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CLINICAL PRACTICE GUIDELINE DOCUMENT

Editor's Choice – European Society for Vascular Surgery (ESVS) 2020 Clinical Practice Guidelines on the Management of Acute Limb Ischaemia

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ABBREVIATIONS AND ACRONYMS

AAO	Acute aortic occlusion
ABI	Ankle brachial pressure index
AC	Anticoagulation
AF	Atrial fibrillation
ALI	Acute limb ischaemia
APTT	Activated partial thromboplastin time
ASA	Acetylsalicylic acid
CDT	Catheter directed thrombolysis
CE-MRA	Contrast enhanced magnetic resonance angiography
CI	Confidence interval
CK	Creatine kinase. (This is the same enzyme as creatine phosphokinase, often abbreviated CPK in older literature, and in some countries.)
COMPASS	Cardiovascular Outcomes for People Using Anticoagulation Strategies
CRP	C reactive protein
CS	Compartment syndrome
CTA	Computed tomography angiography
DOAC	Direct oral anticoagulants
DSA	Digital subtraction angiography
DUS	Duplex ultrasound
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
ESC	Eurpean Society of Cardiology
ESVS	European Society for Vascular Surgery
EVAR	Endovascular aneurysm repair
HR	Hazard ratio
IRI	Ischaemia reperfusion injury
IU	International unit
LMWH	Low molecular weight heparin
MALE	Major adverse limb events
NHDS	National Hospital Discharge Survey
OR	Odds ratio
PA	Popliteal artery aneurysm
PAD	Peripheral artery disease
PMT	Pharmacomechanical thrombolysis
PTA	Percutaneous transluminal angioplasty
RCT	Randomised controlled trial
RR	Relative risk
rtPA	Recombinant tissue plasminogen activator
STILE	Surgery *vs.* Thrombolysis for Ischaemia of the Lower Extremity
TOPAS	Thrombolysis or Peripheral Arterial Surgery
UFH	Unfractionated heparin
VQI	Vascular Quality Initiative
WC	Writing committee

1. INTRODUCTION

1.1. Purpose

The European Society for Vascular Surgery (ESVS) has developed guidelines for treating patients with acute limb ischaemia (ALI). The focus on the guidelines is on lower limb acute ischaemia; however recommendations are also made on acute upper limb ischaemia. The term acute leg ischaemia is not used, in order to avoid confusion, as the same abbreviation, "ALI", may be used. These guidelines will provide guidance for emergency physicians; vascular, cardiovascular and general surgeons; angiologists; interventional radiologists; and radiologists. The target population comprises patients with acute lower and/or upper limb ischaemia. The guidelines, which are developed by specialists in the field, promote a high standard of care (based on evidence, whenever available). Guidelines should not be viewed as a legal standard of care. This document is a guiding support, and the care given to a patient will always be dependent on the individual (symptom variability, comorbidities, age, level of activity), and treatment setting (techniques available, local circumstances, and expertise). To further underline this supportive character of the Guidelines, non-European reviewers were invited to review the document, so that it could serve doctors treating patients globally. This is also the rationale behind the decision to publish all ESVS Guidelines as free to download, and why the ESVS Guidelines app also can be downloaded free of charge from the ESVS website (www.esvs.org).

1.2. Methodology

1.2.1. Writing Committee. Members of the Writing Committee (WC) were selected by the ESVS to represent clinicians involved in the treatment of ALI and included vascular surgeons and interventional radiologists. Members of the WC have provided disclosure statements regarding all relationships that might be perceived as real or potential sources of conflicts of interest. These are filed and available from ESVS headquarters. Members of the WC received no financial support from any pharmaceutical, device, or surgical industry to develop these guidelines. The ESVS Guideline Committee was responsible for

undertaking the review process. The final version was checked and approved by the WC and the Guideline Committee.

1.2.2. Definition of clinically relevant issues. The WC held an introductory meeting on 13/14 June 2018 in Uppsala, Sweden, where the list of topics and author tasks were determined. After the first draft was completed and internally reviewed, the WC met again on 14/15 January 2019 in Hamburg, Germany, to review and approve the wording of each recommendation. The Guidelines then underwent external reviews, and the final version of the document was approved on July 30th, 2019.

1.2.3. Literature search. Members of the WC agreed on a common systematic literature search strategy for each of the assigned chapters. The literature search of articles published from 1 January 1990, published in English, was performed in the PubMed, Embase, Cardiosource Clinical Trials Database, and Cochrane Library databases up to 31 July 2018. The search was performed with the help of an information specialist (a clinical librarian). Reference checking and manual searching by the members of the WC added other relevant literature. In all, 6 549 unique abstracts were retrieved after duplicates were removed. The detailed literature search is described in Appendix S1 (see Supplementary Material).

Selection of the literature was based on the information provided in the titles and abstracts of the retrieved studies. Only peer reviewed published literature and studies with predefined outcomes were considered. The selection process followed the pyramid of evidence, with aggregated evidence at the top of the pyramid (systematic reviews, meta-analyses), followed by randomised controlled trials (RCTs), and, finally, observational studies. Single case reports, abstracts, and *in vitro* studies were excluded, leaving expert opinion at the bottom of the pyramid. Articles published after the search date or in another language were only included if they were of paramount importance to these guidelines. After the second external review the members of the WC were asked to perform a second literature search within their area of responsibility to see if any important publications had been published between 31 July 2018 and 21 June 2019.

1.2.4. Evidence and recommendations criteria. The European Society of Cardiology (ESC) system was used for grading evidence and recommendations. A, B, or C reflects the level of current evidence (Fig. 1) and the strength of each recommendation was then determined to be either class I, IIa, IIb, or III (Fig. 2).

1.2.5. The revision process. The guidelines document underwent revision by members of the ESVS Guidelines Committee, and by external experts in the field. Each draft was revised according to the reviewers' suggestions and the final document was submitted to the *European Journal of Vascular and Endovascular Surgery* (*EJVES*) and the ESVS Guidelines Committee on 4 July 2019.

Level of evidence A	Data derived from multiple randomised clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomised clinical trial or large non-randomised studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, and registries.

Figure 1. Levels of evidence.

Classes of recommendation	Definition
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, and effective.
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.

Figure 2. Classes of recommendation.

1.3. Terminology and definitions

ALI is characterised by a sudden decrease in arterial perfusion of the limb, with a potential threat to the survival of the limb, requiring urgent evaluation and management.[1] ALI is considered when the symptom duration is less than two weeks.[2,3] A symptom duration of greater than two weeks is usually considered to represent chronic limb ischaemia and is covered by other guidelines.[4,5]

The most common causes of ALI are embolism, thrombosis of native arteries or reconstructions, peripheral arterial aneurysm, dissection, and traumatic arterial injury. The ischaemia is graded clinically according to the Rutherford ALI classification system (see Table 2).[2] Assessment determines whether the limb is viable or irreversibly damaged. The distinction between grade IIa and IIb, and between grade IIb and III, can sometimes be challenging. Prompt diagnosis and revascularisation by means of catheter based thrombolysis and/or thrombaspiration or by open surgery reduces the risk of limb loss and death. Primary amputation is recommended in patients with irreversible (Class III) ischaemia. Despite urgent revascularisation, mortality and major amputation rates are high (for details see section 5, Registries and Quality Improvement).

1.3.1. Areas not covered by these guidelines. The general rule for ESVS guidelines is to avoid covering groups of patients in multiple guidelines, as that may result in contradictions. For this reason, the following groups of patients are not covered by these guidelines. (i) Aortic dissection may result in ALI, most often as a result of compression of the true lumen or dynamic / static obstruction of flow in one or both of the iliac arteries. This condition is covered by the Management of Descending Thoracic Aorta Diseases: Clinical Practice Guidelines of the ESVS.[6] (ii) ALI may occur as a complication of aortic surgery, but that issue is covered by the ESVS 2019 Clinical Practice Guidelines on the Management of Abdominal Aorto-iliac Artery Aneurysms.[7] (iii)

The ESVS has advanced plans to develop Clinical Practice Guidelines on Vascular Trauma / Injuries. Thus, ALI secondary to trauma (iatrogenic or not) is not covered by these guidelines, except when discussing ALI in children (section 8, ALI in Children). (iv) Upper limb ALI is covered in section 7 (Diagnosis and Treatment of Upper Limb Acute Ischaemia), but treatment of patients who develop this condition during renal replacement therapy is covered by the Vascular Access 2018 Clinical Practice Guidelines of the ESVS.[8] (v) Ischaemia may also develop secondary to deep venous thrombosis, and secondary low arterial blood flow, but this condition (phlegmasia cerulea dolens) is covered by the 2015 ESVS Venous Guidelines.[9] (vi) Blue toe syndrome, when emboli lodge in the arteries of the toes (or fingers; often referred to as endarteries, as they lack collaterals) is often associated with great pain but is not covered by these guidelines, as the condition does not result in limb ischaemia. When this condition is suspected it is important to identify the source of embolism.[4] (vii) A number of uncommon causes of ALI are only mentioned for the sake of differential diagnosis (Table 1). The management of these rare diseases can be studied in textbooks.

1.4. Historical notes

An invited editorial on the history of the treatment of ALI is published together with these Guidelines: "Where we have come from: a short history of surgery for ALI".[13]

1.5. Epidemiology

The true incidence of ALI is largely unknown owing to heterogeneous forms of presentation and treatment. Frequently, epidemiological studies include both ALI and chronic limb ischaemia, without clear differentiation. Also, there may be significant geographical variations due to ethnicity, accessibility, and quality of health care; most of the data on which these guidelines are based are from Western Europe and North America. Exceptionally, a publication reported on a Chinese population who underwent thrombolysis for ALI, with similar results to those reported from Europe and North America.[14] The EUCLID study (Examining Use of Ticagrelor in Peripheral Artery Disease) was a global RCT on ticagrelor treatment of patients with peripheral artery disease (PAD) and recruited 13 885 patients from 28 countries and 811 sites. They reported on two interesting subgroups: 642 (4.6%) patients who had critical limb ischaemia at baseline,[3] and 232 (1.7%) who developed ALI (0.8 per 100 patient years).[15] Risk factors for the development of ALI in this cohort, with mainly benign chronic limb ischaemia, were previous peripheral revascularisation, atrial fibrillation (AF), and lower ankle brachial pressure index (ABI).

Over the last century, there has been a general shift in aetiology from embolisation due to rheumatic or congenital valve disease in relatively young patients; to embolisation due to cardiac dysrhythmia; or *in situ* thrombosis in elderly patients.[16,17] It is important to note that ALI caused by native artery thrombosis or embolisation into an atherosclerotic vascular bed has increased in incidence, which has important implications for treatment.[13] Validation of charts revealed three distinct categories of ALI: (i) lower limb arterial thrombo-embolism; (ii) acute exacerbation of chronic limb ischaemia; and (iii) iatrogenic ALI after revascularisation procedures. Approximately 70% of patients presented within two weeks of symptom onset, whereas 30% of patients presented with symptoms lasting more than two weeks. The cause of embolisation is usually attributed to AF or left ventricular mural thrombi after acute myocardial infarction, whereas acute thrombotic occlusions occur in individuals with a high atherosclerotic burden.[18] Lower extremity embolisation due to aortic thrombi is a well known source of embolisation, and may be caused by manipulation of devices during endovascular repair of abdominal aortic aneurysm.[19]

Table 1. Uncommon causes of acute limb ischaemia[10–12]

Cause	Pathology	Signs to look for
Vasculitis	Inflammation of the arteries	Bilateral disease. Systemic symptoms (e.g., fever). Signs of connective tissue disease.
Popliteal entrapment syndrome	The popliteal artery is compressed by muscle or tendon during plantar flexion	Young active patient, no atherosclerotic risk factors. History of claudication pain.
Adventitial cystic disease	Cyst in the vessel wall, occluding blood flow	Acute arterial thrombosis (usually popliteal) in a young person. No atherosclerotic risk factors.
Paradoxical embolism	Atrial septal defect, venous thrombo-embolism (often with pulmonary hypertension)	Venous thrombo-embolism, cardiac bruit, and pulmonary embolism
Tumour embolism	Tissue like embolic material	Signs of tumour or malignancy (usually advanced) in heart or lung
Acute compartment syndrome	Swelling of tissues within fascial compartment (especially the anterior compartment of leg) compressing arteries	History of revascularisation or prolonged surgery. Pain on passive movement
Foreign body embolisation	Gangrene in multiple fingers or toes, often associated with infection or intravenous drug use	Intravenous drug users
Thrombophilia	Arterial thrombosis without risk factors	Young patients, often with a family history
Low cardiac output syndromes	Low blood flow to the extremities, worsened by devices. Common causes: hypotension, shock, and sepsis	Patients with severe cardiac failure, intra-aortic pump devices, extracorporeal membrane oxygenation (ECMO)

Table 2. Clinical categories of acute limb ischaemia according to Rutherford[2]

Grade	Category	Sensory loss	Motor deficit	Prognosis	Doppler signals	
					Arterial	Venous
I	Viable	None	None	No immediate threat	Audible	Audible
IIA	Marginally threatened	None or minimal (toes)	None	Salvageable if promptly treated	Inaudible*	Audible
IIB	Immediately threatened	More than toes	Mild/moderate	Salvageable if promptly revascularised	Inaudible	Audible
III	Irreversible	Profound, anaesthetic	Profound, paralysis (rigor*)	Major tissue loss amputation. Permanent nerve damage inevitable	Inaudible	Inaudible

This is an identical replica of the table in the 1997 publication by Rutherford *et al.*,[2] with the exception of the asterisks (*).
* In the original 1997 classification it was stated that arterial Doppler sounds are never present in Stage IIA, and that rigor (mortis) is always present in Stage III. However, it is the opinion of the Writing Committee that exceptions to these rules do exist, and a slight modification of the Rutherford classification from 1997 may be appropriate in the future.

Historical data from Sweden and the UK have suggested an incidence of 3 — 14 per 100 000 person years, with a large majority of individuals being >80 years of age.[20—23] The largest contemporary epidemiological analysis of treatment of ALI used the National Hospital Discharge Survey (NHDS, USA).[18] Some 1 092 811 hospital admissions from 1988 to 1997 were for acute arterial embolism or thrombosis of the lower limb; this was reduced to 670 704 from 1998 to 2007, implying a decrease in the incidence of arterial embolisation or thrombosis from 42.4 per 100 000 person years from 1988 to 1997 to 23.3 per 100 000 person years from 1998 to 2007. Hospital mortality also decreased from 8.3% to 6.3%. Unfortunately, this publication did not differentiate between embolism and thrombosis, and bypass thrombosis was excluded.

In another epidemiological study of treatment of ALI in the Medicare population of the USA between the years 1998 and 2009, the incidence of ALI related hospital admissions decreased from 45.7 to 26.0 per 100 000 person years.[24] The number of patients undergoing open revascularisation was reduced from 57.1% to 52.6%, while endovascular procedures were doubled, from 15.0% to 33.1%. Hospital mortality decreased from 12.0% to 9.0% and amputation rates from 8.1% to 6.4%, although the latter decrease was not statistically significant. One year mortality remained unchanged (41.0% *vs.* 42.5%). The one year amputation rate decreased over time from 14.8% to 11.0%. Similar amputation rates, mortality, and time trends were reported from Sweden.[23,25,26] One investigation from the National Inpatient Sample in the USA studied 162 240 patients with ALI from 2002 to 2013; 33 615 (20.7%) underwent thrombolysis. The authors concluded there could be an association between the increased use of thrombolysis and other endovascular procedures and improved outcome.[27] There are few data on the level of major amputation after ALI, but in one large cohort study 34% of amputations done within 30 days were performed above the knee.[25]

Better detection and medical treatment of AF and atherosclerotic disease has probably contributed to this decrease in the incidence of ALI.[18] Primary prevention strategies, including smoking cessation advice, have also probably contributed.[28]

1.6. Benefit vs. harm

ALI is both a life and limb threatening disease. This makes decisions about best care complex. Often the limb is not salvageable owing to irreversible ischaemia, and amputation may be needed to save the patient's life; sometimes the patient is very frail and an attempt to save the limb will pose a significant risk to the patient's life. In 1994, in Gloucestershire, UK, 24% of individuals with ALI did not undergo a revascularisation attempt.[22] However, these data may not reflect contemporary practice, and it may be questioned whether they are still valid. Decisions about care need to be made in a compassionate and sympathetic way but based on available clinical evidence, and after discussion with patients and their relatives. Patients are often elderly and their ability to comprehend the complexities of their situation, while in pain and often on opiate analgesia, is difficult. There may be issues such as the ability to consent. Clinicians must ensure appropriate consent is obtained before treatment. The following list of factors should be taken into account before deciding on treatment.

1.6.1. Patient's age, fitness, and comorbidities. Patients suffering from underlying or associated diseases may need specific considerations concerning the therapeutic approach. ALI is usually a disease of the elderly, is associated with general frailty, and may be an end of life problem.[29] Recognising when a patient is dying is important, and not always easy. This situation, when the thrombosis is part of ending life, is sometimes referred to as *agonal thrombosis.* For example, in a small series of patients who developed ALI while in hospital with other medical conditions, none survived active treatment.[22] The elderly may tolerate an embolectomy but not do so well if a distal bypass is needed to save the limb. The benefit of revascularisation in nonagenarians with lower limb ischaemia is limited by high mortality at one year.[30] These patients often present with concomitant emboli to other arterial beds, and they may die from embolic stroke or embolic bowel ischaemia.

Arterial thrombosis may also be associated with an underlying malignancy causing prothrombotic states, including patients being actively treated, for example with chemotherapy. The malignancy is usually advanced, and treatment often has dismal results. Limb salvage rates are poor and most patients are not alive six months later, usually as a result of their underlying cancer.[31] Decisions about the management of patients with malignancy should be individualised with the help of oncologists, as active treatment in selected patients can yield good results both from treatment of the leg and the cancer.[32,33] In a prospective study from Denmark with 26 years of follow up, patients with ALI and a newly diagnosed cancer had a higher risk of amputation than similar patients without cancer (hazard ratio [HR] 0.09 *vs.* 0.06), and patients with cancer also had a higher mortality rate (HR 0.67 *vs.* 0.37).[34]

1.6.2. Current and projected quality of life. This is more important than the patient's general fitness. Elderly patients may be living alone and independent but need to move to residential accommodation if they become an amputee. A threat to their independence could be an argument for taking extra risks to try and obtain limb salvage. Similarly, understanding limb function is important. It may not be appropriate to attempt to save the limb of a patient who is wheelchair bound, while doing a brachial embolectomy to ensure good hand and arm function may ensure continued independence.

1.6.3. What can be offered? Unless the limb is irreversibly ischaemic, there is usually some treatment that can be offered to most patients. Options may be surgical or endovascular (thrombectomy or thrombolysis). Medical antithrombotic/anticoagulation (AC) treatment alone may be sufficient, which should be considered especially in frail patients with limited or no ability to be mobilised. The complexity of decision making is where a larger, potentially more hazardous surgical procedure has a greater predicted chance of success, but also a greater risk of complications, including death. This is where experience is required in the treating clinician, and good communication with patient and relatives is vital.

1.6.4. The wishes of patients and their relatives. Many elderly patients with severe ALI will not accept the possibility of leg amputation initially, preferring that their life ends. The situation requires a clear discussion with a vascular surgeon who can explain all the available options, including that good quality of life can be obtained, even as an amputee. Involvement of relatives is paramount as optimal outcomes are achieved if the patient, their relatives, and the surgeon can agree on the proposed management. Occasionally, relatives will adopt a more active approach to treatment and try to persuade the patient to have a procedure that they do not agree to. This is a difficult situation that needs careful handling by an experienced and sympathetic clinician. It is fundamental that the discussion and decisions are clearly recorded in the case notes to avoid later legal challenge by relatives. Irrespective of the decision of whether to amputate or not, patients need psychological support.

Recommendation 1

For patients with acute limb ischaemia it is recommended: that the best interests of the patient are considered before deciding on treatment; to obtain informed consent to management if at all possible; and to record decisions clearly.

Class	Level	References
I	C	Consensus

Recommendation 2

For patients with acute limb ischaemia and underlying malignant disease, active revascularisation in selected patients should be considered, as the immediate post-operative outcome is comparable to patients without malignancy.

Class	Level	References
IIa	B	Mouhayar *et al.* (2014),[32] Tsang *et al.* (2011),[33] Morris-Stiff and Lewis (2010),[31] Nicolajsen *et al.* (2015)[34]

2. DIAGNOSIS

ALI is a medical emergency, and it is important that the diagnosis is confirmed promptly, and proper treatment is started in order to prevent limb loss and other severe complications. Patients with acute on chronic limb ischaemia often have a history of intermittent claudication and have risk factors for PAD, such as smoking, hypertension, renal insufficiency, and diabetes. It is important to include patient history in the clinical assessment. The clinical presentation of ALI depends on the location and duration of the arterial occlusion, the presence of collateral circulation, and the metabolic changes related to tissue ischaemia. Typically, after occlusion of a native artery, the signs of ischaemia are located one level / joint distal to the level of occlusion (Fig. 3).

In a study of the Swedvasc registry comprising 16 229 patients who underwent revascularisation for native artery ALI (thus excluding ALI secondary to re-occlusion of previous vascular surgery), the cause for limb ischaemia was embolic in 44%, thrombotic in 53%, and a popliteal artery aneurysm (PA) in 3%.[23] The clinical differentiation between acute embolic and thrombotic occlusion can sometimes be difficult. A sudden onset of ALI symptoms is typical for arterial embolism. Patients with ALI due to thrombosis will present as a more gradual aggravation of symptoms, because most patients with pre-existing PAD compensate by increased collateral circulation. Most embolic occlusions are caused by cardiac dysrythmias, and two thirds are associated with AF, while 20% originate from ventricular thrombus (that may be of diverse aetiology).[35] In low and middle income countries valvular heart disease remains an important cause of ALI.

2.1. Clinical examination

The classic "six Ps" (pain, pallor, pulselessness, poikilothermia [perishing with cold], paraesthesia, and paralysis) can help to appreciate the clinical severity of ischaemia. However, in

clinical practice all six signs are rarely encountered, unless there is a severe ALI in a patient with otherwise normal arteries. Detection of peripheral pulses is enhanced by determination of the ABI using hand held Doppler.[36,37] ABI in ALI is also a predictor of outcome and an index <0.7 is critical.[38] The loss of sensory and motor function are symptoms of a threatened limb with a need for immediate revascularisation. The Rutherford classification for ALI (Table 2) is the most commonly used to determine whether the limb is viable, threatened, or irreversibly ischaemic, and to guide clinical management.[2] It is important that both legs are examined to exclude bilateral disease and to look for bilateral conditions such as PA. Physical examination should also include all other peripheral pulses and looking for signs of visceral ischaemia (abdominal tenderness). Patients with neurological impairment or deep venous thrombosis may have clinical signs and symptoms similar to ALI. Given the cardiac origin of embolic occlusions, a focused cardiac examination should be performed, without interfering with or delaying the treatment of ALI.

Many patients with ALI are not admitted primarily to vascular specialists. However, after thorough clinical work up (see above) by any competent doctor, the diagnosis of ALI is usually made easily. Early diagnosis is important in order to save time, and increase the chance of successful treatment.

2.2. Imaging modalities

The time needed to obtain any type of imaging should be weighed against the urgency of revascularisation. If non-invasive imaging is chosen, it is important that this does not delay subsequent treatment.

Virtually all data on the diagnostic accuracy of non-invasive imaging modalities come from studies in patients with chronic limb ischaemia, the majority having intermittent claudication. Little is known about the accuracy of imaging of the lower limb arteries in the acute (non-trauma) setting. Although the accuracy of the various imaging modalities in the setting of ALI is unknown, sensitivity and specificity to detect arterial occlusions is unlikely to be significantly different from that seen in chronic PAD. However, the possibility of imaging the outflow arteries is usually more difficult in patients with ALI, owing to the lack of collaterals.

2.2.1. Digital subtraction angiography. In terms of diagnostic accuracy, digital subtraction angiography (DSA) is still considered the standard investigation for ALI.[39] DSA can delineate aetiology and offers the advantage of allowing treatment in the same setting; in modern practice this should be considered in association with endovascular surgery. The presence of a crescent shaped occlusion, or meniscus sign, combined with the normal appearance of the remaining vessels is typical of an embolic occlusion (Fig. 4). Thrombotic occlusion is typified by other areas of atherosclerosis and some existing collaterals. Arterial access for the DSA should be chosen in such a way that both inflow and outflow can be evaluated. Intra-arterial vasodilators can be used to reduce vasospasm in the vessels distal to the site of occlusion, and thus enhance visualisation of the distal arterial bed.[40] In patients with severe renal insufficiency, carbon dioxide angiography may be considered.[41]

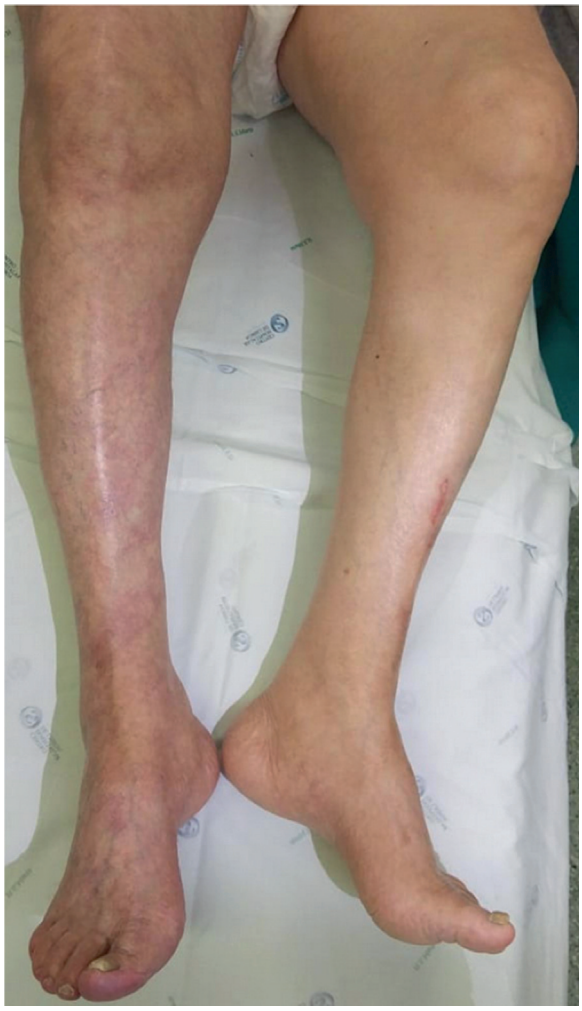

Figure 3. Clinical aspect of acute ischaemia of the right lower limb.

2.2.2. Duplex ultrasound. Data on the diagnostic accuracy of duplex ultrasound (DUS) in the setting of ALI are also scarce. DUS has a sensitivity of 88% (95% confidence interval [CI] 80% — 98%) and a specificity of 96% (95% CI 89% — 99%) to detect a stenosis $>$ 50% or occlusion in patients with chronic PAD.[42] DUS is able to obtain the necessary information in 90% of cases where revascularisation is considered, including patients with ALI, and is an accurate modality with which to detect complete or incomplete obstruction in the common femoral, superficial femoral, and popliteal arteries, and in bypass grafts.[43] The diagnostic accuracy is lower for detection of stenoses or occlusions in the tibial arteries, but ALI is rarely caused by such distal lesions. Therefore, DUS should not be used as a single modality in order to rule out arterial occlusion. In

one study it was shown that in patients with ALI, a 0.5 mm dilatation of the artery above the occlusion, in comparison with the contralateral limb is suggestive of an embolic occlusion, whereas a 0.5 mm diameter reduction correlates well with a thrombotic occlusion.[44] In a retrospective analysis of 181 patients with ALI, 90 patients were treated based on DUS as the sole pre-operative modality, with similar outcomes to those who had pre-operative DSA and computed tomography angiography (CTA).[45] The clinical applicability of DUS is limited in the acute setting, because it is not always available 24/7.

2.2.3. Computed tomography angiography. CTA requires administration of non-ionic contrast to obtain sufficient opacification of the arteries of the legs without venous or tissue enhancement. Although there is an association between the use of iodinated contrast and acute kidney injury, this is a relative problem when facing a potentially life threatening condition. Furthermore, the recent guidelines from the European Society for Urogenital Radiology have lowered the threshold for safe administration of contrast to an estimated glomerular filtration rate of 30 mL/minute/1.73 m^2.[46] In a large cohort of 1 017 patients treated for ALI there was an association between contrast induced acute kidney injury and increased all cause mortality, but there were multiple potential confounders associated with comorbidities.[47]

Anatomical coverage usually extends from just cranial to the origins of the renal arteries down to the feet, with an average scan length of around 120 cm. If the distal vessels are not well opacified (e.g., in the case of femoropopliteal aneurysm or slow flow in the setting of cardiac failure), a secondary acquisition may be necessary.[48] Current CT technology allows coverage of the entire body in a single acquisition, with short acquisition times, high resolution, and the possibility of post-processing axial images into reconstructions that provide similar accuracy to DSA images (Fig. 5).

Most modern hospitals can offer expedited CTA. An advantage of CTA is that it allows evaluation of the thoracic and abdominal aorta to seek a potential embolic source, and also the mesenteric vessels to look for other emboli. Extravascular findings may be seen that are related to the aetiology of ALI (e.g., in some types of popliteal artery entrapment) or are of clinical importance. In one study, relevant findings needing further investigation or treatment were seen in up to 74% of investigations.[49] Four (2.8%) patients in the latter series had previously unknown malignancy.[49] CTA is considered more useful than DSA because it can combine evaluation of the possible primary cause of ALI with high resolution evaluation of the outflow tract and provide a roadmap to guide treatment. In patients with chronic PAD, CTA has a sensitivity of 96% (95% CI 93% — 98%) and a specificity of 95% (95% CI 92% — 97%) for the detection of stenoses $>$ 50% or occlusions from the aorta to the popliteal arteries.[50] In a systematic review including a total of 891 trauma patients, the sensitivity and specificity of CTA were both 100% to detect arterial injury in a single investigation.[51] In the only study in the setting of ALI the sensitivity of CTA was 42/43 (98%) for the detection of an occluded artery *vs.* DSA or surgery.[52]

2.2.4. Contrast enhanced magnetic resonance angiography. In contrast enhanced magnetic resonance angiography (CE-MRA), like conventional angiography, contrast agent injection enables the generation of images that can

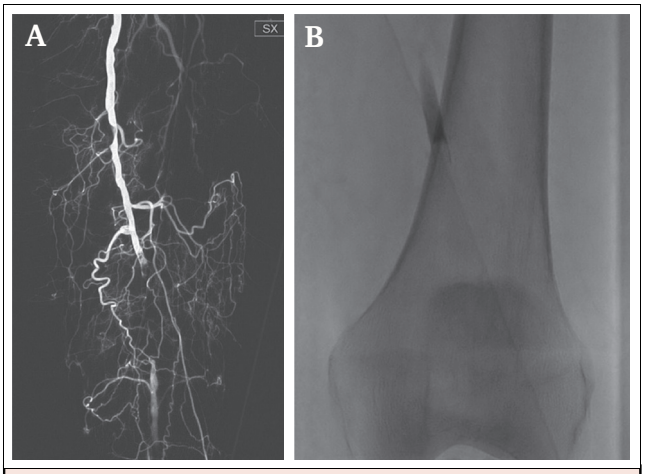

Figure 4. (A) Digital subtraction angiography image of acute on chronic occlusion. Note the irregular proximal margins and collaterals typical of thrombotic occlusion. (B) Fluoroscopic image demonstrating stasis of contrast on embolic occlusion. Note the concave margin typical of embolic occlusion.

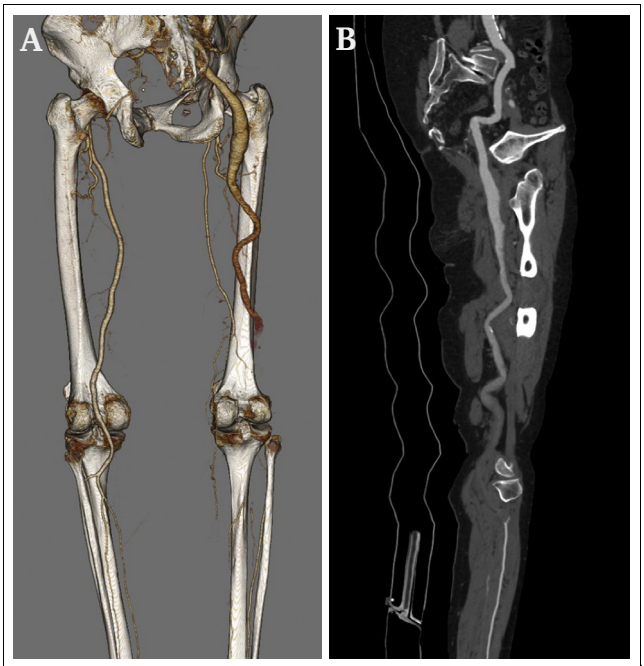

Figure 5. Aneurysmal persistent sciatic artery with acute thrombosis of the popliteal artery. Computed tomography angiography: (A) three-dimensional reconstruction and (B) centre line reconstruction.

visualise both arteries and veins. Arteries are visualised if image acquisition is performed during the arterial phase of the bolus. The vascular enhancement is a transient and dynamic process; hence, the critical element to be set for a CE-MRA, as with CTA, is the proper timing for image acquisition. CE-MRA is characterised by long examination times, limited availability, and therefore not frequently used in ALI. Image quality may be affected by artefacts related to venous return (which might be overcome by four dimensional imaging where contrast media inflow and outflow are used to distinguish between artery and vein), as well as any metallic implants (surgical clips and stents). In patients with chronic PAD the diagnostic accuracy of CE-MRA is similar to that of CTA, with a sensitivity and specificity for the detection of a stenosis > 50% of 93% (95% CI 91% – 95%) and 94% (95% CI 93% – 96%), respectively.[50] To date, no studies have evaluated CE-MRA in the setting of ALI.

2.2.5. Summary of imaging modalities. Based on current evidence, DSA, CTA, DUS, and CE-MRA can all be considered for imaging in patients with ALI, and may be used based on local expertise, availability around the clock, and preference (Table 3). CTA is used most often because of its availability, and should be performed for treatment planning, unless the ischaemia is too severe to allow time for additional imaging. The role of CE-MRA seems limited, mainly because of limited availability out of office hours, and because it has not been evaluated in patients with ALI.

2.3. Laboratory markers of ischaemia

The pre- and peri-operative measurement of biomarkers in ALI could potentially serve to assess the level of ischaemia and predict which patients will not tolerate efforts at limb salvage, or who will have poor functional outcomes after salvage. Few studies in humans have validated the clinical usefulness of markers of ALI and reperfusion.[53] Myoglobin and creatine kinase (CK) are well known markers of skeletal muscle damage, due to ischaemia and rhabdomyolysis, and may help in determining the level of subsequent resuscitative support that is required. Myoglobin is known to precipitate in the renal tubules and cause loss of renal function in patients with rhabdomyolysis, but has not been studied as a prognostic factor in patients with ALI. CK is used widely as marker of ischaemia reperfusion injury (IRI) and might assist the peri-operative management of ALI by estimating the risk of major amputation or limb preservation. Indeed in a series of 97 patients with mild and severe symptoms of ALI, the risk of amputation in patients with normal CK at presentation was 4.6% *vs.* 56.3% in those with elevated CK.[54]

In a series of 46 patients with ALI undergoing embolectomy, cardiac troponin I was > 0.2 ng/mL in 24 but did not have prognostic value with regard to in hospital mortality.[55] A correlation with limb salvage was not studied. C reactive protein (CRP) and alpha-1-acid glycoprotein levels were studied in 75 patients with acute arterial occlusion. Postoperative complications were detected with a sensitivity and specificity of 84% and 95%, respectively, using a CRP level of 49 mg/L as the cut off.[56] In a retrospective analysis of 254 patients who underwent embolectomy for ALI, a neutrophil / lymphocyte ratio > 5.2 had a sensitivity of 83% and a specificity of 63% to detect the need for amputation within 30 days.[57] There are no data in the literature correlating levels of lactate with severity of ALI. The 2017 ESVS Mesenteric Guidelines recommended against using serum lactate to diagnose acute mesenteric ischaemia, as it is a late sign of generalised hypoperfusion, and is often normal in the early acute phase.[58]

Summarising the scarce evidence on the use of biomarkers as prognostic factors in patients with ALI shows that there are no studies that support the routine use of biomarkers to predict limb salvage and survival after ALI.

Recommendation 3

For patients presenting with a possible diagnosis of acute limb ischaemia, it is recommended that clinical assessment is performed urgently by a vascular specialist, who should be responsible for planning further investigation and management.

Class	Level	References
I	C	Consensus

Recommendation 4

For patients presenting with acute limb ischaemia, the Rutherford classification for acute limb ischaemia is recommended for clinical evaluation.

Class	Level	References
I	C	Rutherford *et al.* (1997)[2]

Table 3. Summary of imaging modalities in acute limb ischaemia

Modality	Availability*	Accuracy	Invasiveness	Therapeutic potential	Evaluation of entire vascular tree and adjacent structures
Duplex ultrasound	±	++	−	−	+
Computed tomography angiography	++	+++	−	−	+++
Contrast enhanced magnetic resonance angiography	+	++	−	−	++
Digital subtraction angiography	++	+++	+	+	+

* Availability is very much dependent on local conditions.

Recommendation 5

For patients presenting with acute limb ischaemia, diagnostic imaging is recommended to guide treatment, provided it does not delay treatment, or if the need for primary amputation is obvious.

Class	Level	References
I	C	Weiss *et al.* (2017)[39]

Recommendation 6

For patients presenting with acute limb ischaemia, computed tomography angiography is recommended as the first line modality for anatomical imaging.

Class	Level	References
I	B	Jens *et al.* (2013),[50,51] Jakubiak *et al.* (2009)[52]

Recommendation 7

For patients presenting with acute limb ischaemia, duplex ultrasound or contrast-enhanced magnetic resonance angiography may be considered for alternative imaging before starting treatment, depending on availability and clinical assessment.

Class	Level	References
IIb	B	Jens *et al.* (2013),[50,51] Collins *et al.* (2007),[42] Hingorani *et al.* (2008),[43] Crawford *et al.* (2016)[45]

Recommendation 8

For patients presenting with acute limb ischaemia, it is not recommended to use results of myoglobin and creatine kinase on admission to base the decision to offer revascularisation or primary amputation.

Class	Level	References
III	C	Watson *et al.* (2014),[53] Currie *et al.* (2007)[54]

3. TREATMENT

3.1. Initial management

Initial medical treatment of ALI includes appropriate analgesia and intravenous administration of unfractionated heparin (UFH): initially 5 000 IU, or 70 — 100 IU/kg, followed by infusion, dose adjusted to patient response, and monitored by activated clotting time or activated partial thromboplastin time (APTT). The aim is to reduce further embolism or clot propagation, and to provide an anti-inflammatory effect.[4,59] Although this approach is widely accepted, no recent randomised study has been done to confirm the benefit of UFH for ALI, nor has any randomised study compared unfractionated UFH with other anticoagulants.[60] In an RCT performed in the 1980s, patients undergoing open surgery for emboli either had 5 000 IU UFH pre-operatively, followed by full intravenous heparinisation plus warfarin until they were effectively anticoagulated, or no anticoagulant treatment.[61] This study showed no obvious benefit of this level of AC, but an expected increase in bleeding complications was seen. However, the study design made it impossible to draw any conclusion regarding the benefit and safety of only giving a single dose of pre-operative UFH. A study of 87 patients in the USA who needed transfer to a vascular centre (36% with class IIb ischaemia), showed that although 76 received UFH before transfer, only 44 (58%) reached therapeutic levels, and those not achieving therapeutic levels had a higher re-intervention rate (47%).[62]

In patients with confirmed or suspected heparin induced thrombocytopenia, non-heparin anticoagulants such as lepirudin, argatroban, or danaparoid are options.[63] Advice from a haematologist may be valuable. Other measures that may be beneficial in patients with ALI include intravenous hydration and supplementary oxygen,[64] and lowering the foot end of the bed (anti-Trendelenburg position).

3.2. Adjuvant prostanoid treatment

Studies evaluating the role of other adjuvant pharmacological treatments for ALI have mainly focused on prostaglandin analogues. One study randomised 300 patients to either surgical treatment with peri-operative iloprost (intra-operative intra-arterial bolus plus post-operative intravenous infusion for 4 — 7 days) or placebo.[65] The study did not demonstrate a significant difference in the combined incidence of death and amputation (primary end point), but iloprost used as an adjuvant to surgery significantly reduced peri-operative mortality from 10.6% to 4.7%, as well as the overall rate of cardiovascular major events. A post-hoc analysis showed that the combined incidence of death and amputation was significantly reduced in a subgroup of elderly patients (aged $>$ 70 years) treated with iloprost.[66] A more recent study randomised 204 patients to peri-operative administration of liposomal prostglandin E1 or placebo.[67] The incidence of peri-operative mortality/major adverse limb events (MALE) was significantly reduced in patients receiving liposomal prostaglandin E1 (13.2% — 5.1%). Although these studies report benefit from adjuvant prostanoid therapy, it has not found widespread favour.

Recommendation 9

For patients with acute limb ischaemia awaiting revascularisation, heparin is recommended.

Class	Level	References
I	C	Aboyans *et al.* (2018),[4] Gerhard-Herman *et al.* (2017),[59] Alonso-Coello *et al.* (2012)[60]

Recommendation 10

For patients with acute limb ischaemia awaiting revascularisation, supplemental oxygen is recommended.

Class	Level	References
I	C	Berridge *et al.* (1989)[64]

Recommendation 11		
For patients with acute limb ischaemia awaiting revascularisation, adequate analgesia and intravenous rehydration are recommended.		
Class	**Level**	**References**
I	C	Aboyans *et al.* (2018),[4] Gerhard-Herman *et al.* (2017),[59] Alonso-Coello *et al.* (2012)[60]

Recommendation 12		
For patients with acute limb ischaemia, treated by open surgery, prostacyclin analogues may be considered during and after revascularisation.		
Class	**Level**	**References**
IIb	B	De Donato *et al.* (2006),[65,66] Li *et al.* (2013)[67]

3.3. Decision making

Patients with ALI should be treated by specialists in vascular and endovascular therapies, in centres with a full range of facilities to manage patients with vascular diseases. This may mean that a patient will need to be transferred from a non-vascular centre for treatment, if appropriate.[23] The urgency of transfer will depend on the severity of the ischaemia, with patients with motor or sensory loss (Rutherford IIb) requiring urgent transfer.

The urgency of treatment will depend on the severity of the limb ischaemia, graded using the Rutherford clinical classification (Table 2).[2] If there is a neurological deficit in the limb, particularly involving motor loss (Rutherford IIb), urgent revascularisation is mandatory. Various revascularisation techniques can be used, including surgical thrombo-embolectomy, bypass, percutaneous catheter directed thrombolysis (CDT), thrombus aspiration / mechanical thrombectomy (with or without thrombolysis) and hybrid procedures including thrombendarterectomy. The strategy employed will depend on a number of factors, including the expertise and facilities of the treating team, and patient factors such as the duration and severity of ALI, the location and cause of the occlusion, comorbidities, and therapy related risks.

Other ESVS Guidelines, such as the recently published 2019 Clinical Practice Guidelines on the Management of Abdominal Aorto-iliac Artery Aneurysms,[7] defined minimum volumes for centres treating a certain disease. Data suggest that being able to offer both open and endovascular surgery 24/7 may be associated with improved outcomes, as patients treated by an endovascular first strategy have improved survival.[23,27] Being able to offer both treatment modalities 24/7 requires a certain treatment volume, which is self evident, even if robust data are lacking to substantiate this assumption. There is a difficult trade off between the cost of delay, when a patient is transferred, and the limited expertise that may be available in the local hospital where the patient presents. All these patients can be discussed with a vascular surgeon on call; however, the discussion should take place before the difficult decision is made whether to refer the patient to another centre or treat on site with potentially limited resources. Smaller hospitals, particularly if they are situated in remote areas, should be integrated into a network facilitating rapid referral, whenever indicated.

Recommendation 13		
It is recommended that patients diagnosed with acute limb ischaemia in a non-vascular centre be transferred to a vascular centre that offers the full range of open and endovascular interventions with an urgency that depends on the severity of the ischaemia.		
Class	**Level**	**References**
I	B	Grip *et al.* (2018),[23] Bath *et al.* (2019)[27]

Recommendation 14		
It is recommended that patients with acute limb ischaemia should have access to treatment in a hybrid theatre, or operating theatre with C arm equipment, and by a clinical team able to offer a full range of open or endovascular interventions during a single procedure.		
Class	**Level**	**References**
I	C	Consensus

3.4. Open revascularisation techniques

3.4.1. Thrombo-embolectomy. Since its introduction in 1962 by Fogarty, balloon thrombo-embolectomy has remained the standard treatment of ALI caused by embolic occlusion,[68] particularly when dealing with occlusion of an otherwise normal artery. However, this is an increasing rarity in modern surgical practice, as most patients with AF have co-existing vascular disease. A single femoral incision is usually adequate to perform thrombo-embolectomy of unilateral iliac, femoral or profunda clots. When the occlusion extends up to the aortic bifurcation, it is important to avoid clot dislodgement over the bifurcation into the other leg. Balloon protection of the contralateral common iliac artery under fluoroscopic guidance, or manual compression of the contralateral common femoral artery, are sometimes used to reduce the risk of contralateral embolisation. For more details on acute aortic occlusion (AAO), see section 6, Acute Aortic Occlusion With Bilateral Lower Limb Ischaemia.

If the occlusion is in the popliteal artery or below, complete removal of occluding thrombus may be difficult from the groin, and direct exploration of the below knee popliteal artery should be considered. This enables passage of the embolectomy catheter into all three tibial arteries separately to clear any obstructing clot. A transverse arteriotomy is preferred in the below knee popliteal artery to prevent narrowing when the incision is repaired. Patch angioplasty is recommended for surgeons who prefer longitudinal arteriotomy. In patients with distal embolic occlusions, a few retrospective studies with limited numbers describe microtibial embolectomy via pedal arteries.[69,70]

Femoral embolectomy can be done under local anaesthethia, but an anaesthetist should always be present in theatre, even if the procedure is under local anaesthesia, to administer analgesia and sedation, and to treat any dysrhythmia or cardiac

complication on reperfusion.[31] Popliteal artery exploration usually requires general or regional anaesthesia.

Technical improvements to surgical embolectomy have been introduced with wire guided ballons for a precise approach to specific vessels and to avoid iatrogenic injury (i.e., dissection), ante- and retrograde approach, and fluoroscopic guidance.[71] These approaches are associated with improved vessel clearance.[71–73]

A number of reports describe contemporary outcomes of surgical embolectomy as the primary treatment of ALI due to arterial embolism. In one report of 170 patients, 82 (49%) had AF.[74] In most cases, a femoral approach was used (aortic, iliac, and infra-inguinal emboli), although 10 (6%) required bypass surgery. Additional local thrombolysis was performed in 16% of patients and fasciotomy was needed in 39%. The 30 day mortality rate was 18% and a further 15% had a major amputation within 90 days. The five year freedom from amputation and survival estimates were 80% and 41%, respectively. This study typifies the ongoing high morbidity and mortality of embolic ALI.

Recommendation 15

For patients requiring surgical thrombo-embolectomy for acute limb ischaemia, regional or local anaesthesia may be considered, but always with an anaesthetist present.

Class	Level	References
IIb	C	Morris-Stiff *et al.* (2009)[75]

Recommendation 16

For patients requiring surgical thrombo-embolectomy for acute limb ischaemia, the use of over the wire embolectomy catheters under fluoroscopic control should be considered.

Class	Level	References
IIa	C	Pemberton *et al.* (1999),[71] de Donato *et al.* (2014),[72] Lipsitz and Veith (2001)[73]

3.4.2. Surgical bypass. Surgical bypass may be the primary treatment for ALI, or be used if intravascular recanalisation cannot be achieved. Bypass is more often indicated for acute on chronic ischaemia. The techniques used are generally similar to those for chronic limb threatening ischaemia. The Vascular Study Group of New England reviewed 5 712 infra-inguinal bypasses done between 2003 and 2011, 323 (5.7%) of which were done for ALI.[76] More patients with ALI had previous endovascular interventions (41.1% *vs.* 28.8%) and / or ipsilateral bypasses (32.8% *vs.* 23.5%) than those operated on for chronic limb ischaemia. More prosthetic bypasses were used (40.6% *vs.* 32.6%) and there were more complications after surgery in the ALI group (rate of severe events was 19.8% *vs.* 11.6% in the chronic limb ischaemia group). Overall results at one year were also worse after bypass for ALI (major amputation rate 22.4% *vs.* 9.7%; death 20.9% *vs.* 13.1%; and amputation free survival 62.8% *vs.* 77.4%).

There are no RCTs comparing vein with prosthetic grafts in the acute setting, but two retrospective studies reported better patency rates with vein grafts.[77,78] Preferential use of a prosthetic graft may be considered in a patient with severe ischaemia (Rutherford grade IIB), where urgent revascularisation is necessary.

Recommendation 17

For patients requiring an infrainguinal bypass procedure for acute limb ischaemia, the preferential use of a vein graft should be considered.

Class	Level	References
IIa	C	Marques de Marino *et al.* (2016),[77] Grego *et al.* (2004)[78]

3.4.3. Completion imaging after surgery or embolectomy. There is consensus to recommend completion angiography after thrombo-embolectomy to document the outcome, as residual thrombus is common and its identification is associated with a reduced risk of re-intervention and limb loss.[73,79] If residual thrombus is found after embolectomy, further embolectomy or bypass may be considered. A widely used alternative is intra-operative instillation of thrombolytic agents (e.g., recombinant tissue plasminogen activator [rtPA] 4 — 10 mg) directly into the artery downstream with the aim of dissolving residual thrombus.[80–82] No controlled studies exist, and the benefit to limb salvage remains unclear, but severe bleeding complications are rare.[83–85] There are wide variations in techniques and doses of thrombolytic agents employed, which makes firm conclusions difficult. Although completion imaging is recommended, and is straightforward in most modern operating rooms, there are situations when an exception to the rule can be made, such as in a patient with renal insufficiency and clearly palpable foot pulses.

Recommendation 18

For patients undergoing open and endovascular surgery for acute limb ischaemia, completion angiography is recommended.

Class	Level	References
I	C	Lipsitz and Veith (2001),[73] Zaraca *et al.* (2010)[79]

Recommendation 19

For patients with residual thrombus after open surgery for acute limb ischaemia, intra-operative local thrombolysis may be considered.

Class	Level	References
IIb	C	Gonzalez-Fajardo *et al.* (1995),[84] Witz *et al.* (2002),[82] Comerota and Sidhu (2009),[85] Knaus *et al.* (1993),[80] Beard *et al.* (1993),[81] Garcia *et al.* (1990)[83]

3.4.4. Treatment of acutely occluded bypass grafts. Some patients with acute bypass graft occlusion do not develop critical ischaemia, and in this situation the no treatment option may be safest. In those who are symptomatic, treatment will depend on the situation and material used for the primary bypass. If the occluded graft is vein, both proximal and distal anastomoses usually require surgical exploration. In such cases, over the wire embolectomy catheters can be useful to deal with valve cusps. Identification (and treatment) of the underlying cause of thrombosis is crucial.

Thrombo-embolectomy alone is unlikely to restore the circulation in an occluded vein graft.[86,87] If no anatomical explanation for graft failure can be identified, the prognosis for long term patency and limb salvage is poor. If the cause of the graft failure (e.g., anastomotic stenosis or poor runoff) is identified and addressed, more favourable outcomes have been reported.[88,89] ALI due to early graft occlusion (within 30 days of insertion) is often a technical issue (poor vein quality, inadequate inflow or outflow, anastomotic stenosis, graft torsion, valve defects, or clamp related damage). ALI caused by late graft thrombosis (> 30 days) is usually the result of progression of atherosclerosis proximal or distal to the graft, atherosclerosis within the graft, fibrotic stenosis or intimal hyperplasia in the graft, or aneurysmal dilatation.[86,87] No comparative studies have specifically addressed the optimal treatment for occluded bypasses causing ALI.

CDT is also an effective treatment for acutely occluded bypasses. In a systematic review angiographic patency after CDT was 82% for prosthetic and 61% for venous bypass grafts.[14] In a study from Sweden, 123 patients (67% with a prosthetic graft) were treated between 2000 and 2008.[90] The mean duration of thrombolysis was 19 hours. Only 29% of patients did not require additional intervention after thrombolysis; 21% received open surgery, 39% had endovascular treatment, and 11% a combination of both. Amputation free survival was 89% at one month and 75% at one year. Two haemorrhagic strokes occurred as immediate complications (1.6%), and one was lethal. Major haemorrhage occurred in 13.2%. Mortality was 6.5% after one month and 13% after one year. One advantage of thrombolysis is that it can uncover the reasons for bypass failure, which can help plan secondary intervention to prolong patency (e.g., angioplasty of an anastomotic stenosis). Thrombolysis may also increase the number of outflow vessels available for subsequent bypass.[91]

Recommendation 20		
For patients with acute limb ischaemia caused by graft occlusion, identification and treatment of the cause of graft occlusion is recommended.		
Class	**Level**	**References**
I	C	Shoenfeld *et al.* (1987),[86] Cohen *et al.* (1986),[87] Whittemore et al. (1981),[88] Bandyk *et al.* (1990),[89] Edwards *et al.* (1990),[92] Sanchez *et al.* (1996)[93]

3.4.5. Hybrid treatment. Although simple thrombo-embolectomy or bypass still play a major role in the open treatment of ALI, there is a trend for these patients to have complex, multilevel occlusive disease; they may best be treated by a combination of open and endovascular techniques.[72,94,95] After incomplete thrombo-embolectomy, endovascular techniques such as intra-arterial thrombolysis or thrombus aspiration / mechanical thrombectomy can be used to remove any remaining clot. When completion angiography reveals an underlying chronic stenosis, balloon angioplasty or stenting can be performed to treat the underlying lesion, and prolong patency. Similarly, endovascular treatment may need to be supplemented by open surgery, such as thrombendarterectomy or fasciotomy. For this reason, optimal ALI treatment should take place in a hybrid theatre, or operating theatre with a C arm, and by a clinical team able to offer a full range of open or endovascular interventions during a single procedure. Having said that, there are situations when the patient's condition and / or the local hospital resources makes it necessary to perform the procedure in a conventional operating room or an angio suite in the radiology department.

Although hybrid procedures have gained widespread acceptance, there are few data evaluating their potential benefit for ALI. A recent multicentre retrospective study analysed the short term outcomes of 1 480 patients following open surgical, endovascular, or hybrid treatment for ALI.[96] Endovascular treatment was associated with a reduction in the amputation rate *vs.* open and hybrid procedures. However,

Table 4. Overview of randomised controlled trials comparing intra-arterial recombinant tissue plasminogen activator *vs.* intravenous recombinant tissue plasminogen activator

Reference	Patients *n*	Thrombolytic regimens	Amputation free survival at 30 d *n* (%)	Major bleeding *n* (%)	Stroke *n* (%)	Distal embolisation *n* (%)
Berridge *et al.* (1991)[97]	40	Intra-arterial low dose infusion *vs.* IV infusion at rates of 1, 2, 5, or 10 mg/h	16/20 (80) *vs.* 14/20 (70)	0/20 (0) *vs.* 4/20 (20)	0/20 (0) *vs.* 1/20 (5)	1/20 (5) *vs.* 0/20 (0)
Saroukhani *et al.* (2015)[98]	38	Intra-arterial bolus + infusions *vs.* IV infusion over 2 h	16/20 (80) *vs.* 12/18 (67)	0/20 (0) *vs.* 0/18 (0)	0/20 (0) *vs.* 0/18 (0)	Not applicable

Data are *n* (%). IV = intravenous.

there was no difference in 30 day freedom from re-intervention, or mortality. Another study evaluated 380 patients with ALI of the leg and found that those who had intra-operative angiography after embolectomy had a higher rate of intra-operative re-intervention, a higher rate of additional interventions due to residual stenosis / occlusion and a lower rate of re-occlusion after 24 months.[79]

Recommendation 21		
After open revascularisation for acute limb ischaemia, simultaneous endovascular treatment addressing inflow or outflow stenosis should be considered.		
Class	**Level**	**References**
IIa	C	de Donato *et al.* (2014),[72] Balaz *et al.* (2013),[94] Argyriou *et al.* (2014),[95] Davis *et al.* (2018)[96]

3.5. Thrombolysis

3.5.1. Systemic thrombolysis. Two small RCTs compared intra-arterial with intravenous rtPA for ALI (Table 4).[97,98] Intra-arterial rtPA was more effective than intravenous rtPA in producing complete recovery at 30 days ($n = 16/20$ *vs.* $n = 9/20$; $p = .048$),[97,99] whereas amputation free survival at 30 days appeared similar.[97,98] In one study, there were more bleeding complications after intravenous rtPA ($n = 13/20$; $p < .001$) and intra-arterial streptokinase ($n = 6/20$; $p = .02$) than after intra-arterial rtPA.[97] Complication rates were also similar. Intravenous thrombolysis is no longer in general use for ALI.

Recommendation 22		
For patients with acute limb ischaemia, intravenous thrombolysis is not recommended.		
Class	**Level**	**References**
III	A	Berridge *et al.* (1991),[97] Saroukhani *et al.* (2015),[98] Robertson *et al.* (2013)[99]

3.5.2. Assessment before catheter directed thrombolysis. Intra-arterial CDT can be performed in ALI with equivalent results to surgery (Fig. 6).[91,100,101] Initially, thrombolysis was recommended only for patients with ALI and a limb that was not immediately threatened, and not for those with severe or progressive symptoms. However, a systematic review showed that thrombolysis may also be used in patients with more severe ischaemia (Rutherford class IIb),[14] and that outcomes were no worse for patients with motor deficit. Retrospective studies showed similar results.[102–104] In three studies clinical success and amputation free survival were inferior in patients with Rutherford class IIb than IIa ischaemia, although this was the case for both CDT and surgery.[23,105,106] In patients with more severe ischaemia the administration of thrombolysis may need to be enhanced by increasing the dosage and / or combining it with other endovascular techniques, described in this section.

Patients with acute onset claudication (Rutherford class I) experience significant morbidity and mortality when treated by thrombolysis for a condition that does not threaten their limb.[107] Moreover, many of these patients do not have relief of symptoms in the longer term.[108] Therefore, patients presenting with acute onset claudication should be treated conservatively by best medical treatment and supervised walking therapy.[107] There is a need for future research in this field (as discussed in section 9.3).

In contemporary series of patients with ALI treated by thrombolysis, technical success rates are high (80% — 90%).[17,25] Thrombolysis can be used for native artery occlusions, graft and stent / stent graft thrombosis, and for embolic occlusions and PA thrombo-embolism.[23,26] Major amputation free survival was reported to be 84% at 30 days,[25] and around 75% at one year.[37,104] Significant haemorrhage is the major risk (13% — 30%), and may require the cessation of treatment. There is a small risk of intracerebral haemorrhage (around 0.4% — 2.3%), which is usually fatal.[25,109]

Thrombolysis is contraindicated in patients at increased risk of bleeding, as haemorrhage is the most common complication. The Working Party on Thrombolysis in the

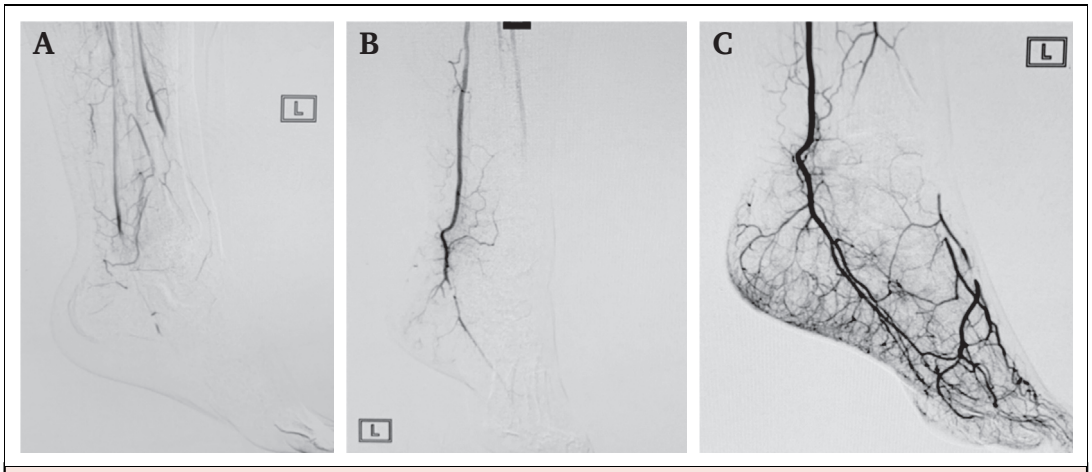

Figure 6. (A) Digital subtraction angiography showing an occlusion of the pedal and posterior tibial arteries. Results after thrombolysis: (B) first control angiogram and (C) second control angiogram.

Management of Limb Ischaemia divided contraindications into absolute and relative, major and minor (Table 5).[110] Cancer was a contraindication in previous guidelines, but this has been removed, opening up potential treatment of this difficult and vulnerable group. Similarly, older age is often considered to be associated with an increased risk of intracranial haemorrhage, but there are confounders explaining this association and therefore older age in itself is not considered a relative contraindication.

Recommendation 23

For patients with acute onset claudication (Rutherford grade I) that does not threaten the limb, (percutaneous) catheter-directed thrombolysis is not recommended.

Class	Level	References
III	B	Braithwaite *et al.* (1999),[107] Korn *et al.* (2001)[108]

Recommendation 24

For patients with Rutherford grade IIa acute limb ischaemia, it is recommended that (percutaneous) catheter-directed thrombolysis is considered as an alternative to surgery.

Class	Level	References
I	A	The STILE trial (1994),[91] Comerota *et al.* (1996),[100] Enezate *et al.* (2017),[11] Ouriel and Veith (1998),[101] Bath *et al.* (2019)[27]

Recommendation 25

For patients with Rutherford grade IIb acute limb ischaemia, (percutaneous) catheter-directed thrombolysis may be considered if initiated promptly, and may be combined with percutaneous aspiration or thrombectomy.

Class	Level	References
IIb	B	Ebben *et al.* (2019),[14] Acosta and Kuoppala (2015),[17] Braithwaite *et al.* (1997),[109] Grip *et al.* (2014),[23] (2018)[25]

3.5.3. Access for percutaneous thrombolysis. Complications as a result of vascular access for thrombolytic therapy are the commonest cause of difficulty during the procedure. Groin haematoma is common following percutaneous puncture of the femoral artery. Through and through puncture of the femoral artery for access (including puncture of the posterior wall) should be avoided. Anterior wall puncture alone is recommended, ideally assisted by ultrasound guidance. Ultrasound guided retrograde puncture was superior to an anatomical landmark approach in pooled results from five RCTs of coronary angiography.[111] Ultrasound guidance leads to fewer attempts (odds ratio [OR] 0.24), reduced risk of venous puncture (OR 0.18), and most importantly, fewer bleeding complications (OR 0.41).

There are no comparative studies on antegrade *vs.* retrograde access to the femoral artery for thrombolysis.

Table 5. Contraindications to thrombolytic treatment for acute limb ischaemia[110]

Absolute
1. Established cerebrovascular event (including transient ischaemic attack) within the last two months.
2. Active bleeding diathesis.
3. Recent gastrointestinal bleeding (<10 d).
4. Neurosurgery (intracranial, spinal) within the last three months.
5. Intracranial trauma within the last three months.
Relatively major
1. Cardiopulmonary resuscitation within the last 10 days.
2. Major non-vascular surgery or trauma within the last 10 days.
3. Uncontrolled hypertension: >180 mmHg systolic or >110 mmHg diastolic.
4. Puncture of non-compressible vessel.
5. Intracranial tumour.
6. Recent eye surgery.
Relatively minor
1. Hepatic failure, particularly those with coagulopathy.
2. Bacterial endocarditis.
3. Pregnancy.
4. Diabetic haemorrhagic retinopathy.

Antegrade access, particularly for distal infrainguinal thrombolysis may facilitate torque and manoeuvrability to traverse an occlusion. Antegrade access from the arm also enables passage of an acutely angled aortic bifurcation, but with modern techniques this is rarely an issue. Retrograde contralateral access offers a stable position of a long crossover sheath, reducing the risk of dislodgement and bleeding.[112] It also avoids the need for compression of the inflow artery of the ischaemic leg once the catheter is removed.

Recommendation 26

For patients with acute limb ischaemia undergoing endovascular therapy, ultrasound guidance for arterial access is recommended.

Class	Level	References
I	A	Marquis-Gravel *et al.* (2018)[111]

3.5.4. Fibrinolytic drugs. Urokinase and rtPA are the most widely used thrombolytic drugs for CDT. Multiple studies have shown that the efficacy and safety of these medications are similar.[99] The feasibility of newer agents such as reteplase and tenecteplase have been described in retrospective cohort studies of CDT, but have never been compared with urokinase or rtPA.[113–120] However, reteplase plus intravenous abciximab was not superior to urokinase plus intravenous abciximab in terms of reduced amputation rates in a RCT.[121]

The guidelines of the Society of Interventional Radiology[122] recommend the use of weight related doses of rtPA (alteplase) for CDT (0.02 — 0.1 mg/kg/hour). Most clinicians use standard non-weight related doses, usually between 0.25 and 1.0 mg per hour for low dose infusions.

Overall, the maximum recommended dose of rtPA for catheter based intra-arterial thrombolysis is 40 mg.[122]

In a recent systematic review a wide variety of treatment protocols was found, and meta-analysis on dosages and outcomes was not possible owing to heterogeneity.[14] There are a number of accelerated methods of CDT using higher doses of thrombolytic drugs. Pooled results from 9 877 patients were not suitable for direct comparison, but accelerated thrombolysis reduced treatment duration: 21.9 hours (95% CI 21.4 — 22.5) for high dose protocols (≥ 75 000 IU/hour urokinase, ≥ 0.8 mg/hour rtPA, or ≥ 1.0 IU/hour rtPA) *vs.* 32.7 hours with low dose protocols (< 75 000 IU/h urokinase or < 0.8 mg/hour rtPA or < 1.0 IU/hour rtPA). Bleeding complications occured in 17.1% (95% CI 16.7 — 17.5) in high dose regimens and in 13.4% (95% CI 12.8 — 14.0) in low dose regimens. Clinical success appeared to be comparable.

Two small RCTs compared accelerated with standard thrombolysis. The first randomised 63 patients with symptomatic peripheral arterial or bypass graft occlusions to high dose (250 000 IU/hour for four hours and then 125 000 IU/hour) or low dose (50 000 IU/hour) urokinase. They found both regimens to be equally effective in achieving thrombolysis. The high dose group had significantly more (mostly minor) bleeding complications (20% *vs.* 2.7%).[123] A second study investigated high dose rtPA (three doses of 5 mg over 30 minutes, then 3.5 mg/hour for up to four hours, then 0.5 — 1.0 mg/hour) *vs.* low dose rtPA (0.5 — 1.0 mg/hour) in 100 patients.[109] The median duration of thrombolysis was significantly shorter for the high dose group (4.0 hours *vs.* 20 hours). Clinical outcome and complications were equivalent.

Recommendation 27

For patients with acute limb ischaemia undergoing thrombolysis, it is recommended that recombinant tissue plasminogen activator or urokinase is used.

Class	Level	References
I	A	Robertson *et al.* (2013)[99]

3.5.5. Monitoring fibrinogen levels during thrombolysis. Fibrinogen is depleted during thrombolysis, and its measurement could be used to predict bleeding complications or guide the dose of thrombolytic agent.[117] While the Surgery *vs.* Thrombolysis for Ischaemia of the Lower Extremity (STILE) trial reported a correlation between low fibrinogen and haemorrhagic complications,[91] the Pro-urokinase *vs.* Urokinase for Recanalisation of Peripheral Occlusions, Safety and Efficacy (PURPOSE) trial found a negative correlation for low fibrinogen and major bleeding but a relative risk of 1.39 for plasma fibrinogen < 1.0 g/L and any bleeding.[124] Three other studies found no association between a drop in or low level of plasma fibrinogen and haemorrhagic complications.[118,125,126]

Although there is some evidence that very low levels of plasma fibrinogen (< 1.0 or < 1.5 g/L) are indicators of bleeding risk, a systematic review concluded the predictive value of plasma fibrinogen for bleeding during thrombolysis is unproven, so regular monitoring is not recommended.[127]

Recommendation 28

For patients undergoing thrombolytic therapy for acute limb ischaemia, routine monitoring of plasma fibrinogen is not recommended.

Class	Level	References
III	B	The STILE trial (1994),[91] Ouriel *et al.* (1999),[124] Arepally *et al.* (2002),[125] Hull *et al.* (2006),[118] Marder *et al.* (2012),[126] Poorthuis *et al.* (2017)[127]

3.5.6. Heparinisation during catheter directed thrombolysis. Some authors recommend continuing UFH treatment during thrombolysis. However, in the Thrombolysis or Peripheral Arterial Surgery (TOPAS) trial, the concurrent use of UFH intravenously with a target activated partial thromboplastin time 1.5 — 2 times baseline was associated with an increased risk of major bleeding (RR 2.19, 95% CI 1.13 — 4.24). One small RCT investigated the effect of 250 IU/hour of intra-arterial UFH,[97] but no benefit (or disadvantage) was observed. Another observational study compared two hospitals with different strategies.[25] All patients received thrombolysis using rtPA and an UFH bolus at the start of the procedure. Bleeding complications were less common in the centre without a continuous UFH infusion (21.4% *vs.* 36.7%), but in multivariable analysis the UFH infusion was not an independent risk factor for bleeding. Treatment success was similar in the two centres. Some authors use a low dose UFH infusion through the catheter sheath to maintain its patency and prevent pericatheter thrombosis, but no controlled studies exist. Likewise, there is no evidence of any benefit from low molecular weight heparin (LMWH) during CDT.

Recommendation 29

For patients undergoing thrombolysis for acute limb ischaemia, continuous systemic therapeutic heparinisation is not recommended.

Class	Level	References
III	B	Berridge (1990),[128] Ouriel and Veith (1998),[101] Grip *et al.* (2014)[25]

3.5.7. Complications after thrombolysis. Patients receiving thrombolysis for ALI are at risk of a number of limb and life threatening complications. They should be managed in a facility by nursing and medical staff familiar with vascular patients and the complications of thrombolysis, but not necessarily intensive care.[129] During the thrombolytic infusion they should undergo regular monitoring to assess both vital signs and, in particular the condition of the treated limb. Specific complications of thrombolysis include bleeding, distal embolisation, progressive ischaemia, and compartment syndrome.

Bleeding is the main complication of thrombolytic therapy, with major bleeding (requiring intervention or blood transfusion) affecting 8% – 10% of the patients.[14,130,131] Bleeding at the arterial access site is the most common bleeding complication. To prevent this it is important to secure the sheath and to immobilise the groin during thrombolytic therapy. Early detection of minor bleeding complications can prevent them becoming major. Interventions such as direct manual pressure, catheter repositioning, or changing to a larger sheath can prevent continued groin bleeding. If there is major bleeding, thrombolysis should usually be stopped. In special circumstances minor bleeding may be managed, and thrombolysis continued (possibly at a lower dose) to salvage the limb.[132]

Distal embolisation can occur while crossing the occlusion with a wire or catheter. Embolisation can also occur during an infusion, and may make the limb more severely ischaemic. Experience is needed to decide whether to continue the infusion at that stage, perhaps to increase the dose and hope the embolus will lyse, or to stop the infusion and adopt an open surgical or other endovascular approach. The course of action will depend on previous progress with lysis, and the state of the patient.[133]

Thrombolysis often takes time, and ischaemia may progress during thrombolytic treatment if the clot is not lysed. Accurate clinical evaluation of the limb is important at baseline, with regular review during infusion. If there is any sign of deterioration in the condition of the limb, or no improvement on angiography over 6 – 12 hours, a change in treatment strategy should be considered.

Recommendation 30

It is recommended that patients undergoing thrombolytic treatment for acute limb ischaemia should be monitored for vital signs, access site complications, and the condition of the limb.

Class	Level	References
I	C	Darwood *et al.* (2018),[130] Wang *et al.* (2016),[131] Ebben *et al.* (2019)[14]

Recommendation 31

For patients treated for acute limb ischaemia, it is recommended that thrombolysis be stopped if major bleeding occurs during treatment.

Class	Level	References
I	C	Darwood *et al.* (2018),[130] Wang *et al.* (2016),[131] Ebben *et al.* (2019)[14]

Recommendation 32

For patients treated for acute limb ischaemia who have minor bleeding during thrombolysis, continued treatment should be considered, after evaluation of the risk and benefit of stopping or continuing.

Class	Level	References
IIa	C	Kuoppala *et al.* (2008),[134] Grip *et al.* (2014)[25]

3.6. Other endovascular techniques

Several additional percutaneous techniques have been described for the treatment of ALI, including mechanical thrombolysis, ultrasound assisted thrombolysis, thrombus fragmentation, thrombo-aspiration, angioplasty, and covered stenting.[135] Technical success rates, when combined with adjunctive techniques, vary from 70% to 100%.[135] The potential advantage of these devices is speedy restoration of blood flow in the ischaemic limb.[136] RCTs comparing percutaneous thrombectomy (by any means) with thrombolysis are not available.[137]

3.6.1. Thrombus aspiration. The first reports of aspiration thrombo-embolectomy described the use of simple large bore (guiding) catheters.[138] Aspiration was done using a 50 mL syringe, usually with a detachable haemostatic valve (Fig. 7).

Several commercial aspiration catheters are now available, typically allowing end hole aspiration. A rapid exchange system commonly used in the coronary vessels can be used for clot in the below knee arteries.[139] There is also an aspiration pump with specifically designed catheters (Indigo; Penumbra, Alameda, CA, USA).[140–144] The vacuum pump uses the direct aspiration first pass technique used in neuro-interventional procedures, where the catheter is allowed to engage the thrombus for a short interval and subsequently withdrawn by retracting the catheter (Fig. 8).[143] Use of adjunctive therapy should be anticipated (thrombolyisis, angioplasty with or without stent placement). A mismatch between the size of the catheter and arterial diameter is the main reason for not achieving complete clot removal. Incomplete removal is more frequent in the above knee *vs.* the below knee arteries.[142] Aspiration techniques are considered to work better when the thrombus is acute (< 14 days old), and when larger bore catheters can be used.[145] Aspiration may also be

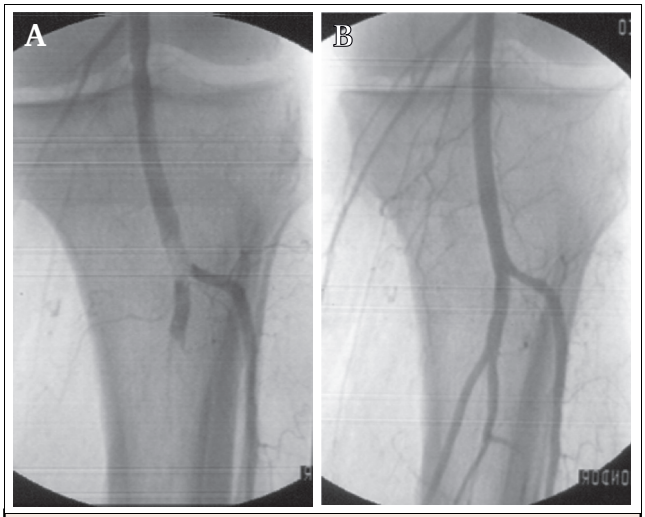

Figure 7. (A) Angiogram showing an embolic occlusion of the below knee popliteal artery and tibioperoneal trunk. (B) Result after aspiration.

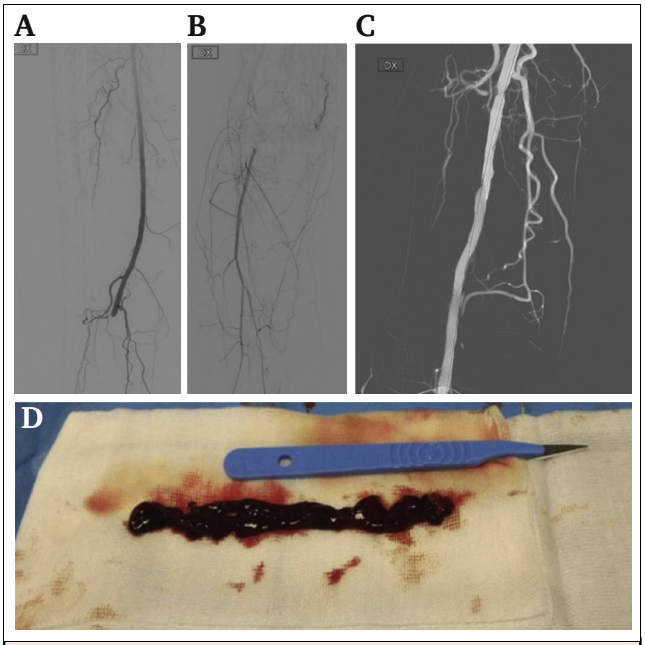

Figure 8. (A, B) Digital subtraction angiography showing an acute femoropopliteal stent occlusion. (C) Result after vacuum assisted thrombo-aspiration and balloon angioplasty of underlying stenosis, demonstrating absence of residual stenosis. (D) Thrombotic material removed with vacuum assisted thrombus aspiration.

effective after failed thrombolysis.[143,146] First line use of aspiration thrombectomy can reduce the need for CDT, without increasing costs.[141,147]

3.6.2. Endovascular mechanical thrombectomy. Several mechanical thrombectomy devices are available commercially. They can be classified according to their working mechanism: rheolytic catheters or microfragmentation catheters.[136]

A study that compared CDT with or without pharmacomechanical thrombolysis (PMT) using the Angiojet device showed that PMT increased technical success rates, but at the cost of more distal embolisation.[148] A matched cohort analysis comparing PMT alone and PMT with thrombolysis showed better outcomes, shorter procedures, and comparable limb salvage in the PMT alone group. The limitation of PMT is the inability to use the device in small calibre arteries in the leg, and the risk that haemolysis may lead to hyperkalaemia, haemoglobinuria, and renal damage.

The Rotarex system (Straub, Wangen, Switzerland) has been studied in several registries. It has a high technical success rate, and can reduce the need for additional catheter directed thrombolysis.[149–151] A comparative (non-randomised) study of Rotarex *vs.* thrombolysis showed similar technical results but better primary and secondary patency rates with fewer complications and shorter hospital stay in the Rotarex group.[152] This device can also aspirate more organised clot but cannot be used in smaller arteries below the knee.[153] Vessel perforation has been described as a device related complication.[153] One study reported that re-thrombosis was more frequent after Rotarex was used for bypass graft thrombosis, longer arterial occlusions, and in the presence of poor runoff.[154]

3.6.3. Ultrasound accelerated thrombolysis. Ultrasound has been used to accelerate thrombolysis. High frequency, low intensity ultrasound can speed enzymatic clot lysis *in vitro* by loosening fibrin strands and thereby increasing thrombus permeability and exposing more plasminogen receptors for binding. A RCT compared endoluminal ultrasound accelerated thrombolysis (EKOS EndoWave system; EKOS, Bothell, WA, USA) along with local urokinase *vs.* standard local urokinase infusion alone (see Table 10).[155] Thrombolysis was accelerated; however, there were three (10.7%) technical ultrasound catheter placement failures. Two (7.1%) intracranial haemorrhages, one of which was fatal, occurred after ultrasound accelerated thrombolysis. The need to withdraw the ultrasound co-axial wire out of the multilumen thrombolysis delivery catheter during control angiography, with manipulation of the introducer sheath, seemed to increase the risk of bleeding. In other studies using the EKOS system, time to full flow restoration and the amount of thrombolytic agent used was reducaed significantly.[156,157] A (non-randomised) comparison of mechanical thrombectomy (Rotarex) and ultrasound assisted thrombolysis showed a higher technical success and shorter treatment in the mechanical thrombectomy group.[158]

All mechanical thrombectomy devices can cause embolisation of both large and small particles. The use of distal embolic protection devices has been considered but not yet advocated. It should be remembered that many of these devices were originally developed for deep vein thrombosis, a situation when minor embolisation has less serious consequences.

The costs of all these endovascular devices are significant in comparison to CDT alone, and it is unclear whether the shorter thrombolytic treatment may make the devices more cost effective.

Recommendation 33

For patients with acute limb ischaemia, aspiration and mechanical thrombectomy should be considered.

Class	Level	References
IIa	C	Kwok *et al.* (2018),[141] Zehnder *et al.* (2000),[147] Byrne *et al.* (2014),[148] Kronlage *et al.* (2017)[152]

3.7. Randomised trials for the treatment of acute limb ischaemia

Over the years, a large number of RCTs have been done to explore the optimal role of thrombolysis in the management of ALI. Initially, there were several large trials done directly comparing thrombolysis with surgery (Table 6). Subsequently, most trials have been smaller and have been concerned with variations in thrombolytic techniques or agents. A summary with Forest plot figures of the results of several meta-analyses are found in Appendix S2 (see Supplementary Material).

Table 6. Randomised controlled trials comparing thrombolysis with surgical revascularisation

Reference	Patients *n*	Thrombolytic agent	Amputation free survival at one year *n* (%)	Major bleeding at 30 days *n* (%)	Stroke at 30 days *n* (%)	Distal embolisation at 30 days *n* (%)
Nilsson *et al.* (1992)[160]	20	High dose rtPA; 30 mg/3 h continuous UFH	NR	0 *vs.* 0	0 *vs.* 0	1/11 (9) *vs.* 0/9 (0)
Ouriel *et al.* (1994)[161]	114	Urokinase; continuous UFH	43/57 (75) *vs.* 30/57 (53)*	6/57 (10) *vs.* 1/57 (2)	1/57 (2) *vs.* 0/57 (0)	5/57 (9) *vs.* 0/57 (0)*
Ouriel *et al.* (1996)[301]	213	Urokinase; continuous UFH	107/155 (69) *vs.* 38/58 (66)	60/155 (38.7) *vs.* 17/58 (30)†	3/155 (1.9) *vs.* 0/58 (0)	NR
Ouriel *et al.* (1998)[159]	544	Urokinase; continuous UFH	177/272 (65.1) *vs.* 191/272 (70.2)	32/272 (11.8) *vs.* 14/272 (5.1)*	4/272 (1.5) *vs.* 0/272 (0)*	36/272 (13.2) *vs.* 0/272 (0)*
The STILE trial (1994)[91]	393	High dose rtPA; 0.05 mg/kg/h or urokinase continuous UFH	NR	14/249 (5.6) *vs.* 1/144 (0.7)*	3/249 (1.2) *vs.* 0/144 (0)	NR

Data are *n* (%) unless otherwise stated. rtPA = recombinant tissue plasminogen activator; UFH = unfractionated heparin; NR = not reported.
* Significant difference.
† Need of blood transfusion.

3.7.1. Surgery *vs.* local thrombolysis. The large and small trials during the 1990s all agree that overall, local intra-arterial thrombolysis and surgery were equivalent treatment options for ALI in terms of amputation free survival up to one year (Table 6).[91,101,159–161] A meta-analysis of five RCTs suggests that thrombolysis was associated with more bleeding complications, including haemorrhagic stroke and distal embolisation. The higher risks of bleeding with thrombolysis should be balanced against the risks of surgery in each patient.[130] There was substantial heterogeneity between included studies in the meta-analysis. It might be argued that the results of these RCTs from the 1990s may not apply to current patients with ALI,[85] but it is unlikely they will be repeated on such a large scale.

The STILE trial was the first large RCT of thrombolysis *vs.* surgery for ALI, but two thirds of the patients had stable ischaemia with a symptom duration > 14 days.[91] There was also a high rate of failed catheter placement (28%),[91] similar to the earlier Rochester study (17%).[161] Even in TOPAS II, the last major RCT of surgery *vs.* thrombolysis for ALI, the rate of thrombo-embolic clot guidewire traversal failure was 11%,[159] much higher than current practice. Since the 1990s, there has been a rapid evolution of vascular imaging, endovascular equipment, techniques, and skills that has driven the endovascular revolution for all vascular therapy. In a modern endovascular practice, patients with ALI can be offered a full range of surgical and endovascular options. In a contemporary, large, nationwide, propensity matched cohort comparing primary endovascular with open revascularisation for ALI, endovascular revascularisation (thrombolysis in most patients) was associated with a higher amputation free survival rate at 30 days (87.5% *vs.* 82.1%) and at one year (69.9% *vs.* 61.1%).[23]

3.7.2. Comparison of thrombolytic regimens. Thrombolysis may be accelerated by increasing the dose of thrombolytic drug or altering the method of administration. An initial bolus of rtPA (15 mg), followed by infusion (3.5 mg/hour for the first four hours, then 1 mg/hour thereafter) significantly accelerated thrombolysis compared with a low dose infusion without comprising the outcome.[109] A pulse spray device to lace the entire thrombus with high dose rtPA also achieves faster thrombolysis than a slow low dose infusion.[38,162] Some 35% ($n = 20/58$) could be treated within two hours in one series.[38]

Table 7. Randomised controlled trials comparing high *vs.* low dose intra-arterial recombinant tissue plasminogen activator

Reference	Patients *n*	Thrombolytic regimen	Amputation free survival 30 d *n* (%)	Major bleeding *n* (%)	Stroke *n* (%)	Distal embolisation *n* (%)
Yusuf *et al.* (1995)[162]	18	High dose pulse spray infusion *vs.* low dose infusion	100 *vs.* 67	0 *vs.* 0	0 *vs.* 0	NR
Braithwaite *et al.* (1997)[109]	93	Initial repeated intrathrombotic bolus + high dose *vs.* low dose infusion	39/49 (80) *vs.* 37/44 (84)	3/49 (6) *vs.* 3/44 (7)	0/49 (0) *vs.* 1/44 (2)	3/49 (6) *vs.* 2/44 (4)
Plate *et al.* (2006)[38]	121	Initial pulse spray high dose infusion + continuous UFH *vs.* low dose infusion plus continuous UFH	49/58 (84) *vs.* 54/63 (86)	4/58 (7) *vs.* 8/63 (13)	2/58 (3) *vs.* 0/63 (0)	10/58 (17) *vs.* 8/63 (13)

Data are *n* (%) unless otherwise stated. NR = not reported; UFH = unfractionated heparin.

Table 8. Randomised controlled trials comparing high dose *vs.* low dose intra-arterial urokinase

Reference	Patients *n*	Thrombolytic regimen	Amputation free survival 30 d *n* (%)	Major bleeding *n* (%)	Stroke *n* (%)	Distal embolisation *n* (%)
Cragg *et al.* (1991)[123]	63; 72 thrombolytic procedures	High dose bolus + high dose infusion *vs.* low dose bolus + low dose infusion	30/35 (86) *vs.* 36/37 (97)*	2/35 (6) *vs.* 0/37 (0)	0/35 (0) *vs.* 0/37 (0)	1/35 (3) *vs.* 2/37 (5)
Kandarpa *et al.* (1993)[163]	25	High dose pulse spray *vs.* initial pulse spray bolus + continuous infusion	10/12 (83) *vs.* 11/13 (85)	3/12 (25) *vs.* 1/13 (8)	1/12 (0) *vs.* 0/13 (0)	5/12 (42) *vs.* 5/13 (38)

Data are *n* (%) unless otherwise stated.
* Six (five in the high dose group) exhibited progression of ischaemia. Five of the six eventually had major amputations. One patient died (not amputated), unclear in which group. Local recombinant tissue plasminogen activator *vs.* urokinase.

Table 9. Randomised controlled trials comparing intra-arterial urokinase with intra-arterial recombinant tissue plasminogen activator

Reference	Patients *n*	Thrombolytic agents	Major amputation 30 days – 6 months *n* (%)	Major bleeding *n* (%)
Meyerovitz *et al.* (1990)[165]	32	Urokinase intrathrombotic bolus + infusion *vs.* rtPA intrathrombotic bolus + infusion	1/16 (6) *vs.* 2/16 (12)	3/16 (19) *vs.* 5/16 (31)
Schweizer *et al.* (1996)[166]	120	Urokinase and continuous UFH *vs.* rtPA intrathrombotic bolus + infusion and continuous UFH	2/50 (4) *vs.* 1/52 (2)	1/60 (2) *vs.* 0/60 (0)
Mahler *et al.* (2001)[164]	234	Urokinase *vs.* rtPA	3/100 (3) *vs.* 11/124 (9)	0/110 (0) *vs.* 1/124 (1)

Data are *n* (%) unless otherwise stated. rtPA = recombinant tissue plasminogen activator; UFH = unfractionated heparin.

However, amputation free survival is not improved by accelerated techniques,[109,162] although the risk of bleeding and distal embolisation was similar (Table 7).[38,109,162]

3.7.2.1. Local high vs. low dose urokinase. High dose CDT with urokinase was as effective as low dose urokinase in terms of duration of thrombolysis and amputation free survival (Table 8),[123,163] but bleeding was more common.[123] Speed of thrombolysis and initial success rates were similar in the high dose and low dose groups.

3.7.2.2. Local recombinant tissue plasminogen activator vs. urokinase. No difference between urokinase and rtPA in terms of major amputation or major haemorrhage has been shown (Table 9).[164–166]

3.7.3. Local *vs.* intravenous recombinant tissue plasminogen activator. Please see section 3.5.1.

3.7.4. Evidence on novel thrombolytic regimens.

3.7.4.1. Abciximab. Abciximab is a potent platelet inhibitor (glycoprotein GP IIb/IIIa receptor antagonist; Reopro [Janssen, Toronto, Canada]). It has been used as an adjunct to thrombolysis in three studies. Patients with acute peripheral artery thrombosis were randomised to received 5 mg rtPA intravenously and 500 IU UFH/hour, along with either an intravenous bolus of 0.25 mg/kg abciximab followed by 10 μg/minute intravenous abciximab over 12 hours, or 500 mg acetylsalicylic acid (ASA).[167] The abciximab group had a significantly lower composite of adverse events (sum of rates of rehospitalisation, re-interventions, and amputations) at six months compared with the ASA group. One major bleed (fatal haemorrhagic stroke) occurred in the ASA group. No distal embolisation occurred in either group (Table 10). A second RCT including patients with both thrombotic and embolic occlusions treated with local urokinase plus intravenous abciximab *vs.* local urokinase plus placebo[168] showed faster thrombolysis and a higher amputation free survival at 90 days (96% *vs.* 80%) without an increase in bleeding complications in the urokinase plus abciximab group (Table 10); this was the dominant strategy at three months.[169] In a third RCT,[121] reteplase, a third generation thrombolytic agent, plus intravenous abciximab, was not superior to urokinase plus intravenous abciximab in terms of reduced amputation rates (Table 10). During the three year follow up, only two patients (1.7%) underwent major amputation, which, according to the authors, may have been attributed to abciximab.

3.7.4.2. Alfimeprase. Alfimeprase is a recombinant protein of the enzyme fibrolase, a zinc metalloprotease originally isolated from the venom of the southern copperhead snake. Alfimeprase directly degrades fibrin alpha chain and has no interaction with plasminogen. In one study, intrathrombus alfimeprase (0.3 mg/kg) in two divided weight based infusions two hours apart was no more effective than intrathrombus placebo in 30 day surgery free survival, whereas the overall rate of adverse events was higher with alfimeprase (Table 10).[170]

Table 10. Single randomised trials comparing different thrombolytic regimens

Reference	Patients *n*	Thrombolytic regimens	Amputation free survival *n* (%)	Major bleeding *n* (%)	Stroke *n* (%)	Distal embolisation *n* (%)
Schrijver *et al.* (2015)[155]	60	Ultrasound accelerated thrombolysis + local urokinase *vs.* standard urokinase infusion	NR	3/28 (11) *vs.* 2/32 (6)	2/28 (7) *vs.* 0/32 (0)	1/28 (4) *vs.* 0/32 (0)
Schweizer *et al.* (2000)[167]	84	5 mg rtPA IV and 500 IU heparin/h, + either 500 mg ASA or an IV bolus of 0.25 mg/kg abciximab followed by 10 μg/min abciximab IV for 12 h	37/42 (88) *vs.* 40/42 (95) at 6 mo	1/42 (2) *vs.* 0/42 (0)	1/42 (2) *vs.* 0/42 (0)	0/42 (0) *vs.* 0/42 (0)
Duda *et al.* (2001)[168]	70	Local urokinase + IV abciximab *vs.* local urokinase + placebo	48/50 (96) *vs.* 16/20 (80) at 90 d	4/50 (8) *vs.* 0/20 (0)	0/50 (0) *vs.* 0/20 (0)	3/50 (6) *vs.* 2/20 (10)
Tepe *et al.* (2006)[121]	120	Reteplase + IV abciximab *vs.* urokinase + IV abciximab	NR	5/50 (10) *vs.* 4/70 (6)	0/50 (0) *vs.* 0/70 (0)	11/50 (22) *vs.* 6/70 (9)
Han *et al.* (2010)[170]	398	Intrathrombus alfimeprase (0.3 mg/kg) *vs.* intrathrombus placebo	NR	10/199 (5) *vs.* 6/199 (3)	1/199 (0.5) *vs.* 0/199 (0)	20/199 (10.0) *vs.* 5/199 (2.5)*
Ouriel *et al.* (1999)[124]	228	Recombinant pro-urokinase *vs.* standard therapy with urokinase	57/61 (93) *vs.* 47/55 (85) *vs.* 45/52 (86) *vs.* 50/60 (83) at 30 d	9/61 (15) *vs.* 11/55 (20) *vs.* 12/52 (23) *vs.* 10/60 (17)	0/61 (0) *vs.* 0/55 (0) *vs.* 0/52 (0) *vs.* 0/60 (0)	12/61 (20) *vs.* 11/55 (20) *vs.* 8/52 (15) *vs.* 6/60 (10)
Poredos and Videcnik (1999)[171]	88	Local streptokinase infusion ± lacing of plasminogen into the thrombus	6/43 (14) *vs.* 8/45 (18)	7/43 (16) *vs.* 5/45 (11)	0/43 (0) *vs.* 0/45 (0)	4/43 (9) *vs.* 6/45 (13)

Data are *n* (%) unless otherwise stated. NR = not reported; rtPA = recombinant tissue plasminogen activator; IV = intravenous; IU = international units; ASA = acetylsalicylic acid; h = hours; min = minutes; mo = months; d = days.
* Significant difference.

3.7.4.3. Pro-urokinase. Recombinant pro-urokinase is a single chain zymogen that is assembled into active two chain urokinase on the surface of the thrombus. This plasminogen activator is a highly fibrin specific agent. In an RCT, four regimens were compared: recombinant pro-urokinase (2 mg/hour, 4 mg/hour, or 8 mg/hour, followed by 0.5 mg/hour in all three arms) *vs.* standard therapy with urokinase.[124] The patients receiving pro-urokinase responded in a dose dependent manner, resulting in a higher frequency of $>$ 95% clot lysis and a lower frequency of $<$ 25% clot lysis at eight hours for those receiving 8 mg/hour compared with the other regimens, accompanied by a non-significant increase in bleeding complications. There was no difference in amputation rates between the four regimens (Table 10).

3.7.4.4. Enrichment with intrathrombus plasminogen. One RCT compared local streptokinase infusion after deposition of plasminogen into the thrombus *vs.* local streptokinase (Table 10).[171] While the duration of thrombolysis was shorter in the former group, there was no difference in successful thrombolysis rates between the groups.

3.8. Primary open surgery or thrombolysis for acute limb ischaemia?

A Cochrane Review addressed the question of whether surgical or thrombolytic therapy should be the preferred initial treatment of ALI.[130,172] Five RCTs with a total of 1 283 patients were included. The authors concluded that a general recommendation for initial treatment of ALI cannot be made for open surgery or thrombolysis, based on the current scientific data. There were no significant differences in limb survival or death between the two treatments after 30 days, six months, or one year. After 30 days, the thrombolysis group had a larger number of haemorrhagic strokes, major bleeding, and episodes of distal embolisation (see Table 6). Yet, these risks must be balanced against the individual risks of surgery, especially as there was no difference in long term survival. Another recent systematic review reported similar results, with no evidence in favour of either thrombolysis or surgery.[11]

The risks of surgery and thrombolysis in the initial treatment of ALI are presented in a meta-analysis. This analysis also supplies the background for the medical guidelines of the American College of Chest Physicians.[60]

A retrospective comparison between endovascular (154 extremities) and surgical (316 extremities) revascularisation for ALI was performed.[103] For Rutherford grade II ischaemia, results were as follows: technical success 90.7% (surgery) *vs.* 79.9% (endovascular); major amputation rate after 30 days 10.0% (surgery) *vs.* 7.2% (endovascular); and after one year 16.3% (surgery) *vs.* 13% (endovascular). Thirty day mortality was 13.2% after surgery and 5.4% after endovascular revascularisation. The authors concluded that in ALI with Rutherford grade II ischaemia, endovascular revascularisation could provide similar

limb survival to surgery, but with lower mortality. These results were confirmed in a propensity score matched analysis of a large contemporary cohort study (see section 3.9.1).

One study reported 322 patients with ALI, who received either surgical embolectomy alone ($n = 112$), or embolectomy in combination with an endovascular procedure ($n = 210$).[72] In addition to embolectomy, these hybrid procedures included percutaneous transluminal angioplasty (PTA) $\pm$ stenting ($n = 90$), direct CDT + PTA $\pm$ stenting ($n = 24$), and fragmentation / aspiration of the thrombus + PTA $\pm$ stenting in 67 patients. Primary patency rates after five years were 87.1% (hybrid procedure) *vs.* 66.3% (embolectomy). Freedom from re-intervention was estimated at 89% *vs.* 73.7%. The authors of this paper concluded a hybrid approach has advantages in selected patients.[72]

3.9. Specific considerations

3.9.1. Long term outcomes after acute limb ischaemia. Knowledge on the impact of revascularisation technique on long term outcomes is scarce. So far, no randomised study has evaluated long term mortality, patency, or amputation rates. The largest retrospective epidemiological analysis of treatment of ALI was based on data from the NHDS in the USA.[18] The authors included 1 092 811 hospital admissions for acute arterial embolism or thrombosis of the leg from 1988 to 1997, but no long term follow up data were reported.

Trends in the treatment of ALI in the Medicare population of the USA were also analysed from 1998 to 2009,[24] including one year follow up. One year mortality remained unchanged (41.0% *vs.* 42.5%), but the amputation rate at one year decreased from 14.8% to 11.0%.[76]

In a retrospective study from the Swedish Vascular Registry, 3 365 patients who underwent endovascular treatment were compared with 3 365 patients who underwent open surgery for ALI below the inguinal ligament after propensity score matching.[23] At 30 days, the endovascular group had better patency (83.0% *vs.* 78.6%) and lower mortality rate (6.7% *vs.* 11.1%), but amputation rates were similar. Five years after surgery, endovascular treatment still showed improved survival (HR 0.78, 99% CI 0.70 — 0.86), although the difference between the two groups occurred mainly in the first year.

Another paper reported the long term follow up of 689 patients who underwent thrombolysis for ALI.[26] During a mean follow up of five years, 33% needed further re-interventions, 16% underwent amputation, and 51% had no re-intervention. There were large differences in need for re-intervention, primary patency, amputation, and survival, depending on the cause of ALI. The amputation rate was lowest after embolus, survival was highest after occluded PA, and amputation free survival was lowest after occluded graft / stent, all at five years.

In an international collaboration between two centres in Finland and Russia, 155 patients treated by CDT for grade I or IIa ischaemia were studied with a mean follow up of 126 months.[173] Only 30% were alive after 10 years; AF and older age were associated with mortality. Re-interventions were common: 190 additional procedures in 122 patients.

3.9.2. Aetiology of the occlusion. Differences in outcome are dependent on the aetiology of the occlusion: arterial thrombosis, embolus, aneurysm, or graft thrombosis.

In the Rochester trial,[161] irrespective of whether the ALI was caused by embolic or thrombotic occlusion, surgery and thrombolysis were equally effective for limb salvage. However, the one year survival rate appeared greater when patients with embolic events were treated by thrombolysis (100% *vs.* 51%). The benefit for patients with thrombotic occlusions was less substantial.

In the TOPAS trial,[159] subgroup analysis showed that surgery and thrombolysis provided comparable outcomes in patients with native arterial occlusion, as well as in those with bypass graft thrombosis. Patients with emboli randomly assigned to initial thrombolysis tended to have improved thrombolysis rates and less need for secondary intervention.

In the STILE trial, patients with acute graft occlusion ($<$ 14 days) had the greatest benefit from thrombolysis.[91,100] There was a trend toward a lower major amputation rate at 30 days, and a significantly lower rate at one year compared with those who had surgery. In the recent Swedish Vascular Registry study,[23] amputation free survival was higher after primary endovascular intervention, irrespective of whether the ALI was caused by embolus or thrombosis.

Collectively, these trials suggest that thrombolysis may have an advantage for the treatment of acute bypass graft occlusions, with initial success rates tending to be better for prosthetic than vein grafts.

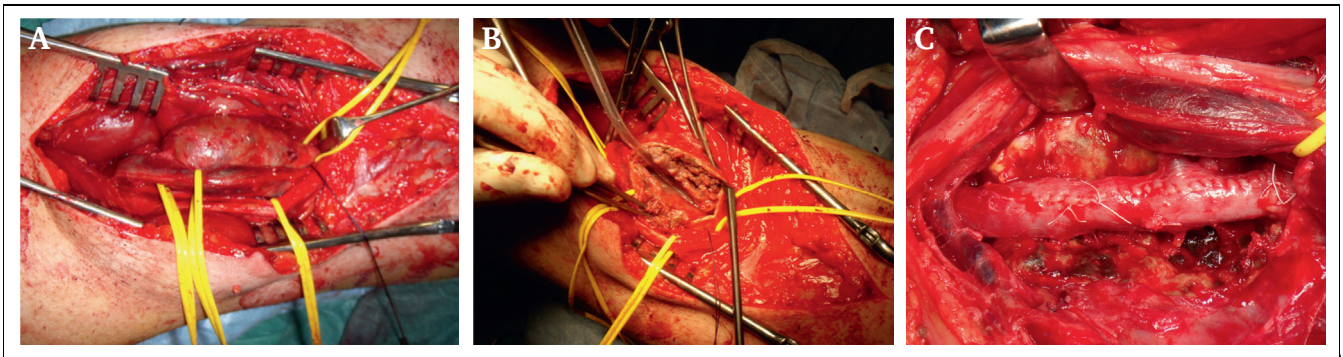

Figure 9. (A) Thrombosed popliteal artery aneurysm (PA). (B) Opened PA showing thrombus. (C) Reconstruction with a doubled vein graft.

3.9.3. Length of occlusion. Data from the TOPAS trial were analysed using a Cox proportional hazard multifactorial model to determine whether baseline variables could be useful in deciding whether patients should be treated by thrombolysis or surgery.[101] The length of occlusion was the only parameter to be significant. Patients with an occlusion of $<$ 30 cm appeared to do better after surgery, with an increased one year amputation free survival rate (79% *vs.* 60%). Patients with occlusions $>$ 30 cm tended to fare better after thrombolysis, with an improved one year amputation free survival (69% *vs.* 61%).

3.9.4. Acute limb ischaemia due to popliteal artery aneurysm. PA may cause ALI by thrombosis and / or embolisation. Distal embolisation may occur to one, two, or all three major lower leg arteries, leading to chronic or acute limb ischaemia. In the latter case the limb may be ischaemic, but with a patent popliteal artery. If the popliteal artery thromboses, leg ischaemia may be mild if distal vessels are preserved, but more often it is severe, as the distal vessels are already occluded. A recent study of 55 patients with ALI due to PA, treated by open surgery, reported that it may be difficult to distinguish grade IIb and grade III ischaemia in these patients.[174] A systematic review reported a high risk of amputation after acute thrombosis of a PA (14.1%).[175] Although femoral and iliac artery aneurysms may cause thrombo-embolism and ALI, this is much less common and will not be discussed in these guidelines.

The diagnosis of PA as the cause of ALI is often clinical, as the aneurysm may be palpable if it has not thrombosed completely, and about half the patients have bilateral PAs. The diagnosis is confirmed by imaging with DUS or CTA. The state of the tibial vessels is critical in management, as the patency of a surgical bypass is dependent on the number of patent tibial arteries. Surgical bypass has been the mainstay of treatment, but endovascular stenting with a covered stent graft is a more recent alternative. Surgical bypass should be done with saphenous vein where possible, as patency rates *vs.* prosthetic bypass are superior after one year .[176] The popliteal artery may be exposed by medial or posterior approaches. A meta-analysis of seven comparative, non-randomised studies including 338 patients undergoing posterior and 1 089 undergoing medial open bypass included a majority of elective repairs. The posterior approach was superior in terms of primary and secondary patency, aneurysm exclusion, and need for re-operation,[177] although it was more often done for short lesions (Fig. 9). Extrapolation of these data to patients with acute ischaemia is not appropriate.

3.9.4.1. The role of thrombolysis in popliteal artery aneurysm with acute limb ischaemia. Adjuvant intra-arterial thrombolysis may be valuable in patients with ALI due to PA thrombosis. Unlike native vessel thrombosis, the aim of peripheral arterial thrombolysis is not to re-open the whole artery, as this risks catastrophic distal embolisation,[133] but to re-open occluded tibial vessels to optimise the potential for surgical bypass.[178] Once partial lysis is achieved, there is an option to continue with endovascular therapy and end the treatment session by placing a stent graft; however, once the distal vessels are patent, most surgeons employ an open vein bypass, particularly if there is a good saphenous vein available in either leg. Alternatively, thrombolytic drugs may be given intra-operatively after popliteal artery exploration in an attempt to re-open tibial vessels occluded by fresh thrombus, before inserting a distal bypass. Intra-operative thrombolysis has been reported to improve limb salvage *vs.* pre-operative thrombolysis and delayed surgery in a univariable analysis.[179] In a systematic review of 33 studies including 895 patients, pre-operative and / or intra-operative thrombolysis improved one year primary graft patency, but did not reduce the risk of amputation compared with surgery (thrombo-embolectomy and bypass) alone.[175] In registry data, thrombolysis for PA was associated with the need for higher doses of rtPA, more bleeding complications needing blood transfusion, a higher fasciotomy rate, a higher major amputation rate at 30 days and lower amputation free survival compared with thrombolysis for ALI due to native vessel or bypass occlusion. The authors concluded this was due to the higher rates of severe ischaemia with a motor deficit at presentation.[25]

3.9.4.2. The role of covered stenting in popliteal artery aneurysm with acute limb ischaemia. Endovascular lining with a covered stent is an option to seal the inside of the popliteal artery as an alternative to surgical bypass. There are no RCTs comparing open surgery with stenting with or without thrombolysis for ALI secondary to PA. Two reports describe outcomes after vein bypass *vs.* endovascular PA repair in patients treated urgently for ALI.[176,180] The pooled 30 day graft occlusion and amputation rate was higher after endovascular stenting than after open vein repair. A nationwide study using the Swedish Vascular Registry suggests compromised runoff is common even after tibial thrombo-embolectomy or local thrombolysis for thrombosed PA, leading to a low flow situation, which contributes to the inferior performance of prosthetic grafts and stent grafts, compared with vein grafts.[176] The two most important factors in multivariable analysis for major adverse events in the mid term after PA repair were fewer patent runoff arteries to the foot and endovascular repair.[180]

Recommendation 34

For patients with acute limb ischaemia secondary to thrombosis of a popliteal artery aneurysm, repair of the aneurysm with a saphenous vein bypass should be considered.

Class	Level	References
IIa	B	Huang *et al.* (2014),[180] Cervin *et al.* (2015)[176]

Recommendation 35

For patients with acute limb ischaemia secondary to popliteal artery aneurysm, pre-operative or intra-operative thrombolysis to improve runoff should be considered.

Class	Level	References
IIa	B	Ravn *et al.* (2007),[178] Gabrielli *et al.* (2015)[179]

Recommendation 36		
For patients with acute limb ischaemia secondary to popliteal artery aneurysm, stent grafting is not recommended as first line treatment.		
Class	**Level**	**References**
III	B	Huang *et al.* (2014),[180] Cervin *et al.* (2015)[176]

3.9.5. Management of compartment syndrome and reperfusion injury

3.9.5.1. Pathophysiology. IRI is the consequence of flow restoration to ischaemic tissue. Tissue damage is initiated in the ischaemic phase but continued, and even aggravated after reperfusion. IRI involves a number of mechanisms, such as the release of oxygen free radicals and infiltration of neutrophils into the reperfused tissues.[181] This provokes vasodilation and capillary leakage, resulting in tissue oedema. Recent research has concentrated on potential IRI biomarkers; these include matrix metalloproteinases, neutrophyl gelatinase associated lipocalin, and inflammatory cytokines.[182]

Compartment syndrome (CS) is a serious complication following ALI revascularisation. The tissue swelling as a result of IRI raises pressure in the limb muscles which are constrained by fascial compartments. Thus, intracompartment pressure rises as a result of swelling and may be sufficiently high to reduce perfusion of already damaged tissues. Untreated, the extremity (usually the foot) becomes ischaemic again, and the limb may be lost, despite previously successful revascularisation. Late diagnosis and treatment are associated with severe morbidity due to irreversible muscle necrosis and ischaemic nerve damage.

3.9.5.2. Incidence. CS can occur after any revascularisation for ALI: embolectomy, thrombolysis, or bypass surgery.[183] However, it is more common after revascularisation of prolonged, severe ischaemia. A high incidence of CS (up to 25% — 30%) has been reported in several studies.[184,185] The main complication is leg amputation, but deaths do occasionally occur.

3.9.5.3. Diagnosis. The diagnosis of CS is usually based on clinical symptoms and signs; however, they have poor sensitivity, which may result in delayed diagnosis.[186] Pain is usually present and is often severe, but it is an unreliable indicator as its intensity can be variable. Pain may be minimal in CS associated with nerve injury. Swelling and tenderness of the muscle compartments are signs, which should suggest the diagnosis, although a haematoma may be an alternative explanation. Sensory symptoms and signs are often present in the extremity at an early stage, but by the time a motor deficit develops, full recovery is unusual, being reported in only 13% of patients.[187]

CS caused by IRI results in muscle damage, accompanied by leakage of myoglobin and CK into the circulation (rhabdomyolysis). Excretion of myoglobin in the urine (myoglobinuria) can cause renal tubular damage and renal failure, in extreme cases.[188] CK can be measured in the blood and high levels (5 000 — 10 000 IU/L) are indicative of severe IRI and CS, with the potential for acute renal failure.[189,190] Rhabdomyolisis is diagnosed once CK reaches 20 000 μ/L. Raised CK occurs relatively late in CS, so it is not very useful for early diagnosis. Other biochemical markers include neutrophil to lymphocyte ratio; a ratio of $>$ 5 is associated with higher mortality rates after ALI.[191,192]

Compartment pressure measurement is straightforward using a needle manometer, but there is little consensus about the threshold value for diagnosis and treatment of CS. Elevated compartment pressure above 20 — 30 mmHg has high sensitivity and specificity (94% — 98%) for CS, but some authors believe the absolute value should be related to mean arterial pressure at the time.[193,194] Compartment pressure is seldom measured routinely;[194,195] indeed routine measurement after reperfusion may even result in overtreatment.[196]

Several authors have attempted to identify risk factors for the development of CS, including ischaemia duration $>$ 6 hours, young age, previous history of ALI, and hypotension.[197] Others found that elevated serum CK, severity of acute ischaemia (Rutherford IIb), inadequate intra-operative backflow and positive fluid balance were associated with CS after ALI treatment.[184] The importance of these findings lies in the possibility of identifying patients who would benefit from immediate fasciotomy after revascularisation for ALI, or at least undergo close monitoring post-operatively, and delayed fasciotomy if necessary.

3.9.5.4. Prevention of compartment syndrome. Slow restoration of the circulation (controlled limb reperfusion) has been extensively investigated to try and reduce IRI. It is thought that thrombolysis might offer this compared with surgical revascularisation. After initial optimistic results,[198] a recent RCT failed to find an improvement in amputation free survival or overall survival at four weeks and one year *vs.* conventional treatment for ALI.[199] Hypothermic, initially oxygen free, controlled limb reperfusion with extracorporeal membrane oxygenation (ECMO) is another possible solution, although not widely available,[185] and poorly investigated.

The main way to prevent CS is to conduct prophylactic fasciotomy after revascularisation. Obviously, this is an easier option for patients who have have had surgical treatment, but must be considered after all urgent revascularisation procedures. Decisions will be individualised for each patient but should take into account the risk factors mentioned above. A recent study reported that patients undergoing delayed fasciotomy were more likely to require major amputation within 30 days than patients having prophylactic fasciotomy (50% *vs.* 5.9%), suggesting that a liberal approach to prophylactic fasciotomy was favourable.[200] However, there are many confounding factors in this comparison, including the timing of on demand fasciotomy, making it difficult to draw firm conclusions from these data.

3.9.5.5. Treatment. Fasciotomy is the treatment for both established CS, and prophylaxis against possible IRI. The lower leg is the most common location of CS. A single incision technique over the anterior compartment was advocated,[201] but this risks leaving the posterior compartments untreated and ischaemic. A full four compartment fasciotomy is the current standard of care, which is typically achieved with two incisions (Fig. 10). The compartments must be decompressed fully, which requires skin incisions of at least 15 cm in length. The wounds should be left open, as early closure of fasciotomy wounds has been associated with recurrent CS. Various

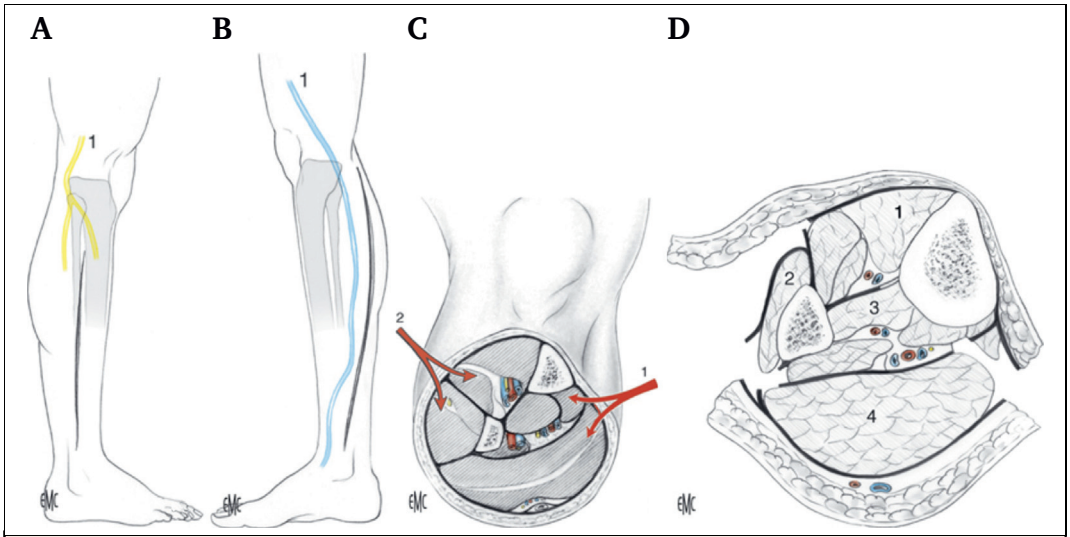

Figure 10. Fasciotomies of the leg: a full four compartment fasciotomy is recommended, which is typically achieved with two incisions. (A) Lateral incision (1 = peroneal nerve). (B) Medial incision (1 = great saphenous vein). (C) Fasciotomies of the superficial posterior and deep posterior compartments (1). Fasciotomies of the anterior and lateral compartments (2). (D) Four compartment fasciotomy, with the wounds left open (1 = anterior compartment; 2 = lateral compartment; 3 = deep posterior compartment; 4 = superficial posterior compartment). Reproduced with permission from Ricco *et al.*[202]

techniques are described for wound closure following fasciotomy, including vacuum assisted wound closure, shoelace suturing, skin stretching, and skin grafting.

Fasciotomy is needed less often in the arm (for details please see section 7). The timing of fasciotomy is critically important in patients who develop CS. Untreated CS compounds ischaemic muscle damage, and risks myoglobinuria and renal failure. In this situation, fasciotomy is an emergency procedure, and should take precedence over most other urgent surgical cases. Performing fasciotomy in the intensive care or high dependency unit should be considered, to avoid delay. Fasciotomy should usually be done within two hours of diagnosis; waiting longer than six hours is not acceptable. Fasciotomy should be done within eight hours of the development of CS,[203] but even that may be too late in some patients. It is probaly too late for fasciotomy if CS has been present for more than eight hours.[204]

Fasciotomy is not entirely without risk. Early skin grafting or coverage by other means may reduce the risk of infection.[205] It has also been shown that approximately half of patients who undergo fasciotomy develop symptoms of deep venous insufficiency, which may become more significant with time.[206] Thus, the decision to perform fasciotomy should always be considered carefully.

Recommendation 37

For patients who have had revascularisation for acute limb ischaemia, clinical examination is recommended to diagnose post-reperfusion compartment syndrome.*

Class	Level	References
I	B	Janzing *et al.* (2007),[186] McQueen and Court-Brown (1996),[194] von Keudell *et al.* (2015),[203] Gourgiotis *et al.* (2007)[193]

* Recommendation refer to the lower limb.

Recommendation 38

Compartment pressure measurement may be considered to diagnose post-reperfusion compartment syndrome, when the clinical diagnosis is uncertain.*

Class	Level	References
IIb	C	Janzing *et al.* (2007),[186] McQueen and Court-Brown (1996)[194]

* Recommendation refer to the lower limb.

Recommendation 39

For patients who have had revascularisation for acute limb ischaemia, routine prophylactic fasciotomy is not recommended, as it is associated with prolonged hospital stay, local infection, and development of late deep venous insufficiency.*

Class	Level	References
III	C	Bermudez *et al.* (1998),[206] Johnson *et al.* (1992)[205]

* Recommendation refer to the lower limb.

Recommendation 40

Prophylactic four compartment fasciotomy should be considered if ischaemia before revascularisation has been profound or prolonged.*

Class	Level	References
IIa	C	Papalambros *et al.* (1989),[197] Orrapin *et al.* (2017),[184] Rothenberg *et al.* (2019)[200]

* Recommendation refer to the lower limb.

Recommendation 41

Emergency four compartment fasciotomy is recommended to treat post-ischaemic compartment syndrome.*

Class	Level	References
I	B	von Keudell *et al.* (2015),[203] Gourgiotis *et al.* (2007)[193]

* Recommendation refer to the lower limb.

Recommendation 42

When post-ischaemic compartment syndrome is diagnosed, fasciotomy should be considered as soon as possible, and always within two hours.*

Class	Level	References
IIa	C	Consensus

* Recommendation refer to the lower limb.

Recommendation 43

When post-ischaemic compartment syndrome of the lower limb is diagnosed, delaying fasciotomy by more than six hours is not recommended.*

Class	Level	References
III	C	von Keudell *et al.* (2015),[203] Finkelstein *et al.* (1996)[204]

* Recommendation refer to the lower limb.

3.9.6. Decision making algorithm in acute limb ischaemia.

The decision making algorithm in acute limb ischaemia is provided in Fig. 11.

4. POST-OPERATIVE MEDICAL TREATMENT AND FOLLOW UP

The high rate of early and late limb loss, as well as the considerable mortality following treatment of ALI are

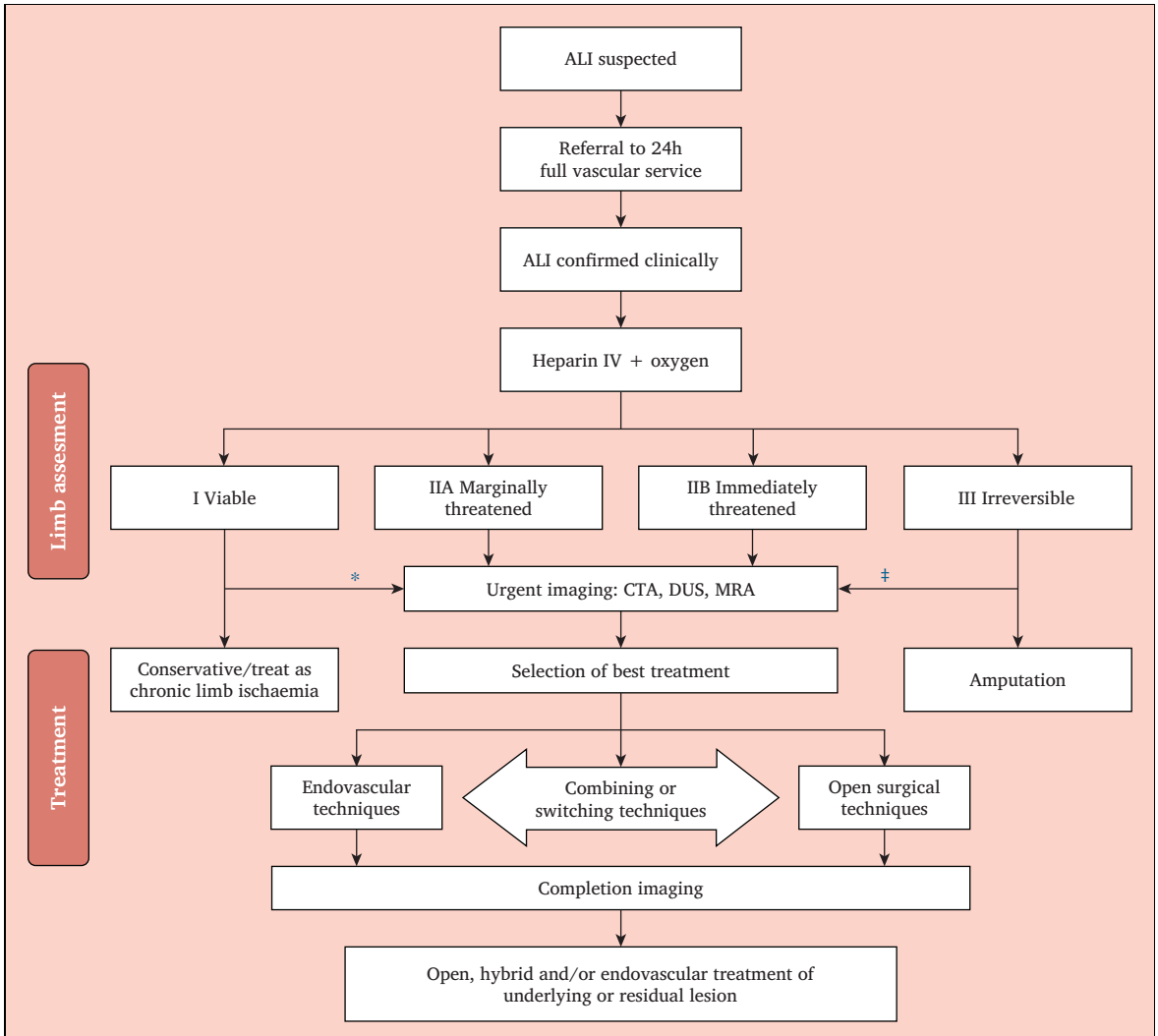

Figure 11. Decision making algorithm in acute limb ischaemia. *In patients with acute onset of claudication conservative treatment is safest. ‡In patients with short duration of motor deficit, there is a small chance of limb salvage. In very selected cases urgent revascularisation can be considered.

indications for follow up after treatment.[29,207] This may include both the patient's cardiovascular condition and an assessment of the functional status of the limb. Although ALI is an important healthcare problem, numbers of patients are limited, which, together with its acute character, makes research more difficult. There are no RCTs comparing different types of follow up, but data from registries and observational studies are available.

The 2017 European Socity of Cardiology (ESC) Guidelines on PAD developed in collaboration with the ESVS did not specifically address issues related to patients treated for ALI.[4] However, there are general principles guiding medical treatment and follow up after embolisation, or surgical bypass in the lower limb. The same WC developed further those recommendations on follow up in a subsequent 2019 publication.[208]

4.1. Follow up after arterial embolisation

As the most common causes of arterial embolisation are AF and intracardiac thrombosis, one of the most important aims of post-operative management is the prevention of recurrent embolisation. The source of the embolus needs to be verified. The evaluation includes electrocardiogram (ECG), other diagnostic methods to identify acute myocardial infarction, 24 hour ECG monitoring when necessary, as well as echocardiography and CTA of the whole aorta if no intracardiac embolic source is identified.[59]

The value of AC for prevention of embolisation in patients with AF is well established.[209,210] In a large registry study post-operative AC treatment with warfarin was associated with a reduced risk of early limb loss after embolectomy for acute arterial occlusion.[16] The Vascular Surgical Society of Great Britain and Ireland carried out an audit after treatment for ALI. It was concluded that recurrent limb ischaemia was less common in patients given warfarin initially (7% *vs.* 17%) and still taking warfarin after one year (3% *vs.* 19%).[29]

Warfarin has been the most commonly used medication for this purpose for decades. A meta-analysis from 2013 reported direct oral anticoagulants (DOACs) to be no more effective in preventing non-haemorrhagic stroke and systemic embolic events in patients with AF, but they were associated with a lower risk of intracranial bleeding than warfarin.[211] A more recent meta-analysis, from 2016, suggested that DOACs may decrease the risk of ALI significantly compared with warfarin in patients with AF.[212]

A review of 50 patients presenting with ALI showed that patients *without* AF or intracardiac thrombus may not carry the same risk of recurrent events as those with these risk factors.[213] Long term AC may not be necessary in this group of patients, as there are few published data supporting this approach. However, this area awaits a properly designed prospective randomised trial that preferably also would consider the importance of cardiac risk factors and concomitant malignant disease.

Early heparinisation after surgery for ALI appears valuable, but there is no evidence of a benefit of short or long term heparin treatment in patients with acute thromboembolic arterial occlusion.[61,214]

Multiple studies report that many patients with AF are not given AC treatment,[215–217] and many others have suboptimal AC levels.[217] The specific treatment of AF and other dysrhythmias is covered by the ESC guidelines.

Recommendation 44

After revascularisation for acute limb ischaemia, follow up should be considered, including the patient's cardiovascular condition and functional status of the limb.

Class	Level	References
IIa	C	Zierler *et al.* (2018),[218] Campbell *et al.* (2000),[29] Ansel *et al.* (2008)[207]

Recommendation 45

For patients revascularised for acute limb ischaemia of embolic origin, it is recommended that, whenever possible, the source of the embolus be investigated, to prevent recurrence.

Class	Level	References
I	B	Kirchhof *et al.* (2016),[219] Gerhard-Herman *et al.* (2016)[59]

Recommendation 46

After revascularisation for acute limb ischaemia caused by an embolus secondary to atrial fibrillation or intracardiac thrombus, long term anticoagulation is recommended.

Class	Level	References
I	B	Ljungman *et al.* (1991),[16] Campbell *et al.* (2000),[29] de Haro *et al.* (2016)[212]

Recommendation 47

For patients who have had revascularisation for acute limb ischaemia of embolic origin, long term anticoagulation may be considered for patients without atrial fibrillation or intracardiac thrombus.

Class	Level	References
IIb	C	Forbes *et al.* (2002)[213]

4.2. Follow up after native arterial thrombosis, or occlusion of an artery treated by endovascular or open surgery

Patients with ALI are prone to repeated major cardiovascular events, often leading to rehospitalisation, re-intervention, and early mortality. In patients with symptomatic PAD, ALI is most often caused by thrombosis of the diseased native vessel, or by acute occlusion of a bypass graft, or an endovascular procedure. Following surgical or endovascular revascularisation for ALI caused by arterial thrombosis, regular follow up may be beneficial, including clinical evaluation and assessment of functional status,[4,208] although specific studies addressing this issue were not identified. During follow up visits, pulse examination and ABI measurements are performed. If clinical symptoms deteriorate, or there is a significant drop in ABI, vascular imaging (DUS, CE-MRA, CTA, or DSA) is required.

4.2.1. Concomitant malignancy or thrombophilia. When young patients (< 60 years of age) are affected by thrombotic ALI, and in particular when patients suffer simultaneous venous and arterial thrombosis, concomitant malignant disease[220] and thrombophilia[221] should be investigated post-operatively.

4.2.2. Smoking cessation. Smoking is a strong risk factor for the development and progression of PAD.[222,223] Several studies suggest that smoking cessation is associated with a lower rate of cardiovascular ischaemic and limb related vascular events, amputations, and death.[224,225] Therefore, patients who smoke should be advised to quit smoking at every follow up visit, and should be offered support from a smoking cessation team, if available.[208,226]

4.2.3. Antithrombotic medication and statins. Following ALI revascularisation for arterial thrombosis, antiplatelet therapy and statins should be administered to decrease cardiac complications and to prevent atherosclerotic disease progression.[227] A meta-analysis of the Antithrombotic Trialists' Collaboration showed that among patients with symptomatic PAD treated with antiplatelet therapy there was a 22% odds reduction for cardiovascular events, including myocardial infarction, stroke, or vascular death.[228] The large British Heart Protection study (2002) provided robust evidence that statins reduce stroke, acute myocardial infarction, and death of patients with PAD.[229] In a systematic review of observational studies, statins were associated with improved infra-inguinal bypass graft patency, reduced restenosis, and amputation rates.[230] The above mentioned studies mainly apply to patients with chronic PAD, but it is expected that similar benefits will also apply to patients who developed ALI as a result of thrombosis.

There are no data showing that UFH, LMWH, or AC treatment is of any benefit for the prevention of a recurrent arterial thrombotic event. In a registry based study, it was concluded that AC was associated with significantly improved secondary patency in patients with prosthetic bypass grafts (HR 0.77);[231] therefore, long term AC after thrombectomy or thrombolysis of an occluded prosthetic bypass might be considered. The combination of low dose DOAC and low dose aspirin, as in the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial, has not primarily been investigated after ALI. However, in patients with stable PAD, an overall benefit from receiving rivaroxaban2 × 2.5 mg plus aspirin 100 mg was demonstrated.[232] A small subgroup of patients within this study who had ALI also had a marked reduction in amputation and mortality rate.[223] Although the COMPASS trial was positive for patients with ALI, this was not the primary end point, and further research with a focus on ALI is needed.

4.2.4. Imaging. DUS is the imaging modality of choice during follow up. It is non-invasive, and the most appropriate method to evaluate degree of stenosis. There are no problems with artefacts after stenting. CTA and CE-MRA are alternative non-invasive tools for follow up. CE-MRA can provide useful information on the remodelling process after endovascular interventions and can also determine patency and restenosis if stents were not used.[233]

DUS surveillance after infrainguinal vein bypass (in general, not specifically after treatment of ALI) has been advocated for over 20 years, however, the evidence for this practice remains contradictory.[234,235] A recent meta-analysis showed that DUS surveillance compared with clinical examination and ABI measurement was not associated with a significant change in vein bypass patency, amputation, or mortality.[236] Although there are no data on optimal timing, many vascular surgeons offer clinical and imaging follow up after four to six weeks, three and six months, and one and two years after bypass surgery.

Recommendation 48

Long term anticoagulation may be considered after thrombectomy or endovascular treatment of a prosthetic bypass graft occlusion.

Class	Level	Reference
IIb	B	Liang *et al.* (2017)[231]

4.3. Follow up after thrombosed popliteal aneurysm

In a registry based study it was observed that the number of surgical procedures for PA, including thrombosed cases with ALI, have almost doubled in Sweden over the past 10 years, probably owing to an increased detection rate.[176] Nonetheless, the proportion of patients with ALI due to thrombosed PA is low. In another large registry study on ALI, only 536 of 16 229 (3.3%) patients treated for ALI had a thrombosed PA.[23] Patients with PA have an increased risk of a new aneurysm formation in the contralateral popliteal region, the aorta, and at other locations.[237] Therefore, these patients should be followed and if a new aneurysm develops, vascular reconstruction should be considered to protect life and limb. In a re-examination of 190 patients, who had another 108 aneurysms at the time of surgery, another 131 aneurysms were identified after a mean of seven years.[238] Six of 138 legs (4.3%) treated with a venous bypass had developed a graft aneurysm. Although the authors recommended life long surveillance, no patient with a normal arterial segment

developed an aneurysm requiring intervention within three years. Therefore, it would be adequate to re-examine the normal arterial segments every three years.

A similar follow up approach can be recommended after endovascular therapy of a thrombosed PA. However, there are no data to support DUS surveillance improving outcome. If DUS detects a severe restenosis, endovascular re-intervention or open surgery is recommended. In patients who undergo endovascular intervention for PA, or open surgery with a medial approach, exclusion of the aneurysmal sac from the blood flow should also be examined, as late expansion is common (33% after a median of seven years of follow up in one study).[238] DUS can detect expansion of the aneurysm sac after PA repair, but CTA is more reliable in detecting the expansion mechanism. There is no specific study to confirm the benefit of platelet inhibitors and/or statins after surgery for a thrombosed PA; however, on the basis of general observations the use of these drugs can be expected to be beneficial.

Recommendation 49

Antiplatelet therapy or anticoagulation and statins are recommended long term to reduce cardiovascular events following acute limb ischaemia revascularisation caused by native artery thrombosis, thrombosis of a popliteal artery aneurysm, or failure of previous revascularisation.

Class	Level	References
I	A	Mangiafico and Mangiafico (2011),[227] Tomoi *et al.* (2013),[239] Paraskevas *et al.* (2013),[230] Aboyans *et al.* (2018),[4] Venermo *et al.* (2017),[240] Proietti *et al.* (2017),[241] Heart Protection Study Collaborative Group (2002)[229]

Recommendation 50

For patients treated for thrombosed popliteal artery aneurysm, regular duplex ultrasound follow up should be considered after open or endovascular surgery.

Class	Level	References
IIa	B	Dawson *et al.* (1991),[237] Ravn *et al.* (2008),[238] Loftus *et al.* (1999)[242]

Recommendation 51

For patients treated by open or endovascular surgery for thrombosed popliteal artery aneurysm, duplex ultrasound imaging of the treated and contralateral arteries, as well as of the aorta, iliac, and femoral arteries, every three years should be considered.

Class	Level	References
IIa	C	Loftus et al. (1999),[242] Ravn *et al.* (2008)[238]

5. REGISTRIES AND QUALITY IMPROVEMENT

5.1. Variables to include in registries

Vascular registries aim to monitor outcomes, improve quality, and form the basis for research. Some registries cover all types of open and endovascular procedures; others are focused on specific operations, such as abdominal aortic aneurysm repair and carotid endarterectomy. The first international collaboration of vascular registries, Vascunet, was created in 1997. It focused on harmonising variables and outcomes suitable for quality improvement projects.[243,244] One of the first Vascunet reports described great international variations in treating > 32 000 patients with infrainguinal bypass for PAD, but, unfortunately, those treated for ALI were excluded from this investigation.[245] However, a later publication on 1 471 patients treated for PA in eight countries reported specifically on those who had been treated for ALI.[58] The proportion of PAs treated as an emergency (including just a few ruptures) varied from 0% in Iceland to 74% in Hungary.

5.1.1. Acute limb ischaemia in existing vascular registries. In 2014 Vascunet joined with the recently founded North American Society for Vascular Surgery Vascular Quality Initiative (VQI) and created the International Consortium of Vascular Registries.[246] Similar to the Vascunet, the focus of the VQI has been on PAD, but it has also reported on the proportion of patients treated for ALI. In a report on 15 338 bypass procedures and 33 926 endovascular procedures, 14% and 10%, respectively, were on patients admitted with ALI.[247] Mortality and major amputation rates did not differ between regions, either after open or endovascular surgery, but there were significant differences in myocardial infarction. Another paper reported that 9% of those who underwent major amputation in 2013 — 2015, were admitted with ALI.[248] They also reported a higher proportion of above knee amputations (57%) in those who had an amputation after ALI than in those who had an amputation for other reasons (43%).

Amputation was also the focus of an extended Vascunet collaboration in 2010 — 2014, which showed great international variation in incidence, by a factor of six, between participating countries.[249] Amputations for acute thrombosis and embolus were included in this investigation.

Many registries still do not capture specific data to monitor and improve outcomes after ALI. However, in the Vascunet study on PA, the authors suggested that vascular registries should capture the following data: diameter of the PA; thrombus in the aneurysmal sac, indication for repair; number of runoff vessels; thrombolysis; and open surgical approach (medial or posterior).[250] They also suggested reporting patency, amputation, and symptoms at 30 days and one year after surgery.

5.1.2. Suggested variables for future registries. One way of improving registry data collection is to reach consensus through a Delphi process, and two such processes took place in 2018. The first paper identified 79 recommended variables to be included in registries on all patients with PAD,[251] including obvious variables such as survival and amputation. The second Delphi process focused on ALI: 23 variables were recommended for the minimum core data

set (Level 1). An additional 12 more specific variables, and more detailed information on the previously mentioned 23 variables, were suggested for registries that are capable of capturing more data (Level 2 — 3).[252]

Recommendation 52		
It is recommended that outcomes after treatment of acute limb ischaemia should be monitored in vascular registries, using variables that have been developed specifically for this group of patients.		
Class	**Level**	**References**
I	C	Behrendt *et al.* (2019)[252]

5.2. Claims data or administrative data

An alternative to prospectively collected vascular registry data is to use existing health insurance claims or statutory hospital episode statistics.[240] While registry data are usually collected specifically for comparative audit driving quality improvement, and for research, claims data consist of heterogeneous information used for reimbursement or administration. Nevertheless, claims data are often sufficiently valid for major events, such as death or amputation. An important advantage is that claims data may have high external validity (i.e., few missing cases) when compared with some registry data with lower quality. In addition, there is usually complete follow up until death, and subsequent hospital episodes can be captured.[253] Furthermore, data collection using claims is not limited to a single society or medical specialty, but includes all healthcare providers. There are also limitations, such as lack of anatomical data or patient reported outcomes. As many countries and regions lack a high quality vascular registry for quality improvement of treating patients with ALI, the use of claims data is an alternative that should be considered.

5.3. Quality improvement projects

Improving outcomes after ALI has not yet been the focus of quality improvement in any of the registries. Simply by monitoring outcomes over time, and comparing units, regions, and nations, results are likely to improve. It is important, for instance, to monitor mortality, amputation, level of amputation, and fasciotomy rates.

It is also possible that specific factors are associated with outcome, such as delay from presentation to revascularisation, or treatment at a centre with both open and endovascular capability. If such factors can be shown to be independently associated with the outcome in prospective registry data collection, they can be used in the future as quality improvement targets. Vascular societies should develop benchmarks for treatment outcomes of patients with ALI.

Recommendation 53		
For patients treated for acute limb ischaemia, quality improvement projects and benchmark indicators should be considered.		
Class	**Level**	**References**
IIa	C	Behrendt *et al.* (2019),[252] Behrendt *et al.* (2018)[249,251]

6. ACUTE AORTIC OCCLUSION WITH BILATERAL LOWER LIMB ISCHAEMIA

6.1. Aetiology and diagnosis

AAO is an immediately life threatening condition. It can be caused by large saddle emboli from the heart (usually a complication of acute myocardial infarction); by thrombosis of an atherosclerotic or aneurysmal aorta (or both the common iliac arteries), sometimes secondary to thrombophilia or low cardiac output, or by an acute occlusion of a previously inserted graft or stent graft. It is a rare condition (see below), which also results in a lack of robust data to guide management. The condition remains a true challenge, even for an experienced clinician.

Aortic dissection may result in AAO, most often a result of compression of the true lumen. This condition is covered by the ESVS Management of Descending Thoracic Aorta Diseases: Clinical Practice Guidelines,[6] and will not be discussed in the present Guidelines.

Diagnosis of AAO is sometimes difficult, in particular when the patient presents with bilateral lower limb paralysis,[254] and delay is associated with poor outcome.[255] Most publications consist of relatively small case series, and in a recent paper the authors concluded that outcome had not improved over time.[256]

6.2. Treatment

One of the explanations for why treatment is not always successful, even if performed in a timely way, is that the IRI is so massive when both lower limbs are affected by ALI.[198,257] AAO is a more serious threat to life than to limb. For further reading on IRI, see section 3.9.5.

In a nationwide study from Sweden, 715 patients were operated on over a 21 year period for AAO, resulting in an incidence of 3.8 per million person years.[258,259] *In situ* thrombosis dominated (64%), followed by saddle embolus (21%) and occluded grafts/stent grafts (15%). Interesting time trends were reported: an increase of the number of occluded grafts/stent grafts; a decrease of *in situ* thrombosis; and a stable proportion of saddle embolus. Overall, within 30 days the amputation risk was 9% and mortality 20%, but results improved over time according to this study (mortality decreased from 25% to 15%).

The rate of surgical revascularisation is dependent on the aetiology. In the Swedish study, 32% underwent thromboembolectomy, 22% CDT, 19% axillobifemoral bypass, and 18% aortobi-iliac or -bifemoral bypass.[258] There are no comparative studies on which revascularisation method is preferable in which situation. The decision making should take into account aetiology, comorbidities, resources, and experience, and is based on standard vascular surgical principles.

6.3. Effect of increased use of endovascular aneurysm repair

The increased use of endovascular aneurysm repair (EVAR) has resulted in an increased risk of aortic occlusion due to

stent graft thrombosis. The EVAR-I trial reported a 3 — 4 times higher rate of graft related complications after endovascular aneurysm repair compared with open aortic surgery.[260] Newer generations of stent grafts may be more flexible and have more kink resistant limbs[261] which may reduce the incidence of EVAR graft limb occlusion. For more details regarding aortic or iliac occlusions after aortic surgery, and recommendations on how to prevent this complication, please consult the ESVS 2019 Clinical Practice Guidelines on the Management of Abdominal Aorto-iliac Artery Aneurysms, in particular section 6.3.2.[7]

Recommendation 54		
For patients with acute limb ischaemia secondary to acute aortic occlusion, it is recommended that revascularisation is performed urgently.		
Class	**Level**	**References**
I	C	Kaschwich *et al.* (2017),[257] Beyersdorf and Schlensak (2009),[198] Grip *et al.* (2019)[258]

Recommendation 55		
For patients who have undergone revascularisation for acute limb ischaemia secondary to acute aortic occlusion, close collaboration is recommended with anaesthetists and intensivists to reduce the complications of ischaemia reperfusion injury.		
Class	**Level**	**References**
I	C	Kaschwich *et al.* (2017),[257] Beyersdorf and Schlensak (2009)[198]

7. DIAGNOSIS AND TREATMENT OF ACUTE UPPER LIMB ISCHAEMIA

Acute upper limb ischaemia is not as common as acute lower limb ischaemia.[262,263] There are a number of other differences: the ischaemia is more likely to be embolic and it is less likely to be limb threatening.[264,265] It is also less likely to be immediately life threatening than lower limb ischaemia, although late mortality rates are high owing to the underlying disease and comorbidities.[266]

The tissue effects of ischaemia are similar to the lower limb, but management and treatment cannot be evidence based, as there are no RCTs and few large cohort studies. There are a number of core principles. Patients should be treated by vascular surgeons with expertise, in units where there is access to a full range of vascular and endovascular therapeutic options.

Acute treatment is similar for upper and lower limb ischaemia: systemic AC; intravenous fluids; oxygen; and medical optimisation (e.g., management of AF).

Cardiac embolism is the most common cause of acute upper limb ischaemia; thrombosis is less often the aetiology (17% in a large UK cohort).[267] There are a number of other rare causes, such as distal thrombosis due to thrombophilia, ischaemia due to the complications of thoracic outlet syndrome, arteritis, stenosis secondary to radiation treatment, and subclavian aneurysm. These guidelines focus on treatment of emboli to the upper limb.

7.1. Diagnostic strategy

The diagnosis is clinical and the level of occlusion can be determined by palpation of pulses. Confirmation is by arterial imaging with DUS or CTA. Arterial imaging may not be necessary before intervention for every patient with acute upper limb ischaemia. If the patient has a typical cardiac embolus (AF, short history, and normal arterial pulses elsewhere), it may be reasonable to proceed to treatment immediately if the limb is immediately threatened and if the axillary artery pulse in the upper arm is easily palpable (i.e., there is inflow for a brachial embolectomy). If the ischaemia is not typically embolic (e.g., in a young patient when thoracic outlet syndrome or a cervical rib is suspected; thrombosis associated with radiotherapy; subclavian aneurysm; or if there is a suspicion of aortic dissection) or the axillary pulse is not palpable, imaging of the proximal upper limb vessels is mandatory before treatment (in most cases a CTA). Blind embolectomy in this situation may not improve the blood flow to the hand and may simply make the ischaemia worse. If the artery is patent it is important to perform an elevation test with DUS or DSA, to verify a thoracic outlet syndrome mechanism, if present.

7.2. Surgical decision making

Some patients with upper limb ischaemia appear to have no immediate threat to their limb, (no motor or sensory loss, no muscle tenderness, audible arterial signals at the wrist on Doppler; Rutherford grade IIa) and conservative treatment with AC alone may be appropriate. The risk is that although the limb may remain viable, the patient may suffer from forearm claudication, which makes use of the arm painful and affects quality of life. As for lower limb ischaemia, there should be a discussion about options, individualised to risks and benefits for each patient. Factors that may be taken into account are whether the dominant hand is affected, the age and condition of the patient, the patient's occupation, and the severity of the ischaemia. If the decision is made to treat upper limb ischaemia conservatively with AC alone, the arm should be reviewed regularly over the next few days to ensure it does not deteriorate. AC alone has been suggested as primary therapy,[268] but a review of 23 studies suggested that poor functional outcomes were reported more often after a conservative approach.[269]

7.3. Open surgery

Most patients with upper limb ischaemia are treated surgically by brachial embolectomy (Fig. 12); bypass surgery is seldom required acutely. The default should be surgery under local anaesthesia, with an anaesthetist present, and with the option for intravenous sedation and resuscitation, if required. Technical details are discussed elsewhere, but controversies include which incision to use in the skin; whether the brachial bifurcation needs formal dissection,[270] and whether both forearm arteries need re-opening; transverse or longitudinal arteriotomy in the brachial artery; size of Fogarty catheter; and method of arterial repair. In a review of 100 patients, it was suggested that intra-operative angiography after embolectomy may reduce the risk of re-occlusion.[271] Alternatively, the ischaemic hand can be placed in a sterile clear plastic bag during the surgery, and if embolectomy restores visible perfusion and a palpable wrist pulse, check angiography may not be needed. Long term functional results after embolectomy[272] and surgical bypass[267] are reassuring.

7.4. Endovascular surgery

Endovascular treatments such as percutaneous thrombectomy,[273] aspiration thrombectomy,[274] or CDT[155] have been used for acute upper limb ischaemia, but only case reports exist to describe their benefits and complications. CDT through a femoral approach, with a catheter in the aortic arch, is associated with the risk of cranial vessel embolism,[275] but it can also be performed with a brachial approach, minimising that risk. Clots may also detach and pass cranially from the proximal end of the occlusion, a phenomenon known as whirlpool embolism.[276] Primary distal thrombosis of the hand (or residual distal ischaemia after embolectomy) may benefit from CDT or intravenous prostaglandin therapy.

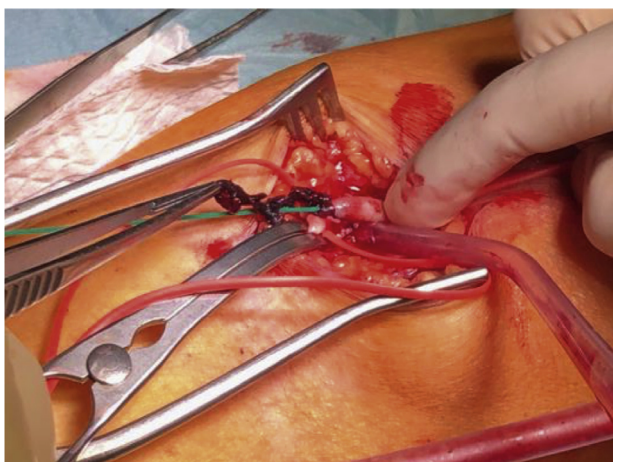

Figure 12. Thrombectomy of the brachial artery using a Fogarty catheter.

7.5. Compartment syndrome and fasciotomy

After successful reperfusion of the upper limb, CS is a rare complication. However, if it occurs it can still result in long term damage by contracture, or even limb loss. Prophylactic fasciotomy is seldom indicated, but if the arm has been ischaemic for many hours and swells considerably after successful embolectomy, fasciotomy is indicated. If it is indicated, volar fasciotomy is suggested, but concurrent dorsal fasciotomy is also recomended by some authors (Fig. 13).[277] Advice and assistance from orthopaedic, hand, or plastic surgeons may be necessary.

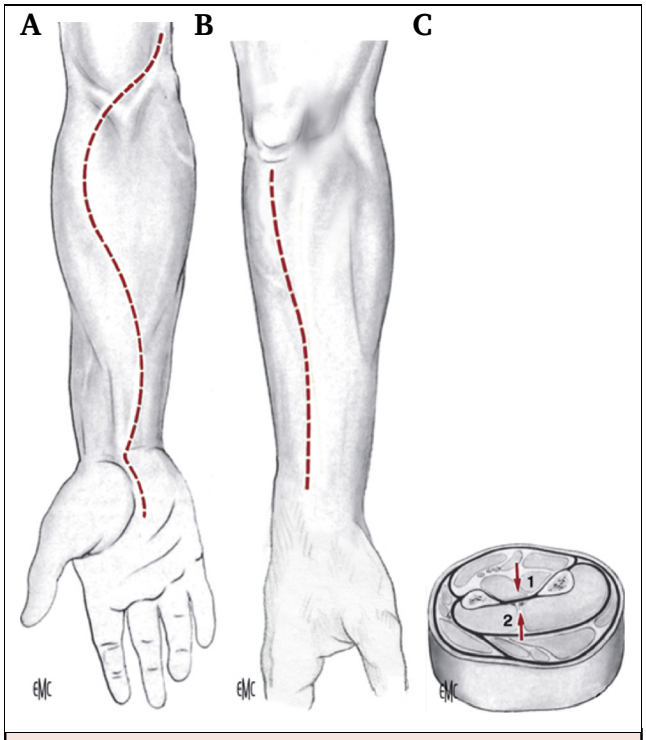

Figure 13. (A, B) Fasciotomies of the forearm. Surgical approach for (A) anterior and (B) posterior fasciotomies. (C) Fasciotomies of the superficial posterior and deep posterior compartments (red arrow, 1), fasciotomies of the anterior and lateral compartments (red arrow, 2). Reproduced with permission from Ricco *et al.*[202]

Recommendation 56

For patients with acute ischaemia of the upper limb, preoperative imaging is recommended, unless embolic occlusion is obvious, the limb is immediately threatened, and axillary or proximal brachial pulses are palpable.

Class	Level	References
I	C	Consensus

Recommendation 57		
For a patient with acute ischaemia of the upper limb, conservative treatment with anticoagulation alone is not recommended if the arm is threatened, or if limb function is important to quality of life.		
Class	**Level**	**References**
III	C	Turner *et al.* (2010),[268] Wong *et al.* (2015)[269]

8. ACUTE LIMB ISCHAEMIA IN CHILDREN

8.1. Epidemiology

ALI in children is a rare but potentially catastrophic event associated with mortality, limb loss, and permanent long term disability. The entity is observed in 26 − 85 of every 100 000 paediatric admissions,[278,279] and in < 1% of paediatric trauma.[280,281] In most instances, ischaemia is iatrogenic and results from thrombosis secondary to umbilical or femoral artery catheterisation, especially in neonates and young infants.[278] Symptomatic thrombotic complications occur in 0.2% of neonates in intensive care units. However, asymptomatic catheter related arterial thrombosis is much more common, ranging from 3% to 90%.[282] Other causes of ALI relate to penetrating or blunt trauma, cardiogenic embolisation in infants with congenital heart or great vessel malformations, inborn coagulation disorders, or intra-uterine extrinsic compression (Table 11).

Table 11. Aetiology of acute limb ischaemia and approximate relative frequencies in children[278–282]

Aetiology	Frequency (%)
Neonates and infants	
Intra-uterine compression	<1
Inborn coagulation disorders	1–2
Iatrogenic	85–95
Umbilical artery catheterisation	
Femoral artery catheterisation	
Embolic	1–2
Great vessel malformations	
Large cardiac defects	
Idiopathic	1–2
Young children	
Iatrogenic	20–50
Femoral artery catheterisation	
Traumatic	50–80
Penetrating trauma	
Blunt trauma (including the pulseless pink hand syndrome)	
Idiopathic	<1

8.2. Diagnosis

Clinical presentation of ALI in neonates and small children may be less obvious than in the adult population. Thus, a high index of suspicion is necessary, especially when arterial catheterisation was performed. This can be explained by limited capacity to verbalise complaints and also by smaller limbs and less developed muscles which are more tolerant of hypoxia. Furthermore, collateralisation may be improved and develops rapidly early in life.[283,284] The most common presentation is cyanosis and delayed capillary refill. Necrotic changes are less frequent. In a large cohort study based on registry claims data, infants, *vs.* older children, had a lower risk of upper extremity ALI, higher mortality, and were more often treated without intervention.[278] Several publications have suggested that DUS is a useful to guide vascular puncture, to minimise the incidence of catheter related arterial thrombosis, and also for the early diagnosis of thrombotic complications.[285–287]

8.3. Treatment options and outcome

Conservative management with systemic heparinisation has been the mainstay of ALI treatment in children, mostly based on expert opinion and small case series, as literature is scarce. AC alone appears to be a relatively safe early strategy in the majority of cases, allowing partial or complete resolution of thrombus, development of collaterals, and recovery of limb perfusion[283,284,288–290] at the price of a small risk of bleeding complications (3% in one investigation).[283] Both UFH and LMWH may be used as anticoagulants. For UFH, a bolus of 75 IU/kg followed by perfusion at 28 IU/kg/hour for infants < 1 year of age and 20 IU/kg/hour for older children is generally used, adjusted to an APTT of 55 − 85 seconds.[291] Succesful treatment by systemic thrombolysis is also reported, although there is a risk of intracranial bleeding, especially in preterm infants.[292–294] Long term outcomes of conservative management have also been evaluated, suggesting that 15% of affected children will have either intermittent claudication or limb discrepancy as a result of impaired growth later in life.[283,295,296]

Up to 17% of children affected by ALI were treated with revascularisation in a population based study, they were older than those treated conservatively, and the aetiology was more often traumatic.[278] Infants and young children present significant technical challenges for revascularisation and the surgical outcomes are worse than those of older children.[289,297] Infants, in particular, do not have improved outcomes after surgery, when compared with those treated conservatively.[278]

There is no evidence to suggest that the same concepts of intervention for ALI used for the adult population should apply to children. A few reports have been published on the use of systemic or CDT, thrombo-aspiration, or surgical thrombectomy. These are mostly small series from single centres, suffering from publication bias, and they do not support a generalised first line approach for intervention. However, endovascular treatment does appear to be a safe strategy, and may be used selectively in the most severe limb threatening cases.[282] In a recent

publication, based on a population based administrative database including nearly 1 600 children with ALI, no differences were found between conservative management and intervention regarding mortality (4% overall), amputation (< 2% overall), or length of hospital stay. Owing to the administrative nature of the database, severity of ischaemia could not be determined and selection bias may be present. Nonetheless, these outcomes compare favourably to the adult population.[278] Similarly, a recent systematic review including all management strategies suggests that limb salvage is 88% (95% CI 1% — 31%) and overall mortality 7% (95% CI 2% — 14%).[298]

From a case series of 25 children aged < 12 months, with ALI mainly caused by iatrogenic injuries following arterial cannulation, the following was reported:[296] in 88% the lower extremity was affected, and the diagnosis was obtained by missing Doppler signals (64%) or cyanosis of the extremity (60%). Whenever possible (80%), primary therapy consisted of AC; two patients were treated by thrombolysis. Three died within 30 days, independently of ALI. One patient needed an above knee amputation. Functional long term results were excellent, which shows that ALI can be treated successfully with AC. As there are no RCTs, no direct comparison can be made regarding conservative management and intervention in paediatric patients. However, a first line conservative management seems justified, with the possible exception of older children with traumatic injuries. No evidence supports the use of one single intervention strategy over another, when considered necessary.

As ALI in small children (aged < 2 years) is very uncommon, and as blood vessels are small, a multidisciplinary approach is warranted. Plastic surgeons and hand surgeons with experience of microsurgery, as well as paediatric surgeons, may be helpful when open surgery is necessary.

In school children, supracondylar fracture of the humerus is a common cause of upper extremity ALI. This entity results from brachial artery injury, and the majority of cases resolve after closed reduction and stabilisation of the fracture. In a systematic review, an overall incidence of vascular compromise in 3% to 14% after supracondylar fractures was identified, which persisted after reduction and stabilisation in 28%.[299] When severe signs of ALI are present, exploration is advisable. However, some limbs remain pulseless despite apparent perfusion of the hand. This is often referred to as the “pulseless pink hand”, and management is more debatable. Many authors recommend watchful waiting, as symptoms usually resolve and the pulse returns within one week. Exploration is reserved for patients who develop additional signs of ischaemia, or for those without improvement after one week.[299] When considered necessary, exploration with release of brachial artery entrapment at the fracture site, primary arterial repair, venous patch angioplasty, or venous interposition grafts appear to be the preferred surgical options.[300]

Recommendation 58

For infants and children younger than 2 years of age with acute limb ischaemia, initial conservative management with heparin is recommended.

Class	Level	References
I	C	Lim *et al.* (2018),[278] Rizzi *et al.* (2018),[288] Sadat *et al.* (2015),[289] Lin *et al.* (2001)[297]

Recommendation 59

For infants and children undergoing femoral catheterisation, ultrasound guided puncture and post-procedural ultrasound examination should be considered.

Class	Level	References
IIa	C	Alexander *et al.* (2016),[285] Kulkarni and Naidu (2006),[286] Knirsch *et al.* (2013)[287]

Recommendation 60

For infants and children with acute limb ischaemia without improvement after conservative therapy with heparin, thrombolysis, or open surgical revascularisation may be considered.

Class	Level	References
IIb	C	Rizzi *et al.* (2016),[288] Sadat *et al.* (2015),[289] Kayssi *et al.* (2014),[283] Matos *et al.* (2012),[284] Downey *et al.* (2013),[290] Wang *et al.* (2018)[296]

Recommendation 61

In school children with a supracondylar humeral fracture and a pulseless, perfused hand, watchful waiting may be considered an alternative to immediate surgical exploration.

Class	Level	References
IIb	C	Griffin *et al.* (2008)[299]

9. UNRESOLVED ISSUES AND FUTURE RESEARCH

9.1. Diagnosis

The ESVS ALI guidelines recommend that a diagnosis of ALI should be made primarily on clinical grounds (typical symptoms and signs). Although most patients with ALI present with a typical constellation of symptoms and signs, it is unknown how frequently the diagnosis is delayed as a result of inexperienced assessment (patients usually initially present to non-vascular specialists) or atypical presentations. Future research should be considered in patients presenting with suspected ALI to establish the

diagnostic utility for non-vascular specialists of a range of clinical symptoms and signs and biomarkers (both novel and those used routinely). The standard for the future diagnosis of ALI in these studies would be CTA.

Theoretically, the role of emergency CTA in a patient with ALI, with or without motor deficit, needs to be evaluated in an adequately powered multicentre RCT. However, it is possible that the window of opportunity has closed, as this has already become a routine in many countries.

9.2. Classification and prognosis

It is important to be able to classify patients presenting with ALI. It aids clinical decision making and allows comparisons to be made for the purposes of clinical audit and interventional studies. The most widespread scheme in general clinical use for patients with ALI is the Rutherford system.[2] This was published some years ago and its development would not stand up to modern rigorous methodologies. Although it has been in widespread use for over 20 years, its clinical performance as a tool for classification (including reliability/repeatability, etc.) and its ability to provide a prognosis have yet to be established. It would be valuable to assess its utility as a clinical classification tool. Currently, no biomarkers (e.g., serum CK or myoglobin) are available to identify patients who require primary amputation. Further research might help to identify patients who have a non-salvageable limb, or in whom attempts at revascularisation may be futile (and/or harmful).

9.3. Interventions

AC with intravenous UFH has become the mainstay of initial therapy for patients presenting with ALI, despite the fact that a small RCT published in 1991 reported no benefit and more bleeding complications with this practice.[61] It is difficult to be certain whether this intervention is effective in improving outcomes and may never be tested in a new trial, unless an alternative with a rapid onset (and offset) of action were to be developed. There are some suggestions that adjunctive therapy with prostacyclin analogues may improve outcomes, but the trials and evidence are weak and more robust data in the form of RCTs would help confirm these observations.

The studies comparing surgery with CDT were reported in the 1990s. Technologies have changed significantly and the population of patients with ALI has also changed (older patients with a greater number of comorbidities and fewer presenting with ALI secondary to embolism). It is difficult to be certain how relevant these RCTs are to contemporary clinical practice. Interestingly, in many countries surgery has become the standard of care, whereas in others CDT is the primary intervention. Ideally, these RCTs could be repeated to inform the optimal revascularisation technique for ALI. This work is closely linked to improvement of the classification system (see section 9.2).

As the RCTs of CDT and surgery were reported in the 1990s a variety of additional endovascular techniques (including ultrasound, aspiration, and mechanical thrombectomy) have come to market and are in regular clinical use. Unfortunately, few of these techniques have been tested in appropriately powered trials and their clinical and cost effectiveness remain to be fully established when compared with standard interventions. Those that were tested have failed to demonstrate that they are as good as standard endovascular therapies. It is the view of the ESVS guideline team that patients receiving modern technologies should be enrolled in trials or clinical registries to monitor safety and effectiveness.

A variety of thrombolytic drugs and techniques are available. Different infusion catheters and lytic dosing regimens exist, including the use of pharmacological (e.g., abciximab) and mechanical adjuncts. Each technique has its merits, but none has been proven to be superior. rtPA and urokinase remain the agents of choice, but newer agents (reteplase and tenecteplase) have become available (and others are also being considered, e.g., plasmin) and should be tested within appropriately designed trials. The search for the ideal thrombolytic drug continues and novel agents should be tested within appropriately powered clinical trials.

Patients who present with ALI due to thrombosis and or embolisation from PA present a unique challenge with a high rate of limb loss and disability. It is recommended that surgery is the primary revascularisation technique for this condition. However, as endovascular techniques become more sophisticated, and algorithms for endovascular interventions such as popliteal stent grafting and CDT become available in these patients, their role requires elucidation in properly constructed clinical trials.

An important subgroup of patients are those who present with acute onset claudication. Data from the 1990s suggested that the prognosis was good with conservative treatment and that complications were not infrequent. Those old data are the basis of the negative recommendation in these guidelines, advising against treating these patients invasively. This issue needs to be re-addressed in a contemporary study, preferably an RCT, as endovascular therapy has developed.

Controlled limb reperfusion for the prevention of IRI has been extensively investigated over the last 20 years. Initial studies concluded that it may reduce the local manifestations of the post-ischaemic syndrome after prolonged ischaemia in salvaged limbs.[198] However, in a recent RCT no difference was found in amputation free survival between conventional treatment of ALI and controlled limb reperfusion.[199] Hypothermic, initially oxygen free controlled limb reperfusion with ECMO was used in a study of patients with ALI, which suggested that this new treatment might limit complications and mortality, but the evidence was not conclusive.[185] Further prospective, RCTs are needed to evaluate this hypothesis.

9.4. Complications

Revascularisation of the ischaemic limb, whether by endovascular methods or open surgery, is associated with a number of key complications. These include, most notably,

bleeding, CS, pericatheter thrombosis, and major systemic complications. Efforts have been made to reduce the incidence of minor and major haemorrhage during the administration of thrombolysis. The use of systemic heparinisation and longer duration of lysis are associated with increased bleeding risk and should be avoided. Minor bleeding during thrombolysis is common. Standard approaches to managing access site bleeding have been to apply compression, adjust the dose of (or stop) the lytic agent, and to increase the sheath size. Innovative systemic therapies to manage minor access site bleeding include the use of desmopressin and these should be evaluated in trials.

CS is associated with significant morbidity and should be prevented by pre-emptive fasciotomy in high risk patients or diagnosed and managed as soon as it develops. Methods to identify patients at high risk of developing CS would be valuable in clinical practice. At present, the reliability of diagnostic techniques, such as the measurement of intracompartmental pressures, is low. The predictive value of different biomarkers needs to be evaluated. Several different methods of wound management after fasciotomy and approaches to delayed wound closure have been described. There is a need for comparative studies to be able to issue recommendations in this important clinical situation.

The development of perisheath thrombosis should be avoided whenever possible. Systemic heparinisation results in an increased bleeding risk; however, it is uncertain whether the local administration of UFH through the access site sheath is superior to regular flushing with crystalloid solutions, or no flushing at all. This important detail needs to be investigated.

ALI is associated with a stubbornly high rate of systemic complications (including renal failure) and death, even after successful revascularisation. Strategies to reduce these complications would be welcome. The best approach to address these problems remains to be determined, including the optimal level of care. Expert interdisciplinary consensus methodology to develop novel interventions and quality improvement programmes could hold the key to improved outcomes.

9.5. Outcomes

Future research in ALI could be enhanced if it was possible to standardise the reporting of studies and outcomes were shown to be highly relevant to patients, healthcare professionals, and healthcare commissioners. ALI is associated with a significant mortality risk and a high rate of subsequent complications. Reporting standard guidelines in PAD were developed with a focus on chronic rather than acute disease. No core outcome set for patients presenting with ALI exist and there are no guidelines on how best to report studies on patients with ALI (reporting standards). Future work should focus on developing both a core outcome set and a core reporting set for patients with ALI. A core reporting set for use in registries has been developed through international and interdisciplinary collaboration, as a spin off effect of developing these Guidelines,[252] but these need to be evaluated in future quality improvement projects. Patient reported outcome measures are important tools to assess the impact of interventions and their delivery on patients. A variety of generic quality of life tools exist for patients with vascular disease; however, none exists specifically for patients with ALI, and this is a clear gap that should be filled.

9.6. Long term therapy

Patients who develop ALI are at increased risk of recurrent ischaemic events. The standard management strategy following limb revascularisation has been to anticoagulate patients and manage the underlying cause (e.g., AF). The duration and dosage of AC in patients in whom no underlying cause has been found is a matter of debate and requires further research. It remains to be established what role antiplatelets and DOACs have compared with standard alternatives (heparins and coumadins) and, specifically, whether they reduce recurrent ALI and improve limb survival. The role of antiplatelet therapy *vs.* AC, and the combination of both therapies, needs to be evaluated in this specific patient group.

Around 25% of patients presenting with PAD (and ALI) have evidence of a thrombophilia. It is unclear whether the outcome of these patients differs and whether they require alternative management strategies to improve outcomes and prevent ALI recurrence.

It remains to be determined whether new drug regimens could be beneficial, such as proprotein convertase subtilisin/kexin type 9 (PCSK-9), rivaroxaban vascular dose, and so on.

9.7. Standards

Standard setting and benchmarking would be valuable in ALI. These would enable enhanced assessment and approval of new interventions for the management of patients with ALI, and appropriate comparative audits in routinely collected data. A more precise characterisation of the degree of ischaemia (see section 8.2) could be used to define the maximum time interval from diagnosis to treatment.

Quality improvement projects in other areas of PAD management have had a beneficial effect. Attempts should be made to design similar projects to improve the outcomes of patients suffering from ALI.

In summary, despite the identification of 28 RCTs from the literature, there is a great need for future research to enable improvement of the management of patients with ALI. Most of these unresolved issues require multicentre collaboration.

10. PLAIN ENGLISH SUMMARY

Acute limb ischaemia (ALI) is a sudden reduction in the arterial blood supply to the arm or leg. There are two main causes: *thrombosis* as a result of blood clot developing within the artery, usually at a site of previous narrowing in people with hardening of the arteries; and *embolus*, where blood clot develops elsewhere in the body (usually the heart), detaches and passes through the arterial circulation to lodge in one of the main blood vessels to a limb. ALI is a serious condition that threatens both the limb itself and the life of the patient. Failure to restore the arterial circulation

often results in limb amputation and can cause death. ALI is more common and more serious in the leg than in the arm.

An international group of specialists has examined the research that has been published on ALI and has summarised the evidence about the best methods of managing this condition. This guideline has been produced to help doctors provide the best care for ALI.

Firstly, it is important that all doctors recognise the signs and symptoms of ALI characterised by the six Ps: painful, pale, pulseless, paraesthesia (numbness), paralysed, and perishingly cold. Secondly, doctors need be able to assess how bad the ALI is. If it causes numbness or paralysis of the limb, it is very severe and the limb may be impossible to save if untreated within around six hours.

Once the diagnosis of ALI has been made, the guideline group has recommended that patients should be treated by experts (usually a vascular specialist) in a hospital where assessment and treatment is available 24/7. Patients may need to be transferred urgently to a specialist hospital. After assessment, the group recommends patients are treated by experts who are able to use all possible treatments that are available. Until 25 years ago the only possible treatment for ALI was surgery. Now there are a variety of clot busting drugs and new methods of aspirating blood clots percutaneously, without needing an operation.

The guideline group has looked at all the scientific research on different methods of treating ALI. Both surgical and non-surgical treatments, such as clot busting drugs, are effective but with subtly different outcomes depending on individual patients. The group has made recommendations about how to use the different treatments to obtain the best outcomes. The best results seem to be achieved in hospitals used to dealing with patients with ALI, and familiar with all the different methods available, choosing the method most suitable for each individual patient.

It is hoped these guidelines will be used by doctors treating patients with ALI to give them the best care, thus giving them the best chance for full recovery without complications.

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APPENDIX A. SUPPLEMENTARY DATA

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