CATHETER-DIRECTED THROMBOLYSIS FOR ACUTE LIMB ISCHEMIA

A.M. Schrijver

Catheter-directed thrombolysis for acute limb ischemia
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Catheter-geleide trombolyse voor acute ischemie van de extremiteit
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op donderdag 24 maart 2016 des middags te 4.15 uur

door

Anne Marjolein Schrijver

geboren op 6 augustus 1983 te Leiden

Promotor:	Prof.dr. F.L. Moll
Copromotor:	Dr. J.P.P.M. de Vries

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Chapter 1

General introduction and thesis outline

ACUTE LIMB ISCHEMIA

Acute limb ischemia is a vascular emergency. The incidence of acute limb ischemia is estimated to be 14 per 100,000 in the general population and to form 10% to 16% of the vascular workload.[1] When not treated promptly and adequately it is associated with significant limb loss and death. Many patients suffering from acute limb ischemia have extensive cardiovascular disease, which makes them high-risk patients. The major cause of acute limb ischemia is thrombosis of underlying atherosclerotic disease. Atherosclerotic plaque rupture causes platelet activation, leading to platelet adherence and altered flow, which results in thrombosis. The second most common cause of acute limb ischemia is embolism, usually of cardiac origin. More rare underlying causes are cystic adventitial disease, popliteal entrapment syndrome, popliteal aneurysm, vasculitis, hyperhomocysteinemia and paraneoplastic syndrome.[2]

Initial clinical examination is crucial in patients with acute limb ischemia. The classical signs and symptoms of patients with acute limb ischemia are categorized by the "six Ps" (pain, pallor, paralysis, pulse deficit, paresthesia, and poikilothermia). In 1986 a clinical classification for acute limb ischemia was published, that was later known as the Rutherford classification (Table).[3]

If sensation and motor function are present, viability of the limb is not immediately threatened and the patient can be treated semi-elective. In case of loss of sensation or muscle weakness, prompt surgical intervention is required, since ultimate limb loss is likely.

Table. Rutherford classification for acute limb ischemia

Class	Clinical signs
I	Viable–not immediately threatened, no sensory loss or muscle weakness, arterial Doppler signal is audible.
IIa	Marginally threatened–salvageable if promptly treated, minimal sensory loss, no muscle weakness, arterial Doppler signal is often inaudible.
IIb	Immediately threatened–salvageable with immediate revascularization, sensory loss associated with rest pain in more than the toes, mild to moderate muscle weakness, arterial Doppler signal is usually inaudible.
III	Irreversible–major tissue loss or permanent nerve damage inevitable if there is significant delay before intervention, profound limb anesthesia and paralysis, arterial and venous Doppler signal is inaudible.

SURGICAL THROMBOEMBOLECTOMY

Over a long period of time, surgical thromboembolectomy has been the standard of care for patients with acute limb ischemia. In 1963 the introduction of the Fogarty catheter (a flexible tube, with a balloon attached to its tip through which thrombus is extracted) allowed large amounts of thromboembolic material to be removed rapidly to restore blood flow to ischemic tissues.[4] Disadvantages of this technique are damaging the endothelium and often leaving the underlying cause of the thrombus, an atherosclerotic plaque, untreated. Furthermore, it can be challenging to treat small arteries in the foot or forearm with a thromboembolectomy catheter. In addition, up to 30% of thromboembolectomies may show residual thrombus on angiogram.[5]

CATHETER-DIRECTED THROMBOLYSIS

Catheter-directed thrombolysis was introduced in the 1980s and its use has widely increased ever since. The benefits of catheter-directed thrombolysis compared with surgery are gentler and more complete clot removal, which allows the preservation of endothelium, its less invasiveness, and the possibility to visualize and, if necessary, to treat an underlying atherosclerotic lesion or anastomotic stenosis by endovascular means. The main limitations include failure to achieve complete lysis, prolonged time to revascularization and the occurrence of hemorrhagic complications. So far, there have been three large randomized controlled trials comparing surgery to catheter-directed thrombolysis.

In the Rochester trial a total of 114 patients with limb-threatening ischemia of less than 7 days' duration were randomized to thrombolytic therapy or surgical therapy. Thrombolytic therapy resulted in complete lysis of the thrombus in 70%. Although limb salvage rate at 12 months did not differ between the groups, cumulative survival rate at 12 months was significantly higher in the thrombolysis group.[6]

In the STILE trial a total of 393 patients with native arterial or bypass graft occlusions were randomized to either optimal surgical treatment or catheter-directed thrombolysis with recombinant tissue plasminogen activator or urokinase. Patients with progressive limb ischemia in the previous 6 months were eligible for inclusion in the study. There was no significant difference in death or major amputation between the groups, but patients that underwent surgical treatment had significantly less ongoing/recurrent ischemia as compared to thrombolysis. A subgroup analysis stratified by duration of ischemia (acute (0-14 days of worsening ischemia) versus chronic (>14 days) ischemia) showed that among patients with acute ischemia, surgery was associated with more major amputations compared with thrombolysis. The authors concluded that combining a treatment strategy of catheter-directed thrombolysis for acute limb ischemia with surgical revascularization for chronic limb ischemia offers the best overall results. It is noteworthy that the study terminated prematurely because of significant failure of placement of the catheter in the thrombolysis group.[7]

In the TOPAS trial a total of 454 patients with acute (<14 days) arterial occlusions of the lower limbs, were randomized to surgical treatment (surgical thromboembolectomy or bypass grafting) or catheter-directed thrombolysis. The amputation-free survival rates at 6 months and 1 year did not significantly differ between the groups. However, during the first 6 months after initial treatment, patients who were assigned to surgery underwent nearly twice as much open surgical procedures, as compared to the patients that were assigned to thrombolysis. A 12.5 percent incidence of major hemorrhage with urokinase was found. Despite its association with a higher incidence of hemorrhagic complications, intra-arterial infusion of urokinase reduced the need for surgical procedures, with no significant increase in amputation or death.[8]

ULTRASOUND-ACCELERATED THROMBOLYSIS

Several methods have been investigated to accelerate thrombolysis with use of ultrasound (US). High- intensity US can be used to mechanically disrupt clots,[9] while low-intensity US speeds enzymatic clot lysis in vitro by loosening fibrin strands and thereby increasing thrombus permeability and exposing more plasminogen receptors for binding, without mechanically disrupting the clot.[10-12] The aim of the latter method is to restore blood flow faster and to reduce the dosage of thrombolytic agent, and thereby possibly reducing thrombolysis-related hemorrhagic complications. Several clinical studies have shown that this technique is safe and effective.[13-16] So far, no randomized controlled trials have been performed.

THESIS OUTLINE

This thesis focuses on catheter-directed thrombolysis in patients with acute limb ischemia. The final three chapters focus on the results of US-accelerated thrombolysis.

Chapter 2 provides an overview of the developments in pharmacomechanical thrombolysis. Available thrombolytic agents, infusion techniques, and pharmacomechanical devices are discussed.

Chapter 3 describes the long-term outcome of catheter-directed thrombolysis for acute occlusions of lower limb native arteries and prosthetic bypass grafts. Several patient-related and occlusion-related factors that might possibly affect the outcome of thrombolysis have been identified. Controversy persists concerning the outcome of catheter-directed thrombolysis in lower limb native arteries compared with bypass grafts. Currently available studies are difficult to compare because different outcome measures are used. However, there is limited evidence that the long-term outcome is better in native arteries.

Although catheter-directed thrombolysis has established its role in the treatment of acute lower limb ischemia, primary surgical intervention is still the most common treatment in acute upper limb ischemia. In **Chapter 4** the outcome of catheter-directed thrombolysis as first-line treatment in patients with acute upper limb ischemia is evaluated. Possible benefits of this form of treatment are its less invasive character, minimal trauma to the intimal wall, clearance of thrombus in small arteries, and the possibility to visualize and treat any underlying cause of occlusions like stenosis in peripheral and collateral arterial territories in the arm.

Catheter-directed thrombolysis is an accepted form of treatment not only in peripheral arterial occlusions, but also in various other thromboembolic conditions, such as stroke, deep venous thrombosis, and pulmonary embolism. An important draw-back of catheter-directed thrombolysis are its (hemorrhagic) complications. Several methods have been investigated to reduce therapy time and thereby reducing treatment related complications. Low-intensity US has been shown to accelerate clot dissolution by affecting the fibrin strands and thereby facilitating the delivery of therapeutic agents into the clot. In **Chapter 5** an overview of the literature

on US-accelerated thrombolysis is presented. A total of 77 reports focusing on catheter-directed US-accelerated thrombolysis, including in vitro, in vivo and clinical studies, were identified and reviewed.

Chapter 6 describes a feasibility study on the use of US-accelerated thrombolysis in arterial thromboembolic occlusions of the lower limbs in preparation of a randomized controlled clinical trial. In this study the EKOS EndoWave system (EKOS Corporation, Bothell, WA, USA) is used. This system facilitates simultaneous delivery of low-intensity US and a thrombolytic agent into an occluded native artery or bypass graft. It consists of a multilumen thrombolysis delivery catheter and a matching US coaxial core wire that delivers low-intensity, high-frequency US over the entire length of the infusion catheter. Both the multilumen thrombolysis delivery catheter and the US coaxial core are available in variable lengths, in order to match the length of the occlusion.

In **Chapter 7** the design and rationale of a randomized trial comparing standard catheter-directed thrombolysis versus US-accelerated thrombolysis for thromboembolic infrainguinal disease (DUET) is described. Thrombosed infra-inguinal native arteries and thrombosed bypass grafts were included. This is the first randomized trial to investigate the application of US-accelerated thrombolysis, and its impact on therapy time as compared with standard catheter-directed thrombolysis.

Finally, **Chapter 8** describes the results of the randomized controlled DUET trial, comparing standard catheter-directed thrombolysis with US-accelerated thrombolysis for thromboembolic infrainguinal disease. Sixty patients (44 men; mean age 64 years) with recently thrombosed infrainguinal native arteries or bypass grafts causing acute limb ischemia (Rutherford class I or IIa) were randomized to standard catheter-directed thrombolysis (n=32) or US-accelerated thrombolysis (n=28). The primary outcome was the duration of catheter-directed thrombolysis needed for uninterrupted flow (>95% thrombus lysis), with outflow through at least 1 below-the-knee artery.

Chapter 9 concludes this thesis providing a summary and general discussion.

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Chapter 2

Pharmacomechanical thrombolysis for acute arterial limb occlusions

A.M. Schrijver, J.P.P.M. de Vries, F.L. Moll

In preparation

HISTORY

A thrombus is composed of platelets and red blood cells that are entangled by fibrin strands. Thrombus formation most frequently occurs superimposed on an atherosclerotic plaque. In 1933, Tillett and Garner[1] discovered the lytic properties of streptokinase (SK) produced by group C β-hemolytic streptococci. The first intravascular infusion of thrombolytic agents was described in 1955 by Tillett;[2] initially, these agents were administered intravenously. The first patient series was described in 1965 by Cliffton.[3] Since the 1980s, thrombolytic agents have been routinely used for several thromboembolic conditions, including stroke, myocardial infarction, pulmonary embolism, and peripheral venous and arterial occlusions.

The goal of catheter-directed thrombolysis is to dissolve thrombus and restore tissue perfusion. An underlying lesion can be identified, and usually be treated by endovascular means. Suggested benefits of catheter-directed thrombolysis are: reestablishment of inflow and outflow for bypasses, establishment of patency for inaccessible small vessels, potentially with limited intimal injury in comparison with surgical embolectomy. Additional benefits include reduction of the need for acute major surgery, and ultimately reducing the level of amputation. Only patients with a nonviably threatened limb are suitable for catheter-directed thrombolysis, because they must be capable of withstanding a prolonged period of ischemia while the pharmacologic agent is administered.[4] Several endovascular treatment modalities are available for patients with acute limb ischemia. Catheter-directed thrombolysis can be used solely pharmacologic or combined with a mechanical thrombectomy device or thrombus aspiration device.

The aim of this article is to provide an overview of available thrombolytic agents, infusion techniques, and pharmacomechanical thrombolysis devices, in order to guide physicians to select the optimal (combination) of pharmacomechanical device(s).

THROMBOLYTIC AGENTS

Thrombolytic agents activate the fibrinolytic system by converting plasminogen into plasmin, which disaggregates fibrin and leads to clot dissolution. All thrombolytic agents are forms of plasminogen activators and do not directly degrade fibrin. Thrombolytic agents initially were non-fibrin-specific agents that activated plasminogen in the circulating blood and also fibrin-bound plasminogen.[5] Newer thrombolytic agents have the ability to distinguish between circulating and bound plasminogen and thereby avoid plasminemia, which is called fibrin specificity.[6] The most commonly used thrombolytic agents are discussed below.

Streptokinase

Streptokinase was the first thrombolytic agent to be described. In 1933, Tillett et al.[1] demonstrated the capacity of broth hemolytic streptococci to rapidly liquefy the fibrin clots of normal

human plasma. Plasma half-life of streptokinase is 30 minutes. A major disadvantage of this agent is its antigenic effect, including anaphylaxis, due to preformed antibodies.[7]

Tissue-type plasminogen activator

Tissue-type plasminogen activator (t-PA) is a naturally occurring fibrinolytic agent produced by endothelial cells. This agent is highly fibrin specific and has a short plasma half-life of 5 to 7 minutes.[7, 8] Currently available agents are alteplase (recombinant t-PA), derived from cloned human t-PA, and reteplase and tenecteplase, genetically engineered mutant forms of t-PA.[9]

Urokinase

Macfarlane et al.[10] first described the fibrinolytic potential of human urine. Urokinase directly activates plasminogen to form plasmin. The agent is non-antigenic.[7] It has low fibrin affinity and specificity and a plasma half-life of approximately 15 minutes.[8] Pro-urokinase is a precursor of urokinase. It is relatively fibrin-specific because it preferentially activates fibrin-bound plasminogen found in a thrombus over free plasminogen in flowing blood.[7]

THROMBOLYSIS CATHETERS

End-hole thrombolysis catheter

Dotter et al.[11] described the first thrombolysis catheter in 1974. This was an end-hole thrombolysis catheter. A disadvantage of this catheter was the need to reposition the tip of the catheter during thrombolysis and to have the tip in the remaining thrombus, with the possible risk of distal embolization because of manipulation of the thrombus.

Multiple side-hole thrombolysis catheter

At the beginning of the 1990s a multiple side-hole catheter was developed. A major advantage of this catheter was that it obviated the need for repeat repositioning of the thrombolysis catheter and thereby reduced the risk of distal embolization.[12, 13] Examples of currently available multiple side-hole catheters are the Prostream Multiple Sidehole Infusion Wire (Covidien, Mansfield, MA, USA), the Cragg-McNamara Valved Infusion Catheter (Covidien, Mansfield, MA, USA), and the UniFuse (AngioDynamics, Queensbury, NY, USA).

INFUSION TECHNIQUES

Continuous infusion

This is the standard method for performing catheter-directed thrombolysis. The thrombolytic agent is infused using a constant infusion pump.[14] Continuous, low-dose infusion is an appropriate infusion technique when prompt revascularization is not warranted.

Graded infusion

With graded infusion, a higher dosage of thrombolytic agents is administered in the first hours of treatment. An advantage of this technique is faster revascularization but it is associated with a higher risk of hemorrhagic complications.[9]

Forced infusion

With forced infusion (i.e., pulse-spray infusion), a high-pressure spray of small pulses of concentrated thrombolytic agents is forced homogeneously and simultaneously into the thrombus. This causes mechanical and enzymatic degradation of the thrombus. An advantage of this technique is even distribution of thrombolytic agents in the thrombus by forceful injection, overcoming thrombus resistance.[15] Greenberg et al.[4] showed that the time to reperfusion was reduced but that lysis was more incomplete and distal embolization was increased compared with continuous infusion. Pulse-spray thrombolysis can be time consuming when applied manually. Examples of currently available pulse-spray infusion systems are the Fountain Infusion Catheter With Squirt Fluid Dispensing System (Merit Medical Systems, Inc., South Jordan, UT, USA) and the Pulse*Spray Infusion System (AngioDynamics, Queensbury, NY, USA).

PERCUTANEOUS THROMBUS ASPIRATION DEVICES

Percutaneous thrombus aspiration devices can be used alone or with catheter-directed thrombolysis. The technique was first reported by Greenfield et al.[16] in 1969. The system consists of a thin-walled guiding catheter, a vascular sheath with a removable hemostatic valve, and a 50-mL Luer lock syringe. The removable hemostatic valve is necessary to prevent retention of aspirated thrombus within the sheath upon removal from the artery.[17] With this technique, the thrombus is passed with a guidewire, and a catheter is passed until it is embedded in the thrombus. The guidewire is removed, and suction of the thrombus is applied with a syringe.[18] Disadvantages of this technique are damage to the arterial wall caused by suction and only fresh thrombi can be treated. An overview of available percutaneous thrombus aspiration devices is provided in the Table.

PERCUTANEOUS MECHANICAL THROMBECTOMY DEVICES

Percutaneous mechanical thrombectomy devices were originally developed for the treatment of occluded hemodialysis grafts. Most percutaneous mechanical thrombectomy devices are used off-label for the treatment of peripheral arterial occlusions. They are generally fast in restoring blood flow but are associated with damage to the vessel wall and creation of sizable emboli.[4] Therefore only high-risk patients who are not candidates for catheter-directed thrombolysis or surgery should be treated with these devices.

Table. Percutaneous thrombus aspiration devices for peripheral arterial occlusions.

Company, Product Name	Maximum Tip Diameter (mm)	Minimum Guide Catheter Size (F)	Catheter Length (cm)
Bayer, Fetch 2 Aspiration Catheter	1.42	6	135
Control Medical Technology, Aspire RX-LP6	1.7	6	136
Maquet Vascular Systems, Thrombuster II	1.35, 1.52	6	140
Medtronic, Inc., Export Catheter	1.73, 1.98	6, 7	140, 145
Merit Medical Systems, Inc., ASAP Aspiration Catheter Kit	1.73	6	140
OptiMed Medizinische Instrumente GmbH, Big Lumen Aspiration Catheter	1.25, 1.48, 1.64, 1.88	5, 6, 7, 8	70, 80, 90, 100, 120
Qualimed Innovative Medizinprodukte GmbH, Aspiration Catheter	0.5	5, 6, 7	135, 141
Spectranetics Corporation, QuickCat Extraction Catheter	1.4	6	145
Terumo Europe, Eliminate	N/A	6, 7, 8	140
Vascular Solutions, Inc., Pronto Extraction Catheter	1.65-2.2	6, 7, 8	138

Hydrodynamic recirculation devices

Hydrodynamic recirculation devices make use of the Venturi-Bernoulli effect. Heparinized saline is retrogradely injected through a catheter with a hairpin loop at the tip. This causes a local reduction in pressure that sucks the thrombus into the aperture of the catheter.[17] Currently available devices are the AngioJet Thrombectomy Set (Possis, Minneapolis, MN, USA), Hydrolyser (Cordis Corporation, Fremont, CA, USA), and Oasis (Boston Scientific Corporation, Natick, MA, USA). The AngioJet Thrombectomy Set consists of an over-the-wire catheter with a high-pressure saline jet at the distal tip that is retracted with high speed, creating a localized vacuum effect. This causes dissociation and entrainment of the thrombus.[19] The Hydrolyser and Oasis are similar systems.

Rotational circulation devices

These devices cause clot disruption by production of a hydrodynamic vortex, which is created by a high-speed rotating impeller or basket. Currently available devices are the Trellis Peripheral Infusion System (Covidien) and the Rotarex S (Straub Medical AG, Wangs, Switzerland). The Trellis device is a pharmacomechanical thrombectomy system (6F or 8F and working length of 80 or 120 cm) that isolates the thrombus between two balloons while exposing the thrombus to a thrombolytic agent and using wire oscillation. This causes fragmentation of the thrombus, after which the thrombus is aspirated.[20] The Rotarex S device is a catheter (6F or 8F and working length of 85 or 110 cm) that contains a rotating steel spiral that fragments the clot while producing a continuous vacuum. The fragmented clot is transported to a collector bag.[21]

ULTRASOUND-ACCELERATED THROMBOLYSIS

A very different approach to catheter-directed thrombolysis is the addition of low-intensity, high-frequency ultrasound. This technique uses ultrasound to increase permeability of the thrombus, and thereby enhances delivery of thrombolytics into the thrombus. Moreover, it increases enzy-

matic activity of thrombolytic agents and thereby accelerates thrombolysis.[22] EKOS Corporation developed the EkoSonic Endovascular System (EKOS Corporation, Bothell, WA, USA) to provide ultrasound-accelerated thrombolysis. This system consists of a 5.2F multilumen drug-delivery catheter with a working length of 106 or 135 cm, a matching ultrasound coaxial core wire with a working zone of 6 to 50 cm, and a portable control unit. The multilumen drug-delivery catheter consists of 3 lumens for dispersion of the thrombolytic agent and a central lumen that accommodates the US core wire. The multiple side holes of the drug-delivery catheter correspond to the miniature US transducers for the delivery of low-intensity (2.2 MHz) high-frequency ultrasound over the entire working zone of the US core wire.[23]

CONCLUSIONS

Thrombolytic agents, thrombolytic catheters, and infusion techniques are under constant development, aiming to provide faster and more complete lysis of thrombus, while reducing hemorrhagic complications. The effect of thrombolytic agents depends on the intricate interaction between the biochemical characteristics of the thrombolytic agent and the individual patient's hemostatic system, the technique used to infuse the thrombolytic agent, and the composition of the thrombus.

Choosing the right pharmacomechanical thrombolysis device depends on thrombus characteristics as well as patient characteristics. A multiple side-hole catheter is currently the standard of care because it provides more even distribution of thrombolytic agents over the thrombus compared with end-hole catheters. Continuous, low-dose infusion is an appropriate infusion technique when prompt revascularization is not warranted and can be useful in overnight infusion treatment strategies. Possible advantages of graded and forced infusion techniques over continuous infusion techniques are faster restoration of blood flow. Disadvantages of these techniques are a higher incidence of hemorrhagic complications and distal embolization due to clot fragmentation in forced infusion techniques. Percutaneous thrombus aspiration can be a useful adjunct to catheter-directed thrombolysis when fast removal of thrombus load is required, for example, to facilitate placement of the catheter prior to initiation of catheter-directed thrombolysis or for small amounts of residual thrombus after discontinuation of catheter-directed thrombolysis. The use of percutaneous thrombectomy devices should be restricted to patients who are not suitable for catheter-directed thrombolysis.

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Chapter 3

Long-term outcomes of catheter-directed thrombolysis for acute lower extremity occlusions of native arteries and prosthetic bypass grafts

A.M. Schrijver, J.P.P.M. de Vries, D.A.F. van den Heuvel, F.L. Moll

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ABSTRACT

Objective

Catheter-directed thrombolysis is a well-accepted treatment for acute lower extremity occlusions of native arteries and bypass grafts. Several variables that affect outcomes of thrombolysis have been identified. The hypothesis of this study was that the long-term outcome after catheter-directed thrombolysis would be better for acute lower extremity occlusions of native arteries compared with prosthetic bypass grafts.

Methods

This observational study retrospectively analyzed 159 consecutive patients (114 men), median age, 65 years (range 57-73 years), with 89 native artery (56%) and 70 prosthetic bypass graft (44%) occlusions of the lower extremity. All patients were treated with catheter-directed thrombolysis between 2006 and 2009 in two vascular referral centers in the Netherlands. The severity of ischemia was Rutherford class I (52%), class IIa (27%), class IIb (12%), and unknown (9%) in native arteries and class I (64%), class IIa (19%), class IIb (1%), and unknown (16%) in bypass grafts. Median (range) duration of symptoms before the start of thrombolysis was 3.5 (1-14) days in native arteries and 3 (1-9) days in bypass grafts. All patients were treated with a continuous dosage of urokinase (100,000 IU/h). Amputation-free survival was estimated by conduit type using the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate analyses were performed using a Cox proportional hazards model.

Results

Complete (>95%) lysis was achieved in 69% of native arteries and bypass grafts (p=1.00). Major hemorrhagic complications occurred in 12% (4% hemorrhagic strokes, of which 2% were fatal) of native arteries and in 7% (0% hemorrhagic stroke) of bypass grafts (p=0.28). The 30-day mortality rate was 6% in native arteries and 1% in bypass grafts (p=0.17), and the 30-day amputation rate was 10% in native arteries and 13% in bypass grafts (p=0.45). Mean follow-up was 27±19 months. Amputation-free survival at 1 year was 76% for native arteries and 78% for bypass grafts and at 5 years was 65% for native arteries and 51% for bypass grafts (p=0.32). Multivariate analysis showed two negative predictors for amputation-free survival: age >65 years and cerebrovascular disease. Conduit type was not an independent predictor for amputation-free survival (p=0.78).

Conclusion

Despite initial promising results, long-term follow-up of catheter-directed thrombolysis for acute lower extremity occlusions showed a disappointing amputation-free survival. In a multivariate analysis, no significant differences in amputation-free survival between native arteries and prosthetic bypass grafts were determined.

INTRODUCTION

Background

Catheter-directed thrombolysis is a well-accepted treatment in selected patients with (semi) acute occlusions of lower extremity native arteries and bypass grafts. Because hemorrhagic complications, and especially hemorrhagic stroke, may occur, identifying and selecting patients who are expected to have the best short-term and long-term outcome after catheter-directed thrombolysis is crucial. Several patient-related and occlusion-related factors have been identified that might possibly affect the outcome of thrombolysis.

Proposed patient-associated factors have been gender, tobacco use, race, age, weight, coronary artery disease, diabetes, hypertension, renal insufficiency, hypercholesterolemia, cerebrovascular occlusive disease, congestive heart failure, malignancy, and pre-existing peripheral arterial occlusive disease (PAOD).[1-8] Proposed occlusion-associated characteristics have been the cause of the occlusion (thrombus versus embolus), level of occlusion (suprainguinal versus infrainguinal), number of occluded segments involved, length of occlusion, Rutherford classification, duration of ischemic symptoms, and number of runoff vessels.[2, 4, 8-10]

Controversy continues in the current literature about the outcome of catheter-directed thrombolysis in occluded lower extremity native arteries compared with bypass grafts. Available studies are difficult to compare because different outcome measures are used. Most studies have used short-term outcomes, such as technical success of thrombolysis, whereas only some studies have investigated long-term outcomes such as amputation-free survival. Most studies have a short duration of follow-up. Although most studies have found no difference in amputation-free survival between native arteries and bypass grafts, there is some evidence that the long-term outcome is better for native arteries.[11, 12]

Hypothesis

The hypothesis of this study was that the long-term outcome after catheter-directed thrombolysis is better for acute lower extremity occlusions of native arteries compared with prosthetic bypass grafts.

MATERIALS AND METHODS

Study design

This was a retrospective cohort study in two vascular referral centers in the Netherlands, the St. Antonius Hospital, Nieuwegein, and the University Medical Center Utrecht, Utrecht. The study included patients with (semi-)acute (<28 days) occlusions of lower extremity native arteries and prosthetic bypass grafts with acute ischemia class I, IIa, and IIb, according to the Rutherford classification for acute lower extremity ischemia.[13] In the event a patient underwent more than one episode of thrombolysis during the study period, the outcome of the first thrombolysis treatment was analyzed.

Procedure

An antegrade approach was used through the ipsilateral common femoral artery, if possible; otherwise, a crossover approach via the contralateral femoral artery was used. Initial angiography included the iliac arteries and femoropopliteal arteries as well as the below-the-knee outflow. All patients received a continuous infusion with urokinase (100,000 IU/h). During thrombolysis, systemic heparin was given at a dose of 100,00 IU/24 hours. Routine blood tests were performed that included fibrinogens, prothrombin times, and activated partial thromboplastin times. Thrombolysis was discontinued in case of complete lysis, in case of no progression of lysis within 24 hours, or in case of complications such as progressive ischemia requiring immediate surgical intervention or hemorrhagic complications.

Any necessary additional procedure, such as percutaneous transluminal angioplasty (PTA), with or without additional stent placement, was performed at any stage in the treatment process if considered appropriate. After successful thrombolysis, systemic heparin was given (25,000 IU/24 hours), and coumarin derivatives were started. The target international normalized ratio (INR) was 2.5 to 3.5. If this value was reached, heparinization was stopped.

Definitions

Complete lysis was defined as >95% clot lysis at angiography.[14] Major hemorrhage was defined as a hemorrhage necessitating discontinuation of thrombolysis, transfusion, or surgical intervention. Diabetes was considered if patients were receiving antidiabetic treatment with diet, oral hypoglycemic agents, or insulin. Tobacco use was defined as current or former tobacco use. Hypertension was defined as systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg, measured on at least two occasions, and/or a previous diagnosis of hypertension or taking antihypertensive drugs. Hyperlipidemia was defined as measured elevated levels of any or all lipids and/or lipoproteins in the blood. Coronary artery disease was considered if patients had a history of angina pectoris, myocardial infarction, or treatment for coronary artery disease. Renal insufficiency was defined as preprocedural creatinine <1.5 mg/dL. Cerebrovascular disease was considered if there was a history of stroke or transient ischemic attack (TIA).

Contraindications for catheter-directed thrombolysis were adopted from the Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II).[15] Absolute contraindications for thrombolysis were (1) an established cerebrovascular event, excluding TIA, within the previous 2 months, (2) active bleeding diathesis, (3) gastrointestinal bleeding within the previous 10 days, (4) intracranial or spinal neurosurgery within the previous 3 months, and (5) head trauma within the previous 3 months.

Data collection

All consecutive patients treated with catheter-directed thrombolysis for occlusions of native arteries and bypass grafts of the lower extremity between January 2006 and December 2009 in the two participating hospitals were included. Patients were identified by the hospital registry

for radiologic procedures. The medical records and the radiologic imaging studies related to the thrombolytic treatment of the included patients were retrospectively reviewed. During the study period 72 patients were registered in our database as primary surgical intervention for acute lower extremity occlusions.

Statistical analysis

Statistical analysis was performed using SPSS 20.0 software (IBM Corp, Armonk, NY). Continuous parametric data are presented as means and standard deviations and continuous nonparametric data as medians with interquartile ranges. Dichotomous data are presented as frequencies with percentages. Amputation-free survival was estimated by conduit type using the Kaplan-Meier method and compared using the log-rank test ($p<0.05$). Univariate and multivariate analyses were performed using a Cox proportional hazards model to identify independent predictors for amputation-free survival and to correct for potential confounders. Proposed predictors for amputation-free survival were entered as covariables in the univariate analysis. Dummy coding was applied for categorical variables. Variables showing a p-value of <0.15 with univariate analysis were included in the multivariable analysis. A p-value of <0.05 was considered statistically significant.

RESULTS

Patients

The study included 159 consecutive patients (114 men), who were a median age of 65 years (range, 57-73 years), with 89 native artery (56%) and 70 prosthetic bypass graft (44%) occlusions of the lower extremity that were treated with catheter-directed thrombolysis. Baseline characteristics are presented in Table 1. There was a significant difference in the presence of hypertension, hyperlipidemia, coronary artery disease, anticoagulation use, and Rutherford class between patients with native arteries and prosthetic bypass grafts.

Technical success

Complete (>95%) lysis was achieved in 69% of native arteries and bypass grafts ($p=1.00$).

Complications

Major hemorrhagic complications occurred in 12% (7% hemorrhage from vascular access site and 5% remote hemorrhage, of which 4% were hemorrhagic strokes) of native arteries and 7% (3% hemorrhage from vascular access site and 4% remote hemorrhage, of which 0% were hemorrhagic strokes) of bypass grafts ($p=0.28$). All four hemorrhagic strokes occurred during thrombolysis. Fibrinogen levels in all four patients were above 1.0 g/L during hemorrhagic stroke. After the occurrence of a stroke, thrombolysis was discontinued immediately. Two patients died of hemorrhagic stroke. No patients died of other hemorrhagic complications.

Table 1. Baseline characteristics of 159 patients undergoing catheter-directed thrombolysis for occluded lower extremity native arteries and prosthetic bypass grafts.

Characteristic	Native arteries (n =89)	Bypass grafts (n =70)	Total (n=159)	P
Age, y	64 (55-75)	65 (59-71)	65 (57-73)	0.931
Gender				0.088
Male	59 (66)	55 (79)	114 (72)	
Female	30 (34)	15 (21)	45 (28)	
Diabetes				0.155
Yes	18 (20)	21 (30)	120 (76)	
No	71 (80)	49 (70)	39 (24)	
Tobacco use				0.791
Yes	56 (63)	41 (59)	50 (31)	
No	30 (34)	20 (28)	97 (61)	
Unknown	3 (3)	9 (13)	12 (8)	
Hypertension				0.025
Yes	47 (53)	49 (70)	61 (39)	
No	41 (46)	20 (29)	96 (60)	
Unknown	1 (1)	1 (1)	2 (1)	
Hyperlipidemia				0.001
Yes	33 (37)	43 (62)	79 (50)	
No	55 (62)	24 (34)	76 (48)	
Unknown	1 (1)	3 (4)	4 (2)	
Coronary artery disease				0.003
Yes	21 (24)	32 (46)	104 (66)	
No	67 (75)	37 (53)	53 (33)	
Unknown	1 (1)	1 (1)	2 (1)	
Renal insufficiency				0.849
Yes	12 (14)	10 (14)	134 (84)	
No	76 (85)	58 (83)	22 (14)	
Unknown	1 (1)	2 (3)	3 (2)	
Cerebrovascular disease				0.695
Yes	11 (12)	10 (14)	137 (86)	
No	78 (88)	59 (85)	21 (13)	
Unknown	0 (0)	1 (1)	1 (1)	
Medication				0.000*
None	31 (35)	3 (4)	34 (21)	
Warfarin	13 (15)	28 (40)	41(26)	
Ascal	44 (49)	33 (48)	77 (48)	
Both	1 (1)	3 (4)	4 (3)	
Unknown	0 (0)	3 (4)	3 (2)	
Duration of symptoms, d	3.5 (1.0-14.0)	3.0 (1.0-8.5)	3.0 (1.0-10.0)	0.115
Rutherford class				
I	46 (52)	45 (64)	91 (57)	
IIa	24 (27)	13 (19)	37 (23)	0.015*
IIb	11 (12)	1 (1)	12 (8)	
Unknown	8 (9)	11 (16)	19 (12)	
Target occlusion				
Suprainguinal	23 (26)	17 (24)	40 (25)	0.822
Infrainguinal	66 (74)	53 (76)	119 (75)	
Number of runoff vessels				
0	17 (19)	9 (13)	26 (16)	
1	19 (21)	7 (10)	26 (16)	
2	20 (23)	23 (33)	43 (27)	
3	31 (35)	26 (37)	57 (36)	
Unknown	2 (2)	5 (7)	7 (5)	

Values represent absolute numbers with percentages (n [%]) for categorical variables and median ± IQR or means (95% confidence intervals) for continuous values. *Pearson χ^2.

Follow-up

The 30-day mortality rate was 6% in native arteries and 1% in bypass grafts (p=0.17). Early (<30 days) and late (>30 days) causes of death are reported in Table 2. The 30-day amputation rate was 10% in native arteries (all of these patients had unsuccessful lysis) and 13% in bypass grafts (7 patients with unsuccessful lysis and 2 patients with successful lysis; p=0.45). Mean follow-up was 27±19 months. Amputation-free survival at 1 year was 76% for native arteries and 78% for bypass grafts and at 5 years was 65% for native arteries and 51% for bypass grafts (p=0.32; Figure 1.).

Table 2. Early (<30 days) and late (>30 days) causes of death in 159 patients undergoing catheter-directed thrombolysis for occluded lower extremity native arteries and prosthetic bypass grafts.

Causes	Early (<30 days) death	Late (>30 days) death*
Cerebro-cardiovascular		
Stroke	2 (hemorrhagic)	1 (ischemic)
Myocardial ischemia	1	0
Congestive heart failure	0	4
Peripheral arterial ischemia	1	2
Bowel ischemia	1	0
Non cerebro-cardiovascular		
Respiratory failure	0	2
Sepsis	1	1
Gastrointestinal	0	1
Malignancy	0	4
Trauma	0	1
Unknown	0	6

Values represent absolute numbers. *Excluding deaths within 30 days.

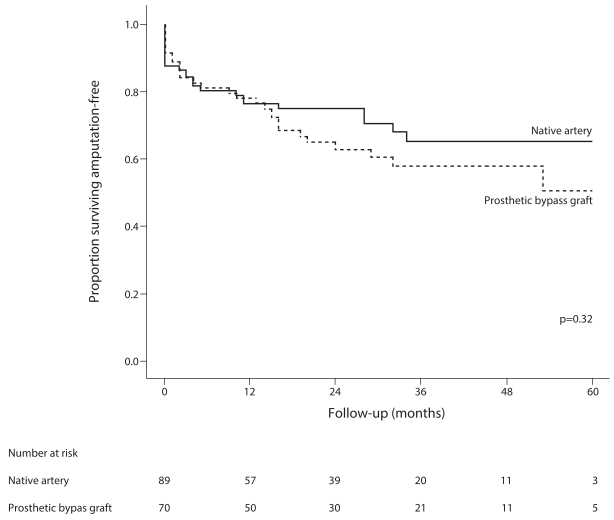

Figure 1. Amputation-free survival in 159 patients undergoing catheter-directed thrombolysis for occluded lower extremity native arteries and prosthetic bypass grafts.

Univariate and multivariate analyses

Results of the univariate and multivariate analyses are summarized in Table 3. In the univariate analysis, age >65 years, diabetes, tobacco use (positive predictor), cerebrovascular disease, anticoagulation use, and Rutherford class were predictors for amputation-free survival. Gender, hypertension, hyperlipidemia, coronary artery disease, renal insufficiency, history of peripheral arterial disease, duration of symptoms, level of occlusion, and number of runoff vessels were not predictors for amputation-free survival. Multivariate analysis showed two independent predictors for amputation-free survival: age >65 years and cerebrovascular disease. Conduit type was not an independent predictor for amputation-free survival (p= 0.78).

Table 3. Univariate and multivariate analysis of variables associated with amputation-free survival.

Characteristic	Univariate analysis		Multivariate analysis†	
	P	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)
Age (>65 years/<65 years)	0.004*	2.2385 (1.322-4.303)	0.038*	2.267 (1.046-4.913)
Gender (female/male)	0.825	0.932 (0.497-1.745)	-	-
Diabetes (yes/no)	0.049*	1.754 (1.002-3.070)	0.137	1.677 (0.848-3.318)
Tobacco use (yes/no)	0.034*	0.533 (0.297-0.954)	0.22	0.651 (0.328-1.293)
Hypertension (yes/no)	0.274	1.398 (0.767-2.550)	-	-
Hyperlipidemia (yes/no)	0.873	1.046 (0.605-1.807)	-	-
Coronary artery disease (yes/no)	0.787	1.081 (0.612-1.911)	-	-
Renal insufficiency (yes/no)	0.359	1.384 (0.691-2.770)	-	-
Cerebrovascular disease (yes/no)	0.002*	2.587 (1.400-4.781)	0.043*	2.127 (1.024-4.416)
Medication				
None (ref category)	0.012*		0.095	
Warfarin	0.035	2.313 (1.059-5.050)	0.111	2.271 (0.829-6.219)
Ascal	0.786	0.895 (0.402-1.993)	0.853	0.916 (0.362-2.317)
Both	0.187	2.816 (0.605-13.109)	0.206	2.983 (0.548-16.244)
History of PAOD	0.314	1.369 (0.743-2.524)	-	-
Duration of symptoms (>14/<14 days)	0.217	0.603 (0.271-1.345)	-	-
Rutherford class				
I (ref category)	0.060*		0.137	
IIa	0.023	2.065 (1.107-3.853)	0.083	1.889 (0.920-3.879)
IIb	0.213	1.791 (0.716-4.482)	0.174	2.376 (0.683-8.267)
Level of occlusion (infrainguinal/suprainguinal)	0.371	1.355 (0.696-2.638)	-	-
Number of run off vessels				
0 (ref category)	0.555		-	-
1	0.318	0.627 (0.251-1.567)		
2	0.33	0.678 (0.310-1.482)		
3	0.162	0.577 (0.268-1.246)		
Conduit type (bypass graft/native artery)	0.293	1.156 (0.882-1.515)	0.778	1.053 (0.735-1.510)

*Statistically significant. †Multivariate analysis is performed with variables showing a p-value <0.15 in the univariate analysis. PAOD; peripheral arterial occlusive disease.

DISCUSSION

This study represents one of the largest published series comparing long-term amputation-free survival after catheter-directed thrombolysis in occluded native arteries and prosthetic bypass grafts of the lower extremity. Initial technical results of catheter-directed thrombolysis in native arteries and in prosthetic bypass grafts were acceptable; however, long-term follow-up showed a disappointing amputation-free survival in both groups. Multivariate analysis found two negative predictors for amputation-free survival: age >65 years and cerebrovascular disease. Conduit type was not an independent predictor for amputation-free survival.

During the study period, only 13 patients with an occlusion of a venous bypass graft were treated with catheter-directed thrombolysis. This group was too small to compare with the current two groups. To prevent heterogeneity in the bypass graft group, we did not include the venous bypass grafts, which is a limitation of this study. During the study period, 16 patients were treated with catheter-directed thrombolysis for chronic (>28 days) arterial lower limb occlusions. These patients were also not included.

An overview of studies comparing short-term and long-term outcome after catheter-directed thrombolysis for lower extremity native arteries and bypass grafts is presented in Table 4.[1, 2, 4, 6-9, 11, 12, 16, 17] Three of these studies were randomized controlled trials. Comparison of native arteries and bypass grafts was based on subgroup analyses.[7, 12, 16] Amputation-free survival is the preferred primary endpoint in reporting results of thrombolytic therapy in lower extremity ischemia.[18] However, most studies have compared short-term outcomes, such as technical success and 30-day patency, in native arteries and bypass grafts. Current literature reporting the short-term outcome of catheter-directed thrombolysis is inconsistent. Some studies have shown higher technical success for native arteries than for bypass grafts,[1, 8, 11] others have shown better results for bypass grafts,[12, 14] and some authors report no difference between native arteries and bypass grafts.[9, 17, 19] None of the studies made a distinction between venous and prosthetic bypass grafts.

A large number of studies describing long-term follow-up after catheter-directed thrombolysis have described death or amputation, or both. The number of studies that have compared amputation-free survival in native arteries and bypass grafts is small. Consistent with our findings, the studies by Breukink et al., Earnshaw et al., Kuoppala et al., and Ouriel et al., found no difference in amputation-free survival between native arteries and bypass grafts.[1, 2, 6, 7] The study by Kuoppala et al.[6] was the only study that made a distinction among native arteries, venous bypass grafts, and prosthetic bypass grafts. The studies by Plate et al. and Geier et al. found a higher amputation-free survival for patients with an occluded native artery compared with a bypass graft.[11, 12] However, these studies made no distinction between venous and prosthetic bypass grafts.

We found that age >65 years and cerebrovascular occlusive disease were independent predictors for amputation-free survival after catheter-directed thrombolysis. These variables might be associated with more extensive (atherosclerotic) disease, and therefore a higher risk of amputa-

Table 4. Overview of studies comparing short- and long-term outcome after catheter-directed thrombolysis for lower extremity native arteries and bypass grafts.

Article	Patients	Study design	Follow-up	Technical success	Amputation-free survival			
	(n)		(mon)	(%)	1 month (%)	6 months (%)	1 year (%)	Last follow-up (%)
STILE[16] 1994	249	RCT	6	70 (no difference)	-	83 (no difference)	-	-
Ouriel et al. 1998[7]	544*	RCT	12	-	85 (no comparison)	-	68 (no difference)	-
Plate et al. 2009[12]	121	RCT	12	72 (favors BG)	85 (no difference)	-	69 (favors NA)	-
Clouse et al. 1994[9]	82	Retrospective	1	77 (no difference)	-	-	-	-
Earnshaw et al. 2004[2]	1133	Prospective	1	46 (no comparison)	75 (no difference)	-		-
Breukink et al. 2004[1]	129	Retrospective	36	72 (favors NA)	-	88 (no comparison)	-	83 (no difference)
Geier et al. 2007[11]	82	Retrospective	52	82	-	-		87 (favors NA)†
Kuoppala et al. 2008[6]	220	Retrospective	32	41 (no comparison)	-	-	-	51(no difference)
Kuhn et al 2011[17]	129	Retrospective	12	74 (no difference)	-	-	-	-
Kashyap et al. 2011[4]	129	Retrospective	17	82 (no comparison)	82 (no comparison)	-	-	-
Vakhitov et al. 2014[8]	149	Retrospective	1	77 (favors NA)	-	-	-	-
Present study	159	Retrospective	27	69	-	-	76 (NA), 78 (BG)	65 (NA), 51 (BG)

Follow-up is presented as mean or median. *50% treated surgically; †Included only patients with initial successful thrombolysis. NA denotes native artery; BG denotes bypass graft.

tion or death, or both.[7] Other studies have also found older age is a predictor for amputation-free survival.[2, 5, 7] Cerebrovascular disease has been reported as a predictor for amputation-free survival.[6, 7] In the study by Kuoppala et al.,[6] cerebrovascular disease was only a predictor for amputation-free survival in the univariate analysis. In their multivariate analysis, cerebrovascular disease was an independent predictor for death but not amputation.

The current guidelines recommended catheter-directed thrombolysis only in acute (<14 days old) thrombus.[18] Interestingly, we found that duration of symptoms was not an independent predictor for amputation-free survival. This finding is consistent with the findings of Breukink et al.[1] Another study found that duration of symptoms was also not an independent predictor for technical success.[9] We found that Rutherford classification was not an independent predictor for amputation-free survival. This finding is consistent with results of the study by Breukink et al.[1]

Hemorrhagic complications remain the largest limitation to catheter-directed thrombolysis. We found no significant difference in the occurrence of hemorrhagic complications between native arteries and bypass grafts. The current overall bleeding complication rate of 10% is comparable to the bleeding complication rates of two large randomized controlled trials in which catheter-directed thrombolysis was compared with surgical intervention.[14, 16] The current technical success rate of approximately 70% in native arteries and in bypass grafts is comparable to these trials as well.[14, 16, 17] The determined amputation-free survival is comparable to the outcome of a large retrospective study by Kuoppala et al.[6]

This study has some limitations. Since the major focus of this manuscript was to describe the long-term outcomes of thrombolysis rather than 30-day complication rate and initial technical success, no detailed information about the amount of fibrinolytics and heparin was included. Patency rates during follow-up were not recorded due to the retrospective character of our study. Moreover, the decision to perform a reintervention is often physician dependent. A number of our patients were referred back to their peripheral hospital after being treated in our tertiary center. Not all follow-up data from the peripheral hospitals could be retrieved, which resulted in some loss to follow-up.

CONCLUSION

Despite initial promising results, long-term follow-up of catheter-directed thrombolysis for acute lower extremity occlusions showed a disappointing amputation-free survival. Hemorrhagic complications remain the largest limitation to catheter-directed thrombolysis. The current results did not show a significant difference in amputation-free survival between native arteries and prosthetic bypass grafts. Catheter-directed thrombolysis should therefore not be withheld from patients based on conduit type. In older patients and patients with cerebrovascular disease, a poor outcome in terms of amputation-free survival is anticipated.

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Chapter 4

Catheter-directed thrombolysis for acute upper extremity ischemia

A.M. Schrijver, G.J. de Borst, J.A. van Herwaarden, E.J. Vonken, F.L. Moll, J.A. Vos, J.P.P.M. de Vries

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ABSTRACT

Background

Acute nontraumatic upper extremity ischemia has significant chronic disability when not treated adequately and timely. As surgical treatment can be challenging, this study evaluates catheter-directed thrombolysis as first-line treatment for acute upper extremity ischemia.

Methods

Between January 2006 and December 2010, 28 patients (22 women; mean age, 63±16 years) underwent catheter-directed thrombolysis for acute upper extremity ischemia, Rutherford class I or IIa. Proximal extent of the occlusion was in the subclavian (32%), axillary (7%), brachial (25%) and forearm arteries (36%). Median occlusion length was 18 cm (range, 12–43). Causes were embolus (14%), thrombus (39%), thoracic outlet syndrome (14%), paraneoplastic (4%), or unknown (29%).

Results

Technical success was 96%, radiologic success (>95% clot lysis) 61%, and clinical success 68%. Median duration of thrombolysis was 24 hours (range, 18-96). Of the 11 radiologically unsuccessful patients (39%), five were treated conservatively and six underwent surgical intervention. In-hospital amputation-rate was 7%. Four complications occurred: embolization to the lower extremity, a transient ischemic attack, a subcapsular splenic hematoma and a pseudoaneurysm. Cumulative amputation-free survival at six months was 93%, standard error (S.E.) 4.87 and at one year 88%, S.E. 6.50.

Conclusions

These results show that catheter-directed thrombolysis is effective in over 60% of patients as first-line treatment of extensive acute upper extremity ischemia and can prevent surgical intervention in these patients.

INTRODUCTION

Acute ischemia of the upper extremity is rare compared with acute ischemia of the lower extremity. The incidence of acute upper extremity ischemia is 1.3/100,000 persons, which accounts for 15% to 18% of patients with acute extremity ischemia.[1, 2] Acute upper extremity ischemia may occur secondary to traumatic or nontraumatic causes. The most common nontraumatic cause of acute upper extremity ischemia is an embolus, most frequently of cardiac origin. The second most common nontraumatic cause is a local thrombus superimposed on underlying atherosclerosis. Less common causes are arterial thoracic outlet syndrome (TOS), paraneoplastic syndrome, vasculitis, and Raynaud phenomenon.[3, 4] Although acute upper extremity ischemia usually does not immediately threaten the limb due to an extensive collateral circulation, it has been associated with a high level of functional impairment and chronic disability if left untreated.[5, 6]

Since the 1960s, the state-of-the-art treatment for acute nontraumatic upper extremity ischemia has been balloon catheter embolectomy, as first described by Fogarty et al.[7] Reported complication rates after balloon catheter embolectomy are low. However, since in the majority of patients no postoperative angiography is performed, some injuries are undetected unless they cause severe symptoms that warrant diagnostic investigation.[8, 9] Reported complications after embolectomy are arterial rupture by over inflation of the balloon, arterial perforation by the catheter tip and pseudoaneurysm formation.[10, 11] Other limitations are the occurrence of reocclusions due to damage to the intimal layer of the arterial wall[12-14] and the inability to remove all of the thrombus, especially in the small arteries of the forearm and hand.[15]

Over the years, the use of catheter-directed thrombolysis to treat acute nontraumatic upper extremity ischemia has gained interest. Advantages of catheter-directed thrombolysis compared with balloon catheter embolectomy include its less invasive character, minimal trauma to the intimal wall, clearance of thrombus in small arteries, and the possibility to visualize and treat any underlying cause of occlusions like stenosis in peripheral and collateral arterial territories in the arm. Although thrombolysis has established its role in the treatment of acute lower extremity ischemia,[16] reports on the use of thrombolysis in the treatment of acute upper extremity ischemia are scarce; moreover, most reports are outdated and include small numbers of patients.[17-28]

This study evaluates the outcome of catheter-directed thrombolysis as first-line treatment in patients with acute nontraumatic upper extremity ischemia in two tertiary vascular referral hospitals in the Netherlands.

METHODS

The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patients and study design

From January 2006 until December 2010, all consecutive patients presenting with acute (complaints <24 hours) nontraumatic upper extremity ischemia class I or IIa according to Rutherford were eligible for inclusion in our study and were prospectively registered. Patients were treated primarily with catheter-directed thrombolysis, unless contraindicated. Contraindications for thrombolysis were adopted from the TransAtlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease II.[29] Patients with acute upper extremity ischemia Rutherford class IIb or III were treated primarily by surgical means and patients with acute upper extremity ischemia caused by trauma were also excluded.

Pre-intervention evaluation

A detailed history and clinical examination were undertaken in all patients. Arterial duplex, Computed Tomography Angiography (CTA) or Magnetic Resonance Angiography (MRA) of the affected extremity was performed to localize the occlusion. CTA of the thoracic aorta and echocardiogram were performed to identify cardiothoracic sources of emboli. Cardiac embolism was assumed to be the cause of the occlusion if a cardiac embolus was identified on echocardiography or if patients had a history of atrial fibrillation, or both, combined with absence of an underlying atherosclerotic lesion of the affected extremity or thoracic aorta on angiography. Arterial TOS was diagnosed when the occlusion was in the subclavian artery at the level of the thoracic outlet and physical examination and electromyography were suggestive for thoracic outlet syndrome. Possible underlying coagulation disorders were identified.

Interventions

Thrombolysis

All patients underwent diagnostic subtraction angiography on presentation. The preferred access was via the common femoral artery. If this was not possible, access was through the axillary, subclavian or brachial artery in an antegrade fashion (proximal of the occlusion). After the occlusive lesion was localized, placement of a thrombolysis catheter was attempted. If placement of a thrombolysis catheter was successful, urokinase was continuously infused in a dosage of 100,000 IU/hour, with systemic heparin in a dosage of 10,000 IU/24 hours. Control angiographies were performed on indication of clinical improvement or deterioration. Thrombolysis was discontinued when lysis was complete (>95% clot lysis),[30] if lysis did not progress after 24 hours of treatment, if progressive arm ischemia occurred that required immediate surgical intervention, or if hemorrhagic complications occurred. After successful thrombolysis, heparin was given and coumarin derivatives were started. During heparinization, the target activated partial thromboplastin time (aPTT) ratio was 1.5 to 2.5 and was measured twice daily. The target international normalized ratio (INR) was 2.5 to 3.5; if this value was reached, heparin was stopped.

Additional interventions

An additional intervention was defined as an intervention to treat an underlying disease that caused the occlusion and included percutaneous transluminal angioplasty (PTA), with or without additional stent placement for pre-existent occlusions, or transaxillary first rib resection in case of TOS.

Secondary interventions

A secondary intervention was defined as an intervention necessary because of incomplete thrombolysis or progressive ischemia, or both, and included embolectomy, bypass grafting, or amputation.

Data collection

Patients were prospectively registered in a database, as described in *Patients and Study Design*, and data analysis was performed retrospectively. Collected data included patient demographics, vascular risk factors, arterial occlusion characteristics, interventions and reinterventions, amputations, complications (i.e. hemorrhage, stroke, distal embolization), and death.

Follow-up

Routine clinical follow-up was scheduled at one month and one year post-procedurally.

Outcomes

The outcome measures included (1) technical success, defined as successful placement of a thrombolysis catheter with the distal tip of the catheter positioned in the occluded segment; (2) radiologic success, defined as complete (>95%) clot lysis as demonstrated with angiography with outflow through at least one forearm artery to the arcus palmaris;[30] (3) clinical success, defined as complete resolution of ischemic symptoms and restoration of radial or ulnar pulse, or both; (4) hemorrhagic complications; (5) reinterventions; (6) amputation; (7) mortality; and (8) amputation-free survival. Radiologic success was determined by two experienced interventional radiologists who evaluated all the pre-intervention and post-intervention angiographies.

Statistical analysis

Analyses were performed using SPSS 19.0 software (SPSS Inc., Chicago, Ill, USA). Categorical variables are presented as numbers and percentages. Continuous variables are reported as means ± standard deviation (SD) and as medians (range) in case of non-normal distributions. A two-sided $P < .05$ was considered statistically significant. Cumulative amputation-free survival was calculated by Life Table analysis.

RESULTS

Patient inclusion

During the 5-year study period, 42 patients presented with acute nontraumatic upper extremity ischemia. Fourteen patients were excluded: two had acute ischemia (Rutherford I) with very mild symptoms and were treated conservatively by their own preference, 12 had acute ischemia that threatened the extremity (Rutherford IIb or III) requiring immediate surgical intervention by embolectomy or bypass grafting, or both. The remaining 28 patients (22 women; mean age, 63 ± 16 years) were indicated for catheter-directed thrombolysis as first-line treatment. Patient characteristics are presented in Table 1. Seventeen patients (61%) were American Society of Anesthesiologists class 3.

Occlusion characteristics are presented in Table 2. Notably in 10 of 28 patients (36%), more than one arterial segment was occluded; in Table II only the proximal extent of the occlusion is indicated. Median length of the occlusion was 18 cm (range, 12–43 cm). The minority of patients suffered from emboli. Most of the patients had pre-existent atherosclerotic disease.

Table 1. Baseline characteristics of 28 patients undergoing catheter-directed thrombolysis for acute upper extremity ischemia.

Characteristic	Patients (n=28)
Age, y	63±16
Female sex	22 (79)
Predisposing factors	
Insulin-dependent diabetes	1 (4)
Smoking, current or recent	13 (46)
Hypertension	9 (32)
Hypercholesterolemia	7 (25)
Coronary artery disease	4 (14)
Stroke or TIA	3 (11)
History of malignancy	
Current (<5 y)	4 (14)
Past	11 (3)
ASA class	
1	4 (14)
2	7 (25)
3	17 (61)
Preprocedural medication	
Warfarin	5 (18)
Acetylsalicylic acid	10 (36)
None	13 (46)
Rutherford class	
I	15 (54)
IIa	13 (46)

ASA, American Society of Anesthesiologists; TIA, transient ischemic attack. Continuous data are presented as mean ± standard deviation, and categorical data as number (%).

Table 2. Occlusion characteristics of 28 patients undergoing catheter-directed thrombolysis for acute upper extremity ischemia.

Characteristic	Occlusions (n=28)
Right sided	15 (54)
Type of conduit	
Artery	25 (89)
Bypass	3 (11)
Proximal level of occlusion	
Subclavian	9 (32)
Axillary	2 (7)
Brachial	7 (25)
Radial/ulnar	10 (36)
Extent of occlusion	
1 segment	18 (64)
>1 segment	10 (36)
Cause	
Embolus	4 (14)
Thrombus	11 (39)
Thoracic outlet syndrome	4 (14)
Paraneoplastic	1 (4)
Unknown	8 (29)

Data are presented as number (%).

Technical success

A thrombolysis catheter was successfully placed in the occluded segment in 27 of 28 patients (96%). Placement of a thrombolysis catheter was technically not feasible in one patient due to inability to transverse an in-stent occlusion of the subclavian artery with a guidewire. This patient, with acute ischemia Rutherford class I, was further managed with medical treatment because of mild complaints.

Radiologic success

In 17 of 28 patients (61%) >95% clot lysis was achieved. Median duration of thrombolysis was 24 hours (range, 18-96 hours). An additional intervention was performed in six of these 17 patients (35%). PTA of an underlying atherosclerotic lesion was performed in four patients, and two patients underwent a transaxillary resection of the first rib at six weeks after thrombolysis because of TOS. In the remaining 11 of 17 patients with radiologic successful thrombolysis, no underlying cause of the acute occlusion could be determined.

Thrombolysis was not successful in 11 of 28 patients (39%). No correlation between failure of treatment and severity of ischemia, duration of ischemic symptoms, location of occlusion or cause of occlusion could be found. Partial lysis was achieved in four of 11 patients. One of these patients was successfully treated with embolectomy, with complete resolution of symptoms. Three patients preferred conservative treatment; of these, two had become asymptomatic and one patient remained mildly symptomatic. No lysis was achieved in seven patients; including

the patient with technical failure of catheter placement, as aforementioned. In the remaining six patients thrombolysis was discontinued because there was no lysis of thrombus after 24 hours. Of these, one patient requested conservative treatment, and the remaining five underwent embolectomy because of persistent ischemic complaints. Embolectomy was successful in three patients, with complete resolution of symptoms. In two patients, embolectomy was not successful, and progressive ischemia resulted in forearm amputation in one patient and upper arm amputation in the other. The first patient had an occlusion of the subclavian artery and multiple thrombi in the radial, ulnar and hand arteries. Thrombolysis of the subclavian artery was successful; however thrombolysis of the forearm and hand was not successful. Two attempts of embolectomy were performed, followed by forearm amputation because of progressive ischemia. The second patient had an occlusion of the forearm arteries. After unsuccessful thrombolysis, embolectomy was performed. Eventually an upper arm amputation was performed, because of progressive ischemia due to residual thrombus.

Of the seven patients that had failed lysis two patients had an embolus of cardiac origin, two patients suffered from a thrombus with pre-existent atherosclerotic disease, and in three patients the etiology of the occlusion could not be determined.

Clinical success

Complete resolution of ischemic symptoms after thrombolysis alone was achieved in 19 of 28 patients (68%), this includes two of the patients with partial clot lysis. After secondary intervention complete resolution of ischemic symptoms was achieved in 23 patients (82%).

In-hospital morbidity and mortality

In-hospital mortality was 0%. The amputation-rate was 7%, as described in the previous section. Four other complications occurred in three patients. In the first patient embolization to the superficial femoral artery and crural arteries of the lower extremity occurred during the completion angiography, which was successfully treated with thrombolysis. This patient had pre-existent single vessel crural outflow. In the second patient, a vertebrobasilar transient ischemic attack (TIA) occurred directly after discontinuation of thrombolysis. Duplex scanning showed an underlying atherosclerotic lesion of the ipsilateral vertebral artery. A CT study of the brain showed no ischemia or hemorrhage. The patient recovered without neurological sequelae. In the third patient, who eventually underwent upper arm amputation because of progressive ischemia, a false aneurysm developed at the puncture site of the femoral artery that thrombosed spontaneously. The same patient developed a subcapsular splenic hematoma one week after thrombolysis. This patient needed blood transfusion. There was no need for (surgical) intervention. Therefore, the major hemorrhagic complication rate was 4%. In all three patients thrombolysis-related complications did not adversely affect secondary interventions.

Follow-up

At one-month follow-up, two patients had developed a reocclusion after an initially successful thrombolysis. One patient was successfully treated with renewed catheter-directed thrombolysis (no cause of reocclusion could be determined), and another patient was treated with thrombosuction and re-PTA of a pre-existent stenosis. Treatment was successful in both patients. No patients died during one-month follow-up, and no amputations were necessary.

Two patients died during follow-up: one patient died of an acute myocardial infarction at 7 months after initial hospitalization. The other patient died of multi-organ failure due to sepsis of unknown cause at one year after initial hospitalization (Figure 1). Cumulative amputation-free survival at six months was 93%, standard error (S.E.) 4.87 and at one year 88%, S.E. 6.50 (Figure 2).

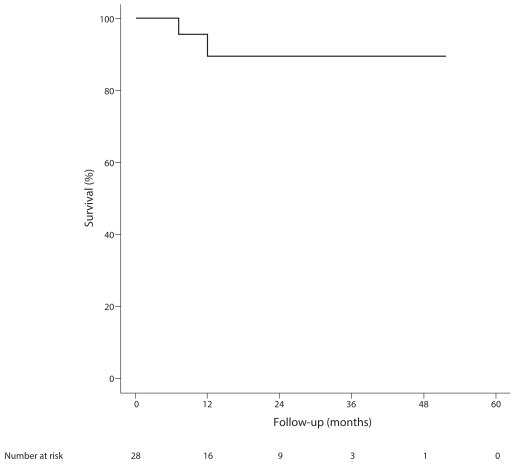

Figure 1. Kaplan-Meier curve of survival.

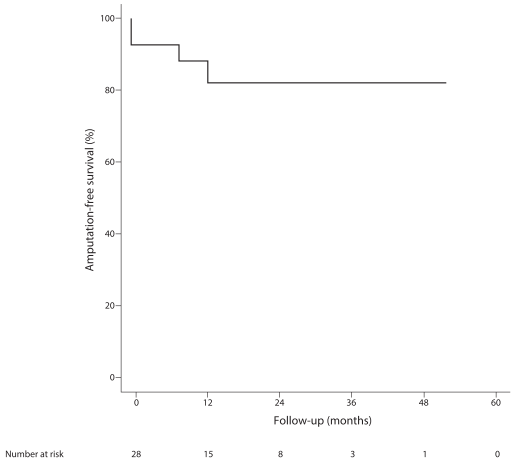

Figure 2. Kaplan-Meier curve of amputation-free survival.

DISCUSSION

In this study, catheter-directed thrombolysis as a first-line treatment in patients with acute non-traumatic upper extremity ischemia was radiologically successful in 61% of patients and clinically successful in 68% of patients. Of the remaining 11 radiologically unsuccessful patients (39%), five were treated conservatively and six underwent surgical intervention. Of the latter group of patients, two subsequently underwent an upper arm and a forearm amputation respectively, due to extensive and progressive ischemia. Despite absence of in-hospital mortality, four complications occurred. In-hospital amputation-rate was 7%.

Women comprised 79% of our study population. This female preponderance in acute upper extremity ischemia has previously been described.[3, 31] The mean age of our study population was 63 years. Patients presenting with acute upper extremity ischemia tend to be older than patients with acute lower extremity ischemia.[2]

In this study the percentage of patients with acute upper extremity ischemia due to a cardiac embolism is relatively low (14% of the total cohort) as compared to current literature. The reported incidence of cardiac embolism as a cause of upper extremity ischemia is up to 90%. Most studies attribute the cause of occlusion to associated cardiac conditions, but often this cannot be confirmed pathologically. Since atherosclerosis in the arteries of the upper extremity is more rare as compared to the lower extremity, some investigators label all non-traumatic upper extremity ischemia as embolic. This could cause over reporting of cardiac embolisms as a cause of upper extremity ischemia.[3]

In more than one- third of our patients, more than one arterial segment was occluded. Median arterial occlusion length was 18 cm. A substantial part of the patients had pre-existent atherosclerotic lesions of the upper extremity arteries. We believe that these long-segment acute on chronic occlusions are particularly suitable for catheter-directed thrombolysis instead of invasive surgical intervention. Embolectomy in diseased arteries might cause intimal damage to the small arm arteries and dislodgement of atherosclerotic plaques.

In our study, a quarter of patients had a history of malignancy. Other studies have shown that patients suffering from cancer have a higher risk of developing arterial thrombosis. This is probably due to the hypercoagulable state associated with malignancy.

Hemorrhagic complications are the main limitation of thrombolytic therapy. However, the hemorrhagic complication rate was low (4%) in our study, as compared to the 9% described in current literature.[16] The risk of hemorrhagic complications should be weighed against the low complication rate of surgical embolectomy for localized emboli.

A TIA occurred in one patient. This patient was treated for a thrombus in the subclavian artery. Cerebral embolization resulting in TIA or stroke can be caused by pericatheter thrombosis from a catheter that is localized in the supra-aortic region[19, 23] or by the underlying thrombogenic lesion.

Our in-hospital amputation rate of 7% is considerable. However, it is comparable to studies in which embolectomy has been described. In 1998 Eyers et al. published a review on the outcome of embolectomy in acute upper extremity ischemia. They reported amputation rates ranging

from 0 to 20%.[3] Over more, a large observational cohort study from Denmark that included 1377 patients that underwent thromboembolectomy of the upper extremity reported an amputation rate up to 3.6%.[32]

The main limitations of this study are its retrospective design and the absence of long-term routine follow-up. Furthermore, a minority of patients with acute ischemia Rutherford class I was managed with medical treatment, because of very mild symptoms. It remains debatable if these patients should have been treated with thrombolysis at all.

Several non-randomized studies on catheter-directed thrombolysis for acute upper extremity ischemia have been published.[17-28] The majority of studies are case reports or small cohort studies with less than 10 patients.[20, 22-28]

The largest case series was published by Cejna et al. in 2001, describing a retrospective cohort study of 38 patients undergoing thrombolysis for 40 acute arterial occlusions of the upper extremity. The overall radiologic success rate was 55%, and for small segment upper arm occlusions the success rate was 100%. No lethal complications occurred and no amputations were required in the follow-up period.[18]

Baguneid et al. reported a retrospective cohort study of 12 patients undergoing thrombolysis for acute upper extremity ischemia. Technical failure occurred in three patients. In all patients an embolectomy could be safely performed. Complete lysis was achieved in six patients. In one patient partial lysis was achieved, but this patient had become asymptomatic. In the remaining patients no lysis was achieved; one patient was treated with embolectomy and one with a bypass graft. No major hemorrhagic complications occurred and no amputations were performed.[17]

Coulon et al. reported a retrospective cohort study of 13 patients. In 8 patients complete lysis was achieved and in five patients partial lysis was achieved. One patient suffered from a TIA, probably due to a cerebral embolism upon catheter withdrawal. No amputations were performed.[19]

Johnson et al. reported 12 patients undergoing thrombolysis for acute arterial occlusions of the upper extremity. In all patients partial lysis was achieved. In four patients a digital amputation was performed; notably all of these patients had presented with Rutherford class III ischemia. No complications occurred.[21]

CONCLUSIONS

This patient series shows that catheter-directed thrombolysis is valuable in around 60% of patients as first-line treatment for long-segment arterial occlusions of the upper extremity to prevent or limit surgical intervention.

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Chapter 5

Advancements in catheter-directed ultrasound-accelerated thrombolysis

D.E. Doomernik, A.M. Schrijver, C.J. Zeebregts, J.P.P.M. de Vries, M.M.P.J. Reijnen

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ABSTRACT

Introduction

Pharmacological catheter derived thrombolysis has evolved into an accepted treatment modality of a variety of thromboembolic conditions. Additional use of ultrasound waves may increase lysis rate, thereby reducing therapy time. The objective of the present study was to review all available literature on catheter-directed ultrasound-accelerated thrombolysis for peripheral arterial occlusions (PAO), stroke, deep venous thrombosis (DVT) and pulmonary embolism (PE).

Materials and Methods

A systematic literature search was performed, using MEDLINE, EMBASE and Cochrane databases. A total of 77 reports focusing on catheter-delivered ultrasound-accelerated thrombolysis were identified.

Results

Experimental studies show that high intensity ultrasound may induce thrombolysis, with and without the addition of plasminogen activators, mainly by acoustic cavitation and mechanical disruption, while low intensity, high frequency ultrasound waves may actually enhance plasmin-mediated thrombolysis. In a total of 340 clinical cases of various thromboembolic conditions, catheter-directed ultrasound-accelerated thrombolysis was related to rapid revascularization and a reduction in treatment time, drug dosage, hospitalization time, and possibly major bleeding complications compared to standard thrombolysis. Reported complication rates, including bleeding and embolization, were low.

Conclusion

Ultrasound-enhanced thrombolysis seems to be a promising concept in the treatment of various thromboembolic conditions. The technique has shown to be safe and efficacious in vitro, in vivo and in clinical studies. Randomized controlled trials are warranted and should be awaited before considering catheter-directed ultrasound-accelerated thrombolysis as a new standard treatment.

INTRODUCTION

In recent years, pharmacological catheter-directed thrombolysis (CDT) has become an accepted treatment modality for a variety of thromboembolic conditions, including infrainguinal arterial thromboemboli, stroke and deep venous thrombosis. Acute infrainguinal arterial thrombosis is related to significant morbidity and mortality. Traditional therapy consists of surgical thrombectomy, which is associated with incomplete thrombus removal, a high rate of re-thrombosis, perforation, pseudoaneurysm formation and intimal hyperplasia.[1-3] Advantages of CDT are its minimal invasive character, gentler clot removal and the opportunity to immediately treat an underlying cause endovascularly. Potential drawbacks of this technique include high costs, an extended time needed for revascularization, hemorrhagic complications, and renal dysfunction related to repeated angiography.[4-7]

Stroke and stroke related death are an increasing cause of concern in the western world. Currently, stroke is the third most common cause of mortality in the western world.[8, 9] In 2008 The American College of Chest Physicians (ACCP) has stated that the preferred treatment of acute ischemic stroke is the intravenous administration of recombinant tissue plasminogen activator (r-tPA), provided that treatment is initiated within 3 hours of clearly defined symptom onset. Additionally, the use of catheter-delivered thrombolytic therapy may be indicated in selected patients with acute middle cerebral artery or acute basilar artery thrombosis in specialized centers, although this indication is still matter of dispute. Limitations of the technique, for instance contraindications for thrombolytic drugs and side effects such as intracranial hemorrhage, emphasize the need to develop adjunctive therapies increasing efficacy and minimizing the administered dose of thrombolytic drugs.[3]

The two major manifestations of venous thromboembolic events are deep venous thrombosis (DVT) and pulmonary embolism (PE). Over 90% of acute PE are caused by emboli originating from proximal veins of the extremities and is the most significant complication of DVT, with a mortality rate of 12%.[10] The vast majority of patients with DVT are treated with low-molecular-weight heparin and coumarin derivatives. Before the introduction of these agents 80% of patients with DVT developed a severe form of post-thrombotic syndrome (PTS),[11] which is associated with a reduced quality of life[12] and chronic venous ulceration.[13] The use of heparin and coumarin derivatives has reduced the incidence of PTS to 20-50% within 1 to 2 years after the symptomatic episode of DVT.[14] However, anticoagulation therapy does only prevent propagation of thrombus and does not resolve existing thrombus.[3] Catheter-delivered thrombolysis of DVT may offer a valid alternative in patients with extensive acute DVT as it might shorten treatment time, reduce acute symptoms and, most importantly, reduce the incidence of PTS.[15, 16] Interventional catheterization techniques of PE may also be indicated in compromised patients who are unsuitable to receive prolonged systemic thrombolytic therapy due to bleeding risk.[3]

Several in vitro studies have suggested a role for ultrasound in accelerating thrombolysis.[17-43, 43-57] In addition, in vivo studies have shown that transcutaneous applied ultrasound waves, either

alone or in combination with thrombolytic agents, are capable to enhance thrombolysis in peripheral arterial occlusions (PAO), DVT,[27, 45, 58-68] stroke,[69] and myocardial infarction.[63, 70-72] However, adverse effects of transcutaneous ultrasound application, including interstitial edema, internal and external tissue damage[45, 65, 66, 73-75] and the disruption of the blood-brain barrier, causing brain edema and infarction,[76, 77] have limited its applicability in common clinical practice.

Recently, catheter-delivered thrombolysis has been combined with catheter-delivered high frequency, low intensity ultrasound in order to accelerate clot dissolution, thereby reducing treatment time and the incidence of thrombolysis-related complications. Ultrasound waves may increase clot permeability by affecting the fibrin strands, thereby facilitating the delivery of therapeutic agents into the clot.[78-83] A rapid restoration of complete blood flow is likely to reduce the risks of treatment and costs.[84, 85] The aim of the present study was to summarize all available evidence on catheter-delivered ultrasound accelerated thrombolysis.

METHODS

A systematic literature search was conducted to identify reports on the application of catheter-delivered ultrasound-accelerated thrombolysis, published until September 1, 2010, using the MEDLINE, EMBASE and Cochrane databases. The following MeSH search terms were used: ultrasonography, ultrasonic therapy, thrombolytic therapy, stroke, pulmonary embolism, venous thrombosis and arterial occlusive diseases. Other non-MeSH terms such as catheter-delivered ultrasound, peripheral arterial occlusions, thrombolysis, and ultrasound enhanced/accelerated thrombolysis, were also used. These terms were applied in various combinations in addition to the use of the 'related articles' and 'citing articles' function. Full-text articles were studied without restriction of language of publication and manual cross-referencing was performed. Reports were classified by in vitro studies, in vivo studies and clinical trials. Experimental studies focusing on transcutaneously applied ultrasound were excluded.

A total of 77 reports on catheter-delivered ultrasound-accelerated thrombolysis were identified; 51 reports presented data from in-vitro studies, 11 reports described results from in vivo studies and 15 reports described clinical results of catheter-delivered ultrasound-accelerated thrombolysis in case series. To date no randomized controlled trials have been published in the area of catheter delivered ultrasound thrombolysis.

RESULTS

In vitro studies

In 1976, Truebestein et al. were the first to demonstrate that ultrasound waves could disrupt clots.[17] Additional animal studies suggested that this approach had the potential for peripheral arterial clot dissolution. Since then two fundamentally different approaches have been evolved in the use of ultrasound for thrombolysis. In the first concept high intensity ultrasound is applied in

order to mechanically disrupt the clot, while in the second concept a lower intensity ultrasound is used to augment enzymatic fibrinolysis by breaking linkage of fibrin strands.[86]

High intensity ultrasound

In the early studies of Truebestein et al. high intensity ultrasound was used in order to disrupt clots.[17, 18] Later studies showed that a simultaneous application of thrombolytic drugs, such as urokinase and t-PA, led to synergistic effect on clot resolution.[28] Several other studies have confirmed the observation that catheter-delivered ultrasound at different intensities (10-150W, 20kHz) could mechanically disrupt clots with[87-89] or without the administration of plasminogen activators.[19-24]

Siegel et al.[22] were the first to demonstrate the effectiveness of catheter-delivered ultrasound in atherosclerotic clot ablation. Treatment, however, was limited by vessel perforation, thermal heating and the generation of microscopic debris. These adverse effects were considered to be related to the thermal heating, the use of continuous wave energy at an intensity of > 20 W, the application of the probe perpendicular to longitudinally opened segments and the use of ultrasound for at least 30s. In addition, other researchers observed that the effects of ultrasound on dissolution rates were inversely related to its intensity.[20, 23] Hong et al.[19] observed that ultrasound waves could disrupt human blood clots by both mechanical and cavitational mechanisms, rather than by fibrinolysis. In contrast, Rosenschein et al.[21] have shown that high-intensity focused ultrasound provided a safe and effective mean to induce thrombolysis.

Low intensity ultrasound

Various experimental studies have shown that low intensity, high frequency ultrasound waves may actually enhance plasminogen activator mediated thrombolysis.[25-31, 31-38] According to Blinc et al.[25] the degree of thrombolysis depends on the plasminogen activator concentration, the intensity of ultrasound waves, the duty cycles and the frequency. A successful thrombolytic effect has been reported for urokinase,[25, 26, 28] r-tPA,[25, 48] t-PA,[27] reteplase,[35] and streptokinase[25, 28, 34, 36] at intensities ranging from 0,125-4 W/cm^2. The lytic effect of streptokinase and reteplase, however, disappeared at intensity levels of 4 W/cm^2 and greater, indicating that the balance between ultrasound waves and pharmacological treatment is crucial.[34-36] In addition, Soltani et al.[90] demonstrated that ultrasound with a frequency of 1MHz and intensities of 2,5-3,1 W/cm2 had no statistically significant effect on the enzymatic activity of the plasminogen activators, urokinase, reteplase, alteplase and streptokinase. Nevertheless, only limited data is available on the ideal concentrations of plasminogen activators necessary for optimal ultrasound enhanced thrombolysis. The highest lytic rates of r-tPA have been reported using a dose of 1-3 µg/mL.[47]

Importantly, a variation in the used ultrasound waves may affect its thrombolytic efficacy. The use of low frequency ultrasound has repeatedly been shown to accelerate fibrinolysis with a reduction of side effects caused by thermal heating.[39-41, 43-47, 49] The use of a pulsed mode ultrasound[29, 33] significantly enhanced thrombolysis when compared to continuous waves and

a rise of duty cycles resulted in increased clot lysis.[48] Moreover, traveling waves significantly[38] accelerated thrombolysis, either in a pulsed[37] or continuous wave mode, when compared to standing waves.[38]

An addition of microbubbles to ultrasound therapy may further increase the thrombolytic effect of ultrasound-accelerated thrombolysis.[55, 91-100] Several in vitro studies have been focusing on the use of catheter-delivered ultrasound as a potential use in the endovascular area. According to Tachibana et al.[26, 53] the use of catheter-delivered ultrasound at respectively 225 kHz and 1.3 MHz combined with urokinase accelerated thrombolysis. Similar results were described by the group of Shlansky-Goldberg[54] using a 640 kHz catheter-mounded transducer with urokinase. In addition, the use of albumin microbubbles in combination with urokinase and pulse-waved ultrasound catheter (170 kHz, 0.5 W/cm^2, 60 sec) significantly enhanced the fibrinolytic effect.[55]

Hartnell et al.[56] evaluated an ultrasonic thrombolysis device for intracoronary use and reported rapid clot lysis, less local heating and little debris release during clot ablation. These results were confirmed by the studies of Muller-Leisse et al.[57] In addition, Fischell et al.[42] showed at moderate power outputs, effective for clot ablation, a dose dependent, reversible vasorelaxant effect of catheter-delivered ultrasound in rabbit thoracic aortas, which was not related to thermal heating or irreversible smooth muscle cell injury. They suggested that this vasorelaxation effect could further enhance the safety and efficacy of catheter directed ultrasound thrombolysis.

In vivo studies

Animal studies using a catheter-delivered external ultrasound transducer for clot dissolution are relatively rare. Rosenschein et al.[21] have described that a pulsed mode ultrasound (20 kHz) significantly reduced obstruction in canine femoral arteries. Histological examination showed no damage to the media or adventitia. Applying the same pulse mode ultrasound, a rapid disruption of occluded arteries, without thermal or cavitation injury, embolization, or perforation, was found in a canine femoral artery model[20, 101] and in xenografts.[101] In addition, an arterial relaxation effect of catheter delivered external ultrasound was found ex-vivo and in-vivo in occluded canine femoral arteries. Histological examination revealed no evidence of perforation, thermal damage, blast injury, re-thrombosis or vessel damage.[42] A case control study, Steffen et al.[87] showed that an activated ultrasound probe was able to completely disrupt a coronary thrombus in 13 out of 15 dogs and partially in 2 out of 15 dogs, while there was no clot lysis in the control group without ultrasound. Again, there was no histological evidence of ultrasound-mediated vessel damage or residual thrombus.

A relative new concept is the catheter-delivered transducer tipped ultrasound. Experiments in the rabbits' aorta using a continuous ultrasound exposure during 10 minutes demonstrated no endothelial damage due to thermal or mechanical factors.[102] Atar et al.[103-105] tested a prototype of a transducer-tipped ultrasound catheter with a local drug delivery capability in 16 bilateral occluded superficial femoral arteries in dogs. Significantly more partial or complete reperfusion ($p=0.0007$), widely patent artery segments ($p=0.0002$) and lower distal embolization rates

(p=0.05) were found in the ultrasound (1,1 MHz, 0,6 W/cm^2) plus low-dose urokinase group compared to urokinase treatment alone. In a similar designed study, Atar et al.[106] and Mitchel et al.[107] confirmed these results using the same catheter. These first comparative studies showed significant more complete perfusion in the combined ultrasound and urokinase treated arteries when compared to controls.[103-107]

Clinical Data

Peripheral arterial occlusions

The first clinical results using ultrasound-accelerated thrombolysis with the EKOS Ultrasound Infusion System (EKOS Corporation, Bothell, WA, USA) were published by Greenberg et al.[108] in 1999 (Table 1). In a small series of 9 patients with acute lower extremity ischemia, they described technical difficulties in 3 patients in which the procedure had to be discontinued. The technical success rate of the 6 remaining cases was 100% after changing the study design. Revascularization was seen in 5 of the 6 cases. In addition, Link et al.[109] reported a technical success rate of 80% using the same system in 5 patients with acute leg ischemia over a mean treatment time of 5.75 hours and 8.5 mg rtPA. Complete lysis was achieved in 3 patients.

In 2007, Wissgott et al.[110] published a retrospective non-randomized trial designed to evaluate the efficacy and safety of the EKOS Peripheral Infusion System (EKOS Corporation, Bothell, WA, USA) in 25 patients with acute thrombotic occlusions of the lower limb (Figure 1). The inclusion and exclusion criteria were matched to the TOPAS protocol to allow comparison to a control group.[111] Early recanalization (>50% thrombus resolving after 6 hours of treatment) occurred in 23 patients (92%), with achieving complete lysis in 8 patients (32%). Complete lysis, defined angiographically as > 95% clot removal and < 30% residual stenosis, was achieved in 22 patients (88%) after 16 hours of treatment. Partial lysis had been realized in one patient and in another patient there was no lysis. In one case treatment had to be ended due to a dislocation of the introducer sheath. Additional treatment, such as percutaneous transluminal angioplasty (PTA), stent placement, thrombectomy and vascular repair, was performed in 12 (48%) patients. The technical success rate, defined as placement of the tip of the catheter distal to the thrombus and simultaneous delivery of ultrasound with lytic infusion, was 100% and no adverse events attributable to the EKOS Peripheral Infusion System were described. The mean time to discharge was 4 days (range 1-6 days). During 1-month follow-up, 2 re-occlusions occurred. No amputations or deaths were reported. The authors concluded that the use of ultrasound-accelerated thrombolysis is a safe, effective and time-saving treatment, achieving rapid recanalization and higher rates of complete lysis. Similar results were obtained by Motarjeme,[112] who reported a complete lysis of 96% with a mean treatment time of 16.4 hours in a group of 24 patients with an occlusion of an iliac, femoral or popliteal artery. They reported a shorter infusion time and higher rate of complete lysis using the Lysis Infusion System (EKOS Corporation) compared to the TOPAS[111] and RELAX[113] trials. There were no procedure-related complications and during a 12 month follow-up a re-occlusion occurred in only one patient.

Table 1. Clinical data on catheter-directed ultrasound-enhanced thrombolysis in arterial and venous occlusions of the extremities.

Study	N	Type	Mean Thrombus Size, cm (range)	Lysis Complete/ Partial/ None	Stopped Procedure	Mean Dose (range)	Mean Time to Complete Lysis, h (range)	Complications	Complications in Follow-up
Peripheral arterial occlusions									
Greenberg 1999[108]	9	A	NR	5 (55.5%)/—/1 (11.1%)	3 (33%)	NR	NR	NR	NR
Link 2000[109]	5	A	NR	3 (60%)/NR/NR	1 (20%)	8.5 mg rtPA	5.75	1 unspecified	NR
Wissgott 2007[110]	25	A	25 (2-70)	22 (88%)/1 (4%)/ 1 (4%)	1 (4%)	17 mg rtPA (5–25)	16.9 (5–24)	1 dislocated catheter, hematoma	2 reocclusions
Motarjeme 2007[112]	24	A,C	NR	23 (96%)/NR/NR	0%	NR	16.4 (3–25)	None	1 reocclusion
Wissgot 2008[114]	10	A	337 (11-50)	9 (90%)/—/—	1 (10%)	15.1 mg rtPA (2–22.5)	15.1 (2–22.5)	1 dislocated catheter, hematoma	1 reocclusion
Kasirajan 2008[115]	27	A,C	29	27 (100%)/—/ —	0%	tPA dosage NR	16.4610	None	None
Crouch 2008[116]	1	A	NR	1 (100%)/—/—	0%	5 U reteplase	21.5	None	None
Raabe 2010[117]	29	A	NR	NR/NR/2 (6.9%)	0%	39.0 mg alteplase	41.4	1 minor access site bleeding, AMI (n=1)	None
Deep venous thrombosis									
Raabe 2006[124]	45	A,C	28.5	32 (71.1%)/ 9(20%)/ 2 (4.4%)	2 (4.4%)	NR	24.7	Major bleeding, hematoma (n=2)	None
Motarjeme 2007[112]	12	A,C	NR	10 (83.1%)/ NR/ NR	0%	NR	21.2	None	1 reocclusion
Parik 2008[126]	53	A, SA, C	NR	37 (69.8%)/11 (20.8%)/5 (9.4%)	0%	2 million U UK 14.0 mg tPA 6.9 U rtPA 9.5 mg TE	22 (6–69) UK: 19.3 tPA: 18.0 rtPA: 24.0 TE: 24.3	Hematoma - increased bleeding risk (n=2)	NR
Kasirajan 2008[115]	10	A, C	29	4 (40%)/4 (40%)/ 2 (20%)	0%	tPA dosage NR	16.4	None	1 reocclusion
Raabe 2010[117]	9	A, SA, C, A-on-C	NR	NR/NR/1 (11.1%)	0%	45.9 mg alteplase	45.3	None	1 reocclusion

A: acute, C: chronic, SA: subacute, NR: not reported, AMI: acute myocardial infarction, A-on-C: acute on chronic.

In a prospective trial, Wissgott et al.[114] compared the EKOS Lysis Peripheral Catheter System (EKOS Corporation) with a rotational mechanical thrombectomy device (Rotarex, Straub Medical, Wangs, Switzerland) in 20 patients with an acute occlusion of a femoropopliteal bypass graft. The mean duration to achieve complete lysis was significant lower ($p<0.05$) in the mechanical thrombectomy group, i.e. 1 hour compared to 15 hours in the lysis group. The technical success rate was 100% in the thrombectomy group and 90% in the ultrasound-accelerated thrombolysis group, due to a dislocation of the introducer sheath, which was successfully treated by open surgery. Additional treatment was performed in both groups (60% in the thrombectomy group compared to 70% in the lysis group). No major complications were reported. The mean hospitalization time was 2.3 days in the mechanical thrombectomy group and 8.5 days in the lysis group. During follow-up, re-intervention was necessary in one patient in the lysis group because of a re-occlusion. The authors concluded that both techniques were very safe and effective in the treatment of acute arterial occlusions.

In 2008 Kasirajan[115] presented data of 37 patients with arterial and venous occlusions, treated with the EKOS EndoWave Endovascular System. Complete lysis was achieved in all arterial patients without any complication related to the EKOS device. In addition, Crouch et al.[116] used the EKOS EndoWave Endovascular System in a 66-year-old woman with a right femoral-tibial peroneal bypass graft occlusion. After 1 hour of treatment, pulses in the dorsalis pedis returned and a patent bypass with minimal residual thrombus had been achieved in 21.5 hours of infusion with in total 5 U reteplase. PTA was performed to treat the underlying atherosclerotic irregularity. The patient was discharged the 4th day post treatment without complications.

Very recently, Raabe has studied the EKOS EndoWave Endovascular System, in combination with alteplase, in 29 patients with a peripheral arterial occlusion. Twenty-seven out of 29 patients achieved either complete or partial lysis without an unusual decline in fibrinogen levels. No major complications were reported. These data suggest that shorter infusion times and lower

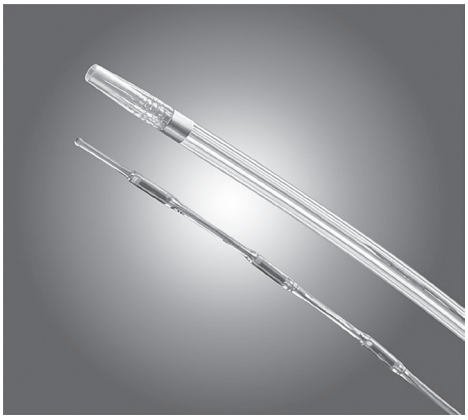

Figure 1. The transducer tipped ultrasound probe of the EKOS EndoWave Endovascular Device. (Kindly provided by EKOS Corporation, Bothell, WA, USA)

administered drug doses related to the use of ultrasound accelerated thrombolysis, may limit fibrinogenolysis, thereby minimizing fibrinogen depletion and reducing the likelihood of bleeding complications.[117]

Stroke

The first clinical experience with the EKOS MicroLysUS Infusion Catheter (EKOS Corporation) for acute embolic stroke was published in 2003 by Mahon et al.[118]. They studied 14 patients with an occlusion of the anterior (n=10) or posterior (n=4) cerebral circulation and symptoms of cerebral ischemia. At the end of ultrasound-accelerated thrombolysis using either tPA or reteplase a complete perfusion was achieved in 36% of patients (n=5), a partial perfusion in 29% (n=4) and 5 patients died. Three patients died within 24 hours after treatment due to cerebral edema (n=1) and intracranial hemorrhage (n=2). In another patient the thrombolysis had to be terminated due to bradycardia and hypotension, followed by cerebral edema which required neurosurgical intervention and the patient died within 4 days because of non-hemorrhagic herniation. A fifth patient died one month after treatment due to intracranial hemorrhage. No adverse events attributable to manipulation of the catheter, such as perforation, dissection, vasospasm and vessel occlusion were seen. During follow-up improvement was noted in all major standardized stroke scores. The group with posterior occlusions performed better on average standard stroke score scales than those with anterior occlusions. It was concluded that ultrasound-accelerated thrombolysis is associated with a similar or slightly better rate of recanalization and neurologic outcome compared to the historical controls using standard thrombolytic therapy.[119-121]

The Interventional Management of Stroke II (IMS II) trial[122] was developed to determine if micro-catheter technology using the EKOS Micro Infusion System (EKOS Corporation) in combination with intra-venous (IV) and/or intra-arterial (IA) administration of thrombolytic drugs is safe and effective in patients with ischemic stroke. Eighty-one patients were enrolled in the study of which 26 patients received only IV administered r-tPA. A combined IV/IA therapy was applied in 55 patients and 36 of them had occlusions accessible for the infusion catheter. Any subject with etiology or arterial occlusion that prevented safe passage of a guidewire through the occlusive lesion were not accepted for treatment with the EKOS catheter. Additionally, patients with thrombus identified in the anterior cerebral artery; posterior cerebral artery; superior cerebellar artery; posterior inferior cerebellar artery; and anterior inferior cerebellar artery could not be treated with the EKOS Micro Infusion System. In total 33 were treated with the EKOS Micro Infusion System and three subjects received r-tPA infusion without ultrasound activation, with a mean drug dose of 56 mg rtPA. A complete or partial perfusion was achieved in 46% of the EKOS-treated patients within the first hour of treatment and in 73% at the end of procedure. Procedure related complications such as dissections and vasospasm were reported in 3 cases and 2 major bleeding complications required transfusion. The overall mortality rate at 3 months was 16% for the whole IMS II population. Significantly better 3-month outcomes were reported at all endpoints when compared to both the placebo-treated subjects and the r-tPA-treated group of

the NINDS r-tPA Stroke Trial.[123] A randomized IMS III trial has been started in 2006 and included the EKOS Micro Infusion System as part of the investigation to further elucidate the role of this technique in ischemic stroke.

Deep venous thrombosis

In an open enrollment registry across seven centers in the US, Raabe et al.[124] studied 40 patients with 45 acute and chronic occlusions of the upper and lower extremity and hepatic veins (Table 1). Using various thrombolytic agents, including reteplase, alteplase, urokinase and tenecteplase, in combination with the EKOS Lysus System (EKOS Corporation, they achieved a complete lysis in 71%, a partial lysis in 20% and only in 9% no lysis occurred. The average time to achieve complete clot clearance was 25 hours and 2 major bleeding complications (4.4%) occurred. The technical success rate, defined as catheter positioning within the clot and simultaneous delivery of ultrasound with lytic infusion, was 100%. It was concluded that the EKOS Lysus System offers a rapid initiation of thrombolytic therapy with lower lytic drug dosage, shorter infusion time compared to traditional catheter-directed thrombolysis, as reported in literature.[125] Similar results were reported by Motarjeme et al.[112] who had a complete lysis in a mixed group of patients, including venous thrombosis, in 83% of the patients with a mean duration of complete lysis of 21 hours, without major complications. Compared to the National Venous Registry,[125] shorter average infusion times and higher rates of complete lysis were seen using the EKOS Lysis Infusion System. During a 12 months follow up, re-occlusion occurred in one patient. In a retrospective study, Parikh et al.[126] investigated the success of lysis and clinical outcomes in patients treated with deep vein thrombosis. Forty-seven patients with 53 occlusions in the upper and lower extremity and hepatic veins were treated with the EKOS EndoWave System. In 37 patients (70%) a complete lysis, defined as ≥90% lysis, was achieved. A partial lysis was noted for 11 patients (21%) and in 5 patients no lysis occurred. Additional treatment, such as PTA, stent placement, mechanical thrombectomy and surgery, was necessary in 40 cases. Two major bleeding complications occurred in patients with relative contraindications for thrombolytic therapy. Both patients successfully completed thrombolysis followed by a surgical evacuation of hematoma. These results showed better efficacy rates, a 3.4 times lower UK drug dosage and half of the infusion time used in the National Venous Registry.[125] Similar results were found when compared to the study of Grunwald and Hofmann.[127] The authors concluded that ultrasound-accelerated thrombolysis appeared to be safe and effective in the treatment of DVT, and it had the potential benefit of complete thrombus resolving behind valves to prevent PTS.

Additionally, Kasirajan[115] reported 10 cases of venous occlusions treated with the EKOS EndoWave System. In that study, a complete lysis occurred only in 40% of the DVT group, a partial lysis was noted in 4 patients (40%) and 2 patients had no changes. Mean duration of tPA infusion was 16 hours. After a six month follow-up, one patient developed an asymptomatic re-occlusion. Recently, Raabe has published the results of 9 patients with venous occlusions of the upper and lower extremities that were treated with the EKOS EndoWave System in combination with

alteplase. Treatment was successful in 8 out of 9 patients and during follow-up 1 re-occlusion occurred 2 months after treatment. Fibrinogen depletion was more pronounced among patients with venous occlusions (26.4% from baseline) than those with arterial occlusions (15.8% from baseline), but no major hemorrhagic complications occurred.[117]

Pulmonary embolism

Publications focusing on ultrasound-accelerated thrombolysis for PE are rare. In 2008, Chamsuddin et al.[128] have evaluated the efficacy of thrombolysis using the EKOS EndoWave Endovascular System in 10 patients with 17 massive PE's (n=17). The EKOS EndoWave System was used in combination with urokinase, tPA or reteplase. Complete lysis, defined as more than 90% thrombus removal, was achieved in 76% of patients (n=13). Near complete thrombolysis, defined as 75%-90% thrombus clearance, was achieved in 18% (n=3), and partial thrombolysis, defined as 50%-75% thrombus removal, was achieved in 6% (n=1). The average treatment time was 25 hours. Two minor complications, a small right groin hematoma and non-fatal hemoptysis were seen. During follow up over a period of 3 days to 1 year, no reocclusions were seen.

Stambo and Montague[129] used the EKOS EndoWave System in a hemodynamic unstable patient with bilateral massive pulmonary embolism. Bilateral infusion of tPA (0.5 mg/hr for eight hours) resulted in complete lysis of both emboli at control angiography, without any complication. This is a fraction of the total amount of 100 mg IV tPA recommended by the ACCP.[3] The patients' hemodynamic status improved and the patient was discharged home after three days. Further, Lin et al.[130] evaluated the outcome of acute massive PE in patients treated with ultrasound accelerated thrombolysis using the EkoSonic Endovascular System (n=15) or catheter directed thrombolysis (CDT, n=18). The EKOS treated group had a significant ($p < 0.02$) better outcome in complete thrombus dissolution compared to the CDT group (100% versus 50%). The time to achieve thrombolysis was significant shorter in the EKOS group ($p < 0.03$), with a mean duration of 17.4 ± 5.2 hours. The mean total dosage of tPA was 17.2 ± 2.4 mg for the EKOS treated group and 25.4 ± 5.3 mg for the CDT group. Comparative analysis showed a significant reduction in treatment time and drug dosage in the EKOS group compared to CDT ($p < 0.001$). No treatment related hemorrhagic complications were seen with the EkoSonic Endovascular System compared to 21.4% for CDT ($p < 0.02$). The authors concluded that, compared to CDT, treatment with the EKOS EkoSonic Endovascular System has the same efficacy but provides faster recanalization and less treatment related complications.

DISCUSSION

In the present review we have shown that ultrasound-accelerated thrombolysis is a promising concept in the treatment of various thromboembolic conditions. This technique has repeatedly been reported to be associated with a rapid revascularization without increased complication rates (Figure 2). It must be stressed, however, that all the available clinical data are complicated

by reporting bias and that this may be one of the reasons for the positive results. Moreover, the EKOS catheter has undergone significant modifications since the 1999 publication, which may have affected outcome of different studies. Randomized trials have not been performed to date. Due to the wide variance in study design of publications concerning ultrasound enhanced thrombolysis, a comparison with results from either the TOPAS or STILE study may not be reliable.[131,133] Additionally, since the publication of these trials treatment protocols have changed, indicating the need for prospective randomized trials.

Catheter-directed thrombolysis is an accepted therapy in different thromboembolic conditions. When compared to surgical thrombectomy, however, the technique is associated with higher costs, longer time needed to revascularization, hemorrhagic complications, a small but significant incidence of stroke, and renal dysfunction related to repeated angiography. The incidence of complications appears to be related to the length of treatment since extended infusion times are associated with increased fibrinogen depletion.[131-134] For this reason a reduction of thrombolytic therapy time would be indispensable. Various reports included in this study note a rapid lysis, when using ultrasound-accelerated thrombolysis.

In the present study a total of 340 patients were included that were treated with catheter-delivered transducer tipped ultrasound- accelerated thrombolysis for various indications. Complete lysis, defined as >90% thrombus removal, or partial lysis defined as <90% thrombus removal, was achieved in 87.9% compared to no lysis in 8.2%. In 4 cases, it was not clear if there was lysis or not, and 2.6% of the procedures had to be discontinued before thrombolysis was achieved. The time to achieve complete lysis differed among indications, partly caused by differences in definitions of lysis time (e.g. time to complete lysis, median lysis time, and early recanalization).

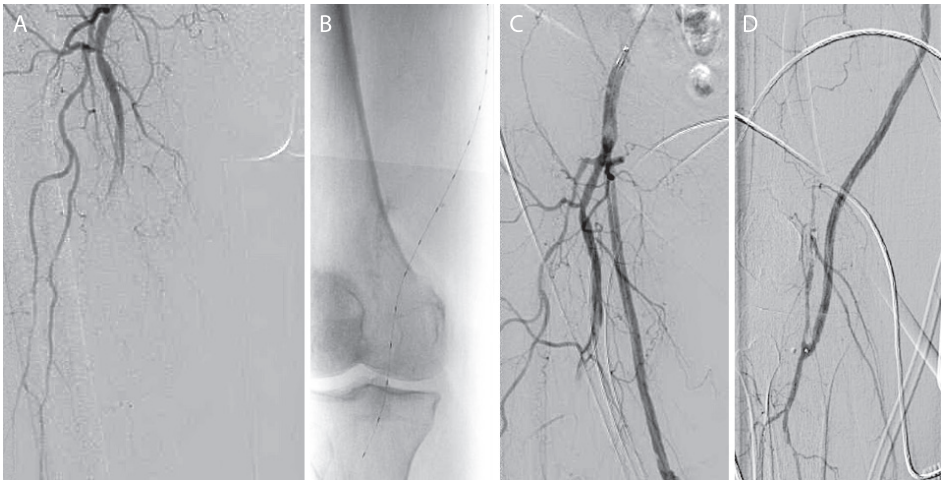

Figure 2. (A) Preprocedural angiography showing an occluded bypass in a 53-year-old patient with a history of renal transplantation, diabetes, and 2 right-sided femoropopliteal bypasses. The patient presented with a pale and painful right leg that had existed for 1 day. (B) The patient was treated with ultrasound-enhanced thrombolysis. (C, D) Control angiography at 6 hours showing complete lysis of the thrombus.

Moreover, the lysis time may have been influenced by the anatomical substrate of the occlusion (arterial or venous), the time of onset of the occlusion (acute, subacute, or chronic), the length of the occlusion, the use of different plasminogen activators and the interval of control angiography. The mean drug dosage was lower when compared to conventional thrombolytic treatment. The overall complication rates are low (7.1%). Bleeding occurred in 4.1% and distal embolization was not described. Procedure related complications, including technical failure, occurred in 1.2% of the cases. In some studies, a shorter hospitalization time was reported. During follow-up, re-occlusion occurred in 2.1% of the cases. None of the studies included in this paper had a proper control group.

The development of an algorithm in the treatment of acute thromboembolic events may be hampered by advances in percutaneous thrombomechanical devices, which are a promising alternative to catheter-delivered pharmacologic thrombolytic therapy and surgical thrombectomy. Combinations of these techniques may prove to be useful in the near future. Current limitations of percutaneous mechanical thrombectomy devices, however, are incomplete thrombus removal, high costs, embolization risks, hemolysis, vessel wall and valve injury, design complexity, its labor intensiveness, effective in fresh thrombi only and the lack of prospective data.[4-6] Randomized studies focusing on different techniques and indications are indicated to elucidate this subject.

Various authors have reported the efficacy of ultrasound-accelerated thrombolysis in the dissolution of chronic clots. A chronic thrombus is less receptive for lytic drugs,[25] because the thrombus composition changes over time as a well-organized fibrin cap developed around the thrombus.[135] The application of high frequency ultrasound may facilitate permeation of the lytic drug into the fibrin cap due to ultrasound mediated changes in the fibrin structure. This mechanism may account for the complete lysis seen in patients with chronic arterial and venous occlusions.[112] The possibility to clear thrombus behind venous valves, thereby preserving their function, may lead to better long-term patency rates and a reduced incidence of PTS.[124, 126] Long term follow-up of patients, however, have not been published, to date.

The reported incidence of complications using ultrasound-accelerated thrombolysis is low. Systemic thrombolysis is associated with a significant increase in major bleeding complications.[85] A reduced lysis time and dose might reduce the incidence of bleeding complications. The reported rate of distal embolization is also low. The absence of mechanical fracturing of the thrombus by the EKOS EndoWave Endovascular System may prevent distal embolization during the procedure.[124] Several devices for arterial revascularization have been reported to cause vasoconstriction or spasm.[136, 137] This could result in turbulent blood flow and high shear rates, which promote platelet aggregation and thrombus formation.[138, 139] In vitro, ex vivo, in vivo and clinical experiments have shown a dose dependent, reversible vasorelaxant effect of catheter-delivered ultrasound. This finding may further enhance the safety and efficacy of ultrasound accelerated thrombolysis, especially when the device is used in the coronary or cerebral circulation.[42, 140]

The mechanism of action of ultrasound-accelerated thrombolysis is not completely clear. The effects of ultrasound on clot dissolution are thought to be based on multiple factors including

(1) acoustic cavitation, (2) microstreaming, (3) mechanical effects, (4) intracellular microcurrents, (5) thermal warming, and (6) increased clot permeability. The chemical effect of ultrasound on thrombus dissolution is most likely based on the cavitation phenomenon: the formation, growth and implosive collapse of cavities in liquids that release large amounts of localized energy.[78, 141]

Acoustic cavitation results in the formation of microscopic bubbles when ultrasound waves pass with an alternating pressure and may either be stable or transient. Both the oscillation of microbubbles and their rapid collapse in the acoustic field result in high local pressure changes,[78] localized thermal heating, acoustic (micro)streaming (liquid micro circulations) and local turbulences.[142-145] An intense shear stress may occur in tissues in the immediate vicinity of the collapsing bubble which could alter the erythrocyte membrane, causing reversible disaggregation of fibrin fibers and affect platelets. Acoustic (micro)streaming and local turbulences may improve transport processes[143, 145] leading to better penetration of enzyme into the thrombus[78, 79] and increasing the total amount and depth of penetration,[80] finally leading to thrombus disruption.[78-83]

The effect of ultrasound-accelerated thrombolysis may be further increased by the addition of various substances (chemical microbubbles), including perfluorocarbon-filled polymer biospheres, perflurocarbon-exposed sonicated dextrose albumin, and galactose-based microbubbles.[94-96] The addition of a glycoprotein IIb/IIIa receptor antagonist to microbubbles, may improve binding of the microbubble at the surface of platelet thrombi.[97, 146] Recent studies have demonstrated that tPA incorporated echogenic liposomes may also enhance thrombolysis.[98, 99] These observations warrant further experimental studies in order to optimize thrombolytic treatment.

CONCLUSION

Catheter-directed ultrasound-accelerated thrombolysis seems to be a promising concept in the treatment of various thromboembolic conditions. However, ultimately this issue can be resolved only by randomized controlled trials. Comparative studies with conventional thrombolysis and other available techniques are indicated before considering ultrasound-accelerated thrombolysis as the new standard treatment. To this end, the Dutch Ultrasound accElerated Trial (DUET), comparing standard catheter-directed thrombolysis with ultrasound accelerated catheter-directed thrombolysis in infra-inguinal arterial occlusion, is designed to provide level 1 evidence.

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Chapter 6

Initial results of catheter-directed ultrasound-accelerated thrombolysis for thromboembolic obstructions of the aortofemoral arteries: a feasibility study

A.M. Schrijver, M.M.P.J. Reijnen, J.A. van Oostayen, A.W.J. Hoksbergen, R.J. Lely, M. van Leersum, J.P.P.M. de Vries

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ABSTRACT

Purpose

To report the 30-day technical and clinical outcome of ultrasound (US)-accelerated thrombolysis in patients with aortofemoral thromboembolic obstructions.

Methods

A prospective cohort study was conducted from December 2008 to December 2009 of patients who were treated with US-accelerated thrombolysis for thromboembolic obstructions of aortofemoral arteries or bypasses. Urokinase was infused in a dosage of 100,000 IU/hour. Twice daily a control angiography was performed. Thirty-day follow-up consisted of duplex scanning, combined with magnetic resonance angiography.

Results

The study included 21 consecutive patients (20 men; median age, 66 years; range 52–80) with 24% artery versus 76% bypass occlusions. Median duration of symptoms was 11 days (7-140). Median occlusion length was 32 cm (6-80). In 20 patients (95%) an US-accelerated thrombolysis catheter could be successfully placed. In 1 patient placement of an US-accelerated thrombolysis catheter was technically not feasible, and therefore a standard catheter was placed. Median thrombolysis time was 26.5 hours (range 8.5-72). Complete thrombolysis (>95% lysis of thrombus) was achieved in 20 patients; in 9 within 24 hours. Median ankle-brachial index (ABI) increased from 0.28 (0–0.85) to 0.91 (0.58-1.35). One patient had a thromboembolic complication, and needed surgical intervention. No hemorrhagic complications and no deaths occurred. At 30-day follow-up, 17 of 21 patients (81%) had a patent artery or bypass.

Conclusion

This feasibility study showed a high technical success rate of US-accelerated thrombolysis for aortofemoral obstructions. US-accelerated thrombolysis led to complete lysis within 24 hours in almost half of patients, with a low 30-day major complication rate.

INTRODUCTION

Thrombosis of a bypass graft or native artery of the lower extremities has been associated with a high rate of limb loss and significant morbidity and mortality.[1] Catheter-directed thrombolysis was introduced in the 1980s and its use has increased. The benefits of catheter-directed thrombolysis compared with surgery are gentler and more complete clot removal that allows the preservation of endothelium, less invasiveness, and the possibility to visualize and, if necessary, to treat an underlying atherosclerotic lesion or anastomotic stenosis by endovascular means. The main limitations include inability to cross the thrombosed segment, failure to achieve complete lysis, occurrence of thrombolysis-related hemorrhagic complications, distal embolization, and a prolonged time to revascularization.[2, 3]

In the STILE trial 393 patients with acute thromboembolic occlusions of native artery or bypass graft of the lower limbs were randomized to catheter-directed thrombolysis or surgery. Major amputation rates at 6 months follow-up were similar for both groups (11.8% in catheter-directed thrombolysis group versus 10.6% in the surgery group, p=0.87) and there were no significantly different mortality rates (16% versus 12%, p=0.54). Major morbidity rates at 1 month follow-up were similar in both groups (20.6% in catheter-directed thrombolysis group versus 16.0% in the surgery group, p=0.266), however there was a significant difference in composite clinical outcome in favor of the surgery group. More than half of thrombolysis patients had a reduction in the need for open surgery ($p < 0.001$).[4]

In the TOPAS trial 548 patients with acute thromboembolic occlusions of native artery or bypass graft of the lower limbs were randomized between catheter-directed thrombolysis and surgery. At 1 year follow-up amputation-free survival rates were similar in both groups (65.0% in catheter-directed thrombolysis group versus 69.9% in the surgery group, p=0.23) and there were no significantly different mortality rates (20.0% versus 17.0%, p=0.39). Major hemorrhage occurred in 12.5% of thrombolysis patients versus 5.5% of surgical patients (p=0.005). However catheter-directed thrombolysis reduced the need for open surgery ($p \leq 0.01$).[5]

A recent systematic review that included a meta-analysis of 3 large randomized controlled trials, including both the TOPAS and STILE trials, totaling 1283 patients comparing surgery with thrombolysis in the management of acute lower limb ischemia showed no significant differences in limb salvage rate or deaths at 30 days, 6 months, or 1 year. However, 30-day hemorrhagic complications and distal embolization were more likely in thrombolysis patients (8.8% and 12.4%, respectively) compared with surgery.[6]

Several methods have been investigated to accelerate thrombolysis with use of ultrasound (US).[7] High intensity ultrasound can be used to mechanically disrupt clots,[8, 9] while low-intensity ultrasound causes an increase in enzymatic activity of thrombolytics [10-18]. The aim of the latter method is to restore blood flow faster and to reduce the dosage of thrombolytic agent, thereby reducing thrombolysis-related hemorrhagic complications. A combination of low-intensity US and thrombolytics accelerated clot lysis by increasing clot permeability and penetration of

the thrombolytic agent into the thrombus both in vitro[13-18] and in vivo,[10-12] without mechanical fragmentation of the clot. The safety of the application of US-accelerated thrombolysis has been shown in the treatment of embolic stroke[19, 20] and deep venous thrombosis.[21-23] So far, 3 studies have been published concerning catheter-directed US-accelerated thrombolysis in the treatment of thromboembolic obstructions of native arteries and bypass grafts of the aortofemoral area.[21, 24, 25]

The present article reports the initial results of catheter-directed low-intensity US-accelerated thrombolysis in patients with arterial thromboembolic obstructions of the aortofemoral area. This was a feasibility study performed in preparation of a multicenter randomized controlled trial comparing standard catheter-directed thrombolysis with US-accelerated thrombolysis in arterial thromboembolic obstructions of the aortofemoral area.

METHODS

This prospective cohort study was conducted between December 2008 and December 2009 in one university medical center and two vascular referral hospitals in the Netherlands. Included were adult patients with a thromboembolic obstruction of an artery or bypass graft of the aortofemoral area that existed for at least 1 week. All the patients were informed concerning the new US-accelerated thrombolysis technique, which is not experimental. Approval had been given by all patients for data collection in this study. Excluded were patients with an immediately threatened limb (i.e. Rutherford class IIb or higher) that required immediate revascularization. Other exclusion criteria were based on the Dutch guidelines, including patients for whom antiplatelet therapy, anticoagulants, or thrombolytic drugs are contraindicated, patients with a recent (less than 6 weeks) ischemic stroke or cerebral bleeding, patients with recent (less than 6 weeks) surgery, severe hypertension (diastolic blood pressure greater than 110 mmHg, systolic blood pressure greater than 200 mm Hg), current malignancy, a history of life-threatening reaction to contrast medium, uncorrected bleeding disorders (gastrointestinal ulcer, menorrhagia, liver failure), and women with childbearing potential not taking adequate contraceptives or currently breastfeeding, and pregnancy.

Data on the following variables were prospectively collected: patient characteristics, occlusion characteristics (including inflow and outflow arteries), therapy time, complications (technical failure, hemorrhage, distal embolization, infection, reocclusion, and conversion to open surgery), additional endovascular procedures, mortality, and 30-day complication and patency rates.

Device

US-accelerated thrombolysis involves simultaneous delivery of low-intensity US and a thrombolytic agent into a thrombosed vessel. US-accelerated thrombolysis was performed with use of the EKOS EndoWave system (EKOS Corporation, Bothell, WA, USA) (Figure 1). This system consists of a 5.2F multilumen thrombolysis delivery catheter with a 106 cm or 135 cm working length and

a matching US coaxial core wire with a working zone of 6 cm to 50 cm. The central lumen of the multilumen thrombolysis delivery catheter accommodates the US core. Urokinase was infused through 3 drug lumens containing multiple side holes. Low-intensity (2.2 MHz) high-frequency US was delivered over the entire length of the infusion catheter. US power and local temperature were automatically controlled by a portable control unit.[21, 24]

Procedure

All procedures were performed under local anesthesia in the angiography suite of the Radiology Department. Arterial access was obtained with a percutaneous antegrade or retrograde femoral approach in all patients using a 6F introduction sheath. Digital subtraction angiography was performed to determine the inflow, obstruction, and outflow of the affected limb. After measurement of the length of the occlusion, a multilumen thrombolysis delivery catheter was navigated over a 0.018-inch hydrophilic guidewire into the thrombosed segment in such a way that the US treatment zone traversed the entire occluded segment and the tip of the infusion catheter was located distal to the thrombosed segment.

After final positioning, the guidewire was exchanged for a length of matching US core wire (EKOS EndoWave system), and thrombolytic therapy was started. Urokinase was infused in a dosage of 100,000 IU/hour. During thrombolysis systemic heparin was given (10,000 IU/24 hours). If placement of the EKOS EndoWave system was technically not feasible (i.e., the entire thrombosed segment could not be passed), the procedure was defined as a technical treatment failure. The vascular surgeon and interventional radiologist decided to switch to an alternative treatment, for instance, standard thrombolysis with the tip of the thrombolytic catheter in the proximal part of the thrombosed segment or conversion to open surgery.

All patients had their first angiography started at 8:00 a.m. A control angiography was performed every 12 ± 2 hours. During the night angiographies were only performed in case

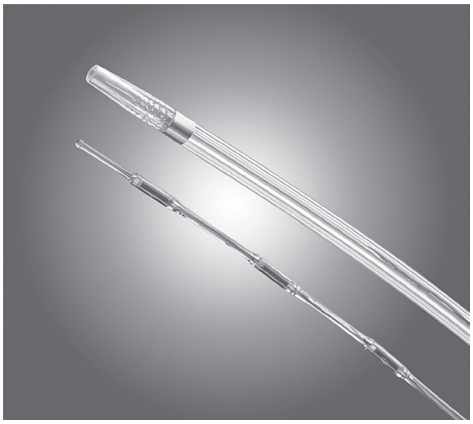

Figure 1. Ultrasound-accelerated thrombolysis catheter (EKOS EndoWave system, EKOS Corporation, Bothell, WA, USA).

of emergencies (i.e. thromboembolic complications). US-accelerated therapy was continued until complete lysis was achieved. If the obstructive clot was successfully thrombolized, a final angiogram of the treated segment was performed. Any necessary additional procedure, such as percutaneous transluminal angioplasty (PTA) with or without additional stent placement, was documented.

After successful thrombolysis, heparin was given in a dosage of 25,000 IU/24 hours and coumarin derivatives were started. Antiplatelet therapy was only started in case of intolerance to coumarin derivatives. During heparinization, the target activated partial thromboplastin time (aPTT) ratio was 1.5 to 2.5 and was measured twice daily. The target international normalized ratio (INR) was 2.5 to 3.5; if this value was reached, heparin was stopped. In case of thrombolysis-related complications, therapy could be stopped on the decision of the physician.

Definitions

Technical success was defined as positioning of the EKOS EndoWave System so that the treatment zone traversed the entire thrombosed segment and the tip of the thrombolysis catheter was positioned distal to the thrombosed segment. Complete lysis was defined as clot lysis exceeding 95% of the thrombosed native artery or bypass graft with outflow through at least 1 crural artery, as determined by digital subtraction angiography. Clinical success was defined as ischemic complaints at least returning to the preacute ischemic state, both after the procedure and at 30-day follow-up.

Follow-up

The 30-day follow-up consisted of a visit to the outpatient clinic, with clinical examination, including ankle-brachial indices (ABI), and duplex US scanning combined with magnetic resonance angiography (MRA) of the treated limb. Any additional procedures, conversion to open surgery, distal thromboembolic complications, and other complications were recorded during follow-up.

Statistical analysis

Statistical analysis was performed using SPSS version 17.0 software (SPSS, Chicago, IL, USA). Patency rates were calculated with Kaplan-Meier life-table estimates. Statistical analysis was performed based on the intention-to-treat principle.

RESULTS

During the study period 21 consecutive patients were treated with US-accelerated thrombolysis for thromboembolic obstructions of a native artery or a bypass graft of the aortofemoral area. Baseline characteristics of the study population are summarized in Table 1. Occlusion characteristics are summarized in Table 2. In 20 of 21 patients (95%), the EKOS EndoWave system could be successfully advanced through the entire thrombosed segment. In only 1 patient placement

Table 1. Baseline characteristics of study population.

Variable	Patients (n=21)
Age, median (range) years	66 (52–80)
Male sex	20 (95)
Risk factors	
Diabetes	2 (10)
Smoking, current or recent	14 (67)
Hypertension	17 (81)
Hypercholesterolemia	11 (52)
Coronary artery disease	10 (48)
Stroke or transient ischemic attack	3 (14)
Body mass index, median (range) kg/m^2	27.5 (23.1–38.8)
Preprocedural medication	
Acetylsalicylic acid	16 (76)
Coumarin	7 (33)
Clopidogrel	4 (19)
Dipyridamole	0 (0)
No anticoagulant	0 (0)
Duration of ischemic complaints	
Acute (<14 days)	10 (48)
Subacute (14-30 days)	9 (42)
Long-lasting (>30 days)	2 (10)
Severity of ischemia	
(Sub)acute ischemia (<30 days)	19 (90)
Rutherford category I	3 (14)
Rutherford category IIa	16 (76)
Long-lasting ischemia (>30 days)	2 (10)
Fontaine category 1	0 (0)
Fontaine category 2a	0 (0)
Fontaine category 2b	1 (5)
Fontaine category 3	1 (5)
Ankle-brachial index, median (range)	0.28 (0–0.85)

Data are presented as number (percentage) unless otherwise indicated.

of the EKOS EndoWave system was technically not feasible because of the inability to navigate the tip of the thrombolysis catheter distal to the entire thrombosed segment. This patient was treated with standard thrombolysis, with placement of the tip of the catheter as far as possible into the thrombosed segment. Thrombolysis was successful, but at 1 month follow-up reocclusion occurred. Because this patient had no clinical signs of ischemia no further reintervention was performed.

Complete lysis was achieved in 20 of 21 patients. Median therapy time until complete lysis was 26.5 hours (range, 8.5 - 72 hours). In 9 patients (43%), complete lysis was achieved within 24 hours. No hemorrhagic complications occurred during treatment. US-accelerated thrombolysis had to be discontinued after 5.5 hours in 1 patient because of distal embolization. This was a class D major complication, according to the Society of Interventional Radiology Classification System for Complications by Outcome (Table 5).[26] The patient was successfully treated with open thrombectomy and revision of the stenotic segment of the bypass graft. Median IU of urokinase

Table 2. Occlusion characteristics.

Variable	Occlusions (n=21)
Type	
Native artery	5 (24)
Bypass graft	16 (76)
Venous	3 (14)
Prosthetic	13 (62)
Location	
Proximal	8 (39)
Aortoiliac	5 (24)
Iliofemoral	1 (5)
Aortofemoral	2 (10)
Femoral	1 (5)
Distal	12 (56)
Above-knee femoropopliteal	2 (9)
Below-knee femoropopliteal	6 (28)
Femorocrural	4 (19)
Number of patent crural arteries	
0	0 (0)
1	1 (5)
2	5 (24)
3	15 (71)
Length thrombosed segment, median (range) cm	32 (6–80)

Values are presented as number (percentage) unless otherwise indicated.

Table 3. Results.

Variable	Patients (n=21)
Technical success	20 (95)
Complete lysis	20 (95)
< 24 hours	9 (43)
< 48 hours	19 (90)
Therapy time, median (range) hours	26.5 (8.5 – 72)
Urokinase dosage, median (range) IU	2,650,000 (850,000 – 7,200,000)
Complications by Outcome	
Minor	0 (0)
Major	1 (5)
Additional interventions	
PTA	14 (67)
Thrombosuction	2 (10)
Surgical revision bypass graft anastomosis	2 (10)
Ankle-brachial index, median (range)	0.91 (0.58-1.35)

Values are presented as number (percentage) unless otherwise indicated.

given was 2,650,000 (range, 850,000 – 7,200,000). Of 21 patients, 14 (67%) needed an additional PTA after successful thrombolysis to treat an underlying atherosclerotic lesion, 3 of them had additional stent placement due to >30% residual stenosis. Two (10%) required additional thrombosuction of localized thrombus in one of the crural arteries, and 2 (10%) underwent a surgical

Table 4. 30-day follow-up.

Variable	Patients (n=21)
Patency	17 (81)
Treatment of reocclusion	
Standard thrombolysis	2 (10)
Bypass graft	1 (5)
Conservative	1 (5)
Complications by Outcome	
Minor	0 (0)
Major	0 (0)
Ankle-brachial index, median (range)	0.85 (0.42 – 1.0)

Values are presented as number (percentage) unless otherwise indicated.

Table 5. SIR Classification System For Complications by Outcome.[26]

Minor Complications
A. No therapy, no consequence.
B. Nominal therapy, no consequence; includes overnight admission for observation only.
Major Complications
C. Require therapy, minor hospitalization (<48 hours).
D. Require major therapy, unplanned increase in level of care, prolonged hospitalization (>48 hours).
E. Permanent adverse sequelae.
F. Death.

revision of a bypass graft anastomosis. One patient required amputation of the lower leg because of progressive ischemia, despite complete lysis of an occluded bypass graft. After additional and/or secondary intervention all 21 patients were discharged with a patent treated native artery or bypass graft.

MRA or duplex scans at the 30-day follow-up showed 17 of 21 patients (81%) had a patent treated artery or bypass graft. These treated limbs had returned to at least their preischemic state. Median ABI was 0.85 (range, 0.42-1). In the remaining 4 patients, a reocclusion of the treated segment had occurred. The reocclusions in 2 patients were treated within 48 hours after complaints with standard thrombolysis, as this was the preferred treatment of the treating physician. In 1 patient, the reocclusion of a native artery was treated with a bypass graft because of the poor quality of his former occluded graft, and in another, this was the patient that was treated with standard thrombolysis, the reocclusion was treated conservatively.

DISCUSSION

This study assessed the safety and efficacy of the application of US-accelerated thrombolysis for thromboembolic obstructions of native arteries and bypass grafts of long-segment occlusions existing for a median of 11 days. The technical success of US-accelerated thrombolysis was 95%. Complete lysis was achieved in 20 of 21 patients, and in 9 of these patients (43%) lysis occurred

within 24 hours. The incidence of treatment-related complications was 5%, the mortality rate was 0%, and the patency rate at 30-day follow-up was 81%.

Catheter-directed thrombolysis is a well-accepted treatment for thromboembolic obstructions of arteries and bypass grafts of the lower extremities. However, this treatment is associated with incidence of hemorrhagic complications of approximately 9% and distal embolization of 12%.[6] The incidences of these sometimes devastating complications are variable amongst literature and influenced by the therapeutic agents which has been used as well as the varying treatment protocols The main focus of current studies is to reduce thrombolysis time and thereby possibly reduce treatment-related hemorrhagic complications.

US may be used to accelerate thrombolysis by using two distinct approaches.[7] First, high-intensity US is used to mechanically disrupt clots. Reported complications of this approach, however, are vessel wall damage and possible distal embolization of clot and plaque fragments.[8, 9] Second, low-intensity US is used to accelerate enzymatic activity of thrombolytics by increasing clot permeability and penetration of the thrombolytic agent into the thrombus, without mechanical fragmentation of the clot.[13-18] This is caused by an increased drug transport, a reversible alteration in fibrin structure, and an increase in binding sites to fibrin.[27] US can be delivered transcutaneously or be catheter-directed.[28] The latter is used with the EKOS EndoWave System, which consists of a multilumen thrombolysis delivery catheter with a US core. This system facilitates simultaneous delivery of low-intensity US and a thrombolytic agent into a thrombosed vessel or bypass graft.

The results of this study are comparable to the results reported by 3 previous studies on the application of US-accelerated thrombolysis in acute thromboembolic obstructions of the lower extremities. In 2007 Wissgott et al. conducted a prospective single-center study that included 25 patients with acute (existing less than 14 days) thromboembolic obstructions of the lower limb arteries who were treated with US-accelerated thrombolysis.[24] The technical success rate was 100%, and mean therapy time was 16.9 ± 10.9 hours. There were no complications related to the catheter system. At the 1-month follow-up, 2 reocclusions had occurred.

In 2008 Wissgott et al. conducted a prospective study that compared mechanical thrombectomy, using a rotational thromboembolectomy device (Rotarex S, Straub, Wangs, Switzerland) with US-accelerated thrombolysis for the treatment of 20 patients with an acute femoropopliteal bypass graft occlusion.[25] Some of the patients in this study had also been included in the previous study by Wissgott et al.[24] The technical success rate was 90% in the US-accelerated thrombolysis group, due to dislocation of the introducer sheath, which was successfully treated by open surgery. Mean therapy time was 904.0 minutes (range, 120–1350 minutes).

Motarjeme et al used US-accelerated thrombolysis in the treatment of 24 subacute arterial occlusions.[21] The technical success rate was 100%, and complete lysis was achieved in 23 (96%) arterial occlusions. Average time to achieve complete lysis was 16.4 hours (range 3–25 hours). During the 12-month follow-up, only 1 femoropopliteal bypass graft rethrombosed. No bleeding or other complications occurred.

Median therapy time in our study was longer compared with previous studies on the application of US-accelerated thrombolysis. Several explanations can be proposed. In contrast to aforementioned studies, only patients with occlusions existing more than 1 week were treated in this study. These were mostly long-segment occlusions, with a length of more than 20 cm.

The interval between control angiographies differed between this study and previous studies. Due to logistic reasons control angiographies were performed every 12 hours in our study compared to every 4 hours in the study by Motarjeme et al. Actual therapy time in our study might have been shorter.

Also, the type and dosage of thrombolytic agent differed between studies. In this study urokinase in a dosage of 100,000 IU/hour has been used. Wissgott et al. used in both trials rtPA in a dosage of 1.0 mg/h. Motarjeme et al. used urokinase dosages of 80,000-120,000 IU/h. Urokinase is a first generation thrombolytic drug, which is non-fibrin specific. In contrast, second and third generation thrombolytics are fibrin specific enzymes. Fibrin specific thrombolytics may be more effective in the treatment of older clots.[29]

One of the limitations of this study is the fact that post-interventional clinical categories of acute and chronic limb ischemia were not recorded, and no comparison could be made with pre-interventional data.

In conclusion, this feasibility study showed that the application of US-accelerated thrombolysis in the treatment of thromboembolic obstructions of arteries and bypass grafts of the aortofemoral area is effective and safe and might be better compared with standard catheter-derived thrombolysis. To this end, we recently started a multicenter randomized trial comparing US-accelerated thrombolysis with standard thrombolysis: Dutch randomized trial comparing standard catheter-directed thrombolysis versus Ultrasound-acceElerated Thrombolysis for thromboembolic infrainguinal disease (DUET) [ISRCTN72676102]. Inclusion is expected to be completed at the end of 2011.

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Chapter 7

Dutch randomized trial comparing standard catheter-directed thrombolysis versus Ultrasound-accElerated Thrombolysis for thromboembolic infrainguinal disease (DUET): design and rationale [ISRCTN72676102]

A.M. Schrijver, M.M.P. J. Reijnen, J.A. van Oostayen, R. P. J. Tutein Nolthenius, P.H.M. van der Valk, A.W.J. Hoksbergen, R.J. Lely, B. Fioole, D. Vroegindeweij, M. van Leersum, J.P.P.M. de Vries

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ABSTRACT

Background

The use of thrombolytic therapy in the treatment of thrombosed infrainguinal native arteries and bypass grafts has increased over the years. Main limitation of this treatment modality, however, is the occurrence of bleeding complications. Low intensity ultrasound (US) has been shown to accelerate enzymatic thrombolysis, thereby reducing therapy time. So far, no randomized trials have investigated the application of US-accelerated thrombolysis in the treatment of thrombosed infra-inguinal native arteries or bypass grafts. The DUET study (Dutch randomized trial comparing standard catheter-directed thrombolysis versus Ultrasound-accElerated Thrombolysis for thromboembolic infrainguinal disease) is designed to assess whether US-accelerated thrombolysis will reduce therapy time significantly compared with standard catheter-directed thrombolysis.

Methods/design

Sixty adult patients with recently (between 1 and 7 weeks) thrombosed infrainguinal native arteries or bypass grafts with acute limb ischemia class I or IIa, according to the Rutherford classification for acute ischemia, will be randomly allocated to either standard thrombolysis (group A) or US-accelerated thrombolysis (group B). Patients will be recruited from 5 teaching hospitals in the Netherlands during a 2-year period. The primary endpoint is the duration of catheter-directed thrombolysis needed for uninterrupted flow in the thrombosed infrainguinal native artery or bypass graft, with outflow through at least 1 crural artery.

Discussion

The DUET study is a randomized controlled trial that will provide evidence whether US-accelerated thrombolysis will significantly reduce therapy time in patients with recently thrombosed infrainguinal native arteries or bypass grafts, without an increase in complications.

BACKGROUND

Thrombosis of an infrainguinal bypass graft or the native lower leg arteries has been associated with a high rate of limb loss and significant morbidity and mortality.[1] Traditional therapy with thrombectomy and eventually additional (bypass) surgery has been associated with moderate long-term patency rates.[2] Catheter-directed thrombolysis was introduced in the early 1980s as a treatment option for occluded bypass grafts. This technique has advantages that make it ideal for acute occlusions, including avoidance of mechanical injury to the endothelium, no need for surgical interventions and more complete lysis of the clot in the bypass graft or outflow arteries. Moreover, it can dissolve platelet-fibrin aggregates in the microcirculation and thrombi in collateral vessels.[3] A recent systematic review that included a meta-analysis of 5 large randomized controlled trials with a total of 1283 patients comparing surgery with thrombolysis in the management of acute lower limb ischemia showed no significant difference between them in limb salvage or death at 30 days, 6 months, or 1 year. However, hemorrhagic complications and distal embolization were more likely at 30 days in thrombolysis patients (8.8% and 12.4%, respectively) than in surgery patients.[4, 5]

The incidence of these complications might be reduced by a reduction in thrombolytic therapy time. In recent years, ultrasound (US) has been used to accelerate thrombolysis. Low-intensity US-accelerated thrombolysis has been shown to accelerate enzymatic clot lysis in vitro by loosening fibrin strands and thereby increasing thrombus permeability and exposing more plasminogen receptors for binding, without mechanically disrupting the clot.[6-8] The safety of this technique has been shown in the treatment of embolic stroke[9] and deep venous thrombosis.[10] Only two prospective series have been published on the use of US-accelerated thrombolysis in the treatment of thromboembolic obstructions of native arteries and bypass grafts of the lower extremities. In a recent study by Wissgott et al, 25 patients with acute obstructions of the native lower limb arteries were treated with US-accelerated thrombolysis. The technical success rate of 100%, and total clot removal was achieved in 88% of the patients within 24 hours. There were no complications related to the catheter system. At the 1-month follow-up, 2 reocclusions had occurred.[11] Motarjeme et al used US-accelerated thrombolysis in the treatment 24 arterial occlusions and 12 venous occlusions, and complete lysis was achieved in 23 (96%) arterial occlusions. Average time to achieve complete lysis was 16.4 hours (range, 3-25 hours). During the 12-month follow-up, only 1 femoropopliteal graft rethrombosed. No bleeding or other complications occurred.[12]

So far, no randomized trials have focused on US-accelerated and standard catheter-directed thrombolysis for arterial thromboembolic disorders of the lower limbs. The DUET (Dutch randomized trial comparing standard catheter-directed thrombolysis versus Ultrasound-accElerated Thrombolysis for thromboembolic infrainguinal disease) study is designed to compare US-accelerated thrombolysis with standard thrombolysis in patients with recently thrombosed infrainguinal native arteries or bypass grafts.

Hypothesis

We anticipate that US-accelerated thrombolysis will result in a significant reduction in thrombolysis time (12 hours or more), without increasing the complication rate.

METHODS/DESIGN

Study objectives

The purpose of the study is to demonstrate that US-accelerated thrombolysis will significantly reduce (by at least 12 hours) therapy time compared with standard thrombolysis, without increasing complication rate.

Primary endpoint

The primary end point is the duration of catheter-directed thrombolysis needed for uninterrupted flow in the thrombosed infrainguinal native artery or bypass graft with outflow through at least 1 crural artery.

Secondary endpoints

1. Technical success, defined as complete lysis of the thrombus of the native artery or bypass graft, without distal thromboembolic complications
2. Number of units of urokinase needed for uninterrupted flow in the thrombosed infrainguinal native artery or bypass graft with outflow through at least 1 crural artery
3. Thrombolysis-induced hemorrhagic complications
4. Thirty-day mortality
5. Duration of hospital admission
6. Costs of hospital admission
7. Thirty-day patency of the target native artery or bypass graft, as evidenced by magnetic resonance angiography (MRA)
8. Drop of serum fibrinogen concentration to below 1.0 g/L during procedure
9. Conversion to open surgery
10. Distal thromboembolic complications
11. Other complications

Definitions

Complete lysis: clot lysis of >95% determined by arteriographic measurements of the thrombosed native arterial segment or bypass graft.[13]

Hemorrhagic complications are defined as:

- hemorrhagic complication requiring interruption or ending of thrombolysis
- hemorrhagic complication requiring surgical intervention
- hemorrhagic complication requiring transfusion

Rutherford classification of acute limb ischemia:[14]

Class I: Viable - not immediately threatened, no sensory loss or muscle weakness, arterial Doppler signal is audible.

Class IIa: Marginally threatened - salvageable if promptly treated, minimal sensory loss, no muscle weakness, arterial Doppler signal is often inaudible.

Class IIb: Immediately threatened - salvageable with immediate revascularization, sensory loss associated with rest pain in more than the toes, mild to moderate muscle weakness, arterial Doppler signal is usually inaudible.

Class III: Irreversible - major tissue loss or permanent nerve damage inevitable if there is significant delay before intervention, profound limb anesthesia and paralysis, arterial and venous Doppler signal is inaudible.

Design of study

This is a multicenter 2-group parallel randomized trial.

Participating centers

Participating centers are Albert Schweitzer Hospital Dordrecht, Free University Medical Centre Amsterdam, Maasstad Hospital Rotterdam, Rijnstate Hospital Arnhem, and St. Antonius Hospital Nieuwegein.

Setting

Patients who will meet the inclusion criteria will be enrolled from 5 teaching hospitals in the Netherlands.

Patients

A total of 60 adult patients with acute lower limb ischemia due to recently (between 1 and 7 weeks) thrombosed infrainguinal native arteries or bypass grafts will be randomized.

Eligibility criteria

Inclusion criteria

1. Men and women older than 18 years and younger than 85 years old.
2. Patients with recently (between 1 and 7 weeks) thrombosed femoropopliteal or femorocrural native arteries or femoropopliteal or femorocrural venous or prosthetic bypass grafts with ischemic complaints.
3. Patients with acute lower limb ischemia class I and IIa according to the Rutherford classification.
4. Patients understand the nature of the procedure and provide written informed consent before enrollment in the study.

Exclusion criteria

1. Patients with isolated common femoral artery thrombosis, including the origin of the superficial femoral artery and profunda femoral artery.
2. Patients with localized (less than 5 cm) emboli or occlusions in the native femoropopliteal arteries.
3. Patients with clinical complaints of acute lower limb ischemia due to thrombosis of the femoropopliteal or femorocrural native arteries, or femoropopliteal or femorocrural venous or prosthetic bypass grafts less than 1 week and more than 7 weeks.
4. Patients with acute lower limb ischemia class IIb and III according to the Rutherford classification.
5. Patients for whom antiplatelet therapy, anticoagulants, or thrombolytic drugs are contraindicated.
6. Recent (less than 6 weeks) ischemic stroke or cerebral bleeding.
7. Patients with recent (less than 6 weeks) surgery.
8. Severe hypertension (diastolic blood pressure greater than 110 mm Hg, systolic blood pressure greater than 200 mm Hg).
9. Current malignancy.
10. Patients with a history of prior life-threatening reaction to contrast medium.
11. Patients with uncorrected bleeding disorders (gastrointestinal ulcer, menorrhagia, liver failure).
12. Women with child-bearing potential not taking adequate contraceptives or currently breastfeeding.
13. Pregnancy.
14. Patients considered hemodynamically unstable at the onset of the procedure.
15. Patients who refuse treatment.
16. Patients who are currently participating in another investigational drug or device study who have not completed the entire follow-up period.
17. Patients younger than 18 years or older than 85 years.
18. Severe comorbid condition with a life expectancy of less than 1 month.
19. Contraindication for magnetic resonance imaging (MRI).

Randomization

Central randomization will take place using a computerized randomization procedure. Block-randomization is used and stratified according to whether a native artery or a bypass graft is involved. Blinding will not be used.

Ethics

This study is conducted in accordance with the principles of the Declaration of Helsinki and good clinical practice guidelines. The study protocol was approved by the Ethics Committee (METC) of

the St. Antonius Hospital Nieuwegein (R-09.17A). Written informed consent will be obtained from all patients, before randomization.

Safety and quality control

Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) is composed of 4 members: 2 independent vascular surgeons and 2 independent interventional radiologists. None of the 4 members is working in one of the hospitals that will include patients. The role of the DSMB is to review safety and to make recommendations regarding the conduct of the study to the steering committee and to the accredited METC that approved the study protocol.

Adverse and serious adverse events

Adverse events (AE) are defined as any undesirable experience occurring to a participant during the study, whether or not considered related to the investigational device. This definition includes events occurring during hospital stay right up to 30 ± 7 days of follow-up. Underlying disease that was present at the time of enrolment is not reported as an AE, but any increase in the severity of the underlying disease will be reported as an AE.

All AEs will be monitored from the time of enrolment through the 30-day follow-up visit. AEs can be classified as moderate or serious and will be recorded on the case record forms (CRFs). A description of the event, including the start date, end date, whether device-related, any action taken, and the outcome will be provided along with the investigator's assessment of the relationship between the AE and the study treatment.

A serious adverse event (SAE) is any untoward medical occurrence or effect that at any dose results in death, or that;

- is life-threatening at the time of the event, or
- requires hospitalization or prolongation of an existing inpatient's hospitalization, or
- results in persistent or significant disability or incapacity, or
- necessitates an intervention to prevent a permanent impairment of a body function or permanent damage to a body structure.

Clinical events to be considered and reported as SAEs include:

- death
- myocardial infarction
- stroke
- bleeding complication requiring interruption or ending of thrombolysis
- bleeding complication requiring surgical intervention
- bleeding complication requiring transfusion

A moderate adverse event (MAE) is any untoward medical occurrence or effect that at any dose will not lead to death, or

- life-threats, or
- significant disability or incapacity, or
- require hospitalization or prolongation of an existing inpatient's hospitalization, or
- necessitate an intervention to prevent a permanent impairment of a body function or permanent damage to a body structure.

Clinical events to be considered and reported as MAEs include:

- groin hematoma
- bleeding complication not requiring interruption or ending of thrombolysis, surgical intervention, or transfusion

Data on SAEs and MAEs will be reported to the DSMB and to the accredited METC via the 'Toetsingonline' website of the website of the Central Committee on Research inv. Human Subjects (CCMO, ccmo.nl).

Statistical analysis

Intention-to-treat

The analysis will be performed in accordance with intention-to-treat principle.

Sample size calculation

The assumption has been made that the mean duration for successful standard thrombolytic treatment of infrainguinal native arteries or bypass grafts is 2.5 ± 1 day, based on retrospective series from the St. Antonius Hospital, Nieuwegein. Given a power of 90% and a 2-tailed significance of 5%, a 2-armed randomized trial including 26 patients in each arm will be needed to prove a significant reduction in therapy time (12 hours or more) with US-accelerated thrombolysis compared with standard thrombolysis. Taking into account 5% to 10% dropouts in each arm, 30 patients need to be included in each study arm. We will analyze the primary outcome by means of Kaplan-Meier and Log-rank test. The sample size calculation is also based on this premise. We will assess imbalance in prognostic factors as a secondary analysis by means of Cox-proportional Hazards multivariate analysis.

An interim analysis on the primary end point (i.e. efficacy) will be performed after 50% of patients have completed their follow-up. The Peto approach will be followed, meaning that the study will only be stopped for beneficial effects in case of a $P < .001$.[15] The study will not be stopped in case of futility. End points in blinded groups will be assessed by the DSMB.

Intervention

Group A (standard thrombolysis)

Standard thrombolysis will be performed with use of a 5F UniFuse Infusion catheter (AngioDynamics, Queensbury, NY, USA) with a working length of 90 cm, with infusion holes around the circumference of the distal 10 cm to 50 cm of the catheter. Access sites may be the contralateral common femoral artery, the ipsilateral common femoral artery, or a brachial approach.

During the initial angiography, the catheter will be navigated over a guidewire and positioned in such way that the entire distal segment with the infusion holes is in the thrombosed segment. At standardized intervals, a control angiography will be performed. During each control angiography, the distal part of the thrombolysis catheter will be repositioned in the remaining thrombosed segment.

Group B (US-accelerated thrombolysis)

US-accelerated thrombolysis involves simultaneous delivery of low-intensity US and a thrombolytic agent into a thrombosed vessel. US-accelerated thrombolysis will be performed with use of the EKOS EndoWave system (EKOS Corporation, Bothell, WA, USA). This system consists of a 5.2F multilumen thrombolysis delivery catheter with a 106 cm or 135 cm working length and a matching US coaxial core wire with a working zone of 6 cm to 50 cm. The central lumen of the multilumen thrombolysis delivery catheter accommodates the US core. Thrombolytics will be infused through 3 drug lumens containing multiple side holes. Low-intensity (2.2 MHz), high-frequency US will be delivered over the entire length of the infusion catheter. US power and local temperature are automatically controlled by a portable control unit.

During the initial angiography, a multilumen thrombolysis delivery catheter will be navigated over a guidewire into the thrombosed segment in such a way that the US treatment zone traverses the entire thrombosed segment and the tip of the infusion catheter is located distal to the thrombosed segment. After final positioning, the guidewire will be exchanged for a matching US core wire, and thrombolytic therapy will be started. Likewise, a control angiography will be performed at standardized intervals.

If placement of the EKOS system is technically not feasible, the procedure will be defined as a technical treatment failure. The vascular surgeon or interventional radiologist, or both, may decide what alternative treatment they will start, for instance, standard thrombolysis or conversion to open surgery. The outcome of these patients will be analyzed in group B according to the intention-to-treat principles.

General

The primary angiography in groups A and B will be started at day 1 at 8.00 a.m. ± 1 hour for logistic reasons. After successful positioning of the thrombolysis catheter, a bolus of 250,000 IU urokinase is given and followed by a continuous infusion with a dose of 100,000 IU urokinase/h. A control angiography will be performed every 6 ± 1 hours. During the night, standard angiog-

raphy will only be performed in emergencies. Angiographies will be performed the next day at 8.00 a.m. ± 1 hour; 2.00 p.m. ± 1 hour, and 8.00 p.m. ± 1 hour. A checklist is completed during each angiography.

The pressure curve from the EKOS monitor will be recorded constantly from the start of the procedure. From the start of thrombolysis until completion angiography, the ankle-brachial indices of the treated leg and a standardized pain score will be recorded every 3 hours by a nurse practitioner or surgical resident. Every day during thrombolysis, the fibrinogen concentration must be checked: if <1.0 g/L the urokinase rate must be lowered to 50,000 IU/h; if the fibrinogen concentration is <0.5 g/L, thrombolysis must be stopped. If the obstructive clot has been successfully thrombolized, any necessary additional procedure, for instance percutaneous transluminal angioplasty (PTA) of the inflow or outflow artery, is performed before the completion angiography, and again, a checklist of the last angiography is completed.

After successful thrombolysis, systemic heparin is given (25,000 IU/24 hours) and coumarin derivatives are started. Activated partial thromboplastin time (aPTT) will be measured daily during heparinization. The target international normalized ratio (INR) will be 2.5 to 3.5; if this value is reached, heparinization can be stopped.

Data collection

Data will be collected by means of a CRF during treatment in the participating centers. The CRF will be completed prospectively during hospital admission and during follow-up. After that, the CRFs will be forwarded to the data coordinating center. There will be regular contact between the study coordinators and the participating centers.

Follow-up

Patients are followed-up during their hospital stay. At 30 ± 7 days after thrombolysis has been completed, there is one follow-up visit in the outpatient department, including a physical examination, ankle-brachial index, treadmill test, and contrast-enhanced magnetic resonance arteriography of the treated leg, according to current guidelines.[16] During follow-up, any additional procedures, conversion to open surgery, duration and costs of hospital admission, death, distal thromboembolic complications, and other complications will be recorded.

DISCUSSION

Several treatment strategies have focused on accelerating thrombolytic therapy to improve its effectiveness and to reduce treatment time and, therefore, adverse effects. US-accelerated thrombolysis, which involves the simultaneous delivery of low-intensity US and a thrombolytic agent into a thrombosed vessel, has been shown to reduce therapy time. The DUET study is designed to compare US-accelerated thrombolysis with standard thrombolysis in patients with recently thrombosed infrainguinal native arteries or bypass grafts.

Only patients with acute lower limb ischemia in class I and IIa, according to the Rutherford classification, will be included in our study, because catheter-directed thrombolysis is the initial treatment chosen in patients with viable or minimally threatened lower limbs. Immediate surgical revascularization is indicated in most patients with acute lower limb ischemia class IIb and III; therefore, these patients will be excluded from the study.

Prolonged thrombolysis therapy might be expected in clots older than 1 week. Most clots that are less than 1 week old can be rather easily and quickly treated with standard catheter-directed thrombolysis or thrombosuction. The additional value of the more expensive US-accelerated thrombolysis in these thrombi may be argued and are these are therefore excluded in this study.

Randomization is stratified according to whether a native artery or a bypass graft is occluded, because it has been shown that thrombolysis of a bypass graft will lead to better outcome than thrombolysis of a native artery.

To test our hypothesis, a control angiography should be performed every 12 hours. Therefore, our sample size calculation is based on a reduction in therapy time of 12 hours or more. Control angiographies at 8:00 a.m. and at 8.00 p.m. would have been sufficient. However, in our study protocol we have incorporated an extra control angiography at 2.00 p.m. to measure our primary outcome more precisely and to reduce any unnecessary exposure to thrombolytics in our study participants.

Two vascular surgeons and 2 interventional radiologists from 2 nonparticipating centers will review all angiographies independently. The vascular surgeons and the interventional radiologists will be blinded for patient characteristics and for the results of the initial reports. They will be asked to classify the degree of lysis, ranging from no lysis, partial lysis, to complete lysis (>95% lysis).

If thrombolysis of the occluded segment is successful, any hemodynamically significant underlying atherosclerotic lesion will be identified and treated. Preferably, the underlying lesion will be treated endovascularly, with PTA with or without stent placement, or both. It will be the vascular surgeon's or interventional radiologists' decision to convert to open surgery if endovascular treatment of the underlying lesion is not feasible or if thrombolysis of the occluded segment is not successful.

CONCLUSION

The DUET study is a randomized controlled trial that will provide evidence whether US-accelerated thrombolysis will significantly reduce therapy time compared with standard thrombolysis in patients with recently thrombosed infrainguinal native arteries or bypass grafts, without an increase in the number of complications.

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Chapter 8

Dutch randomized trial comparing standard catheter-directed thrombolysis and ultrasound-accelerated thrombolysis for arterial thromboembolic infrainguinal disease - DUET

A.M. Schrijver, M. van Leersum, B. Fioole, M.M.P.J. Reijnen, A.W.J. Hoksbergen, A.C. Vahl, J.P.P.M. de Vries

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ABSTRACT

Purpose

To report the results of the Dutch randomized trial comparing standard catheter-directed and ultrasound-accelerated thrombolysis (UST) for the treatment of arterial thromboembolic occlusions.

Methods

The DUET study (*controlled-trials.com*; identifier ISRCTN72676102) was designed to assess whether UST can reduce therapy time significantly compared with standard thrombolysis (ST). Sixty patients (44 men; mean age 64 years) with recently (7–49 days) thrombosed infrainguinal native arteries or bypass grafts causing acute limb ischemia (Rutherford category I or IIa) were randomized to ST (n=32) or UST (n=28). The primary outcome was the duration of thrombolysis needed for uninterrupted flow (>95% thrombus lysis), with outflow through at least 1 below-the-knee artery. Continuous data are presented as means ± standard deviations.

Results

Thrombolysis was significantly faster in the UST group (17.7±2.0 hours) than in the ST group (29.5±3.2 hours, p=0.009) and required significantly fewer units of urokinase (2.8±1.6×106 IU in the ST group vs. 1.8±1.0×106 IU in the UST group, p=0.01) for uninterrupted flow. Technical success was achieved in 27 (84%) patients in the ST group vs. 21 (75%) patients in the UST group (p=0.52). The combined 30-day death and severe adverse event rate was 19% in the ST group and 29% in the UST group (p=0.54). The 30-day patency rate was 82% in the ST group as compared with 71% in the UST group (p=0.35).

Conclusion

Thrombolysis time was significantly reduced by UST as compared with ST in patients with recently thrombosed infrainguinal native arteries or bypass grafts.

INTRODUCTION

Background and rationale

Catheter-directed thrombolysis is a well-accepted treatment for acute occlusions of lower extremity native arteries and bypass grafts.[1] Moreover, several studies have shown that catheter-directed thrombolysis is a valuable treatment option for sub-acute occlusions as well.[2-4] Benefits of thrombolysis over surgical embolectomy are its minimally invasive character, more complete lysis of small side branches and outflow arteries,[5] and the possibility to identify and treat underlying lesions using percutaneous transluminal angioplasty (PTA) and stenting. A major limitation to this treatment is the occurrence of bleeding complications.[6] A meta-analysis of 3 large randomized controlled trials comparing surgical intervention with standard thrombolysis for the treatment of acute lower extremity ischemia showed that limb salvage and death rates were similar for both treatments, with a higher incidence of major bleeding complications in the thrombolysis group.[7]

In recent years, ultrasound (US) has been used to accelerate thrombolysis. High-frequency low-intensity US-accelerated thrombolysis (UST) has been shown to accelerate enzymatic clot lysis in vitro by loosening fibrin strands and thereby increasing thrombus permeability and exposing more plasminogen receptors for binding, without mechanically disrupting the clot.[8-10] Moreover, US accelerates thrombolysis by another nonthermal mechanism, called acoustic cavitation, which refers to the formation and collapse of microscopic bubbles in a liquid due to an acoustic pressure field. The resulting cavitation causes reversible disintegration of fibrin fibers, leading to better penetration of enzyme into the thrombus.[8, 11] Possible benefits of UST are shorter thrombolysis time and eventually reduction in bleeding complications.

The hypothesis of Dutch randomized trial comparing standard catheter-directed thrombolysis versus Ultrasound-accElerated Thrombolysis for thromboembolic infrainguinal disease (DUET) was that UST would result in a significant reduction in thrombolysis time (≥ 12 hours) as compared with standard thrombolysis (ST). We present the final results of this trial, which enrolled patients with recently thrombosed infrainguinal arteries or bypass grafts.

METHODS

Study design and patients

The design and rationale of the DUET study have been previously described in detail.[12] Patients were enrolled in 4 vascular teaching hospitals in the Netherlands; all participating physicians had treated >4 patients with UST before recruitment in the DUET study began to overcome a possible learning curve.

Patients with recently (7–49 days) thrombosed infrainguinal native arteries or bypass grafts presenting with acute limb ischemia (Rutherford acute category I and IIa)[13] were eligible for randomization. Exclusion criteria were isolated common femoral artery (CFA) thrombosis including the origin of the superficial femoral artery (SFA) and deep femoral artery (DFA); localized (<5

cm) femoropopliteal emboli or occlusions; acute ischemia due to thrombosis of the infrainguinal native arteries or bypass grafts <7 or >49 days before treatment; acute lower limb ischemia Rutherford class IIb and III; contraindication to antiplatelet therapy, anticoagulants, or thrombolytic drugs; recent (<6 weeks) ischemic stroke or cerebral bleeding; recent (<6 weeks) surgery; severe hypertension (>110 mmHg diastolic, >200 mmHg systolic blood pressure); current malignancy; history of prior life threatening reaction to contrast medium; uncorrected bleeding disorders; women with child-bearing potential not taking adequate contraceptives; current breastfeeding; pregnancy; hemodynamic instability at the onset of the procedure; refusal of treatment; current participation in another investigational drug or device study that has not completed the entire follow-up period; and age <18 or >85 years. Eligible patients were randomly assigned to treatment groups centrally by the study coordinator using a computerized randomization procedure. Block randomization was used with a concealed block size of 4. All patients provided written informed consent before randomization. Patients were stratified according to whether a native artery or a bypass graft was involved. Prospective data collection was performed by local physicians in the participating centers using case record forms. This study was conducted in accordance with the principles of the Declaration of Helsinki. The institutional review board of each participating hospital approved the study protocol. The trial was registered on the Current Controlled Trials website (*controlled-trials.com*; identifier ISRCTN72676102).

Endpoints and definitions

The predefined primary end point was the duration of catheter-directed thrombolysis needed for uninterrupted flow (> 95% lysis) in the thrombosed infrainguinal native artery or bypass graft with outflow through at least 1 below-the-knee (BTK) artery.[14] All angiographies were evaluated by a team of an interventional radiologist and a vascular surgeon to judge endpoints. Blinding was not used due to the visual difference between the thrombolysis catheters. Secondary end points included technical success, defined as > 95% lysis of the thrombosed native artery or bypass graft with outflow through at least 1 BTK artery;[15] number of units of urokinase needed for uninterrupted flow in the thrombosed infrainguinal native artery or bypass graft; death; major amputation and other adverse events; duration of hospital admission; 30-day patency of the treated native artery or bypass graft.

Adverse events were graded as mild, moderate, or severe according to the recommended standards for reports dealing with lower extremity ischemia.[13] Clinical events regarded as severe were myocardial infarction, major amputation, severe bleeding (including intracranial bleeding), distal embolization, and compartment syndrome. Moderate adverse events included moderate bleeding, pseudoaneurysm, iatrogenic dissection, and renal insufficiency (transient, not requiring hemodialysis). Clinical events regarded as mild were groin hematomas and other bleeding complications without the need for (operative) intervention and/or blood transfusion (mild events were not considered in this analysis).

Additional interventions were those performed after successful thrombolysis to sustain patency, including endovascular, including PTA with or without stenting, additional thrombolysis for remaining thrombus, thrombosuction and surgical (e.g., bypass anastomosis revision) procedures.

Secondary interventions were those performed after failed thrombolysis to achieve revascularization, including thromboembolectomy or bypass grafting.

Intervention

Standard thrombolysis

Initial angiography included the abdominal aorta, iliac arteries and femoropopliteal arteries as well as the BTK outflow. The antegrade approach was used through the ipsilateral CFA if possible; otherwise a crossover approach via the CFA was used. ST was performed with a 5 F UniFuse Infusion catheter (AngioDynamics, Queensbury, NY, USA), which had a working length of 90 cm and circumferential infusion holes along the distal 10 cm of the catheter. After initial angiography, the catheter was navigated over a guidewire and positioned so that the tip of the catheter with the infusion holes was in the thrombosed distal segment. During each control angiography, the distal part of the thrombolysis catheter was repositioned in the remaining thrombosed segment, if necessary. The initial angiography in both groups was started at 8.00 a.m. ± 1 hour for logistical reasons. After successful positioning of the thrombolysis catheter, a 250,000 IU bolus of urokinase was given, followed by a continuous infusion of 100,000 IU urokinase/hour. Moreover, systemic heparin was given (10,000 IU/24 hours) to prevent clot formation at the catheters and infusion lines. Control angiography was performed every 6 ± 1 hours. At night, angiography was only performed in emergencies (e.g., clinical suspicion of distal embolization and bleeding). If the obstructive clot had been successfully thrombolized, a completion angiography was performed, including inflow and outflow arteries. Any necessary additional procedure was performed. After successful thrombolysis, systemic heparin was given (25,000 IU/24 hours) and dosage was adjusted based on activated partial thromboplastin time. Coumarin derivatives were started. The target international normalized ratio (INR) was 2.5 to 3.5. If this value was reached, heparinization was stopped.

Ultrasound-accelerated thrombolysis

UST was performed using the EKOS EndoWave system (EKOS Corporation, Bothell, WA, USA) which consists of a 5.2 F multilumen thrombolysis delivery catheter (106 - or 135-cm working length) and a matching US coaxial core wire with a working zone of 6 cm to 50 cm.[16, 17] The central lumen of the multilumen thrombolysis delivery catheter accommodates the US core wire.

After initial angiography, the thrombolysis delivery catheter was navigated over a guidewire into the target vessel so that the US treatment zone traversed the entire thrombosed segment, with the tip of the infusion catheter located distally in a patent outflow artery. After final positioning, the guidewire was exchanged for the matching US core wire, and thrombolytic therapy

was started. Urokinase was infused through 3 drug lumens containing multiple side holes. Low-intensity (2.2 MHz), high-frequency US was delivered over the entire length of the US core wire and corresponding infusion catheter. US intensity and local temperature were both monitored with thermocouples and automatically regulated by a portable control unit. Control angiography was performed at standardized intervals similar to the ST group. If placement of the EKOS system was technically not feasible, the operating physician decided which alternative treatment was started.

Follow-up

At 30±7 days after completion of thrombolysis, a follow-up visit was planned in the outpatient department, including contrast-enhanced magnetic resonance angiography of the treated leg. During follow-up, any (surgical) reintervention, death, and other (severe) adverse events were recorded.

Safety and quality control

An independent Data Safety Monitoring Board (DSMB) performed an interim analysis on the primary end point after half the required number of patients had been enrolled, using the Peto approach, meaning that the study would only be stopped for beneficial effects in case of a p <.001.[18] End points in blinded groups were assessed by the DSMB. In addition, sequential monitoring was used to monitor the incidence of death from all causes and all severe and moderate adverse events.

Statistical analysis

Sample size calculation was based on the assumption that the mean duration for successful standard thrombolytic treatment of infrainguinal native arteries or bypass grafts is 2.5±1 days. This assumption was based on data from a cohort of 186 patients from the St. Antonius Hospital (Nieuwegein, the Netherlands) undergoing catheter-directed thrombolysis for acute arterial lower limb occlusions from 2001 to 2008 (unpublished data). Given a power of 90% and a 2-tailed significance of 5%, a 2-armed randomized trial including 26 patients in each arm would be needed to prove a 12-hour reduction in therapy time with UST compared with ST. Taking into account 10% dropouts in each arm, 30 patients would be needed in each study arm. This study was not powered on secondary outcomes; no subgroup analyses were predefined.

All analyses were performed according to the intention-to-treat principle, and results were compared between the treatment groups. Primary outcome was analyzed by means of Kaplan-Meier analysis and Log-rank tests. Patients with unsuccessful thrombolysis were censored in the Kaplan-Meier analysis; censored cases were removes from the denominator, that is, the group of patients still receiving thrombolysis.[19] Baseline characteristics were analyzed using chi-square test and Fischer's exact test when appropriate. A p-value <0.05 was considered statistically significant.

Statistical analyses were performed using SPSS software (version 20.0; IBM Corporation, Armonk, NY, USA).

RESULTS

Patient characteristics and treatment assignments

Between November 2009 and November 2012, 67 patients were randomized in the DUET study. Seven patients were excluded after randomization because diagnostic angiography showed a significant stenosis instead of an occlusion. These patients were primarily treated with PTA; none had been treated with thrombolysis. The remaining 60 patients (44 men; mean age 64 years) were included in the analysis (Figure 1): 32 in the ST group and 28 in the UST group. Baseline patient (Table 1) and occlusion characteristics (Table 2) of the treatment groups were similar. Bypass graft thrombosis predominated in both groups.

Outcomes and adverse events

Thrombolysis was significantly faster in the UST group (17.7±2.0 hours) than in the ST group (29.5±3.2 hours, p=0.009; Figure 2) and required significantly fewer units of urokinase (2.8±1.6×10^6

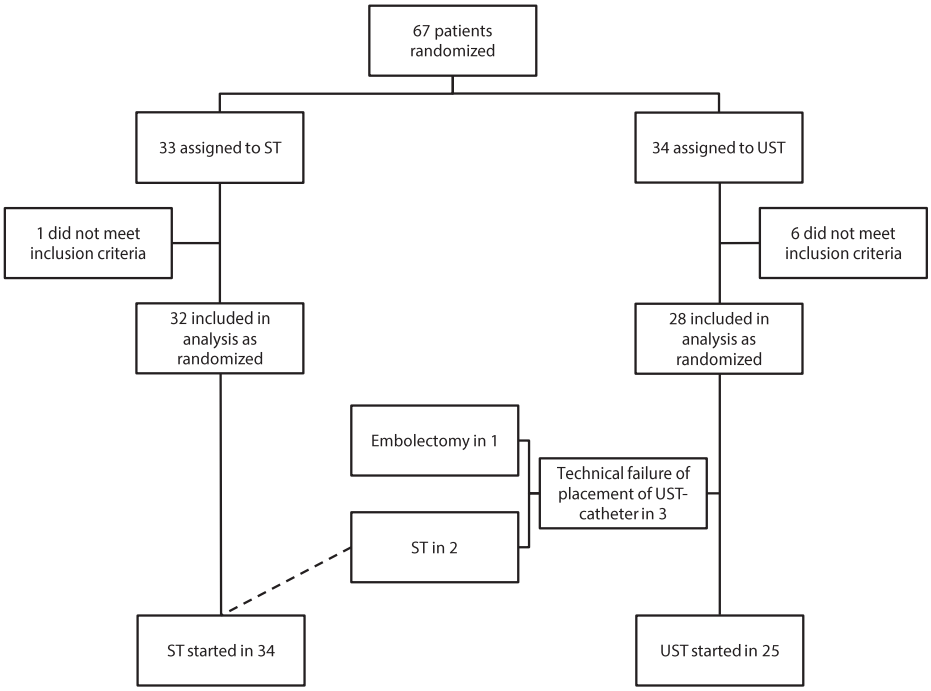

Figure 1. Randomization flowchart. ST, standard thrombolysis; UST, ultrasound-accelerated thrombolysis.

Table 1. Patient characteristics.[a]

Characteristic	Standard thrombolysis (n=32)	US-accelerated thrombolysis (n=28)
Age, y	64.0 ± 11.8	64.8 ± 12.1
Men	25 (78)	19 (68)
Body mass index, kg/m^2	27.1 ± 3.3	27.3 ± 4.5
History of smoking	25 (78)	23 (82)
Comorbidities		
Diabetes	9 (20)	9 (32)
Hypertension	18 (56)	16 (57)
Hypercholesterolemia	18 (56)	15 (54)
Coronary artery disease	8 (26)	10 (36)
TIA or stroke	5 (16)	2 (7)
Renal insufficiency	2 (6)	5 (18)
Pulmonary disease	8 (25)	5 (18)
ASA class		
I	1 (3)	4 (14)
II	23 (72)	13 (46)
III	8 (25)	10 (36)
IV	0 (0)	1 (4)
Prestudy medication		
Coumarin derivatives	14 (32)	11 (39)
Platelet aggregation inhibitors	17 (53)	15 (54)
Statines	18 (56)	15 (54)

Abbreviations: US, ultrasound; TIA, transient ischemic attack; ASA, American Society of Anesthesiologists. [a]Continuous data are presented as the means ± standard deviations; categorical data are given as counts (percentage).

IU in the ST group vs. 1.8±1.0×10^6 IU in the UST group, p=0.01) for uninterrupted flow (Table 3). Mean units of urokinase for all patients was 3.0±1.6×10^6 IU in the ST group and 1.8±1.0×10^6 IU in the UST group (p=0.001). Technical success was achieved in 27 (84%) patients in the ST group vs. 21 (75%) patients in the UST group (p=0.52). Repositioning of the UniFuse catheter was needed in 6 ST patients during control angiography to navigate the infusion holes into the remaining part of the thrombus. There was no significant difference in the use of additional procedures or secondary interventions between the treatment groups. Of the 9 patients with a thrombosed venous bypass graft, 7 had successful thrombolysis (5 UST and 2 ST). The 2 patients who had unsuccessful thrombolysis were both in the ST group. The combined 30-day death and severe adverse event rate (Table 4) was 19% (6/32) in the ST group and 29% (8/28) in the UST group (p=0.54). Combining severe or moderate adverse events with death gave incidences of 22% (7/32) in the ST group and 43% (12/28) in the UST group (p=0.10). One patient died in each group; the ST patient died due to cardiac failure, while the UST patient suffered fatal intracranial bleeding 2 days after successful thrombolysis. Two ST patients experience severe bleeding complications. One had bleeding from a DFA side branch during additional thrombolysis that required embolization and the other had bleeding from a SFA side branch that needed embolization 4 days after thrombolysis. In the UST group, 3 patients had severe bleeding complications. Two had

Table 2. Baseline occlusion characteristics.[a]

Characteristic*	Standard thrombolysis (n=32)	US-accelerated thrombolysis (n=28)
Type of occlusion		
Native artery	10 (31)	9 (32)
Bypass graft	22 (69)	19 (68)
Prosthetic	18 (82)	14 (74)
Venous	4 (18)	5 (26)
Duration of symptoms, d	18.7 ± 12.3	18.9 ± 13.0
Walking distance, m	76.3 ± 116.3	48.6 ± 76.6
Occlusion length, cm	29.8 ± 15.9	32.6 ± 15.3
Rutherford class		
I	19 (59)	15 (54)
IIa	13 (41)	13 (46)
ABI	0.37 ± 0.26	0.24 ± 0.25
Number of outflow arteries		
0	6 (19)	3 (11)
1	7 (22)	7 (25)
2	5 (16)	8 (29)
3	14 (44)	10 (36)
Previous ipsilateral revascularization		
PTA and/or stenting	9 (28)	7 (25)
Thrombolysis	6 (19)	5 (18)
Bypass	22 (69)	19 (68)

Abbreviations: US, ultrasound; PTA, percutaneous transluminal angioplasty; ABI, ankle-brachial index. [a]Continuous data are presented as the means ± standard deviations; categorical data are given as counts (percentage).

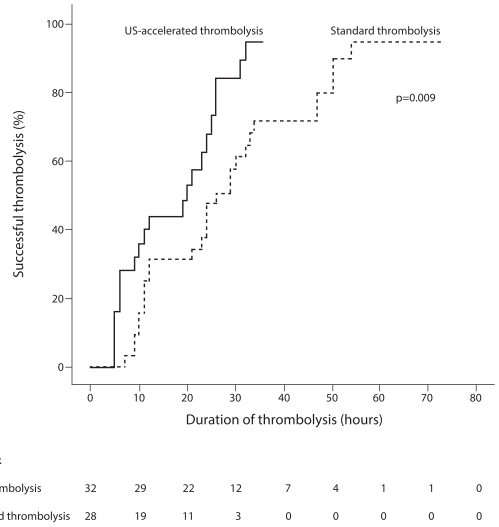

Figure 2. Kaplan-Meier curve of primary endpoint of both treatment groups.

intracranial bleeding (fatal in one as mentioned above) and the other, a patient with a history of recurrent pancreatitis, bled from the gastroepiploic artery during thrombolysis and required laparotomy. During hospitalization, 2 lower leg amputations were performed in ST patients. Both had presented with acute on chronic ischemia and required a lower leg amputation because of progressive Fontaine grade IV ischemia.

Table 3. Procedural details.[a]

	Standard thrombolysis (n=32)	US-accelerated thrombolysis (n=28)	P
Duration of thrombolysis, h	29.5±3.2	17.7±2.0	0.009
Urokinase, IU x 10^6	2.8±1.5	1.8±1.0	0.01
Technical success	27 (84)	21 (75)	0.52
Additional procedures			
PTA ± stenting	17(53)	19 (68)	0.30
Thromboaspiration	0 (0)	1 (4)	0.47
Thrombolysis	4 (13)	3 (11)	1.00
Bypass anastomosis revision	3 (9)	1(4)	0.62
Secondary procedures			
Embolectomy	1 (3)	4 (14)	0.18
Bypass	0 (0)	1 (4)	0.47
Increase in ABI	0.56±0.33	0.57±0.31	0.88
Length of hospital stay, d	8.0±6.3	9.0±7.8	0.48

Abbreviations: US, ultrasound; PTA, percutaneous transluminal angioplasty; ABI, ankle-brachial index. [a]Continuous data are presented as the means ± standard deviations; categorical data are given as counts (percentage).

Table 4. Thirty-day adverse events.[a]

Adverse events[b]	Standard thrombolysis (n=32)	US-accelerated thrombolysis (n=28)	P
Death	1 (3)	1 (4)	1.00
Death and severe adverse events	6 (19)	8 (29)	0.54
Death and severe or moderate adverse events	7 (22)	12 (43)	0.10
Severe adverse events			
Myocardial infarction	1 (3)	0 (0)	1.00
Major amputation	2 (6)	2 (7)	1.00
Severe bleeding	2 (6)	3 (11)	0.66
Intracranial	0 (0)	2 (7)	0.21
Other	2 (6)	1 (4)	1.00
Distal embolization	0 (0)	1 (4)	0.47
Compartment syndrome	0 (0)	1 (4)	0.47
Moderate adverse events			
Moderate bleeding	0 (0)	1(4)	0.47
Pseudoaneurysm	1 (3)	1 (4)	1.00
Iatrogenic dissection	0 (0)	1(4)	0.47
Renal insufficiency[c]	0 (0)	1 (4)	0.47

[a]Data are presented as counts (percentage). [b]All events that occurred in each patient were counted.[13] [c]Defined as transient renal insufficiency without need for hemodialysis.

Follow-up

At 30-day follow-up, patency in the successfully lysed ST patients was 82% (22/27) vs. 71% (15/21) in the UST patients (p=0.35). Among the ST group, 5 patients had a reocclusion. One patient underwent thrombolysis, another had embolectomy, and 3 patients were treated conservatively because of mild claudication symptoms. In the UST group, 6 patients had a reocclusion. Two patients underwent embolectomy, of which 1 patient eventually underwent a transfemoral amputation. One patient had a bypass, another needed a lower leg amputation, and 2 patients were treated conservatively.

DISCUSSION

US-accelerated thrombolysis is a non-mechanical form of thrombolysis that does not damage the intimal wall according to in vitro studies.[20, 21] In addition, UST is thought to have a vasorelaxant effect.[20] Several authors have reported promising results of catheter-directed UST for acute occlusions of lower limb native arteries and bypass grafts, with reported technical success rates between 88% and 96%.[17, 22-25]

The DUET study, the first randomized controlled trial comparing ST with UST in recently thrombosed infrainguinal native arteries or bypass grafts, showed that UST can reduce thrombolysis time significantly. Major bleeding was substantial in both groups, and 30-day patency rates were moderate.

For logistical reasons, patients were randomized prior to initial angiography. Since all of the 7 excluded patients had an initial angiogram that showed a significant stenosis instead of an occlusion, PTA was performed instead of thrombolysis. Therefore, it is very unlikely that selection bias occurred, since allocation did not influence the likelihood that patients received the intervention.[26]

In this trial, patients were included with an occlusion at least 7 days old. Results of standard thrombolytic therapy in acute occlusions are good because the thrombus or emboli are not organized. The added value of UST is expected in the more organized thrombi. Moreover, the literature has shown that the duration of ischemic symptoms does not significantly influence final outcome of thrombolysis,[2-4] and some patients present after 7 days because of mild ischemic symptoms.[27]

This clinical study reflected common practice. Restoration of antegrade flow and dissolution of at least 95% of the thrombus is the consensus definition of technical success.[15] This endpoint was evaluated for every patient in this trial by an interventional radiologist and vascular surgeon. The decision to continue or finish thrombolysis is subjective and was made after the primary endpoint had been reached. The treating physician decided how to treat any residual thrombosis, that is, by endovascular or surgical means.

Control angiography was performed every 6±1 hours; at night, angiography was performed only in case of emergencies. Theoretically, therapy time could have been overestimated in our

study if complete lysis were achieved during the night. Actually, the duration of thrombolysis in the study showed a quite left-skewed distribution, suggesting that most of the UST cases had been successful within the first 12 hours. Since the study protocol was similar for both groups, it is unlikely that bias occurred.

Urokinase was used in this study since this was the most frequently employed fibrinolytic agent in the participating hospitals. A systematic review of fibrinolytic agents for peripheral artery occlusions found no evidence that urokinase is more or less effective or is associated with more bleeding complications as compared to other fibrinolytic agents.[28]

In 3 patients it was technically not possible to advance an US-accelerated catheter through the entire thrombosed arterial segment; in 2 of these patients, it was possible to place a standard catheter in the proximal segment of the thrombus instead. A standard catheter could not be placed in the third case, so embolectomy was performed. The need to advance the US-accelerated catheter through the entire thrombus is one of the limitations of this technique. In addition, the costs of an US-accelerated catheter and the portable unit are substantially higher than those of a standard catheter. While a decrease in overall costs of thrombolytic treatment (i.e., fewer control angiographies, less lytic agent, and shorter hospitalization) is a possible benefit of reduced thrombolysis time, it is unknown if the savings could compensate for the higher costs of the US-accelerated catheter. A cost-effectiveness analysis will be performed to compare overall costs of both treatments.

Although not statistically significant, the rate for combined 30-day death and any severe or moderate complication was higher in the UST group. The 30-day major bleeding complication rates of 6% in the ST group and 11% in the UST group are comparable to the 9% in the meta-analysis of 3 randomized controlled trials comparing standard thrombolysis to surgical intervention.[7] The number of severe bleedings in the UST group was relatively high as compared with the ST group, which might be partially explained by the need to temporarily withdraw the US coaxial core wire during control angiography manipulation of the introducer sheath. The incidence of hypertension did not significantly differ between both groups, and no patient had a systolic pressure >200 mm Hg. In the UST group, 2 of the 3 remote bleeding complications were intracranial. One occurred after 5 hours of thrombolysis and the other 20 days after thrombolytic therapy. It is debatable if the latter event was associated with the initial thrombolysis. In the ST group, only local bleeding complications occurred, most likely due to guidewire trauma.

Limitations

When the trial was started, all hospitals used the 10-cm long catheters for standard thrombolysis, since catheters with other infusion hole lengths were not available in all participating hospitals. The use of only one length of the Unifuse catheter might be a limitation of this study. While major bleeding is an important outcome of catheter- directed thrombolysis, it was not chosen as a primary endpoint in this trial. A study showing a difference in major bleeding would require a very large sample size and is not feasible in the Netherlands.

CONCLUSION

Therapy time for treatment of infrainguinal arterial thrombosis is significantly reduced with UST compared to ST. However, in both treatment groups the number of bleeding complications was substantial with moderate 30-day patency rates. Future studies are needed to assess the clinical significance of reduced therapy time.

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Chapter 9

Summary and general discussion

Acute limb ischemia occurs due to a sudden decrease in blood flow to the limb, usually caused by a thrombus or embolus, resulting not only in a potential threat to the viability of the limb, but also a high risk of death. While over the past decades the rate of limb loss in patients with acute limb ischemia has declined, the mortality rate has not changed. Most likely the rate of limb loss has declined due to improvements in treatment strategies. However, mortality is associated with (cardiovascular) comorbidities and the fragile baseline state of patients with acute limb ischemia.[1] Although surgical techniques have been the standard of care for a long period of time, less invasive endovascular techniques have become the preferred treatment over the last three decades, in particular catheter-directed thrombolysis.

Chapter 2 provides an overview of the current status and new developments of pharmacomechanical thrombolysis for acute arterial lower limb occlusions. Since the introduction of catheter-directed thrombolysis, there has been a vast development of new thrombolysis catheters and different infusion techniques. Different adjuncts to pharmacological thrombolysis are available, such as percutaneous thrombus aspiration devices and percutaneous mechanical thrombectomy devices. Simultaneous delivery of ultrasound and thrombolytic agents, is a relatively new concept in the treatment of acute limb ischemia. The constant innovation of pharmacomechanical thrombolysis catheters, infusion techniques, and thrombolytic agents, is intended to improve and accelerate revascularization and reduce hemorrhagic complications.

Chapter 3 describes the long-term outcome of catheter-directed thrombolysis for acute lower limb occlusions of native arteries and prosthetic bypass grafts. Because (fatal) hemorrhagic complications may occur, identifying and selecting patients who are expected to have the best outcome after catheter-directed thrombolysis is crucial. Based on available literature the hypothesis of the study was that long-term outcome is better for native arteries as compared to prosthetic bypass grafts. Despite initial promising results, long-term follow-up of catheter-directed thrombolysis for acute lower limb occlusions showed a poor amputation-free survival. In our multivariate analysis, no significant differences in amputation-free survival between native arteries and prosthetic bypass grafts were found. Multivariate analysis did show that age >65 years and cerebrovascular disease were significant negative predictors for amputation-free survival. Our results indicate that catheter-directed thrombolysis should not be withheld from patients solely based on conduit type.

In **Chapter 4** we investigated the use of catheter-directed thrombolysis as first-line treatment in patients with acute upper limb ischemia. We found that catheter-directed thrombolysis is effective in over 60% of patients as first-line treatment of extensive acute upper limb ischemia and can prevent surgical intervention in these patients. Although cardiac embolism is found to be the most common cause of acute upper limb ischemia in current literature,[2] we did not find this in our study. It is possible that the cause of acute upper limb ischemia has been falsely attributed to a cardiac embolism in past studies, since most studies did not perform standard diagnostic tests to confirm the origin of the embolus. We believe that computed tomography angiography of the thoracic aorta and echocardiography to identify cardiothoracic sources of emboli, and laboratory

test to identify coagulation disorders should be part of a standard work-up of patients with acute upper limb ischemia. A PET-scan should be performed in case of suspicion of a paraneoplastic syndrome to identify the primary tumor.

Evidence concerning the treatment of acute ischemia of the upper limb is scarce and patient cohorts are often small. In current literature there is controversy about how aggressively acute upper limb ischemia should be treated, particularly when the upper limb appears viable.[2] To date a considerable amount of patients is still treated conservatively or with oral anticoagulants only. Many of these patients are lost to follow-up and data on the outcome of these patients are lacking. Since there is a substantial risk of limb loss, ischemic time of the limb should not be prolonged by only administering oral anticoagulants.

Since hemorrhagic complications are the largest draw-back of thrombolysis, several methods have been investigated to reduce thrombolysis time. Ultrasound-accelerated thrombolysis seems to be a promising concept in the treatment of various thromboembolic conditions. In the 1970s it was demonstrated that ultrasound waves could disrupt clots.[3] Since then, two fundamentally different approaches have evolved in the use of ultrasound for thrombolysis. In the first concept, high-intensity ultrasound is applied to mechanically disrupt the clot, while in the second concept lower intensity ultrasound is used to augment enzymatic fibrinolysis by breaking linkage of fibrin strands.[4] In the review described in **Chapter 5**, a total of 340 patients were treated with catheter-directed transducer-tipped ultrasound-accelerated thrombolysis for various indications. Complete or partial lysis was achieved in almost 90% of patients. The overall (hemorrhagic) complication rates were low. It must be noted that studies on ultrasound-accelerated thrombolysis are difficult to compare, as the EKOS catheter (EKOS Corporation, Bothell, WA, USA) has undergone significant modifications since 1999, which may have affected outcome of different studies.

In preparation of the randomized controlled trial of this thesis, in **Chapter 6** the results of a prospective cohort study of 21 patients undergoing ultrasound-accelerated thrombolysis for acute arterial lower limb occlusions are presented. Complete lysis was achieved in all but one patient. Median therapy time until complete lysis was 26.5 (range, 8.5–72) hours. No hemorrhagic complications or deaths occurred. One patient required major amputation because of progressive ischemia, despite complete lysis of the occluded segment. Based on our study and other available clinical studies, ultrasound-accelerated thrombolysis seems to be feasible and safe in the treatment of acute lower limb ischemia.

In **Chapter 7** the design and rationale of DUET (Dutch randomized trial comparing standard catheter-directed thrombolysis versus Ultrasound-accElerated Thrombolysis for thromboembolic infrainguinal disease) is described. It was designed to assess whether ultrasound-accelerated thrombolysis will reduce therapy time significantly compared with standard thrombolysis. The primary outcome was the duration of thrombolysis needed for uninterrupted flow (>95% thrombus lysis), with outflow through at least 1 below-the-knee artery.

As stated in the study protocol, all angiographies in the trial were assessed by a vascular surgeon and an interventional radiologist independently. We are aware of the fact that there could

be an inter- or intraobserver variability in the assessment of angiographies. For future research it would be interesting to develop a scoring system to calculate thrombus volume, in order to standardize the assessment of angiographies. To our knowledge only one study has described a formula to calculate thrombus volume.[5] Thrombus volume was calculated with independent assessments of radiographs by three physicians; it included the anatomic extent of intra-arterial thrombus, the maximum arterial stenosis produced by residual thrombus, and the volume of residual thrombus (length x [predicted normal arterial diameter/2] x π0. The physicians met as a group and reached a consensus on these end points. It would be interesting to perform an inter- and intraobserver variability study on this scoring system.

The results of DUET are presented in **Chapter 8.** This was a multicenter randomized controlled trial that was conducted in four vascular teaching hospitals in the Netherlands. Sixty patients with recently thrombosed infrainguinal native arteries or bypass grafts causing acute limb ischemia were randomized to standard thrombolysis or ultrasound-accelerated thrombolysis . Thrombolysis time was significantly reduced with 12 hours in the ultrasound-accelerated thrombolysis group as compared to the standard thrombolysis group and subsequently significantly fewer units of urokinase were required in the ultrasound-accelerated thrombolysis group. Technical success rate and 30-day patency rate did not significantly differ between the groups. However there was a trend of higher complication rates in the ultrasound-accelerated thrombolysis group. Most remarkable was the higher occurrence of intracranial hemorrhage in the ultrasound-accelerated thrombolysis group, although not significantly different as compared to the standard thrombolysis group. A possible explanation for this phenomenon is that the lytic properties of urokinase were more enhanced by the addition of ultrasound, caused by a synergistic effect. Furthermore the overall moderate (local) complication rate in the ultrasound-accelerated thrombolysis group was higher. No specific subtype of moderate hemorrhagic complications could be identified. However, it is possible that the higher rate of local complication is caused by the need to reposition the ultrasound-accelerated thrombolysis catheter during control angiographies.

Possibly, a more clinically relevant primary endpoint would have been (hemorrhagic) complication rate. However, in order to reach a statistically significant difference in complication rate, a much larger sample size would have been needed, which was not thought feasible in the Netherlands.

In order to further reduce hemorrhagic complications, studies have investigated the use of a low-dose urokinase regimen. Ebben et al. compared a low-dose urokinase regimen (50,000 IE urokinase per hour) to a high-dose regimen (100,000 IE urokinase per hour), and showed that the low-dose regimen is as effective, while hemorrhagic complications are significantly reduced.[6] A subsequent study by the same authors investigated the addition of contrast-enhanced ultrasound to low-dose thrombolysis in a porcine model and demonstrated that the thrombolytic effect was accelerated, without the occurrence of hemorrhagic complications.[7] Plans are underway to commence a non-randomized clinical trial, DUET II, that will investigate the use of a low-dose urokinase regimen in combination with ultrasound.

FUTURE PERSPECTIVES

Despite several advancements in treatment strategies for patients with acute limb ischemia, complication rates remain high. Since many patients suffer from several underlying cardiovascular comorbidities, acute limb ischemia usually is a sign of end-stage cardiovascular disease and therefore a sign of poor overall prognosis.

Hemorrhagic complications remain a large draw-back of catheter-directed thrombolysis. During thrombolytic therapy hemorrhage occurs due to fibrinolysis and platelet inhibition.[8] The ideal thrombolytic agent should cause fast and complete thrombus lysis, with a minimal risk of both hemorrhage and distal embolization. Further research should focus on developing a thrombolytic agent that has strong lytic capabilities and is highly fibrin specific, and thereby avoid systemic plasminemia. It should have a short circulating half-life and the effects of the thrombolytic agent should be easily reversed in case of hemorrhagic complications. Over more the ideal thrombolytic agent should not be dependent of genetic variations in response to its lytic capacities.

The concept of adding glycoprotein (GP)IIb/IIIa antagonists to thrombolytic therapy to reduce the total amount of thrombolytics needed, especially in platelet rich clots, seems promising. The mechanism of action of GP IIb/IIIa antagonists is inhibition of platelet aggregation and dissolution of platelet rich clot by disrupting fibrinogen-platelet interaction. This combination therapy has been extensively used in the setting of coronary arterial interventions. Current clinical studies that investigated this combination therapy in acute peripheral arterial occlusions, showed faster thrombus resolution, but similar or increased major hemorrhagic complications as compared to thrombolytic therapy alone.[9, 10] Future research should focus on applying this combination therapy only in patients that are more resistant to thrombolysis.

The ideal thrombolysis catheter should be a multiple side hole catheter that reduces the need for repeat repositioning of the catheter and thereby reducing the risk of peripheral embolization. The addition of ultrasound to thrombolytic therapy has been proved to reduce therapy time. Results of DUET II, that investigates ultrasound-accelerated thrombolysis with a lower dosage of urokinase, are eagerly awaited.

Percutaneous thrombomechanical devices are a valuable adjunct to catheter-directed thrombolysis in more organized thrombi. Organized thrombi are less receptive to lytic drugs because a well-organized fibrin cap develops around the thrombus over time. The ideal thrombectomy catheter should be highly steerable and torqueable in order to reach difficult-to-navigate vessels. The catheter should be low-profile, while the robustness of the catheter is maintained in order to reduce endothelial damage, since endothelial damage causes local thrombogenicity.

CONCLUSION

Physicians treating patients with acute limb ischemia should be acquainted with available pharmacomechanical thrombolysis treatment modalities and their (dis-)advantages. Having the complete spectrum of pharmacomechanical thrombolysis treatment modalities in your armamentarium is crucial in order to treat the individual, often fragile, patient in the most optimal way.

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Chapter 10

Nederlandse samenvatting

Acute ischemie (onvoldoende doorbloeding) van de extremiteit is een medisch noodgeval. Indien deze aandoening niet snel en adequaat wordt behandeld, is er grote kans op amputatie en/of dood. De incidentie van acute ischemie van de extremiteit bedraagt 14 per 100.000 in de algemene bevolking en vormt 10 tot 16% van de vasculaire werkbelasting. De meest voorkomende oorzaak van acute ischemie van de extremiteit is vorming van een trombus (bloedstolsel) ter hoogte van een atherosclerotische plaque (slagaderverkalking).

De afgelopen jaren is de kans op amputatie verlaagd door verbeteringen van behandeltechnieken. De mortaliteit is helaas niet verlaagd doordat patiënten met een acute arteriële (slagaderlijke) trombus van de extremiteit vaak uitgebreide hart- en vaatziekten hebben, waardoor er een grote kans is op overlijden tijdens en na de behandeling.

Gedurende lange tijd werden patiënten met acute ischemie van de extremiteit behandeld met een embolectomie (het operatief verwijderen van een bloedprop). Nadelen van deze behandeling zijn het ontstaan van schade aan de vaatwand en incomplete verwijdering van de trombus. In het begin van de jaren 80 werd het gebruik van catheter-geleide trombolyse (het oplossen van een stolsel met medicijnen die via een catheter worden toegediend) geïntroduceerd. Voordelen van deze behandeling ten opzichte van chirurgische embolectomie zijn: meer voorzichtige en complete verwijdering van de trombus, minder schade aan de vaatwand en de mogelijkheid om onderliggende atherosclerose te behandelen met een Dotter-procedure, eventueel in combinatie met plaatsing van een stent. Met drie grote, gerandomiseerde studies, waarbij chirurgische interventie werd vergeleken met catheter-geleide trombolyse, is aangetoond dat er geen significant verschil is in het optreden van amputatie of dood op de korte- en middellange termijn, maar dat het aantal bloedingscomplicaties significant hoger is bij catheter-geleide trombolyse.

Inmiddels is veel onderzoek gedaan naar technieken om de trombolyseduur te reduceren en daarmee het aantal bloedingscomplicaties te reduceren. Met verschillende laboratorium- en klinische studies is aangetoond dat het toevoegen van lage-intensiteit echogeluid leidt tot het sneller oplossen van een trombus. Door de toevoeging van lage-intensiteit echogeluid aan trombolytica (stolseloplossende medicijnen) wordt de trombus op celniveau kapot gemaakt, waardoor de trombus makkelijker kan worden opgelost. Hierdoor wordt de behandelingsduur gereduceerd en mogelijk ook het aantal bloedingscomplicaties.

In **hoofdstuk 2** wordt een overzicht gegeven van de ontwikkelingen van pharmacomechanische trombolyse. Sinds de introductie van catheter-geleide trombolyse is er een snelle ontwikkeling geweest van nieuwe trombolysecatheters en toedieningstechnieken. Daarnaast zijn er verschillende hulpmiddelen beschikbaar, zoals aspiratiecatheters en mechanische trombolysecatheters. De toevoeging van lage-intensiteit echogeluid aan trombolytica is een relatief nieuw concept binnen de behandeling van een acute arteriële trombose. De constante innovatie van nieuwe technieken is gericht op het (sneller) verbeteren van de bloeddoorstroming van de extremiteit en het verminderen van bloedingscomplicaties.

Hoofdstuk 3 beschrijft de lange termijn uitkomsten van catheter-geleide trombolyse bij een acute trombose van arteriën en bypasses in de onderste extremiteit. Ondanks veelbelovende

initiële resultaten, toonde lange termijn follow-up een teleurstellende amputatie-vrije overleving. De amputatie-vrije overleving verschilde echter niet voor acute trombose van een arterie vergeleken met een bypass in de onderste extremiteit. Wel was de amputatie-vrije overleving slechter voor patiënten ouder dan 65 jaar en patiënten met cerebrovasculaire (bloedvaten van de hersenen) ziektes.

In **hoofdstuk 4** hebben we het gebruik van catheter-geleide trombolyse onderzocht bij patiënten met een acute arteriële trombose in de bovenste extremiteit. Resultaten van deze studie toonden dat trombolyse effectief is bij meer dan 60% van de patiënten en daarmee de noodzaak voor chirurgische interventie voorkomt.

Aangezien bloedingscomplicaties het grootste nadeel van trombolyse vormen, zijn er verschillende technieken onderzocht om de behandelingsduur te verkorten en daarmee de totale dosering trombolytica te verkleinen. Eén van deze technieken is het toevoegen van echogeluid aan trombolyse. Daarbij zijn twee verschillende concepten te onderscheiden: bij het eerste concept wordt hoge-intensiteit echogeluid gebruikt om een trombus mechanisch te fragmenteren. Bij het tweede concept wordt lage-intensiteit echogeluid gebruikt om de enzymatische activiteit van trombolytica te vergroten, waardoor de trombus sneller en makkelijker oplost. In de klinische studies in dit proefschrift is onderzoek gedaan naar de toevoeging van lage-intensiteit echogeluid aan catheter-geleide trombolyse. Hierbij is gebruikt gemaakt van het EKOS EndoWave system (EKOS Corporation, Bothell, WA, USA). Dit systeem bestaat uit een trombolysecatheter met meerdere openingen over de gehele lengte, waarin een catheter met corresponderende echo-apparaatjes wordt geplaatst. Hierdoor kan lage-intensiteit echogeluid in combinatie met trombolytica over de gehele lengte van de trombus worden toegediend.

In de review, beschreven in **hoofdstuk 5**, zijn in totaal 340 patiënten met verschillende tromboembolische aandoeningen behandeld met echogeluid-versterkte trombolyse. Bij ongeveer 90% van de patiënten kon de trombus in zijn geheel of gedeeltelijk worden opgelost, met een laag aantal (bloedings-)complicaties.

Ter voorbereiding op de gerandomiseerde studie in dit proefschrift, worden in **hoofdstuk 6** de resultaten beschreven van een prospectieve cohortstudie van 21 patiënten die behandeld zijn met echogeluid-versterkte trombolyse vanwege een acute arteriële trombose van de onderste extremiteit. Bij 20 van de 21 patiënten werd volledige lysis (oplossen) van de trombus bereikt. De mediane behandelingsduur tot complete lysis bedroeg 26.5 (range 8.5–72) uur. Er traden geen bloedingscomplicaties of overlijden op. Bij één patiënt was een amputatie nodig vanwege voortschrijdende ischemie, ondanks complete lysis.

In **hoofdstuk 7** worden de opzet en de rationale van de DUET (Dutch randomized trial comparing standard catheter-directed thrombolysis versus Ultrasound-accElerated Thrombolysis for thromboembolic infrainguinal disease) studie beschreven. Deze studie is ontworpen om vast te stellen of echogeluid-versterkte trombolyse de behandelingsduur significant verkort ten opzichte van standaard trombolyse. De primaire uitkomst van deze studie was de trombolyseduur

tot volledige (>95%) doorgankelijkheid van het getromboseerde segment, met uitstroom via tenminste één onderbeenarterie.

De resultaten van DUET worden beschreven in **hoofdstuk 8**. Dit was een multicenter gerandomiseerde studie in vier vasculaire opleidingsziekenhuizen in Nederland. Zestig patiënten met recent getromboseerde arteriën of bypasses van de onderste extremiteit werden gerandomiseerd tussen echogeluid-versterkte trombolyse en standaard trombolyse. De trombolyseduur was met 12 uur significant gereduceerd in de echogeluid-versterkte trombolysegroep vergeleken met de standaard trombolysegroep. Het technische succes en de doorgankelijkheid van het behandelde segment na 30 dagen verschilde niet tussen de behandelgroepen. Er was een trend zichtbaar van een hoger aantal (bloedings-)complicaties in de echogeluid-versterkte trombolysegroep. Een verklaring voor dit fenomeen is dat er mogelijk sprake is van een synergistisch effect tussen echogeluid en trombolytica, hetgeen de bloedingsneiging verhoogt. Om te onderzoeken of het aantal bloedingscomplicaties kan worden gereduceerd, zijn er plannen om de DUET II studie te starten, een niet-gerandomiseerde studie waarbij een behandeling met een gehalveerde dosering trombolytica in combinatie met echogeluid wordt onderzocht bij patiënten met een acute arteriële trombose van de onderste extremiteit.

Chapter 11

Review Committee

Dankwoord

Author's publication list

Author's curriculum vitae

REVIEW COMMITTEE

Prof. dr. F.L.J. Visseren
Department of Internal Medicine
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Utrecht, The Netherlands

Prof. dr. T. Leiner
Department of Radiology
University Medical Center Utrecht
Utrecht, The Netherlands

Prof. dr. E.J.Th. Rutgers
Department of Surgery
Antoni van Leeuwenhoek Hospital
Amsterdam, The Netherlands

Prof. dr. C.J. Zeebregts
Department of Vascular Surgery
University Medical Center Groningen
Groningen, The Netherlands

Dr. G.J. de Borst
Department of Vascular Surgery
University Medical Center Utrecht
Utrecht, The Netherlands

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Lokale onderzoekers van de DUET studie: dr. A.W.J. Hoksbergen (Arjan), dr. B. Fioole (Bram), dr. M.M.P.J. Reijnen (Michel) en drs. M. van Leersum (Marc). Dank voor jullie warme ontvangst en belangstelling wanneer ik langskwam voor de dataverzameling van de DUET studie. Door jullie inzet en enthousiasme hebben we dit gezamenlijke project tot een mooi einde gebracht.

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AUTHOR'S PUBLICATION LIST

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AUTHOR'S CURRICULUM VITAE

Marjolein Schrijver was born on 6 August 1983 in Leiden, the Netherlands. She entered the Utrecht University Medical School in 2002. After obtaining her medical degree in February 2009, she began working as a surgical resident (not-in-training) at the St. Antonius Hospital, Nieuwegein (Dr. P.M.N.Y.H. Go). During her clinical work, she started a research project on catheter-directed thrombolysis under the supervision of Dr. J.P.P.M. de Vries (Department of Vascular Surgery, St. Antonius Hospital, Nieuwegein) and Prof. Dr. F.L. Moll (Department of Vascular Surgery, University Medical Center Utrecht, Utrecht). As part of this research project, she initiated and coordinated a multicenter randomized controlled trial. Study results have been presented at large national and international congresses. In July 2011, she began her training in surgery at the University Medical Center, Utrecht (Prof. Dr. I.H.M. Borel Rinkes and Prof. Dr. M.R. Vriens) and in July 2013 continued her training at the Elisabeth-TweeSteden Hospital in Tilburg (Dr. P.W.H.E. Vriens and Dr. M.S. Ibelings). During her training, she developed a significant interest for surgical oncology and will do an internship at the Antoni van Leeuwenhoek Hospital, Amsterdam (Prof. Dr. E.J.Th. Rutgers) in 2016 as part of her differentiation in surgical oncology.