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Chapter VI: Follow-up after Revascularisation

F. Dick[a,*], J.-B. Ricco[b], A.H. Davies[c], P. Cao[d], C. Setacci[e], G. de Donato[f], F. Becker[g], H. Robert-Ebadi[g], H.H. Eckstein[h], P. De Rango[i], N. Diehm[j], J. Schmidli[a], M. Teraa[f,k], F.L. Moll[k], M. Lepäntalo[l,m], J. Apelqvist[n,o]

[a] *Department of Cardiovascular Surgery, Swiss Cardiovascular Centre, University Hospital Berne, Switzerland*
[b] *Department of Vascular Surgery, University Hospital of Poitiers, Poitiers, France*
[c] *Academic Section of Vascular Surgery, Imperial College School of Medicine, Charing Cross Hospital, London, United Kingdom*
[d] *Unit of Vascular Surgery, Department of Cardiosciences, Hospital S. Camillo-Forlanini, Rome, Italy*
[e] *Department of Surgery, Unit of Vascular and Endovascular Surgery, University of Siena, Italy*
[f] *Department of Vascular Surgery, University Medical Center Utrecht, The Netherlands*
[g] *Division of Angiology and Hemostasis, Geneva University Hospitals, Geneva, Switzerland*
[h] *Clinic for Vascular Surgery, Klinikum rechts der Isar, Technische Universität München, Munich, Germany*
[i] *Unit of Vascular and Endovascular Surgery, Hospital S. M. Misericordia, Loc. S. Andrea delle Fratte, Perugia, Italy*
[j] *Clinical and Interventional Angiology, Swiss Cardiovascular Centre, University Hospital Berne, Switzerland*
[k] *Department of Nephrology & Hypertension, University Medical Center Utrecht, The Netherlands*
[l] *Department of Vascular Surgery, Helsinki University Central Hospital, Helsinki, Finland*
[m] *Institute of Clinical Medicine, Faculty of Medicine, University of Helsinki, Helsinki, Finland*
[n] *The Diabetic Foot Center at the Department of Endocrinology, Skåne University Hospital, Malmö, Sweden.*
[o] *Division for Clinical Sciences, University of Lund, Sweden*

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Abstract Structured follow-up after revascularisation for chronic critical limb ischaemia (CLI) aims at sustained treatment success and continued best patient care. Thereby, efforts need to address three fundamental domains: (A) best medical therapy, both to protect the arterial reconstruction locally and to reduce atherosclerotic burden systemically; (B) surveillance of the arterial reconstruction; and (C) timely initiation of repeat interventions. As most CLI patients are elderly and frail, sustained resolution of CLI and preserved ambulatory capacity may decide over independent living and overall prognosis. Despite this importance, previous guidelines have largely ignored follow-up after CLI; arguably because of a striking lack of evidence and because of a widespread assumption that, in the context of CLI, efficacy of initial revascularisation will determine prognosis during the short remaining life expectancy. This chapter of the current CLI guidelines aims to challenge this disposition and to recommend evidentially best clinical practice by critically appraising available evidence in all of the above domains, including antiplatelet and antithrombotic therapy, clinical surveillance, use of duplex ultrasound, and indications for and preferred type of repeat interventions for failing and failed reconstructions. However, as corresponding studies are rarely performed among CLI patients specifically, evidence has to be consulted that derives from expanded patient populations. Therefore, most recommendations are based on extrapolations or subgroup analyses, which leads to an

* Corresponding author. Florian Dick, MD, FEBVS, Swiss Cardiovascular Centre, Division of Vascular Surgery, University Hospital Bern Insel, Freiburgstrasse, CH-3010 Bern. *E-mail address*: florian.dick@insel.ch (F. Dick).

almost systematic degradation of their strength. Endovascular reconstruction and surgical bypass are considered separately, as are specific contexts such as diabetes or renal failure; and critical issues are highlighted throughout to inform future studies.

1. Introduction

Follow-up after revascularisation for chronic critical limb ischaemia (CLI) should ensure not only best clinical results including survival, limb salvage and resolution of chronic CLI with sustained functional improvement and improved quality of life, but also timely amputation in case of failure and improved cost-efficiency by structured outcome analysis.[1] Appropriate endpoints for assessment of these goals, however, are still used inconsistently, which handicaps comparisons.[2]

Follow-up after revascularisation needs to address three main issues: (A) best medical therapy, (B) surveillance of arterial reconstruction and (C) indication of repeat revascularisation or timely amputation. As patients with CLI are usually elderly and frail, preserved ambulatory capacity will often decide over independent living, but efforts at limb salvage need to be balanced realistically against the likelihood of continued independence. An associated challenge is the implementation of structured follow-up, which is difficult to achieve even in solid studies with rigorous record-keeping.[3] Most studies are retrospective and use inconsistent reporting standards, and only a few are stratified for presence of CLI. This explains why high-level evidence is scarce, particularly for follow-up after endovascular reconstruction;[2] and why follow-up after revascularisation for CLI has largely been ignored in previous guidelines.[4,5]

Critical issue

There is a need for well-designed clinical studies evaluating follow-up strategies and indications for specific prognostic, diagnostic or therapeutic interventions during follow-up after revascularisation for CLI.

2. Best medical care

Best medical treatment and smoking cessation advice are considered a mainstay of care for all vascular patients, even though this has not been explored specifically in the context of CLI. Monitoring of patient compliance is of paramount importance and an effective way to involve primary care providers into a general therapeutic concept.

2.1. Best medical treatment and cardiovascular risk reduction

The evidence for best medical treatment and systemic cardiovascular risk reduction is addressed in Chapter III (Management of Cardiovascular Risk Factors and Medical Therapy, pp. S33–S42) and should be applied independently of the type of local revascularisation that has been achieved.

A *post hoc* analysis of the PREVENT III cohort[6] investigated the efficacy of statins, beta blockers and antiplatelet agents during follow-up in 1404 patients with CLI undergoing venous bypass grafting. Use of statins was independently associated with a statistically significant survival advantage at 1 year (HR 0.67; 95% CI 0.51–0.90; $p = 0.001$), but none of the drug classes taken separately was associated with a better graft patency in this study. In contrast, daily use of statins in addition to acetylsalicylic acid (ASA) almost halved rates of both restenosis (42% vs. 22%) and lower limb amputation (21% vs. 11%) at 1 year after percutaneous transluminal angioplasty in patients with severe claudication or CLI.[7] A similar favourable effect of statins on graft patency (OR 3.7; 95% CI 2.1–6.4) and amputation rate (OR 0.34; 95% CI 0.15–0.77) has also been observed at 1.5 years after venous bypass grafting (70% CLI patients) in other studies.[8,9]

2.2. Platelet inhibition and antithrombotic therapy

Venous grafts used as arterial bypass suffer the loss of their endothelial layer within days after implantation,[10] which triggers increased expression and exposure of tissue factor within the vein graft. The ensuing thrombogenic process is led primarily by the activated coagulation system, although activated platelets may also play a role.[11] In contrast, introduction of a prosthetic surface such as polyethylene terephthalate (PET), PTFE or endovascular stents initiates a thrombogenic process that is led predominantly by activated platelets.

This may explain consistent observations of a differential efficacy of antiplatelet vs. antithrombotic agents regarding prevention of thrombotic occlusion of vascular reconstructions,[11–13] although none of these Cochrane meta-analyses was stratified for CLI. However, reconstructions for CLI can be assumed particularly prone to thrombotic occlusion due to low flow, suggesting that findings as shown in Table 1 remain pertinent to patients with reconstructed CLI.

2.2.1. Surgical reconstruction

After lower limb bypass, antiplatelet treatment (i.e. ASA alone or in combination with dipyridamole) improves primary patency at 1-year follow-up.[12] However, the size of this effect differs when patients with prosthetic and venous grafts are considered separately. In patients with PTFE or PET bypass, antiplatelet drugs are more efficient and improve primary patency as early as 1 month after surgery with a durable effect thereafter. In contrast, patients with venous bypass benefit less from platelet inhibition and the effect becomes statistically significant only at 1-year follow-up.[12] Ticlopidine, another antiplatelet agent, may be more effective. In a multicentre RCT comparing ticlopidine vs. placebo, ticlopidine significantly improved primary venous graft patency rates at 6, 12 and 24 months but not at 3 months.[14]

In contrast, vitamin K antagonists (VKA) have a strong but time-limited protective effect occurring early on venous graft patency at 3 and 6 months, but disappearing at 1, 2 and 5 years.[11] Attempts to improve venous graft patency with heparin have produced conflicting results: although daily administration of 2500 international units (IU) of low-molecular-weight heparin (LMWH) for 3 months after bypass surgery did not confer any benefit as compared to 300 mg ASA across a single-institution RCT, stratified analysis of the

Table 1 Summary table of randomised controlled trials assessing efficacy of antithrombotic and antiplatelet treatment after revascularisation for CLI[a]

Comparison	(meta)analysis of	No. of patients	Study group	Control group	Effect of intervention
Vein bypass (evidence not stratified for chronic CLI)					
Vitamin K antagonist *vs.* no vitamin K antagonist	Arfvidsson et al., Am J Surg 1990;159:556–60 Johnson et al., *J Vasc Surg* 2002;35:413–21 Kretschmer et al., Arch Surg 1992;127:1112–5 Sarac et al., *J Vasc Surg* 1998;28:446–57	235	Vitamin K antagonist (target prothrombin time <30%, or INR 1.4 to 3.5) with or without acetylsalicylic acid	No vitamin K antagonist, administration of acetylsalicylic acid possible	Positive effect of vitamin K antagonists on primary patency. OR for restenosis/occlusion at 6 months was 0.41 (95% CI 0.17 to 0.96).
Acetylsalicylic acid/dipyridamole *vs.* nothing/placebo	Clyne et al., Br J Surg 1987;74:246–8. McCollum et al., *J Vasc Surg* 1991;13:150–62 Kohler et al., Surgery 1984;96:462–6	723	2–3×325 mg acetylsalicylic acid/2–3×75 mg dipyridamole	Placebo	Moderately positive effect of acetylsalicylic acid on restenosis/occlusion rates with overall OR of 0.69 (95% CI 0.48 to 0.99)
Acetylsalicylic acid *vs.* vitamin K antagonists	BOA Study Group, Lancet 2000;355:346–51 Schneider et al., Angio 1979;2:73–7	1637	80 to 1000 mg acetylsalicylic acid	Vitamin K antagonist (aim for Quick 25–30%; or INR 3.0–4.5)	Sustained favourable effect of vitamin K antagonists on primary patency. OR for restenosis/occlusion at 24 months was 0.59 (95% CI 0.46 to 0.76).
Ticlopidine *vs.* placebo	Becquemin et al., NEJM 1997;337:1726–31	243	250 mg ticlopidine	Placebo	Sustained favourable effect of ticlopidine on primary patency. OR for restenosis/occlusion at 24 months was 0.37 (95% CI 0.21 to 0.64).
Acetylsalicylic acid/dipyridamole *vs.* low molecular weight heparin	Edmondson et al., Lancet 1994;334:914–8	56	3×300 mg acetylsalicylic acid/3×75 mg dipyridamole for 3 months	2500 IU low molecular weight heparin for 3 months	Positive but statistically nonsignificant effect of low molecular weight heparin
Low molecular weight *vs.* unfractionated heparin	Samama et al., Ann Vasc Surg 1995;9:S45–53 Swedenborg et al., Eur J Vasc Endovasc Surg 1996;11:59–64	153	Low molecular weight heparin twice daily for 10 days	Unfractionated heparin	Beneficial effect of low molecular weight heparin: OR for early graft thrombosis at 30 days was 0.41 (95% CI 0.20 to 0.85). Not stratified for graft type.

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Table 1 (*continued*)

Comparison	(meta)analysis of	No. of patients	Study group	Control group	Effect of intervention
Prosthetic bypass (evidence predominantly for intermittent claudication)					
Acetylsalicylic acid/dipyridamole *vs.* nothing/placebo	Green et al., Surgery 1982;92:1016–26 Goldman et al., Vasc Surg 1984;18:217–21 Kohler et al., Surgery 1984;96:462–6 Donaldson et al., Vasc Surg 1985;19:224–30 Clyne et al., Br J Surg 1987;74:246–8.	261	2–3×325 mg acetylsalicylic acid/2–3×75 mg dipyridamole	Placebo	Protective effect of acetylsalicylic acid: OR for restenosis/occlusion at 12 months 0.22 (95% CI 0.12 to 0.38).
Vitamin K antagonist *vs.* no vitamin K antagonist	Arfvidsson et al., Am J Surg 1990;159:556–60 Johnson et al., *J Vasc Surg* 2002;35:413–21	661	Vitamin K antagonist (target prothrombin time <30%, or INR 1.4 to 3.5) with or without acetylsalicylic acid	No vitamin K antagonist, administration of acetylsalicylic acid possible	No statistically significant effect of vitamin K antagonist on primary patency at 24 months (OR 0.72; 95% CI 0.40 to 1.29). Moderate but significant effect at 5 years (OR 0.43; 95% CI 0.26 to 0.73)
Acetylsalicylic acid *vs.* vitamin K antagonists	BOA Study Group, Lancet 2000;355:346–51	1104	80 mg acetylsalicylic acid	Vitamin K antagonist (aim for INR 3.0–4.5)	Advantage for acetylsalicylic acid regarding primary patency. OR for restenosis/occlusion at 24 months was 1.41 (95% CI 1.11 to 1.80).
Acetylsalicylic acid/dipyridamole *vs.* low molecular weight heparin	Edmondson et al., Lancet 1994;334:914–8	144	3×300 mg acetylsalicylic acid/3×75 mg dipyridamole for 3 months	2500 IU low molecular weight heparin for 3 months	Positive but statistically nonsignificant effect of low molecular weight heparin
Low molecular weight *vs.* unfractionated heparin	Samama et al., Ann Vasc Surg 1995;9:S45–53	64	Low molecular weight heparin twice daily for 10 days	Unfractionated heparin	Beneficial effect of low molecular weight heparin: OR for early graft thrombosis at 30 days was 0.41 (95% CI 0.20 to 0.85). Not stratified for graft type.

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Table 1 (*continued*)

Comparison	(meta)analysis of	No. of patients	Study group	Control group	Effect of intervention
Infrainguinal endovascular intervention (evidence predominantly for intermittent claudication)					
Acetylsalicylic acid *vs.* placebo	Heiss et al., Angiology 1990;41:263–9 Study Group, Eur *J Vasc Surg* 1994;8:83–8	356	50 mg to 330 mg acetylsalicylic acid	Placebo	OR for occlusion at 6 months 0.69 (95% CI 0.44 to 1.10), significant only for 330 mg
Acetylsalicylic acid high dose *vs.* low dose	Heiss et al., Angiology 1990;41:263–9 Minar et al., Circulation 1995;91:2167–73 Weichert et al., Vasa 1994;23:57–65 Ranke et al. *Clinical Investigator* 1994;72:673–80.	930	330 mg to 1000 mg acetylsalicylic acid	50 mg to 300 mg salicylsalicylic acid	No positive effect regarding occlusion for high dose at 6 months (OR 0.99, 95% CI 0.71 to 1.38). Similar for other time points up to 24 months. However, more side effects
Acetylsalicylic acid/dipyridamole *vs.* vitamin K antagonist	Pilger et al., Circulation 1991) 83:141–7 Do et al., Radiology 1994;193:567–71	289	75 mg to 3×330 mg acetylsalicylic acid/75 mg to 200 mg dipyridamole	Vitamin K antagonist	No difference regarding occlusion up to 12 months: OR 0.65 (95% CI 0.40 to 1.06)
Ticlopidine *vs.* vitamin K antagonist	Schneider et al., Hans Huber, Fortschr Angiol 1987): 355–6	197	2×500 mg ticlopidine	Vitamin K antagonist	Statistically non-significant advantage of ticlopidine, OR for occlusion at 12 months 0.71 (95% CI 0.37 to 1.36)
Low molecular weight *vs.* unfractionated heparin	Schweizer et al., Angiology 2001;52:659–69	172	Low molecular weight heparin at therapeutic dose (7 days), 6 months 200 mg acetylsalicylic acid	Unfractionated heparin at therapeutic dose (7 days), 6 months 200 mg acetylsalicylic acid	Significant advantage of low molecular weight heparin, OR for restenosis/reocclusion at 6 months 0.35 (95% CI 0.19 to 0.65)
Abciximab *vs.* placebo	Dörffler et al., Radiology 2005;237:1103–9	98	Abciximab perfusion for 12h	Placebo	Positive effect of peri-interventional abciximab on primary patency, OR at 6 months 0.43 (95% CI 0.19 to 0.98)

[a] Adapted from Sasaki et al.,[10] Dörfler-Melly et al.[11] and Brown et al.[12]

subset of CLI patients suggested markedly improved patency rates at 6 and 12 months.[15] However, addition of LMWH to ASA failed to improve primary graft patency in a RCT of 284 CLI patients.[16]

In a comparison of VKA and ASA alone or in combination with dipyridamole, VKA was superior in 1637 patients with venous grafts, whereas antiplatelet agents had a stronger effect on 1104 prosthetic grafts at 2 years.[11]

Finally, the multicentre CASPAR trial[17] randomly assigned 851 patients receiving below-the-knee bypass surgery to ASA alone or to ASA plus thienopyridine (clopidogrel). Endpoints of the study were bypass patency, absence of restenosis, major amputation or death. No difference was observed in this trial among the two groups, but a subgroup analysis suggested a benefit of dual antiplatelet therapy for patients receiving prosthetic grafts (HR 0.65; 95% CI 0.45–0.95; $p = 0.025$). This was achieved without a significant increase of the risk of major bleeding.

The therapeutic range of vitamin K antagonism needs consideration as improved anticoagulation control seems to halve the risk of adverse events.[18] In a general population, the optimum risk–benefit range lies between an international normalised ratio (INR) of 2 and 3,[19] with moderately higher INR still safe. For peripheral artery bypass surgery, patients spending most time during follow-up in an INR range between 3 and 4 had fewest thrombo-embolic or haemorrhagic events in a *post hoc* analysis of the Dutch BOA trial cohort.[20]

To summarise the current literature, it appears that platelet inhibitors improve graft patency rates as compared to placebo. Patients with a prosthetic graft are likely to benefit more from platelet inhibitors than those with a venous graft. On the other hand, patients with a venous bypass appear to benefit more from vitamin K antagonists than platelet inhibitors, particularly following below-the-knee bypass. But these results should be interpreted with caution due to the heterogeneity of the studies including different proportions of patients with CLI and several types of reconstructions.

2.2.2. Endovascular reconstruction

Administration of ASA combined with dipyridamole appears to reduce the incidence of restenosis or occlusion after superficial femoral artery (SFA) endovascular intervention by 60% at 1 year.[13] However, this result could be confounded by a high proportion of claudicants as platelet inhibitors might be less effective in patients with CLI. A meta-analysis of four trials comparing high-dose (300–1000 mg) to low-dose (50–300 mg) ASA regimens indicated that higher doses did not significantly improve patency rates but increased gastrointestinal side effects.[13]

Although platelet inhibitors seem generally superior to VKA, single pathway inhibition may be insufficient to protect extensive endovascular reconstructions.[13,21] According to a small single-centre RCT, GPIIb/IIIa inhibitors such as abciximab are promising to prevent early thrombotic occlusions in high-risk situations.[21] However, abciximab has to be administered intravenously and its long-term effects are unclear.

Another single-centre RCT involved 275 patients undergoing peripheral artery angioplasty to compare the effect of 2500 IU of LMWH in addition to ASA vs. ASA alone for 3 months. Although no effect was observed across the trial, a subgroup analysis of patients with CLI showed a risk reduction from 72% to 45%.[22]

To summarise these findings, there is no high-level evidence regarding the optimum antithrombotic strategy after endovascular interventions for CLI (Table 1). Long-term platelet inhibitors (50–300 mg ASA) appear to be the preferred drug therapy compared to vitamin K antagonists. Platelet inhibitors should be given prior to intervention. Evidence from coronary interventions suggests that more potent platelet inhibitors such as thienopyridines (clopidogrel) or dual antiplatelet therapy might confer additional benefits; however, specific data for CLI are lacking. Finally, time-limited subcutaneous administration of LMWH may improve primary patency following peripheral artery angioplasty.

2.3. Exercise training

There is conclusive evidence that exercise training is beneficial for patients suffering from claudication,[23] particularly if supervised.[24] However, no study has addressed the potential value of supervised exercise training in CLI patients recovering from revascularisation. One reason may be that these frail patients often present with co-existent morbidity, which may compromise compliance with a structured exercise programme or make it impractical. Nonetheless, exercise training may be assumed beneficial in CLI patients who become asymptomatic or with a mild claudication remaining after arterial revascularisation.

Recommendations

Following vein bypass surgery for CLI, ASA or ASA combined with dipyridamole, is efficient in lowering the incidence of thrombotic occlusions **(Level 1b; Grade B)**; however, vitamin K antagonists are superior when closely monitored and should be preferred in suitable patients during early follow-up, particularly for below-the-knee bypass. **(Level 1b; Grade B)**

Ticlopidine is efficient in protecting vein bypass from occlusion **(Level 1b; Grade B)** and may be used as an alternative to vitamin K antagonists. **(Level 3; Grade D)**

Daily administration of 2500 IU of low molecular weight heparin during 3 months after venous bypass may be beneficial **(Level 2b; Grade C)** and is superior to unfractionated heparin. **(Level 1b; Grade B)**

After prosthetic bypass or endovascular revascularisation, ASA, or ASA combined with dipyridamole, should be given daily at low dose (50 to 300 mg) to lower the incidence of bypass or angioplasty occlusions **(Level 1b; Grade B)**. Additional use of thienopyridine (clopidogrel) may be beneficial without increasing the risk of major bleeding. **(Level 2b; Grade C)**

In general, vitamin K antagonists do not seem efficient for prosthetic bypasses **(Level 1b; Grade B)**; however, they may be considered additionally to platelet inhibitors for low-flow (<45 cm/s) prosthetic grafts. **(Level 4; Grade C)**

Vitamin K antagonists should be closely monitored to lower the risk of adverse events **(Level 2b; Grade B)**. An INR between 2 and 4 is efficient for patients receiving surgical bypass, but values between 3 and 4 seem most efficient and are probably safe. **(Level 2b; Grade C)**

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Recommendations (*cont'd*)

Continued use of statins is associated with improved patency rates and limb salvage after venous bypass and endovascular reconstruction. **(Level 2b; Grade C)**

Whenever possible, patients with CLI should be motivated to undergo supervised exercise training following a successful revascularisation. **(Level 5; Grade D)**

Critical issues

- Several studies have suggested an adverse effect of increased homocysteine serum levels on progression of atherosclerosis.[25,26] Homocysteinaemia-lowering therapy is theoretically available; however, its clinical value is still unknown[25] and should be addressed in RCTs.
- Similarly, the value of (supervised) exercise training after revascularisation of CLI should be established.
- In current practice, many vascular centres give platelet inhibitors to patients with a venous bypass, although, regarding graft patency, available evidence favours VKA.[11] Probable reasons are concerns regarding compliance of these elderly patients and anticipated difficulties to ensure safe VKA levels. Besides, local benefits may be considered less important than systemic protective effects of platelet inhibitors, which are detailed in Chapter III. Therefore, it would be interesting to compare a dual antiplatelet regimen to VKA in CLI patients. On any account, optimum duration of VKA after venous bypass needs to be established as protective early effects may be time-limited.
- Similarly, the role of clopidogrel, or clopidogrel in combination with ASA, needs to be evaluated in prosthetic grafts and endovascular reconstructions as does the optimal therapeutic range of VKA and its duration.
- New antithrombotic agents including direct thrombin inhibitors, mega-pentasaccharides, tissue factor/factor VIIa complex inhibitors and oral factor Xa inhibitors might be promising perspectives and should be properly evaluated. Particularly factor Xa inhibitors may be safer and easier to use than vitamin K antagonists, but approval for use outside prevention of thromboembolism is pending.
- For CLI patients, RCTs should not only concentrate on primary patency rates but also integrate other clinically meaningful endpoints such as limb salvage, resolution of CLI and survival.[2]

3. Surveillance

The goal of arterial reconstructions is to improve arterial blood flow. Therefore, surveillance of sustained treatment success usually concentrates on monitoring patency (Table 2). However, sustained patency may not always be needed to achieve limb salvage or to obtain resolution of CLI.[29,36] Conversely, around 10% of patent reconstructions eventually fail despite improved macro-circulation.[37–39] Preoperative factors such as independency and mental capacity may be important independent predictors of functional recovery.[39–41] Therefore, primary patency alone may not be the ideal surrogate measure for treatment success,[29] and other efficacy measures should also be considered.[2]

Prospective analyses suggest that the quality of life of CLI patients depends directly on sustained patency of the reconstruction.[42] As revisions for failing grafts are far more successful than revisions for failed grafts and generate less cost,[43–45] surveillance programmes have been recommended to detect failing grafts and to prevent graft occlusion.[27] But no study has ever examined the value of surveillance programmes as such by comparing surveillance to no surveillance (Table 2). There is also a controversy regarding the best and most cost-effective surveillance method.[46] Regular clinical revaluations including interval patient history, clinical examination and non-invasive assessment of perfusion using ankle-brachial pressure index (ABI) are generally accepted. The controversy exists on whether additional routine screening by duplex ultrasound confers any clinical benefit (Table 2).[1]

3.1. Surveillance of surgical reconstruction

3.1.1. Autologous vein bypass

Venous grafts are prone to stenoses during follow-up precipitating reduced blood flow and graft failure.[47] Most stenoses occur within the first year, and about 25–30% of vein grafts are affected.[44] Nature of failure varies according to its timing.[29] Failure within 30 days is usually attributed to a technical surgical error, whereas failure between 30 days and 1 year is usually due to developing stenosis. Both are obvious targets of surveillance efforts. In contrast, late failure often follows progression of the disease and is conceptually addressed by best medical care.

Duplex ultrasound scanning is the preferred non-invasive method for detecting stenotic lesions (see Chapter II, Diagnostic Methods, pp. S13–S32). A systematic review of 6649 vein grafts concluded that colour duplex (CD) surveillance significantly reduced the total number of occluded grafts as well as the incidence of graft occlusions after 30 days;[27,33] However, overall limb salvage was not improved by CD screening.[27]

Although there is no RCT exploring the potential benefit of CD surveillance specifically among CLI patients, four RCTs have investigated CD in a large population receiving surgical bypass.[1] Three RCTs concentrated on venous bypass,[3,28,29] and one RCT also included prosthetic grafts.[31] The latter randomly assigned 156 patients to either CD screening every 3 months for 2 years or to clinical surveillance including ABI measurements at yearly intervals. At 3 years, assisted primary and secondary patency rates were significantly improved by CD screening (78% vs. 53% and 82% vs. 56%, respectively; $p < 0.05$); however, amputation rates were not affected.[31] In contrast, no difference was found in another trial between CD and ABI measurements at 3-month intervals regarding patency and limb salvage at 1 year even though more grafts had been revised under CD screening.[28] This finding was essentially confirmed by the largest RCT[29] that involved 594 patients receiving vein bypass and demonstrated that CD surveillance failed to confer a clinical benefit in terms of limb salvage or quality of life, but incurred additional costs.

None of these trials was stratified for CLI. Moreover, only patients with a patent graft at 4–6 weeks after surgery were randomised. However, a likely key benefit of CD is the early identification of silent lesions; therefore exclusion of the patients with early graft abnormalities may have missed one

Table 2 Summary table of studies assessing postprocedure duplex surveillance[a]

Study (year)	Study type	No. of patients (limbs)	% with CLI (with prosthetic bypass)	Surveillance strategy	Control group	Outcome measure	Mean follow-up (mo)	Findings	Conclusion
Golledge et al. (1996)[27]	Systematic review of observational studies (n = 43), including uncontrolled studies	Not given (6257 limbs undergoing bypass)	72 (0)	Duplex and clinical surveillance	Clinical follow-up	Rates of graft occlusion, mortality and limb salvage	40–49	Total number of deaths, occluded grafts and occlusions after 30 days were significantly greater in control group. Peri-operative occlusion rates were not significantly different. The numbers of amputations were not significantly different between the two groups	Comparison of surveillance and non-surveillance studies. The patency of infrainguinal vein grafts is improved by surveillance, no improvement can be demonstrated with respect to limb salvage rates.
Ihlberg et al. (1998)[3]	Randomised controlled trial, single centre	179 (185 limbs undergoing bypass)	84 (0)	Duplex and clinical surveillance including ABI measurement at 1, 3, 6, 9 and 12 months	Clinical surveillance including ABI measurement at 1, 3, 6, 9 and 12 months	Rates of primary patency, assisted primary patency, secondary patency and limb salvage	12	56% primary patency in surveillance group *vs.* 68% in control group; 65% assisted primary patency in surveillance group *vs.* 74% in control group; 71% secondary patency in surveillance group *vs.* 84% in control group; 81% limb salvage in surveillance group *vs.* 88% in control group.	This study failed to show any beneficial effect of duplex scanning in a surveillance program. However, occluded grafts and amputees at 1 month were excluded and the main difference in outcome appeared during this first postoperative month, i.e. before the commencement of the surveillance program.
Ihlberg et al. (1999)[28]	Randomised controlled trial, single centre	344 (362 limbs undergoing bypass)	83 (0)	Duplex and clinical surveillance including ABI measurement at 1, 3, 6, 9 and 12 months	Clinical surveillance including ABI measurement at 1, 3, 6, 9 and 12 months	Rates of assisted primary patency, secondary patency and limb salvage	12	78% assisted primary patency in surveillance group *vs.* 77% in control group; 83% secondary patency in surveillance group *vs.* 87% in control group; 93% limb salvage in surveillance group *vs.* 94% in control group.	Includes patients of 1998 publication and reconfirms its findings: intensive surveillance with duplex scanning did not improve the results of any outcome criteria examined
Davies et al. (2005)[29]	Randomised controlled trial, multicentre	594 (594 limbs undergoing bypass)	66 (0)	Duplex and clinical surveillance including ABI measurement at 6 weeks, 3, 6, 9, 12 and 18 months	Clinical surveillance including ABI measurement at 6 weeks, 3, 6, 9, 12 and 18 months	Rates of major amputation, vascular mortality and primary patency	18	7% amputations in surveillance group *vs.* 7% in control group; 3% vascular mortality in surveillance group *vs.* 4% in control group; 69% primary patency in surveillance group *vs.* 67% in control group	Intensive surveillance with duplex scanning did not show any additional benefit in terms of limb salvage rates for patients undergoing vein bypass graft operations, but it did incur additional costs. However, occluded grafts at 1 month were excluded.

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Table 2 (*continued*)

Study (year)	Study type	No. of patients (limbs)	% with CLI (with prosthetic bypass)	Surveillance strategy	Control group	Outcome measure	Mean follow-up (mo)	Findings	Conclusion
Mofidi et al. (2007)[30]	Explorative cohort study, single centre	352 (364 limbs undergoing bypass)	77 (0)	Duplex and clinical surveillance at 6 weeks, 3, 6 and 12 months. Clinical follow-up afterwards	No control group	Rates of primary patency, stenosis progression and major amputations according to degree of flow disturbance at initial scan.	23	82% cumulative patency and 93% limb salvage at 40 months for initially normal grafts; 38% lesion progression/10% occlusion for initially mild stenosis; 56%/16% for initially intermediate stenosis; and 52%/38% for initially critical stenosis	Flow abnormalities at 6 weeks can be used to select grafts for continued duplex surveillance. However, for grafts without any flow abnormality, the yield from continuing with duplex surveillance is likely to be low and probably little better than what is achievable by simple clinical follow-up.
Lundell et al. (1995)[31]	Randomised controlled trial, single centre	156 (156 limbs undergoing bypass)	94 (32)	Duplex and clinical surveillance including ABI measurement at 1, 3, 6, 9, 12, 15, 18, 24, and 36 months	Clinical surveillance including ABI measurement at 1, 12, 24, and 36 months	Rates of assisted primary patency, secondary patency and repeat procedures	36	Vein grafts: 78% (82%) assisted primary (secondary) patency in surveillance group *vs.* 53% (56%) in control group. Prosthetic grafts: 57% (67%) assisted primary (secondary) patency in surveillance group *vs.* 50% (54%) in control group.	Intensive surveillance identified failing vein grafts leading to a significantly higher assisted primary and secondary patency compared with controls. The patency of prosthetic and composite grafts was not influenced by intensive surveillance.
Dunlop et al. (1996)[32]	Explorative case series, single centre	65 (69 limbs undergoing bypass)	61 (100)	Duplex and clinical surveillance including ABI measurement at 3 monthly intervals	No control group	Detection of treatable lesions before graft failure	12	55% 1 year patency (both assisted primary and secondary); 10% detection rate; 86% of failed grafts not identified by surveillance.	Surveillance appears to be of limited benefit in the maintenance of patency of prosthetic grafts.
Fasih et al. (2004)[33]	Cohort study, single centre	97 (106 limbs undergoing bypass)	48 (47)	Duplex and clinical surveillance at 3, 6 and 12 months	Clinical follow-up in 6 monthly intervals	Rates of graft occlusions and major amputations	15	22% occlusions in surveillance group *vs.* 69% in control group; 2% amputations in surveillance group *vs.* 38% in control group	Surveillance of vein grafts helped to improve patency by identifying the correctable lesions

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Table 2 (*continued*)

Study (year)	Study type	No. of patients (limbs)	% with CLI (with prosthetic bypass)	Surveillance strategy	Control group	Outcome measure	Mean follow-up (mo)	Findings	Conclusion
Brumberg et al. (2007)[34]	Explorative case series, single centre	121 (130 limbs undergoing bypass)	86 (100)	Duplex and clinical surveillance including ABI measurement at 1, 3 and 7 months and at 6 monthly intervals thereafter	No control group	Rates of assisted primary patency, secondary patency and limb salvage	17	43% assisted primary patency; 59% secondary patency; 75% limb salvage at 3 years	Low graft flow was a more common mode of prosthetic bypass failure than development of duplex scan-detected stenotic lesions during follow-up. Early duplex scanning may be more important for characterising midgraft velocity and related thrombotic potential and selecting patients for chronic anticoagulation.
Carter et al. (2007)[8]	Explorative case series, single centre	197 (212 limbs undergoing bypass)	38 (23)	Duplex and clinical surveillance at 0, 1, 3, 6, 12, and 18 months	No control group	Rates of stenosis, graft occlusion, and major amputations	18	22% occusions overall. 88% of femoro-popliteal vein grafts preceded by detectable stenosis *vs.* 34% of femoro-crural vein grafts and 4% of prosthetic grafts.	Graft surveillance is a valid method for detecting the presence of significant stenoses in vein grafts at high risk of failure without intervention. Despite the intensive follow-up, the program failed to detect lesions prior to occlusion in a large percentage of prosthetic and femorocrural grafts.
Humphries et al. (2011)[35]	Explorative case series, single centre	156 (198 limbs undergoing endovascular intervention)	100 (–)	Duplex and clinical surveillance including ABI measurement at 3 to 6 monthly intervals	No control group	Rates of primary and secondary patency and amputation-free survival according to degree of flow disturbance at initial scan (30 day).	24	20% major amputations for abnormal early scans *vs.* 5% for normal early scans (significant). However, amputation-free survival not significantly different between groups. In 56% of abnormal early duplex stenosis had been missed during intervention.	Abnormal duplex scan within the first 30 days postprocedure was associated with an increased risk of amputation suggesting a possible role for routine early duplex, close clinical follow-up, and consideration of re-intervention for residual abnormalities in patients treated for CLI.

[a] Adapted from Lane et al.[1]

important advantage of CD. Thus, despite lacking Level 1 evidence, CD screening has a role and should probably be focused on patients with a high risk of graft failure and be initiated immediately after revascularisation.[44,48]

3.1.2. Duplex screening for failing revascularisations

A significant proportion of patients (around 25%) has an abnormal early CD[1,29,49] (i.e. peak systolic velocity of less than 45 cm/s; peak systolic velocity increase to more than 150 to 300 cm/s; or velocity ratio across a suspected stenosis of more than 2.0 to 3.5). This might be occurring despite a normal intraoperative completion angiogram. Half of these patients will eventually need repeat interventions,[8,50] whereas the other half will see these abnormalities on CD remaining stable or even regressing.[49]

Thus, an abnormal initial CD could, together with other risk factors, help to identify patients at a high risk of graft failure who might benefit from continued CD screening.[51–53] The most important additional predictors include falling serial ABI (by more than 0.1 to 0.2), composite or small diameter (<3 mm) vein bypass, redo-bypass grafts, long grafts (>50 cm in length) and alternative autologous venous conduits (i.e. arm or small saphenous veins).[54] Interestingly, absolute ABI was not predictive of failure in a *post hoc* analysis of a large multicentre RCT.[51]

In contrast, patients with normal CD scans at 6 weeks to 6 months had a very low risk for subsequent graft occlusion if clinical surveillance remained normal.[30,55] Others found that the incidence of graft stenosis does not decline significantly during the first year.[56] Therefore, selective CD surveillance for less than 1 year could miss about 30% of lesions eventually leading to revision.

3.1.3. Prosthetic bypass grafts

Although evidence regarding efficacy of CD surveillance for prosthetic bypass is weak,[1] consistent estimates indicate that occlusions of prosthetic grafts are rarely preceded by a detectable stenosis (Table 2). Thus, even intensive surveillance programmes failed to detect salvageable lesions prior to occlusion in a large percentage of prosthetic grafts.[8] If anything, low flow (<45 cm/s midgraft velocity) rather than high flow seems a more common mode of presentation, and early CD may be useful to identify these prosthetic grafts at increased risk, which might benefit from combined antiplatelet and anticoagulant therapy.[34] However, in one RCT that involved prosthetic bypass grafts, no benefit was shown for CD surveillance during 1 year.[31]

3.1.4. Cost

The mean cost for 5-year surveillance including CD has been estimated to be that of the initial bypass graft procedure, whereas the cost of bypass procedure plus surveillance for 5 years approaches the total cost of primary amputation.[43] But revision of a stenotic but patent bypass identified by CD is significantly less expensive than revision for graft occlusion which is also followed significantly more often by a major amputation (33% vs. 2%). Therefore, limb salvage-related expenses[57] appear to be justified in CLI patients.[58] In fact, CD needs to prevent only 5% of patients from an amputation to be economically viable.[29] On the other hand, repeated unsuccessful attempts to revascularise a leg will disproportionally increase the cost without any profit for the patient.[58]

3.2. Surveillance of endovascular reconstruction

A fundamental difference of surveillance for endovascular interventions comes from the obvious challenge to localise the treated arterial segment precisely and not to confound restenosis or re-occlusion with progressive arterial disease elsewhere on the same artery. This is reflected by the distinction between target lesion re-intervention and target extremity re-intervention as important endovascular outcomes.[2] The preservation of collateral vessels during endovascular recanalisation may attenuate the clinical impact of restenosis or reocclusion. Therefore CD could be of less value in an endovascular context. So far, no RCT has investigated the use of routine CD after endovascular interventions. However, by extrapolation, close post-interventional follow-up and timely repeat interventions are generally accepted,[59,60] but the same result could probably be achieved by clinical surveillance alone with similar effectiveness. As with surgical bypass, selective early CD screening may be beneficial after interventions as early duplex is able to detect a residual stenosis missed on completion angiography in up to half of patients. Such stenosis is known to be associated with a higher amputation rate when compared to normal early CD (20% vs. 5%).[35]

3.2.1. Expected ulcer healing

It is important to note that, even after successful revascularisation, ischaemic tissue lesions may heal only slowly. Important therapeutic adjuncts include appropriate removal of ischaemic tissue, dedicated wound management including ultrasound and negative-pressure wound therapy, targeted antibiotic therapy of infections with abscess, and any measure to improve immune-deficient states of any origin. These measures are dealt with in great detail in Chapter V (Diabetic Foot, pp. S60–S74) of these guidelines. Expected median time to complete healing is in the range of 190 days.[61,62] Diabetes and insufficient diabetes control are the most important predictors of delayed healing; these are dealt with in Chapters III and V. Female gender is a risk factor for wound complications after bypass surgery in patients with CLI.[63] However at 1 year, 75% of ulcers can be expected to have healed.[61,62] Lesions at mid- or hindfoot level are the most critical to heal, whereas duration of ulceration before revascularisation is not predictive of healing time. Foot care, mechanical unloading and stump healing (for prosthetic accommodation of amputation) are critical to retain tissue integrity and ambulatory capacity, and are detailed in Chapter V.

Recommendations

An early (30 day) colour duplex scan should be done for venous bypass grafts in CLI patients. However, best level evidence does not support the use of routine long-term colour duplex surveillance for venous bypass grafts that are undisturbed at 1 month **(Level 1b; Grade B)**. Instead, 3- to 6-monthly clinical review with ankle-brachial pressure index measurements should be utilised for at least 2 years. **(Level 2a; Grade B)**

Clinical deterioration and a drop in ankle-brachial pressure index of 0.1–0.2 indicate a failing infrainguinal vein bypass and should trigger focused colour duplex examination. **(Level 1b; Grade B)**

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Recommendations (*cont'd*)

A colour duplex scan at 6 weeks to 6 months helps predicting which venous graft is likely to fail and should benefit from surveillance. **(Level 2b; Grade C)**

Other reconstructions with a likely benefit from colour duplex surveillance include composite vein bypass, redo-bypass grafts, small diameter (<3 mm) venous grafts, long vein bypass (>50 cm) and alternative autologous venous conduits. **(Level 2b; Grade C)**

An early colour duplex scan is useful after endovascular revascularisation for CLI to identify those at risk for failure **(Level 3b; Grade C)**. However, there is no evidence supporting routine long-term colour duplex surveillance after endovascular revascularisation.

Best level evidence does not support the use of colour duplex imaging compared to clinical follow-up with ankle-brachial pressure index measurements every 3 months in patients with prosthetic bypass. **(Level 1b; Grade B)**

Critical issues

- More studies are needed to ensure general applicability of the above findings to patients with CLI, including the preferred duration of CD and/or clinical surveillance.
- The role and duration of CD surveillance after endovascular revascularisation including use of stents, subintimal recanalisation and endarterectomy devices should be better evaluated as compared to clinical surveillance with ABI measurements.
- Cost-effectiveness analyses are lacking regarding preferred surveillance modalities after bypass or endovascular revascularisation in patients with CLI.
- There is a need for stratified analyses comparing prophylactic measures, surveillance or repeat interventions during follow-up between above- and below-the-knee bypass in CLI patients. Available evidence pertains predominantly to below-the-knee reconstructions, but differential outcomes should be explored.

4. Repeat revascularisation

Approximately 40% of CLI patients undergoing vein bypass will need a secondary intervention during follow-up; and in a third of them the contralateral limb will be involved.[52,64] Around 20% of bypass procedures result in graft occlusion or amputation.[53,54,65,66] Overall, this rate corresponds to an estimated average of 1.75 repeat interventions per patient for a 3-year period.[64]

The success rate of secondary procedures for endovascular and surgical techniques is generally high, as long as the bypass or the angioplasty segment is not occluded. In contrast, once a graft has failed long-term patency is poorer after revision and limb salvage rate is moderate.[67] Timing of bypass failure is an important indicator of prognosis: the risk of amputation increases five-fold for early bypass failure (<30 days) as compared to failure after 30 days, as half of patients with early failure will develop untreatable critical ischaemia and immediate amputation.[65] Similarly, early repeat intervention (<120–180 days) is associated with impaired outcome as compared to late re-intervention.[68,69]

4.1. Failing bypass

Stenotic vein bypass can be salvaged with similar success by endovascular or surgical techniques,[54,59,68,70] even though surgical revisions are more durable and necessitate fewer subsequent re-interventions.[71] Midgraft stenoses are more benign than anastomotic stenoses,[70] and late-appearing short lesions have a favourable prognosis as compared to early and extensive stenoses.[68] Overall revision failure is in the range of 30% and is similar between surgical and endovascular approaches.[71]

For stenoses located within the main body of the graft, surgical patch angioplasty and interposition grafting using autologous vein are equally effective in prolonging assisted primary patency. Alternatively, endovascular angioplasty may be used with comparable early results,[71,72] although results are not as good as primary endovascular interventions for native CLI lesion.[73] Thus, the choice of the technique depends on anatomical characteristics and accessibility of the lesion.[47]

Outcome of recurrent stenosis is markedly inferior with endovascular angioplasty, and such lesions probably benefit from surgical revision.[74] Other types of lesions for which surgical repair should be preferred based on its durability include early lesions and lesions within anastomoses.[70] Endovascular revision is probably best suited for short (<2 cm) and late-appearing lesions (>3–4 months) involving the mid-graft, where it reaches similar durability as surgical revision.[58,68–70]

4.2. Failed bypass

Bypass occlusion is a critical event and should undergo urgent revision if the bypass is to be maintained. However, graft salvage attempts fail in up to 65% of patients;[57,65] and about half of graft occlusions will eventually lead to amputation.[34,65]

For occluded vein grafts, surgical revision including placement of a new bypass is preferred, since endovascular revision is less durable.[71] For occluded prosthetic bypasses, graft salvage surgery is associated with acceptable long-term results only for above-the-knee or extra-anatomic grafts. Occluded below-the-knee grafts are preferably replaced by a new bypass to a new outflow artery using an autologous vein.[66]

In some cases, catheter-directed thrombolysis is an appealing alternative. In a recent RCT, a mixed cohort of 124 patients with bypass occlusion was assigned to either surgical revision or intra-arterial thrombolysis.[75] Catheter placement failed in almost 40% of cases and composite clinical outcome at both 30 days and 1 year favoured surgical revision with new graft placement for chronically (>14 days) occluded grafts. However, patients with acute graft thrombosis (<14 days) had a lower amputation rate after successful thrombolysis at 1 year. Other authors have confirmed intra-arterial thrombolysis as a favourable strategy for acute graft occlusions and that it seems to give best results in above-the-knee prosthetic grafts in place at least for 1 year.[76] However, half of these grafts re-occlude within 1 month, particularly if thrombolysis fails to unmask an underlying correctable stenosis.[76,77]

4.2.1. Endovascular reconstruction

In 35% of cases a repeat intervention is needed within 1 year after endovascular revascularisation for CLI.[59,60] Although technical success of second-time endovascular angioplasty is in the range of 95%, its mid-term patency may be limited,[69] particularly in diabetic patients.[59] Therefore, multiple re-interventions may be needed for sustained limb salvage.[59] Early failure (<180 days) of initial endovascular intervention is a predictor of poor success of secondary intervention[69] and indicates that surgical alternatives should be considered. Overall, similar proportions of failed endovascular reconstructions are amenable to surgical or endovascular revision with comparable results.[59,60] Therefore, attempts at revision should be tailored individually.

Recommendations

In venous bypass, an early (<4 months) stenosis or one that involves the anastomosis may benefit from surgical revision **(Level 2b; Grade C)**. In this setting, patch angioplasty using autologous vein and interposition vein grafts are equally effective. **(Level 2b; Grade B)**

Late-appearing and short (<2 cm) stenosis located within the main body of a vein graft can be treated with equivalent efficacy using endovascular intervention or surgical revision **(Level 2b; Grade B)**. However, recurrent stenosis has an inferior outcome when treated by angioplasty and is likely to benefit from surgical revision. **(Level 4; Grade C)**

Following vein graft revision, ongoing clinical and colour duplex surveillance is recommended as the risk of new restenosis appears to be high. **(Level 4; Grade C)**

Following graft occlusion, intra-arterial thrombolysis may be an option in patients without acute critical ischaemia and a recent occlusion (<14 days) of a prosthetic or vein bypass above the knee and in place for at least 1 year, provided that there are no contraindications and that lysis can be accomplished safely. Surgical revision with a new graft using an autologous vein remains the preferred salvage procedure for other types of graft occlusion. **(Level 2b; Grade C)**

Failing or failed endovascular revascularisations can be treated with similar efficacy by endovascular or surgical revision **(Level 2b; Grade C)**. However, early repeated endovascular interventions (<180 days) are associated with a poor outcome. In these cases, a surgical alternative may be preferable. **(Level 4; Grade C)**

Critical issues

- There is a need to study the best available treatment for in-stent restenosis and after graft failure.
- A RCT is needed to evaluate the role of drug-eluting stents for restenosis after angioplasty and for venous graft stenosis.

5. Follow-up in specific contexts

5.1. Diabetic patients

A large proportion of CLI patients are diabetic[59] and may be challenging to manage. Expected clinical outcomes are supposedly similar between surgical and endovascular reconstruction,[59] but as diabetic patients tend to present with an advanced stage of peripheral vascular disease, they may demonstrate reduced primary patency rates.[59,78] However, with timely and repeated use of salvage re-interventions, acceptable secondary patency and limb salvage rates can be reached.[78,79] Therefore, diabetic patients are a subset likely to benefit from close long-term surveillance during follow-up.[59]

5.1.1. Patients with end-stage renal disease

The proportion of patients with both CLI and chronic renal failure is increasing. But with an aggressive repeat revascularisation approach, peri-operative mortality and graft patency rates as well as expected 4-year survival rates tend to approach those of patients with normal renal function.[80] The risk of amputation is however markedly increased in dialysis patients.[80–83] Major amputation despite a patent graft occurs in 10% of patients with end-stage renal disease,[37,39] particularly when prosthetic graft material has been used in non-ambulatory patients with extensive tissue loss.[37,38,80,82,84] In addition, secondary salvage procedures after bypass occlusion have a poor prognosis in patients with end-stage renal disease, and most will need a major amputation within 1 year of graft failure.[67]

5.1.2. Elderly and functionally impaired patients

In elderly patients (⩾80 years), quality of care for CLI is not solely determined by the traditional measures of patency and limb salvage but particularly by functional outcomes. The most important predictor of preserved ambulatory capacity is the patient state at presentation, including mental state, pre-operative ambulatory capacity and independent living status.[40,85] General outlook after open or endovascular revascularisation is fair for aged ambulatory patients with CLI,[86,87] even for below-the-knee reconstructions.[88] At 1 year, 88% of survivors are ambulatory, 85% live at home, and 80% do both, whereas at 5 years, 71% are still ambulatory, and 81% live independently.[40] Therefore, those who were ambulatory and lived at home pre-operatively almost invariably continue to do so. Those with poor ambulatory function or who required assistance pre-operatively, however, are unlikely to improve their status after revascularisation even if technically successful.[40,85,88] These findings question the appropriateness of revascularisation in functionally impaired and chronically ill patients.

Recommendations

Diabetic patients are likely to benefit from close clinical and colour duplex-scan surveillance as primary patency rates are low and ankle-brachial pressure index may be unreliable. **(Level 2b; Grade C)**

Patients with end-stage renal disease and patients who are not ambulatory or are mentally incapacitated are unlikely to profit from any kind of continued limb salvage efforts. This is particularly true if tissue loss is extensive and no adequate autologous vein is available. **(Level 2b; Grade C)**

Conflict of Interest/Funding

None

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