

## Guideline

### PURPOSE AND SCOPE

#### Purpose

The purpose of this Clinical Practice Guideline is to provide guidance on evaluation of the kidney donor and transplant recipient as well as on the management of the recipient in the perioperative period. It is designed to provide information and aid decision-making. It is not intended to define a standard of care, and should neither be construed as one nor should it be interpreted as prescribing an exclusive course of management.

#### Scope and target population

This guideline describes the issues related to selection and evaluation of the kidney donor and transplant recipient. It encompasses aspects of immunological risk assessment and management as well as perioperative care of the recipient. It does not address prevention and treatment of complications that occur after kidney transplantation, nor does it cover immunosuppressive treatment at any stage. For these topics we refer to the Kidney Disease Improving Global Outcomes (KDIGO) guideline on kidney transplantation [1] and the European Renal Best Practice Endorsement of this guideline [2].

Although many of the issues that are important for kidney transplant candidates and their donors are also important for potential recipients of other organs, we intend this guideline for the setting of kidney transplantation only. When discussing aspects of screening for and mediation of risk factors in the kidney transplant candidate, we only assess this in function of the kidney transplant that is to follow. Although many of these are relevant to other surgical procedures and to individuals with chronic kidney disease not opting for kidney transplantation, these aspects of care will not be addressed in this document.

This guideline is targeted to all kidney transplant candidates and their donors irrespective of age. Occasionally, when applicable, only children are targeted, and then this is clearly indicated.

#### Target population perspectives

An effort has been made to capture the perspectives of the target population by adopting two strategies.

Firstly, European Renal Best Practice has a permanent patient representative on its 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 drafts of the final document.

Secondly, the guideline was sent out for public review before publication. All members of the European Renal Association—European Dialysis Transplant Association (ERA-EDTA) received an online questionnaire with a pre-specified answer grid.

In this grid, on a scale from 1 to 5, ERA-EDTA members could express to what extent they felt the individual statements were clear, implementable and to what extent they agreed with the content. In addition, a free text field was provided to allow for additional comments.

#### Target users

This guideline was written for health care professionals dealing with kidney transplantation. This includes nurses, general practitioners, transplant nephrologists, transplant surgeons and other physicians and medical professionals who directly or indirectly care for kidney transplant candidates and their living donors. It is also directly targeted at kidney transplant candidates and their living donors, to help them balance benefits and harms of various management strategies and tailor management to their personal preferences and values.

### COMPOSITION OF THE GUIDELINE DEVELOPMENT GROUP

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## GUIDELINE DEVELOPMENT GROUP AREA OF EXPERTISE AND DECLARATION OF INTEREST

According to the rules of ERA-EDTA, the members of the guideline development group have completed a centralized Declaration of Interest form that is available online at [www.european-renal-best-practice.org](http://www.european-renal-best-practice.org).

This declaration of interest form is kept up-to date.

## METHODS FOR GUIDELINE DEVELOPMENT

### Establishment of the guideline development group

The ERBP Board members appointed the Chair and Co-chair of the guideline development group, who then assembled the guideline development group to be responsible for the development of the guideline. The guideline development group consisted of individuals with expertise in transplant immunology, adult and paediatric nephrology, transplant surgery and medicine. The European Renal Best Practice (ERBP) Methods Support Team provided support in guideline development and systematic review methodology. The ERBP Methods Support Team is a group of young nephrologists trained in guideline development and systematic review methodology. Throughout the process they contributed methodological input and assistance with literature searches— together with methodology experts at the Cochrane Renal Group in Sydney, Australia.

### Defining clinical questions

Specific clinical questions were developed within the guideline development group to reflect the key issues in the management and evaluation of the kidney donor and recipient. They were structured in three chapters and comprised the following questions:

## CHAPTER 1. EVALUATION OF THE KIDNEY TRANSPLANT CANDIDATE

- (1) Should we actively screen for the presence of malignancy in kidney transplant candidates? Is the presence or history of malignancy a contraindication to kidney transplantation?
- (2) Under which conditions can HIV infected patients be enrolled on the waiting list?
- (3) Is there a role for immunization against herpes varicella-zoster (HVZ) prior to kidney transplantation?
- (4) Should Haemolytic Uraemic Syndrome (HUS) as underlying cause of end-stage kidney disease preclude waitlisting for transplantation and does it influence graft and patient survival post-transplantation?
- (5) Should focal segmental glomerulosclerosis (FSGS) as underlying cause of end-stage kidney disease preclude waitlisting for transplantation and does it influence graft and patient survival post-transplantation?
- (6) Does pre-transplant alcohol and drug abuse in patients influence patient or graft survival?
- (7) Does pre-transplant tobacco smoking in patients influence patient or graft survival?
- (8) Should obesity preclude waitlisting for kidney transplantation and is there a difference in outcomes post-transplantation between those with and without obesity?
- (9) Should kidney transplantation be delayed in patients presenting with uncontrolled secondary hyperparathyroidism? Does uncontrolled secondary hyperparathyroidism in the immediate pre-transplant period have an impact on transplant outcomes?
- (10) How should screening for potential cardiovascular disease in the potential recipient be done in a cost-effective way?
- (11) When and for which indications should native nephrectomy be performed in kidney transplant candidates awaiting kidney transplantation?

## CHAPTER 2. IMMUNOLOGICAL WORK-UP OF KIDNEY DONORS AND RECIPIENTS

- (1) How should human leucocyte antigen (HLA) typing be performed in kidney transplant candidates and donors?
- (2) In a kidney transplant recipient, how should HLA matching be used to optimize outcome?
- (3) In kidney transplant candidates, what HLA antigens and non-HLA antigens should be defined in addition to HLA-A, -B and -DR?
- (4) In HLA-sensitized kidney transplant candidates what measures should be attempted to improve the probability of a successful transplantation?

- (5) Should in kidney transplant candidates a failed allograft that still is in place be removed or left in place?
- (6) In kidney transplant candidates, what technique of cross-match should be used to optimize outcomes?
- (7) In kidney transplant candidates planned to undergo living donor transplantation but for whom the available donor is ABO incompatible, what measures can be undertaken to improve outcome after transplantation?
- (8) In previously transplanted patients, what is the effect of repeated mismatches for HLA antigens on outcomes, as compared to avoiding repeated HLA mismatches?

## CHAPTER 3. EVALUATION, SELECTION AND PREPARATION OF DECEASED AND LIVING KIDNEY DONORS

- (1) When is dual transplantation preferred over single transplantation?
- (2) Which perfusion solution is best suited for kidney preservation in recipients of living donation? Which perfusion solution is best suited for kidney preservation in recipients of deceased kidney donation?
- (3) Is machine perfusion superior to standard perfusion?
- (4) Is there a critical cold ischaemic time beyond which a donated organ should be discarded?
- (5) On which criteria should we select living kidney donors to optimize the risk-benefit ratio of their donation?
- (6) What lower limit of kidney function precludes living donation?
- (7) What are the risks of pregnancy in a woman with a single kidney after living donation?
- (8) What is the best surgical approach for living donor nephrectomy for the donor? What is the best surgical approach for living donor nephrectomy for the recipient?

## CHAPTER 4. PERIOPERATIVE CARE OF THE KIDNEY TRANSPLANT RECIPIENT

- (1) What are the indications for additional haemodialysis in the recipient immediately before the transplantation procedure?
- (2) Does the use of central venous pressure measurement as a guidance tool for fluid management in kidney transplant recipients improve the outcome after transplantation?
- (3) In kidney transplant recipients during the perioperative period, does the use of intravenous solutions other than 0.9% sodium chloride improve patient and/or graft outcome?
- (4) Does the use of dopaminergic agents (dopamine and its alternatives) improve early post-operative graft function?
- (5) Should we use prophylactic antithrombotic agents during the perioperative period?

- (6) In kidney transplant recipients, what are the effects of using a JJ stent at the time of operation on outcomes?
- (7) What is the optimal post-operative time for removal of the indwelling bladder catheter in kidney transplant recipients?

The Methods Support Team assisted the guideline development group in framing the clinical questions into a PICO format, a well-accepted methodology which requires breakdown of the clinical question with careful specification of a patient group, the intervention diagnostic test or risk factor, the comparator and the outcomes or target disease of interest [3]. For each question the guideline development group and Methods Support Team agreed upon explicit criteria for the patient group, intervention or risk factor, comparators, outcomes and study design features (Appendix 1).

#### Assessment of the relative importance of the outcomes

For each question, the guideline development group compiled a list of outcomes, reflecting both benefits and harms of alternative management strategies. The guideline development group ranked the outcomes as critical, highly or moderately important according to their relative importance in the decision-making process. As such, outcomes such as patient and graft survival were considered critical. Outcomes such as acute rejection and graft function were considered highly important, and surrogate outcomes such as blood pressure were considered moderately important outcomes (Table 1).

#### Searching for evidence

**Sources.** The Methods Support Team initially searched The Cochrane Database of Systematic Reviews, DARE, CENTRAL and MEDLINE (from 1948) in May 2010. All searches were updated in July 2011 and supplemented by articles identified by the guideline development group members through February 2012. The search strategies combined subject headings and text words for the patient group, and the intervention or risk factor under assessment. The full search strategies are detailed in Appendix 2. We 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 Transplantation to screen the reference lists. Searching was restricted to electronically available information. We did not attempt hand-searching, nor searching grey literature.

**Searching hierarchy and selection criteria.** For questions on treatment, we adopted a hierarchical search strategy in which we first tried to identify eligible systematic reviews of randomized controlled trials. If not available, of insufficient quality or if they did not fully address the question, we searched for individual eligible randomized controlled trials. If the systematic reviews were of sufficient quality but outdated, we restricted our search to the time period since the end of the literature search within the systematic reviews. If randomized controlled trials were not available, underpowered, at moderate to high risk of bias or if they did not fully address the question,

**Table 1. Hierarchy of outcomes**

Hierarchy	Outcomes
Critically important	Patient survival
	Graft survival
Highly important	Acute rejection
	Cardiovascular events
	Cerebrovascular events
Moderately important	Graft function
	Delayed graft function
	New onset diabetes after transplantation
	Length of hospital stay
	Blood pressure

we tried to identify all relevant observational data. For prognostic questions, we tried to identify all relevant observational data irrespective of sample size.

We included all studies conducted in humans without restrictions based on language. Inclusion and exclusion criteria for each question were defined within the PICO-framed questions (Appendix 1). Citations were screened on title and abstract by a member of the Methods Support Team to discard clearly irrelevant ones. A second screening was done a member of the guideline development group. All abstracts that did not meet the inclusion criteria were discarded. Any discrepancies at this stage were resolved by consensus.

Assisted by the Cochrane Renal Group's Information Specialist, the Methods Support Team retrieved full texts for potentially relevant studies. The guideline development group members then examined them for eligibility according to the predefined eligibility criteria.

#### Data extraction and critical appraisal of the literature

For each included study, relevant information on design and conduct and relevant results were collected through a standardized data extraction sheet in Microsoft Excel (2010). Data were extracted by the guideline development group members and further checked by a member of the Methods Support Team. Discrepancies were resolved by consensus. A template is available from Appendix 3. The full tables are available online from Appendix 4.

Risk of bias of the included studies was evaluated using validated checklists, as recommended by the Cochrane Collaboration. These are AMSTAR for Systematic reviews [4], the Cochrane Risk of Bias tool for randomized controlled trials [5] and the Newcastle Ottawa scale for Cohort and Case-control studies [6]. As such, the risk of bias was assessed by study and across outcomes. We defined three categories for the overall assessment of the risk of bias at study level: 'high', 'moderate' and 'low', reflecting the extent to which the guideline

development group members were confident that the effect sizes in the study were close to that of the true effect.

**Formulating and grading recommendations: GRADE**

After the data tables were prepared, revised and approved by the guideline development group three full-day plenary meetings were held in December 2011, February 2012 and May 2012 to formulate and grade the recommendations. We used a structured approach, based on Grading of Recommendations Assessment, Development and Evaluation Working Group (GRADE) methodology to grade the quality of the evidence and the strength of the recommendations [7]. GRADE offers a system for separately rating the quality of the evidence and grading the strength of the recommendations in the guideline. The ‘strength’ of a recommendation indicates the extent to which we are confident that adherence to the recommendation will do more good than harm. The ‘quality’ of the evidence refers to the extent to which we are confident that the estimates of effect across studies are close to the true effects (Figure 1).

**Rating the quality of the evidence for each outcome.** In accordance with GRADE, we—guideline development group together with the Methods Support Team—initially categorized the quality of the evidence for each outcome as high if it originated predominantly from randomized controlled trials and low if it originated from observational data. We subsequently downgraded the quality of the evidence one level if the results from individual studies were at serious risk of bias; there were serious inconsistencies in the results across studies; the evidence was indirect; the data were sparse or imprecise; and publication bias was thought to be likely. If evidence arose from observational data, but effect sizes were large, or there was evidence of a dose–response gradient, or all plausible confounding would either reduce a demonstrated effect or suggest a spurious effect when results showed no effect, we would upgrade the quality of the evidence. The final grade for the quality of the evidence for each intervention or risk and outcome pair would eventually be one of high, moderate, low or very low (Table 2).

**Rating overall quality of the evidence.** Each clinical outcome was ranked by the guideline development group according to its relative importance to the patient. The overall body of evidence was then graded, taking into account the quality of the evidence for each outcome and judgement about

the relative importance of each outcome. This resulted in four aggregated categories A, B, C or D (Figure 1 and Table 3).

**Grading the strength of the recommendation.** Recommendations can be for or against a certain strategy. Following GRADE, we classified the strength of the recommendations as strong, coded ‘1’ or weak, coded ‘2’ [7]. Table 4 shows the implications of strong and weak recommendations for patients, clinicians and policy-makers.

Judgements around four key factors determined the strength of a recommendation: the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence, the variability in values and preferences and ultimately also resource use. We did not conduct formal decision or cost analyses.

**Ungraded statements**

We decided to use an additional category of ‘ungraded statement’ for areas where formal evidence was not available and statements were based on common sense, or expert experience alone. They were termed ‘statement’ to differentiate them from graded recommendations and not meant to be stronger than level 1 or 2 recommendations.

**Writing rationale**

Rationales were written by the guideline development group members according to a pre-specified format. Each question contains one or more specific boxed statements. Within each recommendation the strength is indicated as level 1 or level 2 and the quality of the supporting evidence as A, B, C or D. Ungraded statements are referred to as such, and do not hold an indicator for the quality of the evidence. These are followed by the rationale, which contains a brief section on ‘why this question’ with relevant background and rationale to justify the topic, followed by a short narrative review of the evidence in ‘what did we find’ and finally a justification of how the evidence translated in the recommendations made in ‘how did we translate the evidence into the statement’.

For each question we provided a narrative summary of the relevant recommendations made by a selection of guideline producing organizations issuing recommendations in the area of kidney transplantation in Europe and beyond. It was not meant to be an exhaustive list, but predominantly aimed to represent major bodies in Europe and active ones beyond (Table 5).

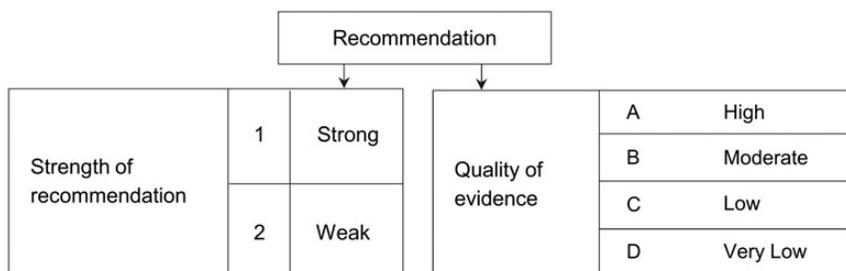


FIGURE 1: Grade system for grading recommendations. \*From [7].

**Table 2. Method of rating the quality of the evidence**

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 Moderate Low Very low
*Adapted from [8]			

**Table 3. Grade for the overall quality of evidence**

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

**Table 4. Implications of strong and weak recommendations for stakeholders**

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
*Adapted from [7].			

**Table 5. Selected guideline producing organizations**

Kidney Disease: Improving Global Outcomes (KDIGO)
Canadian Society of Nephrology (CSN)
Kidney Health Australia – Caring for Australasians with Renal Impairment (KHA-CARI)
The Renal Association (UK)
European Association of Urology (EAU)
British Transplant Society (BTS)
Société Francophone de Néphrologie
Deutsche Gesellschaft für Nephrologie
Società Italiana di Nefrologia
Sociedad Española de Nefrología
Sociedad Española de Diálisis y Transplante

Finally, we attempted to provide relevant suggestions for future research where possible.

## ORGANIZATION OF INTERNAL AND EXTERNAL REVIEW

### Internal review

A first draft of the guideline was sent to experts in transplantation, selected by the chair and co-chair. (in alphabetical order):

- Klinger Marian, Department and Clinic of Nephrology and Transplant Medicine, Medical University of Wrocław, Poland
- Krämer Bernhard, Universitätsklinikum Mannheim, Germany
- Martorell Julio, Servicio de Immunología, Hospital de Clinic de Barcelona, Spain
- Roodnat Joke, Erasmus Medical Center Rotterdam, Rotterdam, the Netherlands
- Watschinger Bruno, Universitätsklinik für Innere Medizin, Nephrologie und Dialyse, Wien, Austria
- Wiseman Alexander, Division of Renal Diseases and Hypertension, University of Colorado, Denver, USA

Internal reviewers were asked to complete a grid-based evaluation of overall appreciation of each individual statement, using a score ranging from 1 to 5. These scores were averaged and colour-coded between red (1) and green (5) to help visualize any problematic part. In addition, internal reviewers were asked to comment on the statements and the rationale within free text-fields limited to 225 characters. All these comments and suggestions were discussed during an additional meeting of the guideline development group in October 2012. For each

comment or suggestion, the guideline development group evaluated whether 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, the variability in values and preferences and ultimately also resource use.

### External review

The finalized version of the guideline was sent to the European Society of Transplantation, with the invitation to select three reviewers from their membership. C.C. Baan, C. Legendre and F. Diekmann were indicated and reviewed the guideline. External reviewers were asked to complete a grid-based evaluation of overall appreciation of each individual statement, using a score ranging from 1 to 5. These scores were averaged and colour-coded between red (1) and green (5) to help visualize any problematic part. In addition, external reviewers were asked to comment on the statements and the rationale within free text-fields limited to 225 characters.

The same evaluation grid, but without potential to write free text comments, was also made publicly available to the ERA-EDTA membership and the members of Descartes working group. In total, 648 ERA-EDTA members and 27 Descartes members responded.

All these valid comments and suggestions were discussed with the subgroups by e-mail, and during a final meeting of the chair of the guideline development group (Daniel Abramowicz) and the chair of ERBP (Wim Van Biesen). As a result, one ungraded statement, that was considered to be inappropriate by the external reviewers, was removed.

### Timeline and procedure for updating the guideline

ERBP plans to update the guideline every 5 years, or when new evidence emerges that might require changes to individual statements. At least every 5 years, they will update its literature searches. Relevant papers will be identified and their data will be extracted using the same procedure as for the initial guideline. The guideline development group will then decide whether or not the original statement needs to be updated. The guideline will then be published as a whole online in the revised version, and a position statement describing the changes will be published with an accompanying rationale in Nephrology, Dialysis and Transplantation.

During the 5-year interval, designated members of the advisory board ('watchdogs') will follow the literature, and signal the chair and co-chair of the guideline development group when new information is published that might require changes to specific statements. The chair and co-chairs of the guideline development group will then decide whether an update is needed. If they deem an update is warranted, data from the additional paper will be extracted and added to the original data extraction table. A position statement will be produced and published in Nephrology, Dialysis and Transplantation.

## FUNDING

This guideline was produced on the budget of ERBP, the guideline producing body of ERA-EDTA. Activities of ERBP are supervised by an advisory board (see [www.european-renal-best-practice.org](http://www.european-renal-best-practice.org) for details and declaration of interests).

ERBP is an independent part of ERA-EDTA, and is funded by an unrestricted grant by ERA-EDTA. The amount of this yearly grant is based on a budget that is proposed on a yearly basis by the chair of ERBP to the ERA-EDTA council for approval.

All these secure ERBP can act independently from industry and other possible influences.

## CONFLICT OF INTEREST POLICY

We required all participants in the guideline development group to fill out a detailed Declaration of Interest Statement. We did not however attach any consequences to these stated interests. All members of the guideline development group were allowed to participate in all the discussions and have equal weight in formulating the statements. All were allowed equal involvement in data extraction and writing the rationales. The declaration of interest forms are available on [www.european-renal-best-practice.org](http://www.european-renal-best-practice.org)

## CHAPTER 1. EVALUATION OF THE KIDNEY TRANSPLANT CANDIDATE

## 1.1. Should we actively screen for presence of malignancy in kidney transplant candidates? Is presence or history of malignancy a contraindication to kidney transplantation?

We recommend screening kidney transplant candidates for cancer according to the recommendations that apply to the general population. (**Ungraded Statement**)

We suggest screening kidney transplant candidates for the presence of kidney cancer by ultrasound. (**Ungraded Statement**)

We suggest screening for the presence of urothelial cancer by urinary cytology and cystoscopy in kidney transplant candidates with an underlying kidney disease associated with an increased risk of this type of cancer. (**Ungraded Statement**)

We recommend screening HCV and HBV-infected kidney transplant candidates for the presence of hepatocellular carcinoma according to the EASL-EORTC Clinical Practice Guideline on the management of hepatocellular carcinoma. (**Ungraded Statement**)

We suggest that patients with current or previous cancer be discussed with an oncologist and considered on a case-by-case basis. The following factors should be considered when determining the appropriate time that wait-listing should be delayed: (a) the potential for progression or recurrence of the cancer according to its type, staging and grade; (b) the age of the patient; (c) the existence of comorbidities, in order to define the appropriate period of time that wait-listing should be delayed. (**Ungraded Statement**)

## Rationale

## Why this question?

Kidney transplantation is associated with an increased risk of cancer. Screening in transplant candidates is aimed at avoiding kidney transplantation, and its associated immune suppression in a patient with an unknown cancer present. To optimize survival of the recipient and of the graft, optimized screening protocols are needed. In transplant candidates diagnosed with cancer, the balance between mortality risk after transplantation and remaining on dialysis should be defined to guide optimal timing of active wait-listing.

## What did we find?

Kidney transplant recipients are approximately three times more likely to develop cancer than the general population [9–14]. Estimates result mostly from large registry analyses

showing standardized incidence rates up to 10 times those seen in the general population, depending on the type of cancer [9–11, 13–23]. Most of these studies included patients without specifying whether the presence of cancer had been excluded before transplantation. Hence, it is unclear whether this higher cancer risk was due to the presence of an undiagnosed cancer, to a true increased risk of developing cancer after transplantation, or a combination of both.

We found no data evaluating the effectiveness of screening protocols in transplant candidates; hence recommendations are made based on extrapolations from the general population taking into account the additional baseline risk of patients with end-stage kidney disease.

Data on the recurrence of pre-existing cancers after kidney transplantation come from two registry analyses with inconsistent results [24, 25]. Historical data gathered in the 1970s, 1980s and early 1990s showed that patients with previous cancer experienced recurrence at an overall rate of 21% [26]. In the majority in whom the cancer recurred, it did so within the first 5 years after transplantation. Analysis for the Australian and New Zealand Transplant Registry found much lower rates of cancer recurrence, ~2–5% [25]. Plausible differences in patient selection and cancer ascertainment make inference problematic. As information on tumour staging in both registries is lacking, any attempt at risk estimation remains crude. No data allowing more precise estimation of risk of recurrence are available at this point.

## How did we translate the evidence into the statement?

Diagnosis of cancer at earlier stages, changes in treatment, and availability of new immunosuppressive agents urge us to re-evaluate risk and prognosis of cancer in transplant candidates. Unfortunately accurate evidence in this field is lacking. The guideline development group judged that, in view of the increased prevalence and severity of cancer in both patients with end-stage kidney disease and those after transplantation, screening should be recommended. In the absence of validated screening protocols for this specific patient group, we advocate the screening recommendations that apply to the general population as a minimal work-up.

Recommendations on how long patients should be withheld from transplantation when a cancer is detected are troublesome. Given the important limitations of the existing registry data, and the changes in medical practice and perhaps prognosis over time, the guideline development group felt that stringent generic recommendations according to the type of tumour were no longer possible. A more reasonable, although arguably a more difficult approach is a case-per-case analysis, taking into account the potential for progression or recurrence of the cancer according to its type, but also its staging, the age of the patient and potential comorbidities. Information to guide this discussion can be found on the website of Adjuvant! online: [adjuvantonline.com](http://adjuvantonline.com), or on the website of the Laboratory for Quantitative Medicine of the Harvard Medical School and Massachusetts Hospital: [lifemath.net/cancer](http://lifemath.net/cancer).

Based on consensus of personal opinion, the guideline development group supported following suggestions:

We suggest that patients with *in situ* cancers of the skin and uterine cervix, and patients with incidentally discovered and successfully removed kidney cancer, can be immediately registered on the waiting list.

We suggest that patients with localized cancer of good prognosis such as cancers of the thyroid, uterus body, uterine cervix or larynx wait 1–3 years before transplantation.

We suggest that patients with a potentially curable cancer such as localized, or curable metastatic or disseminated cancer such as testicular malignancy or lymphoma wait at least 1–3 years before transplantation.

We suggest strongly discouraging transplantation for at least 5 years for cancers with a generally poor prognosis such as lung, stomach, brain and oesophagus cancers, melanoma and mesothelioma.

We suggest strongly discouraging transplantation in patients with metastatic or disseminated forms of any cancer, except for testicular cancer and lymphomas.

### What do the other guidelines state?

The UK Renal Association recommends a general waiting time between successful tumour treatment/remission and transplantation of at least 2 years and for certain malignancies at least 5 years, referring mainly to the Penn database [24]. KHA-CARI agrees on screening in accordance to the general population but does not specifically recommend screening for renal, urothelial and hepatocellular cancer. KHA-CARI provides specific waiting times depending on the type of malignancy, whereas we recommend an individual case-by-case approach [27, 28]. The European Association of Urology endorses similar recommendations to ERBP concerning that the waiting time until transplantation depends on individual patient and cancer-related facts [29].

### Suggestions for future research

Development of prospective registry studies of all transplant candidates reporting detailed information on pre-transplant cancer diagnosis, screening results, acceptance on the waiting list, recurrence and outcome.

Development and rigorous evaluation of screening protocols for transplant candidates.

## 1.2. Under which conditions can HIV infected patients be enrolled on the waiting list?

We recommend that HIV *per se* is not a contraindication for kidney transplantation. (1C)

We recommend waitlisting HIV patients only if

(1) they are compliant with treatment, particularly HAART therapy

(2) their CD4+ T cell counts are >200/ $\mu$ L and have been stable during the previous 3 months

(3) HIV RNA was undetectable during the previous 3 months

(4) no opportunistic infections occurred during the previous 6 months

(5) they show no signs compatible with progressive multifocal leukoencephalopathy, chronic intestinal cryptosporidiosis or lymphoma. (1C)

We suggest that the most appropriate anti-retroviral therapy should be discussed before transplantation with the infectious diseases team in order to anticipate potential drug interactions after transplantation. (Ungraded Statement)

### Rationale

#### Why this question?

Around 1% of patients with chronic kidney disease stage 5D in Europe and the USA are infected with human immunodeficiency virus (HIV) [30]. Since highly active antiretroviral therapy (HAART) became widely available in 1996, the prognosis of HIV infection has dramatically improved. Once contraindicated because of poor prognosis after kidney transplantation [31], many transplant programmes are now routinely transplanting HIV-infected candidates, provided HIV infection is well controlled.

#### What did we find?

Data on >500 carefully selected HIV-infected patients show that patient and graft survival is similar to non-HIV patients up to 3–5 years after transplantation [32–44]. However, most of these studies applied stringent inclusion and exclusion criteria:

CD4 >200 cells/ $\mu$ L for at least 3 months; undetectable HIV viraemia (<50 copies/mL) for at least 3 months; demonstrable adherence overall and with HAART therapy in particular; absence of AIDS-defining illness following successful immune reconstitution after HAART.

The use of immunosuppressive agents does not seem to destabilize HIV control, with patients showing stable CD4+ levels, anecdotal occurrence of viral replication and opportunistic infections. Data on acute rejection rates are higher—up to 2- to 3-fold—in some [38, 40, 41], but not all reports [34, 35, 39, 42].

#### How did we translate the evidence into the statement?

Based on the currently available data, the guideline development group judged that patients should not be denied waitlisting for transplantation based on the presence of HIV infection alone. As so far, the positive results have been observed in highly selected patients, the guideline development group judged that the following criteria should be met: patients are compliant overall and with HAART therapy in particular, CD4+ T cell levels are >200/ $\mu$ L and have been stable during the last 3 months, HIV RNA was undetectable during the last 3 months, no opportunistic infections occurred during the last 6 months, no signs are present compatible with progressive multifocal leukoencephalopathy, chronic intestinal cryptosporidiosis or lymphoma.

The reported higher rejection rate in some studies can potentially be attributed to the difficulty to obtain a good balance between immunosuppression and controlled viral replication. Achieving this balance is further hampered by the potent drug interactions between anti-retroviral and immunosuppressive drugs, e.g. protease inhibitors that potently impair cytochrome P-450 enzyme function leading to calcineurin inhibitor intoxication. For all these reasons, the guideline development group judged that the most appropriate anti-retroviral therapy for an individual patient should be discussed with the infectious diseases team before transplantation. The use of antiretrovirals such as integrase inhibitors that do not inhibit the cytochrome P-450 enzyme system may simplify the use of immunosuppressants in this setting and decrease the frequency of rejection [43].

#### What do the other guidelines state?

KHA-CARI endorses similar recommendations, but demand a CD4+ T cell count >200/ $\mu$ L for 6 months and do not specify a certain time period free of opportunistic infections prior to transplantation [45].

#### Suggestions for future research

Evaluation of effectiveness, safety, pharmacokinetic profiles and drug–drug interactions of new anti-HIV medications and immunosuppressive agents in the context of kidney transplantation.

### 1.3. Is there a role for immunization against herpes varicella-zoster prior to kidney transplantation?

We recommend immunization against varicella-zoster virus in all paediatric and adult patients negative for anti-varicella-zoster antibodies, preferably when they are still waitlisted. (1D)

#### Rationale

##### Why this question?

Varicella may be a severe and even fatal disease in the immunocompromised child and adult. Vaccination is available but not routine in the general population in most countries.

##### What did we find?

Almost 50% of paediatric patients on the waiting list for kidney transplantation are seronegative for antibodies against varicella-zoster virus (VZV) [46]. Three to ten per cent of adult kidney transplant candidates are negative for anti-VZV antibodies [47, 48]. After a single dose of vaccine, 50–82% develop a protective antibody titre [46, 48, 49]. After two doses, separated by 3 to 4 months, 73–94% do so [46, 48–50]. Protective titres may be lost with time and a third dose may be necessary [51]. In chronic kidney failure, the vaccine appears more effective in children younger versus older than 6 years of age [46]. Vaccination before transplantation seems to be well tolerated with mild varicella and flu-like symptoms being the only reactions seen. In transplanted children with versus

without varicella vaccination, varicella infection incidence is lower (12 versus 45%,  $P < 0.001$ ), as is the severity of the illness ( $P < 0.04$ ). Also reactivation (Herpes Zoster) is lower (11 versus 38%,  $P < 0.001$ ) [51]. All these data stem from observational studies uncontrolled for potential confounding such as time effect. A pre-transplant vaccination programme against varicella is reported as cost-effective when compared to treatment with varicella-zoster immunoglobulin [52, 53].

##### How did we translate the evidence into the statement?

Although studies are largely limited by their observational character and univariate analyses, data seem to suggest protective titres are easily achieved after two doses with reduced incidence of both varicella-zoster infection and reactivation. Additionally, reported side-effects appear to be infrequent and benign. The cost of a pre-transplant vaccination programme is relatively low. Taking all this into account, the guideline development group felt that the risk–benefit balance is in favour of vaccinating all sero-negative children and by extrapolation all seronegative adults awaiting kidney transplantation.

##### What do the other guidelines state?

These recommendations correspond with those of KDIGO [1], UK Renal Association [28] and KHA-CARI [54].

##### Suggestions for future research

No suggestions

#### 1.4. Should haemolytic uraemic syndrome (HUS) as underlying cause of end-stage kidney disease preclude waitlisting for transplantation and does it influence graft and patient survival post-transplantation?

We recommend that typical, proven shiga-toxin *Escherichia coli*-associated HUS is not a contraindication to transplantation from either deceased or living donors. **(1B)**

We suggest considering kidney transplantation as an acceptable option (i) in kidney transplant candidates with atypical HUS (aHUS) and a proven membrane cofactor protein (MCP) mutation and (ii) in those displaying anti-complement factor H (CFH) auto-antibodies. **(Ungraded Statement)**

We suggest that kidney transplantation in patients with aHUS should only be undertaken in centres with experience in managing this condition and where appropriate therapeutic interventions are available. **(Ungraded Statement)**

We do not recommend living donation from a genetically related donor in patients who are suspected to have aHUS as their underlying kidney disease unless the responsible mutation has been conclusively excluded in the donor. **(1D)**

We recommend evaluating the potential of living donation from a genetically unrelated donor to a recipient with aHUS on a case-by-case basis. It should only be considered after appropriate counselling of recipient and donor on the risk of disease recurrence in the transplanted graft. **(Ungraded Statement)**

#### Rationale

##### Why this question?

The HUS is a condition that can recur after transplantation. Recently, HUS has been associated with several distinct abnormalities in complement genes, a condition named aHUS. The insights in the underlying pathophysiology of the different forms of aHUS are rapidly evolving, and accordingly so is the evaluation of the risk of recurrence after transplantation.

##### What did we find?

Most cases of HUS, including >90% of those in children, are secondary to infection with *E. coli* serotypes O157:H7 and others, which produce Shiga-like toxin [55].

We found three studies retrospectively reviewing outcomes after transplantation in Shiga-like toxin-associated HUS. All found recurrence rates to be extremely low (0–1%) [55–57]. It has been hypothesized that in the cases in which HUS did recur, the condition was in fact associated with unrecognized genetic mutations, but this has not been directly proven.

aHUS presents as either a familial (<20%) or a sporadic form (>80%) [58]. Both autosomal dominant and recessive patterns of inheritance have been reported. About two-thirds of

familial forms have been linked to distinct complement abnormalities—mutations in CFH 40–45%; in complement factor I (CFI) 5–10%; in C3, 8–10%; in MCP 7–15%; in thrombomodulin (THBD) 9% and in complement factor B (CFB) 1–2% [58]. The genetic abnormalities identified in the sporadic (mainly idiopathic) form of the disease are those that have also been documented in the familial form of aHUS. Of note, at least 10% of affected patients have a combination of two mutations. In addition to mutations, various polymorphisms in genes encoding complement proteins may have some contribution to the degree of susceptibility to HUS. Finally, antibodies to CFH have been found in 6–10% of patients affected by sporadic aHUS.

Altogether, aHUS is reported to recur in ~50–60% of patients who undergo transplantation, and graft failure occurs in 80–90% of those with recurrent disease [58–61]. Importantly, reported post-transplant recurrence rate varies depending on the particular genetic abnormality with 70–90% in CFH and CFI mutations and <20% in patients with MCP mutations.

##### How did we translate the evidence into the statement?

Research has linked aHUS to uncontrolled activation of the alternative complement pathway. Kidney transplantation may trigger aHUS recurrence because of cold ischaemia that induces graft-derived C3 production, endothelial injury due to calcineurin inhibitors, anti-HLA antibodies and infections.

It is sometimes advised that patients should undergo a thorough screening before transplantation for blood levels of C3, CFH, CFI, CFB, the presence of anti-CFH auto-antibodies and membrane CP expression on peripheral blood leucocytes, and be genotyped for mutations in CFH, MCP, CFI, C3, CFB, THBD as well as for CFH-related deletions.

The ERBP guideline development group judged that, while obtaining such a complete work-up would be ideal for research purposes, at present it is expensive, logistically difficult to organize, and may take several months, while the clinical relevance of this information is very low. We believe currently only the presence of an MCP mutation or anti-CFH antibodies is clinically relevant for the discussion of the option of transplantation with the patient. Indeed, MCP-associated aHUS recurs in only 20% of cases, and recurrence due to anti-CFH antibodies is potentially manageable. Still then, it should not be neglected that some patients have more than one mutation. In case of aHUS based on a MCP mutation, living donation from a genetically related donor should only be considered after careful exclusion of aHUS-associated mutations in the donor, not only for MCP, but also all other known mutations.

In any case, we suggest that kidney transplantation should only be undertaken if appropriate therapeutic measures are available post-transplantation. Different therapeutic options [eculizimab, plasma exchange] are currently being explored. Data to support any of these strategies are lacking so far however, and are eagerly awaited.

Living-donor transplantation is contraindicated in patients with aHUS because of the high risk of recurrence. In addition, such procedures may be risky for living-related donors, who

may carry an unrecognized genetic susceptibility factor or be mutations carriers and develop 'de novo' aHUS.

**What do the other guidelines state?**

The British Transplant Society suggests similarly to ERBP that living-related kidney transplantation is not recommended in aHUS [62]. While ERBP suggests that kidney transplantation is an acceptable option in candidates with a proven MCP mutation, the British Transplant Society suggests informing these patients who the risk of recurrence after kidney transplantation is low.

The British Transplant Society does not recommend kidney transplantation in candidates with a factor H or I mutation; it recommends that if either isolated liver or combined liver/kidney transplantation are considered, this should only be done as part of an international clinical trial.

The British Transplant Society suggests informing patients with mutations in C3 and CFB of their high risk of recurrence after transplantation and recommends minimizing antibody titres in patients with anti-factor H autoantibodies before transplantation, whereas ERBP does not provide guidance on these specific mutations.

**Suggestions for future research**

Registries of aHUS patients could refine the association between genotype–phenotype and outcome of transplantation.

Trials investigating the efficacy of eculizumab in the prevention and treatment of post-transplant aHUS recurrences in the different genotypes are needed.

### 1.5. Should focal segmental glomerulosclerosis (FSGS) as underlying cause of end-stage kidney disease preclude wait-listing for transplantation and does it influence graft and patient survival post-transplantation?

We recommend that primary focal segmental glomerulosclerosis *per se* is not a contraindication to kidney transplantation from either a living or a deceased donor. **(1D)**

We recommend informing the recipient and in living donation, the potential donor, about the risk of recurrence of focal segmental glomerulosclerosis in the graft. **(Ungraded Statement)**

We recommend that when a first graft has been lost from recurrent focal segmental glomerulosclerosis, a second graft from either a deceased or a living donor should only be transplanted after an individual risk-benefit assessment and careful counselling of the recipient and potential donor in the case of living donation. **(Ungraded Statement)**

We suggest using an updated management protocol in cases of recurrent focal segmental glomerulosclerosis. **(Ungraded Statement)**

We suggest that children with steroid-resistant nephrotic syndrome undergo appropriate genotyping before wait listing them for kidney transplantation. **(Ungraded Statement)**

#### Rationale

##### Why this question?

FSGS accounts for  $\pm 10\%$  of childhood end-stage kidney disease and, depending on age, 1–5% of adult end-stage kidney disease. Primary FSGS may recur after transplantation and lead to rapid graft loss. As this disease typically occurs in younger patients, it is quite likely that the possibility of living donation will be considered by the patient or his/her family. In the same context, it should be considered that a second transplantation might be needed during the course of the patient's life.

##### What did we find?

Secondary FSGS classically does not recur after kidney transplantation. The reported recurrence rate of primary FSGS however lies between 34 and 56% [63–68].

Graft loss occurs in  $\pm 30\text{--}50\%$  of patients with FSGS recurrence after transplantation, resulting in an overall graft loss due to FSGS recurrence of  $\pm 10\text{--}15\%$  [63, 65, 68, 69]. The reported risk of relapse is high ( $\pm 80\text{--}100\%$ ) in those with a history of allograft loss due to recurrent FSGS [65, 68, 70].

FSGS patients with mutations of the NPHS1 and NPHS2 genes, only rarely experience recurrence after transplantation [65, 67, 71]. Therapy of recurrent disease with high-dose cyclosporine, steroids and PE has been associated with partial or complete remission in 17/42 patients [64].

##### How did we translate the evidence into the statement?

Recurrence of primary FSGS after first transplantation is rather high, but leads to graft loss in only 10–15% of cases. In view of the potential advantages of transplantation over remaining on dialysis, the guideline development group judged that under these conditions there is sufficiently positive risk-benefit to not preclude the option of transplantation. However, the increased risk of recurrence with its associated substantial morbidity and potential need for aggressive interventions need to be clearly communicated to the patient and his next of kin. Potential living donors should be informed about the risk of recurrence and graft loss.

Treating recurrent disease after transplantation can be challenging. Aggressive treatment protocols with high-dose plasmapheresis, cyclosporine and steroids have been advocated with some success in small series. To the opinion of the guideline development group the transplant team should therefore have a well-defined updated management strategy to both detect and treat focal segmental glomerulosclerosis recurrence in order to optimize prognosis by early intervention.

In view of the very high reported recurrence rate for a second transplantation after recurrence in the first graft, the guideline development group judged that regrafting should be strongly discouraged.

##### What do the other guidelines state?

No other guideline body has a statement on this topic.

##### Suggestions for future research

Randomized controlled trials evaluating effectiveness and safety of treatment of recurrent idiopathic FSGS after transplantation.

## 1.6. Does pre-transplant alcohol and drug abuse in patients influence patient or graft survival?

We recommend that women who drink >40 g and men who drink >60 g of alcohol per day stop or reduce their alcohol consumption to below these levels. (1D)

These patients can be waitlisted, but a careful surveillance of reduction of alcohol consumption should be exerted. (Ungraded Statement)

We recommend not waitlisting patients with alcohol 'dependence'. (Ungraded Statement)

Strategies to stop alcohol consumption should be offered, according to the World Health Organization (WHO) Clinical Practice Guideline. (Ungraded Statement)

We recommend not waitlisting patients with an ongoing addiction to 'hard drugs' resulting in non-adherence. (1D)

### Rationale

#### Why this question?

Alcohol consumption is widely accepted and frequent in the general population. Its use puts patients potentially at risk for additional complications after transplantation. Especially adherence, pharmacokinetic interactions and physical and psychosocial consequences are of concern.

Transplantation in patients with drug abuse poses challenging clinical and ethical questions, both for the personal outcome of the individual as for the fair allocation of organs.

#### What did we find?

Various categories of alcohol consumption have been defined and interchangeably used in the literature. The WHO defines three categories: hazardous alcohol drinking (20–40 g/day for women, 40–60 g/day for men), harmful alcohol drinking (>40 g/day for women, >60 g/day for men) and finally alcohol dependence, which refers to a cluster of physiological behavioural and cognitive phenomena in which the use of alcohol takes on a much higher priority for a given individual than other behaviours that once had a greater value [72].

The reported prevalence of alcohol consumption in the transplant population is high, but both harmful drinking and alcohol dependence are low at ~1.5% [73].

We found one retrospective multivariate analysis, based on data from the United States Renal Data System (USRDS) [74]. In this study, alcohol consumption was defined as a dichotomous variable: 'alcohol dependence' declared as yes or no at the time of the first visit to an end-stage kidney disease service. After adjustment for multiple covariates, 'alcohol dependency', was associated with an increased risk of death (HR: 1.56 95% CI: 1.21–2.02) and death-censored graft-loss (HR: 1.38, 95% CI: 1.04–1.08). It was reported

that the increased risk was not present in females; however, this was not formally analysed due to sample-size restrictions. We found one additional retrospective single-centre cohort study, in which both patient and graft survival up to 10 years after transplantation were numerically better for patients with prior history of alcohol dependency [75]. Small numbers and univariate analysis make interpretation of these results cumbersome. We did not find any study evaluating the influence of known alcohol consumption of any category before transplantation on patient adherence and drug-interactions afterwards. Also no studies were found on success of alcohol cessation programmes or risk of relapse after transplantation.

We found three old retrospective cohort studies evaluating the influence of past drug, heroin or cocaine abuse conducted in 424 kidney transplant recipients. Results are conflictive, studies underpowered and generally poorly designed and analysed. Overall there is no evidence that past heroin or cocaine abuse is associated with poorer patient and graft survival. However, as these data come from observational studies, this only indicates that in well selected past heroin or cocaine abusing patients, where the treating physicians judged transplantation feasible, outcome is not jeopardized [75–77].

#### How did we translate the evidence into the statement?

Although results come from one retrospective study with a potential for misclassification due to a vague definition of alcohol dependency, we judged this would have biased the results in favour of no difference, rather than that it would have resulted in an overestimation of the effect. Accordingly, the guideline development group recommend that patients with harmful drinking should reduce their alcohol intake, and that patients with alcohol dependence should stop. There is no evidence that modest alcohol consumption negatively influences patient or graft survival, so complete alcohol abstinence seems, in view of its wide social acceptance, neither realistic, nor necessary. However, the guideline development group judged that patients with alcohol dependence as defined by the WHO, have a high risk for negative outcomes, and that, according to the definition and the data in the general population, a sustained modest consumption is not realistic in this patient group. Accordingly, these patients should stop their alcohol consumption completely.

The mechanisms by which alcohol consumption is associated to graft dysfunction are poorly understood. Alcohol-dependent patients may have lifestyle habits that adversely affect patient and graft survival. Levels of immunosuppressant drugs might be very variable due to non-adherence with post-transplant treatment, and because of pharmacokinetic interactions. However, none of these mechanisms have been investigated so far.

The few available data on the influence of drug abuse on outcome after transplantation indicate that a history of heroin or cocaine abuse is not associated with poorer graft or

recipient survival. In all of these studies however a well-documented complete abstinence was a prerequisite for transplantation. Accordingly, the guideline development group judged that drug addicts should be encouraged to follow a structured rehabilitation programme. The prospect of transplantation can be used as a positive motivator.

**What do the other guidelines state?**

No other guideline body provides a statement on this topic.

**Suggestions for future research**

Studies, stratified for quantity of alcohol consumption and its influence of post-transplant outcome.

### 1.7. Does pre-transplant tobacco smoking in patients influence patient or graft survival?

We recommend patients stop smoking before transplantation. **(1B)**

Smoking cessation programmes should be offered. **(Ungraded Statement)**

#### Rationale

#### Why this question?

Cigarette smoking increases the risk of cancer and cardiovascular disease in the general population and may negatively influence patient and graft survival in kidney transplant recipients.

#### What did we find?

Few studies have specifically addressed the role of pre-transplant tobacco exposure on post-transplant outcomes. However, many retrospective cohort studies have analysed risk factors for post-transplant cardiovascular disease controlling for pre-transplant tobacco exposure. All have shown that tobacco exposure is associated with a decrease in patient (HR: 1.4–7.4) and/or graft survival (HR: 1.3–8.1) [78–109]. In addition, smoking cessation for 5 years or more before transplantation has been associated with improvements in both patient (HR: 0.71, 95% CI: 0.52–0.9) and graft survival (HR: 0.66, 95% CI: 0.52–0.85) [95]. One

study specifically in living donor kidney transplantation showed that any history of smoking was associated with impaired graft and patient survival and a 50% increased risk of early rejection [102].

#### How did we translate the evidence into the statement?

The evidence for a negative influence of smoking on the outcome of kidney transplantation is large and consistent stemming from well-adjusted multivariate analyses of observational data at low risk of bias. However, there was no consensus in the guideline development group to consider active smoking as a contraindication for waitlisting for transplantation. The major argument was that it is very difficult, if not impossible to check smoking status, and even if patients stopped smoking before transplantation, there is always the risk of relapse after transplantation. There was however a consensus to strongly recommend smoking cessation in kidney transplant candidates. The guideline development group feels that, as for the general population, success of smoking cessation can be enhanced by offering structured smoking cessation programmes.

**What do the other guidelines state?** The UK Renal Association supports these recommendations [28]. No other guideline bodies provide a statement on this topic.

#### Suggestions for future research

No suggestions.

### 1.8. Should obesity preclude waitlisting for kidney transplantation and is there a difference in outcomes post-transplantation between those with and without obesity?

We recommend that patients with a body mass index (BMI)  $>30$  kg/m<sup>2</sup> reduce weight before transplantation. (Ungraded Statement)

#### Rationale

##### Why this question?

There is uncertainty around the relation between obesity and outcomes after kidney transplantation. Obese kidney transplant recipients may have poorer outcomes in comparison with non-obese recipients, but perhaps outcomes are better compared with remaining on dialysis. There is no consensus on whether obesity should be an exclusion criterion for kidney transplantation and policies differ among transplant centres.

##### What did we find?

We found 13 observational studies examining the relation between obesity and outcomes after transplantation [110–122]. All used BMI as a measure to discriminate between obese and non-obese recipients, but studies differed widely in their threshold for obesity, and the distinction between different levels of excess weight.

All but one [119] were retrospective in design and included between 130 and  $\pm 52\,000$  kidney transplant recipients. In nine studies, multivariate Cox-regression analysis was used to model time to event data [110, 112, 113, 116–119, 121, 122]. Results varied widely.

Whereas in three studies there was a significant negative association between obesity and death [117, 119, 121], graft loss or death-censored graft loss, in six others results were inconclusive. The difference could not be explained by sample size, variation in the overall risk of bias or the extent to which estimates were adjusted for confounding. However, definition of the reference category and stratification of obesity could be an explanation. In the two studies in which authors distinguished between obesity and morbid obesity ( $n = 79\,304$ ), morbid obesity was consistently associated with a 20% increase in the risk of death and an 20% increase in the risk of graft loss, compared with a reference category of normal weight recipients [116, 121]. Obesity—as defined by a BMI between 30 and 35 kg/m<sup>2</sup>—was not consistently associated with poorer outcomes. Results differed according to how patient groups were pooled and according to which groups were compared with one another.

One study found obese recipients to have a 75% increased risk of developing new onset diabetes after transplantation in comparison with non-obese recipients [112]. Finally one study examined perioperative complications and found obese patients to have 4% more surgical wound breakdowns. However, there was no increase in the number of infections or complete wound dehiscence when corrected for confounders [118].

##### How did we translate the evidence into the statement?

The present data on the association between obesity and patient and graft survival are conflictive.

Although morbidly obese patients have poorer outcomes after transplantation than those who are not obese, the risk of moderate obesity is less clear. Although one could hypothesize on how obesity causally relates to adverse outcomes, we could not identify interventional trials examining the effect of intentional weight loss before transplantation on outcomes after transplantation. In addition, in all of the studies obesity was defined as a BMI  $\geq 30$  kg/m<sup>2</sup>, and yet it is undeniable that some individuals may have increased BMI which is not only due to excess body fat. Finally, registry data have indicated obese patients to benefit from transplantation, with better survival compared with remaining on the waiting list [120, 123, 124].

With this in mind, the guideline development group felt that they could not make a statement regarding the acceptance or refusal for kidney transplantation based on obesity in itself. On the other hand, candidates with morbid obesity do have poorer outcomes after transplantation than those with a normal weight. Although there is no evidence that weight reduction before transplantation improves survival afterwards, it seems reasonable to believe the cardiovascular risk profile would benefit from such an intervention. How weight loss should be achieved is less clear. Although the benefits of dietary treatment will reasonably outweigh the harms, both pharmacological therapy and bariatric surgery will likely cause more adverse events, making the risk–benefit balance more problematic.

##### What do the other guidelines state?

No other guideline body provides recommendations on this topic.

##### Suggestions for future research

Randomized controlled trials to examine the benefits and harms of interventions aimed at losing weight in obese and morbidly obese kidney transplant candidates.

### 1.9. Should kidney transplantation be delayed in patients presenting with uncontrolled secondary hyperparathyroidism? Does uncontrolled secondary hyperparathyroidism in the immediate pre-transplant period have an impact on transplant outcomes?

We recommend not refusing a cadaveric graft only because of uncontrolled hyperparathyroidism in the recipient. (**ID**)

However, for patients on the waiting list, effort should be made to comply with existing chronic kidney disease—metabolic bone disease guidelines, including parathyroidectomy, when indicated. (**Ungraded Statement**)

#### Rationale

##### Why this question?

There is evidence that parathyroid hormone (PTH) concentrations both early and late after kidney transplantation are independently related to PTH levels before transplantation [125]. In addition, persistent hyperparathyroidism following kidney transplantation plays a central role in post-transplant hypercalcaemia through calcium release from bone. As such, there might be a risk of accelerated osteoporosis and vascular calcification, and of nephrocalcinosis potentially leading to graft loss.

##### What did we find?

Resolution of pre-transplantation hyperparathyroidism in the post-transplantation period is reported to be rather uncommon (22.7–50%) in several single-centre retrospective cohorts [125, 126].

Two studies have shown that nephrocalcinosis detected by protocol biopsies 3–6 months after transplantation is related to persisting hyperparathyroidism and higher serum calcium levels post-transplantation. In addition, early nephrocalcinosis detected by protocol biopsies 3–6 months after transplantation influenced graft function 1 year after transplantation in one study, but not in a prospective study with a mean follow-up of 33 months [127, 128].

In a single-centre retrospective cohort study, pre-transplant PTH levels were independently associated with death-censored graft survival and with acute rejection, but not with patient survival [129]. In the same study, pre-transplantation parathyroidectomy was independently associated with a 3-fold risk reduction for death.

In a retrospective analysis, 49 patients with post-transplant hyperparathyroidism had similar graft survival compared with those without hyperparathyroidism (88 versus 84%,  $P = 0.51$ ) [130]. In this study patients who underwent parathyroidectomy after transplantation had lower glomerular filtration rates (GFRs) ( $46 \pm 20$  versus  $58 \pm 21$  mL/min,  $P = 0.04$ ) and poorer graft survival (71 versus 88%,  $P = 0.06$ ) in comparison with those that did not undergo parathyroidectomy.

In a small ( $n = 7$ ) non-randomized observational study, total pre-transplant parathyroidectomy with auto transplantation of a small part of the gland resulted in better preservation of

bone mineral density as assessed by dual energy X-ray absorptiometry (DEXA) testing post-transplantation [131].

In a single-centre prospective cohort study, PTH levels were inversely associated with bone mineral density before transplantation. However, evolution of bone mineral density post-transplantation was not influenced by the pre-transplant PTH level [132].

Patients receiving calcimimetics before transplantation to control severe secondary hyperparathyroidism who discontinue the treatment after transplantation may be at risk of rebound hyperparathyroidism, hypercalcaemia and early nephrocalcinosis.

##### How did we translate the evidence into the statement?

The guideline development group judged that there was insufficient evidence to refuse only because of uncontrolled hyperparathyroidism a cadaveric graft to a patient for whom a kidney becomes available, as studies reporting on the association between pre-transplantation PTH concentrations and graft survival are conflictive, whereas all studies report absence of an association with patient survival. The guideline development group deems that the risk of delaying transplantation in these patients outweighs the risks of transplantation with high PTH levels.

The guideline development group points out that this should not be seen as an excuse not to do any effort to comply with the guidance provided by KDIGO [133] and endorsed by ERBP [134] with regard to management of metabolic bone disease for the following reasons:

Complete resolution of hyperparathyroidism after transplantation occurs rather infrequently.

There appears to be a higher prevalence of nephrocalcinosis in patients with persistent hyperparathyroidism after kidney transplantation, although this may have no influence on graft outcome.

Parathyroidectomy before transplantation in patients with hyperparathyroidism reduced the relative risk of death after transplantation 3-fold, whereas parathyroidectomy after transplantation seems to be associated with worsening graft function. It should be taken into account that there is a high recurrence rate of hyperparathyroidism and hypercalcaemia post-transplantation in patients whose hyperparathyroidism was controlled by calcimimetics before transplantation [135]. In patients who are deemed suitable for kidney transplantation, the risk of parathyroidectomy is low, while it probably is beneficial. Therefore, in patients who are listed on the waiting list, and who have secondary or tertiary hyperparathyroidism, parathyroidectomy in the pre-transplant period should be preferred over controlling PTH with calcimimetics.

##### What do the other guidelines state?

No other guideline body provides a statement on this topic.

##### Suggestions for future research

Influence of pre-transplantation parathyroidectomy in patients with hyperparathyroidism listed for kidney transplantation on outcome (patient and graft survival, GFR, cardiovascular events).

### 1.10. How should screening for potential cardiovascular disease in the potential recipient be done in a cost-effective way?

We recommend that basic clinical data, physical examination, resting electrocardiogram (ECG) and chest X-ray are a sufficient standard work-up in asymptomatic low-risk kidney transplant candidates. (1C)

We recommend performing a standard exercise tolerance test and cardiac ultrasound in asymptomatic high-risk patients (older age, diabetes, history of cardiovascular disease). In patients with a negative test, further cardiac screening is not indicated. (1C)

We recommend performing further cardiac investigation for occult coronary artery disease with non-invasive stress imaging (dobutamine stress echocardiography or myocardial perfusion scintigraphy) in kidney transplant candidates with high risk and a positive or inconclusive exercise tolerance test. (1C)

We recommend performing coronary angiography in kidney transplant candidates with a positive test for cardiac ischaemia. Further management should be according to the current cardiovascular guidelines. (1D)

#### Rationale

##### Why this question?

Cardiovascular death with a functioning graft is considered a prevalent major negative outcome after kidney transplantation. As a consequence, it is tempting to screen patients listed for transplantation thoroughly for cardiovascular disease.

The American College of Cardiology/American Heart Association (ACC/AHA) does not recommend routinely screening asymptomatic patients facing intermediate to high-risk surgery if their functional status allows them to perform four or more metabolic equivalent tasks; however, the relevance of these findings to patients with end-stage kidney disease is not known. As a consequence, ACC/AHA guidelines are in conflict with current practice in many units for end-stage kidney disease patients facing kidney transplant.

The question is of relevance, as not screening can incur an increased risk of cardiovascular morbidity and/or mortality, especially of death with functioning graft. On the other hand, screening might deny a transplant to patients who might benefit from it, can substantially postpone the transplantation, and may lead to increased costs and potential complications.

In addition, it is also unclear what to do when cardiac lesions are found during screening, with regard to the different therapeutic options, and with regard to whether or not patients can be put on the waiting list after their cardiac problem has been intervened upon.

To properly assess the question at hand, a decision-tree analysis should be made, where all components of underlying epidemiology, diagnostic accuracy of the different tests in

different subsets of patients, outcome of different interventions and outcomes after transplantation of all these possible combinations of events are numerically assessed. Such a decision-tree analysis is a tremendous and complex task. Therefore, the guideline development group decided to reformat the problem into some easier to solve subquestions:

- (1) Is it safe in asymptomatic patients at low risk to only screen for cardiovascular risk by physical examination, ECG and chest X-ray?
- (2) What is the negative predictive value of non-invasive tests such as a cardiac exercise tolerance test in asymptomatic patients with a higher risk (diabetes; older age, history of cardiovascular disease)?
- (3) What is the negative predictive value of non-invasive tests such as myocardial perfusion tests or dobutamine stress echocardiography?

By providing the answers to these questions, we hoped to substantially simplify screening for cardiovascular risk in transplant candidates, and reduce the number of patients in need of a coronary angiography, without putting them at jeopardy. As an additional question, we wondered whether there are cardiac tests predictive for increased cardiac mortality due to non-coronary artery disease.

##### What did we find?

Several smaller single-centre cohort studies reported a high negative predictive value for cardiovascular risk obtained by basic history, clinical information, ECG and chest X-ray in non-diabetic, asymptomatic patients [136–138]. Most of the studies consider diabetes, presence of peripheral vascular disease, older age, hypertension and elevated low-density lipoprotein cholesterol as 'high risk'.

In a retrospective analysis, Kasiske *et al.* found that in kidney transplant candidates, who were considered low risk (43% of the cohort) based on history, ECG and clinical findings, and who were thus accordingly not further screened by invasive testing, the actuarial incidence of an event related to ischaemic heart disease was only 5.8% at 5 years after transplantation [139]. In contrast, in patients deemed to be at high risk, and in whom further investigation and work-up was performed, prophylactic angioplasty was performed in 6.2%, and bypass surgery in 2.8% before listing, but still, prevalence of an ischaemic heart disease-related event was 18.9% at 5 years.

Manske *et al.* reported that 31 out of 151 (20.5%) asymptomatic insulin-dependent diabetic kidney transplant candidates had coronary artery stenoses >75%. Of these, 26 were randomized to medical versus coronary bypass; 10/13 in the medical versus 2/13 in the intervention group had a cardiovascular event after a median of 8.4 months ( $P = 0.002$ ), and 4 versus 0 patients died ( $P > 0.05$ ) [140]. In another study by the same group in diabetic type 1 kidney transplant candidates, the combination of age <45, non-smoking, no ST-segment changes on ECG and <25 years of diabetes resulted in a negative predictive value for cardiac events of 98% [141]. At 36 months of follow-up, 55 and 30 % of those with >50% or >75% stenosis on coronary angiogram had experienced a cardiovascular event [142].

De Lima *et al.* reported on a cohort of 1025 patients who were screened in a pre-transplant work up by laboratory tests, resting electrocardiography, transthoracic echocardiography and non-invasive coronary testing [myocardial scintigraphy with dipyridamole, single photon emission computed

tomography (SPECT)], irrespective of symptoms [143]. Patients in whom these tests revealed an increased probability for the presence of coronary artery disease ( $n = 519$ , 51%) were referred for coronary angiogram, where the presence of coronary artery disease was confirmed in 230 (44%). Based on the

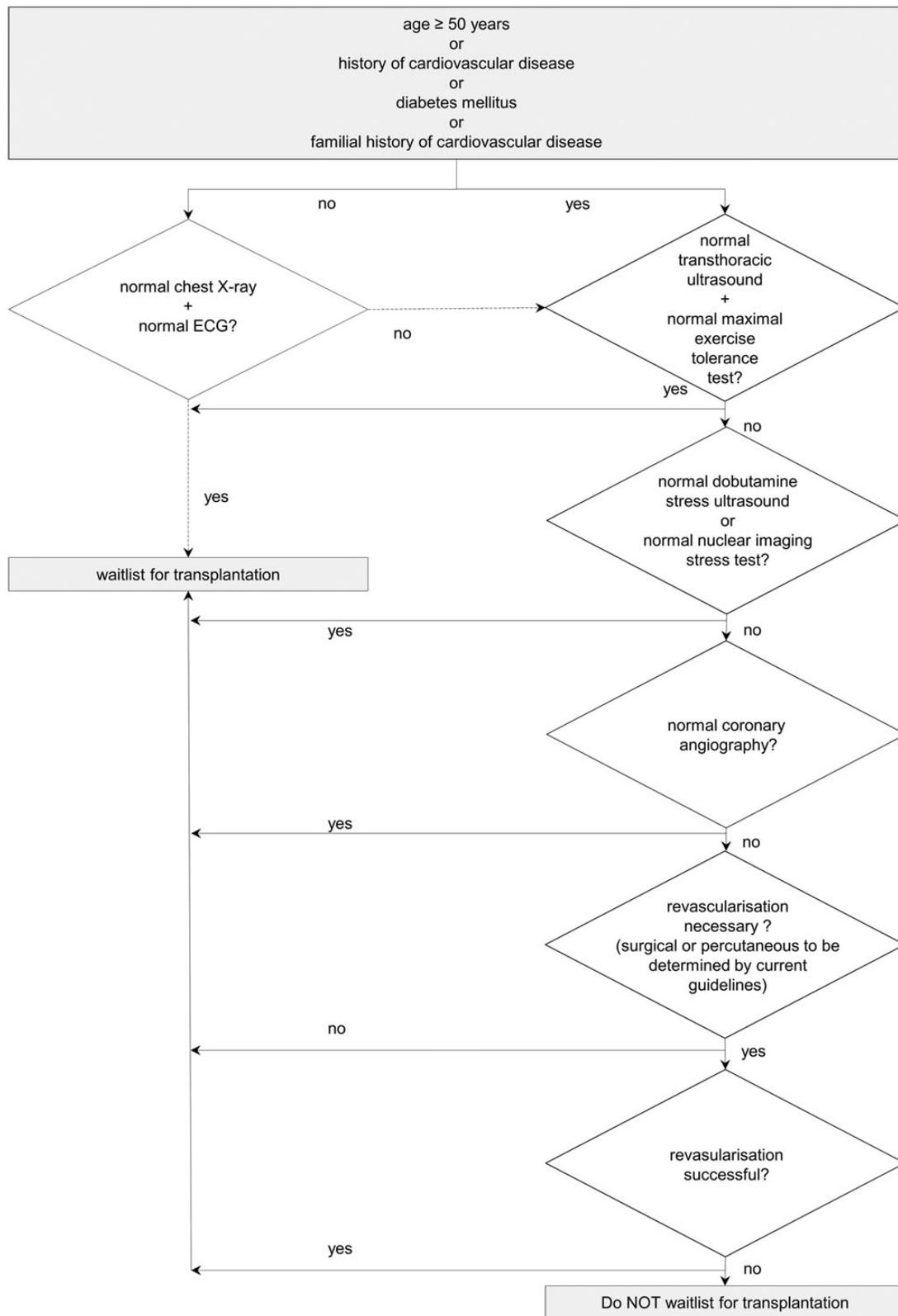


FIGURE 2: Decision-tree pre-transplant cardiovascular screening.

ACC/AHA criteria, these patients were either maintained on medical therapy or referred for revascularization. Event-free survival for patients on medical therapy at 12, 36 and 60 months was 86, 71 and 57%, whereas overall survival was 89, 71 and 50% in the same period, respectively. However, patients who refused intervention had a worse outcome compared with those who actually underwent intervention (cardiac events: HR: 4.50, 95% CI: 1.48–15.10; death: HR: 3.39, 95% CI: 1.41–8.45). Although these are observational data, they suggest that ~50% of patients presenting for kidney transplantation can be safely screened by basic non-invasive screening; for the other 50% who will need a coronary angiogram, about half will need intervention based on ACC/AHA criteria, and half can be maintained on medical therapy; overall, outcomes in these groups should be considered equal. Refusal of treatment in patients needing it based on the ACC/AHA criteria was detrimental however, and maybe these patients should be excluded from the waiting list.

In a single-centre cohort study, 45/429 (10.5%) had a cardiac event post-transplantation [144]. The risk was higher (31.3 versus 6.5%) in the subgroups with versus without pre-transplant angina, myocardial infarction or positive angiography. Five-year patient survival was lower in the high-risk group (82.8 versus 93.1%,  $P = 0.004$ ), as was 5-year overall graft survival (74.8 versus 84.1%,  $P = 0.08$ ). Forty-one per cent of patients who were treated with angioplasty plus stenting or bypass graft prior to transplantation had post-transplant cardiac events, when compared with 28% of those without intervention in the high-risk group and 6.5% of patients in the low-risk group ( $P = 0.001$ ).

Koch *et al.* found a prevalence of coronary artery disease of 36% in diabetic patients; the presence of coronary artery disease was poorly predicted by any clinical or biochemical sign or by ECG; no outcome data were provided however [145].

Barrionuevo reported a prevalence of relevant coronary artery disease in 89/356 patients evaluated for kidney transplantation [146]. Of these, 73 were asymptomatic; no outcome data were reported. Charytan *et al.* evaluated 67 asymptomatic haemodialysis patients with coronary angiogram, and found stenoses in the proximal vessels in 28.5% [147]. The presence of this finding was associated with increased 3-year mortality (HR: 3.1, 95% CI: 1.4–7.3).

When it comes to diagnostic accuracy of non-invasive tests detecting significant coronary artery disease, we found one well-conducted systematic review, published in 2011. It included eleven studies (690 participants) evaluating dobutamine stress echocardiography, 7 studies (317 participants) assessing myocardial perfusion scintigraphy, and two studies (129 participants) evaluating exercise stress electrocardiography. Compared with coronary angiography, dobutamine had pooled sensitivity of 0.80 (95% CI 0.64 to 0.90) and specificity of 0.89 (95% CI 0.79 to 0.94). Myocardial perfusion scintigraphy had pooled sensitivity of 0.69 (95% CI 0.48 to 0.85) and specificity of 0.77 (95% CI 0.59 to 0.89). Indirect comparison suggested that dobutamine stress echocardiography may have higher accuracy compared with stress echocardiography

( $P = 0.07$ ). Power to detect differences in accuracy at the 5% level however was low due to sparse data [148].

In a study including 600 patients, most of them diabetics, the 42-month cardiac event-free survival rate was 97% in patients with normal SPECT images and 85% in patients with abnormal SPECT images (RR: 5.04, 95% CI: 1.4–17.6) [149], comparable with results reported in other studies [150, 151]. In a cohort of 150 transplant candidates, using a multivariate logistic regression model adjusted for age and diabetes mellitus, an abnormal myocardial perfusion imaging test result (either low left ventricular ejection fraction or abnormal perfusion), was a strong independent predictor of all-cause mortality (OR: 2.5, 95% CI: 1.2–5.3), together with diabetes mellitus (OR: 2.2, 95% CI: 1.01–4.8) [152].

Hage *et al.* investigated all-cause mortality in 3698 patients with end-stage kidney disease evaluated for kidney transplantation [153]. Sixty per cent were high risk, but coronary angiography was performed in only 7%. The presence and severity of coronary artery disease on angiogram was not predictive of mortality. Coronary revascularization did not impact survival except in three-vessel disease ( $P = 0.05$ ).

In a study including 300 consecutive patients with end-stage kidney disease referred for pre-transplant cardiac evaluation (222 finally listed on the waiting list, 80 transplanted during the follow-up), patients unable to exercise (Bruce standard exercise tolerance test) or to exercise for a maximum of 6 min exhibited a higher mortality rate after transplantation in the multivariate analysis (adjusted HR: 6.4 and 5.2, respectively,  $P < 0.05$ ) [154]. However, coronary angiography and revascularization were not predictive of mortality.

In a cohort of 653 kidney transplant candidates, a left ventricular ejection fraction  $<45\%$  was associated with a 1.8-fold increased risk of cardiac complications and a 2-fold increased risk of mortality after a mean follow-up of  $3.0 \pm 1.8$  years [106]. In another study, four independent predictors of mortality after kidney transplantation were identified: age  $>50$  years ( $P = 0.002$ ), left ventricular end-systolic diameter  $>3.5$  cm ( $P = 0.002$ ), maximal wall thickness  $>1.4$  cm, ( $P = 0.014$ ) and mitral annular calcification ( $P = 0.036$ ). The 5-year survival estimates for 0, 1, 2 and 3 prognostic factors were 96, 86, 69 and 38%, respectively [155].

In an observational cohort of 253 transplant candidates deemed to be at high cardiovascular risk, mortality was worse in patients not transplanted versus transplanted, even after stratification for the severity of coronary artery disease. However, it is unclear how lead time bias induced by death on the waiting list influenced these results, and the data should be interpreted with caution [156].

#### How did we translate the evidence into the statement?

The guideline development group proposes an algorithms for screening for underlying cardiovascular disease.

In patients with a low cardiovascular risk profile, history, basic ECG and chest X-ray have a very high negative predictive value for the presence of cardiovascular disease.

In patients with diabetes or high cardiovascular risk (elderly, peripheral vascular disease, familial history), additional stress testing has a high negative predictive value. There is no clear evidence for superiority of one method of stress testing over the other (dobutamine stress echocardiography versus myocardial perfusion scanning, physical versus medication induced exercise).

Only patients with high cardiovascular risk with non-negative stress imaging tests should undergo coronary arteriography.

A basic cardiac ultrasound can in high-risk patients give some prognostic information, based on simple criteria.

#### **What do the other guidelines state?**

The UK Renal Association similarly does not recommend full/invasive cardiac work up in asymptomatic patients [28].

KHA-CARI endorses similar recommendations on cardiac work-up before transplantation [157]. The European Association of Urology recommends to rule out coronary artery disease in high-risk patients and to perform any revascularizations prior to transplantation [29].

#### **Suggestions for future research**

A randomized controlled trial comparing routine coronary screening in asymptomatic high-risk patients with care as proposed by the ACC/AHA guidelines would determine whether current recommendations have an impact in outcomes important to patients. It has been shown that such a trial is feasible.

### 1.11. When and for which indications should native nephrectomy be performed in kidney transplant candidates awaiting kidney transplantation?

We recommend native nephrectomy before transplantation (unilateral or bilateral) in patients with autosomal polycystic kidney disease (ADPKD) when there are severe, recurrent symptomatic complications (bleeding, infection, stones). (1C)

We suggest unilateral nephrectomy of asymptomatic ADPKD kidneys when space for the transplant kidney is insufficient. (2C)

We do not recommend routine native nephrectomy, unless in cases of recurrent upper urinary tract infections or when the underlying kidney disease predisposes to enhanced cancer risk in the urogenital tract. (Ungraded Statement)

#### Rationale

##### Why this question?

There is no consensus regarding which kidney transplant candidates should undergo native nephrectomy, whether they should undergo unilateral or bilateral nephrectomy and what is the optimal timing for such a procedure.

##### What did we find?

We identified 12 retrospective cohort studies examining the influence of unilateral or bilateral nephrectomy on outcomes after transplantation [158–169]. With the exception of one old registry study including close to 3000 patients [166], sample sizes were small with 23–75 participants each. Eight studies only included patients with ADPKD [160–162, 164, 165, 167–169].

In all 12 studies removal of one or both kidneys had been for clear reasons of recurrent infections, persistent bleeding, discomfort or lack of space for the kidney graft. In nine studies unilateral or bilateral nephrectomy was compared with not performing planned nephrectomy either before, during or after transplantation ( $n = 3268$ ) [158, 159, 161, 163–168]. Overall, there was no difference in patient and/or graft survival between patients who underwent nephrectomy before transplantation and those that did not undergo planned nephrectomy.

When compared with patients who underwent planned nephrectomy before transplantation, patients who underwent planned nephrectomy during transplantation had similar patient and/or graft survival after transplantation, post-operative complications and duration of hospital stay (five studies,

$n = 2945$ ). Complications and complication rates in case of required nephrectomy after transplantation were not different in comparison with complication rate after planned nephrectomy. Only two small studies ( $n = 85$ ) compared bilateral with unilateral nephrectomy [162, 167]. Overall there was no evidence to suggest outcomes after transplantation or complication rate differed between bilateral and unilateral nephrectomy, but the comparisons were poorly studied.

All studies suffered from selection bias and lack of adequate decision analysis as all studies only included those who were actually transplanted.

##### How did we translate the evidence into the statement?

Overall there was no evidence to suggest that if kidneys were left in place in asymptomatic patients, and surgeons did not consider space to be insufficient, patient or graft survival after transplantation was compromised, complication rate was higher or hospitalization was longer. If they did consider there to be insufficient space to accommodate the kidney graft, then outcomes were not different whether the nephrectomy was done before or during transplantation and whether one or both kidneys were removed. Although subject to selection bias, it suggests that subjecting these patients to an additional surgical procedure does not convey benefit.

When one or both native kidneys were removed before transplantation for reasons other than lack of space, it happened because of recurrent infection, bleeding or pain. Reasonably, the comparator group in whom kidneys were left in place had no such symptoms. Outcomes were similar between those with symptomatic and those with asymptomatic kidneys, provided the symptomatic kidneys had been removed and patients had lived up to transplantation. Although there is no direct evidence to support removal of symptomatic ADPKD kidneys specifically in light of subsequent transplantation, it seems reasonable the strategy would not differ from those who are not considered for transplantation. The guideline development group felt that although not supported by direct evidence, the risk of severe infections under immunosuppression in patients with recurrent urinary tract infections before transplantation could make nephrectomy of a non-ADPKD kidney a reasonable strategy.

##### What do the other guidelines state?

These recommendations are in line with those of the European Association of Urology. None of the other guideline bodies provides a statement on this topic [29].

##### Suggestions for future research

No suggestions.

## CHAPTER 2. IMMUNOLOGICAL WORK-UP OF KIDNEY DONORS AND RECIPIENTS

### 2.1. How should HLA typing be performed in kidney transplant candidates and donors?

We suggest that at least one typing is performed by molecular HLA typing of patients and donors to avoid mistakes in the classification of the HLA antigens. (2D)

We suggest that HLA typing is performed in duplicate, preferentially on separate samples obtained at different occasions to avoid logistical errors. (Ungraded Statement)

In case of sensitized patients, we recommend additional serological typing of the donor cells to be used for cross-matches in order to check the proper expression of the HLA antigens on the target cells. (1D)

For highly sensitized patients with allele-specific antibodies we suggest to consider high-resolution molecular typing in both recipients and donors. (2D)

#### Rationale

#### Why this question?

Good matching potentially improves graft outcome. More precise tests may improve the matching, and thus improve graft outcome. However, they are expensive and laborious.

#### What did we find?

All studies comparing the results of serological HLA typing and molecular typing show a significantly lower discrepancy rate with molecular typing irrespective of the molecular typing technique, i.e. PCR-SSP and PCR-SSO. Especially serological typing for HLA-DR is associated with a high discrepancy rate up to 25% but also for HLA-A and -B typing the error rate is significantly higher when using serological typing [170–173].

The clinical benefit of molecular typing is shown by studies where patients had been transplanted with an HLA compatible donor on the basis of serological typing. One-year graft survival in the group that was also compatible after molecular typing was significantly higher (87 versus 72%,  $P < 0.05$ ) than in the group where molecular typing revealed incompatibilities

[174]. Of course, these data stem from an era with less potent immunosuppressive regimens.

A disadvantage of molecular typing is the fact that this technique does not test the proper expression of the HLA molecules on the cell surface. This is important when cross-matches are performed for sensitized patients as this may lead to false-negative cross-matches in case the target antigen is not adequately expressed on the donor cells used for cross-matching. Serological typing will reveal the expression of the antigens on the donor cells used in the cross-match.

Matching in kidney transplantation is based on low-resolution typing, which means that allelic mismatches could still be present in apparently fully HLA-matched combinations. High-resolution typing can reveal allelic differences between donor and recipient, which may be important for patients with allele-specific antibodies.

#### How did we translate the evidence into the statement?

Despite the fact that there is no direct evidence to prove superiority of molecular typing tests, the guideline development group judged that they can be of benefit because of better accuracy and reproducibility in defining class I and class II antigens.

For highly sensitized patients, high-resolution molecular typing in both recipients and donors is necessary to avoid allocation of kidneys bearing the HLA allele against which the recipient has antibodies.

Duplicate sampling is recommended to avoid administrative and logistic errors.

#### What do the other guidelines state?

The British Transplant Society endorses guidelines for the detection and characterization of clinically relevant antibodies in allo-transplantation in collaboration with the British Society for Histocompatibility and Immunogenetics. They recommend assessing a patient's HLA alloantibody profile to delineate antigens regarded as unacceptable for transplantation [62].

#### Suggestions for future research

To evaluate outcomes of molecular typing versus classic typing, using an intention to treat approach, and with the outcome measures patient survival, graft survival and waiting time.

To conduct health economic analysis of molecular typing.

## 2.2. In a kidney transplant recipient, how should HLA matching be used to optimize outcome?

We suggest matching for HLA-A, HLA-B and HLA-DR whenever possible. (2C)

We recommend balancing the effects of HLA matching with other parameters that affect patient and graft outcomes when deciding the acceptance of a potential graft. (1D)

We recommend giving preference to an HLA identical donor and recipient combination. (1B)

We suggest giving more weight to HLA-DR matching than to HLA-A and HLA-B matching. (2C)

We recommend giving more weight to HLA matching in younger patients, in order to avoid broad HLA sensitization that might impair re-transplantation. (Ungraded Statement)

### Rationale

#### Why this question?

Matching for HLA antigens can potentially improve graft outcomes. However, it can increase waiting time for certain patients, and it can negatively impact on cold ischaemia time (CIT).

#### What did we find?

The current role of HLA matching is controversial. Several epidemiological data from large registries show a benefit with regard to both acute rejection incidence and graft survival when HLA antigens are matched [175–184]. This is in particular true for zero mismatch versus one or more mismatched organs [185]. Other studies fail to demonstrate a difference in rejection rates and graft survival according to HLA matching [186–188]. Overall it seems that HLA matching has a beneficial effect on graft survival, declining with era of transplantation from ~15% after 5 years during the years 1985–94 to 2–8% during the years 1995–2005 [189–191].

Eurotransplant data show that matching primarily for HLA-DR can result in a simpler and more equitable allocation of kidneys [192].

The effect of matching has to be balanced with other factors like time on dialysis. Moreover, waiting for a well-matched kidney can have negative effect on patient survival when compared with earlier transplantation with a poorly matched kidney [186].

An increasingly important criterion for HLA matching is to reduce sensitization. This should be taken into consideration when transplanting a donor with a mismatch of a frequent HLA antigen in a younger recipient with a chance of needing a re-transplant.

#### How did we translate the evidence into the statement

The guideline development group judges that the impact of matching for HLA-A, -B and -DR is too important to be neglected. This beneficial effect is especially observed when a full match is obtained. The impact of DR mismatches is stronger than for HLA-A and -B.

However, also other factors such as estimated CIT, waiting time on the transplant list, eventual technical problems related to dialysis, difference or agreement between age and body size of donor and recipient should be accounted when taking the individual decision to accept an offered organ for a specific patient.

In young patients, it should be considered that re-transplantation might become necessary in the future. Therefore, one should try to have an as optimal organ as possible, to enhance longevity, and to avoid mismatches, to reduce the potential for sensitization, which at a later stage might complicate re-transplantation.

#### What do the other guidelines state?

No other guideline provides specific statements on this topic.

#### Suggestions for future research

More insight in the balance of the impact of CIT and of HLA-mismatching is needed.

### 2.3. In kidney transplant candidates, what HLA antigens and non-HLA antigens should be defined in addition to HLA-A, -B and -DR?

We recommend performing HLA-DQ, HLA-DP and HLA-C typing of the donor only when the intended recipient has HLA antibodies against those antigens. (1D)

We do not recommend routine typing for major histocompatibility complex class I-related chain-A (MICA) and other non-HLA antigens in either recipient or donor. (1D)

#### Rationale

##### Why this question?

Besides the classical HLA antigens, also additional HLA and non-HLA antigens might have an impact on graft outcome. Additional identification of these antigens can however pose logistical problems, and is laborious and expensive. It might also lead to avoiding clinically irrelevant mismatches, and thus increase waiting time in some patients.

##### What did we find?

The effect of HLA-C matching has been poorly studied. As a result of linkage disequilibrium, HLA-C matching is strongly linked with A and B matching. In a small ( $n = 104$ ) retrospective cohort study, an unplanned and univariate analysis showed association between HLA-C mismatching and acute rejection. However there was no pre-specified hypothesis or correction for multiple testing [184]. In a large cohort of 2260 deceased donor kidney transplantations, the Collaborative Transplant Study (CTS) group found that HLA-C mismatch was associated with significantly decreased graft survival in sensitized (2 MM:  $70.3 \pm 7.5\%$ , 1 MM  $79.6 \pm 2.7\%$ , 0 MM  $87.7 \pm 1.7\%$ ,  $P < 0.001$ ) but not in non-sensitized patients ( $P = 0.75$ ) [193].

The influence of HLA-DP matching on transplant outcome has still to be clarified. Around 14% of the patients have HLA-DP antibodies before transplantation [194]. Post-transplant, 5.1% of recipients of a functioning graft and 19.5% of those who have rejected their graft have DP antibodies by Luminex [195]. The CTS group has reported in a cohort of 3600 first transplantation and 1300 re-transplantation that HLA-DP matching is not associated with better allograft survival after a first kidney transplant, but is associated with better 1-year graft survival after a second kidney transplant (83 versus 76 versus 73% in 0, 1 and 2 mismatches respectively [196]. The same team as well as the Leiden group showed later, by studying the amino-acid residues in the hyper variable regions of the DP alleles that matching for certain immunogenic epitopes was more important than the classical matching at the allelic level [194, 197].

Among non-HLA antigens, MICA is the strongest antigenic system. While indirect evidence from small, retrospective studies suggest that MICA antibodies could be a risk factor for acute kidney graft rejection [196, 198–201], the most robust

though contradictory data in kidney transplantation stem from two major studies. In a cohort of 1910 transplanted patients, 11.4% had MICA antibodies before transplantation [202]. MICA immunization significantly correlated with acute rejection and lower 1-year graft survival. Its influence was more evident in first transplantation and in patients well matched for HLA with their donor. In the second study, MICA antibodies were detected in 14.9% of patients with chronic kidney disease, 425 transplanted and 172 dialysed, versus 6.8% in controls [203]. The variables associated with their development were the same as for HLA antibodies: transfusion, pregnancy and previous transplantation. Contrasting with the preceding study, no detrimental effect of MICA immunization on graft survival even at 10 years was found. In a subgroup of patients, MICA antibodies were identified as autoantibodies in 20%.

The pathogenic role of H-Y has been demonstrated in two large studies with a cohort of >100 000 transplantations, one from the CTS group [204] and one from the United States Renal Database [205]. Both found a significantly increased risk of graft failure in the combination male donor/female recipient at 1 year but not at 10 years and female recipients even appeared to have better survival whatever the sex of the donor. Although significant, the H-Y effect was small (HR:  $\sim 1.03$ ). The US study included more covariates in the analysis such as race, peak PRA, cause of end-stage kidney disease and transplant era, but the conclusions were identical apart from a trend to disappearance of the H-Y effect in patients transplanted between 2000 and 2004. Antibodies against two recombinant H-Y molecules have been identified by enzyme-linked immunosorbent assay (ELISA) and western blot in 46% of 26 female recipients of a male donor versus 0–3% in the other sex combinations [206]. These antibodies significantly and strongly correlated with acute rejection, CD38 and CD138 plasma cell infiltrates in the biopsy but not with C4d staining and post-transplant HLA antibody.

A significant effect on acute rejection of certain killer immunoglobulin-like receptor (KIR) mismatches has also been reported. A recent study showed that in 137 kidney transplantations compatible for HLA-A, HLA-B and HLA-DR, KIR-ligand mismatching was associated with a 25% reduction in death-censored graft survival ( $P = 0.043$ ) [207] and was an independent risk factor in multivariate analysis (HR: 2.29). This effect was estimated comparable with that of HLA-A and -B incompatibilities. In HLA-B incompatible transplantations, KIR-ligand mismatches had no additional effect [208].

Other targets for non-HLA antibodies, such as endothelial cell antigens [209], have been suggested but their interest in kidney transplantation still has to be demonstrated. Antibodies against the angiotensin II type 1 receptor (AT1) were reported several years ago as able to induce humoral rejection characterized by malignant hypertension in a small series of 16 patients [210]. However, in 28 patients from a cohort of 433 kidney transplants, having early antibody-mediated rejection, none among the 10 that were not explained by HLA antibodies were associated with AT1 antibodies [211]. Along this line, AT1 antibodies could not be detected among patients who developed C4d-positive rejection [212]. Anti-glutathione

transferase T1 (GSTT1) antibodies have been described in acute and chronic C4d-positive antibody-mediated rejection in patients who do not have the GSTT1 gene (20% of the population) and have received a GSTT1-positive donor [213, 214].

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

Non-classical HLA types (HLA-C, HLA-DP and HLA-DQ) have been associated with acute rejection and worse graft survival. However, most of these data come from older observational cohorts which might not be representative for current transplant practice, and are based on univariate analyses. Taking into account the rather limited effect size, and the potential logistical consequences of routinely typing for these additional HLA antigens, both in terms of financial costs and

increasing the complexity of allocation, the guideline development group recommend performing HLA-C, HLA-DP and HLA-DQ preferentially in high-risk patients, i.e. re-transplantation in highly sensitized patients.

We suggest neither screening for AT I-receptor antibodies or MICA antibodies nor for any other non-HLA antibody.

#### **What do the other guidelines state?**

No other guideline body provides a statement on this topic.

#### **Suggestions for future research**

Prospective studies analysing the impact of matching for HLA-DQ, HLA-DP and HLA-C should be undertaken, with as outcome parameters patient and graft survival, time on the waiting list, CIT and a health economic analysis.

#### 2.4. In HLA-sensitized kidney transplant candidates what measures should be attempted to improve the probability of a successful transplantation?

We recommend establishing programmes to select a donor towards whom the recipient does not produce antibodies. (1C)

In recipients from cadaveric kidney donors, this aim can be achieved by an acceptable mismatch programme. (1C)

In living donation this goal can be achieved by paired exchange. (Ungraded Statement)

We recommend transplanting patients with donor-specific antibodies only if these above-mentioned measures cannot be accomplished and after successful intervention. (2D)

#### Rationale

##### Why this question?

Patients can be HLA sensitized, which might jeopardize their graft survival. Avoiding donors to whom the sensitized recipient produces antibodies can prolong the waiting time, or can lead to abandoning living donation. Several interventions have been described in the last decade to reduce the antibody titres, allowing transplantation of patients with donor-specific antibodies.

##### What did we find?

In deceased donor transplantation, the Acceptable Mismatch programme of Eurotransplant is based on the accurate definition of the HLA antigens or epitopes against which the patient has not formed antibodies; the donor must be compatible with the combination of the HLA type of the recipient and the acceptable antigens. This procedure has increased the transplantation rate for highly immunized patients with good results [215]. France has a similar programme where acceptable antigens are defined according to the positivity and strength of the HLA antibodies by Luminex. In case an incompatible living donor is available, paired donor exchange programmes have shown to be a good tool to find an alternative cross-match negative donor [216].

Several papers have described a progressive or integrative approach in the attribution of the transplant graft and have also specified the associated risk [217, 218]. The first protocols were based on high dose intravenous immunoglobulins (IVIG) [219] or plasmatic exchange with low dose IVIG [220]. Stegall compared both and reported a lower incidence of humoral rejection whenever plasma exchange was used pre- and post-transplant [221]. In some centres, plasma exchange has been replaced by immunoadsorptions [222]. Anti-CD20 antibodies have been added in the most recent protocols for inhibition of antibody production [223, 224]. The association of rituximab, plasma exchange and IVIG has improved the access of immunized patients to a transplant and short-term graft survival. In one study including histological data, the addition of rituximab was also shown to significantly decrease the inflammatory lesions in

the microcirculation, the rate of transplant glomerulopathy and of chronic humoral rejection [224]. Based on a publication of the Mayo Clinic showing that this drug was able to inhibit antibody producing cells in the bone marrow [225], bortezomib has been used in desensitization protocols, but results are equivocal. A multicentre North American trial on this topic is currently on-going. An original approach has recently been proposed by Stegall with the addition of eculizumab, an anti-C5 monoclonal antibody to reduce lesions associated with complement activation by donor-specific antibodies [226]. Although most of these protocols reduce HLA antibodies to a degree that transplantation becomes possible, the long-term outcome of these procedures is still uncertain, as no study has a follow-up longer than 3 years.

##### How did we translate the evidence into the statement?

In addition to poorer graft survival, HLA-sensitized patients, especially the highly sensitized ones, have a poor access to kidney transplantation and accumulate on the waiting list. The search for a compatible donor should be preferred, and optimized with the most accurate characterization of the HLA antibodies and attribution of a suitable donor, living or deceased, through specific programmes.

Transplantation of an HLA incompatible kidney should remain the last step when the search for a compatible donor is unsuccessful. HLA incompatible donors are increasingly proposed to these patients, after elimination of the donor-specific antibodies by desensitization procedures. These procedures allow transplantation, and have a reasonable and acceptable short-term outcome in reported case series. However, these interventions, either applied alone or in combination, do not seem able to significantly and sustainably reduce donor-specific antibody production in patients with high levels of HLA antibodies and there is still concern in the long-term outcome of the transplant and patient survival. Clearly, more studies are needed with larger cohorts and longer-term endpoints.

The strength of HLA antibody titres under or above which desensitization protocols are either not necessary or not efficient has also to be determined.

##### What do the other guidelines state?

The British Transplant Society together with the British Society for Histocompatibility and Immunogenetics endorses recommendations on HLA-specific antibody incompatible transplantation in general (not specifically on kidney transplantation) [62]. They recommend determining the HLA specificity and level of donor-specific antibodies prior to antibody reduction treatment which should follow an established clinical and laboratory protocol.

##### Suggestions for future research

Long-term follow-up observational studies reporting graft and patient survival and complications with protocols bypassing high sensitization are needed.

Head-to-head comparison of different protocols for reduction of antibody titres is needed.

Relevant cut-off points for antibody strength should be defined, and this for different desensitization strategies.

## 2.5. Should in kidney transplant candidates a failed allograft that is still in place be removed or left in place?

Evidence comparing patients with a failed transplant with versus without nephrectomy is insufficient and conflictive, hampering a meaningful general recommendation on whether or not nephrectomy of failed grafts should be recommended. **(Ungraded Statement)**

We suggest that in following conditions an explanation of the failed kidney graft be considered: clinical rejection, chronic systemic inflammation without other obvious cause or recurrent (systemic) infections. **(Ungraded Statement)**

We suggest to continue low level immunosuppression and to avoid a nephrectomy of a failed graft when residual graft urinary output is >500 mL/day and there are no signs of inflammation. **(Ungraded Statement)**

### Rationale

#### Why this question?

Failed graft is an increasingly prevalent reason for start of kidney replacement therapy. Removal of a failed graft can theoretically reduce the inflammation induced by on-going activation of the immune system. The presence of the failing graft might induce sensitization, which might hamper re-transplantation. The net immunological effects of a nephrectomy are unclear, as the failed graft can act as a sponge of already present antibodies, which will become apparent after nephrectomy. In addition, nephrectomy deprives the patient of residual diuresis, if still present.

#### What did we find?

Several studies have compared rejection incidence and graft survival in re-transplant recipients with versus without the failed graft in situ. All these studies showed serious methodological limitations because they were single centre; the management of immunosuppression both before and after nephrectomy varied between reports; the indications of nephrectomy were non-standardized, some being performed electively and others because of clinical indications; and there was a general lack of adjustment for possible confounders such as co-morbidities or time on dialysis before nephrectomy. Some studies did not show any difference in rejection incidence and graft survival or rejection incidence whether transplantectomy was performed or not [227], whereas others show either a beneficial [228] or a detrimental impact of previous transplantectomy [229, 230]. Early data showed a higher anti- HLA sensitization if nephrectomy of the failed graft occurred before instead of during re-transplantation [231]. This was later confirmed when the presence of HLA antibody specificities in the serum of 65 patients from 16 centres was analysed before and after nephrectomy of the failing graft [232]. In the HLA-A, HLA-B and HLA-DRB1 mismatch categories the incidence of DSA reactivity pre- versus post-nephrectomy was 64 versus 87% ( $P = 0.003$ ) and 57 versus 86% ( $P = 0.001$ ), respectively. The frequencies of individual reactive

antigens were also lower before versus after nephrectomy of the failing graft: for HLA-A and HLA-B antigens: 49 versus 75% ( $P < 0.0001$ ) and DRB1 antigens: 48 versus 79% ( $P = 0.0001$ ). The authors speculated that additional antibodies are probably absorbed into the rejected graft and became apparent after removal of the graft.

In a small ( $n = 21$  and 32) retrospective single-centre cohort, graft survival at 1, 3 and 5 years was 83 versus 89%, 64 versus 79% and 45 versus 68% in the nephrectomized versus non-nephrectomized group, respectively. None of these differences was significant, which might be due to the lack of power [233].

In a small ( $n = 89$ ) retrospective cohort study comparing patients who had their failing graft removed (Group 1) versus left in place (Group 2), there was no difference in panel reactive antibody (PRA) titre at the moment of transplantation (37 versus 29%). After a mean follow-up of 4 years, 49.1% of patients in Group 1 versus 31.2% in Group 2 had acute rejection ( $P = 0.20$ ) and 20 (29%) versus 4 (19%) of grafts failed in Group 1 versus Group 2; 1, 3 and 5 years' actuarial graft survival in Group 1 was 83.8, 76 and 66.2%, whereas in Group 2, it was 94.7, 86.8 and 69.5%, respectively ( $P = 0.66$ ). Five-year actuarial patient survival in Groups I and II was 94.1% and 87.5%, respectively ( $P = 0.69$ ) [234].

In a large retrospective analysis of USRDS data, including 3707 early graft failure and 15 400 late graft failure patients (graft survival >12 months), nephrectomy was associated with an increased risk of death (HR: 1.13, 95% CI: 1.01–1.26) in the early transplant failure cohort, whereas in patients with late transplant failure, it was associated with a decreased risk of death (HR: 0.89, 95% CI: 0.83–0.95) [235]. In early transplant failure patients, nephrectomy was associated with a lower risk of re-transplant failure (HR: 0.72, 95% CI: 0.56–0.94), while among late transplant failure patients it was associated with a higher risk (HR: 1.20, 95% CI: 1.02–1.41). In another analysis of the cohort in the USRDS database between 1994 and 2004, included 10 951 transplant recipients who returned to long-term dialysis [236]. Of those, 3451 (31.5%) received an allograft nephrectomy during the follow-up, which was associated with a 32% lower-adjusted relative risk for all-cause death (adjusted HR: 0.68, 95% CI: 0.63–0.74), after adjustment for socio-demographic characteristics, comorbidity burden, donor characteristics, interim clinical conditions associated with receiving allograft nephrectomy and propensity to receive an allograft nephrectomy. Those having versus not having a transplant nephrectomy had a higher probability for re-transplantation (10.0 versus 4.1%,  $P < 0.0001$ ), but there might have been bias by indication, and no outcome data for the re-transplant were provided.

In a small retrospective comparison including only patients who actually underwent re-transplantation, previous nephrectomy ( $n = 141$ ) versus no nephrectomy ( $n = 45$ ) was associated with increased panel reactive antibody titres (37.2 versus 17.8%,  $P = 0.02$ ), increased rates of primary non-function (14.8 versus 4.4%,  $P = 0.05$ ) and acute rejection (29.7 versus 13.6%,  $P = 0.04$ ), and worse re-transplant graft survival (30 versus 15% after a mean of  $67 \pm 29$  months,  $P = 0.03$ ) [230].

Importantly, recent data show that, among patients who underwent early graft nephrectomy and were left without immunosuppression, anti-donor HLA antibodies were produced only after several weeks and continued to increase up to 6 months after graft nephrectomy. This observation suggests that donor-specific antibodies are produced 'de novo' after graft nephrectomy, rather than absorbed by the graft and released in the circulation thereafter [237].

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

Data seem to suggest that removal of a failing graft might either lead to 'de novo' immunization to donor HLA antigens, or reveal the presence of antibodies that were adsorbed by the failing graft while still in place. Data on graft and patient survival after re-transplantation are coming from small observational cohorts, and there is a substantial risk of bias by indication, as presumably, there was mostly a clear reason for removal of the failing graft; however, data on indications for graft removal are not available.

The guideline development group judged that data do not allow to draw any meaningful general conclusion, and that the

decision for nephrectomy of a failed graft should be taken on a case per case basis. Factors to be included in the evaluation are the presence/absence of residual kidney function, and the presence or absence of inflammation or infection.

We suggest that the threshold to perform a nephrectomy should be substantially lower in patients in whom re-transplantation is not an option; in contrast, in patients rescheduled for re-transplantation, the threshold should be higher.

#### **What do the other guidelines state?**

No other guideline body provides a statement on this topic.

#### **Suggestions for future research**

A randomized controlled trial comparing nephrectomy with no nephrectomy of a failed graft should be performed, with post-nephrectomy immunization profile and kinetics, patient survival, time to re-transplantation and graft survival as outcomes. Such a trial should include an evaluation of the impact of continuation of immunosuppression after transplant nephrectomy. A separate analysis should be provided for patients waiting for a re-transplantation, and those not rescheduled for transplantation.

## 2.6. In kidney transplant candidates, what technique of cross-match should be used to optimize outcomes?

We recommend performing a complement-dependent cytotoxic (CDC) cross-match in HLA-sensitized patients to prevent hyperacute rejection. (1B)

We suggest that in HLA antibody negative patients with negative regular quarterly screening samples a cross-match can be omitted, unless a potential HLA-sensitizing event has occurred since last screening. (2B)

We do not recommend performing a Luminex or endothelial cell cross-match because their additional value needs further evaluation. (1D)

We recommend a positive CDC cross-match should only be accepted as truly positive when donor-specific antibodies are known to be present. (1B)

### Rationale

#### Why this question?

A cross-match is used as an *in vitro* test to evaluate compatibility between the individual donor and recipient pair. However, performing the cross-match takes some time, and might increase CIT.

CDC is the most widespread test, but more sensitive tests have been developed over the last years. These tests are however more laborious and expensive, and might lead to false-positive results.

#### What did we find?

Historical data show that a positive CDC cross-match due to donor-specific HLA antibodies is associated with the occurrence of hyperacute rejection [238, 239]. The clinical relevance of a positive CDC cross-match with historical sera only is less clear and such a cross-match is rather a risk factor than a contraindication for transplantation [240]. A more sensitive variant of the CDC cross-match is the one augmented by the addition of anti-human immunoglobulin, the AHG-CDC cross-match, which might be too sensitive for the mere prevention of hyperacute rejection [241]. In order to detect antibodies reactive with donor HLA class II, CDC cross-matches are performed with B cells as target. The relevance of a positive B-cell cross-match is less clear. Le Bas-Bernadet showed a higher incidence of early graft failure in case of a positive B-cell cross-match, whereas Pratico-Barbato did not observe any clinical effect [242, 243]. The reason for this may be the specificity of the antibodies causing the positive B-cell cross-match. In case of a positive B-cell cross-match and proven donor-specific antibodies in antibody screening a high incidence of graft loss is observed whereas a positive B-cell cross-match in the absence of DSA has no effect on graft outcome [244]. Not all HLA antibodies do fix complement, which is the reason why the flow cytometric cross-match was introduced. Several retrospective studies show that the presence of a positive flow cytometric cross-match is not a contraindication for

transplantation but is associated with a higher incidence of rejection although many grafts function well without any complications [245–248]. Other studies could not demonstrate any clinical relevance of a positive flow cross-match in the presence of a negative CDC cross-match [249–251]. A positive flow cross-match in the presence of donor-specific antibodies is shown to be associated with more acute rejection and poor graft function [246], although this was not confirmed by a small study by Bryan *et al.* [252]. A problem associated with flow cross-matching is the detection of irrelevant (non-HLA) antibodies especially reactive with B-cells, which may be prevented by the addition of pronase [253, 254]. Recently two other cross-match tests have been introduced: one for the detection of donor-specific HLA antibodies on the basis of the Luminex technology [255], while the second one uses endothelial cell precursor cells as targets in order to be able to detect non-HLA targets [256]. The clinical relevance of these assays remains to be established.

Recent data suggest that a good antibody screening can help to define non-acceptable mismatches and can predict a positive cross-match [257–261]. Donors expressing these non-acceptable HLA antigens can be excluded without performing an actual cross-match, a policy called a virtual cross-match.

In a cohort of 606 patients [262], no cross-match was being performed before transplantation in 257 non-sensitized patients; a cross-match performed at a later stage proved to be negative in all cases, and CIT was reduced from 16.7 to 14.3 hours, resulting in a decrease (28 versus 18%) in delayed graft function (DGF) in recipients of a brain death donor, but not in recipients of a heart-beating donor (52 versus 54%).

#### How did we translate the evidence into the statement?

A positive CDC cross-match with current serum is considered a contraindication for transplantation. It is however essential to take the results of antibody screening into consideration in the interpretation of the cross-match. A positive B-cell cross-match in CDC is therefore only associated with a higher incidence of rejection when donor-specific antibodies are present. If that is not the case, graft survival and rejection incidence in patients with a positive B-cells cross-match are similar to that of non-sensitized patients. An important aspect of the CDC cross-match is the fact that donor lymphocytes are used as target cells. The consequence is that the antibodies leading to a positive cross-match are not necessarily directed against the HLA antigens. This is one of the reasons that why a positive cross-match in CDC is not always a contraindication for transplantation.

In non-sensitized patients with negative regular quarterly screening samples, the guideline development group accepted that a cross-match can be omitted. This is based on a large cohort of such patients, where in none of the cases, a positive cross-match was observed at a later stage. In this study, omission of the cross-match resulted in a shorter CIT, and in the recipients of a brain death donor even in less DGF. However, it is important that no potentially HLA sensitizing event, such as pregnancy, or blood transfusion has occurred since last screening.

Positive cross-match tests based on flow cytometry are associated with increased, but not unacceptable, risk of graft loss and the guideline development group judged that transplantation under these conditions is possible, but should be done with caution. However, the guideline development group judged that the additional value of flow cytometry remains uncertain, and that especially cost aspects make that it cannot be recommended as a routine procedure. The same line of reasoning was followed for cross-match based on Luminex and on endothelial cell assays.

**What do the other guidelines state?**

The European Association of Urology recommends that a lymphocyte cross-match should be performed to avoid hyperacute rejection. The British Transplant Society in collaboration with the British Society for Histocompatibility and Immunogenetics recommend pre-transplant cross-match unless a

programme exists to confidently identify non-sensitized individuals that have never produced HLA antibodies [62]. According to them, patients with no detectable HLA-specific antibodies can be transplanted on the basis of a negative virtual cross-match without waiting for a cross-match test to be performed; this recommendation is thus in line with that of ERBP. Additionally, a cross-match using flow cytometric techniques on historic samples of the sensitized patient is recommended for sensitized patients.

**Suggestions for future research**

Further evaluation of the additional value of flow cytometric, Luminex and endothelial cell cross-match, including health economic analysis is needed.

Further evaluation of the impact of omitting a cross-match in non-sensitized patients is warranted.

## 2.7. In kidney transplant candidates planned to undergo living donor transplantation but for whom the available donor is ABO incompatible, what measures can be taken to improve outcome after transplantation?

We recommend both inhibition of antibody production and ABO antibody removal before transplantation applied together in one and the same validated protocol. (1C)

We recommend transplantation of an ABO incompatible kidney only if the ABO antibody titre after intervention is lower than 1:8. (1C)

We suggest considering paired exchange when available. (Ungraded Statement)

### Rationale

#### Why this question?

In some cases only an ABO blood group incompatible living donor is available. Allowing ABO incompatibility in living donation could expand the donor pool. However, there might be an increased risk for rejection and worse long-term outcomes.

#### What did we find?

It has long been known that preformed anti-ABO antibodies trigger hyperacute rejection, and ABO incompatibility has been considered an absolute contraindication to kidney transplantation. As a consequence, between 30 and 40% of potential living donors are turned down. An extreme lack of available deceased donor kidneys encouraged investigation into desensitization for ABO incompatible living donation in Japan starting in 1989, using antibody removal and splenectomy. At present, the long-term results between ABO incompatible and compatible transplantation are similar [263, 264]. One report detailed the long-term follow-up on 441 of 494 patients who received an ABO incompatible kidney allograft during the period of 1989 through 2001. In this retrospective multicentre analysis, there was no significant difference in patient or graft survival at Year 1, 3, 5, 7 or 9 compared with historical data from 1055 recipients of ABO compatible living donor allografts [265]. In Europe, the median-term outcomes of 60 consecutive ABO incompatible kidney transplantations after the use of a protocol that incorporated antigen-specific immunoadsorption, rituximab, and IVIG were compared to that of 276 ABO compatible live donor transplant recipients in three centres [266]. At follow-up of up to 61 months, allograft survival was 97% for the ABO incompatible group versus 95% for the ABO compatible recipients. Patient survival was identical for both groups (98%). Of note, there was a significant improvement in ABO incompatible graft survival in patients in the 2000 to 2004 era, following the incorporation of tacrolimus and mycophenolate in the maintenance immunosuppression regimen instead of cyclosporine and azathioprine [267]. In this analysis, statistically superior allograft survival in the most recent period was reported at 1 year (94 versus 78%) and 5 years (90 versus 73%); acute rejection rates had also markedly

improved (15 versus 48%). Along the same line, the combined use of tacrolimus and mycophenolate mofetil allowed to safely and efficiently transplant patients who had initial high titres against A and/or B antigens, in contrast to similar patients previously transplanted under cyclosporine and azathioprine [268].

In most recent reports, the incidence of early acute antibody-mediated rejection is below 10%, and is similar to that observed after ABO compatible transplantation [266, 269–276].

The main principles to allow for efficient ABO incompatible transplantation are first, to reduce circulating ABO antibody titers with either plasmapheresis or immunoadsorption, with the goal of achieving titers  $\leq 1:8$  to  $\leq 1:32$ , depending on centre practice [277]. When plasmapheresis is used, most centres administer 0.1 g/kg of intravenous immunoglobulins (IVIG) after each session [274, 278–284] in order to avoid the depletion of protecting antibody and also to take advantage of the immunomodulatory properties of IVIG [285].

Immunoadsorption was initially described in Sweden using an affinity column coated with A and B blood group antigens (Glycosorb A/B\*, Glycorex Transplantation AB, Sweden), allowing for specific depletion of anti-A/B antibodies [286]. Immunoadsorption is performed daily until antibody titres reach 1:8 or lower. In roughly 80% of patients this is achieved with four sessions of antibody removal. This technique is now widely and successfully used in Europe [269, 272, 287, 288]. Second, immunosuppression should be initiated at least one week prior to transplantation, to inhibit the synthesis of the anti-A/B antibodies depleted by immunoadsorption or plasmapheresis. Third, splenectomy and the use of rituximab, the anti-B-cell depleting monoclonal antibody, have been used as adjunctive therapies to further inhibit post-transplantation antibody synthesis. Several protocols have been published. However, what seems to be essential is the reduction of ABO titres at the time of transplantation, to avoid hyperacute rejection and early acute antibody-mediated rejection during the first post-transplant month. Beyond this period, a rise in isoagglutinin antibody titre to pre-treatment levels or higher is generally not associated with graft damage, a process called accommodation. Although controversial, splenectomy has been commonly used in desensitization protocols for ABO incompatible transplantation to reduce the risk of acute antibody-mediated rejection, mostly in Japan [265, 283, 289, 290] but also in the early experience in the USA [291]. However, the combination of an additional surgical risk and an increased risk of serious infection, especially in the setting of chronic immunosuppressive therapy, lead to a progressive decline of this procedure, which has been often efficiently replaced by rituximab in series from Japan [273, 275, 292], the USA [278, 279] and Europe [266]. Finally, even the use of rituximab seems to be avoidable, as several groups have reported no graft loss and rate of acute antibody-mediated rejection below 10% by using plasmapheresis and IVIG alone [274, 279, 280]. Of note, steroid withdrawal after 1 year in some studies was only successful in 50% and therefore should be used with great caution [287, 293, 294].

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

The guideline development group acknowledges that ABO incompatibility can be a barrier to expansion of living donor programmes. According to the group, there are two ways out: one is to avoid ABO incompatibility by organizing a paired exchange programme. If successful, and with acceptable delays on waiting time, such a programme might have benefits over elimination protocols.

Different protocols for elimination of antibodies have been established, always based on a combination of antibody removal and inhibition of antibody production. As ABO antibodies are subject to accommodation, excellent outcomes have been obtained with these techniques. However, the pros and cons of the procedure should be explained carefully and in depth with

the donor and the recipient. As benefits, one can state the shorter time on dialysis, or even avoidance of dialysis, which is considered to improve long-term outcome. As a drawback, one should stress the potential need for higher levels of immunosuppression and the need to continue long-term steroid therapy.

**What do the other guidelines state?**

This topic is dealt with by the British Transplant Society, which mostly agrees with ERBP recommendations [62].

**Suggestions for future research**

At present, much work remains to be done to establish which strategy: plasmapheresis and IVIG, specific immunoabsorption or anti-CD-20 use is more effective.

## 2.8. In previously transplanted patients, what is the effect of repeated mismatches for HLA antigens on outcome, as compared to avoiding repeated HLA mismatches?

We recommend that repeated HLA mismatches are not considered a contraindication for transplantation in the absence of antibodies against those repeated mismatches. (Ungraded Statement)

We suggest that the presence of antibodies against the repeated mismatch detectable by other techniques than CDC technique be considered as a risk factor rather than a contraindication. (Ungraded Statement)

### Rationale

#### Why this question?

Patients with a previously failed graft might form antibodies against HLA mismatches present in their previous graft. Taking into account previous mismatches can prolong the waiting time. When antibodies are present against a previous mismatch, transplanting a kidney from a donor who also has that HLA pattern can jeopardize graft survival.

#### What did we find?

The available studies were published in the 1990s and their conclusions are difficult to extrapolate to today's situation. Conclusions were conflictive regarding class II repeated mismatches but not class I. Some studies [295–297], but not all [298–302], have suggested that class II repeated mismatches are detrimental. The Eurotransplant group has reported that repeat mismatch of class II had a negative impact on graft survival but only in patients who had lost their first graft in <6 months after transplantation [303]. Others have also found that there was a correlation between the duration of the survival of a first graft and that of the second or further graft [297, 301]. In this previous era, screening of HLA antibodies was more reliable for class I than class II. In addition, donor reactivity against a mismatched antigen was reflected by the positivity of the cross-match but

not all centres performed B-cell cross-matches that are supposed to detect class II immunization. This might explain why class II-repeated mismatches appeared to be detrimental.

Our actual screening, using more sensitive tests such as Luminex or ELISA, is more performant than the methods used previously and is so for any class of HLA antibodies. No study has been reported to date, on the topic of graft survival in re-transplantations with repeated mismatches but this question is linked to the general question of the management of donor-specific antibodies before transplantation.

Repeated mismatch could be harmful in patients having a non-kidney transplant and receiving later a kidney graft. It cannot be excluded that they have donor-specific or non-specific HLA antibodies that are not detected because they are trapped in their first transplant. One study only addressed this question. In a small cohort of patients having a heart, lung or liver transplant and receiving kidney transplantation years later (respectively, 53 and 22 patients), a repeated mismatch was present in 31% of patients, but was not associated with poorer graft survival or lower kidney function at 5 years [304].

#### How did we translate the evidence into the statement?

A repeated mismatch does not contraindicate transplantation if the patient has not developed immunization against this antigen. This reactivity was detected by the cross-match in the past era but our actual screening for identification of HLA antibodies is more sensitive and possibly too sensitive. The question of the repeated HLA mismatch is part of broader discussions on the relevance of donor-specific antibodies detected by the currently available sensitive techniques.

#### What do the other guidelines state?

No other guideline body produced a statement on this topic.

#### Suggestions for future research

Compare outcomes of patients with versus without repeat mismatch, with outcomes patient and graft survival, acute rejection, kidney function, time on the waiting list.

## CHAPTER 3. EVALUATION, SELECTION AND PREPARATION OF DECEASED AND LIVING KIDNEY DONORS

### 3.1. When is dual-kidney transplantation preferred over single-kidney transplantation?

We recommend that before the kidneys of a cadaveric donor are discarded because they are deemed unsuitable for single transplantation, transplantation of both kidneys into one recipient (dual-kidney transplantation) is considered as an option. (1C)

We suggest that in cadaveric donors where there is uncertainty about the quality of the kidneys, the decision to either discard the kidneys, or use them as a dual or a single transplant, is based on combination of the clinical evaluation and history of the recipient and donor, and when available, a standardized assessment of a pre-transplant donor biopsy. (2D)

We recommend that before a kidney from a paediatric donor is discarded because due to low donor age it is deemed unsuitable for single transplantation in an adult recipient, en bloc transplantation is considered. (1B)

We suggest that the option of using kidneys for en bloc transplantation is always considered for donors weighting <10 kg. (1D)

#### Rationale

##### Why this question?

As a result of the shortage of kidneys for transplantation and the increasing number of elderly patients on the waiting list, many organ procurement organizations are increasingly using kidneys from older donors and from donors with risk factors adversely affecting kidney function, such as hypertension or diabetes. This practice carries the risk of using poor-quality organs which might in turn lead to poor graft outcome [305–307]. Apart from the surgical problems related to the presence of severe atherosclerosis in the kidney allograft vasculature, poor allograft outcome has traditionally been attributed to an inadequate number of viable nephrons. This problem also arises when paediatric donors are considered.

To overcome these, dual-kidney transplantation—in which both kidneys are transplanted into a single patient—has been proposed, based on the assumption that the sum of the viable nephrons in the two kidneys approach the number of one standard kidney [308, 309]. Such a strategy should expand the donor pool by recovering kidneys which would otherwise be discarded. Potential drawbacks of dual transplantation are the increased risk of perioperative and surgical complications, and the fact that using two kidney grafts for one

recipient potentially deprives a second person from a scarcely available resource.

##### What did we find?

We retrieved 32 observational cohort studies comparing dual- with single- kidney transplant outcomes [308–339]. The studies differed in the methods of allocating the dual-kidney transplant, which varied as to the type of donors considered for evaluation, the criteria used for such an evaluation (biopsy, clinical, both) and the criteria used for decision-making. Only two studies from the same transplant centre reported explicit criteria for including the recipients as suitable for dual transplantation [321, 339]. In most studies, dual transplantations have been performed using kidneys turned down by other transplant centres, whereas in 10 studies the allocation to dual or single transplantation was based on prospective criteria, which differed among studies [309, 316, 321–323, 326, 327, 335, 336, 339]. One study on Organ Procurement and Transplant Network/United Network for Organ Sharing (UNOS) registry data examined the adherence to current UNOS Guidelines for dual transplantation [330]. Pre-transplant donor biopsies were obtained and used as the sole criteria for allocation of kidneys from marginal donors in all studies from Italy [309, 321, 323, 326, 327, 339] and pre-transplant donor biopsies were performed in 75–95% in North American studies [330, 336], but in a French study, the allocation was based only on the estimated donor's maximum creatinine clearance [335]. Kidney allograft and patient survival was evaluated in all studies, whereas kidney function [i.e. serum creatinine or estimated glomerular filtration rate (eGFR)] and surgical complications were reported in 10 of the 11 aforementioned studies. Follow-up ranged between 1 and 3 years and the number of dual transplants between 21 and 625. No study prospectively evaluated the effects of dual transplantation strategy on the rate of donor recovery and on the time spent by the recipients on the waiting list.

Concerning paediatric donors, we found 10 observational cohort studies [312, 313, 319, 324, 325, 329, 333, 334, 337, 338] comparing en bloc kidney transplantations with single-kidney transplantation outcomes from standard criteria donors [313, 319, 324, 325, 332, 334, 337, 338], extended criteria donors [332] and single kidneys [312, 325, 329, 337]. Kidney allograft and patient survival were evaluated in all studies. In most recent studies [319, 324, 325, 332, 334, 337] follow-up ranged between 5 and 10 years and the number of en bloc kidney transplantations between 66 and 1162. Surgical complications were compared in four studies [312, 313, 329, 338], the incidence of acute rejection in three studies [313, 332, 337], the incidence of proteinuria and hypertension in one study [334].

##### How did we translate the evidence into the statement?

Notwithstanding the less favourable donor characteristics, allograft survival and function of dual transplants approached that observed in transplants from extended criteria donors [330, 335, 336] or even that of standard criteria donors [326], depending on which criteria were used to make the allocation between dual transplant, single transplant or discarding

kidneys. Unfortunately, no study performed so far provided sufficient evidence as to the best method to decide between dual or single transplantation, while ensuring that dual transplantation be restricted to organs that would otherwise be discarded. In fact, no study clearly showed specific prospective criteria for allocation yielding single transplants achieving adequate kidney function, dual transplants achieving the same allograft function as the single transplants, and the donor pool being increased as a result of the implementation of a dual transplantation policy. However, in some transplant centres, the strategy of dual transplantation apparently shortened recipient's expected time on the waiting list [320, 322, 326]. Overall, dual transplantation is a relatively safe option. In fact, when dual transplantation is performed in suitably selected recipients, the increased risk of perioperative and surgical complications seems to be only modest, and not associated with an increased mortality [326, 330, 336, 339]. Dual-kidney transplantation can be carried out by bilateral or unilateral placement of both kidneys. The latter technique offers the advantage of a single surgical access and shorter operating times but it is not technically feasible in all recipients [339].

Concerning paediatric donors, en bloc kidney transplantations have better long-term graft survival and graft function than expanded criteria donor kidneys and standard adult donor kidneys despite a higher graft loss during the first 12 months

post-transplant due to an increased risk of graft thrombosis. The advantage of en bloc kidney transplantation can be appreciated even in extreme donor age <5 years for which en bloc is the transplant technique of choice with respect to the technique of using single organs for paediatric donors [324, 337]. The risk of early graft loss is inversely proportional to donor weight and is highest for donor weight below 10 kg [332]. Donors weighting less than 10 Kg have also the highest discard rate [325]. Surgical expertise and use of heparin can profoundly decrease the incidence of early graft loss due to graft thrombosis in these donors [319]. The incidence of acute rejection for en bloc kidney transplant is similar to standard kidney grafts [319, 332, 337]. From a resource perspective, single kidneys from paediatric donors weighing 10-35 kg used as singles offer more cumulative graft years than when used en bloc [332].

#### **What do the other guidelines state?**

No other guideline body provides a statement on this topic.

#### **Suggestions for future research**

Establish and evaluate strict donor criteria for single or dual-kidney transplantation.

Evaluate the impact of a strictly defined dual-kidney programme on the waiting list.

### 3.2. Which perfusion solution is best suited for kidney preservation in recipients of living donation?

#### Which perfusion solution is best suited for kidney preservation in recipients of deceased kidney donation?

There is insufficient evidence to favour a particular preservation solution for kidneys that carry a low risk of DGF. (Ungraded Statement)

We recommend not using Eurocollins as a preservation solution for kidneys that carry a high risk of DGF (long-projected CIT extended criteria donors). (1B)

#### Rationale

##### Why this question?

Cold storage is the most commonly used procedure for kidney preservation for either living donation or deceased donation after cardiac death. Several types of preservation solutions and fluids have been designed according to their extracellular or intracellular components, viscosity and ability to decrease cell metabolism during preservation while preventing ischaemic reperfusion injuries.

##### What did we find?

We found a recent systematic Cochrane review of sufficient quality on this topic [340].

This review included in total 15 trials, 10 randomized controlled trials (RCTs) and 5 non-RCTs, with a total of 3584 (3004 in RCTs) kidneys, that analysed DGF as primary outcome. Three RCTs compared University of Wisconsin (UW) with Euro Collins (EC), three RCTs compared UW with Celsior, two RCTs and two non-RCTs compared EC with histidine-tryptophan-ketoglutarate (HTK), two RCTs compared UW with HTK. Overall quality of studies was rather low, with

a JADAD [341] score of three ( $n=2$ ), two ( $n=6$ ) and one ( $n=2$ ). The definition of DGF was different in each study.

Euro Collins was associated with a higher risk of DGF than UW solution in two RCTs (114/343 versus 80/352 and 34/44 versus 32/46) and HTK in two RCTs (18/54 versus 0/34 and 119/277 versus 85/292), with moderate risk of bias. UW was associated with an equal risk of DGF compared with Celsior in three RCTs and HTK in two RCTs. These findings are partly supported by registry data.

Eleven studies reported comparable graft survival rate at 1 year for different combinations of perfusion solutions, and one reported worse outcome for EC versus UW (265/300 versus 233/282).

None of the studies was adequately powered to make conclusions on primary non-function or on patient survival.

##### How did we translate the evidence into the statement?

There is a consistent impression that Euro Collins performs worse when compared with other perfusion solutions with regard to DGF. There appears to be no evidence for differences between the other more frequently used perfusions solutions (UW, HTK, Celsior). As a consequence, the guideline development group judged that all solutions can be used when the risk of DGF is low, e.g. in living donation. When additional risk factors for DGF are present, e.g. projected long CIT or non-heart-beating donor, the use of perfusion solutions other than Euro Collins might be advantageous.?

##### What do the other guidelines state?

The European Association of Urology states that UW-solution, HTK-solution and Celsior solution are equally effective for multi-organ and kidney-only donors [29].

##### Suggestions for future research

No suggestions.

### 3.3. Is machine perfusion superior to standard perfusion?

There are conflictive data regarding the generalizability of the benefit of machine perfusion over static cold storage. Until further evidence emerges, no firm recommendation for the use of machine perfusion in preference to cold storage can be made. (Ungraded Statement)

#### Rationale

##### Why this question?

Kidney allografts retrieved from deceased donors may be preserved by either static cold storage or machine perfusion. Machine perfusion is more expensive, and is logistically more laborious, as it requires staff well trained in the procedure.

##### What did we find?

Until recently, studies examining the potential benefits of machine perfusion were small and of poor quality. A meta-analysis of 16 studies with appropriate comparator groups and sufficient data performed between 1971 and 2001 concluded that machine perfusion when compared with cold storage was associated with a small reduction in the risk of DGF (RR: 0.80, 95% CI: 0.67–0.96) [342]. No evidence was found to suggest that this effect was different for allografts retrieved from heart beating versus non-heart-beating donors. There was no significant effect on 1-year graft survival although even when aggregated, the studies were underpowered. In 2009, Moers *et al.* reported the results of a well-designed adequately powered European multicentre randomized controlled study in which one kidney from a donor was assigned to machine perfusion using the LifePort machine ( $n = 359$ ) with the contralateral organ assigned to cold storage ( $n = 359$ ) [343]. However, in 25 donors (4.6%) there were technical difficulties (small aortic patch or multiple arteries) to make connection to the perfusion machine, and the surgical teams were permitted to reverse the randomization. Trained perfusionists were used to transport and set up the machine perfusion device at the donor hospital. In 64% of donors, UW fluid was used for vascular flush and preservation, while HTK solution was used in 32%. Machine perfusion significantly reduced the risk, duration and severity of DGF (adjusted OR: 0.57,  $P = 0.01$ ). The size of the treatment effect was no different after standard-criteria donation versus expanded-criteria donation. While there was no difference in DGF or patient survival at 1 year, allograft survival at 1 year was better in the machine perfusion group (94 versus 90%;  $P = 0.04$ ). Because it was considered that an insufficient number of non-heart-beating donors had been enrolled after initial recruitment for subgroup analysis (heart

beating versus non-heart-beating donors), the investigators extended the study until a total of 82 non-heart-beating kidney pairs had been randomized. In neither the main data set nor the extended data set was a significant difference observed in DGF between machine perfusion and cold storage in kidneys coming from heart beating versus non-heart-beating donors. However, the same group published a subgroup analysis of outcome in the 82 non-heart-beating kidney pairs from the extended data set of the Machine Preservation Trial [344]. In this paper, the incidence of DGF was 53.7% in machine perfusion versus 69.5% in cold storage ( $P = 0.007$ ) with an adjusted OR of 0.43 (95% CI: 0.20–0.89,  $P = 0.025$ ) for the probability of developing DGF in machine perfused kidneys compared with cold storage. There was no difference in 1-year patient and graft survival. In contrast, Watson *et al.* also published in 2010 the results of a multicentre randomized controlled trial of machine perfusion versus cold storage in non-heart-beating donor kidneys using only a sequential study design which stops patient recruitment after there is sufficient evidence to reject the null hypothesis [345]. After 90 transplants from 45 donor pairs, there was no difference in the incidence of DGF or in any secondary endpoints. In contrast to Moers' study, there was standardization of the preservation fluid (UW) and immunosuppression used. Trained perfusionists were not available and when kidney retrieval occurred away from the base transplant centre, kidneys randomized to machine perfusion could first undergo a period of cold storage during transport to the base hospital.

##### How did we translate the evidence into the statement?

Given these conflictive results and in the absence of a pharmaco-economic evaluation of the cost of employing dedicated trained perfusionists as part of the retrieval team, no firm recommendation can be made regarding the optimum method of organ preservation until more evidence emerges from further studies.

##### What do the other guidelines state?

No other guideline bodies provide a statement on this topic.

##### Suggestions for future research

Further adequately powered randomized studies are required of machine perfusion versus static cold storage in both heart beating and non-heart-beating donors, and this using standardized perfusion fluid, with pre-specified subgroups. Ideally, these studies should be international and multicentre, to allow generalizability, and include a pharmaco-economic evaluation.

### 3.4. Is there a critical cold ischaemia time beyond which a donated organ should be discarded?

We suggest that CIT is kept as short as possible. (2D)

We recommend keeping CIT below 24 h when transplanting kidneys from donors after brain death. (1B)

We recommend keeping CIT <12 h when using kidneys from donors after cardiac death. (1D)

We recommend that the decision to use donor kidneys with a CIT of >36 h should be made on a case per case basis. (1D)

#### Rationale

##### Why this question?

CIT is one of the few potentially modifiable donor risk factors that can have a significant influence on transplant outcome. However, keeping CIT as short as possible might pose substantial logistical problems. Also, accepting only a short CIT might lead to loss of otherwise acceptable grafts.

##### What did we find?

Data from the Collaborative Transplant Study (CTS) based on kidney allograft transplants performed between 1990 and 2004 have shown that increasing CIT up to 18 h has no adverse effect on graft outcome [346]. For CIT between 19 and 24 h, the hazard of graft failure increased by 9%, for 25–36 h by 16% and for >36 h by 30%. Maybe as a result of that, the proportion of transplants with CIT >36 h decreased from 8.3% between 1990 and 1991 to 0.6% between 2004 and 2005. Compared with CIT <19 h, 1-year creatinine values were increased significantly only for CIT >36 h but not with CIT between 19 and 36 h. There was no evidence that prolonged CIT was more deleterious for kidneys from elderly donors or from extended-criteria donors. In comparison, UK registry data have shown that for recipients of first kidney allografts from brain-death donors, CIT up to 21 h has no effect on transplant failure up to 5 years of follow-up. However, for every additional hour of CIT over 21 h, the risk of transplant failure increased by 4% [347]. For recipients of kidneys from donors after controlled cardiac death (Maastricht category 3), a CIT >12 h seemed to be associated with worse graft survival, although results were not significant at the 5% level [348]. For recipients of kidneys from both cardiac-death and brain-death donors, a CIT >24 h was associated with an eGFR that on average was ~5 mL/min/1.73 m<sup>2</sup> lower than in patients with a CIT <12 h [348]. In a single-centre cohort study of brain death donor kidney transplants from younger donors (<50 years), CIT, when analysed as a continuous variable, was shown to be an independent risk factor for graft loss (20% increase for every 5 hours of CIT

[349]. When analysed as a categorical variable (less than or longer than 19 hours), a CIT >19 h independently increased the risk of graft failure by 50%.

CIT is associated with DGF, defined as the need for dialysis in the first week after transplantation. UNOS data reveal that the incidence of DGF in recipients of kidneys with a CIT of more than 36 hours was 40% in standard criteria donors and 50% in extended criteria donors [350]. In a single-centre study of brain-death donor kidney transplants using a uniform immunosuppression regimen, CIT was also an important risk factor for the development of DGF. CIT predicted long-term graft survival in grafts that survived for more than 1 year, and this independently of DGF [351]. In another more recent single-centre cohort study, CIT was the single most important independent predictor of DGF, which had an incidence of 42% when the CIT increased to 36 h. CIT was also an independent risk factor for acute rejection, with each hour of CIT increasing the risk of acute rejection by 4%. Although CIT was a significant independent risk factor for graft loss, this effect was almost entirely due to its impact on acute rejection. Similarly, the detrimental effect of DGF on graft survival was explained by an increased incidence of acute rejection [352].

##### How did we translate the evidence into the statement?

CIT is an important modifiable risk factor that can influence outcome. Therefore, every effort should be made to keep CIT to as short as possible. Based on the evidence above, the ERBP group recommends that when transplanting kidneys after brain death, the CIT should be kept below 24 h. Because non-heart-beating donor kidneys are subjected to longer warm ischaemia and have a higher incidence of delayed function, minimizing CIT is even more important in this setting. Based on observational studies, we recommend that when transplanting kidneys after controlled circulatory death (Maastricht category 3) CIT is kept <12 h. There are few data reporting the outcome of kidney transplants with very long CIT, i.e. >36 h. However, it was the opinion of the group that the high incidence of DGF, the worse outcome with increasing CIT and the increased risk of acute rejection means that these kidneys should not usually be used, unless under exceptional circumstances and after full discussion of the risks and benefits with the potential recipient.

##### What do the other guidelines state?

Like ERBP, the European Association of Urology recommends to keep CIT as short as possible [29]. No other guideline body provides any indication on which maximal CIT is acceptable.

##### Suggestions for future research

No suggestions.

### 3.5. On which criteria should we select living kidney donors to optimize the risk–benefit ratio of their donation?

#### **General remarks**

We recommend encouraging living kidney donors to exercise on a regular basis and when relevant, to lose weight and stop smoking. (1C)

We recommend that the individual risk of donation should be carefully discussed with the donor, taking into account the situation of both donor and recipient. Ideally, this should be done using standardized check lists to ensure all items are discussed. (Ungraded Statement)

We suggest that the donor be evaluated by an independent physician who is not part of the transplant team and is not involved in the daily care of the recipient, and when possible, by a psychologist. (Ungraded Statement)

We recommend that the process of donation is stopped should any doubt on donor safety arise, especially in younger donors, or when the benefit for the recipient is limited. (Ungraded Statement)

We recommend that the simultaneous presence of more than one risk factor (hypertension, obesity, proteinuria, impaired glucose tolerance, haematuria) precludes donation. (Ungraded Statement)

#### **Hypertension**

We recommend considering potential donors with a blood pressure <140/90 mmHg on at least three occasions without antihypertensive medication, as normotensive. (1C)

We suggest measuring ambulatory blood pressure in potential donors who have office hypertension (blood pressure  $\geq$ 140/90 mmHg) or who are taking pharmacological treatment for hypertension. (2C)

We suggest well-controlled primary hypertension, as assessed by ambulatory blood pressure <130/85 mmHg, under treatment with maximum two anti-hypertensive drugs (diuretics included) is not considered a contraindication to living kidney donation. (2C)

We recommend discouraging hypertensive donors with evidence of target organ damage such as left ventricular hypertrophy, hypertensive retinopathy and micro-albuminuria. (1C)

We suggest that these potential donors could be re-evaluated for disappearance of this target organ damage after appropriate treatment. (2D)

#### **Obesity**

We suggest a BMI  $>$ 35 kg/m<sup>2</sup> is a contraindication to donation. (2C)

We recommend counselling obese and overweight donors for weight loss before and after donation. (Ungraded statement)

#### **Impaired glucose tolerance**

We recommend diabetes mellitus is a contraindication to donation, other than in exceptional circumstances. (1D)

We suggest impaired glucose tolerance is not an absolute contraindication to donation. (2C)

#### **Proteinuria**

We recommend quantifying urinary protein excretion in all potential living donors. (1C)

We recommend overt proteinuria is a contraindication for living donation [24-h total protein  $>$ 300 mg or spot urinary albumin to creatinine (mg/g) ratio  $>$ 300 ( $>$ 30 mg/mmol)]. (1C)

We recommend further evaluating potential living donors with persistent (more than three measurements with 3 months interval) proteinuria  $<$ 300 mg/24 h by the quantification of micro-albuminuria to assess their risk of living donation. (Ungraded statement)

We suggest considering persistent (more than three measurements with 3 months interval) micro-albuminuria (30–300 mg/24 h) a high risk for donation. (Ungraded statement)

#### **Haematuria**

We recommend considering persistent haematuria of glomerular origin as a contraindication to living donation, because it may indicate kidney disease in the donor. (1B)

However, we acknowledge thin basement membrane disease might be an exception. (Ungraded statement)

#### **Old age**

We recommend that old age in itself is not a contraindication to donation. (1B)

#### **Rationale**

##### **Why this question?**

Owing to the ever increasing waiting times required to receive a kidney transplant from deceased donors, more and more reliance is currently being put on living-donor kidney transplantation as the treatment of choice for end-stage kidney disease. To resolve pressure on the cadaveric waiting list, subjects who in the past were deemed unsuitable for living donation, nowadays are increasingly being considered as suitable candidates, so that donors with medical abnormalities form a significant proportion of the living donors [353]. What exactly the long-term effects of donation are in this population remains uncertain. In particular, it still remains to be answered whether or not donors with relevant risk factors such as hypertension, obesity, old age, impaired glucose tolerance, proteinuria or haematuria, have safe outcomes in the long term. The impact of borderline-normal kidney function in the donor is discussed in a separate paragraph.

### What did we find?

Experience gained with unilateral nephrectomy performed on servicemen, who lost a kidney due to trauma during World War II, showed that the long-term risks inherent to this procedure when compared with non-nephrectomized servicemen are minimal [354]. This finding was later confirmed by a comparison of donors with non-donating siblings [355]. More recently, several studies showed excellent long-term outcomes in donors compared with an age-matched general population [356]. However, these studies were limited to highly selected donors, who were young, white, and generally free from relevant risk factors, in contrast with current donors who are often obese, hypertensive and increasingly older [357]. It is likely that the risk of living donation in individuals with medical disorders varies with race, since it has been shown that after kidney donation black donors, when compared with white donors, have an increased risk of developing hypertension, diabetes and chronic kidney disease [358]. Segev *et al.* examined donor survival over a median of ~6 years follow-up in a cohort of over 80 000 donors from 1994 to 2009 [545 with hypertension and 4473 with BMI  $\geq 30$  kg/m<sup>2</sup>], and compared it with a matched cohort of ~9000 healthy subjects selected from NHANES III [359]. This is the only large study comparing living donors with healthy controls rather than with the general population. Moreover, at variance with previous studies, the population included a significant proportion of black (13%) and Hispanic (12%) individuals. On overall, living donation was not associated with an increased risk of death compared with a healthy matched cohort. However, being retrospective, this study could not fully control for all potential confounding factors. Moreover, there were too few events to provide reliable estimates for each risk subgroup of living donors.

Few multicentre cohort studies have been carried out choosing appropriate control groups, adjusting for all relevant confounding factors, using standardized definitions of donor risk factors and outcomes, and providing sufficient length and completeness of patient follow-up. Moreover, no study was designed to assess the effect of each donor risk factor in the context of the other risk factors which may have an additive effect in increasing the risk of living donation and, finally, no study examined the long-term outcome of young donors with risk factors associated with future development of hypertension or diabetes.

Therefore, the recommendation is mostly based on the natural history of the medical abnormalities, on common sense, and consensus between the guideline development group members.

### Hypertension

A systematic review of the literature until 2008 found six studies involving 115 donors with pre-existent hypertension, and 621 controls from three studies [360]. Overall, quality of the studies was low, with 3/6 not providing a clear definition of hypertension, and only one stating that blood pressure was measured by a professional. Change in blood pressure after donation was quantified in only one study, where blood pressure did not increase 1 year after donation. One study

assessed change in the mean arterial blood pressure after donation, which decreased more often in hypertensive donors.

In the study of Segev *et al.*, out of the ~30 000 donors with blood pressure data available, 545 (1.8%) had pre-existent hypertension. Hypertension was associated with an increased risk of death in living donors (36.7, 95% CI: 4.4–132.6/10 000 donations versus 1.3, 95% CI: 0.4–3.4/10 000 donations) [359]. However, these risk estimates were based on only two deaths in the cohort of hypertensive patients. Textor *et al.* examined the short term, mainly 1-year, change in arterial blood pressure, kidney function and proteinuria of 148 donors with pre-existent hypertension, and compared it with normotensive donors [361]. After 282 days, normotensive donors had no change in awake ambulatory blood pressure monitoring measurements (before 121/75 mmHg versus after 120/75 mmHg), whereas blood pressure in hypertensive donors fell with both non-pharmacological and drug therapy (before 142/85 mmHg to after 132/80 mmHg,  $P < 0.01$ ). After correction for age, no independent effect of hypertension before donation was evident for predicting GFR after nephrectomy. Urine protein including micro-albuminuria did not change after donor nephrectomy. It is worth noting that in the Textor study only a minority of 'hypertensive' patients were taking anti-hypertensive medications, despite blood pressures  $>140/90$  mmHg in 96%, and awake ambulatory blood pressure monitoring  $>135/85$  mmHg in 75% of the donors [361]. Tent *et al.* compared 47 hypertensive donors to 94 control donors [362]. Pre- and early post-donation systolic and mean arterial blood pressures were significantly higher in hypertensive donors. Control donors showed a rise in diastolic blood pressure after donation, and thus the pre-donation difference was lost post-donation. Both at 1 year (29 hypertensive donors, 58 controls) and 5 years after donation (13 hypertensive donors and 26 controls), blood pressure was similar between the groups, and kidney function was similar at all time-points. Both studies involved mainly white donors, whereas African-American living donors were reported to have an increased risk of developing hypertension and chronic kidney disease [358].

### Obesity

A meta-analysis on the effect of obesity on the risk of perioperative complications after living donation compared 294 donors with BMI  $>30$  kg/m<sup>2</sup> to 624 non-obese controls (average BMI 34 kg/m<sup>2</sup> and 24 kg/m<sup>2</sup>, respectively) [360]. In the obese donors, the operative time was on average 20 min longer (95% CI: 14–26 min), and length of hospital stay was 0.1 days longer (95% CI: 0.0–0.3 days). Compared with donors having a BMI  $<25$  kg/m<sup>2</sup>, the crude risk for post-operative wound complications (infection, seroma, hernia) increased from 2 to 4% for donors with a BMI = 25–30 kg/m<sup>2</sup> and ~9% in donors with BMI  $\geq 30$  kg/m<sup>2</sup> [363]. In this study, no differences in micro-albuminuria post-donation were observed with increasing BMI. After adjusting for male sex, anomalies of kidney vessels, right versus left kidney and laparoscopic versus open surgery, a BMI  $>30$  kg/m<sup>2</sup> was associated with an odds ratio of 1.76 (95% CI: 0.66–4.70) for major perioperative complications (45 events in total) in the Norwegian National Hospital Living Donor Registry including data

of 1006 donors (524 and 85 donors with pre-donation BMI  $>25 \text{ kg/m}^2$  and BMI  $>30 \text{ kg/m}^2$ , respectively) [364]. In this registry, post-operative wound infection (event number = 37) was associated with BMI  $>25 \text{ kg/m}^2$ . No study has explicitly examined whether the risk of perioperative complications in obese donors is different according to the type of surgical procedure (laparoscopic donor nephrectomy versus open surgery).

Segev *et al.* compared  $\sim 4400$  donors with BMI  $\geq 30 \text{ kg/m}^2$  with 15 300 donors with BMI  $<30 \text{ kg/m}^2$ , finding that obesity was not associated with increased mortality among living donors in short-to-medium term [359]. In the study of Ibrahim *et al.*, for each unit of BMI there was a 12% increase in the odds of post-donation eGFR  $<60 \text{ mL/min/1.73 m}^2$ , and post-donation hypertension requiring medications [356]. However, the finding of an association between high BMI ( $>30 \text{ kg/m}^2$ ) and the risk of a significant post-donation GFR decline was not confirmed by two other studies [353, 365]. African-American living donors with a BMI  $>35 \text{ kg/m}^2$  might be at particularly high risk of developing a significant kidney function decline post-donation [366].

It is worth mentioning that donors with high BMI have often a further increase in weight following donation [367]. No study estimated the absolute additional long-term risk in the young obese donors when compared with non-donor counterparts. Moreover, all these data being observational, it is unclear whether obese donors were selected among those who were otherwise healthy, i.e. with no additional risk factors such as, e.g., hypertension or diabetes. Finally, it must be stressed that in the same studies the proportion of very obese subjects ( $>35 \text{ kg/m}^2$ ) was generally low. Therefore current available evidence regarding the safety of living donation in such donors is scarce.

#### **Impaired Glucose Tolerance**

Only one study, carried out in Japan, examined the effect of impaired glucose tolerance on living donor outcome [368]. This study compared donors having either impaired glucose tolerance ( $n = 44$ ) or true diabetes mellitus ( $n = 27$ ), with 373 normo-glycaemic donors. However, among the diabetic donors only five were receiving anti-diabetic treatment, while the other glucose-intolerant donors had been classified as diabetics only on the basis of the oral glucose tolerance test (OGTT) performed at the time of evaluation. Donors showing micro-albuminuria, haemoglobin A1c  $\geq 6.5\%$ , or diabetic complications were not included because deemed unsuitable for kidney donation. The follow-up was  $\sim 9$  years on average. Perioperative complications, kidney function and patient survival did not differ according to the presence or not of pre-transplant glucose intolerance. One of the five diabetic donors already on treatment at the time of transplant was lost to follow-up, another donor showed an increase in serum creatinine from the pre-transplant value of 1.04 to 1.44 mg/dL 27 months after transplantation.

#### **Proteinuria**

Only one study examined the role of proteinuria on donor outcome by comparing the changes in kidney function, arterial blood pressure and proteinuria occurring 1 year after

donation in eight subjects having abnormal proteinuria, and in 75 control donors [369]. The study was performed between 1988 and 1998, therefore the definition of abnormal proteinuria was not adherent to the current standard of today (urinary albumin/creatinine  $>10 \text{ mg/mmol}$  or protein/creatinine  $>0.02 \text{ g/mmol}$ ). Anyhow, the borderline-high levels of proteinuria were not associated with any adverse effect on donor kidney function or blood pressure.

#### **Haematuria**

Living donations from individuals having haematuria due to proven glomerular kidney diseases have been reported: three had Immunoglobulin A (IgA) nephropathy [370], two thin basement membrane disease [371] and six were affected mothers donating the kidney to sons suffering from Alport syndrome [372]. Length of follow-up ranged between 1 and 10 years. In this small case series, at least one of the donors with IgA nephropathy, and two of the mothers of patients with Alport syndrome developed hypertension, proteinuria and significant kidney function decline beyond 1 year after donation. There is only one study, performed in Japan, which estimated the increased risk associated with isolated renal haematuria (defined as more than five dysmorphic erythrocytes in urine per high power field) in living donors who were not evaluated by kidney biopsy [373]. In this study, 22 donors with pre-transplant renal haematuria and 220 haematuria-free control donors were retrospectively followed-up for an average of  $\sim 2$  years. The study population included 43 subjects with family history of IgA nephropathy or Alport syndrome. A family history of IgA nephropathy increased the risk of haematuria after donation. In 70% of the donors with renal haematuria before donation, haematuria showed a persistent pattern (i.e. confirmed after  $>3$  month interval). Almost invariably, donors having persistent haematuria before donation continued showing this urinary abnormality after donation. Persistent renal haematuria post-donation was associated with a declining GFR post-donation ( $\pm 2 \text{ mL/min/year}$ ). For the case of haematuria associated with the relatively benign condition of thin basement membrane disease, there are no data in the setting of living donation.

#### **Old Age**

Older living donors, defined in the various studies as aged  $\geq 60$  or  $\geq 65$  years, apparently do not have an increased risk of death after donation compared with the matched healthy population of the same age [359]. In fact, older age is not associated with a significant increase in perioperative complications such as blood loss, intraoperative incidents or wound infections, nor with an increased length of hospital stay [360], although an increased risk of cardiac and pulmonary complications in donors over 60 years has been reported in one study [374].

A meta-analysis on the effect of older age on kidney function after donation [360], including 181 older donors and 666 younger donors, did not find a negative impact of older donor age on kidney function post-donation after a median follow-up of 2 years. On the other hand, Ibrahim [356] reported that older age is a determinant of low (i.e.  $<60 \text{ mL/min per } 1.73 \text{ m}^2$ ) measured GFR post-donation after adjusting for creatinine concentrations before donation. However GFR, which was

measured in a random sample of 7% of the study population, was not available at baseline. Moreover, the finding that older age was associated with an increased risk of renal function decline after donation was not confirmed by a subsequent observation in another transplant centre [375]. Long-term changes in blood pressure and proteinuria in older donors have not been extensively investigated. Two studies comparing older with younger donors [369, 376] reported inconsistent findings on blood pressure. More recently, Ibrahim and colleagues found that older age is a determinant of hypertension requiring medication after donation [356]. The analysis was adjusted for pre-donation systolic and diastolic blood pressure but not for the use of anti-hypertensive medication before donation. One study did not find any effect of age at donation on the albumin:creatinine ratio after 1-year follow-up, a finding confirmed by Ibrahim [369].

It is worth noting however, that in all the above-mentioned studies it is unclear whether the cohorts of older living donors had a lower prevalence of additional pre-donation risk factors compared with younger donors, since no study fully adjusted for all the potential relevant pre-donation confounding factors. Therefore, selection bias cannot be excluded.

#### How did we translate the evidence into the statement?

As presence of comorbidity often precludes donation, the evidence on the impact of these comorbidities on outcome after donation is scarce. Whereas for the presence of single risk factors, some low-quality evidence can be found, the lack of evidence on the impact of a combination of risk factors for donation does not allow exactly quantifying the additional risk for an individual donor with a specified set of comorbidities. The guideline development group judged that, as a general rule, persistent the presence of more than one risk factor should preclude donation in most, if not all, cases.

Some risk factors (blood pressure, obesity, nicotine abuse) can be modified, and effort should be made by the transplant team to obtain this modification before the donation.

In the absence of comorbidities, a blood pressure repeatedly <140/90 mmHg should be considered as 'normotension', as it is unlikely that this person would have higher blood pressures under more normal conditions.

If blood pressures >140/90 mmHg are recorded, 'white coat' or office hypertension should be excluded by ambulatory blood pressure recording.

Patients who have hypertension that is well controlled by medication (<130/85 mmHg on ambulatory blood pressure monitoring with two different drugs at maximal dose) can be considered normotensive. There is some suggestion that, after donation, blood pressure decreases in these patients, maybe because compliance increases.

Although the evidence for the negative impact of hypertension in the setting of living donation is scarce, the strong association between hypertension and negative cardiovascular outcome in the general population is so overwhelming that the guideline development group judged that it can most likely be translated to the peculiar situation of living donation. Potential

donors should be informed that a negative effect is even more likely if they already have end-organ damage at the moment of evaluation (proteinuria, left ventricular hypertrophy, hypertensive retinopathy). As treatment of hypertension in some of these potential donors might have been suboptimal until the moment of evaluation for living donation, a re-evaluation after adequate treatment has been installed should be planned if the wish to donate persists.

Obesity as defined by BMI is associated with a relative increase in peri- and post-operative complications: mainly wound infection and wound healing. However, these problems appear to be relatively minor in relation to the potential gain for the recipient, especially as long as BMI is not >35 kg/m<sup>2</sup>. Attention should be given to presence of other risk factors, especially glucose intolerance, micro-albuminuria and hypertension. It should also be taken into account that a definition of obesity based on BMI does not differentiate between central obesity (fat) and high muscle mass, whereas these two conditions might be distinct in terms of outcome of living donation.

Persistent micro-albuminuria is a marker of kidney disease, and/or enhanced cardiovascular risk. Occasional albuminuria can be present even in normal persons, e.g. after exercise. Therefore, the diagnosis 'micro-albuminuria' should only be made when several samples with some months interval have been positive.

Presence of haematuria is a sign of either glomerular or urological disease, and should be further explored. The ERBP guideline development group judges that haematuria precludes living donation. Haematuria can be a sign of thin basement membrane disease, and it is unclear whether living donation is safe (both for the donor and the recipient) or not in this condition.

Old age by itself should not be considered a contraindication to donation. Indeed, older donors do have a lower expected life span, and 'kidney survival' might be less an issue in these circumstances. Older patients should however be screened for the presence of other comorbidities, which could exacerbate after nephrectomy or jeopardize the remaining kidney (hypertension, proteinuria, diabetes).

#### What do the other guidelines state?

##### *Hypertension*

KHA-CARI provides suggestions for clinical care based on weak evidence which not only suggests 24-h ambulatory blood pressure measurement but also home blood pressure measurements for exclusion of white coat hypertension [377]. KHA-CARI states a different threshold for systolic blood pressure assessed by 24 h ambulatory blood pressure measurement of <135 mmHg as target for potential kidney donors. KHA-CARI suggests excluding hypertensive donors with end-organ damage, but also with other cardiovascular risk factors. They do not state anything on re-evaluating potential donors with target organ damage after appropriate treatment for donation. The Amsterdam Forum on the Care of the live kidney donor considers potential donors with a blood pressure >140/90 mmHg on ambulatory blood pressure measurement as

generally unacceptable [378]. They suggest that under certain conditions (>50 years of age, GFR >80 mL/min and urinary albumin excretion <30 mg/day), such donors can be accepted for donation, after their blood pressure has been controlled. A recommendation on hypertensive donors with target organ damage is not provided by the Amsterdam Forum. Recommendations of the UK Renal Association and the British Transplant Society on this topic are in line with ERBP [28, 62].

### **Obesity**

KHA-CARI provides suggestions for clinical care based on weak evidence and suggests a stricter threshold of BMI >30 kg/m<sup>2</sup> as relative contraindication to donation [379]. They suggest using both the BMI and the waist circumference as tools for clinical assessment of risk of donation. They suggest taking into account eventual additional risk factors to obesity for chronic kidney disease, such as impaired glucose tolerance, hypertension or proteinuria, which are, according to KHA-CARI, contraindications to donation in obese patients.

The Amsterdam Forum on the Care for the live kidney donor endorses guidelines similar to ERBP, but in addition stresses that the contraindication to donation is stronger if additional risk factors are also present [378].

The UK Renal Association and British Transplant Society endorse similar recommendations as ERBP in regard of encouraging the obese donor to lose weight prior to donation and maintain an ideal weight after donation [28, 62]. Like ERBP the UK Renal Association and the British Transplant Society similarly recommend to discourage potential donors with a BMI >35 kg/m<sup>2</sup> from donation. For the UK Renal Association, the presence of additional comorbidities in patients with 'moderate obesity' (BMI 30–35 kg/m<sup>2</sup>) should also be a relative contraindication for donation, and these patients should be counselled about the potential risks of donation.

### **Impaired Glucose Tolerance**

KHA-CARI suggests how to assess blood glucose levels in donors in a very detailed way. In contrast to ERBP, they do not only consider manifest diabetes mellitus, but also impaired glucose tolerance and a history of gestational diabetes an absolute contraindication for living kidney donation, acknowledging the evidence base is weak [380]. The Amsterdam Forum on the Care of the live kidney donor suggests that potential donors with a history of diabetes, an impaired

fasting glucose or OGTT should not donate [378]. Unlike ERBP, the UK Renal Association and British Transplant Society do not consider diabetics as unsuitable for live kidney donation under specific conditions, and after careful assessment of the presence of other risk factors [28, 62]. They do not suggest using diabetic living donors to be routine practice, but rather a possibility in selected, well-informed patients.

### **Proteinuria**

KHA-CARI provides suggestions for clinical care based on weak evidence which are in agreement with ERBP in regard of considering micro-albuminuria and overt proteinuria of >300 mg/day a contraindication [381]. Based on opinion, KHA-CARI suggests that kidney biopsy may help in assessing the donor's risk in the case of minor proteinuria. KHA-CARI also recommends that donors should have their proteinuria checked annually after donation. The Amsterdam Forum on the Care of the live kidney donor agrees on considering proteinuria of >300 mg/day a contraindication for live kidney donation but does not provide a recommendation on micro-albuminuria [378]. The UK Renal Association and British Transplant Society endorse similar recommendations as the Amsterdam forum, except that in regard of the absence of clear data on the role of micro-albuminuria, they suggest a careful evaluation and counselling of these patients on the potential risks, rather than accepting it as a plain contraindication for donation [28, 62].

### **Haematuria**

KHA-CARI suggests excluding urological and kidney disease before donation, based on weak evidence. They indicate that recommendations on thin basement membrane disease cannot be made [382]. Recommendations from the UK Renal Association and British Transplant Society as well as the Amsterdam Forum on the Care of the live kidney donor are in line with ERBP [28, 62, 378].

### **Old Age**

The UK Renal Association and British Transplant Society agree that old age itself is no contraindication for living kidney donation [28, 62].

### **Suggestions for further research**

Decision analysis techniques should be used to quantify the individual risk of each donor in function of comorbidities.

### 3.6. What lower level of kidney function precludes living donation?

We recommend that all potential living kidney donors have their GFR assessed. (1C)

We recommend that in cases where more exact knowledge on GFR is needed or where is doubt regarding the accuracy of GFR from estimation methods, a direct measurement of GFR is undertaken by exogenous clearance methods. (Ungraded Statement)

We recommend that all potential donors should have a predicted GFR that is projected to remain above a satisfactory level after donation within the life-time of the donor as indicated in figure 3. (Ungraded Statement)

#### Rationale

##### Why this question?

Assessment of a potential living donor's kidney function is essential to ensure that they will have sufficient residual kidney function after donation to live out their life without any adverse consequences related to their reduced renal mass. A secondary consideration is ensuring that the transplanted kidney will provide sufficient function for the intended recipient.

##### What did we find?

An accurate assessment of the GFR should be undertaken in all potential kidney donors. Although there is currently no evidence that favours the use of a directly measured GFR (iothalamate, EDTA, DTPA or iohexol) over an estimated GFR in donor assessment, some guidelines organizations make this recommendation, given the imprecision of the estimated methods [62].

Much of the evidence relating to kidney function in living donors comes from underpowered, retrospective cohort studies, with poor follow-up and without suitable matched controls [383]. However, the long-term outcome of a reasonably sized cohort of living donors (2199 out of a total of 3404 who were still alive and consented to provide data) carefully assessed at a single US centre from 1963 to 2007 is widely cited [356]. All donors had a GFR  $>80$  mL/min/1.73 m<sup>2</sup> at the time of donation. The survival of kidney donors was similar to that of controls in the general population, who were matched for age, sex and race or ethnic group. End-stage kidney disease that necessitated dialysis or transplantation developed in 11 donors, a incidence of 180 cases per million persons per year compared with an incidence of 268 per million per year in the general population. A subset of 255 donors randomly selected but stratified by sex and years since donation underwent measurement of their GFR, urinary albumin to creatinine ratio and quality of life assessment. At a mean of  $12.2 \pm 9.2$  years after donation, 86% of this subgroup had a GFR  $\geq 60$  mL/min/1.73 m<sup>2</sup> (none had a GFR  $<30$  mL/min/1.73 m<sup>2</sup>), 32% had hypertension and 13% had albuminuria. Older age and higher body mass index, but not a longer time since donation, were associated with both a GFR that was  $<60$  mL/min/1.73 m<sup>2</sup> and hypertension. A longer time since donation was independently associated with albuminuria. Most donors had quality-of-life scores that were better than those in the general population and the prevalence of co-morbidities was similar to that of controls. However, the mean age of the subset at the time of donation was 41 years, 99% were white and 60% were women.

After the age of 40, kidney function declines at a mean speed of  $\sim 0.9$  mL/min/1.73 m<sup>2</sup>/year [384]. These data have been used for defining minimal age-dependent GFRs in living donors such that the GFR of the remaining kidney will be  $>37.5$  mL/min/1.73 m<sup>2</sup> at the age of 80 [62].

One needs to be careful when extrapolating these data to potential donors from different racial and ethnic groups. In a

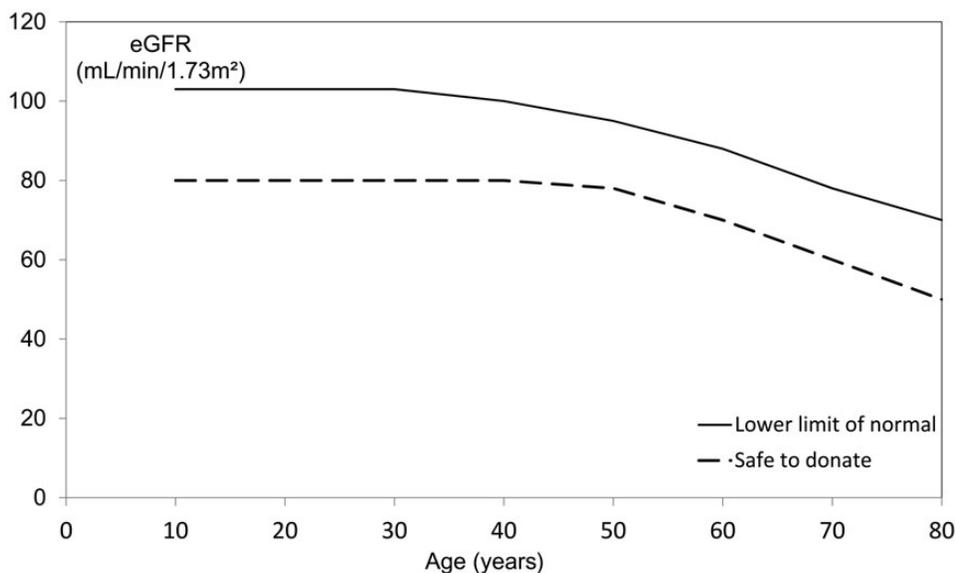


FIGURE 3: Expected decline in kidney function due to ageing. \*Adapted with permission from [386].

large US registry study, the rate of established kidney failure occurring in living kidney donors while being low overall was nearly five times higher for black donors than for white donors (and two times higher for males than for females) [385]. Although the authors note that these ethnic differences are similar to those observed in the general population, the absence of prospective measures of kidney function in black donors after donation with adequate follow-up and appropriately matched controls introduces uncertainty which should be shared with the potential donor during their pre-donation assessment. The growing willingness to consider and accept donors with isolated medical problems such as hypertension, glucose intolerance, obesity etc., should, until appropriate data become available, be avoided in this ethnic group.

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

We recommend that all potential living kidney donors should have their GFR assessed and that where there is doubt regarding the accuracy of GFR from estimated methods, a direct measurement of GFR should be undertaken by exogenous clearance methods. We recommend that all potential donors should have a predicted GFR that will remain above a satisfactory level within their life-time. We suggest using figure 3 as a reference to predict evolution of GFR after donation. The upper line in this graph represents the lower limit of normal at different ages, as determined in 428 living donors (courtesy to British Transplant Society and UK Renal Association) [386]. The lower line depicts the lower boundary of GFR before donation for different ages that will still lead to an acceptable GFR at 80 years. For potential living donors >50 years old, a measured GFR >80 mL/min per 1.73 m<sup>2</sup> will provide sufficient kidney function not to cause ill health in the future.

**What do the other guidelines state?** KHA-CARI provides suggestions for clinical care in regard of donor kidney function but no recommendations based on high level evidence [383]. KHA-CARI suggests that serum creatinine and estimated clearances can be used, as there is no evidence in living donation that more expensive and laborious techniques such as CrEDTA, provide any additional benefit. KHA-CARI does not suggest making an age-dependent cut-off for accepting donors. The Amsterdam Forum on the Care of the live kidney donor recommendations are in line with ERBP [378]. They also state an age-dependent estimated GFR cut-off for not accepting a live kidney donor. The UK Renal Association and British Transplant Society recommend GFR measurement using a reference GFR procedure, e.g. 51Cr EDTA and discourage using eGFR methods, as they state these are not validated in the field of living donation [28, 62]. Concerning a cut-off for the minimum acceptable GFR in a potential donor the UK Renal Association and BTS recommend a predicted GFR of at least 37.5 mL/min/1.73 m<sup>2</sup> at the age of 80 after donation.

#### **Suggestions for future research**

Prospective studies examining long-term kidney function, cardiovascular disease or surrogate markers and complications of chronic kidney disease in older donors with appropriately matched controls.

Prospective studies examining the relationship between pre-donation GFR and long-term kidney function, cardiovascular disease or surrogate markers, and complications of chronic kidney disease with appropriately matched controls in both white and black populations.

### 3.7. What are the risks of pregnancy in a woman with a single kidney after living kidney donation?

We recommend informing women of childbearing age that as they are selected from a very healthy subpopulation, donation increases their individual risk from below that of the general population, to that of the general population. (1B)

#### Rationale

##### Why this question?

In women of child bearing age, the wish for future pregnancy can be an obstacle for living donation. Women with a single kidney might be at enhanced risk during pregnancy, itself a cause of hyperfiltration, proteinuria and hypertension.

##### What did we find?

Buszta *et al.* reported a retrospective, single-centre experience of 39 pregnancies in 23 patients after living kidney donation [387]. Transient proteinuria >300 mg on dipstick was seen in two patients in the third trimester, and trace proteinuria in seven pregnancies. In a larger single-centre retrospective cohort, Ibrahim *et al.* reported 1085 women with in total 3213 pregnancies and 504 women without pregnancy [388]. Foetal and maternal outcomes in post-donation pregnancies were comparable with published rates in the general population. Post-donation versus pre-donation pregnancies were associated with a lower likelihood of full-term deliveries (73.7 versus 84.6%,  $P = 0.0004$ ), a higher likelihood of foetal loss (19.2% versus 11.3%,  $P < 0.0001$ ) and were also associated with a higher risk of gestational diabetes (2.7 versus 0.7%,  $P = 0.0001$ ), gestational hypertension (5.7 versus 0.6%,  $P < 0.0001$ ), proteinuria (4.3 versus 1.1%,  $P < 0.0001$ ) and pre-eclampsia (5.5 versus 0.8%,  $P < 0.0001$ ). In a separate analysis including women who had both pre- and post-donation pregnancies, similar results were observed.

Reisater *et al.* identified a cohort of 326 donors, with 726 pregnancies, of which 106 after donation [389]. In univariate analysis, no differences were observed in the occurrence of pre-eclampsia ( $P = 0.22$ ), but after adjustment, it was more common in pregnancies after than before donation (6/106

versus 16/620,  $P = 0.026$ ). The occurrence of stillbirths was higher after versus before donation (3/106 versus 7/620), where it was equal to controls from the general population. No differences were observed in the occurrence of adverse pregnancy outcome in kidney donors and in the general population in unadjusted analysis.

Wrenshall *et al.* reported 45 pregnancies in 33 women who donated a kidney [390]. Complications incurred during gestation were grossly comparable with those reported in the general population (miscarriage 13.3%, pre-eclampsia 4.4%, gestational hypertension 4.4%, proteinuria 4.4% and tubal pregnancy 2.2%). Foetal abnormalities, persistent hypertension, proteinuria or changes in kidney function were not noted. Infertility was a problem in 8.3% (3/36) of the respondents, compared with a worldwide incidence of 16.7%.

##### How did we translate the evidence into the statement?

There is no evidence for increased problems to conceive for women post-donation, at least when compared with the general population.

There is no evidence that nephrectomy results in serious adverse events during pregnancy. In general, the risk of pregnancy is comparable with that of the general population. However, it should be noted (and explained to the potential living donor), that the results of the general population include outcomes of all types of women, some of which with known or unknown comorbidities, such as diabetes, hypertension, underlying genetic or systemic disease. On the other hand, accepted candidates for living donation are highly selected, and generally have no comorbidity. Therefore in principle, there risk should be much lower than in the general population.

##### What do the other guidelines state?

KHA-CARI states that there is no evidence of increased pregnancy complications after previous donation when compared with the general population. However, they do not draw attention to the fact that live donors are a selected subpopulation that should in principle have a lower risk than the general population [391].

##### Suggestions for future research

No suggestions.

### 3.8. What is the best surgical approach for living donor nephrectomy for the donor? What is the best surgical approach for living donor nephrectomy for the recipient?

For living donor nephrectomy, we suggest either a minimally invasive or laparoscopic approach rather than a flank subcostal retroperitoneal one. The choice between minimal invasive and laparoscopic procedure should be based on the local expertise. (2C)

#### Rationale

##### Why this question?

Different surgical techniques to harvest a kidney from a living donor have been described. It is unclear whether one method has advantages over the other with regard to donor safety, donor comfort or graft function and survival. The major disincentive for relatives and partners contemplating kidney donation is the pain, scarring and morbidity associated with the large incision of a conventional surgical approach [392, 393]. The conventional methods of donor nephrectomy have recently been challenged by potentially less-invasive operations using laparoscopic techniques.

##### What did we find?

Different surgical techniques have been described to harvest kidneys from living donors. In the classic transperitoneal approach, the kidney is harvested through a midline or through a left or right subcostal incision, whereby the peritoneum is opened. The sub or supra costal approach can also be performed without opening the peritoneal space. In the dorsal lumbar technique, an incision is performed underneath the 12th rib, and the 12th rib is resected. As an alternative, the incision goes above the 12th rib; in both cases, the approach is extraperitoneal, and care should be taken not to open the pleural space. Harvesting of the kidney can also be done by laparoscopy. In this case, the approach can be either transperitoneal or retroperitoneal. On the right side, the liver may make dissection difficult in a transperitoneal approach.

A Cochrane review comparing open surgery (different approaches) to laparoscopy (different approaches) for harvesting living donor kidneys has been published in 2011 . Six studies were identified that randomized 596 live kidney donors to either laparoscopic donor nephrectomy or open donor nephrectomy arms. All studies were assessed as having low or unclear risk for selection bias, allocation bias, incomplete outcome data and selective reporting bias. Four of six studies had high risk of bias for blinding. As various different combinations of techniques were used in each study, there was substantial heterogeneity in the results. One to 1.8% of the laparoscopic approaches had to be converted to open donor nephrectomy. Laparoscopic donor nephrectomy was generally found to be associated with reduced analgesia use, shorter hospital stay and faster return to normal physical functioning. The extracted kidney was exposed to longer warm ischaemia periods (2–17 min) with no associated short-term consequences. Open donor nephrectomy was associated with shorter duration of

procedure. For those outcomes that could be meta-analysed there were no significant differences between laparoscopic and open donor nephrectomy with regard to perioperative complications (RR: 0.87, 95% CI: 0.47–4.59), reoperations (RR: 0.57, 95% CI: 0.09–3.64), early graft loss (RR: 0.31, 95% CI: 0.06–1.48), DGF (RR: 1.09, 95% CI: 0.52–2.30), acute rejection (RR: 1.41, 95% CI: 0.87–2.27), ureteral complications (RR: 1.51, 95% CI 0.69–3.31), kidney function at 1 year (SMD: 0.15, 95% CI: –0.11 to 0.41) or graft loss at 1 year (RR: 0.76, 95% CI: 0.15–3.85). The authors conclude that laparoscopic donor nephrectomy is associated with less pain compared with open surgery. However, there are equivalent numbers of complications and occurrences of perioperative events that require further intervention. Kidneys obtained using laparoscopic versus open donor nephrectomy procedures were exposed to longer warm ischaemia periods, although this has not been reported as being associated with short-term consequences.

##### How did we translate the evidence into the statement?

Based on this Cochrane review, it can be concluded that laparoscopic and open approach to harvesting living donor kidney have comparable outcomes with regard to donor safety and graft function [394]. The laparoscopic approach seems to have some advantage in terms of comfort for the donor. It should however be stressed that, as for most surgical techniques, local experience might play an important role. These results are based on randomized controlled trials performed in centres with great experience in the laparoscopic approach, by a limited number of surgeons, which reduces the generalizability of the findings. No health economic analyses have been provided. None of these randomized controlled trials was truly blinded.

The guideline development group concluded that there was insufficient evidence to recommend either open or laparoscopic approach as a general rule.

##### What do the other guidelines state?

KHA-CARI states that recipient outcome is equivalent with laparoscopic and open nephrectomy for living kidney donation and that recommendations in regard to donor mortality and morbidity cannot be made based on high quality evidence [395]. The UK Renal Association and British Transplant Society recommend laparoscopic over minimal invasive open surgery, and, as ERBP, do not prefer a flank subcostal approach [28, 62]. The European Association of Urology describes the possible surgical approaches in more detail [29]. They state that laparoscopic techniques have equal outcomes to open surgery techniques, but result in shorter recovery and less post-operative morbidity, although they add the recommendation that this procedure should only be performed by surgeons with experience with this technique. They do recommend using the flank costal approach with retroperitoneal dissection over the transperitoneal approach.

##### Suggestions for future research

More large-scale, multi-centre randomized controlled trials are needed to establish the safety of the laparoscopic approach when applied in a generalized context, and to better quantify the gain in donor comfort of this approach.

## CHAPTER 4. PERIOPERATIVE CARE OF THE KIDNEY TRANSPLANT RECIPIENT

### 4.1. What are the indications for an additional haemodialysis session in the recipient immediately before the transplantation procedure?

We recommend not routinely performing a haemodialysis session immediately before the actual transplantation procedure unless there are specific clinical indications. (1C)

When additional haemodialysis is performed immediately before the transplantation procedure, we recommend not using ultrafiltration unless there is evidence of fluid overload. (1C)

#### Rationale

##### Why this question?

In some dialysis centres, a routine haemodialysis session immediately before the transplantation procedure is carried out to improve the metabolic status of the patient. However, this is not routinely done in other centres where dialysis is performed only in case of some clinical indications (hyperkalaemia, fluid overload). Performing an additional dialysis before transplantation may increase CIT and activate inflammation. Ultrafiltration during pre-transplant dialysis is avoided in some centres, while some argue for ultrafiltration to improve cardiac function before surgery; it is unclear whether dehydration might jeopardize graft perfusion and diuresis in the perioperative phase.

#### What did we find?

In a small ( $n = 110$ ) randomized control trial, Kikic *et al.* found no influence of haemodialysis without ultrafiltration and using biocompatible membranes versus no haemodialysis on the risk of DGF, and eGFR at Day 5 in deceased kidney transplantation. In this study arm, patients with hyperkalaemia  $>5$  mmol/L were excluded [396].

In a retrospective cohort, Van Loo *et al.* found the use of bio-incompatible dialysis membranes along with the application of ultrafiltration to be associated with the risk of DGF [397]. The negative effect of a haemodialysis session immediately before transplantation, especially when ultrafiltration was performed, on immediate graft function was also pointed out by Schmidt *et al.* [398].

#### How did we translate the evidence into the statement?

There is no evidence for a benefit of performing a haemodialysis session just immediately before transplantation. The logistical organization of such a dialysis session may result in a delay in the surgery and hence increase CIT.

There is evidence that ultrafiltration just prior to transplantation is associated with more DGF after transplantation.

As a consequence, the guideline development group recommends to perform an additional dialysis session immediately before the transplantation procedure only when there is a clear clinical or biochemical indication that cannot be resolved by conservative measures alone.

#### What do the other guidelines state?

No other guideline body provides a statement on this topic.

#### Suggestions for future research

No suggestions.

#### 4.2. Does the use of central venous pressure measurement as a guidance tool for fluid management in kidney transplant recipients improve the outcome after transplantation?

We suggest that central venous pressure (CVP) is measured and corrected in the early post-operative period to prevent hypovolaemia and DGF. (2D)

##### Rationale

##### Why this question?

Assessment of adequate hydration status during first hours and days in kidney transplant patients is important for proper patient management. Dehydration might cause DGF due to decreased renal perfusion; on the other hand, fluid overload might result if fluid loading is done in patients who remain anuric in the post-operative period. It is not clear whether measurement of CVP measurement provides additional information to guide fluid management on top of clinical assessment of the patient.

##### What did we find?

There is limited evidence in the setting of kidney transplantation on the impact of CVP measurement on graft function in adults, both on short and long term. Most of the published trials are retrospective descriptive observations.

Othman *et al.* showed in a small prospective randomized open trial in 40-living donor kidney transplant recipients that hydration with normal saline using CVP >15 mmHg as aim versus at a continuous rate without CVP monitoring is associated with earlier onset of diuresis and better first day graft function measured by serum creatinine [399]. It was unclear whether this manoeuvre was associated with decreased incidence of DGF or better graft survival.

In a retrospective case-control study in deceased donor kidney transplantation, it was demonstrated that CVP <8 mmHg measured during transplantation was associated with a 3.5

times higher risk for DGF defined as the need for dialysis in the first week after transplantation [400]. In another retrospective study, intraoperative hydration aiming at a CVP of 7–9 mmHg had no effect on early kidney graft function [401]. Ferris *et al.* observed that after reperfusion of a transplanted kidney, CVP decreased irrespective of fluid loading [402]. This CVP drop was not associated with DGF.

##### How did we translate the evidence into the statement?

This suggestion is based on low grade evidence. However, there was general consensus in the guideline development group that good hydration is crucial to avoid DGF.

As most recipients of a kidney graft do have a central line in place in the immediate perioperative period, measurement of CVP can easily be obtained. Under these conditions, using CVP as for guiding hydration seems to decrease the occurrence of DGF. Especially sharp increases in CVP should be taken as an indicator of potential overhydration, or at least as a sign that further fluid loading is unlikely to result in improved cardiac output, and that fluid loading should be avoided accordingly.

The guideline development group judges that placement of a central venous line just for the measurement of CVP cannot be defended however. In the same line of reasoning, the central venous line should also not be maintained with the sole aim to measure CVP.

##### What do the other guidelines state?

No other guideline bodies provide a statement on this topic.

##### Suggestions for future research

A randomized controlled trial dealing with hydration according to CVP measurement in deceased donor kidney transplantation, and comparing different levels of CVP, or alternative means to evaluate cardiac filling pressure would be welcomed.

### 4.3. In kidney transplant recipients during the perioperative period, does the use of intravenous solutions other than 0.9% sodium chloride improve patient and/or graft outcome?

There is no evidence to prefer one type of solution (crystalloids versus colloids, normal saline versus Ringer) for intravenous volume management of the recipient during kidney transplant surgery.

In view of the available data in the literature, and in line with the ERBP position on prevention of acute kidney injury, we suggest to be cautious with the use of starches in the kidney transplant recipient during the perioperative period, although specific data in this setting are lacking. (Ungraded Statement)

We recommend monitoring for metabolic acidosis when normal saline is used as the only intravenous fluid in the perioperative and post-operative period. (1B)

#### Rationale

##### Why this question?

Patients receiving kidney grafts should be properly hydrated to allow immediate kidney graft function. Post-operative management differs in various centres and it is unclear whether crystalloid or colloid solutions are the first choice of volume replacement.

##### What did we find?

In a small randomized controlled double blind trial, O'Malley *et al.* compared normal saline versus lactated Ringer's solution for intraoperative intravenous fluid therapy in predominantly living donor kidney transplantation [403]. The study was prematurely stopped since patients treated with normal saline experienced significantly more acidosis and hyperkalaemia. There was no difference between the two solutions on post-operative graft function. Five (19%) patients in the normal saline group versus none in the lactate Ringer group had potassium concentrations  $>6$  mmol/L ( $P < 0.05$ ). Eight (31%) patients in the normal saline group versus none in the Ringer's lactate group were treated for metabolic acidosis ( $P < 0.004$ ).

Another randomized controlled trial compared normal saline, lactated Ringer's solution and Plasmalyte at comparable

infusion rates (20–30 mL/kg/h) in 90 living donor kidney transplant recipients [404]. Normal saline decreased pH ( $7.44 \pm 0.5$  to  $7.36 \pm 0.05$  and base excess from  $0.4 \pm 3.1$  to  $-4.3 \pm 2.1$  mmol/L), whereas Ringer's lactate was associated with increased lactate levels (from  $0.48 \pm 0.29$  to  $1.95 \pm 0.48$  mmol/L). None of the solutions resulted in hyperkalaemia. Although the best metabolic profile was associated with Plasmalyte, kidney function at first post-operative week was similar. Comparable results were reported by Khajavi *et al.* [405].

##### How did we translate the evidence into the statement?

There is evidence that maintenance of adequate perfusion pressure during the perioperative phase is of importance to avoid DGF. There is no evidence comparing crystalloid versus colloid solutions during kidney transplantation. In other areas of medicine, all evidence seems to point towards no advantage of colloid solutions over colloid solutions in patients thought to need volume replacement [406, 407]. If anything, high doses of starches might even be associated with increased mortality and risk for acute kidney injury [407].

The type of crystalloid solution seems to have no impact on graft outcome; however, the use of normal saline can result in metabolic acidosis, and associated with that, increase in potassium. These can be corrected by using 1.4% sodium bicarbonate when appropriate.

##### What do the other guidelines state?

KDIGO suggests using isotonic crystalloids rather than colloids (albumin or starches) as initial management for expansion of intravascular volume in patients at risk for or with acute kidney injury. They have no specific recommendation in the perioperative setting of kidney transplantation [408].

##### Suggestions for future research

The effect of 0.9% saline versus buffered solutions as perfusion fluid in the perioperative phase in kidney transplant recipients needs further investigations with the setting of a randomized controlled trial.

The effect of lower molecular weight iso-osmolar starches when compared with crystalloid solutions in the perioperative phase in kidney transplant recipients needs further investigation within a randomized controlled trial.

#### 4.4. Does the use of dopaminergic agents (dopamine and its alternatives) improve early post-operative graft function?

We do not recommend the use of 'renal doses' of dopaminergic agents in the early post-operative period, since it does not improve graft function or survival. (1B)

##### Rationale

##### Why this question?

Low-dose dopamine (<5 µg/kg/min) and alternative drugs, e.g. fenoldopam, have been proposed to kidney graft recipients as renoprotective agents in the early post-operative period aiming at improving graft function and survival. Such a benefit would decrease the risk of delayed graft function and therefore improve the long-term graft function and survival.

##### What did we find?

In patients with acute kidney injury in the non-kidney transplant population, there is no good evidence for an effect of the use of 'renal dose dopamine' [409].

In a small ( $n = 20$ ) randomized controlled trial (RCT) in the first 9 h after clamp release, patients were randomized to receive low-dose dopamine in the first 3 h and from 6 to 9 h versus only in the period 3–6 h [410]. During low-dose dopamine infusion, urine flow rate, effective renal plasma flow, creatinine clearance and total urinary sodium excretion were enhanced; however, no data on DGF, or later graft function were available. In another largely underpowered RCT ( $n = 18$ ), McCune *et al.* did not find a difference in serum creatinine at 48 h and at 30 days between patients treated with fenoldopam or placebo [411].

Three small randomized controlled trials showed better short-term graft function and reduced risk of DGF with low-dose dopamine in comparison with no dopamine, but all were at high risk of bias (multiple testing, potentially selective outcome reporting, patient selection, immunosuppression era, adjustment from confounding factors, limited information due to congress abstract source, number of patients) [412–414]. Another slightly larger RCT at moderate risk of bias found no evidence for a clear effect of treatment on short-term outcomes [415].

When it comes to outcomes at 3 months to 1 year after transplantation, four small retrospective cohort studies also failed to show evidence suggesting benefit for patients treated with low-dose dopamine, both in terms of patient and graft [416–419].

##### How did we translate the evidence into the statement?

There is no evidence to support that low-dose dopamine can improve graft outcome in terms of relevant outcomes as DGF, or serum creatinine levels in the mid-long and long term. The use of low-dose dopamine might induce arrhythmias. As such, the guideline development group judged that the use of low-dose dopamine could not be recommended. The existing evidence does not support that alternative dopamine agonists, such as fenoldopam, have a more positive profile. As a consequence, also the use of these agents cannot be recommended.

##### What do the other guidelines state?

No other guideline body provides a statement on this topic.

##### Suggestions for future research

No suggestions.

#### 4.5. Should we use prophylactic antithrombotic agents during the perioperative period?

We do not recommend routinely using low-molecular-weight heparin, unfractionated heparin or aspirin before transplantation to prevent graft thrombosis. (1B)

##### Rationale

##### Why this question?

Patients treated with dialysis might be at higher risk for thromboembolic events, especially arterio-venous fistula thrombosis, deep vein thrombosis and embolism for reasons that are poorly understood. In some of those patients graft vein thrombosis or other thromboembolic events may occur after kidney transplantation. Prophylactic use of antithrombotic agents potentially reduces that risk at the cost of increased bleeding in the immediate post-operative period, with the potential need for re-intervention and damage to the transplanted organ.

##### What did we find?

In a randomized trial in 75 living donor kidney transplant recipients, there was no event of thromboembolism in either the treatment arms (low-molecular-weight heparin or unfractionated heparin) or the placebo arm during the first week after transplantation, while there was a small comparable risk for bleeding complications in both arms [420].

In a small moderate quality randomized control trial in deceased donor kidney transplantation, Horvath *et al.* evaluated pre-operative injection of 2500 units of heparin or placebo followed by 17 days of therapy [421]. Three-month graft survival and the number of thrombotic events were similar in both arms. Bleeding events were numerically more frequent in the intervention arm but low event numbers made confidence intervals wide and results not statistically significant (RR: 11.00, 95% CI: 0.65–185).

Lundin *et al.* conducted a retrospective study in 120 kidney transplant recipients [422]. Fifty-six patients received prophylaxis with low-molecular-weight heparin, two patients received low-dose unfractionated heparin and the remaining patients received no prophylaxis. Graft thrombosis occurred in a single case in the control arm. Bleeding events were similar in both arms, and although there were numerically more graft nephrectomies in the control arm (4/64 control versus 0/56), the result was not statistically significant and reasons for this observation were not reported. There was a slightly higher incidence of ultrasonographically diagnosed lymphoceles in the interventional arm (RR: 2.11, 95% CI: 1.19–3.74), but the number of lymphoceles needing intervention was similar (10/56 versus 11/64).

We found one retrospective cohort study ( $n = 200$ ) in which low-dose heparin given just before vascular clamping was compared with no prophylaxis [423]. Although both the number of patients experiencing graft thrombosis and the

number needing blood transfusions were numerically higher in the control group, results were not statistically significant and confidence intervals wide.

We found one study in which 105 patients treated with aspirin during the first 3 months along with low-molecular-weight heparin for first 5 days after transplantation were compared with 121 historical controls [424]. They found numerically fewer events of graft thrombosis and biopsy-proven chronic allograft nephropathy at 1 year. None of these results was adjusted for confounding or statistically significant and confidence intervals were very wide.

In another retrospective cohort study, Nagra *et al.* found similar numbers of graft thrombosis leading to graft loss after heparin prophylaxis compared with no prophylactic anticoagulation. Among the 254 patients, there was one bleeding incident leading to graft loss [425].

Finally, we found two retrospective cohort studies comparing low-dose aspirin with no prophylaxis during the first month after transplantation. Both found fewer cases of graft thrombosis but used a historical control group and did not attempt adjustment for potential confounding in their analysis [426, 427].

##### How did we translate the evidence into the statement?

There is no consistent and convincing evidence for routine antithrombotic therapy by unfractionated or low-molecular-weight heparin. There is no study dealing with low dose heparin or low-molecular-weight heparin prophylaxis in patients with obvious risk of thrombosis such as genetic mutation of factor V Leiden, prothrombin mutation or those already on anticoagulation therapy. As these patients do have an indication for anticoagulation anyway, and as there is no convincing consistent evidence for an increased bleeding risk, we suggest such patients to receive low-molecular-weight heparin prophylaxis for 4 weeks as recommended by the Haematological Society. (2B)

Aspirin with the sole purpose of preventing renal vein thrombosis should not be started in patients who are not already on the treatment for other indications. In patients who have an indication for chronic antiplatelet drugs, aspirin should not be stopped, as the pharmacodynamic action on platelet activity lasts >7 days.

##### What do the other guidelines state?

No other guideline body provides a statement on this topic.

##### Suggestions for future research

We need an adequately powered randomized controlled study to clarify the risks and benefits of prophylactic treatment with low-molecular-weight heparin in the perioperative period in kidney transplantation.

Insufficient evidence is reported on safety and bleeding risk of kidney biopsy in kidney transplant patients under antiplatelet aggregating drugs, and more reports in this regard are needed.

#### 4.6. In kidney transplant recipients, what are the effects of using a JJ stent at the time of operation on outcomes?

We recommend prophylactic JJ stent placement as a routine surgical practice in adult kidney transplantation. **(1B)**

We suggest that if a JJ stent is in place, cotrimoxazole is given as antibiotic prophylaxis. **(2D)**

We suggest removing the JJ stent within 4–6 weeks. **(Ungraded Statement)**

#### Rationale

##### Why this question?

Placement of a prophylactic ureteric stent is mostly done to protect the connection of the donor ureter with the bladder of the recipient, to avoid urinary leakage in the post-operative phase and to avoid strictures. However, placement of a JJ stent enhances the risk of infection and reflux. In addition, the removal of the JJ stent in a second stage can pose logistical problems and cause inconvenience and discomfort for the recipient.

##### What did we find?

A recent Cochrane review on this topic included seven randomized controlled trials (total 1154 patients) of low or moderate quality [428]. In this systematic review, the incidence of major urological complications was significantly reduced (RR: 0.24, 95% CI: 0.07–0.77,  $P = 0.02$ , NNT 13) in patients who had a prophylactic stent in place. However, the authors pointed out that the result was dependent on whether the same surgeon performed or attended the operations, so there might be a decreased effect in surgeons with high experience. However, also in the subgroup where all interventions were done by the same surgeon, a beneficial effect of prophylactic stenting was observed (RR: 0.39, 95% CI: 0.08–1.86, NNT = 30). The incidence of major urological complications in the non-stented group differed widely between the different studies (0–17%), whereas this was far less in the stented group (0–4%). Two patients lost their grafts to infective urinary tract complications in the stented group. Urinary tract infections were more common in stented versus not stented patients (RR: 1.49, 95% CI: 1.04–2.15), unless the patients were prescribed co-trimoxazole 480 mg/day. In that

case, the incidence was equivalent (RR: 0.97, 95% CI: 0.71–1.33).

In a recent retrospective single-centre study cohort ( $n = 961$ , 32% of whom did not receive a stent), ureteral complication rate was 1.9% in stent versus 5.8% in the no-stent group ( $P = 0.007$ ) [429]. Urinary tract infection rate was 14% with stent versus 8% without stent ( $P = 0.003$ ). Stent use was independently associated with reduction in ureteral complications (incidence rate ratio 0.40, 95% CI: 0.17–0.96) and an increase in risk for urinary tract infection (RR: 1.79, 95% CI: 1.18–2.74). Stent protective effect was primarily related to reduction in stricture risk (RR: 0.23, 95% CI: 0.05–0.99). Stents were reported in this study to be associated with a decrease in ureteral complications in deceased donor recipients (RR: 0.34, 95% CI: 0.13–0.88), but not living donors (RR: 1.24, 95% CI: 0.15–10.2), but only 10% of living donation recipients (23/263) did actually receive a stent, so there is a high risk for bias by indication and lack of power for this subgroup analysis.

There is no evidence for such a benefit in children and there is no consensus among paediatric transplant surgeons for using prophylactic ureteral stenting.

##### How did we translate the evidence into the statement?

In view of the published evidence, prophylactic placement of a stent should be recommended. In experienced hands, the expected benefits are lower, but still present.

Some members of the guideline development group judged that in experienced hands, and when logistical circumstances to remove the stent in a second stage are difficult, performing a transplant without placement of a stent can be acceptable.

The major complication of stenting is urinary tract infection. As the risk seems to be similar for those who do not receive a stent when patients are given cotrimoxazole, we suggest cotrimoxazole is given as antibiotic prophylaxis.

##### What do the other guidelines state?

No other guideline body provides a statement on this topic.

##### Suggestions for future research

It is deemed unlikely that further RCTs will change the evidence we have so far. However, RCTs on the most optimal timing of removal of the stent are needed. Also studies to clarify under which conditions and/or in which type of patients no JJ stent might be a safe option, would be welcomed.

#### 4.7. What is the optimal post-operative time for removal of the indwelling bladder catheter in kidney transplant recipients?

We suggest removing the urinary bladder catheter as soon as possible after transplantation, balancing the risk of urinary leak against that of urinary tract infection. (2D)

We recommend monitoring adverse event rates (urinary tract infection, urinary leakage) in each centre, to inform the decision over when to remove the indwelling bladder catheter. (1D)

#### Rationale

##### Why this question?

An indwelling bladder catheter can protect the fresh suture of the ureter on the bladder and reduce major urological complications. On the other hand, it can be an additional source of infection, prolonging the initial hospitalization due to urinary tract infection [430]. There is still a controversy as to the most optimal post-operative day to remove the indwelling catheter [431].

##### What did we find?

We did not find any randomized trial on this topic.

A single-centre retrospective analysis compared patients in whom the bladder catheter was removed on the second post-operative day ( $n = 66$ ) to those in whom it was removed later ( $n = 75$ ) [432]. All patients had also a ureteral JJ stent. The median length of stay was 3 days in group A compared with 5 days in group B ( $P = 0.001$ ). Urinary retention requiring reinsertion of the urethral catheter occurred once in group A (1.5%) and twice in group B (2.6%). There were no urine leaks in neither of the groups. Readmission within 30 days of transplantation was significantly associated with DGF ( $P = 0.016$ ) and longer post-transplant length of stay ( $P = 0.001$ ), but not with the post-operative day of urethral catheter removal ( $P = 0.14$ ). By its design this study was highly prone to bias by indication however. This risk of bias is also substantial in two other reports demonstrating a similar ( $2.6 \pm 1.4$  versus  $2.4 \pm 1.1$  days in those with versus without urinary tract infection in the first months post-transplantation) [431] and a longer bladder catheterization ( $6.5 \pm 5.5$  versus  $5.2 \pm 2.9$  days in those with versus without urinary tract infection in the first year after transplantation) in kidney recipients, respectively [433].

In a small ( $n = 57$ ) observational single-centre cohort, the odds ratio for developing a urinary tract infection while having a bladder catheter in place for  $>3$  days was 1.48 (95% CI: 0.35–6.19) [434]. The analysis was, however, not adjusted for potential confounders. Finally, we found one retrospective cohort study comparing catheter removal between the second and third day with leaving the bladder catheter in place for  $>1$  week. On average, the risk for developing urinary tract infection was twice as large for patients in the early catheter removal group. Both groups had, however, received antibiotic prophylaxis and the analysis was not corrected for possible confounding [435].

#### How did we translate the evidence into the statement?

The evidence came only from a few retrospective studies, with poor design and probable bias. Nevertheless, early catheter removal (2 days) was associated with shorter length of the hospital stay, and less risk of infection. There were no numbers to assess the potential influence on urological complications of early removal of the bladder catheter.

As such, the guideline development group judged that pros and cons of removal of the bladder catheter should be weighed on an individual patient basis daily from the second post-operative day onwards. As information, even observational, is grossly lacking, centres should document their own experience to help steering the decision process. It is important that this is done by individual centres, as the ideal day might be dependent upon factors related to local procedures and techniques.

#### What do the other guidelines state?

No other guideline body provides a statement on this topic.

#### Suggestions for future research

A randomized clinical trial on the adverse event rates (urinary tract infection, urinary leakage) in patients in whom the bladder catheter is removed early versus later in the post-operative period is highly needed.

Transplant centres should be stimulated to register their own complication rates (infections and urological complications), and adapt timing of removal of the indwelling bladder catheter accordingly.

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