Outcome After Leg Bypass Surgery for Critical Limb Ischemia Is Poor in Patients With Diabetes

A population-based cohort study

JONAS MALMSTEDT, MD[1]
KARIN LEANDER, PHD[2]
ERIC WAHLBERG, MD, PHD[1]
LARS KARLSTRÖM, MD, PHD[3]
LARS ALFREDSSON, PHD[2]
JESPER SWEDENBORG, MD, PHD[1]

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 versus those without.

RESEARCH DESIGN AND METHODS — We did a population-based cohort study by linking nationwide databases in Sweden. We identified 1,840 patients in the Swedish Vascular Registry who had their first leg bypass procedure for critical lower-limb ischemia between 1 January 2001 and 31 December 2003—742 with and 1,098 without diabetes. Our primary end point was first major amputation of the limb on which bypass was done or death. Individuals were followed up until 31 December 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 events/100 person-years; crude hazard ratio [HR] 1.32 [95% CI 1.17–1.50]). Similarly, individuals with diabetes had a shorter amputation-free survival period than individuals without (2.3 years, range 1.9–2.8 vs. 3.4 years, range 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 [95% CI 1.26–1.69]). The effect was more pronounced in male (1.75 [1.47–2.08]) than in female (1.35 [1.11–1.64]) patients 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 Care 31:887–892, 2008

Diabetes is a common cause of mortality and morbidity, largely due to a fourfold increase in cardiovascular disease in those with diabetes (1). The effect of diabetes seems especially pronounced for peripheral arterial disease (PAD) and lower-limb amputations (2). Most nontraumatic lower-limb amputations in the Western world are performed on patients with diabetes, whose relative risk of major amputation is 12- to 24-fold compared with that for 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 and 80% (5), whereas the prevalence of diabetes in comparable age-groups in the population is ~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 times 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 (6–8), whereas others have found results to be worse in patients with diabetes (9–11). Most of these studies are single-center studies from referral centers and are associated with inconsistencies and methodological problems, making 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-

From the [1]Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden; the [2]Division of Cardiovascular Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; and the [3]Department of Vascular Surgery, Sahlgrenska University Hospital, Gothenburg, Sweden.

Corresponding author: Jonas Malmstedt, Department of Vascular Surgery, N1:06, Karolinska University Hospital, SE-17176 Stockholm, Sweden. E-mail: jonas.malmstedt@karolinska.se.

Received for publication 20 December 2007 and accepted in revised form 5 February 2008.

Published ahead of print at http://care.diabetesjournals.org on 11 February 2008. DOI: 10.2337/dc07-2424.

Additional information for this article can be found in an online appendix at http://dx.doi.org/10.2337/dc07-2424.

Abbreviations: CDR, Cause-of-Death Registry; NHPR, National Hospital Patient Registry; PAD, peripheral arterial disease; Swedvasc, Swedish Vascular Registry.

© 2008 by the American Diabetes Association.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

term outcome of lower-limb revascularization (5).

Data on this issue are important because 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 amputation-free survival after leg bypass surgery for critical ischemia. To assess this hypothesis 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 diabetic patients with nondiabetic patients and determined amputation-free survival time.

RESEARCH DESIGN AND METHODS

— 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) and 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, including complete nationwide coverage since 1987. Each discharge record contains information on diagnoses according to the ICD and up to 12 surgical procedures coded according to the Swedish version of the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures (NCSP) (www.nordclass.uu.se/index_e.htm), as well as dates for admission and discharge. Personal identification number was complete in 99.3% of NHPR records, and 98% of surgical procedures were coded correctly (16). CDR covers all deaths of Swedish residents, including primary and contributory causes of death.

We included patients from the Swedish Vascular Registry database 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 1 January 2001–31 December 2003. Patients with concomitant leg disorders such as popliteal aneurysms, acute thrombosis, acute embolus, or traumatic injury were excluded in order 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.

To study amputation-free survival, we designated our primary outcome as 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 no event occurred, until 31 December 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 (transtibial 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.

Earlier validation of the Swedvasc database has shown over 90% accuracy of variables (15). We performed further validation with 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 (see the online appendix available at http://dx.doi.org/10.2337/dc07-2424). The accuracy was over 90% for all variables except cardiac disease, hypertension, and pulmonary disease. While examining the diabetes variable, we found that two hospitals accounted for 77 out of 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%) patient records left with missing values for diabetes status in the final cohort were assumed to correspond with individuals without diabetes in analyses.

Our study required a sample size of ~800 patients with diabetes according to a power calculation based on a 90% probability that the study would detect an outcome difference between patients with and without diabetes at a two-sided 5% significance level, an assumed true hazard ratio (HR) of 1.2, and 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 by calculating the crude HR for primary outcome using a Cox proportional hazards model; we subsequently adjusted the HR for prespecified 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 patient's own vein or not), pulmonary disease, and smoking (ongoing or quit less than 5 years ago). We performed prespecified sex subgroup analysis and estimated interaction effects according to the methodology of 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, including renal disease (serum creatinine >150 mmol/l), cardiac disease (previous myocardial infarction, angina pectoris, atrial fibrillation, heart failure, ischemic signs on electrocardiogram, or previous heart surgery), hypertension, and cerebrovascular disease (stroke or transient ischemic attack). These factors were not regarded as confounders.

We used secondary outcome measures to test the robustness of our findings. First, we extended the outcome event to also include contralateral amputations in the amputation-free survival end point. Second, we repeated the analysis for limb salvage by censoring for death

Table 1—*Baseline characteristics of 1,840 patients with leg bypass for critical limb ischemia*

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

Data are means ± SD or *n* (%).

Errata: 82%

to ascertain that any associations found in amputation-free survival were not an effect of different mortality rates between patients with and without diabetes.

Both visual inspection of log–log plots and a supremum test based on Schoenfeld residuals ($P = 0.61$) indicated that the proportional-hazard assumption was not violated. All HRs were reported with 95% CI, 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 6,869 patients in whom vascular procedures were performed and whose lower-limb ischemia manifested as rest pain or tissue loss. Of these patients, we selected individuals who had their first unilateral leg bypass operation to an artery below the knee, yielding a final cohort of 1,840 patients—742 with and 1,098 without diabetes. Patients with diabetes were younger (73.9 vs. 77.8 years; $P < 0.0001$), and a higher proportion of patients with diabetes had tissue loss (82 vs. 67%) than those without diabetes. Demographic, procedural, and risk factors recorded in connection with surgery are listed in Table 1. Cardiac disease and renal insufficiency were more common in patients with diabetes than in those without (65 vs. 55% and 20 vs. 8%, respectively), 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 4,015 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 1,004 outcome events. The rate of ipsilateral amputation or death per 100 person-years was higher in patients with diabetes (30.2 [95% CI 26.6–34.2]) than in patients without (22.0 [19.4–24.9]). Almost one-half of the patients with diabetes and one-third of those without had lost their leg or were deceased 2 years after index procedure (Fig. 1). The median time to this event was 2.3 years (95% CI 1.9–2.8) in patients with diabetes and 3.4 years (3.1–3.7) in those without.

The crude and age-adjusted HRs for ipsilateral amputation or death for patients with diabetes compared with patients without diabetes were 1.32 (95% CI 1.17–1.50) and 1.55 (1.37–1.77), respectively. 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 [95% CI 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 [95% CI 1.19–1.56]) (online appendix).

The effect of diabetes on amputation-free survival was more pronounced in male patients (age-adjusted HR 1.75 [95% CI 1.47–2.08]) than in female patients (1.35 [1.11–1.64]). The relative excess risk due to interaction between sex and diabetes was 0.32 (95% CI 0.04–0.60).

Analysis of secondary end points 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 (age- and sex-adjusted HR 1.67 [95% CI 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 (1.57 [1.39–1.78]). Diabetes was also associated with a higher risk of death (1.49 [1.30–1.71]).

CONCLUSIONS — We observed that patients with diabetes had 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. On average, patients with diabetes had 1 less year to live without amputation. The apparent reduction in amputation-free survival for patients with diabetes was also evident after controlling for confounding factors. Further adjustments for intermediate factors did not influence results substantially. Moreover, similar results were obtained when using the secondary end points survival, limb salvage, and any major amputation irrespective of side. Our findings also emphasize that the rate of major amputation and death after vascular reconstruction is high in patients with critical limb ischemia, both for 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 for a number of reasons that our results are likely to be a proper estimate of amputation-free survival after leg bypass. First,

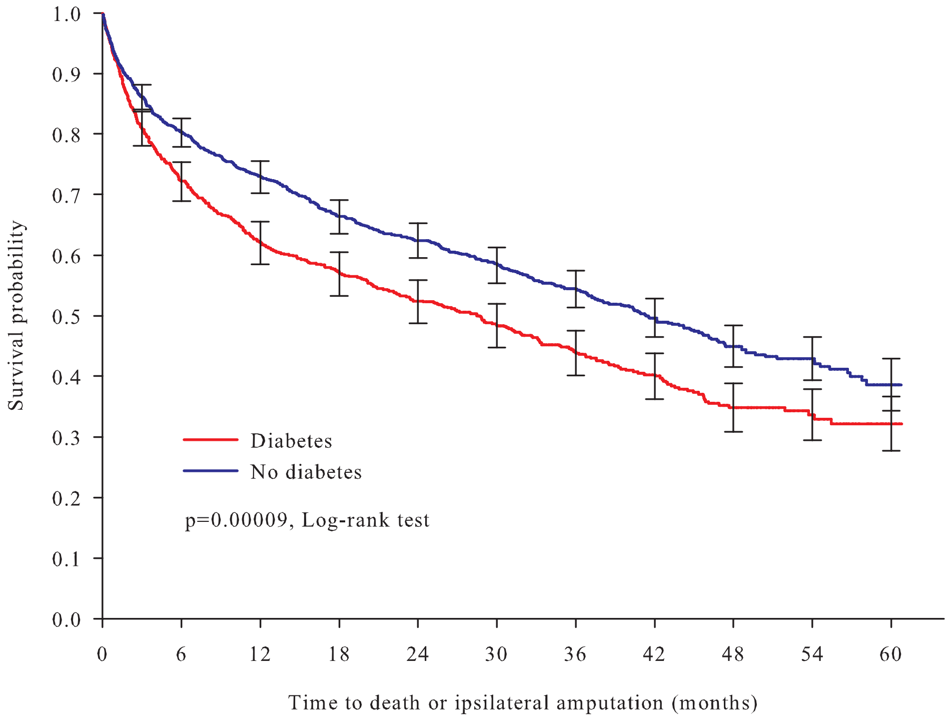

Figure 1—*Kaplan-Meier plot of amputation-free survival after leg bypass for critical limb ischemia in patients with and without diabetes. Vertical bars show 95% CI at selected time points.*

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 that provides free access to health care. Second, diabetes diagnosis was found to have a sensitivity of 96% and a specificity of 99%. Third, 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 degrees 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 likely explained by different outcome measures (i.e., limb salvage instead of amputation-free survival) by inclusion of younger patients and patients with less severe degrees of ischemia.

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 am-

Table 2—*Absolute rates and hazards for amputation and death after leg bypass surgery in patients with diabetes compared with patients without diabetes*

	Diabetes*		No diabetes†		HR (95% CI) of diabetes relative to no diabetes		
Outcome	*n*	Rate (95% CI)‡	*n*	Rate (95% CI)‡	Unadjusted	Age and sex adjusted	Adjusted for confounders§
Ipsilateral amputation or death	446	30.2 (26.6–34.2)	558	22.0 (19.4–24.9)	1.32 (1.17–1.50)	1.55 (1.37–1.77)	1.46 (1.26–1.69)
Ipsilateral amputation	156	10.6 (8.5–13.2)	159	6.3 (5.0–7.8)	1.57 (1.26–1.96)	1.67 (1.34–2.10)	1.68 (1.30–2.18)
All-cause mortality	486	27.7 (24.1–31.6)	378	13.4 (11.7–15.4)	1.23 (1.09–1.41)	1.49 (1.30–1.71)	1.39 (1.19–1.63)
Any amputation or death	463	32.5 (28.8–36.8)	577	23.2 (20.6–26.3)	1.34 (1.19–1.52)	1.57 (1.39–1.78)	1.45 (1.26–1.68)
Any amputation	192	13.5 (11.0–16.5)	188	7.6 (6.2–9.3)	1.65 (1.35–2.02)	1.77 (1.44–2.17)	1.69 (1.33–2.14)

*n = 742; †n = 1098; ‡rate is per 100 person-years; §adjusted for age, sex, smoking, pulmonary disease, degree of limb ischemia, type of graft and level for distal anastomosis.

putations (12,14). All these factors have a 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 only followed for 30 days.

As a result of 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 duration of amputation-free survival in our study is in accordance with the overall amputation-free survival of the BASIL (Bypass Versus Angioplasty in Severe Ischemia of the Leg) trial (55% at 3 years) and in the Veterans Affairs National Surgical Quality Improvement Program (57% at 3 years), which recruited participants comparable with 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 is more pronounced in male compared with female patients. Other studies support this finding regarding PAD outcome (14) and amputations (19). Biological differences, including delayed onset of cardiovascular disease in women, may perhaps explain this effect. According to a 2004 population-based study of 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 underuse of revascularization in women; 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. We therefore did not identify individuals 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 toward the null hypothesis. Finally, we were also 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 with hyperglycemia have been shown to augment the atherosclerosis process. Activation of the protein kinase C pathway by hyperglycemia seems to be an important initial step leading to oxidative stress and endothelial dysfunction (25). Hyperglycemia also induces formation of advanced glycation end products and upregulates the receptor for advanced glycation end products, activation of which 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 aspects of patient care. 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 the earliest possible stage.

In summary, diabetes diminishes the chances of survival and of 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.

Acknowledgments— J.M. was supported by a Swedvasc Research grant and the Gore Research Award. J.M. also obtained funding for this work from the Swedish Heart and Lung foundation and through the regional agreement on medical training and clinical research (ALF) between Stockholm County Council and the Karolinska Institutet. The study was supported by the Swedvasc steering committee.

All vascular surgeons in Sweden who meticulously registered their procedures are gratefully acknowledged for their effort. We thank research nurses M. Johansson and M. Hensäter for assistance with medical record retrieval.

References

1. Huxley R, Barzi F, Woodward M: Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. *BMJ* 332:73–78, 2006
2. American Diabetes Association: Peripheral arterial disease in people with diabetes. *Diabetes Care* 26:3333–3341, 2003
3. The Global Lower Extremity Amputation Study Group: Epidemiology of lower extremity amputation in centres in Europe, North America and East Asia. *Br J Surg* 87:328–337, 2000
4. Carmona GA, Hoffmeyer P, Herrmann FR, Vaucher J, Tschopp O, Lacraz A, Vischer UM: Major lower limb amputations in the elderly observed over ten years: the role of diabetes and peripheral arterial disease. *Diabetes Metab* 31:449–454, 2005
5. Weiss JS, Sumpio BE: Review of prevalence and outcome of vascular disease in patients with diabetes mellitus. *Eur J Vasc Endovasc Surg* 31:143–150, 2006
6. Akbari CM, Pomposelli FB Jr, Gibbons GW, Campbell DR, Pulling MC, Mydlarz D, LoGerfo FW: Lower extremity revascularization in diabetes: late observations. *Arch Surg* 135:452–456, 2000
7. Panneton JM, Gloviczki P, Bower TC, Rhodes JM, Canton LG, Toomey BJ: Pedal bypass for limb salvage: impact of diabetes on long-term outcome. *Ann Vasc Surg* 14:640–647, 2000
8. Wolfle KD, Bruijnen H, Loeprecht H, Rumenapf G, Schweiger H, Grabitz K, Sandmann W, Lauterjung L, Largiader J, Erasmi H, Kasprzak PM, Raithel D, Allenberg JR, Lauber A, Berlakovich GM, Kretschmer G, Hepp W, Becker HM, Schulz A: Graft patency and clinical outcome of femorodistal arterial reconstruction in diabetic and non-diabetic patients: results of a multicentre comparative analysis. *Eur J Vasc Endovasc Surg* 25:229–234, 2003
9. Feinglass J, Pearce WH, Martin GJ, Gibbs J, Cowper D, Sorensen M, Khuri S, Daley J, Henderson WG: Postoperative and amputation-free survival outcomes after femorodistal bypass grafting surgery: findings from the Department of Veterans

Affairs National Surgical Quality Improvement Program. *J Vasc Surg* 34:283–290, 2001
10. Goshima KR, Mills JL Sr, Hughes JD: A new look at outcomes after infrainguinal bypass surgery: traditional reporting standards systematically underestimate the expenditure of effort required to attain limb salvage. *J Vasc Surg* 39:330–335, 2004
11. Taylor SM, Kalbaugh CA, Blackhurst DW, Cass AL, Trent EA, Langan EM 3rd, Youkey JR: Determinants of functional outcome after revascularization for critical limb ischemia: an analysis of 1000 consecutive vascular interventions. *J Vasc Surg* 44:747–755, 2006
12. Virkkunen J, Heikkinen M, Lepantalo M, Metsanoja R, Salenius JP: Diabetes as an independent risk factor for early postoperative complications in critical limb ischemia. *J Vasc Surg* 40:761–767, 2004
13. Hallett JW Jr, Byrne J, Gayari MM, Ilstrup DM, Jacobsen SJ, Gray DT: Impact of arterial surgery and balloon angioplasty on amputation: a population-based study of 1155 procedures between 1973 and 1992. *J Vasc Surg* 25:29–38, 1997
14. Al-Omran M, Tu JV, Johnston KW, Mamdani MM, Kucey DS: Outcome of revascularization procedures for peripheral arterial occlusive disease in Ontario between 1991 and 1998: a population-based study. *J Vasc Surg* 38:279–288, 2003
15. Bergqvist D, Troeng T, Elfstrom J, Hedberg B, Ljungstrom KG, Norgren L, Ortenwall P, the Steering Committee of Swedvasc: Auditing surgical outcome: ten years with the Swedish Vascular Registry–Swedvasc. *Eur J Surg Suppl* 3–8, 1998
16. Nilsson AC, Spetz CL, Carsjo K, Nightingale R, Smedby B: [Reliability of the hospital registry: the diagnostic data are better than their reputation]. *Lakartidningen* 91:598:603–595, 1994. [in Swedish]
17. Andersson T, Alfredsson L, Kallberg H, Zdravkovic S, Ahlbom A: Calculating measures of biological interaction. *Eur J Epidemiol* 20:575–579, 2005
18. Adam DJ, Beard JD, Cleveland T, Bell J, Bradbury AW, Forbes JF, Fowkes FG, Gillepsie I, Ruckley CV, Raab G, Storkey H: Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. *Lancet* 366: 1925–1934, 2005
19. van Houtum WH, Lavery LA, Harkless LB: The impact of diabetes-related lower-extremity amputations in the Netherlands. *J Diabetes Complicat* 10:325, 1996
20. Sigvant B, Wiberg-Hedman K, Bergqvist D, Rolandsson O, Andersson B, Persson E, Wahlberg E: A population-based study of peripheral arterial disease prevalence with special focus on critical limb ischemia and sex differences. *J Vasc Surg* 45: 1185–1191, 2007
21. Coutinho M, Gerstein HC, Wang Y, Yusuf S: The relationship between glucose and incident cardiovascular events: a metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes Care* 22:233–240, 1999
22. Treweek SP, Condie ME, Gilmour DG: Screening for diabetes in lower limb amputees: a pilot study. *J R Coll Surg Edinb* 43:93–94, 1998
23. Moss SE, Klein R, Klein BE: The 14-year incidence of lower-extremity amputations in a diabetic population: the Wisconsin Epidemiologic Study of Diabetic Retinopathy. *Diabetes Care* 22:951–959, 1999
24. Morrish NJ, Wang SL, Stevens LK, Fuller JH, Keen H: Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes. *Diabetologia* 44: S14–S21, 2001
25. Creager MA, Luscher TF, Cosentino F, Beckman JA: Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy. Part I. *Circulation* 108:1527–1532, 2003