Outcome after leg bypass surgery for critical limb ischemia is poor in patients with diabetes: a population-based cohort study

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Running Title: Diabetes and outcome after bypass for leg ischemia

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ABSTRACT

Objective: Our aim was to assess the risk of major amputation or death after leg bypass surgery for critical limb ischemia in patients with diabetes compared to patients without diabetes.

Research Design And Methods: We did a population-based cohort study by linking nationwide databases in Sweden. We identified 1840 patients in the Swedish Vascular Registry who had their first leg bypass procedure for critical lower limb ischemia from January 1, 2001 to December 31, 2003, 742 with, and 1098 without diabetes. Our primary endpoint was a composite of first major amputation of the limb on which bypass was done, or death. Individuals were followed up until December 31, 2005 through the National Hospital Patient Registry and the Cause-of-death Registry.

Results: Incidence of ipsilateral amputation or death was higher in patients with diabetes than in patients without (30.2 vs. 22.0 events per 100 person-years; crude hazard ratio [HR] 1.32; 95% CI 1.17-1.50). Similarly, individuals with diabetes had shorter amputation-free survival than individuals without (2.3 years; 1.9-2.8 vs. 3.4 years; 3.1-3.7). Adjustment for demographic characteristics, comorbidities and risk factors for amputation or death did not substantially affect the risk (HR 1.46; 1.26-1.69). The effect was more pronounced in male (HR 1.75; 1.47-2.08) than in female patients (1.35; 1.11-1.64) after adjustment for age.

Conclusions: Diabetes is associated with lower amputation-free survival after leg bypass for critical limb ischemia. Patients with diabetes and limb ischemia need intensified treatment of diabetes-related risk factors to improve outcome.
Diabetes is a common cause of mortality and morbidity, largely due to a four-fold increase in cardiovascular disease (1). The effect of diabetes seems especially pronounced for peripheral arterial disease (PAD) and lower limb amputations (2). Most non-traumatic lower limb amputations in the western world are performed on patients with diabetes, whose relative risk of major amputation is 12-24-fold compared to patients without diabetes (3). Amputations in patients with diabetes are usually preceded by critical limb ischemia (4). The prevalence of diabetes among patients with leg bypass surgery for critical limb ischemia varies between 30-80% (5), whereas the prevalence of diabetes in comparable age groups in the population is approximately 10%. Patients with critical limb ischemia commonly require leg bypass surgery to distal arteries to prevent major amputation.

Inferior outcome after leg bypass surgery could partly explain the higher amputation and mortality rates in patients with diabetes, but there is no standard for reporting outcome after lower limb vascular reconstruction. Outcome is predominately reported as the proportion of limbs without amputation (limb salvage) at different time after the vascular procedure. This is a problematic, and not always relevant, measure in an elderly population with high mortality. Patients with the highest risk for amputation may die shortly after vascular reconstruction, and diabetes per se will increase that risk. Thus, by focusing on the fate of the limb, the fate of the patient will be more or less neglected and is better evaluated by amputation-free survival.

There is an abundance of observational studies on this issue, some reported excellent results after leg arterial bypass surgery with no difference between patients with and without diabetes (68) whereas others have found results to be worse in patients with diabetes (911). Most of these studies are single centre studies from referral centres and are associated with inconsistencies and methodological problems, which makes it difficult to draw conclusions from results for patients with diabetes.

Population-based studies on the outcome after infrainguinal revascularization in patients with diabetes and critical limb ischemia are lacking. Indirect data from other population-based studies, including patients with various degrees of lower limb ischemia and a broad range of vascular interventions, suggest either equal (12) or worse (13, 14) outcome for patients with diabetes. The conclusion of most reports, however, is that diabetes does not negatively influence the long-term outcome of lower limb revascularization (5).

Data on this issue are important as they could promote the understanding of both diabetes and critical limb ischemia, and provide further insight into the clinical course of patients with diabetes.

Bearing in mind the generally elevated risk for amputation and mortality in patients with diabetes, we postulated that diabetes decreases the amputation-free survival after leg bypass surgery for critical ischemia. To assess this we undertook a nationwide population-based cohort study of outcome after leg bypass surgery in a well-defined high-risk population with critical limb ischemia. We compared patients with diabetes to patients without diabetes and determined amputation-free survival time.

**RESEARCH DESIGN AND METHODS**

**Setting and data sources.** The patient cohort was established using the Swedish Vascular Registry (Swedvasc). Outcomes were assessed by linking this cohort with the National Hospital Patient Registry (NHPR) and the Cause-of-death Registry (CDR) in Sweden. Unambiguous record linkage between all registries is possible through use of the unique personal identification number assigned to all Swedish residents. Swedvasc is a population-based vascular surgery registry, covering more than 95% of...
all arterial vascular procedures performed in the Swedish population (8.5 million), containing detailed prospectively registered information on indications, risk factors and surgical procedures for each individual(15). NHPR contains individually based information on inpatient care since 1964, with complete nationwide coverage since 1987. Each discharge record contains information on (a) diagnoses according to the International Classification of Diseases, (b) up to 12 surgical procedures coded according to the Swedish version of NOMESCO Classification of Surgical Procedures (NCSP) (see www.nordclass.uu.se/index_e.htm); and (c) dates for admission and discharge. Personal identifier was complete in 99.3% of NHPR records and 98.0% of surgical procedures were coded correctly(16). CDR covers all deaths of Swedish residents, with primary and contributory causes of death.

Patients and diabetes status. We included patients who had their first infrainguinal distal bypass procedure for critical limb ischemia, defined as rest pain or tissue loss (ulcer or gangrene), during the period January 1, 2001 to December 31, 2003 from the Swedvasc database. Patients with concomitant leg disorders such as popliteal aneurysms, acute thrombosis, acute embolus or traumatic injury were excluded to assess only patients with critical limb ischemia due to PAD. The index date was defined as the date for the bypass procedure. We used data from Swedvasc regarding demographic characteristics, presence of diabetes at time of surgery, other major comorbidities, potential risk factors for amputation or death and operative details including operated side.

Study outcomes. In order to study amputation free survival, our primary outcome was ipsilateral amputation defined as first amputation above the ankle (i.e. major amputation) in the limb on which bypass was performed (i.e. ipsilateral limb) or death from any cause, whichever occurred first. The observation period began on the index date and continued until the primary outcome event occurred or if uneventful until December 31, 2005. Secondary outcomes were death from any cause and first amputation irrespective of side.

We assessed amputation status and survival status by linking each patient by their personal identification number to the NHPR and CDR databases respectively. Amputation above the ankle was defined as a discharge record after index date with NCSP code NFQ09 (hip exarticulation), NFQ19 (transfemoral amputation), NGQ09 (knee exarticulation) or NGQ19 (transfibial amputation). We ascertained each amputation found in NHPR by retrieving medical records from the surgical procedure. We checked that level and date for amputation were correct and recorded information on which side the amputations was done.

Data validation. Earlier validation of the Swedvasc database has shown over 90% accuracy of variables(15). We did further validation in a randomly selected sample of 140 patients (7.6%), from the study cohort. Data from Swedvasc were compared with corresponding medical records to assess agreement for operative details and risk factors. We calculated sensitivity, specificity and accuracy with patient charts used as standard (Online-only appendix 1). The accuracy was over 90% for all variables except cardiac disease, hypertension and pulmonary disease. Examining the diabetes variable, we found that two hospitals accounted for 77/146 (53%) of missing values. Having checked the medical records relating to the hospitalization for the bypass procedure of these 77 patients, 73 were considered not to have diabetes. The remaining 70 (3.8%) records left with missing values for diabetes status in the final cohort were assumed individuals without diabetes in analyses.

Statistical analysis. Our study required a sample size of about 800 patients with diabetes according to a power calculation based on 1) a probability of 90% that the study would detect an outcome difference
between patients with and without diabetes at a two-sided 5% significance level, 2) an assumed true hazard ratio of 1.2, 3) an accrual period of 3 years. Cumulative event rates and survival curves were calculated with the Kaplan-Meier method, with the index date as time zero. We compared patients with diabetes to patients without known diabetes calculating the crude hazard ratio for primary outcome using a Cox proportional hazards model and subsequently adjusted the hazard ratio for pre-specified potential confounders: age at index operation, sex, severity of limb ischemia, level of distal anastomosis (popliteal artery below knee, crural vessels or pedal artery), type of graft (use of patients own vein or not), pulmonary disease and smoking (ongoing or quitted less than 5 years ago). We did pre-specified gender subgroup analysis and estimated interaction effects according to Andersson et al.(17). Age was entered as a continuous variable and all other variables were entered as dichotomous variables in the adjusted models. We also evaluated the influence of several risk factors assumed to be in the causal pathway to diabetes complications: renal disease (serum creatinine >150mmol/L), cardiac disease (previous myocardial infarction, angina pectoris, atrial fibrillation, heart failure, ischemic signs on ECG, previous heart surgery), hypertension and cerebrovascular disease (stroke or TIA). These factors were not regarded as confounders. We used secondary outcome measures to test the robustness of our findings. Firstly, we extended the outcome event to include also contralateral amputations in the amputation-free survival endpoint. Secondly, we repeated the analysis for limb salvage by censoring for death to ascertain that any associations found in amputation-free survival was not an effect of different mortality rates between patients with and without diabetes. Both visual inspection of log–log plots and the supremum test based on Schoenfeld residuals (P = 0.61) indicated that the proportional-hazard assumption was not violated. All hazard ratios were reported with 95% confidence intervals and all tests were two-tailed with a p-value of 0.05 judged statistically significant. The study was approved by the research ethics committee at Karolinska Institutet, Stockholm, Sweden.

RESULTS

During the 3-year accrual period, we identified 6869 vascular procedures performed in patients with lower limb ischemia manifested as rest pain or tissue loss. Of these, we selected individuals who had their first unilateral leg bypass operation to an artery below the knee, yielding a final cohort of 1840 patients, 742 with and 1098 without diabetes. Patients with diabetes were younger (73.9 vs. 77.8 years, p<0.0001), and a higher proportion had tissue loss (82% vs. 67%) than those without this disease. Demographic, procedural and risk factors recorded in connection with surgery are listed in table 1. Cardiac disease and renal insufficiency were more common among patients with diabetes (65% vs. 55%, and 20% vs. 8%) whereas smoking and pulmonary disease were more prevalent in patients without diabetes. Other factors were similarly distributed in patients with and without diabetes. The median duration of follow-up was 2.2 years, equivalent to 4015 person-years of observation. The shortest event-free follow up was 2 years and the longest 4.9 years. A total of 446 patients with diabetes and 558 without underwent ipsilateral amputation or died, giving a total of 1004 outcome events. The rate of ipsilateral amputation or death per 100 person-years was higher in patients with diabetes (65% vs. 55%, and 20% vs. 8%) whereas smoking and pulmonary disease were more prevalent in patients without diabetes. Other factors were similarly distributed in patients with and without diabetes. The median time to this event was 2.3 years, 1.9-
2.8 (95% CI) in patients with diabetes and 3.4 years, 3.1-3.7 (95% CI) in patients without diabetes. The crude and age-adjusted hazard ratio for ipsilateral amputation or death for patients with diabetes compared to patients without diabetes was 1.32; 1.17-1.50 and 1.55; 1.37-1.77. Adjustment for sex, smoking, pulmonary disease, degree of limb ischemia, type of graft and level of distal anastomosis did not substantially affect this finding, HR 1.46; 1.26-1.69, (Table 2).

Several other factors in the causal pathway to diabetes complications were also related to ipsilateral amputation and death, including renal disease, cardiac disease, hypertension and cerebrovascular disease. Additional adjustment for these factors did not substantially influence the effect of diabetes, (HR 1.36; 1.19-1.56). (Online-only appendix 2).

The effect of diabetes on amputation-free survival was more pronounced in male patients, HR_{age-adj} 1.75; 1.47-2.08 than in female HR_{age-adj} 1.35; 1.11-1.64. The relative excess risk due to interaction between gender and diabetes was 0.32, 0.04-0.60 (95% CI).

Analysis of secondary endpoints showed consistently higher risk for amputation or death in patients with diabetes. When censoring for death (i.e. limb salvage), the association between diabetes and risk for amputation was accentuated, (HR_{age-and sex-adj} 1.67; 1.34-2.10). Diabetes was associated with a higher risk for amputation of any leg in analysis of amputation-free survival including both ipsi- and contralateral amputations (HR_{age-and sex-adj} 1.57; 1.39-1.78). Diabetes was also associated with a higher risk of death (HR_{age-and sex-adj} 1.49; 1.30-1.71).

CONCLUSIONS
We observed that diabetes was associated with a 55% increase in the risk for major amputation or death after leg bypass surgery for critical lower limb ischemia compared with patients without diabetes. Patients with diabetes had one year shorter time to live without amputation on average. The apparent reduction in amputation-free survival for patients with diabetes was evident also after controlling for confounding factors. Further adjustments for intermediate factors did not influence results substantially. Moreover, similar results were obtained when using the secondary endpoints survival, limb salvage and any major amputation irrespective of side. Our findings also emphasize the fact that the rate of major amputation and death after vascular reconstruction is high in patients with critical limb ischemia, both in patients with and without diabetes(18).

This is the first nationwide population-based study of amputation-free survival after leg vascular reconstruction for critical limb ischemia comparing patients with and without diabetes. We believe that our results are likely to be a proper estimate of amputation-free survival after leg bypass for the following reasons. Firstly, we used nationwide data with complete coverage for identification of the cohort, thereby minimizing selection bias. Referral and diagnostic bias are also almost completely avoided in a setting with a national health care service with free access to health care. Secondly, the diabetes diagnosis was found to have a sensitivity of 96% and a specificity of 99%. Thirdly, we were able to achieve complete and accurate follow-up of amputation status and death using nationwide registry data. Moreover, our cohort consisted exclusively of patients with critical ischemia undergoing distal bypass surgery, thus avoiding confounding due to the inclusion of patients with less severe degree of ischemia or more proximal procedures.

Our results seem plausible considering the substantial body of evidence of increased cardiovascular risk(1) and markedly elevated risk for amputation(3) in patients with diabetes. The difference between our results and those obtained from numerous case series(5) showing equal outcome in patients with and without diabetes is most probably explained by
different outcome measures, i.e. limb salvage instead of amputation-free survival, by inclusion of patients with less severe degree of ischemia and younger patients. Several studies have examined factors contributing to postoperative amputation and mortality in patients with and without diabetes, but all have specific limitations such as including only patients with diabetes, small sample size, short or incomplete follow up, combined analysis of patients with claudication and critical limb ischemia, supra- and infrainguinal procedures and inability to distinguish between ipsilateral and contralateral amputations(1214). All these factors have profound effect on outcome after leg bypass surgery.

We found only one population-based study aiming to investigate outcome after vascular procedures for critical limb ischemia in patients with and without diabetes(12). This study found higher amputation rates in patients with diabetes, but patients were followed only for 30 days. Due to the scarce use of amputation-free survival as outcome measure in contemporary case series and trials, we found it difficult to compare our results with those from these studies. The short amputation-free survival in our study is in accordance with the over-all amputation-free survival of the BASIL trial (55% at 3 years) and in The Veterans Affairs National Surgical Quality Improvement Program (57% at 3 years), which recruited participants comparable to our cohort in terms of age distribution and proportion of patients with diabetes(9, 18).

Our results indicate that the impact of diabetes on amputation-free survival was more pronounced in male as compared to female patients. Other studies support this finding regarding PAD outcome (14) and amputations (19). Biological differences, with delayed onset of cardiovascular disease in women, may perhaps explain this effect. According to a recent, (2004), population-based study on PAD in Sweden, the prevalence of critical limb ischemia is higher among women(20). This higher prevalence is not reflected in our cohort suggesting a relative under-use of revascularization in women. If true, a selection bias of healthier women for revascularization could explain our observed better outcome in women.

There are several limitations to this study that merit discussion. The observational design might have permitted uncontrolled confounding factors to affect the results. A second limitation involves our definition of diabetes, which is based on clinical overt disease reported to Swedvasc, and therefore did not identify people with undiagnosed diabetes. The risks for cardiovascular events or death and amputation are elevated in patients with undiagnosed diabetes (21, 22), thus the possible misclassification of exposure would lead to falsely high estimates of amputation and death in our reference group without diabetes, biasing our results towards the null hypothesis. Lastly, we were unable to distinguish between type 1 and type 2 diabetes. As the risk for amputation(23) and the risk for cardiovascular death(24) are approximately equal in type 1 and 2 diabetes, this limitation has probably not affected our results.

The impact of diabetes on cardiovascular disease is greater than can be explained by higher prevalence of traditional atherosclerotic risk factors(2). Several mechanisms coupled to hyperglycaemia have been shown to augment the atherosclerosis process. Activation of the protein kinase C pathway by hyperglycaemia seems to be an important initial step leading to oxidative stress and endothelial dysfunction(25). Hyperglycaemia also induces formation of advanced glycation end products (AGE) and up-regulates receptor for advanced glycation end products (RAGE). Activation of RAGE by AGE has multiple effects in vascular tissue; it is proinflammatory, augments smooth muscle migration and proliferation, and causes endothelial dysfunction and oxidative stress(25). Diabetes is also
characterized by distinctive atherogenic lipid disturbances, increased platelet activation and a hypercoagulable state(25). These are all potentially modifiable mechanisms, pointing to the possibility that improved glucose control and targeted therapies could improve outcome after vascular reconstruction in patients with diabetes.

An additional explanation of our findings is the high proportion of tissue loss in patients with diabetes and lower limb ischemia, which may indicate an undue delay in recognition of ischemia. This delay is probably explained by masking of ischemic symptoms from concomitant peripheral neuropathy(2).

Our findings might have consequences for research and care of patients. Patients with diabetes presenting with limb ischemia should be treated as having very high mortality risk and require intense treatment of cardiovascular risk factors at earliest possible stage.

In summary, diabetes diminishes the chances of survival and avoiding amputation in patients with critical lower limb ischemia undergoing leg bypass procedures. Further studies in this group of patients should be directed to find ways to reduce this excess risk.

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REFERENCES

### TABLE 1. Baseline characteristics of 1840 patients with leg bypass for critical limb ischemia

<table>
<thead>
<tr>
<th></th>
<th>Diabetes</th>
<th>No diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>742 (40)</td>
<td>1 098 (60)</td>
</tr>
<tr>
<td><strong>Demographic factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>73.9 ± 9.8</td>
<td>77.8 ± 8.9</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>434 (58)</td>
<td>543 (49)</td>
</tr>
<tr>
<td>Length of stay (days)</td>
<td>11.7 ± 10.5</td>
<td>11.6 ± 10.2</td>
</tr>
<tr>
<td><strong>Degree of limb ischemia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest pain</td>
<td>130 (18)</td>
<td>362 (33)</td>
</tr>
<tr>
<td>Tissue loss (ischemic ulcer or gangrene)</td>
<td>612 (72)</td>
<td>736 (67)</td>
</tr>
<tr>
<td><strong>Procedure factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal anastomosis, popliteal artery</td>
<td>261 (35)</td>
<td>500 (46)</td>
</tr>
<tr>
<td>Distal anastomosis, crural artery</td>
<td>441 (59)</td>
<td>573 (52)</td>
</tr>
<tr>
<td>Distal anastomosis, foot artery</td>
<td>40 (5)</td>
<td>25 (2)</td>
</tr>
<tr>
<td>Vein as graft material</td>
<td>601 (81)</td>
<td>881 (80)</td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>144 (19)</td>
<td>196 (18)</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>485 (65)</td>
<td>599 (55)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>443 (60)</td>
<td>608 (55)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>151 (20)</td>
<td>89 (8)</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>68 (9)</td>
<td>156 (14)</td>
</tr>
<tr>
<td>Smoking</td>
<td>144 (19)</td>
<td>146 (13)</td>
</tr>
</tbody>
</table>

Data are means ± SD or n (%).
### TABLE 2. Absolute rates and hazards for amputation and death after leg bypass surgery in patients with diabetes compared to patients without diabetes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Diabetes (n=742)</th>
<th>No diabetes (n=1098)</th>
<th>Hazard ratio (95% CI) of diabetes relative to no diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate* (95% CI)</td>
<td>Rate* (95% CI)</td>
<td>Unadjusted Age and sex adjusted Adjusted for confounders†</td>
</tr>
<tr>
<td>Ipsilateral amputation or death</td>
<td>30.2 (26.6 - 34.2)</td>
<td>22.0 (19.4 - 24.9)</td>
<td>1.32 (1.17 - 1.50) 1.55 (1.37 - 1.77) 1.46 (1.26 - 1.69)</td>
</tr>
<tr>
<td>Ipsilateral amputation</td>
<td>10.6 (8.5 - 13.2)</td>
<td>6.3 (5.0 - 7.8)</td>
<td>1.57 (1.26 - 1.96) 1.67 (1.34 - 2.10) 1.68 (1.30 - 2.18)</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>27.7 (24.1 - 31.6)</td>
<td>13.4 (11.7 - 15.4)</td>
<td>1.23 (1.09 - 1.41) 1.49 (1.30 - 1.71) 1.39 (1.19 - 1.63)</td>
</tr>
<tr>
<td>Any amputation or death</td>
<td>32.5 (28.8 - 36.8)</td>
<td>23.2 (20.6 - 26.3)</td>
<td>1.34 (1.19 - 1.52) 1.57 (1.39 - 1.78) 1.45 (1.26 - 1.68)</td>
</tr>
<tr>
<td>Any amputation</td>
<td>13.5 (11.0 - 16.5)</td>
<td>7.6 (6.2 - 9.3)</td>
<td>1.65 (1.35 - 2.02) 1.77 (1.44 - 2.17) 1.69 (1.33 - 2.14)</td>
</tr>
</tbody>
</table>

* Rate is per 100 person years. † Model adjusted for age, sex, smoking, pulmonary disease, degree of limb ischemia, type of graft and level for distal anastomosis. CI=confidence interval.
FIGURE LEGEND

Figure 1. Kaplan-Meier plot of amputation-free survival after leg bypass for critical limb ischemia in patients with and without diabetes. Vertical bars show 95% confidence intervals at selected time points.
Diabetes and outcome after bypass for leg ischemia

![Graph showing survival probability over time for diabetes versus no diabetes.](image)

- **Survival probability**
- **Time to death or ipsilateral amputation (months)**

**Number at risk**
- **Diabetes**: 742, 461, 389, 217, 99, 5
- **No Diabetes**: 1098, 802, 685, 413, 176, 22

*p = 0.00009, Log-rank test*