention (*n*) Comparator(*n*) Duration	Outcome(s)	Results *P > 0.05	Quality of evidence
				not deviating >30% from the mGFR)	MDRD = 79.5; CKD-EPI = 79.1 LM revised was more stable in terms of bias and accuracy across age and BMI groups than MDRD and CKD-EPI	
Liu *et al.* [42] 2013	Inclusion: >65 years with CKD Exclusion: published elsewhere	*N* = 378 Age 72.8 ± 5.7 mGFR 39.5 ± 20.2 DM 42.8%	Reference mGFR: 99mTc-DTPA Comparator eGFR equations: Asian formula; Tai formula; Japanese formula; Korean formula; Chinese formula 1; Chinese formula 2	For each comparator: Bias (median difference between eGFR and mGFR) Precision (IQR of bias) Accuracy (percentage of eGFR not deviating >30% from the mGFR)	Bias (median): Asian formula = 2.59; Tai formula = 3.74; Japanese formula = −6.71; Korean formula = 11.72; Chinese formula 1 = 2.22; Chinese formula 2 = 3.69 Precision (IQR): Asian formula = 21.4; Tai formula = 22.48; Japanese formula = 13.14; Korean formula = 22.06; Chinese formula 1 = 23.06; Chinese formula 2 = 15.53 Accuracy (%): Asian formula = 49.2; Tai formula = 48.4; Japanese formula = 54; Korean formula = 37.8; Chinese formula 1 = 47.4; Chinese formula 2 = 59.3	Moderate risk of methods and outcomes bias—uses DPTA as gold standard
Marx *et al.* [43] 2004 UK	Inclusion: oncology patients >70 referred for EDTA GFR No exclusion data	*N* = 225 Age 74 (70–89) mGFR 76 (23–172) mL/min/1.73 m^2	Reference mGFR: [51Cr]-EDTA Comparator eGFR equations: Jelliffe; CG; Wright	For each comparator: Bias (mean % error) Precision (mean absolute % error)	All 3 eGFR equations tested have imprecision and bias at the extremes of renal function. Wright showed least bias	No data on GFR <50 mL/min/1.73 m^2 cancer patients with no data on nutrition or edema, cachexia scores
Bevc *et al.* [44] 2011	Inclusion: adults >65 years referred for EDTA GFR assessment Exclusion: no data	*N* = 317 Age 72.7 ± 5.1 mGFR 34 ± 22.6 mL/min/1.73 m^2	Reference mGFR: 51Cr-EDTA Comparator eGFR equations: MDRD; CKD-EPI$_{Cr}$; CKD-EPI$_{Cr\text{-}Cyst}$ Simple Cystatin-C formula	For each comparator: Bias (mean difference between eGFR and mGFR) Precision (SD of bias) Accuracy (percentage of eGFR not deviating >30% from the mGFR)	Bias (mean): MDRD = −20.2; CKD-EPI$_{Cr}$= −22.2; CKD-EPI$_{Cr\text{-}Cyst}$= −20.8; Simple Cystatin-C formula = 7 Precision (SD): MDRD = 14.9; CKD-EPI$_{Cr}$= 14.9; CKD-EPI$_{Cr\text{-}Cyst}$= 12.3; simple Cystatin-C formula = 17.8 Accuracy (%) (stage 3 CKD): MDRD = 77.9; CKD-EPI$_{Cr}$= 71.6; CKD-EPI$_{Cr\text{-}Cyst}$= 76.8; simple Cystatin-C formula = 47.4 Accuracy (%) (stage = 4 CKD): MDRD = 56.6; CKD-EPI$_{Cr}$= 54; CKD-EPI$_{Cr\text{-}Cyst}$= 60.2; simple Cystatin-C formula = 28.3 Accuracy (%) (stage 5 CKD): MDRD = 55.2; CKD-EPI$_{Cr}$= 39.7; CKD-EPI$_{Cr\text{-}Cyst}$= 63.8; simple Cystatin-C formula = 6.9 All formulae lacked precision, Cystatin-C was no worse than Cr-based and Cr-Cyst-based formulae	Moderate risk of selection bias No gold standard

Terpos *et al.* [21] 2013 Greece	Inclusion: newly diagnosed symptomatic myeloma Exclusion: no data published	*N* = 220 Age: 69 (36–94)	?	?	?	
Fontsere *et al.* [23] 2009	Inclusion: outpatients, age 60+, and plasma Cr >1.5 mg/dL Exclusion: heart failure, asthma, corticosteroid therapy, thyroid disorders	*N* = 40 Age 73.9 (8.5) mean (SD) mGFR 36.9 (9.2)	Reference mGFR: ^{51}Cr-EDTA Comparator eGFR: cystatin-C based: Hoek; Larsson; Stevens Cr based: MDRD-isotope dilution mass spectrometry (IDMS); CG	For each comparator eGFR equations: Bias (mean difference between eGFR and mGFR) Precision (95% range of Bias) Accuracy + precision Lin coefficient	Bias (mean): Hoek = −0.2; Larsson = −2.9; Stevens = 2.6; MDRD-IDMS = −14.6; CG = −12.5 Precision (95% range): Hoek = (−27.9, 27.4); Larsson = (−32.7, 26.7); Stevens = (−37.1, 42.3); MDRD-IDMS = (−23.8, −4.2); CG = (−22.5, −2.1) Accuracy and Precision Lin's Coefficient: Hoek = 0.48; Larsson = 0.44; Stevens = 0.58; MDRD-IDMS = 0.35; CG = 0.4 Cr-based, predictive formula (MDRD and CG) significantly underestimated GFR (negative bias) compared with Cystatin-based which was down to the influence of lean mass	Moderate risk of selection bias
Lamb *et al.* [17] 2005 UK	Inclusion: unclear	*N* = 46 Age = 80 ± 4.9 mGFR 54.7 ± 17 mL/min/1.73 m^2	Reference mGFR: ^{51}Cr-EDTA Comparator eGFR: CG; MDRD Reference Cr method: IDMS Comparator Cr analysis Enzymatic (ortho); Enzymatic (Roche); Jaffe rate (Roche)	To assess the contribution of creatinine method differences to variation in estimates of GFR	Estimates of GFR depend critically on the accuracy and precision of the creatinine measurement used in their calculation	Moderate risk of selection bias
Verhave *et al.* [16] 2005 France	Inclusion: serum Cr <1.5 mg/dL Exclusion: atherosclerosis (stroke, coronary and peripheral artery disease), heart failure, proteinuria, diabetes mellitus, alcohol abuse, cimetidine, trimethoprim, fibrate therapy	*N* = 850 Age 48.1 ± 15 mGFR 99.3 ± 20.2 mL/min/1.73 m^2	Reference mGFR = 99mTc-DTPA Comparator eGFR equations: CG; MDRD Comparator Cr analysis: Enzymatic; Jaffe	Bias of renal function estimates according to age and BMI	In obesity both CG and MDRD are unreliable. MDRD performance better in older subjects and CG in younger. Use of enzymatic versus Jaffe Cr analysis significantly affected results	Moderate risk of selection bias excluded patients with significant CKD

Table A10. Q2. Prognostic scores: what is the most reliable risk prediction score to predict progression of CKD in older patients with advanced CKD (eGFR <45 mL/min/1.73 m^2)?

Study Year Location	Design	Inclusion criteria Exclusion criteria	Patients' characteristics	Intervention (*n*) Comparator (n) Duration	Outcome(s)	Results	Quality of evidence
Dalrymple *et al.* [45] 2011 USA	Prospective cohort study	Inclusion: ≥65 years and eGFR <60 Exclusion: institutionalization, use of a wheelchair within the home, hospice care, current chemotherapy or radiation for cancer	Community-dwelling older people from the CHS: mean age 75 years mean eGFR 51	eGFR <60–45 (*n* = 985) eGFR <45 (*n* = 283)	ESKD (need for RRT) All-cause mortality CV mortality	Event rates/100 person-years: eGFR <60-45: ESKD 0.3 (0.2, 0.4); mortality 6.1 (5.6, 6.6); CV mortality 2.6 (2.3, 3.0) eGFR <45: ESKD 1.8 (1.2, 2.4); mortality 10.3 (8.8, 11.7); CV mortality 4.8 (3.8, 5.8) Independent risk factors for ESKD: male, African-American, BMI ≥25, lower eGFR Independent risk factors for death: older age, male, BMI <18.5, hypertension, diabetes, cardiovascular disease, heart failure, former and current tobacco use	Good quality study but no measure of proteinuria available No risk score Subgroup with eGFR <45 small. Primary purpose of study was to study epidemiology of cardiovascular disease
De Nicola *et al.* [46] 2012 Italy	Prospective cohort study	Inclusion: eGFR <60; attendance at nephrology clinic >1 year Exclusion: AKI within 6 months	Consecutive patients attending 25 nephrology clinics Mean age 67 years Mean eGFR 31 mL/min/1.73 m^2	Age <65 years (*n* = 481) Age 65–75 years (*n* = 410) Age >75 years (*n* = 357)	ESKD (start of RRT) Death without ESKD	Overall risk of ESKD exceeded risk of death without ESKD Event rates in 3 age groups: ESKD: 9.0 (95% CI: 7.8–10.4), 7.3 (95% CI: 6.1–8.8), 7.9 (95% CI: 6.4–9.8) Death without ESKD: 1.2 (95% CI: 0.8–1.7), 5.2 (95% CI: 4.2–6.5), 12.6 (95% CI: 10.7–14.9) Independent risk factors for ESKD: age, male, lower BMI, lower Hb, higher phosphate, interactions between age and proteinuria, age and CVD Independent risk factors for death without ESKD: age, CVD, ESKD, higher uric acid, lower Hb Interaction between diabetes and age	Good quality study Highly selected study population All Caucasian No risk score
Drawz *et al.* [48] 2013 USA	Retrospective cohort study	Inclusion: age ≥65 years; eGFR <30 Exclusion: on dialysis or with kidney transplant	Elderly male patients from two VA hospitals Developmental cohort: mean age 77.5 years; 95% male; 12% Black; mean GFR 25 Validation cohort: mean age 78.1 years; 98% male 8% Black; mean GFR 25	Developmental cohort: *n* = 1866 Validation cohort: *n* = 819	ESKD within 1 year of index GFR ESKD = GFR <15 or RRT	Final predictive model included: eGFR, age, CHF, SBP (average of last 5), most recent potassium and albumin, and interactions between age and eGFR and eGFR and CHF. *c*-statistic = 0.854 *c*-statistic in validation cohort = 0.823 *c*-statistic for Tangri risk score in both cohorts = 0.780	Predominantly male study population GFR range lower than in PICO Retrospective study Validation cohort similar to developmental cohort, therefore external validation required
Faller *et al.* [47] 2013 France	Prospective multicenter cohort study	Inclusion: age ≥80 years; creatinine 170 µmol/L (males) or 150 µmol/L (females); new referral to nephrology or <9 months follow-up Exclusion: dialysis initiation planned within 3 months	Mean age 85 years; mean GFR 24	*n* = 155	Initiation of dialysis or death at 2 years	Cox proportional hazards model: only eGFR <23 predicted ESKD Fine and Gray analysis: eGFR <23 and DBP predicted ESKD	Poor quality study: small study population 25 participants lost to follow-up or no longer followed up No risk score
Tangri *et al.* [50] 2011		Inclusion: age >65 years; eGFR <45	NA	NA	Initiation of RRT	4-variable model included age, sex, eGFR, albuminuria 8-variable model included: age, sex, eGFR, albuminuria, serum calcium, serum phosphate, serum bicarbonate and serum albumin *c*-statistic for 4- and 8-variable model for risk at 2- and 5-years 0.86–0.88 Calibration factor required to improve performance in European populations	Likely good quality study with inclusion criteria that exactly match the PICO

Q3. What is the most reliable risk prediction model to predict mortality in older and/or frail patients with advanced CKD (eGFR <45 mL/min/1.73 m^2)

Table A11. 3.1. Descriptive data from included studies

Development studies							
Study Year	Index	Population	CKD stage*	Participants (*n*)	Events, [*n*] (%)	Predictors (*n*)	Time span of prediction (years)
Inouye *et al.* [62] 2003		≥70 years, hospital admission	–	525	145 (28%)	5	1
Carey *et al.* [59] 2004		≥70 years, community dwelling	–	4516	464 (10%)	6	2
Porock *et al.* [67] 2005		≥65 years, nursing home residents	–	32 599	7485 (23%)	14	0.5
Lee *et al.* [64] 2006	Lee index	>50 years, community dwelling	–	11 701	1361 (12%)	12	4
Mazzaglia *et al.* [66] 2007		≥65 years, community dwelling	–	2470	108 (4%)	5	1.25
Levine *et al.* [65] 2007	Levine index	≥65 years, hospitalized	–	2739	722 (26%)	9	1
Johnson *et al.* [52] 2007		≥20 years	–	6541	298	6	5
Carey [58] 2008		>55 years, community dwelling eligible for nursing home care	–	2232	290 (13%) 821 (37%)	8	1 3
Walter *et al.* [70] 2001		≥70 years, hospitalized	–	1495	492 (33%)	5	1
Schonberg [68] 2009		>65 years, community dwelling	–	16 077	2930 (18%)	11	5
Couchoud [74] 2009	REIN score	≥75 years, incident ESKD	5d	2500	470 (19%)	10	0.5
Lee *et al.* [63] 2009	USRDS index–Liu score	All ages, nursing home residents	–	1820	985 (54%)	5	5
Liu *et al.* [76] 2010	Liu score	All ages, incident ESKD, 9 months on RRT	5d	33 077	26/100 patient years	15	1–6
Gagne *et al.* [60] 2011	Romano/Charlson score	≥65 years, community dwelling	–	123 855	9289	3	1
	Van Walraven/ Elixhauser score					3	
	Combined score					3	
Han *et al.* [61] 2012	PROMT	>65 years, self-reported declining health	–	21 870	3295 (15%)	11	0.5
Sharifi *et al.* [69] 2012	OPMI	All ages, nursing home residents no financial resources	–	247	74 (30%)	4	3
van Diepen [78] 2014		All ages, incident ESKD with diabetes, 3 months on RRT	5d	394	82 (21%)	7	1
Cheung *et al.* [73] 2014	Modified Hec score	≥67 years, incident ESKD on RRT	5d	44 109	10 289	5	0.5
	Combined Liu/Hec score	≥67 years, incident ESKD on RRT	5d	44 109	10 289	2	0.5
	REIN score + age	≥67 years, incident ESKD on RRT	5d	44 109	10 289	2	0.5
	Liu score + age	≥67 years, incident ESKD on RRT	5d	44 109	10 289	2	0.5
	Modified Hec score + age	≥67 years, incident ESKD on RRT	5d	44 109	10 289	2	0.5
	Combined Liu/Hec score + age	≥67 years, incident ESKD on RRT	5d	44 109	10 289	3	0.5
Bansal *et al.* [71] 2015	Bansal score	≥65 years, community dwelling	>2	828	283 (34%)	9	5
Weiss *et al.* [72] 2015	Model 1	≥65, ≤79 years, community dwelling	≥4 not 5D	4054	1276 (31%)	12	1
	Model 2	≥80 years, community dwelling					
Thamer *et al.* [77] 2015	Simple risk score	≥67 years, incident ESKD on RRT	5D	52 796	6477 (12%) 10 718 (20%)	7	0.25 0.5
	Comprehensive risk score	≥67 years, incident ESKD on RRT	5D	52 796	6477 (12%) 10 718 (20%)	14	0.25 0.5
		≥75 years, incident ESKD	5d	12 500	1296 (10%)	9	0.25

Continued

Table A11. 3.1. Continued

Development studies							
Study Year	Index	Population	CKD stage*	Participants (*n*)	Events, [*n*] (%)	Predictors (*n*)	Time span of prediction (years)
Couchoud *et al.* [188] 2015							
Validation studies							
Internal validation							
Carey *et al.* [59] 2004		≥70 years, community dwelling	–	2877	358 (12%)	6	2
Porock *et al.* [67] 2005		≥65 years, nursing home residents	–	10 878	2147 (20%)	14	0.5
Lee *et al.* [64] 2006	Lee index	>50 years, community dwelling	–	8009	1072 (13%)	12	4
Mazzaglia *et al.* [66] 2007		≥65 years, community dwelling	–	1722	114 (7%)	5	1.25
Levine *et al.* [65] 2007	Levine-index	≥65 years, hospitalized	–	3643	950 (26%)	9	1
Schonberg *et al.* [68] 2009		>65 years, community dwelling	–	8038	1650 (21%)	11	5
Carey *et al.* [58] 2008		>55 years, community dwelling eligible for nursing home care	–	1667	245 (15%) 670 (40%)	8	1 3
Couchoud *et al.* [74] 2009	REIN score	≥75 years, incident ESKD	5d	1642	307 (19%)	10	0.5
Liu *et al.* [76] 2010	Liu score	All ages, incident and prevalent ESKD, 9 months on RRT	5d	33 166 *incident 1999* 35 891 *incident 2001* 142 517 *prevalent 2000*	26 per 100 py 26 per 100 py 25 per 100 py	15	1–6
Han *et al.* [61] 2012	PROMT	>65 years, self-reported declining health	–	21 870	NA	11	0.5
van Diepen *et al.* [78] 2014		All ages, incident ESKD with diabetes, 3 months on RRT	5d	394 bootstrapping	82 (21%)	7	1
Weiss *et al.* [72] 2015		≥65 years, community dwelling	≥4 not 5d	4054	1276 (31%) (multiple imputation)	12	1
Thamer *et al.* [77] 2015	Simple risk score	≥67 years, incident ESKD on RRT	5d	23 626	2081 (9%) 3396 (14%)	7	0.25 0.5
	Comprehensive risk score	≥67 years, incident ESKD on RRT	5D	23 626	2081 (9%) 3396 (14%)	14	0.25 0.5
Couchoud *et al.* [188] 2015		≥75 years, incident ESKD	5d	11 848	1255 (11%)	9	0.25
External validation							
Inouye *et al.* [62] 2002		≥67 years, discharged confirmed pneumonia	–	1246	488 (39%)	5	1
Walter *et al.* [70] 2001		≥70 years, hospitalized	–	1427	398 (28%)	5	1
Cruz 2013	Lee index (2006) 10 year	>50 years, community dwelling	–	8009	2508	12	10
Cheung *et al.* [73] 2014	Rein-score	≥67 years, incident ESKD on RRT	5d	44 109	1014 (2%)	10	0.5
	Liu score	≥67 years, incident ESKD on RRT	5d	44 109	1014 (2%)	12	0.5
Bansal *et al.* [71] 2015	Bansal score	≥70 ≤79 years, community dwelling without major functional impairment	>2	789	125 (16%)	9	5

Table A12. 3.2. Performance characteristics of included studies

Development studies						
Study Year	Index	Calibration[a]	Discrimination[b]	Model fit[c]	Diagnostic characteristics reported[d]	Validation
Inouye *et al.* [62] 2003		NA	0.83	NA	NA	External
Carey *et al.* [59] 2004		NA	0.76	NA	NA	Internal
Porock *et al.* [67] 2005		NA	0.76	NA	NA	Internal
Lee *et al.* [64] 2006	Lee-index	NA	0.84	NA	NA	Internal
Mazzaglia *et al.* [66] 2007		NA	0.75 (95% CI: 0.72–0.78)	NA	NA	Internal
Johnson *et al.* [52] 2007		NA	0.7	NA	NA	NA
Levine *et al.* [65] 2007	Levine-index	NA	0.67	NA	NA	Internal
Carey *et al.* [58] 2008		NA	0.66	NA	NA	Internal
Walter *et al.* [70] 2001		NA	0.75	NA	NA	External
Schonberg *et al.* [68] 2009		NA- other	0.75	NA	NA	Internal
Couchoud *et al.* [74] 2009	Rein-score	NA	NA	NA	NA	Internal
Liu *et al.* [76] 2010	USRDS index/Liu score	NA	NA	NA	NA	Internal
Gagne *et al.* [60] 2011	Romano/Charlson score	NA	0.78 (95% CI: 0.776–0.780)	NA	NA	NA
	van Walraven/Elixhauser score	NA	0.77 (95% CI: 0.770–0.775)	NA	NA	NA
	Combined score	NA	0.79 (95% CI: 0.786–0.791)	NA	NA	NA
Han *et al.* [61] 2012	PROMPT	NA	NA	NA	NA	Internal
Sharifi *et al.* [69] 2012	OPMI	NA	NA	NA	NA	NA
Cheung *et al.* [73] 2014	Modified Hec score	NA	0.65	NA	NA	NA
	Combined Liu/Hec score	NA	0.67	NA	NA	NA
	REIN score + age	NA	0.66	NA	NA	NA
	Liu score + age	NA	0.65	NA	NA	NA
	Modified Hec score + age	NA	0.68	NA	NA	NA
	Combined Liu/Hec score + age	NA	0.70	NA	NA	NA
Bansal *et al.* [71] 2015	Bansal score	7.8 (P = 0.4)	0.72 (95% CI: 0.68–0.74)	NA	NA	External
Weiss *et al.* [72] 2015	Model 1 (aged 65–79)	12,2 (P = 0.14)	NA	NA	NA	Internal
	Model 2 (aged ≥80)	5.2 (P = 0.74)	NA	NA	NA	Internal
Thamer *et al.* [77] 2015	Simple risk score	NA	0.68	36 981	NA	Internal (temporal)
	Comprehensive risk score	NA	0.71	36 132	NA	Internal (temporal)
Couchoud *et al.* [188] 2015		NA	NA	NA	NA	Internal
Validation studies						
Internal validation						
Carey *et al.* [59] 2004		NA	0.74	NA	NA	
Porock *et al.* [67] 2005		P = 0.16	0.75	NA	NA	
Lee *et al.* [64] 2006	Lee index	NA	0.82	NA	NA	
Mazzaglia *et al.* [66] 2007		NA	0.75 (95% CI: 0.73–0.78)	NA	NA	
Levine *et al.* [65] 2007	Levine index	NA	0.65	NA	NA	
Schonberg *et al.* [68] 2009		NA	NA	NA	NA	
Carey *et al.* [58] 2008		NA	0.69	NA	NA	
Couchoud *et al.* [74] 2009	REIN score	P = 0.93	0.7	NA	NA	
Liu *et al.* [76] 2010	USRDS index/Liu score	NA	0.67	438 240	NA	
Han *et al.* [61] 2012		NA	0.75	NA	YES	
van Diepen *et al.* [78] 2014		Calibration slpe	0.79	NA	NA	
Weiss *et al.* [72] 2015		NA	0.68	NA	NA	
Thamer *et al.* [77] 2015	Simple risk score Comprehensive risk score	NA	0.69 0.72	11 753 NA	NA NA	

Continued

Table A12. 3.2. Continued

Development studies						
Study Year	Index	Calibration[a]	Discrimination[b]	Model fit[c]	Diagnostic characteristics reported[d]	Validation
		Correlation coefficient				
External validation						
Inouye *et al.* [62] 2003		NA	0.77	NA	NA	
Walter *et al.* [70] 2001		NA	0.79	NA	NA	
Cruz 2013		P = 0.38	0.83 (95% CI: 0.83–0.84)	NA	NA	
Cheung *et al.* [73]	REIN score	NA	0.63	NA	NA	
2014	Liu score	NA	0.62	NA	NA	
Bansal *et al.* [71] 2015		3.96; P = 0.9	0.69 (95% CI: 0.64–0.74)	NA	NA	
Couchoud *et al.* [74] 2009		NA	0.75 (95% CI: 0.74–0.76)	NA	NA	

[a]Hosmer Lemeshow.
[b]c-statistic or AUROC.
[c]−2 log likelihood or the Akaike–Bayes information criterion.
[d]Sensitivity/specificity; PPV/NPV.

Table A13. Q4a. What is the best method to assess functional decline in older and/or frail patients with advanced CKD?

Study Year Location	Inclusion criteria Exclusion criteria	Patients' characteristics	Outcome(s)	Results
Kutner *et al.* [89] 1994 USA	On dialysis, >60 years old	287 patients, mean age 68.6 ± 5.9, 31% black men, 19% black men, 28% black women, 23% white woman	Functional status index: ADLS, time in bed or chair and KPS Outcome: mortality	Functional status associated with survival in multivariate cox regression model (−0.002, P = 0.01)
McClellan *et al.* [90] 2010	Population-based cohort 59.2% were white and 45.3% were male	28 923 CKD, mean age 65.3 years; hypertension 58.6%, diabetes mellitus 21.2%, dyslipidemia 58.6%, coronary heart disease 22.8%, cerebrovascular disease 9.9%, and cancer 14.5%.	Inactivity question SF12	OR for inactivity: GFR <30 versus CKD 60–89 = 3.72 (2.88–4.79). Adjusted OR = 1.67 (0.78, 2.86). SF12 PCS: mean score 46.4 (10.4). The fully adjusted PCS declined from 40.9 to 37.3 as GFR declined from >90 to 15–29 mL/min/1.73 m^2
Farrokhi *et al.* [91] 2013	Exclusion: unable or unwilling to participate, or resident in a long-term institutional setting	167 patients aged >65 years, chronic in-center hemodialysis (57% men) mean age of 74.8 ± 5.9 years (range, 64.5–93.9 years)	Intervention: 4 item ADL scale Comparator: Barthel index Outcome: survival	Agreement: κ 0.78 for 4 item scale versus Barthel index Sensitivity: 83.2%; specificity 100%. Positive and negative predictive values: 100 and 76.9%. Internal consistency 0.66 Severe disability (score 4 on 4 item scale) = associated with higher risk of death (4 versus 0: OR = 12.58 (95% CI: 2.44–65.01)
Bowling *et al.* [92] 2014	Community-dwelling Medicare beneficiaries from the University of Alabama at Birmingham Study of Aging who had sCrea measured during a baseline in-home study visit and completed at least one telephone follow-up	390 older adults, mean age 77.6 ± 5.8 years, 41% African American, 50.5% women	UAB Study of Aging Life-Space Assessment is a validated measure that reflects mobility and social participation	Risk of decline in life space score OR: 1.33 (95% CI: 1.05–1.70) when GFR <45 versus >60 mL/min/1.73 m^2
Kutner *et al.* [93] 2014	>18 years, English or Spanish speaking, dialysis vintage <3 months, able to give consent Excluded: on PD or home HD	*N* = 742, mean age 57.2 (14.1), >65 years 28.4%, male 59.4%, 50.7% diabetic	Fried index used to assess frailty.	Prefrail (OR 1.93; 95% CI: 1.01–3.68) and frail (OR 11.32; 95% CI: 5.49–23.32) associated with need for ADL assistance
Anderson *et al.* [94] 1993	Unclear	228 nursing home residents on HD between 4/1990 and 12/1991. Age 17–101 years 60.5% >65 years 25% admitted to NH. 51% male, 86.7% HD, 37.4% white	Modified ADLS to assess functional status Outcome: survival	Poor ADLS score (<8) associated with higher risk of death (HR 2, 95% CI: 1.6–2.6)
Kutsuna *et al.* [95] 2011	HD patients. Excluded: hospitalized <3 months prior to the study, recent MI, uncontrolled cardiac arrhythmias, hemodynamic instability, uncontrolled hypertension, severe arthralgia or myalgia, severe motor paralysis or dementia, or had been performing regular exercise training for >3 months prior to the study, missing data for one or more of the analytical variables	*N* = 65 (study 1), *n* = 83 (study 2), *n* = 29 (study 3). study 1: age = 66 ± 10 years, *M* = 24/65; study 2 age = 66 ± 8 years, *M* = 40/83. study 3 exercise grp: 63 ± 8, *M* = 4/14, control: 64 ± 7, *M* = 4/15	QDUE-HD, FIM, muscle grip strength	QDUE-HD: Cronbach alpha: light work 0.92, holding activities 0.87 Correl. versus hand grip strength: light work 0.42 P < 0.001, Holding activities 0.31, P < 0.01, FIM 0.19 ns
Painter *et al.* [98] 2000	Exclusion criteria: angina, lower extremity amputation, orthopedic disorder exacerbated by activity, chronic lung disease, and cerebral vascular disease manifested by transient ischemic attacks Inclusion: adult on HD for at >3 months	286 HD patients; age 55.9 ± 15.15 (int) versus 52.8 ± 16.8 (ctrl) Female: 57.1% (int) versus 65.4% (ctrl), no. of comorbidities: 3.0 ± 1.4 (int) versus 2.6 ± 1.7 (ctrl) time on dialysis: 33.7 ± 35.6 (int) versus 40.2 ± 62.4 (ctrl) months	Gait speed, STS, 6-min walk test (6MWT) used to assess functional status SF36 QoL	Improvement in scores over time in the intervention group compared with ctrl
		27 HD (24 completed the study), age 61.3 ± 9.0 years, female 8/27, diabetes 6/27, 4 or more	6MWT grip strength, pinch strength, chair-rising time and	No significant change in grip strength, chair-rising time, 6MWT or FIM among ambulatory HD patients

Continued

Table A13. Q4a. Continued

Study Year Location	Inclusion criteria Exclusion criteria	Patients' characteristics	Outcome(s)	Results
Hsieh *et al.* [97] 2010	Inclusion criteria: able to walk independently for 6 min, MMSE >23 exclusion: infection, angina or arrhythmia in the last 3 weeks	comoridities 16/27, dialysis vintage 63 (6–240) months	FIM used to measure functional status, WHOQOL-BREF—QoL	at the 16-month follow-up assessment No correlation between pinch strength, QoL and age, sex, duration of dialysis, diabetes, functional performance or VO_2 peak
DeOreo *et al.* [104] 1997	Unclear inclusion criteria	1000 HD patients assessed between 1994 and 1995; age 58.2 ± 15.4 years 50% men, 23% white, 36% diabetes	Outcome: survival and hospitalization SF36 used to assess physical function	SF36 PCS associated with survival (HR = 10.4, 95% CI: 1.1–18), and hospital days (HR = 5.8, 95% CI: 4.0–7.7
Kutner *et al.* [96] 2010	Included: patients from CDS cohort who were working in the year before starting dialysis	585 dialysis patients from cohort of 1643, mean age 59.6 ± 14.2, male 55%, black 28.4%, diabetes 52.7%	Human activity profile (HAP) to assess functional status	HAP associated with higher likelihood of continued employment = OR 1.04, 95% CI: 1.02–1.05
Walker *et al.* [106] 2013	Systematic review	20 332 patients from 7 studies 10 592 from the 2 studies that related frailty to a patient relevant outcome	Roshanravan score Modified Fried Frailty Criteria	Wilhelm-Leen score: mortality in frail versus non frail patients HR 2.0, 95% CI: 1.5–2.7 Roshanravan score: Frail versus non frail death or dialysis HR 2.5, 95% CI: 0.9–2.87
Saito *et al.* [99] 2007	All patients admitted to the Geriatric Dialysis Rehabilitation Program regardless of initial ambulatory status	$N = 30$, mean age was 74.6 ± 7.5 years Male 19/30; dialysis vintage 4.4 ± 3.7 years CCI 7.1 ± 2.4	STS compared with FIM as gold standard	Reliability: ICC 0.89 (95% CI: 0. 80–0.94). Inter-rater reliability: 0.99 (95% CI: 0.98–0.99 The change in STS scores correlated inversely with the absolute change in FIM scores ($r - 0.875$, $P = 0.000$)
Lo *et al.* [100] 2008	All >65 years of age on dialysis, admitted between June 2007 and Aug. 2007 Assesses functional status before and 1 week after hospitalization	$N = 35$, age 72.9 ± 5.9 years, male 62.8%, PD 29%	Basic ADLS, Lawton score, timed up and go, handgrip strength, trail test, clock test	73.3% of patients (95% CI: 54.1–87.7) experienced a decline in personal functional independence in association with hospitalization
Kutner *et al.* [101] 2015	Adults, treated by HD for at least 3 months, giving informed consent. Exclusion criteria: PD or home HD; active malignancy; expected relocation. Persons with significant mental illness Probably not representative patient group (selection bias)	756 prevalent HD patients aged 20–92 years	Gait speed used to assess physical function 4 groups: <0.6 m/s, 0.6 to <0.8 m/s, 0.8 to <1.0 m/s, ≥1.0 m/s	Increase of 0.1 m/s in gait speed higher mortality risk (HR 1.17; 95% CI: 1.05–1.31) Cox model (adjusted at baseline): gait speed <0.6 versus >0.6 m/s HR = 2.17 (1.19–3.98); unable versus able to mobilize HR = 6.93 (4.01–11.96) At 12 months baseline walk speed ≥1.0 m/s versus 0.6 to <0.8 m/s hospitalization OR 2.04 (95% CI: 1.19–3.49) and ADL difficulty OR 3.88 (95% CI: 1.46–10.33) and an estimated change in SF36 PCS of 8.20 (95% CI: 13.57–2.82)
Lopes *et al.* [102] 2014	Dialysis patients enrolled in the DOPPS study Excluded: missing data on comorbidity, physical activity, HRQoL, and depression symptoms, or unable to walk	$N = 5763$ Age: never active 68.6 ± 12.8, infrequently active 62.7 ± 14.7, sometimes active 62.0 ± 14.5, often active 61.9 ± 14.5, very active 59.5 ± 14.9	RAPA to assess functional status Outcomes: mortality, depression (CESD), HRQoL (KdQoL)	HRQoL scores very active versus never/rarely active: 6.7 points (95% CI: 5.79–7.56) for PCS, 3.7 points (95% CI: 2.76–4.65) for MCS, and 9.9 points (95% CI: 7.75–11.99) for KDB The associations of muscle strength and flexibility activity with HRQoL and depression symptoms were weak and inconsistent Compared with never/rarely active patients, the extensively adjusted HR was 0.89 (95% CI: 0.72–1.10) for infrequently active, 0.84 (95% CI: 0.67–1.05) for sometimes active, 0.81 (95% CI: 0.68–0.96)

				for often active, and 0.60 (95% CI: 0.47–0.77) for very active (P for trend <0.001)
Torino *et al.* [105] 2014	Included adult dialysis patients (HD and PD) enrolled in the EXCITE trial, who completed 6-min walk test at baseline	296 participants, dialysis vintage-median = 44 months (IQR 26–83). HD = 247. Age 65 ± 13 years, 68% male, 21% diabetic, 76% cardiovascular comorbidities	6MWT Outcome: composite end-point including mortality, fatal and non-fatal cardiovascular events and hospitalizations	Increase in walk distance by 20 m associated with lower risk of composite endpoint: HR: 0.94, CI: 0.91–0.98 death: HR 0.89, CI: 0.84–0.94 hospitalizations: HR 0.96, CI: 0.92–0.99. CV events: HR 0.96, CI: 0.91–1.01
Segura-Orti *et al.* [103] 2011	Hemodialysis patients; inclusion/exclusion unclear	*N* = 39 (32 male); age 60.3 ± 15.8 years, dialysis vintage 25 (range 6–152) months, median number of comorbidities 3 (range 1–5)	6MWT, STS-10, STS-60, one-leg heel-rise test and handgrip strength test	Intraclass coefficient: STS 10 0.88 (0.78–0.94), STS 60 0.97 (0.94–0.98), 6MWT 0.94 (0.89–0.97),one leg heel raise (right) 0.97 (0.92–0.99), one leg heel raise (left) 0.94 (0.85–0.97). Hand grip strength dominant 0.96 (0.88–0.99) and nondominant 0.95 (0.83–0.98)
Osthus *et al.* [107] 2012 Norway	Primary aim was to determine association between HRQoL (SF36 and SF12) and mortality	All patients ≥18 years on HD or PD >2 months. Exclusion criteria: impaired cognitive function, psychosis, or drug abuse 252 patients, 60.2 ± 15.5 years, 65.9% males, dialysis vintage 9.0 (IQR 5.0–23.0) months. Mortality during follow-up was 33.7% (85 deaths) SF36 PCS: 36.6 ± 10.4 (range 9.6–58.2); SF36 MCS 47.3 ± 11.0 (16.9–70.7); SF12 PCS 35.5 ± 9.9 (13.3–56.6); and SF12 MCS 46.9 ± 10.9 (16.7–70.4)	Mortality Follow-up 4.5 years	SF36 PCS versus SF12 PCS: $\rho = 0.93$, $P < 0.001$ SF36 MCS versus SF12 MCS: $\rho = 0.95$, $P < 0.001$ Mortality rate was highest in patients in the lowest quartile of SF12 PCS ($\chi^2 = 15.3$, $P = 0.002$) and SF36 PCS ($\chi^2 = 16.7$, $P = 0.001$). MCS was not associated with mortality Adjusted hazard ratios for mortality highest versus lowest quartile: SF12 PCS: 2.5 (95% CI: 1.0–6.3); SF36 PCS: 2.7 (95% CI: 1.1–6.4) A one unit increase in the SF12 PCS and of the SF36 PCS score was related to 3.2 and 2.3% lower adjusted HR of death
Lacson*et al.* [108] 2010 USA	Validate SF12 versus SF36 Patients who had scorable SF36 and SF12 from 1/2006 to 12/2006, treated at Fresenius Medical Care, North America facilities	44 395 patients (55% response rate) age 61.2 ± 15.1 years; 46% female; 57% white; 51% diabetes; mean vintage 3 years, HD 94%	Death and first hospitalization followed for up to 1 year from the date of survey.	SF36 PCS versus SF12 PCS and SF36 MCS versus SF12 MCS: both Pearson coefficients 0.94, $P < 0.0001$). The risk profiles are similar with SF36 PCS and SF12 PCS as well as between SF36 MCS and SF12 MCS Each incremental SF12 PCS and SF36 PCS point: 2.4% lower adjusted HR of death and 0.4% decline in HR for first hospitalization (both $P < 0.0001$). For each MCS point: 1.2 (SF12 MCS) and 1.3 (SF36 MCS)

Table A14. Q4b. Are interventions aimed at increasing functional status in patients with renal failure (eGFR <45 mL/min/1.73 m^2 or on dialysis) and/or the frail and older of benefit?

Study Year Location	Inclusion criteria Exclusion criteria	Patients' characteristics	Intervention (n) Comparator (n) Duration	Outcome(s)	Results	Quality of evidence	Notes
RCTs							
Chen *et al.* [111] 2010 Boston	Inclusion: - ≥30 years - Serum albumin <4.2 g/dL - HD 3 times a week for >3 m Exclusion: - Unstable cardiovascular disease - Any uncontrolled chronic condition - Cardiac surgery <6 m - Myocardial infarction <6 m - Joint replacement or lower extremity fracture <6 m - Severe cognitive impairment - Lower extremity amputation - Current strength training	HD patients Mean age: 71.1 ± 12.6 years (intervention)– 66.9 ± 13.4 years (control) M/F: 10/12–11/11 Duration of HD: 2.6 ± 2.6–4.8 ± 5.2 years	Intervention: - 2 times a week during the 2 h of dialysis - 48 exercises sessions - Supervised sessions - 5 min warm-up, 5 min cool-down - Only lower body exercises with ankle weights and pelvic tilt without using free weights - Allocated to strength training (n = 25), received intervention (n = 19), testing n = 25-22-19-8 (0–24 s – 36–48 s) Comparison: 'Attention-control participants' - Stretching exercises with light resistance bands. - Allocated to attention control (n = 25), received intervention (n = 20), testing n = 25-22-20-12 (0–24 s to 36–48 s)	* Short physical performance battery (SPPB) * Knee extensor strength (kg) * Whole body lean mass (kg) * Leg lean mass (kg) * Whole-body fat mass (kg) * Leisure-time physical activity (PASE score) * SF36 physical component * SF36 mental component * ADL disability score	Strength (P value) Pre: 5.0–6.0 (P = 0.05) Post: 7.0–6.5 %change: 21.1–0.2 (P = 0.03) Pre: 11.4–14.8 (P = 0.08) Post: 15.8–12.1 %change: 44.9 to −18.1 (P = 0.0001) Pre: 45.8–47.8 (P = 0.5) Post: 4.9–46.3 %change: 4.2 to −3.2 (P = 0.0001) Pre: 6.9–7.2 (P = 0.5) Post: 7.2–6.9 %change: 5.0 to −3.2 (P = 0.0001) Pre: 31.3–30.8 (P = 0.9) Post: 29.6–33.1 %change: −2.6–11.0 (P = 0.02) Pre: 47.5–28.6 (P = 0.2) Post: 57.5–22.7 %change: 10.3 to −30.5 (P = 0.0001) Pre: 46–52 (P = 0.08) Post: 54–50 %change: 21 to −2 (P = 0.02) Pre: 37–39 (P = 0.6) Post: 37–38 %change: 6–1 (P = 0.6) Pre: 6.3–6.8 (P = 0.2) Post: 7.0–6.7 %change: 10.5 to −2.6 (P = 0.02)	1. Sequence generation: MR. Unknown 2. Allocation concealment: MR. Unknown 3. Blinding: HR. No blinding 4. Incomplete data asses: LR adequate 5. Selective outcome reporting: LR 6. Intention to treat: MR, chance of primary outcome (post versus final testing) 7. Sponsor: LR No sponsoring	- Initially they have intended to use the final-testing SPPB score (after 48 sessions) for the primary outcome, but based on the number of interruptions in training, they used the post testing SPPB score (after 36 sessions) or mid-testing score as necessary (24 sessions) - SPPB improvement was due to an reduction in chair stand time. Balance and gait speed did not change in either group - Adherence: 89% in the strength group, 90% in the control group
Prospective interventional trial							
Anding *et al.* [110] 2015 Germany	Inclusion: - Maintenance HD ≥3 m - Dialysis 3 times a week for 4–5 h - Stable medical condition Exclusion: - Symptomatic ischemic heart disease - Orthopedic or musculoskeletal problems interfering with exercise training	HD patients Mean age: 63.4 ± 13.8 years – M/F: 11/8–6/6–7/8 Duration of HD: 4–4.5 years Mean Hb: 10.78 g/dL	Intervention: - Combined endurance (bed-cycle ergometer) and resistance training (8 muscle group, with individual target repetition rate), 2 times a week, during the first 2 h of dialysis - Direct supervision of an experienced exercise specialist - Regular maximal exercise tests provided new individual baseline parameters for the next training - 1 year - 5 year for participation rate	Strength Strength improvement after 12 m (R12/R0–1) (%) *Leg extensor * Leg curl * Back * Adductor * Abdomen * Biceps * Triceps * Abductor Endurance improvement after 3 m (P3/P1-1) (%)	HA (P-value) MA (P-value) HA: 89 ± 15 (P ≤ 0.0001) MA: 74 ± 22 (P ≤ 0.002) HA: 34 ± 10 (P ≤ 0.0001) MA: 48 ± 30 (P ≤ 0.09) HA: 112 ± 31 (P = 0.0004) MA: 79 ± 58 (P ≤ 0.19) HA: 100 ± 21 (P ≤ 0.0001) MA: 61 ± 32 (P ≤ 0.045) HA: 140 ± 32 (P ≤ 0.0001) MA: 74 ± 32 (P ≤ 0.033) HA: 33 ± 7.9 (P ≤ 0.0001)	1. Sequence generation: HR. No controlled trial 2. Allocation concealment: HR. No controlled trial 3. Blinding: HR. No blindation 4. Incomplete data asses: LR Adequate 5. Selective outcome reporting: LR	- LA group: None showed a significant improvement over the 12 months - Participation rate: 36 of 46 patients were still exercising after 1 year, 20 patients were still exercising after 5 years, 18 forced drop out (died or transplanted), 8 unforced drop out 'Adherence rate of 80% after 5 y' - Costs for training: 8 euro/patient/day

			High adherence (HA)
			>80% of the target sessions completed in the first year
			(*n* = 19)
			Moderate adherence (MA)
			60–80% of the sessions completed
			(*n* = 12)
			Low adherence (LA)
			<60% of the sessions completed
			(*n* = 5)
			Drop out After 1 year:
			(*n* = 10)
				* 6 min walking test (m)
				* Timed up and go (s)
				* Sit to stand 60 s (STS60) (rep/min)
					MA: 16 ± 15 (P ≤ 0.28)
					HA: 47 ± 11 (P ≤ 0.0001)
					MA: 5.6 ± 11 (P = 0.59)
					HA: 129 ± 29 (P ≤ 0.0001)
					MA: 43 ± 16 (P = 0.0007)
					HA: 55% (P = NS)
					MA: 45% (P = NS)
					360 ± 132//374 ± 134 (NS)//403 ± 141 (P = 0.0002) 10.1 ± 4.0//9.1 ± 3.5 (P = 0.002)//7.5 ± 2.8 (P ≤ 0.0001)
					16.7 ± 8.3//20.5 ± 8.8 (P = 0.0053)//24.2 ± 10.2 (P ≤ 0.0001)
						6. Intention to treat: LR
						7. Sponsor: LR. No sponsoring	

Heiwe *et al.* [112] 2001 Sweden	Inclusion: - Age >60 years - GFR <25 mL/min/1.73 m^2 iohexol clearance - K <5.5 mmol/L - Bic >21 mmol/L Hb >10 g/dL - Stable medical condition Exclusion: - Orthopedic disability - Neurological symptoms of disease which could affect their ability to participate in the exercise training program	Elderly pre-dialysis patients Mean age: 72–79 years Mean GFR uremic group: 16–18 mL/min/1.73 m^2	Intervention: Regular exercise program - Individually strength training (dynamic/static) by sets of knee extensions with a weight of 60% of 1RM. The weight was adjusted every other week - A low-intensive group exercise program followed for 30 min for general muscle endurance, balance, co-ordination and stretching - The session was concluded with 10 min of relaxation - 3 times a week for 12 weeks - Uremic exercise group (16) - Healthy exercise group (18) Comparison: - Sedentary lifestyle during 12 weeks - Uremic comparison group (9) - Healthy comparison group (5)	- Bicycle ergometer test (baseline only) * 1 RM quadriceps (kg) * Dynamic musc. endurance (repetitions) * Statistic musc. endurance (s) * 6-min walking test (m) * Timed 'Up & go' (s) * Sickness impact profile	Intervention group: U: 87% (range 64–113%; H: 89% (range 83–187%) Before (range) – After (range) (P) U: 8 ± 5–13 ± 5 (P < 0.0001) H: 10.1 ± 4.0–17 ± 4 (P = 0.004) U: 37 (14–57)–48 (30–101) (P = 0.004) H: 38 (18–187)–69 (40–227) (P = 0.004) U: 28 (12–60)–32 (15–150) (P = NS) H: 40 (17–158)–57 (10–147) (P = NS) U: 390 ± 128–452 ± 99 (P = 0.002) H: 466 ± 101–534 ± 109 (P< 0.001) U: 11(9–46)–9 (7–27) (P = 0.004) H: 11(6–36)–9 (6–21) (P = 0.0007) U: No sign change H: No sign change In the uremic and the healthy comparison group the scores remained unchanged	1. Sequence generation: HR. No RCT 2. Allocation concealment: HR. No RCT 3. Blinding: HR. No blindation 4. Incomplete data asses: LR Adequate 5. Selective outcome reporting: LR 6. Intention to treat: LR 7. Sponsor: LR No sponsoring	- Small group size - There were sign. differences between the predialysis patients and the healthy subjects at baseline: the predialysis patients had significant lower scores in strength, static muscular endurance and 6-min walking test. - The aim of the study was to compare the effect of an exercise program between healthy and uremic group
Kutsuna *et al.* [95] 2011 Sagamihara, Japan	Inclusion: 'Outpatients who went to the HD center 3/week to receive maintenance HD' Exclusion: Hospitalization 3 m prior to the study; recent myocardia; infarction/angina pectoris; uncontrolled arrhythmias;	HD patients Mean age: 63 ± 8–64 ± 7 years M/F: 4/10–4/11 Duration of HD: 20.6–21.7 m	Intervention: (EG) - The training session was carried out 3/week before HD sessions; Consist of 4 resistance training exercises with elastic tubing, shoulder external rotation, seated row, chest press, biceps curl (*n* = 14) - The physical therapist prescribed the	Physical function * Handgrip strength * Biceps strength * Palmar pinch strength * Key pinch strength * Active ROM shoulder * Active ROM hand - QDUE-HD	* Sign. Improvement in EG * Sign. Improvement in EG * No sign. Improvement * No sign. Improvement * No sign. Improvement * No sign. Improvement	1. Sequence generation: HR. Unclear selection of EG/CG 2. Allocation concealment: HR. No RCT 3. Blinding:	The primary aim of the study was to develop a novel questionnaire evaluating disability in the ADL in the upper extremities of HD patients ->QDUE-HD, composed of 11 items Only 29 of 88 patients agreed to participate in the 3rd part of the study (exercise study)

Continued

Table A14. Q4b. Continued

Study Year Location	Inclusion criteria Exclusion criteria	Patients' characteristics	Intervention (n) Comparator (n) Duration	Outcome(s)	Results	Quality of evidence	Notes
	uncontrolled hypertension; hemodynamic instability; severe arthralgia/myalgia; severe motor paralysis/dementia; being performing regular training >3 m; missing data for one of more of the analytic variables	Hb: 10.7–10.5 g/dL	exercise training. - If the patient had a rating ≥14 for perceived exertion, the intensity and repetitions were reduced. - 6 week, 3 times a week Comparison: (CG) - Control group, not performing such training during 6 week (n = 15)	* Light work *Holding activity - FIM score	*Sign. Improvement EG * Sign. Improvement EG No sign improvement	HR. No blindation 4. Incomplete data asses: LR adequate 5. Selective outcome reporting: LR 6. Intention to treat: MR It was not the primary goal of the study 7. Sponsor: LR No commercial funding	All patients were able to complete the 6-week exercise training without suffering arthralgia
Mercer *et al.* [113] 2002 UK Manchester	Inclusion: - Hb >10 g/dL - Kt/V urea >1 - Interdialytic weight gain <2.5 kg - Predialysis potassium <5.5 mmol/L Exclusion: - Recent myocardial infarction (<6 weeks) - Uncontrolled arrhythmias - Uncontrolled hypertension - Unstable angina - Sympt. LV dysfunction - Uncontrolled DM - Neurological disorder with functional deficit	HD/PD (16/6)–patient (Exercise – Control) Mean age: 63 ± 14.559 ± 12.3 years M/F: 6/1–5/2 Duration of dialysis: 2.5 ± 1.5–3.8 ± 2.8 years Hb: 11.0 ± 0.7–10.7 ± 0.6 g/dL	Intervention: (ER) - 2 sessions per week (HD patients on dialysis days before dialysis; PD patients with 2 L of fluid in the abdominal cavity) - In hospital under supervision of a physician, a physiotherapist, and a exercise physiologist - Combination of intermittent aerobic exercises on a cycle ergometer and a local muscular endurance circuit of eight exercises - Intensity was adjusted when subjects reported reductions in exercise training RPE - 10–15 min warm-up and cool-down components (n = 7: 13 recruited, 12 presenting for initial exercise tolerance assessment, 3 drop out before intervention, 2 drop out of the exercise program because of lack of interest) - 12 weeks Comparison: (CO) - Normal activity during 12 weeks (n = 7: 9 were recruited, 7 completed both assessment)	Walk: North Staffordshire Royal Infirmary walking-stair-climbing test: = 50 m walk, 22 steps up, 22 steps down, 50 m walk * Total time (s) * Stair climb(s) * Stair descent(s) * Rating of perceived exertion overall (6–20) * Rating of perceived exertion legs (6–20) Interviewer-admixture Walking Impairment Questionnaire Self-reported degree of difficulty: Perceived Walking Capability * Walking speed (%) * Walking distance (%) Perceived exercise Tolerance * Leg weakness (%) * Breathlessness (%)	Pre – Post – Mean change (%) *P< 0.05 ER: 146.0–126.0* – 15 CO: 139.1–141.7 – -2 ER: 18.8 – 14.8*–22 CO: 17.5–18.2 – -2 ER: 21.7–17.8* – 18 CO: 19.8–20.9 – -5 ER: 12–11.8 CO: 11.7–11.9 ER: 12.1–11.6 CO: 12.0–12.6 ER: 28–43* – 15 CO: 38–35 – -3 ER: 53–65–12 CO: 58–62–4 ER: 64–89*–25 CO: 75–65 – -10 ER: 50–82*–32 CO: 71–68 – -3	1. Sequence generation: HR. No RCT 2. Allocation concealment: HR. No RCT 3. Blinding: HR. No blindation 4. Incomplete data asses: LR Adequate 5. Selective outcome reporting: LR 6. Intention to treat: LR 7. Sponsor: LR No sponsoring	* Small group size * Important drop out (before start) in the intervention group.
Ota *et al.* [114] 1997 Japan Okayama	Inclusion: - >60 years - HD for at least 6 months, at least 2–3 times a week for 3–4 h - Inactive lifestyle before Exclusion: Not mentioned	HD patients Mean age: 68 ± 6–69 ± 4 years M/F: 3/10–4/2 Duration of dialysis: 57 ± 45–58 ± 21 m Hematocrit: 26.5 ± 2.5–27.8 ± 3.3 Number of patient hospitalized more than 6 m in 1991: 5–0	Intervention: (ER) - At least 2/week gymnastic regimen on the days patients received dialysis including stretching and isotonic muscle conditioning using 2 tennis balls (low intensity) - Each 30-min session was supervised by an occupational therapist and a physical instructor - Plus a walking regiment on nondialysis days spent at home (13 of 17 that started with exercise rehabilitation) Comparison: (CO)	* Bicycle ergometer: VO_2 at VT (mL/min/kg) * Bilateral grip strength (kg) * Sit-and-reach test * Dual-photon absoptiometry scanner (% fat) Lawton's IADL scales * Mean IADL	Exercise: 0-1-2 years Control: 0-1-2 years #P<0.05 ER: 9.7–10.3#–10.8 (only 8 of 13 patients) CO: 9.3–8.8–not done (only 5 of 6 patients) ER: 20.5–21–23.8# CO: 22.4–20.7–21.3 ER: 1.8–2.9–3.9# CO: 2.1 – -1.8 – -1.6 ER: 34.2–30.5–29.2 CO: 23.8–22.7–21 ER: 8–10–10	1. Sequence generation: HR. No RCT 2. Allocation concealment: HR. No RCT 3. Blinding: HR. No blinding 4. Incomplete data asses: LR adequate 5. Selective outcome reporting: MR missing the subscores for IADL	* Small group size * Long term follow-up * Clear inclusion/ exclusion criteria are missing

			- Pt who did not participate in the rehabilitation program (6 of 33 patients who did notparticipate) - 2 years study		CO: 9–9–9 ER: 3 out of 5 patients were discharged CO: –	6. Intention to treat: LR 7. Sponsor: LR: No sponsoring	
Esteve Simo *et al.* [116]	Inclusion: - ≥18 years - ≥3 m treatment in their HD unit - Clinical and HD stability in the last 3 months Exclusion: - Recent cardiovascular event - Physical incapacity - Refusal to grant signed informed consent	HD patients Mean age: 67.9 ± 15.9–68.7 ± 16.6 years Men (%): 43–48% Duration of dialysis: 58.8 ± 70.1–69 ± 78.9 m Charlson index: 7.5 ± 0.9–7.8 ± 0.6	Intervention: (ER) - Intradialysis endurance program, 2/week during the first 2 h of HD, 5-min warm up, 5-min cool down; 45–50 min exercises: shoulder press, side shoulder press, external shoulder rotation, triceps extension, biceps curl, double-leg lifts, seated knee raises, knee extension, straight-legged raise, hip flexion, hip abduction and hamstring curl; do as many repetitions, sets and exercises as possible - Controlled by own nursing staff (n = 16, 2 drop out) Comparison: (CO) - Regular care in HD (n = 24, 3 drop out) - 6 Months	* Handgrip (kg) * Maximum quadriceps length strength (kg) * 6MWT (m) * STS10 (s)	Pre – Post (P-value) ER: 22.1 ± 13.2–24.1 ± 15.8 (P = 0.045) CO: 25.1 ± 10.3–24.1 ± 11.1 (P = 0.474) ER: 15.6 ± 10.7–17.7 ± 12.5 (P= 0.040) CO: 20.9 ± 9.3–16.2 ± 8.4 (P = 0.010) ER: 293.1 ± 192.3–368 ± 217.5 (P = 0.001) CO: 350 ± 176.4–315 ± 152.1 (P = 0.004) ER: 32.1 ± 18.5–28.7 ± 20.6 (P = 0.506) CO: 31.5 ± 17.9–36.4 ± 19.8 (P = 0.230)	1. Sequence generation: HR. No RCT 2. Allocation concealment: HR. No RCT 3. Blinding: HR. No blinding 4. Incomplete data asses: LR; Adequate 5. Selective outcome reporting: LR 6. Intention to treat: LR 7. Sponsor: LR; No sponsoring	* Small group size
Esteve Simo *et al.* [115] 2015 Spain Barcelona	Prospective non randomized controlled trial Inclusion: - Informed consent - ≥80 years - ≥3 m treatment in their HD unit - Clinical and HD stability in the last 3 months Exclusion: - Recent cardiovascular event - Physical incapacity - Frequent symptomatic hypotension (BP <90/70) at HD session - No written consent	HD patients Mean age: 83.9 ± 3.9–82.4 ± 4.6 years Men (%): 36–64% Duration of dialysis: 37.3 ± 27.6 m – 50.9 ± 81.2 m Charlson index: 9.7 ± 1.1–9.3 ± 1.4	Intervention: (ER) - Adapted physical exercise program developed with the physical rehabilitation department, supervised by the nurses, 2 times a week during the first 2 h of the HD session - 5-min warm up, 5-min cool down - 45–50 min exercises: anaerobic capacity, coordination and flexibility of different muscle groups of the extremities with elastic resistance bands, medicine balls, elastic balls, … and aerobic capacity with electric cycloergometer - Exercises were adapted individually. - Intensity was adapts by the nursing staff (n = 11) Comparison: (CO) - Regular care in HD (n = 11)	* Handgrip (kg) * Maximum quadriceps length strength (kg) * 6MWT (m) * STS10 (s) *EuroQOL-5D - Mobility - Personal hygiene - Daily activities - Pain/malaise - Anxiety/depression - Visual scale * Beck depression scale	Pre – Post (P-value) ER: 16.6 ± 8.7–18.2 ± 8.9 (P = 0.019) CO: 19.9 ± 9.4–18.3 ± 10.6 (P = 0.011) ER: 10.5 ± 7.6–12.9 ± 10.1 (P = 0.061) CO: 11.9 ± 7.5–10.3 ± 5.6 (P = 0.442) ER: 234.4 ± 117.7–274.7 ± 144.9 (P = 0.004) CO: 213.9 ± 104.4–210.8 ± 126.5 (P = 0.801) ER: 29.9 ± 10.6–25 ± 7.8 (P = 0.004) CO: 44 ± 14.2–45.9 ± 13.8 (P = 0.265) ER: 1.81 ± 0.4–1.81 ± 0.4 (P = 0.999) CO: 1.88 ± 0.6–1.77 ± 0.4 (P = 0.347) ER: 1.81 ± 0.9–1.91 ± 0.7 (P = 0.678) CO: 1.22 ± 0.6–1.44 ± 0.7 (P = 0.169) ER: 2.32 ± 0.6–1.99 ± 0.6 (P = 0.081) CO: 1.88 ± 0.66–1.89 ± 0.9 (P = 0.999) ER: 1.92 ± 0.7–1.91 ± 0.6 P = 0.999) CO: 2.11 ± 0.6–2.11 ± 0.6	1. Sequence generation: HR. No RCT 2. Allocation concealment: HR. No RCT 3. Blinding: HR. No blinding 4. Incomplete data asses: LR adequate 5. Selective outcome reporting: LR 6. Intention to treat: LR 7. Sponsor: LR No sponsoring	* Small sample size * Only frail/elderly

Continued

Table A14. Q4b. Continued

Study Year Location	Inclusion criteria Exclusion criteria	Patients' characteristics	Intervention (*n*) Comparator (*n*) Duration	Outcome(s)	Results	Quality of evidence	Notes
					(P = 0.999) ER: 1.61 ± 0.8–1.41 ± 0.5 (P = 0.168) CO: 1.66 ± 0.8–1.77 ± 0.8 (P = 0.594) ER: 49 ± 19.1–59.5 ± 20.3 (P = 0.049) CO: 58.8 ± 31.4–52.7 ± 31.3 (P = 0.243) ER: 14.4 ± 13.6–11.7 ± 10.8 (P = 0.048) CO: 14.1 ± 13.6–15.1 ± 15.6 (P = 0.368)		

Q5a. Which is the best alternative to evaluate nutritional status in older patients with CKD stage 3b or higher or on dialysis with advanced CKD (eGFR <45 mL/min/1.73 m^2)

Study Year Location	Inclusion criteria Exclusion criteria	Patients' characteristics	Intervention (*n*) Comparator (*n*) Duration	Outcome(s)	Results	Quality of evidence
Longitudinal cohort studies						
Cheng *et al.* [122] 2009 China	Inclusion: PD patients from a previous study on nutritional status attending the dialysis clinic between April 11th–May 19th 2007 -Exclusion: conversion to HD of receiving a transplant after been included in the previous study	Consecutive PD patients attending: *n* = 59 mean age 56 ± 10 years male 48% duration RRT: not reported	SCG versus MIS comparison of SCG versus MIS for follow-up of nutritional status in PD patients	Change in SGA over 12 months versus change in MIS	Change in SGA: 5.9 ± 0.7–5.8 ± 0.9 (P = 0.5) Change in MIS: 6.8 ± 3.0–7.1 ± 3.29 (P = 0.6) Cohen's κ 0.274 between change MIS/SGA (MIS as ref for detection of detoriation in nutritional standard) sens SGA 62% spec 87% PPV 72% NPV 81%	Intermediate quality - Longitudinal data - Both MIS and SGA assessed by same investigator and single measurement -Inter-observer difference ? (*n* = 4) examiners - Selection bias: 60/136 included for follow-up - Primary purpose of previous study was to study the MIS - One of the few studies in PD
Lawson *et al.* [127] 2001 UK	Inclusion: inpatients with AKI, CKD or RRT (incl HD/PD/Transpl) Exclusion: mental incapacity for informed consent In B. Exclusion if hip/knee replacement/PM and amputees	Hospital patients with renal disease of 3 renal inpatient wards Overall n = 276;male 51% A. Validity cohort n = 190; mean age 65 years; 30% RRT B. Construct cohort *n* = 46; mean age 61 years 45% RRT C. Reliability cohort *n* = 40; mean age 64 years 35% RRT	SCG versus MUS and MST	-Validity of MUST and MST -Inter-rater reliability of MUST and MST	- 50% patients malnourished - SGA reference test > MUST sens 54%, spec 78%, acc 65%, PPV 74%, NPV 60%, K 0.316 > MST sens 49%, spec 86%, acc 66%, PPV 79%, NPV 60%, K 0.335	Poor quality: - bias of 20% missing tests - tertiary single center - no external validation. - spectrum of included patients in terms of eGFR, (type of) RRT, RRT y/n is very broad and even includes AKI
Maggiore *et al.* [131] 1996 Italy	Inclusion: HD patients >6 months on RRT Exclusion: unclear (not described)	All HD out patients of 3 dialysis units *n* = 131; age 63 ± 14 years Male 62%; duration RRT 75 ± 59 months *n* = 272 controls: healthy subjects matched for age/sex recruited from hospital personnel and volunteers general population	Bio-impedance indices (resistance/reactance and PA) versus nutritional indices (alb, nPCR, SGA) and anthropometric parameters (UAC, TS, MAMC, MAC, BMI, UAR, TBW)	Correlation bio-impedance indices and nutritional markers	(Focussed on PICO outcome SGA) - SGA sign (P < 0.01) predictor of resistance and phase angle (PA) - in lowest PA angle quartile sens 67%, spec 78% for severely impaired SGA	Moderate quality: - no exclusion criteria described - multicenter - all clinical assessments by single observer, but blinded for other nutritional tests - SGA categorized in 3 outcomes (normal/moderately impaired/severely impaired)
Cross-sectional cohort studies						
Cooper *et al.* [135] 2002 Australia	-Inclusion: RRT (PD and HD) patients -Exclusion: not described	Consecutive RRT patients attending 1 clinic (*n* = 52 HD, *n* = 24 PD): total *n* = 76 Mean age 64 ± 15 years;	TBN (reference gold standard) compared with SCG	Validity of SCGA as a marker of nutritional status	Moderate level of inter-observer agreement on SGA (*K* = 0.6) Sensitivity SGA (cutoff SGA B) in prediction malnutrition for O1: sens 68%; spec 61%; PPV 42%;	- Good quality study - High methodological value - SGA determined by 2 independent, blinded examiners (Observer 1 = O1 Observer 2 = O2)

Continued

Q5a. Continued

Study Year Location	Inclusion criteria Exclusion criteria	Patients' characteristics	Intervention (*n*) Comparator (*n*) Duration	Outcome(s)	Results	Quality of evidence
		male 60%; duration RRT 34 ± 30 months			NPV 83% for O2: sens 50%; spec 65%; PPV 41%; NPV 80%	
Desbrow *et al.* [128] 2005 Australia	Inclusion: HD Exclusion: >80 years and those that could not stand independently excluded from anthropometric investigations	All HD patients attending private tertiary single-center dialysis unit *n* = 60; mean age 64 ± 16 years; male 53% duration RRT 18 ± 29 months	Comparison of PG-SGA ≥9 with SGA, alb, corrected AMA and TSF	Validity of PG-SGA as a nutrition assessment tool in HD	PG-SGA ≥9: sens 83% spec 92% in prediction SGA classification PPV 71% NPV 96% sign. Correlation between PG-SGA ≥9 and alb, % weight loss past 6 months	Poor quality: - single center - selection bias (tertiary/private) - binary outcome PG-SGA - low prevalence of malnutrition - single measurements - all assessments verified by dietician
Hou *et al.* [123] 2012 China	Inclusion: maintenance HD of the university Hospital Exclusion: serious infection, malignancy, liver disease, therapy for active renal disease, HD, 1 month, metal stent or pacemaker	HD patients of the University Hospital dialysis unit *n* = 84 Mean age 51 ± 16 years Male 64% duration RRT 26 ± 22 months	M(Q)SGA (reference) versus MIS and BIA	Comparison of the agreement between the 3 tools to determine malnutrition	Correlation between M(Q)SGA and MIS: $r = 0.924$ r^2 0.855 P ≤ 0. Correlation between M(Q)SGA and BIA: $r = -0.169$ r^2 0.029 P = 0.124	Poor quality study: - single center -single measurements -assessments of the nutritional tests was not described (single observer? blinded? trained?)
Kalantar-Zadeh *et al.* [129] 1999 US	Inclusion: PD/HD patients with no other previous RRT modality Exclusion: hospitalization <1 month; active infection or disease activity	Randomly selected RRT patients (PD and HD) who never changed treatment modality *n* = 41 Mean age 57 ± 12 years Male 48% duration RRT 36 ± 25 months	- development of 7-item quantitative malnutrition score [M(Q)SGA] using the components of the SGA: weight change, dietary intake, GI symptoms, functional capacity, comorbidity, sc fat, muscle wasting - Comparison of M(Q)SGA with SGA, PCR, BDW, URR, BST, TST, MAC, MAMC, BMI, alb, TYBC, TP, lipids, BUN (*)	Development of new score/tool M(Q)SGA -Correlation between tool and qualitative nutritional scores and parameters*	[No head-to-head comparison M(Q)SGA versus SGA] No correlation M(Q)SGA and URR or PCR Sign correlation between M(Q)SGA and TYBC, alb, TP, MAC, MAMC, BST, BMI and age (!) -> higher age = stronger tendency towards malnutrition ($r = 0.343$, P = 0.028)	Poor quality: - the evidence to incorporate these 7 components of M(Q)SGA is lacking - small sample size - no head-to-head comparison M(Q)SGA versus SGA, only indirect with single nutritional parameters - single center - small size
Piratelli *et al.* [130] 2012 Brazil	Inclusion: patients initiating HD Exclusion: hospitalization <1 month, parental nutrition, active infection or dementia	HD patients of a private dialysis unit *n* = 48 Age range 25–75 years Male 65% Duration RRT ?	Modified SGA BMI, TST, UAC, UAMC, albumin, transferrin	Frequency of malnutrition using other nutritional markers (anthropometry/biochem) Correlation between these various methods	-Modified SGA: 98% at risk of mild malnutrition or mild malnutrition and 2% moderately malnourished - No correlation between modified SGA and other nutritional markers - Lack of sensitivity to detect moderate-severe malnutrition [e.g. shown by BMI (54%) or UAC (42%)]	Poor quality: - small sample size - single measurements taken before initiating RRT - lack of baseline characteristics - missing statistics on correlations - poorly representative (single center, private dialysis unit)
Enia *et al.* [132] 1993	Inclusion: RRT (HD of CAPD) for ≥4 months Exclusion: unclear (not described)	*n* = 59 Age 58 ± 10 years Male 64% duration RRT 45 (range 4–46) months	SCG versus ST, fat%, MAMC, nPCR, BIA (PA)	Validating SGA in RRT patients	- Univariate analysis-> sign association SGA with Alb P < 0.001, $r = -0.51$ PA P < 0.001, $r = -0.58$ MAMC P = 0.028, $r = -0.28$ nPCR P = 0.027, $r = -0.29$ %fat P = 0.042, $r = -0.27$	Moderate quality: - First validation study of SGA in RRT patients - SGA performed by observer blind of objective measurements - no exclusion criteria

					Lacking for edema and weight loss In multivariate analysis relation SGA (dependent) and the objective measurements (covariates) much stronger (multiple $r = 0.77$ F statistics significant at $P < 0.0001$) with adjusted R^2 56%.	
Chan *et al.* [124] 2007 China	Inclusion: PD patients Exclusion: unclear (not described) 8 patients self-declined	Prevalent PD patients from 1 renal unit in Hong Kong attending the clinic from April to May 2006 $n = 165$ Age 59 ± 12 years Male 42% duration RRT ?	Correlation MIS versus SGA	Validation of MIS in PD patients Explore cutoff for MIS to defining degree of malnutrition	Correlation MIS versus SGA: - $r = -0.667$ $P < 0.001$ - 80% similar classification of nutritional status SGA sign correlation with nPCR ($r = 0.326$, $P < 0.001$), Kt/V (r −0.171, $P = 0.048$) and residual eGFR ($r = 0.247$, $P = 0.004$), no sign. correlation with albumin ($P = 0.18$) If taking cut-off MIS ≥9 and SGA 3–5 as reference (to predict moderate malnutrition) MIS sens 70%; spec 85% PPV 69%; NPV 86%	Poor quality study - single center - nutrition scored by 3 observers, level of agreement from previous study noted - no patient with severe malnutrition in cohort and over 67% only mildly malnourished-normal; cut-off MIS for severe malnutrition could not be explored - adds to limited at on PD with considerable cohort size
Gurreebun *et al.* [133] 2007 UK	Inclusion: HD Exclusion: no specific inclusion or exclusion criteria	All HD patients from 2 renal units in UK asked to participate, 70% agreed $n = 141$ Age 60 (range 19–89 years) Male 52% duration RRT?	SGA versus BMI/alb/unintended weight loss ('gold standard')	Sensitivity of SGA to detect malnutrition versus 3 nutritional parameters BMI<18.5 and alb <35 and Unintentional edema free weight loss >10% past 6 months	Sensitivity of combined 3 nutritional parameters 100%, spec 78% Sensitivity of SGA 32%, spec 100% Conclusion authors: SGA has no additional value over basic nutritional parameters	Poor quality study - Poor 'gold standard' - all data collected by 1 researcher, not blinded - unclear who scored SGA - no exclusion of patients with specific reasons for malnutrition - selection bias (30% declined participation) - limited baseline characteristics
Szeto *et al.* [125] 2010 Hong Kong	Inclusion: adult PD patients Exclusion: not described	X-sect $n = 314$ unselected PD patients from single renal unit in hospital Hong Kong Age 60 ± 12 years Male 48% Duration RRT 39 ± 38.6 month Longitudinal $n = 106$ randomly selected patients who remained on PD during 1 year follow-up from the same cohort	GNRI versus MIS versus SGA	Validation of GNRI (in PD) Reliability of GNRI to detect change in nutritional status	X-sect - GNRI sign correlation with SGA ($r = 0.234$, $P < 0.001$) - When SGA ≤5 (as definition for malnutrition) the sensitivity of GNRI ≤93 was 55%, spec 71%. AUC of ROC 0.643 Longitudinal - Change in GNRI correlated with change in SGA ($r = 0.266$, $P = 0.006$) - When decrease in SGA (as definition for worsening nutrition) sens 42% and spec 87% of GNRI (AUC ROC 0.66) - When increase in SGA (as definition for improvement in	Intermediate quality - single center - large PD population - unique for geriatric risk tool, but tool was designed and validated in elderly medical patients. Therefor a sensitivity analysis in patients >65 year - no data about data collection observers: number? blinded? - single measurements

Continued

Q5a. Continued

Study Year Location	Inclusion criteria Exclusion criteria	Patients' characteristics	Intervention (*n*) Comparator (*n*) Duration	Outcome(s)	Results	Quality of evidence
Campbell *et al.* [126] 2007 Australia	Inclusion: adult CKD stage 4 and 5 patients with eGFR MDRD ≤30 Exclusion: expected RRT within 6 months, malnutrition due to other diseases than CKD	Consecutive patients of one predialysis clinic in Queensland *N* = 56 Age 70 ± 12 years Male 61% eGFR 22 ± 7	SGA, mSGA, MIS, PG-SGA, BMI, alb and TIBC versus BCM measured with TBK	Comparability of SGA based tools against original SGA and BCM (TBK)	nutrition) sens 53% and spec 81% of GNRI (AUC ROC 0.68) - No association of SGA with alb, eGFR or CRP, neither of BMC with these parameters - BCM only sign. Difference in ♀ (P = 0.05) - No better performance of 7-SGA to SGA	Poor quality study: - single center - small study group - all assessments by single dietician, who was blinded for BCM - lack of power for malnutrition, only *n* = 11 malnourished patients (SGA B), no SGA C - selection bias? 80% well-nourished by SGA (A)
Gama-Axelsson *et al.* [134] 2012 Sweden	Inclusion: incident and prevalent RRT (PD and HD) patients Exclusion: current hospitalization, infection, vasculitis patients Not able to give consent	Pt from 2 independent cohorts Stockholm Uppsala area Incident *n* = 458 Age 54 ± 13 years Male 61% eGFR 6.6 ± 0.3 Prevalent *n* = 383 Age 62 ± 14 years Male 56% Duration of RRT ? PD *n* = 34 HD *n* = 347	Albumin versus creatinine, SGA, handgrip strength, skinfold thickness, dual X-ray absorptiometry)	Correlation of serum albumin with markers of nutritional status NB SGA scored in 4 categories (1 = normal to 4 = severe malnutrition)	Incident - Correlation of alb with SGA>1: β = −0.15, P < 0.001 - AUC ROC 0.62 Prevalent: - Correlation of alb with SGA>1: β = −0.16, P < 0.001. - AUC ROC 0.64 - No significant increase expl power in adding albumin over SGA (pseudo r/r^2 0.2 for incident and 0.1 for prevalent patients)	Good-quality study: - large sample size - both PD/HD, but small PD subgroup - different time frames - 2 centers - remarkable cutoffs SGA 1–4

Q6. Table A16. Q6. What is the benefit of RRT for older patients with CKD stage 5 ?

Study Year Location	Population			Intervention	Comparator	Outcomes				
	Patients (*N*); follow-up (months)	Comorbidity	Functional status			Mortality/survival	QoL and related measures	Health economics	Other factors	Bias
Retrospective cohort studies										
Brown *et al.* [161] 2015 Australia	467; 50	Stoke score higher prevalence in CM	Not stated	PD, HD	CM	316 versus 33 months	SF36 better in RRT	Not stated		Low
Carson *et al.* [162] 2009 UK	202; 96	CCI score no sig diff	Not stated	PD, HD	CM	14 versus 38 months	Not stated	Not stated	Improved death outside hospital in CM	Moderate
Chan *et al.* [164] 2007 Hong Kong	107; 24	Total comorbidities assigned	Not stated	CM only	None	Mean survival 97 days	Not stated	Not stated		High
Chandna *et al.* [163] 2011 UK	844; 216	Total comorbidities higher in CM	Not stated	HD, PD	CM	21 versus 67 months	Not stated	Not stated		Low
Da-Silva Gane *et al.* [190] 2012 UK	170; 36	Total comorbidities higher in CM	High Karnofsky score in lower % of CM	HD, PD	CM	76 versus 110 months	SF36 physical scores equal; mental scores better for RRT; HADS anxiety/depression scores better for RRT	Not stated		Low
De Biase *et al.* [166] 2008 Italy	15; 27	Total comorbidities higher in CM	Karnofsky score deteriorated more in CM	HD	CM	45% death during follow-up	SF36 physical and emotional scores lower for CM; more depressed patients in CM	Not stated		High
Ellam *et al.* [167] 2009 UK	69; 50	Stoke score	Not stated	CM only	None	21 months	Not stated	Not stated		High
Gracia-Garcia *et al.* [168] 2012 Spain	75; 48	Total comorbidities measured	WHO score worsened through study	CM only	None	13 days	Not stated	Not stated		High
Hussain *et al.* [169] 2013 UK	441; 84	Stoke score equal; CCI higher in CM	WHO score worse in CM	HD, PD	CM	29 months increased survival in RRT	Not stated	Not stated	Survival advantage lost with increasing comorbidity, dependency and age >80; improved death outside hospital and palliative care input for CM	Low
Joly *et al.* [170] 2003 France	146; 144	Stoke score higher in CM	Karnofsky worse in CM	HD	CM	9 versus 29 months	Not stated	Not stated		Moderate
Murtagh *et al.* [171] 2010 UK	74; 18	Stoke score measured	Not stated	CM only	None	Not stated	Not stated	Not stated		High

Continued

Q6. Continued

Study Year Location	Population			Intervention	Comparator	Outcomes				
	Patients (*N*); follow-up (months)	Comorbidity	Functional status			Mortality/survival	QoL and related measures	Health economics	Other factors	Bias
Murtagh *et al.* [172] 2007 UK	129; 66	Stoke score equal	Not stated	HD, PD	CM	76 versus 47% 24 months survival	Not stated	Not stated		Low
Rodriguez Villarral *et al.* [173] 2014 Spain	56; 42	CCI equal	Greater dependence for ADLs in CM	HD, PD	CM	25 versus 17% mortality during study	Not stated	Not stated		Moderate
Seow *et al.* [174] 2013 Hong Kong	101; 24	CCI equal	Karnofsky equal	HD, PD	CM	62 versus 13% mortality during study	KDQOL stable and no sig diff in CM versus RRT except worse at time of RRT start for RRT	Not stated		Moderate
Shum *et al.* [175] 2014 Hong Kong	199; 102	CCI no sig diff	Equal dependence for ADLs	PD	CM	45 versus 28 months	Not stated	Not stated	Increased likelihood of intubation, endoscopy, CPR, and tube feeding in last month of life in RRT	Low
Smith *et al.* [176] 2003 UK	321; 57	CCI higher in CM	Karnofsky worse in CM	HD, PD	CM	8 versus 6 months	Not stated	Not stated		Low
Teo *et al.* [177] 2010 Singapore	168; 12	Not stated	Not stated	HD, PD	CM	69 versus 23% survival during study	Not stated	Admissions 3× more expensive for RRT		Low
Verberne *et al.* [178] 2016	311; 120	Stoke score higher in CM	Not stated	HD, PD	CM	18 versus 37 months	Not stated	Not stated	Survival advantage lost in age >80 and increasing comorbidity	Low
Echevers *et al.* [180] 2016 Spain	314; 60	CCI	Not stated	Stage 4/5 CKD and dialysis	CM	Kaplan–Meier survival analysis: ≥70 years (93 versus 69 patients with dialysis, log-rank: 15, $P < 0.001$); patients ≥75 years (74 versus 46 patients with dialysis, log-rank: 8.9, $P = 0.003$); patients ≥80 (40 versus 15 patients with dialysis) and $P = 0.2$	Not stated	Not stated		Moderate
Wong *et al.* [179] 2007	73; 24	Stoke score measured	Not stated	CM only	None	23 months	Not stated	Not stated		High