National Audit of Thrombolysis for Acute Leg Ischemia (NATALI): Clinical factors associated with early outcome

Jonothan J. Earnshaw, DM, FRCS, Birgit Whitman, BA (Hons), and **Chris Foy, MSc, for the Thrombolysis Study Group**

Objective: **The National Audit of Thrombolysis for Acute Leg Ischemia (NATALI) database is a consecutive series of patients who underwent intra-arterial thrombolysis to treat acute leg ischemia in one of 11 centers in the United Kingdom. The purpose of the study was to analyze the factors associated with outcome after 30 days.**
Methods: **The data were collected over 10 years on standard pro formas, and registration was completed at the end of 1999. Since then, data from each unit have been verified and missing data included when available. Univariate and multivariate analyses were performed, with the outcomes of amputation-free survival (AFS), amputation with survival, and death.**
Results: **A total of 1133 thrombolytic events were included. Outcome results at 30 days for the entire group were AFS, 852 (75.2%); amputation, 141 (12.4%); and death, 140 (12.4%). Results for the entire group improved from the first half of the database, when AFS ranged from 65% to 75%, to almost 80% for the last few years of the study, although this was not statistically significant. Preintervention factors associated with lower AFS at multivariate analysis included diabetes ($P = .002$), increasing age ($P < .001$), short-duration ischemia ($P = .027$), Fontaine grade ($P = .001$), and ischemia with neurosensory deficit ($P = .004$). AFS was improved in patients receiving warfarin sodium at the time of the arterial occlusion ($P = .04$). Mortality was higher in women ($P = .006$) and in older patients ($P < .001$), and in patients with native vessel occlusion ($P < .001$), emboli ($P = .02$), or a history of ischemic heart disease ($P < .001$). Amputation risk was greatest in younger men ($P < .001$) and in patients with more severe ischemia ($P = .02$), graft occlusion ($P < .001$), or native vessel thrombotic occlusion ($P = .02$).**
Conclusion: **Experienced surgeons and radiologists can achieve an AFS of about 80% in selected patients with acute leg ischemia. Information from the NATALI database can be used in selection of an appropriate intervention in the individual patient. (J Vasc Surg 2004;39:1018-25.)**

Thrombolytic therapy was developed as a means to open arteries or veins occluded by fresh thrombus. For patients with acute leg ischemia it has become an alternative to surgical treatment, such as embolectomy or vascular reconstruction. Since 1974, when Dotter et al[1] first described the intra-arterial technique, vascular surgeons and radiologists have explored methods and indications for local thrombolysis of acute leg ischemia. A large literature exists, including open and randomized trials, yet the exact role of lysis remains elusive.[2] The aim of the present study was to use a large prospective database collected over a decade to explore the indications for thrombolysis in acute leg ischemia.

The Thrombolysis Study Group (TSG) was formed in 1990 by a group of surgeons and radiologists from various hospitals in the United Kingdom who wished to conduct research into peripheral thrombolysis. The group met and defined the indications and outcomes for thrombolysis in acute leg ischemia, and agreed to collect data, using standard forms, in a computer database, The National Audit of Thrombolysis for Acute Leg Ischemia (NATALI).[3] The group has previously published information from the database concerning various methods of lysis, the effects of aspirin on thrombolysis, and the treatment of acute-onset claudication.[4-6]

The database was completed at the end of 2000, the year in which more than 1000 episodes of thrombolysis had been recorded. Since then an extensive program of data verification has been undertaken for the current statistical analysis.

METHODS

In the 10 years that data have been collected by the TSG, 43 vascular surgeons and radiologists from 14 hospitals in the United Kingdom have contributed. Both district hospitals and teaching hospitals are included; a full list of participants is presented in the Appendix. Participants agreed to collect data on consecutive patients undergoing intra-arterial lysis to treat acute leg ischemia, defined as "sudden deterioration in the circulation to a leg, which has previously been adequate at rest." Patients treated conservatively and those who underwent primary surgery were excluded. Some centers joined after 1990, and not all centers collected data continuously to the end of the decade. Data were returned to the NATALI database coordi-

From the Gloucestershire Royal Hospital, Gloucester, England.
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Reprint requests: Mr J. Earnshaw, Gloucestershire Vascular Group, Gloucestershire Royal Hospital, Great Western Road, Gloucester GL1 3NN, UK (e-mail: Earnshaw@rudford.demon.co.uk).
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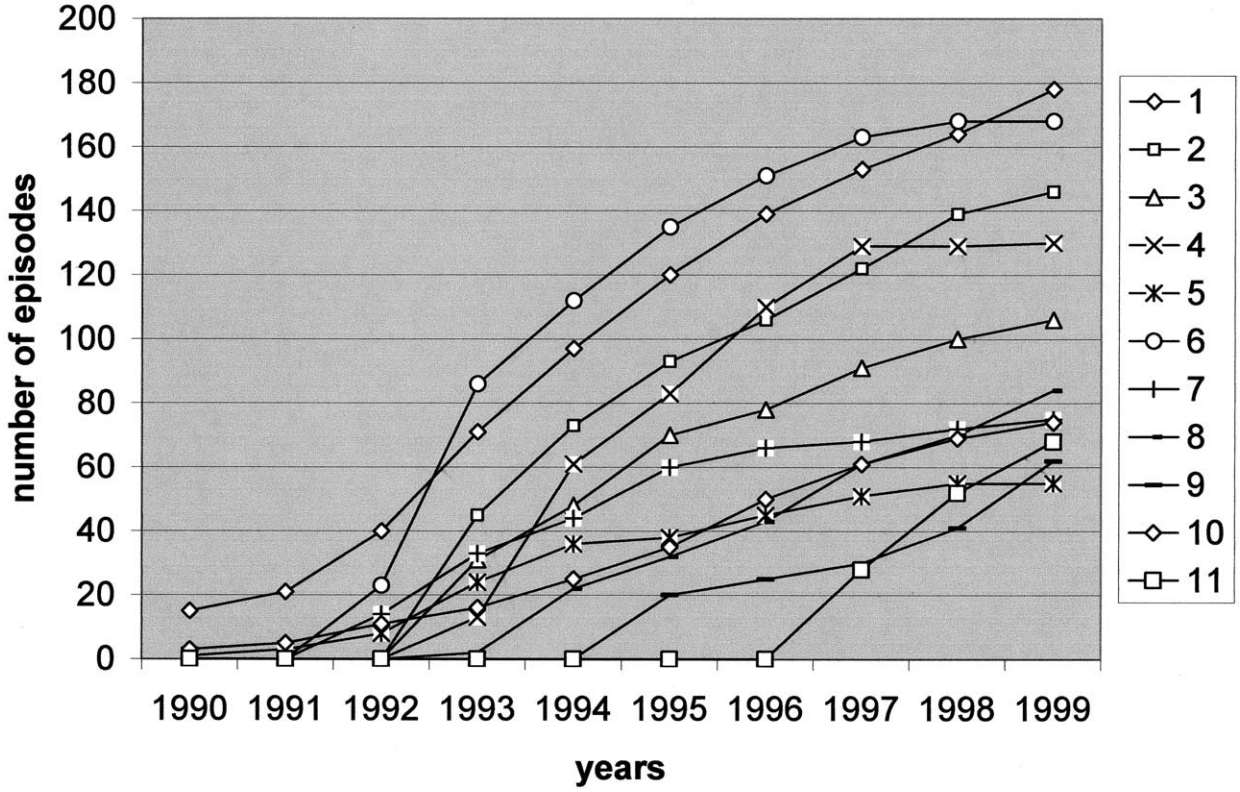

Fig 1. Recruitment to the National Audit of Thrombolysis for Acute Leg Ischemia database by year for the 11 participating centers in the final clinical analysis.

nator in batches, either electronically (five larger centers received satellite computer links) or on paper, to be entered centrally by the database coordinator. Most of the data were collected contemporaneously, but some missing information was entered retrospectively during verification. Results were returned annually to participating centers as part of the audit process. Each center received copies of their own outcome results, together with results from the group overall, for comparison. National meetings were held annually to discuss these results and to define projects for further study.

It was agreed to close the database after 1000 episodes of intra-arterial lysis had been collected, and this was achieved in 2000. Final data entry was agreed to be on December 31, 2000. There followed an extensive program of verification. The NATALI database coordinator visited each hospital with an independent observer (consultant vascular nurse). Radiology department records, vascular databases, and any other available sources were checked to ensure that consecutive patients had been included. Missing data and patients captured retrospectively were included and entered into the database. A sample of approximately 10% of the completed records at each hospital was reviewed to determine whether there were any significant data mismatches. Overall, fewer than 10% of the sampled records were changed or upgraded as a result of the verification process. Most of the changes were the result of missing, rather than inaccurate, data.

The present analysis was undertaken to determine whether preoperative patient-related factors could be used to predict outcome. An analysis of outcomes related to methods of thrombolysis and specifics of the thrombolytic regimens are the subject of a separate analysis. To be included in the current analysis, centers had to have submitted consecutive patients for several years, to have entered at least 50 episodes, and to have agreed to the verification process. Eleven of the 14 centers fulfilled these criteria. Recruitment details to the NATALI database are shown in Fig 1. Recruitment was maximal in the mid-1990s, then trailed off over the last few years of the study. The principal outcomes analyzed were defined 30 days after treatment: amputation-free survival (AFS), major amputation with survival (amputation), and death, including death after amputation. Initially, univariate analysis (cross-tabulation with χ^2 tests) was performed with AFS as the primary end point. Significant variables were then subjected to multivariate analysis with binary logistic regression. Finally, patients with the end points of amputation or death were compared, again with binary logistic regression, to determine the additional risk factors for these categories. Significance was accepted at $P = .005$. All statistical analysis

performed with SPSS for Windows, version 10 (SPSS, Chicago, Ill).

RESULTS

The present analysis included verified data from 11 centers that fulfilled the criteria for inclusion and collected information on 1147 episodes of intra-arterial thrombolysis. Outcome data were lacking in 14 episodes, which were therefore excluded, leaving 1133 episodes for analysis. There were 631 men and 380 women, mean age 68.5 years (range, 17-97 years). All had acute leg ischemia as defined, and 11% of patients had more than one episode in the database. For purposes of analysis, each episode was treated separately. Patient risk factors identified included diabetes (n = 172, 15.2%), ischemic heart disease (n = 353, 31.1%), known peripheral vascular disease (n = 678, 59.8%), and previous stroke (n = 91, 8%). At admission 322 patients (28.4%) were taking aspirin and 118 (10.4%) were receiving oral anticoagulation therapy with warfarin sodium.

Symptoms of ischemia (known in 1132 episodes) were present for less than 8 hours in 288 episodes (25.4%), 8 to 48 hours in 336 episodes (29.6%), 48 hours to 1 week in 231 episodes (20.4%), and more than 1 week in 277 episodes (24.4%). Severity of ischemia (known in 1078 episodes), as defined according to Fontaine grade, was grade II in 214 patients (19.8%), grade III in 746 patients (69.2%), and grade IV in 104 patients (9.6%). At presentation 519 patients (48.5%) had acute critical ischemia with complete or partial neurosensory deficit, and 556 patients (51.5%) had subacute critical ischemia, without any evidence of neurosensory loss.[7] These data were recorded in 1069 episodes.

All patients underwent local catheter-directed intra-arterial thrombolytic therapy. Some early patients received streptokinase (n = 59), but since 1994 all received tissue plasminogen activator. Urokinase was not widely available in the United Kingdom and was more expensive than tissue plasminogen activator, and hence was used in only 23 episodes. A number of thrombolytic techniques were used, including standard low-dose infusion, initial high-dose bolus infusion,[8] and pulsed-spray thrombolysis.[9] Initial outcome at the end of the infusion (Table I) was complete lysis in 516 episodes (45.5%), partial (clinically useful) lysis in 314 episodes (27.7%), lysis but no runoff in 141 episodes (12.4%), and no lysis in 162 episodes (14.3%).

After 30 days the final clinical outcome in the series overall was AFS in 852 patients (75.2%), amputation in 141 patients (12.4%), and death in 140 patients (12.4%). Results for the group overall improved from the early part of the study (AFS, 65%-75% in 1990-1993) to AFS of almost 80% in the last few years, although this was not statistically significant (Fig 2).

The outcome was complicated after 299 episodes of intra-arterial thrombolysis (complete data in 1108 episodes). Major hemorrhage that required transfusion or operation was seen after 87 episodes (7.85%), of which five were fatal; minor hemorrhage occurred after 70 episodes (6.3%) episodes. Stroke occurred in 26 patients (2.3%), which proved fatal in 20 patients. Other significant complications included distal embolization in 27 patients (2.4%), reperfusion injury in 20 patients (1.8%), pericatheter thrombosis in 9 patients (0.8%), and allergy in a single patient. The cause of death was recorded in 76 of 140 episodes (54%). The commonest known causes were myocardial infarction or failure (n = 24), stroke (n = 20), pneumonia (n = 7), and renal failure (n = 6). Only five patients died of hemorrhage. There was no systematic effort to verify cause of death; the cause documented on the NATALI form by the local clinician was accepted. This may have included autopsy data, but it may simply have been a clinical diagnosis.

Table I. Outcome definitions after thrombolysis used in NATALI database

Initial result
Complete lysis: Clearance of occluded vessel, with restoration of flow to runoff and restoration of peripheral pulses.
Partial lysis: Partial clearance of thrombus that relieved rest pain or improved ankle-brachial pressure index by at least 0.2; or partial clearance that enabled a smaller operation to be undertaken than was possible before lysis or that enabled a procedure to be performed when prior to therapy none was possible.
Lysis, but no runoff: Successful lysis of acute thrombus (usually an occluded bypass graft), but without establishing runoff flow into major distal vessels.
No lysis: No improvement after lysis, or deterioration in state of limb perfusion.

Data from Braithwaite BD, Ritchie AWS, Earnshaw JJ. NATALI: a model for national computer databases in the investigation of new therapeutic techniques. J R Soc Med 1995;88:511-5.
NATALI, National Audit of Thrombolysis for Acute Leg Ischemia.

Univariate and multivariate analyses. Preoperative factors that could be predictive of outcome were subjected to univariate analysis, with the outcome being AFS at 30 days (Table II). Preoperative patient-related factors that affected outcome included age, diabetes mellitus, and use of warfarin before the onset of acute ischaemia. AFS deteriorated progressively with age, from 87% for episodes in patients younger than 60 years to 65% for episodes in those older than 80 years ($P < .001$). AFS was reduced to 66% in the 172 episodes in patients with diabetes ($P = .003$). In 118 episodes the patient was taking warfarin at the time of onset of acute ischemia; AFS was improved to 83% in this group ($P = .04$).

The duration of leg ischemia also affected outcome significantly; the shorter the duration the higher the risk for death or amputation (Table III). AFS improved from 69% for ischemia of less than 8 hours' duration to 80% for ischemia for longer than 1 week ($P = .02$). The severity of leg ischemia had a marked effect on outcome. AFS diminished with increasing Fontaine grade, and was also significantly related to the presence of a neurosensory deficit. AFS was 80% in episodes with no deficit, and decreased to 56% when complete neurosensory deficit was reported ($P < .001$). There was no significant difference in the rate of AFS when graft and native vessel occlusions were compared, nor

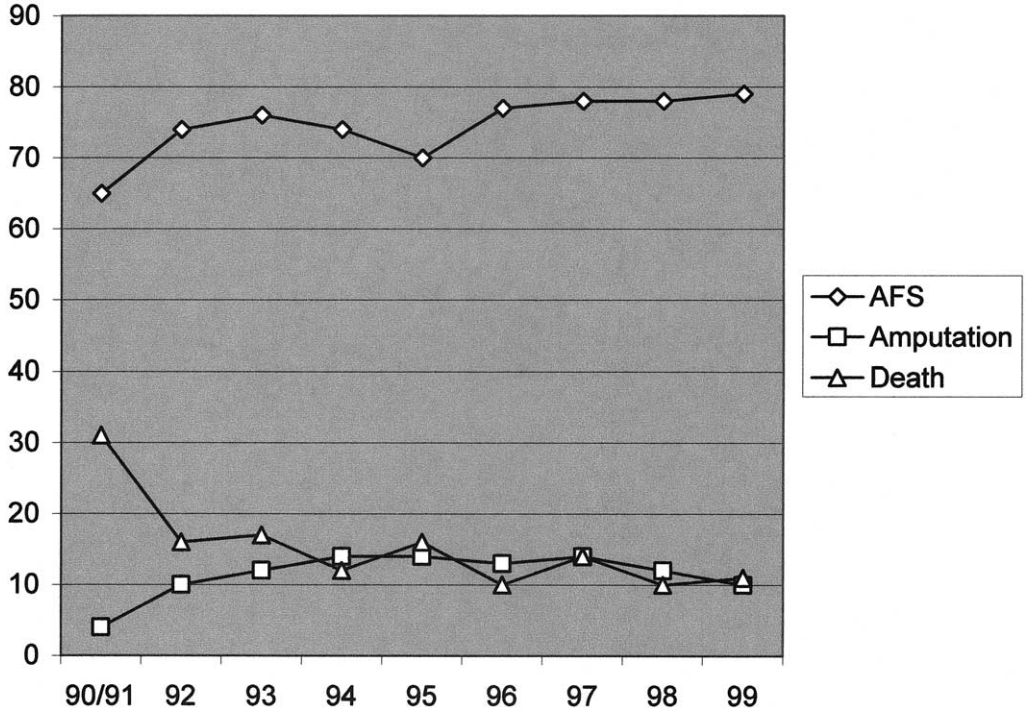

Fig 2. Thirty-day outcomes after thrombolysis to treat acute leg ischemia, by year of treatment.

for occlusions thought to be emboli or thromboses. Finally, and not surprising, AFS was 91% after successful intra-arterial lysis, and decreased to 39% when an occluded graft could be reopened, but without evidence of distal runoff.

At multivariate analysis the pretreatment factors that remained significantly related to AFS were age ($P < .001$), diabetes ($P = .002$), duration of ischemia ($P = .027$), Fontaine grade ($P = .001$), and presence of a neurosensory deficit ($P = .004$).

In a second analysis, data for patients who died were compared with data for those who required amputation but survived, again using multivariate analysis (Table II). Factors that increased the risk for death included sex (women were less likely to survive; $P = .006$), increasing age ($P < .001$), ischemic heart disease ($P < .001$), native vessel occlusion ($P < .001$), and occlusion caused by embolus ($P = .02$). Conversely, factors that increased the risk for amputation were male sex, younger age, increasing Fontaine grade ($P = .02$), graft occlusion, and occlusion caused by thrombosis.

DISCUSSION

It has been 30 years since intra-arterial thrombolysis was described to treat acute leg ischemia, yet it has still to find a clear role. Suggestions that it may replace surgery for treatment of all acute limb ischemia have been overoptimistic.[10] The technique is widely used by many clinicians who believe it has a significant role, but others have doubts.[11] Whereas randomized controlled trials have not identified an overall advantage for thrombolysis,[12-14] meta-analysis has demonstrated benefit in selected patients.[15,16] The purpose of this analysis of the NATALI database was to try to define the role of intra-arterial thrombolysis more clearly. The strengths of the project include the size of the database, which is larger than all the randomized trials combined. It has also been extensively checked and verified. The results can be compared with a combined review of lysis and surgery[17] and data from the national inpatient sample in the United States.[18] It is reassuring that AFS rates in the present database are similar to those achieved in randomized trials.

The NATALI database is, however, limited in the information it contains. It cannot be used to examine individual indications for thrombolysis, because patients who underwent surgery were not included, and clinicians were free to choose which patients received thrombolysis. All patients had acute ischemia, though clearly in some the situation was not critical. Indeed, the TSG has previously published data that show a high adverse outcome rate in patients with acute-onset claudication treated with thrombolysis.[6] Whereas AFS may not be the most appropriate means for assessing outcome in this group of patients, all had borderline rest pain that required intervention, and other end points were similar to those for other patients in the database. From the wide variation in the duration of ischemia recorded it is obvious that a small number of more chronic occlusions were treated, although 75% of episodes had been present for less than 1 week. Similarly, the database gives no information about patients who underwent surgery. Only a relatively small proportion had symptoms

Table II. Univariate analysis of factors associated with amputation-free survival 30 days after peripheral thrombolysis to treat acute leg ischemia

	Thrombolytic events (N = 1133)	*AFS (n = 852, 75%)*		*Death or amputation (n = 281, 25%)*		P
		n	*%*	*n*	*%*	
Patient factors						
Sex						.25
Female	380	276	73	104	27	
Male	631	479	76	152	24	
Age (y)						<.001
≤59	236	206	87	30	13	
60-69	308	232	75	76	25	
70-79	369	269	73	100	27	
≥80	208	135	65	73	35	
Diabetes	172	114	66	58	34	.003
In-hospital dialysis	353	265	75	88	25	.95
Peripheral vascular disease	678	516	76	162	24	.39
Stroke	91	68	75	23	25	.91
Aspirin	322	251	78	71	22	.18
Warfarin	118	98	83	20	17	.04
Leg factors						
Duration						.02
≤8 h	288	200	69	88	31	
8-48 h	336	261	78	75	22	
48 h-1 wk	231	170	74	61	26	
>1 wk	277	221	80	56	20	
Fontaine grade (n = 1078)						<.001
II	214	178	83	36	17	
III	746	555	74	191	26	
IV	104	63	61	41	39	
Neurosensory deficit (n = 1069)						<.001
None	550	441	80	109	20	
Partial	428	320	75	108	25	
Complete	91	51	56	40	44	
Vessel						.11
Native	655	481	73	174	27	
Graft	478	371	78	107	22	
Type of occlusion						.46
Thrombus	679	519	76	160	24	
Embolus	211	156	74	55	26	
Unknown	243	177	73	66	27	Not in analysis
Lysis factors						<.001
Complete	516	470	91	46	9	
Clinically useful	314	246	78	68	22	
Lysis but no runoff	141	55	39	86	61	
No lysis	162	81	50	81	50	

for less than 24 hours, and it is likely that many patients with short-duration severe ischemia underwent thromboembolectomy. The database does, however, include a large number of threatened legs; almost half of the episodes included a neurosensory deficit. The current study did not analyze the contribution of the various radiologic techniques to outcome; this will be the subject of future research. Earlier analysis of the database failed to find differences in outcome among the various thrombolytic techniques.[4] Finally, even after verification there remained data gaps; thus the numbers varied in each statistical analysis.

There is evidence that members of the TSG changed the threshold or indication for thrombolytic therapy during the 10-year study.[19] Recruitment to the database was maximal during the first half of the decade, then trailed off in many centers. The validation exercise proved that the change was real and not just a reduction in the number of cases registered. This reduction could have been due to changing enthusiasm for the project, or it could have been because the audit process and publication of early results focussed inclusion toward more suitable patients. Additional evidence that the latter explanation was responsible comes from the fact that the outcome results for the TSG overall improved over the decade of the study. Numbers for each hospital were too small to determine whether this improvement was seen in all or just some of the centers. There may be a significant learning curve for the technique

Table III. Univariate analysis of factors associated with amputation or death 30 days after peripheral thrombolysis to treat acute leg ischemia

	Thrombolytic events (n = 281)	*Amputation*		*Death*		
		n	*%*	*n*	*%*	P
Patient factors						
Sex						.006
Female	78	29	37	49	63	
Male	126	72	57	54	43	
Age (y)						<.001
≤59	27	21	78	6	22	
60-69	59	36	61	23	39	
70-79	73	32	44	41	56	
≥80	54	18	33	36	67	
Diabetes	38	24	63	14	37	.11
In-hospital dialysis	70	23	33	47	67	<.001
Peripheral vascular disease	127	69	54	58	46	.17
Stroke	21	9	43	12	57	.5
Aspirin	58	32	55	26	45	.44
Warfarin	16	10	63	6	37	.44
Leg factors						
Duration						.67
≤8 h	65	32	49	33	51	
8-48 h	64	29	45	35	55	
48 h-1 wk	44	24	55	20	45	
>1 wk	41	23	56	18	44	
Fontaine grade						.02
II	25	9	36	16	64	
III	145	68	47	77	53	
IV	34	24	71	10	29	
Neurosensory deficit						.89
None	78	40	51	38	49	
Partial	90	46	51	44	49	
Complete	26	12	46	14	54	
Vessel						<.001
Native	129	52	40	77	60	
Graft	86	56	65	30	35	
Type of occlusion						.02
Thrombus	160	88	55	72	45	
Embolus	55	20	36	35	64	
Unknown						Not in analysis

of intra-arterial thrombolysis, and the improvement seen could just have been due to increasing expertise in the participating centers. There was, however, no difference in outcomes when centers that contributed more than 100 episodes to the database were compared with those who submitted fewer than 100 episodes.

The goal of the present study was to help clinicians identify which factors are associated with better outcome after thrombolysis. The best predictor of outcome is whether the procedure is successful, but it is self-evident that this information is not available before treatment is started. Acute leg ischemia is complex, with multifactorial causes and wide variation in patient status. Outcomes are different for the patient and the limb. AFS is the ideal composite end point, first used in the Surgery vs Thrombolysis for Ischemic Lower Extremity trial,[13] but it ignores that the two main adverse outcomes, amputation and death, have different risk factors.

Previous reports have highlighted that differences in outcome were dependent on the cause of the occlusion. In the Surgery vs Thrombolysis for Ischemic Lower Extremity trial, patients with a graft occlusion had a higher chance for successful AFS than did those with native vessel occlusions[13]; this was also confirmed with meta-analysis.[15] The fate of reopened grafts remains dubious, inasmuch as follow-up studies have shown a low rate of retained patency at 1 year.[20,21] For native vessel occlusions, standard teaching is that patients with emboli are at higher risk for death because of associated cardiac disease, and patients with thrombosis are at higher risk for amputation because of poor runoff.[22,23] The cause of occlusion was also a significant factor that determined differences between amputation and death in the present study.

In the current investigation, factors that influenced AFS were increasing age, diabetes, duration and severity of ischemia (both Fontaine grade and presence of neurosensory deficit). This information enables clinicians to build a clinical picture of patients with acute leg ischemia unlikely to do well with thrombolysis, who could perhaps undergo surgery instead, although as yet there is no evidence that

this group would fare better from operation. Another alternative in these patients with severe acute ischemia is a percutaneous thrombectomy device, although its use is not widespread in the United Kingdom. In addition, female sex, ischemic heart disease, and embolic occlusion were associated with higher mortality. These are also factors to take into account when making management decisions. Acute leg ischemia is a common condition in elderly women, who are already recognized as a group at high risk.[24]

One reason why thrombolysis is not widely used is the perceived hazard. Clearly there are risks from local bleeding from arterial puncture sites, but there were only five deaths in the present database. Stroke is the most feared complication, and followed 2.3% of episodes in the NATALI database. A previous analysis suggested that approximately half were hemorrhagic and half were thromboembolic; most occurred during anticoagulation after thrombolysis.[25] In the randomized trials there was little difference in morbidity and mortality from surgery and thrombolysis. It is noteworthy that the rates of distal embolization and pericatheter thrombosis were low, even though most radiologists did not use heparin during thrombolysis.

It has been argued that thrombolysis has not proved superior to surgery, and therefore should not be seen as a standard treatment.[11] Others, particularly enthusiasts, believe it is an effective treatment, with an important role in selected patients, and that it belongs at the center of the options available to a good vascular interventional department. Experts have joined to produce guidelines for its use.[26] All new techniques go through an enthusiast phase before settling into mainstream practice. Thrombolytic therapy is now widely used in many vascular radiology departments throughout the world. Previous work has suggested this is a cost-effective approach.[27] The present research shows that much can be learned from carefully collected databases and randomized trials, and that experts can achieve creditable results; the TSG achieved almost 80% AFS at the end of the study. The past decade of research has begun to identify which patients with acute leg ischemia will do well with thrombolysis, and clinicians can use this information to tailor appropriate therapy to individual patients.

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APPENDIX

The following are members of the Thrombolysis Study Group:

Ms S. Baker (Bournemouth), Prof J. Belch (Dundee), Prof P. R. Bell (Leicester), Dr A.-M. Belli (London), Mr J. D. Beard (Sheffield), Mr D. C. Berridge (Leeds), Dr P. Birch (Gloucester), Mr B. D. Braithwaite (Nottingham), Dr T. Buckenham (London), Dr N. Chalmers (Manchester), Mr N. Cheshire (London), Mr K. Dawson (London), Prof J. Dormandy (London), Dr J. Dyett (Hull), Ms L. Earby (Northampton), Mr J. J. Earnshaw (Gloucester), Dr P. A. Gaines (Sheffield), Mr R. B. Galland (Reading), Mr A. E. B. Giddings (London), Dr I. Gillespie (Edinburgh), Dr R. H. S. Gregson (Nottingham), Mr G. Hamilton (London), Mr B. P. Heather (Gloucester), Prof B. P. Hopkinson (Nottingham), Ms M. Ireland (Sheffield), Ms C. Judge (London), Ms M. Kerle (London), Dr R. Kendrick (Northampton), Dr D. Kessell (Leeds), Dr H. Loose (Newcastle), Mr T. Loosemore (London), Ms P. Morris Vincent (London), Dr J. Moss (Glasgow), Dr R. Morgan (London), Mr S. Parvin (Bournemouth), Dr A. Platts (London), Mr D. Ratcliff (Northampton), Dr K. Reddy (Gillingham), Ms A. Reed (Leicester), Dr B. Riddler (Exeter), Dr J. Rose (Newcastle-upon-Tyne), Mr J. Thompson (Exeter), Dr P. Torrie (Reading), Dr T. Tottle (Gloucester), Dr T. Watkinson (London), Mr P. Wenham (Nottingham), Ms B. Whitman (Gloucester), Dr S. Whittaker (Nottingham), Ms L. Wilson (Newcastle), Mr J. H. N. Wolfe (London), and Mr M. Wyatt (Newcastle).

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