HIGH-RISK PATIENTS AND HIGH-RISK GRAFTS IN INFRAINGUINAL BYPASS FOR CRITICAL LIMB ISCHAEMIA

Eva Arvela

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Helsinki 2011
To my family
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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which will be referred to in the text by their Roman numerals.


IV Arvela E, Venermo M, Söderström M, Albäck A, Lepäntalo M. Outcome of infrainguinal single segment great saphenous vein bypass for CLI is superior to alternative autologous vein bypass especially in patients with high operative risk. Accepted for publication (Ann Vasc Surg).


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**ABBREVIATIONS AND DEFINITIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>ABI</td>
<td>Ankle-brachial index</td>
</tr>
<tr>
<td>ADP</td>
<td>Arteria dorsalis pedis</td>
</tr>
<tr>
<td>AFS</td>
<td>Amputation-free survival</td>
</tr>
<tr>
<td>APP</td>
<td>Assisted primary patency</td>
</tr>
<tr>
<td>ASA</td>
<td>Acetosalisylic acid</td>
</tr>
<tr>
<td>ATA</td>
<td>Arteria tibialis anterior</td>
</tr>
<tr>
<td>ATP</td>
<td>Arteria tibialis posterior</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the (ROC) curve</td>
</tr>
<tr>
<td>CABG</td>
<td>Coronary artery bypass grafting</td>
</tr>
<tr>
<td>CAD</td>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>CG</td>
<td>Cockcroft-Gault</td>
</tr>
<tr>
<td>CGSV</td>
<td>Contralateral great saphenous vein</td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>CLI</td>
<td>Critical limb ischaemia</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>CTA</td>
<td>Computed tomography angiography</td>
</tr>
<tr>
<td>CVD</td>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td>DM</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>DSA</td>
<td>Digital subtraction angiography</td>
</tr>
<tr>
<td>eGFR</td>
<td>Estimated glomerular filtration rate</td>
</tr>
<tr>
<td>ESRD</td>
<td>End-stage renal disease</td>
</tr>
<tr>
<td>GSV</td>
<td>Great saphenous vein</td>
</tr>
<tr>
<td>IDMS</td>
<td>Isotope dilution-mass spectrometry</td>
</tr>
<tr>
<td>IGSV</td>
<td>Ipsilateral great saphenous vein</td>
</tr>
<tr>
<td>LMWH</td>
<td>Low molecular weight heparin</td>
</tr>
<tr>
<td>LS</td>
<td>Leg salvage</td>
</tr>
<tr>
<td>LSV</td>
<td>Lesser saphenous vein</td>
</tr>
<tr>
<td>MDRD</td>
<td>Modification of Diet in Renal Disease</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>MRA</td>
<td>Magnetic resonance angiography</td>
</tr>
<tr>
<td>N.A</td>
<td>Not assessed/not available</td>
</tr>
<tr>
<td>PTFE</td>
<td>Polytetrafluoroethylene</td>
</tr>
<tr>
<td>ROC</td>
<td>Receiver operating characteristic</td>
</tr>
<tr>
<td>Scr</td>
<td>Serum creatinine</td>
</tr>
<tr>
<td>SCS</td>
<td>Spinal cord stimulation</td>
</tr>
<tr>
<td>SMC</td>
<td>Smooth muscle cell</td>
</tr>
<tr>
<td>SE</td>
<td>Standard error</td>
</tr>
<tr>
<td>SP</td>
<td>Secondary patency</td>
</tr>
<tr>
<td>TASC</td>
<td>Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease</td>
</tr>
</tbody>
</table>

**Primary patency**
Graft patency is uninterrupted

**Assisted primary patency**
Graft is patent, but additional procedures have been performed to maintain patency

**Secondary patency**
Graft patency has been restored after occlusion
ABSTRACT

Background
Patients with critical limb ischaemia (CLI) usually have several comorbidities affecting the outcome. Complex and sometimes multiple infrainguinal bypasses are required for limb salvage. Therefore, the lack of optimal graft material is an increasing clinical problem. The type and quality of the vein graft are major determinants of bypass patency. Revascularization for CLI is meaningless unless both life and limb are preserved. Therefore, the knowledge of both patient- and bypass-related risk factors is of paramount importance in clinical decision-making, patient selection and resource allocation.

Aims of the study
The aim of this study was to identify patient- and graft-related predictors of impaired outcome after infrainguinal bypass for critical limb ischaemia. The purpose was to assess the outcome of high-risk patients undergoing infrainguinal bypass and to evaluate the usefulness of specific risk scoring methods. The results of bypasses in the absence of optimal vein graft material were also evaluated, and the feasibility of the new method of scaffolding suboptimal vein grafts was assessed.

Patients and methods
I A retrospective study of 603 infrainguinal bypasses for critical limb ischaemia comparing serum creatinine (SCr) and estimated glomerular filtration rate (eGFR) as predictors of outcome.
II A retrospective study comparing the outcome of octogenarian patients with CLI undergoing either infrainguinal percutaneous transluminal angioplasty (PTA) (n=277) or infrainguinal bypass (n=307).
III A total of 1,425 patients undergoing infrainguinal PTA or bypass for CLI were analysed retrospectively and the usefulness and accuracy of two risk scoring methods, the Finnvasc score and modified Prevent III (mPIII) score, as predictors of outcome were assessed.
IV In a retrospective analysis of 1,109 patients undergoing infrainguinal vein bypass for critical limb ischaemia, the patency and leg salvage rates of different types of autologous vein grafts were assessed. Risk factors for graft failure were also evaluated.
V A single-centre study compared the results of arm vein (n=130) and prosthetic (n=160) infrainguinal bypasses for CLI.
VI A prospective, multicentre, observational study from six centres assessed the feasibility of the new method of external scaffolding for suboptimal infrainguinal vein grafts in 50 patients.
Main results
Estimated GFR <30 ml/min/1.73 m² and serum creatinine >200 mmol/l predicted mortality (the adjusted hazard ratio [HR] 4.0 [95% CI 2.22–7.39] and 3.5 [95% CI 1.82–6.84], respectively) and limb loss (the adjusted HR 6.5 [95% CI 2.71–15.59] and 6.2 [95% CI 2.47–15.56], respectively) (I).

In 95 propensity-score-matched pairs, PTA achieved significantly better leg salvage (88% vs. 75%, \( p = 0.010 \)) and amputation-free survival (AFS) (53% vs. 45%, \( p = 0.033 \)) rates than bypass in octogenarians with CLI (II).

In patients undergoing infrainguinal revascularization for CLI, the Finnvasc score predicted leg salvage (RR 1.431, 95% CI 1.319–1.551), survival (RR 1.233, 95% CI 1.116–1.363) and amputation-free survival (RR 1.422, 95% CI 1.319–1.534). The modified PIII score also predicted leg salvage (RR 1.190, 95% CI 1.108–1.277), survival (RR 1.245, 95% CI 1.193–1.300) and amputation-free survival (RR 1.223, 95% CI 1.176–1.272) (III).

Primary patency, assisted primary patency, secondary patency and limb salvage at 1 year were significantly better in the single-segment great saphenous vein (GSV) graft group than in the alternative autologous vein graft group: 74.4% vs. 53.7% (\( p<0.0001 \)), 82.4% vs. 67.2% (\( p<0.0001 \)), 84.8% vs. 69.9% (\( p<0.0001 \)) and 88.9% vs. 83.0% (\( p<0.0001 \)), respectively. Non-single-segment GSV graft was the only independent risk factor for graft stenosis development (RR 2.62, 95% CI 1.56–4.38, \( p<0.0001 \)) (IV).

High-risk patients (age >80, coronary artery disease, eGFR<30) who underwent bypass with a risk graft (arm vein or spliced vein) had extremely poor one-year survival (28.6%) (IV).

In infrapopliteal revascularizations for CLI, primary patency, assisted primary patency and secondary patency rates at three years were significantly better in the arm vein group than the prosthetic group: 28.3% vs. 9.6% (\( p=0.031 \)), 56.8% vs. 10.4% (\( p=0.000 \)) and 57.4% vs. 11.2% (\( p=0.000 \)), respectively. Leg salvage and survival at 3 years were 75.0% vs. 57.1% (\( p=0.005 \)) and 58.8% vs. 39.5% (\( p=0.007 \)), respectively (V).

The six-month primary, assisted primary and secondary patency rates of bypasses using external mesh support due to a suboptimal quality of vein grafts were acceptable: 82.3%, 88.6% and 92.1%, respectively. No adverse effects related to polyester mesh were detected (VI).

Conclusions
Low estimated GFR is an independent marker of poor prognosis after infrainguinal bypass in patients with critical limb ischaemia. Estimated GFR is a more accurate predictor of survival and leg salvage than serum creatinine alone (I).

The overall outcome of octogenarians with critical limb ischaemia undergoing infrainguinal revascularization is poor. Endovascular treatment
seems to be associated with better survival, leg salvage and amputation-free survival than bypass. If feasible, an endovascular first option should be considered in patients ≥ 80 years of age, especially in the presence of coronary artery disease (II).

The Finnvasc and modified Prevent III risk scoring methods predict the long-term outcome of patients undergoing both surgical and endovascular infrainguinal revascularization for CLI. The Finnvasc score also seems to perform well in predicting immediate postoperative outcome. Both risk scores may be useful as additional information in decision-making (III).

A single-segment great saphenous vein graft is superior to any other autologous vein graft in terms of mid-term patency and leg salvage. A single-segment GSV graft requires fewer maintenance procedures than alternative autologous vein grafts. Acceptable patency and leg salvage rates can be achieved with alternative autologous vein grafts (IV).

The outcome of patients with both a high operative risk and a risk graft bypass is very poor (IV).

Arm vein conduits are superior to prosthetic grafts for infrapopliteal bypasses in patients with CLI. Despite only moderate patency rates, a prosthetic bypass on infrapopliteal arteries may be worthwhile as a last resort option for limb salvage (V).

In a prospective, multicenter study of 50 patients, polyester mesh seems to be a safe and feasible adjunct to infrainguinal bypass using suboptimal autologous vein grafts, and it may enable the use of vein grafts of compromised quality (VI).
Peripheral arterial disease (PAD) can be defined as a disparity between tissue oxygen demand and supply. Critical limb ischaemia (CLI) is an end-stage PAD where chronic lack of sufficient blood supply eventually leads to ischaemic rest pain and/or a tissue lesion. According to Norgren et al. (2007), the estimated incidence of CLI varies between 500 and 1,000/million annually.

Asymptomatic PAD and claudication are markers of increased cardiovascular risk (Shammas 2007) but infrequently lead to limb loss (Dormandy and Murray 1991). Critical limb ischaemia (ischaemic rest pain or ischaemic tissue lesion) often leads to limb loss without revascularization (Wolfe and Wyatt 1997).

The main purpose of revascularization procedures for CLI is to preserve the leg and sustain the patient’s ambulatory status. Other goals are ischaemic pain relief and healing of ischaemic ulcers. CLI patients who undergo successful revascularization sustain their mobility and independent status longer (Luther 1998) and have better survival and quality of life (Klevsgård et al. 2001, Brosi et al. 2007) than those treated conservatively or with primary amputation. An active revascularization policy for CLI reduces amputation rates (Eskelinen et al. 2004) and has proven cost-effective in ambulatory patients (Luther 1997). Therefore, revascularization should be offered to all CLI patients if the procedure can be tolerated and the patient is ambulatory and living independently preoperatively (Varu et al. 2010). According to the first TransAtlantic Inter-Society Consensus (TASC) document (2000), primary amputation should be considered in the presence of an unreconstructable disease, extensive necrosis involving weight-bearing areas, a fixed and irremediable flexion contracture of the leg, a terminal illness, or a very limited life expectancy because of co-morbid conditions.

Endovascular revascularization procedures have challenged bypass surgery as the first-line treatment for CLI (Nasr et al. 2002, Kudo et al. 2004). This is mainly due to their less invasive nature and subsequent better short-term survival especially in elderly patients (Dosluglu et al. 2009). Despite rapidly evolving endovascular techniques, there are still patients with multilevel infrainguinal disease not amenable to endovascular procedures. The latest TASC II Document still recommends bypass surgery as the treatment of choice for long multisegmental lesions (Norgren et al. 2007). The BASIL Trial—a large randomised trial comparing bypass and endovascular revascularization—suggests that bypass provides more durable results than the endovascular approach and, therefore, a bypass-first strategy should be considered if there is a good vein and the patient is relatively fit with a life expectancy more than two years (Adam et al. 2005, Bradbury et al. 2010).

Despite the technical success and acceptable patency rates of bypass procedures, advanced age and co-morbid conditions may limit the benefit
from bypass procedures. Advanced age is associated with decreased peri-and postoperative survival after vascular surgery procedures (Plecha et al. 1985). Renal insufficiency is an independent predictor of impaired outcome. Especially patients with end-stage renal disease (ESRD) and critical limb ischaemia undergoing infrainguinal bypass have poorer post-operative survival and higher amputation rates (Sanchez et al. 1992, Johnson et al. 1995). The combination of ESRD, coronary artery disease, hypoalbuminaemia and critical limb ischaemia seems to be a marker of extremely poor outcome (Biancari et al. 2002).

In addition to patient characteristics, several graft-related factors affect the outcome. Outflow is one of the most important determinants of bypass outcome (Albäck et al. 1998). Graft type, size and quality are also major contributors to bypass patency. The great saphenous vein (GSV) is the conduit of choice for infrainguinal bypass due to its superior long-term patency and limb salvage rates (Klinkert et al. 2004, Perreira et al. 2006). As a result of a previous infrainguinal bypass, coronary artery bypass grafting, or varicose vein surgery or ablation, however, the GSV may be lacking or can be of poor quality due to varicosities or small calibre. In these cases, either alternative autologous veins or prosthetic material can be used as conduits. Acceptable patency and leg salvage rates can be achieved with alternative autologous veins (Gentile et al. 1996, Faries et al. 2000a–c). The patency and leg salvage of prosthetic bypasses are promising in the femoro-popliteal level and in the short term (Veith et al. 1986, Bosiers et al. 2006, Peeters et al. 2006), but the long-term outcome of infrapopliteal prosthetic bypasses is still poor (Kashyap et al. 2002). Adjunctive methods such as heparin-bonding (Peeters et al. 2006) and anastomotic modifications (Gulkarov et al. 2008) have been introduced to improve the results of prosthetic bypasses.

As the population is aging and the incidence of diabetes increasing, even more elderly patients with CLI and numerous co-morbidities will be referred to vascular surgery units (Conte et al. 2001, Diehm et al. 2004). This emphasizes the role of patient selection and preoperative risk assessment in the future. The estimation of the risk of adverse postoperative outcome is important as it helps decision-making between different treatment modalities, allows appropriate resource allocation and provides patients with information of their individual operative risk.

This study evaluates patients undergoing infrainguinal bypass for CLI. The aim was to uncover patient- and graft-related predictors of poor outcome and to assess whether the results of infrainguinal bypasses in suboptimal circumstances are good enough to justify these high-risk procedures. The results of this study might be helpful in every-day clinical practise, guiding vascular surgeons in patient selection and clinical decision-making in regard to which treatment modality should be chosen and when to refrain from any type of reconstruction.
REVIEW OF THE LITERATURE

1 OUTCOME OF PATIENTS WITH CRITICAL LIMB ISCHAEMIA

1.1 Natural outcome

Manifestations of PAD can be classified according to the severity of ischaemia by using the Fontaine classification (Fontaine et al. 1955; Table I) or the Rutherford classification (Rutherford et al. 1986; Table II). Asymptomatic PAD (Fontaine I, Rutherford 0) or claudication (Fontaine II a-b, Rutherford 1-3) are markers of increased cardiovascular risk (Shammas et al. 2007) but only seldom lead to limb loss (Dormandy and Murray 1991). In contrast, ischaemic rest pain (Fontaine III, Rutherford 4) or an ischaemic tissue lesion (Fontaine IV, Rutherford 5–6) often leads to limb loss without revascularization procedures (Wolfe and Wyatt 1997).

Table I. Fontaine classification

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>IIa</td>
<td>Mild claudication</td>
</tr>
<tr>
<td>IIb</td>
<td>Moderate-severe claudication</td>
</tr>
<tr>
<td>III</td>
<td>Rest pain</td>
</tr>
<tr>
<td>IV</td>
<td>Ulcer or gangrene</td>
</tr>
</tbody>
</table>

Table II. Rutherford classification

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>1</td>
<td>Mild claudication</td>
</tr>
<tr>
<td>2</td>
<td>Moderate claudication</td>
</tr>
<tr>
<td>3</td>
<td>Severe claudication</td>
</tr>
<tr>
<td>4</td>
<td>Rest pain</td>
</tr>
<tr>
<td>5</td>
<td>Minor tissue loss</td>
</tr>
<tr>
<td>6</td>
<td>Severe tissue loss</td>
</tr>
</tbody>
</table>

The international consensus on the definition of CLI is as follows: any patient with chronic ischaemic pain, an ulcer or gangrene attributable to objectively proved arterial occlusive disease (Norgren et al. 2007). Patients with CLI are estimated to represent approximately 1% of the total number of PAD patients (Hirsch et al. 2006). Patients with CLI are not only at a high risk of losing their limb, but also at risk for other cardiovascular events, such as myocardial infarction and stroke (Howell et al. 1989, McKenna et al. 1991, Criqui et al. 1992, Murabito et al. 2002). Up to 80% of CLI patients die from a vascular event; over 60% from coronary artery disease (CAD) and approximately 10% from stroke (Regensteiner and Hiatt 2002). High mortality rates associated with diagnosed CLI even exceed those seen in patients with symptomatic coronary artery disease (Caro et al. 2005, Steg et al. 2007), which emphasizes
the role of the severe diffuse atherosclerotic burden of CLI. CLI is therefore a predictor of poor prognosis for both life and limb. The prognosis of CLI is even compared to that of some malignant diseases as the mortality is 20% in the first year after presentation and seems to continue at the same rate, reaching 50% at 5 years and 90% at 10 years (Norgren et al. 2007). Moreover, studies on patients diagnosed with CLI reveal that at 1 year, only 50% patients will remain amputation-free, some of them still symptomatic, whereas 25% will require a major amputation and the remaining 25% will die (Norgren et al. 2007). An observational study of 105 patients with unreconstructed CLI published by Lepäntalo and Mätzke (1996) demonstrates an even worse outcome, as the 1-year survival and leg salvage rates were 46% and 54%, respectively. The one-year amputation-free survival was only 28%. Seventy-two percent of patients died due to cardiovascular events. Similarly, data from multicentre pharmacotherapy trials on patients with CLI who are unreconstructable or in whom reconstruction attempts have failed show that within 6 months approximately 40% lose their limb and 20% die (Norgren et al. 2007). The fate of the unreconstructed CLI patient is reported to be dismal in other series as well (Table III).

The degree of ischaemia is a major contributor to the fate of the leg. According to Wolfe and Wyatt (1997), the amputation rate in the presence of subcritical (rest pain and/or ankle pressure > 40 mmHg) versus critical limb ischaemia (tissue loss and/or ankle pressure < 40 mmHg) without reconstruction at one year was 70% versus 95%, respectively.

Table III. Fate of unreconstructed CLI

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>n</th>
<th>FU (months)</th>
<th>amputation (%)</th>
<th>mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norgren et al. (1990)</td>
<td>103a</td>
<td>6</td>
<td>39</td>
<td>13</td>
</tr>
<tr>
<td>Jivégård et al. (1995)</td>
<td>51b</td>
<td>18</td>
<td>45</td>
<td>31</td>
</tr>
<tr>
<td>Lepäntalo &amp; Mätzke (1996)</td>
<td>105</td>
<td>12</td>
<td>46</td>
<td>54</td>
</tr>
<tr>
<td>Klomp et al. (1999)</td>
<td>120c</td>
<td>24</td>
<td>45</td>
<td>33</td>
</tr>
<tr>
<td>Amann et al. (2003)</td>
<td>112d</td>
<td>12</td>
<td>35</td>
<td>-</td>
</tr>
</tbody>
</table>

FU=follow-up
*aprostanoid treatment n=50, placebo n=53
*bspinal cord stimulation (SCS) n=25, control n=26
*cSCS n=60, control n=60
*dSCS n=73, control n=39

The effect of alternative treatment modalities has also been studied in patients with CLI not eligible for revascularization. Placebo-controlled studies have evaluated the use of prostacyclin analogues in the treatment of CLI. Neither Norgren et al. (1990) nor Brass et al. (2006) found any difference in amputation rates between the prostacyclin analogues and the placebo group. Therefore,
these pharmacologic agents seem to have no role in the management of CLI. Spinal cord stimulation (SCS) has been introduced as an alternative to amputation in CLI patients with severe ischaemic pain. Ubbink et al. (2006) reported positive effects of SCS on pain relief, but concluded that the risks and high cost must be weighed against the marginal benefits. Klomp et al. (1999) concluded that spinal cord stimulation in addition to the best medical care does not prevent amputation in patients with critical limb ischaemia. Dedicated wound care may increase limb salvage in some patients who are unfit for surgery (Marston et al. 2006).

1.2 Outcome of infrainguinal bypass
The outcome of infrainguinal bypass can be defined in many ways. The purpose of revascularization is to relieve ischaemic pain, heal ischaemic tissue lesions, prevent amputation and therefore sustain ambulatory status, as well as to improve the quality of life and prolong survival. According to Nicoloff and co-workers (1998), an ideal endpoint—i.e., a patent graft, healed wound, freedom from reoperations, independent living status and continued ambulation—was rarely achieved in patients with CLI, as only 14% of the patients met all these criteria for success. Similarly, Colledge and colleagues (2001) used the same criteria for successful revascularization and reported that only 22% of CLI patients achieved the ideal outcome.

Both patient- and bypass-related factors affect the overall outcome. Bypass patency and leg salvage are largely dependent on arterial anatomy and bypass graft-related factors, such as graft type and quality. Table IV summarizes the patency and leg salvage expectations for different types of infrainguinal bypasses as reported in a review by Dahlman (2000). Patient survival and functional outcome, on the other hand, are affected mostly by co-morbidities and medication. Death usually predominates in patients with CLI and, therefore, other endpoints, such as wound healing, are not easily assessed.

There is controversy regarding the most appropriate endpoint in the evaluation of patients with CLI. The preservation of both life and limb is of paramount importance, and therefore amputation-free survival (AFS) is a justifiable endpoint. Furthermore, the TASC II Document (Norgren et al. 2007) suggests AFS as a primary outcome endpoint. In a large randomised, multicentre trial including 1,166 patients undergoing infrainguinal bypass for CLI, Schanzer et al. (2009) reported a 79% AFS at 1 year. In the largest randomised trial comparing bypass versus angioplasty in the treatment of severely ischaemic leg (the BASIL Trial), one-year amputation-free survival after bypass was reported to be 68% (Adam et al. 2005). Similarly, Feinglass and co-workers (2001) reported 1-year and 3-year amputation-free survival rates of 74% and 56%, respectively, in their series from Veterans Affairs
hospitals including 4,288 male veterans undergoing femorodistal bypass (63% of study population had CLI). Due to the high incidence of severe comorbidities, perioperative (<30-day) mortality is relatively high in CLI patients undergoing infrarenal bypass. A meta-analysis reviewing 31 studies involving bypass for CLI (Albers et al. 2006) revealed considerably high immediate postoperative mortality up to 11.6% (weighted average 2.3%).

In a review of 10 studies reporting the outcomes of femoropopliteal bypass grafting, Hunink et al. (1994) published a 3.6% overall perioperative mortality rate. In the large Prevent III study, the overall perioperative mortality rate was 2.7% (Conte et al. 2005).

**Table IV.** Patency and leg salvage expectations for different types of infrainguinal bypasses (Dahlman 2000).

<table>
<thead>
<tr>
<th></th>
<th>PP</th>
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<th>SP</th>
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<td>1Y</td>
<td>3Y</td>
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<tr>
<td>A-K FEMOROPOPLITEAL</td>
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</tr>
<tr>
<td>GSV*</td>
<td>84%</td>
<td>73%</td>
<td>-</td>
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<td>-</td>
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<tr>
<td>arm vein</td>
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<td>60%</td>
<td>-</td>
<td>-</td>
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<td>-</td>
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<tr>
<td>PTFE</td>
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<td>66%</td>
<td>-</td>
<td>-</td>
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<tr>
<td>B-K FEMOROPOPLITEAL</td>
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<tr>
<td>GSV**</td>
<td>80%</td>
<td>73%</td>
<td>96%</td>
<td>86%</td>
<td>99%</td>
<td>83%</td>
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<tr>
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<td>-</td>
<td>83%</td>
<td>73%</td>
<td>-</td>
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</tr>
<tr>
<td>PTFE</td>
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<td>-</td>
<td>68%</td>
<td>44%</td>
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<tr>
<td>INFRAPoplITEAL</td>
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<td>GSV</td>
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<tr>
<td>reversed</td>
<td>77%</td>
<td>66%</td>
<td>84%</td>
<td>78%</td>
<td>85%</td>
<td>82%</td>
</tr>
<tr>
<td>in-situ</td>
<td>82%</td>
<td>74%</td>
<td>89%</td>
<td>84%</td>
<td>91%</td>
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<tr>
<td>arm vein</td>
<td>-</td>
<td>-</td>
<td>73%</td>
<td>58%</td>
<td>-</td>
<td></td>
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<tr>
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<td>46%</td>
<td>-</td>
<td>68%</td>
<td>56%</td>
</tr>
<tr>
<td>PEDAL/PLANTAR</td>
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</tr>
<tr>
<td>GSV*</td>
<td>81%</td>
<td>-</td>
<td>85%</td>
<td>76%</td>
<td>83%</td>
<td>84%</td>
</tr>
</tbody>
</table>

*A-K= above-knee, B-K= below-knee
GSV=great saphenous vein, PTFE= polytetrafluoroethylene
PP= Primary patency, SP= Secondary patency, LS= Leg salvage
2 FACTORS AFFECTING THE OUTCOME OF INFRAINGUINAL BYPASS

2.1 Patient-related risk factors
Patients with CLI often also have other manifestations of cardiovascular disease (CAD, cerebrovascular disease [CVD]) as well as other comorbidities such as diabetes, chronic obstructive pulmonary disease (COPD) and renal insufficiency, which affect the outcome negatively and largely determine the fate of the patient regardless of the success of the bypass procedure alone.

2.1.1 Coronary artery disease
Coronary artery disease has been estimated to be present in over 50% of patients with CLI (Feringa et al. 2007, Norgren et al. 2007). The risk of cardiac events in patients with CLI seems to be at least equal that of patients with symptomatic CAD (Criqui et al. 1992, Newman et al. 1999). High cardiac event and mortality rates with a 5-year survival of 60%–70% in CLI patients undergoing revascularization are reported in several series (Dawson et al. 1993, Farkouh et al. 1994). Myocardial infarction (MI) is the most common life-threatening complication of vascular surgery, with a reported perioperative incidence ranging from 8% to up to 40%, depending on the diagnostic criteria (Kim et al. 2002, Landenburg et al. 2003, Hobbs et al. 2005). The severity of PAD is clearly connected to the risk of coronary events (Criqui et al. 1992, Newman et al. 1999), and CLI definitely represents the worst phase of the condition. One explanation for the high perioperative MI rate in CLI might be that patients undergoing surgery for CLI have even greater levels of platelet and monocyte activation than those being treated for acute MI (Burdess et al. 2010). Conte and co-workers (2005) reported a 4.7% perioperative myocardial infarction rate after infrainguinal bypass for CLI, and the notable finding was that 24% of the patients had no kind of antithrombotic medication. The best medical treatment is of paramount importance in order to reduce perioperative adverse cardiac events. Pharmacological treatment with β-blockers, statins and aspirin are demonstrated to have beneficial effects (Poldermans et al. 2009). However, according to two randomised controlled trials, CARP (Coronary Artery Revascularization Prophylaxis; McFalls et al. 2004) and the DECREASE-V Trial (Poldermans et al. 2007), prophylactic coronary artery revascularization in cardiac stable patients does not seem to provide any significant extra benefit in terms of postoperative outcome, with an exception for patients with left main coronary artery stenosis. Therefore, in the most recent European Society for Cardiology (ESC) guidelines, it is only recommended to consider prophylactic coronary artery revascularization...
in patients undergoing high-risk surgery, such as lower extremity open revascularization (Poldermans et al. 2009).

### 2.1.2 Diabetes

Diabetes increases the prevalence of symptomatic peripheral arterial disease 3.5-fold in men and 8.6-fold in women (Kannel and McGee 1985). Poor glucose control accelerates the manifestation of peripheral arterial disease. For every 1% increase in haemoglobin A1c, there is a corresponding increase of 25%–28% in the relative risk of peripheral arterial disease (Selvin et al. 2004). Among patients with PAD, diabetes is associated with an approximately fourfold increase in the risk of developing CLI (Norgren et al. 2007). Ten to twenty years ago, roughly one third of patients undergoing infrainguinal bypass for CLI had diabetes (Da Silva et al. 1996), but currently there are as many diabetics as non-diabetics among patients with CLI (Conte et al. 2001, Eskelinen et al. 2004), and in the future diabetics will overtake non-diabetics, especially if the more liberal definition of CLI is used (Apelqvist et al. 2008). Diabetes does not seem to have an effect on graft patency (Biancari 2000a, Wölfle et al. 2003, Monahan and Owens 2009). The effect of diabetes on leg salvage and survival is, however, controversial. According to previous studies, the clinical results of lower extremity bypass surgery seem to be worse in diabetics in terms of increased mortality (Stirnemann et al. 1991, Karacagil et al. 1995, Luther and Lepäntalo 1997a, Biancari et al. 2000a, Wölfle et al. 2003) and inferior limb salvage rates (Taylor et al. 1990, Da Silva 1996, Luther and Lepäntalo 1997a). The manifestation of peripheral arterial disease is often different in diabetics and nondiabetics. The combined effect of diabetic neuropathy and ischaemia, so-called neuroischaemia, affects the foot perfusion in a variety of ways (Schaper et al. 2000). Infection and impaired wound healing are evidently major determinants of leg salvage in diabetic patients. Unfortunately, up to 30% of diabetics have gangrene at admission to a vascular surgery unit due to a lack of recognition of ischaemia, an underestimation of the severity of the lesion and a subsequent delay in referral (Mills et al. 1991). The prevalence of diabetic foot ulcers has been estimated to be 3%–8% (Abbot et al. 1998, Reiber et al. 1998). Approximately 40%–60% of all amputations of the lower extremity are performed on patients with diabetes (Larsson and Apelqvist 1995, Adler et al. 1999) Up to 85% of these amputations are precipitated by a foot ulcer which deteriorates to deep infection or gangrene (Larsson et al. 1995, Reiber et al. 1998). In the series of Carsten et al. (1998), persistent overwhelming soft tissue infection despite a patent bypass was the reason for early amputations in 4.4% of patients. Similarly, Virkkunen and co-workers (2004) reported that after bypass for CLI, significantly more diabetics than non-diabetics underwent amputation despite successful revascularization.
There are, however, recent studies suggesting that diabetic patients with CLI could achieve an equal outcome after infrainguinal bypass as non-diabetic patients with an aggressive, multidisciplinary approach, including experience in extremely distal revascularizations as well as aggressive treatment of infection, frequent debridement, biomechanical off-loading, blood glucose control and treatment of co-morbidities (Akbari et al. 2000, Dorweiler et al. 2002, Awad et al. 2006).

2.1.3 Renal insufficiency
Approximately 5% of patients with end-stage renal disease (ESRD) develop critical limb ischaemia (Albers et al. 2001), and bypass surgery for CLI on patients with renal insufficiency, especially ESRD, is challenging. Cardiovascular mortality is higher among patients with end-stage renal disease in comparison to the normal population (Sarnak and Levey 2000). Diabetes and hypertension are not only risk factors for both ESRD and CLI, but may further worsen the prognosis (Longenecker et al. 2002, Kronenberg et al. 2003). However, renal insufficiency per se seems to be an independent risk factor for poor outcome (Naidu et al. 2003, Go et al. 2004).

Dialysis-dependent patients usually have extremely calcified arteries, and their wound healing is impaired due to several factors, such as anaemia, malnutrition, impaired immunity and a susceptibility to infection (Sanchez et al. 1992, Whittemore et al. 1993, Peltonen et al. 1998). Therefore, patients with critical limb ischaemia and ESRD undergoing infrainguinal bypass have poorer post-operative survival and higher amputation rates. The patency rates of ESRD patients are comparable to patients with normal kidney function (Hakaim et al. 1998), but a 10%–37% amputation rate due to persistent gangrene despite a patent bypass has been reported in ESRD patients (Edwards et al. 1988, Taylor et al. 1991, Johnson et al. 1995, Simsir et al. 1995, Albers et al. 2007). A meta-analysis by Albers et al. (2007) yielded a 5-year pooled estimate of 50.4% for primary patency, 50.8% for secondary patency and 66.6% for leg salvage. Five-year survival was only 23%. Especially in diabetic patients with ESRD, the outcome has been discouraging because of high perioperative mortality rates (3%–17%) and low 3-year leg salvage rates (40%–76%) (Edwards et al. 1988, Harrington et al. 1990, Whittemore et al. 1993, Johnson et al. 1995, Harpavat et al. 1998). Furthermore, the life expectancy after bypass in this patient group has been reported to be dismal, with an average of 60% survival at 1 year, 50% survival at 2 years, and 0%–40% survival at 3 years (Harpavat et al. 1998, Edwards et al. 1988, Chang et al. 1990, Harrington et al. 1990, Whittemore et al. 1993, Johnson et al. 1995, Simsir et al. 1995, Hakaim et al. 1998). End-stage renal disease is evidently a marker of poor prognosis, but the impact of mild to moderate renal insufficiency on outcome after infrainguinal
bypass for CLI is less well known. O’Hare et al. (2004) reported that PAD patients on dialysis, but not patients with milder degrees of renal insufficiency, are at higher risk of limb loss after revascularization when compared to patients with normal renal function.

The measurement of serum creatinine is the most commonly used method to assess renal function, but it is an inaccurate estimate of actual renal function, especially in early renal insufficiency (Diskin 2007). Direct measurement of glomerular filtration rate is the gold standard, but it is not practical in clinical use. The glomerular filtration rate can be estimated with serum-creatinine-based equations; either the Modification of Diet in renal Disease (MDRD; Levey et al. 1999) or the Cockcroft-Gault (Cockcroft and Gault 1976) formula. These formulas take age, sex and body size into consideration and are therefore more accurate in estimating renal function than serum creatinine alone. Maithel et al. (2006) showed that, independently of dialysis status, estimated GFR, but not serum creatinine, also predicted long-term survival after lower limb revascularization.

2.1.4 Age
As a result of the increasing life expectancy of the population, more octogenarians and even older patients with critical limb ischaemia are being referred to vascular surgery units (Pomposelli et al. 1998, Diehm et al. 2004). Several studies have demonstrated that equal patency and limb salvage rates after infrainguinal bypass can be achieved in octogenarians as in younger patients (Luther and Lepäntalo 1997a and 1997b, Pomposelli et al. 1998, Chang and Stein 2001, Brosi et al. 2007). Doslouglu and co-workers (2009) even reported superior limb salvage rates in octogenarians compared to those of younger patients undergoing infrainguinal bypass. The explanation for this is probably the patient selection, with a smaller proportion of diabetics, active smokers and patients with ESRD in octogenarians. Furthermore, infrainguinal bypass for CLI in patients aged 80 years and older is justified because limb preservation is likely to sustain ambulatory status and independent living (Luther and Lepäntalo 1997b, Pomposelli et al. 1998, Zdanowski et al. 1998). Despite its proven effectiveness, the overall benefit from infrainguinal bypass may, however, be limited in the very elderly because advanced age is associated with increased perioperative and postoperative mortality after vascular operations (Plecha et al. 1985). Perioperative mortality rates in series of octogenarians undergoing infrainguinal bypass is reported to be relatively high, 2%–16% (Scher et al. 1986, O’Mara et al. 1997, Pomposelli et al. 1998, Chang and Stein 2001, Doslouglu et al. 2009). Five-year survival rates for octogenarians with CLI are reported in the literature to range from 25 to 54 percent (Pomposelli et al. 1998, Chang and Stein 2001, Doslouglu et al. 2009),
which is considerably worse than the 77% 5-year survival rate reported in a series of patients of the same age undergoing coronary artery bypass grafting (Nissinen et al. 2010). This again underlines the negative effect of not just age but also the presence of CLI on outcome. Advanced age in combination with advanced CLI seems to predict cardiovascular complications. Conte et al. (2005) presented pooled data from prospective multicentre trials of bypass for CLI (Prevent III, Circulase II and BASIL) and concluded that age >80 years in combination with tissue loss was associated with a 3.1-fold risk of major adverse cardiac events.

### 2.1.5 Smoking

Smoking is one of the major risk factors for CLI (Dormandy et al. 1999). It is associated with an approximately threefold increase in the risk of developing CLI in patients with PAD (Norgren et al. 2007). Tobacco smoking accelerates atherosclerosis in both the peripheral and the coronary arteries (Doll and Peto 1976, Kannel 1981). The mechanism is speculated to be vasospasm, hypoxia or endothelial cell loss (Davies et al. 1985, Cough 1986) and platelet activation (Hawkins 1972). In vitro and animal studies of intimal hyperplasia have demonstrated the potential of tobacco derivatives to stimulate the proliferation of smooth muscle cells (Davies 1985, Higman et al. 1993) and to inhibit the activity of endothelial nitric oxide synthase (Higman et al. 1996), thereby causing focal vein graft stenosis. Furthermore, several clinical series have demonstrated that smoking is associated with vein bypass graft stenosis (Wiseman et al. 1989, Powel et al. 1993, Cooke and Ma 1995, Cheshire et al. 1996). Smoking has been associated with an increased risk of occlusion of femoropopliteal saphenous vein grafts. Wiseman et al. (1989) reported a 1-year patency of 63% for smokers as opposed to the 84% rate for non-smokers. Gentile et al. (1997) reported that of the traditional cardiovascular risk factors, only smoking was associated with early graft flow disturbances. Willigendael et al. (2005) published a meta-analysis including 29 studies (4 randomized clinical trials, 12 prospective studies and 13 retrospective studies) assessing the effect of smoking on vein graft failure. Based on the results of randomized clinical trials and other prospective studies, they concluded that continued smoking after lower limb bypass surgery results in a threefold increased risk of graft failure. According to Bluman and co-workers (1989), current smoking increases the risk of postoperative pulmonary complications nearly sixfold. This risk seems to exist even with no diagnosed chronic pulmonary disease.
2.1.6 Chronic obstructive pulmonary disease

Data concerning the impact of chronic obstructive pulmonary disease (COPD) on the outcome of patients undergoing infrainguinal bypass for CLI is sparse in the literature. Diagnosed chronic lung disease is, however, the most significant patient-related risk factor for postoperative pulmonary complications. The relative risk is reported to range from 3% to 6% (Smetana 1999). McAllister and co-workers (2003) reported that patients with COPD had an up to 300%–700% higher risk of postoperative pulmonary complications than those without COPD. Despite the increased risk of postoperative respiratory complications, there seems to be no prohibitive level of lung function below which surgery would be absolutely contraindicated (Stein 1970, Smetana 1999). Bronchodilators, smoking cessation, antibiotics and/or corticosteroids along with chest physical therapy reduce the risk of pulmonary complications in COPD patients undergoing surgical procedures (Stein 1970, Tarhan 1973). Furthermore, epidural anaesthesia is associated with a reduced risk of pulmonary complications when compared to general anaesthesia in COPD patients (van Lier et al. 2011).

2.1.7 Hypercoaguable states

Hypercoaguable states can be the underlying cause of accelerated peripheral arterial disease (Donaldson 1993) and should be suspected in cases of arterial thrombosis in unexpectedly young patients or without traditional risk factors for PAD. Resistance to activated protein C (factor V Leiden mutation), antithrombin deficiency, protein C and protein S deficiency as well as antiphospholipid antibody syndrome are the most common hypercoaguable states associated with an increased risk of arterial and venous thrombosis (Girolami et al. 1997). Hyperhomocysteinaemia can also be considered a hypercoaguable state. High serum homocysteine levels have been correlated with increased incidence of peripheral vascular disease, coronary artery disease and cerebrovascular disease (Clarke et al. 1991). The prevalence of hypercoaguable states is higher in patients undergoing peripheral vascular procedures. According to Donaldson and colleagues (1990), up to 10% of patients screened at their centre were found to have a serologically proven hypercoaguable state, whereas Ray et al. (1997) reported that as many as 35% of patients undergoing elective bypass surgery for leg ischaemia (CLI 77%) were found to have coaguability abnormalities preoperatively. Coagulation disorders are a risk factor not only for early (Ray et al. 1997) but also late vein graft failure (Curi et al. 2003). Curi et al. (2003) reported in their series of 456 patients undergoing infrainguinal bypass that patients with hypercoaguability were significantly younger and more likely to have undergone prior revascularization attempts. Patients with hypercoaucluable states had poorer
primary patency (28% vs. 35%; p=0.004), assisted primary patency (37% vs. 45%; p=0.0001), secondary patency (41% vs. 53%; p=0.0001), limb salvage (55% vs. 67%; p=0.009) and survival (61% vs. 74%; p=0.02) rates at 5 years. In addition to screened coagulopaties, neoplasia, stress and inflammation can also induce a hypercoaguable state (Monahan and Owens 2009). Another clinically relevant phenomenon is resistance to antiplatelet therapy. Some patients have adverse cardiovascular events despite having dual antiplatelet therapy. Lepäntalo et al. (2009) concluded that concomitant aspirin and clopidogrel treatment failed to suppress platelet activity in 20% of patients.

2.1.8 Degree of ischaemia

There is evidence that not all cases of critical limb ischaemia are similar from the point of view of outcome. The status of the foot in addition to comorbidities is a major determinant of outcome, especially in terms of leg salvage. Sometimes major amputation is required despite a patent bypass graft because of irreversible ischaemic tissue changes and infection (Biancari et al. 2000b, Mätzke et al. 2001). Gangrene seems to be a stronger predictor of not only amputation but also inferior patency than rest pain or ulcer. Nasr et al. (2003) reported different outcomes for different manifestations of CLI in their series of 128 patients with CLI undergoing 152 infrainguinal bypasses. The 5-year primary patency, assisted primary patency and secondary patency rates were 33%, 52% and 51% (p = 0.04); 46%, 70% and 72% (p = 0.01) and 48%, 76% and 75% (p = 0.003) for gangrene, ulceration and rest pain, respectively. The limb salvage rates also differed significantly: the respective 5-year limb salvage rates were 59% for gangrene, 87% for ulceration and 83% for rest pain (p = 0.01). Therefore, the authors concluded that gangrene is a distinct subcategory of critical limb ischaemia with a clearly worse prognosis than ulceration and rest pain.

2.2 Risk assessment

Estimation of the risk of impaired postoperative outcome is of paramount importance in bypass surgery for CLI, as it may guide the clinician in the decision-making process, provide the patients with information on their individual operative risk, allow the planning of resource utilization and enable comparison between different institutions or surgeons. Two specific risk scoring methods have been introduced and validated in literature; the Finnvasc (Biancari et al. 2007) and the Prevent III score (Schantzer at al 2008).

The Finnvasc score was derived from a large national series of 3,925 patients who underwent infrainguinal bypass for CLI and whose data were included in the nationwide Finnvasc registry (Biancari et al. 2007). Diabetes,
coronary artery disease, foot gangrene and urgent operation were independent predictors of 30-day postoperative mortality and/or major lower-limb amputation, and the Finnvasc risk scoring method was therefore developed by assigning 1 point each to these four risk factors (Figure 1).

<table>
<thead>
<tr>
<th>RISK FACTOR</th>
<th>POINTS</th>
</tr>
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<tbody>
<tr>
<td>Diabetes</td>
<td>1</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1</td>
</tr>
<tr>
<td>Foot gangrene</td>
<td>1</td>
</tr>
<tr>
<td>Urgent operation</td>
<td>1</td>
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</table>

Figure 1. Finnvasc score calculation and thirty-day combined mortality or limb loss rates according to different risk scores in the derivation and validation datasets (Biancari et al 2007).

The Prevent III (PIII) risk scoring method was originally derived from a prospective, randomized study on the efficacy of edifoligide in preventing autologous vein graft failure in 1,404 patients who underwent infrainguinal vein bypass surgery for CLI (Schantzer et al 2008). This risk score was validated both internally and externally with three independent cohorts in a total of 3,286 patients with CLI (Shanzer et al. 2009) to predict AFS in CLI patients undergoing infrainguinal bypass. Points for the calculation of original PIII score were assigned to each patient for the presence of dialysis (4 points), tissue loss (3 points), age >75 years (2 points), hematocrit <30% (2 points) and coronary artery disease (1 point). A score was calculated as the total sum of points. According to this score, patients were categorized in the low- (score < 3), medium- (score 4–7), or high-risk (score > 8) category (Figure 2a). A modified version of the PIII score was published a year later by the same authors (Schantzer et al. 2009). In this modified version, baseline hematocrit was not included due to a large proportion of missing values. Points for the calculation of the modified PIII were assigned to each patient for the presence of dialysis...
(4 points), tissue loss (3 points), age >75 years (2 points) and coronary artery disease (1 point). A score was calculated from the total sum of points similarly to the original version, and patients were categorized in the low- (score < 3), medium- (score 4–7), or high-risk (score > 8) category (Figure 2b).

<table>
<thead>
<tr>
<th>RISK FACTOR</th>
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<tbody>
<tr>
<td>Dialysis</td>
<td>4</td>
</tr>
<tr>
<td>Tissue loss</td>
<td>3</td>
</tr>
<tr>
<td>Age &gt;75 years</td>
<td>2</td>
</tr>
<tr>
<td>Hematocrit &lt;30%</td>
<td>2</td>
</tr>
<tr>
<td>CAD</td>
<td>1</td>
</tr>
</tbody>
</table>

**Figure 2a.** The original Prevent III score calculation and one-year amputation-free survival rates according to different risk score categories (Schanzer et al. 2008).

**Figure 2b.** A modified Prevent III score calculation and one-year amputation-free survival rates according to different risk score categories (Schanzer et al. 2009).
2.3 Bypass-related factors

Patient-related factors are major contributors to overall postoperative survival, whereas bypass-related factors mostly determine graft patency and subsequently influence the leg salvage, although graft occlusion does not always lead to limb loss.

2.3.1 Run-off

Run-off status is evidently an important determinant of bypass outcome. A lack of a suitable outflow vessel makes the revascularization impossible. Inadequate outflow is a well-reported predictor of bypass failure (Donaldson et al. 1990, Varty et al. 1993). There are several ways of describing run-off. The run-off score is a scoring method that has been developed to grade outflow according to angiographic findings. This scoring method published by the Ad Hoc Committee in 1986 and revised in 1997 (Rutherford et al. 1986, 1997) gives a run-off 1–10 points, 1 being normal outflow and 10 meaning no outflow at all (blind loop). The predictive value of the run-off score is somewhat controversial. There are studies where this run-off score is a strong predictor of bypass outcome (Albäck et al. 1998, Biancari et al. 1999, Seeger et al. 1999). In contrast, studies by Plecha et al. (1993), Tordoir et al. (1993) and Takolander et al. (1995) found no effect of run-off score on graft patency. The explanation for this discrepancy between studies might be the limited accuracy of the Ad Hoc Committee’s run-off score due to its dependency on the quality of angiography images. All in all, the assessment of angiographic scoring appears subjective, as illustrated by the problems in repeatability in such scoring methods (Kukkonen et al. 2010).

2.3.2 Type of conduit

The type of conduit is a major determinant of bypass outcome (Schanzer et al. 2009). An autologous vein is superior to prosthetic grafts as bypass material for infrainguinal reconstructions due to long-term patency and resistance to infections (Klinkert et al. 2004).

2.3.2.1 Vein grafts

The great saphenous vein

Kunlin performed the first bypass with an autologous saphenous vein in 1949 (Kunlin 1951). A single-segment great saphenous vein (GSV) is the preferred graft for infrainguinal revascularizations in terms of long-term patency and limb salvage (Klinkert et al. 2004, Perreira et al. 2006). Excellent long-term results in a series of 2,058 patients undergoing infrainguinal in situ saphenous vein bypass (Indication was limb salvage in 91% of patients) were reported by
Shah et al. (1995). They reported 1-, 5- and 10-year secondary patency rates of 91%, 81% and 70%, respectively. Leg salvage at one, five and ten years was 97%, 95%, and 90%, respectively. The great saphenous vein is superior to prosthetic material in terms of patency even in an above-knee position (Johnson et al. 2000) and especially in infrapopliteal revascularizations (Bergan 1982, Veith 1986). Klinkert et al. (2004) reviewed 25 articles comparing the patency of femoral to above-knee popliteal saphenous vein against PTFE bypasses. They reported 2- and 5-year primary patency rates of 81% and 69%, respectively, for venous bypasses, and for PTFE bypasses the adjacent rates were 67% and 49%, respectively. When only randomized trials were considered, venous bypasses were again superior to PTFE bypasses at all intervals studied: the 2- and 5-year primary patency rates of venous versus PTFE bypasses were 80% vs. 69% and 74% vs. 39%, respectively. Since both randomized and retrospective studies comparing venous with PTFE bypasses showed that vein grafts were superior PTFE prostheses, the authors concluded that the saphenous vein should be used as graft material whenever it is available and of adequate quality. Therefore, it seems that a single-segment great saphenous vein is the conduit of choice in both supra- and infrapopliteal revascularizations for CLI. Table V summarizes randomised clinical trials comparing saphenous vein bypasses and PTFE bypasses.

**Table V.** Randomised clinical trials comparing vein conduit and PTFE prosthesis in infrainguinal bypasses

<table>
<thead>
<tr>
<th>Author, year (n)</th>
<th>CLI %</th>
<th>PATENCY</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Above-knee fem-pop</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klinkert 2003 (n=151)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GSV</td>
<td>55</td>
<td>-</td>
<td>76%</td>
</tr>
<tr>
<td>PTFE</td>
<td>61</td>
<td>-</td>
<td>52%</td>
</tr>
<tr>
<td>Johnson 2000 (n=752)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vein</td>
<td>69</td>
<td>81%</td>
<td>-</td>
</tr>
<tr>
<td>PTFE</td>
<td></td>
<td>69%</td>
<td>-</td>
</tr>
<tr>
<td>Veith 1986 (n=176)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GSV</td>
<td>100</td>
<td>-</td>
<td>61%</td>
</tr>
<tr>
<td>PTFE</td>
<td></td>
<td>-</td>
<td>38%</td>
</tr>
<tr>
<td>Below-knee fem-pop</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Veith 1986 (n=153)</td>
<td>100</td>
<td>-</td>
<td>76%</td>
</tr>
<tr>
<td>GSV</td>
<td></td>
<td>-</td>
<td>54%</td>
</tr>
<tr>
<td>PTFE</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Infrapopliteal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Veith 1986 (n=204)</td>
<td>100</td>
<td>-</td>
<td>49%</td>
</tr>
<tr>
<td>GSV</td>
<td></td>
<td>-</td>
<td>12%</td>
</tr>
<tr>
<td>PTFE</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

CLI% = proportion of critical limb ischemia patients

GSV = great saphenous vein

PTFE = polytetrafluoroethylene
According to the randomized studies available, there seems to be no difference in patency regardless of whether the saphenous vein is used as a reversed conduit or in situ (Watelet et al. 1986, Wengerter et al. 1991, Harris et al. 1993, Watelet et al. 1997). All four of these studies demonstrated no difference in secondary patency between in situ and reversed saphenous vein bypasses (Table VI).

**Table VI. Patency of reversed versus in situ bypass**

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>n</th>
<th>Bypass type</th>
<th>PATENCY</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reversed</td>
<td>In-situ</td>
<td>p-value</td>
</tr>
<tr>
<td>Watelet (1986)</td>
<td>100</td>
<td>AK/BK popliteal</td>
<td>88%</td>
<td>71%</td>
<td>ns</td>
</tr>
<tr>
<td>Wengerter (1991)</td>
<td>125</td>
<td>infrapopliteal</td>
<td>67%</td>
<td>69%</td>
<td>ns</td>
</tr>
<tr>
<td>Harris (1993)</td>
<td>215</td>
<td>AK/BK popliteal</td>
<td>77%</td>
<td>68%</td>
<td>ns</td>
</tr>
<tr>
<td>Watelet (1997)</td>
<td>91</td>
<td>AK/BK popliteal</td>
<td>70%</td>
<td>65%</td>
<td>ns</td>
</tr>
</tbody>
</table>

**AK=above-knee**  
**BK=below-knee**

Alternative autologous veins

The great saphenous vein is evidently the best conduit for infrainguinal revascularizations due to its superior patency. Unfortunately, a great number of patients who would need a bypass procedure for limb salvage lack the GSV. This may be due to previous coronary artery bypass grafting, lower extremity bypasses or varicose vein surgery. Furthermore, even if not absent, the GSV can be unusable due to a too small calibre, varicosities or postphlebitic vein wall pathology. The usable ipsilateral GSV (IGSV) is reported to be absent in approximately 20%–45% of patients (Taylor et al. 1987, Holzenbein et al. 1996, Chew et al. 2002). In these situations, the contralateral GSV (CGSV) can be used unless the donor limb is also critically ischaemic. If so, or if both the IGSV and CGSV are absent or of poor quality, other autologous conduit options are arm veins (basilic vein or cephalic vein) or the lesser saphenous vein (LSV).

Arm veins

The first bypass using arm veins, specifically the cephalic vein, as a conduit was described by Kakkar in 1969. Subsequently, clinical series over the past 25 years have introduced good long-term results for arm vein bypasses, with patency and leg salvage rates at 3 years ranging from 40% to 73% and 63% to 92%, respectively (Andros et al. 1986, Balshi et al. 1989, Harvard et al. 1992, Sesto et al. 1992, Flamme et al. 1995, Gentile et al. 1996, Tisi et al. 1996, Holzenbein et al. 1996, Faries at al 2000a-c, Chew et al. 2001). Arm veins are relatively easy to harvest, and one advantage of using arm veins as conduit is the avoidance of possible surgical wound problems in donor
limbs and the preservation of the CGSV for subsequent contralateral limb revascularization or CABG. Therefore, some groups (Holzenbein et al. 1996, Faries et al. 2000a, c) have even introduced a policy of using arm veins as the first alternative if the ipsilateral GSV is absent. In contrast, those who favour the use of the contralateral GSV first can defend their policy based on reports where the need for subsequent contralateral limb revascularization is only 20%–23% (Stonebridge et al. 1991, Poletti et al. 1998). The need for subsequent CABG is even lower, 2%–3% within 5 years, as reported by Chew et al. (2002) and Poletti et al. (1998). The basilic vein or at least the cephalic vein is usually long enough for femoral-to-popliteal bypass or for popliteal-to-distal bypass. However, in femorodistal bypasses, splicing is usually required. According to reports by Armstrong et al. (2004), spliced arm vein grafts were the most prone to stenosis development, whereas several other groups (Gentile et al. 1996, Holzenbein et al. 1996, Faries et al. 2000c, Chew et al. 2001) have demonstrated that splicing does not have an effect on the patency. An alternative for splicing in some cases where a longer vein graft is needed might be the use of a cephalic-basilic loop, a technique described by, for instance, Holzenbein and co-workers (1995).

Other autologous veins

The lesser saphenous vein (LSV) is also one graft option in the absence of the GSV. The first reports using the LSV in infrainguinal bypass grafting were published by Shandall et al. (1987) and Weaver et al. (1987). The relative shortness of the LSV, however, limits its usability, but the LSV can be used as a part of spliced vein grafts if the calibre and quality is sufficient. One solution for the shortness of the LSV is to use it in combination with its thigh extension, the vein of Giacomini, as introduced by Delis et al. (2004).

The results of using lesser saphenous vein grafts are sparse in the literature—however, Belkin et al. (1995) published a series of 300 re-operations where 34 grafts predominantly constructed from the LSV were used. The five-year secondary patency and leg salvage rates were both 55% and the authors reported that the results with LSV grafts were equal to those of arm vein bypasses. Chang et al. (1992) achieved a 55% 3-year primary patency rate in a series of 69 LSV infrainguinal bypasses, 73% of which were secondary bypasses.

In the absence of usable superficial veins, the femoral vein can also be used for bypass grafting. Schulman et al. (1986) published a series of 80 femoropopliteal bypasses using the deep veins of the leg as conduits, with rather good results; the 1-, 3- and 5-year patency rates were 89%, 70% and 60%, respectively. The morbidity, such as venous stasis or ulceration, related to deep vein harvesting was very low. Recently, Kaczynski and Gibbons (2011) reported on their series of 20 infrainguinal bypasses using femoral vein as a
conduit. At five years, the primary, assisted primary and secondary patency rates were 36%, 66% and 78% respectively. Five-year limb salvage was 83%. In this series as well, late venous morbidity was only mild or moderate, although temporary leg swelling after femoral vein harvesting was common.

2.3.2.2 Prosthetic grafts
Despite the superior long-term patency and leg salvage rates of vein grafts, the use of a prosthetic graft may be necessary in patients with CLI and with no available autologous vein material. Approximately 20%–45% of patients with critical limb ischaemia lack a suitable saphenous vein. When secondary bypasses are performed, the rate of patients who have no suitable vein material is reported to be as high as 50% (Belkin et al. 1995).

Prosthetic grafts, either expanded polytetrafluoroethylene (ePTFE) or polyester (Dacron), are widely used for infrainguinal bypasses. Clinical series from 25 years ago (Sterpetti et al. 1985, Veith et al. 1986) report excellent patency and leg salvage rates for above-knee femoropopliteal bypasses. In a meta-analysis by Hunink et al. (1994), a 5-year primary patency of 47% for above-knee PTFE bypasses was reported. Expanded polytetrafluoroethylene has been the most popular and widely used prosthetic material; however, several studies ten years ago demonstrated that in above-knee femoropopliteal bypasses, polyester and ePTFE are equal in terms of patency (Robinsson et al. 1999, Green et al. 2000, Post et al. 2000). Furthermore, a more recent randomized study (Jensen et al. 2007) concluded that polyester is at least as good or even better and more durable than ePTFE for above-knee bypasses. A Cochraine review (Mamode and Scott 2000) of nine trials including 1,334 patients reported no difference between ePTFE and Dacron. According to Gupta and co-workers (1991), ring-support does not affect the patency of ePTFE bypasses in the femoro-popliteal (above- or below-knee) position.

Although widely accepted in above-knee bypasses where the outflow is usually rather good, the use of prosthetic material in infrapopliteal bypasses is controversial. Prosthetic material is more thrombogenic than an autologous vein graft, especially in low-flow circumstances, and, mainly due to this aspect, the results of infrapopliteal prosthetic bypasses have been disappointing or only moderate. A meta-analysis of PTFE infrapopliteal bypasses published by Albers et al. (2003) yielded pooled 3-year primary patency, secondary patency and limb salvage rates of 41%, 51% and 66%, respectively. The pooled weighted data for 1-, 3- and 5-year primary patency rates of 70%, 35%, and 25%, respectively, for femorodistal prosthetic bypass are reported in TASC II (Norgren et al. 2007).

Prosthetic grafts tend to occlude especially during the first months after bypass (Devine et al. 2006). This has probably been the most important reason
REVIEW OF THE LITERATURE

for the development of technical improvements, such as heparin coatings and anastomotic modifications (pre-cuffed prostheses). Indeed, heparin coating seems to have improved at least the short-term results of not only femoropopliteal, but also infrapopliteal prosthetic bypasses. In the past five years, one-year primary and secondary patency rates for femoropopliteal bypasses using heparin-bonded prostheses are reported to range from 78% to 84% and from 89% to 96%, respectively. For infrapopliteal bypasses, the corresponding rates are 74%–75% and 85%–100%, respectively (Bosiers et al. 2006, Peeters et al. 2006, Scharn et al. 2008). A recent Scandinavian, randomised multicentre trial showed, that heparin coating was associated with significant graft failure reduction compared to average ePTFE, especially in femoro-popliteal bypasses for CLI, where graft failure reduction was reported to be 50% (Lindtholt et al. 2011).

A vein cuff is suggested to improve prosthetic bypass patency especially at the infrapopliteal position. The Joint Vascular Research Group (JVRG) of the UK has published two series demonstrating the beneficial effect of a vein cuff on patency. The first series reported improved patency and a trend towards better limb salvage in below-knee bypasses (Stonebridge et al. 1997). In the latter randomised controlled trial, Griffiths et al. (2004) reported higher 3-year patency rates for Miller vein cuff vs. non-cuff in below-knee femoro-popliteal bypasses. In contrast, a recent randomised Scandinavian Miller Collar Study (SCAMICOS 2011) failed to demonstrate any influence of a vein cuff on patency or leg salvage in below-the-knee bypasses for CLI. Furthermore, a concomitant AV fistula has been introduced to improve prosthetic bypass patency, but no major additional benefit has been demonstrated (Laurila et al. 2004).

2.3.3 Quality of vein graft
The quality of the vein graft as a determinant of graft patency has been demonstrated in several studies—first decades ago by Szilagyi et al. in 1973 and LoGerfo et al. in 1977 and later by others (Pannetta et al. 1992, Wilson et al. 1996). Saphenous veins are reported to have several pre-existing pathological conditions, such as increased wall thickness, postphlebitic changes and varicosities, which may predispose to graft failure. The incidence of such saphenous vein “disease” and subsequent unsuitability for bypass grafting is reported to be 2%–12% (Panetta et al. 1992). The aetiology of the venous diseases seems to be multifactorial in origin, and, in addition to a gross morphological appearance of vein, there is no clear indicator to identify those veins which should be rejected as grafts (Panetta et al. 1992, Varty et al. 1993). Miller et al. (1990) described the presence of intraluminal webs and bands as signs of incomplete recanalisation after thrombophlebitis in angioscopic
evaluations of vein grafts. Wilson and co-workers (1996) published a series of 52 vein bypasses, 38 of which included angioscopy for the detection of vein abnormalities. The angioscopic findings included intraluminal strands and fibrotic webs, bands, thrombi and haemorrhagic mural plaques. Most of these abnormalities were not detected in preoperative duplex scanning. Similarly, Pannetta and colleagues (1992) reported that duplex failed to identify as many as 38% of the abnormal veins. Davies et al. (1993) histologically studied veins used for bypass and concluded that significant pathological changes, such as intimal thickening and histological evidence of early atheromatous changes in the intima, are seen in long saphenous and cephalic veins which are considered normal. However, the effect of pre-existing intimal thickening alone on later graft stenosis development is controversial, as there are reports questioning the association between pre-existing vein wall thickness and later vein graft stenosis development. Varty et al. (1996) reported no difference in either intimal or medial thickness between stenosed and non-stenosed grafts.

Varicosity is usually considered a contraindication to autologous vein bypass grafting due to increased formation of intimal hyperplasia, the risk of aneurysm formation and even subsequent graft rupture. Varicotic dilatation may involve the entire saphenous vein or just an isolated segment. Cephalic and basilic veins are often thin walled which may predispose them to ectatic dilatation in the long term. Arm vein grafts are especially prone to stenosis development and aneurysm formation (Armstrong et al. 2004). Moreover, Armstrong et al. (2004) reported the incidence of vein graft abnormalities in arm vein bypasses to be as high as 55% and, similarly, Maraccaio et al. (1993) also reported a high incidence of vein graft disease among arm veins.

2.3.4 Size of vein graft
Not only the quality, but also the adequate size of the vein graft is a major determinant of graft patency. Several studies have demonstrated that a small calibre of the vein graft is an independent risk factor for vein graft failure (Towne et al. 1989, Varty et al. 1993, Idu et al. 1999). A small GSV is associated with a twofold risk of early failure (Schanzer et al. 2007). Several factors are suggested as an explanation for the increased risk of failure in vein grafts of less than 3.5 mm. The calibre of the vein may be small because of wall thickness, some other vein wall abnormality or as a result of previous phlebitis. Furthermore, small-calibre veins may be more prone to damage during vein harvest, dilatation and valve lysis (Panetta 1992, Marin 1993). Idu et al. (1999) suggested that a small calibre is a greater risk factor for graft failure than the use of arm or composite vein grafts and that these alternative veins should be preferred if the GSV is less than 3.5 mm in diameter.
Observations from a large multicentre trial suggest that vein graft type and size are major factors affecting the outcome of infrainguinal bypass grafts (Schanzer et al. 2007).

2.3.5 Adjunctive methods for poor-quality vein grafts
Poor-quality vein grafts are prone to stenosis development and subsequent graft occlusion. The application of external support has been proposed to allow the use of suboptimal-quality veins otherwise unacceptable for bypass grafting. External scaffolding is supposed to stabilise the vein, minimise the arterial stress and thus reduce the rate of stenosis development, therefore improving graft patency. Preclinical animal studies employing external support of suboptimal-quality vein bypasses have shown a less pronounced neointima formation, with subsequently improved long-term patency rates compared to unsupported grafts (Bambang et al. 1997, Dashwood et al. 2002, Vijayan et al. 2002, Jeremy et al. 2004). The use of external polyester reinforcement of a vein graft was first introduced in clinical use by Parsonet and Shah (1963). Later, several small clinical series (Bednarkiwicz et al. 1998, Souyry et al. 1999, Moritz et al. 1992 and 1993) have reported the use of both polytetrafluoroethylene (PTFE) and polyester prosthetic reinforcement of varicose vein grafts, with acceptable results. Melliere et al. (1995) published a small series of patients with critical limb ischaemia undergoing bypass, where dilated segments of greater saphenous veins were wrapped in short segments of PTFE prosthesis or polyester mesh. Neufang et al. (2003) reported over 80% 1-year secondary patency rates for infrainguinal bypasses using varicotic vein grafts reinforced with PTFE. According to a more recent report by Melliere and colleagues (2007), patency rates using varicotic vein grafts with prosthetic reinforcement were higher than those achieved using prosthetic grafts.

2.3.6 Vein graft failure
The pattern of infrainguinal vein graft failure has remained largely similar since the report by Darling and Linton (1972) nearly three decades ago. Vein graft failure can be divided into three phases, depending on the timing of failure: early (<30 days), intermediate (30 days–2 years) and late (>2 years). Early failures are usually due to technical mistakes, such as poorly constructed anastomosis, insufficient inflow or outflow, retained venous valves, or a poor-quality vein. Any of these reasons can reduce graft flow below the thrombotic threshold velocity, with subsequent graft occlusion. In addition to flow, the other elements of the Virchow triad—endothelial damage and hypercoaguable states—may cause early vein graft failure (Monahan and Owens 2009).
Intermediate vein graft failure is due to intimal hyperplasia. Carrel and Guthrie (1906) described this phenomenon more than a hundred years ago. As a response to the arterialization of the vein graft and surgical trauma, vascular smooth muscle cells (SMSs) migrate from the media to the intima and switch phenotype to a more proliferative form (Cox et al. 1991, Davies and Hagen 1995), which leads to a production of excessive amounts of extracellular matrix and subsequent intimal hyperplasia. All vein grafts probably undergo some degree of intimal hyperplasia. However, it remains partly unclear why some vein grafts are affected more than others (Landry et al. 2002). Twenty to twenty-five percent of infrainguinal vein grafts develop significant stenosis during the first postoperative year due to intimal hyperplasia (Szilagyi et al. 1973, Sladen et al. 1981, Whittemore et al. 1981, Grigg et al. 1988, Wilson et al. 1996). These stenoses are usually asymptomatic and, if not corrected, may limit the graft flow and lead to subsequent graft thrombosis (Idu et al. 1999).

Late vein graft failure (after 2 years) is commonly attributed to dyslipidaemia and the progression of atherosclerosis, compromising either inflow or outflow vessels. The progression of atherosclerosis can also directly affect the vein graft itself, as described in regard to saphenous grafts in coronary artery bypass grafting (Motwani and Topol 1989) and in lower extremity bypass grafting (DeWeese and Rob 1977, Reifsnyder et al. 1993).

According to Monahan and Owens (2009), patient-related risk factors predisposing to vein graft stenosis development are different from traditional cardiovascular risk factors (Table VII). The early presentation of atherosclerosis is considered as a somewhat different, more virulent form than that which occurs in older patients (Aronson 1989, Harris et al. 1996, Levy 1996). Young age can thus be considered a risk factor for vein graft failure. Elevated C-reactive protein (CRP) seems to be a risk factor for vein graft failure. Hispanics and African Americans have elevated levels of CRP, which might explain why they have an increased risk of vein graft failure. Moreover, Monahan and Owens (2009) speculated that many of the other observed risk factors, such as a redo operation and CLI as an indication, can also be considered as increased inflammatory states. This might explain the finding that statin use seems to reduce graft stenosis development (Porter and Turner 2002). Smoking is not only a risk factor for atherosclerosis, but, it also has adverse effect on graft patency due to endothelial dysfunction and impaired nitric-oxide-mediated vasodilatation (Higman et al. 1993, 1996).
Table VII. Patient-related risk factors for vein graft failure (Monahan and Owens 2009).

<table>
<thead>
<tr>
<th>EARLY FAILURE</th>
<th>INTERMEDIATE FAILURE</th>
<th>LATE FAILURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>young age</td>
<td>young age</td>
<td>dyslipidaemia</td>
</tr>
<tr>
<td>hypercoaguable state</td>
<td>hypercoaguable state</td>
<td></td>
</tr>
<tr>
<td>African American ethnicity</td>
<td>redo bypass</td>
<td></td>
</tr>
<tr>
<td>CLI as indication</td>
<td>smoking</td>
<td></td>
</tr>
<tr>
<td>smoking</td>
<td>African American or Hispanic ethnicity</td>
<td></td>
</tr>
<tr>
<td>inflammation</td>
<td>inflammation</td>
<td></td>
</tr>
</tbody>
</table>

2.3.7 Vein graft surveillance

Despite surveillance, 10%–20% of vein grafts within the first year and up to 25% within 3 years after bypass will fail (Idu et al. 1988 and 1992, Bandyk et al. 1989, Bergamini et al. 1995, Lundell et al. 1995). As the graft salvage after occlusion is poor, with 2-year patency rates as low as 19%–31% (Seabrook et al. 1991, Hye et al. 1994, Nackman et al. 1997, Robinsson et al. 1997), the identification and revision of significant stenoses prior to graft occlusion is crucial. There is data suggesting that grafts can fail with no warning signs, and the positive predictive value of the ankle-brachial index (ABI) alone in detecting a failing graft is only 12%–34% (Bandyk 1990). Stenoses can be easily detected with ultrasonography, which is, however, time-consuming and expensive. The efficacy and cost-effectiveness of intensive vein graft duplex surveillance is still controversial to some extent. It has been estimated that to be cost-effective, a surveillance programme should improve limb salvage rate by approximately 5% (Chesire and Wolfe 1993). The latest TASC consensus document suggests routine surveillance of vein grafts but does not recommend duplex scanning (Norgren et al. 2007). There are few randomised controlled trials assessing the efficacy of duplex surveillance. Lundel et al. (1995) studied both vein graft and prosthetic bypasses and reported a better identification of failing vein grafts by intensive duplex surveillance, which led to significantly better assisted primary and secondary patency rates when compared to clinical surveillance. However, leg salvage rates did not differ between the groups. Ihlberg et al. (1998), on the other hand, failed to demonstrate any difference in assisted primary patency, secondary patency or limb salvage rates between the duplex and clinical surveillance groups in their series of 185 consecutive vein grafts. In a large multicentre trial published by Davies et al. (2005), 594 patients were randomised to either clinical (n= 290) or duplex (n=304) surveillance. More graft stenoses were detected in the clinical surveillance group, but primary, assisted primary or secondary patency rates did not differ between the groups.

Tinder et al. (2008) assessed the characteristics of graft failure to find those
grafts that would most benefit from intensive duplex surveillance. They found that warfarin therapy, a non-single-segment saphenous vein conduit and redo bypass were predictive for stenosis development. There is also data suggesting that risk grafts, such as arm vein grafts prone to stenosis development, benefit significantly from duplex surveillance. Armstrong et al. (2004) reported that duplex surveillance revealed graft stenosis in almost half of the study population, which resulted in a 48% graft revision rate. An excellent 3-year assisted primary patency rate of 91% was achieved due to efficient duplex surveillance and early correction of detected stenoses.

According to the literature, there is no clear evidence to date supporting duplex surveillance of prosthetic grafts (Lundel et al. 1995, Hobollah et al. 1997). The mechanism of failure of prosthetic grafts is believed to be anastomotic stenosis and subsequent low graft flow. These anastomotic stenoses would be easily detected with duplex, but evidence of its cost-effectiveness is lacking. According to Brumberg et al. (2007), early duplex scanning of infrapopliteal prosthetic grafts might, however, be reasonable—not for detecting stenoses but for identifying low-flow grafts predisposing to thrombosis, thereby selecting patients for anticoagulation.
AIMS OF THE PRESENT STUDY

The purpose of this study was to assess the results and outcome of infrainguinal bypasses for critical limb ischaemia, especially in high-risk patients or in cases of non-optimal vein grafts. The primary aim was to evaluate those patient- and graft-related factors that negatively affect the outcome and thereby to find patients whose benefit from infrainguinal bypass is remarkably limited. This knowledge could be useful in clinical decision-making, treatment modality and patient selection as well as resource allocation. The specific aims were to assess:

1. The effect of renal insufficiency on outcome and to evaluate the usefulness of estimated glomerular filtration rate (eGFR) in predicting poor outcome after infrainguinal bypass (I)

2. The effect of age on outcome and the results of surgical versus endovascular revascularization in patients ≥ 80 years of age with critical limb ischaemia (II)

3. The usefulness and accuracy of specific risk scoring methods (III)

4. Predictors of extremely dismal survival to aid in determining when not to perform bypass (I–IV)

5. The results of alternative autologous vein graft bypasses, the risk factors for graft failure and the rate of graft revision procedures (IV)

6. The outcome of high-risk patients undergoing infrainguinal bypass with a risk graft (IV)

7. The results of arm vein conduits in comparison to prosthetic grafts when an optimal vein graft is not available (V)

8. The feasibility of external polyester mesh scaffolding of compromised quality vein grafts (VI)
MATERIAL AND METHODS

All retrospective studies (I–V) were approved by the Institutional Review Board of Helsinki University Central Hospital (HUCH). For a prospective, multicentre feasibility trial (VI), the approval of the Ethics Committee was obtained.

1 PATIENTS AND STUDY DESIGNS

**Study I** is a retrospective single-centre cohort study of 603 consecutive patients who underwent infrainguinal bypass for critical limb ischaemia between 2002 and 2005 at Helsinki University Central Hospital (HUCH). The purpose was to evaluate the effect of renal insufficiency on outcome and to compare serum creatinine and estimated glomerular filtration rate as predictors of outcome. The main outcome endpoint was amputation-free survival.

**Study II** is a retrospective single-centre cohort study of 584 patients aged at least 80 years who underwent infrainguinal endovascular (n=277) or surgical (n=307) revascularization for critical limb ischaemia between 2000 and 2007. The purpose was to compare the results of PTA and bypass in octogenarians with CLI. Ninety-five propensity-score-matched pairs were created to minimize the effect of confounding factors. Classification and regression tree analysis were performed to further verify the effect of treatment modality on outcome. The main outcome endpoints were one-year survival, leg salvage and amputation-free survival.

**Study III** is a retrospective cohort study from a single centre, and it includes 1,425 patients with CLI who underwent infrainguinal surgical (47.6%) or endovascular (52.4%) revascularization between 2000 and 2007 at HUCH. The aim was to evaluate the Finnvase score and Prevent III score as predictors of outcome. In order to assess the accuracy of these scoring methods in predicting intermediate outcome, they were tested by the receiver operating characteristic (ROC) curve. The main outcome end points were leg salvage, overall survival and amputation-free survival.

**Study IV** is a retrospective cohort study from a single centre. All infrainguinal, autologous vein bypasses for CLI between 2000 and 2007 (n=1109) at HUCH were included. The aim was to assess and to compare the outcome of bypasses with different types of vein grafts and to assess risk factors for vein graft stenosis and vein graft failure. The outcome endpoints of interest were primary, assisted primary and secondary patency. Subgroup analysis of high-risk patients with a risk graft was performed.

**Study V** is a retrospective cohort study. A total of 290 consecutive infrainguinal bypasses for CLI using an arm vein conduit (n=130) or prosthetic
graft (n = 160) between January 2000 and December 2006 in a single centre (HUCH) were analysed. The outcomes of arm vein grafts and prosthetic grafts were compared in terms of primary, assisted primary and secondary patency. Leg salvage was also assessed.

Study VI is a prospective, multicentre observational feasibility study of 50 patients. The patient inclusion period was from May 2005 to March 2008. The participating centres were:
1. Helsinki University Central Hospital, Finland (20 patients)
2. Johannes Gutenberg University Hospital Mainz, Germany (13 patients)
3. J.W.Goethe University Hospital, Frankfurt, Germany (12 patients)
4. Municipal Hospital Muehldorf, Germany (three patients)
5. Verbundkrankenhaus Bernkastel/Wittlich, Wittlich, Germany (one patient)
6. Kath. Kliniken Essen-Nord, Essen, Germany (one patient)

The aim of this study was to evaluate the feasibility of external polyester scaffolding in infrainguinal bypass grafting when the available vein material is suboptimal due to varicosity or dilatation. The primary objectives were short-term primary patency, assisted primary patency and secondary patency. Secondary objectives were to assess the rate of graft stenoses, infections and possible other adverse effects related to the use of external scaffolding.

Demographic data of all patients included in all the studies is presented in Table VIII. The flow chart for patients in Studies I–V is shown in Figure 3.
Table VIII. Demographic data of patients in studies I–VI.

<table>
<thead>
<tr>
<th>Demographics</th>
<th>STUDY I</th>
<th>STUDY II</th>
<th>STUDY III</th>
<th>STUDY IV</th>
<th>STUDY V</th>
<th>STUDY VI</th>
</tr>
</thead>
<tbody>
<tr>
<td>number of patients</td>
<td>603</td>
<td>277</td>
<td>1425</td>
<td>1109</td>
<td>290</td>
<td>50</td>
</tr>
<tr>
<td>age (years)</td>
<td>73 (65-80)*</td>
<td>86 (±4.0)**</td>
<td>85 (±3.7)**</td>
<td>73 (±11.7)</td>
<td>74 (36-107)*</td>
<td>74 (41-95)*</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73 m²)</td>
<td>67 (46-89)*</td>
<td>58 (±21)**</td>
<td>62 (±23)**</td>
<td>66 (±34)**</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>SCr (µmol/l)</td>
<td>86 (86-117)*</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>87 (29-1161)*</td>
<td>n.a.</td>
</tr>
<tr>
<td>follow-up time (months)</td>
<td>5 (0-46)*</td>
<td>24 (0-49)*</td>
<td>24 (0-49)*</td>
<td>29 (0-95)*</td>
<td>37 (0-121)*</td>
<td>35 (0-118)*</td>
</tr>
<tr>
<td>female sex</td>
<td>330 (55%)</td>
<td>77 (28%)</td>
<td>99 (32%)</td>
<td>707 (49%)</td>
<td>643 (58%)</td>
<td>122 (42%)</td>
</tr>
<tr>
<td>CAD</td>
<td>359 (63%)</td>
<td>196 (71%)</td>
<td>227 (74%)</td>
<td>909 (64%)</td>
<td>691 (62%)</td>
<td>691 (62%)</td>
</tr>
<tr>
<td>diabetes</td>
<td>276 (47%)</td>
<td>143 (52%)</td>
<td>114 (37%)</td>
<td>819 (58%)</td>
<td>548 (49%)</td>
<td>113 (39%)</td>
</tr>
<tr>
<td>hypertension</td>
<td>397 (68%)</td>
<td>212 (77%)</td>
<td>236 (77%)</td>
<td>1077 (76%)</td>
<td>785 (71%)</td>
<td>218 (75%)</td>
</tr>
<tr>
<td>hyperlipidaemia</td>
<td>229 (48%)</td>
<td>75 (27%)</td>
<td>85 (27%)</td>
<td>584 (41%)</td>
<td>440 (40%)</td>
<td>126 (44%)</td>
</tr>
<tr>
<td>COPD</td>
<td>111 (19%)</td>
<td>n.a.</td>
<td>215 (15%)</td>
<td>152 (14%)</td>
<td>51 (18%)</td>
<td>n.a.</td>
</tr>
<tr>
<td>CVD</td>
<td>116 (20%)</td>
<td>61 (22%)</td>
<td>40 (13%)</td>
<td>277 (20%)</td>
<td>199 (18%)</td>
<td>44 (15%)</td>
</tr>
<tr>
<td>current smoking</td>
<td>173 (30%)</td>
<td>19 (7%)</td>
<td>20 (7%)</td>
<td>n.a.</td>
<td>302 (27%)</td>
<td>74 (26%)</td>
</tr>
<tr>
<td>CLI % (FIII/FIV)%</td>
<td>100 (40/60)</td>
<td>100 (17/83)</td>
<td>100 (29/71)</td>
<td>100 (21/79)</td>
<td>100 (32/68)</td>
<td>100 (41/59)</td>
</tr>
</tbody>
</table>

*median (range), **mean (±SD)
CAD=coronary artery disease
COPD=chronic obstructive pulmonary disease
CVD=cerebrovascular disease
CLI%=proportion of critical limb ischemia patients
FIII=Fontaine class II (ischaemic rest pain)
FIV=Fontaine class IV (ulcer/gangrene)
n.a.=not available/not assessed

Figure 3. Flow chart of the study populations (studies I–V)
2 INVESTIGATIONAL PRODUCT (VI)
The polyester mesh tube (ProVena®, B. Braun Aesculap, Germany) is manufactured from multifilament polyester yarn (polyethylene terephthalate). It is supplied in various diameters and lengths. ProVena® is a porous prosthesis with a honeycomb-like structure, and it is designed for the intra-operative external scaffolding of autologous veins of non-optimal quality due to varicosities or ectatic dilatation.

3 METHODS

3.1 Data collection and validation
All the retrospective studies (I–V) are registry-based studies. Data were collected prospectively into our institutional database of surgical and endovascular revascularizations (Husvasc) and scrutinized retrospectively. The registry includes patient demographics, comorbid conditions, indications for surgery, specific operative details, complications and outcome at discharge. Follow-up data includes graft patency and dates of any graft revisions or graft occlusion as well as the dates of major amputation or death. Registry data of all patients included in the study were cross-checked against patient records, and any missing data in the registry was retrieved from the patient’s records and completed in registry. The dates of death were retrieved from the Finnish national population registry, Statistics Finland. Data on late amputations have been completed retrospectively from the files of the National Institute for Health and Welfare.

For the prospective, multicentre pilot study (VI), clinical data were collected at the time of patient enrolment, at the time of the procedure, at discharge and at planned follow-up visits. Data were collected using patient record forms. Data from all six participating centres from two countries were combined and analysed.

3.2 Estimation of renal function (I, II, III)
Serum creatinine levels were measured using the IDMS (isotope dilution-mass spectrometry) traceable enzymatic assay (Roche Diagnostics, Basel, Switzerland). Glomerular filtration rate was estimated using the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation for creatinine results traceable to an IDMS method: eGFR (mL/min/1.73 m²) =175 x (Scr/88.4)^1.154 x (Age)^0.203 x 0.742 (if female) x 1.210 (if African American) (SI units) (Peake and Whiting 2006, Levey et al. 2005 and 2006). Chronic kidney disease (CKD) is divided into five stages according to The National
Kidney Foundation – Kidney Disease Outcomes Quality Initiative (NKF KDOQI) guidelines. Stages 1 and 2 as well as stages 4 and 5 were summed up to establish three categories (Table IX).

Table IX. Staging of renal insufficiency according to the National Kidney Foundation – Kidney Disease Outcomes Quality Initiative (NKF KDOQI) guidelines and our modification.

<table>
<thead>
<tr>
<th>Stage</th>
<th>eGFR</th>
<th>Description (NKF KDOQI)</th>
<th>Our modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>90</td>
<td>Normal renal function</td>
<td>&gt; 60 no or mild insufficiency</td>
</tr>
<tr>
<td>2</td>
<td>60–89</td>
<td>Mild renal insufficiency</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>30–59</td>
<td>Moderate renal insufficiency</td>
<td>30–60 moderate renal insufficiency</td>
</tr>
<tr>
<td>4</td>
<td>15–29</td>
<td>Severe renal insufficiency</td>
<td>&lt; 30 severe renal insufficiency or renal failure</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15</td>
<td>End-stage renal disease (uraemia)</td>
<td></td>
</tr>
</tbody>
</table>

3.3 Risk score assessment (III)

As Biancari et al. (2007) demonstrated, diabetes, coronary artery disease, foot gangrene and urgent operation were independent predictors of 30-day postoperative mortality and/or major lower-limb amputation. Therefore, the Finnvasc scoring method was developed by assigning 1 point each to these four risk factors.

In a modified version of the PIII score, published by Schantzer et al. (2009), points were assigned to the presence of dialysis (4 points), tissue loss (3 points), age >75 years (2 points) and coronary artery disease (1 point). The sum total of points was converted to a score which places the patient in the low- (score < 3), medium- (score 4–7) or high-risk (score> 8) category. We did not have the information of the number of patients on dialysis—therefore, for the calculation of the modified PIII score, dialysis was categorized as CKD class 5 (eGFR <15ml/min/1.73m2) because it appropriately includes patients with the most severe degree of renal failure (Levey et al. 2003).

3.4 Revascularization procedure

The suitability of inflow and outflow vessels for bypass was evaluated by means of magnetic resonance angiography (MRA), conventional digital subtraction angiography (DSA) or computed tomography angiography (CTA). In Studies II–III, the angiograms were evaluated retrospectively and the runoff score was calculated using the grading scheme proposed by Rutherford and co-workers (1997).

The size and quality of usable vein material was preoperatively mapped
with ultrasonography. Autologous vein grafts were used whenever possible. The best available vein graft to treat the immediate problem was preferred. Therefore, in the absence of the ipsilateral great saphenous vein (IGSV), the contralateral great saphenous vein (CGSV) was the preferred conduit unless the donor limb was ischaemic. Arm veins or the lesser saphenous vein were used if a usable GSV was absent. The operating surgeon decided whether the vein graft was to be used in a reversed or non-reversed position. If a spliced vein graft was needed, vein segments were employed in a reversed or non-reversed position to minimize size mismatch of vein-to-vein anastomoses and artery-to-vein anastomoses. The vein-to-vein anastomoses were sutured with 7-0 interrupted sutures.

A prosthetic graft, either expanded polytetrafluoroethylene (ePTFE) or polyester (Dacron) was applied if usable autologous veins were completely unavailable. In prosthetic bypasses to infrapopliteal arteries an adjunctive vein cuff, either Miller cuff (Miller 1984; Figure 4.) or St. Mary’s boot (Tyrrel and Wolfe 1991; Figure 4.) was used, except in cases where precuffed ePTFE prosthesis was used.

Figure 4. An illustration of distal anastomosis of prosthetic bypass without vein cuff (above), with Miller cuff (middle) and with St. Mary’s boot (below).
In Study VI, polyester mesh (Provena®) was used as external support for vein grafts. Prior to suturing the anastomoses, an appropriate length of polyester mesh tube was drawn over the vein graft with a special instrument. Fibrin glue was used to fix the mesh to the outer layer of the vein graft to facilitate anastomosis suturing if the mesh tube was extended to cover the anastomoses.

Studies II and III also include endovascular revascularizations for CLI. They were performed mostly by interventional radiologists. The technique was mainly intraluminal, and subintimal angioplasty was used only in a minority of cases. Drug-eluding balloons were not applied, and stents were not used routinely but were employed selectively for long occlusion or in cases of target lesion dissection.

Transit time flow measurement was used to ensure adequate graft flow (mL/min) perioperatively. The measurements were performed with a transit time flowmeter (CardioMed CM4006; Medistim A/S, Oslo, Norway), which is based on an ultrasonic pulsed-beam technique. The idea is to measure volume flow within the conduit. A precalibrated probe of the correct size to fit the vein graft is placed around the conduit to measure the flow. In the case of compromised graft flow, intraoperative duplex scanning was performed to exclude vein wall abnormalities and technical defects in anastomoses. Angioscopy or intraoperative angiography was used only selectively. The threshold criteria for duplex or angiography were the following: for femoropopliteal grafts, rest flow <150 mL/min; for crural bypasses, rest flow <50 mL/min or maximum flow capacity (flow after injection of 40 mg papaverine) <110 mL/min; and for pedal reconstructions, maximum flow capacity <45 mL/min.

Intraoperative heparin was administered to all patients according to weight, and the adequacy of heparinization was controlled using activated clotting time (ACT) assessment. At the end of the procedure, if needed, prothamine sulphate was administered to antagonize the heparin. All patients received weight-adjusted doses of low-molecular-weight heparin (LMWH) twice a day postoperatively until discharge and ASA 100 mg per day indefinitely if there were no contraindications. Some patients received clopidogrel instead of aspirin (aspirin allergy, previous coronary balloon angioplasty, etc.). Warfarin was used only if there was a clear indication (atrial fibrillation, trombofilia, etc.) for it.

3.5 Follow-up
In all studies, the follow-up protocol was similar. The follow-up visits were carried out routinely at 1, 6 and 12 months postoperatively and thereafter annually. The evaluation protocol included the inspection of limb status, pulse palpation and the measurement of ankle-brachial indices (ABI) and
MATERIAL AND METHODS

toe pressures (TP). For vein grafts, duplex scanning of the entire graft, anastomoses as well as inflow and outflow arteries was performed. If duplex scanning revealed significant focal stenosis (peak systolic velocity ratio [Vr] ≥3, peak systolic velocity [PSV] over 300 cm/s or overall graft velocity <45 cm/s in a normal-calibre graft), angiography was performed. The patency of a prosthetic graft was ensured by ABI and TP measurements and Doppler auscultation. The graft was considered patent if ABI remained improved (>0.15) in comparison to the preoperative value and the Doppler flow signal from at least two points over the graft was audible. The duplex scanning of prosthetic bypass was performed only if the patency was uncertain.

The clinical follow-up after endovascular procedures was similar, but duplex scanning or DSA was performed only if foot status was worsening or there was otherwise a suspicion of target lesion re-stenosis or occlusion.

3.6 Definition of outcome endpoints
In all studies (I–VI), the terms survival, leg salvage and amputation-free survival as well as the criteria for patency and the definitions of primary, assisted primary and secondary patency are as recommended by the revised Ad Hoc Committee on Reporting Standards, SVS/NA-ISCVS (Rutherford et al. 1997).

3.7 Statistical methods
Statistical analyses were performed using SPSS for Windows, versions 13.0 (I), 15.0 (II-III), 16.0 (VI), 17.0 (V) and 19.0 (IV) (SPSS Inc., Chicago, IL, USA).

Comparisons between the SCr and eGFR groups were made using the Kruskal-Wallis test for continuous variables and Chi-squared test for categorical variables (I). In Studies II–V, Pearson’s Chi-square test and Fisher’s exact test (if n<5) were used for analyses of categorical data; non-parametric variables were analysed with the Mann-Whitney test.

Patency rates (IV–VI), leg salvage (I–V), survival (I–IV) and amputation-free survival (I–IV) were estimated using the Kaplan-Meier method, and comparisons between curves were performed with the aid of the Mantel-Cox log rank test.

Crude and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) of mortality, limb loss and amputation and/or death were calculated for both eGFR and creatinine using Cox regression analysis (I).

The propensity score (the risk of a patient to be included in either the PTA or the bypass group) was calculated by means of logistic regression. Variables with a p value of less than 0.2 in univariate analysis were included.
in the regression model. Hosmer-Lemenshow’s test was used to assess the regression model fit. Receiver operating characteristics (ROC) curve analysis was applied to estimate the area under the curve of the model, predicting the probability of being included in the PTA or bypass group. Areas under the curve (AUC) were calculated with 95% CIs. Propensity score was used for one-to-one matching as well as to adjust for other variables in estimating their impact on the postoperative outcome on multivariable analysis. Classification and regression tree (CART) analysis was employed to identify independent risk factors for 1-year AFS and to even further verify the impact of treatment method on outcome (II).

The ROC curve analysis was used to estimate the predictive value of the Finnvasc and PIII risk scoring methods in predicting 30-day and 1-year amputation-free survival. Cox regression analysis was applied to adjust these risk scores for the anatomic level of revascularization and type (endovascular vs. bypass) of revascularization (III).

A p value of <0.05 was considered statistically significant.
RESULTS

1 RENAL INSUFFICIENCY AS AN INDEPENDENT PREDICTOR OF POOR AMPUTATION-FREE SURVIVAL (I)

If estimated GFR was used, 40% of the study population was found to have some degree of renal insufficiency. When the upper level of normal serum creatinine level alone was used as a criterion, only 23% of patients had impaired renal function.

Severe renal insufficiency (eGFR<30 or SCr >200) was an independent predictor of poor survival, leg salvage and amputation-free survival. Moderate renal insufficiency was also associated with an approximately 2-fold risk of death, amputation or amputation/death (Table X).

Table X. Adjusted hazard ratios (HR) with corresponding 95% CIs of impaired survival, leg salvage and amputation-free survival in different eGFR and SCr categories.

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR 30–60</td>
<td>1.87 (1.22–2.87)</td>
<td>0.004</td>
</tr>
<tr>
<td>eGFR &lt;30</td>
<td>4.05 (2.22–7.39)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Scr 120–200</td>
<td>2.18 (1.33–3.59)</td>
<td>0.002</td>
</tr>
<tr>
<td>Scr &gt;200</td>
<td>3.53 (1.82–6.84)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Leg salvage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR 30–60</td>
<td>1.61 (0.78–3.35)</td>
<td>0.199</td>
</tr>
<tr>
<td>eGFR &lt;30</td>
<td>6.51 (2.71–15.59)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Scr 120–200</td>
<td>2.27 (1.01–5.13)</td>
<td>0.048</td>
</tr>
<tr>
<td>Scr &gt;200</td>
<td>6.20 (2.47–15.56)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Amputation-free survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR 30–60</td>
<td>1.66 (1.12–2.47)</td>
<td>0.012</td>
</tr>
<tr>
<td>eGFR &lt;30</td>
<td>3.99 (2.40–6.63)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Scr 120–200</td>
<td>1.82 (1.16–2.85)</td>
<td>0.010</td>
</tr>
<tr>
<td>Scr &gt;200</td>
<td>3.56 (2.03–6.25)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*HRs are relative to the baseline renal groups of eGFR >60 or SCr < 120

Kaplan-Meier estimates of amputation-free survival showed that according to eGFR, both severe and moderate renal insufficiency were associated with decreased AFS when compared to normal eGFR (Figure 5a). According to SCr, only severe renal insufficiency indicates poor outcome, whereas moderate renal insufficiency does not differ in comparison to normal kidney function. (Figure 5b)
Figure 5a. One-year amputation-free survival for eGFR >60, eGFR 30-60 and eGFR <30 was 73.2%, 54.7% and 38.7%, respectively.

Figure 5b. One-year AFS for Scr <120, Scr 120–200 and >200 was 69.8%, 46.2% and 42.2%, respectively.
RESULTS

2 OUTCOME OF OCTOGENARIANS WITH CLI UNDERGOING INFRAINGUINAL REvascularization (II)

The life-expectancy of octogenarians with CLI is short (median 2.5 years). Five-year survival in the overall series was 36%.

Cox regression analysis showed that advanced age (RR 1.05 95% CI 1.02–1.08), decreased eGFR (RR 0.99, 95% CI 0.99–1.00), diabetes (RR 1.30, 95% CI 1.08–1.62), coronary artery disease (RR 1.36, 95% CI 1.05–1.75) and bypass surgery (RR 1.55, 95% CI 1.24–1.93) were associated with decreased amputation-free survival.

In the overall series, PTA achieved a significantly better early and late outcome than bypass surgery among octogenarians with CLI (Table XI).

Furthermore, in the 95 propensity-score-matched pairs of patients who underwent either PTA or bypass, leg salvage and amputation-free survival were significantly better in those who underwent PTA (Table XII).

Classification and regression tree analysis further suggested that PTA was associated with better 1-year AFS than bypass surgery, especially in patients with CAD (63.8% vs. 48.9% p=0.008).

Table XI. Kaplan-Meier’s estimates of early and late outcome in octogenarians (overall series)

<table>
<thead>
<tr>
<th></th>
<th>30-day</th>
<th>1-year</th>
<th>2-year</th>
<th>3-year</th>
<th>4-year</th>
<th>5-year</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SURVIVAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTA</td>
<td>94.9%</td>
<td>66.7%</td>
<td>57.7%</td>
<td>50.4%</td>
<td>42.3%</td>
<td>39.9%</td>
<td>0.014</td>
</tr>
<tr>
<td>Bypass</td>
<td>90.5%</td>
<td>64.8%</td>
<td>52.3%</td>
<td>40.4%</td>
<td>36.0%</td>
<td>31.5%</td>
<td></td>
</tr>
<tr>
<td><strong>LS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.039</td>
</tr>
<tr>
<td>PTA</td>
<td>97.4%</td>
<td>88.8%</td>
<td>85.4%</td>
<td>82.6%</td>
<td>80.2%</td>
<td>78.3%</td>
<td></td>
</tr>
<tr>
<td>Bypass</td>
<td>95.0%</td>
<td>79.3%</td>
<td>78.7%</td>
<td>75.4%</td>
<td>73.3%</td>
<td>73.7%</td>
<td></td>
</tr>
<tr>
<td><strong>AFS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.005</td>
</tr>
<tr>
<td>PTA</td>
<td>93.1%</td>
<td>62.4%</td>
<td>53.0%</td>
<td>44.3%</td>
<td>35.3%</td>
<td>32.9%</td>
<td></td>
</tr>
<tr>
<td>Bypass</td>
<td>86.9%</td>
<td>55.2%</td>
<td>44.9%</td>
<td>33.2%</td>
<td>29.2%</td>
<td>26.1%</td>
<td></td>
</tr>
</tbody>
</table>

PTA = percutaneous transluminal angioplasty, LS = leg salvage, AFS = amputation-free survival

Table XII. Kaplan-Meier’s estimates of early and late outcome in octogenarians (95 propensity-matched pairs)

<table>
<thead>
<tr>
<th></th>
<th>30-day</th>
<th>1-year</th>
<th>2-year</th>
<th>3-year</th>
<th>4-year</th>
<th>5-year</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SURVIVAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTA</td>
<td>94.7%</td>
<td>67.5%</td>
<td>57.5%</td>
<td>53.3%</td>
<td>46.4%</td>
<td>42.8%</td>
<td>0.210</td>
</tr>
<tr>
<td>Bypass</td>
<td>91.5%</td>
<td>62.2%</td>
<td>53.5%</td>
<td>48.7%</td>
<td>40.4%</td>
<td>40.4%</td>
<td></td>
</tr>
<tr>
<td><strong>LS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.010</td>
</tr>
<tr>
<td>PTA</td>
<td>98.9%</td>
<td>92.1%</td>
<td>87.8%</td>
<td>87.8%</td>
<td>83.4%</td>
<td>83.4%</td>
<td></td>
</tr>
<tr>
<td>Bypass</td>
<td>92.5%</td>
<td>76.9%</td>
<td>74.6%</td>
<td>70.7%</td>
<td>62.4%</td>
<td>62.4%</td>
<td></td>
</tr>
<tr>
<td><strong>AFS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.033</td>
</tr>
<tr>
<td>PTA</td>
<td>93.6%</td>
<td>63.0%</td>
<td>53.1%</td>
<td>49.1%</td>
<td>40.2%</td>
<td>40.2%</td>
<td></td>
</tr>
<tr>
<td>Bypass</td>
<td>86.2%</td>
<td>52.1%</td>
<td>45.1%</td>
<td>37.3%</td>
<td>27.6%</td>
<td>26.1%</td>
<td></td>
</tr>
</tbody>
</table>

PTA = percutaneous transluminal angioplasty, LS = leg salvage, AFS = amputation-free survival
3 ACCURACY OF THE FINNVASC SCORE AND MODIFIED PREVENT III SCORE AS PREDICTORS OF OUTCOME (III)

In the overall series, the accuracy of the Finnvasc and mPIII scoring methods in predicting early (30-day) and late (1-year) amputation-free survival (AFS) was rather good. The Finnvasc score also seems to be accurate in predicting 30-day amputation (Table XIII). Both risk scoring methods also predicted 1-year AFS when isolated endovascular and isolated surgical procedures were analysed separately (Table XIV).

Kaplan-Meier estimates for amputation-free survival also show that the higher the risk score, the worse the outcome (Figures 6a and b).

Cox regression analysis showed that when adjusted for anatomic level and type of revascularization, the Finnvasc score and mPIII score were independent predictors of leg salvage, survival and amputation-free survival (Table XV).

Table XIII. Areas under the ROC curve with corresponding 95% CIs for different outcome endpoints for the Finnvasc and mPIII score. All procedures are included.

<table>
<thead>
<tr>
<th></th>
<th>FINNVASC SCORE</th>
<th>mPIII SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day amputation</td>
<td>0.609 (95% CI 0.549–0.677; p =0.003)</td>
<td>0.533 (95% CI 0.457–0.609; p =0.37)</td>
</tr>
<tr>
<td>30-day AFS</td>
<td>0.622 (95% CI 0.573–0.671; p &lt; 0.0001)</td>
<td>0.588 (95% CI 0.533–0.642; p =0.001)</td>
</tr>
<tr>
<td>1-year AFS</td>
<td>0.630 (95% CI 0.597–0.663; p &lt; 0.0001)</td>
<td>0.634 (95% CI 0.600–0.667; p &lt; 0.0001)</td>
</tr>
</tbody>
</table>

AFS=amputation-free survival

Table XIV. Areas under the ROC curve with corresponding 95% CIs for 1-year AFS for the Finnvasc and mPIII score. Endovascular and surgical procedures are analysed separately.

<table>
<thead>
<tr>
<th></th>
<th>FINNVASC SCORE</th>
<th>mPIII SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-year AFS: PTA</td>
<td>0.627 (95% CI 0.584–0.671; p &lt;0.0001)</td>
<td>0.595 (95% CI 0.550–0.640; p &lt;0.0001)</td>
</tr>
<tr>
<td>1-year AFS: bypass</td>
<td>0.658 (95% CI 0.612–0.704; p &lt;0.0001)</td>
<td>0.677 (95% CI 0.629–0.725; p &lt;0.0001)</td>
</tr>
</tbody>
</table>

AFS=amputation-free survival, PTA= percutaneous transluminal angioplasty

Table XV. Adjusted Risk ratios (RRs) with corresponding 95% confidence intervals (CIs) of the Finnvasc and mPIII score for different outcome endpoints.

<table>
<thead>
<tr>
<th></th>
<th>FINNVASC SCORE</th>
<th>mPIII SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS</td>
<td>RR 1.322 (95% CI 1.122–1.558; p= 0.001)</td>
<td>RR 1.160 (95% CI 1.080–1.247, p &lt; 0.0001)</td>
</tr>
<tr>
<td>SURVIVAL</td>
<td>RR 1.483 (95% CI 1.344–1.636; p &lt;0.0001)</td>
<td>RR 1.241 (95% CI 1.189–1.295; p &lt; 0.0001)</td>
</tr>
<tr>
<td>AFS</td>
<td>RR 1.422 (95% CI 1.319–1.534; p &lt;0.0001)</td>
<td>RR 1.219 (95% CI 1.170–1.270; p &lt; 0.0001)</td>
</tr>
</tbody>
</table>

LS=leg salvage, AFS= amputation-free survival
RESULTS

Figure 6a. Kaplan-Meier estimates for amputation-free survival according to different Finnvasc risk scores.

Figure 6b. Kaplan-Meier estimates for amputation-free survival according to different modified PIII risk score categories.
4 RESULTS OF ALTERNATIVE AUTOLOGOUS VEIN GRAFT BYPASSES (IV)

Primary patency, assisted primary patency and secondary patency at 1 and 3 years were significantly better in the single-segment GSV graft group than the alternative autologous vein graft group: 74.4% and 67.1% vs. 53.7% and 42.0% (p<0.0001), 82.4% and 78.1% vs. 67.2% and 57.8% (p<0.0001), and 84.8% and 80.7% vs. 69.9% and 61.4% (p<0.0001), respectively. Similarly, leg salvage at 1 and 3 years was better in the single-segment GSV group: 88.9% and 87.0% vs. 83.0% and 77.2% (p<0.0001), respectively. The patency, survival and leg salvage rates of the different graft types is presented in Table XVI.

Table XVI. Kaplan–Meier estimates of patency rates and leg salvage with corresponding Standard errors (SEs) for different vein graft types. Numbers in parentheses indicate the number of patients at risk.

<table>
<thead>
<tr>
<th>GSV</th>
<th>PP</th>
<th>APP</th>
<th>SP</th>
<th>LS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-year</td>
<td>74.4 ± 1.6 (471)</td>
<td>82.4± 1.4 (508)</td>
<td>84.8± 1.3 (521)</td>
<td>88.9± 1.1 (600)</td>
</tr>
<tr>
<td>3-year</td>
<td>67.1 ± 1.8 (279)</td>
<td>78.1 ± 1.6 (279)</td>
<td>80.7 ± 1.6 (287)</td>
<td>87.0 ± 1.3 (397)</td>
</tr>
<tr>
<td>LSV</td>
<td>1-year</td>
<td>53.3 ± 17.3 (4)</td>
<td>77.8 ± 13.9 (6)</td>
<td>77.8 ± 13.9 (6)</td>
</tr>
<tr>
<td></td>
<td>3-year</td>
<td>53.3 ± 17.3 (2)</td>
<td>77.8 ± 13.9 (2)</td>
<td>77.8 ± 13.9 (2)</td>
</tr>
<tr>
<td></td>
<td>p&gt;0.001</td>
<td>p&gt;0.001</td>
<td>p&gt;0.001</td>
<td>p=0.008</td>
</tr>
<tr>
<td>arm vein</td>
<td>1-year</td>
<td>62.1 ± 7.7 (24)</td>
<td>74.7 ± 6.9 (29)</td>
<td>74.7 ± 6.9 (29)</td>
</tr>
<tr>
<td></td>
<td>3-year</td>
<td>43.2 ± 8.2 (12)</td>
<td>55.4 ± 8.6 (15)</td>
<td>58.5 ± 8.4 (16)</td>
</tr>
<tr>
<td></td>
<td>p&gt;0.001</td>
<td>p&gt;0.001</td>
<td>p&gt;0.001</td>
<td>p=0.008</td>
</tr>
<tr>
<td>spliced vein</td>
<td>1-year</td>
<td>51.8 ± 3.2 (82)</td>
<td>64.8 ± 3.4 (108)</td>
<td>68.1 ± 3.3 (109)</td>
</tr>
<tr>
<td></td>
<td>3-year</td>
<td>40.9 ± 3.8 (44)</td>
<td>56.9 ± 3.7 (54)</td>
<td>60.7 ± 3.7 (69)</td>
</tr>
<tr>
<td></td>
<td>p&gt;0.001</td>
<td>p&gt;0.001</td>
<td>p&gt;0.001</td>
<td>p=0.008</td>
</tr>
</tbody>
</table>

p-values: compared to the single-segment GSV conduit (Mantel–Cox log rank test)
GSV = great saphenous vein, LSV = lesser saphenous vein
PP= primary patency, APP= assisted primary patency, SP= secondary patency, LS=leg salvage

The revision rate of non-single-segment GSV conduits was higher than that of single-segment GSV grafts (18% vs. 12%, p= 0.007; Table XVII). In multivariate analysis, non-single-segment GSV graft was the only independent risk factor for graft stenosis development (RR 2.62, 95% CI 1.56–4.38, p<0.0001), graft occlusion (RR 2.27, 95% CI 1.52–3.40, p<0.0001) and graft failure (stenosis or occlusion; RR 2.00, 95% CI 1.39–2.88, p<0.0001).
Table XVII. Rates and types of revision procedures in different graft types.

<table>
<thead>
<tr>
<th>REVISION TYPE</th>
<th>GSV</th>
<th>LSV</th>
<th>Arm vein</th>
<th>Spliced vein</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=818)</td>
<td>(n=10)</td>
<td>(n=42)</td>
<td>(n=239)</td>
<td>(n=1109)</td>
</tr>
<tr>
<td><strong>Endovascular</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTA for graft stenosis</td>
<td>65</td>
<td>0</td>
<td>4</td>
<td>23</td>
<td>92</td>
</tr>
<tr>
<td>inflow PTA</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>outflow PTA</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td><strong>Surgical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>distal extension</td>
<td>8</td>
<td>2</td>
<td>2</td>
<td>9</td>
<td>21</td>
</tr>
<tr>
<td>patch angioplasty</td>
<td>9</td>
<td>0</td>
<td>1</td>
<td>9</td>
<td>19</td>
</tr>
<tr>
<td>interposition</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>98 (12%)</td>
<td>2 (20%)</td>
<td>7 (17%)</td>
<td>43 (18%)</td>
<td>150 (14%)</td>
</tr>
</tbody>
</table>

PTA = percutaneous transluminal angioplasty, GSV = great saphenous vein, LSV = lesser saphenous vein
5 PREDICTORS OF DISMAL OUTCOME AFTER INFRAINGUINAL BYPASS FOR CLI (I–IV)

1. One-year survival and amputation-free survival in patients with eGFR<30 were only 45.7% and 38.7%, respectively (I).
2. Octogenarians undergoing infrainguinal bypass for CLI have poor long-term survival (at 5 years 31.5%) (II).
3. Of octogenarians with CAD and diabetes undergoing infrainguinal bypass for CLI, only 42% are alive with the leg intact at 1 year (II).
4. Patients with a Finnvasc score of 4 or an mPIII score of 8–10 achieved an only <40% 1-year AFS (III).
5. High-risk patients (age >80, coronary artery disease, eGFR<30) who underwent bypass with an arm vein or spliced vein conduit had extremely poor 1-year survival compared to average-risk patients: 28.6% vs. 76.6% (p=0.024), respectively (Figure 7) (IV).

Figure 7. Survival estimates for high-risk vs. average-risk patients when an arm or spliced vein is used.
6 ARM VEIN CONDUITS VERSUS PROSTHETIC GRAFTS IN INFRAINGUINAL REVASCULARIZATIONS FOR CLI (V)

When the patency calculations for the whole study population were performed, primary patency at 3 years did not differ statistically significantly between arm vein grafts and prosthetic grafts. However, assisted primary patency and secondary patency at 3 years were clearly better in the arm vein group (Table XIV). In the overall series, the use of a prosthetic graft was a significant risk factor for graft occlusion (OR 1.76, 95% CI 1.05–2.90; \(p = 0.031\)).

In a subgroup analysis of infrapopliteal bypasses, primary patency, assisted primary patency and secondary patency rates at 3 years were significantly better in the arm vein group (Table XVIII and Figure 7.a-c). The use of a prosthetic graft for infrapopliteal revascularization was a significant risk factor for graft occlusion (OR 2.95, 95% CI 1.41–6.20; \(p = 0.004\)). At three years, leg salvage was significantly better in the arm vein than the prosthetic bypass group (Table XIV).

Splicing did not affect patency. One year primary, assisted primary, and secondary patency rates for single-piece, two-piece and three- or four-piece arm vein grafts were 61.3%, 49.9%, and 46.3% (\(p = 0.108\)), 74.4%, 76.7% and 67.1% (\(p = 0.759\)) and 74.7%, 78.2%, and 67.1% (\(p = 0.734\)), respectively.

Table XVIII. Outcome of arm vein versus prosthetic bypasses.

<table>
<thead>
<tr>
<th></th>
<th>ALL (n=290)</th>
<th>FEMOROPOPLITEAL (n=145)</th>
<th>INFRAPOPLITEAL (n=145)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arm vein (n=130)</td>
<td>Prosthesis (n=160)</td>
<td>Arm vein (n=27)</td>
</tr>
<tr>
<td>PP 1-year</td>
<td>55.5%</td>
<td>59.2%</td>
<td>70.3%*</td>
</tr>
<tr>
<td>pp</td>
<td>0.762</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PP 3-year</td>
<td>31.4%</td>
<td>30.3%</td>
<td>43.4%*</td>
</tr>
<tr>
<td>p</td>
<td>0.524</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APP 1-year</td>
<td>75.4%</td>
<td>63.7%</td>
<td>84.0%</td>
</tr>
<tr>
<td>p</td>
<td>0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APP 3-year</td>
<td>58.1%</td>
<td>34.8%</td>
<td>63.0%*</td>
</tr>
<tr>
<td>p</td>
<td>0.128</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SP 1-year</td>
<td>76.0%</td>
<td>66.5%</td>
<td>84.0%</td>
</tr>
<tr>
<td>p</td>
<td>0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SP 3-year</td>
<td>58.6%</td>
<td>38.1%</td>
<td>63.0%*</td>
</tr>
<tr>
<td>p</td>
<td>0.200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS 1-year</td>
<td>85.4%</td>
<td>86.8%</td>
<td>95.7%</td>
</tr>
<tr>
<td>p</td>
<td>0.631</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS 3-year</td>
<td>77.2%</td>
<td>79.7%</td>
<td>84.7%</td>
</tr>
<tr>
<td>p</td>
<td>0.953</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* standard error > 10%

PP= primary patency, APP= assisted primary patency, SP= secondary patency, LS= leg salvage
Figure 7a-c. In infrapopliteal bypasses a) primary patency (p=0.031), b) assisted primary patency (p=0.000) and c) secondary patency (p=0.000) rates were significantly better in the arm vein than the prosthetic bypass group.
7 FEASIBILITY OF EXTERNAL POLYESTER SCAFFOLDING FOR COMPROMISED-QUALITY VEIN GRAFTS (VI)

The primary, assisted primary and secondary patencies with standard errors (SEs) at 6 months were 82.3% (SE ± 6.2%), 88.6% (SE ±4.8%) and 92.1% (SE ±4.4%), respectively (Figure 8). In a subgroup of patients with critical limb ischaemia, survival and limb salvage at 1 year were 88.2% (SE±6.4%) and 90.0% (SE ±6.7%), respectively.

![Figure 8. Primary, assisted primary and secondary patency rates of polyester-scaffolded bypasses](image)

A total of six graft stenoses were detected under duplex surveillance. The only immediate failure occurred on the third postoperative day and was treated by thrombectomy and patch angioplasty of distal anastomosis. There were four graft occlusions at 2, 4, 5 and 9 months postoperatively, only one of them leading to limb loss. This patient was operated on for critical limb ischaemia. In addition to this, another major amputation was performed due to persistent gangrene despite patent bypass 6 months after revascularization. There were no severe infections related to the polyester mesh tube.
DISCUSSION

1 LIMITATIONS OF THE STUDY

Study I: The Modification of Diet in Renal Disease formula has been developed and validated for populations with chronic kidney disease. It may not be as accurate in patients with no known kidney disease. The estimated GFR seems to underestimate actual renal function in patients with normal kidneys. It may also overestimate renal function in underweight patients.

Study II: Despite the propensity score assessment, there were several potential confounding factors. Data on preoperative ABI or toe pressures were not available for all patients, so it is unclear whether the severity of ischaemia was similar in both groups. Differences in the length of the treated arterial segments may have occurred, as lesion length was not assessable. Data on functional status was lacking due to the retrospective study setting.

Study III: We did not have the data on dialysis status, a risk factor included in the modified PIII risk score. Therefore, we assigned 4 points to class V of the CKD classification.

Study IV: This is a retrospective study, and the number of patients in the subgroups of different vein graft materials, especially in the LSV group, is rather small; therefore, there is a possibility of type two statistical errors.

Study V: This is a retrospective analysis, and the number of patients is relatively small. One shortcoming of this study is the difference in surveillance programmes for vein and prosthetic grafts. Moreover, there might be some conduit selection bias, as both arm veins and prostheses were alternatives in the femoropopliteal region, but in infrapopliteal bypasses, the arm vein was selected whenever not absent.

Study VI: The limitations of this feasibility study are the lack of a control group, a rather short follow-up time and the heterogeneity of the study population due to some differences in the indications for polyester mesh use between the participating centres.

2 GENERAL DISCUSSION

2.1 Treatment options for CLI and future prospects

As the population ages, increasingly elderly patients with CLI are referred to vascular surgeons (Conte et al. 2001, Diehm et al. 2004). The increasing number of endovascular revascularizations for CLI (Kudo et al. 2004 ) probably directs the patients with the most advanced PAD and a need for the most complex revascularizations to vascular surgeons (Norgren et al. 2010). Indeed, there is evidence suggesting that the technical complexity of infrainguinal
revascularizations has increased compared to the past decades, as is reflected by a greater incidence of gangrene as an indication, an increased need for alternative conduits and a more distal outflow (Conte et al. 2001). Furthermore, the demographics of patients undergoing infrainguinal revascularizations are reported to have changed. In addition to higher age and a greater proportion of females, the incidence of comorbidities—diabetes, renal failure and previous CABG—is reported to have increased (Conte et al. 2001). Vascular surgeons are therefore faced with the mounting challenges of treating older, more morbid patients with the most advanced forms of CLI. A new challenge for vascular surgeons will be the fast increase in the number of ischaemic and neuroischaemic ulcerated diabetic feet, in which the healing potential is decreased by infection, microvascular dysfunction and other manifestations of neuropathy (Boulton et al. 2004). The number of these patients will amplify the need for revascularizations, especially in the infrapopliteal region, to a large extent.

In recent years, there has been continuous discussion concerning the best revascularization method. Those favouring the endovascular approach refer to studies where superior early outcome and lower short-term costs are clearly pointed out (Singh 1996, Adam et al. 2005). These advantages are mainly due to a lower cardiovascular complication rate and shorter hospital stay associated with angioplasty (Nasr 2002, Faglia 2005). In addition to these reasons, the rapidly evolving endovascular techniques along with device improvement have led to a widespread utilization of the endovascular-first approach (Nasr et al. 2002, Salas et al. 2004, Faglia et al. 2005 Brosi et al. 2007). Admittedly, a limitation of the endovascular approach is the inferior durability and subsequent need for repeated interventions (Norgren et al. 2010). Due to re-operations, however, the survival advantage (Brosi et al. 2007) and cost-effectiveness (Adam et al. 2005) of angioplasty may diminish in the long term.

The great improvements in the endovascular means for revascularization underline the importance of the selection of the right patients for the right treatment modalities, as bypass surgery is no longer the only available option. Despite advanced endovascular techniques, bypass surgery is and probably will remain the treatment of choice for complex, multi-level PAD (Norgren et al. 2007 and 2010). Moreover, the opponents of infrainguinal bypass usually defend their preference by referring to the better durability and subsequent improved freedom from re-operations (Adam et al. 2005, Norgren et al. 2007). Indeed, this was also confirmed in our Study II, which suggests that patients undergoing bypass had better freedom from further bypasses. However, acceptable leg salvage rates can be achieved with both endovascular and surgical revascularization. The selection between these treatment modalities should be based on patient characteristics (Schanzer et al. 2009, Varu et al. 2010) and not on lesion characteristics, as is the case in the TASC classification (Norgren et
The most important issue is not which treatment modality is best, but which patients gain the most benefit from angioplasty and who are best treated with bypass surgery.

The older the patients treated, the more important is the selection of the right treatment modality. According to Plecha et al. (1985), advanced age is associated with increased postoperative mortality after vascular surgery. In Study II, bypass and angioplasty in CLI patients aged 80 years or older were compared. Angioplasty achieved a better outcome in terms of survival, leg salvage and amputation-free survival. A notable finding was that the overall life-expectancy of octogenarians with CLI was short. Hence, the results of Study II can be considered similar to those of the Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial (Adam et al. 2005): patients with a short life expectancy achieve better AFS if treated by endovascular intervention. Death is a more common endpoint than amputation in very elderly patients, which may diminish the influence of treatment modality on leg salvage. Furthermore, it seems that it is the higher mortality rate after bypass surgery that mostly contributes to the significantly better overall outcome of patients treated with angioplasty first. In our Study II, perioperative mortality was also much greater after bypass surgery than angioplasty. The early survival difference favouring endovascular treatment has been reported by others as well (Chang 2001, Salas et al. 2004, Brosi et al. 2007, Doslougly et al. 2009). In contrast to these findings, a Swedish population-based study (Zdanowski et al. 1998) of patients aged 76 years and older reported equal perioperative mortality rates of six percent for both endovascular and bypass interventions. This probably reflects the severe cardiovascular co-morbidity of these very elderly patients as the major determinant of outcome, rather than the treatment modality alone.

New treatment options and improvements in present strategies for CLI is a great challenge because a significant proportion of patients may not be eligible for revascularization, and medical management at the moment is suboptimal. Not only the rapidly evolving endovascular field and device improvements, but also the enhanced possibilities of hybrid vascular procedures and the continuous improvement in vascular graft technology should be taken into consideration in the decision-making. Optimal, best medical treatment will probably improve the outcome of both patient and bypass graft. The Prevent III (Schanzer et al. 2008) study demonstrated that statin use was associated with better one-year survival after revascularization for CLI. There is also increasing evidence that statins are beneficial in the reduction of graft stenoses as well (Carter et al. 2007).

great interest. Both gene- and cell-based new therapies in CLI seem promising in some patients, but larger randomised trials are needed to prove the efficacy and safety of these therapies.

2.2 High-risk patient
Renal insufficiency, especially end-stage renal disease, is one of the most documented independent predictor of poor outcome after bypass surgery for CLI (Naidu et al. 2003, Go et al. 2004). Similarly, severe renal insufficiency was a marker of dismal prognosis in Study I. However, the effect of moderate renal insufficiency on the outcome of CLI patients is less well documented in the literature. Study I demonstrated that not only severe renal insufficiency but also moderate renal impairment is a predictor of impaired outcome. Although renal insufficiency is a strong independent predictor of dismal outcome, other co-existing morbidities further worsen the outcome, as demonstrated by Biancari et al. (2000b, 2002).

Coronary artery disease (Dawson et al. 1993, Farkouh et al. 1994) and diabetes (Taylor et al. 1990, Karacagil et al. 1995, Da Silva 1996, Luther and Lepäntalo 1997a, Wölfe et al. 2003) are also well-documented risk factors that affect the outcome of CLI patients. These factors were not analysed separately in the present study. However, Study II demonstrated in octogenarians with CLI undergoing infrainguinal bypass that coronary artery disease and diabetes further increased the risk of impaired amputation-free survival. End-stage renal disease seems to be the only risk factor that per se is a marker of dismal prognosis. When outcome is considered, the impact of risk factors seems to be more or less cumulative, as was well demonstrated in Study III: the higher the score, the poorer the outcome.

2.3 Outcome assessment
Estimation of the risk of adverse postoperative outcome is of utmost importance in patients with CLI, as the outcome of these patients is rather poor with and without revascularization procedures (Adam et al. 2005, Lepäntalo and Mätzke 1996). Hence, several studies during last decades have assessed the outcome of lower extremity revascularization procedures and reported a number of risk factors associated with poor outcome. The identification of high-risk patients by specific risk scores might allow more critical decision-making, patient selection and a better allocation of resources towards those patients who are more likely to benefit from revascularization. Providing the ideal risk scoring method is difficult, as the outcome of revascularizations is multi-factorial. In addition to the traditional patient- and bypass-related factors discussed in this thesis, other aspects such as referral pathway, a multidisciplinary approach
(Rith-Najarian et al. 1998) and the activity of the revascularization policy (Eskelinen et al. 2003, 2004) have a definite impact on outcome. Furthermore, functional status seems to be a major contributor to outcome, particularly in elderly patients. There is data suggesting that declining functional status in patients aged 80 years is associated with poorer survival, leg salvage and AFS (Taylor et al. 2005). Goodney et al. (2009) studied the ability to predict preoperatively which patient would be ambulatory at 1 year after bypass and concluded that advanced age, preoperative non-ambulatory status, dependent living status, CLI as indication, graft thrombosis and amputation were predictors of amputation and non-ambulatory status. Moreover, dependent status combined with age of at least 80 years was associated with an 87-fold increase in perioperative death in a recent study by Crawford et al. (2010).

The inclusion of all possible risk factors into a risk scoring method would result in a complicated score not useful in clinical practice. Both risk scoring methods evaluated in Study III, the Finnvasc and the mPIII score, are easy to use but still rather accurate. This study also demonstrated that although these scoring methods were originally derived from a series of CLI patients undergoing bypass, they seem to be usable in the risk assessment of patients undergoing endovascular revascularization as well.

The most important benefit of these scoring methods might be their ability to aid in identifying the patients in whom extremely poor outcome estimates would suggest that any revascularization is contraindicated and a conservative approach being more appropriate. The results of Study III demonstrate that a Finnvasc score of 4 and modified PIII score of ≥ 8 are associated with remarkably low 1-year amputation-free survival. However, the number of these patients with the highest risk was very small (4%–6%).

2.4 High-risk graft

The superiority of the single-segment great saphenous graft in terms of long-term patency and leg salvage is indisputable. Unfortunately, optimal graft material is not always available. Several studies have introduced characteristics of risk grafts: non-single-segment saphenous vein graft (Londrey et al. 1994, Alexander et al. 2002, Schazer et al. 2007, Tinder et al. 2008), small-calibre vein graft (Idu et al. 1999, Towne 1991 Varty et al. 1993, Wengerter et al. 1991) and poor-quality vein graft (Pannetta et al. 1992, Wilson et al. 1996) are all associated with lower patency rates. Tinder et al. (2004) reported that redo bypass was also a risk factor for graft stenosis development. Similarly, in the present study (Study IV), a non-single segment great saphenous vein was a predictor of graft failure. Although clearly inferior to a single-segment GSV, several studies prefer arm veins over prosthetic grafts (Calligaro et al. 1997, Faries et al. 2000a, b). Similarly, in Study V, arm veins, even
when spliced, were superior to prosthetic grafts especially in infrapopliteal bypasses. Furthermore, Study IV suggests that arm veins are prone to stenosis development and require duplex surveillance and revision procedures to maintain patency. A similar finding was published by Armstrong et al. (2004). Arm veins are thin-walled and usually have a large diameter especially at proximal portions, which might predispose them to ectatic dilatation and stenosis development. Indeed, Armstrong et al. (2004) detected both stenoses and aneurysmal lesions in arm vein grafts. Most of the stenoses developed within one year, but aneurysms developed later, suggesting that arm vein bypasses benefit even from lifelong duplex surveillance. Moreover, arm vein bypass is usually the last possible autologous bypass, which should be taken into consideration in surveillance activity and risk factor management. Study VI suggests that external scaffolding might be useful in arm veins and in spliced vein grafts with segments of different sizes, although a larger randomised study and longer follow-up will be needed to prove the effect on the incidence of vein graft stenosis and graft patency.

2.5 High-risk bypass
The complexity of infrainguinal bypasses largely depends on several factors. Compromised inflow or outflow, scar tissue due to previous bypass procedures, obesity and a lack of optimal graft material, among other things, make revascularization procedures more challenging. Simple prosthetic femoropopliteal bypass with good run-off is a completely different operation than a redo bypass with a spliced vein graft. Bypasses using alternative autologous veins are complex because they are often redo-procedures (Belkin et al. 1995). Furthermore, harvesting sometimes several vein segments and suturing vein-to-vein anastomosis when creating a spliced vein graft is time-consuming. It also predisposes the patient to some degree of hypothermia, and perioperative bleeding might also be more profuse. Moreover, arm vein harvesting usually necessitates general anaesthesia. Therefore, secondary bypasses and the use of alternative autologous vein grafts can be considered high-risk bypasses. The duration and complication risk of these operations might be reduced by having at least two surgeons (one harvesting the vein, one preparing anastomosis sites), using preoperative vein marking and harvesting arm veins in local tumescent anaesthesia.

2.6 Decision-making
The outcome expectations for CLI treatment are not similar for all patients. For relatively fit patients, ulcer healing, pain relief and subsequently sustained or improved ambulatory status may be the main goal, whereas for high-risk
patients limb preservation and prolonged survival may be a reasonable result. The outcome of bypass is largely multifactorial, with varying predominating factors, depending on the specific outcome of interest. Graft patency and subsequent limb salvage are largely determined by the characteristics of the graft (graft type and size) and arterial anatomy (run-off). In contrast, patient survival is more affected by comorbidities and medication (Schanzer 2009). With modern infrainguinal bypass techniques, patency and leg salvage rates are good and durable even in suboptimal circumstances. Patient co-morbidities largely determine the overall outcome and should therefore be prioritised in the decision-making because a patent bypass is meaningless unless both life and limb are preserved. Considering the high-risk nature of CLI per se as well as the increasing variety of treatment options, outcome estimation with risk assessment is of paramount importance. For low-risk patients with multilevel PAD not amenable to endovascular revascularization, it is reasonable to perform infrainguinal bypass even in complex circumstances (i.e., redo-operation with arm or spliced vein graft). In contrast, for high-risk patients, such high-risk bypasses should be avoided and other options such as an endovascular approach, even in the presence of technical challenges, should be attempted. If endovascular revascularization is not feasible, a prosthetic bypass under local or regional anaesthesia might be considered. In elderly high-risk patients, compromises in patency and revascularization durability may be justified, as the life expectancy is short. For non-ambulatory, dependent, high-risk patients with limb-threatening ischaemia, primary amputation for decreasing mortality might be the most appropriate option. The findings of Studies I–VI, with respect to data from the literature, suggest that either the patient’s overall condition, the quality of the graft or outflow should be good. If all these factors are suboptimal, the outcome expectations are extremely poor. Moreover, high-risk patients (presence of CAD, low eGFR and age >80 years) who underwent bypass with an arm or spliced vein graft had extremely poor perioperative and 1-year survival, suggesting that patients with the highest operative risk should not be exposed to high-risk procedures.

In the future, the need of vascular surgery will increase significantly as the elderly and diabetic population increases, which emphasises the importance of focusing on those patients that will gain benefit from infrainguinal bypass. Therefore, in conclusion, the individual risk of the patient, ambulatory status, outcome expectations, the risk of bypass procedure as well as technical factors such as the suitability of outflow anatomy and the available vein material should all be assessed and taken into consideration when deciding on the best revascularization strategy.
CONCLUSIONS

In summary, the findings of Studies I–IV suggest that either the patient’s overall condition or the quality of the graft should be acceptable. If both patient and graft are considered risky, the outcome expectations are extremely poor. The specific conclusions were:

1. Renal insufficiency—not only renal failure but also moderate impairment in renal function—seems to be a significant risk factor for both limb loss and death after infrainguinal bypass in patients with critical limb ischaemia. Low estimated GFR (<30 ml/min/1.73 m²) is a strong independent marker of poor prognosis. Estimated GFR is a more accurate predictor of survival and leg salvage after infrainguinal bypass in CLI patients than serum creatinine alone. Therefore, GFR estimation should be used instead of creatinine level alone in the risk evaluation of patients undergoing infrainguinal revascularization for critical limb ischaemia (I).

2. The overall outcome of octogenarians with critical limb ischaemia undergoing infrainguinal revascularization is poor. Endovascular treatment seems to be associated with a better outcome than bypass in terms of survival, leg salvage and amputation-free survival in this fragile patient group and should therefore be considered as the first option, especially in the presence of coronary artery disease (II).

3. The Finnvasc and modified Prevent III risk scoring methods both predict the long-term outcome of patients undergoing both surgical and endovascular infrainguinal revascularization for CLI. The Finnvasc score seems to be more accurate in predicting immediate postoperative outcome. Both risk scoring methods are rather easy to use and might be helpful in clinical practice as an aid in preoperative patient selection and decision-making (III).

4. Low estimated eGFR alone, and especially in combination with advanced age and CAD, is a marker of dismal survival and AFS. A Finnvasc score of 4 and mPIII score of >8 are predictors of particularly poor AFS (I–V).

5. A single-segment great saphenous vein graft is superior to any other autologous vein graft in terms of mid-term patency and leg salvage. It requires significantly fewer maintenance procedures than alternative autologous vein grafts. A non-single segment GSV graft is an independent predictor of both graft stenosis development and graft failure. However, due to active duplex surveillance and graft maintenance procedures, acceptable patency and leg salvage rates can also be achieved with alternative autologous vein grafts (IV).
6. Patients with the combination of high operative risk due to severe comorbidities and risk graft have extremely poor survival, suggesting that only relatively fit patients should undergo complex bypasses with risk grafts (IV).

7. Arm vein conduits, even when spliced, are superior to prosthetic grafts for infrapopliteal bypasses in patients with CLI. Arm veins are often the last-resource autologous veins for bypass, and they are prone to focal stenoses, indicating that the surveillance and maintenance of these “high-risk grafts” is important (V). The patency rates of prosthetic bypasses on infrapopliteal arteries are only moderate, but the acceptable limb salvage rates justify prosthetic infrapopliteal bypasses as a last means of limb salvage. This applies especially to high-risk patients with a short life expectancy who do not tolerate long, complex procedures with arm or spliced vein grafts (IV, V).

8. In the prospective, multicentre study on 50 patients, polyester mesh seemed to be a safe and feasible adjunct to infrainguinal bypass using suboptimal autologous vein grafts. However, larger prospective, randomised series and longer follow-up will be required to prove its safety and benefit with respect to the incidence of vein graft stenosis and graft patency. External scaffolding may, however, enable the use of vein grafts of compromised quality otherwise unsuitable for bypass grafting (VI).
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