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ORIGINAL RESEARCH

Comparison of Outcomes After Revascularization for Acute Lower Limb Ischemia in Patients with and without Type 2 Diabetes Mellitus – A Nationwide Registry Study

Emil Karonen[1,2], Frida Eek[3], Isabel Drake[4], Talha Butt[1,2], Hanne Krage Carlsen[5], Björn Eliasson[6], Anders Gottsäter[1,7], Stefan Acosta[1,2]

[1]Department of Clinical Sciences, Lund University, Malmö, Sweden; [2]Vascular Centre, Department of Cardiothoracic and Vascular Surgery, Skåne University Hospital, Malmö, Sweden; [3]Department of Health Sciences, Lund University, Lund, Sweden; [4]Diabetes and Cardiovascular Disease-Genetic Epidemiology, Department of Clinical Sciences, Malmö, Lund University, Malmö, Sweden; [5]Centre of Registers, National Diabetes Register, Göteborg, Sweden; [6]Department of Molecular and Clinical Medicine, Institute of Medicine, University of Gothenburg, Göteborg, Sweden; [7]Department of Medicine, Skåne University Hospital, Malmö, Sweden

Correspondence: Emil Karonen, Department of Clinical Sciences, Lund University Ruth Lundskogs Gata 10, Malmö, 205 02, Sweden, Email emil.karonen@med.lu.se

Introduction: Acute lower limb ischemia (ALI) is a life and limb threatening event often affecting patients with type 2 diabetes mellitus (T2DM). Little is known about how T2DM affects the risk of adverse events in patients revascularized for ALI. This study aimed to investigate if there were differences in major outcomes between ALI patients with and without T2DM.

Methods: Between 2010 and 2014, 615 patients underwent revascularization for ALI, according to the Swedish Vascular Registry (SWEDVASC). Using the National Diabetes Registry (NDR), 245 (39.8%) of the patients were identified as having T2DM. Uni- and multivariable Cox or logistic regression analyses were performed to evaluate risk differences for major amputation, mortality, major adverse cardiovascular events (MACE), and fasciotomy between patients with and without T2DM.

Results: The rates of major amputation and mortality at one year were 32.7% and 21.6% in the T2DM group, compared to 21.9% and 31.9% in the non-DM group, respectively, resulting in a hazard ratio (HR) of 1.52 (95% confidence interval [CI] 1.12–2.07) for major amputation and HR of 0.64 (95% CI 0.46–0.88) for mortality. At one year, the HR for major amputation was 1.45 (95% CI 0.99–2.11), HR for mortality 0.92 (95% CI 0.61–1.39), HR for combined major amputation/mortality 1.27 (95% CI 0.94–1.72), and HR for MACE 1.24 (95% CI 0.92–1.67) for those with T2DM compared to those without in the multivariable Cox-regression analyses. The multivariable logistic regression analysis showed significantly lower odds of fasciotomy, OR 0.1 (95% CI 0.01–0.51) in the T2DM-group.

Conclusion: T2DM was not significantly associated with higher hazard of major amputation, mortality, combined major amputation/mortality, or MACE after revascularization for ALI, compared to patients without T2DM. Patients with T2DM had significantly lower odds of fasciotomy.

Keywords: acute lower limb ischemia, type 2 diabetes mellitus, major amputation

Introduction

Type 2 diabetes mellitus (T2DM) is a major risk factor for the development of coronary heart disease, cerebrovascular disease, and peripheral artery disease (PAD).[1–3] Patients with T2DM and PAD often have both more distal atherosclerosis, which may limit potential revascularization options, and higher rates of major amputation and mortality.[4] Acute lower limb ischemia (ALI) is an umbrella term for the acute onset of reduced limb perfusion with a maximum duration of 14-days in patients with or without pre-existing PAD.[5] The two main causes of ischemia are thrombotic occlusions in an atherosclerotic or aneurysmatic artery, and cardiac embolization.[6] Urgent revascularization is recommended for patients with Rutherford category IIA and IIB ALI, however in patients with Rutherford category III revascularization is not

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advised, and in selected cases with Rutherford category I, a conservative approach is suitable.[7] The revascularization procedure, either open-, endovascular, or hybrid vascular surgery, is chosen with regard to the severity of ischemia according to the Rutherford classification, the etiology and anatomical site of the occlusion, and the patient's characteristics.[7] After emergency revascularization, the patient is at risk of developing acute compartment syndrome (ACS) with increased pressure inside the muscle compartments caused by swelling of the calf muscles restrained in compartments by the fascia, resulting in ischemia necessitating urgent fasciotomy to save the limb and prevent foot drop.[7]

The potential effects of T2DM on ALI outcomes have not been thoroughly investigated, and it is unknown whether the higher rates of major amputation and mortality seen in PAD translate to worse outcomes in ALI. It is also of interest to know if T2DM modifies the risk of major adverse cardiovascular events (MACE) and ACS after revascularization for ALI.

This study aimed to investigate potential differences in major amputation and mortality after revascularization for ALI in patients with and without T2DM. A secondary aim was to investigate potential differences in MACE and fasciotomy between the two groups, as a proxy for ACS following revascularization for ALI.

Methods

Study Design and Setting

This was a nation-wide registry-based cohort study of patients with or without T2DM undergoing revascularization for ALI at all hospitals in Sweden between January 1, 2010, and December 31, 2014. The Swedish Vascular Registry (SWEDVASC) was used to identify all patients who underwent revascularization for ALI in Sweden during the inclusion period. Information about coexistence of T2DM was collected through cross-referencing the national diabetes registry (NDR) using the patient's personal identity number. Follow-up for mortality ended December 31, 2017. The study complied with the Strengthening the Reporting of Observational Studies in Epidemiology statement for cohort studies (Supplementary Table S1). This study was approved by the Regional Ethical Review Board in Lund, Sweden (DNR: 2016–232 and 2016–544) and the data was handled according to local data protection and privacy regulations.

Data Collection and Registries

All Swedish patients undergoing any type of vascular surgery are supposed to be included in SWEDVASC, the Swedish National Registry for Vascular Surgery, which in this study was used to retrieve information about the ischemic severity (Trans-Atlantic Inter-Society Consensus Class [TASC]), revascularization procedure(s), and fasciotomy. SWEDVASC includes around 15000 patients yearly[8] and has been shown to have a high degree of accuracy when reporting in validated fields: "carotid surgery" and "abdominal aortic aneurysm repairs".[9,10]

NDR aims to include all patients with diabetes mellitus (DM), including T2DM, in Sweden and collects data on treatment and risk factors for diabetes-related complications.[11] Reporting to NDR is based on information collected from medical records at least once a year at hospital outpatient and primary health care clinics. NDR includes data from around 470000 patients with all types of diabetes.[12]

The National Patient Register was used to access comorbidities at admission, as well as follow-up data regarding major amputation, MACE, acute myocardial infarction, stroke, and ischemic heart disease.[13] The *National Patient Register* uses International Classification of Disease, tenth revision (ICD-10) for diagnosis. Longitudinal Integration Database for Health Insurance and Labor Market Studies was used for socioeconomic background information.[14] The Cancer Registry was used for cancer diagnosis.[15] The Swedish Cause of Death Register was used to determine the date and cause of death.[16]

Sample Selection

All consecutive patients with infrainguinal ALI treated with revascularization and registered in SWEDVASC during the inclusion period were included in the study. Patients who died prior to revascularization, or were under the age of 18 at admission, underwent primary amputation, conservative treatment, or palliative care were excluded. If a patient underwent consecutive treatments, only the index procedure was included in the study. No power calculations were performed prior to the initiation of the study due to its exploratory nature.

Variables

Socioeconomic Variables

Marital status was divided into married, separated, single, and widowed. Income was ordered into quartiles. Education was divided into non-complete elementary education (<9 years), complete elementary education to complete upper secondary school (9–12 years), or higher-level education (>12 years). Country of birth was defined as Sweden, Europe outside of Sweden, and the rest of the world.

Background Characteristics and ALI Definition

T2DM was defined as dietary treatment only or use of oral antihyperglycemic agents only, or patients diagnosed with diabetes at the age of ≥40 years taking insulin with or without non-insulin antihyperglycemic agents.[17] For patients with T2DM, diabetes treatment and HbA1C levels were collected from the NDR (Supplementary Table S2). PAD was defined as ICD-10 codes: I70.2 and I73.9 (all subgroups accepted except I73.9A). Data on current smoking status was retrieved from SWEDVASC. Atrial fibrillation/flutter, cerebrovascular disease, chronic obstructive pulmonary disease, coronary heart disease, heart failure, kidney disease, liver disease, prior stroke, and psychiatric disorders were defined as having a prior diagnosis in the *National Patient Registry* at admission. The following ICD-10 codes were used for ALI diagnosis: I74.0–5, I74.8–9.

Treatment Variables

Open vascular surgery was defined as any type of open vascular surgery performed for revascularization, including hybrid procedures. Endovascular revascularization was defined as revascularization using any type of endovascular procedures, including catheter directed thrombolysis. For fasciotomy, the Swedish standardized system for coding health care procedures Klassifikation Av Vårdåtgärder (KVÅ) codes were used: NGM09 (fasciotomy of the lower leg), NFM09 (fasciotomy of the thigh and/or glutes).

Outcome Variables

Major amputation was defined as a tibial or more proximal amputation of the ipsilateral limb. MACE was defined as cardiovascular mortality (defined as death through I00-I99, R570, R960, R961 [ICD-10]), coronary revascularization FNA' 'FNB' 'FNC' 'FND' 'FNE' 'FNG' 'FNP12B' 'FNQ05B' 'FNQ12B' 'FNR22B' (KVÅ), ischemic heart disease I20-I25 (ICD-10), or stroke I61, I62, I63, I64 (ICD-10). Acute myocardial infarction was defined as I21 (ICD-10).

Statistical Methods

R 4.2.0 (http://cran.us.r-project.org/) was used for statistical analysis. Chi-square test was used to compare the proportion of immediately threatened limbs. Uni- and multivariable Cox-regression were used to analyze time-to-event outcome variables and presented as hazard ratios (HR) with 95% confidence intervals (CI). Kaplan–Meier curves of cumulative events with life tables were used to accompany the Cox regression analyses. For non-time dependent outcome variables, uni- and multivariable logistic regressions were performed with results presented as odds ratios (OR) with 95% CI. A directed acyclic graph (Supplementary Figure S1) was used to identify an appropriate multivariable model (Supplementary Figure S2) that adjusts for potential confounding in all multivariable analyses in the present study.[18] The covariates included in multivariable regression analyses were age, civil status, country of birth, sex, smoking, level of education, and income. As the study population have multiple comorbidities and have a high overall mortality rate, a multivariable Fine-Gray Subdistribution Hazard Model was used to address the potential impact of competing risks from mortality in the analyses of non-fatal outcomes; major amputation, MACE, acute myocardial infarction, and stroke. All statistical tests were two-sided and p-values < 0.05 were considered statistically significant.

Results

Study Cohort

All consecutive patients with infrainguinal limb-threatening ischemia (chronic or acute) who underwent revascularizations during the study's inclusion period (n=6936) were included in SWEDVASC infra-inguinal module. For this study, patients undergoing revascularization for non-acute ischemia (ie chronic limb threatening ischemia) (n=6321) were

excluded (Supplementary Figure S3). A total of 615 patients who underwent revascularization for ALI meeting the study's inclusion criteria remained for analysis. After cross-referencing with NDR, it was found that 245 (39.8%) of these patients had T2DM.

Baseline Characteristics

The group with T2DM had a lower mean age (73.7 years, SD 11.3 years), lower rates of smoking 26.4%, and lower proportion of women 41.6%, compared to a mean age 79.2 years (SD 10.4 years), 32.8% smokers, and 54.1% women in the group without T2DM (Table 1). The T2DM group also had a higher prevalence of prior acute myocardial infarction, coronary heart disease, cerebrovascular disease, heart failure, kidney disease, and lower prevalence of chronic obstructive pulmonary disease, atrial fibrillation, and cancer prior to admission than the group without T2DM (Table 2). Ischemic severity was not reported in 77.5% of patients with T2DM, and not in 64.3% of patients without T2DM. Among patients with reported ischemic severity, the proportions of immediately threatened limbs did not differ significantly between groups (with T2DM: 29/52 versus without T2DM: 66/126; p=0.68).

Revascularization Procedures

In the T2DM group, 34.3% (84/245) underwent open/hybrid surgery and 65.7% (161/245) underwent endovascular procedures, compared to 40.5% (150/370) open/hybrid and 59.5% (220/370) endovascular surgery in the group without T2DM. Catheter directed thrombolysis was performed in 17.1% (42/245) of patients with T2DM and 21.4% (79/370) of patients without T2DM.

Table 1 Socioeconomic Background Data

Variable	All (n=615)	T2DM (n=245)	Non-T2DM (n=370)
Age, Mean (SD)	77.0 (11.1)	73.7 (11.3)	79.2 (10.4)
Female sex % (n)	49.1 (302)	41.6 (102)	54.1 (200)
Smoking % (n)	29.9 (139)	26.4 (56)	32.8 (83)
Marital status % (n):			
Married	33.8 (208)	39.2 (96)	30.3 (112)
Separated	19.8 (122)	21.6 (53)	18.6 (69)
Single	13.5 (83)	13.5 (33)	13.5 (50)
Widowed	32.8 (202)	25.7 (63)	37.6 (139)
Country of origin % (n):			
Sweden	85.7 (527)	85.3 (209)	85.9 (318)
Europe outside of Sweden	8.0 (49)	5.3 (13)	9.7 (36)
Rest of the world	6.3 (39)	9.4 (23)	4.3 (16)
Education duration % (n):			
<9 years	47.4 (284)	47.9 (114)	47.1 (170)
9–12 years	41.2 (247)	42.0 (100)	40.7 (147)
>12 years	11.4 (68)	10.1 (24)	12.2 (44)
Income quartile % (n)			
1	24.7 (152)	26.5 (65)	23.5 (87)
2	25.4 (156)	21.6 (53)	27.8 (103)
3	21.1 (130)	22.0 (54)	20.5 (76)
4	28.8 (177)	29.8 (73)	28.1 (104)

Abbreviations: ALI, Acute lower limb ischemia; SD, Standard deviation; T2DM, Type 2 Diabetes Mellitus.

Table 2 Health Burden at Admission

Variable	All % (n=615)	T2DM % (n=245)	Non-T2DM % (n=370)
Atrial fibrillation/flutter % (n)	31.1 (191)	24.5 (60)	35.4 (131)
Cancer % (n)	11.1 (68)	8.6 (21)	12.7 (47)
Cerebrovascular disease % (n)	31.9 (196)	40.0 (98)	26.5 (98)
Chronic obstructive pulmonary disease % (n)	12.7 (78)	9.8 (24)	14.6 (54)
Coronary heart disease % (n)	39.7 (244)	51.0 (125)	32.2 (119)
Heart failure % (n)	31.4 (193)	35.1 (86)	28.9 (107)
Kidney disease % (n)	13.7 (84)	19.2 (47)	10.0 (37)
Liver disease % (n)	2.3 (14)	3.3 (8)	1.6 (6)
Peripheral artery disease % (n)	79.0 (486)	82.9 (203)	76.5 (283)
Prior acute myocardial infarction % (n=615)	22.0 (135)	29.4 (72)	17.0 (63)
Prior stroke % (n)	14.0 (86)	16.3 (40)	12.4 (46)
Psychiatric disorders % (n)	4.1 (25)	3.3 (8)	4.6 (17)

Abbreviation: T2DM, Type 2 Diabetes Mellitus.

Comparison of Major Outcomes

In the T2DM group, 21.6% of patients died and 32.7% underwent major amputation during the first year of follow-up, resulting in a combined major amputation/mortality rate of 44.9%, compared to a mortality rate of 31.9%, major amputation rate of 21.9% and a combined major amputation/mortality rate of 44.3% in the group without T2DM (Table 3). Only 1.2% of patients in the T2DM group underwent fasciotomy, whereas fasciotomy was performed in 3.8% of patients in the group without T2DM (Table 3). In the crude analysis, the T2DM-group had a lower hazard of mortality (HR 0.64 [95% CI: 0.46–0.88]) (Figure 1), but a higher hazard of major amputation (HR 1.52 [95% CI 1.12–2.07]) (Figure 2) and acute myocardial infarction (HR 2.24 [95% CI 1.05–4.78]). None of these differences

Table 3 Major Adverse Events During the First Year of Follow-Up After Revascularization for ALI, Including Uni- and Multivariable Regression Analyses

Variable	All % (n=615)	T2DM % (n=245)	Non-T2DM % (n=370)	Model A (Crude)		Model B (Multivariable Regression)		Model C (Fine-Gray Subdistribution Hazard)	
				HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Mortality 1 year % (n)	26.2 (161)	21.6 (53)	31.9 (108)	0.64 (0.46–0.88)	0.01	0.92 (0.61–1.39)	0.69	-	-
Cardiovascular mortality 1 year % (n)	4.1 (25)	4.1 (10)	4.1 (15)	0.95 (0.43–2.11)	0.90	0.88 (0.29–2.64)	0.82	-	-
Major amputation 1 year % (n)	26.2 (161)	32.7 (80)	21.9 (81)	1.52 (1.12–2.07)	0.01	1.45 (0.99–2.11)	0.05	1.38 (0.96–1.99)	0.08
Major amputation/ mortality 1 year % (n)	44.6 (274)	44.9 (110)	44.3 (164)	1.03 (0.81–1.32)	0.79	1.27 (0.94–1.72)	0.12	-	-
MACE 1 year % (n)	44.6 (274)	47.3 (116)	42.7 (158)	1.12 (0.88–1.42)	0.37	1.24 (0.92–1.67)	0.15	1.25 (0.93–1.69)	0.13
Acute myocardial infarction 1 year % (n)	4.6 (28)	6.9 (17)	3.0 (11)	2.24 (1.05–4.78)	0.04	2.15 (0.86–5.38)	0.10	2.20 (0.88–5.54)	0.09

(*Continued*)

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Table 3 (Continued).

Variable	All % (n=615)	T2DM % (n=245)	Non-T2DM % (n=370)	Model A (Crude)		Model B (Multivariable Regression)		Model C (Fine-Gray Subdistribution Hazard)	
				HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Stroke 1 year % (n)	5.7 (35)	6.9 (17)	4.9 (18)	1.32 (0.68–2.57)	0.46	1.36 (0.60–3.09)	0.46	1.39 (0.62–3.15)	0.4
-	-	-	-	OR (95% CI)	p-value	OR (95% CI)	p-value	–	–
Fasciotomy % (n)	2.8 (17)	1.2 (3)	3.8 (14)	0.24 (0.06–0.73)	0.02	0.1 (0.01–0.51)	0.01	–	–

Abbreviations: ALI, Acute lower limb ischemia; CI, Confidence interval; HR, Hazard ratio; MACE, Major adverse cardiovascular event; OR, odds ratio; T2DM, Type 2 diabetes mellitus.

remained statistically significant after adjusting for potential confounders (Table 3), or after accounting for the competing risk of mortality (Table 3). Combined major amputation/mortality did not differ significantly in crude or adjusted analysis (Figure 3 and Table 3). Odds of fasciotomy were significantly lower in the T2DM-group in both the crude analysis (OR 0.24 [95% CI: 0.06–0.73]) and after adjustment for potential confounders (OR 0.1 [95% CI 0.01–0.51]) (Table 3).

Discussion

In the present study, patients with T2DM had higher hazard of major amputation and acute myocardial infarction, but lower hazard of mortality during the first year after revascularization for ALI compared to those without T2DM. However, these differences were attenuated and no longer statistically significant in adjusted analyses. The odds of fasciotomy were significantly lower in both crude and adjusted analysis for patients with T2DM, and the overall rate of fasciotomy in this cohort was lower than previously reported in the literature.[7]

In line with the present study, a recent population-based study on revascularized and non-revascularized patients with ALI covering the years 2015–2018[19] reported that DM was not associated with increased rate of combined major amputation/mortality at one year. A similar finding was reported after 843 revascularizations for ALI covering the period

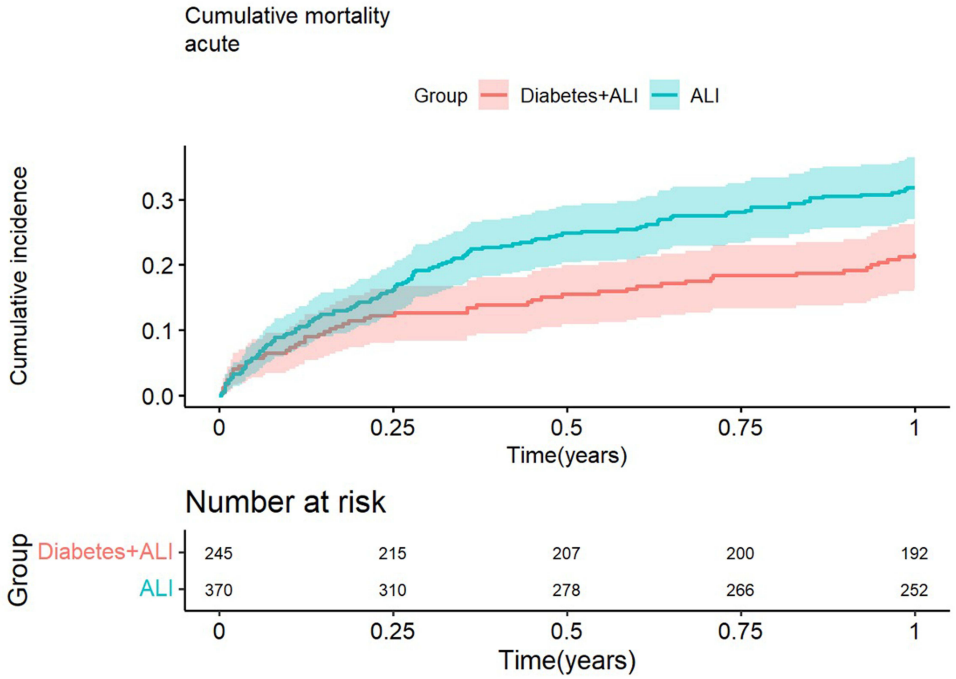

Figure 1 Cumulative mortality during the first year after revascularization for acute lower limb ischemia for patients with and without type 2 diabetes mellitus. Shaded areas represent 95% CI.

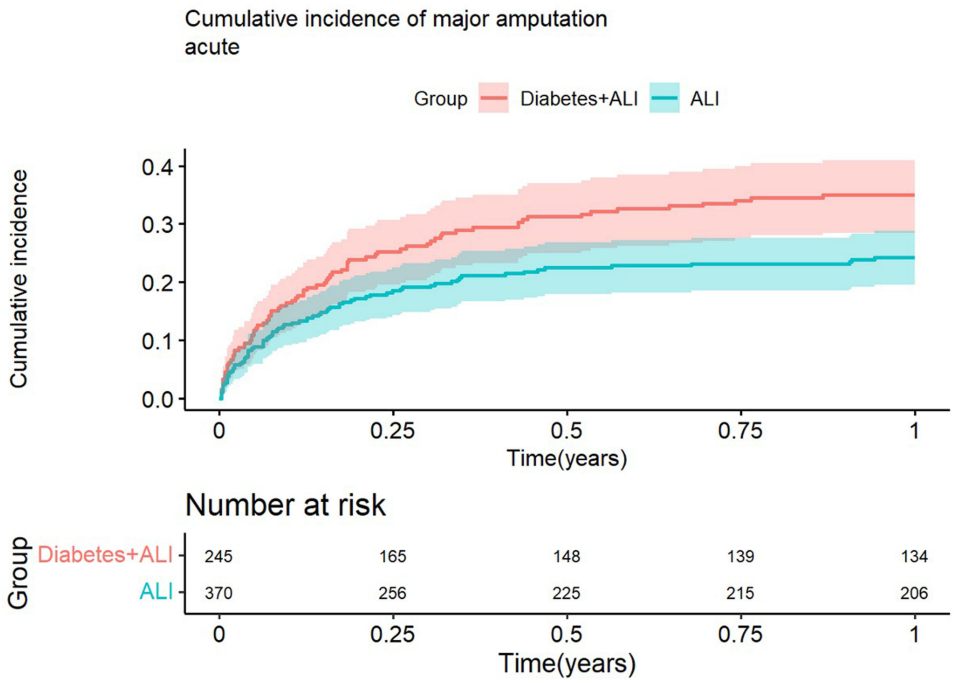

Figure 2 Cumulative major amputation during the first year after revascularization for acute lower limb ischemia for patients with and without type 2 diabetes mellitus. Shaded areas represent 95% CI.

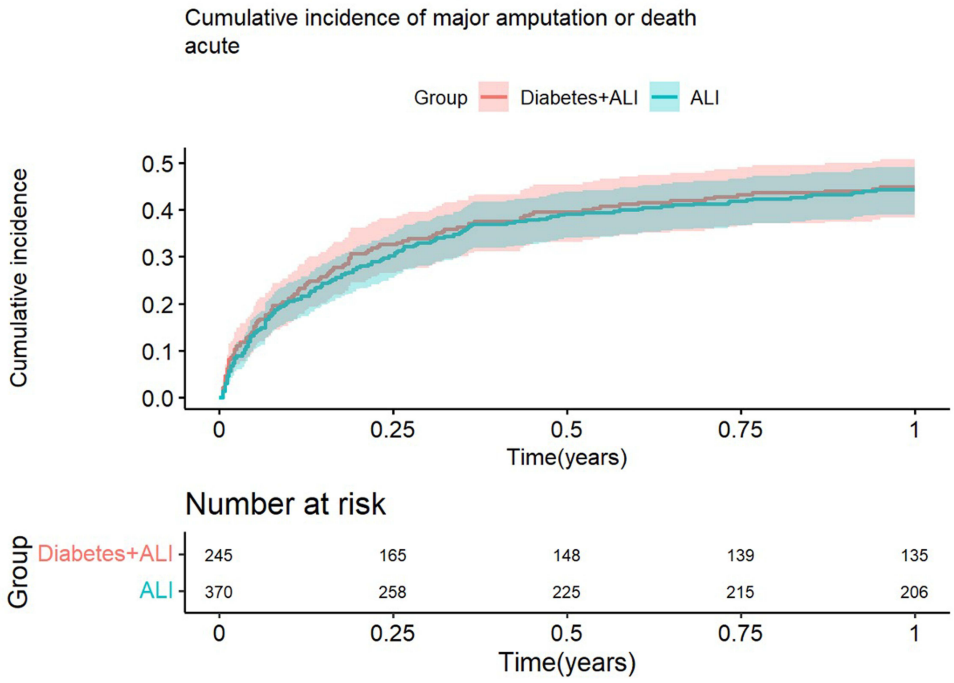

Figure 3 Cumulative combined major amputation/mortality during the first year after revascularization for acute lower limb ischemia for patients with and without type 2 diabetes mellitus. Shaded areas represent 95% CI.

from 2001 to 2018.[20] However, in another report on patients undergoing catheter-directed thrombolysis, patients with diabetes had a higher rate of major amputation at one year and higher combined major amputation/mortality at three years in the adjusted analysis compared to those without DM.[21] In the present study, the small subset of patients undergoing catheter-directed thrombolysis in the present study was not evaluated separately. The hazard for all-cause

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mortality, which acts as a competing risk, was higher in the group without T2DM in the crude analysis, which could have led to an underestimation of the risk of major amputation rate in this group. Therefore, a subsequent Fine-Gray subdistribution hazard model was used to estimate the subdistribution HR after accounting for the competing risk of all-cause mortality. Results suggested that failure to account for the competing risk of all-cause mortality may to some extent overestimate the risk of major amputation in the T2DM group compared to the group without T2DM.

The odds of fasciotomy, a proxy for treatment or prevention of ACS, was lower in the T2DM group. The development of ACS is caused by an increased intracompartmental pressure (ICP), where ischemia arises when the ICP is high enough to impede blood flow. There is no set ICP at which ACS arises, but its development seems to be dependent on the perfusion pressure.[22] Models have been used to set cut offs for the difference between either diastolic pressure or mean arterial pressure minus ICP, and a pressure difference of <30mmHg between diastolic pressure and ICP has been most widely used to indicate ACS.[23,24] Patients with DM are more prone to arterial stiffness[25] with less arterial compliance, leading to increased blood pressure and thus an increased perfusion pressure in the tissue.[26] With a higher perfusion pressure, the threshold ICP for the development of ACS would need to be higher. DM has also been associated with a higher risk of sarcopenia.[27] With less muscle mass, the muscle of the lower leg might have more room to expand without a significant increase in ICP. Furthermore, compared to patients without DM, those with DM often have more extensive and lengthy atherosclerotic occlusive lesions in the calf arteries,[28] which hypothetically may prevent the possibility of obtaining larger reperfusion volumes of the lower leg after emergency revascularization, and hence ACS and the need for fasciotomy. Such mechanisms could potentially contribute to the fact that patients with T2DM in this study had lower odds of fasciotomy. In a large retrospective study of ALI,[20] patients with DM did not undergo fasciotomy less often than those without DM. To clarify whether DM is a protective factor for ACS and fasciotomy, large prospective studies focused on risk factors for ACS with preset defined variables would be worthwhile.

Strengths and Limitations

The main strength was the study design, as we used data from a combination of nationwide registries. The loss of follow-up data was minimal. The use of directed acyclic graphs enabled standardized evaluation of possible relations between different variables, the choice of variables necessary to adjust for address potential confounding,[29] and increased transparency in the choice of variables for the multivariable analyses, which is often lacking in retrospective studies.[28] The use of the Fine-Gray subdistribution hazard models may have helped to mitigate some of the effects of possible competing risks from mortality.[30]

Registry data needs to be validated regularly to be trustworthy. As data on patients with acute or chronic limb ischemia registered in SWEDVASC have not yet been validated, there might be misclassification of these two conditions. It is highly likely that registrations of patients undergoing vascular procedures for ALI are both fewer and less accurate than for patients with chronic limb ischemia. The SWEDVASC infra-inguinal module has no registration of anatomic level of the arterial occlusion, and it would have been interesting to obtain the distribution of femoro-popliteal and infra-popliteal occlusions in those with and without T2DM. Unfortunately, severity of limb ischemia was insufficiently reported in SWEDVASC, but there were no significant differences in the available registered data. Validation of the SWEDVASC infrainguinal module would be advisable.

Even with a quite large cohort, there may still be a risk of statistical error due to insufficient power, especially regarding endpoints with fewer events. No consideration of duration of diabetes, glycemic control, or type of treatment for T2DM was made in the present study, resulting in a heterogeneous group of patients with T2DM. In a report on patients with DM and chronic limb-threatening ischemia, increased HbA1c levels were associated with increased risk of limb loss.[31] Thus, the hazard of adverse events might be underestimated for T2DM patients with poor glycemic control in the present study. Figures regarding smoking might also be inaccurate, as previous studies have shown low levels of reporting of this variable in SWEDVASC.[32]

Generalizability

The results are applicable to high-income countries with similar access to urgent vascular and endovascular surgery including supportive care, similar demographics, similar access to primary health care, and affordable costs of prescribed drugs. Only patients with infra-inguinal ALI were included, and the results are therefore not representative of patients with supra-inguinal arterial disease. In the last decade, new drugs have been introduced in the treatment of T2DM, such as sodium-glucose transporter-2 inhibitors and glucagon-like peptide-1 analogs, contributing to a decreased risk of cardiovascular mortality and MACE in patients with T2DM.[3,33–35] Since the inclusion period in the present study was 2010–2014, the results related to cardiovascular mortality and MACE may be less applicable to patients with T2DM treated with these drugs.

Conclusions

T2DM was associated with an increased hazard for major amputation and acute myocardial infarction, but a lower hazard for mortality, in the first year after revascularization for ALI. However, after adjusting for potential confounders, none of these differences remained statistically significant. T2DM was significantly associated with lower odds of undergoing fasciotomy after revascularization for ALI. Further large-scale prospective cohort studies comparing patients with ALI with and without DM are warranted.

Disclosure

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