Clinical practice guideline on peri- and postoperative care of arteriovenous fistulas and grafts for haemodialysis in adults

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ABBREVIATIONS AND ACRONYMS

AV	arteriovenous
CPG	clinical practice guideline
CKD	chronic kidney disease
CSN	Canadian Society of Nephrology
DOPPS	Dialysis Outcomes and Practice Patterns Study
EBPG	European Best Practice Guidelines
EDTNA/ ERCA	European Dialysis and Transplant Nurses Association/European Renal Care Association
ERBP	European Renal Best Practice
ESKD	end-stage kidney disease
ESVS	European Society for Vascular Surgery
GEMAV	Grupo Español Multidisciplinar del Acceso Vascular
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	hazard ratio
IQR	interquartile range
IRR	incidence rate ratio
KDIGO	Kidney Diseases: Improving Global Outcomes
NKF-KDOQI	National Kidney Foundation Kidney Diseases Outcomes Quality Initiative
KHA-CARI	Kidney Health Australia – Caring for Australasians with Renal Insufficiency
MD	mean difference
N	number of
NICE	National Institute for Health and Care Excellence
OR	odds ratio
PTFE	polytetrafluoroethylene
RCT	randomized controlled trial
RD	risk difference
RR	relative risk
95% CI	95% Confidence Interval
SIGN	Scottish Intercollegiate Guidelines Network
SD	standard deviation
SMD	standardized mean difference
UKRA	UK Renal Association
VAS	Vascular Access Society

DEFINITIONS

Interpreting evidence in the arteriovenous (AV) access literature is challenged by the heterogeneity in terminology and the lack of standardization in outcomes. Below some of the terms used in this guideline are listed and how they have been interpreted in the context of this document. Because guideline development necessarily relies on aggregate data from systematic reviews and other individual studies, we can only hope to provide the user with conceptual definitions for certain concepts and outcome domains. At present, there is insufficient consensus to go beyond that point and define specific outcome measures or measurements.

AV access	Overarching term referring to both AV fistulas and AV grafts.
AV access thrombosis	Blood clot obstructing the AV access; indicates loss of anatomic, haemodynamic and clinical patency.
AV fistula	Surgically created autogenous vascular access used for chronic haemodialysis consisting of an anastomosis between an artery and a vein, with the vein serving as the accessible conduit (synonym: native AV fistula).
AV graft	Surgically created vascular access used for chronic haemodialysis, whereby an artificial or biological prosthetic segment is used to connect an artery and a vein, with the prosthetic segment serving as the accessible conduit.
Cannulation	Placement of a dialysis needle in the AV access to provide haemodialysis.
Clinical monitoring	Clinical assessment of an AV access at regular intervals; it is distinct from technical surveillance and includes examination of the access AV thrill and bruit, haemostasis time after needle removal and outflow appraisal after arm elevation.
Clinical practice guideline (CPG)	A set of statements that include recommendations intended to optimize patient care, which are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options (synonym: guideline).
Maturation	Process leading to a newly created AV access being usable for haemodialysis; it encompasses enlargement and thickening of the draining fistula vein, increases in the blood flow and absence of thrombosis and bleeding as mechanisms of AV access failure (synonym: suitability for dialysis).
Recommendations	Graded statements within a CPG intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options.
Patency	See primary unassisted patency or secondary patency.
Pre-emptive intervention	Intervention aimed at resolving a stenosis or another problem in an AV access that is still adequately providing dialysis; the intention is to avoid the AV access becoming dysfunctional.
Primary AV access failure	An AV access that, despite radiological or surgical intervention, cannot be used successfully for dialysis by a given time point (usually up to three months) following its creation (synonym: dialysis suitability failure).
Primary unassisted patency	The time of AV access creation or placement until any first intervention (endovascular or surgical) to maintain or restore blood flow or the first occurrence to AV access thrombosis (synonym: intervention-free AV access survival; primary patency).
Secondary patency	the time of AV access creation or placement until AV access abandonment or permanent

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	loss of the AV access (synonym: cumulative AV access survival; secondary assisted patency).
Surveillance	Overarching term referring to both clinical monitoring and technical surveillance of an AV access; it includes haemodialysis parameters such as pump speed, dialyser inlet and transmembrane pressure and indices of dialysis adequacy (K_t/V urea); sequential measurements with trend analysis of intra-access flow, dynamic or static dialyser outlet pressure, AV access recirculation or AV access duplex ultrasound assessment.
Technical surveillance	Assessment of an AV access at regular intervals using a specialized apparatus; distinct from clinical monitoring.

PREFACE

Vascular access remains one of the most challenging aspects of renal replacement therapy. If the vascular access does not function properly, then haemodialysis will not remove uraemic retention solutes adequately, and if all access possibilities have been exhausted, then haemodialysis is no longer possible. The consequences for patient survival may be severe if kidney transplantation or peritoneal dialysis are not an option either. Every professional who has been active in haemodialysis long enough will remember at least a few patients in whom haemodialysis had to be abandoned for lack of access. They will also remember many more in whom a series of procedures was necessary, often without ensuring adequate dialysis for prolonged periods.

For patients, the 'umbilical cord' keeping them alive can be a constant source of stressful experiences [1].

In 2007, during the second round of recommendations for haemodialysis from the European Best Practice Guidelines (EBPG)—the predecessor of the current European Renal Best Practice (ERBP)—the first set of essentially clinically oriented vascular access recommendations was drafted by a small group of experts in vascular access surgery, interventional radiology and haemodialysis [2]. Guideline development has changed profoundly since then, with more rigorous methodology having been introduced and a greater emphasis placed on evidence-based medicine [3].

One of the caveats in the present clinical practice guideline (CPG) is that even today high-quality data on vascular access are scarce, partly because there are still too few sufficiently powered and well-designed controlled trials and partly because adoption of evidence-based medicine in the field of vascular access is maturing and changing the landscape. It is well recognized that the heterogeneity of the patient samples studied and the many associated confounders may bias the study results, including differences in surgical procedures, skills and experience; differences in patient education; variability in patient genetic predisposition of thrombogenicity; variation in cannulation procedures, uraemic status and vessel quality and many others. It made offering strong treatment guidance difficult. However, in addition to helping clinicians make decisions based on what is known today, we hope this text will stimulate researchers to explore what is still unknown and the nephrology community at large to develop uniform definitions and assess more clinically relevant vascular access outcomes [4].

This text is intended for nephrologists and for the other stakeholders in the field whose participation was sought during the development process: dialysis nurses, vascular access surgeons, radiologists, researchers, pharmacists and, importantly, patients and their caregivers [5]. It specifically covers peri- and postoperative care of AV fistulas and grafts. The second part—under development when this guideline went to press—will cover aspects related to access choice, preoperative vessel assessment and central venous catheters. We hope the current and planned CPG will assist the professional community in making decisions about vascular access processes, pathways and care; help patients and caregivers gain insight and facilitate joint decision making in this field.

SUMMARY OF THE RECOMMENDATIONS

Chapter 1. Medical treatments for promoting arteriovenous fistula maturation

1.1. We suggest any decision to give aspirin, ticlopidine or clopidogrel in adults with end-stage kidney disease (ESKD) during the first 2 months after arteriovenous fistula creation for the sole purpose of improving maturation must balance a reduction in thrombosis against uncertain effects on maturation and bleeding. (2C)

1.2. We suggest any decision to give perioperative heparin in adults with end-stage kidney disease during arteriovenous fistula creation must balance an increase in arteriovenous fistula patency at 1 month against an important increase in bleeding complications. (2C)

1.3. We suggest any decision to apply far infrared therapy in adults with end-stage kidney disease during the first 3 months after arteriovenous fistula creation must balance a possible reduction in thrombosis against uncertain effects on maturation and bleeding. (2C)

1.4. There are insufficient randomized controlled trial (RCT) data to make a recommendation for ticagrelor, prasugrel, dipyridamole, sulphinpyrazone, warfarin or other oral anticoagulants, fish oil, statins, vonapanitase, glyceryl trinitrate, iontophoretic injection of *Salvia miltiorrhiza* or prednisolone for improving arteriovenous fistula maturation in adults with end-stage kidney disease. (-D)

Advice for clinical practice:

• Do not stop mono-antiplatelet treatment in adults undergoing AV access creation.

Chapter 2. Surgical and endovascular interventions for promoting arteriovenous fistula maturation

2.1. We suggest using regional block anaesthesia rather than local anaesthesia for arteriovenous fistula creation in adults with end-stage kidney disease. (2C)

2.2. We suggest there is insufficient evidence to support end-of-vein to side-of-artery over side-of-vein to side-of-artery anastomosis for arteriovenous fistula creation in adults with end-stage kidney disease (2C)

Chapter 3. Surgical and endovascular interventions for non-maturing arteriovenous fistulas

3.1. We suggest there is insufficient evidence to support open surgical over endovascular interventions as the preferred treatment for non-maturing arteriovenous fistulas in adults with end-stage kidney disease. (2D)

Advice for clinical practice:

- Decisions on how to treat non-maturing arteriovenous fistulas are likely best based on local resources, experience and success rates.
- Institutions likely benefit from building a dedicated multidisciplinary vascular access team, with clinical experience in various techniques available for non-maturing arteriovenous fistulas.

Chapter 4. Self-administered interventions for arteriovenous fistula maturation

4.1. We suggest that a standardized exercise programme involving hand-and-arm exercises may improve arteriovenous fistula maturation in adults with end-stage kidney disease. (2C)
4.2. There is insufficient evidence to support specific exercise programmes or physical interventions to promote AV fistula maturation in adults with end-stage kidney disease. (-D)

Advice for clinical practice:

- Involving patients more actively in preparing for haemodialysis may improve self-management skills and health literacy and thereby well-being.

Chapter 5. Perioperative prophylactic antibiotics for preventing arteriovenous access infection

5.1. We recommend giving preoperative antibiotic prophylaxis for arteriovenous graft insertion in adults with end-stage kidney disease. (1C)
5.2. We suggest giving preoperative antibiotic prophylaxis for complex arteriovenous access procedures in adults with end-stage kidney disease. (2D)
5.3. We suggest not giving preoperative antibiotic prophylaxis for simple arteriovenous access procedures in adults with end-stage kidney disease. (2D)

Advice for clinical practice:

- Simple arteriovenous access procedures include the creation of a native radiocephalic or native brachiocephalic arteriovenous fistula.
- Complex arteriovenous access procedures include those that are not considered simple.

Chapter 6. Timing of first cannulation

Arteriovenous fistulas

6.1. In adults requiring haemodialysis, we suggest arteriovenous fistulas can be cannulated 4 weeks after creation if they are considered suitable for cannulation on clinical examination. (2C)
6.2. In adults requiring haemodialysis, we recommend against cannulating arteriovenous fistulas sooner than 2 weeks after their creation. (1B)
6.3. In adults requiring haemodialysis, we suggest against cannulating arteriovenous fistulas 2–4 weeks after their creation unless this will avoid placement of a central venous catheter for haemodialysis. (2C)

Arteriovenous grafts

6.4. In adults requiring haemodialysis, we recommend that 'early cannulation type' arteriovenous grafts can be cannulated as soon as wound healing permits. (1B)
6.5. In adults requiring haemodialysis, we suggest against cannulating a 'standard type' arteriovenous graft sooner than 2 weeks after insertion unless this will avoid placement of a central venous catheter for haemodialysis. (2B)

Advice for clinical practice:

- In practice, suitability for cannulation on clinical examination is determined by the presence of a palpable vein and good thrill.
- If clinical examination is inconclusive, then ultrasound with flow measurement may help in deciding whether to cannulate.
- Bedside ultrasound-guided cannulation may be helpful in avoiding complications and decreasing the number of failed cannulations.
- Using single-needle dialysis, low dialysis blood flows and smaller needles (17 gauge) may prevent harm to arteriovenous fistulas that are cannulated early.
- Wound healing refers to the tissue around the body of the graft rather than the incision site.

Chapter 7. Vascular access surveillance

Arteriovenous fistulas

7.1. We suggest the evidence for technical surveillance in addition to clinical monitoring of a functional arteriovenous fistula to detect and pre-emptively correct a haemodynamically important arteriovenous access stenosis in adults is inconclusive and needs more research. (2C)

Arteriovenous grafts

7.2. We suggest against technical surveillance in addition to clinical monitoring of a functional arteriovenous graft to detect and pre-emptively correct a haemodynamically important arteriovenous access stenosis in adults unless it occurs in the context of a clinical study. (2C)

Chapter 8. Medical treatments for maintaining long-term arteriovenous access patency

Arteriovenous fistulas

8.1. We suggest any decision to give fish oil to adults with end-stage kidney disease in the year following arteriovenous fistula creation must balance improved patency at 1

year against an unknown risk of bleeding and other side effects. (2C)

8.2. We suggest far infrared therapy may be considered for improving long-term arteriovenous fistula patency in adults with end-stage kidney disease. (2C)

8.3. There are insufficient randomized controlled trial data to make a recommendation for aspirin, clopidogrel, ticlopidine, warfarin, sulphinpyrazone, vonapanitase, beraprost sodium, cholecalciferol, statins, dipyridamole or dipyridamole combined with aspirin to be given for maintaining long-term arteriovenous fistula patency in adults with end-stage kidney disease. (-D)

Arteriovenous grafts

8.4. We recommend against warfarin in combination with antiplatelet agents and against clopidogrel in combination with high-dose aspirin for reducing arteriovenous graft thrombosis in adults with end-stage kidney disease. (1C)

8.5. We suggest any decision to give fish oil in the year following arteriovenous graft creation in adults with end-stage kidney disease must balance any improvement in graft patency at 1 year against an unknown risk of bleeding. (2C)

8.6. There are insufficient randomized controlled trial data to make a recommendation for aspirin, clopidogrel, ticlopidine, warfarin, beraprost sodium, statins, dipyridamole or dipyridamole combined with aspirin to be given for maintaining long-term arteriovenous graft patency in adults with end-stage kidney disease. (-D)

Chapter 9. Cannulation techniques for arteriovenous fistulas

9.1. We suggest against using the area technique for cannulating arteriovenous fistulas in adults treated with haemodialysis. (2D)

9.2. We suggest using either a rope-ladder or buttonhole technique for cannulating arteriovenous fistulas in adults treated with haemodialysis and letting the choice be dependent on local expertise and arteriovenous fistula characteristics. (2D)

Advice for clinical practice:

- Antiseptic measures and practical aspects of the cannulation procedure are important in reducing the infection risk associated with buttonhole cannulation.
- Arteriovenous grafts are usually only cannulated using a rope-ladder technique.

Chapter 10. Needle types for arteriovenous fistulas

10.1. We suggest using either sharp needles or plastic cannulas for cannulating arteriovenous fistulas in adults treated with haemodialysis. (2C)

10.2. We recommend using blunt needles only for buttonhole cannulation of arteriovenous fistulas in adults treated with haemodialysis. (1D)

Advice for clinical practice:

- A quality improvement programme including recording and monitoring of the needle types and cannulation techniques alongside arteriovenous access outcomes can help to monitor quality, guide changes in cannulation practice, if needed, and improve quality of vascular access care.
- Arteriovenous grafts are usually only cannulated using sharp steel needles.

Chapter 11. Timing of intervention for arteriovenous fistula thrombosis

11.1. We suggest attempting to declot a thrombosed arteriovenous fistula in adults as soon as possible under optimal conditions and before the next haemodialysis treatment. (2D)

11.2. We suggest attempting to declot a thrombosed arteriovenous fistula in adults even if there has been a delay of days to weeks. (2D)

Chapter 12. Surgical and endovascular interventions for arteriovenous access thrombosis

12.1. We suggest the choice between surgical and endovascular interventions for arteriovenous access thrombosis be defined by the condition of the patient and their vascular access, as well as local expertise, as there is no evidence one approach improves outcomes over another. (2B)

COMPOSITION OF THE GUIDELINE DEVELOPMENT GROUP

ERBP's Advisory Board appointed the co-chairs and invited a small group of content experts to a steering committee to direct the guideline development process. These content experts were chosen based on their previous involvement with EBPG or their close association with national or international vascular access societies [3]. The group was supplemented with selected members of ERBP's methods support team to supervise the project and provide methodological expertise in guideline development throughout the process. The steering committee convened in May 2013 and February 2014 and decided on the composition of the Guideline Development Group (GDG), taking into account the clinical and research expertise of each proposed candidate and their willingness to invest the necessary time and effort to perform the task according to the proposed deadlines and the agreed methodology. The group ultimately consisted of 44 participants, including 25 nephrologists, 9 surgeons, 3 radiologists, 5 researchers, 2 nurses and 8 methodologists (categories not mutually exclusive). It included 29 men and 15 women (see Supplement 1—Guideline Development Group area of expertise).

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CONFLICT OF INTEREST POLICY AND DECLARATION OF INTEREST FORMS

We required all participants in the GDG to fill in a detailed 'declaration of interest statement' including all their current and future conflicts of interest as well as past interest restricted to the two years before joining the guideline development process. Declaration of interest statements of individual GDG members are enclosed in Supplement 2 (see Supplement 2—Declaration of interest statements).

Because it was felt that excluding every individual with some degree of possible conflict of interest would make assembling a GDG impossible, we allowed members of the GDG to have past financial and/or intellectual conflicts of interest. We did not attach any consequences to the stated interests, but rather insisted

on transparency. All members of the GDG could 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.

PURPOSE AND SCOPE OF THIS GUIDELINE

Topic selection

The process of identifying and prioritizing all relevant treatment decisions along the vascular access care pathway (vascular access 'topics') comprised three phases [5]. In Phase 0, we created a preliminary list of topics based on the literature review and input from a multidisciplinary expert group. Its members did not necessarily participate in later stages of the guideline development process. The group consisted of two kidney patients, two nephrologists, a renal nurse, two surgeons and a radiologist. In Phase 1, an international panel of 85 kidney patients, 687 nephrologists, 194 nurses and 140 surgeons/radiologists rated the priority of these topics on a 5-point Likert scale through an online survey and suggested additional topics to complement the preliminary list. The additional topics were prioritized in Phase 2 by rating 42 vascular access–related topics on a 5-point Likert scale in an electronic questionnaire. Details of the scoping procedures and its results have been published separately [5].

The group estimated that it would be feasible to select 20 topics for further elaboration and selected these from the list of 42 topics, guided by a preference for prioritizing topics that had been covered by EBPG and by the priority ratings they had received from patients and clinicians in the scoping procedure [2]. Although the group initially developed all 20 topics simultaneously, the guideline was later split into two parts for reasons of feasibility.

Why was this guideline produced?

The purpose of this CPG was to provide guidance on the management and preservation of AV fistulas and grafts for haemodialysis. It was designed to provide information and assist decision making related to this topic. It was not intended to prescribe a standard of care and should not be construed as such. It should also not be interpreted as prescribing an exclusive course of management.

This CPG was developed by ERBP, the guidance body of the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) and is a collaborative effort of various stakeholders within the field, including representatives of the Vascular Access Society (VAS), nephrologists, vascular access surgeons, radiologists, dialysis nurses, researchers, patients and their caregivers.

All these stakeholders agreed that there was a need for up-to-date guidance on vascular access management. The current document is an update of EBPG for haemodialysis published in 2007 [2]. An attempt to adhere to increasingly stringent guideline development methodology has required certain sacrifices in terms of scope. As a result, the current document does not necessarily cover the same topics as the previous version. Some are shared, but some were archived in favour of new questions

prioritized by both health care providers and the people they care for [5].

Who is this guideline for?

This guideline aims to support clinical decision making for any health care professional treating or caring for haemodialysis vascular access, including nephrologists, vascular access surgeons, radiologists, dialysis nurses and pharmacists dealing with vascular access in both outpatient and in-hospital settings and general practitioners, internists and surgeons who are not directly practicing in the nephrology or dialysis access field but who may be confronted indirectly with haemodialysis access issues and systems.

The guideline is also developed for policymakers, for informing standards of care at national and international levels, and for haemodialysis patients, to improve their views on what dialysis access is about and how they can participate in its maintenance and preservation.

What is this guideline about?

This CPG covers aspects related to vascular access that are necessary for successful long-term haemodialysis. A rigorous multilayered phased selection procedure drove identification of the specific clinical questions this guideline aims to answer [5].

Population

The guideline covers aspects related to vascular access that are necessary for successful chronic haemodialysis in adults of all ages with ESKD. It does not cover vascular access in children because the GDG felt essential differences exist between the two patient groups, requiring a targeted guideline development process. Not only would priorities for guideline development likely differ, interventions would have an appreciably different risk–benefit balance and require exploration of lower-level evidence generated specifically in children, which would be beyond the limits of our resources available at present.

Conditions

This guideline covers aspects related to maturation and maintenance of AV fistulas and grafts used in long-term haemodialysis. It specifically deals with interventions for promoting maturation of the AV access, perioperative antibiotic therapy for preventing AV access infection, timing of first cannulation, cannulation techniques and needle types, medical treatments for long-term AV access patency, AV access surveillance and pre-emptive intervention and surgical and endovascular interventions for AV access thrombosis.

Health care setting

This guideline targets outpatient, in-hospital and out-of-hospital haemodialysis unit settings dealing with adults who need to have an AV access for long-term haemodialysis.

Clinical management

This guideline deals with educational, pharmaceutical and interventional tools for promoting successful use of an AV access and interventions aimed at preventing failure of the vascular access by the use of specific treatment strategies tailored to

the underlying problem. This guideline covers treatment for adults with acute or chronic vascular access problems and strategies to prevent or treat, regardless of the underlying cause of kidney disease, any pre-existing systemic vascular condition or any specific haemodialysis strategy.

In line with the mission statement of ERBP, this guidance document intends to inform all involved stakeholders and to stimulate shared decision making. It also highlights topics for which additional research data are needed and offers suggestions for how research might be pursued [3].

METHODS FOR GUIDELINE DEVELOPMENT

Establishment of the GDG

A steering committee consisting of the chair of ERBP at that time (Wim Van Biesen), selected members of ERBP's methods support team (Christiane Drechsler, Maria Haller, Muguet Koobasi, Evi Nagler and Sabine van der Veer), the co-chairs of the GDG appointed by ERBP's Advisory Board (Maurizio Gallieni and Anna Marti I Monros) and selected content experts (Markus Hollenbeck, Nicholas Inston, Mick Kumwenda, Steve Powell, Jan Tordoir, Matthias Widmer) convened in May 2013 and February 2014 and decided on the composition of the GDG, taking into account the clinical and research expertise of the proposed candidates. The GDG consisted of content experts that included individuals with expertise in vascular access. In its composition, the GDG aimed to be multidisciplinary, including nephrologists, surgeons, radiologists, researchers, a nurse and a patient. ERBP's methods support team provided methodological input and practical assistance throughout the guideline development process.

Developing clinical questions

With the scope of the guideline as the point of departure, the GDG identified specific clinical research questions for which a systematic review was conducted.

Development of review questions

The methods support team assisted in developing review questions, that is, framing the clinical questions into a searchable format, by applying the PICO procedure. This required careful specification of the patient group (P), the intervention (I), the comparator (C) and the outcomes (O) for intervention questions and the patient group, index tests, reference standards and target conditions for questions of diagnostic test accuracy [6]. For each question, the GDG agreed upon explicit review question criteria, including study design features (see Supplement 3 for detailed review questions and PICO tables).

Assessment of the relative importance of the outcomes

For each intervention question, the GDG compiled a list of outcomes, reflecting both benefits and harms of alternative management strategies. The GDG ranked the outcomes as critical, highly or moderately important according to their relative importance in the decision-making process. As such, patient-important health outcomes, such as patient survival and quality of life, as well as permanent loss of the vascular access, were

considered critical. Outcomes such as AV access thrombosis, infections, hospitalizations and temporary central venous haemodialysis catheter use were considered highly important, but less important than the critically important clinical outcomes (Table 1).

Target population perspectives

Efforts were made to capture the target population's perspectives by adopting three strategies.

To identify and prioritize all relevant treatment decisions along the vascular access care pathway (vascular access 'topics'), we conducted an extensive survey in three phases, including participants with kidney disease in every phase of the process [5]. We ultimately elicited responses from 85 patients residing in Austria (15%), Belgium (24%), Spain (14%), The Netherlands (29%) and the UK (18%).

Second, one of the GDG members, a researcher in the field of vascular access and actively involved with the evidence review and guideline development process, had previously been treated with chronic haemodialysis and, as such, was very familiar with many of the challenges faced by people with ESKD.

Third, ERBP has a permanent patient representative on its board. Although he was not included in the GDG or in the evidence review process, drafts of the guideline document were sent out for his review and his comments were considered in revising and drafting the final document.

Searching for evidence

Sources and search strategy

We used a hierarchical strategy whereby the ERBP's methods support team first searched the Cochrane Database of Systematic Reviews (up to April 2018) for reviews that were either up to date or could be updated by our review team. If such a review did not exist, then the methods support team subsequently searched Database of Abstracts of Reviews of Effects (DARE) (up to April 2018) Cochrane Controlled Register of Trials (CENTRAL) (up to April 2018) for other systematic reviews and randomized trials, respectively. If no randomized trials were available, then an additional search was conducted in MEDLINE (up to April 2018) for identifying non-randomized studies that fit the inclusion criteria set for each research question.

Search strategies combined subject headings and text words for the patient population and intervention. The detailed search

Table 1. Hierarchy of outcomes

Hierarchy	Outcomes
Critically important	Death
	Technique/vascular access failure, major cardiovascular events, major infections, quality of life, uninterrupted dialysis sessions
Highly important	Hospitalization, pain, physical limitations, blood flow (in AV access or in dialysis machine)
Moderately important	Anxiety/distress, pressures (in AV access or in dialysis machine), dialysis adequacy, recirculation

strategies and dates are available in Supplement 4—Search strategies.

Study selection

We used the Early Reference Organisation Software (http://www.eros-systematic-review.org) to organize the initial step of screening and selection of papers. The title and abstract of all papers retrieved by the search were made available to those responsible for screening through this system. For each research question, two GDG members independently screened all titles and abstracts. Abstracts that did not meet the inclusion criteria were discarded. Any discrepancies at this stage were resolved by group consensus.

In a second step, the methods support team retrieved full texts of potentially relevant studies and two mutually independent reviewers examined them for eligibility, according to the preset eligibility criteria independent of each other. Any discrepancies were resolved by consensus. If no consensus could be reached, then the disagreement was settled by group arbitrage.

The flow diagram depicting the paper selection process for each research question is presented in Supplement 5—Study selection and flow diagrams.

Data extraction and critical appraisal of individual studies

For each included study we collected relevant information on design, conduct and relevant results through standardized data extraction forms. These forms were developed in Salesforce (Salesforce, San Francisco, CA, USA), a customer relationship platform, customized to fit our needs. We introduced closed questions with drop-down answer lists whenever possible to improve data quality. The tool allowed automatic collection of the entered data into a database and semi-automatic cross-checking of the data independently entered by two reviewers. It also facilitated the generation of the summary evidence tables directly from the collated dataset. As no data required manual copying into a different format after it has been entered by the reviewer, we believed this would reduce error in handling of the data. For each question, two reviewers extracted all data independent of each other. The methods support team produced tables displaying the extracted data for both reviewers by question. The member of the methods support team checked all the data and any discrepancies were discussed and resolved by consensus, and if no consensus could be reached, disagreements were resolved by an independent referee. From these tables we produced merged consensus evidence tables for informing the recommendations. The summary evidence tables are available from Supplement 6—Summary evidence tables.

The risk of bias of the included studies was evaluated using various validated checklists as recommended by the Cochrane Collaboration. These were Assessing the Methodological Quality of Systematic Reviews (AMSTAR) for systematic reviews [7], the Cochrane Risk of Bias tool 2.0 for RCTs [8], the Newcastle-Ottawa scale for cohort and case–control studies [9] and Quality Assessment of Diagnostic Accuracy Studies (QUADAS) for diagnostic test accuracy studies [10]. Data were compiled centrally by ERBP's methods support team.

Rating the quality of the evidence for each outcome across studies

The evidence for outcomes on therapeutic interventions from the included systematic reviews of randomized trials was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox developed by the international GRADE working group [11]. In accordance with GRADE, the GDG initially categorized the quality of the evidence for each outcome as high if it originated predominantly from RCTs and low if it originated from observational data. The quality of the evidence was subsequently downgraded one or two levels if results from individual studies were at serious or very serious risk of bias, there were serious inconsistencies in the results across studies, the evidence was indirect, the data were sparse or imprecise or publication bias was thought to be likely. If evidence arose from observational data, but effect sizes were large, then 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, the quality of the evidence would be upgraded (Table 2). Uncontrolled case series and case reports automatically received downgrading from 'low' to 'very low' level of evidence for risk of bias, so that no further reasons for downgrading were checked. By repeating this procedure, an overall quality of evidence for each outcome and each intervention was obtained. See Table 3 for the list of definitions [12].

Formulating statements and grading recommendations

Recommendations

After the summary tables were prepared and the evidence assessed, recommendations were formulated and graded. Recommendations can be in favour of or against a certain strategy. The GDG drafted the recommendations based on their interpretation of the available evidence. Judgements around four key factors determined the strength of the recommendation: the balance between desirable and undesirable consequences of alternative therapeutic or diagnostic strategies, the quality of the evidence and the variability in values and preferences. Formal decision or cost analysis was not conducted. In accordance with GRADE, the strength of the recommendations was classified as strong, coded '1', or weak, coded '2' (Table 4) [11]. The strength of a recommendation is determined not only by the certainty of evidence, but also by other, often complex judgements regarding the size of the net medical benefit, values and preferences and costs. Individual statements were made and discussed to reach a group consensus.

Advice for clinical practice

An additional category of ungraded statements was used for areas where formal evidence was not sought and statements were based on common sense or expert experience alone. These were termed 'advice for clinical practice' to differentiate them from graded recommendations and do not hold an indicator for the quality of the evidence. Advice for clinical practice is only for improving practical implementation. It contains some elaboration on one of the statements, clarifying how the statement can be implemented in clinical practice. The ungraded statements were generally written as simple declarative statements but were not meant to be stronger than level 1 or 2 recommendations.

Table 3. Grade for the overall certainty of evidence

Grade	Quality level	Definition
A	High	We are confident that the true effects lie 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

Adapted from Guyatt *et al.* [11].

Table 2. Method of rating the certainty of the evidence for an outcome

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	Risk of bias	Large effect	High (four plus: ++++)
	−1 Serious	+1 Large	Moderate (three plus: +++)
Observational studies = low	−2 Very serious	+2 Very large	Low (two plus: ++)
	Inconsistency	Dose response	Very low (one plus: +)
	−1 Serious	+1 Evidence of a gradient	
	−2 Very serious	All plausible confounding	
	Indirectness	+1 Would reduce a demonstrated effect	
	−1 Serious	+1 Would suggest a spurious effect	
	−2 Very serious	when results show no effect	
	Imprecision		
	−1 Serious		
	−2 Very serious		
	Publication bias		
	−1 Likely		
	−2 very likely		

Adapted from Balshem *et al. J Clin Epidemiol* 2011; 46: 401–406 [12].

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 as a 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	Policymaking will require substantial debate and involvement of many stakeholders

Adapted from Guyatt *et al.* [11].

Writing rationale

Recommendations and advice for clinical practice for each of the clinical questions were collated in separate chapters structured according to a specific format. Each question resulted in one or more specific boxed statements. Within each recommendation, the strength was indicated as level 1 o level 2 and the quality of the supporting evidence as A, B, C or D as prescribed by the GRADE methodology (Tables 3 and 4) [11]. These statements are followed by advice for clinical practice and the rationale. The rationale contains a brief section with relevant background and justification of the topic, followed by a short narrative review of the evidence and finally a justification of how the evidence was translated in the recommendations made. When areas of uncertainty were identified, the GDG considered making suggestions for future research based on the importance to patients or the public and on ethical and technical feasibility. Finally, each chapter provides an overview of recommendations made by other guideline bodies. The list is not meant to be exhaustive, but rather is intended to provide a concise overview of other recommendations made. Any grading was reprinted as reported in the respective clinical practice guideline. These may and do differ for some organizations from the GRADE system used for the ERBP guideline development process. The reader is referred to the original publication for further details regarding the grading system for coding individual recommendations.

Internal and external review

Internal review

Both the VAS and ERBP nominated experts in vascular access and members of their governance bodies. Internal referees were asked to complete a standardized internal review survey online (see Supplement 7—Internal review). Referees were asked whether statements were clear, implementable and to what extent they agreed with the content on a scale of 1–5. These scores were averaged and colour-coded from red (1) to green (5) to help visualize problematic areas. In addition, internal reviewers were asked to comment on the statements and the rationale within free-text fields. All these comments and suggestions were discussed with the GDG group. For each comment

or suggestion, the GDG evaluated if the statement needed to be adapted, again considering the balance between desirable and undesirable consequences of the alternative management strategies, the quality of the evidence and the variability in values and preferences.

External review

The draft guideline was posted on the ERBP website and the public was invited to comment using the same standardized review form as was used for the internal review process. Anyone was invited to comment, but reviewers had to provide basic information to identify their background or stakeholder position. The public consultation period lasted for 4 weeks to ensure adequate time for responses. In addition to public consultation, the guideline was sent to the council of the ERA-EDTA, the VAS, Kidney Diseases: Improving Global Outcomes (KDIGO), Kidney Health Australia – Caring for Australasians with Renal Impairment (KHA-CARI), the National Institute for Health and Care Excellence (NICE), the European Dialysis and Transplant Nurses Association/European Renal Care Association and the European Society of Vascular Surgery (ESVS) for review. Referees used the same standardized review form as for the internal review process. All comments were summarized by ERBP's methods support team and provided to the guideline group chair to determine the appropriate course of action as part of finalizing the guidelines. As part of the final approval process, the ERBP chair and co-chair ensured that all comments had been appropriately addressed.

Timeline and procedure for updating the guideline

ERBP aims to update its clinical practice guidelines at least every 5 years. New evidence requiring additional recommendations or changes to existing statements could instigate an earlier update. At least every 5 years, ERBP's methods support team will aim to update its literature searches. Relevant studies will be identified and their data will be extracted using the same procedure as for the initial guideline. During a 1-day meeting, the GDG will decide whether the original statements require updating. ERBP will aim to publish an updated version of the guideline online.

CHAPTER 1. MEDICAL TREATMENTS FOR PROMOTING AV FISTULA MATURATION

Recommendations

We suggest any decision to give aspirin, ticlopidine or clopidogrel in adults with end-stage kidney disease during the first 2 months after arteriovenous fistula creation for the sole purpose of improving maturation must balance a reduction in thrombosis against uncertain effects on maturation and bleeding. (2C)

We suggest any decision to give perioperative heparin in adults with end-stage kidney disease during arteriovenous fistula creation must balance an increase in arteriovenous fistula patency at 1 month against an important increase in bleeding complications. (2C)

We suggest any decision to apply far infrared therapy in adults with end-stage kidney disease during the first 3 months after arteriovenous fistula creation must balance a possible reduction in thrombosis against uncertain effects on maturation and bleeding. (2C)

There are insufficient randomized controlled trial data to make a recommendation for ticagrelor, prasugrel, dipyridamole, sulphinpyrazone warfarin or other oral anticoagulants, fish oil, statins, vonapanitase, glyceryl trinitrate, iontophoretic injection of *Salvia miltiorrhiza* or prednisolone for improving arteriovenous fistula maturation in adults with end-stage kidney disease. (-D)

Advice for clinical practice:

- Do not stop mono-antiplatelet treatment in adults undergoing AV access creation.

Rationale

- **Background**

Non-maturation is defined as a process leading to a newly created AV access that cannot be used for haemodialysis; it does not apply to AV grafts. Non-maturation may cause various problems, such as a need for reintervention or for a temporary central venous haemodialysis catheter to be inserted. An AV fistula may fail because of thrombosis or because of the feeding artery or the draining vein failing to enlarge. Medications that influence these processes could result in improvement of maturation, provided their adverse effects do not counterbalance their benefits either locally or systemically. For instance, anticoagulant and antithrombotic agents may prevent clotting, but they may also cause bleeding. Vasoactive agents may prevent vasospasm, stimulate vasodilation and increase blood flow in the newly created AV fistula, but they may also lower systemic blood pressure. As maturation problems in the first months may result from different pathophysiological mechanisms rather than patency problems in the longer term, the two issues are discussed in two different chapters of this guideline. The current chapter specifically covers AV fistula maturation. Chapter 8 covers long-term patency of AV fistulas and AV grafts.

- **Summary of the evidence**

(Supplement 3 | Review questions – PICO format—Chapter 1)
(Supplement 4| Search strategies—Chapter 1)
(Supplement 5| Study selection flow diagrams—Chapter 1)
(Supplement 6| Summary evidence tables—Chapter 1)

We identified seven systematic reviews of RCTs assessing benefits and harms of various medical adjuvant treatments to increase overall patency of AV fistulas and AV grafts [13–19]. All these reviews were judged to be of moderate to high quality with AMSTAR scores of 8–10/11. The reviews included studies measuring maturation outcomes after 6–12 weeks and patency outcomes measured several months later. Unfortunately the meta-analyses did not separate studies reporting maturation outcomes from studies reporting longer-term patency outcomes. The next paragraph describes the nature and the content of the included systematic reviews that were used to identify relevant randomized trials. Based on group consensus, for this chapter we chose to only consider RCTs and meta-analyses measuring patency outcomes before or at 12 weeks as an arbitrary cut-off to distinguish maturation from long-term patency and only in those studies assessing AV fistulas.

The first was a Cochrane systematic review with content assessed as being up to date through 23 March 2015 [14]. It included 15 RCTs comprising 2230 participants at the time of access creation. Seven trials included patients with an AV fistula, six with an AV graft and two with either an AV fistula or an AV graft. All but one enrolled participants at the time of AV access creation [20]. Tested medical interventions included aspirin, ticlopidine, dipyridamole, dipyridamole plus aspirin, warfarin, fish oil, clopidogrel, sulphinpyrazone and human type I pancreatic elastase (vonapanitase). Studies mostly included participants of all ages and follow-up ranged from 1 to 18 months after AV access insertion. Most studies only assessed AV access thrombosis as the primary outcome of interest.

The second was also a Cochrane systematic review, which specifically covered antiplatelet agents to prevent vascular access failure and other outcomes in people with chronic kidney disease (CKD). Its content was assessed as being up to date through 24 January 2011 [15]. The review included 12 RCTs assessing the effect of antiplatelet agents in a newly created AV access and another 9 in an already functioning AV access. Nine of these were also included in the first review [14]. Of the remaining three studies, the largest was excluded [21]. The RCT

tested dipyridamole plus aspirin versus placebo, but included participants in whom aspirin was started prior to study inclusion and did not require discontinuation in the placebo group. The other two did not contribute to any of the meta-analyses of interest [22, 23]. Medical interventions included aspirin, ticlopidine, dipyridamole, dipyridamole plus aspirin, clopidogrel and sulphinpyrazone [15]. The Cochrane review resulted in a derivative review assessing only vascular access outcomes [13].

Four other systematic reviews each assessed a specific treatment, such as fish oil [16], far infrared therapy [17, 18] or intra-operative anticoagulation during AV access formation [19].

In addition to these reviews, we identified six RCTs published after 2013 and not included in any of the considered systematic reviews, assessing various adjuvant medical treatments for improving AV access patency [24–29].

Antiplatelet agents

Palmer *et al.* found that, overall, antiplatelet agents seemed to reduce AV fistula thrombosis at 8 weeks, although the certainty of the evidence was compromised by risk of bias in the underlying studies and serious imprecision, with a total sample size below the optimal information size {five RCTs; $n = 1005$; relative risk [RR] 0.43 [95% Confidence Interval (CI) 0.26–0.73]; I square (I^2) = 25%} [13]. Effects on AV fistula maturation failure were uncertain [two RCTs; $n = 794$; RR 0.57 (95% CI 0.13–2.51)]. Definitions for AV fistula maturation varied widely.

Aspirin

One RCT compared 500 mg of aspirin versus placebo given the day before until 28 days after construction of a Brescia–Cimino fistula in 92 patients [30]. Aspirin reduced AV fistula thrombosis at 1 month by 81% [$n = 92$; RR 0.19 (95% CI 0.04–0.81)]. The sample size was low and risk of bias unclear. Numerically, more people complained of gastric pain and epistaxis in those taking aspirin, but the CI was wide [11% versus 4% (95% CI 4% fewer to 18% more)]. The risk of gastrointestinal bleeding or wound haematoma was the same in both groups (4%).

Ticlopidine

Three RCTs compared ticlopidine 250 mg twice daily versus placebo for 1 month in 339 patients undergoing AV fistula creation [14]. By combining results, it appeared ticlopidine might reduce AV access thrombosis, but the certainty of the evidence was low due to risk of bias in the primary studies and serious imprecision [three RCTs; $n = 339$; odds ratio (OR) 0.45 (95% CI 0.24–0.85); $I^2 = 20$%]. There was no clear information about adverse events.

Clopidogrel

Seventy-five milligrams of clopidogrel was compared versus placebo in two RCTs, indicating it may reduce AV fistula thrombosis up to 6 weeks after AV fistula creation [2 RCTs; $n = 959$; OR 0.40 (95% CI 0.13–1.19); $I^2 = 54$%)] [14]. The certainty of the evidence was low however, due to risk of bias in both studies, and serious imprecision, with the CI spanning the line of no effect. Both studies indicated a similar proportion of bleeding events and mortality.

We identified an additional RCT including 96 participants randomized to either clopidogrel plus a prostacyclin analogue (epoprostenol) or placebo for 7 days before and up to 1 year after surgery [24]. The investigators described an important improvement in fistula maturation—in this study defined as a blood flow >300 mL/min or velocity >70 cm/s—for those taking dual anti-platelet treatment (87% versus 67%), but the certainty of the evidence was low due to unclear denominators. The investigators reported no bleeds, but the external validity of the results was considered low because of stringent exclusion criteria. Only 25% of all people set to undergo AV fistula creation were finally enrolled.

Dipyridamole and sulphinpyrazone

There were no studies assessing outcomes at 12 weeks for dipyridamole or sulphinpyrazone.

Anticoagulants

Warfarin or other oral anticoagulants

There were no studies assessing outcomes at 12 weeks for warfarin or other oral anticoagulants.

Perioperative anticoagulants

We identified one systematic review on systemic intra-operative anticoagulation during AV access formation [19]. The review included three randomized trials that used systemic heparin during AV fistula creation and found the intervention increased AV fistula patency at 6 weeks, but the quality of evidence was low due to a high risk of bias in the underlying studies and large imprecision of the summary effect estimate [three RCTs; RR 0.57 (95% CI 0.33–0.97)]. Importantly, systemic heparin increased bleeding events in all access trails including an additional RCT with both AV fistulas and grafts [four RCTs; $n = 411$; RR 7.18 (95% CI 2.40–21.40)].

Another RCT assessed the combined use of heparin and anisodamine (an anticholinergic and α1 adrenergic receptor antagonist used in the treatment of acute circulatory shock in China) given immediately after AV fistula creation and found it reduced the risk of early thrombosis in AV fistulas compared with placebo or heparin alone, but the study was at high risk of bias [31].

Other

Fish oil—omega 3 polyunsaturated fatty acids

We identified a systematic review comparing fish oil versus placebo or no treatment, with content assessed as being up to date through January 2017 [16]. In addition to two RCTs identified by Tanner and Da Silva [14], this review included four additional RCTs assessing dosages ranging from 3 g three times weekly to 6 g daily. Only one study assessed the effect in AV fistulas and the others were in AV grafts [32]. Outcomes were measured at 12 months; there were no data on outcomes measured within the pre-specified time period of 12 weeks.

Statins

There were no studies assessing outcomes at 12 weeks for statins.

Vonapanitase—recombinant type I pancreatic elastase

Two RCTs assessed the effect of recombinant type I pancreatic elastase applied directly to the adventitia of the AV vessels at the time of AV fistula creation [14]. For AV fistulas there was

no difference in unassisted maturation at 6 weeks, regardless of the definition of maturation. At 3 months, more AV fistulas had matured in the group that had received vonapanitase, but a large loss to follow-up and multiple testing issues reduced the certainty of the evidence. Both studies listed several adverse events including local symptoms secondary to the creation of a new AV fistula, but according to the study authors, there were no significant differences between placebo and recombinant type I pancreatic elastase–treated participants.

We found an additional trial that randomized 313 people to locally dripped vonapanitase or placebo at the time of AV fistula creation. The report provided no outcome data for maturation [25].

Far infrared therapy
We found one systematic review on far infrared treatment for increasing the patency of AV fistulas, with the content assessed as being up to date through January 2017 [18]. The review included 21 RCTs comprising 1899 participants at the time of AV access creation. Although not clearly reported, it appears all studies included participants with an AV fistula. Investigators used different techniques for delivering far infrared rays; most commonly a device generating wavelengths between 5 and 25 mm set at a height of 20 cm above the AV fistula with a treatment time of 40 min during each haemodialysis session. Most studies assessed blood volume, vessel diameter or primary patency at various time points up to 1 year after fistula creation. We awarded the review an 8 of 11 score on the AMSTAR checklist, limited by the absence of a registered protocol, unclear search methods and incomplete reporting of excluded studies.

Eight studies assessed outcomes earlier than or at 3 months after AV fistula creation, but only four could be included in the meta-analysis.

Although the certainty of the evidence was compromised by the small number of studies and research groups these data were derived from, the risk of bias in the underlying studies and the heterogeneity in the results, overall, far infrared therapy modestly increased blood flow [three RCTs; $n = 328$; mean difference (MD) 57.2 (95% CI 9.1–105.2); $I^2 = 93\%$]. In addition, two trials comprising 180 participants showed results for AV fistula occlusion rates. Overall, therapy with far infrared radiation decreased AV fistula occlusion rates [two RCTs; $n = 180$; RR 0.29 (95% CI 0.06–1.35); $I^2 = 0\%$]. There was no evidence of heterogeneity in these trials.

Cholecalciferol
One RCT randomized 52 participants to receive either 200 000 IU oral cholecalciferol or matching placebo [26]. High-dose cholecalciferol had uncertain effects on AV fistula maturation at 6 months [one RCT; $n = 52$; RR 0.79 (95% CI 0.45–1.38)].

Glyceryl trinitrate
Glyceryl trinitrate was tested in a placebo-controlled clinical trial including 200 participants [27]. An active or a placebo patch was applied 5 cm proximal to the AV anastomosis immediately after completing the surgical procedure and left in place for 24 h. The trial provided moderate-certainty evidence for no meaningful difference in patency at 6 weeks or change in venous diameter as a surrogate for maturation. There were no major differences in side effects, resulting in similar numbers dropping out in both groups, but no formal analysis was presented.

Iontophoretic intradermal injection of Salvia miltiorrhiza
We found one Chinese trial randomizing 20 participants who had undergone radiocephalic AV fistula creation to iontophoretic intradermal injection (a technique that uses low-level current to drive charged compounds across the skin) of *Salvia miltiorrhiza*, a Chinese root that contains salvianolic acid B as a potentially vasculoprotective and anti-inflammatory agent [28]. It found the experimental treatment increased the number of successfully matured AV fistulas by 35% at 1 month [one RCT; $n = 20$; RR 1.07 (95% CI 1.06–2.73)]. We considered the evidence of low certainty because of the sample size and concerns about changes in the primary outcome, originally to be measured at 6 months rather than 1 month.

Prednisolone
Finally, we identified a protocol for an RCT set to assess the effect on radiocephalic AV fistula maturation of intravenous liposomal prednisolone 150 mg given twice after surgery (days 1 and 14) [29]. To the best of our knowledge, results of this study were not yet available upon publication of the guideline.

- ### Translation of the evidence into recommendations

Interpreting the available data in the context of maturation is challenging for various reasons. Most studies assessing antiplatelet agents report on short-term vascular access thrombosis rather than successful dialysis. This is problematic, as a reduction in AV fistula thrombosis does not necessarily translate into improved maturation. It is true that fistula thrombosis precludes successful use of the AV access for dialysis, but if the current treatments, predominantly aimed at reducing platelet aggregation and coagulation, increase the risk of bleeding, a local haematoma may cause irremediable loss of the access even before it has ever been used. In addition, access thrombosis may be treated using endovascular or surgical techniques and antiplatelet agents have uncertain effects on reducing interventions for assisting maturation.

Authors use different definitions for the concept of AV fistula maturation, and that also complicates interpretation of the data. Some investigators treat maturation as a pre-cannulation outcome based on surrogate measures of vessel diameter and blood flow. Whether or not an AV fistula is successfully used for dialysis later is often ignored. The GDG judged that an improvement in maturation using pre-cannulation definitions would not be enough to issue a supporting recommendation.

Lastly, many studies report primary unassisted patency after 1 year and do not distinguish between the maturation phase and long-term patency of a matured AV fistula. As harmful effects of treatments may change over time, differences in primary unassisted patency may well be non-proportional too. In other words, what benefits the maturation process may be different from what benefits the matured AV fistula.

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The GDG felt that for a positive recommendation, interventions had to improve successful use of the AV access. We judged that in the absence of evidence for a positive effect of successful cannulation, evidence for an effect on intermediate outcomes such as AV access thrombosis would not be enough to advocate treatment. But rather than formulating a neutral statement, the group also wanted to highlight existing ambiguity by communicating the items to be weighed in decision making.

After initial recommendations were drafted, the group decided to add a statement advising not to stop antiplatelet treatment in adults already treated with antiplatelet agents for other reasons. Although this chapter did not directly aim to answer that question, it was felt that the current evidence supporting continuation of antiplatelet treatment in adults undergoing non-cardiac surgery would tip the uncertain benefit for maturation in favour of continuing treatment [33].

Other guidelines on this topic

ESVS [34]

We suggest individualizing the indication of antiplatelet agents to prevent thrombosis of native AV fistulas, given that although a reduction in the risk of thrombosis was demonstrated, the adverse effects have not been well studied.

Grupo Español Multidisciplinar del Acceso Vascular (GEMAV) [35]

We suggest that antiplatelet therapy for thrombosis prophylaxis of native AV fistula be indicated on a case-by-case basis, because although it shows a decrease in the risk of thrombosis, we believe that adverse effects have not been studied with sufficient accuracy.

Canadian Society of Nephrology (CSN), KDIGO, National Kidney Foundation Kidney Diseases Outcomes Quality Initiative (NKF-KDOQI), KHA-CARI and NICE provide no current recommendations on this topic.

Suggestions for future research

Large heterogeneity in reported trial outcomes limits our ability to interpret the evidence correctly. Therefore we welcome initiatives like Standardized Outcomes in Nephrology–Hemodialysis (SONG–HD), which aim to develop standardized outcomes in vascular access [4]. Implementing consensus outcomes in future trials will be the key for improving the ability of systematic reviewers and guideline developers to better assess the benefits and harms of proposed treatments. Routinely collected data on vascular outcome data in registries might be of benefit to assess strategies and practices.

Most studies assess AV access thrombosis rather than AV access maturation or the ability to perform dialysis using a newly created AV access. In the presence of an adverse effect that could counter the intermediate outcome, a trial including maturation would be informative. Such a trial would likely capture other causes of maturation failure, which are currently not taken into consideration.

CHAPTER 2. SURGICAL AND ENDOVASCULAR INTERVENTIONS FOR PROMOTING AV FISTULA MATURATION

Recommendations

> We suggest using regional block anaesthesia rather than local anaesthesia for arteriovenous fistula creation in adults with end-stage kidney disease. (2C)
>
> We suggest there is insufficient evidence to support end-of-vein to side-of-artery over side-of-vein to side-of-artery anastomosis for arteriovenous fistula creation in adults with end-stage kidney disease. (2C)

Advice for clinical practice:

• None.

Rationale

• **Background**

Non-maturation is defined as a process leading to a newly created AV access that cannot be used for haemodialysis; it does not apply to AV grafts. Non-maturation may cause various problems, such as a need for reintervention or for a temporary central venous haemodialysis catheter to be inserted. An AV fistula may fail because of thrombosis or because of the feeding artery or the draining vein failing to enlarge.

Physical interventions that influence these processes may result in improvement of maturation, provided their adverse effects do not counterbalance their benefits. Such interventions include different types of anaesthetic procedures, balloon-assisted maturation, use of devices to connect the artery and the vein, ligation of accessory draining veins, dilatation of the main draining vein or specific surgical techniques to make the anastomosis.

• **Summary of the evidence**

(Supplement 3| Review questions—PICO format—Chapter 2)
(Supplement 4| Search strategies—Chapter 2)
(Supplement 5| Study selection flow diagrams—Chapter 2)
(Supplement 6| Summary evidence tables—Chapter 2)

Two systematic reviews [36, 37] and 16 RCTs assessing eight different interventions were identified [38–53]. One systematic review and meta-analysis included six studies with 870 participants comparing the effects of regional versus local anaesthesia on several AV fistula outcomes [36]. With respect to maturation, the authors found that regional block anaesthesia produced an average 25 mL/min increase in blood flow [two RCTs; $n = 78$; MD = 25.08 mL/min (95% CI 19.40–30.76); $I^2 = 53\%$] and a 22% increase in primary unassisted patency [three RCTs; $n = 246$; RR 1.22 (95% CI 1.08–1.37); $I^2 = 45\%$]. Conversely, there were no important differences for AV fistula thrombosis and primary fistula failure. Certainty of the evidence was low and the number of studies included in the pooled analysis was limited.

Five RCTs compared regional block anaesthesia versus local site anaesthesia [38–42]. The first RCT included 126 participants and reported better outcomes with block anaesthesia for primary patency at 3 months [$n = 126$; OR 3.3 (95% CI 1.4–

7.6)] and immediate patency at the time of hospital discharge [$n = 126$; OR 4.3 (95% CI 1.5– 15.5)] [38].

In the second RCT including 60 patients, the authors found no meaningful differences in primary patency after brachial plexus block or local infiltration anaesthesia [39]. They did report wider diameters of the AV fistula vein and improved haemodynamic parameters, including blood flow at 6 months, for brachial plexus block. However, no actual numbers and no further details on outcome assessment were provided, thereby limiting our ability to assess the certainty of these findings.

The third RCT found no differences in thrombosis, maturation, time to maturation or time to first cannulation after vertical infraclavicular block or local anaesthesia in 123 individuals undergoing creation of a first AV fistula [40]. However, the study did not report numeric data and specific details on study design and conduct were missing. The remaining two studies had a smaller sample size, including 60 and 34 participants each, and described improvements in surrogate outcomes in the group that received regional block anaesthesia [41, 42]. The first of the two reported improved blood flow for patients in the infraclavicular block group but recorded similar access failures in both groups [41].

One RCT assessed whether stellate ganglion blockade with ropivacaine given for 7 days after surgery improved outcomes after radiocephalic fistula creation [43]. In comparison with usual care, stellate ganglion blockade reduced the frequency of thrombosis up to 24 h after surgery from eight to two events ($n = 50$; denominators not reported). Time until maturation was also shorter in the intervention group (41 ± 7 versus 77 ± 11 days). However, the number of participants in whom the outcome was assessed was not reported and definitions of maturation were variable.

A recent systematic review and meta-analysis collecting data from seven studies and 986 participants found no differences in AV fistula patency at 3, 6, 12 and 24 months after an end-of-vein to side-of-artery or side-of-vein to side-of-artery surgical approach [37]. The overall outcome certainty of this review was very low due to the small number of studies included, most of which were observational and non-randomized trials. Three RCTs, two of which were included in the review, compared a side-of-vein to side-of-artery anastomosis versus an end-of-vein to side-of-artery anastomosis [44–46]. The first RCT included 71 participants and reported no difference in access patency and fistula thrombosis at 3 and 9 months [44]. The second RCT enrolled 60 participants and found no difference in patent fistulas at 6 months [45]. The third enrolled 336 adults and found no meaningful differences in patency at 6 months [46].

No study addressed end-of-vein to end-of-artery anastomosis or other newer techniques that are less often performed.

There were three RCTs that compared clips versus sutures in performing an end-to-side anastomosis for AV fistula creation [47–49]. All three found uncertain effects on primary patency or AV fistula maturation.

One RCT compared ligation versus no ligation of the distal vein after side-to-side anastomosis in 60 patients [50]. The investigators reported 90% access survival at 90 days in the intervention group versus 83% in the control group (P-value (P) > 0.05). However, important aspects of study design and conduct were not reported, making any inference problematic.

One RCT assessing the type of suture was identified [51]. The investigators compared continuous versus interrupted suture of the AV fistula in 40 participants. Access survival at 2 years was found to be similar in both groups.

A small RCT comparing one-stage versus two-stage procedures for creating a brachiobasilic vein AV fistula found no differences in primary and secondary patency or in non-thrombotic postoperative complications [52]. Conversely, the transposed brachiobasilic vein fistula maturation rate after one-stage procedures was lower compared with the maturation rate after two-stage procedures (33% versus 100%; $P = 0.01$), which led to premature termination of the trial. However, serious limitations in the trial design, hamper meaningful inference.

Finally, a small trial including 40 participants compared balloon angioplasty of cephalic veins with a diameter ≤ 2 mm with hydrostatic dilatation and ligation of collateral veins [53]. The trial was considered at high risk of bias due to its small sample size, incomplete analysis, lack of outcome definitions, omitting of indications for interventions to prevent loss of access and unclear blinding procedures.

• Translation of the evidence into recommendations

RCTs provided low to medium-certainty evidence overall. However, lack of standardization in outcome reporting made inference particularly difficult.

Five RCTs were found to provide evidence for block anaesthesia compared with local anaesthesia. Only one RCT was considered at low risk of bias, while the other four were considered at high risk of bias. All studies suggested the benefit of using regional block anaesthesia, but there were several considerations that limited the strength of the recommendation to a discretionary one. First, the risk of bias in these studies was generally high and outcome data were mostly limited to surrogate outcomes. Second, switching from local anaesthesia to regional block anaesthesia could unwantedly complicate the procedure, may increase costs and may possibly even delay the access procedure. Third, the main advantage of regional block anaesthesia was felt to be vein dilation, which could also be achieved by other means, such as creating warm conditions.

For the comparison of end-of-artery to side-of-vein versus side-to-side anastomosis, there were two reports, which were considered at medium risk of bias, with available results insufficient to recommend one type of anastomosis over another but equally insufficient to indicate equipoise between the two.

Three reports were available on the comparison of clips versus sutures for AV fistula creation. Sample sizes were small and the studies had important shortcomings, leaving important uncertainty as to the benefit of one technique over the other. Considering this uncertainty, the GDG felt that technique choice should be left to the surgical team based on experience and personal preference. It was felt any recommendation would confuse the end user rather than clarify any ambiguity, such that no recommendation was formulated.

The guideline group considered the other trials to be preliminary at best, providing a limited basis for formulating a recommendation in either direction. Hence they decided to refrain from making statements related to vein ligation, suture

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technique, angioplasty or techniques for creating a brachiobasilic AV fistula.

Other guidelines on this topic

ESVS [34]

Regional anaesthesia should be considered in preference to local anaesthesia for vascular access surgery because of a possible improvement in access patency rate..

The CSN, GEMAV, KDIGO, NKF-KDOQI, KHA-CARI and NICE provide no current recommendations on this topic.

Suggestions for future research

The available reports do not resolve the uncertainty about long-term effects and only do so incompletely with regards to side effects. New multicentre trials comparing regional block anaesthesia with other anaesthetic techniques would help strengthen the evidence base. Larger trials comparing different anastomotic techniques are also advocated. Standardization of outcomes and estimation of adequate sample sizes are needed.

CHAPTER 3. SURGICAL AND ENDOVASCULAR INTERVENTIONS FOR NON-MATURING AV FISTULAS

Recommendations

> We suggest there is insufficient evidence to support open surgical over endovascular interventions as the preferred treatment for non-maturing arteriovenous fistulas in adults with end-stage kidney disease. (2D)

Advice for clinical practice:

- Decisions on how to treat non-maturing AV fistulas are likely best based on local resources, experience and success rates.
- Institutions likely benefit from building a dedicated multidisciplinary vascular access team with clinical experience in various techniques available for non-maturing AV fistulas.

Rationale

- **Background**

To allow successful use of a newly created AV fistula, the outflow vein needs to enlarge sufficiently to allow insertion of one or two needles and sustain the blood flow required for adequate dialysis. Unfortunately, up to a quarter of newly constructed AV fistulas fail to mature [54]. The outflow vein may not enlarge for many reasons, some of which can be remedied by surgical or radiological endovascular interventions. If unsuccessful, however, then such treatments may reduce quality of life by increasing the number of interventions, increase workload and inflate costs. This may also delay creation of an alternative permanent AV access.

- Summary of the evidence

(Supplement 3| Review questions—PICO format—Chapter 3)
(Supplement 4| Search strategies—Chapter 3)
(Supplement 5| Study selection flow diagrams—Chapter 3)
(Supplement 6| Summary evidence tables—Chapter 3)

No RCTs were identified comparing the benefits or harms of surgical or radiological endovascular interventions versus one another or versus no treatment.

A recent narrative review that included an attempt at comprehensively searching multiple databases found 28 non-randomized uncontrolled studies recording clinical success, 1-year primary patency or 1-year secondary patency of various surgical and radiological endovascular techniques (Table 5 and 6) [54].

Thirteen studies used balloon angioplasty, defined as any technique, whereby a catheter is inserted in the AV fistula to dilate a stenotic vessel, mostly at the juxta-anastomotic or the draining vein. It led to clinical success in 43–97% of procedures, with 1-year primary unassisted patency of 28–72% and 1-year secondary patency of 68–97%. Rupture of the venous wall occurred in ∼15% of cases, the majority of which could be managed with prolonged balloon inflation. In two studies, clinicians dilated diseased radial arteries feeding a radiocephalic AV fistula, which resulted in 1-year primary unassisted patency of 65 and 83% and 1-year secondary patency of 86 and 96%. Balloon-assisted maturation is a technique whereby the vein of an AV fistula is subjected to staged, serial, long-segment balloon angioplasty dilations (e.g. every 2 weeks) until it reaches the desired diameter and flow rate. It was investigated in four studies and was considered clinically successful in 55–89% of interventions, but none of the studies provided data for 1-year primary unassisted or secondary patency. Adverse effects, including local

Table 5. Summary of case series assessing the effect of radiological endovascular interventions for non-maturing AV fistulas

Technique	Target lesion	No. of studies	No. of patients	Clinical success (range) (%)	1-year primary patency (%)	1-year secondary patency (%)
Balloon angioplasty	Stenosis in draining vein or juxta-anastomotic region	14	657	43–97	28–72	68–97
Balloon angioplasty	Stenosis in arterial inflow	2	99	91–98	65–83	86–96
Balloon-assisted maturation	Non-dilating veins	4	156	55–89	–	–
Endovascular accessory vein obliteration	–	1	34	65	–	–
Balloon angioplasty + endovascular accessory vein obliteration	Stenosis in draining vein or juxta-anastomotic region	6	538	78–92	62	68–94
Balloon angioplasty+ stent deployment	Long segment stenosis in draining vein	1	12	100	65	72

Table 6. Summary of case series assessing the effect of surgical interventions for non-maturing AV fistulas

Technique	Target lesion	No. of studies	No. of patients	Clinical success (range) (%)	1-year primary patency (%)	1-year secondary patency (%)
Proximal neo-anastomosis	Stenosis in juxta-anastomotic region	2	71	90	71–78	87–95
Accessory vein ligation	–	3	66	82–89	–	75
Proximal neo-anastomosis + accessory vein ligation	Stenosis in juxta-anastomotic region	2	62	87–94	68	85–86

bleeding, rupture and thrombosis, occurred frequently (>40% of procedures) [55]. Endovascular accessory vein obliteration is a procedure whereby a metal coil is inserted in a collateral competing vessel to increase blood flow through the AV fistula. It can be performed as an isolated intervention or in addition to balloon angioplasty, with variable results. Finally, balloon angioplasty has been conducted in combination with stent deployment in cases of stenosis of long venous segments with moderate 1-year primary and secondary patency (65 and 72%, respectively).

Surgical intervention usually involves (i) proximal AV neo-anastomosis, defined as any technique, whereby a new connection is created between the inflow artery and outflow vein; (ii) accessory vein ligation, defined as any procedure whereby collateral competing vessels are tied to increase blood flow through the AV fistula; or (iii) a combination of both. One-year patency in uncontrolled studies varies from 68 to 78% for primary patency and from 85 to 95% for secondary patency. Several other techniques for aiding AV fistulas that are failing to mature have been experimented with during the last 5 years, including radial artery deviation and reimplantation or placement of an internal or external anastomotic device. Individual studies are small and obtained success rates of similar magnitude to other surgical interventions.

A small retrospective study including 46 participants compared surgical proximal neo-anastomosis with endovascular intervention [56]. The group that had undergone surgical intervention had a cumulative AV fistula survival of 83% compared with 43% for those who had undergone an endovascular treatment. However, effect estimates were not adjusted for baseline patient and vessel characteristics. A second retrospective study that compared surgical proximal neo-anastomosis versus balloon angioplasty found similar results, with primary patency of 71% in the group treated with surgery versus 41% in the group treated with balloon angioplasty [57]. However, results for secondary patency were of similar magnitude and, again, results were not adjusted for baseline differences between the study groups. There was no information on the number of reinterventions.

- **Translation of the evidence into statements**

Several surgical and endovascular interventions are available to help non-maturing AV fistulas reach a stage where they can be used successfully for haemodialysis. Both surgical and endovascular procedures achieve moderate primary patency and rather good secondary patency at 1 year. The variability in outcome for both categories is large, probably due to differences in the study population, and perhaps also due to differences in expertise of the vascular access team. The trade-offs from aggressive efforts to maximize AV fistula maturation may be prolonged catheter use, as creation of an alternative permanent vascular access is delayed. Multiple reinterventions may be taxing for patients and ultimately reduce quality of life in comparison with rapid creation of an alternative access or even permanent catheter use. Many of these questions remain unanswered to date.

Also, data are limited to primary and secondary patency at 1 year and seldom provide insight into true longevity of the AV access. AV fistulas that require intervention before maturation have shorter secondary patency duration than those that mature without an intervention [58]. The cumulative AV fistula survival is markedly inferior in patients requiring two or more interventions to achieve maturation as compared with those requiring one or no intervention. In addition, AV fistulas requiring more than one intervention to achieve maturation need more interventions to maintain long-term patency once haemodialysis using that AV fistula is started [56].

Comparative studies between surgical and endovascular interventions are scarce, retrospective and uncontrolled for some of the baseline characteristics that may influence both the choice of procedure and outcome. With the data currently at hand, the guideline group felt the available evidence to be insufficient to suggest one approach over another.

It seems reasonable to assume that clinical multidisciplinary expertise in the absence of clear guidance may be even more important than it is for other areas. Building and nurturing a team of dedicated vascular access specialists may be what maximizes success. It allows team members to gain experience in the various techniques available and to monitor success as well as complications at a local level. In the absence of clear evidence that favours one intervention over another, or even comparative studies assessing the trade-offs and harms associated with interventions to aid the non-maturing fistula, at least having a structured approach may benefit outcomes.

Other guidelines on this topic

GEMAV [35]

We recommend a clinical check-up be performed at 4–6 weeks after creation to definitively detect a delay in or absence of AV fistula maturation from its creation to this moment and elective treatment proposed. We recommend confirming the suspected lack of maturation by Doppler ultrasound.

We suggest early treatment of the non-matured native AV fistula to favour maturation and to prevent thrombosis and definitive loss. We recommend percutaneous or surgical techniques not be used systematically to promote maturation of native AV fistulas.

We suggest surgery as the first treatment option (proximal reanastomosis) in native AV fistulas with maturation failure associated with juxta-anastomotic stenosis. In cases where this is not possible, endovascular treatment (percutaneous angioplasty) should be proposed.

We suggest significant accessory veins associated with maturation failure be disconnected by percutaneous ligation, surgical ligation or endovascular embolization with coils. We suggest endovascular treatment be used in the presence of stenosis and surgical treatment when there is no stenosis as the first option, given the lower complexity and health care costs.

We recommend angioplasty in cases of non-matured native AV fistulas with proximal venous stenosis.

We suggest angioplasty of the arterial stenosis when this is the cause of non-maturation of the AV fistula in cases in which the vascularization of the limb is not compromised.

The CSN, ESVS, KDIGO, NKF-KDOQI, KHA-CARI and NICE provide no current recommendations on this topic.

Suggestions for future research

Given the absence of comparative data, a randomized trial comparing surgical versus radiological endovascular interventions would be informative. Investigators should assess long-term outcomes and record the timing, type and incidence of interventions required to achieve both maturation and long-term access patency. Only centres experienced in both options should participate. Careful reporting of adverse events and patient quality of life will be instrumental to inform future guidance in this field.

CHAPTER 4. SELF-ADMINISTERED INTERVENTIONS FOR AV FISTULA MATURATION

Recommendations

We suggest that a standardized exercise programme involving hand and arm exercises may improve arteriovenous fistula maturation in adults with end-stage kidney disease. (2C)

There is insufficient evidence to support specific exercise programmes or physical interventions to promote arteriovenous fistula maturation in adults with end-stage kidney disease. (-D)

Advice for clinical practice:

- Involving patients more actively in preparing for haemodialysis may improve self-management skills and health literacy and thereby well-being.

Rationale

- **Background**

Successful maturation of a newly created AV fistula is essential to allow its use for adequate haemodialysis. Unfortunately the newly created AV fistula fails to mature in up to a quarter of cases, leading to additional invasive procedures and reduced quality of life. Interventions that ensure improved maturation would surely be welcomed by all. Simple interventions that can be performed by patients themselves, including hand exercises and self-surveillance, seem attractive, presuming they would cause fewer adverse events than medical or surgical interventions. Past guidance suggested performing isometric hand exercise before and following creation of the AV fistula, as it was thought to increase blood flow and, therefore, enlarge vein diameter [59]. The evidence base supporting these recommendations was patchy and required updating.

- **Summary of the evidence**

(Supplement 3| Review questions—PICO format—Chapter 4)
(Supplement 4| Search strategies—Chapter 4)
(Supplement 5| Study selection flow diagrams—Chapter 4)
(Supplement 6| Summary evidence tables—Chapter 4)

We identified three RCTs involving hand or other exercises to enhance maturation of newly created AV fistulas [60–62] and one RCT assessing a device developed to apply reliable intermittent pneumatic compression to the outflow veins [63].

We found no RCTs assessing other forms of patient education, patient behaviour or self-monitoring.

The first RCT compared simple exercises with opening and closing of fingers versus a structured exercise programme that included squeezing a tennis ball and exercising with a dumbbell and flex-band with a tourniquet positioned proximal to the AV fistula. In the per protocol analysis of 25 participants in both groups, 17 patients performing the simple exercises and 22 following the structured programme had matured fistulas 2 weeks after creation (P = 0.14) [60]. The study was considered at high risk of bias because of subjective outcome definition and inadequate random sequence generation.

The second RCT included 18 participants and compared the use of a handgrip versus a soft ball for hand-squeezing exercises. This study only reported surrogate outcomes such as the increase in vein diameter before and after exercising. The number of matured fistulas overall and within each group were not reported [61]. The trial was considered at high risk of bias because of selective outcome reporting and lack of information on important elements in the design and conduct of the study.

The third RCT included 72 participants who were randomized after proximal or distal AV fistula creation to either a structured programme, which consisted of repeated flexion and extension of the elbow and wrist in addition to opening and closing of the hand, or usual lifestyle without specific exercises [62]. After 1 month there were more people with a clinically mature AV fistula in the group that had exercised than in the group that had not (95% versus 81%; P = 0.07). Also, more AV fistulas were considered ultrasonographically mature among the people who had exercised than among those who had not (82% versus 74%; P = 0.45). Importantly though, results were not statistically significant and maturation definitions were based on clinical and radiological criteria rather than on successful dialysis. In addition, although an attempt was made to adequately randomize the participants due to sample size

restrictions, important imbalances existed between the groups that could have biased the results. In particular, there were fewer diabetic patients with peripheral vascular disease in the intervention group.

A final RCT assessed a new device developed to apply reliable intermittent pneumatic compression to the outflow veins [63]. The device consists of a miniaturized control unit attached to a wearable pneumatic cuff that inflates to a pressure of 60 mmHg, held for 20 s, and subsequently deflates to 10 mmHg for 55 s before the cycle repeats. Forty-eight participants were randomized to either the real or a sham device 1 week after successful AV fistula creation and were asked to wear the device 6 h a day for 4 weeks. After 1 month there was a statistically significant 20% greater increase in venous diameter 5 cm proximal to the AV anastomosis for the participants in the experimental group. At 10 cm, the average difference was 7% and was no longer statistically significant and at 15 cm there was no difference between the groups. There was no information on maturation. There were no important adverse events reported in the experimental group.

- **Translation of the evidence into recommendations**

We found two RCTs, both comparing different self-administered hand exercises. Neither indicated one intervention to be superior over another, but data were sparse and the studies were at high risk of bias. In addition, we found one RCT comparing a structured exercise programme versus no exercises, which provided some evidence that such a programme may be beneficial. We found this evidence to be of low certainty due to the risk of selection bias and wide CIs from sample size restrictions. More importantly, outcome measures were of a surrogate nature, using clinical and ultrasonographic criteria-based maturation rather than successful dialysis. One month may be too soon to assess the finality of a maturation process and data might have been different if the AV fistulas had been reassessed 2 weeks later.

The GDG felt it would be unlikely that simple exercises, such as hand squeezing, could have any harmful outcomes, provided that the patients waited until sufficient wound healing had occurred. Indeed, the no-exercise controlled trial did not report any important adverse events. Despite the study limitations, the GDG felt there was some indication that a structured exercise programme could be useful, and would not represent important resource implications, such that in the absence of important adverse events they supported the use of such programmes in the postoperative phase of AV fistula creation.

There was one trial testing a new pneumatic device, but the results were considered preliminary and outcomes surrogate in nature.

Other guidelines on this topic

ESVS [34]

Structured postoperative hand exercise programmes should be considered to increase AV fistula maturation. (IIa-B)

NKF-KDOQI [59]

Fistula hand–arm exercise should be performed. (B)

GEMAV [35]

We suggest that the patients do exercises before and after the creation of native AV fistulas to promote maturation.

The CSN, KDIGO, KHA-CARI and NICE provide no current recommendations on this topic.

Suggestions for future research

Given the scarcity of evidence on self-administered interventions to promote maturation, randomized trials comparing various exercise programmes versus no exercise with adequate sample sizes and standardized outcomes would be informative for future recommendations in this field.

CHAPTER 5. PERIOPERATIVE PROPHYLACTIC ANTIBIOTICS FOR PREVENTING AV ACCESS INFECTION

Recommendations

> We recommend giving preoperative antibiotic prophylaxis for arteriovenous graft insertion in adults with end-stage kidney disease. (1C)
>
> We suggest giving preoperative antibiotic prophylaxis for complex arteriovenous access procedures in adults with end-stage kidney disease. (2D)
>
> We suggest not giving preoperative antibiotic prophylaxis for simple arteriovenous access procedures in adults with end-stage kidney disease. (2D)

Advice for clinical practice:

- Simple AV access procedures include the creation of a native radiocephalic or native brachiocephalic AV fistula.
- Complex AV access procedures include those that are not considered simple.

Rationale

- **Background**

Creation of an AV access for haemodialysis can be considered a clean surgical procedure. Accordingly, preoperative antibiotics should not be necessary and overuse may induce bacterial resistance. However, patients with ESKD have impaired immunity with an increased risk of infection. In addition, the risk and consequences may be dependent on the type of AV access procedure. If prosthetic material is inserted and becomes infected during surgery, then the newly created AV access may be jeopardized. As such, recommendations for antibiotic prophylaxis may be different for AV fistula and AV graft procedures and must balance benefits and harms appropriately.

- **Summary of the evidence**

(Supplement 3| Review questions—PICO Format—Chapter 5)
(Supplement 4| Search strategies—Chapter 5)
(Supplement 5| Study selection flow diagrams—Chapter 5)
(Supplement 6| Summary evidence tables—Chapter 5)

We identified two RCTs assessing perioperative antibiotics for AV graft insertion [64, 65]. No studies were found that assessed prophylactic antibiotics for AV fistula creation.

The first RCT included 38 participants who were randomized to either cefamandole or placebo before insertion of an AV graft in the radiocephalic ($n = 19$) or femorosaphenous ($n = 19$) position [64]. Cefamandole or placebo was given intravenously 30 min prior to surgery and 6–12 h postoperatively. The overall infection rate was 26%. Two of 19 participants treated with antibiotics and 8 of 19 participants given placebo developed an infection (RD = −0.32; P < 0.04). The study was considered at unclear risk of bias for not reporting the randomization procedure.

The second RCT included 206 patients who underwent a total of 408 procedures to create a permanent vascular access [65]. Patients were randomized to either a single intravenous dose of 750 mg of vancomycin ∼6–12 h before the vascular access placement procedure (206 procedures) or to no prophylactic antibiotics (202 procedures). Within 30 days, and before using the AV access for chronic dialysis, infection developed twice in the antibiotics group and 12 times in the group that had not received antibiotic prophylaxis (RD = −0.05; P < 0.01). All 14 infections occurred in upper limb polytetrafluoroethylene (PTFE) grafts. The study was considered at high risk of selection bias as the allocation was based on the hospital record number.

- **Translation of the evidence into recommendations**

There are no randomized trial data on perioperative antibiotic prophylaxis for AV fistula creation. The GDG felt that in the absence of direct evidence they should rely on extrapolation of evidence for antibiotic prophylaxis for preventing surgical site infections in general. They drew on an evidence review conducted by NICE in January 2017 [66]. The review process found evidence supporting antibiotic prophylaxis to patients before clean surgery involving the placement of a prosthesis or implant; this was based predominantly on the evidence for a clinically relevant reduction in surgical site infections for this category. There is far less evidence related to clean and simple procedures, a single randomized trial indicating evidence for no effect. Our GDG considered the creation of a native fistula to be a 'clean' and short surgical procedure in a non-contaminated area. Hence they judged antibiotic prophylaxis non-mandatory in this setting.

In cases where prosthetic materials are used, two RCTs provided low-certainty evidence for a clinically relevant reduction in surgical site infections. This is in line with the conclusion from the evidence review conducted for the NICE guideline [66]. We found no evidence for preferring one type of antibiotic over another in this setting. The GDG judged both first-generation cephalosporins as well as vancomycin, or teicoplanin could be considered, depending on the local practice and epidemiology of methicillin resistance.

Other guidelines on this topic

ESVS [34]

We recommend that broad-spectrum antibiotics should be given prior to the insertion of an AV graft, including prophylaxis for *Staphylococcus aureus*. (IA)

In carriers or in units with a high incidence of methicillin-resistant *S. aureus*, the administration of a parenteral glycopeptide is recommended. (IB)

GEMAV [35]

Due to the risk of infection associated with the prosthetic AV fistula, we recommend the use of perioperative prophylactic antibiotics.

The CSN, KDIGO, NKF-KDOQI, KHA-CARI and NICE provide no current recommendations on this topic.

Suggestions for future research

An adequately powered RCT comparing routine administration of antibiotics versus no antibiotic prophylaxis before the creation of native AV fistulas would be helpful to resolve the remaining uncertainty.

CHAPTER 6. TIMING OF FIRST CANNULATION

Recommendations

AV fistulas

> In adults requiring haemodialysis, we suggest arteriovenous fistulas can be cannulated 4 weeks after creation if they are considered suitable for cannulation on clinical examination. (2C)
>
> In adults requiring haemodialysis, we recommend against cannulating arteriovenous fistulas sooner than 2 weeks after their creation. (1B)
>
> In adults requiring haemodialysis, we suggest against cannulating arteriovenous fistulas 2–4 weeks after their creation unless this will avoid placement of a central venous catheter for haemodialysis. (2C)

AV grafts

> In adults requiring haemodialysis, we recommend 'early cannulation type' arteriovenous grafts can be cannulated as soon as wound healing permits. (1B)
>
> In adults requiring haemodialysis, we suggest against cannulating a 'standard type' arteriovenous graft sooner than 2 weeks after insertion unless this will avoid placement of a central venous catheter for haemodialysis. (2B)

Advice for clinical practice:

- In practice, suitability for cannulation on clinical examination is determined by the presence of a palpable vein and good thrill.
- If clinical examination is inconclusive, ultrasound with flow measurement may help in deciding whether to cannulate.
- Bedside ultrasound-guided cannulation may be helpful in avoiding complications and decreasing the number of failed cannulations.
- Using single-needle dialysis, low dialysis blood flows and smaller needles (17 gauge) may prevent harm to AV fistulas that are cannulated early.
- Wound healing refers to the tissue around the body of the graft rather than the incision site.

Rationale

• Background

It has been standard practice to avoid cannulating an AV fistula during the first 6 weeks after its creation. For standard PTFE AV grafts, this period has always been 2 weeks, but new-generation grafts have been marketed for their early cannulation properties, allowing use as an alternative to central venous catheters for prompt access [67]. On the one hand, cannulating a newly created vascular access too early may result in perforation, haematoma or even destruction of the access site. On the other hand, waiting may cause needless insertion of haemodialysis catheters and lead to delays in searching for causes of non-maturation or in creating an alternative AV access.

We wanted to assess when the different AV access types may be reasonably cannulated successfully and whether certain easily measured variables indicate the first attempt at cannulation is likely to be successful. These variables included clinical observations and ultrasound-based measurements such as vessel diameter, blood flow, wall thickness and depth of the AV access.

• Summary of the evidence

(Supplement 3| Review questions—PICO format—Chapter 6)
(Supplement 4| Search strategies—Chapter 6)
(Supplement 5| Study selection flow diagrams—Chapter 6)
(Supplement 6| Summary evidence tables—Chapter 6)

AV fistulas

We found no RCTs assessing the effect of the timing of first cannulation on outcome in AV fistulas.

Eight observational studies assessed the effect of the time point of first cannulation after AV fistula creation on outcome [68–75] and the results were conflicting.

Two studies based on the Dialysis Outcomes Practice Patterns Study (DOPPS) provided centre-level information on the timing of first cannulation [68, 69]. When analysing all patients who started haemodialysis with an AV fistula ($n = 894$), the median time to first cannulation varied greatly between countries, averaging 25 days for Japan, 27 days for Italy, 42 days for Germany, 80 days for Spain, 86 days France, 96 days for the UK and 98 days for the USA [68]. No association was found between cannulating sooner versus later than 28 days after AV fistula creation and age, sex and 15 different classes of variables reflecting comorbidity. Cannulating an AV fistula sooner than 14 days after its creation was associated with a 2-fold increased risk of subsequent fistula failure versus cannulating after 14 days ($P < 0.01$). There was no difference for AV fistulas cannulated within 15–28 days compared with fistulas cannulated within 43–84 days.

Based on the same cohort, investigators analysed the influence of time to first cannulation and blood flow rate at first cannulation on primary fistula failure [69]. For newly created AV fistulas, the first attempt at cannulation occurred within 2 months after placement in 36% of US, 79% of European and 98% of Japanese facilities. There was no indication that centres that cannulated their AV fistulas within 4 weeks after creation had higher risks of later fistula failure. The facility median blood flow rate was not significantly associated with access failure either.

A retrospective study including 190 Moroccan haemodialysis patients found no difference in the risk of fistula thrombosis whether cannulation occurred before or after 21 days following AV fistula creation [70]. However, the authors did not provide numeric data, there was no attempt at adjusting for confounders and it was unclear when or how outcomes were measured.

A prospective cohort study enrolled 118 people with a newly created AV fistula [71]. In contrast to the DOPPS data, postponing cannulation until 1 month after fistula creation reduced the risk of thrombosis by 60% [RR 0.40 (95% CI 0.19–0.84)]. This finding was supported by a second prospective cohort including 535 people with newly created AV fistulas [72]. In this study, which adequately controlled for possible confounders, cannulating AV fistulas within 30 days of their creation was associated with twice the hazard for primary AV fistula failure.

Two studies published by a group from the UK retrospectively reviewed fistula patency in 1167 fistulas created between 2002 and 2015 with different cut-off points to define early cannulation [73, 74]. Both analyses were unadjusted comparisons using the AV fistula as the unit of analysis rather than the individual patient. The first report used a cut-off of 30 days after fistula creation to define early and late cannulation and found no difference in fistula failure within 90 days following first cannulation between the two groups ($P = 0.35$) [73]. The second report separately analysed AV fistula survival in pre-dialysis patients and patients on maintenance haemodialysis with a definition of early cannulation as an attempt that happened within 4 weeks after fistula creation. It found no difference in fistula survival between the cohorts [74].

One study prospectively included all adults with CKD set to undergo upper extremity AV fistula creation at one of seven US centres to assess the association between a variety of clinical processes, cannulation and successful haemodialysis [75]. In a subset already treated with chronic haemodialysis at the time of AV fistula creation, the investigators analysed the influence of timing to first cannulation on overall maturation, broadly defined as successful dialysis during a 4-week period. They found that for every month a first cannulation attempt was delayed beyond 2 months, the odds for successful dialysis gradually diminished [OR 0.93 (95% CI 0.89–0.98)]. The certainty of the evidence was affected by possible residual confounding and inflated type 1 error from multiple analyses.

Four studies assessed the value of clinical assessment or ultrasound-based measures in determining readiness for first cannulation [76–79].

The first study assessed whether ultrasound and clinical evaluation of AV fistulas at 4 weeks after creation predicted future successful cannulation [76]. Clinical appreciation, by experienced nurses unaware of the ultrasound findings, consisted of examining the flow characteristics (categorized as thrill/pulse/audible bruit with or without a palpable thrill), the vein calibre and the straightness and depth of the vein. Clinical appreciation, a vein diameter >5 mm and arterial end diastolic velocity >110 cm/s had a positive predictive value for successful cannulation of 81, 90 and 87%, respectively. The negative predictive value, however, was only 63, 53 and 37%, respectively. Importantly, this study excluded patients with AV fistulas that had already thrombosed prior to or at 4 weeks.

A second, single-centre consecutive cohort of 20 patients assessed whether venous wall thickness and circumferential

stress could predict successful cannulation, defined as successful dialysis without substantial extravasation of blood at the cannulation site [77]. The investigators used very high frequency–based assessment (55 MHz probe) of intima-media thickness, defined as the sum of a thin blood–intimal interface and a uniform hypoechogenic media. A minimum threshold intima-media thickness of 0.13 mm was associated with successful cannulation without extravasation (sensitivity 87%, specificity 92%). Importantly, patients were only cannulated if the venous diameter was >6 mm, the blood flow >600 mL/min and the depth of the fistula <6 mm for a segment >6 cm 6 weeks after AV fistula creation.

A third cohort study retrospectively assessed the maturation surveillance ultrasound examinations of 69 patients performed within 4 months of AV fistula creation [78]. A venous diameter >0.4 cm or a blood flow >500 mL/min were reasonable predictors of successful cannulation within 4 months. In patients who met both criteria, cannulation was successful in 19 of 20, while in those who failed both criteria, successful cannulation occurred in only 5 of 15. In this study, clinical assessment by experienced nurses correctly predicted successful cannulation in 24 of 30 patients (accuracy of 80%).

Finally, a fourth study recorded fistula flow and diameter for 12 weeks following creation of the AV fistula. None of 14 fistulas with a diameter increase <0.4 cm 14 days after creation matured, while all 38 fistulas with a diameter increase >0.4 cm were successfully cannulated within 12 weeks. The same results were seen with a cut-off blood flow <400 or >400 mL/min [79].

AV grafts

We found one RCT comparing cannulation within 1–2 days versus 10–14 days after insertion of an upper limb standard PTFE AV graft in 36 patients requiring semi-urgent dialysis. There were no meaningful differences in the number of participants with haematomas, thrombosis or infection. There was no meaningful difference in compression time to control bleeding or venous back pressure. Evidence was considered moderate to low certainty because of unclear risk of bias and wide CIs [80].

We found an additional six observational studies covering AV grafts [69, 70, 81–84]. All directly assessed the effect of the time point of first cannulation after AV graft creation on outcome: four in prospective [69, 71, 83, 84] and 2 in retrospective cohort studies [81, 82].

Two prospective cohort studies reported on cannulation within the first 3 days after creation [83, 84]. The first study assessed 76 stretch-expanded PTFE grafts and found no meaningful difference in primary patency after 3 and 12 months for those cannulated after 1–2 days versus those cannulated after 2 weeks [84]. The second study from the USA reported an unadjusted comparison of early cannulation within 72 h of graft placement to late cannulation >21 days following graft placement in 87 patients, using a multilayer graft designed for early cannulation. They found no meaningful difference in cumulative graft patency rates up to 12 months of follow-up (76% versus 77.5%; P = 0.7) [83].

Three studies reported on cannulation of standard AV grafts within 14 days and compared the results with AV grafts cannulated after 14 days [69, 81, 82].

In the DOPPS, the first cannulation of AV grafts typically occurred within 2–4 weeks at 62% of US, 61% of European and 42% of Japanese facilities [69]. In 17% of US, 16% of European and 42% of Japanese facilities that cannulate their AV graft within 2 weeks of creation, overall risk of AV graft failure, defined as the time to first thrombosis or access salvage procedure, did not differ from those cannulating at later times.

A retrospective study reported on the 12-month failure of 64 AV grafts in 58 people who had their standard AV graft's first cannulation at different times after insertion, starting from the second week after surgery. The study results suggested that the timing of the first cannulation of a standard AV graft had no significant impact on graft survival [81]. The overall incidence of primary AV graft failure, defined as the first occurrence of graft thrombosis or need of any invasive access procedure, and of cumulative graft failure, defined as irreparable loss of the graft, at 12 months was 72 and 41%, respectively. There was no association between the time of first cannulation and cumulative graft loss. Primary graft failure seemed to decrease as the interval between the procedure and the first cannulation increased, but results were not statistically significant and the certainty of the evidence was very low due to the requirement of successful first cannulation as an inclusion criterion and censoring for patient mortality (15% grafts), disproportionally present in the later time groups. A third and retrospective study in 270 people receiving a standard AV graft found secondary patency rates up to 15% lower in grafts cannulated within versus after 14 days. The certainty of the evidence was very low, as we considered the study at high risk of bias, with comparisons of raw numbers not adjusted for confounders [82].

Finally, a prospective cohort in North America enrolling 147 people with AV grafts found first cannulation after versus within 1 month had uncertain effects on the risk of thrombosis within 1 year of cannulation [n = 147; RR 0.77 (95% CI 0.43–1.38)]. The analysis had been adequately adjusted for the main confounding factors [71].

- **Translation of the evidence into recommendations**

Several observational studies consistently indicate that cannulating an AV fistula within 14 days of its creation increases—almost doubles—the risk of unsuccessful dialysis and/or later AV fistula failure compared with cannulating an AV fistula after 14 days. The evidence for waiting another 14 days is less impressive and not consistent. In addition, the negative effects of a further delay, that is, the need for urgent central venous catheter placement, have never been studied and may counterbalance the positive effects of fistula longevity. In the absence of this evidence, the GDG felt that in this case, avoiding placement of a catheter weighed more heavily and by allowing another 14 days for further maturation weighed less in comparison with the previous case. In the absence of the need for urgent dialysis, it seems reasonable to allow for an additional 14 days of further maturation before attempting to cannulate the AV fistula. This also holds true for those already receiving dialysis via a tunnelled catheter unless a problem with the catheter should arise.

AV fistulas with a palpable vein and good thrill at 4 weeks after their creation can be cannulated successfully in most cases. In this situation, additional ultrasound measures are unlikely to be helpful. However, in the absence of such a thrill, there is low-quality evidence in line with clinical practice suggesting that an AV fistula diameter >4–5 mm or a blood flow >500 mL/min indicates the fistula has matured and can be cannulated successfully. In the absence of a thrill, a diameter <4 mm and a blood flow <400 mL/min make it highly suspicious that the AV fistula will fail without intervention. Although other techniques to assess AV fistula characteristics have been proposed, further study is needed to assess their added value.

One small RCT and several observational studies provide moderate-certainty evidence that cannulating an AV graft within 2 days of its insertion has no negative consequences for short- or long-term AV graft outcome, including infection rates. This is the case even with standard PTFE grafts. There does not seem to be an increase in the complication rate, but early cannulation of standard PTFE grafts has never found its way into routine practice around the world. RCTs of the new grafts designed for early cannulation are not available. One retrospective study showed no increase in complications when cannulation of an early cannulation graft within the first 72 h was compared with cannulation after 3 weeks. How this influences the added benefit of avoiding temporary and tunnelled central venous catheter placement is unclear, but it can only be expected to further tip the benefit–harm balance in favour of supporting early cannulation when necessary.

Other guidelines on this topic

ESVS [34]

AV fistulas should be considered for cannulation 4–6 weeks after creation and standard AV grafts after 2–4 weeks. (IIa-B)

AV fistula cannulation before 2 weeks should generally not be done. (III-C)

AV fistula cannulation 2–4 weeks after creation may be considered in selected patients under close supervision. (IIIb-B)

GEMAV [35]

We recommend that cannulation of the native AV fistula not be initiated in the first 2 weeks following creation and that the optimal time for the first cannulation be decided on a case-by-case basis.

We recommend that cannulation of the prosthetic AV fistula be initiated 2–4 weeks following construction, except in those of immediate cannulation.

The CSN, KDIGO, NKF-KDOQI, KHA-CARI and NICE provide no current recommendations on this topic.

Suggestions for future research

Given the lack of high-quality comparative data, randomized trials comparing decision rules to determine optimal time points for first cannulation in grafts and fistulas would be informative. These trials should take care to investigate objective and reproducible criteria for deciding upon the timing of first cannulation of a vascular access. Long-term access outcomes, adverse events and quality of life measures should be reported transparently.

CHAPTER 7. VASCULAR ACCESS SURVEILLANCE

Recommendations

AV fistulas

> We suggest the evidence for technical surveillance in addition to clinical monitoring of a functional arteriovenous fistula to detect and pre-emptively correct a haemodynamically important arteriovenous access stenosis in adults is inconclusive and needs more research. (2C)

AV grafts

> We suggest against technical surveillance in addition to clinical monitoring of a functional arteriovenous graft to detect and pre-emptively correct a haemodynamically important arteriovenous access stenosis in adults unless it occurs in the context of a clinical study. (2C)

Advice for clinical practice:

• None.

Rationale

• **Background**

AV fistulas or grafts can develop stenotic lesions anywhere in the arteriovenous circuit due to neointimal hyperplasia. This may lead to dysfunction or thrombosis of the vascular access, making it unfit for use. It happens quite often and is associated with an increased risk of irremediable access failure [85]. Clinical monitoring is defined as clinical assessment of an AV access at regular intervals, including examination of the AV access thrill and bruit, haemostasis time after needle removal and outflow appraisal after arm elevation. Technical surveillance is defined as the assessment of an AV access at regular intervals using a specialized apparatus. Both clinical monitoring and technical surveillance have been advocated under the assumption that detection of a haemodynamically important AV access stenosis (>50% reduction in luminal diameter) and subsequent intervention to prevent further vessel narrowing and thrombosis leads to improved longevity of the AV access compared with salvage interventions deferred to when the access becomes dysfunctional [2, 86]. However, such a practice may inadvertently lead to more invasive diagnostic and therapeutic interventions and expose patients to the complications thereof.

• **Summary of the evidence**

(Supplement 3| Review questions—PICO format—Chapter 7)
(Supplement 4| Search strategies—Chapter 7)
(Supplement 5| Study selection flow diagrams—Chapter 7)
(Supplement 6| Summary evidence tables—Chapter 7)

A Cochrane systematic review, with content assessed as up to date through 30 November 2015, included 30 reports of 14 RCTs comprising 1390 participants [87]. Nine studies enrolled

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adults without a documented or suspected access stenosis (primary prophylaxis) and five enrolled adults with either a documented or suspected stenosis in a functioning access (secondary prophylaxis). In primary prophylaxis, pre-emptive correction followed the identification of a stenosis using various technical surveillance strategies: Doppler ultrasound, sequential access blood flow measurements or measurements of dialyser outlet pressure, often in addition to clinical monitoring. In secondary prophylaxis, participants were randomized either before or after angiographic confirmation of a stenosis to pre-emptive correction or continued monitoring until the access became dysfunctional. Five studies included only AV fistulas, eight only AV grafts and one included both. Follow-up ranged from 6 months to 3 years. Attaining a maximum 11/11 on the AMSTAR checklist, we considered the review to be of high quality and its results trustworthy. In what follows, we summarize the findings of that review.

A meta-analysis including data from five randomized trials indicated that pre-emptive correction had uncertain effects on patient death. The point estimate favoured no intervention, but the CI spanned a potentially important reduction and increase in risk, such that the overall level of evidence for the effect was very low [87].

Pre-emptive correction may have slightly reduced permanent access loss. Both because of the high risk of bias in the included studies and the width of the CI, the certainty of the evidence was low. The authors of the review decided to subgroup studies according to whether participants had an AV fistula or an AV graft and concluded that pre-emptive correction may reduce the risk of permanent access failure in AV fistulas but may make little or no difference in AV grafts. From visual inspection of the forest plots, we understand the decision to conduct the subgroup analysis, although there was no statistical indication of heterogeneity in the primary analysis. Hence the evidence supporting a claim of differential effect remains low. Similarly, the effect does not seem to have depended on whether studies covered primary or secondary prophylaxis, on the type of surveillance strategy used or on the type of remedial procedure performed.

Twelve RCTs assessed the effect of pre-emptive correction on access thrombosis (possibly remediable access failure). Overall, pre-emptive correction slightly reduced the risk of access thrombosis, but there was a moderate degree of heterogeneity in the analysis that could be explained by the modifying effect of access type. In the subgroup analysis, there was moderate-certainty evidence for an important reduction in the risk of possibly remediable failure of an AV fistula. Conversely, there seemed to be little or no effect on the risk of possibly remediable failure of an AV graft. Another source of heterogeneity involved the aim of prevention. In the subgroup analysis, the data indicated that the effect may be different for people in whom a stenosis was already suspected or documented (secondary prophylaxis) versus those in whom that was not the case (primary prophylaxis), but a lot of heterogeneity remained in the analyses. In primary prophylaxis, the type of surveillance strategy had no visual or statistical influence on the effect of pre-emptive strategies.

For infections, the evidence was very limited. Only three RCTs included in the review assessed this outcome, but all three defined the outcome differently: one did not provide a definition, one included only access infections and one only catheter-related infection. Given that pre-emptive correction may decrease catheter use (see below), effects on catheter-related infection and AV access infection are expected and indeed appeared to be in opposite directions, invalidating meta-analysis of these studies in our view. At this point in time, it remains unclear how the intervention affects net infection risk, as no study assessed both outcomes in the same study.

Pre-emptive correction probably increases the number of diagnostic angiograms in people that receive primary surveillance of their AV access, and undoubtedly in those who already have a suspected stenosis based on the clinical monitoring or other technical surveillance strategies (moderate certainty evidence). It may decrease catheter use, and the risk of hospital admission, but the level of evidence remains low due to the risk of bias in the primary studies and a large amount of unexplained heterogeneity in the analysis with point estimates on opposite sides of the line of no effect.

In addition to the Cochrane review, we identified two reports of another recent randomized trial that had not yet been included in the systematic review [88, 89]. The study enrolled 212 adults who had dialysed successfully via an AV fistula for the past 3 months. Participants were randomized to a 'classic' or 'access blood flow-based' surveillance programme. The classic surveillance programme included clinical monitoring, that is, physical examination of the AV fistula before every dialysis, and 'first-generation' or 'classic' technical surveillance through effective blood flow, dynamic dialyser inlet and outlet pressure measurement during every dialysis, weekly K_t/V assessment and recirculation measurement using the urea method every 3 months. The presence of any of the seven alarm criteria would trigger fistulography and subsequent percutaneous transluminal angioplasty or surgical intervention depending on the findings. The access blood flow-based surveillance programme included Doppler ultrasound and Doppler dilution methods to assess blood flow in addition to what was used in the classic surveillance programme on a 3-month basis. Classic criteria would trigger additional access blood flow measurement. A set of three criteria (blood flow decrease >25%; blood flow <500 mL/min, >50% reduction in vessel diameter plus either peak systolic blood velocity >400 cm/s or pre-: post-stenosis ratio >3) would trigger fistulography and subsequent treatment if necessary. At the end of a 3-year follow-up—with staggered censoring—they found an important increase in thrombosis-free patency [Hazard Ratio (HR) 0.38 (95% CI 0.11–0.82)] and access survival until abandonment [HR 0.49 (95% CI 0.26–0.93)] for those receiving access blood flow–based surveillance. Intervention-free access survival was similar [HR 0.98 (95% CI 0.57–1.61)]. Also, the number of interventions during the entire follow-up was not different (0.14/patient/year in both groups).

• **Translation of the evidence into recommendations**

For a screening programme to be successful, two important elements are needed. Not only should the screening test be effective at detecting the presence of an underlying significant stenosis, there should also be evidence that subsequent correction of the stenosis prolongs AV access survival.

In weighing benefits against harms, the GDG assigned the most value to patient survival and permanent access loss.

The evidence to date indicates that technical surveillance and subsequent pre-emptive correction of an AV access stenosis may possibly and slightly reduce the risk of permanently losing an AV fistula. It also appears that this effect may be smaller for AV grafts, if it exists at all. This is regardless of which surveillance technique is used or which intervention is subsequently performed. In addition, there is moderate quality evidence that even possible remediable access failure is probably not importantly reduced by pre-emptive intervention, whatever the intervention may be.

For AV fistulas, technical surveillance and pre-emptive correction seem to have a larger effect than the overall estimate indicated, but caution is required in interpreting both the relative and absolute effect sizes obtained by the review. First, although visual inspection of the forest plot indicated effect modification by access type, there was no statistical indication that heterogeneity truly exists. Translating the obtained subgroup effect estimate may thus overestimate the true effect. A more conservative estimate assumes the overall relative risk of 0.8 with its CI. The corresponding absolute effect heavily depends on the baseline risk of access failure in the control group, which is expected to be (much) larger in the people already suspected to have an access stenosis than in those who are not. By estimating the baseline risk from the studies, the relative effect of 0.8 translates into an estimated five fewer AV fistulas being lost for every 100 patients screened and an estimated six fewer for every 100 patients undergoing pre-emptive correction of a documented stenosis after 1 year. There is better quality evidence for AV fistula thrombosis. There is moderate quality evidence that surveillance and pre-emptive correction moderately reduce the risk of fistula thrombosis, the RR of 0.5 translating into an estimated absolute 15 fewer AV fistula thromboses for every 100 patients surveilled for 1 year and an estimated 23 for every 100 patients undergoing pre-emptive correction of a documented stenosis. This needs to be weighed against the increased number of diagnostic angiograms, which may ultimately not change the number of invasive procedures a person needs to undergo. The value patients put on being able to have these planned—in case of surveillance—rather than having to undergo them in an emergency setting—in the case of access thrombosis—may sway the balance of perceived benefits and harms. Fewer catheters may be required, but the overall effect on the infection rate remains unclear to date. Additional demands on individual radiology services may also limit the feasibility of routine surveillance programmes. Because of uncertainties around the absolute reduction in risk of AV fistula failure, which needs to be weighed against an increased number of diagnostic angiograms, the GDG ultimately refrained from speaking out for or against technical surveillance.

A more recent RCT compared two strategies of surveillance: 'classic' or first-generation versus 'classic plus access blood flow–based' or second-generation surveillance [88]. There was moderate evidence that access blood flow–based surveillance resulted in reduced access thrombosis and reduced AV fistula abandonment without increasing the total number of interventions the patients had to undergo. Although this does not directly answer the question, it seems to indicate the superiority of access blood flow–based surveillance over classic surveillance methods. However, the guideline development group felt that at this stage more research was needed before any specific recommendation could be made.

Other guidelines on this topic

ESVS [34]

Routine physical examination is recommended for vascular access surveillance and maintenance. (I-B)

It is recommended that vascular access monitoring be performed by flow measurement of AV grafts monthly and AV fistulas every 3 months. (I-B)

When AV fistula blood flow measurement during dialysis indicates the presence of a vascular access stenosis, that is, Q_a is <500 mL/min, angiographic assessment of stenosis should be considered. (IIa-B)

Venous pressure adjusted for a mean arterial pressure >0.50 (or derived static venous pressure >0.55) is not a reliable indicator of stenosis and intervention based on this finding is not recommended. (III-C)

When haemodialysis efficiency is impaired, investigation and correction of an underlying vascular access stenosis should be considered. (IIa-B)

Surveillance of AV fistulas with duplex ultrasound at regular intervals and pre-emptive balloon angioplasty should be considered to reduce the risk of AV fistula thrombosis. (IIa-A)

Surveillance of AV grafts with duplex ultrasound at regular intervals and pre-emptive balloon angioplasty is not recommended to prevent thrombosis or improve AV graft functionality. (III-A)

CSN [90]

Measure access flow bimonthly in AV fistulas and venous pressure or access flow monthly in AV grafts. (Grade D)

Perform angiography if fistula flow decreases to <500 mL/min or drops to >20% from baseline (Grade D) or if AV graft flow decreases to <650 mL/min or drops >20% from baseline. (Grade D)

NKF-KDOQI [86]

Prospective surveillance of fistulas and grafts for haemodynamically significant stenosis, when combined with correction of the anatomic stenosis, may improve patency rates and may decrease the incidence of thrombosis.

The work group recommends an organized monitoring/surveillance approach with regular assessment of clinical parameters of the AV access and HD adequacy. Data from the clinical assessment and HD adequacy measurements should be collected and maintained for each patient's access and made available to all staff. The data should be tabulated and tracked within each HD centre as part of a quality assurance programme.

Physical examination should be used to detect dysfunction in fistulas and grafts at least monthly by a qualified individual. (B)

Techniques, not mutually exclusive, that may be used in surveillance for stenosis in grafts include:

- Preferred:
  ○ intra-access flow by using one of the several methods that are outlined in Table 7 using sequential measurements with trend analysis (A)

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○ directly measured or derived static venous dialysis pressure by one of the several methods (A) (Protocol provided in Table 8 for using transducers on haemodialysis machines to measure directly; criteria in Table 9 for derived methods.)
○ duplex ultrasound (A).

- Acceptable:
  ○ physical findings of persistent swelling of the arm, presence of collateral veins, prolonged bleeding after needle withdrawal or altered characteristics of pulse or thrill in a graft (B).

- Unacceptable:
  ○ unstandardized dynamic venous pressures should not be used.

Techniques, not mutually exclusive, that may be used in surveillance for stenosis in AV fistulas include:

- Preferred:
  ○ direct flow measurements (A)
  ○ physical findings of persistent swelling of the arm, presence of collateral veins, prolonged bleeding after needle withdrawal or altered characteristics of pulse or thrill in the outflow vein (B)
  ○ duplex ultrasound (A).

- Acceptable:
  ○ recirculation using a non-urea-based dilutional method (B)
  ○ static pressures (B) direct or derived (B).

One should not respond to a single isolated abnormal value. With all techniques, prospective trend analysis of the test parameter has greater power to detect dysfunction than isolated values alone (A).

Persistent abnormalities in any of the monitoring or surveillance parameters should prompt referral for access imaging (A).

There should be an access flow rate <600 mL/min in grafts and <400–500 mL/min in fistulas (A).

There should be a venous segment static pressure (mean pressures) ratio >0.5 in grafts or fistulas (A).

There should be an arterial segment static pressure ratio >0.75 in grafts (A).

NICE [91]

Quality standard: Adults receiving haemodialysis have their vascular access monitored and maintained using systematic assessment.

GEMAV [35]

We recommend performing a complete physical examination of the AV access in every advanced CKD clinic visit to assess maturation and to detect early on any complication before the first cannulation.

We recommend that Doppler ultrasound be performed if insufficient development of a native AV fistula is observed during physical examination in regular advanced CKD outpatient check-ups.

We recommend that haemodialysis units have protocolized programmes for AV fistula follow-up, involving multidisciplinary participation. These programmes should include methods for early diagnosis of AV fistula dysfunction and locate its origin, as well as performing the elective treatment.

We recommend that the application of programmes for AV fistula follow-up must involve periodic assessment of the parameters obtained by each monitoring and/or surveillance method applied.

We recommend that repeated alteration of any monitoring and/or surveillance parameter be used as a criterion to perform an imaging examination of the AV fistula in front of suspected pathology.

We recommend that both Doppler ultrasound and dilution screening methods be used interchangeably to assess AV fistula function, as they have an equivalent performance for blood flow determination.

We recommend that Doppler ultrasound be used as the first-choice imaging test in the hands of an experienced examiner, without the need for confirmatory fistulography, to indicate elective treatment in the event of suspected significant stenosis.

We recommend that fistulography be reserved as a diagnostic imaging exploration only for cases with inconclusive Doppler ultrasound findings and persistent suspicion of significant stenosis.

According to the current concept of significant stenosis, we do not recommend that surveillance of the prosthetic AV fistula be performed using second-generation screening methods, whether there are dilution methods to estimate the blood flow or Doppler ultrasound.

According to the current concept of significant stenosis, we recommend that first-generation screening methods be used for monitoring the prosthetic AV fistula.

According to the current concept of significant stenosis, we recommend that both first- and second-generation methods be used for monitoring and surveillance of the native AV fistula.

We recommend that a stenosis be considered significant when there is any reduction in the vascular lumen in native or prosthetic AV fistulas, shown by Doppler ultrasound, that meets all the criteria for high risk of thrombosis (the two main criteria and at least one additional criterion).

We recommend that an elective intervention be performed without delay by percutaneous transluminal angioplasty and/or surgery when the diagnosis of significant AV fistula stenosis is established because of the high risk of thrombosis.

We recommend that a stenosis be considered non-significant when there is any reduction in the vascular lumen in native and prosthetic AV fistulas, shown by Doppler ultrasound, that does not meet all the criteria for high risk of thrombosis.

We recommend that an elective intervention not be performed when a diagnosis of non-significant stenosis is established in an AV access because of the low risk of thrombosis.

We recommend that all non-significant AV fistula stenosis be strictly controlled using second-generation screening methods, because the risk of progression is significant.

We recommend that an elective intervention be performed on the dysfunctional AV fistula with significant stenosis instead of restoring after thrombosis.

We suggest surgical treatment of juxta-anastomotic stenosis of the native AV fistula be performed provided a central venous catheter does not need to be placed.

We suggest venous juxta-anastomotic stenosis of the prosthetic AV fistula be treated indistinctly by angioplasty or surgical intervention.

We suggest non-juxta-anastomotic stenosis of the native AV fistula initially be treated using angioplasty, because it is less invasive than surgery.

We recommend fistulography be performed if central venous stenosis is clinically suspected.

We recommend only central vein stenoses that are symptomatic be treated.

We recommend endovascular therapy be performed using percutaneous transluminal angiography with balloon as the first treatment option for central stenosis.

We suggest the use of stents be limited to selected cases where there is technical failure of angioplasty and frequent relapse of stenosis, and we recommend they be not used in venous confluents.

We suggest that angioplasty be used as the initial treatment in stenosis in the cephalic vein arch. Treatment by stent placement or by surgical transposition of the cephalic vein may also be considered.

UK Renal Association [92]

We recommend that all patients on long-term haemodialysis should have their vascular access monitored and maintained to minimize failure, to allow timely planning for subsequent replacement with definitive vascular (or peritoneal) access and to avoid the need for emergency access. (1B)

We suggest that systematic observation and advanced surveillance should be employed to predict and prevent access failure. (1C)

The KDIGO and KHA-CARI provide no current recommendations on this topic.

Suggestions for future research

Given the possible, but insufficiently clear, benefits of screening and subsequent pre-emptive correction of an established stenosis in functioning AV fistulas, an adequately powered RCT assessing the right outcomes (AV fistula loss, death, quality of life, infections) would be informative. As screening can only be useful if interventions for correcting established AV fistula stenosis are effective, it would be pragmatic to enrol only participants with a suspected or documented access stenosis. An informative RCT would include meticulous records of how many patients were screened, how often, what monitoring and surveillance methods were used and how much staff time was spent on access screening, data collection and interpretation. Ravani *et al*. [87] estimated that based on the findings of their review, an RCT of 1020 participants per arm recruited over 1 year and followed for 3 years would have a power of 90% to detect a 30% reduction in the HR for access loss as significant at a two-sided P-value of 0.01, assuming a baseline risk of 10% and a withdrawal rate of 10%. To better inform the best practice recommendations in this field, patient preferences concerning the various outcomes and their views on elective versus urgent intervention should be included in future research.

CHAPTER 8. MEDICAL TREATMENTS FOR MAINTAINING LONG-TERM AV ACCESS PATENCY

Recommendations

AV fistulas

> We suggest any decision to give fish oil to adults with end-stage kidney disease in the year after arteriovenous fistula creation must balance improved patency at 1 year against an unknown risk of bleeding and other side effects. (2C)
>
> We suggest that far infrared therapy may be considered for improving long-term arteriovenous fistula patency in adults with end-stage kidney disease (2C)
>
> There are insufficient RCT data to make a recommendation for aspirin, clopidogrel, ticlopidine, warfarin, sulphinpyrazone, vonapanitase, beraprost sodium, cholecalciferol, statins, dipyridamole or dipyridamole combined with aspirin to be given for maintaining long-term arteriovenous fistula patency in adults with end-stage kidney disease (-D)

AV grafts

> We recommend against warfarin in combination with antiplatelet agents and against clopidogrel in combination with high-dose aspirin for reducing arteriovenous graft thrombosis in adults with end-stage kidney disease (1C)
>
> We suggest that any decision to give fish oil in the year following arteriovenous graft creation in adults with end-stage kidney disease must balance any improvement in graft patency at 1 year against an unknown risk of bleeding. (2C)
>
> There are insufficient RCT data to make a recommendation for aspirin, clopidogrel, ticlopidine, warfarin, beraprost sodium, statins, dipyridamole or dipyridamole combined with aspirin to be given for maintaining long-term arteriovenous graft patency in adults with end-stage kidney disease (-D)

Advice for clinical practice:

- None.

Rationale

- **Background**

AV fistulas or grafts can develop stenotic lesions anywhere in the AV circuit, mostly due to neointimal hyperplasia. This may lead to dysfunction or thrombosis of the vascular access, making it unfit for use. AV access thrombosis happens quite often and is associated with an increased risk of irremediable access failure [85]. Several medications, including antiplatelet agents and vitamin K antagonists, are thought to prevent AV access thrombosis and increase AV access patency and longevity but may also cause bleeding [93]. As immediate maturation problems in the first weeks and months after access creation may result from different pathophysiological factors than patency problems in the long run, the two

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issues are discussed in two different sections. In this chapter we assess long-term patency; maturation is discussed in Chapter 1.

- **Summary of the evidence**

(Supplement 3| Review questions—PICO format—Chapter 8)
(Supplement 4| Search strategies—Chapter 8)
(Supplement 5| Study selection flow diagrams—Chapter 8)
(Supplement 6| Summary evidence tables—Chapter 8)

Five systematic reviews of RCTs assessing benefits and harms of various medical adjuvant treatments to increase patency of AV fistulas and AV grafts were identified. We judged all these reviews to be of moderate to high quality, with AMSTAR scores of 8–10/11 [14–18]. All the reviews included both studies measuring patency outcomes after 6–12 weeks as well as patency outcomes measured several months later. Based on group consensus, for this section we chose to only consider studies measuring patency outcomes after 12 weeks, as an arbitrary cut-off to distinguish maturation from long-term patency.

The first was a Cochrane systematic review with content assessed as up to date through 23 March 2015 [14]. It included 15 RCTs comprising 2230 participants. Seven trials included people with an AV fistula, six with an AV graft and two with either an AV fistula or AV graft. After exclusion of the studies on maturation (outcomes registered within 12 weeks of creation), nine studies remained for consideration in the present section. Three of these included AV fistulas and the remaining six included AV grafts. All but one enrolled participants at the time of AV access insertion [20]. Tested medical interventions included aspirin, dipyridamole, dipyridamole plus aspirin, warfarin, fish oil, clopidogrel and human type I pancreatic elastase. Studies mostly included participants of all ages, follow-up ranged from 5 to 18 months after AV access insertion. Most studies only assessed AV access thrombosis as the primary outcome of interest.

The second was also a Cochrane systematic review that covered specifically anti-platelet agents to prevent vascular access failure and other outcomes in people with CKD, with content assessed as up to date through 24 January 2011 [15]. Most of the data contained in that review were not included in this section, as outcomes were mostly registered within 3 months of AV access creation. This systematic review focused only on the effect of anti-platelet agents, and the included studies largely overlapped with the ones that Tanner *et al.* [14] later included in their review. In contrast to that review, the second review also included existing access systems [15], which resulted in the identification of two additional RCTs for this guideline section [94, 95].

Three other systematic reviews each assessed a specific treatment: fish oil [16] and far infrared therapy [17, 18].

In addition to these reviews, a further three RCTs, published after 2013 and not included in any of the included systematic reviews, assessing various adjuvant medical treatments for improving patency were identified [24, 25, 96].

Aspirin

Two RCTs compared different doses of aspirin versus placebo in AV grafts with overall very uncertain effect on AV access thrombosis [20, 97]. The two included studies were small and at unclear risk of bias, results were very inconsistent and the CI was very wide, spanning the line of no effect.

A third RCT compared 30 mg of aspirin daily versus placebo in a random crossover design in 137 patients who had been on haemodialysis for >6 weeks while treated with erythropoietin [95]. The investigators found no appreciable difference in thrombosis or loss of patency. They reported no data on adverse outcomes.

Clopidogrel

A first RCT assessed the combination of clopidogrel and aspirin versus placebo for AV graft outcomes in newly inserted AV grafts [94]. The study was terminated early after 12 months because of excessive bleeding risk in the active treatment arm. Antiplatelet treatment did not alter thrombosis or loss of patency.

A second study randomized 96 participants to receive either clopidogrel plus a prostacyclin analogue or placebo for 7 days before until 1 year after AV fistula creation [24]. The investigators described an important reduction in primary fistula failure at 1 year. They reported no bleeding, but the external validity of the results was considered low because of stringent exclusion criteria. Only 25% of all the people set to undergo AV fistula creation had been enrolled.

Dipyridamole

One RCT tested the effect of dipyridamole or dipyridamole plus aspirin versus placebo on thrombosis within 18 months in people with newly inserted AV grafts [97]. The point estimate favoured dipyridamole in both cases, but the certainty of the evidence was low due to an unclear risk of selection and selective reporting bias, as well as a very wide CI spanning both an important reduction and increase in graft thrombosis. Again, the publication contained no clear data on adverse events.

Anticoagulants

One RCT assessed low-dose warfarin in newly inserted AV grafts, targeted to an international normalized ratio of 1.4:1.9 [98]. Warfarin did not decrease graft thrombosis, and the study was terminated early for major bleeding complications in the treatment group. Five patients (11% of participants) on warfarin developed severe bleeding (including upper gastrointestinal bleeding and cerebral haematoma). All five patients were concurrently treated with antiplatelet agents. Those in the placebo arm had no severe bleeding.

Fish oil, omega 3 polyunsaturated fatty acids

One systematic review compared fish oil versus placebo or no treatment, with the content assessed as up to date through January 2017 [16]. In addition to two RCTs identified by Tanner *et al.* [14], this review included four additional RCTs assessing dosages ranging from 3 g three times weekly to 6 g daily. Only one study assessed the effect in AV fistulas, the others were in AV grafts. In the meta-analysis, the authors found moderate-certainty evidence suggesting that fish oil treatment using 1.6–3.4 g of polyunsaturated fatty acids for 12–52 weeks prevented primary patency loss. There was no evidence for a differential effect between AV fistulas and grafts. It was very uncertain whether fish oil increased the risk of

bleeding. No data were provided for the severity or nature of bleeding for most studies.

Statins

There were no RCTs for long-term outcomes of statins.

Vonapanitase, recombinant type I pancreatic elastase

Three RCTs assessed the effect of recombinant type I pancreatic elastase applied directly to the adventitia of the AV vessels at the time of access creation [14]. At 12 months, the agent seemed to reduce the odds for AV access thrombosis, although the certainty of the evidence was low due to a risk of bias in the included studies and important imprecision with a CI spanning the line of no effect.

All three studies listed several adverse events including local symptoms secondary to the creation of a new AV access, but according to the study authors, there were no significant differences between placebo and recombinant type I pancreatic elastase–treated participants.

We found an additional trial that randomized 313 people to locally dripped vonapanitase or placebo [25]. At 1 year, the authors found very little evidence for a difference in their primary outcome of unassisted patency. Secondary patency was 13% higher in the group treated with vonapanitase, but no absolute numbers were given and the risk of bias assessment was hampered by the study being published as an abstract only.

Beraprost sodium

One RCT assessed the effect of beraprost sodium, an oral synthetic analogue of prostaglandin I_2, on 2-and 1-year primary unassisted patency in 55 patients with a previously failed AV access. In 75% the new access was an AV fistula and in the remaining quarter an AV graft. After 2 years, those who had received beraprost were about three times as likely to have a patent AV access than those who had not. However, the study was considered at high risk of bias due to unclear randomizing, lack of blinding and insufficiently detailed numeric outcome reporting. The authors reported no important bleeding events in either group, but external validity may be questioned since people considered at increased risk of bleeding had been excluded from the study.

Far infrared therapy

There was one systematic review on far infrared treatment to increase the patency of AV fistulas, with content assessed as up to date through January 2017 [18]. The review included 21 RCTs comprising 1899 participants at the time of access creation. Although not clearly reported, it appears all studies included people with an AV fistula. Investigators used different strategies for delivering far infrared rays; most commonly, a device generating wavelengths between 5 and 25 mm, set at a height of 20 cm above the AV fistula, with a treatment time of 40 min during each haemodialysis session. Most studies assessed blood volume, vessel diameter or primary patency at various time points up to 1 year after fistula creation. Although the reliability of the evidence was compromised by the small number of studies and research groups these data were derived from and the risk of bias in the underlying studies, overall far

infrared therapy seemed to increase primary unassisted patency at 12 months. In addition, five trials comprising 510 participants showed results for AV fistula occlusion rates. Overall, therapy with far infrared radiation decreased AV fistula occlusion rates. There was no evidence of heterogeneity in these trials.

An older review included only four RCTs, comprising 666 patients [17]. Primary unassisted patency was assessed in 610 patients and far infrared therapy for 40 min three times weekly seemed to improve primary unassisted patency compared with controls. In addition, the two studies that reported secondary patency rates indicated a small difference in favour of far infrared therapy. The reliability of the results was mainly limited due to the high risk of bias by being open-label, being conducted by the same research group and being industry sponsored.

- **Translation of the evidence into recommendations**

The GDG felt that for a positive recommendation, interventions had to improve successful use of the AV access. It was judged that in the absence of evidence for a positive effect of successful cannulation, evidence for an effect on access thrombosis would not be enough to advocate treatment. Although it is true that access thrombosis precludes successful use of the fistula for dialysis, a reduction in access thrombosis does not necessarily translate into improved patency. If these interventions, predominantly aimed at reducing platelet aggregation and coagulation, increase the risk of bleeding, then a local haematoma may cause irremediable access loss. In contrast, access thrombosis may be treated with endovascular or surgical procedures, whereby patency is maintained or restored. In general, there were very few studies suggesting a positive effect of a given intervention and positive outcomes were rarely confirmed by independent sources. Often though, rather than formulating a neutral statement, the group also wanted to highlight existing ambiguity by communicating the items to be weighed in decision making.

Other guidelines on this topic

ESVS [34]

Long-term antithrombotic therapy should not be used to prolong vascular access patency in haemodialysis patients. (III-C)

GEMAV [35]

We suggest that antiplatelet therapy for thrombosis prophylaxis of native AV fistula be indicated on a case-by-case basis, because although it shows a decrease in the risk of thrombosis, we consider that adverse effects have not been studied with sufficient accuracy.

We suggest that antithrombotic prophylaxis not be used in patients with prosthetic AV fistulas because there is no benefit in preventing thrombosis and the adverse effects have not been studied with sufficient accuracy.

UK Renal Association [92]

We recommend that pharmacological and mechanical strategies are in place to maintain or restore access patency. (1C)

The CSN, KDIGO, KHA-CARI, NKF-KDOQI and NICE provide no current recommendations on this topic.

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Suggestions for future research

The small number of studies with their short follow-up, few participants and mostly single-centre approach precluded the formulation of any definitive recommendation. Many studies did not assess bleeding, infection or obstruction of the in- or outflow. Adverse events were often not considered or inadequately reported (e.g. systemic bleeding). Any future controlled study should try and close this gap.

Assessment of the evidence highlights the ambiguity of 'maturation' as an outcome. Some studies assess outcomes up to 1 year after the creation of an AV access and still refer to the study as evaluating maturation. Given that principles governing maturation may be different from those maintaining long-term patency, a decision was made to assess the two outcomes separately. To allow the distinction, we required >3 months of follow-up for including studies in the current chapter. To facilitate interpretation, future work should focus on establishing clear definitions for concepts that are frequently used but currently ill-defined. Determining core outcomes and harmonizing their measurement would facilitate comparison and interpretation of study results. Perhaps the SONG initiative, which aims to establish core outcomes in CKD, will bring more consistency in the terminology of outcome reporting in dialysis access studies [4].

CHAPTER 9. CANNULATION TECHNIQUES FOR AV FISTULAS

Recommendations

We suggest against using the area technique for cannulating arteriovenous fistulas in adults treated with haemodialysis. (2D)

We suggest using either a rope-ladder or buttonhole technique for cannulating arteriovenous fistulas in adults treated with haemodialysis and letting the choice be dependent on local expertise and arteriovenous fistula characteristics. (2D)

Advice for clinical practice:

- Antiseptic measures and practical aspects of the cannulation procedure are important in reducing the infection risk associated with buttonhole cannulation.
- AV grafts are usually only cannulated using a rope-ladder technique.

Rationale

• Background

Proper cannulation of the AV access is the key to its preservation and prevents vascular access–related morbidity. While AV grafts are only cannulated using a rope-ladder technique, three different methods for puncture site selection exist for AV fistulas: the area, rope-ladder and buttonhole techniques (Figure 1). The area technique refers to cannulating the same general area, but not necessarily the same point, session after session. In the rope-ladder technique, the cannulator rotates needle placement sites for each dialysis along the entire length of the cannulation segment. Both these techniques require the use of sharp—cutting—needles and allow skin healing after each haemodialysis session. In the buttonhole method, haemodialysis needles are inserted at the same site, angle and depth for consecutive dialysis sessions, using blunt—non-cutting—needles in a fibrotic track previously created by sharp needles.

The buttonhole technique has been advocated to facilitate cannulation, decrease needling pain, reduce bleeding at the end of the haemodialysis session and prevent aneurysm development. However, it is unclear whether these benefits really exist, how they balance with infection risk and whether technique choice influences long-term AV fistula patency.

• Summary of the evidence

(Supplement 3| Review questions—PICO format—Chapter 9)
(Supplement 4| Search strategies—Chapter 9)
(Supplement 5| Study selection flow diagrams—Chapter 9)
(Supplement 6| Summary evidence tables—Chapter 9)

Three systematic reviews were identified [99–101], including six reports of five RCTs comparing buttonhole with 'control' cannulation in AV fistulas [102–107]. The included RCTs reported on patient survival, access survival, quality of life, needling pain, infection, bleeding during or after dialysis and aneurysm development. Outcome definitions and measures varied, hampering formal meta-analysis. All studies included both incident and prevalent dialysis patients dialysed through an AV fistula. Buttonhole cannulation was compared with other—often ill-defined—cannulation techniques. One RCT defined the comparator as 'different-site technique', a mix of rope-ladder and area cannulation not further specified [102]. Another compared buttonhole with standard or control cannulation not further specified [103]. Three RCTs compared buttonhole versus rope-ladder cannulation [104–106]. In all these studies, by definition, buttonhole cannulation was performed with blunt needles and the comparator cannulation technique with sharp needles. Four of five RCTs included only in-centre haemodialysis patients [102–104, 106]. Only one included both home and in-centre patients [105]. Sample sizes were generally small, including between 56 and 140 participants.

Patient survival

One RCT reported eight and five deaths, respectively, in the groups using buttonhole and other cannulation techniques after 1 year (MD 7%, no statistical testing) [102]. The second RCT assessed 140 in-centre haemodialysis patients over an 8-week period, which reported one death in each group [106]. Its 12-month follow-up study equally reported similar number of deaths in both groups [107]. Finally, two RCTs also had similar event numbers in both groups at 6 months [104, 105].

Access survival

After 1 year of follow-up, one RCT had no AV fistula failures in the buttonhole group. In the group using other cannulation techniques, the median Interquartile range (IQR) time to fistula failure was 268 days (IQR 143–292) [102]. In another RCT, the median access survival was similar for both groups (~17 months) [107].
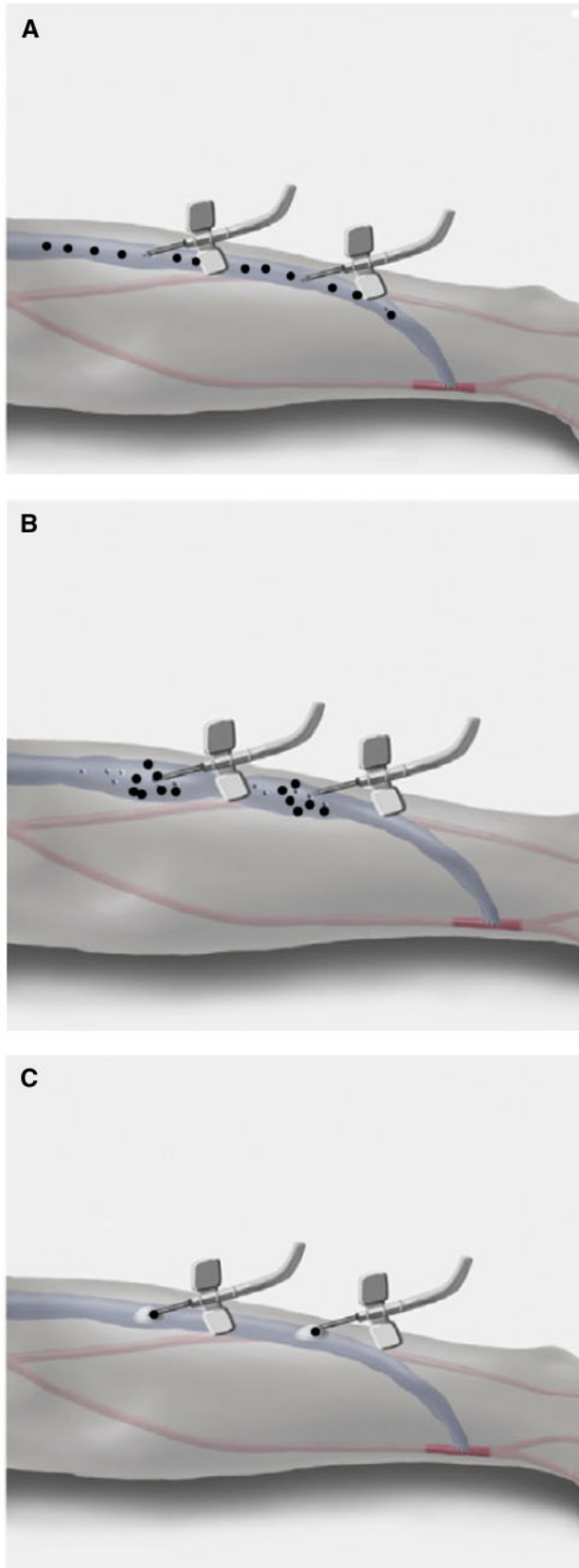
FIGURE 1: Cannulation techniques: (**A**) rope-ladder technique, (**B**) area technique and (**C**) buttonhole technique. Reprinted from Schmidli *et al.* [33], with permission from Elsevier.

Primary unassisted patency and secondary patency

In one RCT, both primary unassisted and secondary patency were substantially better in the buttonhole group than in the usual practice group (73% versus 48%, no statistical testing; 100% versus 86%; P = 0.005) [102]. However, a second RCT reported no difference in unassisted primary and secondary patency for buttonhole versus another technique [107].

Thrombosis

One RCT found no difference in thrombosis and the event rate was generally low [107]. A second RCT observed six cases of thrombosis with usual practice versus none with buttonhole [102]. A third RCT found one fistula thrombosis in both groups [104].

Quality of life

Only one RCT measured quality of life. They randomized 70 adults from multiple in-centre and home training units to either buttonhole or rope-ladder cannulation. After 6 months, they found no difference in any of the measures between the groups [105].

Cannulation pain

In a systematic review that also included non-randomized studies, buttonhole was associated with reduced needling pain in observational studies [standardized mean difference (SMD) −0.76 (95% CI −1.38 to −20.15 Standard Deviation (SD))] but not among RCTs [three RCTs; SMD 0.34 (95% CI −0.76–1.43)] [100].

All five included RCTs assessed patient-reported pain. None of these were blinded, due to the nature of the intervention, and all studies were at high risk of detection bias.

One RCT found similar pain scores for buttonhole and rope-ladder cannulation over an 8-week period (median score 1.5 versus 1.2; P = 0.57), but there was some evidence suggesting more people in the buttonhole group who experienced severe pain (pain score >3) (28.6% versus 15.7%; P = 0.07) [106]. Of note, the investigators only specified rope-ladder being the control group cannulation technique in the title of the paper; detailed information was missing from the methods. All participants in this study used a topical 5% lidocaine gel. It can be argued that the standard use of lidocaine decreased the pain scores, possibly explaining why a difference between cannulation techniques was not seen.

In the second RCT, 8 of 10 patients reported buttonhole to be less painful than their previous cannulation technique [103]. The remainder reported similar pain levels. Although randomized, the trial did not compare pain levels directly and did not provide the pain scores measured in the control group. One may also question whether the assessment time frame should be longer than 1 week.

The third RCT reported a median pain score of 3/10 before and 2.5/10 after 6 months for patients cannulated using the buttonhole technique. The rope-ladder group reported pain scores of 1/10 at both time points [104]. No statistical analysis was provided. The use of local anaesthetics was allowed and could have influenced the pain scores. Patients randomized to the buttonhole technique used local anaesthetics less frequently.

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The fourth RCT found people using the buttonhole technique reported similar pain scores compared with controls after 1 year [102]. The use of local anaesthetics was similar in both groups. And finally, a fifth RCT also found no meaningful difference in pain scores between the buttonhole and rope-ladder techniques at baseline or at the final follow-up [105]. Fewer people in the buttonhole group used xylocaine (44% versus 76.7%; P = 0.01). However, five patients using the buttonhole technique reported site pain during dialysis (P = 0.01).

Infections

A meta-analysis that included data from four RCTs indicated buttonhole cannulation to be associated with a 3-fold increase in infectious risk with other cannulation techniques [four RCTs; RR 3.34 (95% CI 0.91–12.20)] [101]. Event rates varied substantially and CIs crossed the line of no effect [101].

The first RCT reported one infection—defined as erythema, redness, swelling, tenderness, exudates or pus—in 37 patients in the buttonhole group versus none in the control group during 3 months of follow-up [103]. The investigators did not define the cannulation technique used in the control group. A second RCT reported one infection in 28 patients in the buttonhole group during a 6-month follow-up period [104]. There were no infections in the rope-ladder group. In contrast, a third RCT reported two cases of bacteraemia in the control group versus none in the buttonhole group during 1 year of follow-up. There were, however, two cases of local infection in the buttonhole group and none in the control group [102]. A fourth study documented localized infection twice as often in those using buttonhole versus other techniques during an 8-week observation period (P < 0.01) [106]. *Staphylococcus aureus* bacteraemia was noted once in the buttonhole group and not in the control group. An 18-month follow-up report described 12 patients using buttonhole experiencing an infection versus none with standard care (P < 0.001) [107]. Three of these infections were local infections and nine were *S. aureus* bacteraemia. The median time to first infection was ~11 months. A fifth RCT reported four infections in 34 patients in the buttonhole group and one infection in 35 patients in the rope-ladder group during a 6-month observation period (P = 0.11) [105]. However, the patient with the infection in the rope-ladder group had been cannulated using a buttonhole technique at the time of infection.

Bleeding from cannulation sites during dialysis

One RCT reported severe bleeding (needing an astringent) at the puncture site during the haemodialysis session in 2.7% of people using buttonhole versus 4.6% using another cannulation technique. An additional 11% of people using buttonhole experienced mild bleeding, versus none in the control group [103]. The authors reported that no statistical analysis and the cannulation technique in the control group were not defined. The second RCT reported 11 episodes of bleeding in two patients during dialysis in the buttonhole group compared with 17 episodes in the control group. The number of patients affected in the control group was not reported [104].

Haemostasis after needle removal

Time until haemostasis was <5 min in 54% of patients using buttonhole compared with 28% for those using the undefined control technique [103]. The four other RCTs included in the systematic review by Wong *et al.* [100] found no appreciable differences in post-dialysis bleeding times [102, 104–106].

Haematomas

One RCT reported 19 haematomas in the buttonhole group (8 of which occurred before creation of the buttonhole tract, 7 while creating the buttonhole tract and 4 in established tracks) compared with 27 hematomas in the rope-ladder group [104]. The second RCT found fewer haematomas with buttonhole cannulation (295/1000 dialysis sessions with buttonhole versus 436/1000 dialysis sessions with standard cannulation) (P = 0.03) [106]. Also, a greater proportion of patients in the standard group had at least one haematoma (36% versus 17%; P = 0.01). In contrast, the third RCT reported four haematomas in 34 patients in the buttonhole group and none in the usual care group (P = 0.03) [105].

Aneurysm development

One RCT assessed the average increase in maximum transverse fistula diameter based on measurements from photographs taken at baseline and after 6 months [104]. Overall, in the buttonhole group, AV fistulas did not increase in size. In the rope-ladder group, AV fistulas widened by 30% on average, corresponding to an absolute increase of 5 mm. The second RCT found new aneurysms in 4% of patients using a buttonhole cannulation technique and in 17% of people using the control technique [102]. Enlargements of pre-existing aneurysms were found in 23% of patients in the buttonhole group and in 67% in the control group. An aneurysm was defined as a swelling of 0.5 cm or an increase in size ≥0.5 cm. Aneurysms were assessed based on photographs on a 3-month basis. No studies used ultrasound to assess aneurysm formation.

• Translation of the evidence into recommendations

The technique used for cannulation of an AV fistula has uncertain effects on patient and access survival. RCT data are scant and contradictory, making any inference for critical outcomes quite problematic. Similarly, high-certainty data for quality of life that could steer judgement in decision making are currently not available. The supposition that the buttonhole technique causes less cannulation pain is not supported by current RCTs. However, the use of local analgesic treatment possibly influenced the extent to which pain could be objectively measured. In addition, the cannulation technique used in control groups was ill-defined for most studies.

There is evidence suggesting that the buttonhole technique leads to an increased risk of local and systemic infections as compared with rope-ladder cannulation. However, the GDG felt that risk may be somewhat modified through appropriate antiseptic measures. There is also low-certainty evidence from two studies suggesting that buttonhole cannulation causes less extensive aneurysm formation, although patency rates appear to be similar.

The GDG felt the RCT evidence base did not allow a clear recommendation in favour of a specific cannulation technique. In the absence of such evidence, they felt their advice should incorporate a large observational study including >7000 patients, indicating the area technique to be associated with poorer AV fistula survival than the other two techniques [108].

The group felt it reasonable to support both rope-ladder and buttonhole cannulation techniques according to centre expertise, AV fistula characteristics and patient preference. Often the length of the fistula cannulation segment will dictate whether to opt for buttonhole or rope-ladder. The GDG also agreed that all centres would benefit from maintaining a minimal level of experience with the different techniques within the vascular access team.

From the observational data, it becomes apparent that there is large variability in how different techniques are applied in clinical practice. A single label (buttonhole, rope-ladder, area cannulation) often covers different practices, which complicates interpretation of the evidence that is available. In that perspective, the GDG advised to have a quality improvement programme in place where outcomes of cannulation are registered and analysed at regular intervals.

Other guidelines on this topic

CSN [109]

For adult end-stage renal disease patients receiving intensive home haemodialysis with an AV fistula, we suggest the use of rope-ladder cannulation over buttonhole cannulation unless topical antimicrobial prophylaxis is used. (2D)

For adult end-stage renal disease patients using buttonhole cannulation for intensive home haemodialysis, we suggest the use of mupirocin antibacterial cream to reduce the risk of infection. (2D)

ESVS [34]

In patients with a short cannulation segment, the use of the buttonhole technique should be considered over other techniques. (IIIa-C)

KHA-CARI [110]

Compared with the rope-ladder technique, the buttonhole technique is associated with an increased risk of local and systemic infection and should not be routinely performed. (Level II evidence)

NKF-KDOQI [86]

Patients with fistula access should be considered for buttonhole cannulation and for self-cannulation, the buttonhole is the preferred technique.

GEMAV [35]

We recommend that the rope-ladder technique be used as the method for cannulating a prosthetic AV fistula.

We recommend that the rope-ladder technique be used as the preferred method for cannulating native AV fistulas.

We recommend that the buttonhole technique be reserved for cannulating tortuous or deep native AV fistulas and/or those with an extremely short venous length.

UK Renal Association [92]

We recommend that the rope-ladder and buttonhole techniques should be used for cannulation of AV fistulas and rope-ladder for AV grafts. (2B)

KDIGO and NICE provide no current recommendations on this topic.

Suggestions for future research

Long-term RCTs are needed for comparing buttonhole with other cannulation techniques in incident haemodialysis patients. Such studies should measure pain using validated methods [111]; be adequately powered for infection, patency and quality of life and include detailed reporting of complications.

CHAPTER 10. NEEDLE TYPES FOR AV FISTULAS

Recommendations

> We suggest using either sharp needles or plastic cannulas for cannulating arteriovenous fistulas in adults treated with haemodialysis. (2C)
>
> We recommend using blunt needles only for buttonhole cannulation of arteriovenous fistulas in adults treated with haemodialysis. (1D)

Advice for clinical practice:

- A quality improvement programme including recording and monitoring of the needle types and cannulation techniques alongside with AV access outcomes can help monitor quality, guide changes in cannulation practice if needed and improve the quality of vascular access care.
- AV grafts are usually only cannulated using sharp steel needles.

Rationale

• Background

Sharp steel needles are routinely used for cannulating AV grafts with a rope-ladder technique. In contrast, various methods are used for cannulating AV fistulas. Besides differences in the location and direction of needle insertion and differences in cannulation technique, the shape of the needle (sharp or blunt, with or without side or back holes) and the material of the conduit (steel needle or plastic cannula) may influence AV access longevity. Most units use sharp or dull steel needles, which remain *in situ* during the dialysis session, providing a conduit for the blood flow throughout each treatment. A sharp bevelled needle can cause trauma to the vessel if inserted or placed incorrectly. It can even perforate the AV fistula should the patient move inadvertently. In some haemodialysis units, a synthetic cannula is inserted together with a sharp steel introducer that is withdrawn once the cannula sits within the vessel. The cannula is then used as the conduit during the dialysis session. Other needling systems based on synthetic materials also exist. Theoretically these synthetic needling systems should result in fewer physical fistula injuries, but the benefits and harms of these alternative systems require assessment.

• Summary of the evidence

(Supplement 3| Review questions—PICO Format—Chapter 10)
(Supplement 4| Search strategies—Chapter 10)

(Supplement 5| Study selection flow diagrams—Chapter 10)
(Supplement 6| Summary evidence tables—Chapter 10)

Three RCTs assessing different needle designs were identified. One study, published only as an abstract, compared large-gauge hollow-bore sharp steel needles (referred to in the study as standard needles) versus Nipro SafeTouch sharp steel needles (referred to as safety needles) [112]. The second RCT compared sharp versus blunt steel dialysis needles using a buttonhole cannulation technique [113]. The third study compared plastic cannulas with sharp needles using the rope-ladder technique [114]. All three RCTs were conducted in a single centre and reported outcomes after 1 and 6 months up to 1 year. Sample sizes were generally small, including 33–39 participants.

All included RCTs reported outcomes considered relevant to this guideline: cannulation difficulty or complications, needling pain, infection, bleeding during or after dialysis, need for interventions and patient preference. Outcome definitions and measures varied. Two studies included prevalent haemodialysis patients [112, 113] and one study included incident patients [114].

One RCT assessed a composite primary outcome of 'acute access-associated complications', including needlestick injuries, fistula 'blows' (not otherwise defined) and needle dislodgement [112]. 39 participants were randomized to standard needles or safety needles. No needle stick injuries occurred in either group. In the standard needle group, 24 infiltrations—not otherwise defined—occurred during cannulation and dialysis, while 15 infiltrations occurred in the safety needle group. According to the authors, the result was not statistically significant, but no analysis was provided.

A second RCT reported data after <1 month in 35 participants and 335 dialysis sessions [113]. Participants were randomized at each session to have their AV fistula cannulated using a buttonhole technique with a blunt needle or a sharp needle. Resultant important carry-over between the interventions made inference particularly challenging. Overall, among 169 AV fistula cannulations randomized to blunt needles, 12 were ultimately cannulated with a sharp needle due to failed cannulation. Of the 166 AV fistulas randomized to sharp needles, four were ultimately cannulated with a blunt needle because the patient refused cannulation with a sharp needle or experienced pain during cannulation. Overall, the difference in failed cannulation was not statistically significant for the downstream needle. For the upstream needle, a blunt needle resulted in cannulation failure more frequently than a sharp one (6% versus 0%; P = 0.001). There were no meaningful differences in needling pain, bleeding time or infection rate between the two treatment groups [113].

A third study randomized 33 participants to have their AV fistula cannulated either with plastic cannulas or sharp needles [114]. Effects on the number of people having undergone a procedure for stenosis, thrombosis or aneurysm formation were uncertain due to wide CIs and an imbalance in baseline event rates. With plastic cannulas, there seemed to be 50% fewer patients experiencing complications, defined as infiltration either during cannulation or dialysis itself [RR 0.53 (95% CI 0.29–0.97)]. Again, however, the certainty of the evidence was low due to sample size restrictions.

- **Translation of the evidence into recommendations**

The type of needle used for cannulation of an AV fistula has very uncertain effects on patient and access survival. RCT data are scant, making any inference for critical outcomes quite problematic. Similarly, high-certainty data for quality of life that could steer judgement in decision making are currently not available. It appears that sharp steel needles less often result in failed cannulation than blunt ones. In addition, the professed benefit of less cannulation pain with blunt steel needles in buttonhole cannulation is not supported by current RCT data. Unfortunately, those data are sparse. Only one very small trial tested sharp needles in AV fistulas cannulated using the buttonhole technique, and the buttonhole technique was originally described using blunt needles—the aim being not to injure the cannulation tract [113].

There is only one small RCT assessing the proposition that synthetic materials used for cannulation result in less damage to the AV fistula vessel. Again, however, sample size limitations prevent a preference of one material over another [114].

Other guidelines on this topic

The CSN, ESVS, GEMAV, KDIGO, NKF-KDOQI, KHA-CARI and NICE provide no current recommendations on this topic.

Suggestions for future research

Adequately powered multicentre randomized trials assessing the benefits and harms of sharp steel needles versus other needling systems using standardized outcomes would be informative. The currently available reports do not resolve the uncertainty about long-term effects and incompletely describe possible adverse events.

CHAPTER 11. TIMING OF INTERVENTION FOR AV FISTULA THROMBOSIS

Recommendations

> We suggest attempting to declot a thrombosed arteriovenous fistula in adults as soon as possible under optimal conditions and before the next haemodialysis treatment. (2D)
>
> We suggest attempting to declot a thrombosed arteriovenous fistula in adults, even if there has been a delay of days to weeks. (2D)

Advice for clinical practice:

- None.

Rationale

- **Background**

Thrombosis of the AV fistula occurs quite often (one per person every ≥four years) and is one of the most frequent causes of access failure (Helthuis et al., submitted for publication). Thrombosis causes vessel wall inflammation and structural injury to the vascular endothelium. On the assumption that the longer a blood clot is present, the more damage it inflicts, many consider an attempt at declotting the AV fistula an emergency procedure to be performed as quickly as possible.

However, such a strategy inevitably creates logistical challenges and may inadvertently lead to worse outcomes if less experienced operators must intervene in suboptimal conditions during out-of-office hours. Understanding the trade-offs is the key in decision making.

In AV graft thrombosis, the blood clot is relatively inert. While it is widely agreed that a timely attempt at declotting the AV graft must be made to avoid central venous catheters, thrombosis is generally not considered an emergency. Therefore this chapter only covers AV fistula thrombosis [115].

• **Summary of the evidence**

(Supplement 3| Review questions—PICO format—Chapter 11)
(Supplement 4| Search strategies—Chapter 11)
(Supplement 5| Study selection flow diagrams—Chapter 11)
(Supplement 6| Summary evidence tables—Chapter 11)

There were no RCTs comparing the benefits and harms of earlier versus later interventions for declotting a thrombosed AV fistula.

There were four retrospective analyses assessing the effect of time to intervention on outcome of the AV fistula [116–119]. All were inherently at very high risk of bias through selection, attrition and failing to reach the optimal information size. AV fistula outcomes were mostly reported in terms of technical success and data on primary or secondary patency were largely absent.

A first, nested case–control study including 188 AV fistulas indicated that surgical thrombectomy within 24 h of diagnosing thrombosis of the AV fistula resulted in 50% technical success [116]. If deferred to any time during the first week, then only 20% of thrombectomy procedures remained successful. After that, the probability of success dropped to 10%. The investigators provided univariable comparison data only and no attempt was made to accommodate factors influencing clinical decisions.

A second, retrospective analysis included 59 people with thrombosis of their AV fistula who had all been referred to vascular surgery as quickly as possible [117]. Surgical thrombectomy with percutaneous transluminal angioplasty or stent placement resulted in technically successful declotting of the AV fistula in 84% of participants treated within 6 h of diagnosis. In those treated after that time, the procedure was successful in 74% [RR 1.14 (95% CI 0.87–1.49)]. Again, the comparison was univariable with data unadjusted for possible confounding variables and CIs very wide.

In a third study, investigators retrospectively reviewed all 60 episodes of vascular access failure within a 3-year time frame [118]. More than half were treated with thrombolysis, about a third with a combination of thrombolysis and angioplasty and one-tenth with angioplasty alone. When comparing interventions executed within 48 h of diagnosis versus those performed after 48 h, they found the odds of intervention failure to be about half in the group with a 2-day delay versus the group in which the intervention had occurred within 2 days [OR 0.55 (95% CI 0.31–0.99)]. This corresponded with an estimated 32% relative lower odds for access failure at 3 months [OR 0.68 (95% CI 0.36–1.27)]. The study included both AV fistulas and grafts. Although the analysis attempted to adjust for possible confounders, interaction tests or subgroup data were not available.

Finally, a group of investigators retrospectively reported their experience with streptokinase intravascularly infused at the site of the thrombosis [119]. Of the 19 participants treated within 4 days of diagnosis, the procedure was successful in 16 (84%). For the eight treated afterwards, thrombolysis was successful in three (38%) [RR 2.25 (95% CI 0.90–5.61)]. The sample size was small, cut-offs arbitrarily chosen and analyses univariable.

• **Translation of the evidence into recommendations**

AV access failure is a common and serious complication leading to increased temporary catheter use, access creation at multiple sites and, after many years, of multiple access failures, to a catastrophic inability to provide haemodialysis in some cases. Thrombosis is one of the most frequent causes of access failure, and successful declotting can save the access from permanent failure.

Intuitively, one would think that the earlier the intervention (surgical or radiological) is undertaken, the more likely it will result in successful access salvage, as delay can only result in clot organization, retraction and fibrosis. Indeed, for this reason, many have considered AV access thrombosis an emergency, necessitating immediate intervention. However, the evidence to support this assumption is very sparse. There have been no randomized trials assessing the effect of increasing the time to intervention (within a reasonable time frame) on access outcome, and the observational data are limited and at high risk of being biased.

In addition, there may be biologic reasons for challenging the existing paradigm. Given that acute thrombosis is associated with vessel wall inflammation and endothelial injury, and such early active inflammation may be prothrombotic in itself, it is biologically plausible that some delay in intervention may in fact avoid rapid recurrence of thrombosis after intervention.

Also, a recommendation favouring the shortest possible window for intervention may have important implications for service delivery and health care resources. One of the included studies assessed the causes for delay in intervention—the majority were due to the lack of interventional radiology unit availability [120]. A statement favouring rapid intervention could also inadvertently lead to worse outcomes if less experienced operators must intervene in suboptimal conditions during out-of-office hours. Finally, most cases of access thrombosis are associated with an outflow stenosis, which may not be amenable to surgical treatment. Adequate imaging of the inflow and outflow should be performed and thrombectomy and stenosis treated simultaneously [120–123].

In the absence of a clear understanding of the trade-offs at present, it seems reasonable that the timing of the intervention is determined by different factors, including the urgency for a functioning dialysis access and the availability of optimal logistical conditions to perform the best possible intervention.

Whereas there seems to be little data to support an aim for the maximum time to intervention, the existing data support intervention, irrespective of the time delay. Even after 2 days, 70% of procedures are still technically successful (corresponding to a 3-month primary patency in 63%), and up to 1 week, still about one in five can technically be salvaged [116, 118].

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This challenges the widely held view that late intervention is likely to be futile. Modern mechanical thrombectomy devices could be even more effective in restoring patency several days after the thrombotic event [124, 125].

Other guidelines on this topic

ESVS [34]

We recommend that for vascular access salvage after early thrombosis, thrombectomy and revision should be performed as soon as possible. (IC)

NKF-KDOQI [86]

Thrombectomy of a fistula should be attempted as early as possible after thrombosis is detected, but can be successful even after several days. (B)

GEMAV [35]

We recommend a priority be placed on attempting to restore the patency of potentially recoverable thrombosed AV fistulas, preferably within the first 48 h. In all cases, the priority should be to salvage the AV fistula and avoid central venous catheter placement.

UK Renal Association [92]

We recommend that each centre should have facilities for surgical and radiological intervention for prompt and timely treatment of AV fistula/graft stenosis; a local standard policy should be developed. (1B)

The CSN, KDIGO, KHA-CARI and NICE provide no current recommendations on this topic.

Suggestions for future research

An adequately powered prospective observational trial aimed at assessing standardized outcome measures according to increasing time to intervention analysed as a continuous variable could be informative for answering this question. An integrated health–economic evaluation would be required to assess the desirability of implementing the service change required to meet a set maximum time-to-intervention threshold.

CHAPTER 12. SURGICAL AND ENDOVASCULAR INTERVENTIONS FOR AV ACCESS THROMBOSIS

Recommendations

> We suggest the choice between surgical and endovascular interventions for AV access thrombosis be defined by the condition of the patient and their vascular access as well as local expertise, as there is no evidence one approach improves outcomes more than any other. (2B)

Advice for clinical practice:

- None.

Rationale

• Background

Traditionally an occluded AV access was always treated surgically. However, over the past 20 years, endovascular techniques have increasingly been developed and are used as an alternative to salvage thrombosed vascular accesses. Most centres tend to prefer either surgery or endovascular intervention, depending on and at the same time determined by local availability and experience with either technique. We aimed to determine which interventions—surgical or endovascular—has the best risk–benefit balance in the setting of AV access salvage, both for AV fistulas and AV grafts.

• Summary of the evidence

(Supplement 3| Review questions—PICO format—Chapter 12)
(Supplement 4| Search strategies—Chapter 12)
(Supplement 5| Study selection flow diagrams—Chapter 12)
(Supplement 6| Summary evidence tables—Chapter 12)

Three RCTs were identified comparing either surgical versus endovascular intervention or different types of endovascular intervention with one another. Populations, interventions, comparators and outcomes varied across studies. All trials included participants with AV grafts.

The first RCT compared the efficacy of a mechanical thrombectomy device (Amplatz) versus conventional surgical thromboembolectomy for declotting 174 thrombosed AV grafts [126]. Between the 109 patients randomized to mechanical thrombectomy and the 65 individuals treated with a surgical approach, there was no difference in immediate thrombectomy success and short- or long-term graft patency with successful dialysis. No extensive details of differences in minor and major adverse events between the two groups were provided. Information on sequence generation (computer-based) was given, but the study remained at unclear risk for most of the other sources of bias. Of note, there was no information on whether the surgical approach included construction of a new anastomosis, that is, proximalization of the AV access.

The second RCT was a multicentre study including 120 adults with recently thrombosed AV grafts who were randomized to hydrodynamic thrombectomy ($n = 62$) or pulse spray thrombolysis ($n = 58$), both endovascular procedures [127]. No statistically significant differences were noticed in either technical success (as defined by $\geq$80% thrombus removal) or clinical success (technical success plus being able to provide successful dialysis) at 30 and 90 days. Similarly there were no meaningful differences in procedure-related blood loss and early or late complications. Conversely, thrombus treatment times were shorter for thrombectomy than for thrombolysis (16.8 versus 23.4 min; P < 0.01), suggesting that hydrodynamic thrombectomy could be useful for reducing treatment procedure time with no impact on efficacy over thrombolysis. The study was unclear with respect to selection bias, as no details were provided on randomization and allocation concealment. However, there was a high risk of funding bias due to a declaration of interest by one of the co-authors.

The third RCT randomized 40 patients with clotted AV grafts to a lyse-and-wait technique with 4 mg of the tissue plasminogen activator alteplase ($n = 20$) or to a percutaneous thrombectomy device (Arrow-Trerotola), also both endovascular interventions [128]. In addition, 20 non-consecutive patients with thrombosed synthetic AV grafts who were randomized to

undergo the lyse-and-wait technique with urokinase (250 000 U) as part of an earlier clinical study served as historical controls. The immediate anatomic success rate was 95% in both the tissue plasminogen activator lyse-and-wait and percutaneous thrombectomy device groups. The mean in-room time until restored flow was significantly lower for lyse-and-wait with tissue plasminogen activator than the percutaneous thrombectomy device (10 versus 19 min; $P < 0.01$), although there were no differences in the mean in-room procedure time. No bleeding complications occurred in the percutaneous thrombectomy device group. Conversely, seven episodes of bleeding occurred in 6 patients treated with tissue plasminogen activator and 4 of the 20 patients undergoing lyse-and-wait with urokinase had minor puncture site bleeding during the procedure. The 3-month primary patency rates were 65, 65 and 60% for lyse-and-wait with tissue plasminogen activator, percutaneous thrombectomy device and lyse-and-wait with urokinase, respectively. Given the lack of information provided, the study risk of bias remained unclear for most of the items considered.

- **Translation of the evidence into recommendations**

There is little randomized evidence available addressing this issue. The three RCTs found were mostly designed to evaluate the efficacy or superiority and safety of specific (endovascular) techniques or devices rather than comparing, more generally, surgical over endovascular approaches for AV access thrombosis. In addition, no study compared any of the available procedures in AV fistulas, all participants had AV grafts. Lastly, surgical outcomes are biased if a new anastomosis, that is, proximalization of the AV access, is included in the surgical treatment. Observational studies suggest that thrombectomies with adjuvant treatment to correct an underlying problem result in better outcomes than endovascular intervention [129]. The appropriate comparator is surgical balloon thrombectomy (without altering the anastomosis) versus endovascular intervention. Such a study has not been conducted. This heterogeneity of procedures employed, type of interventions and comparators and outcomes analysed prevent us from drafting definitive conclusions or recommendations favouring one approach over the other.

Other guidelines on this topic

CSN [90]
Correct thrombosis of an AV graft with pharmacomechanical or mechanical thrombolysis or surgical thrombectomy. (Grade D)

ESVS [34]
Surgery or endovascular methods should be considered for treatment of late thrombosis of vascular accesses depending on the centre's expertise. (IIa-B)

Treatment of vascular access thrombosis should include perioperative diagnosis and treatment of any associated stenosis. (I-C)

GEMAV [35]
We recommend an imaging test be carried out after restoring AV fistula patency. This should be performed immediately after thrombectomy to detect any possible stenoses requiring treatment.

We initially recommend native AV fistula with thrombosis secondary to juxta-anastomotic stenosis be treated by surgical treatment as long as the technique does not require central venous catheter placement.

We recommend the patency of native AV fistula in thromboses not associated with juxta-anastomotic stenosis be restored by surgical treatment or by endovascular therapy using mechanical thrombectomy or aspiration devices, if necessary.

We recommend it be attempted to restore the patency of thrombosed prosthetic AV fistulas by surgical or endovascular treatment.

We recommend elective intervention be performed on the dysfunctional AV fistula with significant stenosis instead of restoring after thrombosis.

We recommend attempting to restore the patency of thrombosed AV fistulas rather than creating a new AV fistula and place a central venous catheter, as this is associated with lower health costs, lower hospitalization rates and lower morbidity and mortality.

The KDIGO, NKF-KDOQI, KHA-CARI and NICE provide no current recommendations on this topic.

Suggestions for future research

Given the lack of evidence proving the superiority of surgical over endovascular treatment for treating fistula thrombosis, adequately powered RCTs providing data on the same type of vascular access/problem (e.g. primary or recurrent thrombosis, native fistula/grafts) and any type of procedure would be highly informative. Studies should ideally target the same core set of outcomes that should be considered essential for answering this research question, such as targeted efficacy endpoints (including but not limited to anatomic and clinical success rate at established time points, procedure duration and long-term patency with successful dialysis) and the safety profile, particularly in terms of peri- and post-procedural bleeding. Population selection and minimization of potential biases are also crucial issues given the impossibility, due to the nature of the intervention, of eliminating performance and detection bias by blinding patients, investigators and outcome assessors.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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