Cardiovascular Diabetology

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Reamputation risk and mortality after lower-limb amputation in patients with diabetes: predictors, effects of antidiabetic medications and temporal trends

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Abstract

Background Diabetes is associated with a high incidence of diabetic foot and peripheral artery disease and with markedly increased lifetime amputation risk. Here we investigated predictors of reamputation risk and mortality including antidiabetic medication in patients undergoing non-traumatic lower limb amputation (LLA).

Methods In an observational longitudinal study, we analyzed 607 patients with diabetes and 500 patients without diabetes who underwent non-traumatic LLA between 2006 and 2022. The primary endpoint was reamputation-free survival. Predictors of subsequent amputations or mortality were analyzed using Cox regression and joint frailty models.

Results Diabetes was independently associated with increased combined reamputation and mortality risk (HR *1.28*, 95% CI [1.08, 1.52], $p=0.004$). Reduced reamputation-free survival in patients with diabetes was triggered by a marked higher reamputation risk. Higher HbA1c levels were associated with lower reamputation-free survival. Older age, presence of atrial fibrillation and chronic kidney disease were associated with increased reamputation risk in patients with diabetes. Metformin usage in patients with type 2 diabetes was associated with a marked reduction in combined risk of reamputation and mortality (HR *0.59*, 95% CI [0.43, 0.81] $p=0.001$). While overall sodium-glucose transporter 2 inhibitor (SGLT2i) usage was low in this cohort, it was associated with an increased reamputation risk (HR 2.00, 95% CI [1.47, 2.72], $p>0.001$) although safe with respect to mortality. Over time, reamputation risk peaked between 2020 and 2022, whereas mortality declined compared with the period from 2006 to 2010 in patients with diabetes.

Conclusion Diabetes remains to be associated with reduced reamputation-free survival; an association that is independent of increased prevalence of comorbidities in our data. Although reamputation risk has increased in recent years, overall survival has improved in patients with diabetes. Metformin usage is associated with improved reamputation-free survival while our limited data suggest increased risk of reamputation but safety with respect to

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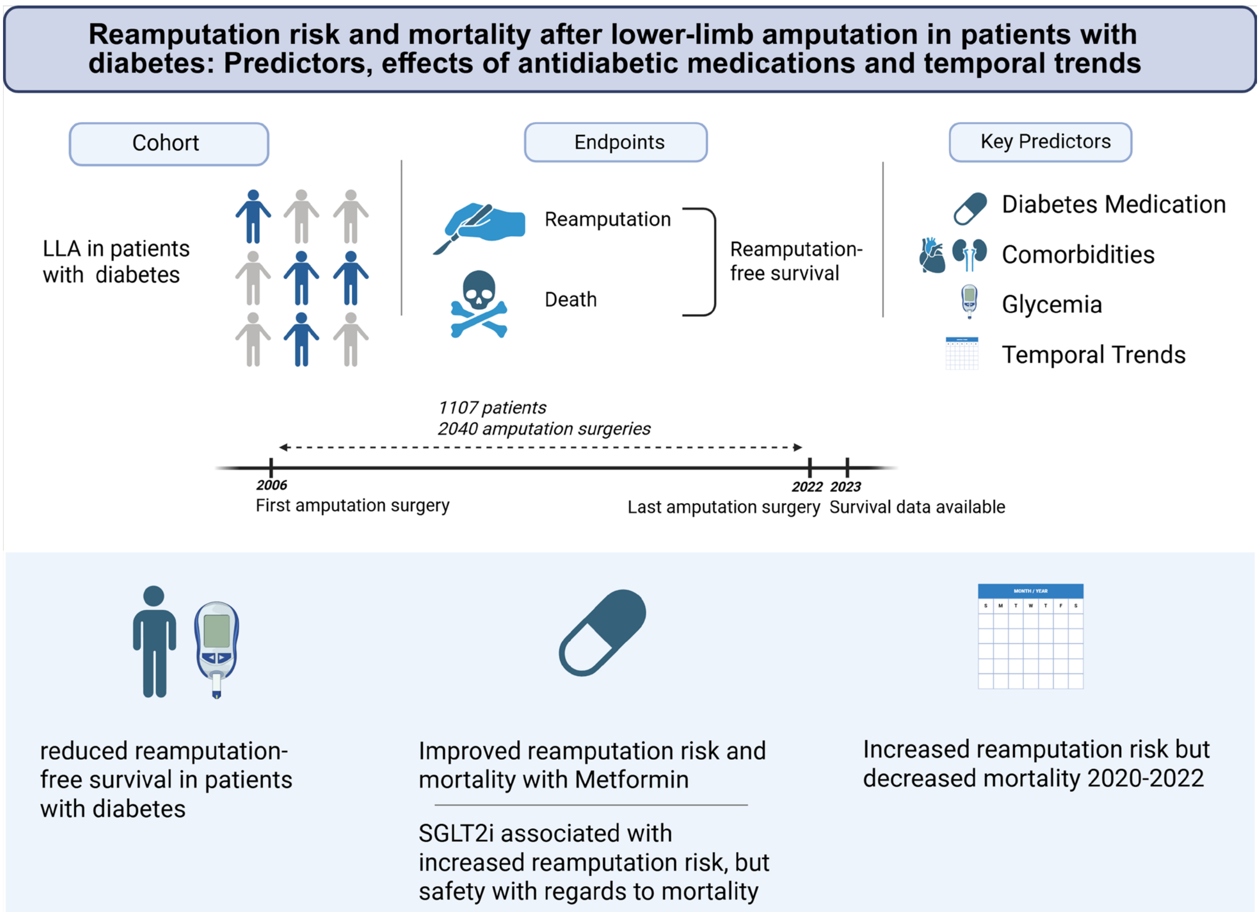
mortality in patients treated with SGLT2i. Further studies are warranted to evaluate the effect of SGLT2i therapy on outcome in patients undergoing LLA.

Keywords Lower-limb amputation, Diabetes, Risk factors, Mortality, Reamputation risk

Graphical abstract



Research insights

What is currently known about this subject?

- Need for amputation surgery represents a severe and frequent comorbidity of the diabetic foot syndrome.
- Need for amputation surgery severely affects quality of life for affected patients.

What is the key research question?

- Does presence of diabetes and/or type of antidiabetic medication influence reamputation-free survival, isolated reamputation risk or mortality following amputation surgery due to diabetic foot syndrome and/or peripheral arterial disease?.

What is new?

- Diabetes is associated with reduced reamputation-free survival with increased HbA1c levels, presence of atrial fibrillation or chronic kidney disease and older age at time of first amputation as predictors of worse outcome in patients with diabetes.
- Metformin usage is associated with improved reamputation-free survival, while limited data indicate that SGLT-2 inhibitor usage might be associated with increased reamputation risk but safety with respect to mortality.
- Reamputation risk has increased over time with a peak during SARS-CoV2 pandemic years, however post-amputation mortality has substantially improved from 2006 to 2022.

How might this study influence clinical practice?

- Findings support careful treatment of modifiable risk factors and critical appraisal of pharmacological interventions in patients with diabetic foot syndrome.

Background

Lower limb amputation (LLA) is the most severe complication of diabetic foot syndrome and/or peripheral artery disease (PAD) and is associated with high morbidity and mortality [1, 2]. In patients with diabetes, the lifetime risk for diabetic foot syndrome is high with estimations between 19 and 34% [3]. Despite tighter treatment goals and novel treatment options recent data suggest that the incidence of hospitalization for diabetic foot syndrome has even increased in the past decades [4]. Increasing rates of LLA due to diabetic foot syndrome were reported in the post-pandemic period [5]. In contrast, in a Danish type 2 diabetes cohort incidence of PAD, lower-extremity revascularization and LLA decreased from 1996 to 2015 [6]. Decreasing rates of LLA were also reported from a Polish registry [7].

Several data are available on prevalence and risk factors of LLA in patients with diabetes [8–11], however only little information is available on predictors of outcome. While depression and frailty index were identified as risk factors for mortality in patients following major amputations [12, 13], most data on predictors of outcome are predominantly available from the acute preoperative or perioperative setting. In various studies, albumin levels, smoking, hypertension, diabetes duration, number of debridements after surgery, preoperative red blood cell distribution width, and a high neutrophil-to-lymphocyte ratio (NLR) were identified as predictors of reamputation risk or mortality, respectively [14–16]. In a systemic review considering 22 publications on 2334 patients, comorbidities and type of amputation predicted poor outcome in patients with diabetic foot ulcers [17]. In patients with type 1 diabetes, increasing age, comorbidities and female sex were associated with increased in-hospital mortality [18].

Only recently, uncertainties came up regarding the use of antidiabetic medication in patients with diabetic foot ulcers and/or PAD. Following increased amputation rates reported in the CANVAS trial, regulation authorities informed about potentially increased amputation risk in type 2 diabetics on SGLT2i [19]. Meanwhile, several studies and meta-analyses have put into perspective or have refuted the warning [20–26]. However, only recently a retrospective study in US veterans suggested that SGLT2i use is associated with an increased risk for amputations in patients with diabetes and PAD. In another study risk for major adverse limb events was higher in SGLT2i treated patients than in glucagon-like peptide 1 receptor agonist (GLP1-RA) treated patients, while amputation rate was comparable between the groups [27]. Increased risk of PAD surgeries was also reported in patients treated with SGLT2i when compared to dipeptidyl peptidase 4 inhibitor (DPP4i) therapy [28].

Here we aim to characterize the effect of diabetes on outcome in patients with LLA and define both, long-term and immediate risk factors for subsequent amputations and mortality in these high-risk patients.

Methods

Study design

Medical records of patients who had undergone non-traumatic LLA for complications of PAD and/or diabetic foot syndrome between 2006 and 2022 at the Department of Vascular Surgery at the Medical University of Innsbruck, Austria, were assessed retrospectively. In this study, first we evaluated the impact of diabetes on clinical outcomes by comparing diabetic and non-diabetic patients undergoing lower limb amputations and second, within the diabetic cohort, we identified risk factors for mortality and reamputation, specifically examining the influence of various antidiabetic medications. Additionally, temporal trends in outcome and clinical characteristics from 2006 to 2022 were investigated in the diabetes cohort. For the latter, the observation time was divided into four periods [2006–2010, period 1 (P1), 2011–2015 period 2 (P2), 2016–2019 period 3 (P3), and 2020–2022 period 4 (P4)]. The SARS-CoV2 pandemic years (P4) were analyzed separately to avoid bias due to partly limited access to health care.

Study population

Patients with and without diabetes who underwent non-traumatic LLA for complications of PAD, arterial embolism and/or diabetic foot syndrome were analysed. Patients with LLA due to oncologic indication or implantation-related infection or trauma were excluded from analysis. Demographic and clinical data including laboratory data, comorbidities and medication were obtained from medical records. Vital status was available from 1087 patients up until end of 2023. Data on vital status were obtained from the death registry of Statistics Austria. Data from patients with missing vital status (20 of 1107) was not further used for survival analysis. Body mass index (BMI) and body weight were determined before surgical intervention. Age at first amputation was used for descriptive and adjusted Cox analysis. Laboratory values were considered as eligible for analysis when obtained within a maximum of 3 months before the first amputation. PAD was classified according to Fontaine [29] and Rutherford classifications [30]. Defect size was classified according to the Society of Vascular Surgery (SVS)-Wound-Ischemia-Foot Infection (WIFI) classification [31]. Details on inclusion and exclusion criteria and study procedures were described elsewhere [32]. The study was approved by the local ethics committee of the Medical University of Innsbruck (1108/2023).

Study outcome and definitions

The primary outcome was reamputation-free survival after non-traumatic LLA. A reamputation was defined as any osseus tissue dislodging after a previous amputation. Amputations distal to the ankle joint were classified as minor amputations, while major amputations were defined as amputations above the ankle.

Statistical analysis

For the combined end-point "reamputation-free survival" time to event analysis was performed with time to either next amputation or death, whichever appeared first. Data were right-censored after follow-up (end of 2022 for analysis of repeated amputation and end of 2023 for mortality analysis). Survival analysis was done as implemented in the *survival* R package (Version 3.8–3). For plotting reamputation risk we used the Fine and Gray method with death set as competing risk from the *cmprsk* R package (Version 2.2–12).

Predictors of outcome were analysed using an adjusted Cox model. Established risk factors as well as potentially outcome-modifying medication were included as variables in the adjusted Cox models. These include non-modifiable risk factors (age, sex), comorbidities (diabetes, chronic kidney disease, hypertension, arterial fibrillation and underweight or obesity), amputation type (major, minor), indications of LLA according to the SVS-WIFI classification and medications that have been evaluated to affect outcome (antiplatelet therapy, anticoagulants, ACEi/ARB, β blocker, lipid lowering therapy). In the diabetic cohort, presurgical HbA1c was included as variable in the adjusted Cox model. In an extended adjusted Cox model, antidiabetic medication, which had been shown to affect outcome in clinical trials were included (SGLT2i, metformin, insulin). GLP-1 RA and glitazone treatment were excluded due to too small sample size.

To assess the risk for reamputation and account for the competing risk of death a generalized joint frailty model as implemented in the R package *frailtypack* (Version 3.7.0) was used on the full dataset of 2040 amputations. Risk for repeated amputation surgery (repeated event) and risk for death (terminal event) was modeled with a shared frailty term to account for within-patient correlation. To report results from joint frailty models, robust standard errors were calculated.

For propensity score matching (PSM) the *MatchIt* R package was used. We used two separate PSM analyses to minimize impact of selection bias: one for Metformin and one for SGLT2i use as the main exposure. All covariates from the "Diabetes" Cox Model (Fig. 2a) were used here including HbA1c (per 10 mmol/mol), sex, age per 10 years, BMI, amputation type, comorbidities (chronic kidney disease, hypertension, atrial fibrillation), indications of LLA amputation according to the SVS WIFI classification (infection, ischemia, defect size) and medication (antiplatelet therapy, oral anticoagulant therapy, ACEi/ARB, β blocker, lipid lowering therapy). We employed a nearest-neighbour matching algorithm without replacement, using a 3:1 ratio (up to three controls for every treated patient). To ensure good-quality matching and reduce bias, a caliper of 0.2 SDs was applied. The shown Cox models in the matched cohort were adjusted for all covariates for doubly robust estimation. Matching weights were also incorporated in the Cox model to account for the 3:1 ratio data structure. For all modelling approaches complete-case analysis was used, and all covariates included in the model were plotted in the corresponding graphs.

For the descriptive analysis of the dataset, data is presented as median with interquartile (Q25, Q75) ranges provided. Kruskal–Wallis test and Chi-Squared test were used to compare groups. For trend testing Spearman's rank correlation was used.

Statistical analysis, creation of tables and figures were done in R (R-Version 4.4.1).

Results

Clinical characteristics

607 patients with diabetes and 500 patients without overt diabetes at time of first LLA were analysed [32]. Baseline characteristics are shown in Table 1.

579 patients suffered from type 2 diabetes, 25 from type 1 diabetes, and 3 from other specific diabetes forms, respectively. Median age was lower and median BMI was higher in the diabetes cohort when compared to patients without diabetes. Median low-density lipoprotein cholesterol (LDL-C) levels were lower in the diabetes cohort but were markedly above current treatment targets of 1.4 mmol/l for patients with diabetes-associated organ damage [33]. Prevalence of chronic obstructive pulmonary disease (COPD) and median serum creatinine levels were higher in patients with diabetes. Unexpectedly, atrial fibrillation was less common in patients with diabetes compared to patients without diabetes.

A minor amputation was the first amputation in 78.9% of patients with diabetes but only in 54.6% of non-diabetic patients (Table 1). In patients with diabetes, a major amputation as first surgical intervention was significantly more often performed in females than in males (34.9% vs. 15.9%). Similar sex differences in amputation type were found to a lesser extent in patients without diabetes as well.

Table 1 Overview of cohort according to diabetes status

	Diabetes			
	[ALL]	no	yes	p.overall
	N = 1107	N = 500	N = 607	
Age	73.6 [64.7;81.5]	76.2 [67.3;83.3]	71.4 [63.3;79.5]	< 0.001
Female Sex	345 (31.2%)	179 (35.8%)	166 (27.3%)	0.003
BMI (kg/m^2)	24.9 [22.0;28.5]	23.2 [20.5;26.8]	26.2 [23.3;29.8]	< 0.001
Smoking	280 (28.1%)	142 (30.7%)	138 (25.8%)	0.226
LDL-C (mmol/L)	2.05 [1.53;2.64]	2.12 [1.61;2.59]	1.97 [1.48;2.67]	0.295
< 1.4 mmol/L	130 (20.7%)	50 (19.2%)	80 (21.9%)	0.470
> 1.4 mmol/L	497 (79.3%)	211 (80.8%)	286 (78.1%)	
HbA1c (%)	6.40 [5.60;8.00]	5.60 [5.30;5.90]	7.20 [6.20;8.60]	< 0.001
HbA1c (mmol/mol)	46.4 [37.7;63.9]	37.7 [34.4;41.0]	55.2 [44.3;70.5]	< 0.001
Hypertension	857 (77.5%)	367 (73.4%)	490 (80.9%)	0.004
Coronary heart disease	401 (36.3%)	167 (33.5%)	234 (38.6%)	0.092
Heart failure	182 (16.5%)	81 (16.3%)	101 (16.7%)	0.934
Chronic kidney disease	630 (57.7%)	265 (53.8%)	365 (61.0%)	0.018
Creatinine (μmol/L)	94.6 [71.6;143]	90.2 [69.0;134]	98.1 [74.3;148]	0.002
eGFR (ml/min/1.73m^2)	54.8 [33.1;77.4]	57.7 [35.5;79.9]	53.1 [32.6;72.4]	0.023
Atrial fibrillation	268 (24.2%)	141 (28.2%)	127 (21.0%)	0.006
COPD	177 (16.0%)	104 (20.8%)	73 (12.1%)	< 0.001
Antiplatelet therapy	912 (85.0%)	406 (84.1%)	506 (85.8%)	0.489
Oral anticoagulant therapy	256 (23.9%)	123 (25.5%)	133 (22.5%)	0.287
Lipid lowering therapy	590 (54.6%)	254 (52.5%)	336 (56.4%)	0.223
ACE/ARBi	594 (55.5%)	226 (47.0%)	368 (62.4%)	< 0.001
β-blockers	392 (36.6%)	180 (37.3%)	212 (35.9%)	0.679
Insulin			362 (59.6%)	
Metformin			142 (23.4%)	
SGLT2i			48 (7.91%)	
DPP4i			79 (13.0%)	
Secretagogues			119 (19.6%)	

Medications (ACEi/ARB, betablocker, oral anticoagulants, antiplatelet therapy, lipid-lowering therapy), COPD chronic obstructive pulmonary disease, SGLT2i, Sodium glucose transporter 2 inhibitors; DPP4i, Dipeptidyl-peptidase 4 inhibitors

Table 2 Underlying disease, local findings and amputation types in patients with and without diabetes

	Diabetes			
	[ALL]	no	yes	p.overall
	N = 1107	*N = 500*	*N = 607*	
PAD stage (Fontaine):				< 0.001
0	133 (12.3%)	49 (10.0%)	84 (14.2%)	
1	19 (1.75%)	0 (0.00%)	19 (3.20%)	
2	25 (2.31%)	6 (1.22%)	19 (3.20%)	
3	37 (3.42%)	12 (2.45%)	25 (4.22%)	
4	869 (80.2%)	423 (86.3%)	446 (75.2%)	
PAD stage (Rutherford): 1–3	0	0	0	0.058
4	21 (3.80%)	14 (5.79%)	7 (2.26%)	
5	61 (11.1%)	30 (12.4%)	31 (10.0%)	
6	470 (85.1%)	198 (81.8%)	272 (87.7%)	
Gangrene	450 (40.9%)	184 (37.1%)	266 (44.1%)	0.022
Ulcer	522 (47.7%)	167 (33.8%)	355 (59.1%)	< 0.001
Infection	717 (77.1%)	291 (70.6%)	426 (82.2%)	< 0.001
Ischemia	773 (70.5%)	364 (73.4%)	409 (68.1%)	0.063
Revascularisation Indication:				< 0.001
ALI	174 (23.9%)	127 (34.3%)	47 (13.2%)	
CLI	553 (76.1%)	243 (65.7%)	310 (86.8%)	
Defect size:				0.112
minor	119 (12.3%)	55 (13.4%)	64 (11.5%)	
major	539 (55.7%)	212 (51.8%)	327 (58.6%)	
extensive	309 (32.0%)	142 (34.7%)	167 (29.9%)	
Amputation type:				< 0.001
minor	752 (67.9%)	273 (54.6%)	479 (78.9%)	
major	355 (32.1%)	227 (45.4%)	128 (21.1%)	
neuropathy	383 (35.0%)	120 (24.3%)	263 (43.9%)	< 0.001

ALI, acute limb ischemia; CLI, chronic limb ischemia; PAD stages according to Fontaine [29] and Rutherford classifications [30]

Reamputation-free survival, reamputation risk and mortality

Overall study population

Overall, reamputation-free survival was low in this patient cohort with even poorer outcome in the diabetes cohort. Underlying diseases and local findings at time of amputation are shown in Table 2. Median time to either reamputation or death was 0.652 years (95%CI [0.463–0.939]) in patients with diabetes and 0.909 years (95%CI [0.646–1.437]) (Log-rank $p = 0.011$) in patients without diabetes (Fig. 1a). Diabetes remained to be associated with adverse outcome in a multivariate analysis that included severity of vascular disease and other known risk-factors for lower-limb amputations as covariates. Presence of diabetes was an independent risk factor for subsequent amputation or death (HR 1.28, 95%CI [1.08–1.52]). Multivariate Cox regression further identified presence of atrial fibrillation (HR 1.28, 95%CI

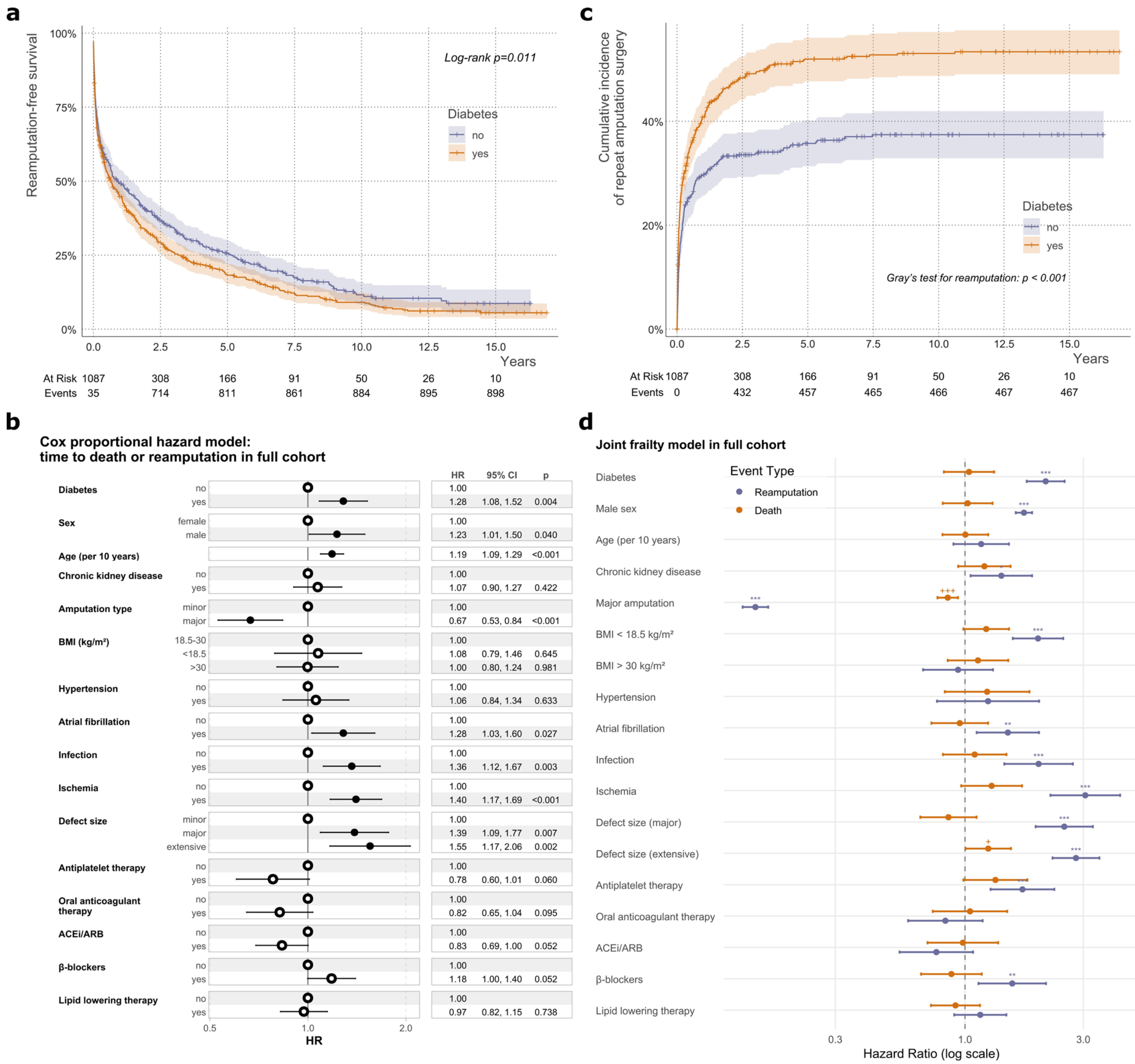


Fig. 1 Reamputation-free survival and predictors of outcome in patients with and without diabetes. **a** Kaplan–Meier plot of reamputation-free survival with and without diabetes at time of first amputation. The composite endpoint consists of either reamputation or death, whichever appears first. Censoring is indicated by ticks on the survival curves. Log-rank test was used to compare survival curves. **b** Cox proportional hazards model for the combined endpoint reamputation or death. Age at first amputation was centered around 60 years and scaled for 10 years. Hazard ratios indicate combined risk of reamputation or death. **c** Cumulative incidence of reamputation surgery. Cumulative incidence of a second amputation was modelled using the Fine and Gray method accounting for death as competing risk. Censoring is indicated by ticks on the survival curves. Grays test was used to compare cumulative incidence functions. **d** A joint frailty model for reamputation risk and death is shown. The model uses a joint frailty term clustering all amputation surgeries around individual patients. Hazard ratios and 95% confidence intervals are shown for all model covariates and for both reamputation risk (reoccurrence) and death (terminal event). For better readability reference levels of covariates are not plotted here. The BMI category 18.5–25 kg/m^2 was used as the reference group. Age at first amputation was centered around 60 years and scaled for 10 years. "*" indicates statistical significance for reamputation risk; "+" indicates statistical significance levels for mortality risk. */+ $p < 0.05$; **/+ + $p < 0.01$; ***/+ + + $p < 0.001$

[1.03–1.60]), male sex (HR 1.23, 95%CI [1.01–1.50]) and age at first amputation (per 10 years: HR 1.19, 95%CI [1.09–1.29]) as significant predictors of the combined endpoint (Fig. 1b). Presence of infection, ischemia and defect size were also associated with reduced reamputation-free survival driven by an increased reamputation risk. Overall, reamputation risk was significantly higher in patients with diabetes than in non-diabetic controls (Fig. 1c). Results from a joint frailty model, which simultaneously models risk for repeated surgery and also takes the competing risk of death into account using a shared frailty term, confirmed the enhanced reamputation risk in patients with diabetes without significantly affecting mortality (Fig. 1d).

Unadjusted in-hospital mortality was similar in patients with and without diabetes, but 30-day and 365-day mortality was lower in patients with diabetes compared to those without (ESM Table 1).

Diabetes study cohort

A J-shaped association between HbA1c levels and reamputation-free survival was found in the diabetes cohort, with an increase in presurgical HbA1c levels per 10 mmol/mol resulting in a reduction of reamputation-free survival by 7% (Fig. 2a, c). Besides presurgical presence of ischemia, infection and an extended defect size, older age and presence of atrial fibrillation were associated with decreased reamputation-free survival in patients with diabetes (Fig. 2a).

Unadjusted Kaplan–Meier curves suggest an early effect on mortality after amputation surgery in patients with diabetes, with no significant impact on long-term outcome (ESM Fig. 1a). In the joint frailty model, presence of chronic kidney disease, atrial fibrillation and male sex were also associated with increased reamputation risk without affecting mortality (Fig. 2b). Remarkably, aside a low BMI < 18.5 kg/m^2, local infection, ischemia and a larger defect size, male sex was associated with the highest increase in amputation risk (Fig. 2b).

There was a strong association between repeated surgeries and mortality from the joint frailty model [theta (association between recurrences and terminal event) = 0.30, $p < 0.001$)].

Analysis of the joint frailty hazard function showed the increased risk for repeated amputation surgery drops after 3 to 4 years and remains relatively low afterwards (ESM Fig. 1b). In contrast, mortality after amputation surgery exhibits a j-shaped relationship with time after first surgery (ESM Fig. 1c).

Effect of antidiabetic medication on outcome in patients with diabetes

Use of antidiabetic medication and temporal trends are shown in Tables 2 and ESM Table 2. In total, 23.4% of patients were treated with metformin, 59.6% with insulin, 13% with DPP4i and 7.9% with SGLT2i. Secretagogue usage drastically dropped during the observation period while SGLT2i usage markedly increased over time. GLP-1 RA and pioglitazone usages were low.

Notably, metformin treatment was associated with a marked decrease in combined reamputation and mortality risk even after adjusting for confounding factors including chronic kidney disease (HR 0.59, 95%CI [0.43–0.81]) (Fig. 3a). Improved primary outcome in metformin treated patients was driven by a reduced reamputation risk as shown in joint frailty analysis (Fig. 3b). In unadjusted survival analysis, both, reamputation-free survival and mortality were improved in metformin treated patients (Fig. 3c, d).

In contrast, SGLT2i treatment was associated with a borderline but non-significant increase in the combined

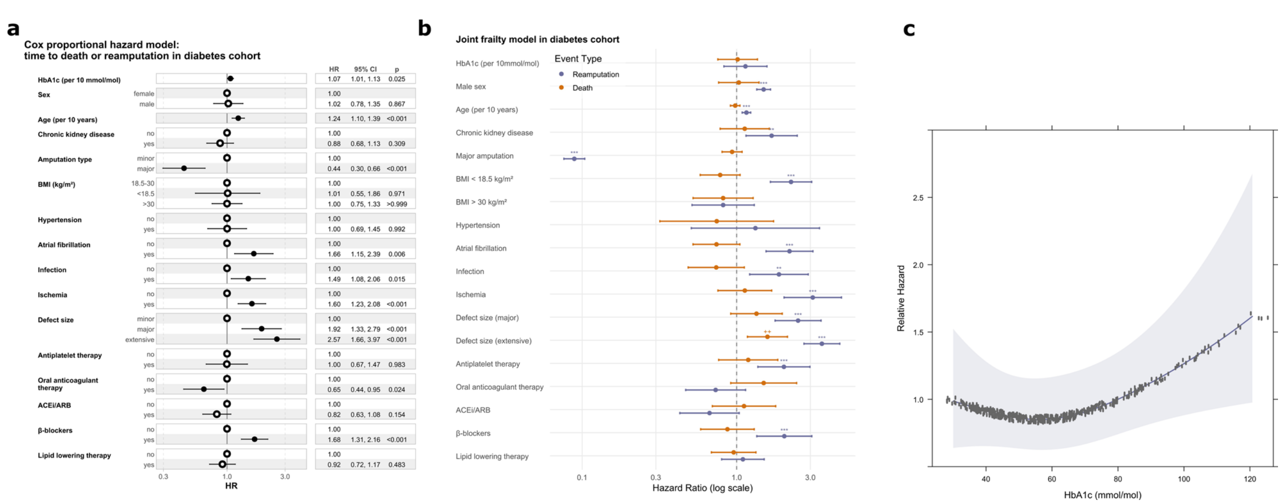


Fig. 2 Reamputation-free survival and predictors of outcome in patients with diabetes. **a** Cox proportional hazards model for the combined endpoint reamputation or death. Age at first amputation was centered around 60 years and scaled for 10 years. Hazard ratios indicate combined risk of reamputation or death. **b** A joint frailty model for reamputation risk and death is shown. The model uses a joint frailty term clustering all amputation surgeries around individual patients. Hazard ratios and 95% confidence intervals are shown for all model covariates and for both reamputation risk (reoccurrence) and death (terminal event). For better readability reference levels of covariates are not plotted here. The BMI category 18.5–25 kg/m^2 was used as the reference group. Age at first amputation was centered around 60 years and scaled for 10 years. "*" indicates statistical significance for reamputation risk; "+" indicates statistical significance levels for mortality risk. */+ $p < 0.05$; **/+ + $p < 0.01$; ***/+ + + $p < 0.001$. **c** Correlation between presurgical HbA1c levels (per 10 mmol/mol) and relative risk of either reamputation or survival is shown

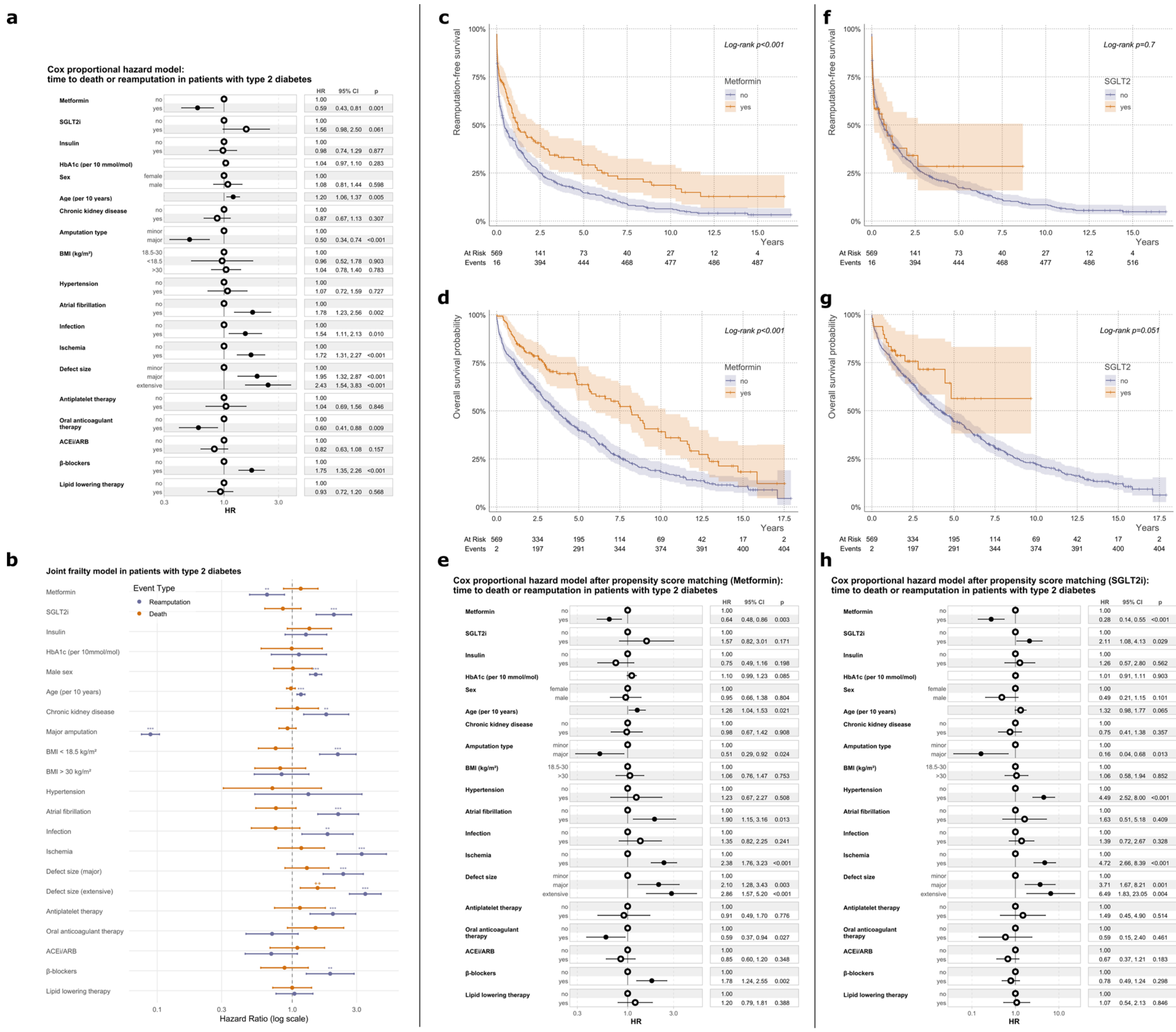


Fig. 3 (See legend on next page.)

endpoint of reamputation and mortality (*HR 1.56*, 95%CI [0.98–2.5], $p = 0.061$) in the adjusted Cox analysis (Fig. 3a). Joint frailty analysis revealed increased reamputation risk while mortality remained unaffected in SGLT2i treated patients (Fig. 3b). In unadjusted survival analysis a non-significant trend towards improved survival was found (Fig. 3 g). As a sensitivity analysis, in order to rule out selection or prescription bias we re-ran the analysis after propensity score matching for either metformin or SGLT2i exposure, which basically confirmed findings in our primary analysis (Fig. 3e, h and ESM Table 3). Importantly, overall number of patients on SGLT2i treatment was low in this cohort (n = 48). Insulin therapy did neither affect reamputation-free survival nor isolated mortality risk (Fig. 3a, b and ESM Fig. 2a and b). Characteristics of metformin, SGLT2i and insulin-treated patients are shown in ESM Tables 4–6.

Temporal trends in outcome

Temporal trends in clinical characteristics are shown in Table 2. In summary, in patients with diabetes LDL-C levels decreased and prevalence of hypertension, coronary heart disease and atrial fibrillation increased over time. Median HbA1c was near target with median levels overall being 55.2 mmol/mol (7.2%). HbA1c did not significantly change over time, while LDL-C significantly decreased over time from median 2.2 mmol/L in P1 (2006–2010) to 1.86 mmol/L in P4 (2020–2022). Still, only 31.1% of patients achieved the LDL-C target of < 1.4 mmol/L in P4. Interestingly, male preponderance in patients undergoing LLA even increased during the observation period.

Surprisingly, reamputation-free survival decreased over time (Fig. 4a). In a Cox regression model including sex, age at first amputation, amputation type, presence

(See figure on previous page.)

Fig. 3 Effects of antidiabetic medication on reamputation-free survival and mortality in patients with type 2 diabetes. **a** Cox proportional hazards model for the combined endpoint reamputation or death in patients with diabetes including antidiabetic medication as covariates. Age at first amputation was centered around 60 years and scaled for 10 years, HbA1c levels are analysed per 10 mmol/mol changes. Hazard ratios indicate combined risk of reamputation or death. **b** A joint frailty model for reamputation risk and death in patients with type 2 diabetes including antidiabetic medication as covariates is shown. The model uses a joint frailty term clustering all amputation surgeries around individual patients. Hazard ratios and 95% confidence intervals are shown for all model covariates and for both reamputation risk (reoccurrence) and death (terminal event). For better readability reference levels of covariates are not plotted here. The BMI category 18.5–25 kg/m^2 was used as the reference group. Age at first amputation was centered around 60 years and scaled for 10 years, HbA1c levels are analysed per 10 mmol/mol changes. Hazard ratios indicate combined risk of reamputation or death. "*" indicates statistical significance for reamputation risk; "+" indicates statistical significance levels for mortality risk. */+ $p<0.05$; **/+ + $p<0.01$; ***/+ + + $p<0.001$. **c** Kaplan–Meier plot of reamputation-free survival in patients with type 2 diabetes according to metformin treatment. The composite endpoint consists of either reamputation or death, whichever appears first. Censoring is indicated by ticks on the survival curves. Log-rank test was used to compare survival curves. **d** Kaplan–Meier plot of overall survival in patients with type 2 diabetes according to metformin usage. Censoring is indicated by ticks on the survival curves. Log-rank test was used to compare survival curves. **e** Propensity score analysis was performed by employing a nearest-neighbor matching algorithm without replacement, using a 3:1 ratio (up to three controls for every treated patient) for metformin treatment. After matching, the cohort consisted of 224 total matched patients. Age was centered around 60 years and scaled for 10 years. HbA1c was scaled for an increase of 10 mmol/mol. "*" indicates statistical significance for reamputation risk; "+" indicates statistical significance levels for mortality risk. */+ $p<0.05$; **/+ + $p<0.01$; ***/+ + + $p<0.001$. **f** Kaplan–Meier plot of reamputation-free survival in patients with type 2 diabetes according to SGLT2-I treatment. The composite endpoint consists of either reamputation or death, whichever appears first. Censoring is indicated by ticks on the survival curves. Log-rank test was used to compare survival curves. **g** Kaplan–Meier plot of overall survival in patients with type 2 diabetes according to SGLT2i treatment. Censoring is indicated by ticks on the survival curves. Log-rank test was used to compare survival curves. Censoring is indicated by ticks on the survival curves. Log-rank test was used to compare survival curves. **h** Propensity score analysis was performed by employing a nearest-neighbor matching algorithm without replacement, using a 3:1 ratio (up to three controls for every treated patient) for SGLT2-i treatment. After matching, the cohort consisted of 111 total matched patients. Age was centered around 60 years and scaled for 10 years. HbA1c was scaled for an increase of 10 mmol/mol. "*" indicates statistical significance for reamputation risk; "+" indicates statistical significance levels for mortality risk. */+ $p<0.05$; **/+ + $p<0.01$; ***/+ + + $p<0.001$

of chronic kidney disease and BMI as covariates, reamputation-free survival was significantly lower during the SARS-CoV2 pandemic P4 (2020–2022) when compared to P1 (2006–2010) (HR *1.66*, 95% CI [1.05–2.61]) (Fig. 4b). A joint frailty model showed a divergent effect on mortality and reamputation risk according to time of first amputation surgery (Fig. 4c). Risk for reamputation was significantly higher in P2 and P4 when compared to P1 (P4 vs P1 reamputation risk HR *2.21*, 95% CI [1.48–3.29]). However, risk of mortality was significantly lower in P2, P3 and P4 with the highest HR in the time period from 2016 to 2019 (P3) (P4 vs. P1 mortality risk HR *0.52*, 95% CI [0.34–0.79]).

Discussion

Patients with diabetes are at high risk for foot ulcers with an estimated lifetime risk up to 34%. Besides a high recurrence rate, the lifetime incidence of LLA is about 20% in affected patients. The latter is not only associated with a marked decrease in quality of life but also with a drastic reduction in life span [34]. While critical limb ischemia including arterial embolism in PAD is the most frequent cause for LLA in non-diabetic patients, severe-life-threatening infections, tissue loss or uncontrolled osteomyelitis are common causes for LLA in patients with diabetic foot syndrome, sometimes even in the absence of PAD [35].

Here we report an analysis of 1107 well-characterized patients with and without diabetes who underwent LLA for diabetic foot syndrome or PAD between 2006 and 2022. In our analysis we focused on I) investigating the impact of diabetes and other clinical predictors on the primary outcome defined as reamputation-free survival, II) the effect of antidiabetic medication on reamputation and mortality risk and III) on temporal trends in management and outcome of patients with diabetes. Importantly, we used two different statistical methods for evaluation of risk factors for reamputation and mortality. While we used identical covariates including established long-term and immediate risk factors and outcome-modifying medication to control for confounding factors, the contribution of covariates to the first reamputation or death was evaluated in the adjusted Cox model, while the contribution to any consecutive reamputation or death was assessed in the joint frailty model analysis Table 3.

Firstly, we report that reamputation-free survival is significantly lower in patients with diabetes when compared to patients without diabetes. The difference is driven by a markedly higher reamputation rate is patients with diabetes. However, minor amputations were performed far more frequently as first surgical intervention in patients with diabetes than in those without suggesting that patients with diabetes are at higher risk for recurrent minor amputations. Importantly, in regression analysis diabetes remained a significant predictor of reamputation-free survival even when corrected for presence of relevant comorbidities, disease modifying medications and local findings further underlining the clinical significance of diabetes in this high-risk study cohort. Besides presence of diabetes, chronic kidney disease and atrial fibrillation, male sex and older age at first amputation were negative predictors of reamputation-free survival. Expectedly, ischemia, infection and wound defect size were also associated with poorer outcome.

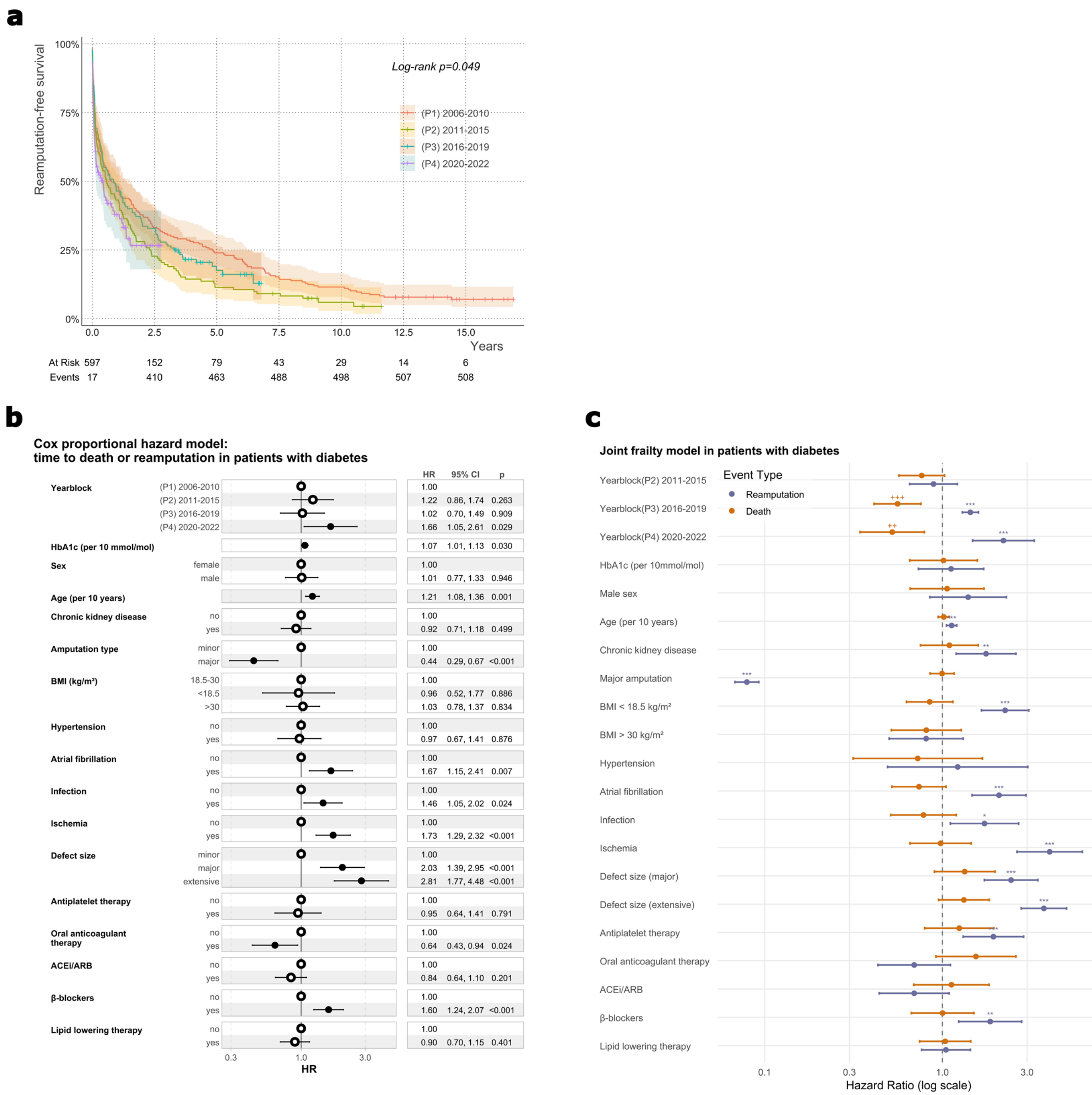


Fig. 4 Difference in outcome from 2006 until 2022 in patients with diabetes. **a** Reamputation-free survival in time clusters P1 (2006–2010), P2 (2011–2015), P3 (2016–2019) and P4 (2020–2022) in patients with diabetes is shown in a Kaplan–Meier plot. Time of first surgery was used for categorizing patients into corresponding time clusters. The composite endpoint consists of either reamputation or death, whichever appears first. Censoring is indicated by ticks on the survival curves. Log-rank test was used to compare survival curves. **b** Cox proportional hazards model for reamputation-free survival in patients with diabetes. Time of first surgery was used to categorize patients and clinically relevant covariates were used. Age was centered around 60 years and scaled for 10 years. HbA1c was scaled for an increase of 10 mmol/mol. **c** Joint frailty model in patients with diabetes with the addition of time of first surgery for each patient, categorized as time clusters. Hazard ratios and 95% confidence intervals are shown for all model covariates and for both reamputation risk (reoccurrence) and death (terminal event). For better readability reference levels of covariates are not plotted here. P1 (2006–2010) was used as the reference level for time clusters. The BMI category 18.5–25 kg/m^2 was used as the reference group. Age was centered around 60 years and scaled for 10 years. HbA1c was scaled for an increase of 10 mmol/mol. "*" indicates statistical significance for reamputation risk; "+" indicates statistical significance levels for morality risk. */+ $p<0.05$; **/++ $p<0.01$; ***/+++ $p<0.001$

Table 3 Changes in different time periods P1–P4

	[ALL]	P1 2006–2010	P2 2011–2015	P3 2016–2019	P4 2020–2022	p.overall	p.trend
	N = 607	*N = 224*	*N = 133*	*N = 142*	*N = 108*		
Age	71.4 [63.3;79.5]	70.5 [61.2;79.0]	72.9 [64.9;80.1]	70.1 [62.0;78.1]	73.4 [66.4;80.6]	0.089	0.121
Female sex	166 (27.3%)	70 (31.2%)	40 (30.1%)	30 (21.1%)	26 (24.1%)	0.135	0.046
BMI (kg/m^2)	26.2 [23.3;29.8]	26.3 [23.0;29.0]	25.2 [23.1;29.4]	27.8 [24.6;30.4]	25.0 [22.9;29.4]	0.008	0.437
Smoking	138 (25.8%)	46 (29.5%)	39 (30.0%)	29 (20.4%)	24 (22.4%)		0.007
LDL-C (mmol/L)	1.97 [1.48;2.67]	2.20 [1.71;2.80]	1.86 [1.37;2.58]	1.99 [1.48;2.59]	1.86 [1.35;2.43]	0.027	0.015
< 1.4 mmol/L	80 (21.9%)	13 (12.9%)	23 (26.7%)	25 (21.2%)	19 (31.1%)	0.028	0.019
> 1.4 mmol/L	286 (78.1%)	88 (87.1%)	63 (73.3%)	93 (78.8%)	42 (68.9%)		
HbA1c (%)	7.20 [6.20;8.60]	7.05 [6.20;8.38]	6.95 [6.00;8.70]	7.35 [6.30;8.97]	7.40 [6.10;8.70]	0.466	0.217
HbA1c (mmol/mol)	55.2 [44.3;70.5]	53.6 [44.3;68.0]	52.5 [42.1;71.6]	56.8 [45.4;74.6]	57.4 [43.2;71.6]	0.466	0.217
Hypertension	490 (80.9%)	168 (75.3%)	107 (80.5%)	118 (83.1%)	97 (89.8%)	0.015	0.001
Coronary heart disease	234 (38.6%)	75 (33.5%)	42 (31.6%)	64 (45.1%)	53 (49.1%)	0.005	0.001
Heart failure	101 (16.7%)	34 (15.2%)	18 (13.5%)	32 (22.5%)	17 (15.7%)	0.183	0.358
Chronic kidney disease	365 (61.0%)	129 (58.9%)	83 (62.4%)	96 (68.6%)	57 (53.8%)	0.102	0.989
Creatinine (µmol/L)	98.1 [74.3;148]	97.3 [72.5;157]	99.9 [76.9;158]	105 [83.8;141]	89.7 [67.2;130]	0.097	0.318
eGFR (ml/min/1.73m^2)	53.1 [32.6;72.4]	54.8 [30.3;75.7]	51.5 [28.1;70.7]	50.3 [33.2;64.8]	58.7 [37.5;80.6]	0.191	0.485
Atrial fibrillation	127 (21.0%)	34 (15.2%)	24 (18.0%)	38 (27.0%)	31 (28.7%)	0.007	0.001
COPD	73 (12.1%)	23 (10.3%)	12 (9.02%)	21 (14.9%)	17 (15.9%)	0.223	0.072
Amputation type:						0.937	0.521
Minor	479 (78.9%)	174 (77.7%)	105 (78.9%)	113 (79.6%)	87 (80.6%)		
Major	128 (21.1%)	50 (22.3%)	28 (21.1%)	29 (20.4%)	21 (19.4%)		

While prevalence of chronic kidney disease was higher in patients with diabetes, male preponderance was more pronounced in patients without diabetes.

In a recent meta-analysis presence of chronic kidney disease doubled the amputation risk in patients with PAD [36]. Additionally, an association between chronic kidney disease with diminished wound healing of foot ulcers and mortality was reported in several studies [1, 32, 37–40]. Our data, identifying chronic kidney disease as major driver of reamputation risk in both the overall and diabetes cohorts, underline the clinical significance of chronic kidney disease in patients at high amputation risk.

Importantly, atrial fibrillation was associated with poorer outcome in the overall cohort and in the diabetes cohort. This relation might be explained by common pathophysiological aspects of PAD and atrial fibrillation and underlines previous studies reporting worse outcome in patients suffering from both conditions [41]. Noteworthy, anticoagulant therapy improved reamputation-free survival in patients with diabetes, which might reflect increased risk of arterial embolism in patients with diabetes [42]. Supporting our finding of overall very high risk in patients with diabetes, increased mortality after lower limb surgery in this population has recently been described by another group [43].

In the diabetes cohort, a J-shaped association between HbA1c levels and reamputation-free survival was found. Higher perioperative HbA1c levels might, on the one hand, increase the risk of major limb events as shown previously by another group [44], but on the other hand, might also indicate long-term poor glycemic control. The relevance of glycemic control on LLA rate has impressively been shown in the National Health and Nutrition Examination Survey (NHANES) where improved HbA1c levels over a longer time period were inversely related to the LLA risk [45]. Male sex was significantly associated with increased reamputation risk in patients with diabetes, while its effect on mortality was neutral. Interestingly, Lopez-de-Andres and colleagues reported increased short time mortality in female patients with type 1 diabetes after LLA [18]. However, in our cohort, 1-year mortality was comparable in male and female patients as described recently [32].

In the past years, effects of antidiabetic medication, especially of SGLT2i on amputation risk have been widely discussed. Several, but not all studies suggested a slight increase in amputation risk in SGLT2i treated patients [19–28]. In our study, overall SGLT2i use was low, thus limiting the validity of results. As shown in the Kaplan Meier plot, SGLT2i use was associated with an increased reamputation rate but a trend towards lower mortality, albeit missing statistical significance. While neutral effects on outcome were found in the adjusted Cox model, SGLT2i treatment was associated with increased reamputation rate in the joint frailty model. Limited data from our study support previous findings reporting increased reamputation risk in SGLT2i treated patients but at the same time suggest that SGLT2i use is safe with respect to mortality in these high-risk patients. Importantly, further larger studies are warranted to prospectively investigate the effect of SGLT2i in this high-risk population in order to allow weighing up cardio- and renoprotective effects of SGLT2i with potential increases in reamputation risk in patients with diabetic foot syndrome or PAD.

Metformin use was associated with increased reamputation-free survival and reduced reamputation risk in adjusted regression models. Unadjusted survival curves show a marked difference in survival < 10 years after first surgery in patients using metformin with less effect in the long-term. Beneficial effects on reamputation-free survival remained significant even when controlling for preexisting comorbidities including chronic kidney disease and obesity or older age. These data clearly contradicts that metformin should be discontinued in all patients with diabetes at high risk for reamputation. Despite HbA1c levels and BMI being significantly higher in insulin-treated patients reamputation-free survival was similar in patients with and without insulin therapy.

When analysing temporal trends in reamputation-free survival we found significantly worse outcomes during SARS-CoV2 pandemic years 2000 to 2022 (P4) which were driven by a markedly increased reamputation risk. Joint frailty analysis revealed higher risk for reamputation in periods 2 and 4 (2011–2016 and 2020–2022). However, mortality risk was significantly lower between 2011 and 2022 when compared to the time period from 2006 to 2010 despite increased prevalences of coronary heart disease and atrial fibrillation. Accordingly, our data suggest that no improvement in amputation prevention has been achieved in the past decade, however, more efficient treatment or earlier diagnosis of comorbidities have contributed to reduced mortality in these high-risk patients.

Study limitations

A selection bias cannot be ruled out due to the retrospective design of the study. Due to the very small number of pioglitazone and GLP-1 RA treated patients with diabetes, these drug classes were not included in the analysis. SGLT2i use significantly increased over time but in total SGLT2i use was low, thus limiting conclusions on SGLT2 use on outcome.

As only a small number of patients with type 1 diabetes or specific diabetes types were included in the analysis, data and conclusions mainly result from and apply to elderly patients with type 2 diabetes. For the medication related analysis, only patients with type 2 diabetes were analyzed. Data on smoking behavior were available at time of first amputation only.

Only presurgical HbA1c levels were available in this study, thus not allowing conclusions to be drawn on long-term glycemic control. Prevalence of diabetic neuropathy might be underestimated in our study as we cannot ensure that regular screening tests have been performed in all patients. No data on retinopathy and reliable information on diabetes duration were available in this study.

While death represents a competing risk problem when analyzing repeated surgeries and gets accounted for both with the Fine and Gray method and in the joint frailty analysis, major amputation also represents a competing risk. While there are patients with multiple major amputations in this cohort, which in turn limits the effect, compared with minor amputation the calculated HRs for major amputation are probably overestimated in the analysis. We still opted to include amputation type in the model, as it is a clinically important factor and differs in patients with or without patients and finally, inclusion significantly improved the models.

Conclusions

In summary, our data underline the importance of diabetes as negative predictor of reamputation-free survival. Presence of diabetes, atrial fibrillation, chronic kidney disease, and male sex are significantly associated with increased reamputation risk. In patients with diabetes, metformin therapy is associated with improved reamputation-free survival and reamputation risk. Our limited data suggest that SGLT2i treatment might be associated with higher reamputation risk but neutral effect on mortality in these high-risk patients. Larger studies are warranted to confirm these findings. Finally, we found that reamputation risk has increased in the past years, however, mortality has significantly improved in parallel.

Abbreviations

BMI	Body mass index
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
DPP4i	Dipeptidyl peptidase-4 inhibitors
GLP-1 RA	Glucagon like peptide 1 receptor agonist
HbA1c	Glycated hemoglobin
HR	Hazard ratio
KM	Kaplan–Meier
LLA	Lower limb amputation
LDL-C	Low-density lipoprotein cholesterol
PAD	Peripheral artery disease
SGLT2i	Sodium-glucose transporter 2 inhibitor

Supplementary Information

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Supplementary Material 1

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Author contributions

BR, GG, JK and SK conceptualized the study. All authors performed analysis and interpretation of the study. BR, JB, NK, VS, LK and EB performed data curation, BR, FA and GG performed statistical analysis. BR, ML, HS, FA, GG, JK and SK wrote the first draft of the manuscript. All authors had full access to all data and approved the final version of the manuscript. JK and SK were the co-principal investigators.

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Data availability
All data supporting the findings of this study are available within the paper and its Supplementary Information.

Declarations

Ethics approval and consent to participate
This study was approved by the local ethics committee of the Medical University of Innsbruck (Reference: 1108/2023). All study procedures complied with the Declaration of Helsinki.

Competing interests
As no specific funding was collected for the conduction of this study, no potential conflict of interest can be reported from authors.

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