Long-term prognostic factors after thrombolysis for lower limb ischemia

Monica Kuoppala, MD, Sofia Franzén, MD, Bengt Lindblad, MD, PhD, and **Stefan Acosta, PhD, MD,**
Malmö, Sweden

Objective: **This study assessed prognostic factors regarding long-term outcome for amputation and death among patients who underwent intra-arterial thrombolysis due to lower limb ischemia.**
Methods: **Consecutive patients with intra-arterial thrombolysis due to lower limb ischemia treated at the Department of Vascular Diseases, University Hospital of Malmö, between January 1, 2001, and December 31, 2005, were retrospectively reviewed. A multivariate Cox regression analysis was performed to determine independent predictors for amputation and death.**
Results: **A total of 220 intra-arterial thrombolysis procedures were performed in 195 patients (46% women). Median age was 73 years. Complete and partial thrombolysis was obtained in 41% and 38%, respectively. Hemorrhagic complications were documented in 33%, but only 6% (13 of 220) were interrupted. The amputation rate was 26% and mortality was 35% during a median follow-up of 32 months. Degree of lysis (hazard ratio [HR], 4.8; 95% confidence interval [CI], 2.4-9.7; $P < .001$), motor deficit at admission (HR, 4.0; 95% CI, 1.8-8.7; $P = .001$), foot ulcers (HR, 7.2; 95% CI, 2.2-23.4; $P = .001$), and ischemic heart disease (HR, 2.3; 95% CI, 1.1-4.8; $P = .024$) remained as independent factors associated with amputation. Renal insufficiency (HR, 2.4; 95% CI, 1.4-4.2; $P = .003$), ischemic heart disease (HR, 2.1; 95% CI, 1.2-3.7; $P = .007$), cerebrovascular disease (HR, 2.2; 95% CI, 1.2-4.0; $P = .009$), foot ulcers (HR, 3.2; 95% CI, 1.2-8.6; $P = .019$), and acute lower limb ischemia (HR, 3.4; 95% CI, 1.1-10.1; $P = .028$) remained as independent factors associated with mortality.**
Conclusions: **Thrombolysis is successful, with few major complications in most patients with lower limb ischemia. Patients with ischemic heart disease and foot ulcers are at higher long-term risk for both amputation and death. A lesser degree of lysis and motor deficit were associated with higher amputation rates. The presence of such negative prognostic factors may help clinicians to deny further invasive vascular treatment. Renal insufficiency, cerebrovascular disease, and acute lower limb ischemia were associated with increased mortality. (J Vasc Surg 2008;47:1243-50.)**

Patients with advanced vascular disease are increasingly being treated with endovascular techniques at the expense of a continuous decline in open surgery.[1] Most endovascular procedures can be performed under local anesthesia, which makes it possible to treat the most fragile patients.[2,3] Parallel to the rapid development of high-resolution imaging techniques, there has also been a clear shift towards increased diagnostic resources in both magnetic resonance (MR) and computed tomography (CT) angiographies before intervention in patients with acute lower limb ischemia.

Taken together, imaging-based catheter-directed thrombolytic therapy has evolved as the treatment modality of choice in patients with acute lower limb ischemia in our department. In contrast with open surgery, the level of occlusion and cause can be determined in a more detailed manner, and the locally dissolved clot can be cleared with less risk of injuring the sensitive underlying endothelium and occurrence of rethrombosis.[4]

Nevertheless, the Fogarty balloon-catheter thromboembolectomy device[5] may be preferable to use in patients with motor deficit to be able to rapidly remove the thromboembolic material and to achieve early reperfusion of severe ischemic areas. Thrombolysis can be followed by endovascular, open, or hybrid treatment, whereas open surgery seldom can be performed before thrombolysis. The main aim of the present study was to assess the long-term prognostic factors associated with leg amputation and death after local intra-arterial thrombolysis for lower limb ischemia.

From the Vascular Center, Malmö University Hospital.
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Correspondence: Dr Stefan Acosta, Vascular Center, Malmö University Hospital, S205 02 Malmö, Sweden (e-mail: stefan.acosta@telia.com).
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METHODS

Setting. The Vascular Center, Malmö-Lund has a primary catchment population of approximately 756,000 inhabitants.[6] Patients requiring endovascular interventions, including intra-arterial thrombolysis, are all relocated to Malmö. The clinic also serves as a referral center for patients with complicated vascular disease from other hospitals within the regions in the southernmost part of Sweden. In 2002, there were 265,000 inhabitants in Malmö (128,000 men; 137,000 women).[6]

Study population. This study comprised all patients with lower limb ischemia who underwent intra-arterial thrombolysis between January 1, 2001, and December 31, 2005. The patients were identified in the prospective database for endovascular intervention. Of the 237 patients identified, 17 were excluded because of misclassification (n = 2), local thrombolysis in other arterial segments (n = 4), or double registration during the same thrombolysis (n =

11). There were 220 thrombolysis procedures remaining for further analysis.

Local intra-arterial thrombolysis. According to a local memo,[7] the presence of any absolute or relative contraindication for thrombolysis is checked. The absolute contraindications are the following risk factors for bleeding during thrombolysis: operation or organ biopsy ≤2 weeks, cerebral infarction ≤6 weeks, cerebral metastasis, known arteriovenous cerebral malformations, and epidural catheter or puncture of the dura ≤3 days.

A number of predetermined blood tests are taken immediately before thrombolysis, including levels of creatinine, hemoglobin, aspartate aminotransferase, alanine aminotransferase, bilirubin, lactate dehydrogenase, activated partial thromboplastin time (APTT), prothrombin complex, and platelet count. A prothrombin complex value >1.5 international normalized ratio (INR) is generally not accepted before arterial puncture. A patient will not be treated with thrombolysis if no patient bed is available in the intensive care unit (ICU).

Any prior MR or CT imaging of the patient's vascular tree is scrutinized. Arterial puncture is performed in the common femoral artery in the nondiseased leg, and a long thrombolysis catheter, equipped with multiple side holes, is advanced to the diseased leg and positioned in the occlusion to be able to deposit high concentrations of lytic agent. Infusion of alteplase (Actilyse; Boehringer Ingelheim, Stockholm, Sweden), a recombinant tissue plasminogen activator (rt-PA), commences at the ICU, with repeated measurements of coagulation status throughout the treatment. Initially, a dosage of 1 to 2 mg/h is administered during the first 4 hours, followed by 0.5 to 1 mg/h, depending on the age and extent of the occlusion, the degree of ischemia, and the patient's age. Parallel with this, heparin (Heparin Leo, LEO Pharma, Malmö, Sweden) is first given as a bolus dosage of 5000 IU and then continuously through the side hole of the introducer, which is placed with its tip above the occlusion. The heparin infusion is adjusted according to APTT values, which should be two to three times above the reference value during therapy.

Retrieval of patient data. Apart from prospectively collected data from the endovascular database, data were retrieved from patient records at the clinics of emergency care, internal medicine, surgery, orthopaedics, neurology, and the ICU. All patients registered in the municipality of Malmö entered the epidemiology analysis. Results from MR, CT, and angiography/thrombolysis were scrutinized.

Follow-up. All patients were monitored from the day of thrombolysis until death or January 24, 2007. Median follow-up time was 32 months. Information about amputations was retrieved from case records from the Departments of Orthopaedics in Malmö-Trelleborg, Lund, Ystad, Helsingborg, Kristianstad, Karlskrona, Karlshamn, Kalmar, and Växjö. In addition, a senior orthopedic surgeon provided us with data from his personal on-going amputation register in Lund. Four patients lived in cities in the middle part of Sweden, and their amputation status could not be evaluated, either through denial of medical records or uncertainties about the follow-up hospital. Follow-up mortality data were retrieved from the Swedish Population Registry.

The analysis of long-term outcome in terms of leg and patient survival encompassed all primary amputations and deaths, respectively, occurring between the date of thrombolysis and end of follow-up. The causes of deaths were obtained from the National Board of Health and Welfare. Information on mortality was not possible to achieve in one patient living in the United States. This study was approved by the Research Ethics Committee at the University of Lund.

Definitions. Hypertension was defined as systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg, or both, on at least two different occasions. Hypertension was also considered if the patient previously had been diagnosed with hypertension or was taking antihypertensive medication. Cerebrovascular disease was considered if there was a history of stroke (cerebral bleeding or infarction) or transient ischemic attack (TIA). Other vascular disease was present if the patient had any history of ischemic heart disease, cerebrovascular disease, or aortic aneurysm or dissection. This definition also included patients who received antiplatelet drugs or lipid-lowering agents. Ischemic heart disease was considered if there was a history of myocardial infarction, angina pectoris, coronary artery bypass graft, or percutaneous coronary angioplasty. Diabetes mellitus was noted if the patient had antidiabetic treatment with diet, oral hypoglycemic agents, or insulin. Smoking included both current and former tobacco smokers. Hemoglobin (Hb) and creatinine levels at admission were analyzed. Anemia was defined as Hb <134 g/L in men and <117 g/L in women, and renal insufficiency was present if serum creatinine reached levels >105 μmol/L in men and >90 μmol/L in women.

Acute ischemia in the lower limb was defined as a sudden decrease in or deterioration of limb perfusion causing a potential threat to viability of the extremity.[8] Duration of symptom was counted in hours from the time of onset to the start of thrombolysis. Degree of lysis was stated as complete, partial, lysis but no run-off, or no lysis.[9]

Complementary procedures after thrombolysis were defined as endovascular (aspiration of thromboembolic material, percutaneous transluminal angioplasty, stenting), open (bypass grafting, thromboembolectomy, thromboendarterectomy, other vascular reconstruction), or hybrid (endovascular and open) interventions.

Statistical methods. Data management and statistical analysis were performed using SPSS 14.0 software (SPSS Inc, Chicago, Ill). Total and sex-specific incidence rates of thrombolysis were determined by the number of thrombolysis and were expressed as number of cases per 100,000 person-years. The 2002 Malmö population was used as reference population. Confidence intervals (CI) were calculated from the formula for normal approximation ($n \pm 1.96\sqrt{n}$). Differences in proportions were evaluated using

Table I. Patient characteristics and comorbidities

Variable	*No. (%) or mean (IQR)*
Age, years	73 (62-80)
Sex	
Male	118 (54)
Female	102 (46)
Comorbidity	
Hypertension	166/218 (76)
Smoking	143/191 (75)
Diabetes mellitus	49/220 (22)
Ischemic heart disease	74/219 (34)
Cerebrovascular disease	39/219 (18)
Atrial fibrillation	68/218 (31)
Anemia	63/210 (30)
Renal insufficiency	84/213 (39)
Medication	
β-Adrenoceptor antagonists	72/219 (33)
ACE inhibitors	45/219 (21)
Lipid-lowering agents	71/219 (32)
Antiplatelet drugs	123/219 (56)
Warfarin	35/220 (16)

ACE, Angiotensin-converting enzyme; *IQR,* interquartile range.

the χ^2 test, or when using an ordinal variable such as degree of lysis, the Kendall τ-b test was used.

Age, ankle-brachial pressure index, duration of symptoms and thrombolysis, and total dosage of alteplase and heparin were expressed as median and interquartile range (IQR), and comparisons between groups were made with the Mann-Whitney *U* test. Leg and patient survival was analyzed according to the Kaplan-Meier method. Variables associated with amputation or death during follow-up were further tested in a multivariate Cox regression model, with all variables entered into the model. Significant associations were expressed in terms of hazard ratios (HR) with 95% CI; and $P < 0.05$ was considered significant.

RESULTS

Incidence of thrombolysis. During the 5-year study period, 220 intra-arterial thrombolytic interventions were performed in 195 patients, of which 15 patients received thrombolysis more than once (1 patient, 6 times; 2 patients, 4; 2 patients, 3; and 10 patients, 2 times). Thrombolysis was administered to 87 patients (40 men, 47 women) registered in the municipality of Malmö. The overall incidence of thrombolysis in Malmö due to lower limb ischemia was estimated to be 6.6 (95% CI, 5.2-8.0) per 100,000 person-years. The incidence for men and women was 6.2 (95% CI, 4.3-8.2) and 6.9 (95% CI, 4.9-8.8) per 100,000 person-years, respectively. The highest incidence rates per 100,000 person-years were found in the age category 75 to 84 years; overall, 41.8 (95% CI, 28.7-54.8); men, 50.9 (95% CI, 27.4-74.3); and women, 36.2 (95% CI, 20.7-51.7).

Patients. The median age in the study population was 73 years (IQR, 62-80 years), with 75 years for women and 71 years for men ($P = .10$). The burden of cardiovascular risk factors in the study patients are listed in detail in Table I. In all, 123 patients at admission were receiving antiplatelet drug therapy, including acetylsalicylic acid in 109, clopidogrel in 21, and dipyridamole in one. Vascular disease other than peripheral arterial insufficiency in the legs was found in 167 of 220 patients (76%).

Table II. Symptoms and clinical findings before thrombolysis

Variable	*Total No.*	*No (%) or mean (IRQ)*
Symptoms		
Previous claudication	208	112 (54)
Symptom duration, hours		
All	197	72 (26-168)
Acute ischemia	160	67 (24-149)
Nonacute ischemia	31	144 (48-744)
Clinical findings		
Foot ulcer	218	27 (12)
Heel ulcer	218	8 (4)
Motor deficit	192	44 (23)
Sensory deficit	193	108 (56)
ABPI index	174	0.0 (0.0-0.26)
Acute ischemia	212	167 (79)

ABPI, Ankle-brachial pressure index; *IQR,* interquartile range.

Symptoms and clinical findings at admission. The median time from onset of symptoms to start of thrombolysis was 67 hours for patients with acute leg ischemia and 144 hours for those with nonacute leg ischemia ($P = .001$). In patients with acute leg ischemia, symptom duration was 58 hours in patients with motor deficit and 72 hours in those without motor deficit ($P = .47$). Patients with diabetes mellitus had a higher prevalence of foot ulcer (29% [14 of 48]) compared with all study patients ($P < .001$). The spectrums of clinical findings are summarized in Table II.

Nature of the occlusions. Duplex ultrasound (DUS), and MR and CT angiographies were performed in 28% (61 of 218), 10% (22 of 220), and 3% (7 of 220), respectively, of the patients before thrombolysis. In patients with leg ischemia and motor deficit, DUS and CT angiography were performed in 10 and two cases, respectively. The nature of the acute occlusions is reported in Table III. Acute thromboembolic occlusions in native vessels occurred in 139 cases and were located in the infrarenal aorta in 2, common iliac artery in 9, external iliac artery in 9, common femoral artery in 12, profunda femoral artery in 7, superficial femoral artery in 45, popliteal artery in 45, tibioperoneal trunk in 2, anterior tibial artery in 5, peroneal artery in 1, and posterior tibial artery in 2.

Thrombolysis. The median duration of thrombolysis was 19 hours (IQR, 16-31 hours) in case of thrombosis and 20 hours (IQR, 14-33 hours) for embolus ($P = .89$). Six patients received thrombolysis for >48 hours. The median dosage of alteplase was 21.2 mg (IQR, 16.0-29.0 mg) in case of thrombosis and 18.9 mg (IQR, 13.8-26.1 mg) for embolus ($P = .14$). According to the radiologists' descriptions and conclusions at completion angiogram, 80% (170 of 213) of the thrombolysis succeeded in complete or partial lysis (Table III). Regional thrombolysis with the help of the heart–lung machine was performed in three

Table III. Nature of the occlusions and thrombolysis characteristics

Variable	*Total No.*	*No. (%) or mean (IRQ)*
Etiology	220	
Embolus		61
Thrombus		148
Uncertain		11
Occluded venous graft	219	9 (4)
Occluded synthetic graft	219	58 (26)
Occluded stent/stent graft	217	15 (7)
Popliteal aneurysm	218	15 (7)
Thrombolysis		
Duration, hours	212	20 (16-32)
Dosage of alteplase, mg	211	20.5 (15.7-28.6)
Dosage of heparin, IU	198	19400 (13900-26800)
Degree of lysis		
Complete lysis	213	88 (41)
Partial lysis	213	82 (38)
No lysis	213	30 (14)
Lysis, but no run-off	213	13 (6)
Ad mortem	220	2 (1)
Supplementary interventions	220	164 (75)
Open		29
Endovascular		112
Hybrid		23

IQR, Interquartile range.

cases.[10] Thrombolysis of thromboembolic complications due to popliteal aneurysm was followed by successful bypass operations in 11 cases. Diabetes mellitus was associated with a lesser degree of lysis ($P = .002$). The quantity of complementary procedures to thrombolysis is specified in Table III. In all, endovascular treatment without need for open surgery was performed in 167 cases (76%).

Complications and early failures of thrombolysis. During thrombolysis, two patients died, respectively, of cerebral hemorrhage and acute myocardial infarction. It was not possible to complete the thrombolytic treatment as planned in four patients due to unavailable beds at the ICU. The frequency of bleeding complications was 33%, but only 13 of 220 (6%) thrombolysis resulted in premature interruption of ongoing treatment. In 66 patients (30%), no or insufficient effect of the endovascular treatment resulted in open surgery in 38, in-hospital amputation in 25, and three deaths at the ICU after leg ischemia without any complementary action taken. The duration of thrombolysis ($P = .30$) and the dosage of heparin ($P = .43$) were not associated with bleeding complications, whereas the dosage of alteplase ($P = .041$) was related to bleeding complications.

Factors associated with amputation during follow-up. Median follow-up was 32 months, during which 57 of 216 (26%) thrombolysis resulted in amputation of the ischemic leg. The amputations were above knee in 19, ex-articulation of the knee in 5, below knee in 27, and toe in 6. In 12 patients, a reamputation at a higher level was required, resulting in amputations above the knee in 7, ex-articulation of the knee in 1, below the knee in 3, and metatarsal in 1. Duration of symptoms was not associated with amputation ($P = .60$). There was no difference in amputation rate at end of follow-up in 59 patients with suprainguinal vs 159 with infrainguinal arterial occlusion ($P = .10$).

Factors associated with amputation were motor deficit ($P < .001$), degree of lysis ($P < .001$), diabetes mellitus ($P < .001$), presence of foot ulcers ($P = .001$), thrombotic occlusion ($P = .002$), sensory deficit ($P = .004$), ischemic heart disease ($P = .007$), female gender ($P = .008$), anemia ($P = .012$), fasciotomy in the lower leg due to compartment syndrome ($P = .018$), and renal insufficiency ($P = .02$; Table IV). When these 11 variables were included in a multivariate Cox regression analysis, degree of lysis (HR, 4.8; 95% CI, 2.4-9.7; $P < .001$), motor deficit (HR, 4.0; 95% CI, 1.8-8.7; $P = .001$), presence of foot ulcer (HR, 7.2; 95% CI, 2.2-23.4; $P = .001$), and ischemic heart disease (HR, 2.3; 95% CI, 1.1-4.8l; $P = .024$;) remained as independent factors associated with amputation.

At time of admission to the hospital, the median level of C-reactive protein (CRP) was 26 mg/L in 53 patients who underwent amputation compared with 9 mg/L in 129 who did not ($P = .001$). The highest concentration of lactate in plasma registered per patient (lactate max) during thrombolysis was not associated with amputation ($P = .10$). Hemorrhagic complication during thrombolysis was related to a lower amputation rate ($P = .027$). Fig 1 illustrates amputation-free survival.

Factors associated with in-hospital mortality. There were 11 in-hospital deaths. Factors associated with in-hospital mortality after testing the 22 variables stated in Tables IV to VI were degree of lysis ($P < .001$), renal insufficiency ($P = .007$), cerebrovascular disease ($P = .014$), and motor deficit ($P = .036$). When all four variables were included in a multivariate Cox regression analysis, degree of lysis (HR, 1.2; 95% CI, 2.7-63.8; $P = .001$) and renal insufficiency (HR, 5.4; 95% CI, 1.1-26.6; $P = .039$) remained as independent factors associated with death.

Factors associated with death during follow-up. In all, 77 of 219 patients (35%) died during follow-up. In 31 thrombolysis (14%), lower limb ischemia was considered either as primary or contributory cause of death. According to death certificates, 40 patients (53%) died as a consequence of cardiovascular event, and six patients died of lung cancer. Duration of symptoms was not associated with mortality ($P = .20$). There was no difference in the mortality rate at end of follow-up in 59 patients with suprainguinal vs 159 with infrainguinal arterial occlusion ($P = .60$). Factors associated with mortality during follow-up were ischemic heart disease ($P = .001$), motor deficit ($P = .003$), age ≥80 years ($P = .003$), acute ischemia ($P = .007$), renal insufficiency ($P = .008$), cerebrovascular disease ($P = .008$), medication with warfarin ($P = .010$) and presence of foot ulcers ($P = .027$; Table V).

When all eight variables were included in a multivariate Cox regression analysis, renal insufficiency (HR, 2.4; 95% CI, 1.4-4.2; $P = .003$), ischemic heart disease (HR, 2.1; 95% CI, 1.2-3.7; $P = .007$), cerebrovascular disease (HR, 2.2; 95% CI, 1.2-4.0; $P = .009$), presence of foot ulcer

Table IV. Factors associated with amputation during follow-up after thrombolysis

Factor	*Proportion, No. (%)*	*Amputation, No. (%)*	P
All thrombolysis	220	57/216 (26)	
Comorbidity			
Age ≥ 80 years	64/220 (29)	13/62 (21)	.25
Woman	102/220 (46)	35/100 (35)	.008
Diabetes mellitus	49/220 (22)	23/49 (47)	<.001
Ischemic heart disease	74/219 (34)	27/72 (38)	.007
Warfarin	35/220 (16)	13/35 (37)	.12
Cerebrovascular disease	39/215 (18)	12/39 (31)	.46
Anemia	63/210 (30)	23/62 (37)	.013
Renal insufficiency	83/213 (39)	28/81 (35)	.02
Degree of ischemia			
Foot ulcer	27/214 (22)	14/27 (52)	.001
Motor deficit	44/192 (23)	24/44 (55)	<.001
Sensory deficit	107/193 (55)	36/106 (34)	.004
Acute ischemia	166/212 (78)	43/164 (26)	.88
Etiology			
Thrombosis	148/209 (71)	47/145 (32)	.002
Native artery occlusion	139/219 (63)	35/135 (26)	.80
Occluded venous graft	9/219 (4)	3/9 (33)	.64
Occluded synthetic graft	58/219 (26)	19/57 (33)	.17
Popliteal aneurysm	15/218 (7)	5/14 (36)	.42
Degree of lysis			
Complete lysis	88/213 (41)	14/88 (16)	
Partial lysis	82/213 (38)	15/79 (19)	
Lysis, but no run-off	13/213 (6)	9/13 (69)	
No lysis	30/213 (14)	16/29 (55)	<.001
Complementary interventions	164/220 (75)	43/161 (27)	.86
Complications			
Bleeding	72/220 (33)	12/71 (17)	.027
Distal embolization	26/220 (12)	5/25 (20)	.44
Fasciotomy (compartment syndrome)	9/220 (4)	5/8 (62)	.018

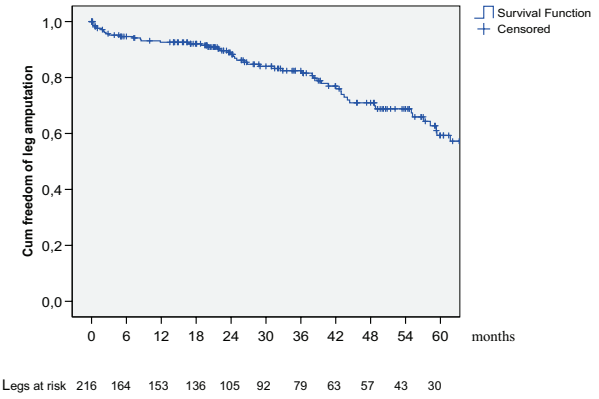

Fig 1. Amputation-free survival after thrombolysis for lower limb ischemia. Numbers below time axis denote patients at risk at the respective time point. The *tick marks* indicate censored data.

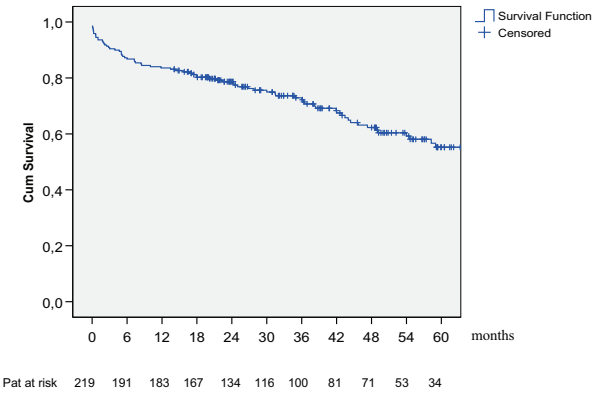

Fig 2. Long-time survival after thrombolysis for lower limb ischemia. Numbers below time axis denotes patients at risk at respective time point. The *tick marks* indicate censored data.

(HR, 3.2; 95% CI, 1.2-8.6; $P = .019$), and acute ischemia (HR, 3.4; 95% CI, 1.1-10.1; $P = .028$) remained as independent factors associated with mortality.

At time of admission to the hospital, the median level of CRP was 25 mg/L in 62 patients who subsequently died during follow-up vs 9 mg/L in 119 who survived ($P < .001$). Lactate max in patients who died was 1.3 mmol/L in 64 compared with 1.1 mmol/L in 131 of those who did not ($P = .027$). Amputation was associated with higher mortality rate ($P = .005$). Fig 2 illustrates long-term survival.

Factors associated with late adverse outcome in terms of either amputation or death. The amputation-free survival rate during follow-up was 51% (111 of 217). When the 11 variables associated with either amputation or mortality, in the univariate analysis (Table VI), were included in a multivariate Cox regression analysis, degree of

Table V. Factors associated with mortality during follow-up after thrombolysis

Factor	*Proportion, No. (%)*	*Death, No. (%)*	P
All thrombolysis	220	77/219 (35)	
Comorbidity			
Age ≥ 80 years	64/220 (29)	32/64 (50)	.003
Woman	102/220 (46)	35/101 (35)	.88
Diabetes mellitus	49/220 (22)	18/49 (37)	.79
Ischemic heart disease	74/219 (34)	37/74 (50)	.001
Cerebrovascular disease	39/218 (18)	21/39 (54)	.008
Warfarin	35/220 (16)	19/35 (54)	.010
Anemia	63/210 (30)	25/63 (41)	.40
Renal insufficiency	83/213 (39)	38/83 (48)	.008
Degree of ischemia			
Foot ulcer	28/218 (13)	15/28 (54)	.027
Motor deficit	44/192 (23)	23/44 (52)	.003
Sensory deficit	107/193 (55)	41/107 (38)	.068
Acute ischemia	166/212 (78)	65/166 (40)	.007
Etiology			
Thrombosis	148/209 (71)	46/146 (32)	.15
Native artery occlusion	139/219 (63)	45/138 (33)	.27
Occluded venous graft	9/219 (4)	3/9 (33)	.90
Occluded synthetic graft	58/219 (26)	24/57 (42)	.21
Popliteal aneurysm	15/218 (7)	2/14 (15)	.089
Degree of lysis			
Complete lysis	88/213 (41)	31/88 (35)	
Partial lysis	82/213 (38)	25/82 (30)	
Lysis, but no run-off	13/213 (6)	3/13 (23)	
No lysis	30/213 (14)	14/29 (48)	.28
Complementary interventions	164/220 (75)	55/163 (34)	.45
Complications			
Bleeding	72/220 (33)	25/71 (35)	.99
Distal embolization	26/220 (12)	9/26 (35)	.95
Fasciotomy[a]	9/220 (4)	1/9 (11)	.12

[a]Compartment syndrome.

lysis (HR, 2.6; 95% CI, 1.6-4.4; $P < .001$), motor deficit (HR, 2.5; 95% CI, 1.5-4.1; $P < .001$), renal insufficiency (HR, 2.4; 95% CI, 1.5-4.04; $P = .001$), ischemic heart disease (HR, 2.1; 95% CI, 1.3-3.4; $P = .003$), and foot ulcers (HR, 3.2; 95% CI, 1.4-7.2; $P = .005$) remained as independent factors for late adverse outcome.

DISCUSSION

This large study population allowed evaluation of important factors associated with amputation and mortality during follow-up in patients receiving thrombolysis for lower limb ischemia. Ischemic heart disease was shown to be an independent risk factor for both amputation and mortality. The presence of ischemic heart disease may be seen as a marker for advanced generalized atherosclerosis, and its strong association with peripheral arterial occlusive disease is well documented.[11] In fact, to reduce the mortality rates after planned leg revascularization, it has been proposed to perform coronary angiography and subsequent myocardial revascularization in severe surgically correctable coronary artery disease before arterial reconstructions due to lower limb ischemia.[12] However, a better medical treatment and clearance of risk factors such as smoking[13] are of greater importance and more feasible in reducing manifestations of atherosclerotic disease in almost all patients. The present study showed, in similarity with other studies,[14] that there was a clear underuse of antiplatelet and lipid-lowering agents before admission among patients with lower limb ischemia and signs of general atherosclerosis.

The two main adverse events, amputation and death, have different risk factors associated with both early[9] and, as the present study has shown, late outcome after thrombolysis. Risk factor analysis is very seldom matched against a follow-up period longer than 1 year, and, in particular, long-term data on leg salvage are scarce. The reported limb salvage rate of 82% in one study[15] and up to 88% in other studies[9,16] at 1 year is within the range of our results, whereas the Kaplan-Meier curve in the present study shows a continuous decline towards a limb salvage rate of only 60% at 5 years. Motor deficit and presence of foot ulcer at admission, as well as degree of lysis, were independent factors associated with amputation, which is in accordance with the findings by Earnshaw et al.[9] The amputation rate among patients with diabetes mellitus receiving thrombolysis was as high as 47%, which seems to be highly associated with a lesser degree of lysis and the high prevalence of foot ulcers among diabetic patients. Hence, diabetic patients who have poor run-off and foot ulcers seem to be unsuitable candidates for thrombolysis.

The patients with motor deficit at admission need an urgent treatment either with thrombolysis or open revas-

Table VI. Factors associated with late adverse outcome in terms of either amputation or mortality during follow-up after thrombolysis

Factor	*Proportion, No. (%)*	*Amputation or death, No. (%)*	P
All thrombolysis	220	106/217 (49)	
Comorbidity			
Age ≥ 80 years	64/220 (29)	38/62 (61)	.020
Woman	102/220 (46)	53/100 (53)	.26
Diabetes mellitus	49/220 (22)	31/49 (63)	.022
Ischemic heart disease	74/219 (34)	49/73 (67)	<.001
Cerebrovascular disease	39/218 (18)	27/39 (69)	.004
Warfarin	35/220 (16)	24/35 (69)	.011
Anemia	63/210 (30)	39/62 (63)	.009
Renal insufficiency	83/213 (39)	54/83 (65)	<.001
Degree of ischemia			
Foot ulcer	28/218 (13)	21/27 (78)	.001
Motor deficit	44/192 (23)	33/44 (75)	<.001
Sensory deficit	107/193 (55)	57/106 (54)	.021
Acute ischemia	166/212 (78)	85/165 (52)	.13
Etiology			
Thrombosis	148/209 (71)	70/146 (48)	.96
Native artery occlusion	139/219 (63)	65/136 (48)	.62
Occluded venous graft	9/219 (4)	4/9 (44)	.78
Occluded synthetic graft	58/219 (26)	33/58 (57)	.16
Popliteal aneurysm	15/218 (7)	6/14 (43)	.63
Degree of lysis			
Complete lysis	88/213 (41)	35/88 (40)	
Partial lysis	82/213 (38)	35/80 (44)	
Lysis, but no run-off	13/213 (6)	10/13 (77)	
No lysis	30/213 (14)	20/29 (69)	.003
Complementary interventions	164/220 (75)	81/162 (50)	.56
Complications			
Bleeding	72/220 (33)	31/71 (44)	.29
Distal embolization	26/220 (12)	12/26 (46)	.77
Fasciotomy[a]	9/220 (4)	6/9 (67)	.28

[a]Compartment syndrome.

cularization. However, the long median time of 58 hours of severe lower limb ischemia in patients with motor deficit, witnesses of both a patient delay and a rather slow work-up, may reflect logistic organizational problems such as unavailable beds in the ICU for the purpose of thrombolysis or insufficient operative resources for surgical intervention.

Physician-caused delay was also identified, in that some patients with motor deficit were referred for inappropriate diagnostic imaging such as DUS and CT angiography studies before thrombolysis. The high-resolution CT and MR capabilities that are increasingly available are very useful and comfortable tools for physicians, if timely used, to outline the best treatment option for the patient. However, there is a risk to exaggerate the value of these imaging modalities and to further postpone treatment in patients with already severely compromised peripheral circulation. In patients with motor deficit, it may be better to operate on the patient immediately[17] and to perform an initial on-table angiogram instead of pursuing with diagnostic examination and late administration of thrombolysis. In addition, the present study showed that 24% of the thrombolytic events needed to be supplemented with open vascular surgery.

Interestingly, occurrence of bleeding complications during thrombolysis was associated with lower amputation rates in the present study. The occurrence of minor bleeding episodes, locally or distant, should not automatically equal discontinuation of thrombolysis. Hence, it may be important to accept minor bleeding complications during thrombolysis to be able to achieve the best possible limb perfusion and to prevent some amputations. Another center has reported a higher bleeding complication rate with a high-dose regimen of rt-PA, compared with our study, but was able to achieve a successful thrombolysis in 86% of the limbs.[18] Even though high-dose bolus therapy of rt-PA seems to accelerate thrombolysis without compromising outcome,[19] the risk of bleeding must be weighed against the risk of surgery in each patient.[20]

Renal insufficiency was a strong factor associated with death after thrombolysis in the present study. The administration of a contrast agent during angiographies may be a negative factor in this subgroup of patients. However, renal insufficiency is also clearly associated with poorer outcome in patients after open vascular surgery.[21] In addition, warfarin treatment was also associated with increased mortality, probably due to an increased burden of cardiovascular illnesses among these patients.

The limitations of the present study are attributed to its retrospective design. In a few patients, it was not possible to determine whether a patient had acute lower limb ischemia

according to the predefined criteria. The number of amputations may still be underestimated, even though we actively searched for available amputation data, because in-hospital registers for this variable are often deficient.[22]

CONCLUSION

Thrombolysis is often successful, with few major complications in most patients with lower limb ischemia. Patients with ischemic heart disease and foot ulcers are at higher long-term risk for both amputation and death. A lesser degree of lysis and motor deficit were associated with higher amputation rates. The presence of such negative prognostic factors may help clinicians to deny further invasive vascular treatment. Renal insufficiency, cerebrovascular disease, and acute lower limb ischemia were associated with increased mortality.

AUTHOR CONTRIBUTIONS

Conception and design: MK, SF, BL, SA
Analysis and interpretation: MK, SF, BL, SA
Data collection: MK, SF
Writing the article: MK, SF, BL, SA
Critical revision of the article: MK, SF, BL, SA
Final approval of the article: MK, SF, BL, SA
Statistical analysis: SA
Obtained funding: SA
Overall responsibility: SA

REFERENCES

1. Acosta S, Lindblad B, Zdanowski Z. Predictors for outcome after open and endovascular repair of ruptured abdominal aortic aneurysm. Eur J Vasc Endovasc Surg 2007;33:277-84.
2. Dias NV, Ivancev K, Malina M, Resch T, Lindblad B, Sonesson B. Does the wide application of endovascular AAA repair affect the results of open surgery? Eur J Vasc Endovasc Surg 2003;26:188-94.
3. EVAR Trial participants. Endovascular aneurysm repair and outcome in patients unfit for open repair of abdominal aortic aneurysm (EVAR trial 2): randomised controlled trial. Lancet 2005;365:2187-92.
4. Berridge DC, Kessel D, Robertsson I. Surgery versus thrombolysis for initial management of acute limb ischaemia. Cochrane Database Syst Rev 2002;1:1-24.
5. Fogarty TJ, Cranley JJ. Catheter technic for arterial embolectomy. Ann Surg 1965;161:325-30.
6. Region Skåne. Skåne i kartor och tabeller. Hämtad 30 april, 2007, från. http://www.skane.se/upload/Webbplatser/Statistik/Dokument/Befb-18-02.xls. Accessed Dec 18, 2007.
7. Gottsäter A, Mattiasson I. PM Trombolysbehandling. Kliniken för kärlsjukdomar Malmö-Lund, Universitetssjukhuset MAS, 2006.
8. Management of peripheral arterial disease (PAD). TransAtlantic Inter-Society Consensus (TASC). Section C: acute limb ischemia. Eur J Vasc Endovasc Surg 2000;19(suppl A):S115-43.
9. Earnshaw JJ, Whitman B, Foy C. National Audit of Thrombolysis for Acute Leg Ischemia (NATALI): clinical factors associated with early outcome. J Vasc Surg 2004;39:1018-25.
10. Greenberg R, Wellander E, Nyman U, Uher P, Lindh M, Lindblad B, Ivancev K. Aggressive treatment of acute limb ischemia due to thrombosed popliteal aneurysms. Eur J Radiol 1998;28:211-18.
11. Hertzer NR. Fatal myocardial infarction following lower extremity revascularization. Two hundred seventy-three patients followed six to eleven postoperative years. Ann Surg 1981;193:492-8.
12. Hertzer NR, Beven EG, Young JR, O'Hara PJ, Ruschhaupt WF 3rd, Graor RA, et al. A classification of 1000 coronary angiograms and results of surgical management. Ann Surg 1984;199:223-33.
13. Gottsäter A. Managing risk factors for atherosclerosis in critical limb ischaemia. Eur J Vasc Endovasc Surg 2006;32:478-83.
14. Barani J, Mattiasson I, Lindblad B, Gottsäter A. Suboptimal treatment of risk factor for atherosclerosis in critical limb ischemia. Int Angiol 2005;24:59-63.
15. Plate G, Jansson I, Forssell C, Weber P, Oredsson S. Thrombolysis for acute lower limb ischaemia-a prospective, randomised, multicentre study comparing two strategies. Eur J Vasc Endovasc Surg 2006;31:651-60.
16. Ouriel K, Skortell CK, DeWeese JA, Green RM, Francis CW, Azodo MV, et al. A comparison of thrombolytic therapy with operative revascularization in the initial treatment of acute peripheral arterial ischemia. J Vasc Surg 1994;19:1021-30.
17. Eliason J, Wainess R, Proctor M, Dimick J, Cowan J, Upchurch G, et al. A national and single institutional experience in the contemporary treatment of acute lower extremity ischemia. Ann Surg 2003;238:382-90.
18. Swischuk JL, Fox PF, Young K, Hussain S, Smouse B, Castaneda F, et al. Transcatheter intraarterial infusion of rt-PA for acute lower limb ischemia: results and complications. J Vasc Interv Radiol 2001;12:423-30.
19. Braithwaite BD, Buckenham TM, Galland RB, Heather BP, Earnshaw JJ. Prospective randomized trial of high-dose bolus versus low-dose tissue plasminogen activator infusion in the management of acute lower limb ischaemia. Thrombolysis Study Group. Br J Surg 97;84:646-50.
20. Braithwaite BD, Davies B, Birch PA, Heather BP, Earnshaw JJ. Management of acute leg ischemia in the elderly. Br J Surg 1998;85:217-20.
21. Maithel SK, Pomposelli FB, Williams M, Sheahan MG, Scovell SD, Campbell DR, et al. Creatinine clearance but not serum creatinine alone predicts long-term postoperative survival after lower extremity revascularization. Am J Nephrol 2006;26:612-20.
22. Apelqvist J, Larsson J. Towards less amputations in diabetic patients. Acta Orthop Scand 1995;66:181-92.

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