Original article

Outcome and complications after intra-arterial thrombolysis for lower limb ischaemia with or without continuous heparin infusion

O. Grip[1], M. Kuoppala[2], S. Acosta[2], A. Wanhainen[1], J. Åkeson[3] and M. Björck[1]

Uppsala University, Department of Surgical Sciences, [1]Section of Vascular Surgery, Uppsala, and Lund University, Department of Clinical Sciences Malmö, [2]Vascular Centre , and [3]Anaesthesiology and Intensive Care Medicine, Skåne University Hospital, Malmö, Sweden
Correspondence to: Professor M. Björck, Department of Surgical Sciences, Section of Vascular Surgery, Uppsala University, SE 75185 Uppsala, Sweden (e-mail: martin@bjorck.pp.se)

Background: **Thrombolysis is a common treatment for acute leg ischaemia. The purpose of this study was to evaluate different thrombolytic treatment strategies, and risk factors for complications.**

Methods: **This was a retrospective analysis of prospective databases from two vascular centres. One centre used a higher dose of heparin and recombinant tissue plasminogen activator (rtPA).**

Results: **Some 749 procedures in 644 patients of median age 73 years were studied; 353 (47·1 per cent) of the procedures were done in women. The aetiology of ischaemia was graft occlusion in 38·8 per cent, acute arterial thrombosis in 32·2 per cent, embolus in 22·3 per cent and popliteal aneurysm in 6·7 per cent. Concomitant heparin infusion was used in 63·2 per cent. The mean dose of rtPA administered was 21·0 mg, with a mean duration of 25·2 h. Technical success was achieved in 80·2 per cent. Major amputation and death within 30 days occurred in 13·1 and 4·4 per cent respectively. Bleeding complications occurred in 227 treatments (30·3 per cent). Blood transfusion was needed in 104 (13·9 per cent). Three patients (0·4 per cent of procedures) had intracranial bleeding; all were fatal. Amputation-free survival was 83·6 per cent at 30 days at both centres. In multivariable analysis, preoperative severe ischaemia with motor deficit was the only independent risk factor for major bleeding (odds ratio (OR) 2·98; $P < 0·001$). Independent risk factors for fasciotomy were severe ischaemia (OR 2·94) and centre (OR 6·50). Embolic occlusion was protective for major amputation at less than 30 days (OR 0·30; $P = 0·003$). Independent risk factors for death within 30 days were cerebrovascular disease (OR 3·82) and renal insufficiency (OR 3·86).**

Conclusion: **Both treatment strategies were successful in achieving revascularization with acceptable complication rates. Continuous heparin infusion during intra-arterial thrombolysis appeared to offer no advantage.**

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Introduction

Acute leg ischaemia caused by arterial embolism or thrombosis of native vessels and grafts is a common and potentially serious condition. Treatment is often initiated by local administration of thrombolytic therapy, recombinant tissue plasminogen activator (rtPA), through an indwelling intra-arterial catheter. Intra-arterial thrombolysis can be performed under local anaesthesia, which makes it possible to treat patients with co-morbidities in a safer way[1–3]. Intra-arterial thrombolysis is not without risk: approximately 10 per cent of the patients suffer from haemorrhage, sometimes requiring blood transfusion or reoperation, which may even be fatal[4–6].

The role of anticoagulation during thrombolysis remains debated. One randomized study[7] compared 30 patients treated with either low-dose heparin or no heparin during thrombolysis. Additional heparin did not increase the efficacy of the lysis but the study was not large enough to draw definitive conclusions[8]. Other studies[9–14] have observed an increased incidence of bleeding complications with prolongation of the activated partial thromboplastin time (APTT).

A recent study of thrombolytic procedures at Malmö University Hospital, Sweden, recorded a high rate of bleeding complications (33 per cent)[15,16]. At Uppsala University Hospital, Sweden, a different treatment algorithm was used during the thrombolytic procedure, with lower doses of both heparin and rtPA. The fact that two hospitals have adopted different schedules for intra-arterial thrombolysis, and have treated large numbers of patients with consistent regimens, offered an opportunity to compare the results between the two centres. The aim of this study was to evaluate the outcomes with regard to limb salvage, bleeding complications and survival, taking into account differences in case mix and method of treatment.

Methods

Uppsala University Hospital and the Vascular Centre, Malmö, are tertiary referral centres for vascular disease, with a combined primary catchment area of approximately 1·1 million and a tertiary catchment area of approximately 3·5 million.

Local intra-arterial thrombolysis for lower limb ischaemia

Baseline coagulation tests such as platelet count, APTT and prothrombin complex were performed before thrombolysis. Vascular imaging (computed tomography angiography, ultrasonography, magnetic resonance angiography) was used to plan thrombolysis. Arterial access was achieved through puncture of the common femoral artery in the non-diseased leg. A long thrombolysis catheter was advanced over the aortic bifurcation and positioned in the occlusion. In Uppsala, arterial puncture was monitored using ultrasound guidance. In Malmö, micropuncture sets were used, but ultrasound imaging was not employed routinely.

The lytic agent used was rtPA (Actilyse®; Boehringer Ingelheim, Ingelheim, Germany). The total dose of rtPA was decided individually depending on the duration and extent of the arterial occlusion, the degree of ischaemia and the patient's age. In Uppsala, the thrombolytic procedure generally started with a bolus dose of 4 mg rtPA, followed by 0·5 mg/h. In Malmö, the procedure generally started with 1–2 mg/h for the first 4 h, followed by 0·5–1·0 mg/h. The thrombolytic treatment seldom exceeded 48 h.

At the start of the endovascular procedure all patients were given 5000 units heparin intravenously (Heparin LEO®; LEO Pharma, Malmö, Sweden). In Uppsala they received only one bolus dose, whereas in Malmö the bolus dose was followed by continuous infusions of heparin, adjusted according to APTT values, aiming for two to three times baseline.

Study population

All patients who received intra-arterial thrombolytic therapy for lower limb ischaemia, with occlusions below the abdominal aorta, between 1 January 2001 and 30 September 2012 in Uppsala, and between 1 January 2001 and 31 December 2010 in Malmö, were included. Patients were identified through the local Swedvasc registry (a national register for vascular procedures, with high validity)[17–19] and local endovascular databases. The regional ethics review board in Lund approved the study.

Retrieval of patient data

Patient records were retrieved and analysed according to a predetermined protocol. The data had been entered prospectively, but the case records were analysed retrospectively. All bleeding complications, both major and minor, were noted during the thrombolytic intervention and for up to 7 days afterwards. All patients who had blood transfusion in relation to the thrombolytic procedure, or during the following 7 days, were noted. The hospital register of all blood transfusions used the same unique personal identity number (PIN). Patients were followed from the day of admission until death or to 30 September 2012 in Uppsala, and to 17 January 2012 in Malmö. The date, side and level of any leg amputation in these patients were recorded. Information on patient mortality was reported automatically within 2 weeks from the Swedish Population registry, based on the patient's PIN, to the Swedvasc registry (Uppsala) and the inpatient database (Malmö).

Definitions

Definitions are shown in *Table S1* (supporting information)[20–22]. Critical limb ischaemia was defined according to European Society for Vascular Surgery guidelines[20].

Statistical analysis

Data management and statistical analysis were done with SPSS® software package version 21·0 (IBM, Armonk, New York, USA). Differences in variables associated with different outcomes were evaluated using univariable analysis (cross-tabulation with χ^2 test). Variables associated ($P < 0{\cdot}200$) with complications, amputation or death were further tested in a multivariable analysis with binary logistic regression, with all variables entered into the model.

Significant associations were expressed in terms of odds ratios (ORs) with 95 per cent confidence intervals (c.i.) $P < 0{\cdot}010$ was considered significant, adjusting for multiple comparisons.

Results

A total of 749 thrombolysis episodes were performed in 644 patients, 318 in Uppsala and 431 in Malmö. Some patients underwent thrombolytic therapy more than once. Some 353 (47·1 per cent) of the procedures were done in women. The median age of the patients was 73 (range 27–97) years; men were younger than women (70 *versus* 74 years respectively; $P < 0{\cdot}001$).

The aetiology of arterial occlusions differed between the two hospitals ($P < 0{\cdot}001$); graft occlusions were more common in Malmö, and thromboembolic occlusions, as well as popliteal aneurysms, were more common in Uppsala (*Table 1*). To avoid confounding factors further analysis was made on the whole group, as well as in subgroups according to aetiology. Co-morbidity data are shown in *Table 1*.

The majority of patients had acute limb ischaemia (589 (78·6 per cent) of 749 procedures) or critical limb ischaemia (92 (12·3 per cent) of 749). Among the 68 patients who had symptoms only of claudication (68 (9·1 per cent) of 749), 41 had an occluded vascular graft, 22 an arterial thrombosis, two a popliteal aneurysm, and for three of these patients the information on aetiology was missing. Of the 280 patients with an occluded vascular graft or stent, 150 (53·6 per cent) were synthetic bypass grafts, 34 (12·1 per cent) were vein grafts, 50 (17·9 per cent) were stents, and 46 (16·4 per cent) were stent-grafts. This distribution was similar at the two centres ($P = 0{\cdot}114$).

The number of patients who had a neurological deficit on presentation was similar in Uppsala and Malmö (21·5 *versus* 21·7 per cent respectively; $P = 0{\cdot}937$). There were differences in the rates of motor deficit depending on aetiology, although these were not significant ($P = 0{\cdot}080$).

Thrombolysis

The mean dose of rtPA administered was 21·0 (range 2·0–76·0) mg, 17·5 mg in Uppsala and 23·6 mg in Malmö ($P < 0{\cdot}001$). The mean duration of thrombolysis was 25·2 (range 1–93) h (27 h in Uppsala *versus* 23 h in Malmö; $P = 0{\cdot}001$). Details are shown in *Table 2*.

Successful lysis was defined as complete or partial lysis of the occlusion; procedures were successful in 79·6 per cent in Uppsala and 81·1 per cent in Malmö ($P = 0{\cdot}595$). In Uppsala 188 (59·1 per cent) of the 318 procedures were followed by a subsequent endovascular intervention, and in Malmö 310 (71·9 per cent) of the 431 procedures ($P < 0{\cdot}001$). In Uppsala 47 thrombolytic procedures (14·8 per cent) were followed by fasciotomy, compared with 23 (5·3 per cent) in Malmö ($P < 0{\cdot}001$).

Unsuccessful thrombolysis requiring conversion to open operation and/or immediate major amputation occurred after 56 episodes (17·6 per cent) in Uppsala and 94 episodes (21·9 per cent) in Malmö ($P = 0{\cdot}151$). Major amputation was needed in hospital in 34 patients (10·7 per cent) in Uppsala and in 44 (10·2 per cent) in Malmö ($P = 0{\cdot}831$).

Bleeding complications (*Table 3*)

As a validation, all blood transfusions were verified with hospital case records in Uppsala; 98·1 per cent consistency with the blood transfusion registry was found.

The incidence of bleeding complications was 21·4 per cent in Uppsala and 36·7 per cent in Malmö ($P < 0{\cdot}001$). Bleeding complications requiring blood transfusion occurred in 11·6 per cent in Uppsala, and in 15·6 per cent in Malmö ($P = 0{\cdot}123$). Bleeding complications necessitated discontinuation of thrombolysis in 5·0 per cent in Uppsala and 6·3 per cent in Malmö ($P = 0{\cdot}473$).

The most common site for any bleeding complication was the femoral access site: 15·7 per cent in Uppsala *versus* 28·6 per cent in Malmö ($P < 0{\cdot}001$). Haemorrhage at distant sites was reported in 8·2 per cent in Uppsala and 15·8 per cent in Malmö ($P = 0{\cdot}002$). These involved skin or subcutaneous tissue (40), the urinary tract (27), gastrointestinal tract (26), iatrogenic injury with the intra-arterial catheter (5) and brain (3). All patients with intracranial haemorrhage died, one in Uppsala and two in Malmö; these were aged 65, 74 and 91 years, and had multiple co-morbidities. They received 12, 12 and 16 mg of rtPA respectively, less than the overall mean of 21 mg. Two of the intracranial haemorrhages occurred during thrombolysis; the third was diagnosed after 2 weeks and had a less clear association with the thrombolysis.

Thirty-day outcome

Within 30 days of thrombolysis 42 patients (13·2 per cent) treated in Uppsala required a major amputation, compared with 56 (13·1 per cent) of 429 patients in Malmö ($P = 0{\cdot}938$). The major amputations were performed below (59), through (5) or above (34) the knee. Fourteen patients (4·4 per cent) from Uppsala and 19 (4·4 per cent) from Malmö died within 30 days ($P = 0{\cdot}988$). In the subgroup of patients treated for occluded grafts, stents and stent-grafts, the overall risk of amputation was 13·8 per cent. The frequency of amputation was 15·2 per cent when venous bypass grafts were treated, 18·2 per cent after synthetic

Table 1 Characteristics of patients with lower limb ischaemia treated with thrombolysis in Malmö and Uppsala

	All procedures ($n = 749$)	Acute arterial thrombosis ($n = 232$)	Embolus ($n = 161$)	Popliteal aneurysm ($n = 48$)	Graft occlusion ($n = 280$)	P†
Centre						< 0·001
Malmö	431 (57·5)	122 (29·0)	75 (17·8)	24 (5·7)	200 (47·5)	
Uppsala	318 (42·5)	110 (36·7)	86 (28·7)	24 (8·0)	80 (26·7)	
Mean age (years)	71·6	70·8	77·5*	70·4	68·8	< 0·001
Sex ratio (M : F)	396 : 353	116 : 116	70 : 91*	45 : 3*	152 : 128	< 0·001
Co-morbidities						
Hypertension	484 (64·6)	151 of 231 (65·4)	99 (61·5)	24 (50)	189 (67·5)	0·103
Diabetes	135 (18·0)	57 (24·6)*	25 (15·5)	2 (4)*	47 (16·8)	0·003
Ischaemic heart disease	243 (32·4)	56 of 231 (24·2)*	60 (37·3)	14 (29)	106 (37·9)	0·005
Atrial fibrillation	217 (29·0)	37 of 231 (16·0)*	104 (64·6)*	6 (13)	61 (21·8)*	< 0·001
Cerebrovascular disease	100 (13·4)	29 of 231 (12·6)	26 (16·1)	7 (15)	33 (11·8)	0·599
Renal insufficiency	243 (32·4)	65 of 227 (28·6)	71 (44·1)*	12 (25)	86 of 275 (31·3)	0·005
Anaemia	214 (28·6)	66 of 224 (29·5)	47 of 158 (29·7)	11 (23)	80 of 274 (29·2)	0·853
Medications						
Aspirin	400 (53·4)	101 (43·5)*	84 (52·2)	19 (40)	185 of 279 (66·3)*	< 0·001
Warfarin	113 (15·1)	18 (7·8)*	28 (17·4)	1 (2)*	64 (22·9)*	< 0·001
Degree of ischaemia						
Mean duration of symptoms (h)	254	447*	99	157	210	< 0·001
Motor deficit	155 (20·7)	46 of 221 (20·8)	39 of 154 (25·3)	15 of 47 (32)	48 of 271 (17·7)	0·080
Acute limb ischaemia	589 (78·6)	150 (64·7)*	160 (99·4)*	45 (94)*	216 (77·1)	< 0·001
Critical limb ischaemia	92 (12·3)	60 (25·9)*	1 (0·6)*	1 (2)	23 (8·2)	< 0·001
Claudication	68 (9·1)	22 (9·5)	0 (0)*	2 (4)	41 (14·6)*	< 0·001

Values in parentheses are percentages of all procedures or of the relevant aetiological group. In 28 patient records the information regarding aetiology of occlusions was missing and these patients were not included in the comparisons between aetiological groups. *$P < 0·010$ *versus* other groups; †comparisons of all groups (cross-tabulation with χ^2 test for dichotomous variables and one-way ANOVA for continuous variables).

Table 2 Thrombolytic procedure according to aetiology of arterial occlusion

	All procedures ($n = 749$)	Acute arterial thrombosis ($n = 232$)	Embolus ($n = 161$)	Popliteal aneurysm ($n = 48$)	Graft occlusion ($n = 280$)	P†
Continuous heparin infusion	473 (63·2)	140 (60·3)	79 (49·1)*	26 (54)	215 (76·8)*	< 0·001
Mean rtPA dose (mg)	21·0	20·2	18·6	25·5*	22·6	< 0·001
Mean duration of thrombolysis (h)	25·2	25·4	23·1	28·0	26·3	0·056
Successful lysis	601 (80·2)	179 (77·2)	131 (81·4)	34 (71)	241 (86·1)*	0·017

Values in parentheses are percentages of all procedures or of the relevant aetiological group. rtPA, recombinant tissue plasminogen activator. *$P < 0·010$ *versus* other groups; †comparisons of all groups (cross-tabulation with χ^2 test for dichotomous variables and one-way ANOVA for continuous variables).

bypass grafts, 2·3 per cent for stent-grafts and 10·2 per cent for stents. The difference between synthetic bypasses and stent-grafts was significant ($P = 0·012$).

Multivariable analyses

Of the 749 procedures included in the study, 227 were followed by a bleeding complication related to the thrombolysis (*Table 3*). Factors associated with any bleeding complication in univariable analysis were male sex ($P = 0·060$), non-embolism ($P = 0·036$), popliteal aneurysm ($P = 0·006$), graft thrombosis ($P = 0·125$), atrial fibrillation ($P = 0·125$), treatment with aspirin ($P = 0·086$), continuous heparin infusion ($P < 0·001$), centre ($P < 0·001$) and total dose of rtPA ($P = 0·001$). When all nine variables were included in a multivariable binary logistic regression analysis, two demonstrated a trend towards being independent risk factors: popliteal aneurysm (OR 2·24, 95 per cent c.i. 1·15 to 4·39; $P = 0·018$) and centre (Malmö: OR 2·68, 1·15 to 6·27; $P = 0·023$).

Blood transfusion was required after 104 procedures (13·9 per cent). Factors associated with this major complication were severe ischaemia (motor deficit) ($P < 0·001$), acute arterial thrombosis ($P = 0·049$), embolism ($P = 0·039$), popliteal aneurysm ($P = 0·017$), graft thrombosis ($P = 0·015$), ischaemic heart disease ($P = 0·065$), preoperative anaemia ($P = 0·002$), continuous heparin infusion ($P = 0·163$), centre ($P = 0·123$) and total dose of rtPA ($P = 0·038$). In multivariable analysis, severe ischaemia remained an independent risk factor (OR 2·98, 95 per cent c.i. 1·79 to 4·96; $P < 0·001$) and preoperative anaemia showed a trend (OR 1·91, 1·16 to 3·16; $P = 0·011$).

Table 3 Outcomes and complications according to aetiology of arterial occlusion

	All procedures ($n = 749$)	Acute arterial thrombosis ($n = 232$)	Embolus ($n = 161$)	Popliteal aneurysm ($n = 48$)	Graft occlusion ($n = 280$)	P†
Any bleeding complication	227 (30·3)	63 of 231 (27·3)	38 (23·6)	23 (48)*	94 (33·6)	0·005
Bleeding requiring transfusion	104 (13·9)	23 of 231 (10·0)	14 (8·7)	12 (25)*	49 (17·5)*	0·002
Interruption of thrombolysis owing to bleeding	43 (5·7)	12 (5·2)	3 (1·9)	6 (13)	19 (6·8)	0·024
Fasciotomy	70 (9·3)	14 (6·0)	13 (8·1)	9 (19)	32 (11·4)	0·022
Amputation within 30 days	98 (13·1)	33 of 231 (14·3)	9 of 159 (5·7)*	14 (29)*	38 (13·6)	< 0·001
Died within 30 days	33 (4·4)	8 (3·4)	15 (9·3)*	1 (2)	7 (2·5)	0·004
Amputation-free survival at 30 days	626 (83·6)	194 of 231 (84·0)	136 of 158 (86·1)	33 (69)*	240 (85·7)	0·025

Values in parentheses are percentages of all procedures or of the relevant aetiological group. *$P < 0·010$ *versus* other groups; †comparisons of all groups (cross-tabulation with χ^2 test for dichotomous variables and one-way ANOVA for continuous variables).

In total, 43 thrombolytic procedures (5·7 per cent) were terminated because of bleeding complications. Risk factors were: non-embolism ($P = 0·020$), popliteal aneurysm ($P = 0·029$), atrial fibrillation ($P = 0·120$) and total dose of rtPA ($P = 0·114$). In multivariable analysis, popliteal aneurysm (OR 2·92, 95 per cent c.i. 1·12 to 7·63; $P = 0·028$) and total dose of rtPA (OR 0·96, 0·92 to 1·00; $P = 0·047$ – lower usually as a result of interruption) remained trends towards independent risk factors.

A total of 70 fasciotomies (9·3 per cent) were done during or immediately after thrombolysis. Factors associated with need for fasciotomy were severe ischaemia ($P = 0·001$), hypertension ($P = 0·053$), acute arterial thrombosis ($P = 0·032$), popliteal aneurysm ($P = 0·022$), graft thrombosis ($P = 0·144$), continuous heparin infusion ($P < 0·001$), centre (Uppsala: $P < 0·001$) and total dose of rtPA ($P = 0·122$). In multivariable analysis, two variables remained independent risk factors: severe ischaemia (OR 2·94, 95 per cent c.i. 1·65 to 5·26; $P < 0·001$) and centre (Uppsala: OR 6·50, 2·31 to 18·50; $P < 0·001$). Trends were identified for graft thrombosis (OR 2·72, 1·25 to 5·91; $P = 0·012$), total dose of rtPA (OR 1·03, 1·01 to 1·06; $P = 0·016$) and popliteal aneurysm (OR 2·81, 1·03 to 7·67; $P = 0·044$).

Within 30 days of thrombolysis, 98 episodes (13·1 per cent) were followed by a major amputation. Associated with this event were severe ischaemia ($P = 0·002$), age ($P = 0·066$), non-embolism ($P = 0·002$), popliteal aneurysm ($P = 0·001$), ischaemic heart disease ($P = 0·174$), preoperative anaemia ($P = 0·001$) and total dose of rtPA ($P = 0·032$). In multivariable analysis, embolism remained an independent negative risk factor, with a decreased risk of amputation (OR 0·30, 95 per cent c.i. 0·14 to 0·66; $P = 0·003$). Age (OR 1·03, 1·01 to 1·06; $P = 0·014$), anaemia (OR 1·84, 1·12 to 3·03; $P = 0·016$), total dose of rtPA (OR 1·03, 1·01 to 1·05; $P = 0·016$) and severe ischaemia (OR 1·89, 1·12 to 3·19; $P = 0·018$) were identified as trends for increased risk of amputation.

Within 30 days, 33 deaths (4·4 per cent) followed the thrombolytic procedure. Risk factors were: severe ischaemia ($P = 0·001$), age ($P < 0·001$), non-embolism ($P < 0·001$), graft thrombosis ($P = 0·058$), atrial fibrillation ($P = 0·178$), cerebrovascular disease ($P = 0·001$), renal insufficiency ($P < 0·001$), anaemia ($P = 0·048$), warfarin treatment ($P = 0·142$) and total dose of rtPA ($P = 0·026$). In multivariable analysis, two variables remained independent risk factors: cerebrovascular disease (OR 3·82, 95 per cent c.i. 1·53 to 9·57; $P = 0·004$) and renal insufficiency (OR 3·86, 1·50 to 9·96; $P = 0·005$). Trends were identified for age (OR 1·06 per year, 95 per cent c.i. 1·00 to 1·11; $P = 0·046$) and severe ischaemia (OR 2·88, 1·3 to 6·79; $P = 0·015$).

When death at 30 days and/or major amputation were combined as one composite endpoint, popliteal aneurysm (OR 3·28, 1·54 to 6·99; $P = 0·002$) and anaemia (OR 2·13, 1·35 to 3·38; $P = 0·001$) were identified as independent risk factors in multivariable analysis.

Discussion

This study offered an opportunity to evaluate two different treatment strategies of intra-arterial thrombolysis, with or without continuous heparin, and to evaluate which factors were associated with success and bleeding. The success rates for the two hospitals with two different treatment strategies were similar at 30 days in terms of limb salvage and survival. The reported amputation-free survival rate of 83·6 per cent in this study is similar to that in previous reports[14,23,24].

A number of studies have shown rtPA to be effective over a wide range of doses, and the lowest effective dose has not yet been determined[8]. A higher dose of rtPA can accelerate the thrombolysis and achieve faster restoration of blood flow, a potential advantage to patients with acute ischaemia[14,25,26]. Faster thrombolysis with a higher dose of rtPA is counterbalanced by a higher rate of bleeding complications[16,25]; the risk of bleeding must be weighed

against the risk of surgery or amputation for each patient[27]. The two hospitals in the present study used significantly different amounts of rtPA, but had equivalent success rates. In multivariable analysis, the dose of rtPA was not a significant risk factor for all complications, or for major bleeding complications.

Many clinicians are concerned about the risk of bleeding associated with intra-arterial thrombolysis. Local bleeding from the arterial puncture site is common, but most of the reported bleeding episodes in this study were mild and could be managed without surgical intervention. Few episodes of bleeding required blood transfusion (13·9 per cent of total episodes) or thrombolysis to be discontinued (5·7 per cent). A previous study[28] reported an even higher bleeding complication rate (47 per cent), but was also accompanied by a higher success rate (86 per cent). Another study[15] reported bleeding complications to be associated with lower amputation rates, suggesting that it is important to accept minor bleeding complications in order to achieve optimal limb salvage.

Both minor and major bleeding complications were more common in Malmö. It is not possible to conclude, however, that this difference was simply the effect of using more heparin and rtPA. There were also differences in case mix, as can be seen in *Table 1*, and in the technique used to puncture the artery or graft. Previous studies[23,29] have reported differences in outcome dependent on the type of arterial occlusion. When confounding factors were addressed in multivariable analyses, popliteal aneurysm and treatment in Malmö remained independent risk factors for any bleeding complication, but use of continuous heparin infusion and the total dose of rtPA did not. The difference in the documented rate of minor bleeding might simply be due to the fact that patients in Uppsala were monitored in a high-dependency unit, whereas patients in Malmö were monitored in intensive care. To avoid this potential bias, it was decided when planning the study to have a clear definition of major bleeding – the patient needing blood transfusion – and to retrieve robust data from the blood transfusion register. When this more strict definition of bleeding was used, there was still a numerical trend towards a higher risk in Malmö, but the difference lost statistical significance; a type II statistical error cannot be excluded.

The finding that patients who had thrombolysis interrupted because of bleeding received less rtPA was expected. In multivariable analysis, the total dose of rtPA administered was shown to be a risk factor for both fasciotomy and amputation. This is also expected as, when unsuccessful, thrombolysis can be prolonged.

Several published studies[9–13] have reported different dosages of concomitant heparin and the risk of bleeding complications. In the Thrombolysis Or Peripheral Arterial Surgery (TOPAS) trial[30], comparing thrombolysis with surgery for acute lower limb ischaemia, heparin was found to be an independent risk factor for major haemorrhage. Owing to the high rate of intracranial haemorrhage, heparin use was stopped prematurely in the trial. Stroke occurred in 1–2 per cent of the procedures in other, larger studies[23,24]; in the present study of 749 thrombolytic procedures there were only three cases (0·4 per cent) of intracranial haemorrhage.

Although heparin did not remain an independent risk factor for bleeding complications in any of the multivariable analyses, there was a trend towards heparin being a risk factor in all of the univariable analyses. A type II error, as well as uncontrolled confounding factors, cannot be ruled out. Continuous heparin infusion requires regular monitoring of APTT values, and adjustment of the infusion rate. Continuous heparin infusion is still standard treatment during intra-arterial thrombolysis at many hospitals[5,8,31]. A small randomized study[7], involving 30 patients treated either with rtPA alone (0·5 mg/h; mean duration 26 h) or rtPA plus heparin (rtPA 0·5 mg/h plus heparin 250 units/h; mean duration 32 h) suggested that the addition of heparin had no significant benefit, consistent with the present study.

Fasciotomy was more common in Uppsala, where the duration of the thrombolysis was also longer. Prolonged ischaemia will result in a higher degree of reperfusion injury, and the need for fasciotomy. It is also possible, however, that surgeons in Uppsala had a lower threshold for performing fasciotomy.

The potential advantages and disadvantages of the two management strategies should ideally have been evaluated in a prospective randomized trial. The fact that some data were collected retrospectively, and that comparisons may have been confounded by differences in case mix, are a major limitation of the study. Patients were registered prospectively in the Swedvasc registry and/or the local endovascular database, however, assuring good external validity[17–19]. Data on blood transfusion were also registered prospectively, and survival or death was confirmed with the population registry.

Local rtPA infusion with, or without continuous heparin was successful for the majority of patients, and was associated with few major bleeding complications. The difference in case mix at the two hospitals underlines the value of the multivariable analysis, as a direct comparison between the hospitals could have led to misleading conclusions regarding the optimal treatment strategy.

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Supporting information

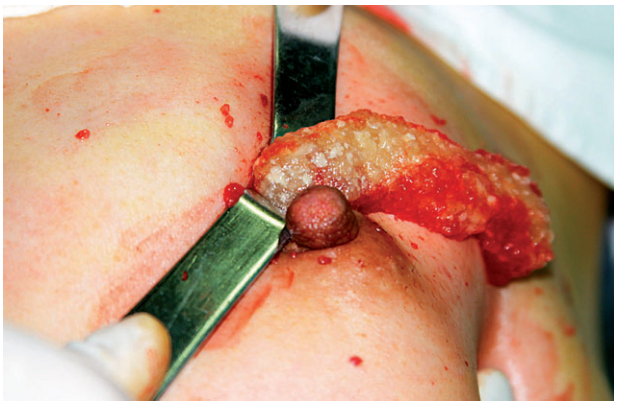
Additional supporting information may be found in the online version of this article:

Table S1 Definitions

Snapshot quiz

Snapshot quiz 14/12

Question: What is the material being removed from this woman's breast?



The answer to the above question is found on p. 1182 of this issue of *BJS*.

Ma F: Plastic Surgery Hospital of Weifang Medical University, 288 Shenglidongjie, Kuiwen District, Weifang, Shandong, China, 261042 (e-mail: fushunma@hotmail.com)

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