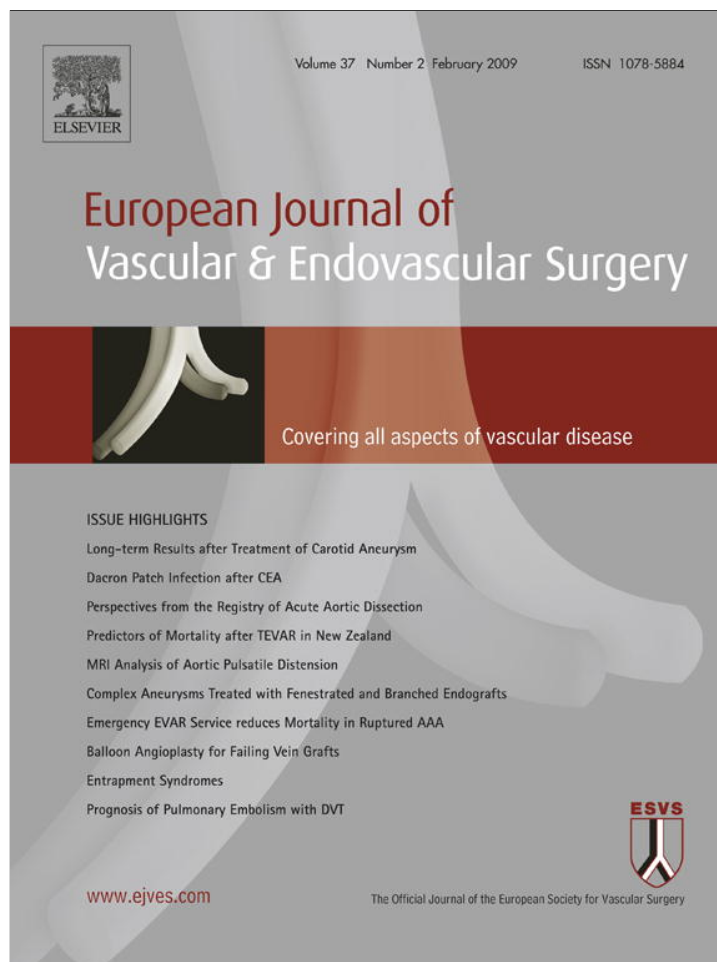


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When is Thrombolysis for Acute Lower Limb Ischemia Worthwhile?

G. Plate^{a,*}, S. Oredsson^a, J. Lanke^b

^a Department of Surgery, Central Hospital, SE-251 87 Helsingborg, Sweden

^b Department of Statistics, Lund University, Sweden

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KEYWORDS

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Abstract Objectives: To find variables associated with outcome following thrombolytic treatment for acute lower limb ischemia.

Design: Re-analysis of a prospective multicentre study.

Material and methods: One hundred and twenty-one patients with acute lower limb ischemia previously included in a randomised study comparing high- with low-dose thrombolysis were re-analysed ignoring the mode of lytic treatment. All possibly predictive variables were subjected to multivariate analyses to find associations with outcome.

Results: Previous successful thrombolysis, ankle–brachial index over 0.33, absence of motor dysfunction, presence of cardiac arrhythmia, and lysis of a vascular graft were all associated with successful thrombolysis ($p = 0.003$). Previous thrombolysis, age less than 70 years, and ankle–brachial index over 0.33 were all perfect predictors of absence of life-threatening complications or death. Successful lysis, age < 70, and lysis of a native artery as opposed to a vascular graft were all associated with clinical success (preserved patency, limb, and life) after one year ($p = 0.002$).

Conclusions: Previous thrombolysis, age under 70 years, and non-severe ischemia predict successful thrombolysis free from severe complications. Successful thrombolysis is strongly predictive of amputation-free survival with vascular patency for at least one year. Occluded grafts could often be reopened, but long-term outcome is better after thrombolysis of native arteries.

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Introduction

Thrombolysis has been used in the treatment of acute lower limb ischemia since the 1950s. Comparative analyses with other modes of treatment, e.g. anticoagulation treatment or surgical intervention, have produced conflicting results.^{1,2} Various refinements of technical details and

* Corresponding author. Tel.: +46 424061528; fax: +46 424061593.
E-mail address: gunnar.plate@skane.se (G. Plate).

a better patient selection have improved the outcome with all modes of treatment. Currently, thrombolytic treatment is generally recommended for acute or semi-acute cases without severe loss of sensory and motor function.^{3,4} Still, failed lysis and early or late recurrences are common despite adjunctive surgical and medical interventions.^{1,4-7} In addition, thrombolytic treatment is afflicted with risks of adverse events mostly related to bleeding but also to induced embolisation for instance from the heart. Hence, the preferable choice of treatment very much depends on expected success and risk of complications in the individual patient.

Most previous attempts to predict the outcome of thrombolytic treatment have consisted of retrospective analyses of the degree of thrombolysis and of early clinical results.⁸⁻¹⁴ Conclusions have been most variable depending upon a great diversity in thrombolytic agents and techniques used, definitions of radiological and clinical success, duration of follow-up and also due to the low accuracy of retrospective and univariate investigations usually employed.¹⁵

We have previously published a prospective, randomised, multicentre study comparing two well-established modes of thrombolysis (low-dose, end-hole infusion versus high-dose, pulse-spray infusion).¹⁶ This study failed to demonstrate a significant difference in outcome except for a lower incidence of re-interventions with the latter technique. The present study is an initially planned continuation of the previous investigation lumping the two treatment groups together in order to identify variables associated with successful or failed thrombolysis, severe complications, or a satisfactory clinical outcome. We have chosen not to include any analysis of mode of thrombolytic technique in the present communication, since this was extensively covered in the previous report.

Material and Methods

Setting

Four Swedish vascular centres at the county hospitals of Eskilstuna, Helsingborg, Västerås, and Växjö included the patients in a prospective randomised study performed during 1997–2000. The ethical committees of the Universities of Lund, Göteborg, Linköping, and Örebro, Sweden approved the study. The present, initially planned, re-analysis of the same patient material was performed at the Department of Surgery in Helsingborg in co-operation with the Department of Statistics at Lund University, Sweden.

Participants

One hundred and twenty-one patients with sudden onset of lower limb ischemia within 30 days were included. Presumed thrombotic and embolic occlusions of native arteries as well as vascular grafts were accepted if the proximal occlusion level was located distal to the aortic bifurcation. Patients with contra-indications to thrombolysis, urgent need for revascularisation, irreversible ischemia, and patients not amenable to follow-up were excluded (Table 1). The present

study comprises a re-analysis of all included patients ignoring the mode of thrombolysis initially employed. The demographic and clinical data of the patients are presented in Tables 2 and 3. The proximal occlusion level was located in the iliac arteries in 17 patients (14%), femoral arteries in 83 patients (69%), and in the popliteal or crural arteries in 21 patients (17%).

Objectives

To find variables associated with successful or failed thrombolysis, severe complications, as well as a good clinical outcome up to one year after the initial event.

Interventions

The techniques of angiography and thrombolysis in the two treatment groups are described in detail in the previous report.¹⁶ The adjunctive medical treatment and interventions provided are summarised in Table 4.

Outcomes

Successful thrombolysis was defined as removal of >75% of the thrombus with re-establishment of an antegrade flow through the previously occluded vascular segment as demonstrated on the completion angiogram. Failed thrombolysis was defined as removal of <25% of the thrombus without re-establishment of an antegrade flow. The remaining patients were considered to have partial thrombolysis.

Life-threatening complications included all severe and lethal complications occurring during the first month. In the presence of multiple complications, only the underlying or most important was registered. Minor bleedings were not considered as life-threatening.

A successful clinical outcome was defined as an amputation-free survival combined with at least secondary patency of the initially occluded vessel. This was analysed at one month and one year after the initial event.

Table 1 Exclusion criteria

Major surgery < 10 days
Haematuria < 10 days
Gastrointestinal bleeding < 10 days
Stroke < 3 months
Coagulopathy
Pregnancy
Brain tumour
Malignant hypertension
Dacron prosthesis implanted < 3 months
Graft infection
Contrast allergy
Irreversible ischemia
Life-expectancy < 30 days
Age < 18 years
Non-cooperative patient

Table 2 Demographic data

Variable	Number of patients
Age (mean; range)	72; 47–97
Female sex	58 (48%)
Smoking ^a	43 (36%)
Diabetes	20 (17%)
Heart disease	76 (63%)
Hypertension	43 (36%)
Cerebrovascular disease	23 (19%)
Hypertlipidaemia ^a	16 (13%)
Previous ipsi-lateral surgery	51 (42%)
Previous ipsi-lateral thrombolysis	13 (11%)
Occluded vessel = graft	35 (29%)
Occluded vessel = native artery	86 (71%)

^a Information missing in several patients.

Table 4 Adjunctive treatment

Treatment	Number of patients
Medical ^a	
Antiplatelet drugs	63 (61%)
Oral anticoagulation	38 (37%)
None	3 (3%)
Intervention	
PTA ^b	72 (60%)
Stenting	6 (5%)
Aneurysm exclusion ^c	2 (2%)
Endarterectomy ^d	1 (1%)

^a Information missing in 17 patients.

^b Percutaneous transluminal angioplasty.

^c Popliteal aneurysms.

^d Outflow in groin.

Statistical methods

Nineteen variables were considered potentially associated with successful or failed thrombolysis (Table 5). Nine of these were binary. Each of the other ten was dichotomised in all possible ways selecting the dichotomisation that had the best association to the evaluation variable (univariate analysis, Fisher's exact test). The 19 binary variables so obtained were used in logistic regression with backward elimination until all remaining variables had *p*-values < 0.05. The *p*-value of the final model can of course not be taken at face value, the model being the result of an extensive search among a large number of possible models. This was compensated for with another statistical method (permutation testing) to achieve a more reliable evaluation. This was performed by randomly permuting the values of the outcome variable among the patients, then repeating the whole selection and analysis procedure, and finally registering the *p*-value of the model so obtained. This was repeated 1000 times. The *p*-value of the permutation test is the fraction of repetitions that resulted in a more "significant" model than did the

analysis of the original data. The same statistical methods were used for the analysis of life-threatening complications and for clinical outcome. Two variables, degree of lysis and post-treatment prophylaxis, were added in the latter analyses.

Results

Overall outcome

Information on the degree of lysis is missing in two patients in whom a post-treatment angiogram was not obtained. Successful thrombolysis (>75% of the thrombus removed combined with antegrade flow) was accomplished in 86/119 patients (72%). Seventeen of 119 patients (14%) had partial thrombolysis and in 16/119 patients (13%) the thrombolysis failed (<25% lysis without antegrade flow).

Fifteen patients (12%) experienced life-threatening complications within one month (Table 6). Only two of them survived. The clinical outcomes after one month and one year are presented in Table 7.

Logistic regression (Table 8)

Degree of lysis

Previously performed thrombolysis was a perfect predictor of another successful thrombolysis. That is, all 13 patients who had previously received thrombolysis had a successful thrombolysis this time also. This variable and these 13 patients were then excluded from further analysis of predicting the degree of lysis.

Four other variables were highly predictive of successful thrombolysis: Ankle-brachial index > 0.33, no loss of motor function, presence of cardiac arrhythmia, and target vessel = occluded vascular graft (as opposed to a native artery). Permutation testing of this model revealed a *p*-value = 0.003.

Logistic regression for analysis of failed thrombolysis revealed only one variable with a *p*-value < 0.05 (loss of motor function). The permutation testing of this model gave a *p*-value = 0.25.

Table 3 Clinical data

Variable	Number of patients
Symptom:	
claudication	18 (15%)
Rest pain	92 (76%)
Tissue loss	11 (9%)
Duration:	
<1 day	29 (24%)
1–3 days	28 (23%)
4–7 days	32 (26%)
8–30 days	32 (26%)
Loss of motor function:	
none	76 (63%)
Mild	38 (32%)
Severe	6 (5%)
ABI ^a median (range).	0.1 (0–0.8)

^a Ankle-brachial index.

Table 5 Variables in logistic regression analysis

Age
Sex
Duration (of symptoms)
Presenting symptom (severity)
Previous (ipsi-lateral) vascular surgery
Previous (ipsi-lateral) thrombolysis
Smoking
Diabetes
Cerebrovascular disease
Heart disease
Cardiac arrhythmia
Hypertension
Ankle-brachial index
Limb coldness (proximal level)
Loss of sensation (severity)
Loss of motor function (severity)
Proximal level of occlusion
Occluded vessel (graft or native artery)
Guide-wire passage through thrombus
Post-treatment prophylaxis ^a
Degree of lysis ^a

^a For analysis of life-threatening complications and clinical outcome.

Life-threatening complications

Previously performed thrombolysis, age less than 70 years, and ankle-brachial index over 0.33 were all three perfect predictors of absence of life-threatening complications or death. The 61 patients who had either of these characteristics were then excluded from further analysis. The multivariate analysis of the remaining 60 patients disclosed only loss of motor function as predictive of life-threatening complications. The permutation testing of this model had a p -value > 0.06 .

Clinical success at one month

Five variables were highly predictive of a successful clinical outcome at one month: degree of lysis $> 75\%$, age < 70 years, claudication or rest pain without ulcer or gangrene, limb coldness only below the knee, and no previous vascular operation. Permutation testing of this model revealed a p -value < 0.001 .

Clinical success at one year

Three variables were highly predictive of a successful clinical outcome at one year: degree of lysis $> 75\%$, age < 70 years, and occluded vessel = native vessel (as opposed to a vascular graft). The permutation testing of this model had a p -value = 0.002.

Discussion

It is obvious that the outcome of thrombolytic treatment very much depends on the efficacy of the treatment, i.e. the ability to reopen the occluded vessel.¹ Supporting this, we recorded that successful thrombolysis correlated to clinical success for at least one year. It is therefore not surprising that many previous reports have focused on

Table 6 Life-threatening complications (one month)

Type	Number of patients
Cardiac	7 (6%)
Cerebrovascular	3 (2%)
Bleeding	3 (2%)
Other ^a	2 (2%)

^a Urosepsis and peritonitis, respectively.

factors associated with the immediate success of thrombolysis. As in our study, radiological success has usually been defined as removal of 70–95% of the thrombus material with creation of an antegrade flow of blood in the previously occluded graft or vascular segment. Associations with such radiological success have been recorded for location and extension of the occlusions, for vascular run-off, for duration and severity of the ischemia, and for several other variables.^{4,10,12,17} Some investigations have failed to find any parameters predicting successful thrombolysis.^{8,13,18} Most reports consist of a univariate analysis of a retrospectively collected material, which is generally considered as less reliable.¹⁵ We have found only four studies^{19–22} that include a multivariate analysis of variables considered possibly predictive of success or failure with thrombolytic treatment.

In 1994, Clouse et al.¹⁹ retrospectively analysed 82 patients treated with high-dose urokinase combined with angioplasty (11%) or surgery (47%). Their end point was a combination of radiological (antegrade flow) and clinical (clearance of symptoms for 30 days) success. They found only two variables (bad vascular run-off and presence of coronary artery disease) that possibly predicted outcome, basically clinical failure. This small study seems less conclusive mainly because of its retrospective nature.

In the same year, Ouriel et al.²⁰ reported on both uni- and multivariate analyses of predictors for clot dissolution using catheter-directed urokinase thrombolysis. As expected, the outcome of the univariate analysis differed from the multivariate analysis. Diabetes, catheter passage into the thrombus, guide-wire traversal through the thrombus (positive guide-wire test), number of segments thrombosed, and type of conduit maintained associations with the degree of lysis following multivariate analysis. Their results differ from ours, the reason for which is not obvious. Their inclusion criteria, thrombolytic agents used, study design, and statistical methods were slightly different, whereas the end points seem to have been similar.

Earnshaw et al.²¹ reported clinical factors associated with early outcome from a large national audit of thrombolysis for acute leg ischemia (NATALI). A total of 1133 thrombolytic events were included making this study most reliable. They started with univariate analysis and performed the multivariate analysis only on those variables that were significant. The main end point was amputation-free survival after 30 days. They found that a low amputation-free survival was associated with diabetes, increasing age, short-duration and severe ischemia. This fairly well agrees with our recorded predictors of early clinical success, except for thrombolytic outcome that was not included in their predictor analysis. They still

Table 7 Outcome

Outcome	1 month	1 year
Failure	16/119 (13%)	16/119 (13%)
Re-occlusion	16 (13%)	30 (25%)
Re-intervention	24 ^a (20%)	36 ^b (30%)
Secondary patency	83/108 (77%)	65/95 (65%)
Amputation	7 (6%)	15 (12%)
Death	13 (11%)	26 (21%)
Amputation-free survival	103 (85%)	84 (69%)
Clinical success ^c	83 (69%)	61 (50%)

Number of patients (%).

^a 30 procedures.

^b 50 procedures.

^c Amputation-free survival with at least secondary patency of target vessel.

considered that the best predictor of outcome is whether the procedure is successful or not. In a secondary analysis, they recorded female sex, ischemic heart disease, native vessel occlusion, and embolism as predictive of early death. This differs from our predictors of life-threatening complication. The reason for this is not clear, but the definitions of this end point were not the same.

In a most recent report, Kuoppala et al.²² retrospectively analysed prognostic factors for long-term clinical outcome (median follow-up of 32 months) in 195 consecutive patients treated with thrombolysis for acute as well as non-acute limb ischemia. Multivariate analysis, which was only performed in factors with significant outcome in the initial univariate analysis, revealed degree of lysis,

severity of ischemia, presence of foot ulcers, and ischemic heart disease as predictive of amputation. Presence of cardiac, renal, or cerebrovascular disease, foot ulcers, and acute ischemia predicted early or late death. It is not surprising that these results differ a great deal from our findings, since their study design, inclusion criteria, statistical methods, and end points were quite different. It is noteworthy from their study, that long-term survival seemed more related to co-morbidity, whereas limb salvage was more related to severity of ischemia and to therapeutic success. This agrees with the findings in the NATALI-study.²¹

McNamara and Fischer²³ already in 1985 recorded that thrombolytic treatment had a much greater chance of success when a guide-wire could be passed through the thrombus (positive guide-wire test). This finding was later corroborated by the multivariate analysis performed by Ouriel et al.²⁰ who recorded a better chance of success also when placement of the thrombolysis catheter into the thrombus was possible. In our study, we did not include patients in whom the catheter could not be passed into the thrombus but accepted patients with a negative guide-wire test. Our univariate analysis, which is not presented due to its inferior reliability, demonstrated a trend towards better lysis with a positive guide-wire test. Successful thrombolysis was achieved in 80% versus 63% ($p = 0.053$, Fisher's exact test). This association was not verified with the multivariate analysis. We now consider catheter placement within the thrombus as essential and a positive guide-wire test as indicative for successful thrombolysis. This conclusion is supported by the standards of practice presented by Rajan et al.⁴

Table 8 Results, logistic regression

Outcome	Predictive variables	Odds ratio	Permutation test
Successful thrombolysis ^a	Previous lysis	Perfect ^c	$p = 0.003$
	Ankle-brachial index > 0.33	5.04 ^d	
	No loss of motor function	5.10 ^d	
	Cardiac arrhythmia	8.97 ^d	
	Occluded vessel = graft	4.33 ^d	
Failed thrombolysis ^b	Loss of motor function	5.70	n.s.
Absence of life-threatening complication	Previous lysis	Perfect ^c	$p < 0.001$
	Age < 70 years	Perfect ^c	
	Ankle-brachial index > 0.33	Perfect ^c	
	No loss of motor function	21.5 ^d	
Clinical success, ^e one month	No ulcer or gangrene	38.6	$p < 0.001$
	Degree of lysis > 75%	19.9	
	Age < 70 years	8.11	
	Limb coldness only below knee	11.4	
	No previous vascular surgery	8.89	
Clinical success, ^e one year	Degree of lysis > 75%	8.95	$p = 0.002$
	Age < 70 years	4.37	
	Occluded vessel = native artery	4.78	

^a >75% of the thrombus with re-establishment of antegrade flow.

^b <25% of the thrombus without re-establishment of antegrade flow.

^c Perfect: all patients with this predictive variable had the noted outcome.

^d Patients with perfectly predicted outcome excluded.

^e Amputation-free survival with target vessel patency.

Gender and age do not seem to have a significant influence on the initial outcome of thrombolytic treatment.^{19–22} In our study, age was a strong predictor of clinical success free of complications, however (Table 8). This is supported by the large NATALI-study²¹ and several other reports,^{7,19,20} while Kuoppala et al.²² did not find any association between increasing age and long-term clinical outcome.

We did not find any association between smoking habits and the early or intermediate outcome of thrombolytic treatment. Smoking habits were not either recorded as predictive of outcome in any of the four multivariate analyses.^{19–22} We have found only one report of smoking as independently associated with failure of thrombolytic treatment.¹ Hence, no clear-cut conclusion can be drawn regarding the influence of tobacco use on the outcome of thrombolytic treatment.

From the Stile trial, Weaver et al.¹⁰ reported that diabetes was associated with a poor outcome following thrombolytic treatment. Two multivariate analyses support this concept.^{20,21} Our study did not reveal any association between diabetes and outcome following thrombolytic treatment. Also others have failed to find an association between diabetes and successful thrombolysis.^{7,13,19}

All our patients who had a history of previous (most probably successful) thrombolytic treatment experienced a successful lysis this time also. In comparison, thrombolysis was successful in 69% of patients who had not been treated with thrombolysis before. We have not found this association in any other report.

Most authors^{10,19–22} have reported a strong correlation between the severity of ischemia and clinical outcome with thrombolytic treatment. Limb viability is especially threatened in the presence of peripheral neurosensory deficits. This agrees with our findings (Table 8). Many patients with a greatly disturbed motor function are probably better treated with urgent surgical intervention. All patients with irreversible ischemia are best treated with primary amputation to decrease the risk of death.^{3,4}

Palfreyman et al.² performed a meta-analysis of randomised trials comparing surgery with thrombolytic treatment. Based on a sub-group analysis, they suggested better outcome in patients treated with thrombolysis if the duration of ischemia did not exceed 14 days. This basically supports the concept that thrombolytic treatment should be restricted to patients with acute ischemia.^{3,4} Only dealing with acute cases, Earnshaw et al.²¹ found that shorter duration of ischemia was associated with a decreased amputation-free survival after 30 days. Kuoppala et al.²² and Korn et al.¹² did not find any association between outcome and the duration of acute ischemia. This agrees with our findings. The reason for this discrepancy regarding the influence of duration of ischemia is not clear. Still, most authors agree that more chronic cases are less suited for thrombolytic treatment.^{3,4,22}

We recorded a greater chance for successful thrombolysis in patients with cardiac arrhythmia, which could indicate that emboli are better amenable for this treatment. Unfortunately, the presence of atrial fibrillation, which is a common cause for embolism, is generally considered as a relative contra-indication to thrombolytic treatment due to the risk of inducing more emboli. Actually, Earnshaw et al.²¹ reported a higher mortality in patients with

embolism. We could not confirm this in the present multivariate analysis, but two of our patients with chronic atrial fibrillation died from ischemic stroke.¹⁶ It seems preferable to perform surgical embolectomy in patients with presumed embolism from the heart to the extremities.^{1–4}

Although we did not analyse these variables, it is reasonable to assume that the outcome of thrombolytic treatment is dependent on the extension of thrombotic involvement and on the quality of vascular run-off. This concept is corroborated by several studies.^{17–20} DeMaiores et al.,⁸ Weaver et al.,¹⁰ and Korn et al.¹² recorded better outcomes for lysis of more proximal occlusions as compared to distal occlusions. No such association was recorded in the thorough radiographic analysis performed by Braithwaite et al.,¹⁸ in none of the multivariate analyses,^{19–22} or by us. It is therefore likely that more extensive thromboses and a bad run-off make thrombolytic treatment less successful whereas thrombus location has less impact on outcome.

Palfreyman et al.² demonstrated better outcomes following thrombolysis of graft occlusions as compared to native artery occlusions. Ouriel et al.²⁰ were more successful with initial lysis of prosthetic grafts and native arteries as opposed to vein grafts. Clouse et al.,¹⁹ Earnshaw et al.²¹ and Swischuk et al.¹³ did not find any significant differences in early results related to type of conduit. Contrary to their study, we noted significantly better thrombolytic success with prosthetic as well as venous grafts. Still, 66% of our native arteries were successfully thrombolysed. Many authors have observed that although vascular graft occlusions could be successfully reopened with thrombolysis, the recurrence rate is high, the need for additional procedures is great, and long-term patency is poor, especially with prosthetic grafts.^{7,9,11,14,24–26} This was confirmed in our study, in which patient with native artery occlusions had a better one-year clinical outcome than those with occluded vascular grafts (Table 8).

In conclusion, previous thrombolysis, age less than 70 years, and non-severe ischemia predict initially successful thrombolysis free from complications. Successful thrombolysis and age under 70 years are in turn strongly associated with clinical success. Catheter placement within the thrombus is essential, but a negative guide-wire test does not preclude successful lysis. Occluded vascular grafts could often be reopened, but long-term outcome is better after thrombolysis of native arteries. Sex and smoking habits barely affect outcome and neither did we find any obvious associations with co-morbidity.

Conflict of Interest

The authors have no conflict of interest.

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