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MAJOR LOWER LIMB AMPUTATION IN PERIPHERAL ARTERIAL DISEASE

TREATMENT OUTCOME, RISK FACTORS, AND
HEALTH-RELATED QUALITY OF LIFE

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Major lower limb amputation in peripheral arterial disease Treatment outcome, risk factors, and Health-Related Quality of Life

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” Don ’t put off until tomorrow what you can do today ”

Benjamin Franklin

To Daniel, Ebba & Adam, with love

ABSTRACT

Critical limb ischemia is the end stage of peripheral arterial disease. These patients have a high risk of amputation and death regardless of revascularization. One of the most important questions for the patient and the surgeon is the risk of amputation despite a revascularization attempt. Some patients with poor vascular anatomy may be better served by a primary below knee amputation than by a high-risk revascularization procedure. Furthermore, patients with critical limb ischemia that undergo an amputation have a high risk of stump complications and re-amputation. An amputation below knee is associated with more complications related to wound healing than an above knee amputation. On the other hand, a patient with an amputation below knee has a 50% higher chance to learn to walk compared to those having an above-knee amputation.

Mobility has been found to be an important factor for the patient's Health-Related Quality of Life after an amputation. However, the association between mobility, use of prosthesis and perceived Health-Related Quality of Life among those amputated due to peripheral arterial disease is largely unknown. Furthermore, knowledge regarding the patients' experience of the amputation decision and the first time after an amputation is sparse. Most of the performed studies consist of patients referred to a rehabilitation ward, resulting in a selection of healthier patients. As patients amputated due to peripheral arterial disease are older with significant comorbidities, transferring results from studies of populations with trauma or cancer as indication is problematic.

The overall aims with this thesis was to study patient-related risk factors for amputation and re-amputation in patients revascularized for critical limb ischemia and to enhance the knowledge regarding the use of prosthesis, its impact on the patients' perceived Health-Related Quality of Life, and their experience of having had an amputation.

Paper I assessed risk factors for amputation in 855 patients amputated after a revascularization due to critical limb ischemia. It was a population-based cohort study using data from the Swedvasc Registry in 2009-2013 with follow-up data until 2017. Risk factors for amputation were assessed using a competing risk analysis and compared to a Cox's proportional-hazards regression. Age (subdistribution hazard ratio [sub-HR], 0.98; confidence interval [CI], 0.97-1.00), preoperative ambulatory status (independent versus bedridden) (sub-HR, 4.10; CI, 2.14-7.86) and ischaemic wound versus rest pain (sub-HR, 3.03; CI, 1.72-5.36) were associated with an increased risk in the analysis using competing risk regression. In

comparison, in the analysis using Cox regression, female versus male sex (hazard ratio [HR], 0.77; CI, 0.64-0.94), age (HR, 1.02; CI, 1.01-1.03), renal impairment (HR, 2.08; CI, 1.61-2.67), preoperative ambulatory status (independent versus bedridden) (HR, 3.45; 2.30-5.18) and ischaemic wound versus rest pain (HR, 2.41; CI, 1.78-3.25) were risk factors associated with an increased risk for amputation.

Paper II assessed risk factors for re-amputation in 288 patients amputated in 2007-2013 due to critical limb ischemia. Fifty patients had a re-amputation during the follow-up (2007-2017). Those having ischemic pain as indication for their amputation had a nearly four times higher risk of a re-amputation compared to those with a non-healing ulcer (subdistribution hazard ratio (sub-HR), 3.55; CI, 1.55-8.17).

Paper III was a prospective cohort study of 98 patients undergoing a major amputation due to peripheral arterial disease 2014-2018. The patients were included at the hospital in connection with their amputation. An interview regarding the patients' functional level the week before the amputation as well as an assessment of Health-Related Quality of Life using the EQ-5D-3L questionnaire was performed at baseline. At the one-year follow-up a semi-structured interview by telephone was performed. Health-Related Quality of Life was measured using the EQ-5D-3L questionnaire. Prosthesis use and prosthesis wearing habit were evaluated using the Stanmore Harold Wood mobility scale and the Houghton scale. Out of the 73 patients that completed the one-year follow-up, 23 were classified as walkers. All patients had an increased Health-Related Quality of Life at follow-up in comparison to their baseline measure. The largest difference in EQ-5D-3L value index was in the group that walked with a prosthesis, 0.12 (IQR =0.09-0.36) at baseline compared to 0.78 (IQR=0.52-0.82) at follow-up, $p<.001$.

Paper IV was an interview study of 13 patients who had undergone a major amputation due to peripheral arterial disease. The interviews were analyzed using content analysis and resulted in three themes: "From irreversible problem to amputation decision", "A feeling of being in a vacuum" and "Adaptation to the new life". The patients expressed a feeling of lack of knowledge of the process after the amputation and what to expect in the future. They did not feel that the healthcare givers had taken enough time to explain the whole process to them. Even so, the patients felt satisfied with their amputation decision, and some expressed that the decision should have been made earlier.

In conclusion: There is a risk for biased estimates using standard survival methods in cohorts with a high mortality. A competing risk regression that takes the competing event of death into account may improve the prediction of the actual risk of amputation. Patients with ischemic pain as indication for their amputation have a high risk of a re-amputation. Prosthesis use is important for the patients' perceived Health-Related Quality of Life. Patients who walked or were able to use their prosthesis for independent movement had an increased level of Health-Related Quality of Life at follow-up compared to baseline. The patients need more information regarding the whole process of the amputation in order to increase their feeling of being involved in the care. To reduce unnecessary suffering and increase the patient's Health-related Quality of Life, amputation may be presented earlier in the process as a treatment alternative.

SUMMARY IN SWEDISH

(svensk sammanfattning)

Bakgrund

Benartärsjukdom orsakas av dålig blodtillförsel i benen och beror vanligtvis på åderförkalkning. Det är en vanlig sjukdom, cirka 10% av Sveriges befolkning över 65 år beräknas vara drabbade. Det otillräckliga blodflödet medför att patienten drabbas av smärta i benen och i vissa fall utvecklar sår. Den allvarligaste formen av sjukdomen kallas för kritisk ischemi och innebär att blodcirkulationen är så dålig att patienten har smärta i benen även i vila. Patientgruppen har en förhöjd risk att drabbas av en amputation till följd av den vävnadsdöd som den nedsatta blodcirkulationen medför. Patienter med benartärsjukdom har även en ökad dödlighet, då det är vanligt att åderförkalkningen påverkar hela hjärt-kärlsystemet.

De behandlingsmetoder som finns att tillgå för att förbättra blodflödet till det drabbade benet är endovaskulära metoder, där behandlingen utförs via blodkärl, eller öppen kirurgi. Dessa behandlingar kombineras med rådgivning om livsstilsförändringar och minskning av eventuella riskfaktorer. Trots kärlkirurgisk behandling behöver ungefär 10% av patienterna genomgå en amputation. Hos vissa patienter saknas möjligheten till en kärlkirurgisk behandling vilket medför att en primär amputation behöver utföras.

I Sverige genomgår ca 3000 patienter en amputation på den nedre extremiteten varje år och majoriteten av dessa utförs på grund av att patienten har benartärsjukdom och/eller diabetes. Amputationer kan utföras på olika nivåer, i denna avhandling ingår amputationer som är på underben-, knä- eller lårbensnivå. Att genomgå en amputation innebär en stor förändring för patienten och studier har visat att det är ett svårt beslut att fatta för såväl patient som läkare. Möjlighet till att lära sig att gå med en protes är viktig för patientens upplevelse av självständighet. Valet av amputationsnivå har stor betydelse för om patienten ska kunna lära sig att gå med en protes, då en underbensamputation bland annat kräver mindre muskelstyrka hos patienten än en lårbensamputation. Nackdelen med en amputation på underbenet är att det innebär en större risk för att patienten behöver genomgå en re-amputation. Val av amputationsnivå är ett kliniskt beslut som tas av den behandlande läkaren då det idag saknas riktlinjer som stöd för beslutet.

Den övergripande målsättningen med avhandlingen var att belysa följande frågeställningar:

1. Vilka riskfaktorer finns för amputation hos patienter som genomgått ett kärlkirurgiskt ingrepp?
2. Vilka är riskfaktorerna för att patienten ska behöva genomgå en re-amputation?
3. Påverkar protesanvändning efter en amputation patienternas livskvalitet?
4. Hur ser patienternas upplevelse av att genomgå en amputation ut?

Delarbete I analyserade 855 patienter som genomgått kärlkirurgisk behandling för kritisk ischemi under åren 2009–2013. Under studieperioden som sträckte sig från 2009–2017 genomgick 178 patienter (21%) en amputation, varav majoriteten gjordes inom ett år efter den kärlkirurgiska behandlingen. Dödligheten i patientgruppen var hög, under studieperioden avled 49%.

Riskfaktorer för amputation analyserades med en competing risk regression och jämfördes med en Cox regressions analys. Riskfaktorer för amputation skiljde sig åt mellan de två analysmetoderna. I analysen med competing risk regression fann vi att patienter med nedsatt gångförmåga, hög ålder samt ischemiskt sår som indikation hade en ökad risk för att behöva genomgå en amputation trots kärlkirurgisk behandling.

Delarbete II analyserade 288 patienter som genomgått en amputation under åren 2007–2017 efter ett kärlkirurgiskt ingrepp. Under uppföljningstiden genomgick 50 patienter en eller flera re-amputationer till en högre nivå. Patienter med ischemisk smärta som indikation till amputationen hade nästan fyra gånger så hög risk att behöva genomgå en re-amputation jämfört med patienter som hade sår som indikation (sHR, 3.55; CI 1.55 – 8.17).

Delarbete III var en prospektiv studie där 98 patienter som genomgått en amputation under åren 2014–2018 inkluderades. Vid inklusionen fyllde patienterna i en enkät om upplevd livskvalitet (EQ-5D-3L) samt svarade på frågor om deras gångförmåga veckan innan operation. Efter ett år följdes patienterna (n=73) upp via telefon. Intervjun utgick från EQ-5D-3L samt frågor om eventuell protesanvändning. Samtliga patienter skattade en högre livskvalitet ett år efter amputation jämfört med värdet innan de genomgått sin amputation. Den största skillnaden i upplevd livskvalitet efter ett år var i gruppen som klassades som gångare (0.78; IQR 0.52-1.00 vid ett år jämfört med 0.12; IQR -0.04-0.59, $p<.001$ vid inkludering).

Delarbete IV var en intervjustudie där 13 patienter från delarbete III ingick. Intervjun utfördes två månader efter amputationen och utgick utifrån patienternas upplevelse av att genomgå en amputation. Intervjuerna analyserades med innehållsanalys och resulterade i tre teman: "Från irreversibla symtom till amputationsbeslut", "En känsla av att befinna sig i ett vacuum" samt "Anpassning till sin nya livssituation". Patienterna upplevde en informationsbrist då beslutet om en amputation fattades. De ansåg inte att hälso- och sjukvårdspersonalen hade tagit sig tid att förklara hela processen kring amputationen. Trots detta upplevde samtliga patienter sig nöjda med sitt beslut att genomgå en amputation, vissa uttryckte även en önskan om att beslutet om amputation skulle fattats tidigare i processen.

Sammanfattning: Det finns en risk för felaktiga uppskattningar av riskfaktorer vid användandet av en Cox regression i patientgrupper med hög dödlighet. Nedsatt gångförmåga innan kärlkirurgisk behandling är en stark riskfaktor för att patienten behöver genomgå en amputation. Patienter som har en ischemisk smärta som indikation till sin amputation har hög risk för att drabbas av en re-amputation. Det är viktigt för patientens livskvalitet att kunna bli protesanvändare efter en amputation. Det gäller även den gruppen som enbart kan använda sin protes för förflyttningar mellan säng och rullstol. Patienter som ska genomgå en amputation behöver informeras om hela processen i samband med amputationen för att underlätta att de upplever sig delaktiga i sin vård. För att undvika onödigt lidande bör beslutet om en amputation fattas i ett tidigare skede för vissa av våra patienter.

LIST OF SCIENTIFIC PAPERS

- I. **Risk factors for amputation are influenced by competing risk of death in patients with critical limb ischemia**
Torbjörnsson E, Blomgren L, Fagerdahl A-M, Boström L, Ottosson C, Malmstedt J.
Journal of Vascular Surgery, 2019. Epub ahead of print.
Doi.org/10.1016/j.jvs.2019.07.074
- II. **Risk factors for re-amputations in patients amputated after revascularization for critical limb ischemia**
Torbjörnsson E, Fagerdahl A-M, Blomgren L, Boström L, Ottosson C, Malmstedt J.
Submitted manuscript
- III. **Health-Related Quality of Life and prosthesis use among patients amputated due to peripheral arterial disease – a one-year follow-up.**
Torbjörnsson E, Ottosson C, Boström L, Blomgren L, Malmstedt J, Fagerdahl A-M
Submitted manuscript
- IV. **The patient's experience of amputation due to peripheral arterial disease**
Torbjörnsson E, Ottosson C, Blomgren L, Boström L, Fagerdahl A-M
Journal of Vascular Nursing. 2017; 35(2):57 - 63.

CONTENTS

1. INTRODUCTION.....	1
2. BACKGROUND.....	2
2.1 Peripheral arterial disease.....	2
2.1.1 Survival analysis in patients with critical limb ischemia.....	2
2.1.2 Patients' experiences of living with critical limb ischemia	3
2.2 Lower limb amputation	3
2.2.1 Identifying patients with high risk of amputation and re- amputation	4
2.2.2 The experience of an amputation.....	5
2.2.3 Prosthesis use and Health-Related Quality of Life after a major lower limb amputation	5
2.3 Health-Related Quality of Life.....	6
2.4 Thesis conceptual framework	6
3. AIMS OF THE THESIS	8
4. METHODS AND PARTICIPANTS.....	9
4.1 Study design	9
4.1.1 Swedish National Registry for Vascular Surgery (Swedvasc)	9
4.1.2 Swedish National In-Patient Registry (IPR)	10
4.1.3 Chart review	10
4.1.4 The EQ-5D-3L questionnaire	10
4.1.5 Prosthesis use	11
4.1.6 Definitions used in the papers.....	12
4.2 Participants and data collection.....	12
4.2.1 Paper I.....	12
4.2.2 Paper II	13
4.2.3 Paper III.....	13
4.2.4 Paper IV.....	14
4.3 Data analysis.....	15
4.3.1 Paper I and II	15
4.3.2 Paper III	16
4.3.3 Paper IV.....	16
4.4 Ethical permits and considerations	17
5. RESULTS.....	19
5.1 Paper I.....	19
5.2 Paper II.....	19
5.3 Paper III	20
5.4 Paper IV	21
6. DISCUSSION	23
6.1 General discussion and main findings	23

6.1.1	Amputation and mortality among patients with critical limb ischemia	23
6.1.2	Survival analysis and absolute risk.....	24
6.1.3	Risk factors for amputation after revascularization	24
6.1.4	The amputation decision	25
6.1.5	Risk factors for complications after a major amputation.....	26
6.1.6	The experience of having an amputation.....	27
6.1.7	Prosthesis use and its importance for the patient's perceived Health-Related Quality of Life	28
6.2	Methodological considerations	29
6.2.1	Internal validity	29
6.2.2	External validity	32
6.3	Implications for clinical practice.....	33
6.4	Implications for the research field.....	33
7.	CONCLUSIONS	34
8.	FUTURE PERSPECTIVES.....	35
9.	ACKNOWLEDGEMENTS.....	36
10.	REFERENCES.....	39

LIST OF ABBREVIATIONS

AKA	Above knee amputation
AFS	Amputation-free survival, time to death or major amputation, whichever occurs first
BKA	Below knee amputation
CI	Confidence interval
CLI	Critical Limb Ischemia
CLTI	Chronic Limb-Threatening Ischaemia
EQ-5D-3L	EuroQol Group trademark for a standardized instrument for use as a measure of health outcome
EQ-5D index	Summary index in EQ-5D-3L index
HR	Hazards ratio
HRQoL	Health-Related Quality of Life
IPR	The Swedish National In-Patient Registry
IQR	Inter quartile range
PAD	Peripheral arterial disease
P-value	Probability value
SD	Standard Deviation
sHR	Subdistribution hazard ratio
Swedvasc	Swedish National Registry for Vascular Surgery
WIFI-score	Risk stratification based on Wound, Ischemia and foot Infection

1. INTRODUCTION

Peripheral arterial disease (PAD) is a disease with a large impact on the patient's Health-Related Quality of Life (HRQoL) as it is associated with a high risk of lower extremity amputation, morbidity and death (1-3). Revascularization in older patients is primarily intended to relieve pain, maintain the patient's ambulatory function, improve the HRQoL and preserve an independent living (4). A major amputation is often seen as the last alternative when all treatments to salvage the leg have failed (5). However, some patients may benefit from an earlier amputation (6). Patients have described that the path towards an amputation is characterized by pain and problems with wound healing (7, 8). Another important factor is that the possibility to learn to walk with a prosthesis increases if the patient is ambulatory before the amputation (9).

The overall research questions during this work has been if there is a certain group of patients that is likely to undergo an amputation despite a revascularization and if there are better ways to predict those that will have complications that will lead to a re-amputation. Further, I have tried to gain information of the patient's experience of becoming an amputee.

During my work with this thesis I have met many patients who have expressed their situation as an amputee with the words "I should have made this decision much earlier". On the other hand, there have also been a few patients who have expressed the opposite "I do not wish that this should happen to my worst enemy". These quotes exemplify the difficulties in decision making, the surgeon and the patient know how the situation is today, but it is hard to tell how the future will appear and how the patient will react to his/her situation. My intention with this thesis has been to bring valuable information that can guide within the choice between a revascularization or a primary amputation.

2. BACKGROUND

2.1 PERIPHERAL ARTERIAL DISEASE

PAD is becoming more frequent, with an estimated prevalence of 237 million people worldwide. Smoking, diabetes, hypertension and hypercholesterolemia are risk factors associated with PAD. The need of vascular surgery will probably increase in the future due to an aging population and an increased prevalence of type 2 diabetes (10). PAD is divided into three stages: asymptomatic disease, intermittent claudication, and critical limb ischemia (CLI). CLI, defined as chronic ischemic rest pain or non-healing ulceration or gangrene, is the most severe form (11). The term CLI is debated, as it fails to include all patients treated for limb-threatening ischemia. The Global Guidelines, published in 2019, recommended term and abbreviation is Chronic Limb-Threatening Ischemia (CLTI) as it includes a broader group of patients with varying degrees of ischemia having an increased risk of amputation (6). However, as CLI was the most common abbreviation when this project started, it has been used throughout the papers in this thesis for consistency.

Patients with CLI is a patient group with multiple chronic co-morbidities, especially diabetes and cardiovascular disease (12). The mortality is 16-35% in the first year after diagnosed with CLI and it seems to continue at the same level (13, 14).

There are few available data to support the optimal treatment strategy in patients with CLI (15). The Bypass versus Angioplasty in Severe Ischemia of the Leg (BASIL-1) trial is a randomized controlled multicenter study designed to try to answer the question of whether bypass surgery first or balloon angioplasty first is the recommended treatment for patients with CLI (16). It showed no short-term differences in time to death or major amputation (amputation-free survival, AFS), between those treated with bypass first or angioplasty first. However, the study indicated that open surgery has an advantage over time (17).

2.1.1 Survival analysis in patients with critical limb ischemia

Within vascular research, the composite outcome AFS has been recommended as an outcome measure, as disregarding of mortality (in for example limb salvage) may yield a biased result (4, 17). To understand the risk of an amputation after revascularization, it is important to consider which patients are at risk. A risk factor that is associated with an increased risk of death may give a biased estimate of the risk of amputation, as the outcome AFS includes and is dominated by mortality. Competing risk analysis is a method to study specific outcomes

(such as amputation) and at the same time take a competing event (death) into consideration and has been shown to give less biased estimates (18, 19). The use of a competing risk regression is uncommon within vascular research. One recently published study of 164,000 patients undergoing revascularization has compared the Cox proportional hazards regression with a competing risk regression. The study showed that the 5-year risk of amputation was overestimated when using standard survival methods compared to a competing risk regression (20).

2.1.2 Patients' experiences of living with critical limb ischemia

Research in CLI has traditionally focused on evaluating the outcome of the treatment in graft patency, amputation, and mortality. However, it is a disease that has a large impact on the patient as it is associated with a high risk of amputation, morbidity and death (1-3, 21). Studies have reported lower scores in HRQoL in patients with CLI compared to the general population, especially in the dimensions including physical functioning, physical activity, and bodily pain (22-24). Further, some evidence supports a decreased HRQoL in patients with CLI regardless of treatment. A two-year follow-up study of patients with CLI showed no significant difference in HRQoL whether the patients had had endovascular, open surgical, or conservative treatment (25). Additionally, the BASIL-1 trial evaluated differences in cost-effectiveness or HRQoL in patients treated with bypass surgery first or balloon angioplasty first. Both treatment groups had an increased HRQoL the first three months after intervention, with no further improvement during followup. Patients with an amputation during follow-up had a slightly decreased HRQoL compared to those without. However, data on HRQoL were missing for about one third of the patients, which may have affected the result (22). Repeated interventions seems to have a negative impact on the patients' HRQoL (26).

2.2 LOWER LIMB AMPUTATION

The yearly incidence of major amputations in Sweden is 33-37 per 100,000 inhabitants, and 90% are due to PAD or diabetes (27). A transtibial amputation is the most common level, followed by a transfemoral amputation. The level of the amputation contributes to the ability to learn to walk with a prosthesis (28, 29). A below knee amputation (BKA) is preferable as those patients have a 50% higher chance to learn to walk again and thereby receive a good functional outcome (30). However, the possibility of a BKA is dependent on existing gangrene, necrosis, or infection in the patient's limb. Additionally, a BKA involves more problems with complications related to wound healing (31).

In patients where revascularization is inappropriate, primary amputation is an option (32). A patient with poor distal vascular status may be better served with a BKA than with a high-risk bypass, as a failed bypass might lead to a higher amputation level, making it harder for the patient to learn to walk again (9). Studies show that in patients with little likelihood of wound healing there is an equal, or sometimes better, perceived HRQoL after an amputation than after extensive revascularization (33).

2.2.1 Identifying patients with high risk of amputation and re-amputation

As the mortality in patients with CLI is high regardless of revascularization, one of the most important questions for the surgeon and the patient is the risk of amputation despite a revascularization attempt. There are risk assessment scores aiming at providing surgeons and patients with information regarding the risk of an amputation (34, 35), but these scores are seldom used in the clinical setting (36). The Prevent III score was developed to predict AFS at one year after treatment. The score includes five independent predictors: dialysis, tissue loss, age >75, hematocrit <30, and a history of cardiac disease (35). The Finnvasc risk score found that a patient with at least three of the following risk factors: diabetes, cardiac disease, gangrene or an urgent operation, had an increased risk of AFS within 30 days (34). Both the Prevent III score and the Finnvasc score have some methodological limitations as they are developed from cohorts that only contain patients undergoing open surgery. Further, there are few reliable data regarding their application on different populations (15).

The Society for Vascular Surgery has developed a risk score named the WIfI classification system. The score predicts the risk of amputation within one year and aims, in combination with the individual patient's co-morbidities and risk factors, at providing knowledge to support the decision whether the patient would benefit from an intervention or not. It is based on three independent risk factors: wound extent, degree of ischemia, and extent of foot infection (37). The advantage compared to earlier risk scores is that the WIfI classification system is developed to be applied to patients across a broad spectrum of atherosclerotic occlusive disease of varying severity and distribution.

There are no guidelines or risk scores developed to support the decision regarding amputation level. Previous research is hard to compare due to lacking consensus regarding variables and outcome. Furthermore, the performed studies have a heterogeneity in the study populations, with an inclusion criterion of either all non-traumatic amputations or a mix of patients undergoing both minor and major amputation (38-41).

2.2.2 The experience of an amputation

To undergo an amputation is often seen as the last alternative when all other treatment options to preserve the leg have failed. The aim is then to save life and reduce pain for the patient (5). The fact that an amputation will have a large impact on the patient's HRQoL contributes to the difficulty of the decision (9, 42, 43).

Few studies have described the patient's experience of the early phase of the amputation process. Madsen et al. have developed a theory called "Pendulating", with the aim to describe the process a patient experiences the first weeks after an amputation. They used grounded theory, a method aiming at developing a theory after collection and analysis of data (44). The theory includes three phases, "losing control", "digesting the shock", and "regaining control". During the first phase, "losing control", the patients described a feeling of losing control, as they felt overwhelmed by the situation. They were worried about their future in a combination of feeling relief, gratefulness, panic, and injustice. In the next phase, "digesting the shock", the patients described how they, emotionally and cognitively, processed the shock of having become an amputee. The last step of the process was called "regaining control". The patients expressed the phase as a period where they had taken back control of their situation and had started to build up hope for the future (45).

2.2.3 Prosthesis use and Health-Related Quality of Life after a major lower limb amputation

To obtain and learn how to use a prosthesis is an important factor for the overall HRQoL in patients who have undergone a major amputation (46, 47). To learn to walk with a prosthesis is often the key for the patients' ability to go on living in their home (28). Walking ability with a prosthesis depends on several factors such as the patient's physical and mental status (48), and the rehabilitation and prosthesis-fitting procedure (49). Several issues make it hard to compare results from previous studies. Most of the studies on HRQoL and prosthesis use consists of patients referred to a rehabilitation ward, which gives a selected population, as those with little prerequisite to learn to walk with a prosthesis are not included (50). It has been common to evaluate surgical success after a BKA in numbers of persons who receive a prosthetic limb (9). Some studies have used ability to stand on one leg and physical fitness as a predictor of success in prosthetic use (51). However, it is important to consider that receiving a prosthetic limb is not necessarily the same as using it (52). Furthermore, patients with PAD are generally old and have significant co-morbidities which have an impact on their possibilities to learn to walk with a prosthesis. This makes it hard to transfer results from studies of populations with trauma or cancer as indication for amputation (53).

2.3 HEALTH-RELATED QUALITY OF LIFE

HRQoL involves those aspects of well-being that affect a person's physical and mental health. Within health research, measuring the HRQoL has become an important part of outcome measures in patients with chronic diseases (54). The concept of HRQoL is used with different meanings in the literature. This thesis uses the following definition: *Quality of Life refers to a patient's appraisal of and satisfaction with their current level of functioning as compared to what they perceive to be possible* (55). It is an individual experience, no one else can tell how the individual will react to a situation.

When choosing an instrument to measure the perceived HRQoL, it is important that the questions cover the aim of the study and are valid and reliable (56). Commonly, both a generic instrument that measures patients' overall HRQoL and a disease-specific instrument measuring problems unique for a disease or a condition are used. The benefit with a generic instrument like the EQ-5D-3L questionnaire is that it allows comparing a population in a study to other patient groups and diagnoses (57). On the other hand, the use of a disease-specific instrument increases the specificity and sensitivity within the study (57).

Unfortunately, unlike for PAD where a validated questionnaire named Vascular Quality of Life Questionnaire-6 (58) is available, there is no validated disease-specific instrument for amputees including both patients that uses a wheelchair and those who walk with a prosthesis (47).

2.4 THESIS CONCEPTUAL FRAMEWORK

The framework within this thesis of patients undergoing a major amputation due to PAD is presented in Figure 1. As the amputation decision is a complex situation, the process has been studied in this thesis from different perspectives, the patient's and the surgeon's. A vascular intervention that fails to heal the patient's wound or to reduce ischemic pain can decrease the patient's HRQoL for a long time. On the other hand, an unnecessary amputation could lead to a severe disability. The decision of the amputation level is important for the individual patient. A BKA increases the patient's opportunity to learn to walk with a prosthesis. On the other hand, a BKA contributes to a higher risk of stump complications and re-amputations.

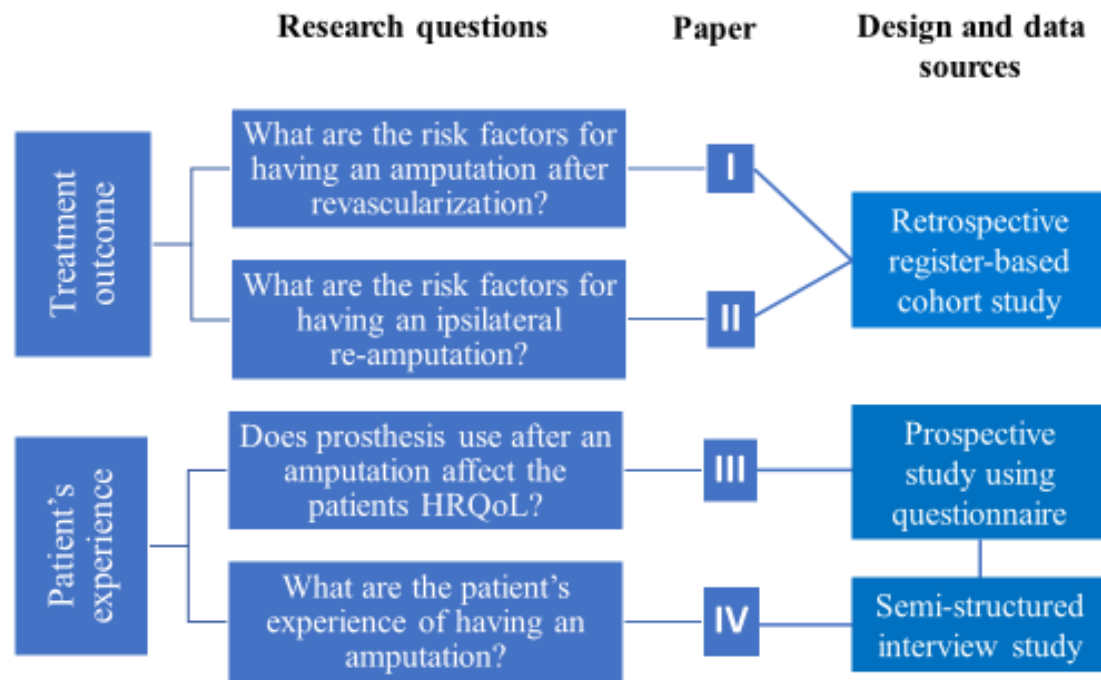


Figure 1. Thesis conceptual framework

3. AIMS OF THE THESIS

The overall aim with this thesis was to study patient related risk factors for amputation and re-amputation in patients revascularized for critical limb ischemia, and to enhance the knowledge regarding the patients' experience of an amputation and the impact on their HRQoL.

The specific aims were:

Paper I

- To estimate risk factors specific for amputation after revascularization in a competing risk framework in patients with critical limb ischemia.

Paper II

- To study risk factors that predict ipsilateral re-amputations after a major limb amputation in patients revascularized due to critical limb ischemia.

Paper III

- To compare the HRQoL between walkers and non-walkers after a major amputation due to peripheral arterial disease.

Paper IV

- To describe the patient's experience of an amputation due to peripheral arterial disease.

4. METHODS AND PARTICIPANTS

4.1 STUDY DESIGN

Different designs and methods have been used depending on the aim and research question with the study (Table 1). All studies in this thesis were conducted with adult patients (> 18 years) treated at Södersjukhuset, Stockholm, Sweden.

Table 1. Overview of the designs and methods used in the included Papers

	Paper I	Paper II	Paper III	Paper IV
Study period	2009-2017	2007-2017	2014-2019	2014-2015
Design	Retrospective cohort study	Retrospective cohort study	Prospective cohort study	Qualitative interview study
Data sources	Swedvasc IPR Chart review	Swedvasc IPR Chart review	EQ-5D-3L The Stanmore Harold Wood mobility grade The Houghton scale	Semi-structured face-to-face interviews
Population	855	288	98	13
Main analysis methods	Competing risk regression Cox regression	Competing risk regression Cox regression	Mann Whitney U-test Two-way ANOVA	Content analysis

4.1.1 Swedish National Registry for Vascular Surgery (Swedvasc)

The Swedish National Registry for Vascular Surgery (Swedvasc) is a population-based, prospective registry covering more than 95% of all arterial vascular procedures performed in Sweden since 1987. Swedvasc is linked with the National Population Registry which contains data on all death certificates signed by a physician, and the coverage of mortality is therefore

100%. Swedvasc has an external validity of 93% for infrainguinal procedures (59), and contains information regarding technical details of the procedures, co-morbidity and demographic details.

To ensure the quality of the data in Paper I and II, we performed a validation using a random sample of 103 patients. Data on operative details and co-morbidity from Swedvasc were compared to the corresponding medical records to assess the accuracy of the data. Sensitivity, specificity, and accuracy were calculated. All variables had an accuracy of $\geq 90\%$ except cardiac disease, and the conclusion was that there was a low risk of misclassification (Supplementary Table I, Paper I).

4.1.2 Swedish National In-Patient Registry (IPR)

Follow-up data in Swedvasc are collected at 30 days and at one year after intervention. When comparing the data from Swedvasc with performed amputations at Södersjukhuset, it appeared that data on amputations were underreported in Swedvasc. Therefore, data for analysis of the primary outcome in Paper I and II, major amputation, was retrieved from the Swedish National In-Patient Registry (IPR). The IPR contains individual information regarding level and date of amputation according to the Swedish version of the Nordic Medico-Statistical Committee (NOMESCO) surgical procedure codes (www.nordclass.uu.se/index_e.htm). The IPR has nearly 100% national coverage and is highly validated (98% correct diagnosis for major amputations) (60).

4.1.3 Chart review

Medical records from all patients who were registered as having had an amputation in the IPR were reviewed. The aim was to ascertain the laterality of the amputation for Paper I and II and to retrieve data on re-amputations for Paper II. Data from the medical chart were also used as a complement in those cases where a variable was missing in Swedvasc. In Paper III, data on the patients' co-morbidity were retrieved from their medical charts.

4.1.4 The EQ-5D-3L questionnaire

EQ-5D-3L is a standardised non-disease-specific instrument for describing and evaluating the patients' HRQoL (61). The questionnaire contains five health dimensions: mobility, self-care, role activity, pain, and anxiety/depression. Each dimension is measured on a three-point Likert-scale (no problem, some problems, or extreme problems). Patients are asked to indicate the level that corresponds to their current level of functioning or experience of each

dimension. The different dimensions can be converted to a summary index, to describe a health status profile. The summary index is based on value sets derived from a representative sample of the general population. As there is no validated value set for EQ-5D-3L (using TTO score) for the Swedish population (62), the United Kingdom value set was used in this thesis (63). Higher values on the summary index indicate better health status, the possible index values range between -0.594 and 1 , where 1 is perfect health and a value less than 0 is a health state worse than death.

The EQ-5D-3L has previously been applied to patients with lower limb amputation, but the ability to detect changes over time in this population has not been evaluated (64, 65).

4.1.5 Prosthesis use

The Stanmore Harold Wood mobility grade (66) and the Houghton scale (67) are two disease-specific questionnaires that assess prosthetic use and wearing habits among patients with lower limb amputation. The questionnaires are self-reported.

The Stanmore Harold Wood mobility grade (66) consists of a question “How is the grade of your mobility?” with six grades of mobility. In this study, level four or higher has been used to define a person who walks with the prosthesis.

1. Does not wear a prosthesis, or uses it only as cosmetic
2. Wears prosthesis only for transfer or help with nursing
3. Walks indoors only using walking aids
4. Walks indoors and outdoors, but regularly uses walking aids
5. Walks independently with no walking aids except occasionally
6. Normal or near normal gait

The Houghton scale is a validated scale with the aim to capture prosthetic wearing habits among patients with lower limb amputation (67). The questionnaire originally consists of four questions with a four-point scale. However, in this study only question one to three were used as the fourth was not recommended for in a validation study (68). The questions used in this paper were “How much time are you using your prosthesis”, “When do you use it” and “Do you use walking aids or a similar tool?”, with four response categories ranging 0-3 (Supplementary Table II, Paper III).

The Houghton scale has a significant test-retest reliability ($p=.01$), a good internal consistency (i.e. measures what it is meant to measure) with a Cronbach’s alpha of 0.71 (an

estimate of consistency) and a good responsiveness (the scale's ability to detect relevant changes).

4.1.6 Definitions used in the papers

Ambulatory status: walking ability two weeks preoperative (independent, walking with aid, wheelchair-bound, or bedridden)

Cardiac disease: current heart failure, angina pectoris, myocardial infarction, coronary bypass- or percutaneous coronary intervention

Current smoker: smoking at the time of, or within 4 weeks prior index operation

Diabetes: type 1 and 2 treated with oral antidiabetics or insulin

Hypertension: systolic blood pressure > 150 mmHg or on antihypertensive medication

Index procedure: the patient's first surgical procedure

Ischaemic status: categorized according to The Society for Vascular Surgery WIfI system (69). Grade 0 (no ischemia): ankle brachial index (ABI) $\geq 0,80$; toe pressure ≥ 60 mmHg, grade 1 (mild ischemia): ABI $\geq 0,6-0,79$; toe pressure 40–59 mmHg, grade 2 (moderate ischemia): ABI $\geq 0,4-0,59$; toe pressure 30–39 mmHg and grade 3 (severe ischemia): ABI $\leq 0,39$; toe pressure <30 mmHg (Paper I)

Major amputation: an amputation above the ankle

Minor amputation: an amputation at, or below, the ankle

Pulmonary disease: chronic obstructive pulmonary disease or emphysema

Renal impairment: a serum-creatinine of >150 mmol/L

Walker (with a prosthesis): being able to walk both indoor and outdoor using walking-aids (Stanmore Harold Wood mobility grade 4 or more)

4.2 PARTICIPANTS AND DATA COLLECTION

4.2.1 Paper I

From the Swedvasc register 855 patients with CLI, who underwent their first-time arterial revascularization in the index leg during 2009-2013 at Södersjukhuset in the Stockholm County region, were identified. Patients with CLI secondary to acute ischemia or

femoral/popliteal aneurysms were excluded.

The outcome was time to first ipsilateral major amputation.

4.2.2 Paper II

From the Swedvasc register we identified 1533 patients treated with infrainguinal revascularization for CLI in one centre for vascular surgery in the Stockholm County region during 2007-2013. Data were crosslinked to the IPR, and 290 patients were identified as having had a major amputation during 2007-2017. Patients with an amputation secondary to any other indication than PAD were excluded (n=2), so the final study population consisted of 288 patients, where 50 patients needed a re-amputation.

Primary outcome was time to ipsilateral re-amputation. Secondary outcome was death from any cause.

4.2.3 Paper III

In Paper III all patients over 18 years who underwent a major amputation at Södersjukhuset, Stockholm, September 2014 – May 2018, were retrieved based on the inclusion criteria: having had an index amputation at tibial, knee, or femoral level and being able to speak Swedish (n=315). In total, 148 patients were contacted by the researcher at the hospital ward in connection with their amputation. After oral and written information about the study, 98 patients accepted to participate, out of which 73 patients completed the one-year follow-up (Figure 2).

Baseline data were collected via personal interviews at the hospital ward and included an interview regarding the functional level the week before the amputation as well as an assessment of HRQoL using the EQ-5D-3L questionnaire (61). Data on co-morbidity and perioperative characteristics on the patients were retrieved from the patients' medical charts.

After 12 months all patients were followed-up by a telephone interview. HRQoL was measured using the EQ-5D-3L. All patients with a prosthesis were asked questions regarding their walking ability and prosthesis wearing habits according to the Stanmore mobility grade (66) and the Houghton scale (67). Both the baseline interviews and the 12 months' follow-up were performed by the same researcher not involved in the patients' care (ET).

With the aim to have a complete follow-up, proxy was used in two patients (70). A caregiver involved in the patient's daily care answered the questions instead of the patient in those cases where they were not capable to explaining their situation.

The primary outcome was HRQoL according to EQ-5D-3L one-year post-amputation. Secondary outcome was to evaluate prosthesis use after a major amputation.

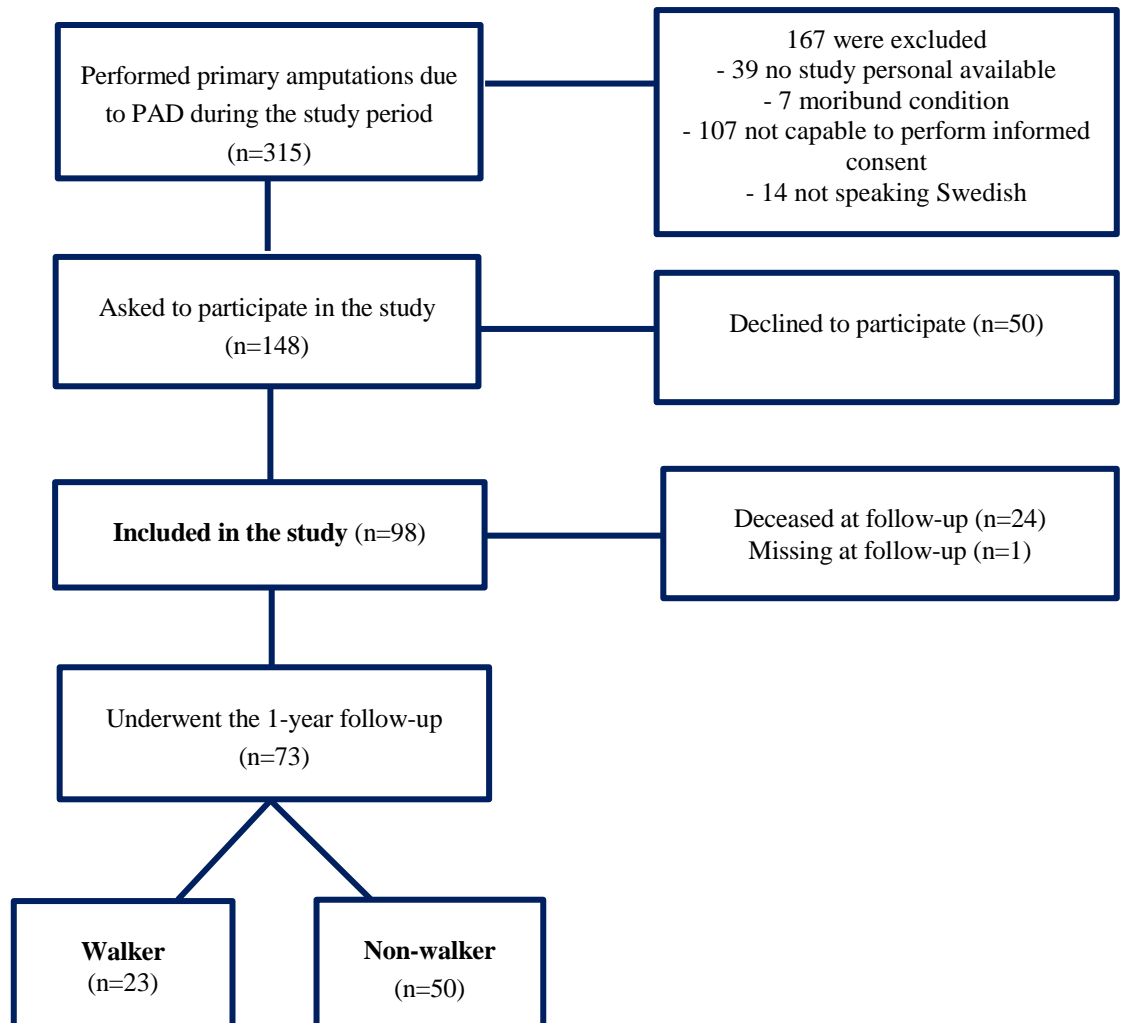


Figure 2. Enrolment and Follow-up in Paper III

4.2.4 Paper IV

A total of 15 patients from Paper III, selected based on age, sex, diagnosis, and level of amputation, were also included in Paper IV. One patient died before the interview was to take place, and one patient repented the consent, so in total 13 interviews were performed.

A qualitative method with semi-structured interviews was used as the aim of the study was to get a deeper understanding of the experience of becoming an amputee. The interviews were performed two months after the amputation. The timing was chosen to give the participants a chance to accept their new situation as well as minimizing the risk of recall bias. The

interviews were performed by one researcher not involved in the patients' care (ET) at a place chosen by the participants. The interviews started with an open-ended, narrative question: "Please tell me about the experiences of the decision of the amputation". To increase the knowledge and to be sure that the participants' comments were correctly understood additional questions were asked for clarification, along with probing questions (71).

4.3 DATA ANALYSIS

Statistical methods were mainly performed using IBM SPSS statistics version 25 (IBM Inc., Chicago, IL, USA). The software R statistical analyses, version 3.4.3 (Foundation for Statistical Computing, Vienna, Austria; <http://www.R-project.org>), was used for the competing risk analysis in Paper I and II and for the analysis of the differences in HRQoL between walkers/non-walkers in Paper III. NVivo Pro qualitative data analysis Software (QSR International PTY Ltd. Version 11, 2015) was used to help structuring the data for the analysis in Paper IV.

In Paper I-III continuous variables with normal distribution were presented with mean and standard deviation (SD) and non-normally distributed data with median and interquartile range (IQR). Baseline differences in categorical variables were evaluated using the Pearson's Chi Square test. In Paper I-II the cumulative incidence function was used to estimate the rate of amputation. A two-tailed *P*-value < .05 was considered statistically significant.

4.3.1 Paper I and II

Censoring occurs when a study ends before a patient reaches the event of interest or a patient leaves the study before the end of follow-up (by death or drop out) (72). Survival methods as the Kaplan Meier and the Cox proportional hazards regression depends on the assumption that the censored data are independent or noninformative, i.e. those who are censored having equal risk of the event as those that remain in the study. However, in patients with CLI, the censoring due to mortality is not independent as the risk of amputation is influenced by the patients' morbidity (73). Thus, the impact of risk factors on amputation was estimated using Fine-Gray competing risks regression and the significance was assessed with Gray's test. Risk factors for mortality were estimated using the Cox regression. The proportional hazards assumption was confirmed by including an interaction term with time in the competing risk model and using Schoenfeld residuals in the Cox regression.

In Paper I we also performed a Cox regression using AFS to estimate risk factors for amputation. The aim was to compare the results from the analysis using competing risk regression. The different models were compared using the Bayes Information Criterion.

4.3.2 Paper III

The Mann-Whitney U-test was used to compare health status between walkers and non-walkers, and Bonferroni's post-hoc test for multiple comparisons was used. A two-way analysis of variance (ANOVA) was performed to explore the differences between HRQoL and prosthetic use. Eta-square was used as the effect size measure.

Sample size

Sample size in studies is based on how many participants are needed to enable detection of a difference between two or more groups. The power calculation in Paper III was based on the null hypothesis that the average EQ-5D-3L index is the same between walker and non-walker (74). As we found no other study to base our calculation on, we estimated the difference of 0.1 in the EQ-5D-3L index between the two groups. To get a power of 80%, 128 patients needed to be included in the study. The inclusion was planned to take part during a period of three years, however it was harder to include patients than we had planned even though we extended the inclusion to another hospital in the Stockholm county region. In May 2018, 98 patients had been included after nearly four years. The research group decided to perform an interim analysis which showed a higher difference in EQ-5D-3L index than estimated, indicating power well above 80% at this sample size. The decision was to end the study.

4.3.3 Paper IV

The interviews in Paper IV were analysed using qualitative content analysis as described by Krippendorff. Content analysis is a technique enabling the researcher to draw replicable and valid inferences from interviews. It enables the researcher an increased understanding of a phenomenon. As the purpose of the study was to seek the how and why beyond the experience of being an amputee, an interview study was found as a preferable method (75). All interviews were transcribed verbatim, read and re-read several times to become familiar with the content and gain a sense of the whole. The analysis did not start until all interviews were performed to achieve stability in the process (75).

Next step was to find the meaning units corresponding to the aim of the study while still preserving the core and label the content with a code. The codes were compared according to

differences and similarities and sorted into sub-themes, after which they were analysed in relation to three different time sequences: the period before the decision, the surgical phase, and the period up to two months after the amputation. The last step in the analysis was to reflect on and discuss the interpretation of the findings within the research group as a way to reach consensus and enhance the credibility (Figure 3). The analysis took the latent underlying meaning of the text into account (75).

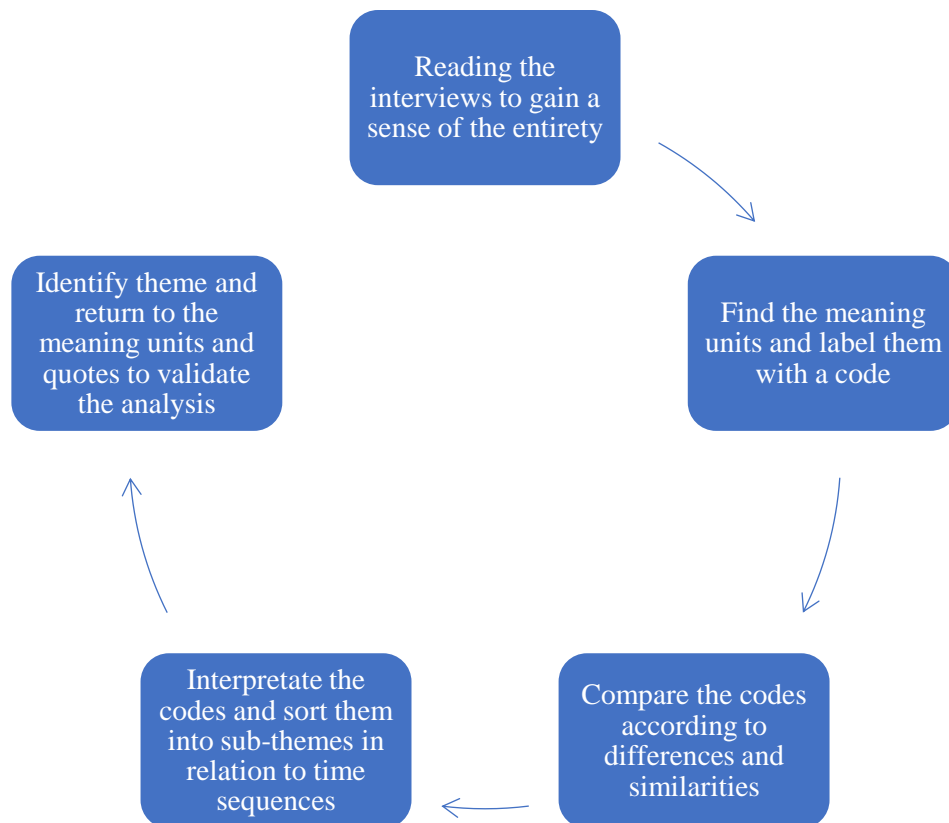


Figure 3. Illustrations of the analysis process in Paper IV

4.4 ETHICAL PERMITS AND CONSIDERATIONS

All studies were conducted according to the principles outlined in the Declaration of Helsinki concerning Ethical Principles for Medical Research involving human subjects (76). To ensure confidentiality, all patients were provided with a code number. The identifying code list was stored in a locked cabinet and kept separate from the data files and the completed questionnaires and interviews. All four studies were approved by the Regional Ethical Review Board, Stockholm, Sweden with the following reference numbers: 2014/801-31/1

(Paper I, II, III and IV), 2015/586–32 (Paper I and II), 2016/2209–32 (Paper I) and 2017/2062-32 (Paper III). Paper III was registered in Clinical Trials.gov ID NCT03570788.

Study I and II were retrospective studies, and as the project did not cause the patient any discomfort no informed consent was seen necessary. All patients who participated in study III and IV were provided with oral and written information, and they signed an informed consent prior to participation. The patients were included in connection with their surgery and many of them were affected by anxiety. As there was a risk that the patients were in a vulnerable situation the information on the study was repeated at the follow-up. The participants were informed that they at any time could withdraw their consent to participate in the study.

5. RESULTS

5.1 PAPER I

During the study period, 178 (21%) patients had an ipsilateral major amputation and 415 (49%) patients died. Most of the amputations were performed during the first year after revascularization (15% of the patients underwent an amputation during the first year). Patients with an amputation during follow-up had a lower 5-year survival compared to them without amputation, 38% compared to 59% ($p < .001$, Log-rank).

Risk factors for amputation were assessed using competing risk and compared to a Cox regression. Overall there were less risk factors associated with major amputation in the competing risk analysis as compared to the one using Cox regression. The multivariable model using competing risk regression identified age (sub-HR 0.98, 95% CI 0.97-1.00), ambulatory status (independent versus bedridden) (sub-HR 4.10, 95% CI, 2.14-7.86), and ischaemic wound versus rest pain (sub-HR 3.03, 95% CI, 1.72-5.36) as risk factors associated with amputation. The Cox regression using AFS as outcome identified female sex (hazard ratio [HR], 0.77; CI, 0.64-0.94), age (HR, 1.02; CI, 1.01-1.03), renal impairment (HR, 2.08; CI, 1.61-2.67), ambulatory status (independent versus bedridden) (HR, 3.45; 2.30-5.18), and ischaemic wound versus rest pain (HR, 2.41; CI, 1.78-3.25) as risk factors.

The patient's ambulatory status prior to revascularization was associated with an increased risk of having an amputation. The multivariable analysis showed that a patient using walking aids had nearly two times higher risk (sub-HR, 1.79; CI, 1.27-2.52) of an amputation compared to those who walked independently two weeks pre-operatively.

5.2 PAPER II

During the study period (2007 – 2017), 50 patients (17%) had a re-amputation. Of those, a third ($n=18$) needed a second re-amputation, performed at a higher level. The mortality in the cohort was 77% ($n=222$) during the eleven-year follow-up.

The multivariable model using competing risk showed that patients having ischemic pain as indication for amputation had an increased risk of re-amputation (sub-HR, 3.55; CI, 1.55–8.17) when compared to those with a non-healing ulcer. Risk factors associated with mortality in the univariable analysis using Cox regression were age, a history of cardiac disease, renal impairment, acute ischemia as indication to vascular surgery, and an

amputation level above knee. Age was the only risk factor that remained associated with mortality in the multivariable analysis (HR, 1.03; CI, 1.02–1.04).

5.3 PAPER III

In Paper III, 73 patients completed the one-year follow-up, of whom 23 were categorized as walkers (walking indoor and outdoor using a prosthesis). The patients had a median value of EQ-5D-3L index at baseline at 0.16 (IQR=-0.46 – 0.54), with no significant difference between walkers and non-walkers ($p=.338$). Contrary to the baseline measure, the patients classified as walkers had a significantly increased HRQoL at the one-year follow-up (0.78, IQR=0.52- 0.82) compared to the non-walkers (0.21, IQR= 0.20-0.40), ($p<.001$). To evaluate the minimal important clinical difference, eta-square was used as effect measure, showing that 20% of the differences in EQ-5D-3L index between walkers and non-walkers at follow-up were accounted for by the ability to walk with a prosthesis.

A prespecified sub-analysis was performed between those classified as a non-user (Stanmore Harold Wood 0-1), a prosthesis-user (Stanmore Harold Wood 2-3), and a walker (Stanmore Harold Wood 4-6). The aim was to evaluate the impact of independent movement. At baseline there were no differences in EQ-5D-3L index between the three groups ($p=.139$). However, the perceived HRQoL was improved at follow-up among those classified as prosthesis-users ($p<.001$) and walkers ($p<.001$). In the group that did not use a prosthesis we could not see any improvement at follow-up ($p=.245$, Figure 4).

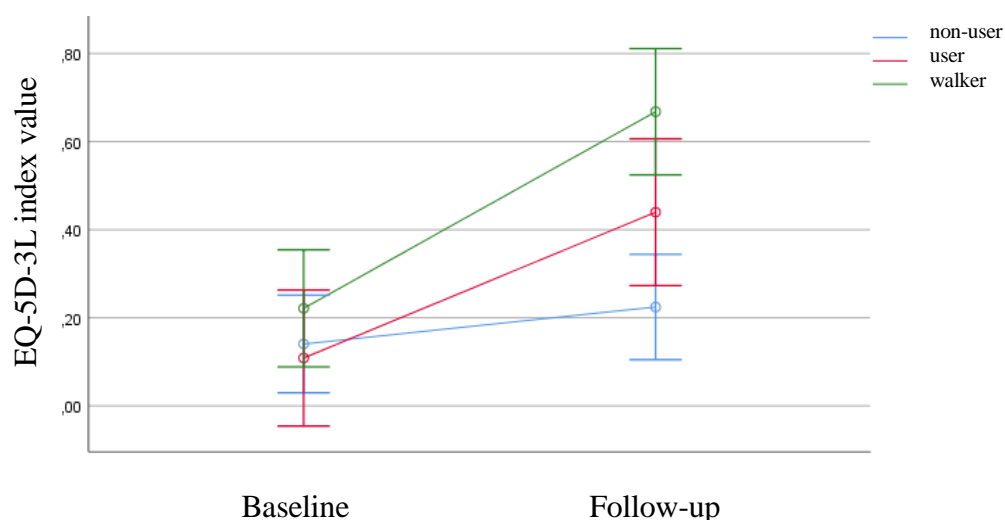


Figure 4. HRQoL using EQ-5D-3L index with 95% CI at baseline and follow-up between non-user (Stanmore 0-1), user (Stanmore 2-3), and walker (Stanmore 4-6)

5.4 PAPER IV

Paper IV was based on the same cohort as Paper III. The patients had a mean age of 75 years, half of the patients had a vascular intervention prior to amputation, and the majority were men (n=9). The analysis was performed according to time sequences (Figure 5).

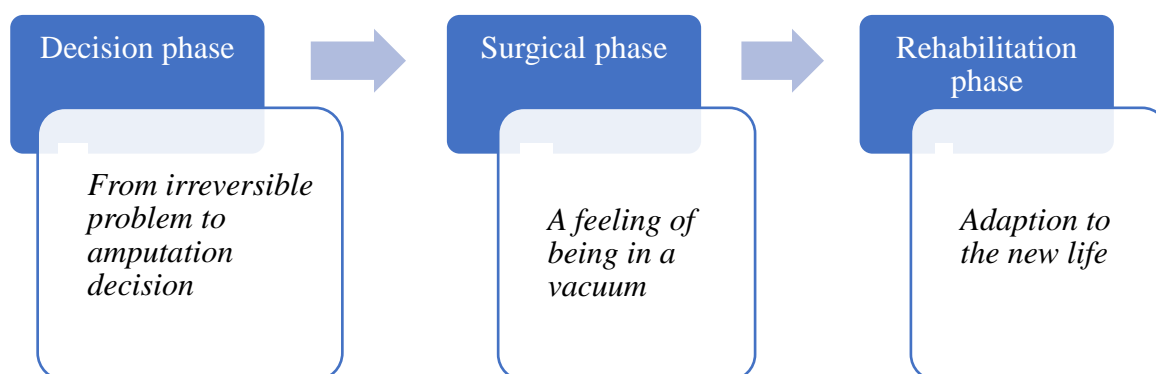


Figure 5. Overview of result; Time sequences and themes

Irreversible problem to amputation decision was the theme for the time period before the amputation decision. Half of the patients had thought of the fact that their situation might lead to an amputation. They described their life before the amputation as a period marked by a tearing pain that took almost all their energy. Others who had an acute occlusion as indication, described that the information that an amputation was needed came as a shock. The patients were not satisfied with the information they got. They missed someone taking time to discuss their future, how their new life as an amputee would be.

The theme for the surgical phase was *a feeling of being in a vacuum*. The period was marked by the patients' new situation as an amputee. They longed for the time when they could get a prosthesis and become "normal" again. None of the patients thought that they had got enough information about the coming plans. They missed information regarding the normal pattern after an amputation. Additionally, several of the patients expressed that they had a feeling of abandonment, as the surgeon who had performed the amputation had not visited or talked to them after the surgery.

The theme of the rehabilitation phase was *adaption to the new life*. The period was characterized by a feeling of anxiety about how the future would be, should they be able to learn to use a prosthesis? The patients struggled to become independent again, they were longing for a time when they would not have to rely on others. The patients felt frustrated

before the training started at the prosthetic centre. They lacked information and felt that they were just waiting, thus they did not know for what or for how long the waiting would be. The feeling of anxiety was increased by the fact that they had very little information regarding the prosthesis, how it looked, how it worked, and so on. The patients who had been to the prosthetic centre talked about how important it was to use a prosthesis, it was a symbol for normality.

Despite their experiences of obstacles, most of the patients were satisfied with their amputation decision and felt hope for the future. Those having pain or a non-healing ulcer as indication thought that their life had become better, they experienced a relief compared to the period before the amputation.

6. DISCUSSION

6.1 GENERAL DISCUSSION AND MAIN FINDINGS

The four studies in this thesis have highlighted different aspects of major lower limb amputation in patients with CLI. Paper I and II focused on risk factors for amputation and re-amputation with the aim to provide knowledge to support the clinical decision regarding a primary amputation and amputation level. Paper III and IV have highlighted different aspects aiming us to better understand the amputees' view of their situation.

6.1.1 Amputation and mortality among patients with critical limb ischemia

Results from Paper I and II emphasize the severity of having CLI. In Paper I, the cumulative incidence function of having an amputation at one year was 15% despite revascularization. This is in line with earlier results. A population-based study, including all patients treated with revascularization in Sweden during 2008-2013, showed an amputation rate of 15% during the first year after revascularization in patients with CLI (13).

The overall mortality was high in all four studies. Paper I had a cumulative incidence function of death at one year at 13%. That is lower than in the population-based study from Sweden that showed that the cumulative incidence of death at 1 year was 21% (13). The BASIL trial found that survival was significantly increased in patients treated with an attempt of balloon angioplasty prior to bypass surgery, in comparison with those treated with bypass surgery first (77). According to these findings, an explanation of the differences in mortality can be the design of our study. As it is a single-centre study, the result can depend on selection bias. Another explanation may be that our study is performed at a high-volume centre, a factor that has been shown to have implications on the result in studies within carotid endarterectomy (78).

The cumulative incidence function of death at one year was 29% in Paper II, and 24% in Paper III. Previous studies of patients undergoing major amputation have also reported data on the cumulative mortality one year after amputation at 21-48% (79). The high proportion of major co-morbidities among patients with CLI is probably an explanation of the high mortality. Paper II and III showed a high risk of re-amputation during follow-up. These results highlight the need of an evaluation of the health status in patients undergoing an amputation in order to minimize future complications (80).

6.1.2 Survival analysis and absolute risk

The research question in Paper I was if there is a certain group of patients who are more likely to have an amputation despite a revascularization. In studies where the research question includes the actual risk for having an event, an analysis using the cause-specific subdistribution function is recommended (18, 81, 82). Unlike for example cardiovascular research, the use of a competing risk regression is sparse within vascular research. We performed a competing risk regression and compared the result to a Cox regression using AFS. The competing risk regression identified age, ambulatory status (independent versus bedridden), and ischaemic wound versus rest pain as risk factors associated with amputation. In comparison, the analysis using Cox regression identified female sex, age, renal impairment, ambulatory status (independent versus bedridden), and ischaemic wound versus rest pain as risk factors. Our conclusion was that the differences in risk factors between the two analyses are probably due to the use of AFS as the outcome measure in the analysis using Cox regression. A combined endpoint that includes mortality may be dominated by risk factors affecting the survival and not the specific amputation risk (73).

Patients who are censored due to death before the end of a study can give biased estimates of the absolute risk of the event of interest (73). Kaplan Meier and Cox proportional hazards regression depends on the assumption that the censoring is independent and non-informative. The patients in Paper I that died during follow-up had an increased risk of amputation. We thereby concluded that the censoring due to mortality was not independent. To avoid the risk of biased estimates we thereby recommend the use of a competing risk approach when the research question is based on decision-making in cohorts with high mortality (18).

6.1.3 Risk factors for amputation after revascularization

Age, ischaemic wound as indication, and preoperative ambulatory status were risk factors associated with amputation despite revascularization in Paper I. Older age and an ischaemic wound are known predictors of a poor outcome after vascular interventions. Ambulatory status as a risk factor is rarely used within vascular research, however it has been shown to have an impact on graft occlusion and amputation (83). One explanation of the strong association between preoperative walking ability and risk for amputation in Paper I, could be that it reflects the patient's frailty, a factor that has been seen as a predictor of the individual's surgical risk (84-86). Frailty is a concept that is based on the idea that there is a subset of an older person who has an increased risk for complications. It is a multidimensional concept involving psychological, physical, social, and environmental factors (87, 88). Frailty has been

seen as a predictor of discharge to a higher level of care, loss of independence, and decreased mobility after an intervention for PAD (89).

Predicting poor outcome after intervention for CLI is difficult as several technical, disease-, and patient-related factors interplay (90). A validated score, that provides an evaluation of the individual patient's risk, can be a valuable tool for the decision between vascular intervention or primary amputation in the individual patient. Paper I showed that it is important to consider the patients absolute risk for having an event when the research question includes decision-making, in populations with a high risk of death (18). However, the current risk scores with the aim to predict an amputation (34, 35, 37)) are not taking the competing risk of death into account (73). Further, preoperative ambulatory status, a variable strongly associated with the risk for amputation in Paper I, is not included.

Thus, a risk score developed in a competing risk framework that involves the three components from the WIfI classification system (wound extent, degree of ischemia, and extent of foot infection) and preoperative ambulatory status may increase the ability to predict an amputation. The motivation to use the variables from the WIfI classification system instead of The Finnvasc and Prevent III score is that the WIfI-score is developed from a cohort undergoing both endovascular and open surgery. Further, it has been validated during a retrospective study (91). Ambulatory status may be used as a proxy for co-morbidity, and frailty to avoid too many variables in the risk score making it inconvenient to use. Unfortunately, as we only had data on ankle- and toe-pressures and lacked information regarding the size of the wound and the presence of infection, we were not able to test this assumption in our study.

6.1.4 The amputation decision

In Paper I we found that most of the amputations were performed during the first year after revascularization. Some of these patients would probably have benefitted from a primary amputation instead of a revascularization. A patient with a good vein conduit but with severe co-morbidity may not be able to heal the wounds even with an intervention, and will thereby not be helped with a revascularization (33). Additionally, it is important to consider that a primary amputation below knee may be preferable to a high-risk bypass, as a failed bypass might lead to a higher amputation level (9). There is no evidence whether a vascular intervention or a primary amputation is the best option for the patient's HRQoL. A reasonable assumption is that a vascular intervention where the patient's wound heals, or the ischaemic pain improves, is always preferable when the improvement takes a limited time. The question

is if an aggressive treatment strategy, where the patient risks to spend a lot of time at hospital due to for example problems with wound healing, is the best treatment option. Maybe a primary amputation, where the patients learn to walk with a prosthesis is preferable in some patients with CLI, especially as they often have a short life expectancy. A study of patients two-years after an intervention for CLI shows that the patients had a reduced HRQoL compared to the normal population (92). It is necessary to keep the primary goal with the treatment in mind, i.e. the patient's right to have as good quality of life as possible. These thoughts are supported by the result from Paper IV where the patients said that they wished the amputation decision had been taken earlier in the process, to avoid unnecessary suffering.

The patients in Paper IV expressed the importance of having an active role during the decision-making process before the amputation. None of the patients thought that they had got enough information of how the future as an amputee might be. They wished that someone had taken the time to sit down and present the normal pattern, so they knew what to expect. Other studies support that patients, regardless of indication for amputation, miss information regarding the overall process (93-95). One possible explanation of the patient's experienced lack of information in Paper IV is that the vascular surgeons at the current hospital do not perform amputations. The patients had to discuss their options with an orthopedic surgeon that they had not met earlier, when they are in an emotionally stressful situation. The orthopedic surgeon in turn does not know the patient's previous struggles. The result emphasizes that the health-care personnel needs to develop an organization where the patient has an opportunity to discuss different treatment alternatives and how these will affect their future in order to increase their feeling of participating in the care.

6.1.5 Risk factors for complications after a major amputation

In Paper II and III, we found a high incidence of re-amputations (24-29% at one year). The incidence of re-amputations is in line with earlier studies (41, 96, 97). The high incidence of complications is a problem, as it causes a delay in the patient's rehabilitation and an additional burden on an already vulnerable patient group.

An amputation level below knee is an important factor if the patient shall obtain and learn to use a prosthesis (46, 47). On the other hand, having a BKA is related to more wound-related complications (31, 96). There is no definitive method that can predict the wound healing potential or failure at the site of amputation (6). In Paper II the aim was to evaluate if there was a certain group of patients who had a higher risk of having a re-amputation. We found that patients with ischemic pain as indication had a nearly four times higher risk of a re-amputation than those having a non-healing ulcer. One explanation is that having pain

without an ulcer may be indicative of an ongoing ischaemia and a decreased blood flow, which will impair the patients' opportunity to heal their amputation stump. Another explanation can be that the decision to perform an amputation may be delayed, as a patient without an ulcer may have harder to accept an amputation as he/she does not feel prepared for it. Rest pain and having a nonreconstructable arterial disease have earlier been shown as predictors of stump complications (41). These findings strengthen our interpretation of the result that this subgroup of patients should be offered an extended evaluation before the decision of amputation level.

Patients with diabetes have been seen to be more likely of having a re-amputation (98). Our findings do not support that. One explanation can be the difference in inclusion criteria, as Dillingham et al. (98) had a mix of patients with minor and major amputations and lacked full information regarding laterality of the re-amputations. Another reason for the higher rates in their study may be related to differences in the medical and surgical care of the diabetic population in Sweden and in the United States of America.

6.1.6 The experience of having an amputation

Having an amputation is often a major life change for the patient. The patients in Paper IV described that it was an overwhelming situation for them to lose a part of their body. They longed for the time when they could get a prosthesis and thereby have a normal body again. The prosthesis was more than a tool for walking, it had become a symbol of normality. The patient's expressed that the wheelchair was an obstacle in their longing for a normal life as it forced them to be dependent on others. The result is in line with the theory 'Pendulating' that Madsen et al. (45) have developed. The phases "digesting the shock" and "regaining control" express how the patients start with processing the shock of becoming an amputee followed by a phase where they are taking back control of their life and starts to build up hope for the future (45). The patients in Paper IV described that the amputation decision was marked by a feeling that they had no other choice than to go through with the amputation, it was a choice between life or death. Some of the patients felt that having a major amputation had been presented as a threat earlier in the process, rather than as a treatment alternative. That made the decision even harder. The results support the importance of having the patient involved early in the discussion regarding treatment plan and to use a shared decision-making (99).

6.1.7 Prosthesis use and its importance for the patient's perceived Health-Related Quality of Life

At the one-year follow-up, 53 (73%) of the patients in Paper III used a prosthesis. However, only 23 (32%) used it to walk both indoor and outdoor. This is in line with earlier findings that patients who have a prosthesis differ in usage time (52).

The patients in Paper III had a median value of EQ-5D index at baseline that was significantly lower than results from populations with CLI. However, at the one-year follow-up, the group who walked with a prosthesis had a value of EQ-5D index comparable with, or even better than, data on patients who have undergone intervention with endovascular or bypass surgery (22). This supports our findings from Paper IV, that in the choice between a high-risk bypass and a primary amputation, an amputation is sometimes preferable.

An interesting finding in Paper III was that the group that used a prosthesis in order to move independently had an increased level of the EQ-5D index at follow-up compared to their baseline measure. In the group with non-prosthesis users, we could not see any significant improvement. These results reflect the importance of prosthesis use that supports independent mobility to for example a wheelchair. A generous prescription of prostheses and rehabilitation after amputation will give the patient a chance to learn to use the prosthesis and thereby increase his/her HRQoL. However, we could not see any significant difference in improvement from baseline to follow-up between those who did not use a prosthesis, the prosthesis users, and the walkers, probably due to low sample size.

6.2 METHODOLOGICAL CONSIDERATIONS

This thesis contains of studies that use both quantitative and qualitative methods. A quantitative method is useful when the aim is to measure the incidence of events in large populations. It gives an opportunity to investigate and develop the choice and the outcome of treatment. Qualitative methods on the other hand, is a way to give the patients an opportunity to share their experience of a treatment. It is a way to gain a deeper understanding of the individual patient's situation and experiences. The use of a combination of the two methods in this thesis has given a broader perspective of the population with severe PAD.

6.2.1 Internal validity

Selection bias/Credibility

Selection bias occur if the association between the exposure and outcome differs between those who participate in the study compared to those in the general population.

In Paper I we used revascularization due to CLI as inclusion criteria. To confirm the classification of the ischaemic status we used The Society for Vascular Surgery's WIfI system (69). Patients categorized with WIfI grade 0 (ankle brachial index (ABI) $\geq 0,80$; toe pressure ≥ 60 mmHg) were reviewed in their medical charts to validate their inclusion.

Most of the amputations in Paper II were performed at a high-volume centre, which may lead to more experienced personnel regarding the choice of amputation level and the timing of re-amputations. On the other hand, in a large centre there are more surgeons performing the amputations, which may affect the result negatively.

In Paper III and IV the patients were included in connection with their amputation. An amputation is for most of the patients an overwhelming situation. This fact is probably a contributor to the high number of patients who did not want to participate. To ensure that the non-included patients did not differ in baseline data compared to those included, we performed a prespecified analysis that showed no differences except for a higher number of men among those included in the study.

Prospective studies may have a problem with loss to follow-up. There was only one patient in Paper III and one patient in Paper IV, except those who died, who did not complete the study. The use of proxy in the two patients who were not capable of explaining their situation contributed to the response rate. The use of proxy in the assessment of HRQoL can be questionable, as it can be hard for another person to express the individual experience. However, a study of the level of agreement between caregiver and patient with mild vascular

cognitive impairment showed a high level of agreement in self-care and a fair agreement for the domains mobility, pain and anxiety in EQ-5D-3L (70).

Credibility refers to how well the data and the analyses addresses the aim of the study (100). In Paper IV we included patients with various experiences regarding amputation level, gender, and age, to increase the possibility of shedding light on the research question (101). The quality of the data in qualitative research depends on the interviewer's technique. In order to increase the quality of the data in Paper IV an interview guide was used to give the interviewer a chance to ensure that all topics were covered in each interview. The use of a semi structured interview guide will give the researcher the possibility to use the guide and still be free to explore, probe, and ask questions to elucidate the topic (71).

Information bias/Dependability

Information bias occur when variables are incorrectly collected or falsely measured. Paper I and II are register-based which may lead to an inherent problem as they are restricted to what the registers contain. To enhance the quality of the data, a validation was performed using a random sample of 103 patients from Paper I. All variables had an accuracy of $\geq 90\%$ except cardiac disease. We thereby concluded that there was a low risk of misclassification.

The Swedvasc register has a problem with follow-up data on amputations. To overcome that problem, we cross-linked the study cohort in Paper I and II with the IPR. IPR has a high validity as it has been mandatory in Sweden to report all performed operations to the register since 2007 (60). To ascertain the level, laterality, and date of amputation, all amputations were reviewed in the medical chart, which resulted in a complete follow-up in the primary outcome.

In Paper III we used a data management software, EpiData Entry (The EpiData Association, Odense, Danmark). EpiData includes tools for double data verification and quality assurance measure which minimizes the risk for incorrect measures.

In research involving HRQoL it is important to choose an instrument that has content validity and includes relevant dimensions. The EQ-5D-3L questionnaire has been validated for several diagnoses and countries, which increases the validity despite that it has not been validated for patients with major amputations (63). Earlier studies of patients with a major amputation has found that physical function, emotional function, role function and social function are important dimensions of HRQoL (47). These dimensions are all included in EQ-5D-3L. One limitation with the questionnaire is that it only consists of five questions making it less sensitive than for example SF-36 (102). The discriminant validity between EQ-5D-3L,

the modified Health Assessment Questionnaire, the Hospital Anxiety and Depression Scale, and a self-assessed index of joint pain has been tested among patients with rheumatoid arthritis in England. The conclusion was that there were clinically relevant correlations between these instruments, and the EQ-5D-3L questionnaire appeared to measure both the current clinical symptoms and changes in symptoms over time. One limitation with the validation is that it did not show how sensitive to change the EQ-5D-3L is (103).

Test-retest reliability, that the patients' answer should be the same if they re-do the questionnaire, has been tested in the EQ-5D-3L. The conclusion was that it is stable over time where the domains mobility, usual activity, and self-care had very high reliability. Pain and anxiety showed a weaker, but acceptable, reliability (104, 105).

The Stanmore Harold Wood mobility grade has not been validated, but, it is frequently used (106). The advantage of the scale is that it covers the amputee's experience of his/her mobility, and measures not only the maximum endurance on a specific day. It also has a wide range as it covers the mobility from totally confined to bed to fully mobile without aids, which gives valid data.

The Houghton scale has been validated, showing a good internal consistency (that it measures what it is meant to measure) with a Cronbach's alpha of 0.71 (an estimate of consistency, 71% of the variance in the scores is reliable variance), a good responsiveness (the scale's ability to detect relevant changes) and a significant test-retest reliability (The Kendall rank coefficient=.95, $p=.01$) (68).

In qualitative studies there is a risk of inconsistency during data collection. The interviewing is a changing process and the interviewer acquires new insight over time. This could lead to a change in the follow-up questions (100). To decrease this risk, all interviews in Paper III and IV were performed by the same person, and the analysis was not performed until all interviews were completed. Earlier studies performed on amputees have asked patients up to several years after the amputation, which entails a risk for recall bias. To minimize this risk, all interviews in Paper IV were performed two months post-amputation (71). The analysis was discussed within the research group as a way to reach consensus (107).

Confounding

Confounding occurs when the effect on a variable changes the effect of another variable. A confounding variable shall be related to both the exposure and the disease. In Paper I and II we tried to control for possible confounders by using a multivariable regression analysis. Age, smoking status, and sex were kept in the models based on their clinical relevance.

6.2.2 External validity

Generalizability / Transferability

All studies in this thesis consisted of patients treated at one single centre in Sweden, which may have an effect of the generalizability as the cohorts may not be representative for all patients with CLI. However, the department of vascular surgery at Södersjukhuset has a well-defined catchment area covering half of the inhabitants in Stockholm county (2.2 million) which increases the possibility to generalize the result.

Transferability refers to how well the result can be transferred to other groups (100). In Paper III and IV, the selection of patients was thoroughly described with the aim to increase the opportunities to transfer the results to other populations. One limitation was our inclusion criteria that the patients needed to speak Swedish. This could have an impact on the transferability, as people from other cultures may have different experiences and perspectives on the phenomena studied. The motivation for the decision was that the use of an interpreter in interviews has been shown as a threat to the validity of qualitative studies (108).

6.3 IMPLICATIONS FOR CLINICAL PRACTICE

This thesis has shown that it is important to undertake a careful preoperative assessment of the patient's ambulatory function and the expected durability of the revascularization procedures for the specific patient. A patient does not benefit from an intervention when there is little chance of success. In these cases, a primary amputation is a better treatment, to give the patient a chance to become ambulant with a prosthesis instead of continuing to suffer from ischaemic pain. It is important to remember that a patient with a poor distal vascular anatomy may be better served with a primary amputation than spending a long time in hospital for repeated revascularizations.

The patients in Paper IV expressed that they experienced a lack of knowledge regarding the amputation process. They missed information regarding different treatment alternatives and their impact on their future life. The development of a multidisciplinary ward, consisting of an orthopedic and a vascular surgeon, a physiotherapist, and an orthopedic technician, may increase the patients' feeling of being participating in their care.

6.4 IMPLICATIONS FOR THE RESEARCH FIELD

The results from this thesis highlight the importance of using a proper methodology to avoid bias and misinterpretations of results. A competing risk regression that takes the absolute risk of an event into account is the recommended tool in studies of populations with a high mortality, when the aim is to support clinical decision-making.

The development of a risk score with the aim to support the decision of a primary amputation or revascularization is important to decrease unnecessary suffering for the patient. Further, guidelines that identify patients with a high risk of complications after an amputation are important.

As the patients experienced a lack of knowledge regarding the amputation process, more studies regarding patients involvement is important. Additionally, further knowledge regarding the optimal care organization around this patient group is recommended.

7. CONCLUSIONS

- ✓ There is a risk for biased estimates using standard survival methods in cohorts with a high mortality. The use of competing risk regression that takes the competing event of death into account may improve the prediction of the actual risk of amputation. It can thereby be a valuable tool to support treatment strategy in individual patients.
- ✓ Age, preoperative ambulatory status, and ischaemic wound as indication for vascular surgery are risk factors associated with risk of amputation after revascularization.
- ✓ Patients with ischemic pain as indication for an amputation has a high risk of a re-amputation.
- ✓ Prosthesis use is important for the patient's perceived HRQoL
- ✓ Vascular patients need better information on lower limb amputation and its consequences so as to be better prepared for the whole process.
- ✓ It is important for the patient's well-being to have the opportunity to discuss different treatment alternative and its impact on their future life with the surgeon to increase their feeling of being participating in the care.

8. FUTURE PERSPECTIVES

Despite there being several studies performed within patients with CLI, there are still questions that need to be answered in order to improve the care of patients undergoing a major amputation.

- ✓ Can we increase the precision in the developed risk scores, aiming to support the clinician decision regarding primary amputation, using competing risk regression instead of standard survival methods? Will the outcome be more precise if we also include preoperative ambulatory status?
- ✓ Can a prospective study of HRQoL over time in patients with CLI, comparing those having revascularization with those having a primary amputation, increase our knowledge regarding treatment selection?
- ✓ What is the best way to evaluate tissue perfusion in patients undergoing an amputation? Can it help us to better predict the wound healing potential or failure in the stump?
- ✓ Can the use of a structured information facilitate the decision to undergo an amputation?
- ✓ Can a validated disease-specific instrument measuring HRQoL in amputees yield information that could support the health-care organization for rehabilitation and the prosthetic training centre?

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