Outcomes of invasive treatment in Chronic Limb-Threatening Ischaemia

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Cover illustration: Limestone plinth with the feet of a colossal statue, Cyprus, 6th century BC. Open access from the Metropolitan Museum of art.

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Kanske det går
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Pippi Långstrump

Abstract

Background

In chronic limb-threatening ischaemia (CLTI), obstruction of the arterial blood flow causes ischaemic rest pain, ulcers or gangrene in the lower extremities. Patients with CLTI have a substantial risk of amputation unless the blood flow is improved, which requires invasive treatment through either open surgery or endovascular intervention.

Methods

This thesis aimed to analyse the outcomes of invasive CLTI treatments in terms of survival, major amputation rates, development of ischaemic symptoms, disease-specific health-related quality of life (HRQoL) and cost-effectiveness. An observational study was conducted in 190 patients with CLTI whose main vessel lesion was located in the femoropopliteal artery. The patients underwent either bypass surgery or endovascular intervention according to existing treatment guidelines and were followed up prospectively.

Results

The amputation-free survival (AFS) rates were 65% at 2 years, 41% at 5 years and 17% at 10 years after intervention. Survival and regression analyses showed worse AFS in patients who underwent endovascular intervention compared with those who underwent bypass surgery (adjusted hazard ratio 1.51). Most non-amputated survivors were free from CLTI symptoms at both 2 years (98/121) and 5 years (48/56) after intervention and reported substantially improved disease-specific HRQoL, which remained relatively constant during follow-up (mean VascuQoL scores of 2.68 at baseline, 4.58 at 2 years and 4.63 at 5 years after intervention). The cumulative hospital cost at 2 years of follow-up was approximately twice as high in the bypass cohort as in the endovascular cohort (SEK 355 000 versus SEK 184 000), whereas the corresponding gain in quality adjusted life years (QALYs) was small (1.04 versus 0.95), resulting in a very high incremental cost-effectiveness ratio.

Conclusions

In this study, patients with CLTI who underwent femoropopliteal revascularisation reported low baseline HRQoL levels, had a low average survival time and sustained a high risk of major limb amputation. However, those who remained alive with a preserved leg were to a large extent free from CLTI symptoms and reported enduring positive effects on disease-specific HRQoL after revascularisation. Bypass surgery was associated with a favourable AFS compared with endovascular intervention, also after controlling for baseline intergroup differences, but the incremental cost-effectiveness ratio for bypass surgery was very high.

Keywords

chronic limb-threatening ischaemia, critical ischaemia, bypass surgery, endovascular intervention, amputation-free survival, health-related quality of life, cost effectiveness

Sammanfattning på svenska

Den här boken handlar om nedsatt blodcirkulation i fötterna på grund av åderförkalkning i benens pulsådror, om resultaten av olika typer av operationer av pulsådrorna, om hur patienterna mår om de får berätta det själva (eller iallafall svara på väl valda frågor) och lite grann om vad allt detta kan kosta för sjukvården.

Bakgrund

Vid åderförkalkning av pulsådrorna i benen försämras blodflödet eftersom det blir trångt i kärlen. Fötterna, som är längst bort från hjärtat, drabbas hårdast av bristen på syresatt blod. Det kan leda till smärta, försämrad sårläkning eller i värsta fall kallbrand. Detta kallas för extremitetshotande ischemi (ischemi=syrebrist). Om man inte lyckas förbättra blodflödet med någon form av kärloperation är risken stor att benet kan behöva amputeras.

Åderförkalkning drabbar de flesta människor med stigande ålder, i olika omfattning och i olika kärl i kroppen. Om åderförkalkningen drabbar kärlen till eller i hjärnan kan det leda till stroke och om den drabbar hjärtats kärl kan det orsaka hjärtinfarkt. Eftersom åderförkalkningssjukdomen ofta finns i flera kärl i kroppen löper människor med extremitetshotande ischemi därför inte bara risk att behöva amputeras, de har också en ökad risk för hjärtinfarkt och stroke, och därmed också kortare förväntad livslängd än genomsnittet. Diabetes och rökning är några av de viktigaste faktorerna som ökar risken för åderförkalkning.

Det finns två principiellt olika sätt att operera pulsådrorna i benen för att förbättra blodflödet. Den ”gamla goda” metoden är en bypassoperation. Precis som ordet antyder, kopplar man då förbi det förträngda partiet av kärlet med hjälp av ett annat kärl (från patienten eller konstgjort). Det ”moderna” alternativet är ett s k endovaskulärt ingrepp, då man tar sig in i pulsådern via ett stick i ljumsken och sedan med hjälp av röntgengenomlysning kan ta sig igenom förträngningen med en vajer och vidga den genom att blåsa upp en ballong som man trär på vajern. (Se bild 4 och 5, sidan 15) Den endovaskulära metoden har den stora fördelen att den går att genomföra i lokalbedövning och det blir inga långa operationssår, dvs det är ett mindre påfrestande ingrepp, vilket har stor betydelse eftersom de som behöver operationen alltså ofta är gamla och sjuka. Det finns dock en misstanke om att de endovaskulära ingreppen inte är lika effektiva och/eller inte håller lika länge som en bypassoperation.

Metod

Den här avhandlingen bygger på en studie av 190 patienter med extremitetshotande ischemi som opererades antingen med en bypass eller ett endovaskulärt ingrepp, som därefter har följts i nästan tio år.

Resultat

Fem år efter kärloperationen hade 22% av patienterna genomgått en amputation och 50% av patienterna hade avlidit. Efter ungefär tio år hade 24% amputerats och 78% avlidit. Medan risken att dö var ungefär lika stor under hela uppföljningstiden, var risken att amputeras störst det första året efter kärlingreppet. Den amputationsfria överlevnaden, dvs andelen patienter som både lever och har benet i behåll, var 41% efter fem år och 17% efter tio år. Den amputationsfria överlevnaden var bättre hos dem som opererats med en bypass jämfört med dem som gjort ett endovaskulärt ingrepp. Det beror sannolikt till stor del på att de som behandlats endovaskulärt var sjukare på andra sätt eftersom man valt den typ av operation man tror är skonsammast till de sjukaste och svagaste. Med statistiska metoder kan man räkna bort sådana skillnader mellan grupperna och då var också skillnaden i amputationsfri överlevnad mindre, men fortfarande lite grann till bypassoperationens fördel.

Patienterna fick också besvara frågeformulär om sin livskvalitet. Dessa visade att livskvaliteten vid extremitetshotande ischemi är väldigt dålig och motsvarar den nivå man ser vid många cancersjukdomar. Efter behandling förbättrades dock livskvaliteten märkbart och detta höll i sig under hela uppföljningen (hos dem som inte blev amputerade). Det förelåg inga märkbara skillnader i livskvalitet mellan de olika behandlingsmetoderna.

Slutligen beräknades kostnadseffektiviteten för de olika behandlingsalternativen. I studien ingick alla kostnader inom sjukhuset under två år, vilka var ungefär dubbelt så stora vid bypassoperation som vid ett endovaskulärt ingrepp. I hälsoekonomiska sammanhang relateras den ökade kostnaden till den eventuella vinsten i form av ökad livskvalitet, vilket resulterar i en kostnadseffektivitetskvot (kostnad per extra år med optimal livskvalitet). Eftersom bypassoperation ledde till påtagligt högre kostnader men ingen större skillnad i livskvalitet blev den här kvoten långt över vad som brukar anses kostnadseffektivt.

Slutsats

Kronisk extremitetshotande ischemi är ett tillstånd förenat med dålig livskvalitet, hög dödlighet och stor risk för amputation. Även efter kärlkirurgiska ingrepp i syfte att förbättra blodcirkulationen är risken för amputation betydande och livslängden kortare än för genomsnittsbefolkningen. Hos de patienter som överlever och inte amputeras ses dock en betydlig förbättring av både symptom och livskvalitet, vilket är bestående även under 5–10 års uppföljning. Det är därför viktigt att inkludera livskvalitet i bedömningen både före och efter operation.

En jämförelse av patientgrupperna som genomgår bypassoperation respektive endovaskulär behandling visar något bättre amputationsfri överlevnad efter bypassoperation, men ingen skillnad i livskvalitet hos dem som lever och har benet i behåll. Skillnaden i amputationsfri överlevnad beror sannolikt till stor del på att de patienter som är sjuka och svaga av annan anledning oftare behandlas endovaskulärt eftersom det generellt sett är ett skonsammare ingrepp. Ytterligare studier krävs för att addera till den kunskap och erfarenhet som finns när det gäller att avgöra vilken patient som är bäst betjänt av vilken typ av ingrepp. Det är dock rimligt att tro att det finns patienter som har förutsättningar att klara en mer påfrestande bypassoperation och samtidigt dra nytta av ett troligen mer långvarigt resultat samt där den högre sjukvårdskostnaden kan anses motiverad.

List of papers

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Perlander A, Jivegard L, Nordanstig J, Svensson M, Osterberg K.
Amputation-free survival, limb symptom alleviation, and reintervention rates after open and endovascular revascularization of femoropopliteal lesions in patients with chronic limb-threatening ischemia.
J Vasc Surg. 2020; 72:1987-95.

II. Perlander A, Osterberg K, Nordanstig J, Svensson M.
Cost-Effectiveness Of Endovascular Intervention Versus Bypass Surgery in Patients with Chronic Limb-Threatening Ischemia and Principal Target Lesion in the Femoropopliteal Segment.
J Crit Limb Ischem. 2022; 2:19-26.

III. Perlander A, Broeren M, Osterberg K, Svensson M, Nordanstig J.
Disease Specific Health Related Quality of Life in Patients with Chronic Limb Threatening Ischaemia Undergoing Revascularisation of Femoropopliteal Lesions.
Eur J Vasc Endovasc Surg. 2023; 66: 245-251

IV. Perlander A, Svensson M, Osterberg K, Nordanstig J.
Ten-year follow-up after lower limb revascularisation in patients with chronic limb-threatening ischaemia and main target lesions in the femoropopliteal segment.
Manuscript.

Content

Abbreviations

ABI	Ankle brachial index
AP	Ankle pressure
AFS	Amputation-free survival
CLTI	Chronic limb-threatening ischaemia
CTA	Computer tomography angiography
DSA	Digital subtraction angiography
DUS	Duplex ultrasound
EQ-5D	EuroQol 5 dimensions instrument
HR	Hazard ratio
HRQoL	Health-related quality of life
IC	Intermittent Claudication
ICER	Incremental cost-effectiveness ratio
LEAD	Lower extremity arterial disease
MID	Minimally Important Difference
MRA	Magnetic resonance angiography
PAD	Peripheral arterial disease
PTA	Percutaneous transluminal angioplasty
SRM	Standardized Response Mean
$TcPO_2$	Transcutaneous oxygen pressure
TP	Toe pressure
QALY	Quality adjusted life year
VascuQoL	Vascular Quality of life questionnaire

Introduction

Background

Chronic limb-threatening ischaemia (CLTI) is the most severe stage of peripheral arterial disease (PAD) in the lower extremities and is mainly caused by atherosclerosis, which obstructs the blood flow and results in ischaemia in the peripheral tissues, leading to rest pain, impaired wound healing and gangrene.

Atherosclerosis

Atherosclerosis, the main cause of PAD, is a chronic condition in which fatty streaks in arterial walls gradually develop into plaques that may cause obstruction or occlusion of the artery lumen. The formation of atherosclerotic plaques is a complex mechanism involving multiple patho-physiological processes (including injury to the vessel wall, lipoprotein retention, inflammation, smooth muscle cell proliferation, calcification, plaque rupture and thrombosis)[1]. Atherosclerosis develops over a long period, generally decades, and is considered a systemic condition that often affects multiple vascular beds[2-4]. The terms peripheral arterial disease (PAD) and lower extremity arterial disease (LEAD) are alternately used to describe atherosclerosis in the lower extremities, although PAD, by definition, also includes other peripheral vascular beds such as the carotid, renal and visceral arteries.

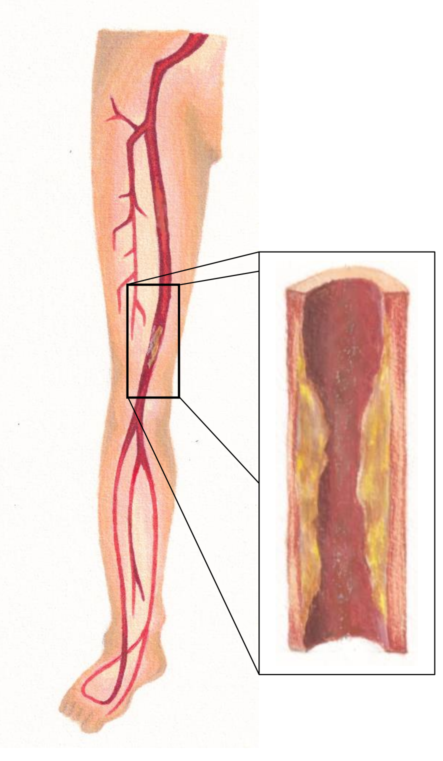


Figure 1 Arteries of the lower limb with atherosclerotic lesion.

Peripheral arterial disease

Most people with PAD are asymptomatic. The most common clinical presentation of PAD is intermittent claudication (IC). In IC, the arterial oxygenated blood flow to the lower extremities is sufficient at rest but becomes insufficient during exercise due to the increased metabolic demand, typically resulting in muscle pain upon walking. A more severe obstruction of the lower limb arteries may result in inadequate supply of oxygenated blood to the peripheral tissues (i.e., the feet) even at rest. This may cause ischaemic pain, impair normal wound healing and eventually lead to the development of gangrene. This condition is known as chronic limb-threatening ischaemia.

In a previous meta-analysis, 7% of patients with asymptomatic PAD progressed to IC within 5 years, and 21% of patients with IC developed CLTI[5]. However, the progression from asymptomatic to symptomatic PAD is not a strict step-by-step process. CLTI is not necessarily proceeded by symptoms of IC. For example, immobility or neuropathy can mask IC and a minor traumatic injury may drive an asymptomatic patient directly into the CLTI stage.

Incidence and prevalence

The prevalence of CLTI in individuals aged >60 years in western populations is approximately 1%[6-9], which corresponds to approximately 25 000 individuals in Sweden. The annual incidence of CLTI varies across studies, but between 500 and 3500 per 1 million has been reported in Europe and North America[7,9,10]. The overall prevalence of PAD, including both asymptomatic and symptomatic patients, has been estimated to be approximately 10–15% above the age of 60 years[2,4,6,7,11,12] which means that over 230 million people worldwide are estimated to have PAD. The prevalence has increased prominently over the past decades, mainly in low- and middle-income countries, but also in high-income countries, presumably as a result of an increased life expectancy and an increased prevalence of type 2 diabetes mellitus[11,12].

Risk factors

The risk factors for PAD coincide with the risk factors for atherosclerosis, which include smoking, diabetes mellitus, hypertension, hyperlipidaemia and chronic kidney disease[10,11,13-15]. The most important modifiable risk factors associated with PAD are smoking and diabetes mellitus. Current smoking has been shown to increase the risk of PAD by 2–4 times, depending on its duration and intensity[11,13,14]. A similar increased risk of PAD is observed in patients with diabetes mellitus, which increases with disease severity and duration[10,13,14]. Diabetes mellitus is also the strongest negative predictor of both disease progression to CLTI and worsening of CLTI[7,10]. This may be due to concomitant peripheral neuropathy and decreased resistance to infection, which negatively affect wound healing[9].

Diagnosis

Clinical diagnosis

Ischaemic rest pain is often first noted at night due to the horizontal position commonly practiced during sleep, enhanced by a physiologically lower systemic blood pressure at night. The anamnestic information of a patient tending to hang their lower leg over the edge of the bed to relieve pain, indicates the diagnosis of ischaemia. Ischaemic wounds are typically located peripherally, i.e., in the toes or heel. The easiest way to objectively assess arterial insufficiency is to measure the blood pressure at the level of the ankle (ankle pressure [AP]). The ankle pressure divided by the systemic blood pressure, as measured in the upper arm, is known as the ankle-brachial index (ABI). Generally, an ABI of <0.9 is considered to confirm a clinical diagnosis of lower limb PAD[16]. In patients with diabetes mellitus, thickening of the medial layer of the arteries may prevent complete compression with a tourniquet resulting in a falsely high AP despite severe arterial insufficiency. When suspecting incompressible arteries, complimentary tests such as toe pressure (TP) or transcutaneous oxygen pressure ($TcPO_2$) should be performed to establish the diagnosis. TP and $TcPO_2$ provide information on the peripheral tissue perfusion and are useful to assess the probability of wound healing. The hemodynamical definition of CLTI is usually set at AP <50–70 mmHg, TP <30–50 mmHg or $TcPO_2$ <20–40 mmHg[3,9,17].

Clinical classification systems

Two PAD classification systems based on clinical presentation are used in parallel: the Rutherford and the Fontaine classifications. Patients with ischaemic rest pain without tissue loss are categorized as Rutherford 4/Fontaine 3 and those with ulcerations are categorized as Rutherford 5–6/Fontaine 4 [18] (Figure 2). In the early versions of the classification systems, patients with diabetes were considered a separate category, owing to their more complex clinical presentation. However, in modern series of patients undergoing lower limb revascularisation, the prevalence of diabetes is approximately 50–70%[19-23]. Furthermore, it has been highlighted how the risk of amputation is multifactorial; in addition to ischaemia, the extent of tissue loss and presence of infection are important prognostic factors. Consequently, there was a need for a system that could include the full spectrum of patients and better describe the burden of disease and of risk of amputation and hence the WIfI classification system was introduced[24] (*W*ound, *I*schaemia, *f*oot*I*nfection), which is now the recommended classification system[3,9,13].

Rutherford	Symptoms of limb ischaemia	Fontaine
0	Asymptomatic	1
1	Mild claudication	2a
2	Moderate claudication	2b
3	Severe claudication	
4	Rest pain	3
5	Ischaemic ulcers	4
6	Ulcers/gangrene with severe tissue loss	

Figure 2. Correlation between the two clinical classification systems of PAD: the Rutherford classification (which was used in the study presented in this thesis) and the Fontaine classification. Chronic limb-threatening ischaemia refers to Rutherford 4-6 or Fontaine 3-4.

Imaging

Vascular imaging should be performed to determine the extent and distribution of atherosclerotic lesions and guide revascularisation decisions. Duplex ultrasound (DUS) is a first-line method owing to its non-invasive nature and combination of anatomical (distribution, degree of calcification etc) and physiological (flow velocity, doppler pulse wave etc) assessments of vascular lesions. However, DUS is time consuming and the diagnostic accuracy is high mainly in the iliac- and femoral artery segments while lower in the infrapopliteal arteries[25]. In CLTI, particularly in the presence of wounds, complete imaging of the arterial tree from the aortic bifurcation to the foot is important for adequate planning of an intervention; thus, DUS is rarely used as the only imaging modality[9]. High quality images of the whole arterial tree can be obtained via magnetic resonance angiography (MRA) or computer tomography angiography (CTA) which both have their pros and cons [26,27]. CTA is rapid and usually easily accessible but requires the use of iodinated contrast agents which can cause nephropathy, especially in patients with pre-existing renal insufficiency. Calcifications visualized by CTA may be difficult to distinguish from contrast media but are relevant for surgical decision making. MRA on the other hand, is more time consuming, which may limit its usefulness in patients with severe rest pain, and it is contraindicated in patients with metal implants (e.g., most pacemakers). MRA also tends to overestimate stenoses. Both CTA and MRA have slightly lower sensitivity and specificity for lesions below the knee and in the foot[9]. Hence, in complex cases, complimentary information may be provided using digital subtraction angiography, which has long been considered the gold standard for the imaging of lower extremity arteries but is currently mainly used for interventions due to its invasive nature.

Anatomical classification systems

The Transatlantic Intersociety Consensus for the Management of Peripheral Arterial disease (TASC II) classification is an established system used to describe and compare arterial lesions in terms of their anatomical distribution and complexity[10]. Femoropoliteal lesions are divided into four categories (i.e., TASC A–D) depending on the severity of lesions (Figure 3). Recently, a more comprehensive anatomical grading system has been developed, the Global Limb Anatomical Staging System (GLASS)[9]. The GLASS system aims to consider the full complexity of the lower limb arterial disease typically present in CLTI and to help define the optimal revascularisation approach.

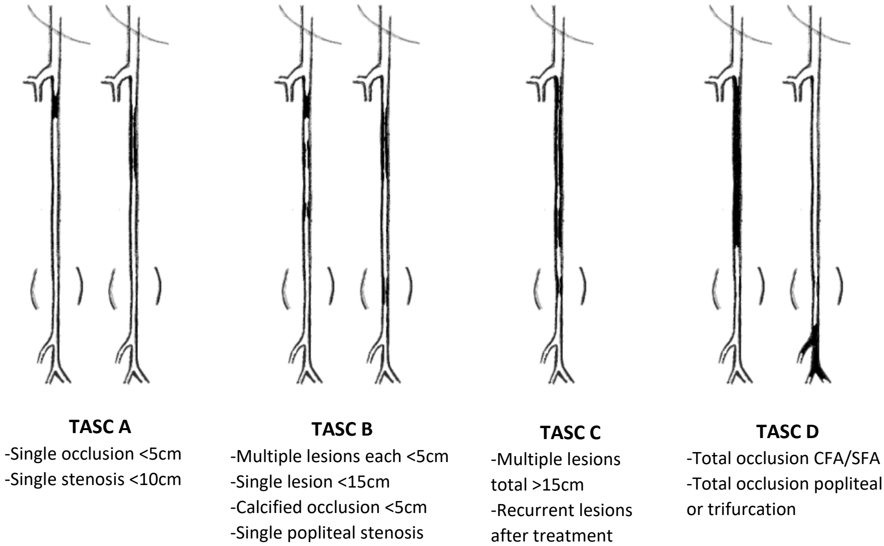


Figure 3. The Transatlantic Intersociety Consensus for the Management of Peripheral Arterial disease (TASC II) classification describes the anatomical distribution and complexity of the arterial lesions.

Prognosis

A serious complication of CLTI is major limb amputation. The natural history of CLTI in patients who do not undergo revascularisation is not well described in the literature, but a meta-analysis reported an average 1-year amputation rate of >20%[14]. However, even after revascularisation, amputation rates have been reported to remain high during follow-up periods of 1–4 years, at approximately 15–20%[23,28-30]. The risk of amputation increases with the severity of limb ischaemia and may reach 60% within 1 year in cases of extensive tissue loss or gangrene[29]. The presence of local infection also considerably increases the risk of amputation, especially among patients with diabetes mellitus[31].

In addition to the risk of amputation, patients with CLTI have an increased risk of cardiovascular events and death from vascular causes due to coexisting cardiovascular and cerebrovascular atherosclerotic disease[3,4,8,32-35]. A 1-year mortality rate of approximately 20% and 5-year mortality rate of approximately 50% have been reported in the literature[28,30,36-38]. The importance of addressing and treating cardiovascular risk factors is discussed further in the *Assessment of risk factors* section below.

A composite endpoint of mortality and amputation, known as amputation-free survival (AFS), is a commonly reported outcome measure in CLTI studies. The AFS rate at 1 year after invasive CLTI treatment has been reported to be approximately 70%, and that at 3–5 years after intervention approximately 50%[19,23,37,39]. Factors that negatively affect AFS in CLTI include increased age, male sex, severe renal failure, heart failure, diabetes mellitus and previous myocardial infarction or ischaemic stroke[9,23,36,40].

Assessment of risk factors

An important aspect of treating CLTI is to address the increased risk of cardiovascular and cerebrovascular events and death. The benefits of smoking cessation are well-established[3,9,13]. Smoking cessation reduces the risk of myocardial infarction and stroke exponentially, with a rapid decline in the relative risk after smoking cessation that reaches to a level just above that of never-smokers within a few years[15]. Glycaemic control, hypertension treatment and lipid-lowering therapy are recommended for all patients with PAD[3,9,13]. Antithrombotic therapy is recommended for patients with symptomatic PAD. The recently published ESVS Clinical Practise Guidelines on Antithrombotic Therapy for Vascular Diseases recommend single antiplatelet therapy with clopidogrel as first choice, or, in patients with high ischaemic risk, a combination of aspirin and low-dose rivaroxaban[41].

Revascularisation

The second component of treating CLTI is revascularisation, which should be attempted whenever possible, to alleviate limb symptoms and reduce the risk of amputation[3,9,13]. The preoperative evaluation should include an assessment of the patient´s risk (per- and postprocedural risks, life expectancy, limb function etc), grading of the severity of limb ischaemia (tissue loss, benefit of revascularisation etc) and description of the anatomical pattern of disease[3,9,13]. The primary goal of revascularisation is to establish a direct inline blood flow to the foot. This can be accomplished through open surgery, endovascular intervention, or a combination of the two techniques.

Open surgery

Bypass surgery is a primary open surgical technique used in the lower extremities. The bypass technique was developed in the mid-twentieth century and has been considered the gold standard for femoropopliteal artery disease since the 1960s. The principle of bypass surgery is that a stenosed or occluded segment of an artery is bypassed using a conduit anastomosed to the artery above and below the occlusion, thereby allowing the blood flow to pass by the affected artery segment. (Figure 4) The preferred conduit material is an autologous vein (particularly the great saphenous vein) which has better patency than prosthetic grafts[26,27,42]. Open surgical techniques also include endarterectomy which is the method of choice for the common femoral artery, which is easily accessible, but not an option for longer femoropopliteal lesions.

Endovascular intervention

Endovascular techniques use X-ray guidance to perform balloon angioplasty (percutaneous transluminal angioplasty [PTA]) or stenting of an artery through a percutaneous puncture of the common femoral artery, thus providing a minimally invasive treatment option. (Figure 5) The first PTA was performed in the 1960s[43]. The development of endovascular techniques accelerated in the 1980s and by the end of the century, a clear shift towards an endovascular approach was noticeable for the treatment of PAD.

Comparing open and endovascular revascularisation

Only two randomised controlled trials have compared the outcomes of open bypass surgery and endovascular recanalisation in patients with CLTI and femoropopliteal lesions. The early results of the first study, the Bypass versus angioplasty in severe ischaemia of the leg (BASIL) study, published in 2005, showed no significant differences in AFS or overall survival between patients who underwent endovascular intervention or bypass surgery, but long-term follow-up showed that bypass surgery was associated with a reduced risk of future amputation or death in patients who were alive 2 years after the intervention[19,44]. Thus, bypass surgery was recommended as a first line treatment in patients with an expected remaining lifetime exceeding 2 years[44,45]. The results were most evident when a suitable vein was available for a conduit.

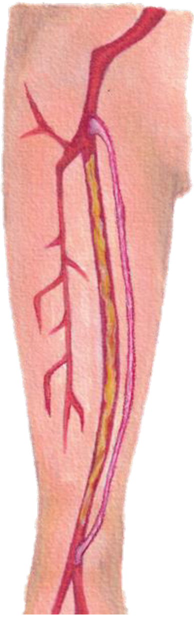


Figure 4. Occlusion of the superficial femoral and popliteal arteries, with vein bypass from the common femoral artery to the popliteal artery (left). Photo of upper anastomosis (below).

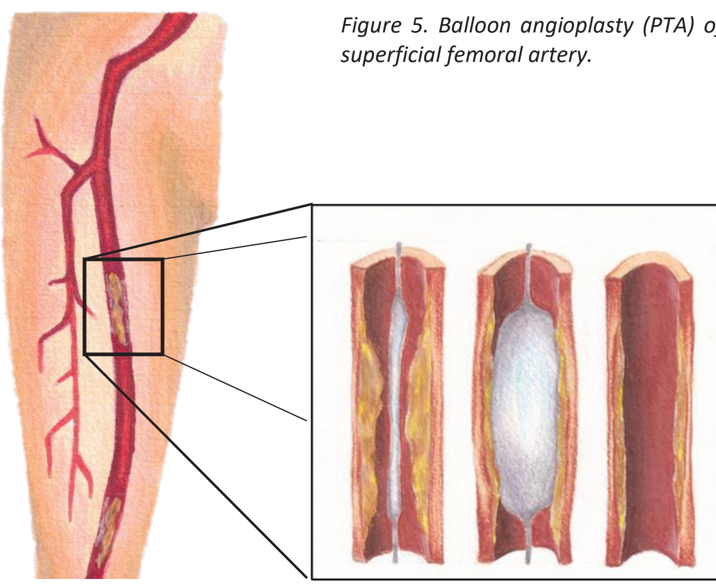


Figure 5. Balloon angioplasty (PTA) of stenosis in the superficial femoral artery.

The second study, the Best Endovascular versus Best Surgical Therapy in Patients with CLTI (BEST-CLI) study, published in 2022, included patients with and without a good-quality great saphenous vein for use as a conduit in two separate cohorts[46]. In patients with a suitable vein, bypass surgery was associated with superior results in preventing a composite outcome of major adverse limb events (amputation above the ankle or major limb reintervention) or death from any cause[46]. In patients without a great saphenous vein suitable for conduit, however, there was no significant difference between treatment methods[46]. A third randomised study on invasive treatment in CLTI patients was published in 2023, i.e, the BASIL-2 study[20]. This study targeted patients with CLTI who required infrapopliteal revascularisation (with or without a femoropopliteal procedure). In contrast to the BASIL-1 and BEST-CLI trials, the BASIL-2 study showed better AFS after endovascular treatment[20]. In addition to these seminal studies, observational studies and meta-analyses conducted over the past 20 years have shown broadly comparable AFS using bypass surgery and endovascular intervention for CLTI[37,39,42,47-49].

Health-related quality of life

Traditionally, the outcomes of patients with CLTI have been measured based on hard endpoints such as patency, limb salvage or AFS. Gradually there has been a growing interest also in patient-reported endpoints. Health-related quality of life (HRQoL) refers to a person´s own perception of life, including physical, psychological and social aspects, and how this perception is affected by their health status. Studies have shown that patients with CLTI have lower HRQoL scores than the general population[50-54]. Revascularisation has been shown to improve HRQoL, especially during the first months after the intervention, but this effect tends to reduce over time and studies with longer follow-up are rare[50,55-58].

HRQoL instruments

Numerous instruments (i.e., questionnaires) are available to assess HRQoL and can be divided into generic and disease specific. Generic questionnaires can be used regardless of the medical condition being studied and have their main application in assessing general health status within and across populations.

The EuroQoL-5-dimensions (EQ-5D) is a generic instrument commonly used in cost-effectiveness analyses[59,60]. (Appendix 1) Disease-specific questionnaires focus on issues of importance in a specific disease, making them more sensitive to longitudinal changes, such as before and after treatment. The Vascular Quality of life (VascuQoL) questionnaire is a commonly used PAD-specific instrument that has been validated in Swedish patients[61-63]. (Appendix 2)

Cost-effectiveness assessments

As described above, the prevalence of PAD is increasing, with a growing impact on healthcare resources worldwide. As health care resources are limited, economic evaluations need to be considered, alongside other aspects, when planning and allocating health care. However, cost effectiveness analyses in patients with CLTI are scarce. Invasive revascularisation has been shown to be cost-effective compared with conservative treatment or primary amputation[64,65] but there are limited data to support the choice between open surgery and endovascular treatment in terms of cost-effectiveness in cases where both modalities can be used[66,67].

Incremental cost-effectiveness ratio

Cost-effectiveness assessments are based on the comparison of two alternative treatments, expressed as an additional cost per gained effect, also known as the incremental cost-effectiveness ratio (ICER).

$$ICER = \frac{cost_A - cost_B}{effect_A - effect_B} = \frac{cost_A - cost_B}{QALYs_A - QALYs_B}$$

The effect can be measured using different outcomes, e.g., patency or limb salvage. However, such disease-specific outcomes do not allow comparisons with other areas of health care. Therefore, the use of a generic measure of health gain is recommended. The most common method is the measure of quality adjusted life years (QALYs). QALYs refer to the product of the health state measured using a scale from 0 (equal to dead) to 1 (best possible health), named the QALY weight, multiplied by the time spent in that health state. Accordingly, one QALY would correspond to one whole year of perfect health. There are different methods for estimating the QALY weight, but in daily practice it is common to use generic HRQoL questionnaires where responses have been converted into QALY weights in prespecified tariffs[68].

A common outcome of the cost-effectiveness analysis of a new treatment in health care is that it is both more expensive and more effective than the old treatment. The next step is to determine the additional cost per gained effect (i.e., the ICER) that could be considered cost effective. In the United Kingdom, the National Institute for Health and Clinical Excellence (NICE) uses a cost-effectiveness threshold of £20 000–30 000 (approximately SEK 260 000–390 000)[69]. The Swedish National Board of Health and Welfare (Socialstyrelsen) has no specific threshold but rather guidelines on what might be considered a high or low cost per QALY. A general interpretation of these guidelines and how they have been implicated is that SEK 500 000 per QALY could be considered cost effective[70].

Aims

The aim of this thesis was to survey outcomes of invasive treatment in patients with Chronic Limb-Threatening Ischaemia (CLTI) and the main target lesion in the femoropoliteal artery segment and to compare the outcomes of patients revascularised using open bypass surgery and endovascular intervention.

Specifically, this thesis aimed to evaluate

- amputation-free survival and limb symptom development (Papers I and IV)
- reintervention rates (Paper I)
- health-related quality of life (Papers III and IV)
- cost-effectiveness (Paper II)

of invasive treatment of femoropopliteal lesions in patients with CLTI.

Patients and Methods

Patients

All analyses in this thesis are based on an observational study of 190 patients with CLTI who underwent invasive revascularisation at Sahlgrenska University Hospital or a nearby district hospital (Södra Älvsborg hospital or Skaraborg hospital) between March 2011 and January 2015. To be included, patients had to (i) have ischaemic rest pain, ulcerations or gangrene for at least 14 days, (ii) be scheduled for an invasive treatment, and (iii) have their main vessel target lesion in the superficial femoral or popliteal artery, based on computer tomography angiography (CTA) or magnetic resonance angiography (MRA). The femoropopliteal lesions were categorised based on the TASC II guidelines (Figure 3).

Revascularisation

The revascularisation technique (i.e., open bypass surgery or endovascular intervention) was selected by the vascular team. The decision was guided by the TASC II guidelines, which recommend endovascular treatment for short SFA lesions (TASC A) and bypass surgery for long occlusive lesions involving the popliteal artery (TASC D). In cases of multiple or medium long lesions (TASC B and C), the guidelines open up for both treatment methods depending on both vessel- and patient-related factors. Since vessel disease is regularly multilevel in CLTI, both inflow and outflow lesions were accepted and treated according to protocol when considered important for the outcome and patency. In cases where endovascular intervention was performed, balloon angioplasty was the primary treatment and stenting was only performed in cases of suboptimal angiographic result. In bypass surgery, the great saphenous vein was the preferred bypass conduit. Synthetic graft material was used in the absence of suitable vein material.

Surveillance

All patients underwent the same follow-up program, including repeated duplex ultrasound examinations during the first year post intervention. Significant stenoses rendered reintervention to maintain patency. Reintervention rates were recorded during the first 2 years of follow-up. Clinical status (Rutherford category) and patient-reported HRQoL were assessed at follow-up visits by a vascular surgeon at 1 month and 1, 2 and 5 years after the intervention. Survival and amputation rates were recorded up to approximately 10 years by reviewing hospital records. The median follow-up time was 9.6 years (range 7.7-11.6).

Survival analyses

Survival analysis using Kaplan Meier plots was conducted to analyse time-to-event data for major amputation, overall survival and the AFS composite endpoint. Cox proportional hazards regression analysis was used to adjust for baseline differences between the groups. The most important confounding factors for major amputation or death were identified using univariable analysis and were then sequentially added using multivariable Cox regression analysis. The proportional hazard assumption was confirmed graphically.

Patient-reported outcomes

Health-related quality of life (HRQoL) was assessed using one generic instrument, the EQ-5D questionnaire, and one PAD-specific instrument, the VascuQoL-25 questionnaire.

The EQ-5D instrument (Appendix 1) is a short questionnaire with five questions concerning different health aspects: mobility, self-care, ability to perform activities of daily living, pain/discomfort and anxiety/depression. In this study the original EQ-5D instrument with a 3-point response scale was used. The Dolan tariff was used to convert the combination of responses of each patient to a QALY weight ranging from 0 (equivalent to being dead) to 1 (best possible health)[68]. QALYs were then calculated by multiplying the QALY weight by the time spent in that health state. The EQ-5D questionnaire was primarily used for the health economic evaluation.

The VascuQol-25 questionnaire (Appendix 2) was developed for longitudinal clinical evaluation of disease specific changes in QoL[61]. The questionnaire consists of 25 questions divided into five domains (pain, activity, symptoms, emotional and social), each with a 7-point response scale ranging from 1 (worst) to 7 (best). The questionnaires were completed by the patients at baseline (before treatment) and at each follow-up visit (1 month, 1 year, 2 years and 5 years after intervention).

The effect size of the changes in HRQoL over time was analysed by calculating the standardized response mean (SRM) and the clinical impact of the HRQoL changes was explored by estimating the minimally important difference (MID). The SRM is calculated by dividing the difference in mean VascuQoL score over time by the standard deviation of the same difference and thus also accounts for variability in questionnaire responses. The MID is defined as an estimated threshold of improvement (or worsening) considered important to patients and was calculated using the distribution-based method, where an increase (or decrease) in the VascuQoL score by at least 50% of the standard deviation from the baseline mean value is considered a minimally important improvement (or worsening)[71-73].

Health economic evaluations

The health economic evaluation was limited to the cohort of patients treated at Sahlgrenska University Hospital and included 160 patients, of whom 105 underwent an endovascular intervention and 55 underwent bypass surgery. The cost-effectiveness analysis was conducted from the health care provider´s perspective. All hospital costs for vascular surgical care, consecutive geriatric care and, in case of amputation, orthopaedic care, during 2 years from the index procedure were collected.

The incremental cost-effectiveness ratio (ICER) was calculated as the cost per gained QALY (difference in mean costs divided by the difference in mean QALYs) and as cost per major amputation avoided (difference in mean costs divided by the difference in amputation rate) over 2 years. QALY-weights were calculated from EQ-5D questionnaires. Intergroup differences at baseline were adjusted for in a linear regression analysis.

Ethical considerations

This study investigated outcomes after invasive treatment as provided according to existing guidelines and clinical routine. Participation in the study did not change the treatment provided and thus did not put the patients at any additional risk of harm. All patients received oral and written information and signed informed consent prior to entering the study.

The study was approved by the Gothenburg Regional Ethical Review Board (Dnr 316-09). Supplementary approval for extended follow-up after the initially planned two years, was obtained in 2017 and 2023.

Results

Patient population and baseline data

A flow chart of the patients included in the study is presented in Figure 6. Among 385 patients screened for inclusion, 190 were included in the study (inclusion rate of 50%). Only six patients withdrew consent during the study. Baseline demographics and comorbidities are presented in Table 1. A total of 117 patients underwent endovascular intervention and 73 patients underwent bypass surgery. Most patients in the endovascular treatment group presented with short stenoses/occlusions (TASC A or B) whereas most patients in the bypass group had complex long vascular lesions (TASC C or D), consistent with the TASC II recommendations regarding the choice of revascularisation method.

	Total n=190	**Endovascular intervention** n=117 (62)	**Bypass surgery** n=73 (38)	**p-value**
Age, mean ± SD	74 ± 9.6	75 ± 9.4	73 ± 9.9	.13
Male/female (%)	51/49	54/46	47/53	.37
BMI, mean ± SD	25 ± 4.4	25 ± 4.0	25 ± 4.8	.49
Coronary artery disease	64 (34)	37 (32)	27 (37)	.53
Chronic heart failure	31 (16)	25 (21)	6 (8.2)	.025
Diabetes mellitus	65 (34)	42 (36)	23 (32)	.64
Endstage renal disease	13 (6.8)	10 (8.5)	3 (4.1)	.38
Active smoking	41 (22)	21 (18)	20 (28)	.15
Previous stroke or TIA	31 (16)	17 (15)	14 (19)	.42
Antithrombotic medication	152 (80)	97 (83)	55 (75)	.26
Lipid-lowering medication	103 (54)	65 (56)	38 (52)	.66
TASC A	31 (16)	31 (27)	0	
TASC B	72 (38)	59 (50)	13 (18)	
TASC C	39 (21)	18 (15)	21 (29)	
TASC D	48 (25)	9 (7.7)	39 (53)	
Run-off vessels 0	34 (18)	26 (22)	8 (11)	.054
Run-off vessels 1-2	122 (64)	77 (66)	45 (62)	.64
Run-off vessels 3	34 (18)	14 (12)	20 (27)	.011
Rutherford 4	51 (27)	26 (22)	25 (34)	.069
Rutherford 5	131 (69)	87 (74)	44 (60)	.041
Rutherford 6	8 (4.2)	4 (3.4)	4 (5.5)	.49

Table 1. Baseline demographics and comorbidities. Numbers (%)

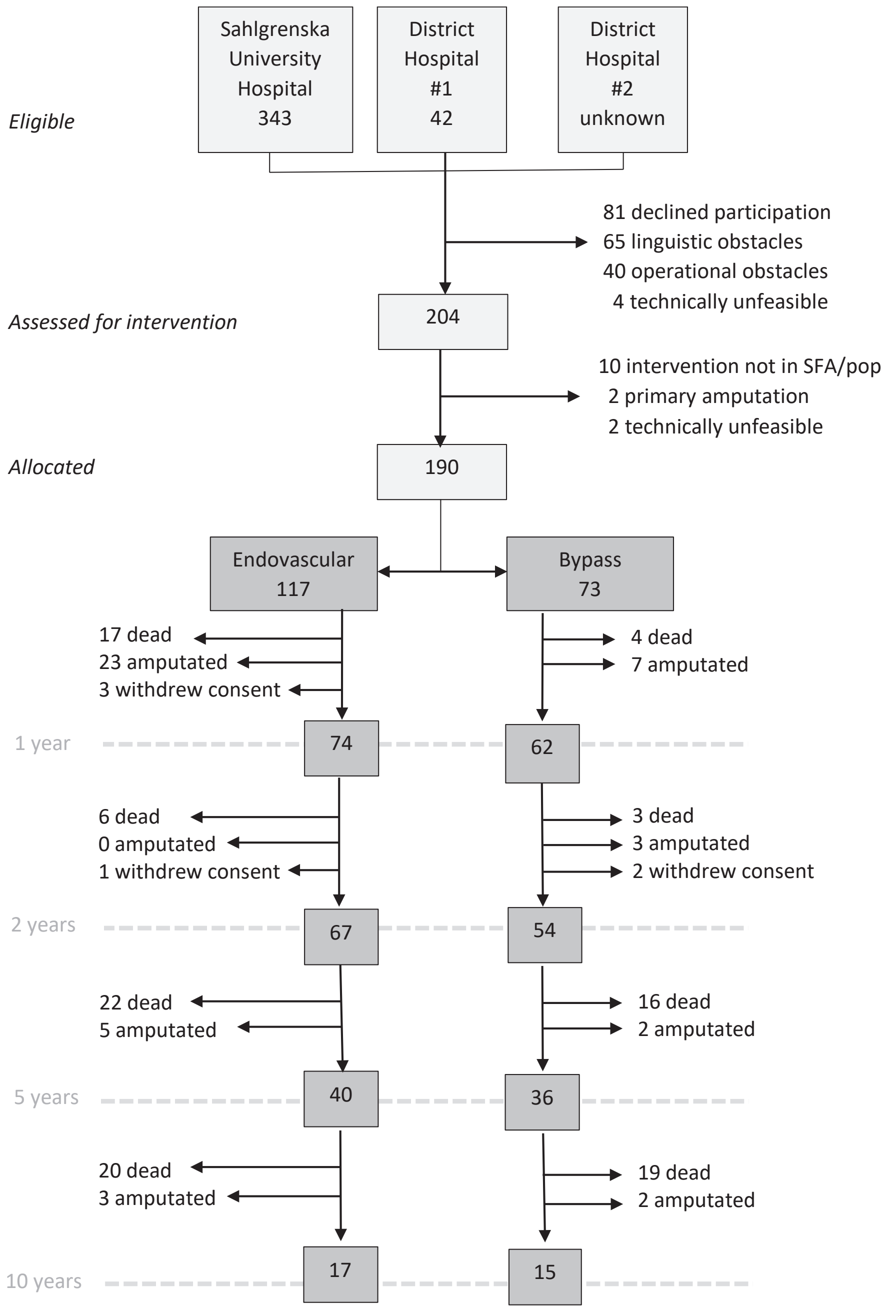
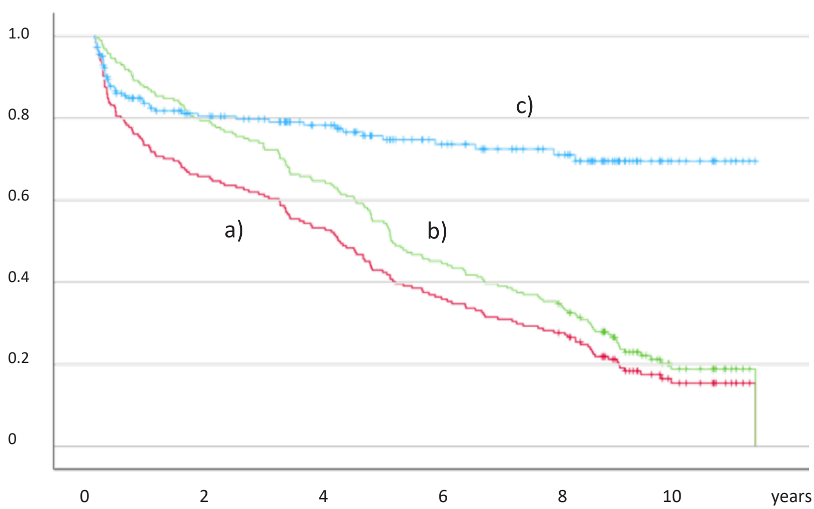


Figure 6. Flow chart of patients in the study

Survival and amputation rates

The overall survival was 86% at 1 year, 79% at 2 years, 50% at 5 years and 22% at 10 years after intervention. The amputation rates were 16% at 1 year, 18% at 2 years, 22% at 5 years and 24% at 10 years after intervention. This resulted in an AFS of 73% at 1 year, 65% at 2 years, 41% at 5 years and 17% at 10 years after intervention. A Kaplan-Meier plot of survival and amputation rates for the entire study cohort is presented in Figure 7. AFS was higher among patients who underwent bypass surgery than among patients who underwent endovascular intervention. Separate Kaplan-Meier curves for the endovascular and bypass cohorts are shown in Figure 8. Survival analysis showed a statistically significant difference in AFS between the two treatment groups during the 10 years of follow-up (p=0.017; log-rank test).



N at risk

	0	2	4	6	8	10
a)	190	119	95	64	46	12
b)	190	144	117	80	57	13
c)	190	119	95	64	46	12

Figure 7. Kaplan-Meier curves for a) amputation free survival, b) overall survival and c) freedom from amputation after revascularisation in the entire study cohort.

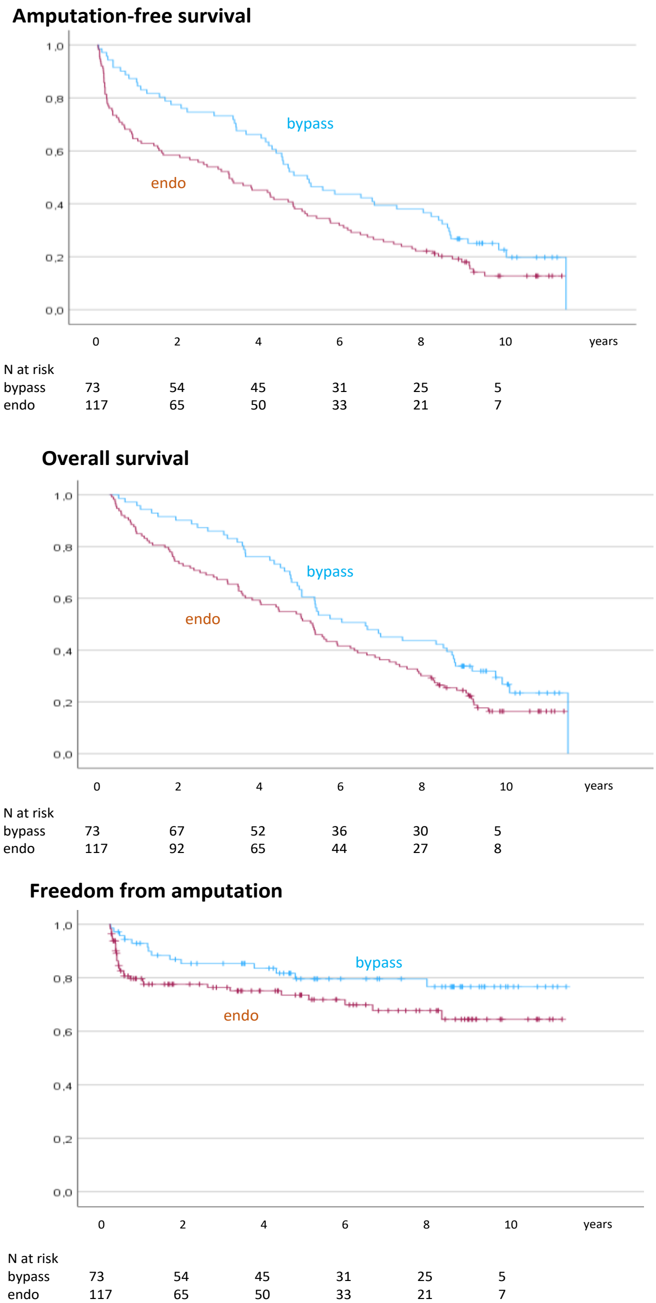


Figure 8. Kaplan-Meier curves for amputation-free survival, overall survival and freedom from amputation in the bypass and endovascular patient cohorts, separately.

Regression analysis

To analyse the impact of treatment modality on AFS, Cox proportional hazards regression analyses were performed to adjust for intergroup differences at baseline. Potential confounders of time until major amputation or death were analysed in a univariable regression model which indicated increasing age, heart disease, end-stage renal disease, diabetes mellitus and presence of tissue loss as the factors most strongly and statistically significantly associated with a higher risk of major amputation or death within 10 years. In a multivariable analysis, adjusting for the above listed background variables, the hazard ratio (HR) of major amputation or death was higher in the endovascular treatment cohort (HR 1.51). A 5-year analysis indicated the same variables as the most important confounders and a corresponding multivariable Cox model generated a HR value of 1.58. In a 2-year perspective, the corresponding Cox regression analysis resulted in a HR at 1.93. However, in this shorter-time perspective, male sex was significantly associated with higher risk of major amputation or death, whereas heart disease and diabetes mellitus were not. However, adjusting for male gender but not heart disease or diabetes mellitus did not substantially change the HR (HR 1.88).

Reintervention rates

A total of 74 patients underwent reintervention to enhance patency during the first two years of follow-up. The reintervention rates were comparable between the endovascular cohort and the bypass cohort (39% and 38%, respectively). Most of the patients underwent one or two reinterventions. Only one patient in the endovascular group but seven patients in the bypass group underwent more than two reinterventions.

CLTI symptom development

At inclusion, all patients in the study suffered from ischaemic rest pain and/or tissue loss. Most patients had minor tissue loss (Rutherford 5). Figure 9 shows the evolution of limb symptoms over time according to the Rutherford classification. A total of 24 (21%) patients in the endovascular cohort, and 5 (6.8%) in the bypass cohort presented with CLTI symptoms 1 year after the intervention. Two years after the intervention, 13 (11%) in the endovascular cohort and 6 (8.2%) in the bypass cohort presented with CLTI symptoms.

Among the 56 patients who attended the five-year follow-up visit, only six patients in the endovascular cohort (n= 33) had ischaemic wounds and one had rest pain, whereas in the bypass cohort (n=23) no patients had wounds and only one had rest pain.

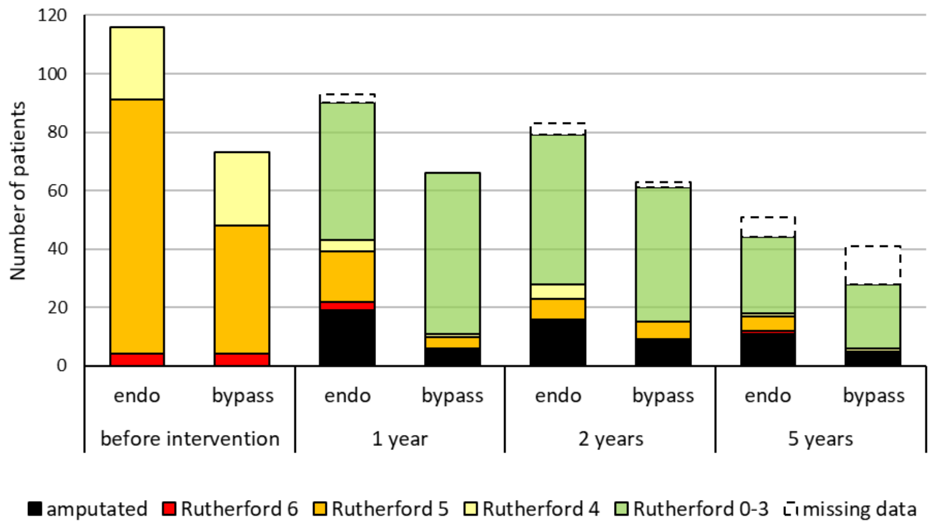


Figure 9. Distribution of CLTI symptoms at each follow-up time point.

Health-related Quality of Life

The baseline mean VascuQoL total score was 2.68. After the invasive procedure, the mean VascuQoL total score among patients who were alive and did not undergo a major amputation, was 4.75 at 1 year, 4.58 at 2 years and 4.63 at 5 years. This resulted in a statistically significant improvement compared with baseline at all measured points. There were no differences in the mean VascuQoL scores between patients who received endovascular treatment and those who underwent bypass surgery at either baseline (p=0.53), 1 year (p=0.18), 2 years (p=0.53) or 5 years (p=0.12). The mean VascuQoL scores (both total and domain specific scores) are shown in Figure 10 for each measured point.

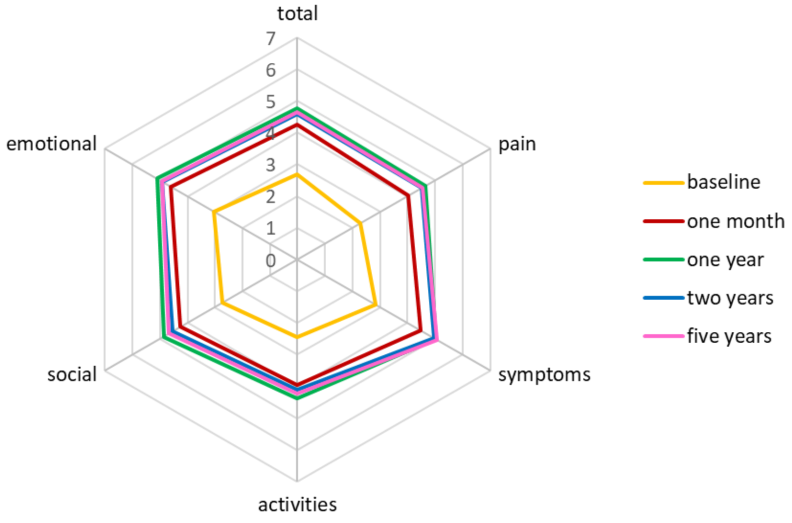


Figure 10. Spider plot showing the mean VascuQoL score at baseline and at each time point after intervention.

The standardized response mean (SRM) scores, estimating the observed effect size in VascuQoL scores, were large at all measured points (1.36 at 1 year, 1.08 at 2 years and 1.15 at 5 years) according to Cohen´s proposed effect size index, where an effect size of <0.5 is considered small, 0.5-0.8 moderate and >0.8 large.

The minimally important difference (MID) corresponded to a change of ≥ 0.51 in the VascuQoL total score. The number of patients who reached the MID for improvement was 101 at 1 year, 78 at 2 years and 44 at 5 years. That corresponds to 53%, 41% and 23%, respectively, of the entire patient cohort (n=190) and 74%, 64% and 58% of the patients alive with a preserved leg.

Cost effectiveness

The mean total cost per patient during two years from intervention was SEK 355 000 in the bypass group and SEK 184 000 in the endovascular group. Mean QALYs per patient during the same period were 1.04 years in the bypass group and 0.95 years in the endovascular group. This resulted in an ICER of approximately SEK 2 million per gained QALY with bypass surgery. After adjusting for age, sex, EQ-5D score at baseline, smoking, diabetes mellitus, chronic heart failure, tissue loss and TASC category in a linear multiple regression analysis, the difference in costs between the treatment groups was SEK 120 000 and the difference in QALYs was 0.02, which resulted in an ICER of approximately SEK 6 million per gained QALY using bypass surgery.

Discussion, Limitations and Future Perspectives

Study design

The study population consisted of an unselected cohort of patients with CLTI who underwent invasive treatment according to existing guidelines during a 4-year period. The main reasons for conducting an observational study were to target a broad population of CLTI patients and to avoid problems with a low and slow inclusion rate which is an acknowledged problem with randomised trials.

Internal validity

A total of 190 patients were included in the study, i.e., approximately 50% of the eligible patients. The main reasons for not including a patient were that patients declined to participate or were unable to fully comprehend the information. Difficulties associated with involving old and frail patients in clinical trials is a well-known problem[74-76]. Previous studies have reported that patients may be overwhelmed by their condition, lack the cognitive reserves to handle information overload when introduced to the study or feel discouraged from participating due to additional hospital visits[76]. These aspects are well applicable to CLTI patients and may have introduced a certain degree of selection bias in this study sample. The number of patients who withdrew consent after the start of the study, and who were consequently excluded from further analysis, was small.

External validity

To analyse whether the study sample was representative of the target population, the baseline data were compared with data from the Swedish National Registry for Vascular Surgery (Swedvasc)[23], two observational studies with a similar design[37,39], and three randomised trials on invasive treatment in patients with CLTI[19,20,46]. (Table 2)

According to the Swedvasc registry, approximately 2500 patients were annually registered for an infrainguinal vascular procedure for CLTI in Sweden at the time of this study. Approximately 70% of the patients were treated with an endovascular technique, indicating a marginally larger proportion of patients than that in our study. In both the German CRITISCH study[39] and Japanese SPINACH study[37] the decision regarding treatment modality was made by the treating physicians, which resulted in a distribution between open and endovascular treatment similar to that in our study. Except for a slightly lower prevalence of diabetes mellitus and heart failure, baseline data in our study were comparable to national Swedvasc data, as reported by Baubeta Fridh et al[23]. Presence of tissue loss was not reported by Baubeta Fridh, but the latest annual Swedvasc report showed the same proportion as recorded in this study (73%). The German study population was grossly comparable with the present study population in terms of comorbidities, but the proportion of patients with severe tissue loss was larger. The Japanese study cohort presented a high prevalence of diabetes mellitus and a very large proportion of patient in dialysis, which is more common in Japan than in Europe[77]. The randomised BEST-CLI study[46] reported a younger study population, but despite that, to a larger extent burdened by cardiovascular disease, diabetes mellitus, chronic renal disease and current smoking. Notable in the more recent BEST-CLI[46] and BASIL-2[20] studies are the relative predominance of male patients and the high prevalence of diabetes mellitus.

	Present study	**Swedvasc 2008-2013 (23)**	**CRITISCH registry* (39)**	**SPINACH study (37)**	**BASIL trial (19)**	**BEST-CLI trial (46)**	**BASIL-2 trial (20)**
Number of patients	190	10 617	926	548	452	1830	345
Endo/bypass (%)	62/38	76/24	69/31	64/36	50/50	50/50	50/50
Age, years (mean)	74	77	74	73	67%>70y	68	73
Male sex %	51	49	64	68	60	72	81
Coronary artery disease %	34	20/28**	45	41	17/18**	45	19/12**
Heart failure %	16	28	-	19	-	5.8	-
Diabetes mellitus %	34	47	48	74	42	69	69
Severe renal insufficiency %	6.8	6.7	8.4	53	-	11	4.3
Current smoking %	22	13	20	15	36	35	21
Tissue loss % Severe tissue loss %	73 4.2	- -	- 21	68 19	74 -	- -	88 -

*Table 2. Comparison of baseline data in the patient cohorts of six published studies on invasive treatment in CLTI. *Data refer to patient group I (endovascular treatment) and II (bypass surgery) only. **previous myocardial infarction/angina pectoris*

Overall, the patient cohort included in this study does not differ markedly from that of the Swedvasc registry. It is reasonable to consider the study cohort to be representative of Swedish patients treated invasively for CLTI symptoms and it may also be considered reasonably representative of European CLTI populations. However, differences in risk factor profiles and comorbidities should always be considered, especially when comparing and interpreting results from different CLTI studies worldwide.

Power

The target number of study participants was 250. However, the study was ended prior to that, mainly because of the start of a national randomised controlled study that concomitantly involved the same patient population. Inclusion in parallel studies proved unfeasible and it also seemed unethical as some patients did not comprehend that they were signing consent to separate studies. The study could thus be considered under-dimensioned, which may have influenced the results.

Amputation-free survival

Amputation-free survival (AFS) is a common composite endpoint in studies on CLTI and the ability to compare results with those of other studies was the primary reason for presenting AFS rates in this study. The AFS rates at 2 and 5 years after the intervention in this study were largely consistent with previous results[20,23,37,39,44,45] (Table 3). To the best of our knowledge, this is the first study to present prospectively obtained AFS rates and time-to-event graphs up to 10 years of follow-up (Figure 7).

However, composite endpoints should be interpreted with caution, especially when the occurrence of one event is dominant[78,79]. In this study, the composite endpoint was primarily driven by the high mortality rate, especially during the long-term follow-up. To avoid misinterpretation, the composite endpoint (AFS) as well as the individual component endpoints (death and major amputation) are presented in the survival analyses and accordingly discussed separately below.

	Present study		Swedvasc 2008-2013 (23)	CRITISCH registry* (39)	SPINACH study (37)	BASIL trial (44,45)	BEST-CLI trial** (46)	BASIL-2 trial (20)
Follow-up (years)	2	5	3	1	3	3-7	2.7***	3.3***
AFS (%)	65	41	54	74	52	38	-	42
Mortality (%)	21	50	-	18	43	56	35	49
Amputation (%)	18	22	19	12	8.6	-	13	19

Table 3. Amputation-free survival, overall mortality and amputation rates in the present study and six previously published studies on invasive treatment in CLTI.
**Data refer to patient group I (endovascular treatment) and II (bypass surgery) only.*
***Data refer to study cohort 1 only (patients with a great saphenous vein accessible for conduit)*
****median*

Mortality

The 5-year mortality rate in this study was 50%, which largely corroborates the current literature[28-30,38]. As shown in table 3 however, there is a variation in mortality rates between studies, presumably due to varying comorbidity status, as described above. The observed mean survival time of 5 years for the patients in this study, is less than half that of age-matched Swedes and corresponds with many cancer diagnoses, further illustrating the pessimistic prognosis for the CLTI patient population[80,81]. Approximately one third of the study population had a concomitant diagnosis of coronary artery disease, which is the main cause of death among patients with PAD[82,83] and the leading cause of death worldwide according to the World Health Organization[84]. The Kaplan Meier survival curves showed that the mortality rate was relatively constant over time, reflecting a generalized atherosclerotic disease and an enhanced risk of death from cardiovascular or cerebrovascular events throughout life. This emphasizes the importance of treating risk factors for atherosclerosis also in this elderly patient group. In this study, approximately 80% of the patients were on antithrombotic medication or anticoagulation and approximately 50% were on lipid-lowering medication when they entered the study. Among the patients who attended the 5-year follow-up, 96% were on antithrombotic or anticoagulation and 86% were on lipid-lowering medication.

Major amputation

The rate of lower limb major amputation in this study was 16% at 1 year, 22% at 5 years and 24% at 10 years after the intervention. One third of the patients had diabetes mellitus, which is a leading cause of amputation according to both the Swedvasc registry[85] and the Swedish amputation and prosthesis registry[86]. Notably, the risk of amputation was the highest during the first year after the intervention, whereas after that first year the amputation rate was very low, regardless of the initial invasive treatment approach. This reflects the critical nature of CLTI and the need for urgent revascularisation to reverse the destructive ischaemic tissue process and salvage the limb. Patients with a successful outcome from the initial limb-threatening situation had a remarkably good prognosis of limb salvage in our study.

Bypass surgery or endovascular intervention

The observational nature of this study limits the possibility of directly comparing treatment modalities due to differences in baseline comorbidities between treatment groups. While the groups were reasonably well balanced in terms of age, sex and prevalence of coronary artery disease and diabetes mellitus, the endovascular group included more patients with congestive heart failure, end-stage renal disease, tissue loss and a worse lower leg runoff vessel situation. These differences are likely a result of selection of the frailer patients for endovascular intervention assuming they would benefit from the potential advantages of a minimally invasive treatment option, which inevitably introduces a confounding effect. Nevertheless, the study reflects the everyday clinical situation where treatment decisions are made according to established knowledge as available in guidelines, and as such the study provides valuable information that justify a comparison of the treatment groups.

Survival analyses showed better AFS in the bypass cohort throughout follow-up, as shown in the Kaplan-Meier curves (Figure 8), with statistical significance as determined by the log-rank test. It is reasonable to suspect that a decisive part of this difference is related to differences in baseline data between the groups. However, also after adjusting for known and potential confounding factors in a Cox proportional hazards regression analysis, the risk of amputation or death remained higher in the endovascular group compared with the bypass group throughout the study. The influence of treatment modality on AFS was the largest during the first two years and smaller when analysed after five and ten years. Suggestively, bypass surgery results in a more complete revascularisation compared with endovascular intervention, possibly reversing the ischaemic situation faster, resulting in wound healing and a lower risk of amputation. This may contribute to higher AFS in the bypass cohort during the first two years, but after that, regardless of treatment modality, the amputation rate was low. Besides, the difference in AFS appears to be driven mainly by a difference in mortality. It is hardly intuitive why the initial invasive treatment method would affect mortality five or even ten years later. Presumably, there are additional confounding factors, such as physical functioning, mobility and cognitive reserves, that are evaluated and considered by the physician when recommending treatment modality, although not always explicit or documented, which may consequently affect survival outcomes.

Two randomised controlled studies have recently been published, comparing open and endovascular treatment in CLTI patients, that report partly diverging results. After a median follow-up time of approximately 3 years, the BEST-CLI study[46] showed overall better results in the bypass cohort than in the endovascular cohort (provided that a good-quality great saphenous vein was available) whereas the BASIL-2 study[20] presented reverse results. Further evaluations will be required before these diverging results can be fully explained. A data sharing agreement between the investigators of the two studies has been announced, that will allow deeper comparison and analysis before final conclusions can be drawn. One important aspect to consider is that both study patient cohorts were highly selected, as only patients deemed equally suitable for open and endovascular intervention were eligible for inclusion, and it may be questioned as to what extent the studied patient cohorts reflect the true diversity of the CLTI patient group.

Surveillance and reintervention

All patients in this study were included in a comprehensive duplex ultrasound surveillance (DUS) program and reintervention was performed in the event of significant restenosis, regardless of symptoms and of the primary treatment modality. This resulted in comparable reintervention rates after endovascular treatment and bypass surgery during the first two years from the primary intervention. However, while it was very uncommon to have more than two reinterventions in the endovascular patient cohort, nearly one in ten patients in the bypass cohort needed repeated (≥3) reinterventions.

It is well known that most vein graft restenoses occur within the first two years, and current guidelines recommended DUS surveillance to detect graft failure before occlusion[13,87,88]. After endovascular interventions, however, restenoses often present with ischaemic symptoms and it is uncertain whether reintervention is indicated in asymptomatic stenoses[88]. In this study, reintervention was performed also in asymptomatic patients which is likely to have increased the reintervention frequency, especially in the endovascular cohort. There is no consensus on DUS surveillance after endovascular interventions in current guidelines; a single DUS within a month after intervention depicting the need for repeated examinations has been suggested[88] as has DUS only in selected patients who may be considered particularly vulnerable to treatment failure[87]. There are also no solid recommendations on surveillance for prosthetic grafts[87]. In this study, peak systolic velocity was used to indicate restenosis both in synthetic and vein grafts, but low mid-graft flow has been suggested as a better predictor of graft failure in prosthetic grafts[89], which may be considered in future studies.

Development of clinical symptoms

This study is one of the few to report on the development of clinical symptoms of CLTI after revascularisation. Figure 9 shows that most patients who were alive and with a preserved leg, were free from CLTI symptoms at both one and two years after the revascularisation procedure, irrespective of the initial treatment modality. Even after five years, few of the patients presented with symptoms of CLTI. Despite the discouraging fact that five years after the intervention half the patients had died and another ten percent were amputated, it is still important to remember that after successful vascular surgery there is a good chance of a durable alleviation of the CLTI symptoms.

Classification and grading systems

It is of crucial importance both for clinical and research purposes, to use commonly accepted classification systems to describe and grade CLTI symptoms. At the time of this study, the Rutherford classification[18,90] was the most common clinical classification system and the TASC II classification[10] was mostly used to describe the extent of the lower limb arterial lesions. Since then, both systems have been evolved and largely replaced in existing guidelines, which may negatively affect the possibilities of comparing studies that use different classification systems.

The current recommended clinical classification system in both the Global Vascular Guidelines on CLTI[9] and the European (ESC/ESVS) PAD guidelines[13] is the WIfI system, which grades the extent of the wound (W), degree of ischaemia (I) and presence of foot infection (fI)[24]. The WIfI system describes the burden of disease but also estimates the risk of amputation and the likelihood of benefiting from revascularisation.

In parallel, also a more elaborated anatomical staging system has been introduced, the GLASS (Global Limb Anatomic Staging System), which defines the target arterial path all the way to the foot including both the femoropopliteal and infrapopliteal artery segments [9]. However, the GLASS system was developed from an endovascular perspective and further studies are warranted to determine how the system can be applied to open surgical procedures. In a retrospective analysis of the BASIL-1 study cohort, the GLASS stage was associated with AFS, survival and limb salvage in the endovascular cohort, but not in the bypass cohort[91].

Health-related quality of life

In this study, disease-specific HRQoL was measured using the VascuQoL-25 questionnaire, which is one of the most common disease-specific HRQoL instruments in CLTI. The mean VascuQoL score at baseline was consistent with other studies on CLTI [20,57,58,92,93]. The pain domain had the lowest score at baseline, which could be expected given that ischaemic rest pain is a primary indication for invasive treatment in CLTI. Despite differences in comorbidity, no significant difference in VascuQoL score at baseline was observed when comparing the endovascular and the bypass cohort, supporting that the instrument reflects CLTI specific QoL values and is not significantly affected by overall comorbidity. The mean VascuQoL score improvement after treatment was statistically significant and the magnitude of the observed VascuQoL changes (displayed as SRM effect size) was considered large at all measurement points. The distribution-based MID value in this study was relatively consistent with that reported in the limited number of other publications on longitudinal VascuQoL score development after invasive treatment in CLTI[58,73]. Most patients who were alive and had a preserved leg experienced long-term clinically meaningful improvement.

The VascuQoL-25 instrument was developed for both IC and CLTI and it has been questioned to what extent it measures the burden of disease accurately at all stages of PAD[92]. However, to the best of our knowledge, no CLTI specific HRQoL instrument is currently available; hence, VascuQoL-25 and the short version VascuQoL-6 have been suggested as most appropriate in patients with CLTI[94]. VascuQoL-6 was developed after the start of this study to meet the demand for a less comprehensive instrument for everyday clinical use[95]. Although response rates in this study may be deemed satisfactory, low response rates are an issue due to the age and complexity of the CLTI patient group, that may be overcome using a shorter questionnaire, however at the expense of some information and nuance.

Cost-effectiveness

The mean hospital cost during two years from intervention was approximately twice as high for bypass surgery as for endovascular intervention. Several studies have reported hospital costs approximately 1.5-2 times higher for bypass surgery during the first 1-3 years after intervention[96-100]. Costs were related to HRQoL in terms of gained QALYs during the two years of follow-up, which were retrieved from the generic HRQoL instrument EQ-5D. A very small difference in HRQoL between the groups resulted in a very high ICER: SEK 6 000 000 per gained QALY, which is far more than what is generally considered cost-effective[69,70,101]. The BASIL study remains the only randomised controlled study yet to have published cost-effectiveness data on invasive treatments in CLTI [50,102]. The initial in-patient hospital costs for bypass surgery were approximately one third higher in the bypass group compared with the endovascular group, but the difference decreased over time and after three years it was no longer significant. Possibly, this could be attributed to a shift towards outpatient costs. Also in the BASIL study, the difference in QALYs between treatment methods was negligible, resulting in a high ICER despite the nonsignificant difference in costs at 3 years. Cost-effectiveness evaluations are planned for both the BEST-CLI study and the BASIL-2 study that will contribute further to our understanding in this area.

It is evident that it is the small denominator, i.e., small differences in HRQoL rather than large differences in costs, that drives up the ICER. Generic HRQoL instruments, such as the EQ-5D consisting of only five questions, provide a broad measure of QoL that is suitable for general estimates of health status, for example in population surveys, but they are not sensitive to smaller changes over time in specific populations defined by a particular condition. For this purpose, disease-specific instruments are recommended[55]. The dilemma is that there are currently no tariffs transferring for example VascuQoL scores into QALYs, which is the recommended outcome measure in cost-effectiveness analyses. Instead, various outcome measures (patency, limb salvage, length of hospital stay) are used in the literature, limiting combined conclusions. Future studies should focus on generating adequate tariffs for directly converting VascuQoL scores into QALYs.

The cost-effectiveness analysis in this study was conducted from the health care payer´s perspective, which is the most common approach in the literature, despite a widespread belief that a societal perspective would be a more accurate way to account for health care costs. In a Markov model-based study, Barshes et al evaluated the cost-effectiveness of various treatment strategies in CLTI from a societal perspective[103]. Bypass-first strategies showed the highest initial costs, but the lowest subsequent annual costs and were associated with the lowest ICER in a 10-year perspective. The authors then performed a sensitivity analysis that simulated the payers´ perspective which conversely resulted in a lower ICER for endovascular-first strategies compared with bypass-first strategies[103]. While a societal approach may result in a more comprehensive description of the total cost consequences that would be of interest for example from a welfare perspective, the health care payer´s perspective may be of greater importance regarding resource allocation within a defined health care system.

Conclusion

Patients with CLTI and the main occlusive arterial target lesion located in the femoropopliteal segment, have a low amputation-free survival also after revascularisation, whether performed with endovascular technique or bypass surgery. The composite amputation-free survival endpoint was mainly driven by high mortality rates, which were relatively constant during a follow-up period of approximately ten years. The risk of major limb amputation was most markedly high during the first year after the revascularisation procedure.

After adjusting for baseline differences between the patients who were treated with endovascular technique and those who had bypass surgery, the average risk of major limb amputation or death from any cause was higher in the endovascular treatment group.

Patients who remained alive and did not suffer a major amputation, showed enduring positive effects on both CLTI symptoms and disease-specific health-related quality of life.

The hospital costs during the first two years after revascularisation were approximately twice as high after bypass surgery compared to endovascular intervention. A very small corresponding gain in quality adjusted life years suggested that bypass surgery would not be considered a cost-effective treatment option in the studied CLTI population.

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Appendix

Appendix 1

EQ-5D; Swedish version

Rörlighet
□ jag går utan svårigheter
□ jag kan gå men med viss svårighet
□ jag är sängliggande

Hygien
□ jag behöver ingen hjälp med min dagliga hygien, mat eller påklädning
□ jag har vissa problem att tvätta eller klä mig själv
□ jag kan inte tvätta eller klä mig själv

Huvudsakliga aktiviteter (arbete, studier, hushållssysslor, familje- och fritidsaktiviteter)
□ jag klarar av mina huvudsakliga aktiviteter
□ jag har vissa problem att klara av mina huvudsakliga aktiviteter
□ jag klarar inte av mina huvudsakliga aktiviteter

Smärtor/besvär
□ jag har varken smärtor eller besvär
□ jag har måttliga smärtor eller besvär
□ jag har svåra smärtor eller besvär

Oro/nedstämdhet
□ jag är inte orolig eller nedstämd
□ jag är orolig eller nedstämd i viss utsträckning
□ jag är i högsta grad orolig eller nedstämd

Appendix 2

VascuQoL-25; Swedish version

1. Under de senaste 2 veckorna har jag haft ont i benet eller foten när jag gått:
    1 □ hela tiden
    2 □ största delen av tiden
    3 □ en del av tiden
    4 □ ibland
    5 □ lite av tiden
    6 □ nästan aldrig
    7 □ aldrig

2. Under de senaste 2 veckorna har jag varit orolig för att jag skulle kunna skada benet
    1 □ hela tiden
    2 □ största delen av tiden
    3 □ en del av tiden
    4 □ ibland
    5 □ lite av tiden
    6 □ nästan aldrig
    7 □ aldrig

3. Under de senaste 2 veckorna har kalla fötter gett mig
    1 □ väldigt mycket obehag eller besvär
    2 □ mycket obehag eller besvär
    3 □ en del obehag eller besvär
    4 □ måttligt obehag eller besvär
    5 □ något obehag eller besvär
    6 □ mycket lite obehag eller besvär
    7 □ inget obehag eller besvär alls

4. Under de senaste 2 veckorna har min förmåga att kunna motionera eller delta i någon sport på grund av den dåliga cirkulationen i benen varit
    1 □ fullständigt begränsad
    2 □ väldigt mycket begränsad
    3 □ mycket begränsad
    4 □ måttligt begränsad
    5 □ lite begränsad
    6 □ nästan inte alls begränsad
    7 □ inte begränsad alls

5. Under de senaste 2 veckorna har jag känt trötthet eller svaghet i benen
    1 □ hela tiden
    2 □ största delen av tiden
    3 □ en del av tiden
    4 □ ibland
    5 □ lite av tiden
    6 □ nästan aldrig
    7 □ aldrig

6. Under de senaste 2 veckorna har min förmåga att vara tillsammans med mina vänner eller släktingar varit begränsad på grund av den dåliga cirkulationen i benen

1 □ hela tiden
2 □ största delen av tiden
3 □ en del av tiden
4 □ ibland
5 □ lite av tiden
6 □ nästan aldrig
7 □ aldrig

7. Under det senaste 2 veckorna haft ont i foten eller benet efter det att jag har gått och lagt mig på kvällen

1 □ hela tiden
2 □ största delen av tiden
3 □ en del av tiden
4 □ ibland
5 □ lite av tiden
6 □ nästan aldrig
7 □ aldrig

8. Under de senaste 2 veckorna har stickningar och domningar i benet eller foten gett mig

1 □ väldigt mycket obehag eller besvär
2 □ mycket obehag eller besvär
3 □ en del obehag eller besvär
4 □ måttligt obehag eller besvär
5 □ något obehag eller besvär
6 □ mycket lite obehag eller besvär
7 □ inget obehag eller besvär alls

9. Under det senaste 2 veckorna har sträckan jag kan gå ökat

1 □ inte alls (oförändrad eller har minskat)
2 □ mycket lite
3 □ något
4 □ måttligt
5 □ en hel del
6 □ mycket
7 □ väldigt mycket

10. Under de senaste 2 veckorna har min förmåga att gå på grund av den dåliga cirkulationen i benen varit

1 □ fullständigt begränsad
2 □ väldigt mycket begränsad
3 □ mycket begränsad
4 □ måttligt begränsad
5 □ lite begränsad
6 □ nästan inte alls begränsad
7 □ inte begränsad alls

11. Under de senaste 2 veckorna har jag oroat mig över att jag är eller håller på att bli bunden vid hemmet

1 □ väldigt mycket
2 □ mycket
3 □ en hel del
4 □ måttligt
5 □ något
6 □ mycket lite
7 □ inte alls

12. Under de senaste 2 veckorna har jag bekymrat mig över att jag har dålig cirkulation i benen

1 □ hela tiden
2 □ största delen av tiden
3 □ en del av tiden
4 □ ibland
5 □ lite av tiden
6 □ nästan aldrig
7 □ aldrig

13. Under de senaste 2 veckorna har jag känt smärta i foten eller benet när jag varit stillasittande

1 □ hela tiden
2 □ största delen av tiden
3 □ en del av tiden
4 □ ibland
5 □ lite av tiden
6 □ nästan aldrig
7 □ aldrig

14. Under de senaste 2 veckorna har min förmåga att gå uppför trappor på grund av den dåliga cirkulationen i benen varit

1 □ fullständigt begränsad
2 □ väldigt mycket begränsad
3 □ mycket begränsad
4 □ måttligt begränsad
5 □ lite begränsad
6 □ nästan inte alls begränsad
7 □ inte begränsad alls

15. Under de senaste 2 veckorna har min förmåga att delta i aktiviteter tillsammans med andra människor på grund av den dåliga cirkulationen i benen varit

1 □ fullständigt begränsad
2 □ väldigt mycket begränsad
3 □ mycket begränsad
4 □ måttligt begränsad
5 □ lite begränsad
6 □ nästan inte alls begränsad
7 □ inte begränsad alls

16. Under de senaste 2 veckorna har min förmåga att utföra vanligt hushållsarbete på grund av den dåliga cirkulationen i benen varit

1 □ fullständigt begränsad
2 □ väldigt mycket begränsad
3 □ mycket begränsad
4 □ måttligt begränsad
5 □ lite begränsad
6 □ nästan inte alls begränsad
7 □ inte begränsad alls

17. Under de senaste 2 veckorna har sår på benet eller foten gett mig smärta eller obehag

1 □ hela tiden
2 □ största delen av tiden
3 □ en del av tiden
4 □ ibland
5 □ lite av tiden
6 □ nästan aldrig
7 □ aldrig

18. På grund av den dåliga cirkulationen i mina ben har de aktiviteter som jag skulle ha velat ägna mig åt under de senaste 2 veckorna varit

1 □ väldigt mycket begränsade
2 □ mycket begränsade
3 □ måttligt begränsade
4 □ lite grann begränsade
5 □ mycket lite begränsade
6 □ knappast begränsade alls
7 □ inte alls begränsade

19. Under de senaste 2 veckorna har problem på grund av dålig cirkulation i benen gjort att jag har känt mig irriterad

1 □ hela tiden
2 □ största delen av tiden
3 □ en del av tiden
4 □ ibland
5 □ lite av tiden
6 □ nästan aldrig
7 □ aldrig

20. När jag under de senaste 2 veckorna fått ont i benet eller foten har det gett mig

1 □ väldigt mycket obehag eller besvär
2 □ mycket obehag eller besvär
3 □ en del obehag eller besvär
4 □ måttligt obehag eller besvär
5 □ något obehag eller besvär
6 □ mycket lite obehag eller besvär
7 □ inget obehag eller besvär alls

21. Under de senaste 2 veckorna har jag haft skuldkänslor för att jag är beroende av vänner eller släktingar

1 □ hela tiden
2 □ största delen av tiden
3 □ en del av tiden
4 □ ibland
5 □ lite av tiden
6 □ nästan aldrig
7 □ aldrig

22. På grund av den dåliga cirkulationen i benen har min förmåga att gå och handla eller bära kassar under de senaste 2 veckorna varit

1 □ fullständigt begränsad
2 □ väldigt mycket begränsad
3 □ mycket begränsad
4 □ måttligt begränsad
5 □ lite begränsad
6 □ nästan inte alls begränsad
7 □ inte begränsad alls

23. Under de senaste 2 veckorna har jag oroat mig för risken att förlora en del av benet eller foten

1 □ hela tiden
2 □ största delen av tiden
3 □ en del av tiden
4 □ ibland
5 □ lite av tiden
6 □ nästan aldrig
7 □ aldrig

24. Under de senaste 2 veckorna har sträckan jag kan gå minskat

1 □ väldigt mycket
2 □ mycket
3 □ en hel del
4 □ måttligt
5 □ något
6 □ mycket lite
7 □ inte alls

25. Under de senaste 2 veckorna har jag känt mig nedstämd på grund av den dåliga cirkulationen i benen

1 □ hela tiden
2 □ största delen av tiden
3 □ en del av tiden
4 □ ibland
5 □ lite av tiden
6 □ nästan aldrig
7 □ aldrig