Surgical or endovascular revascularization in patients with critical limb ischemia: Influence of diabetes mellitus on clinical outcome

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Objective: **The optimal revascularization strategy in diabetic patients with chronic critical limb ischemia (CLI) is unclear. This study assessed the efficacy of tailored endovascular-first vs surgical-first revascularization stratified for the presence of diabetes.**

Methods: **This prospective cohort study, with 1-year follow up, was conducted in a tertiary referral center in a consecutive series of 383 patients (45.7% had diabetes) presenting 426 limbs with chronic CLI. Interventions were endovascular (PTA cohort, 207 limbs) or surgical (SURG cohort, 85 limbs) revascularization. Conservatively treated patients without revascularization (NON REVASC cohort, 108 limbs) were used as a reference. The main outcome measures were sustained clinical success, defined as survival without major amputation or repeated target extremity revascularization (TER), and a categoric upward shift in clinical symptoms according to the Rutherford classification.**

Results: **Sustained clinical success of revascularization was significantly better in nondiabetic patients (hazard ratio [HR], 0.48; 95% confidence interval [CI], 0.29 to 0.72; *P* = .001 [SURG cohort]; HR, 0.53; 95% CI, 0.35 to 0.78; *P* = .002 [PTA cohort]) compared with diabetic patients (HR, 0.78; 95% CI, 0.44 to 1.43, *P* = .45 [SURG cohort]; HR, 0.83; 95% CI, 0.55 to 1.27, *P* = .40 [PTA cohort]). Repeated TER significantly improved clinical success, which became equivalent between diabetic and nondiabetic patients (HR, 1.02; 95% CI, 0.7 to 1.4). In multivariate analysis, treatment success was not influenced by mode of initial revascularization, neither in diabetic nor in nondiabetic patients. Cumulative 1-year mortality was 30.4%, with a trend of increased mortality in patients with diabetes (HR, 1.45; 95% CI, 0.98 to 2.17; *P* = .064). Limb salvage rates were similar in treatment cohorts, also if stratified for diabetes (HR, 1.04; 95% CI, 0.62 to 1.75).**

Conclusion: **Diabetic patients with chronic CLI benefit from early revascularization. To achieve this benefit, multiple revascularization procedures may be required, and close surveillance is therefore mandatory. Choice of initial revascularization modality seems not to influence clinical success. (J Vasc Surg 2007;45:751-61.)**

Diabetes mellitus is one of the major risk factors of peripheral arterial occlusive disease (PAOD)[1-3] and affects the arterial tree in a centrifugal pattern.[4,5] Its prevalence is particularly high in patients with chronic critical lower limb ischemia (CLI).[6,7] Considering the dismal natural course of CLI,[8] there is no doubt that arterial revascularization improves the prognosis, even in diabetic patients.[9] Indeed, current recommendations call for attempts of arterial reconstruction in any patient with CLI if the 1-year probability of survival and limb salvage can be estimated at >25%.[10,11]

Many authors now consider percutaneous transluminal angioplasty (PTA), with or without stenting, as the first-line approach for CLI because results are similar to reconstructive surgery even in the infrapopliteal segment and it potentially offers advantages such as minimal access trauma, low infection rates, and shorter hospital stays.[10,12-16]

Surprisingly little is known about the impact of diabetes on the efficacy of either treatment modality in a nonselected patient population with CLI.[17,18] Data from randomized coronary revascularization trials clearly show a disadvantage of endovascular treatment for diabetic patients.[19-21] It is unclear whether this finding is reflected by peripheral arterial interventions, especially if small-calibre vessels are treated. Recommendations are therefore controversial,[5,12,14,16,22,23] and the optimal treatment of diabetic patients with CLI remains to be determined. Objective of this study was to prospectively assess the efficacy of PTA or reconstructive surgery as the first-line treatment for CLI in patients with or without diabetes in a single-center cohort study.

METHODS

All patients with chronic CLI presenting to the Swiss Cardiovascular Center (SCVC), at the University Hospital Berne, between January 1999 and June 2004 were prospectively followed for 12 months. Recorded patient details included demographic characteristics, risk factors, clinical presentation, imaging studies, treatment modality, and prospective follow-up data. Approval of the responsible Ethical Committee (Ministry of Health, Canton of Berne,

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Competition of interest: none.

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0741-5214/$32.00

doi:10.1016/j.jvs.2006.12.022

Switzerland, KEK-No. 108/02) was obtained before the study started. The study was conducted according to the Declaration of Helsinki,[24] and patients gave informed consent before inclusion into the study.

Definition of CLI followed current consensus[11,23]: (1) presence of ischemic rest pain for >2 weeks or ischemic tissue loss associated with (2) an absolute ankle pressure of <50 mm Hg or great toe pressure of <30 mm Hg. Patients with acute limb ischemia were excluded.

Assessment of the peripheral circulation was performed at baseline and at 2, 6, and 12 months, respectively. This consisted of a complete noninvasive vascular work-up, including measurements of systolic blood pressures of both the anterior and posterior tibial arteries, calculation of ankle-brachial index (ABI), and imaging studies consisting of duplex scan, angiography, computed tomography angiography, or magnetic resonance angiography. Great toe pressure measurements by photoplethysmography were added in cases when arteries were considered incompressible (ABI >1.15)[25] or oscillometric readings showed poor pulsatility despite absolute ankle pressures >50 mm Hg. Transcutaneous partial oxygen tissue pressures ($tcpO_2$) of the forefoot were also recorded in supine and sitting positions.

In view of advanced age and comorbidities of CLI patients, a range of about 3 weeks around each scheduled study visit was tolerated; however, patients were followed up more frequently according to individual clinical needs. Repeated imaging studies were limited to patients where recurrent stenosis or occlusion or additional arterial lesions were suspected clinically or hemodynamically. Experienced vascular technicians performed all vascular laboratory measurements. Grading of the severity of ischemia followed the classification system proposed by Rutherford et al.[26] Patients were not followed up systematically after end of the study, but according to clinical needs.

All patients were evaluated on a case-by-case basis by a dedicated multidisciplinary vascular board that included interventional angiologists, radiologists, and vascular surgeons. This panel was established according to international recommendations[11] and had convened since 1998 for daily conferences. Departmental guidelines for optimal revascularization were continuously adapted to recommendations,[11,23] and a strategy "to treat patients with chronic CLI by endovascular means whenever technically possible rather than to operate" was adopted from the beginning of the recruitment period.

Although relative contraindications for endovascular treatment, such as a long iliac artery or superficial femoral artery (SFA) occlusions (especially if they started at the origin of the SFA), heavily affected calf vessels, and heavily calcified lesions, were more often operated on in the beginning, advances in endovascular techniques changed the situation over time. In general, TransAtlantic Inter-Society Consensus C and D lesions and obstructions spanning more than a single anatomic level (ie, femoropopliteal, below the knee) were not excluded from endovascular therapy.

The intervention decision was determined by clinical presentation, urgency of therapy, general condition of the patient, including presence of limiting comorbidities as well as anatomic distribution and morphologic nature of vascular lesions, availability of autologous veins, and access for endovascular therapy.[27] The same panel was involved in treatment decisions during follow-up for need for repeated or delayed target extremity revascularizations (TER) and major amputations. Decisions on repeated TER were invariably based on vascular imaging in addition to clinical findings.

In cases of prohibitive lesion pattern, patient's refusal, or if the overall clinical situation suggested an expectant attitude, CLI was handled conservatively by best medical treatment, including analgesic, antibiotic and antiplatelet and antithrombotic therapy, as well as lipid-lowering, antihypertensive, and diabetes medications, and infrequently, prostaglandins.[3,27]

Patients who underwent primary amputation owing to irreversible ischemic damage were registered for descriptive analysis but were excluded from analyses. Data sets with missing baseline information, without follow-up, or patient refusal were excluded from analysis.

Treatment cohorts. Patients were included into one of the following cohorts according to the primary therapeutic approach: SURG cohort, open revascularization by reconstructive surgery; PTA cohort, endovascular revascularization by PTA with or without stenting; or NON REVASC cohort, conservative treatment without revascularization. Best medical therapy was applied equally to all treatment cohorts and consisted of the previously mentioned pharmacologic treatment. All treatment cohorts were called at 2, 6, and 12 months for the same follow-up visits.

Study end points. The primary efficacy end point of the study was sustained clinical success,[28] defined as survival without major amputation or repeated TERs, and improvement of clinical symptoms according to Rutherford et al,[26] which is a categoric upward shift of at least one clinical category for all categories except for baseline category 5 (upward shift of at least 2 clinical categories), in combination with hemodynamic improvement of either ABI (≥0.1), toe pressure, or oscillometric reading. Secondary clinical success followed the same criteria but was not censored for repeated TER. The secondary end points analyzed were individual cumulative rates of all cause mortality, limb salvage, repeated TER, and sustained clinical improvement.

Definitions. The following definitions were used:

- Arterial hypertension was assumed when the measurement of arterial blood pressure was >140 mm Hg (systolic) or 90 mm Hg (diastolic), or both, at least on two different occasions, or if the patient was taking antihypertensive medication.
- Hyperlipidemia was defined by a total serum cholesterol level of >5 mmol/L, serum high-density lipoprotein cholesterol level of <1 mmol/L, or serum triglyceride level of >2 mmol/L. Hyperlipidemia was also assumed if a patient was taking lipid-lowering medication.

Table I. Demographic data of patients consisting of 383 patients with 416 critically ischemic limbs

*Data**	*All (N= 416) n (%)*	*Diabetic (n=190) n (%)*	*Nondiabetic (n = 226) n (%)*	P
Female	176 (42.3)	71 (37.4)	105 (46.5)	.073†
Male	240 (57.7)	119 (62.6)	121 (53.5)	
Age, years	75.5 ± 10.9 (40.3-94.9)	75.4 ± 10.1 (41.5-94.9)	75.6 ± 11.5 (40.3-94.7)	.47§
Blood pressure				
Systolic	144 ± 25	143 ± 25	145 ± 26	.66§
Diastolic	74 ± 11	73 ± 11	75 ± 11	.25§
Arterial hypertension	312 (75.2)	154 (81.5)	158 (69.9)	.009‡
Smoking	220 (53.0)	92 (48.7)	128 (56.6)	.12‡
Renal insufficiency	115 (27.6)	62 (32.6)	53 (23.5)	.047‡
Creatinine, μmol/L	102 (27-757)	104 (54-723)	101.5 (27-757)	.05§
Dialysis	27 (6.6)	13 (6.9)	14 (6.3)	.84‡
Hyperlipidemia	233 (56.1)	103 (54.4)	130 (57.4)	.58‡
Cholesterol, mmol/L	5.05 (2.10-11.58)	4.92 (2.10-10.83)	5.08 (2.42-11.58)	.27§
HDL, mmol/L	4.11 (0.85-11.13)	4.42 (0.85-10.60)	4.04 (1.71-11.13)	.11§
Homocysteine, μmol/L	17 (6-47)	17 (6-47)	18 (9-40)	.89‡
Fibrinogen, g/L	4.00 (1.5-9.0)	4.2 (1.5-8.4)	3.86 (1.8-9.0)	.097§
Platelet inhibitor	217 (52.4)	98 (51.6)	119 (53.1)	.77‡
Anticoagulation	122 (29.5)	56 (29.5)	66 (29.5)	1†

*Continuous and normally distributed variables are reported as mean ± standard deviation, asymmetrically distributed variables as median (range), and categoric variables numbers (percentages).
†All except 2 diabetic patients had adult onset diabetes (type II).
‡Two-tailed Fisher exact test.
§Mann-Whitney *U* test.

- Diabetes mellitus was defined by fasting blood sugar levels >120 mg/dL, or a hemoglobin A_{1c} level >6%. The presence of diabetes mellitus was also assumed if the patient was taking hypoglycemic medications.
- Current smoking habits were divided into either smoking or nonsmoking.
- Renal insufficiency was defined by serum creatinine levels >130 μmol/L.
- The ABI calculation was performed by division of the highest systolic arterial pressure reading of the tibial arteries through systemic blood pressure. Tibial artery incompressibility was assumed when ABI was >1.15 because this cutoff value has been reported to be invariably associated with heavy continuous calcification of tibial vessels.[25]
- Amputations were considered major and thus registered if performed above the ankle.
- Limb salvage was defined as absence of major amputation during the observation period and thus preservation of a functional lower extremity.

Statistical methods. Continuous and normally distributed variables are reported as mean ± standard deviation, and asymmetrically distributed variables as median (range). Categoric variables are presented as numbers (percentages). Differences between continuous variables were assessed by two-tailed unpaired *t* test if normally distributed, and by Mann Whitney *U* test if asymmetrically distributed. Differences of categoric variables were assessed by the two-tailed Fisher exact test. A value of $P < .05$ was considered to indicate statistical significance, except for situations where the *P* value had to be adjusted according to Bonferroni to keep the accepted α error at 5%, such as when more than two samples were compared.[29] In these situations, the Kruskal-Wallis test was used and the adjusted values of *P* are especially indicated.

Clinical success rates and secondary end points were assessed by cumulative outcome estimates according to Kaplan-Meier[30] as recommended by Rutherford et al.[26] Patients were uncensored in the event of death, major amputation, repeated TER, and whenever clinical improvement was either never reached or lost. The bivariate assessment of interdependency of diabetes and revascularization modality on influencing outcome was performed by applying log-rank tests. Statistical control of potentially confounding factors was reached by stepwise multivariate analysis (Cox proportional regression). Differences are expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). All time-to-event analyses were performed according to the intention to treat. All analyses were performed using the SPSS 12.0.1 OG software (SPSS Inc, Chicago, Ill).

RESULTS

During the study period, 383 consecutive patients with 426 chronic critically ischemic limbs were treated at the SCVC, a tertiary referral center for a population of about 1.1 million people, accounting for 2% to 5% of all patients seen with PAOD during the same period. Ten data sets (2%) were excluded from analysis owing to missing baseline information because of patient's refusal to undergo vascular imaging (n = 2) or any form of treatment (n = 2), withdrawal of informed consent (n = 1), and lack of any follow-up data owing to relocation to other cantons (n = 3) or countries (n = 2).

Demographic information on the remaining 416 limbs (376 patients) are summarized in Table I. In 16 patients

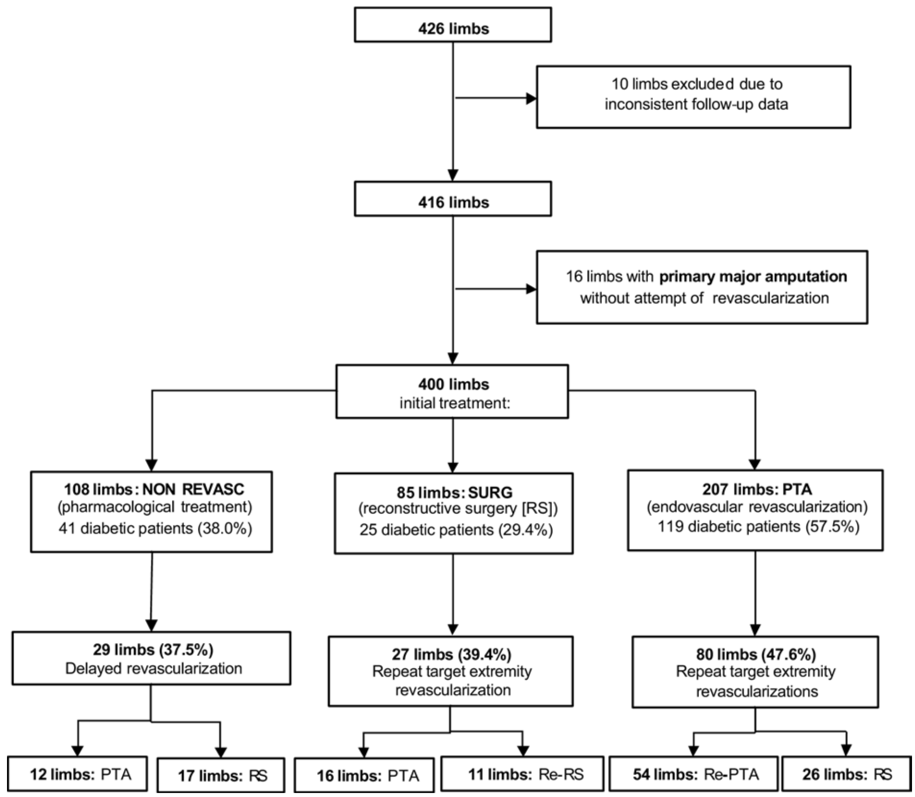


Fig 1. Decision flow chart. *PTA,* Percutaneous transluminal angioplasty.

(4%), primary major amputation was necessary because of CLI unsuitable for revascularization or advanced foot necrosis with or without secondary infection. Treatment decisions on the remaining 400 limbs are summarized in Fig 1. In 108 cases, attempts at revascularization were initially refused because revascularization deemed not immediately necessary in 41, missing consent to any intervention in 14, local disease considered to be inaccessible for both surgery and PTA in 39, or only for PTA whilst unfit for surgery in 6, or prevalent comorbidities in 8. Delayed arterial revascularization was performed in 29 limbs after a median of 49 days (mean, 82 ± 80 days; range, 1 to 327; cumulative 37.5%) because of change of mind about initial refusal in 8, change of clinical situation in patients initially deemed not urgent in 15, and improved general condition either rendering open surgery possible in 4 or endovascular therapy reasonable in 2.

Table II summarizes information on clinical presentation and hemodynamic findings, including Rutherford categories, ABI measurements, $tcpO_2$, oscillometric readings, arterial obstructive pattern, and treatment modalities.

Patients complied with follow-up visits very consistently. Rates of missing follow-up were 3% at 2 months, 3% at 6 months, and 4% at 12 months, and were evenly distributed between treatment cohorts ($P > .05$ by the Fisher exact test).

Primary efficacy end points. Arterial revascularization, regardless of whether PTA or open surgery, was associated with a significantly higher sustained clinical success rate at 1 year, with a higher amputation-free survival associated with clinical improvement compared with conservative therapy alone in nondiabetic patients ($P = .0004$), but not in diabetic patients ($P = .3$; Fig 2, *A*). If repeated TER was applied as needed, clinical success considerably improved ($P = .0014$, Fig 2, *B*) and became equivalent between diabetic and nondiabetic patients (HR, 1.02; 95% CI, 0.7 to 1.4). In multivariate analysis, success was not influenced by the mode of the initial revascularization, neither in diabetic nor in nondiabetic patients. Delay of arterial revascularization was associated with poorer outcome than immediate revascularization. This difference was statistically significant in nondiabetic patients ($P = .003$) and showed a strong trend in diabetic patients ($P = .056$, Fig 2, *C*).

In multivariate analysis of sustained clinical success, advanced age and diabetes were independent predictors of poor outcome. Immediate revascularization, regardless of whether it was PTA or reconstructive surgery, was independently associated with favorable outcome compared with delayed revascularization or no revascularization ($P < .01$ for both). Presence of diabetes had no influence on secondary clinical success when repeated TER was included into multivariate analysis. Table III summarizes the results of multivariate outcome analyses on primary study end points.

Secondary end point analysis. During follow-up, 100 patients died, for a calculated, cumulative 1-year mor-

Table II. Clinical, hemodynamic, and morphologic data of treated patients at first presentation with stratification for treatment modality and diabetes

Data	*SURG (n = 85)*	P*	*PTA (n = 207)*	P*	*NON REVASC (n = 108)*	P*	P†
Diabetes	25 (29.4)		119 (57.5)		41 (38.0)		.0001¶ [.017]
Age, years	72.3 ± 10.9	.78§	77.1 ± 9.7	.009§	74.4 ± 12.1	.24§	.002¶ [.017]
Clinical presentation		.4‖		.23‖		.06‡	.2¶ [.017]
Rutherford 4	17 (20.0)		30 (14.5)		24 (22.2)		
Rutherford 5	65 (76.5)		175 (84.5)		84 (77.8)		
Rutherford 6	3 (3.5)		2 (1.0)		—		
Hemodynamic presentation							
ABI	0.41 (0.21-1.07)	.31§	0.45 (0.15-1.47)	.64§	0.44 (0.17-1.18)	.81§	.028¶ [.017]
ABI not measurable, n	12 (14.0)	.9‡	67 (32.0)	.0001‡	34 (31.0)	.21‡	.005¶ [0.017]
$TcPO_2$ (mm Hg)	6 (1-52)	.31§	5 (1-64)	.28§	9 (1-52)	.42§	.18¶ [0.017]
Nonpulsatile oscillometric reading	61 (72.6)	.4‖	115 (56.7)	.32‖	70 (66.7)	.2‖	.027¶ [0.017]
Distribution of revascularized lesions							
Pelvic axis	23 (27.1)	.43‡	30 (14.5)	.69‡			.018‡
Infrainguinal above knee	83 (97.6)	.9‡	147 (71.0)	.54‡			.0001‡
Infrainguinal below knee	58 (68.2)	.13‡	123 (59.4)	.09‡			.16‡
PTA data							
Primary technical success			196 (94.7)	.53‡			
Stent			21 (10.1)	.9‡			
Surgery data							
Y-prosthesis	5 (5.9)	.9‡					
Common femoral endarterectomy	5 (5.9)	.15‡					
Crossover bypass	5 (5.9)	.9‡					
Bypass above knee	29 (34.1)	.19‡					
Bypass below knee	49 (57.6)	.19‡					
Conduit materials		.37‖					
Autologous vein	41 (52.6)						
Synthetic graft	35 (44.9)						
Biograft	2 (2.6)						
Bypass in history on same leg	14 (17)	.34‡					

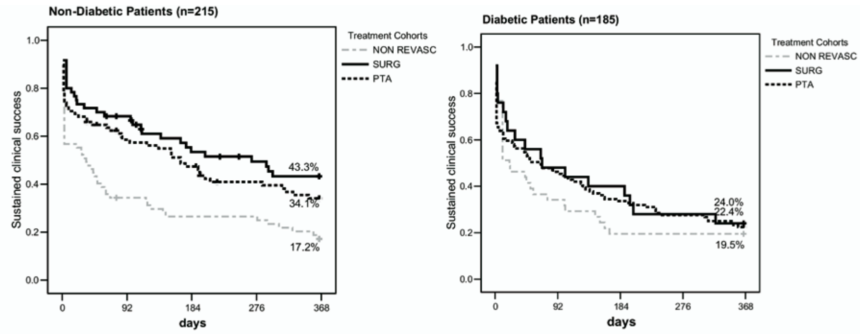
SURG, Surgical-first cohort; *PTA,* (percutaneous transluminal angioplasty) endovascular-first cohort; *NON REVASC,* best medical therapy only cohort; *ABI,* ankle-brachial index; $TcPO_2$, transcutaneous oxygen pressure.
Continuous and normally distributed variables are reported as mean ± standard deviation, asymmetrically distributed variables as median (range), and categoric variables numbers (percentages)
**P* value for diabetes.
†*P* value for cohorts. Values in brackets indicate adjusted significance levels to keep α error at 5% according to Bonferroni.
‡Two-tailed Fisher test.
§Mann-Whitney test.
‖Pearson χ^2 test.
¶Kruskal-Wallis test.

tality rate of 30.4%. Causes of death are summarized in Table IV. Multivariate analysis showed age and renal insufficiency to be independent predictors of higher mortality, and arterial revascularization of lower mortality. Diabetes was associated with higher mortality as a trend but missed statistical significance (HR, 1.45; 95% CI, 0.98 to 2.17; $P = .064$).

Limb salvage rates during the first year of follow-up were similar in all treatment cohorts (Fig 3), also if stratified for diabetes (HR for major amputation in diabetic patients, 1.04; 95% CI, 0.62 to 1.75; $P = .89$). Indeed, no independent predictive risk factors for major amputations could be identified in multivariate analyses. Exact rates for survival and major amputations as well as clinical improvement are summarized in Table V.

Cumulative early and late rates of repeated TER are given in Table V. Repeated TERs were performed in both PTA and SURG cohorts significantly more often in diabetic patients than in nondiabetic patients (HR, 1.64; 95% CI, 1.15 to 2.33; $P = .007$). Similarly, an advanced stage of PAOD was independently associated with higher rates of repeated TER (HR, 1.85; 95% CI, 1.27 to 2.7; $P = .002$). In the NON REVASC cohort, delayed revascularizations were performed in similar frequency in patients with and without diabetes. Distributions of repeated and delayed TER are depicted in Fig 1.

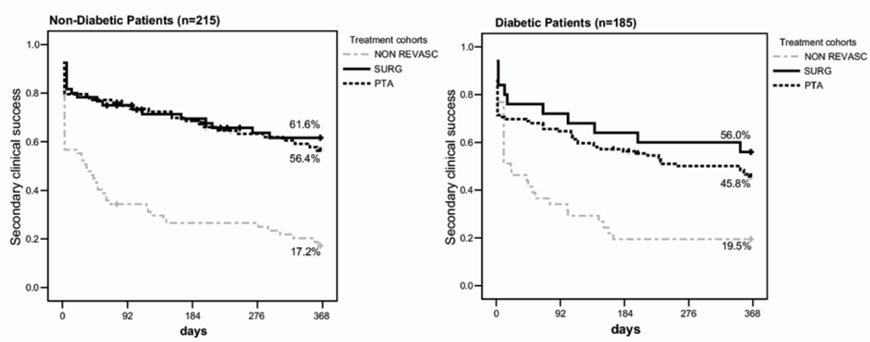
Primary amputation. Mean age of those patients (6 women, 10 men) undergoing primary amputation, and therefore not included in the analysis, was 80 years (range, 52 to 94 years). All were categorized as having Rutherford category 6 severity of PAOD. Three patients (19%) had infectious gangrene, five (31%) were diabetic, and 8 (50%) were heavy smokers. Thirteen patients had an amputation limited to below the knee, and three nondiabetic patients required primary amputation above the knee.



No at risk (days)	0	92	184	276	368	No events	0	92	184	276	368	No events
NON REVASC	67	22	17	17	11	55	41	14	17	8	8	33
SURG	60	39	29	24	21	32	25	12	10	7	6	19
PTA	88	47	38	30	25	55	119	55	40	32	26	92

Log rank test	SURG vs NON REVASC	PTA vs NON REVASC	SURG vs PTA	SURG vs NON REVASC	PTA vs NON REVASC	SURG vs PTA
P-value	*P= .0004*	*P= .004*	*P= .273*	*P= .300*	*P= .293*	*P= .759*

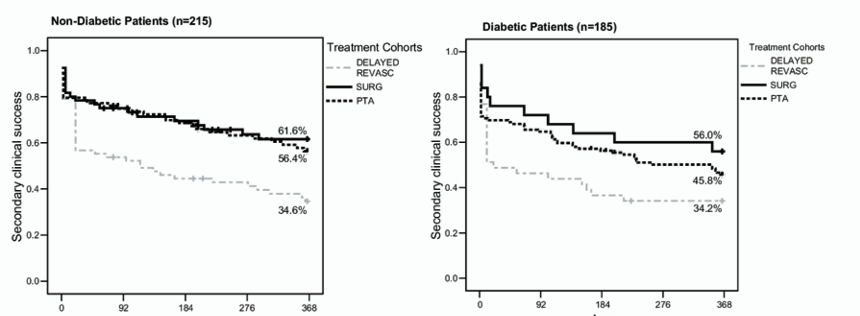
A



No at risk (days)	0	92	184	276	368	No events	0	92	184	276	368	No events
NON REVASC	67	22	17	17	11	55	41	14	8	8	8	33
SURG	60	43	37	31	30	22	25	18	16	15	14	11
PTA	88	60	55	46	41	36	119	77	66	57	53	64

Log rank test	SURG vs NON REVASC	PTA vs NON REVASC	SURG vs PTA	SURG vs NON REVASC	PTA vs NON REVASC	SURG vs PTA
P-value	*P= .000*	*P= .000*	*P= .645*	*P= .001*	*P= .000*	*P= .367*

B



No at risk (days)	0	92	184	276	368	No events	0	92	184	276	368	No events
NON REVASC	67	35	29	26	21	44	41	19	15	13	13	27
SURG	60	43	37	31	30	22	25	18	16	15	14	11
PTA	88	60	55	46	41	36	119	77	66	57	53	64

Log rank test	SURG vs DELAYED REVASC	PTA vs DELAYED REVASC	SURG vs PTA	SURG vs DELAYED REVASC	PTA vs DELAYED REVASC	SURG vs PTA
P-value	*P= .003*	*P= .004*	*P= .645*	*P= .056*	*P= .087*	*P= .367*

C

Table III. Multivariate comparison of clinical success relative to best medical therapy (NON REVASC cohort) including stratification for diabetes

	*Adjusted relative risk of surgery**		*Adjusted relative risk of PTA**	
	Risk ratio (95% CI)	P	*Risk ratio (95% CI)*	P
Sustained clinical success†				
Overall	0.59 (0.41-0.84)	.003	0.65 (0.50-0.86)	.002
Diabetic patients	0.78 (0.44-1.43)	.450	0.83 (0.55-1.27)	.400
Nondiabetic patients	0.48 (0.29-0.72)	.001	0.53 (0.35-0.78)	.002
Secondary clinical success†				
Overall	0.34 (0.22-0.51)	<.001	0.38 (0.28-0.51)	<.001
Diabetic patients	0.39 (0.20-0.79)	.009	0.5 (0.32-0.78)	.002
Non-Diabetic patients	0.29 (0.17-0.49)	<.001	0.29 (0.18-0.45)	<.001
Secondary clinical success (including delayed revascularizations)				
Overall	0.53 (0.35-0.81)	.001	0.58 (0.42-0.79)	.001
Diabetic patients	0.58 (0.28-1.19)	.140	0.72 (0.44-1.16)	.170
Nondiabetic patients	0.47 (0.28-0.81)	.006	0.48 (0.30-0.75)	.002

PTA, percutaneous transluminal angioplasty.
*Adjusted for age, sex, Rutherford-category at presentation, smoking status, renal insufficiency, hypertension, and hyperlipidemia.
†No differences were found between PTA and SURG cohorts after multivariate adjustment for risk factors (relative risk of SURG cohort, 0.9, 95% confidence interval, 0.64 to 1.25; $P = .5$).

Table IV. Causes of death (percentage of patients included)

Cause of death	*n (%)*
Cardiogenic (HF, MI)	35 (9.1)
Renal failure	9 (2.3)
Multiorgan failure	5 (1.3)
Pulmonary embolism	3 (0.8)
Respiratory failure (pneumonia)	8 (2.2)
Stroke	4 (1.0)
Carcinoma	7 (1.8)
Sepsis	9 (2.3)
Unknown	20 (5.2)

HF, Heart failure; *MI,* myocardial infarction.

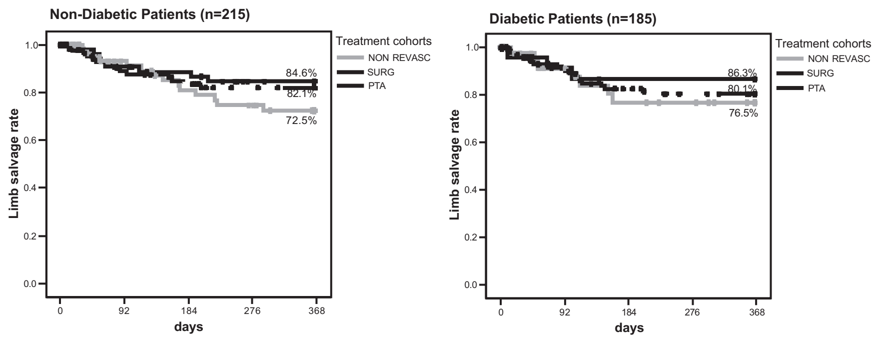
DISCUSSION

This prospective cohort study illustrates the clinical outcome of endovascular-first vs surgical-first revascularization in 383 consecutive patients with chronic CLI stratified for the presence of diabetes. The key finding was that diabetic patients with CLI could benefit from revascularization, regardless of the technique used. To achieve this benefit, however, multiple revascularization procedures may be required, and it was shown that clinical outcome can be improved to the same degree as in nondiabetic patients by means of close follow-up and timely repetition of TER as needed.

Diabetes is the most important risk factor for PAOD apart from smoking.[5] Its prevalence in symptomatic forms of PAOD has been estimated at 20%,[31] and was 13% in the overall patient population treated for PAOD in the SCVC during the study period. In contrast, estimates in chronic CLI are 27% to 76%,[10,13,14,17,32,33] well in accordance with our finding of 45.7% diabetic patients. Diabetic patients tend to have an accelerated form of atherosclerosis and show faster progression of intimal hyperplasia at anastomoses or angioplasty sites. The consequences are earlier and higher rates of restenoses, which become even more pronounced in vessels with a smaller calibre.[4-7] This renders diabetes one of the key factors to be observed when choosing the adequate treatment strategy for a patient with CLI.

The influence of diabetes on vascular interventions has been impressively shown on coronary artery disease (CAD). In the Bypass Angioplasty Revascularization Investigation (BARI) trial, diabetic patients with multivessel disease had a significantly higher cardiac mortality up to 7 years after percutaneous transluminal coronary angioplasty compared with coronary artery bypass grafting.[20] A meta-analysis confirmed this finding, although the difference faded after 6.5 years.[19] It is not known whether this unfavorable

Fig 2. Cumulative outcome estimates of primary efficacy study end points with bivariate analysis of treatment modality and diabetes by log-rank test. *NON REVASC,* Best medical therapy only cohort; *SURG,* surgical-first cohort; *PTA* (percutaneous transluminal angioplasty), endovascular-first cohort. **A,** Sustained clinical success of endovascular-first or surgical-first therapy compared with best medical therapy. Sustained clinical success was defined as survival without major amputation or repeated target extremity revascularizations (TERs), and improvement of clinical symptoms according to Rutherford et al.[26] **B,** Secondary clinical success of endovascular-first or surgical-first therapy compared with best medical therapy. Secondary clinical success was defined as survival without amputation, and improvement of clinical symptoms according to Rutherford et al[26] allowing repeated TERs. **C,** Secondary clinical success of endovascular-first or surgical-first therapy compared with best medical therapy, including delayed revascularization procedures.



No at risk (days)	0	92	184	276	368	No events	0	92	184	276	368	No events
NON REVASC	67	47	39	35	30	14	41	27	21	19	14	7
SURG	60	48	43	35	33	8	25	19	16	16	15	3
PTA	88	69	62	52	49	14	119	90	75	66	61	20

Log rank test	SURG vs NON REVASC	PTA vs NON REVASC	SURG vs PTA	SURG vs NON REVASC	PTA vs NON REVASC	SURG vs PTA
P-value	*P= .207*	*P= .327*	*P= .687*	*P= .468*	*P= .725*	*P= .580*

Fig 3. Cumulative limb salvage estimates over one year with bivariate analysis of treatment modality and diabetes. *NON REVASC,* Best medical therapy only cohort; *SURG,* surgical-first cohort; *PTA* (percutaneous transluminal angioplasty) endovascular-first cohort.

Table V. Kaplan Meier risk estimates for survival, major amputation, repeated target extremity revascularization, and sustained clinical improvement at the 30-day and 1-year follow-up

		Cumulative survival (%)		*Cumulative limb salvage (%)*		*Repeated TER (cumulative) (%)*		*Sustained clinical improvement (cumulative)*	
Cohort	*n*	*30 days*	*1 year*	*30 days*	*1 year*	*30 days*	*1 year*	*30 days*	*1 year*
NON REVASC	108	**88.60**	**61.00**	**99.00**	**73.90**	**6.10**	**37.50**	**49.10**	**20.40**
Diabetic	41	82.50	55.20	97.20	76.50	5.40	27.70	46.30	19.50
Nondiabetic	67	92.40	64.60	100	72.50	6.40	42.30	50.80	20.80
SURG	85	**92.80**	**78.00**	**97.50**	**85.10**	**10.10**	**39.40**	**69.40**	**40.90**
Diabetic	25	92.00	71.20	95.70	86.30	21.10	61.70	60.00	24.00
Nondiabetic	60	93.20	80.80	98.20	84.60	5.40	30.40	73.30	48.60
PTA	207	**94.00**	**70.60**	**96.50**	**81**	**16.70**	**47.60**	**61.40**	**32.00**
Diabetic	119	94.00	67.20	95.60	80.10	17.80	54.40	56.30	26.80
Nondiabetic	88	94.30	75.40	97.70	82.10	15.10	38.90	68.20	39.30
Multivariate analysis of diabetes,* RR (95% CI)		1.47 (0.98-2.17) $P = .064$		1.04 (0.57-1.64) $P = .89$		1.64 (1.15-2.33) $P = .007$		1.41 (1.10-1.82) $P = .009$	
Other independent risk factors*		Age, renal insufficiency, revascularization		None		Rutherford category		Rutherford category, age	

NON REVASC, Best medical therapy only cohort; *SURG,* surgical-first cohort; *PTA,* endovascular-first cohort; *TER,* target extremity revascularization; *RR,* relative risk; *CI,* confidence interval.
Bold face values indicate all patients of the cohort (diabetic and nondiabetic).
Bivariate analysis for influence of treatment modality by log-rank test.
*Multivariate analysis for independent influence of risk factors including diabetes by Cox regression analysis.

reaction to angioplasty is paralleled in diabetic patients treated for PAOD, especially in chronic CLI, with often small-calibre multivessel disease showing some similarities with symptomatic CAD.

Only a few studies have investigated the impact of diabetes on revascularization in consecutive, nonselected patient populations with chronic CLI,[17] and conflicting data have prevented the establishment of accepted guidelines.[5] Some authors remain sceptical about whether diabetic patients really benefit from arterial revascularization at all, whereas others recommend surgery because of unacceptably high restenosis rates after distal PTA.[23,34] However, technical feasibility, safety and interventional success of PTA have been established for CLI in a number of series,[14,15] including diabetic patients.[12,17] Results were equivalent to nondiabetic patients and were achieved by aggressive therapeutic measures and refinement of catheter techniques.

Findings in our series were consistent with the previously mentioned observations. Unlike nondiabetic patients, diabetic patients seem not to benefit durably from arterial revascularization, and the indication should be restrictive if the patient's compliance or circumstances rule out close follow-up and secondary interventions as needed. However, with clinical implementation of close surveillance and aggressive reintervention if needed, differences in clinical success were no longer observed between diabetic and nondiabetic patients. Neither modality of first nor of subsequent revascularization influenced outcome, which is consistent with series that show equivalent results of PTA and surgery.[17,33]

The Bypass Versus Angioplasty in Severe Ischemia of the Leg (BASIL) trial compared surgery-first and angioplasty-first treatment for severe limb ischemia in a prospective, randomized, controlled multicenter trial.[33] In that highly selected patient population—about 30% of patients qualified for randomization—neither approach was superior to the other. The mean age of patients and prevalence of diabetes were similar to our series. Rates of mortality and amputation-free survival at 1 year were almost identical to our PTA and SURG cohorts (20% and 70%, respectively), and no clear cut advantage of one or the other treatment modality was observed even as the ideal treatment modality was chosen individually, indicating that interventional treatment must be considered at least equivalent to surgical reconstruction in the therapy of severe lower limb ischemia.

In the BASIL trial, rate of repeated TER was significantly higher in the angioplasty-first arm. After multivariate adjustment, we could not reproduce this finding in our series. The presence of diabetes was independently associated with a statistically significant higher rate of repeated TER, however, reflecting the higher incidence of early restenosis in diabetic patients.[7] Of interest was that repetition of TER improved clinical success in diabetic patients not only significantly but also to the same level as in nondiabetic patients. Furthermore, the outcome of all patients was significantly better after immediate revascularization than after delayed revascularization, as shown in Fig 2. Rates of repeated TER and their distribution on PTA and surgery were very similar to findings in the BASIL trial (Fig 1).

One of the principal problems of comparing results of surgery and PTA in chronic CLI is the vast heterogeneity of end points used in the literature. Validation of therapy depends on the definition of treatment success. Isolated or combined limb salvage or mortality rates are investigated in most surgical series, whereas patency rates are assessed in most endovascular series. None of these measures reflect patients' quality of life during their remaining lifetime. Indeed, from a patient's perspective, it certainly does not seem sufficient just to postpone amputation until after death.[35] Clinical success, rather, depends on survival without major amputation (ie, preservation of a functional lower limb), but only if associated with symptomatic improvement, desirably, without repetition of an intervention.

A composite end point combining these parameters therefore was chosen to compare clinical success in the different treatment cohorts in our series. The strictness of this approach may explain the seemingly poor treatment results, but reflects the real-life outlook of individual patients, as shown by others.[15] Individually comparing mortality, major amputation, or repeated TER, our results are well in accordance with other series.[15,18,33] Comparing cumulative outcome data for each of the individual end point components (Table V, Fig 2) reveals the predominant influence of clinical improvement, an important measure that has seldom been included in other series. However, the importance of this primary functional outcome measure has been emphasized in a recent expert's consensus document on reporting outcomes of endovascular treatment.[28]

Overall mortality in our series was 30% at 1 year, which reflects the poor prognosis of patients with chronic CLI and is well in accordance with the literature.[10,13,15] Most deaths were due to cardiovascular events (39%) or pulmonary and generalized infections (17%). In 20% of our patients, the cause of death was either not sought (patients who died at home or in nursing homes) or could not be revealed.

Survival was seemingly improved by arterial revascularization. This has often been claimed to be due to lower amputation-related death and more rapid ambulation after revascularization. Because the decision for revascularization was operator dependent, there might have been a relevant selection bias for less aggressive revascularization in high-risk patients prone for a higher mortality in our series.

One striking finding, after adjustment for risk factors, was that we did not find an independent influence of revascularization on isolated limb salvage rates. The same finding is depicted in the bivariate analysis in Fig 3. Others have also made this observation.[17,32] Bertele et al[32] found no influence of revascularization on limb salvage in a large epidemiologic study of 1560 CLI patients. The most likely explanation is the composition of our NON REVASC cohort, which included patients suitable for reconstruction and also those who either initially declined an invasive treatment or in whom reconstruction was not considered urgently necessary. This explains the nearly 40% of patients with delayed revascularization who were retained in the NON REVASC cohort for the purpose of an intention-to-treat analysis.

Conversely, it is important to note that patients with unsalvageable ischemic limbs were *not* included in our analysis because they constitute a subset of CLI patients with no other option than amputation. Their prevalence was very low in our series, at 4% compared with 16% to 19% in other series,[8,11,36] probably because patients with obviously unsalvageable limbs have already undergone amputation in primary or secondary health care centers in a dense health care system such as exists in central Europe. As a result, together with exclusion of delayed revascularizations, this would have increased the 1-year amputation rate to about 50% in the NON REVASC cohort, as is commonly reported.[8,23] Remarkably, the presence of diabetes did not constitute an independent risk factor for amputation, an observation also made by others when primary amputations were excluded from analysis[16,17,32,37] or when outcome of unreconstructable CLI was studied.[8]

Limitations. Assignment of treatment in this controlled, prospective cohort study was based on clinical judgement, rather than on randomization; hence, all disadvantages of nonrandomized outcome studies are possibly present. Conversely, randomization of a seemingly homogeneous patient population to treatment modalities that essentially address different lesion pattern creates an important ethical dilemma. In case of chronic CLI, either only patients with lesion pattern equally suitable for both endovascular *and* surgical revascularization are included (70% of patients had to be excluded in the BASIL trial), thereby possibly *creating* rather than preventing an important selection bias, or randomization of unselected patients to unsuitable and possibly harmful treatment must be accepted. Thus, even results from randomized controlled trials cannot be easily translated to the general population, and it is at least doubtful whether another randomized controlled trial will be performed focusing in more depth on subgroups of patients with chronic CLI.

The declared aim in the present series was to investigate a representative sample of patients with chronic CLI, questioning whether diabetes influences clinical outcome in patients with an individually tailored revascularization strategy within a dedicated vascular center. It is remarkable that results from our series were almost identical to the main results of the BASIL trial despite completely different limitations in methodology. From an evidence-based perspective, this finding is very reassuring since the validity of the conclusions is corroborated from the other side.

Consistency in the decision-making process regarding treatment assignment can be regarded as one of the most critical issues in any nonrandomized outcome study. Consensus in the present series was sought for every individual patient in a dedicated multidisciplinary vascular board, and the involved consultants did not change during the study period. Advances in endovascular materials and techniques,[14,15] however, increased the probability of patients—especially diabetic patients—being assigned to the PTA cohort over time. Comparing first and second part of the study period, rates of endovascular revascularization increased from 47% to 58%, whereas assignment to surgical revascularization decreased from 25% to 17%. This progress has also been described by others[10,38] and highlights another typical limitation of observational cohort studies in fields with rapidly evolving technologies.

Although clinical presentation in terms of Rutherford classification and hemodynamic assessment was very comparable, the distribution of arterial lesions differed considerably between treatment cohorts (Table II). As expected, surgically treated patients had a higher prevalence of multilevel disease because of higher occurrence of pelvic axis and suprapopliteal disease, whereas distribution of arterial lesions in the infrapopliteal segment was alike between the SURG and PTA cohorts.

As in other series, diabetic patients were assigned to PTA significantly more often[17] and were therefore underrepresented in the other treatment cohorts. Diabetic patients often have comorbidities that make minimally invasive treatment modalities look more favorable. Concerns about impaired healing of surgical wounds, increased risks of infection, or silent CAD are important factors to refuse surgery. In line with experiences of our own group and of others,[14,15] infrapopliteal disease was not considered to be a contraindication for endovascular treatment, not even in diabetic patients.

The uneven distribution of diabetes probably did not influence the results, because most demographic characteristics, distribution of risk factors, and lesion characteristics were widely comparable between diabetic and nondiabetic patients, apart from a significant association of hypertension and renal insufficiency with diabetes (Tables I and II). For analysis, these differences were statistically controlled by multiple regression analysis.

CONCLUSION

The study confirms the poor prognosis of chronic CLI, with diabetes being one of the major risk factors. Revascularization should be intended without delay in both nondiabetic and diabetic patients. Clinical outcome is improved, regardless of endovascular-first or surgical-first revascularization, as long as treatment is individually tailored to the patient and his or her vascular morphology. To achieve long-term benefit, however, multiple revascularization procedures may be required in diabetic patients, and a dedicated interdisciplinary surveillance program is mandatory.

We thank Jolanda Vögele, RN, for assistance in data preparation, and Brigitta Gahl, MSC, for assistance in statistical analysis.

AUTHOR CONTRIBUTIONS

Conception and design: FD, ND, JS, IB
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Writing the article: FD, ND
Critical revision of the article: AG, MH, JS, IB
Final approval of the article: FD, ND, AG, MH, JS, IB
Statistical analysis: FD, ND, IB
Obtained funding: Not applicable
Overall responsibility: IB
FD and ND contributed equally to this work.

REFERENCES

1. Marso SP, Hiatt WR. Peripheral arterial disease in patients with diabetes. J Am Coll Cardiol 2006;47:921-9.
2. Reynolds K, He J. Epidemiology of the metabolic syndrome. Am J Med Sci 2005;330:273-9.
3. Diehm C, Diehm N. Non-invasive treatment of critical limb ischemia. Curr Drug Targets Cardiovasc Haematol Disord 2004;4:241-7.
4. Diehm N, Shang A, Silvestro A, Do DD, Dick F, Schmidli J, et al. Association of cardiovascular risk factors with pattern of lower limb atherosclerosis in 2659 patients undergoing angioplasty. Eur J Vasc Endovasc Surg 2006;31:59-63.

5. American Diabetes Association. Peripheral arterial disease in people with diabetes. Diabetes Care 2003;26:3333-41.
6. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. JAMA 2002;287: 2570-81.
7. Jude EB, Oyibo SO, Chalmers N, Boulton AJ. Peripheral arterial disease in diabetic and nondiabetic patients: a comparison of severity and outcome. Diabetes Care 2001;24:1433-7.
8. Lepantalo M, Matzke S. Outcome of unreconstructed chronic critical leg ischaemia. Eur J Vasc Endovasc Surg 1996;11:153-7.
9. Ebskov LB, Schroeder TV, Holstein PE. Epidemiology of leg amputation: the influence of vascular surgery. Br J Surg 1994;81:1600-3.
10. Nasr MK, McCarthy RJ, Hardman J, Chalmers A, Horrocks M. The increasing role of percutaneous transluminal angioplasty in the primary management of critical limb ischaemia. Eur J Vasc Endovasc Surg 2002;23:398-403.
11. Second European Consensus Document on chronic critical leg ischemia. Eur J Vasc Surg 1992;6(suppl A):1-32.
12. Faglia E, Dalla Paola L, Clerici G, Clerissi J, Graziani L, et al. Peripheral angioplasty as the first-choice revascularization procedure in diabetic patients with critical limb ischemia: prospective study of 993 consecutive patients hospitalized and followed between 1999 and 2003. Eur J Vasc Endovasc Surg 2005;29:620-7.
13. Danielsson G, Albrechtsson U, Norgren L, Danielsson P, Ribbe E, Thorne J, et al. Percutaneous transluminal angioplasty of crural arteries: diabetes and other factors influencing outcome. Eur J Vasc Endovasc Surg 2001;21:432-6.
14. Soder HK, Manninen HI, Jaakkola P, Matsi PJ, Rasanen HT, Kaukanen E, et al. Prospective trial of infrapopliteal artery balloon angioplasty for critical limb ischemia: angiographic and clinical results. J Vasc Interv Radiol 2000;11:1021-31.
15. Balmer H, Mahler F, Do DD, Triller J, Baumgartner I. Balloon angioplasty in chronic critical limb ischemia: factors affecting clinical and angiographic outcome. J Endovasc Ther 2002;9:403-10.
16. Hynes N, Mahendran B, Manning B, Andrews E, Courtney D, Sultan S. The influence of subintimal angioplasty on level of amputation and limb salvage rates in lower limb critical ischaemia: a 15-year experience. Eur J Vasc Endovasc Surg 2005;30:291-9.
17. Awad S, Karkos CD, Serrachino-Inglott F, Cooper NJ, Butterfield JS, Ashleigh R, et al. The impact of diabetes on current revascularisation practice and clinical outcome in patients with critical lower limb ischaemia. Eur J Vasc Endovasc Surg 2006;32:51-9.
18. Bailey CM, Saha S, Magee TR, Galland RB. A 1 year prospective study of management and outcome of patients presenting with critical lower limb ischaemia. Eur J Vasc Endovasc Surg 2003;25:131-4.
19. Hoffman SN, TenBrook JA, Wolf MP, Pauker SG, Salem DN, Wong JB. A meta-analysis of randomized controlled trials comparing coronary artery bypass graft with percutaneous transluminal coronary angioplasty: one- to eight-year outcomes. J Am Coll Cardiol 2003;41:1293-304.
20. Influence of diabetes on 5-year mortality and morbidity in a randomized trial comparing CABG and PTCA in patients with multivessel disease: the Bypass Angioplasty Revascularization Investigation (BARI). Circulation 1997;96:1761-9.
21. Weintraub WS, Stein B, Kosinski A, Douglas JS Jr, Ghazzal ZM, Jones EL, et al. Outcome of coronary bypass surgery versus coronary angioplasty in diabetic patients with multivessel coronary artery disease. J Am Coll Cardiol 1998;31:10-9.
22. Pomposelli FB Jr, Marcaccio EJ, Gibbons GW, Campbell DR, Freeman DV, Burgess AM, et al. Dorsalis pedis arterial bypass: durable limb salvage for foot ischemia in patients with diabetes mellitus. J Vasc Surg 1995;21:375-84.
23. Dormandy JA, Rutherford RB. Management of peripheral arterial disease (PAD). TASC Working Group. TransAtlantic Inter-Society Concensus (TASC). J Vasc Surg 2000;31:S1-S296.
24. World Medical Association Declaration of Helsinki as amended by the 48th World Medical Assembly, October, 1996. Available at: http://www.expertiseireland.com/pdfs/WMAHelsinki.pdf. Accessed Sep 16, 2006.
25. Emanuele MA, Buchanan BJ, Abraira C. Elevated leg systolic pressures and arterial calcification in diabetic occlusive vascular disease. Diabetes Care 1981;4:289-92.
26. Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg 1997;26:517-38.
27. Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary. J Am Coll Cardiol 2006;47:1239-312.
28. Diehm N, Baumgartner I, Jaff M, Do DD, Minar E, Schmidli J, et al. A call for uniform reporting standards in studies assessing endovascular treatment for chronic ischemia of lower limb arteries. Eur Heart J 2007; in press.
29. Bland JM, Altman DG. Multiple significance tests: the Bonferroni method. BMJ 1995;310:170.
30. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Ass 1958;53:457-81.
31. Murabito JM, D'Agostino RB, Silbershatz H, Wilson WF. Intermittent claudication. A risk profile from The Framingham Heart Study. Circulation 1997;96:44-9.
32. Bertele V, Roncaglioni MC, Pangrazzi J, Terzian E, Tognoni EG. Clinical outcome and its predictors in 1560 patients with critical leg ischaemia. Chronic Critical Leg Ischaemia Group. Eur J Vasc Endovasc Surg 1999;18:401-10.
33. Adam DJ, Beard JD, Cleveland T, Bell J, Bradbury AW, Forbes JF, et al. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. Lancet 2005;366:1925-34.
34. Gutteridge W, Torrie EP, Galland RB. Cumulative risk of bypass, amputation or death following percutaneous transluminal angioplasty. Eur J Vasc Endovasc Surg 1997;14:134-9.
35. Bosiers M, Deloose K, Verbist J, Peeters P. Percutaneous transluminal angioplasty for treatment of "below-the-knee" critical limb ischemia: early outcomes following the use of sirolimus-eluting stents. J Cardiovasc Surg 2006;47:171-6.
36. Thompson MM, Sayers RD, Varty K, Reid A, London NJM, Bell PRF. Chronic critical leg ischaemia must be redefined. Eur J Vasc Surg 1993;7:420-6.
37. Pomposelli FB, Kansal N, Hamdan AD, Belfield A, Sheahan M, Campbell DR, et al. A decade of experience with dorsalis pedis artery bypass: analysis of outcome in more than 1000 cases. J Vasc Surg 2003;37:307-15.
38. Kudo T, Chandra FA, Kwun WH, Haas BT, Ahn SS. Changing pattern of surgical revascularization for critical limb ischemia over 12 years: endovascular vs. open bypass surgery. J Vasc Surg 2006;44:304-13.

Submitted Sep 16, 2006; accepted Dec 11, 2006.