Factors related to outcome of neuroischemic/ischemic foot ulcer in diabetic patients

Jan Apelqvist, MD, PhD,[a] Targ Elgzyri, MD,[a] Jan Larsson, MD, PhD,[b] Magnus Löndahl, MD, PhD,[a] Per Nyberg, MD, PhD,[c] and Johan Thörne, MD, PhD,[d] *Malmö, Lund, and Helsingborg, Sweden*

Objectives: **Peripheral vascular disease (PVD) is an important limiting factor for healing in neuroischemic or ischemic diabetic foot ulcer. The purpose of this study was to identify factors related to healing in patients with diabetes with foot ulcers and severe PVD.**

Methods: **Patients with diabetes with a foot ulcer, consecutively presenting at a multidisciplinary foot center with a systolic toe pressure <45 mm Hg or an ankle pressure <80 mm Hg were prospectively included, followed according to a preset program, and with the exception of specified exclusions, subjected to angiography offered vascular intervention when applicable. All patients had continuous follow-up until healing or death irrespective of the type of vascular intervention.**

Results: **One thousand one hundred fifty-one patients were included. Eighty-two percent had a toe pressure <45 mm Hg and 49% had an ankle pressure <80 mm Hg. Eight hundred one patients (70%) underwent an angiography. Out of these, 63% had vascular intervention, either percutaneous transluminal angioplasty (PTA; 39%) or reconstructive surgery (24%). Nine percent of the patients had one or more complications after angiography. PTA was multisegmental in 46% and to the crural arteries in 46%. Reconstructive surgery was distal in 51%. Age ($P < .001$), renal function impairment ($P = .005$), congestive heart failure ($P = .01$), number and type of ulcer ($P < .001$), and severity of PVD ($P = .003$) affected the outcome of ulcers. PTA and reconstructive vascular surgery increased the probability of healing without amputation (odds ratio [OR], 1.77 and 2.05, respectively).**

Conclusion: **Probability of ulcer healing is strongly related to comorbidity, extent of tissue involvement, and severity of PVD in patients with diabetes with severe PVD. (J Vasc Surg 2011;53:1582-8.)**

The diabetic foot can be defined as infection, ulceration, and/or destruction of deep tissues associated with neurological abnormalities and various degrees of peripheral vascular disease (PVD) in the lower limb in patients with diabetes.[1] Foot complications in diabetes present a particularly troubling picture, and it has been claimed that every 30 seconds a lower limb is amputated due to diabetes.[2] The population of patients with diabetes that present with foot ulceration is heterogeneous. The complexity of diabetic foot necessitates a profound knowledge of underlying pathophysiology and a multifactorial approach.[1] However, there are a limited number of studies presenting data on current outcomes and determinants of outcome in individuals with diabetic foot ulcers, especially regarding ischemic or neuroischemic foot ulcers.[1,3,4] Most studies in ischemic conditions are focused on limb salvage after a specific intervention.[5,6]

From the Department of Endocrinology, Skåne University Hospital, Malmö[a]; the Department of Orthopaedic Surgery,[b] and Department of Occupational Medicine,[c] Skåne University Hospital, Lund; and the Department of Surgery, Helsingborg's Hospital, Helsingborg.[d]

Competition of interest: none.

Reprint requests: Targ Elgzyri, MD, Department of Endocrinology, Skåne University Hospital, Lund University, 20502 Malmö, Sweden (e-mail: Targ.Elgzyri@med.lu.se).

Additional material for this article may be found online at www.jvascsurg.org.

The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a competition of interest.

0741-5214/$36.00

doi:10.1016/j.jvs.2011.02.006

PVD is considered to be the most important limiting factor for healing of ischemic or neuroischemic diabetic foot ulcers.[1,4,7,8] Noninvasive vascular testing has been shown to predict probability for healing of diabetic foot ulcers.[1,7,9] Few studies evaluate outcome in ischemic or neuroischemic foot ulcers irrespective of vascular intervention. The purpose of this study was to identify factors related to healing of ulcers and the possibility for vascular intervention in consecutively presenting patients with diabetes with foot ulcers and severe PVD treated in a multidisciplinary system, both in and out of the hospital until healing is achieved or death unhealed.

METHODS

Study population. Consecutively, presenting patients with diabetes and foot ulcer (Wagner grades 1-5, at or below the ankle) admitted to a multidisciplinary foot center (n = 1151) were prospectively included between years 1984 to 2006, treated, and followed up according to a standardized protocol until healing or death. The study was designed to follow every patient for 5 years after intervention with regard to recurrence ulceration, new ulcers, amputation, and death.

Inclusion criteria. Individuals with diabetes mellitus and foot ulcer and a systolic toe pressure <45 mm Hg, a systolic ankle pressure <80 mm Hg, or in case of nonmeasurable pressure levels, nonpalpable foot pulses with ulcer Wagner grades 4 to 5 or pain at rest. All patients fulfilled Fontaine grade 4.[10]

Study design. Patients were followed and treated according to a preset standardized protocol by a multidisciplinary team both in and out of the hospital until healing

with or without amputation was achieved, or until the patient died with an unhealed ulcer. All lesions were assessed and documented by the same team. Outpatient treatment was carried out in collaboration with primary health care and home nursing services. Physical examination of the foot was performed at inclusion and regularly during the study by the multidisciplinary team.

The core team consisted of a diabetologist, an orthopedic surgeon, an orthotist, a podiatrist, and a registered nurse educated in diabetes. Vascular investigation was carried out according to a prescheduled program by a vascular surgeon integrated in the team on a regular basis. Specially trained casting technicians provided continuous service for total contact casting. A specialist in infectious disease was available for consultations when required.

All data were recorded on standardized case record forms; these forms were both computerized and transformed into files. At study, entry data were collected on previous management, referral, patient characteristics, comorbidities, ulcer characteristics, and laboratory investigations.

Each patient was represented by one lesion below the ankle. Patients with several concurrent lesions were represented by the one with the worst outcome. Patients with three or more ulcers on the same foot were classified as having multiple ulcers. The most superficial ulcer included was a full thickness skin ulcer penetrating into the subcutaneous layer.

A detailed description of definitions, and the medical and surgical management is available in the Supplementary Information (online only).

Measurements. Systolic toe and ankle blood pressure was measured using strain gauge and Doppler techniques at the vascular laboratory.[9] Signs of sensory polyneuropathy were tested using biothesiometer (BioMedical Instruments, New Burry, Ohio) and defined as present at biothesiometer values of ≥25 V.[11] At the time of the design of the study, vibratory pressure threshold measured by biothesiometer was the most commonly used technique to establish the presence of sensory polyneuropathy and was used as routine in our center for screening for neuropathy in the foot as it predicts subsequent ulceration, although it does not evaluate all modalities of neuropathy.[1,11]

Vascular intervention. Angiography was performed at the discretion of a vascular surgeon according to a written program that was jointly agreed upon in advance. A retrograde aortofemoral angiography, routinely visualizing distal vessels as well as the pedal arch, was performed if medical condition allowed and if informed consent was given by the patient. The catheter was placed as far distally as possible and delayed and magnified lateral foot views were routinely obtained. The popliteal and crural arteries were selectively catheterized if possible. Simultaneous percutaneous transluminal angioplasty (PTA) was performed when possible.

Exclusion criteria for angiography were:

- Medical condition not allowing angiography.
- Extensive gangrene (Wagner grade 5) but not ulcer location.
- Major amputation performed before angiography.
- Subjective life expectancy of the patient <6 months.
- Signs of ulcer healing before angiography.
- Lack of walking capacity before occurrence of ulcer, restitution not expected.
- Informed consent for angioplasty refused.

All patients undergoing angiography with or without PTA were treated according to a program before and after intervention regarding hydration and choice of pharmaceutical drugs to avoid renal failure.[12] After patients with PTA were put on low molecular heparin for a minimum of 3 months.[13] All patients were treated with acetylsalicylic acid or clopidogrel if no contraindication was present.

In patients where PTA was not possible or not successful, reconstructive surgery was considered and performed at the discretion of the vascular surgeon, provided their medical condition allowed surgery and informed consent could be obtained. Distal reconstructive surgery was defined as bypass to or distal to the truncal tibiofibular artery. Postoperative care and follow-up were performed in cooperation and supervision by the team according to the program.

Patients not available for angiography or revascularization after angiography were considered for treatment with low molecular heparin or ketanserin, if feasible, according to comorbidity.[13,14] All patients, irrespective of intervention, were followed by the team according to protocol until a final outcome.

Statistics. Values are given as median and range. Comparisons between groups were made using the Mann-Whitney or χ^2 test. Statistical significance was defined as a P value $< .05$. The simultaneous influence of possible risk factors on a binary outcome (primary healing and amputation) was investigated by means of backward logistic regression analysis. Statistical analysis was performed using SPSS version 14.0 (SPSS, Chicago, Ill).

RESULTS

Vascular intervention and complications. One thousand one hundred fifty-one patients were included in the study. After 5 dropped out, 1146 continued to follow-up in the study (2 years, 0.5-5). Out of these (age 75 years, 40-92), 61% were males, 69% were treated with insulin, and 18% were smokers. Intermittent claudication was present in 26% of patients and pain at rest in 52%. Systolic toe pressure <45 mm Hg and an ankle pressure <80 mm Hg were seen in 82% and 49%, respectively (Table I). Wagner grade at inclusion did not correlate to ankle-brachial or toe-brachial pressure indexes (data not shown).

In 345 patients (30%), no angiography was done (Fig), while 801 patients had an angiography. Fourteen patients were excluded (dropped out) among those who did not have an angiography done. Patients who did not have an angiography done continued with conservative treatment at the diabetic foot clinic according to the program.

Angiography vs no angiography. Patients with no angiography more often had cerebrovascular disease

Table I. Clinical characteristics of the subjects

	All patients (n = 1146)	*No angiography (n = 345)*	*Angiography (n = 801)*	P[1]	*Medical treatment (n = 297)*	*PTA (n = 314)*	*Reconstructive surgery (n = 190)*	P[2]/P[3]
Age (years)	75 (40-92)	77 (46-87)	74 (40-92)		75 (44-90)	74 (44-90)	72 (46-92)	
Male gender	61% (700)	59% (203)	62% (495)		63% (186)	63% (117)	58% (111)	
Duration of diabetes (years)	15 (0-58)	15 (1-58)	15 (0-56)		15 (0-48)	16 (1-56)	15 (1-54)	
Insulin therapy	69% (786)	62% (213)	71% (569)	[b]	67% (200)	73% (229)	73% (138)	
HbA1c (%)	7.6 (3.6-16.0)	7.5 (4.3-14.3)	7.7 (3.6-16.0)		7.6 (3.6-15.1)	7.6 (4.3-16.0)	7.9 (4.3-12.4)	
Serum creatinine (μmol/L)	139 (41-1101)	149 (43-996)	135 (41-1101)		137 (46-755)	137 (43-883)	123 (41-1101)	
Current smokers	18% (204)	16% (53)	19% (151)		15% (45)	17% (53)	28% (52)	P^{2a}
Peripheral edema	57% (638)	55% (186)	57% (452)		56% (166)	58% (177)	58% (110)	
Retinopathy	49% (557)	43% (148)	51% (405)		49% (144)	53% (165)	50% (94)	
Nephropathy	37% (419)	34% (118)	38% (299)		35% (104)	41% (129)	34% (65)	
CVD	33% (337)	41% (143)	29% (234)	[c]	30% (89)	29% (90)	29% (54)	
CHF	28% (323)	30% (102)	28% (221)		28% (83)	28% (88)	26% (50)	
IHD	44% (501)	43% (148)	44% (351)		47% (138)	42% (131)	43% (82)	
Intermittent claudication	26% (303)	19% (64)	30% (239)	[c]	22% (66)	32% (101)	38% (72)	P^{2b}
Rest pain	52% (585)	35% (118)	59% (465)	[c]	49% (145)	63% (195)	67% (126)	P^{2c}
Toe pressure (mm Hg)	32 (0-145)	33 (0-125)	31 (0-145)		32 (0-90)	32 (0-145)	29 (0-90)	
Toe pressure <30 (mm Hg)	49% (557)	48% (164)	51% (411)		50% (148)	51% (159)	55% (104)	
Toe pressure <45 (mm Hg)	82% (939)	82% (283)	81% (652)		81% (240)	81% (255)	82% (156)	
Ankle pressure (mm Hg)	86 (0-235)	89 (0-235)	85 (0-230)		90 (20-230)	87 (10-215)	74 (0-160)	
Ankle pressure <50 (mm Hg)	13% (148)	10% (33)	14% (115)		10% (31)	14% (43)	22% (41)	
Ankle pressure <80 (mm Hg)	49% (558)	50% (172)	48% (386)		43% (127)	46% (145)	61% (116)	
Superficial ulcer	24% (276)	28% (96)	22% (179)		22% (66)	21% (67)	25% (47)	
Deep ulcer	21% (242)	23% (81)	20% (161)		19% (56)	21% (67)	20% (38)	
Abscess/osteitis	16% (181)	15% (52)	16% (130)		18% (52)	18% (57)	11% (20)	P^{3c}
Minor gangrene	33% (376)	27% (92)	35% (284)	[b]	33% (98)	36% (113)	38% (73)	P^{2c}
Major gangrene	6% (71)	7% (24)	6% (47)		8% (25)	3% (10)	6% (12)	
Ulcer of big toe	21% (247)	23% (80)	21% (166)		21% (62)	21% (67)	19% (37)	
Ulcer of other toes	24% (281)	23% (81)	25% (198)		28% (84)	24% (74)	21% (40)	
Fore/midfoot plantar ulcer	7% (82)	10% (33)	6% (49)		7% (21)	6% (20)	5% (9)	
Heel ulcer	14% (159)	19% (66)	12% (97)	[a]	11% (34)	11% (34)	15% (29)	
Dorsal surface ulcer	6% (70)	6% (19)	6% (47)		6% (18)	6% (18)	5% (9)	
Multiple ulcers	27% (312)	19% (66)	31% (245)	[c]	26% (78)	32% (101)	35% (66)	P^{2a}

CHF, Congestive heart failure; *CVD,* cerebrovascular disease; *IHD,* ischemic heart disease.
Data are % (n) or median (range), P^1 = angiography vs no angiography, P^2 = medical treatment vs percutaneous transluminal angioplasty (PTA) + reconstructive surgery, P^3 = PTA vs reconstructive surgery.
[a] $P < .05$.
[b] $P < .01$.
[c] $P < .001$.

(transient ischemic attack/stroke; $P < .001$) and patients with angiography more often had intermittent claudication ($P < .001$), rest pain ($P < .001$), multiple ulcers ($P < .001$), and minor gangrene ($P < .01$; Table I). Patients who had PTA or reconstructive vascular surgery more often had intermittent claudication ($P < .01$), rest pain ($P < .001$), minor gangrene ($P < .001$), and multiple ulcers ($P < .05$), and more often were current smokers compared with patients who had an angiography but no vascular intervention (Table I). In total, a dropout rate of 5% was seen; 14 patients before and 46 after angiography. There were various reasons why angiography was not performed (Supplementary Table I) of which lack of mobility and presence of extensive comorbidity were the most common. In 14% of cases, patients did not give consent for either an angiography or an angioplasty.

After an angiography, 72 of 801 patients (9%) had 99 complications: renal impairment (n = 56), hemorrhage (n = 26), vascular occlusion (n = 1), and other various complications (n = 16).

Percutaneous angioplasty. In 314 patients, a PTA was performed with an average of 1.5 procedures per extremity. The levels of interventions were at the iliac artery

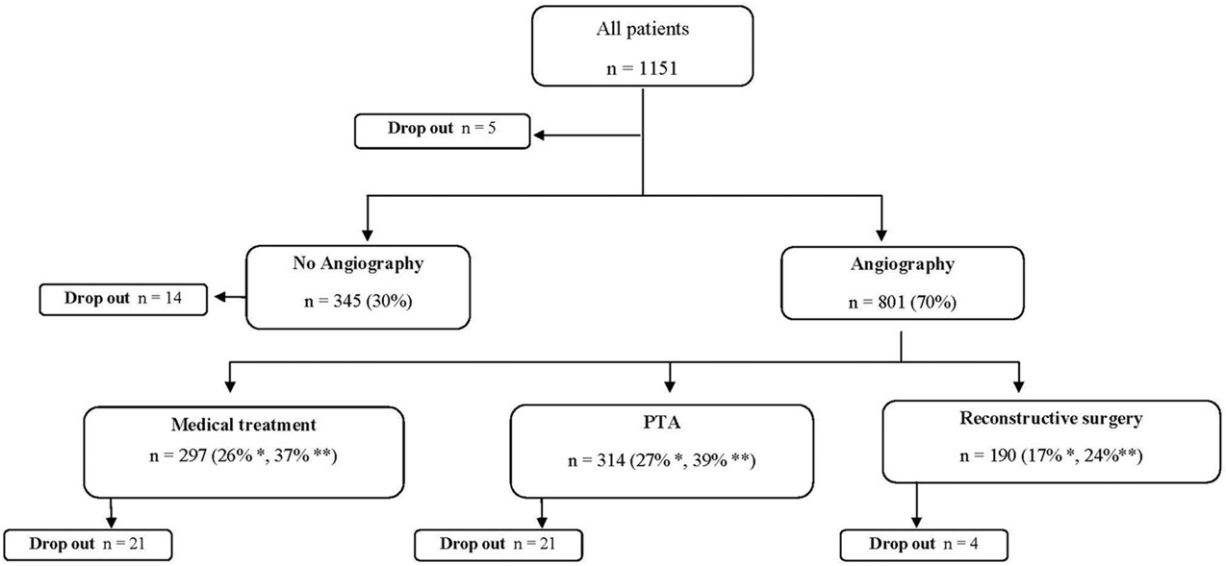

Fig. Flow chart of study population with regard to angiography, percutaneous transluminal angioplasty (*PTA*), and vascular reconstructive surgery performance. *Of all cases; **after angiography.

(10%), femoral artery (53%), popliteal artery (35%), and at the crural arteries in 46% of cases.

Interventions were at a single level in 54% of cases, at two levels in 35%, at three levels in 10.5%, and at four levels in 0.5%. After angiography with PTA, 64 complications in 51 patients (16%) were reported; hemorrhage (n = 30), arterial reocclusion (n = 10 of whom 5 patients needed surgery), and miscellaneous (n = 24). Three patients died within 30 days after intervention.

Reconstructive vascular surgery. Reconstructive vascular surgery was performed in 190 cases of which 51% were distal procedures – tibiotruncal or below (Supplementary Table II). After reconstructive surgery, 41 general complications were reported within 30 days in 30 patients (16%): cardiovascular (n = 16), cerebrovascular (n = 6), pneumonia (n = 3), and miscellaneous (n = 16). Four patients died within 30 days after intervention. Local complications (n = 47) after surgery were seen in 36 cases (19%); hemorrhage (n = 13), arterial occlusion (n = 20 of whom 10 needed a reoperation), and infection (n = 14).

No vascular intervention after angiography. In 297 patients, invasive vascular intervention was not performed after angiography. The reasons are included in Supplementary Table III. In 33% of these cases, the intervention was not feasible according to angiography. These patients continued treatment with the foot care team according to the program.

Vascular intervention and outcome. To evaluate the outcome, patients were divided into four groups: those who had no angiography (n = 345), those treated with PTA (n = 314), those treated with reconstructive vascular surgery (n = 190), and those who received medical treatment only after angiography (n = 297). Forty-six patients were lost to follow-up after angiography and 34 had not reached the end point (healing with or without amputation or death).

In total, 36% of patients healed primarily, 16% healed after minor amputation, 13% healed after a major amputation, and 27% died unhealed. Median time to healing was 27 weeks (1-292 weeks). Among patients with nonmeasurable peripheral ankle pressure (n = 110), primary healing was seen in 36 patients (32.7%), minor amputation in 15 patients (13.6%), major amputation in 13 patients (11.8%), 44 patients (40%) died unhealed, and 2 patients dropped out (1.8%). At the end of the study, there was a dropout rate of 5%, and 3% of patients were still in treatment (unhealed). Out of the surviving patients, 72% healed without a major amputation (Table II).

Factors related to outcome. A multiple regression analysis was performed, including factors of demographic data, clinical characteristics, comorbidity, and local characteristics (Table I) to identify factors related to primary healing (Table III). PTA and vascular surgery increased the probability for primary healing with an odds ratio (OR) of 1.77 and 2.05, respectively. Severity of PVD, age, comorbidity (congestive heart disease and/or renal impairment), and extent of tissue destruction at inclusion were also related to probability of healing.

DISCUSSION

In this large prospective study of individuals with diabetes, foot ulcers, and severe PVD treated at a multidisciplinary foot center, the healing rate without major amputation in surviving patients was 72%. Probability for healing without major amputation was strongly related to severity of PVD, comorbidity, and extent of tissue destruction.

Table II. Outcome in relation to intervention (n = 1146)

	No angiography (n = 345)		*Medical treatment (n = 297)*		*PTA (n = 314)*		*Vascular surgery (n = 190)*	
	n	*%*	*n*	*%*	*n*	*%*	*n*	*%*
Primary healing (n = 415)	127	37	96	32	121	39	71	37
Minor amputation (n = 184)	36	10	43	14	60	19	45	24
Major amputation (n = 143)	33	10	45	15	34	11	31	16
Deceased (n = 310)	128	37	84	28	63	20	35	18
Dropouts (n = 60)	14	4	21	7	21	7	4	2
Still under treatment (n = 34)	7	2	8	3	15	4	4	2

Table III. Factors related to ulcer primary healing

	OR (95% CI)	P *value*
Age <75 years	1.03 (1.02-1.05)	<.001
Serum creatinine <130 μmol/L	1.59 (1.15-2.2)	.005
Ankle pressure >50 mm Hg	1.62 (1.18-2.23)	.003
No congestive heart failure	1.81 (1.26-2.95)	.01
Single ulcer vs multiple ulcers	2.75 (1.93-3.92)	<.001
Ulcer of Wagner grades I–II	2.86 (2.06-3.94)	<.001
PTA	1.77 (1.24-2.53)	.02
Reconstructive vascular surgery	2.05 (1.33-3.16)	.001

CI, Confidence interval; *OR,* odds ratio; *PTA,* percutaneous transluminal angioplasty.

Angioplasty or reconstructive vascular surgery seems to increase the probability of healing.

During the study period, the foot center received approximately 3000 new patients with diabetes with a foot ulcer. At the time of the design of the study, 30% of the patients with a foot ulcer had severe PVD according to the criteria for the present study. At present, the corresponding figure is 49%.

In recent cohort studies, approximately 50% of diabetic foot ulcers are of ischemic or neuroischemic origin.[4,15,16] However, the main focus of diabetic foot treatment is usually on neuropathy and its consequences.[17] There are substantial numbers of suggested classification systems for the diabetic foot ulceration, but none of them completely covers the need for classification and prediction of outcome that can be used both in clinical practice as well as research.[18]

Assessment of the need for vascular intervention (reconstructive vascular surgery or angioplasty) in patients with ischemic or neuroischemic diabetic foot ulcers has frequently been based on the presence of progressive claudication, rest pain, or the extent of tissue loss (using the Fontaine classification). However, pain at rest and claudication in individuals with diabetic foot ulcers are substantially less frequent than in individuals with ischemia without diabetes.[19]

In the absence of symptoms, these patients may present late, and as a result, vascular intervention is often considered too late in the progress of a diabetic foot lesion. It is reported that 30% to 50% of individuals with diabetes and foot ulcers already have gangrene (a score of 4-5 on the Wagner scoring system) when the question of revascularization is raised, and these patients are, therefore, considered unsuitable for this intervention.[20]

The perspective of the present study was to intervene in an earlier phase to achieve ulcer healing, and thereby reduce the risk of amputation. To address the problem of late presentation, noninvasive vascular testing, such as toe pressure and ankle pressure, has been suggested as a screening for the need of earlier vascular intervention because the findings in such testing has been shown to be related to the outcome of diabetic foot ulcers.[7,9] The level of ankle and toe pressure as inclusion criteria, in the presence of an ulcer, in our study, were defined according to previous studies of diabetic foot ulcers as they relate to the risk of amputation.[1,9]

In our study, the healing rate without major amputation was 72% among survivors. In 13% of patients, a major amputation could not be avoided. Comparisons between studies are difficult due to differences in design, setting, patient selection, definitions, follow-up time, and other confounding factors. In the limited number of studies, including patients with diabetes with ischemic or neuroischemic ulcers, the focus is on limb salvage after a specific intervention and they often include patients with and without diabetes, and with and without ulcers.[21-23] However, our results with regard to healing are similar to other published results,[5,24] where healing rates were 70% to 73%. The present study was not designed to assess limb salvage but rate of ulcer healing in all consecutively presenting patients with diabetes and an ischemic or neuroischemic ulcer. Higher healing rates have been reported in other studies in diabetic populations with both neuropathic and neuroischemic ulcers.[4,15,25]

In the present study, 56% of patients had no angiography or invasive vascular intervention (30% and 26%, respectively), most commonly due to comorbidity, poor general condition, and short life expectancy. Feasibility for angioplasty or reconstructive vascular surgery according to angiography was the limiting factor in 33% of cases after angiography. Although lack of walking capacity is not per se a contraindication for angiography, it was used as such due to our policy not to consider vascular inter-

vention if the patient had permanently lost the use of his limbs.

When compared to other studies, it has to be recognized that the present study was stopped with regard to recruitment when magnetic resonance angiography, computed tomography angiography, and subintimal angioplasty (recanalization) became routine procedures. Comparison with other studies is further hampered by the fact that most studies report outcome after a specific intervention.[20,21,26] The present study indicates that the window of opportunity for vascular intervention to achieve healing is strongly related to comorbidity and extent of tissue involvement at the time of intervention.

PTA, frequently multi-segmental (46%) and to the crural arteries (46%), was done in 27% of patients and reconstructive vascular surgery in 17%. In most cases, complications were related to comorbidity rather than the vascular intervention per se. This was in agreement with other studies.[6,20] However, we cannot compare the outcome of PTA vs vascular surgery in the present study, because, according to the design of the study, vascular surgery was performed in patients not feasible for PTA. In the extended follow-up of the bypass versus angioplasty in severe ischemia of the leg trial, 452 patients with severe PVD were followed up for up to 5 years; 42% of the patients were diabetic.[27] In patients who survived for at least 2 years, vascular surgery was associated with significant increase in subsequent overall survival. Furthermore, PTA had a higher early failure rate.[28]

An observation from the present study is that only a limited number of patients could be eligible for a randomized controlled trial comparing PTA with vascular surgery due to patients' comorbidity and the requirement of feasibility for both interventions in such a study.

In the present study, a multiple regression analysis showed a substantially higher probability for primary healing without major amputation after vascular intervention as compared to those who did not have such intervention. However, this finding is still to be confirmed by an interventional comparative study. Comorbidity (congestive heart failure and/or renal impairment), severity of PVD (ankle pressure $\leq$50 mm Hg), and extent of tissue involvement (Wagner grades 3-5 and multiple ulcers) were related to a low probability for primary healing. Presence of foot ulcers in individuals with diabetes has to be recognized as a sign of multiorgan disease. This is confirmed by a substantial number of studies and is further emphasized by the present findings.[5,16,29]

Some methodological issues need to be considered when evaluating the present cohort study. A potential negative selection bias has to be taken into account, because the patients were admitted to a university-based foot center, and no exceptions were made with regard to age, comorbidity, or expected survival, whereas it cannot be excluded that a few and possibly many superficial ulcers were treated in primary health care without the knowledge of the foot team. Definitions of outcome can be very complex, an issue that has been previously analyzed.[15] Patients in our study were divided into groups according to outcome; primary healing, minor amputation, major amputation, and death unhealed. In some studies, minor amputations are included in the group primarily healed.[5,24] In many health care systems, there are limited possibilities for following up patients until healing is achieved. The Swedish system, due to its geographic responsibilities and reimbursement system, makes it possible to follow up patients until a specific end point, irrespective of the care provider.[30] This may explain the present dropout rate of 5%. Our patients are comparable with regard to comorbidity and demographic data, but are somewhat older than patients in other studies regarding vascular intervention.[23,24,26]

In large cohort studies of patients with diabetes and foot ulcers, the outcome has been measured with regard to the possibility of primary healing (healing without amputation) or of avoiding major amputation at or above the ankle.[15,25] In some studies of patients with diabetes, about 10% to 15% (and sometimes as many as 30%) of patients who were considered not suitable for vascular surgery have been shown to heal without any amputation or without a major amputation, which is confirmed by the present findings.[1,13,25] As mentioned previously, studies with regard to vascular intervention, on the other hand, have focused on "limb salvage" and graft survival,[23,24,31] indicating a need to recognize and introduce decreased perfusion or impaired circulation as an indication for intervention in the diabetic foot to achieve and maintain healing and to avoid or delay a future amputation.[4,25,32,33]

In conclusion, comorbidity, severity of PVD, and extent of tissue involvement were the most important factors that negatively affected the probability of healing. Furthermore, the present study indicates the value of revascularization in patients with diabetes with neuroischemic or ischemic ulcers to achieve healing. A higher primary healing rate was seen in those who had vascular intervention.

This study was supported by grants from the Research Funds Malmö University Hospital, the Skåne Research Foundation and Thelma Zoega's Foundation, Helsingborg, Sweden. The authors express their gratitude to M.-B. Johansson, I. Dupros, G. Larsson, Å. Asmundsson, L. K. Bengtsson, and M. Jonsson for their help by providing data for the database, and S. Gershater for providing data management support.

AUTHOR CONTRIBUTIONS

Conception and design: JA, JT
Analysis and interpretation: JA, TE, JL, PN, JT
Data collection: JA, JL, ML, JT
Writing the article: JA, TE
Critical revision of the article: JA, TE, JL, ML, PN, JT
Final approval of the article: JA, TE, JL, ML, PN, JT
Statistical analysis: PN, JT
Obtained funding: JA, JT
Overall responsibility: JA

REFERENCES

1. International Working Group. On the diabetic foot: international consensus on the diabetic foot and practical guidelines on the management and the prevention of the diabetic foot. Amsterdam, The Netherlands, on CD-ROM (http://www.idf.org/bookshop); 2007.
2. Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. Lancet 2005;366:1719-24.
3. Marston WA, Davies SW, Armstrong B, Farber MA, Mendes RC, Fulton JJ, et al. Natural history of limbs with arterial insufficiency and chronic ulceration treated without revascularization. J Vasc Surg 2006; 44:108-14.
4. Prompers L, Huijberts M, Apelqvist J, Jude E, Piaggesi A, Bakker K, et al. High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study. Diabetologia 2007;50:18-25.
5. Alexandrescu V, Hubermont G, Philips Y, Guillaumie B, Ngongang Ch, Coessens V, et al. Combined primary subintimal and endoluminal angioplasty for ischaemic inferior-limb ulcers in diabetic patients: 5-year practice in a multidisciplinary 'diabetic-foot' service. Eur J Vasc Endovasc Surg 2009;37:448-56.
6. Faglia E, Dalla Paola L, Clerici G, Clerissi J, Graziani L, Fusaro M, 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.
7. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg 2007;45;Suppl S:S5-67.
8. Williams DT, Price P, Harding KG. The influence of diabetes and lower limb arterial disease on cutaneous foot perfusion. J Vasc Surg 2006;44: 770-5.
9. Apelqvist J, Castenfors J, Larsson J, Stenström A, Agardh CD. Prognostic value of systolic ankle and toe blood pressure levels in outcome of diabetic foot ulcer. Diabetes Care 1989;12:373-8.
10. Fontaine R, Kim M, Kieny R. [Surgical treatment of peripheral circulation disorders.] [Article in German] Helv Chir Acta 1954;21:499-533.
11. Armstrong DG, Lavery LA, Vela SA, Quebedeaux TL, Fleischli JG. Choosing a practical screening instrument to identify patients at risk for diabetic foot ulceration. Arch Intern Med 1998;158:289-92.
12. Apelqvist J, Torffvit O, Agardh CD. The effect of the non-ionic contrast medium iohexol on glomerular and tubular function in diabetic patients. Diabet Med 1996;13:487-92.
13. Kalani M, Apelqvist J, Blombäck M, Brismar K, Eliasson B, Eriksson JW, et al. Effect of dalteparin on healing of chronic foot ulcers in diabetic patients with peripheral arterial occlusive disease: a prospective, randomized, double-blind, placebo-controlled study. Diabetes Care 2003;26:2575-80.
14. Apelqvist J, Castenfors J, Larsson J, Stenström A, Persson G. Ketanserin in the treatment of diabetic foot ulcer with severe peripheral vascular disease. Int Angiol 1990;9:120-4.
15. Jeffcoate WJ, Chipchase SY, Ince P, Game FL. Assessing the outcome of the management of diabetic foot ulcers using ulcer-related and person-related measures. Diabetes Care 2006;29:1784-7.
16. Oyibo SO, Jude EB, Tarawneh I, Nguyen HC, Armstrong DG, Harkless LB, et al. The effects of ulcer size and site, patient's age, sex and type and duration of diabetes on the outcome of diabetic foot ulcers. Diabet Med 2001;18:133-8.
17. Apelqvist J, Bakker K, van Houtum WH, Schaper NC; International Working Group on the Diabetic Foot (IWGDF) Editorial Board. Practical guidelines on the management and prevention of the diabetic foot: based upon the International Consensus on the Diabetic Foot (2007) Prepared by the International Working Group on the Diabetic Foot. Diabetes Metab Res Rev 2008;24 Suppl 1:S181-7.
18. Karthikesalingam A, Holt PJ, Moxey P, Jones KG, Thompson MM, Hinchliffe RJ. A systematic review of scoring systems for diabetic foot ulcers. Diabet Med 2010;27:544-9.
19. Apelqvist J, Larsson J, Agardh CD. The importance of peripheral pulses, peripheral oedema and local pain for the outcome of diabetic foot ulcers. Diabet Med 1990;7:590-4.
20. 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.
21. Biancari F, Salenius JP, Heikkinen M, Luther M, Ylönen K, Lepäntalo M. Risk-scoring method for prediction of 30-day postoperative outcome after infrainguinal surgical revascularization for critical lower-limb ischemia: a Finnvasc registry study. World J Surg 2007;31:217-25; discussion 226-7.
22. Wölfle KD, Bruijnen H, Loeprecht H, Rümenapf G, Schweiger H, Grabitz K, et al. 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 2003;25: 229-34.
23. Zhu YQ, Zhao JG, Liu F, Wang JB, Cheng YS, Li MH, et al. Subintimal angioplasty for below-the-ankle arterial occlusions in diabetic patients with chronic critical limb ischemia. J Endovasc Ther 2009;16:604-12.
24. Jacqueminet S, Hartemann-Heurtier A, Izzillo R, Cluzel P, Golmard JL, Ha Van G, et al. Percutaneous transluminal angioplasty in severe diabetic foot ischemia: outcomes and prognostic factors. Diabetes Metab 2005;31(4 Pt 1):370-5.
25. Gershater MA, Löndahl M, Nyberg P, Larsson J, Thörne J, Eneroth M, et al. Complexity of factors related to outcome of neuropathic and neuroischaemic/ischaemic diabetic foot ulcers: a cohort study. Diabetologia 2009;52:398-407.
26. Faglia E, Mantero M, Caminiti M, Caravaggi C, De Giglio R, Pritelli C, et al. Extensive use of peripheral angioplasty, particularly infrapopliteal, in the treatment of ischaemic diabetic foot ulcers: clinical results of a multicentric study of 221 consecutive diabetic subjects. J Intern Med 2002;252:225-32.
27. Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FG, Gillespie I, et al. Bypass versus angioplasty in severe ischaemia of the leg (BASIL) trial: an intention-to-treat analysis of amputation-free and overall survival in patients randomized to a bypass surgery-first or a balloon angioplasty-first revascularization strategy. J Vasc Surg 2010;51(5 Suppl):5S-17S.
28. Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FG, Gillespie I, et al. Bypass versus angioplasty in severe ischaemia of the leg (BASIL) trial: analysis of amputation free and overall survival by treatment received. J Vasc Surg 2010;51(5 Suppl):18S-31S.
29. Apelqvist J, Agardh CD. The association between clinical risk factors and outcome of diabetic foot ulcers. Diabetes Res Clin Pract 1992;18: 43-53.
30. Norlund A, Apelqvist J, Bitzén PO, Nyberg P, Scherstén B. Cost of illness of adult diabetes mellitus underestimated if comorbidity is not considered. J Intern Med 2001;250:57-65.
31. Conrad MF, Kang J, Cambria RP, Brewster DC, Watkins MT, Kwolek CJ, et al. Infrapopliteal balloon angioplasty for the treatment of chronic occlusive disease. J Vasc Surg 2009;50:799-805.
32. Armstrong DG, Lavery LA, Harkless LB. Validation of a diabetic wound classification system. The contribution of depth, infection, and ischemia to risk of amputation. Diabetes Care 1998;21:855-9.
33. Prompers L, Schaper N, Apelqvist J, Edmonds M, Jude E, Mauricio D, et al. Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE Study. Diabetologia 2008;51: 747-55.

Submitted Nov 4, 2010; accepted Feb 5, 2011.

Additional material for this article may be found online at www.jvascsurg.org.

SUPPLEMENTARTY INFORMATION (ONLINE ONLY)

Definitions. An ulcer was defined as a skin lesion with or without necrosis penetrating the full thickness of the dermis. Gangrene was defined as a continuous necrosis of the skin and underlying structures (muscle or bone) indicating irreversible damage that would be unlikely to heal without loss of some part of the extremity (Wagner grades 4-5).[1] Major gangrene (Wagner grade 5) was defined as a gangrene involving most of the foot.

Cardiovascular diseases. Hypertension, angina pectoris, myocardial infarction, congestive heart failure, nonischemic heart disease, and cerebrovascular disease were defined as previously described.[2] Diabetic retinopathy was recorded after retinal photography by an ophthalmologist. Diabetic nephropathy was considered present at persistent urine albumin >300 mg/L.[2]

Outcomes were classified as (1) primary healing, defined as healing without any amputation with intact skin for 6 months or intact skin at the time of death; (2) minor amputation, defined as amputation of one or more toes or some part of the foot at or below the ankle; (3) major amputation, defined as amputation above the ankle[3]; and (4) death unhealed, defined as death without healing with or without any amputation.

Sensory/motor neuropathy was defined as vibratory pressure threshold values ≥25V. Peripheral edema was considered present when swelling of the foot was so pronounced as to leave imprint after pressure by a finger. Deep foot infection (Wagner grade 3) included osteomyelitis/osteitis, deep foot abscess, and purulent soft tissue infection. All patients considered to have osteomyelitis had an open lesion fulfilling at least three of the following criterion: cellulitis, positive bacterial culture, radiological and/or scintigraphic evidence, and pathologic anatomic diagnosis.[4]

Rest pain was defined as severe persistent pain localized to the foot and relieved by lowering of the foot. Claudication was defined as recurrent cramping pain or tightness in the calf induced by exercise and relieved by rest.[5] Neuroischemic/ischemic ulcers were considered present at ankle pressure <80 mm Hg or toe pressure <45 mm Hg or at Wagner grades 4 to 5 if distal pressure was not obtained.[6]

MANAGEMENT/TREATMENT

The patients were treated as outpatients, but in case of deep infection associated with septic condition, foot surgery, amputations, vascular surgery, or exacerbation of intercurrent disease, they were treated as inpatients under the supervision of the foot team.

Patients were offered medical treatment to improve metabolic control and optimize treatment of comorbidity.[7] When needed, patients were also given supplementary nutrition and rehydration treatment.[8] When clinical signs of infection were present, oral treatment with antibiotics was provided, often according to ulcer microbiological culture or combining cephalosporin, quinolone, or metronidazole with dicloxacillin or clindamycin. Patients with deep abscess or acute osteomyelitis were hospitalized and intravenous antibiotics were used.[9] A differentiated program for analgesia was used related to cause and intensity of pain.

SURGICAL TREATMENT

Surgery was performed when deemed necessary by an orthopedic surgeon. Local surgical debridement of the lesions was performed when required. Whenever absence of infection and pain so allowed, dry necrosis was left to mummify. Incision and drainage were mandatory in case of a deep plantar abscess, and resection was performed in cases of osteitis/osteomyelitis not responding to antibiotic treatment.

Amputation was performed at the discretion of the orthopedic surgeon according to a preset protocol were indications were progressive gangrene, septic condition, and rest pain not responding to conservative treatment. A nonhealing ulcer was not considered as an indication for amputation. The level of amputation was chosen on clinical grounds as the most distal level possible where healing could be anticipated, the minimal requirement being intact skin with no signs of local infection or severe ischemia. The lowest level used for amputation was at the metatarsophalangeal level. All indications for amputation were recorded according to protocol. Resection of less than the distal phalanx was not considered an amputation.

OFF-LOADING

All patients were offered off-loading equipment adjusted to their individual needs. Protective or therapeutic shoes for indoor and outdoor use and individually fitted insoles were used in the majority of patients. In cases of plantar or heel ulcers, total contact casting was used when appropriate. Specially made orthotic appliances (orthoses) were used in cases of severe midfoot or ankle deformities. Off-loading by crutches or wheel chair was occasionally used.

TOPICAL TREATMENT

According to the individual wound bed condition, different topical treatments were prescribed in written form by the multidisciplinary team. Dressing changes were performed under supervision of a registered nurse in primary health care or home nursing services. The team maintained daytime telephone service for support 5 days a week. Most commonly used dressings were foam dressings, hydrofiber, hydrogels, silicon net, or hydrophobic gauze. Silver and Cadexomere iodine were used as topical antimicrobial agents when appropriate. External compression bandages or intermittent compression therapies were used in the presence of peripheral edema.[7]

REFERENCES

1. Wagner FW Jr. The dysvascular foot: a system for diagnosis and treatment. Foot Ankle 1981;2:64-122.
2. Apelqvist J, Agardh CD. The association between clinical risk factors and outcome of diabetic foot ulcers. Diabetes Res Clin Pract 1992;18:43-53.

3. Larsson J, Agardh CD, Apelqvist J, Stenstrom A. Long-term prognosis after healed amputation in patients with diabetes. Clin Orthop Relat Res 1998;350:149-58.
4. Colwell JA, Bingham SF, Abraira C, Anderson JW, Kwaan HC. V. A. Cooperative Study on antiplatelet agents in diabetic patients after amputation for gangrene: III. Definitions and review of design and baseline characteristics. Horm Metab Res Suppl 1985;15:69-73.
5. Cannon JA. Intermittent claudication. What it is and isn't. Calif Med 1965;102:301-5.
6. Apelqvist J, Castenfors J, Larsson J, Stenström A, Agardh CD. Prognostic value of systolic ankle and toe blood pressure levels in outcome of diabetic foot ulcer. Diabetes Care 1989;12:373-8.
7. Consensus. International Consensus on the Diabetic Foot and Practical Guidelines on the management and the Prevention of the Diabetic Foot. International Working Group on the Diabetic Foot; 2007 the Netherlands: Amsterdam; On CD-Rom (http://www.idf.org/bookshop); 2007
8. Eneroth M, Larsson J, Oscarsson C, Apelqvist J. Nutritional supplementation for diabetic foot ulcers: the first RCT. J Wound Care 2004;13:230-4.
9. Eneroth M, Larsson J, Apelqvist J. Deep foot infections in patients with diabetes and foot ulcer: an entity with different characteristics, treatments, and prognosis. J Diabetes Complications 1999;13:254-63.

Supplementary Table I. Reasons why angiography was not performed (n = 345)

	n	*%*
Sustained lack of walking capacity	74	21
Medical condition not allowing angiography	68	20
Signs of ulcer healing before angiography	47	13
Informed consent not given	44	13
Deceased	16	5
Major amputation performed before angiography	17	5
Other confounding reasons	41	12
Drop out	14	4
Unknown reasons	24	7

In cases where more than one reason was recognized, only the most important reason is mentioned.

Supplementary Table II. Levels of vascular reconstructions performed

Vascular reconstruction	*n = 190*	*%*
Aortobifemoral	8	4
Femorofemoral cross-over	3	1
Femoropopliteal[a]	36	20
Femoro-truncal	5	3
Femoro-ant. tibial	42	24
Femoro-post. tibial	14	9
Femoro-fibular	13	5
Femoro-pedal	30	13
TEA common femoral	25	9
Exploration	20	12

In 6 cases (1 with an aortobifemoral reconstruction and 5 with TEA) an additional distal procedure was performed.
TEA, thrombendarterectomy.
[a]All are below knee popliteal bypass.

Supplementary Table III. Reasons for not performing surgical or endovascular treatment after angiography (n = 297)

	N	*%*
Not feasible according to angiography	99	33
Vein graft not present[a]	33	11
Poor general condition	50	17
Consent not given	29	10
Healed ulcer	21	7
Location of ulcers[a]	17	6
Major amputation	4	1
Deceased	6	2
Unknown reasons	38	13

[a]In cases where PTA was not feasible.