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Editor's Choice – Impact of Comorbidity, Medication, and Gender on Amputation Rate Following Revascularisation for Chronic Limb Threatening Ischaemia

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WHAT THIS PAPER ADDS

This paper describes how sex, comorbidities, and medication influence the relative risk of amputation and mortality in patients revascularised for chronic limb threatening ischaemia (CLTI), using data from a population based observational cohort, containing all revascularised CLTI patients, in Sweden during a five year period.

Objective/background: Chronic limb threatening ischaemia (CLTI) has a high risk of amputation and mortality. Increased knowledge on how sex, comorbidities, and medication influence these outcomes after revascularisation may help optimise results and patient selection.

Methods: This population based observational cohort study included all individuals revascularised for CLTI in Sweden during a five year period (10,617 patients in total). Data were retrieved and merged from mandatory national healthcare registries, and specifics on amputations were validated with individual medical records.

Results: Mean age at revascularisation was 76.8 years. Median follow up was 2.7 years (range 0–6.6 years). Male sex (hazard ratio [HR] 1.20, 95% confidence interval [CI] 1.09–1.33), renal insufficiency (HR 1.57, 95% CI 1.32–1.87), diabetes (HR 1.45, 95% CI 1.32–1.60), and heart failure (HR 1.17, 95% CI 1.05–1.31) were independently associated with an increased amputation rate, whereas the use of statins (HR 0.71, 95% CI 0.64–0.78) and low dose acetylsalicylic acid (HR 0.77, 95% CI 0.70–0.86) were associated with a reduced amputation rate. For the combined end point of amputation or death, an association with increased rates was found for male sex (HR 1.25, 95% CI 1.18–1.32), renal insufficiency (HR 1.94, 95% CI 1.75–2.14), heart failure (HR 1.50, 95% CI 1.40–1.60), and diabetes (HR 1.31, 95% CI 1.23–1.38). The use of statins (HR 0.74, 95% CI 0.67–0.82) and low dose acetylsalicylic acid (HR 0.82, 95% CI 0.77–0.88]) were related to a reduced risk of amputation or death.

Conclusions: Renal insufficiency is the strongest independent risk factor for both amputation and amputation/death in revascularised CLTI patients, followed by diabetes and heart failure. Men with CLTI have worse outcomes than women. These results may help govern patient selection for revascularisation procedures. Statin and low dose acetylsalicylic acid are associated with an improved limb outcome. This underlines the importance of preventive medication to reduce general cardiovascular risk and increase limb salvage.

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INTRODUCTION

Lower extremity artery disease (LEAD) affects millions of people.[1,2] The rising global prevalence during the last few decades has increased the functional disability and mortality caused by LEAD.[3]

Chronic limb threatening ischaemia (CLTI) is the most severe manifestation of LEAD, defined as lower limb ischaemic rest pain and/or ischaemic wound or gangrene, threatening limb viability. Patients with CLTI are also at high risk of other cardiovascular events.[4,5] Current strategies in CLTI management rely on risk factor modification, pain control, secondary preventive medication, and invasive revascularisation to relieve symptoms and prevent limb loss.[6–8] In a recently published Swedish nationwide cohort, the amputation rate after revascularisation for CLTI was 12% during the first 6 months, but then levelled out.[9]

Female patients are older at the time of revascularisation and have previously been reported to have worse outcomes.[10] However, more recent work contradicts this, with a more favourable outcome in women than in men.[11,12]

It is well established that smoking and comorbidities such as hypertension and diabetes increase the risk of CLTI,[13] whereas the relative impact of concurrent diseases on limb prognosis following revascularisation is less well known. A better understanding of this may improve patient selection and guide clinicians when evaluating patients with CLTI for invasive procedures.

It has also been established that secondary preventive medication reduces the risk of major cardiovascular events (myocardial infarction, ischaemic stroke, and cardiovascular death) in patients with CLTI.[14–17] Again, there is a knowledge gap regarding the influence of pharmacological treatment on limb outcome. Despite a high risk of cardiovascular events, many patients with LEAD are undertreated with respect to pharmacological secondary prevention.[4,18,19]

The aim of this study was to evaluate the impact of sex, comorbidities, and medication on amputation rate and survival after revascularisation for CLTI.

MATERIALS AND METHODS

This observational cohort study analysed prospectively collected data on all revascularisations in Sweden for CLTI between 12 May 2008 and 1 May 2013, with a total of 10,617 patients. The analysis included all patients >50 years of age with lower limb revascularisation by either open surgical or endovascular techniques for CLTI. The age cut off was applied to lower the risk of including revascularisation procedures performed for reasons other than atherosclerosis. Patients were only included in the study once, even though some had additional subsequent revascularisations. Additional revascularisations during the study period were not analysed.

Patients were followed from the first revascularisation, defining the index date, up to 31 December 2013, or death, if this occurred earlier. Outcomes were ipsilateral amputation above the ankle and all cause mortality. The composite end point of time to ipsilateral amputation or death was calculated from the index date to the date of the first event.

Data sources

Registries. The studied cohort was identified in the Swedish National Registry for Vascular Surgery (Swedvasc).[20,21] Swedvasc was launched in 1987, receiving full national coverage in 1994, and has repeatedly been validated with high accuracy and data quality.[22,23] Data regarding risk factors, patient characteristics, peri-procedural details, and follow up are prospectively collected at all vascular centres in Sweden.

Pre-operative comorbidities and post-operative amputations were identified in the Swedish National Patient Register (NPR). The register is kept at the National Board of Health and Welfare. It is mandatory for all Swedish caregivers to report diagnosis and operation codes to NPR. The registry was founded in 1964, and has >99% coverage.[24] The International Classification of Diseases, 10th revision (ICD-10) has been used for coding of diagnoses since 1997. The operation codes are based on a national Swedish coding system in which all health interventions get a specific code based on the type of intervention and anatomical location. These codes are mandatory to report since 2007.

Data on prescribed and dispensed drugs were acquired from the Prescribed Drug Register, also kept at the National Board of Health and Welfare. This mandatory registry has been active with full national coverage since 2005.[25] The registry contains nearly 100% of dispensed drugs in Swedish pharmacies.

Dates of deaths were collected from the Cause of Death Register, at the National Board of Health and Welfare. The register was founded in its present form in 1961 and contains information on all deaths in Sweden. Studies performed with cardiovascular patient populations have previously demonstrated high data accuracy when combining the Cause of Death Register with the NPR.[26]

Data management

Merging the registries and searching the medical records was possible by using unique personal identification numbers. Data in the national registries and medical records are kept under strict confidentiality and shared only after thorough legal and ethical considerations.

The data from the Swedvasc registry contained information on patient characteristics, including smoking habits, symptomatology, laterality (right or left limb), technical procedural details, and date of revascularisation. CLTI was defined as chronic LEAD with ischaemic rest pain, ischaemic wounds, and/or gangrene, i.e., Rutherford 4–6 or Fontaine III or IV.[27,28]

The Swedvasc data file was subsequently merged with data from the NPR, adding information on comorbidities and amputations performed. The pre-operative comorbidities were searched using the ICD-10 classification codes and included the time period from 1997 to the index date. Amputation procedure codes were searched from the index date until 31 December 2013.

Data on the patients' drugs were added from the Prescribed Drug Register using the Anatomical Therapeutic Chemical classification system.[29] Only dispensed drugs from

the pharmacy were included in the analysis. Prescribed drugs that were not collected by the patient were not included. The time period for dispensed drug analysis included from four months prior to the day before the index procedure for all drugs except for low dose acetylsalicylic acid (LDASA) and statins, as these drugs are often initiated during the same hospital admission as the CLTI revascularisation procedure.[4] The time period for analysis of LDASA and statins included 4 months prior to and one month after the revascularisation. Dates of deaths were added from the Cause of Death Register.

Medical records

The aim of merging data with the NPR was to get longer follow up times than the one year follow up that is registered in Swedvasc. As the NPR is code based, information on the amputation side, left or right leg, was not always possible to determine. Therefore, for all amputations performed >one year after index date, or when data were not consistent with Swedvasc, a review of the patient's individual records, kept at the treating hospital, was made to acquire accurate data. In total, the medical records of 1366 patients were reviewed.

Outcomes

Outcomes are presented as the relative risk of amputation and/or death. Amputation was defined as an amputation performed above the ankle (e.g., major amputation). In the combined end point of amputation or death, the first occurring event defined the date of the outcome.

The study design is presented in Fig. 1.

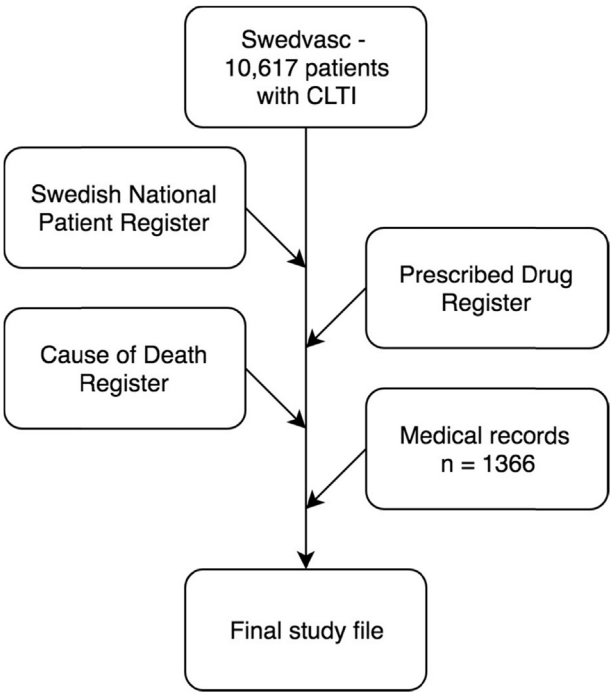

Figure 1. Flow chart of study design. *Note.* Swedvasc, the Swedish National Quality Registry for Vascular Surgery; CLTI = chronic limb threatening ischaemia.

Ethical considerations

The Regional Ethical Review Board at the University of Gothenburg, Gothenburg, Sweden, approved the study (reference number 873-14 and T084-16).

Statistical analysis

Descriptive statistics are presented for demographic and baseline variables as mean ± SD, median, and range. Time to amputation and the combined endpoint of amputation or death were analysed using Cox proportional hazards models applied to both endpoints. The analyses were done in a three step process. First, a series of univariable models were performed where each covariate was included separately. Second, a multivariable regression analysis was followed where each covariate with a p value $< .05$ was entered. Thirdly, a stepwise model was performed where the optimal model was defined as the model with the minimum Akaike information criteria value. As no presented p values or confidence intervals (CIs) were adjusted for multiple comparisons the results should be interpreted as exploratory rather than confirmatory. Patients with amputation registered in the NPR but with uncertainties regarding laterality were included in the analysis and censored at the date of the registered amputation. A sensitivity analysis was also performed, in which these patients were analysed as having an amputation. Statistical programming and analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA) and R version 3.2.3 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study population

Patient demographics, clinical characteristics, and comorbidities are presented in Table 1.

Median follow up was 2.7 years (range 0—6.6 years), with a total of 29,640 person-years accumulated.

Pharmacological treatment

The most frequently used medications were LDASA (62.2%), opioids (59%), statins (55.3%), beta blockers (50.8%), and diuretics (50.6%). Data on pharmacological treatment are presented in Table 2.

Risk of amputation

The uni- and multivariable regressions analysing the risk of amputation are presented in Table 3. The cumulative incidence of amputation based on revascularisation technique, endovascular or open, is presented in Table S1 (Supplementary Material).

Male sex (hazard ratio [HR] 1.20, 95% CI 1.09—1.33 [$p < .001$] in stepwise selected Cox regression) was associated with an increased risk of amputation.

A pre-operative diagnosis of renal insufficiency (HR 1.57, 95% CI 1.32—1.87; $p < .001$), diabetes (HR 1.45, 95% CI 1.32—1.60; $p < .001$), heart failure (HR 1.17, 95% CI 1.05—1.31; $p = .006$), or atrial fibrillation (HR 1.15, 95% CI 1.03—

Table 1. Baseline demographics and comorbidities on admission for revascularisation (n = 10,617).

Sex, n (%)	
Female	5390 (50.8)
Male	5227 (49.2)
Mean ± SD age (y)	76.8 ± 9.6
Women	78.5
Men	75.0
Median (range)	78 (50–103)
Smoking, n (%)[a]	
Current smoker	1370 (12.9)
Former smoker	2765 (26.0)
Never smoked	1996 (18.8)
Smoking status not confirmed	4486 (42.3)
Comorbidity, n (%)[b]	
Hypertension	9024 (85.0)
DM	5010 (47.2)
HF	2944 (27.7)
Angina pectoris	2936 (27.7)
AF	2564 (24.1)
MI	2114 (19.9)
Cancer	2068 (19.5)
Ischaemic stroke	1548 (14.6)
COPD	1476 (13.9)
Chronic renal insufficiency	713 (6.7)
TIA	708 (6.7)
Aortic aneurysm	436 (4.1)
Dementia	279 (2.6)
Arterial embolism and thrombosis	131 (1.2)
Surgical method, n (%)[a]	
Endovascular	8027 (75.6)
Open surgery	2586 (24.4)

Note. DM = diabetes mellitus; HF = heart failure; AF = atrial fibrillation; MI = myocardial infarction; COPD = chronic obstructive pulmonary disease; TIA = transient ischaemic attack.
[a] Data from the Swedvasc registry.
[b] Data from the National Patient Register.

Table 2. Pharmacological treatment (n = 10,617).

	n (%)
Antihypertensives	8906 (83.9)
Beta blockers	5391 (50.8)
Diuretics	5377 (50.6)
ACEi	3819 (36.0)
Calcium channel blockers	3339 (31.4)
ARBs	2266 (21.3)
Analgesics	7631 (71.9)
Opioids	6266 (59.0)
Mild opioids	3397 (32.0)
Strong opioids	4305 (40.5)
Antiplatelets	
LDASA[a]	7778 (73.3)
Clopidogrel	770 (7.3)
DAPT	566 (5.3)
Cilostazol	56 (0.5)
Ticagrelor	19 (0.2)
Prasugrel	8 (0.1)
Anti-dyslipidaemics	
Statins[a]	6883 (64.8)
Fibrates	56 (0.5)
Anti-diabetics	4004 (37.7)
NIAD	1841 (17.3)
Nitrates	2079 (19.6)
Anticoagulants	1083 (18.2)
Warfarin	1076 (10.1)
LMWH	844 (8.0)

Note. ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; LDASA = low dose acetylsalicylic acid; DAPT = dual antiplatelet therapy; NIAD = non-insulin anti-diabetic drug; LMWH = low molecular weight heparin.
[a] Including prescriptions 30 days post-operatively.

1.29; p = .014) were independently associated with an increased rate of amputation. In contrast, previous ischaemic stroke (HR 1.13, 95% CI 1.00–1.28; p = .058) and previous myocardial infarction (HR 1.11, 95% CI 0.98–1.25; p = .091) were not associated with amputation rates in the multivariable analysis, and angina pectoris was not associated with amputation rate, even in the univariable analysis.

The use of statins (HR 0.71, 95% CI 0.64–0.78; p < .001) and LDASA (HR 0.77, 95% CI 0.69–0.87; p < .001) were associated with a reduced risk of amputation. Patients who used strong opioids had an increased amputation risk (HR 1.44, 95% CI 1.31–1.58; p < .001).

Risk of amputation or death

The uni- and multivariable regression analysis of the combined end point amputation or death is presented in Table 4. The cumulative incidence of amputation or death based on revascularisation technique, endovascular or open, is presented in Table S1 (Supplementary Material).

Male sex (HR 1.25, 95% CI 1.18–1.32; p < .001) was associated with an increased risk of amputation or death.

Renal insufficiency was the strongest independent risk factor for the combined end point of amputation or death (HR 1.94, 95% CI 1.75–2.14; p < .001), followed by heart failure (HR 1.50, 95% CI 1.40–1.60; p < .001). Also, diabetes (HR 1.30, 95% CI 1.23–1.38; p < .001), atrial fibrillation (HR 1.25, 95% CI 1.17–1.34; p < .001), previous myocardial infarction (HR 1.21, 95% CI 1.13–1.30; p < .001), previous ischaemic stroke (HR 1.22, 95% CI 1.13–1.31; p < 0.001), and chronic obstructive pulmonary disease (HR 1.21, 95% CI 1.12–1.31; p < .001) were independently associated with an increased risk, whereas angina pectoris (HR 0.94, 95% CI 0.89–1.01; p = .086) was not.

The use of LDASA (HR 0.82, 95% CI 0.77–0.88; p < .001) and statins (HR 0.69, 95% CI 0.65–0.73; p < .001) were associated with a decreased risk of amputation or death, whereas strong opioids (HR 1.33, 95% CI 1.26–1.41; p < .001) were associated with an increased risk.

DISCUSSION

The main findings of this study are that renal insufficiency, diabetes, heart failure, atrial fibrillation, and male sex are independently associated with an increased risk of amputation following revascularisation for CLTI and that treatment with statins and LDASA is associated with a decrease in amputation rate.

There was an equal distribution of men and women, but the revascularised women were older. However, in the multivariable analysis that included age, men had an increased risk of

Table 3. Relative risk of amputation—stepwise regression.

	Univariable analysis			Multivariable adjusted[a]			Stepwise selected		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Age	1.01	1.01—1.02	<.001	1.01	1.01—1.02	<.001	1.01	1.01—1.02	<.001
Male sex	1.24	1.13—1.37	<.001	1.21	1.09—1.33	<.001	1.20	1.09—1.33	<.001
Chronic renal insufficiency	1.87	1.59—2.21	<.001	1.57	1.32—1.87	<.001	1.57	1.32—1.87	<.001
HF	1.54	1.39—1.70	<.001	1.16	1.04—1.31	.009	1.17	1.05—1.31	.006
AF	1.53	1.38—1.69	<.001	1.14	1.01—1.29	.030	1.15	1.03—1.29	.014
DM	1.48	1.34—1.62	< .001	1.45	1.31—1.60	<.001	1.45	1.32—1.60	<.001
MI	1.30	1.16—1.45	<.001	1.09	0.96—1.23	.176	1.11	0.98—1.25	.091
Ischaemic stroke	1.24	1.09—1.40	.001	1.13	0.99—1.28	.065	1.13	1.00—1.28	.058
Hypertension	1.13	0.99—1.30	.079						
Angina pectoris	1.08	0.97—1.20	.150						
Atherosclerosis in other arteries	1.06	0.87—1.30	.540						
COPD	0.91	0.79—1.05	.206						
Strong opioids	1.50	1.37—1.65	<.001	1.44	1.31—1.58	<.001	1.44	1.31—1.58	<.001
Anticoagulants	1.46	1.28—1.68	<.001	1.02	0.86—1.20	.849			
Beta blockers	1.18	1.07—1.29	.001	1.03	0.93—1.14	.553			
DAPT	1.13	0.92—1.38	.248						
ACEi/ARB	1.07	0.98—1.18	.149						
Other antiplatelet	1.06	0.89—1.27	.510						
Calcium channel blockers	0.86	0.78—0.96	.005	0.90	0.81—1.00	.042	0.90	0.81—1.00	.042
LDASA	0.66	0.59—0.72	<.001	0.77	0.69—0.87	<.001	0.77	0.69—0.87	<.001
Statins	0.65	0.59—0.72	<.001	0.70	0.64—0.78	<.001	0.71	0.64—0.78	<.001

Note. HR = hazard ratio; CI = confidence interval; HF = heart failure; AF = atrial fibrillation; DM = diabetes mellitus; MI = myocardial infarction; COPD = chronic obstructive pulmonary disease; DAPT = dual antiplatelet therapy; ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; LDASA = low dose acetylsalicylic acid.
[a] *p* values < .05 in the univariable analysis are included.

both amputation and amputation/death after revascularisation. These findings contradict the view that women have a worse outcome after revascularisation.[10] Instead, the study supports the results of more recent work in this field.[11,12]

Renal insufficiency has previously been identified as a risk factor for amputation and death in patients with CLTI with diabetes[30,31]; and similarly, dialysis dependence has been determined to be a risk factor for amputation.[12] In the

Table 4. Relative risk of amputation or death — stepwise regression.

	Univariable analysis			Multivariable adjusted[a]			Stepwise selected		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Age	1.04	(1.03—1.04)	<.001	1.03	(1.03—1.04)	<.001	1.03	(1.03—1.04)	<.001
Male sex	1.18	(1.12—1.25)	<.001	1.25	(1.18—1.32)	<.001	1.25	(1.18—1.32)	<.001
HF	2.15	(2.03—2.27)	<.001	1.50	(1.40—1.60)	<.001	1.50	(1.40—1.60)	<.001
Chronic renal insufficiency	2.14	(1.94—2.36)	<.001	1.93	(1.75—2.14)	<.001	1.94	(1.75—2.14)	<.001
AF	1.93	(1.82—2.04)	<.001	1.25	(1.17—1.34)	<.001	1.25	(1.17—1.34)	<.001
MI	1.55	(1.46—1.65)	<.001	1.21	(1.13—1.30)	<.001	1.21	(1.13—1.30)	<.001
Ischaemic stroke	1.36	(1.27—1.46)	<.001	1.21	(1.13—1.31)	<.001	1.22	(1.13—1.31)	<.001
COPD	1.28	(1.19—1.38)	<.001	1.21	(1.12—1.30)	<.001	1.21	(1.12—1.31)	<.001
DM	1.27	(1.20—1.34)	<.001	1.30	(1.23—1.38)	<.001	1.30	(1.23—1.38)	<.001
Angina pectoris	1.25	(1.18—1.33)	<.001	0.94	(0.88—1.01)	.082	0.94	(0.89—1.01)	.086
Hypertension	1.21	(1.11—1.31)	<.001	.93	(0.85—1.01)	0.104	.93	(0.85—1.02)	.107
Atherosclerosis in other arteries	1.10	(0.98—1.24)	0.089						
Strong opioids	1.48	(1.40—1.56)	<.001	1.33	(1.26—1.41)	<.001	1.33	(1.26—1.41)	<.001
Anticoagulants	1.46	(1.35—1.59)	<.001	0.90	(0.81—0.99)	.024	0.90	(0.81—0.99)	.024
Beta blockers	1.33	(1.26—1.40)	<.001	1.09	(1.03—1.16)	.003	1.09	(1.03—1.16)	.004
DAPT	1.02	(0.90—1.16)	.751						
ACEi/ARB	1.01	(0.96—1.07)	.640						
Other antiplatelet	1.01	(0.91—1.12)	.832						
Calcium channel blockers	0.85	(0.80—0.90)	<.001	0.94	(0.88—1.00)	.040	0.94	(0.88—1.00)	.041
LDASA	0.68	(0.64—0.72)	<.001	0.82	(0.77—0.88)	<.001	0.82	(0.77—0.88)	<.001
Statins	0.58	(0.55—0.62)	<.001	0.69	(0.65—0.73)	<.001	0.69	(0.65—0.73)	<.001

Note. HR = hazard ratio; CI = confidence interval; HF = heart failure; AF = atrial fibrillation; MI = myocardial infarction; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; DAPT = dual antiplatelet therapy; ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; LDASA = low dose acetylsalicylic acid. [a] *p* values < .05 in the univariable analysis are included.

present study, renal insufficiency, even without dialysis dependence, doubled the risk of an adverse outcome after lower limb revascularisation for CLTI. Interestingly, in the multivariable analysis, renal failure had the highest hazard ratio for amputation of all recorded comorbidities.

Diabetes is the most widely recognised risk factor for LEAD, and it is associated with fatal coronary heart disease and affected revascularisation patency.[32,33] However, many studies have failed to show differences in limb salvage rates among patients with diabetes versus those without diabetes.[33,34] The present study, representing a large and unselected cohort of revascularised patients with CLTI, showed a 45% relative risk increase of amputation among patients with diabetes versus patients without.

Heart failure and atrial fibrillation were associated with a somewhat lower increase in amputation rate. However, heart failure and atrial fibrillation had stronger associations with the combined end point of amputation or death, with a 50% risk increase among patients with heart failure. The combined effect of pre-existing heart failure and atrial fibrillation thus amounts to the same level of risk as that posed by renal insufficiency for either amputation or death.

No significant association was observed between ischaemic stroke, angina pectoris, or myocardial infarction and the risk of amputation. Angina pectoris did not affect the risk of the composite end point of amputation or death either. This is interesting, as both ischaemic stroke and coronary artery disease, as well as CLTI, are manifestations of atherosclerotic disease. The presence of polyvascular disease could indicate an increased global atherosclerotic burden that ultimately would increase the future risk. This was not confirmed in the present analysis, indicating that the pathophysiology and the risk of CLTI are complex.

The majority of patients with CLTI have several comorbidities, and thus, they are exposed to more than one risk factor, accumulating/increasing the overall risk. Consequently, based on the present results, the combination of renal insufficiency, diabetes, and heart failure results in an almost threefold increased in the risk of amputation, and an almost fourfold increase the risk of amputation or death following a CLTI revascularisation procedure. Importantly, this may guide vascular specialists in risk benefit evaluation and help patients with CLTI make informed decisions when facing a revascularisation procedure.

Current knowledge regarding the influence of pharmacological therapy on secondary prevention and limb prognosis is inconclusive.[8,32,35] In unselected LEAD populations, statin therapy has been associated with a decreased risk of amputation.[36–38] In patients with defined CLTI, no protective effects have previously been demonstrated, even though some non-significant trends have been found.[39,40] In the randomised BASIL trial, it was decided not to include statins in the risk stratification analysis owing to the low number of patients receiving best medical treatment.[41] As shown previously, many patients are being prescribed statins and LDASA for the first time during hospital admission for revascularisation.[4] To make sure these patients were included in the analysis, dispensing of these drugs was counted up to 30 days after the procedure. This, in combination with the large number of patients in the present study, enabled a statistically robust analysis and an inverse association was found between statin use and amputation rate, corresponding to a 29% risk reduction.

LDASA has previously been shown to have a limb protective effect after bypass surgery for CLTI.[42,43] The results support this finding and suggest that this effect is also applicable to other types of lower leg revascularisation (i.e., endovascular treatment).

The observed correlation between use of strong opioids and an increased risk of amputation is probably not causal, as a more advanced limb ischaemia is likely to increase the need for more potent analgesics.

Some frail patients may be non-compliant with prescribed medication owing to severe illness. This could affect the observed association between medication and amputation or death. To evaluate this potential confounding factor the multivariable regression analysis was run excluding patients who died or were amputated within 30 days of the revascularisation procedure. However, the results were only marginally changed (Tables S2 and S3; Supplementary Material).

Amputation rates did not differ between patients revascularised by endovascular or open surgery. A slight difference in mortality was observed whereby patients revascularised by open surgery had a slightly higher mortality rate. This finding should be interpreted with caution as the comparison was made without controlling for any of the reasons and decisions underpinning the choice of revascularisation method.

This study was based on all patients revascularised for CLTI in Sweden during a 5 year period and represents nationwide outcomes among all types of caregivers within the country. Therefore, results have high external validity. However, there are some limitations, including the risk of incomplete or missing registry data. In particular, lifestyle variables, such as smoking habits, are less well documented in registries in general, which also applies to the present data, with missing data in 42% of patients. Therefore, smoking habits were not included in the Cox regression model. For other important variables such as comorbidities, medications, and the main outcomes, efforts were made to minimise the ambiguity. Data on mortality are 100% accurate, data on medications are solid,[25] and for amputations the missing data were $<$10% (220 patients, 9.7% of patients with amputation and 2.1% of the total cohort, with remaining uncertainties regarding the laterality of the performed amputation after the review of medical records). In a sensitivity analysis, counting unknown amputations as events, the results only marginally changed. The data on medication are based on actually dispensed drugs that left the pharmacy. Finally, definitions for registrations of comorbidities, i.e., renal insufficiency, are somewhat less well defined compared with a controlled prospective study, and are based on the judgments of the care giving physicians.

Clinical scores can help determine the prognosis of an individual patient in terms of amputation or mortality based on the aggregated outcome of many similar patients treated previously. This may be valuable for clinicians in every day decision making in the frail group that patients with CLTI

represent. However, the existing scores (i.e., FINNVASC score and the modified PREVENT III)[44,45] are constructed on other types of cohorts and/or are based on variables that are not consistent with those recorded in the present database. This limits the relevance of applying these scores to the present study cohort. Developing better scoring methods is an important task for the future to facilitate everyday decision making in the care of patients with CLTI.

CONCLUSIONS

In this large population based study, renal insufficiency was the strongest independent risk factor of both amputation and amputation or death in patients with CLTI, followed by diabetes and heart failure. Men with CLTI had a worse limb outcome than women. Secondary prevention medication with statins and LDASA was associated with improved limb salvage. These findings may guide patients and caregivers in treatment decisions and strongly motivate efforts to improve preventive medication in this patient group.

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CONFLICTS OF INTEREST

P.H. is a current and S.J. a former fulltime employee of AstraZeneca. An independent statistical consultant company, Statisticon, of which AstraZeneca is a client, employs M.T.

The other authors report no conflict of interests.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejvs.2018.06.003.

REFERENCES

1 Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet* 2013;**382**:1329—40.

2 Alberts MJ, Bhatt DL, Mas JL, Ohman EM, Hirsch AT, Rother J, et al. Three-year follow-up and event rates in the international REduction of Atherothrombosis for Continued Health Registry. *Eur Heart J* 2009;**30**:2318—26.

3 Sampson UK, Fowkes FG, McDermott MM, Criqui MH, Aboyans V, Norman PE, et al. Global and regional burden of death and disability from peripheral artery disease: 21 world regions, 1990 to 2010. *Glob Heart* 2014;**9**:145—158 e21.

4 Sigvant B, Kragsterman B, Falkenberg M, Hasvold P, Johansson S, Thuresson M, et al. Contemporary cardiovascular risk and secondary preventive drug treatment patterns in peripheral artery disease patients undergoing revascularization. *J Vasc Surg* 2016;**64**. 1009—10017 e3.

5 Iida O, Nakamura M, Yamauchi Y, Fukunaga M, Yokoi Y, Yokoi H, et al. 3-year outcomes of the OLIVE Registry, a prospective multicenter study of patients with critical limb ischemia: a prospective, multi-center, three-year follow-up study on endovascular treatment for infra-inguinal vessel in patients with critical limb ischemia. *JACC Cardiovasc Interv* 2015;**8**:1493—502.

6 Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA task force on practice guidelines (Writing committee to Develop Guidelines for the management of patients with peripheral arterial disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *Circulation* 2006;**113**:e463—654.

7 Rooke TW, Hirsch AT, Misra S, Sidawy AN, Beckman JA, Findeiss LK, et al. ACCF/AHA focused update of the guideline for the management of patients with peripheral artery disease (updating the 2005 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *J Am Coll Cardiol* 2011;**58**:2020—45.

8 Aboyans V, Ricco JB, Bartelink MEL, Bjorck M, Brodmann M, Cohnert T, et al. 2017 ESC Guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS). *Eur J Vasc Endovasc Surg* 2018;**55**:305—68.

9 Baubeta Fridh E, Andersson M, Thuresson M, Sigvant B, Kragsterman B, Johansson S, et al. Amputation rates, mortality, and pre-operative comorbidities in patients revascularised for intermittent claudication or critical limb ischaemia: a population based study. *Eur J Vasc Endovasc Surg* 2017;**54**:480—6.

10 Norman PE, Semmens JB, Lawrence-Brown M, Holman CD. The influence of gender on outcome following peripheral vascular surgery: a review. *Cardiovasc Surg* 2000;**8**:111—5.

11 Hedayati N, Brunson A, Li CS, Baker AC, Pevec WC, White RH, et al. Do women have worse amputation-free survival than men following endovascular procedures for peripheral arterial disease? An evaluation of the California state-wide database. *Vasc Endovascular Surg* 2015;**49**:166—74.

12 Vierthaler L, Callas PW, Goodney PP, Schanzer A, Patel VI, Cronenwett J, et al. Determinants of survival and major amputation after peripheral endovascular intervention for critical limb ischemia. *J Vasc Surg* 2015;**62**:655—664 e8.

13 Howard DP, Banerjee A, Fairhead JF, Hands L, Silver LE, Rothwell PM, et al. Population-based study of incidence, risk

factors, outcome, and prognosis of ischemic peripheral arterial events: implications for prevention. *Circulation* 2015;**132**:1805—15.
14 Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;**324**:71—86.
15 Heart Protection Study Collaborative Group. Randomized trial of the effects of cholesterol-lowering with simvastatin on peripheral vascular and other major vascular outcomes in 20,536 people with peripheral arterial disease and other high-risk conditions. *J Vasc Surg* 2007;**45**:645—54.
16 CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet* 1996;**348**:1329—39.
17 Armstrong EJ, Chen DC, Westin GG, Singh S, McCoach CE, Bang H, et al. Adherence to guideline-recommended therapy is associated with decreased major adverse cardiovascular events and major adverse limb events among patients with peripheral arterial disease. *J Am Heart Assoc* 2014;**3**:e000697.
18 Subherwal S, Patel MR, Kober L, Peterson ED, Jones WS, Gislason GH, et al. Missed opportunities: despite improvement in use of cardioprotective medications among patients with lower-extremity peripheral artery disease, underuse remains. *Circulation* 2012;**126**:1345—54.
19 Zeymer U, Parhofer KG, Pittrow D, Binz C, Schwertfeger M, Limbourg T, et al. Risk factor profile, management and prognosis of patients with peripheral arterial disease with or without coronary artery disease: results of the prospective German REACH registry cohort. *Clin Res Cardiol* 2009;**98**:249—56.
20 Swedvasc. The Swedish national Registry for Vascular Surgery. Available at: http://www.ucr.uu.se/swedvasc (accessed 6 May 2018).
21 Bjorck M, Bergqvist D, Eliasson K, Jansson I, Karlstrom L, Kragsterman B, et al. Twenty years with the Swedvasc registry. *Eur J Vasc Endovasc Surg* 2008;**35**:129—30.
22 Troeng T, Malmstedt J, Bjorck M. External validation of the Swedvasc registry: a first-time individual cross-matching with the unique personal identity number. *Eur J Vasc Endovasc Surg* 2008;**36**:705—12.
23 Venermo M, Lees T. International vascunet validation of the Swedvasc registry. *Eur J Vasc Endovasc Surg* 2015;**50**:802—8.
24 Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011;**11**:450.
25 Wettermark B, Hammar N, Fored CM, Leimanis A, Otterblad Olausson P, Bergman U, et al. The new Swedish Prescribed Drug Register—opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf* 2007;**16**:726—35.
26 Koster M, Asplund K, Johansson A, Stegmayr B. Refinement of Swedish administrative registers to monitor stroke events on the national level. *Neuroepidemiology* 2013;**40**:240—6.
27 Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg* 1997;**26**:517—38.
28 Fontaine R, Kim M, Kieny R. Surgical treatment of peripheral circulation disorders. *Helv Chir Acta* 1954;**21**:499—533 (in German).
29 WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2017. Available at: https://www.whocc.no/atc_ddd_index/ (accessed 6 May 2018).
30 Hoffstad O, Mitra N, Walsh J, Margolis DJ. Diabetes, lower-extremity amputation, and death. *Diabetes Care* 2015;**38**:1852—7.
31 Faglia E, Clerici G, Clerissi J, Gabrielli L, Losa S, Mantero M, et al. Early and five-year amputation and survival rate of diabetic patients with critical limb ischemia: data of a cohort study of 564 patients. *Eur J Vasc Endovasc Surg* 2006;**32**:484—90.
32 Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. *BMJ* 2006;**332**:73—8.
33 DeRubertis BG, Pierce M, Ryer EJ, Trocciola S, Kent KC, Faries PL. Reduced primary patency rate in diabetic patients after percutaneous intervention results from more frequent presentation with limb-threatening ischemia. *J Vasc Surg* 2008;**47**:101—8.
34 Dick F, Diehm N, Galimanis A, Husmann M, Schmidli J, Baumgartner I. Surgical or endovascular revascularization in patients with critical limb ischemia: influence of diabetes mellitus on clinical outcome. *J Vasc Surg* 2007;**45**:751—61.
35 Harris SK, Roos MG, Landry GJ. Statin use in patients with peripheral arterial disease. *J Vasc Surg* 2016;**64**:1881—8.
36 Klingelhoefer E, Bergert H, Kersting S, Ludwig S, Weiss N, Schonleben F, et al. Predictive factors for better bypass patency and limb salvage after prosthetic above-knee bypass reconstruction. *J Vasc Surg* 2016;**64**:380—388 e1.
37 Kumbhani DJ, Steg PG, Cannon CP, Eagle KA, Smith Jr SC, Goto S, et al. Statin therapy and long-term adverse limb outcomes in patients with peripheral artery disease: insights from the REACH registry. *Eur Heart J* 2014;**35**:2864—72.
38 Arya S, Khakharia A, Binney ZO, DeMartino RR, Brewster LP, Goodney PP, et al. Association of statin dose with amputation and survival in patients with peripheral artery disease. *Circulation* 2018;**137**:1435—46.
39 Suckow BD, Kraiss LW, Schanzer A, Stone DH, Kalish J, DeMartino RR, et al. Statin therapy after infrainguinal bypass surgery for critical limb ischemia is associated with improved 5-year survival. *J Vasc Surg* 2015;**61**:126—33.
40 Westin GG, Armstrong EJ, Bang H, Yeo KK, Anderson D, Dawson DL, et al. Association between statin medications and mortality, major adverse cardiovascular event, and amputation-free survival in patients with critical limb ischemia. *J Am Coll Cardiol* 2014;**63**:682—90.
41 Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FG, Gillespie I, et al. Multicentre randomised controlled trial of the clinical and cost-effectiveness of a bypass-surgery-first versus a balloon-angioplasty-first revascularisation strategy for severe limb ischaemia due to infrainguinal disease. The Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial. *Health Technol Assess* 2010;**14**. 1—210, iii—iv.
42 Collins TC, Souchek J, Beyth RJ. Benefits of antithrombotic therapy after infrainguinal bypass grafting: a meta-analysis. *Am J Med* 2004;**117**:93—9.
43 Nolan BW, De Martino RR, Stone DH, Schanzer A, Goodney PP, Walsh DW, et al. Prior failed ipsilateral percutaneous endovascular intervention in patients with critical limb ischemia predicts poor outcome after lower extremity bypass. *J Vasc Surg* 2011;**54**:730—5.
44 Biancari F, Salenius JP, Heikkinen M, Luther M, Ylonen K, Lepantalo M. Risk-scoring method for prediction of 30-day postoperative outcome after infrainguinal surgical revascularization for critical lower-limb ischemia: a Finnvasc registry study. *World J Surg* 2007;**31**:217—25.
45 Schanzer A, Goodney PP, Li Y, Eslami M, Cronenwett J, Messina L, et al. Validation of the PIII CLI risk score for the prediction of amputation-free survival in patients undergoing infrainguinal autogenous vein bypass for critical limb ischemia. *J Vasc Surg* 2009;**50**:769—75.