# Remote endarterectomy for arterial occlusive disease

## Determinants for success

Suzanne Sarah Gisbertz

**Remote endarterectomy for arterial occlusive disease. Determinants for success**
SS Gisbertz

Thesis, University of Utrecht, with a summary in Dutch


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# Remote endarterectomy for arterial occlusive disease

## Determinants for success

Remote endarteriëctomie voor perifeer arterieel vaatlijden
Determinanten voor succes
(met een samenvatting in het Nederlands)

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door
**Suzanne Sarah Gisbertz**
geboren op 29 april 1974 te Breda

**Promotoren:** Prof.dr. F.L. Moll
Prof.dr. G. Pasterkamp

**Copromotoren:** Dr. J.P.P.M. de Vries
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# 1 General introduction and thesis outline

Peripheral arterial disease remains a significant health care problem and a demanding challenge for the vascular surgeon in a multidisciplinary setting. The prevalence in the general population is approximately 3-10%, and increases with age.[1] In an aging population, the incidence of peripheral arterial disease therefore increases. The most affected artery is the superficial femoral artery (SFA); in 70% of patients, an occlusion is observed here, preferentially at the level of the adductor canal hiatus.[2,3] Moreover, complicating treatment and demonstrating the need for a multidisciplinary approach, patients presenting with a SFA obstruction often reveal other manifestations of cardiovascular disease due to generalized atherosclerosis. As a result of this challenging complexity of factors, surgical and endovascular techniques are evolving, simultaneously with the development of supportive medical therapies and prevention strategies. This has lead to the introduction of a minimally invasive surgical procedure: remote superficial femoral artery endarterectomy (RSFAE), restoring the SFAs continuity. RSFAE is eligible for long SFA occlusions (Trans-Atlantic Inter-Society Consensus[1] [TASC] C and D lesions), which are unsuitable for endovascular procedures. A remaining concern is the significant restenosis rate; a considerable amount of reinterventions is needed to maintain patency.

RSFAE needs to be compared against the current most implemented surgical procedure, the supragenicular bypass, to establish it as a true alternative treatment for SFA occlusive disease. Furthermore, risk factors predicting failure ought to be identified, and moreover, strategies need to be developed to improve patency.



## Thesis outline

The aim of this thesis was to evaluate determinants for successful RSFAE and define its definite role in the spectrum of treatment options for SFA occlusive disease.

In **chapter 2** the literature will be reviewed concerning all aspects of femoropopliteal occlusion treatment. Both medical and interventional strategies will be discussed. Moreover, a view to future perspectives will be provided.

To establish RSFAE as a true alternative for bypass surgery in the treatment of long-segment SFA occlusive disease, the multicentre, randomised controlled REVAS trial (**r**emote **e**ndarterectomy **v**ersus **a**bove-knee **b**ypass **s**urgery), including 116 patients with a TASC C or D SFA obstruction, was initiated, and short-term results will be presented in **chapter 3**. After prolongation of the follow-up, medium-term results will be described in **chapter 4**.

To improve patency following RSFAE a novel treatment strategy has been developed. Cryoplasty provokes apoptosis in arterial smooth muscle cells, preventing migration and proliferation of smooth muscle cells, and thus reducing neointimal

hyperplasia.[4] In a pilot study including 17 patients, concomitant cryoplasty of the desobstructed SFA following RSFAE has been studied, and in **chapter 5**, the 1-year results will be presented.

Several risk factors for cardiovascular disease have been established. Moderate alcohol consumption has been consistently associated with a lower risk for cardiovascular events and peripheral arterial disease.[5,6] Atherosclerotic plaques containing more inflammation and larger lipid cores, are related to unstable coronary syndromes and symptomatic cerebrovascular disease.[7,8] Whether a relationship exists between alcohol intake, atherosclerotic plaque formation and the occurrence of cardiovascular events remains subject of investigation. In **chapter 6** the interrelationship between alcohol consumption, atherosclerotic plaque characteristics and the occurrence of cardiovascular events will be investigated in a prospective cohort study including 224 patients following femoral endarterectomy and 693 patients following carotid endarterectomy. Results after a median follow-up of 25 months will be described.

To improve patency rates and to be able to select these patients that would benefit most from RSFAE, risk factors predicting failure ought to be identified. In **chapter 7** this issue will be addressed. In 90 patients undergoing RSFAE, patient characteristics will be evaluated that might be predictive of restenosis during the first year postoperatively.



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# 2

SS Gisbertz, RJ Hissink, JPPM de Vries, FL Moll

# Future perspectives in the treatment of femoro-popliteal occlusions

J Cardiovasc Surg (Torino) 2005;46:371-84

# Abstract

Femoro-popliteal occlusive disease represents the most frequent localization of atherosclerosis in the lower extremities. Treatment of this disease has changed remarkably in the last decade. A definite treatment strategy has still to be established. The pathophysiology is described. A general overview of the state-of-the art treatment modalities and the most recent developments is given. This is divided into non-interventional preventive and supportive therapy, endovascular interventional therapy, and surgical interventional therapy. The development of medical therapy has expanded enormously and is progressing still. In the wide range of interventional treatment modalities, there has been a change from invasive bypass surgery to more refined techniques like endarterectomy and percutaneous endovascular therapy. This trend towards restoring the patency of the artery using the vessel wall itself as a conduit, leads to a term encompassing all these treatment modalities, known as restorative intervention. Peri-procedural risks of restorative interventions are of a much lesser degree compared to bypass surgery. Reports of patency rates show a steady increase. It is expected that patency rates will eventually equal or even surpass those of bypass surgery.

In conclusion, a treatment strategy for femoro-popliteal occlusions in the future is proposed as follows: the first line of interventional therapy in femoro-popliteal occlusions should be a restorative intervention. With adequate adjuvant medical therapy and sufficient monitoring, this will be the definite treatment for the majority of patients. Bypass surgery should be regarded as the second line of interventional therapy and should be reserved for those patients in whom restorative interventions fail.

# Introduction

Femoro-popliteal occlusive disease represents the most frequent localization of atherosclerosis in the lower extremities with a prevalence of up to 1% in the general population. Historically, femoro-popliteal bypass has been considered the preferential treatment for superficial femoral artery (SFA) and popliteal occlusive disease.[1-5] More than 35 years ago Dotter and Judkins introduced endovascular therapy.[6] With the development of endovascular techniques and the introduction of new devices and concomitant drug therapy, we must consider: what is state of the art and what are the future perspectives? During last decade, modern vascular surgery has made remarkable progress in the management of supragenicular femoro-popliteal occlusions. With the introduction of digitalized vascular imaging, meticulous visualization of the vascular tree has become routine and in the majority of patients atherosclerotic induced disability can be identified. In the wide range of treatment modalities, there has been a change from invasive bypass operations to more refined techniques like endarterectomy and percutaneous dilatation of arterial stenoses. In addition to this, the development of preventive medical therapy has expanded enormously. In this study we review the current state of art in the treatment of femoro-popliteal occlusive disease and give an insight into the future perspectives.



# Literature search

The literature was reviewed for studies focusing on the treatment of SFA occlusive or symptomatic stenotic disease (TASC type C and D lesions). Databases consulted were PubMed and the Cochrane library. Search criteria included SFA, treatment, occlusive disease, symptomatic, intervention, endovascular, surgery, drugs, and risk factors. The outcomes of most of these studies are difficult to relate because of lack of standardization. Many variables (e.g. stenotic versus occluded segments, differences in length of stenosis, non-comparable patient groups and failure measurements to use standard or objective outcome) greatly influence clinical and technical results. Therefore, this review is neither intended to be a meta-analysis, nor for directly comparing the efficacy of different treatment modalities.

# Pathophysiology of femoro-popliteal occlusions

The causative mechanism behind atherogenesis in the SFA and popliteal artery is poorly understood, but the general idea is that besides general atherogenic factors, local factors play an important role.

Considerable progress has been made recently in understanding the pathophysiology of atherosclerosis and has provided us multiple opportunities for influencing arterial injury, and the response to it. It is mainly an inflammatory disease of the vessel wall. Progression of atherosclerosis or its stabilization depends on the balance between cytokines and effectors that play both an inhibiting and a facilitating role in the progression of atherosclerosis. These include platelet-derived growth factor (PDGF), interleukin-1, tumor necrosis factor (TNF) -alpha, MCP-1, and the recently described Toll-like receptors (TLR4).



The response to injury model remains central to our understanding of atherogenesis. Numerous factors may initiate endothelial injury, including homocysteine, oxidized low-density lipoprotein (LDL), possibly infectious agents such as Chlamydia, viruses, and toxins such as nicotine. Mechanical factors such as hypertension and high shear stress in the artery also play a considerable role in the injury to the vessel wall. These factors lead to endothelial cells' increasing expression of receptors for LDL and increased adherence of monocytes and macrophages and T cells.[7]

Progression of atherosclerosis leads to focal accumulation of lipid-filled smooth muscle cells surrounded by lipid, collagen, elastic fibers, and proteoglycans. This forms a fibrous cap that covers deeper deposits of free extracellular lipids intermixed with cell debris. The fibrous plaque is altered as a result of hemorrhage, rupture, calcification, cell necrosis, and mural thrombus. These lesions will eventually cause stenosis of the artery. The actual occlusion however is caused by thrombosis superimposed on the plaques.

Occlusions and stenoses are not equally divided in the different arterial segments. The most affected artery is the SFA: 70% of all patients with intermittent claudication have vascular disorders in this vessel.[8] The proximal part of the popliteal artery is affected only half as many times, although it is direct a continuation of the SFA. The deep femoral artery and the part of the popliteal artery below the knee are affected in only 4-5% of the cases. The main predilection site for initiating occlusive vascular

disease is the distal segment of the SFA. This coincides with the level of the adductor hiatus where the artery crosses the sharp edge of the adductor magnus tendon, also known as Hunter's canal (Figure 1[9]). In one third of the cases occlusions of the distal SFA progress in a proximal direction as far as the origin of the deep femoral artery. Distal progression is not often observed.[9]

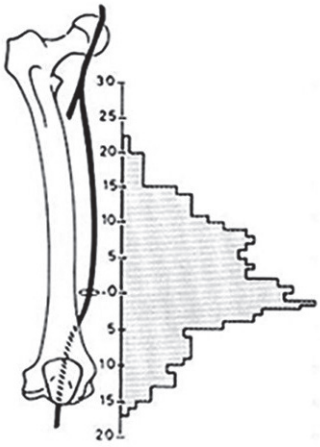


**Figure. 1** Histogram showing the location of femoropopliteal occlusions related (in cm) to the level of the adductor canal hiatus (=zero level). Duplex analysis in 50 patients with femoropopliteal occlusions.



The clear localization of occlusions in the adductor hiatus region implicates that besides general atherogenic causes, local changes in flow hemodynamics play a large role in the prominent atherogenesis at this specific location.

Increasing tortuosity of a vessel alters the local flow hemodynamics, creating great differences of flow velocity profile. This will lead to turbulence and high shear stress at endothelial level in certain segments of the vessel wall. Eventually this leads to the repetitive mechanical injury responsible for the initiation of atherogenesis.[10] Tortuosity of the SFA, especially at the level of the adductor canal is caused by three main pathophysiological mechanisms. Length excess occurs during knee flexion because of the position of the artery inside the axis of movement (Figure 2). The excess in length will mainly be compensated by longitudinal elasticity of the vessel, but if this mechanism reaches its limits the artery will have to meander. Secondly, an increase of tortuosity occurs with age due to natural elongation and loss of longitudinal arterial elasticity. Finally, the gliding mechanism of the SFA within the adductor canal consists of perivascular sheaths that are connected with the canal walls by lamellae. This mechanism becomes more and more rigid with age, creating a junction of a fixed and flexible part of the vessel, accentuating tortuosity at this level of the SFA.

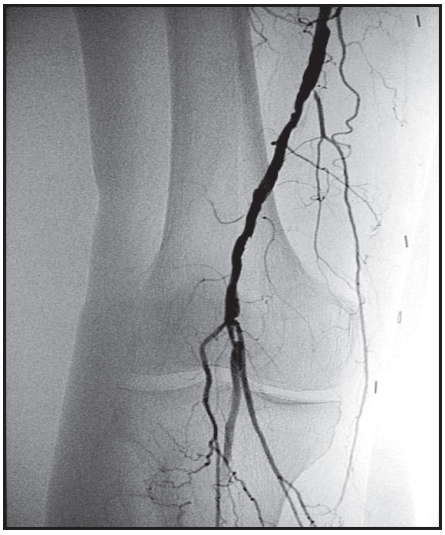

Figure 2a

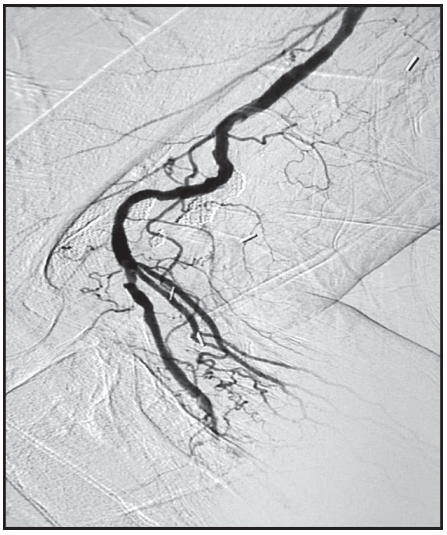

Figure 2b

**Figure. 2** SFA at knee level in extension (a) and flexion (b).



Measurements of flow patterns in the SFA show a helical flow pattern running down the vessel in a clockwise direction. Interestingly the early atherosclerotic lesions in the SFA are found spiralling through the artery in a similar fashion. The implication of this in the cause of distal SFA lesions is unclear, but is an aide to a better understanding of the atherosclerotic plaque formation.

# Treatment modalities

## Non-interventional preventive and supportive therapy

### Exercise therapy

Exercise therapy is safe and less expensive compared to other more invasive therapies for SFA occlusions. A Cochrane review analyzing 10 trials involving 250 patients with intermittent claudication shows that exercise therapy significantly improves pain free walking time with an overall improvement of walking ability of approximately 150% (ranging from 74-230%).[11] These results are better compared to angioplasty or anti-platelet therapy, but do not differ significantly from surgical interventions.[11] Another

review reveals the same results, even in unsupervised series.[12] Comparison of supervised versus non-supervised exercise therapy shows an advantage for supervised therapy in both walking time and onset of leg pain.[13,14] A regimen of thrice weekly, 30 minutes at a time to near maximum pain, for a minimum of 6 months provides the best improvement.[11,15]

## Pharmacologic therapy

### Antiplatelet therapy and oral anticoagulants

Antiplatelet therapy is mainly used to prevent cardial and cerebrovascular events and death. Aspirin is most widely studied and is protective in patients at increased risk of occlusive vascular events as are other antiplatelet drugs (ticlopidine, clopidogrel).[16] Addition of dipyridamole to aspirin produced no significant further reduction in vascular events compared to aspirin alone.[16] Among patients at high risk of immediate coronary occlusion, short term addition of an intravenous glycoprotein IIb/IIIa antagonist to aspirin prevented additional events.[16] A trial comparing aspirin and clopidogrel in prevention of cardiovascular events in patients at risk showed that patients assigned to clopidogrel had a significant reduction in the combined risk of stroke, myocardial infarction, or vascular death compared to aspirin. Patients gaining the most benefit using clopidogrel were the ones with symptomatic peripheral arterial occlusive disease.[17] A trial comparing aspirin and clopidogrel compared with clopidogrel alone for patients at risk showed a non-significant difference in reducing major vascular events. However, the risk of major bleeding is increased.[18] As therapy for intermittent claudication ticlopidine has demonstrated improvement of pain-free and maximum walking distances as well ankle-brachial indexes compared with placebo.[19]



Antiplatelet therapy and oral anticoagulants are also used to prevent re-stenosis or graft occlusion. Administration of antiplatelet agents improves graft patency compared to no treatment, especially when using prosthetic graft.[16] Johnson et al. found no difference in patency rates for 8 mm prosthesis when using aspirin and warfarin or aspirin alone, when using 6 mm prosthesis they found an advantage for the combination over aspirin alone. No differences were encountered using vein.[20] The Dutch BOA study group on the contrary found better patency rates for vein when using oral anticoagulants versus better patency rates for prosthetic when using aspirin.[21] In a meta-analysis by the Cochrane reviewers the safety and effectiveness of aspirin has been confirmed after endovascular treatment.[22] An additional effect for clopidogrel is suspected but data are lacking.

**Pentoxifylline**

Pentoxifylline reduces blood viscosity by improving red cell flexibility, and reduces fibrinogen concentration and platelet adhesiveness. One trial shows improvement in initial and absolute claudication distances.[23] A review by Hood et al. shows no significant difference however, although there is a trend towards a positive effect on walking capacity using pentoxifylline.[24]

**Cilostazol**

Cilostazol has several mechanisms of action that may be beneficial for patients with peripheral arterial disease, including inhibition of platelet aggregation, arterial vasodilatation, decrease in triglycerides, LDL, and total cholesterol and increase in HDL as well as vascular antiproliferative responses.[25] Several double-blind, placebo-controlled trials have established a marked increase in initial and absolute claudication distances as compared to both placebo and pentoxifylline.[25-28] Due to its antiproliferative properties it might become an important novel drug in the prevention of intimal hyperplasia as well.[29-31] It is a promising new agent in the treatment of intermittent claudication.

**Ginkgo biloba**



Ginkgo biloba extract has vasoregulatory effects and prevents damage to cells caused by free radicals. A meta-analysis included 8 trials comparing ginkgo biloba to placebo and found improvement in pain free and maximum walking distance,[32] the effect was marginal however, making clinical relevance uncertain.

**Policosanol**

Policosanol has both antiplatelet activity and cholesterol-lowering effects. It has been shown to increase initial and absolute claudication distances.[33] Patient numbers are small however, ruling out wide application.

**Naftidrofuryl**

Naftidrofuryl acts through vasodilation and improved aerobic metabolism by inhibiting serotonin type 2 receptors (5-HT2Rs). Jacoby et al. described various trials, including a meta-analysis, comparing naftidrofuryl to placebo and found positive results not only on pain-free and maximum walking distance but also improved daily living, pain and social live.[34]

**Propionyl-L-carnitine**

Claudicants with maximal walking distance of 250 m benefit from the use of propionyl-L-carnitine describes a study by Brevetti et al., with improvement in walking

distance and quality of life. However, patients with mild functional impairment showed no response.[35-37]

**L-carnitine**

A study by Brevetti *et al*. demonstrated that chronic treatment with L-carnitine improves walking performance in patients with intermittent claudication. Carnitine supplementation may be critical for removal of acetyl-CoA excess and improvement of oxidative metabolism in patients with peripheral arterial disease.[38,39]

**L-arginine**

L-arginine has effects on nitric oxide formation, which restores endothelium-induced vasodilatation. One study showed an increased pain-free walking distance and normalization of endogenous nitric oxide formation.[40]

**Prostaglandin E1**

Different studies reveal benefits for prostaglandin E1. When treating patients for 2 months with intravenous prostaglandin E1, walking distance increased with 101% compared to 60% in the placebo group.[41] A meta-analysis of 8 trials revealed the same positive effect on pain free walking distance.[42] This intravenously applied therapy is, however, time-consuming and therefore a severe strain for patients, reason to develop oral forms, which are currently being studied.



**Vasodilator therapy**

Vasodilator therapy does not seem to be very beneficial although some clinical trials suggest an increase in maximal walking distance using verapamil or glyceryl trinitrate.[43,44]

**Angiogenic growth factors**

Impressive results have been described using different growth factors in the treatment of peripheral vascular disease. First in animal models fibroblast growth factor, basic fibroblast growth factor and vascular endothelial growth factor were tested, showing marked augmentation of collateral vessel formation.[45-47] When applied to human subjects the same results were shown as well as an interesting clinical improvement: healing ulcers, limb salvage and resolution of rest pain have all been described.[48-51] The development of angiogenesis induced by progenitor cell transplantation is still in the experimental phase, but shows promising results.

**Smoking cessation**

Cigarette smoking is a significant independent risk factor for development of peripheral arterial occlusive disease and is associated with progression of established disease.[52-55] A dose-response relationship exists.[55] In addition, studies report poorer patency of lower extremity vascular reconstructions among smokers.[56-58] One trial assessed the results of smoking cessation on intermittent claudication and found a significant improvement in maximum walking distance in patients with intermittent claudication who stopped smoking.[59] There is however no associated rapid risk reduction of developing peripheral arterial disease after cessation of smoking and, moreover, patients with peripheral arterial disease tend to be less successful in smoking cessation then are patients after myocardial infarction.[55]

**Treatment of hypertension**

A cohort study with more than 5000 patients and a follow-up of 38 years revealed that hypertension conferred a more then two-fold increased risk of developing intermittent claudication,[60] thereby confirming the need to treat this condition thoroughly.



**Treatment of Diabetes mellitus**

Several studies have demonstrated an association between the development of peripheral arterial disease and diabetes mellitus.[60-62] In an article based on the Framingham Heart Study by Murabito et al. diabetes mellitus presented a more then two-fold increased risk of developing intermittent claudication.[60] A narrow glucose regulation is of importance in this patient group.

**Treatment of hypercholesterolemia**

Hyperlipidemia has a high prevalence among patients with peripheral arterial disease. Percentages of 50% have been described in this specific population.[63] There is sufficient proof that lowering lipid levels decreases the incidence of cardiovascular events. This benefit is seen in all patient subgroups.[64,65] Lipid lowering should be considered in all patients with SFA occlusive disease, while statins significantly reduce cardiovascular events and mortality even in patient with normal cholesterol levels.[65] Moreover, no adverse effects have been described.[66] Some trials show a beneficial effect on walking distance and leg functioning, both in patients with and without hypercholesterolemia.[67,68] Whether statins are an adjunct in the prevention of restenosis after treatment of SFA occlusive disease remains uncertain at this point. The latest developments concern drugs that increase the level and activity of HDL in

combination with statins. This might be a powerful adversary in the stabilization or even reversal of the process of atherogenesis.

## Endovascular interventional therapy

### Percutaneous transluminal angioplasty

Percutaneous transluminal angioplasty (PTA) is applicable for stenoses or occlusions of 5-20 cm. This technique shows low morbidity and mortality due to its less invasive character and is, therefore, especially suitable in the elderly population with severe co-morbidity, and a high operation risk.[69] The procedure does not prohibit surgical procedures at a later stage.[70]

The initial technical success rate of percutaneous transluminal angioplasty is approximately 80% for the treatment of SFA occlusions.[71] Longer lesions are technically more difficult and more stents will have to be used. Accordingly, length of occlusion as well as length of stented segment are independent risk factors of failure and re-stenosis.[70-73] Although short-term benefit is evident, a Cochrane review concerning 2 randomized trials showed no significant difference in walking ability or quality of life at long-term follow-up between PTA and control groups, but the PTA group was more likely to have a patent artery.[74]



#### Stents

Stents were introduced to resolve sub-optimal procedures and early success of PTA will be improved using stents. Long-term effects on patency rates still need proof.[73,75-85] The first stents used in 1980's were balloon-expandable. These stents showed poor results with a primary patency rate of 52% at 4 years.[86] This was mainly due to significant intimal hyperplasia.[86] No difference in patency was found between stenting and PTA alone using these bare stents.[78,87,88] The first generation self-expanding stents (e.g. Wallstent) have low primary patency rates (22-55%) compared to the new generation nitinol self-expanding stents.[76,82,89-92] New generation nitinol stents have a thermal memory and are highly flexible, therefore kink and crush resistant. They also have less surface metal area, minimizing blood-metal contact. Recent studies using these stents show promising results: primary and secondary patency of 93% and 85% at 1 year respectively have been described.[93-97] However, these concern relatively short lesions. To prevent re-stenosis new stents are under development, focusing on minimizing intimal hyperplasia. Stent fractures are another possible problem considering stents. Rates between 10.7-53.3% have been reported, allowing further investigations in the mechanical performance of nitinol stents (Figure 3).[98]

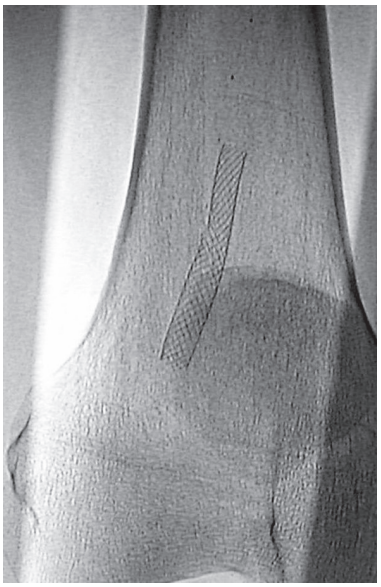

**Figure. 3** Stent fracture of a Wallstent in the distal SFA seven months after placement.

### Covered stents



A polymer cover over a nitinol skeleton supposedly reduces tissue ingrowth hence preventing re-stenosis. Different studies show varying results, with one year patency rates around 70%.[99-106] Best results have been reported with ePTFE covered stents with primary patency rates ranging from 58-79% at one year.[85,103-105]

### Drug eluting stents

One of the most recent developments is drug-eluting stents, which showed promising initial results. Unfortunately after 2 years no difference in re-stenosis was found when comparing bare versus drug eluting stents.[96,107] There was however an inhibition of in-stent proliferation in these drug eluting stents.

### Absorbable stents

Absorbable stents are currently under investigation. The theoretical benefit is to leave no permanent prosthetic material in situ. However, clinical proof will need to be assessed before widespread use is acceptable. Nano-spinning is another new technology based on the principle of absorbable drug eluting material lining the arterial wall to apply temporary therapy in order to create a long lasting solution.

## Percutaneous intentional extraluminal recanalization

Percutaneous intentional extraluminal recanalization (PIER) or subintimal angioplasty

was first described by Bolia *et al.* and four years later by Reekers et al.[108,109] A false lumen is created between the media and intima with re-entry into the true lumen beyond the occlusion. This new lumen is supposedly disease free and therefore less likely to occlude. Patency rates between 49-59%[109-112] after 1 year have been reported on an intention-to-treat basis. When only technically successful procedures are taken into account, patency increases to 71-77%.[111,113] Primary success is observed to be between 74-90% in specialized centres.[109-111] Even if patency rates are mediocre, limb salvage rates are acceptable in patients with critical ischemia (89.5% at 1 year), probably due to a decreased oxygen demand after tissue healing.[114-116]

### Brachytherapy

Brachytherapy could be helpful in preventing re-stenosis after revascularization. Radiation prevents neo-intimal proliferation.[117] Several randomized controlled trials have suggested beneficial effects of brachytherapy. However, routine use is not current, since there are associated risks and practical logistic problems.[118-120]

### Excimer laser

When used prior to PTA laser therapy contributes to the use of fewer stents and a lower rate of distal embolization. Technical success rates of 85.5-90.5% have been described.[121,122] The primary patency rate was only 22.3%, with a primary assisted patency of 40.9% and secondary patency of 43.2% at 2 years.[121,122] Although initial recanalization may be better with the use of the excimer laser, long-term patency rates do not seem to differ.[123] Randomized data are lacking however, so no conclusions can be drawn before further research data are available.



## Surgical interventional therapy

### Femoro-popliteal bypass

The femoro-popliteal bypass is probably the most thoroughly attempted treatment for femoro-popliteal occlusions. The 5 year secondary patency is approximately 70-80% for vein and 50-55% for prosthetic bypasses.[3,86,124,125] Although many authors have suggested that the saphenous vein should be saved for coronary or below-knee bypass grafting a study by Klinkert *et al.* revealed that only once this vein was used for a coronary bypass graft in a series of over 150 patients with a follow-up of 5 years.[3] They suggest the saphenous vein should be used unless there is no alternative, despite the longer operation time needed.

### In situ vein graft versus reversed vein graft

The in situ vein graft is converging versus the diverging reversed vein graft. This leads to improved hemodynamic flow characteristics because of a better diameter match between the vein and arteries both at the proximal and distal anastomosis. This leads to decreased turbulent flow and possibly to a reduced incidence of intimal hyperplasia and, therefore, graft occlusion. This however, is probably only a disadvantage in the below-the-knee bypass graft because the vein is of comparable diameter at the knee and in the groin.[126]

In the reversed vein graft there is no need to lyse valves, which could lead to damage of endothelium and smooth muscle cells which in turn, may lead to graft occlusion.[127] Accordingly, reversed vein grafts are technically easier to prepare. Also there will be no missed tributaries, which may necessitate repeat intervention although, with angioscopically directed techniques this will be minimized.[128]

Randomized trials failed to demonstrate a difference in patency rates for both techniques.[129-131] A recently published trial by Davidovic *et al*. showed better patency rates at 2 and 10 follow-up years for the in situ technique. Additionally this technique proved to be better in patients with one patent crural artery.[132]



### Vein diameter and quality

Calcified or varicose veins could adversely affect patency, even in normal looking veins approximately 20% demonstrate intimal and medial thickening predisposing to graft failure.[133] The optimum diameter for a bypass graft remains unclear, with an overall agreement that smaller grafts are at greater risk of failure. Most authors agree on a minimum diameter of 2-2.5 mm.[134,135]

### Prosthetic graft

In the absence of a suitable vein (small caliber, used for a different procedure like coronary artery bypass grafting) prosthetic grafts can be used. Alternatives to autologous vein are Dacron, PTFE, human umbilical vein, and polyurethane grafts. A Cochrane review could not reveal evidence to favor one graft type over the other, despite encouraging results for human umbilical vein.[136]

## Semi-closed endarterectomy

Van der Heyden et al. described 231 semi-closed endarterectomies retrospectively and found a 5 year overall cumulative patency of 71%, with an acceptable complication and mortality rate (10% and 0.8%).[137] However, the popularity of this technique is declining since the introduction of the remote endarterectomy, which has all the

advantages of the semi-closed endarterectomy needing only a single groin incision.

## Remote endarterectomy with additional stent placement

Remote endarterectomy is the ultimate combination of minimally invasive surgery and an endovascular procedure. It was first described by Moll et al. with a 2 year cumulative assisted primary and secondary patency rate of 86%.[138] Since then the technique has been standard procedure in certain clinics in the Netherlands with reproducible

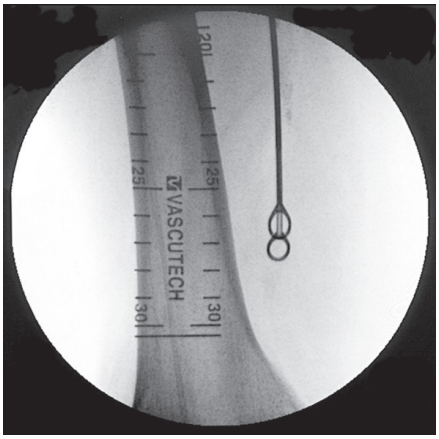


**Figure. 4** Cutting the intimacore at the distal SFA during remote endarterectomy using the Mollringcutter.



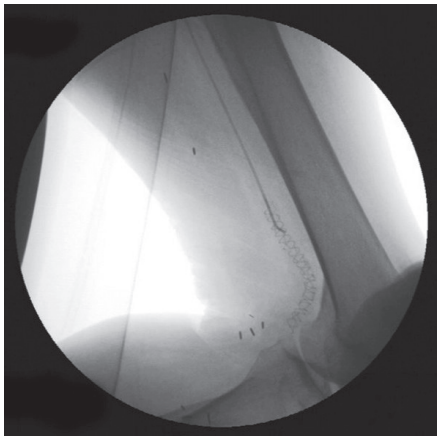

Figure 5a

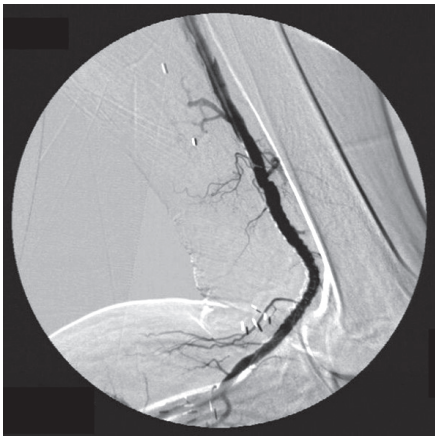

Figure 5b

**Figure. 5** aSpire stent at distal transection zone after remote endarterectomy of the SFA with the knee joint in flexion, showing a preserved collateral. Without (a) and with (b) contrast.

patency rates.[139,140] Furthermore, this operation does not prohibit future surgical bypass or additional endovascular interventions. After dissection, distal transection and removal of the intima core using the Vollmar Ring and Mollring Cutter (Figure 4), a stent is placed at the distal transection zone to prevent further dissection. The recently developed aSpire stent is suitable for use at the knee joint. This is a spiral open architecture stent-graft composed of a double helix nitinol skeleton covered by a thin sleeve of ePTFE. The spiral design is chosen for better hemodynamic compatibility with the native vessel and the concept of partial coverage is intended to inhibit intimal hyperplasia. The ePTFE prevents blood-metal contact. Furthermore the double helix configuration makes the stent flexible and therefore, kink and crush resistant with preserving side branch access and maintaining collaterals (Figure 5). An aggressive approach to re-intervention using PTA in the first year after operation is needed to obtain better primary assisted patency rates.[141-143]

**Endolining**

Endolining is the combination of remote superficial artery endarterectomy with endoluminal grafting. Some reports show some promise.[140,144,145] Its goal is to exclude the exposed thrombogenic endarterectomized surface, possibly thereby lessening the effect of intimal hyperplasia. In a review by Dorucci, reported weighted mean primary and secondary patencies of the Gore Hemobahn Endoprosthesis at 3 years were 64% and 80% respectively.[86]

# Discussion

Femoro-popliteal occlusion is a multifactorial disease that encompasses a large part of the workload in our daily practice. The treatment of femoro-popliteal occlusions remains a dynamic challenge in vascular surgery today. The scope of therapeutical modalities is increasing and changing continuously. In this consideration a general overview of the current strategies of treatment and the future perspectives is given. Their different strengths and durability have for a large part still to be proven. It is however clear that there is not one definite golden treatment, nor will there be in the future.

In the past decades, a shift has occurred in the three main treatment modalities: non-interventional preventive and supportive therapy, endovascular interventional therapy, and bypass surgery.

Initially treatment of the specific lesion with bypass surgery alone was considered the optimal treatment, leaving the rest of the diseased vascular system without proper attention. As knowledge of the pathophysiological mechanisms of atherosclerotic occlusive disease increased, pharmacological therapy gained terrain. At first, this was mainly geared towards anti-thrombotic therapy. Causative treatment of atherosclerosis and plaque stabilization has only evolved in the last decade. With the upsurge of interventional radiology and the rapid development of increasing technical possibilities in this field, a dramatic shift has occurred in the selection of treatment modalities in treating femoro-popliteal occlusions. The shift in present treatment strategies compared to the recommendations given in the TASC 2000 document is only illustrative of this.[146] So what does the future hold?



When analyzing the changes of opinion in the past decade on how femoro-popliteal occlusions should primarily be treated, a clear trend can be recognized. Classical bypass surgery has for a large part been replaced by percutaneous interventions (PTA, PIER, with or without stents) or minimal invasive procedures (remote and semi-closed endarterectomy). The common denominator in these treatment modalities is restoring the patency of the artery using the vessel wall itself as a conduit. 'Restorative interventions' is a term that would cover the full scope of these treatment modalities, concurrently giving a more descriptive term, which clarifies the philosophy behind these treatment modalities.

The main advantage of restorative interventions is that in most cases they do not preclude a surgical bypass at the same site at a later stage. The risk profile of restor-

ative interventions with respect to anesthesia, infection, and hospital stay are of a much lesser degree when compared to bypass surgery. The patency rates reported up to now, do not yet match those of surgery. However with the rapid progress made in recent years it is only a question of time that patency rates will equal or even surpass those of bypass surgery.

The additional value of drug therapy geared towards suppression of intimal hyperplasia and re-stenosis, by systemic or local effects, is an essential aid in reaching this goal. Already clinical trials in phase three have been started in which the efficacy of a statin alone is compared with a statin in combination with a drug to increase the level of HDL to reduce intima hyperplasia and even atheromatous plaque formation.
Better understandings of flow hemodynamics in the SFA and studies on the early onset of atherosclerosis have both supported the optimal design of stent frames, such as the Coiltrac and aSpire stents. These stents respect the spiral flow characteristics within the SFA and keep the shear forces within the stent as low as possible.
In addition, the search for the ideal stent material is under full investigation and making fast progress. Whether this material should be a self-expandable memory metal alloy, such as nitinol, attempting to match the extreme three-dimensional forces to which the distal SFA and the popliteal artery are exposed or that the stent material should be biodegradable is in debate. Even stent constructions with ultra-thin degradable fibers, using nanotechnology, loaded with drugs are currently being tested in animal studies.



The developments given in this article lead to the following conclusion with respect to the proposed treatment strategy for femoro-popliteal occlusions in the future.
The first line of interventional therapy in femoro-popliteal occlusions should be a restorative intervention, specifically tailored to the patient and the length and localization of the lesion. With adequate adjuvant medical therapy and sufficient monitoring, this will be the definite treatment for the majority of patients, requiring no further interventional treatment. Bypass surgery should be regarded as the second line of interventional therapy and should be reserved for those patients in whom restorative interventions fail.

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# 3

SS Gisbertz, M Ramzan, RP Tutein Nolthenius, L van der Laan, TThC Overtoom, FL Moll, JPPM de Vries

# Short-term results of a randomized trial comparing remote endarterectomy and supragenicular bypass surgery for long occlusions of the superficial femoral artery [the REVAS trial]

Eur J Vasc Endovasc Surg. 2009;37:68-76

# Abstract

## Objective

Techniques for surgical repair of Trans-Atlantic Inter-Society Consensus (TASC) C and D lesions of the superficial femoral artery (SFA) are supragenicular bypass grafting or the less invasive remote endarterectomy (RSFAE). This trial compares the patency rates of both techniques.

## Design

Randomized, multicenter trial.

## Materials and methods

116 patients were randomized to RSFAE (n = 61) and supragenicular bypass surgery (n = 55). Indications for surgery were claudication (n = 77), rest pain (n = 21), or tissue loss (n = 18).

## Results

Median hospital stay was 4 days in the RSFAE group compared with 6 days in the bypass group (p = 0.004). Primary patency after 1-year follow-up was 61% for RSFAE and 73% for bypass (p = 0.094). Secondary patency was 79% for both groups. Subdividing between venous (n = 25) and prosthetic grafts (n = 30) shows a primary patency of 89% and 63% respectively at 1-year follow-up (p = 0.086).

## Conclusion

RSFAE is a minimally invasive adjunct in the treatment of TASC C and D lesions of the SFA, with shorter admittance and a comparable secondary patency rate to bypass. The venous bypass is superior to both RSFAE and PTFE bypass surgery, but only 45% of patients had a sufficient saphenous vein available.

This study is registered with ClinicalTrials.gov, number NCT00566436.

# Introduction

Different treatment modalities exist for Trans-Atlantic Inter-Society Consensus[1] (TASC) C and D lesions of the superficial femoral artery (SFA). Every possible procedure still has a significant reobstruction rate, which might result in major lower limb amputation. Patency rates for percutaneous transluminal angioplasty (PTA) are discouraging.[2] The use of additional stents has not improved these results.[3] Subintimal angioplasty is only performed with acceptable patency rates in specialized centres.[4] The most implemented and established procedure for treatment of TASC C and D SFA obstructions is prosthetic or venous bypass grafting, with patency rates of 39-57% for prosthetic and 70-77% for venous bypass grafts.[5-10] An alternative surgical technique has been developed since 1994, the remote SFA endarterectomy (RSFAE).[11,12] Patency rates of retrospective studies so far are promising, with reported patency rates of 61-69% at 18-33 months.[13] Furthermore, this procedure might offer several advantages over bypass surgery, including shorter hospital stay and fewer wound-related problems. To compare patency rates of both surgical techniques, the randomized Remote Endarterectomy Versus Above-knee bypass Surgery (REVAS) trial was performed and short-term results are reported in this article.



# Materials and methods

## Study design

Study inclusion was between October 2004 and March 2007 in 1 university medical centre and 3 major teaching hospitals. The randomization of the study is closed. Included were consecutive patients presenting with severe claudication, critical ischemia, or tissue loss (Rutherford category 3-5)[14] with a TASC C or D lesion of the SFA and a patent popliteal P1 segment with at least 1 crural runoff vessel. Only patients with chronic (> 6 months) complaints originating from atherosclerotic disease were included. Exclusion criteria were previous surgery or PTA with additional stent placement of the target SFA and a SFA diameter < 4 mm.[15] Heavily calcified vessels were not excluded. The treating vascular surgeon established the feasibility of patients by checking the inclusion criteria. All indications for revascularization were discussed

in a multidisciplinary team. Randomization was done at a central telephone number, using sealed envelopes, in a permuted-block sequence and balanced by participating centre. The vascular surgeons were completely blinded on the sequence of the randomization list. Patients were randomly assigned to RSFAE or bypass with the ipsilateral saphenous vein. When the saphenous vein was not available or, when the vein was of inadequate diameter, patients received a polytetrafluoroethylene graft (PTFE bypass®, W.L. Gore and Associates, Inc., Flagstaff, AZ, USA). The primary endpoint was the primary patency at 5 years. This article is an interim report, presenting short-term results. Secondary endpoints were assisted primary patency, secondary patency, limb-salvage, operation time, postoperative complications, and hospital stay. Moreover, possible prognostic factors concerning the primary patency for both study arms will be analysed. Patency is defined in conformity with the guidelines by Rutherford *et al.*[14] Primary patency is defined as uninterrupted patency without any procedures performed on the treated segment. Assisted primary patency is the situation in which patency was never lost but maintained by prophylactic intervention. Secondary patency is restored patency after occlusion, excluding redo or secondary reconstruction operations that do not preserve most of the original graft and at least 1 anastomosis. Patency was determined by duplex ultrasound imaging. A stenosis was considered

significant if the peak systolic velocity ratio exceeded 2.5 or the end-diastolic velocity was higher than 60 cm/s.[14] The medical ethics board of all participating hospitals approved the study protocol. Informed consent was obtained from all patients. This study is registered with ClinicalTrials.gov, number NCT00566436.

## Procedure

The preoperative evaluation consisted of medical history, including risk factors; physical examination, including peripheral pulses; ankle-brachial indices (ABIs), and a treadmill test; color flow duplex ultrasound scanning; and a magnetic resonance angiography (MRA), including crural outflow and mapping of the ipsilateral greater saphenous vein. The decision whether the greater saphenous vein was applicable for grafting (diameter >3.0 mm)[16] was made during preoperative venous mapping using a tourniquet and also assessed during surgery.

### General

Vascular surgeons who had executed RSFAE previously in at least 10 patients, and venous and prosthetic bypasses in 30 patients, performed all the surgical procedures. Ceftriaxone (2 g) was administered intravenously, general or regional anesthesia was used, and the patient underwent systemic heparinization (5000 IE) before the femoral artery was excluded from circulation.

**RSFAE**

Exposure of the common femoral, superficial femoral, and profunda femoris arteries through a single groin incision. Arteriotomy in the proximal SFA followed by dissection of the intima core beyond the occluded SFA segment using the Vollmar ring stripper (Vollmar Dissector, Aesculap®, South San Francisco, CA, USA) under fluoroscopic guidance. The ring stripper is exchanged for a Mollring Cutter (Mollring Cutter®, LeMaitre Vascular, Inc., Burlington, MA, USA), with which transection of the intima core is done remote from the site of entry (Fig. 1). After removal of the intima core, the transection zone is passed by a 0.035-inch. Terumo guidewire (Terumo®, Terumo Corporation, Tokyo, Japan) and secured with an aSpire stent (aSpire stent®, LeMaitre Vascular, Inc., Burlington, MA, USA). This stent has a PTFEcovered nitinol framework with a DNA helical structure, offering the possibility of preserving collaterals. It is flex-

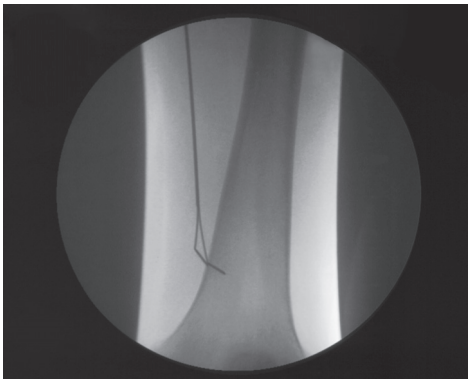


**Figure 1** The Mollring cutter is shown transecting the intima core under fluoroscopic guidance



ible and has high radial strength that makes it eligible for use in proximity of the knee joint with its torsion and flexion forces. By means of a completion arteriography, eventual distal thromboemboli can be verified and embolectomy performed if necessary. A common femoral and profunda femoris endarterectomy can be performed, and the arteriotomy may be closed with or without patch.

**Bypass surgery**

Vertical groin and supragenicular incisions, implantation of a deep-tunnelled reversed saphenous vein or PTFE graft with end-to-side anastomoses. In case of multilevel disease a simultaneous procedure could be performed, such as PTA or endarterectomy of iliac, common femoral or popliteal arteries.

All patients were given antiplatelet therapy before the procedure consisting of acetylsalicylic acid (100 mg daily) or coumarin derivatives on indication. This regimen was continued after the operation.

## Follow-up

Follow-up was scheduled at 3, 6, 12, 18, and 24 months and annually thereafter. Routine surveillance consisted of history, physical examination, ABIs, and duplex ultrasound scanning, with additional angiography or MRA as indicated. In the first year after the procedure, even asymptomatic restenoses were treated because previous studies have shown that revision of early restenoses will improve long-term patency rates.[15]

## Statistical analysis

Based on a primary patency rate of 70% at 2 years and accepting a difference of 25%, it was calculated that the study needed to include 116 patients to obtain sufficient statistical power ($\alpha = 0.05$, two-sided; power = 0.8). The study was planned as a non-inferiority trial. Data were calculated based on intention to treat. Patency rates were calculated with Kaplan-Meier life-table estimates. Multivariate analysis was performed in both study arms separately, to identify prognostic factors influencing primary patency depending on operative strategy. Multivariate analysis was performed using the Cox hazard regression method. The univariate analysis, including all baseline parameters (Table 1), served as the basis for the multivariate Cox hazard regression model. Variables showing association ($p < 0.10$) with the primary patency in univariate analysis were included in the multivariate analysis. Age, sex, indication for operation and outflow were included in all multivariate analyses. Results are presented as hazard ratio with exact 95% confidence interval (95% CI). A log-rank test, Mann-Whitney U test, or $\chi 2$ test was used as indicated to compare both groups. A value of $p < 0.05$ was considered statistically significant. Statistical analysis was performed with SPSS 15.0 software (SPSS, Inc., Chicago, IL, USA).

| Variable | RSFAE (n = 61) | Bypass (n = 55) | P-value¥ |
|---|---|---|---|
| **Age, mean (range) y** | 68 (50-84) | 68 (44-86) | 0.801 |
| **Sex** | | | |
| Male | 47 (77) | 40 (73) | 0.591£ |
| Female | 14 (23) | 15 (27) | |
| **Indication for operation** | | | |
| Rutherford category 3 | 47 (77) | 30 (55) | 0.025£ |
| Rutherford category 4 | 7 (12) | 14 (25) | |
| Rutherford category 5 | 7 (11) | 11 (20.0) | |
| **Initial claudication distance, mean (range) m** | 82 (5-300) | 81 (0-500) | 0.407 |
| **ABI, mean (SD)** | 0,62 (0.14) | 0,58 (0.15) | 0.185 |
| **Treadmill test, mean (SD)** | 0,32 (0.21) | 0,34 (0.22) | 0.759 |
| **Previous ipsilateral procedures** | | | |
| Central | 8 (13) | 7 (13) | 0.950£ |
| Iliacal | 8 (13) | 8 (15) | 0.823£ |
| Femoral† | 11 (18) | 18 (33) | 0.068£ |
| **Risk factors** | | | |
| Coronary artery disease | 29 (48) | 23 (42) | 0.536£ |
| Diabetes | 15 (25) | 9 (17) | 0.297£ |
| Stroke or TIA | 13 (21) | 21 (38) | 0.046£ |
| Smoking, current or recent | 52 (91) | 35 (75) | 0.021£ |
| Hypertension | 45 (74) | 36 (66) | 0.330£ |
| Hypercholesterolemia | 49 (82) | 34 (64) | 0.035£ |
| **Serum creatinine, mean (SD) µmol/L** | 105 (49) | 109 (125) | 0.210 |
| **BMI, mean (SD) kg/m2** | 27 (3.3) | 26 (3.8) | 0.644 |
| **Contralateral amputation** | 1 (2) | 1 (2) | 0.941£ |
| **Preoperative occlusion of SFA** | 56 (91) | 52 (95) | 0.561£ |
| **Length of SFA occlusion, mean (range) cm** | 24 (19-30) | 24 (20-28) | 0.901 |
| **Runoff arteries** | | | |
| 1 | 3 (5) | 9 (16) | 0.018£ |
| 2 | 15 (25) | 18 (33) | |
| 3 | 43 (70) | 28 (51) | |
| **Preoperative medication** | | | |
| Statin | 47 (78) | 29 (55) | 0.008£ |
| Acetylsalicylic acid | 45 (74) | 40 (73) | 0.899£ |
| Coumarin | 16 (26) | 10 (18) | 0.299£ |
| Clopidogrel | 3 (5) | 2 (4) | 0.734£ |
| Dipyridamole | 3 (5) | 6 (11) | 0.228£ |
| No anticoagulant | 2 (3) | 4 (7) | 0.332£ |

**Table 1.** Baseline Characteristics of Study Population§

§Data are presented as No.(%), unless otherwise indicated

¥Mann-Whitney *U* test, unless otherwise indicated

£$\chi^2$ test

†PTA of the SFA without stent placement

# Results

357 consecutive patients with a TASC C or D lesion of the SFA were assessed for eligibility. 118 patients were included and randomly assigned to RSFAE or bypass. Two patients were excluded from the bypass group; therefore 116 patients were included in the final analysis (Fig. 2). All patients were operated within 6 weeks of randomization. The randomization was conducted in a 2.5-year period. The first 6 months only the St. Antonius Hospital had been authorized to randomize patients and included 13 patients. The first year thereafter the St. Antonius Hospital included 19 patients, the University Medical Centre 22 patients, the Albert Schweitzer Hospital 15 patients, and the Amphia Hospital 2 patients. The last year of the study the inclusion was 17, 18, 7 and 3 patients respectively.

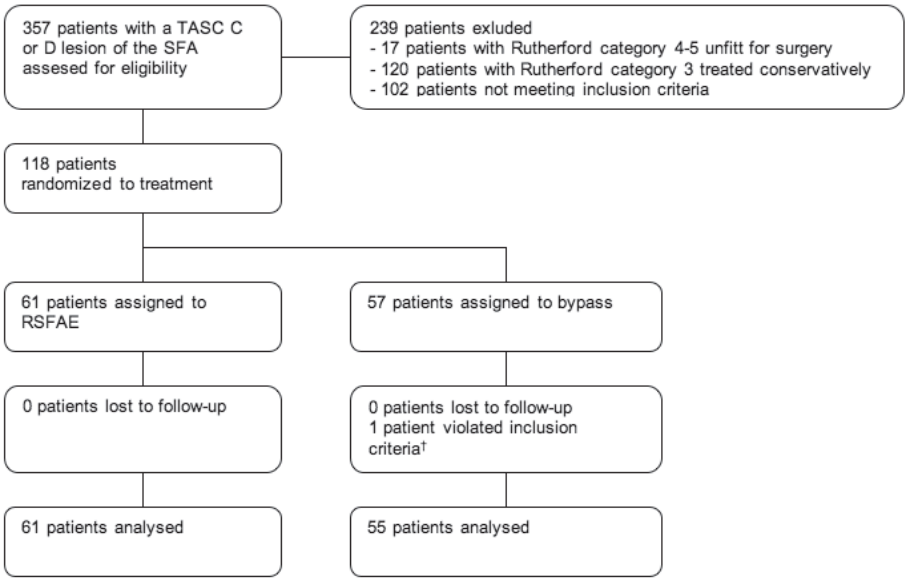



**Figure 2.** Trial profile

†The occlusion of the SFA in this patient extended below the level of the knee in spite of earlier review of the MRA as 'patent popliteal artery'

§This patient suffered from a myocardial infarction and was considered unfit for surgery

Baseline characteristics of the study population are summarized in Table 1. Despite randomization, significantly more patients scheduled for bypass surgery had a single vessel runoff and consequently more severe symptoms than patients scheduled for RSFAE. The bypass group had more patients with a history of TIA or stroke, and the RSFAE group had more smokers and more patients with hypercholesterolemia.

## Intraoperative results

Intraoperative results are reported in Table 2. Operation time and blood loss were not statistically different between groups. The mean length of the endarterectomized intima core was 30 cm (range, 20-44 cm). Only 25 patients (45%) in the bypass

| Variable | RSFAE (n=61) | Bypass (n=55) | P-value¥ |
|---|---|---|---|
| **Operation time, mean (SD) min** | 134 (32.6) | 125 (32.6) | 0.159 |
| **Blood loss, mean (SD) mL** | 270 (186.7) | 208 (150.5) | 0.092 |
| **Intima core, mean (range) cm** | 30 (20-44) | | |
| **aSpire stent** | | | |
| Length, median (range) cm, | 5 (5-15) | | |
| Diameter, median (range) mm | 7 (5-8) | | |
| **Graft** | | | |
| Venous | | 25 (45) | |
| Prosthetic | | 30 (55) | |
| **Additional procedure** | | | |
| None | 6 (10) | 6 (14) | 0.755£ |
| Common femoral and/or profundaplasty | 49 (80) | 46 (80) | |
| Iliacal PTA or remote endarterectomy | 5 (8) | 2 (4) | |
| Popliteal PTA or remote endarterectomy | 1 (2) | 1 (2) | |
| **Patch closure** | 50 (89) | | |

**Table 2.** Intraoperative Results§

§Data are presented as No.(%), unless otherwise indicated

¥Mann-Whitney *U* test, unless otherwise indicated

£$\chi^2$ test

group had a sufficient saphenous vein suitable for bypass grafting. The other 30 patients received a PTFE graft. Initial technical success was 92% in the endarterectomy group versus 100% in the bypass group. Reasons for conversion in the RSFAE group were perforation of the SFA during endarterectomy (n = 3), dissection distally from the transaction zone (n = 1), or heavy calcification (n = 1). These patients received either an above-knee PTFE bypass (3 patients, all with perforation) or a below-knee PTFE bypass (2 patients). During the operation, distal thromboemboli were found

in 4 RSFAE patients, and all were successfully treated with embolectomy during the procedure.

## Postoperative data

Postoperative data are reported in Table 3. Postoperative haemorrhage occurred in 5 RSFAE patients (1 requiring reoperation) and in 4 bypass patients (3 reoperations). Superficial wound infection was observed in 9 RSFAE patients and 4 bypass patients, all treated with oral or intravenous antibiotics. Three RSFAE patients versus 4 bypass patients sustained a deep wound infection requiring surgical debridement. No association could be determined between postoperative infection rate and Rutherford classification. Explantation of an infected PTFE bypass was necessary in 1 patient.

| Variable | RSFAE (n = 61) | Bypass (n = 55) | P-value[¥] |
|---|---|---|---|
| **Postoperative haemorrhage** | 5 (8) | 4 (7) | 0.257 |
| **Superficial wound infection** | 9 (15) | 4 (7) | 0.202 |
| **Deep wound infection** | 3 (5) | 4 (7) | 0.595 |
| **Pneumonia** | 1 (2) | 1 (2) | 0.941 |
| **Urinary tract infection** | 2 (3) | 2 (4) | 0.916 |
| **Postoperative renal failure[†]** | 0 (0) | 0 (0) | |
| **Oedema** | 9 (15) | 13 (24) | 0.223 |
| **Seroma** | 6 (10) | 5 (9) | 0.891 |
| **ABI, mean (SD)** | 0.90 (0.18) | 0.92 (0.23) | 0.945[£] |
| **Hospital stay, median (range) days** | 4 (1-21) | 6 (3-28) | 0.004[£] |
| **Re-admittance** | 6 (10) | 7 (13) | 0.622 |
| **Early reocclusion (<30 days)** | 3 (5) | 2 (4) | 0.734 |

**Table 3.** Postoperative Data[§]

[§]Data are presented as No.(%), unless otherwise indicated

[¥]$\chi^2$ test, unless otherwise indicated

[£]Mann-Whitney *U* test

[†]Defined as a >20% decrease in serum creatinine clearance compared to baseline, the presence of new-onset dialysis, or both

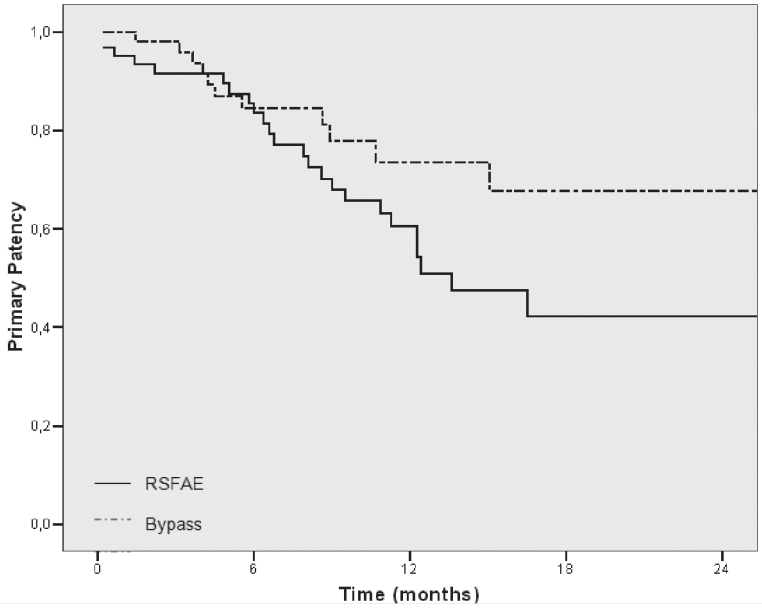
Median hospital stay was significantly shorter for RSFAE: 4 days (range 1-21 days) versus 6 days (range 3-28 days; p = 0.004), whereas re-admittance differed not statistically significant between the two groups. (Re)occlusion within 30 days occurred in 3 RSFAE patients and 2 bypass patients. Of the 3 RSFAE patients, 1 patient had only mild claudication symptoms (Rutherford category 2) and no reintervention was necessary, 1 patient received an infragenicular bypass, and 1 early reocclusion oc-

curred in a RSFAE patient with a primary conversion (due to heavy calcification) to an infragenicular bypass. No vascular reconstruction could be performed, and below-knee amputation was necessary. The initial indication for this operation was gangrene (Rutherford category 5). The two patients in the bypass group with early occlusion were both successfully treated with thrombectomy. One patient in the bypass group was readmitted with persistent ischemia and underwent PTA of the popliteal artery and partial foot amputation. None of the patients died in the hospital or within 30 days after operation.

## Patency and survival

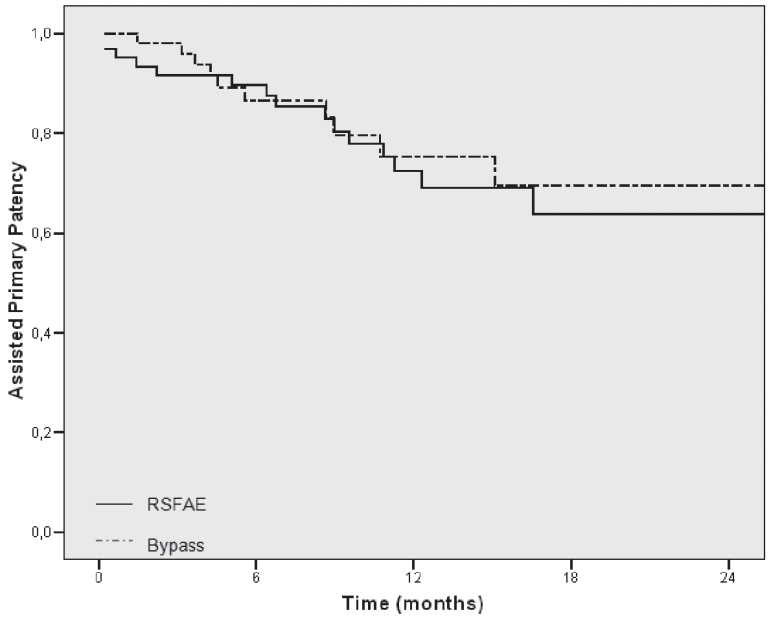
Mean follow-up was 12 months in both groups. Primary patency rate after 1 year of follow-up was 61% for RSFAE and 73% for femoropopliteal bypass (p = 0.094). Assisted primary patency rates were 73% and 75%, respectively (p = 0.698). Secondary patency was 79% for both groups (p = 0.953; Figs. 3-5). Limb salvage was 98%,






| Numbers still at risk | | | | | |
|---|---|---|---|---|---|
| **RSFAE** | 61 | 53 | 42 | 37 | 37 |
| **Bypass** | 55 | 48 | 45 | 44 | 44 |

**Figure 3.** Kaplan-Meier survival estimate comparing primary patency of remote superficial femoral artery endarterectomy (RSFAE) with supragenicular femoropopliteal bypass (Log-Rank test: p = 0.094)

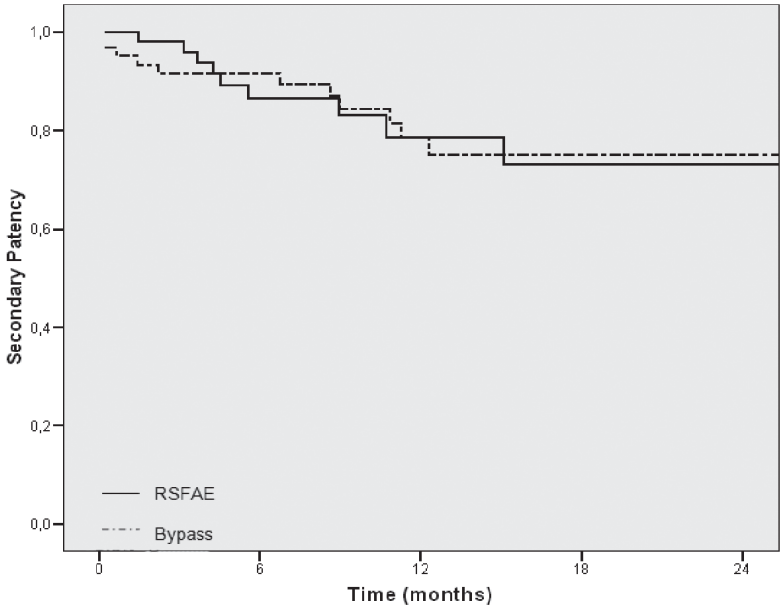



| Numbers still at risk | | | | | |
|---|---|---|---|---|---|
| **RSFAE** | 61 | 55 | 48 | 46 | 46 |
| **Bypass** | 55 | 49 | 46 | 45 | 45 |



**Figure 4.** Kaplan-Meier survival estimate comparing assisted primary patency of remote superficial femoral artery endarterectomy (RSFAE) with suprageniculate femoropopliteal bypass (Log-Rank test: p = 0.698)

with 1 major below-knee amputation performed in both groups. Subdividing between venous and prosthetic grafts shows primary patency rates of 89% and 63%, respectively, compared with 61% for RSFAE (p = 0.086), assisted primary patency rates of 94% and 63% compared with 73% (p = 0.104), and secondary patency rates of 94% and 63% compared with 79% (p = 0.137) at 1 year of follow-up. Treatment of the 15 reoccluded SFA's in the RSFAE group and the 8 occluded bypasses in the bypass group is shown in Fig. 6. Of the 9 restenoses in the RSFAE group, 8 were treated with PTA, and 1 was treated with endarterectomy of the femoral bifurcation. Restenosis was equally distributed within the SFA and was not restricted to the stent. Of the 2 stenoses in the bypass group, 1 was treated with PTA and the other had multiple stenoses and was reoperated on with a proximal patch plasty and a distal bypass jump graft to maintain patency. Stenosis in the graft was not limited to the anastomoses. At 1-year follow-up, 5 patients had died: 4 (7%) in the RSFAE group and 1 (2%) in the bypass group. One death in the RSFAE group was related to the operation. This




| Numbers still at risk | | | | | |
|---|---|---|---|---|---|
| **RSFAE** | 61 | 56 | 51 | 50 | 50 |
| **Bypass** | 55 | 49 | 47 | 46 | 46 |



**Figure 5.** Kaplan Meier survival estimate comparing secondary patency of remote superficial femoral artery endarterectomy (RSFAE) with suprageniculate femoropopliteal bypass (Log-Rank test: p = 0.953)

patient developed a saccular aneurysm of the common femoral artery (not mycotic) and underwent endovascular stent placement. This operation was complicated by recurrent septic bleeding, and the patient eventually died.

## Influence of risk factors

Univariate analysis revealed that primary patency survival in the RSFAE group was not influenced by BMI, serum creatinine level, runoff, previous vascular procedures on target leg, medication, diabetes, hypertension and hypercholesterolemia, coronary artery disease, stroke or TIA, age and smoking. Sex and indication for operation showed an association with the primary patency ($p < 0.10$) and were consequently analysed in a Cox hazard regression model. Multivariate analysis showed only female gender as a significant predictor of reocclusion and restenosis with a hazard ratio of 3.47 (95% CI 1.17-10.35; $p = 0.025$). For the bypass group, no independent risk factors influencing patency could be determined.

# Discussion

This report describes the short-term results of the first randomized trial between RSFAE and supragenicular femoropopliteal bypass for TASC C and D lesions of the SFA. Although not significant, the trial results show a difference in primary patency rates in favour of bypass. The assisted primary and secondary patency rates, however, are comparable in both groups. Subdividing between vein and prosthetic grafts shows superiority for vein, with comparable primary patency rates for RSFAE and prosthetic grafts. In only 45% of patients scheduled for bypass surgery could the ipsilateral greater saphenous vein be used. A study by Johnson et al. found that 11% of patients lacked a sufficient saphenous vein, excluding these used for previous cardiac procedures.[7] The role of preoperative venous mapping as a possible application in the preoperative decision-making, needs to be addressed further. In the postoperative course, there were no statistically significant differences in complications between the 2 groups, although 1 patient required explantation of an infected PTFE bypass. Hospital stay, on the other hand, was significantly shorter for RSFAE: 4 versus 6 days ($p = 0.004$).



Our study has several limitations. Despite randomization, significantly more patients with critical ischemia were allocated to the bypass group. In addition, more patients in the bypass group presented with a single vessel runoff. It is well established that patients presenting with claudication perform better, although this could not be demonstrated in this trial.[5,6,17] There were more differences between the 2 groups in baseline characteristics, with significantly more current or recent smokers and patients with hypercholesterolemia in the RSFAE group but fewer patients with a history of stroke or TIA. When we assessed this imbalance by use of Cox Hazard regression analysis, the adjusted patency rates remained unchanged (data not shown). Initial technical success of the RSFAE group was high, with only 5 conversions to bypass; however, compared with recent literature, our results show a lower primary patency for RSFAE than expected. A recent report by Martin et al. showed a primary patency rate of 70% at 30 months.[18] Knight et al. described an 84% primary patency rate at 18 months compared with 61% at the 1-year follow-up in our trial.[19] Other authors show less favourable results for RSFAE: Ali et al. reached a primary patency of only 42% after RSFAE in combination with covered endografts at 12 months[20]; however, this study population consisted of only 18 patients. Rosenthal et al. performed a retrospective multicenter analysis of 40 patients treated with RSFAE, resulting in a primary patency

rate of 69% at 18 months, and from the same authors, a multinational retrospective analysis among 210 patients revealed a primary patency of 61% at 33 months.[11,13] Our results for bypass surgery are consistent with recent literature, with associated primary patency rates reaching 57-83% at 1 or 2 years of follow-up, depending on the used graft, with superior results for autologous vein.[2,5-10] This is however, an interim report, long-term results will have to prove durability of both procedures. A possible explanation for the lower primary patency in the RSFAE group could be the prospective setting, in an unselected population. Remarkable in the present study is the high percentage of smokers, with current or recent smoking in 91% of patients allocated to RSFAE. The present RSFAE study population shows significant comorbidity, with 48% coronary artery disease, 25% diabetes, 21% history of stroke or TIA, 82% hypercholesterolemia, and 74% hypertension. Although the difference with other study populations is marked, an independent relation affecting patency could not be demonstrated here.[17,18,21] In our series, regression analysis revealed no independent risk factors predicting failure, besides female gender, influencing primary patency in the RSFAE group, with a hazard ratio of 3.47 (95% CI 1.17-10.35; p = 0.025). Female gender as an independent risk factor has not been shown previously. An explanation could be the smaller diameter of the SFA in women, although we have no data to support this. Early restenosis within 1 year after RSFAE caused by presumed aggressive neointimal hyperplasia remains the Achilles heel of the RSFAE procedure, with 83% of restenosis detected within 1 year.[15] After the first year, the restenosis rate declines and is thought to be caused by progression of atherosclerosis rather than neointimal hyperplasia.[15] Therefore, future prevention of neointimal hyperplasia seems to be the key to successful preventing restenosis progressing to reocclusion. Recent research is focussing on this subject, with the development of gene and drug therapy, cryotherapy, drug eluting stents, endothelial cell seeding, and radiation or brachytherapy. A recent randomized trial by Tepe et al. showed promising results with balloon catheters for PTA coated with Paclitaxel. They found significantly less lumen reduction at 6 months and a remarkable lower reintervention rate at 6 and 24 months of 4% and 15%, respectively, for the Paclitaxel group versus 37% and 52% for the control group.[22] Perhaps results will improve after surgically debulking the SFA, which leaves the proliferative cells bare and therefore possibly more sensitive to drug treatment. The role of cryoplasty is not yet defined, with conflicting results and no randomized trials performed so far.[23] Karthik et al. described a 100% restenosis rate within 1 year after PTA with additional cryoplasty for recurrent stenoses, but again, surgically debulking the SFA might improve outcome.[24] Graft material for bypasses is evolving as well. Heparin-bonded Dacron grafts have been introduced to bypass the SFA, with better outcome compared with PTFE. Differences in patency rates were not significant at 5

years of follow-up, but limb salvage was 86% for heparin-coated Dacron versus 74% for PTFE.[5]

RSFAE is a minimal invasive adjunct in the treatment of chronic long occlusions of the SFA, with significantly shorter hospital stay and comparable assisted primary and secondary patency rates to bypass surgery. However, the venous bypass is superior to both RSFAE and prosthetic bypass grafts, but only 45% of patients had a sufficient saphenous vein available. For patients lacking the saphenous vein, RSFAE could be the procedure of choice because prosthetic material can be avoided.

# Acknowledgements

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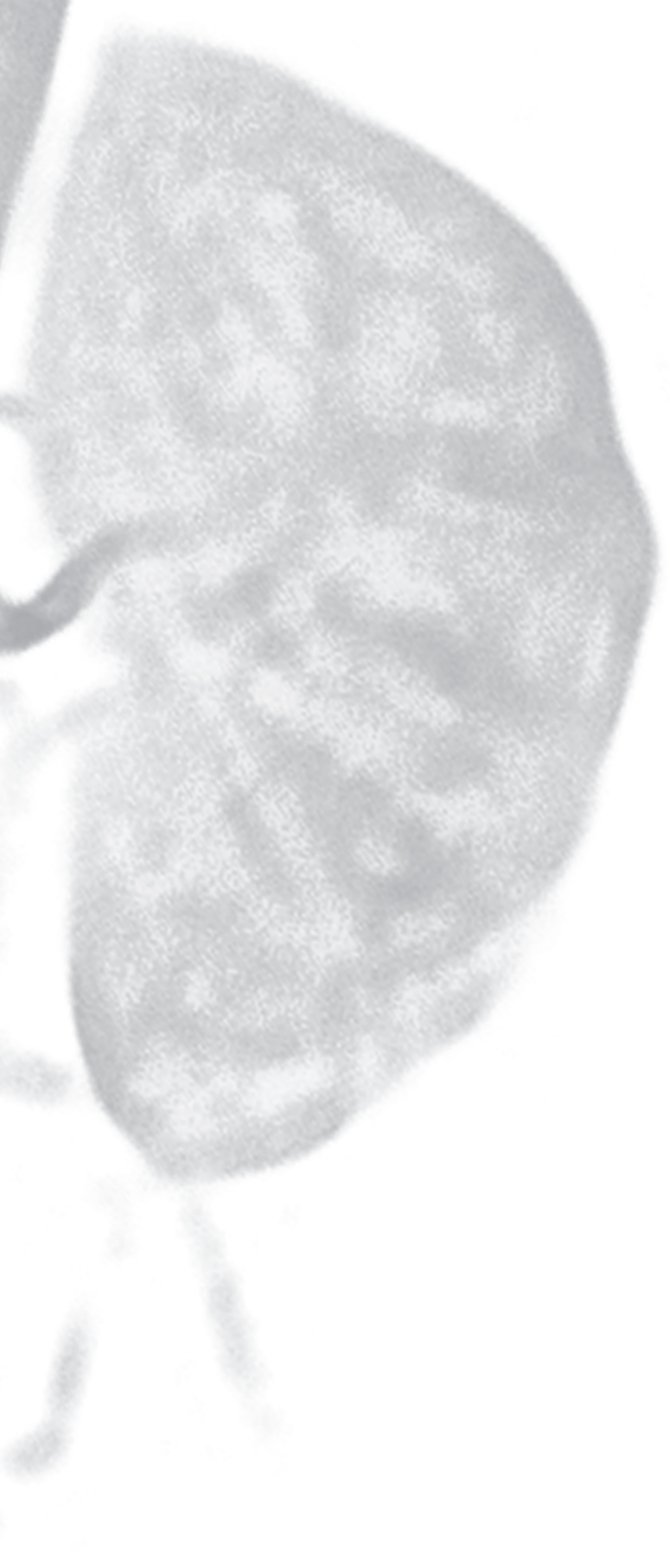


# 4

SS Gisbertz, RP Tutein Nolthenius, GJ de Borst, L van der Laan, TThC Overtoom, FL Moll, JPPM de Vries

# Remote endarterectomy versus supragenicular bypass surgery for long occlusions of the superficial femoral artery: medium-term results of a randomized controlled trial [The REVAS trial]

Submitted

# Abstract


## Objective

To investigate the optimal surgical treatment, remote superficial femoral artery endarterectomy (RSFAE) or supragenicular bypass, for Trans-Atlantic Inter-Society Consensus (TASC) C and D lesions of the superficial femoral artery (SFA). Medium-term results will be presented.

## Design

Randomized, multicenter trial.

## Methods

The study randomized 116 patients: 61 to RSFAE and 55 to supragenicular bypass surgery. Indications for surgery were claudication in 77, rest pain in 21, or tissue loss in 18.

## Results

Primary patency after 3 years of follow-up was 47% for RSFAE and 60% for bypass ($p = 0.107$), assisted primary patency was 63% and 69% ($p = 0.406$), and secondary patency was 69% versus 73% ($p = 0.541$), respectively. For venous ($n = 25$) and prosthetic grafts ($n = 30$) at the 3-year follow-up, primary patency was 65% and 56% versus 47% for RSFAE ($p = 0.143$), assisted primary patency was 84% and 56% versus 63% for RSFAE ($p = 0.052$), and secondary patency was 89% and 59% versus 69% for RSFAE ($p = 0.046$), respectively. Limb salvage was 97% after RSFAE and 95% after bypass surgery ($p = 0.564$).

## Conclusion

RSFAE is a minimally invasive option for surgical repair of TASC C and D SFA obstructions, with assisted primary and secondary patency rates comparable with bypass surgery. Venous bypass grafting is superior to both RSFAE and polytetrafluoroethylene grafting, but only 45% of patients had a sufficient saphenous vein available. If the saphenous vein is not applicable, RSFAE should be considered because it is less invasive and prosthetic graft material can be avoided.

This study is registered with ClinicalTrials.gov, number NCT00566436.

# Introduction

A variety of endovascular and surgical procedures exist to treat occlusions of the superficial femoral artery (SFA). Trans-Atlantic Inter-Society Consensus[1] (TASC) A and B lesions are usually successfully treated by endovascular means; however, results are discouraging for TASC C and D lesions.[2-5]

For long-segment SFA occlusions, bypass grafting is the most established surgical procedure. Patency rates for venous grafts are superior to prosthetic grafts, with 5-year primary patency rates of 69% to 77% for venous grafts and 39% to 57% for prosthetic grafts.[6-14]

Remote SFA endarterectomy (RSFAE) has been shown to be a valuable minimally invasive option in treating TASC C and D SFA obstructions.[15-17] Recently reported primary patency is 35% at 5 years of follow-up, improving to an assisted primary patency of 50% when maintained by endovascular means.[18] Furthermore, RSFAE has been shown to shorten hospitalization significantly.[19] Thus far, however, no randomized trials have compared RSFAE with the most established surgical procedure.

The aim of this study was to compare patency rates of bypass surgery and RSFAE. Therefore, the randomized Remote Endarterectomy Versus Above-knee bypass Surgery (REVAS) trial was initiated, and medium-term results are reported in this article.



# Materials and methods

## Study design

The design and rationale of the REVAS study have been described in detail elsewhere.[19] Inclusion was between October 2004 and March 2007 in a university medical center and 3 major teaching hospitals. REVAS included consecutive patients presenting with severe claudication, critical ischemia, or tissue loss (Rutherford category 3-5)[20] with a TASC C or D lesion of the SFA, a patent popliteal P1 segment, and at least 1 crural runoff vessel. Chronic (>6 months) complaints originating from atherosclerotic disease had to be demonstrated.

Exclusion criteria were previous surgery or percutaneous transluminal angioplasty (PTA) with additional stent placement of the target SFA, and a SFA diameter

< 4 mm.[21,22] The beginning of the SFA occlusion had to start in the first 4 cm of the proximal SFA because otherwise dissection of the proximal intima core could not be performed. Patients were randomized to RSFAE or bypass with the ipsilateral saphenous vein. When the saphenous vein was not available or not suitable (diameter < 3 mm)[23], patients received a polytetrafluoroethylene graft (PTFE bypass®, W. L. Gore and Associates Inc, Flagstaff, AZ, USA).

Randomization was done in a permuted-block sequence, balanced by participating center, at a central telephone number, using sealed envelopes.

The primary end point was the primary patency at 5 years. This article presents medium-term results. Secondary end points were the assisted primary patency, the secondary patency, limb salvage, operation time, postoperative complications, and hospital length of stay. Possible prognostic factors concerning the primary patency for both study arms will also be analyzed.

Patency is defined in conformity with the guidelines by Rutherford *et al*.[20] Primary patency is defined as uninterrupted patency without any procedures performed on the treated segment. Assisted primary patency is the situation in which patency was never lost but was maintained by prophylactic intervention. Secondary patency is restored patency after occlusion, excluding redo or secondary reconstruction operations that do not preserve most of the original graft and at least 1 anastomosis.



Patency was determined by duplex ultrasound imaging. A stenosis was considered significant if the peak systolic velocity ratio exceeded 2.5 or the end-diastolic velocity was higher than 60 cm/s.[20]

The medical ethics board at each participating hospital approved the protocol. All patients gave written informed consent. This study is registered with ClinicalTrials.gov, number NCT00566436.

## Procedure

Patient evaluation and surgical technique have been described before and will be briefly summarized.[19] The preoperative evaluation included color flow duplex ultrasound scanning and a magnetic resonance angiography (MRA).

### General

Ceftriaxone (2 g) was administered intravenously before anesthesia, the procedures were performed with the patient under general or regional anesthesia, and the patient underwent systemic heparinization (5 000 IE) before the femoral artery was excluded from circulation.

### RSFAE

RSFAE is conducted through a single groin incision. After transection and removal of the intima core with the Mollring Cutter (Mollring Cutter®, LeMaitre Vascular Inc, Burlington, MA, USA, Figure 1), the transection zone is secured with an aSpire stent (aSpire stent®, LeMaitre Vascular Inc., Burlington, MA, USA).

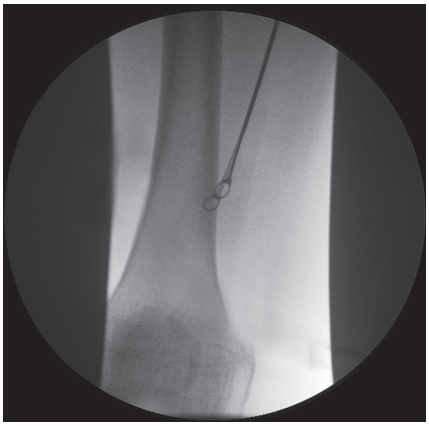


**Figure 1** Transection of the intima core with the Mollring cutter is shown under fluoroscopic guidance.

### Bypass surgery



After vertical groin and supragenicular incisions, a deep-tunnelled reversed saphenous vein or PTFE graft is implanted with end-to-side anastomoses.

All patients were given antiplatelet therapy before the procedure, consisting of acetylsalicylic acid (100 mg daily) or coumarin derivatives when indicated. This regimen was continued after the operation.

## Follow-up

Follow-up was scheduled at 3, 6, 12, 18, and 24 months and annually thereafter. Follow-up visits took place at all participating centers and were conducted by the patient's treating vascular surgeon. Follow-up data were obtained prospectively. Routine surveillance consisted of a medical history, physical examination, ankle-brachial index, and duplex ultrasound scanning. Duplex ultrasound scanning that revealed a significant restenosis was verified by additional MRA or angiography. The mean follow-up included patients who lost patency and patients who died.

## Statistical analysis

Statistical analysis was performed with SPSS 15.0 software (SPSS Inc, Chicago, IL, USA). On the basis of a primary patency rate of 70% at 5 years and accepting a difference of 25%, we calculated that the study needed to include 116 patients to obtain

sufficient statistical power ($\alpha = 0.05$, two-sided; power = 0.8).

The RSFAE group was compared with the bypass group for primary and secondary end points. In addition, patients with venous and prosthetic grafts were analyzed separately. Data were analyzed based on intention to treat. Patency rates were calculated with Kaplan-Meier life-table estimates. Multivariate analysis was performed in both study arms separately to identify prognostic factors influencing primary patency, depending on operative strategy. Multivariate analysis was performed using the Cox hazard regression method. The univariate analysis, including all baseline parameters (Table I), served as the basis for the multivariate Cox hazard regression model. Variables showing association ($p < 0.10$) with the primary patency in univariate analysis were included in the multivariate analysis. Age, sex, indication for operation, and outflow were included in all multivariate analyses. Results are presented as hazard ratio (HR) with the 95% confidence interval (CI). A log-rank test, Mann-Whitney U test or $\chi 2$ test was used as indicated to compare both groups. A value of $p < 0.05$ was considered statistically significant.

# Results



Of 357 consecutive patients with a TASC C or D lesion of the SFA who were assessed for eligibility, 118 met the inclusion criteria and were randomized to RSFAE or bypass. Two patients were excluded from the bypass group; therefore, 116 patients were included in the final analysis (Figure 2). Baseline characteristics of the study population are summarized in Table I.

Despite randomization, there were differences in baseline characteristics: The bypass group had significantly more patients with single-vessel runoff and, consequently, more severe symptoms, and more patients had a history of transient ischemic attack or stroke. The RSFAE group had more smokers and more patients with hypercholesterolemia.

## Perioperative results

The perioperative results have been described before.[19] Length of operation and blood loss were comparable between groups. Only 25 patients (45%) in the bypass group had a sufficient saphenous vein suitable for bypass grafting. The other 30 patients received a PTFE graft. Technical success was 92% in the RSFAE group versus 100% in the bypass group. Postoperative complications did not differ significantly between

| Variable | RSFAE (n = 61) | Bypass (n = 55) | P-value[†] |
|---|---|---|---|
| **Age, mean (range) y** | 68 (50-84) | 68 (44-86) | 0.801 |
| **Sex** | | | |
| Male | 47 (77) | 40 (73) | 0.591[‡] |
| Female | 14 (23) | 15 (27) | |
| **Indication for operation** | | | |
| Rutherford category 3 | 47 (77) | 30 (55) | 0.025[‡] |
| Rutherford category 4 | 7 (12) | 14 (25) | |
| Rutherford category 5 | 7 (11) | 11 (20) | |
| **Initial claudication distance, mean (range) m** | 82 (5-300) | 81 (0-500) | 0.407 |
| **ABI, mean (SD)** | 0.62 (0.14) | 0.58 (0.15) | 0.185 |
| **Treadmill test, mean (SD)** | 0.32 (0.21) | 0.34 (0.22) | 0.759 |
| **Previous ipsilateral procedures** | | | |
| Central | 8 (13) | 7 (13) | 0.950[‡] |
| Iliac | 8 (13) | 8 (15) | 0.823[‡] |
| Femoral[§] | 11 (18) | 18 (33) | 0.068[‡] |
| **Risk factors** | | | |
| Coronary artery disease | 29 (48) | 23 (42) | 0.536[‡] |
| Diabetes | 15 (25) | 9 (17) | 0.297[‡] |
| Stroke or TIA | 13 (21) | 21 (38) | 0.046[‡] |
| Smoking, current or recent | 52 (91) | 35 (75) | 0.021[‡] |
| Hypertension | 45 (74) | 36 (66) | 0.330[‡] |
| Hypercholesterolemia | 49 (82) | 34 (64) | 0.035[‡] |
| **Serum creatinine, mean (SD) µmol/L** | 105 (49) | 109 (125) | 0.210 |
| **BMI, mean (SD) kg/m2** | 27 (3.3) | 26 (3.8) | 0.644 |
| **Contralateral amputation** | 1 (2) | 1 (2) | 0.941[‡] |
| **Preoperative occlusion of SFA** | 56 (91) | 52 (95) | 0.561[‡] |
| **Length of SFA occlusion, mean (range) cm** | 24 (19-30) | 24 (20-28) | 0.901 |
| **Runoff arteries** | | | |
| 1 | 3 (5) | 9 (16) | 0.018[‡] |
| 2 | 15 (25) | 18 (33) | |
| 3 | 43 (70) | 28 (51) | |
| **Preoperative medication** | | | |
| Statin | 47 (78) | 29 (55) | 0.008[‡] |
| Acetylsalicylic acid | 45 (74) | 40 (73) | 0.899[‡] |
| Coumarin | 16 (26) | 10 (18) | 0.299[‡] |
| Clopidogrel | 3 (5) | 2 (4) | 0.734[‡] |
| Dipyridamole | 3 (5) | 6 (11) | 0.228[‡] |
| No anticoagulant | 2 (3) | 4 (7) | 0.332[‡] |

**Table I.** Baseline Characteristics of Study Population[*]

ABI, Ankle-brachial index; BMI, body mass index; SFA, superficial femoral artery; TIA, transient ischemic attack

[*]Data are presented as No. (%), unless otherwise indicated

[†]Mann-Whitney *U* test, unless otherwise indicated

[‡] $^2$ test

[§]PTA of the SFA without stent placement

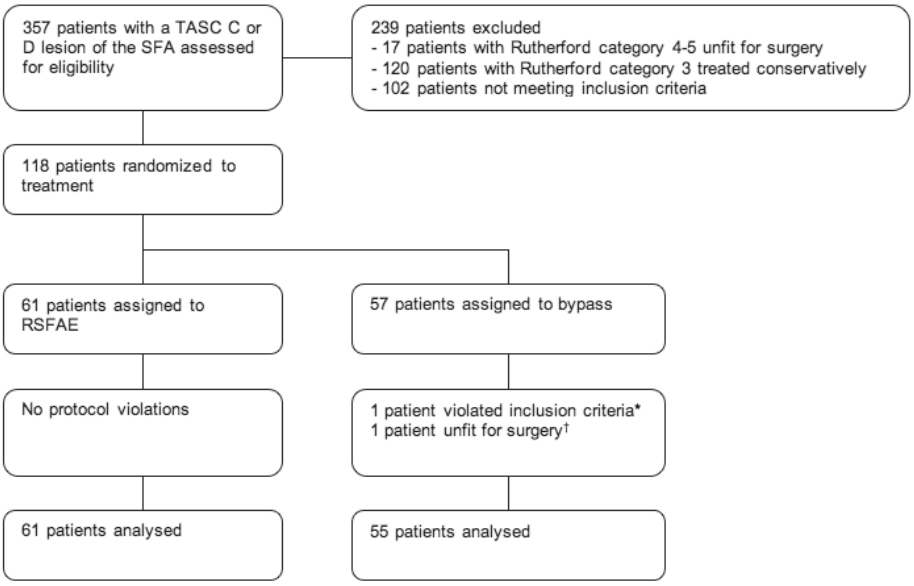



**Figure 2.** Profile of the remote superficial femoral artery endarterectomy (RSFAE) trial.



*The occlusion of the SFA in this patient extended below the level of the knee despite an earlier review of the magnetic resonance angiography as "patent popliteal artery."

†This patient had sustained a myocardial infarction and was considered unfit for surgery.

groups. Three RSFAE patients versus 4 bypass patients sustained a deep wound infection requiring surgical débridement (p = 0.595). One patient required explantation of an infected PTFE bypass.

Median hospital length of stay was significantly shorter for RSFAE: 4 days (range, 1-21 days) versus 6 days (range, 3-28 days; p = 0.004).

## Survival and patency

Median follow-up was 37 months (range, 3-66 months) in both groups. Three patients (4.2%) were lost to follow-up. Nineteen deaths occurred during follow-up, 8 in the RSFAE group (13.1%) after a median follow-up of 10 months (range, 3-40 months) and 11 in the bypass group (20%; p = 0.317) after a median follow-up of 20 months (range, 2-40 months). Causes of death were related to the operation in 1 patient in the RSFAE group and in 2 patients in the bypass group (p = 0.829). In the RSFAE group, 1 patient died of recurrent septic bleeding after a reintervention for a saccular aneurysm in the common femoral artery. In the bypass group, 1 patient died because

of progressive ischemia of the leg after occlusion of a PTFE bypass and 1 patient died with persistent sepsis after an above-knee amputation performed for an occluded venous bypass. Other causes of death included cardiac disease in 7, pulmonary disease in 1, other vascular causes in 2, and oncologic disease in 3. The exact cause of death in 3 patients could not be determined. The causes of death did not differ between groups.

The Kaplan-Meier estimate of the primary patency rate after 3 years of follow-up was 47% for RSFAE and 60% for femoropopliteal bypass (p = 0.107). The assisted primary patency rate was 63% for RSFAE and 69% for femoropopliteal bypass (p = 0.406). Secondary patency was 69% and 73%, respectively (p = 0.541; Figures 3a-3c). When the imbalance in baseline characteristics was assessed by Cox hazard regression analysis, the adjusted patency rates remained unchanged (data not shown). Restenosis after RSFAE was equally distributed within the SFA and not restricted to the region of the stent. Stenosis in bypass grafts after femoropopliteal bypass was not limited to the anastomosis (data not shown).

Limb salvage after 3 years of follow-up was 97% after RSFAE and 95% after bypass surgery, with 1 below-knee amputation performed in both groups, 1 above-knee amputation after RSFAE, and 2 above-knee amputations after femoropopliteal bypass (p = 0.564).



Subdividing between venous and prosthetic grafts at 3 years of follow-up shows primary patency rates of 65% and 56%, respectively, compared with 47% for RSFAE (p = 0.143), assisted primary patency rates of 84% and 56% compared with 63% (p = 0.052), and secondary patency rates of 89% and 59% compared with 69% (p = 0.046; Figures 4a-4c). The standard error in this analysis does not exceed 0.1.

In the RSFAE group, 17 SFAs reoccluded and 11 restenosed. Of the 17 reoccluded SFAs, 2 were treated with PTA (1 reoccluded again, no reintervention). Four patients with reocclusion received a supragenicular bypass, in 3 cases followed by more revisions leading to permanent occlusion in 2 cases. Five reocclusions were followed by infragenicular bypass grafting, 3 of which occluded (2 no reintervention, 1 infragenicular bypass). Three reocclusions were treated with thrombolysis, all followed by other interventions, consisting of 1 infragenicular bypass followed by PTA, 1 infection resulting in sartorius plasty and vein patch plasty, and multiple interventions in 1 patient that eventually resulted in above-knee amputation. One reocclusion was treated with thrombectomy, a below-knee amputation was performed in 1 patient, and no reintervention was necessary in 1 patient because only mild mild claudication symptoms were demonstrated.

Of the 11 restenosed SFAs, 10 were treated with PTA, 3 followed by another intervention (2 PTAs, 1 supragenicular bypass, followed by PTA). One restenosis was

redressed surgically. Of the 5 conversions during the initial operation, 4 reoccluded and 1 restenosed (all described above).

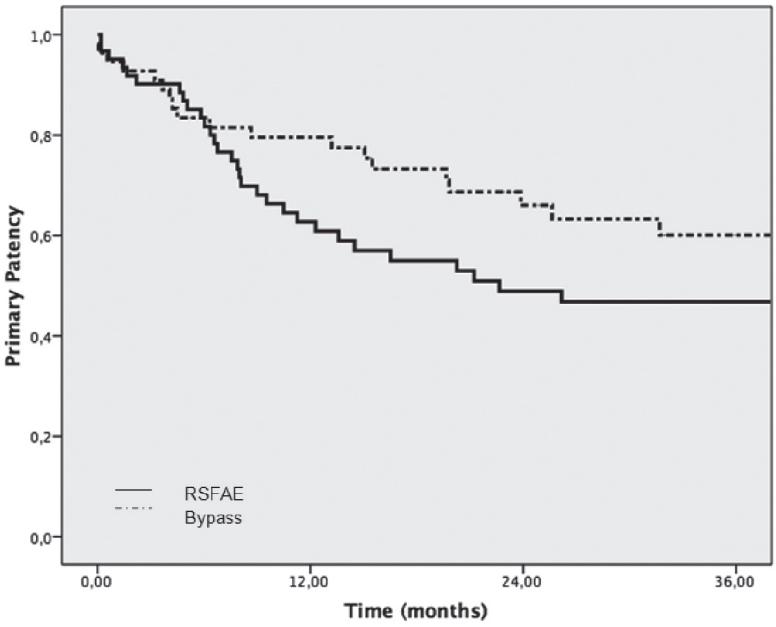
In the bypass group, 15 bypasses occluded and 6 stenosed. Of the 15 occluded bypasses, 8 were treated with thrombolysis, all but 2 (1 patent and 1 occluded) underwent several other reinterventions, including 1 femorocrural bypass, 1 profunda plasty, 1 PTA (followed by a revision operation and multiple thrombolyses), 1 revision operation leading to permanent occlusion, and 1 infected bypass explantation after multiple revisions. One patient died awaiting an above-knee amputation. Two occlusions were treated with thrombectomy, and both procedures were followed by multiple vascular reinterventions such as renewed bypasses, ultimately leading to an above-knee amputation in 1 patient. One occlusion concerned an infected bypass, which was explanted. One occlusion underwent endovascular treatment, followed by a below-knee amputation because of persistent ischemia. In 3 occlusions, no reintervention was performed; these patients had mild symptoms of intermitted claudication only.

Of the 6 stenosed bypasses, 4 were treated with 1 or 2 PTAs, and 1 eventually required an above-knee amputation. One stenosed bypass was revised, and 1 patient with a stenosed bypass had mild claudication symptoms only and no intervention was performed.



## Influence of risk factors

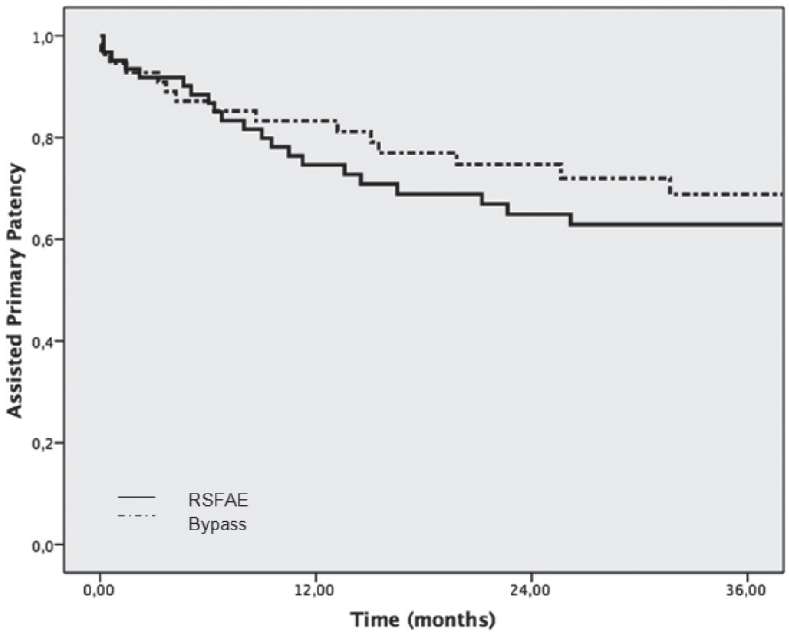
Univariate analysis revealed that primary patency survival in the RSFAE and the bypass groups was not influenced by any of the baseline characteristics (see Table I). Multivariate analysis, including age, sex, indication for operation, and runoff showed no independent risk factors influencing patency in either group.




| Numbers still at risk | | | | |
|---|---|---|---|---|
| **RSFAE** | 61 | 34 | 24 | 15 |
| **Bypass** | 55 | 38 | 25 | 13 |



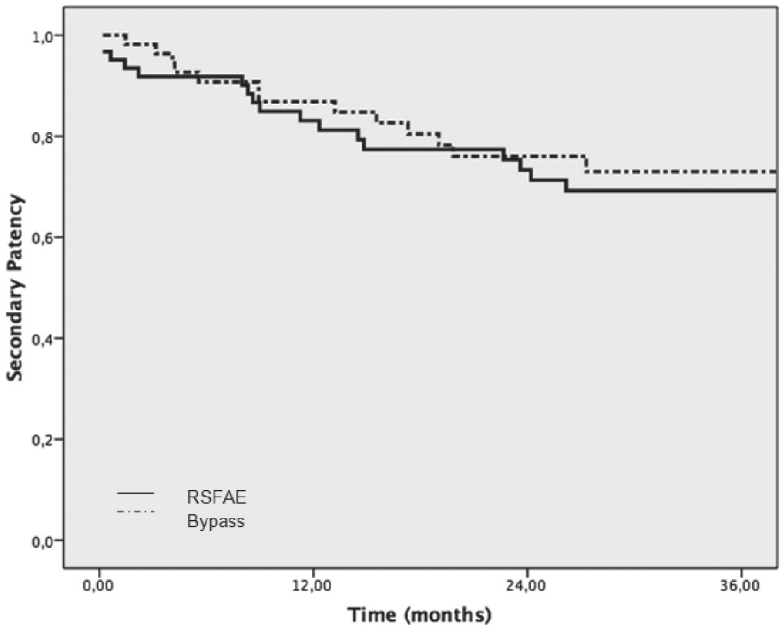
**Figure 3a.** Kaplan-Meier survival estimate comparing the primary patency of remote superficial femoral artery endarterectomy (RSFAE) with supragenicular femoropopliteal bypass (log-rank test: p = 0.107).






| Numbers still at risk | | | | |
|---|---|---|---|---|
| **RSFAE** | 61 | 41 | 33 | 22 |
| **Bypass** | 55 | 40 | 28 | 15 |

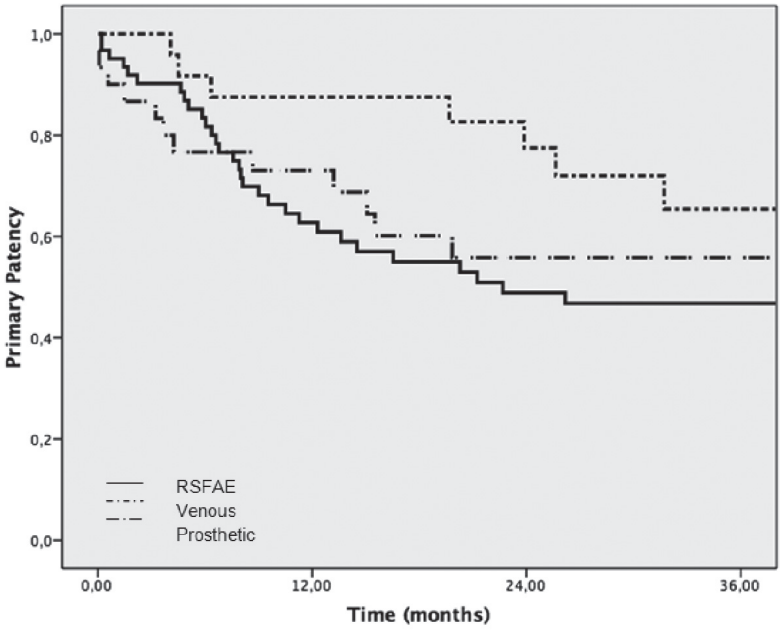
**Figure 3b.** Kaplan-Meier survival estimate comparing assisted primary patency of remote superficial femoral artery endarterectomy (RSFAE) with supragenicular femoropopliteal bypass (log-rank test: p = 0.406).




| Numbers still at risk | | | | |
|---|---|---|---|---|
| **RSFAE** | 61 | 45 | 36 | 24 |
| **Bypass** | 55 | 42 | 29 | 16 |



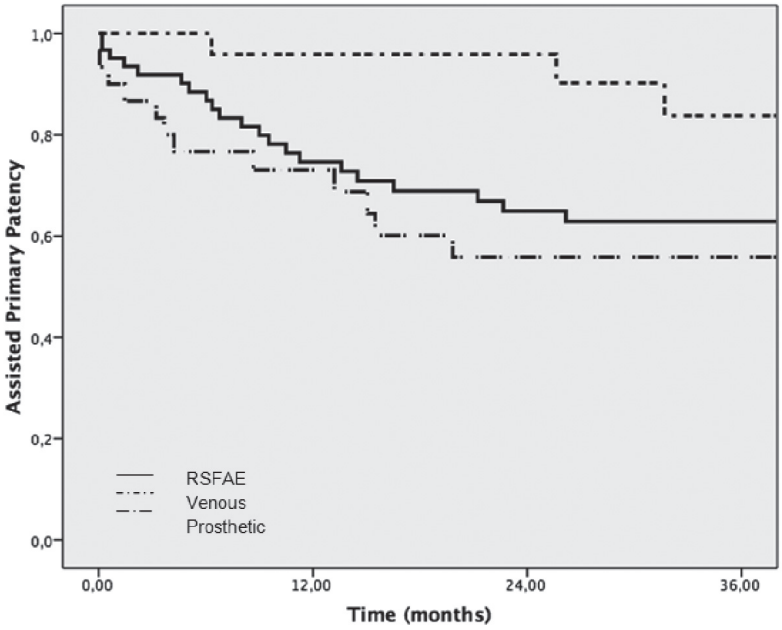
**Figure 3c.** Kaplan-Meier survival estimate comparing secondary patency of remote superficial femoral artery endarterectomy (RSFAE) with supragenicular femoropopliteal bypass (log-rank test: p = 0.541).






| Numbers still at risk | | | | |
|---|---|---|---|---|
| **RSFAE** | 61 | 34 | 24 | 15 |
| **Bypass** | 25 | 21 | 15 | 8 |
| **Prosthetic** | 30 | 17 | 10 | 5 |

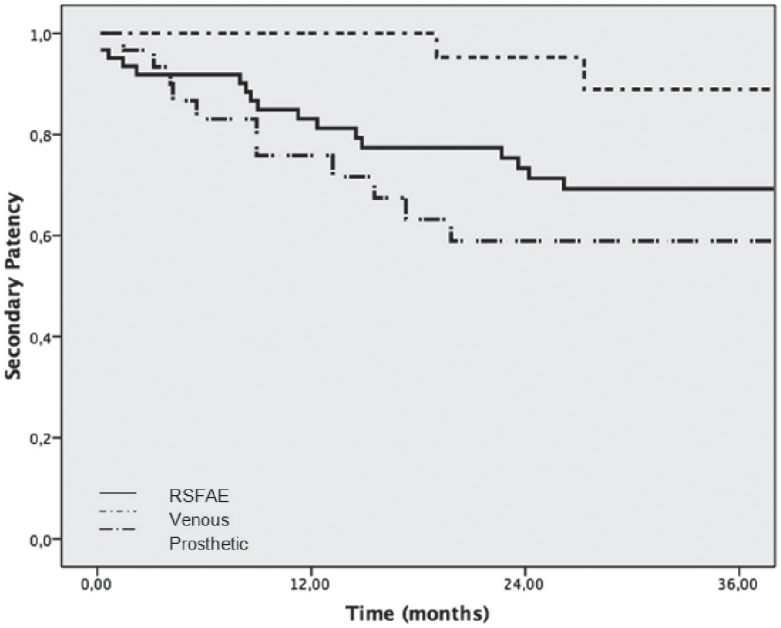
**Figure 4a.** Kaplan-Meier survival estimate comparing primary patency of remote superficial femoral artery endarterectomy (RSFAE) with supragenicular venous femoropopliteal bypass and supragenicular prosthetic femoropopliteal bypass (log-rank test: p = 0.143).




| Numbers still at risk | | | | |
|---|---|---|---|---|
| **RSFAE** | 61 | 41 | 33 | 22 |
| **Bypass** | 25 | 23 | 18 | 10 |
| **Prosthetic** | 30 | 17 | 10 | 5 |



**Figure 4b.** Kaplan-Meier survival estimate comparing assisted primary patency of remote superficial femoral artery endarterectomy (RSFAE) with supragenicular venous femoropopliteal bypass and supragenicular prosthetic femoropopliteal bypass (log-rank test: $p = 0.052$).






| Numbers still at risk | | | | |
|---|---|---|---|---|
| **RSFAE** | 61 | 45 | 36 | 24 |
| **Bypass** | 25 | 25 | 18 | 10 |
| **Prosthetic** | 30 | 18 | 11 | 6 |

**Figure 4c.** Kaplan-Meier survival estimate comparing secondary patency of remote superficial femoral artery endarterectomy (RSFAE) with supragenicular venous femoropopliteal bypass and supragenicular prosthetic femoropopliteal bypass (log-rank test: $p = 0.046$).

# Discussion

This study describes the medium-term results of a multicenter, randomized trial between RSFAE and supragenicular femoropopliteal bypass for TASC C and D SFA occlusions. The trial results show a nonsignificant difference in the primary patency rate in favor of bypass. This difference declines when the assisted primary and secondary patency rates are considered.

When venous and prosthetic grafts are analyzed separately, venous grafts are superior to both prosthetic grafts and RSFAE. However, statistical significance could only be reached for the secondary patency rate, with borderline statistical significance for the assisted primary patency rate, taking into account that our study was not powered for this end point. It is remarkable though, how few patients had an available ipsilateral saphenous vein. In only 45% of patients was this vein applicable for bypass grafting. In the early postoperative period, complications did not differ between groups. Meanwhile, hospital stay was significantly shorter in the RSFAE group.

Our study has several limitations, as has been addressed before.[19] Despite randomization, significantly more patients with critical ischemia, single vessel runoff, and a history of stroke or transient ischemic attack were allocated to the bypass group. On the other hand, more smokers and patients with hypercholesterolemia were randomized to RSFAE. Patency rates remained unchanged when Cox hazard regression analysis was used to assess these differences (data not shown).



Our results for RSFAE are comparable to recent reports, where a 57% rate for the primary patency was demonstrated at 2 years of follow-up and 35% at 5 years of follow-up in a systematic review.[18] Our results for bypass surgery are also in concordance with published reports, showing a 2- to 5-year primary patency rate of 69% to 83% for vein and 39% to 70% for prosthetic bypasses.[6-14, 24-26]

Although a higher reocclusion rate for RSFAE was demonstrated compared with bypass surgery, limb salvage was 97% after RSFAE and 95% after femoropopliteal bypass ($p = 0.564$), supporting the results by Smeets et al., who showed that 80% of patients had improved or unchanged symptoms after SFA reocclusion.[27] Rosenthal et al. revealed similar results, indicating a preserved or improved collateral network after RSFAE.[16]

In this trial, restenoses after RSFAE were treated aggressively by endovascular means because Smeets et al. showed that early recurrent stenoses seem to progress to reocclusion.[28] The decline in restenosis and reocclusion after the first year (pri-

mary patency of 63% at 1 year versus 47% at 3 years) confirms the results by Ho et al., who showed that 83% of all restenosis occurred in the first year postoperatively, although our results are less pronounced.[29] Despite aggressive treatment of recurrent stenoses, the reintervention rate remains considerable, even after the first year. In addition, it is remarkable that 9 of 17 reoccluded SFAs were treated with bypass surgery instead of thrombolysis. Although thrombolysis seems the optimal treatment for newly thrombosed arteries, our experience with reoccluded SFAs after RSFAE seems not significant.

Apparently, other strategies are needed to maintain patency and prevent neointimal hyperplasia from occurring. Perhaps solutions ought to be sought in supportive medical treatment. Dual antiplatelet therapy consisting of clopidogrel and acetylsalicylic acid has been shown to improve outcome in patients after endovascular treatment for femoropopliteal occlusions compared with acetylsalicylic acid alone.[30] However, comparisons were made with a historical cohort and randomized trials on this issue are lacking.[31] Other studies demonstrate beneficial effects of adding clopidogrel to an acetylsalicylic acid regimen, especially in preventing future cardiovascular events.[32] Furthermore, a potential synergistic effect of aspirin and clopidogrel on platelet function has been shown in experimental trials.[33,34] Whether these results can be applied to RSFAE patients remains to be investigated.



Cilostazol may have additional advantages over other platelet inhibitors. It has been demonstrated to inhibit neointimal formation by improving endothelial function and induction of apoptosis in smooth muscle cells.[35,36] Cilostazol has been shown to improve walking distance in individuals with intermittent claudication and reduce restenosis in coronary arteries after endovascular treatment.[37]

Other methods that possibly inhibit neointimal formation have been addressed.[19] Cryoplasty after RSFAE was recently tested in a pilot study of 17 patients. The primary patency at the 1-year follow-up was 74% compared with 63% in this trial (unpublished data). These results are promising, but need confirmation in a randomized trial. In addition, adjuvant treatment of the desobstructed SFA with paclitaxel-coated balloons might improve outcome even more, given the impressive results from a randomized trial of angioplasty, described by Tepe et al.[38] The REVAS group is preparing a randomized trial where patients will be assigned to RSFAE with or without additional paclitaxel treatment.

Cox hazard regression analysis in our series revealed no independent risk factors predicting failure in both study arms. This in contrast to most reports that demonstrate poor runoff as an independent variable predicting failure after bypass surgery.[8-10] Some studies show that younger age, smaller graft diameter, and smoking predict reocclusion after supragenicular bypass grafting,[14,25] whereas Berglund et al. demon-

strate prosthetic graft material and critical ischemia as risk factors for graft failure in a retrospective analysis.[39] Burger et al. also failed to demonstrate any variable predicting failure after bypass surgery.[24]

The study by Lenti et al. of RSFAE demonstrates critical ischemia as the only factor influencing secondary patency.[40] In our previous series, regression analysis revealed female gender as a risk factor for failure that influenced the primary patency in the RSFAE group, with a HR of 3.47 (95% CI, 1.17-10.35; p = 0.025).[19] After prolonged follow-up, female gender as a risk factor for failure could no longer be demonstrated.

# Conclusion

RSFAE is a minimally invasive additive for surgical repair of TASC C and D SFA obstructions, with comparable assisted primary and secondary patency rates compared with bypass surgery at 3 years of follow-up. The venous bypass graft is superior to both RSFAE and PTFE grafts, but only 45% of patients had a sufficient saphenous vein available. If the saphenous vein is not applicable, RSFAE should be considered because it is less invasive and prosthetic graft material can be avoided.



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SS Gisbertz, GJ de Borst, TThC Overtoom, FL Moll, JPPM de Vries

# Initial results of concomitant cryoplasty after remote endarterectomy of the superficial femoral artery; a feasibility study

Vasc Endovasc Surg. 2009 Oct 14

# Abstract


## Objective

Remote endarterectomy is a less invasive technique compared with supragenicular bypass surgery for superficial femoral artery occlusive disease. Early restenosis remains one of the drawbacks of this procedure. To prevent restenosis following remote endarterectomy, concomitant cryoplasty of the desobstructed superficial femoral artery was introduced.

## Methods

A prospective cohort study was initiated of 17 patients treated with cryoplasty of the superficial femoral artery after remote endarterectomy. Indications for surgery were claudication (n = 12), rest pain (n = 3), or tissue loss (n = 2).

## Results

There were no technical failures. The Kaplan-Meier estimate of the primary and assisted primary patency rate after 1 year of follow-up was 74%. Secondary patency was 89%. Limb salvage was 100%. No aneurysmal degeneration and no other adverse events occurred during follow-up.

## Conclusions

This pilot study showed that cryoplasty after remote superficial femoral artery endarterectomy is a safe procedure, with promising patency rates.

# Introduction

Several strategies exist in the treatment of Trans-Atlantic Inter-Society Consensus (TASC)[1] C or D lesions of the superficial femoral artery (SFA). Patency rates for percutaneous transluminal angioplasty (PTA) with or without additional stent placement are discouraging.[2,3] Subintimal angioplasty is only performed with acceptable patency rates in specialized centres.[4] Remote endarterectomy of the superficial femoral artery (RSFAE) is a less invasive technique compared with supragenicular bypass surgery, with comparable short-term assisted primary patency rates.[5] Early restenosis within 1 year after surgery caused by presumed aggressive neointimal hyperplasia remains one of the drawbacks of this procedure, with 83% of restenoses detected within 1 year.[6] Cryoplasty was introduced to try to overcome recurrent intimal hyperplasia and subsequently restenosis. Cryoplasty is thought to provoke apoptosis in arterial smooth muscle cells rather than necrosis, preventing migration and proliferation of smooth muscle cells, and thus reducing myointimal hyperplasia.[7]

Recent literature reports conflicting results when cryoplasty is combined with PTA for SFA occlusive disease. Patency rates vary between 0% and 83% after 9 to 24 months of follow-up.[7-12] No randomized trials have been performed so far comparing PTA with cryoplasty.[13] In addition, cryoplasty after RSFAE has not been described. The combination of these techniques could be of particular additional value, because debulking of the SFA leaves the proliferative cells of the remaining medial layer bare and possibly more sensitive to supercooling. This pilot study shows preliminary results of the first 17 patients treated with RSFAE, followed by cryoplasty of the entire SFA, in two Dutch hospitals.



# Patients and methods

## Study design

Study inclusion was between March 2008 and October 2008 in one university medical center and one major vascular teaching hospital. Included were patients presenting with severe claudication, critical ischemia, or tissue loss (Rutherford category 3 to 5),[14] a TASC C or D lesion of the SFA, and a patent popliteal P1 segment with at least

one crural runoff vessel. Exclusion criteria were previous surgery or PTA with additional stent placement in the target SFA and a SFA diameter <4 mm.

The primary end point was primary patency at 1 year. Secondary end points were assisted primary patency, secondary patency, limb salvage, perioperative adverse events, and postoperative complications. Patency was defined in conformity with the guidelines by Rutherford et al.[14] Patency was determined by duplex ultrasound imaging. A stenosis was considered significant if the peak systolic velocity ratio was >2.5 or the end-diastolic velocity was >60 cm/s.[14]

## Technique

The common femoral, superficial femoral, and profunda femoris artery are exposed through a single groin incision. An arteriotomy in the proximal SFA is followed by dissection of the intima core beyond the occluded segment using the Vollmar ring stripper (Vollmar Dissector, Aesculap, South San Francisco, Calif) under fluoroscopic guidance. The ring stripper is exchanged for a Mollring Cutter (LeMaitre Vascular Inc, Burlington, Mass), with which transection of the intima core is performed remote from the site of entry. After removal of the intima core, the transection zone is passed by a 0.035-inch Terumo guidewire (Terumo Corp, Tokyo, Japan). A 10-cm PolarCath balloon (Boston Scientific, Natick, Mass) with a comparable diameter to the desobstructed SFA is introduced (all under fluoroscopic guidance), after which cryoplasty is performed of the transection zone. If a >30% stenosis persists, the transection zone is secured with an aSpire stent (LeMaitre Vascular Inc., Burlington, Mass).[5]



The entire SFA up to 3 cm from the arteriotomy in the proximal SFA is treated with cryoplasty. Each cryoplasty dilation is performed at 8 atmosphere (atm) of pressure and delivered at –10°C for 20 seconds. A common femoral and profunda femoris endarterectomy can be performed, and the arteriotomy may be closed with or without patch.

All patients were receiving an antiplatelet drug before the procedure or coumarin derivatives on indication. This regimen was maintained after the operation.

## Follow-up

Follow-up was scheduled at 3, 6, and 12 months. Surveillance consisted of clinical examination, including ankle brachial indices, and duplex ultrasound scanning of the target SFA and popliteal artery.

## Statistical analysis

Statistical analysis was performed with SPSS 15.0 software (SPSS Inc, Chicago, Ill). Patency rates were calculated with Kaplan-Meier life-table estimates.

# Results

Seventeen patients with a TASC C or D lesion of the SFA were treated with RSFAE with concomitant cryoplasty. Baseline characteristics of the study population are summarized in Table I. Twelve patients (71%) were operated on for disabling claudication that did not respond to supervised walking exercise for at least 6 months, three (18%) for critical ischemia, and two (12%) for gangrene. Runoff was through three crural arteries in 11 patients (65%), two crural arteries in four patients (24%) and through one crural artery in 2 patients (12%). Patients in this pilot study presented with considerable comorbidities and risk factors, including 12 patients (71%) with coronary artery disease and 14 patients (88%) with current or recent smoking.

Intraoperative results are reported in Table II. RSFAE, followed by cryoplasty of the SFA, was technically successful in all patients. There were no intraoperative adverse events. In all cases, the arteriotomy in the proximal SFA was closed with a bovine or prosthetic patch, and in 11 patients (64%), an additional common femoral and/or profunda femoris plasty was performed. The mean length of the SFA desobstruction was 30 cm (range, 26-34 cm).



Postoperative data are reported in Table III. Superficial wound infection was observed in three patients, and all were treated with oral or intravenous antibiotics. One patient sustained a deep wound infection and was treated with surgical debridement, musculus sartorius plasty, and additional replacement of the bovine patch for a venous patch. Median hospital stay was 3 days (range, 2-14 days).

Four patients had to be readmitted. Two patients had superficial wound infection and one had a deep wound infection (as described). One patient was readmitted with a late leakage of the proximal anastomosis of a simultaneously created iliacofemoral bypass. This patient was treated in an endovascular manner with a covered stent. There were no reocclusions of the desobstructed SFA within 30 days after surgery. None of the patients died in-hospital, within 30 days after operation, or during follow-up.

The Kaplan-Meier estimate of the primary and assisted primary patency rate after 1 year of follow-up was 74%. Secondary patency was 89%. After a mean follow-up of 12 months, two of the desobstructed SFAs had reoccluded. One patient with a reocclusion 7 months after surgery had only mild symptoms, and no reintervention

| Variable | Patients (n = 17) |
|---|---|
| **Age, mean (range) y** | 67 (45-79) |
| **Sex** | |
| Male | 16 (94) |
| Female | 1 (6) |
| **Indication for operation** | |
| Rutherford category 3 | 12 (71) |
| Rutherford category 4 | 3 (18) |
| Rutherford category 5 | 2 (12) |
| **Initial claudication distance, mean (range) m** | 72 (30-100) |
| **ABI, mean (SD)** | 0.61 (0.15) |
| **Treadmill test, mean (SD)** | 0.30 (0.16) |
| **Previous ipsilateral procedures** | |
| Central | 4 (24) |
| Iliacal | 8 (47) |
| Femoral | 4 (24) |
| **Risk factors** | |
| Coronary artery disease | 12 (71) |
| Diabetes | 8 (47) |
| Stroke or TIA | 1 (6) |
| Smoking, current or recent | 14 (88) |
| Hypertension | 13 (77) |
| Hypercholesterolemia | 17 (100) |
| **Serum creatinine, mean (SD) µmol/L** | 90 (17) |
| **BMI, mean (SD) kg/m2** | 25 (3.5) |
| **Contralateral amputation** | 1 (6) |
| **Preoperative occlusion of SFA** | 17 (100) |
| **Length of SFA occlusion, mean (range) cm** | 17 (8-25) |
| **Runoff arteries** | |
| 1 | 2 (12) |
| 2 | 4 (24) |
| 3 | 11 (65) |
| **Preoperative medication** | |
| Statin | 17 (100) |
| Acetylsalicylic acid | 15 (88) |
| Coumarin | 3 (18) |
| Clopidogrel | 2 (12) |
| Dipyridamole | 0 (0) |
| No anticoagulant | 0 (0) |

**Table I.** Baseline Characteristics of Study Population[a]

ABI, Ankle-brachial index; BMI, body mass index. TIA, transient ischemic attack; SFA, superficial femoral artery

[a]Data are presented as No.(%), unless otherwise indicated

was performed. The other patient was treated with a thrombectomy 10 months after the initial operation. Restenosis occurred in one patient who was treated with PTA 16 months after surgery. Limb salvage was 100%.

A comparison between cryoplasty with additional stent placement (9 patients) and cryoplasty without additional stent placement (8 patients) shows one reocclusion and one restenosis (located in the proximal SFA) in the stent group. One reocclusion (located in the proximal SFA) occurred in the no-stent group.

| Variable | Patients (n = 17) |
|---|---|
| **Operation time, mean (SD) min** | 117 (38.1) |
| **Blood loss, mean (SD) mL** | 210 (106) |
| **Intima core, mean (range) cm** | 30 (26-34) |
| **Cryoplasty complete SFA** | 17 (100) |
| **Balloon diameter, median (range) mm** | 7 (5-7) |
| **Distal stent placement** | 9 (53) |
| **Additional procedure** | 13 (77) |
| Common femoral and/or profundaplasty | 11 (64) |
| Iliacofemoral bypass | 1 (6) |
| Femoral interposition graft | 1 (6) |
| Transmetatarsal amputation | 1 (6) |
| PTA iliac | 12 (12) |
| PTA and stent tibiofibular trunk | 1 (6) |
| **Patch closure** | 17 (100) |
| Prosthetic | 3 (18) |
| Vein | 0 (0) |
| Bovine | 14 (82) |

**Table II.** Intraoperative Results[a]

PTA, percutaneous transluminal angioplasty; SFA, superficial femoral artery

[a]Data are presented as No.(%), unless otherwise indicated

| Variable | Patients (n = 17) |
|---|---|
| **Postoperative hemorrhage** | 0 (0) |
| **Superficial wound infection** | 3 (18) |
| **Deep wound infection** | 1 (6) |
| **Pneumonia** | 0 (0) |
| **Urinary tract infection** | 0 (0) |
| **Postoperative renal failure**[b] | 0 (0) |
| **Edema** | 3 (18) |
| **Seroma** | 0 (0) |
| **ABI, mean (SD)** | 0.95 (0.17) |
| **Hospital stay, median (range) days** | 3 (2-14) |
| **Readmittance** | 4 (23) |
| Wound infection | 3 (18) |
| Leakage proximal anastomosis iliacofemoral bypass | 1 (6) |
| **Early reocclusion (<30 days)** | 0 (0) |

**Table III.** Postoperative Data[a]

ABI, ankle-brachial index

[a]Data are presented as No.(%), unless otherwise indicated

[b]Defined as a >20% decrease in serum creatinine clearance compared to baseline, the presence of new-onset dialysis, or both



# Discussion

This pilot study describes the 1-year results of concomitant cryoplasty of the entire SFA combined with remote endarterectomy. The combined procedure was technically successful in all patients, and there were no intraoperative adverse events. The Kaplan-Meier estimates of the primary and assisted primary patency rates after 1 year of follow-up were 74%, and secondary patency was 89%. These short-term results are promising compared to recent literature, which shows a 1-year primary patency of 61%, an assisted primary patency of 73%, and a secondary patency of 79% after RSFAE alone.[5] Furthermore, there were no perioperative adverse events. Safety of the procedure is therefore confirmed; however, our study results are limited by small sample size and short follow-up.

Debulking of the intima core during RSFAE seems the optimal preliminary treat-

ment to maximize the effect of cryoplasty. Dissection on the level of the internal elastic lamina leaves the proliferative cells of the media bare and possibly more sensitive to the apoptotic effect of supercooling and therefore reduces the stimulus for cellular migration and proliferation into the vessel lumen. Debulking may also decrease elastic recoil, another aspect of the restenosis process.

Comparison with recent literature is not easily made, because this is the first study describing cryoplasty after RSFAE. However, after PTA without debulking, results for cryoplasty are conflicting. Karthik et al describes a 100% restenosis rate after cryoplasty for restenosis of the iliofemoral tract.[8] Fava et al, on the other hand, shows a primary patency rate of 83.3% for femoropopliteal arterial lesions at 14 months.[7] Although no randomized trials have been performed, a few large case series have been presented.[9-12] In a cohort described by Laird et al, 101 patients were included with femoropopliteal disease and treated with cryoplasty accordingly. Primary patency at 9 months was 70.1% and well maintained after prolonged follow-up.[9,10] The 12-months results of a study population described by Samson et al were excellent, with only five restenoses in 32 patients with 47 lesions treated, a primary patency rate of 84%.[11] However, a reappraisal after expanding their cohort to 64 patients with 92 lesions led to different conclusions at 16 months of follow-up. The primary patency rate was 47% at 1 year and 38% at 2 years.[12] In their first cohort, 94% of lesions were in the SFA, 2% in the popliteal artery, and 4% in a vein graft, whereas in their second cohort, only 67% of lesions were in the SFA, 27% in the popliteal artery, and 6% in a vein graft. This might explain part of the difference found in their patency percentages.[11,12]



In the eight patients in our study without additional stent placement, no technical failure occurred perioperatively. One SFA reoccluded after 16 months, but the occlusion was limited to the proximal SFA. We therefore assume that if the residual stenosis at the transection zone is <30%, the distal intima core can be safely secured with cryoplasty alone and additional stent placement can be omitted (Figure 1). Reduction in the use of stents can reduce associated risks such as stent fracture and may also reduce costs. Moreover, omitting stents might have future surgical implications because supragenicular bypass grafting is not being compromised. Removal of the stent at the level of the distal anastomosis during supragenicular bypass surgery carries the risk of damaging the vessel wall, which in turn could lead to intimal hyperplasia.

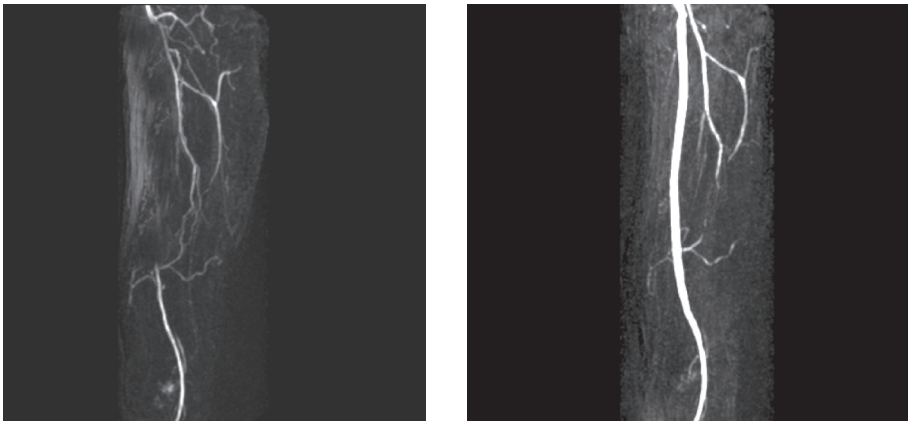

**Figure 1** Preoperative and 12-month postoperative magnetic resonance angiography of the superficial femoral artery of a patient treated with remote endarterectomy of the superficial femoral artery with concomitant cryoplasty, without distal stent placement.



# Conclusion

Cryoplasty after RSFAE is a safe procedure, with promising patency rates in this pilot study. However, long-term results and a larger, randomized trial will have to prove the durability and true additional value of this procedure.

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# 6

SS Gisbertz, WJM Derksen, DPV de Kleijn, A Vink,
ML Bots, Y van der Graaf, WE Hellings, JPPM de Vries,
FL Moll, G Pasterkamp

# Alcohol use is associated with atherosclerotic plaque composition and with a reduced cardiovascular event risk in patients with peripheral arterial occlusive disease, but not in patients with cerebrovascular disease

Submitted

# Abstract


## Objectives

To examine the association between alcohol use, the occurrence of cardiovascular events, and plaque phenotype in patients diagnosed with femoral or carotid artery disease.

## Background

Alcohol has been shown to have cardiovascular protective effects, in patients with cardiovascular disease as well as in healthy individuals. Whether alcohol consumption induces changes in atherosclerotic plaque composition, has not been investigated before.

## Methods

Consecutive femoral (n = 224) and carotid (n = 693) endarterectomy specimens underwent histologic examination for the presence of collagen, calcifications, smooth muscle cells, macrophages, fat, and intraplaque thrombus. Primary outcome was the composite end point "major cardiovascular event." Alcohol consumption was categorized as no alcohol use, 1-10 U/wk, or >10 U/wk.

## Results

The Kaplan-Meier estimate of the major cardiovascular event rate after 3 years of follow-up in the femoral group was 35% for no alcohol use and 21% for 1-10 U/wk, whereas only 10% of the group >10 U/wk sustained a major cardiovascular event (p = 0.010). The plaques of alcohol consumers in the femoral group contained significantly smaller lipid cores and less macrophage infiltration than in abstainers. In the carotid group the major cardiovascular event rate was similar in all 3 groups; a difference in plaque composition could not observed.

## Conclusions

This study shows an inverse relationship between alcohol use and major cardiovascular events after endarterectomy for peripheral arterial occlusive disease, accompanied by a more stable plaque phenotype. However, no such relationship could be observed for patients with cerebrovascular disease.

# Introduction

Moderate alcohol consumption (10-20 U/wk) has been consistently associated with a lower risk for myocardial infarction, stroke, peripheral arterial occlusive disease, and type 2 diabetes.[1-13] In addition to a beneficial effect in patients with known coronary heart disease, a cardioprotective effect of alcohol has been demonstrated in healthy individuals.[1,2,8-12]

The mechanisms behind the cardiovascular protective effects of alcohol are not fully understood, but are thought to be attributable to an anti-inflammatory effect on low-grade inflammatory diseases such as atherosclerosis.[14,15] Alcohol consumption changes the lipid profile, including increases in high-density lipoprotein cholesterol.[16,17] Alcohol also affects thrombus formation by inhibitory effects on platelet aggregation and function combined with increased fibrinolytic activity and lower fibrinogen levels.[18-20] Moreover, alcohol influences antioxidant capacity and insulin sensitivity, thus restraining atherosclerosis.[6,18,21]

Atherosclerosis is a generalized condition and is therefore associated with an increased risk of secondary cardiovascular events when a primary symptomatic lesion has been diagnosed. Whether patients with clinical presentation of peripheral arterial occlusive disease or cerebrovascular disease would benefit from the beneficiary effects of alcohol consumption remains unknown. Whether alcohol use is associated with plaque composition is also unknown. The objective of this study was to investigate the association between alcohol intake, cardiovascular events, and plaque characteristics in patients undergoing femoral or carotid endarterectomy.



# Methods

## Study design of the Athero-Express Biobank

The design of the Athero-Express study has been reported in detail previously.[22] Inclusion for the current substudy was between April 2002 and March 2007. Included were subsequent patients undergoing (1) remote superficial femoral artery endarterectomy or endarterectomy of the femoral bifurcation with or without additional bypass graft for severe intermittent claudication, critical ischemia, or tissue loss

**Alcohol use is associated with atherosclerotic plaque composition and with a reduced cardiovascular event risk in patients with peripheral arterial occlusive disease, but not in patients with cerebrovascular disease.**

(Rutherford category 2-5)[23] with atherosclerotic lesions (TransAtlantic Intersociety Consensus [TASC] A-D)[24] of the femoral artery, and (2) patients undergoing carotid endarterectomy for (a)symptomatic carotid artery stenosis with more than 70% lumen diameter reduction.

Clinical parameters were recorded at baseline. Patients completed a detailed validated questionnaire, including alcohol consumption habits.[22] This questionnaire is based on the validated Rose questionnaire.[25] For the assessment of alcohol intake, a quantity–frequency method was used.[26] Alcohol consumption was a priori categorized as no alcohol use, 1-10 U/wk, or >10 U/wk. One unit was defined as 12 grams of alcohol. Subgroup analyses were not performed by type of beverage due to lack of such detailed information.

## Atherosclerotic Plaque Characterization

During surgery, the atherosclerotic plaques were excised and directly processed in the laboratory for histologic examination. The plaques were evaluated for the presence of collagen, calcifications, smooth muscle cells, macrophages, fat, and thrombus, as described previously, and independent of knowledge on alcohol consumption.[22] The plaque was divided in 5-mm-thick segments along the longitudinal axis. The segment with the greatest plaque burden was subjected to histologic examination. The plaque morphology of this segment has been shown to be relatively good representative and uniform from within each subject.[27] Comparison of the histologic scorings of adjacent segments revealed a mean $\kappa$ (weighted kappa) of 0.40 (range, 0.33 to 0.60). When the culprit segment was compared with the more distant segment, the mean $\kappa$ was 0.24; however, in 91% of cases, the difference between the culprit segment and the distal segment was one category or less.[27] Macrophage infiltration (CD-68), smooth muscle cell infiltration (alpha $\alpha$-actin), the amount of collagen (Picrosirius red), and calcification (hematoxylin and eosin) were semiquantitatively scored as (1) none or minor or (2) moderate or heavy staining. The criteria for classification were defined as follows: for macrophages: (1) absent or minor CD-68 staining with negative or few scattered cells, or (2) moderate or heavy staining, defined as clusters of cells with more than 10 cells present; for smooth muscle cells: (1) minor $\alpha$-actin staining over the entire circumference with absent staining at parts of the circumference of the arterial wall, or (2) positive cells along the entire circumference of the luminal border; and for collagen staining: (1) none or minor staining along part of the luminal border of the plaque or (2) moderate or heavy staining along the entire luminal border. Luminal thrombus and intraplaque bleeding were examined in hematoxylin and eosin and fibrin stainings (Mallory staining) and rated as being absent or present. The size of the lipid core was visually estimated as the percentage of total plaque area using

hematoxylin and eosin and Picrosirius red stainings, with a division in 2 categories of less than 10% and more than 10%. The histologic examination was performed by 2 independent observers who were blinded for the clinical data. The intraobserver and interobserver semiquantitative analysis of atherosclerotic plaque histology is well reproducible.[27] CD68 and α-actin stainings were scored as the percentage of the plaque area using AnalySIS 3.0 software (Olympus, Tokyo, Japan). This computerized analysis revealed an excellent correlation with the semiquantitative observations. The α-values (weighted kappa) for intraobserver variability of fat, macrophages, smooth muscle cells, collagen, calcifications, thrombus, and overall phenotype were 0.83, 0.85, 0.71, 0.63, 0.81, 0.80, and 0.86, respectively, and values for interobserver variability were 0.68, 0.74, 0.54, 0.59, 0.82, 0.75, and 0.71, respectively.[27]

## Follow-up

Once a year, patients were asked to complete a questionnaire during the follow-up for 3 years after the initial surgery. The general practitioner was contacted when patients did not respond. Clinical end points included incidence of cardiovascular and cerebrovascular death, myocardial infarction, coronary artery bypass graft operation, coronary angioplasty, and stroke. When patients revealed an event during follow-up, the correct diagnosis was obtained from discharge summaries and medical records. Cardiovascular events were validated by 2 vascular surgeons from different institutions who were blinded for each other's judgment.



The primary outcome was a composite end point "major cardiovascular event" and included cardiovascular and cerebrovascular death, myocardial infarction, coronary artery bypass grafting, coronary angioplasty, and stroke. Secondary end points were cardiovascular death and a composite end point "all cardiovascular events," including major cardiovascular events and death as described previously, transient ischemic attacks, and peripheral interventions, including peripheral bypasses or desobstruction procedures, aneurysm rupture and repair, renal artery procedures, and leg amputation.

The medical ethics boards of the participating hospitals approved the study, and all patients provided written informed consent.

## Data analysis

Statistical analysis was performed with SPSS 15.0 software (SPSS Inc, Chicago, IL, USA).

Event rates (the primary and secondary end points) were calculated with Kaplan-Meier life-table estimates in the two cohorts separately. Being interested in the effect on the primary endpoint (major cardiovascular events) of alcohol consumption only,

multivariate Cox proportional hazard regression models were used to adjust for possible confounders. Every baseline characteristic (see Table 1) was entered first in the univariate analyses. Only if a baseline characteristic showed an association ($p < 0.1$) with the primary endpoint this characteristic was entered as covariate in multivariate analysis. Age and sex were included in all multivariate models. Univariate and multivariate analysis was performed in the two cohorts apart. Results are presented as hazard ratios with exact 95% confidence interval (CI). A log-rank test, Mann-Whitney *U* test, or $\chi 2$ test was used as indicated to compare both groups. A value of $p < 0.05$ was considered statistically significant. The relation with plaque characteristics was studied in a similar manner, using univariable and multivariable models. The latter included adjustments for age, gender, smoking history, diabetes and body mass index.

# Results

A total of 1167 consecutive patients in the Athero-Express Biobank were followed up for a minimum of 1 year postoperatively and were assessed for eligibility (Figure 1). Owing to malignant disease, permanent extramural care, or lack of informed consent, 23 of 302 patients in the femoral group and 51 of 865 patients in the carotid group were excluded. An additional 52 patients in the femoral group and 116 patients in the carotid group were excluded because information on alcohol use was lacking or plaque material was insufficient. Three patients in the femoral group and 5 patients in the carotid group were lost to follow-up. The final analysis therefore included 224 patients operated on for peripheral arterial occlusive disease and 693 patients operated on for cerebrovascular disease.

Baseline characteristics of the study population are summarized in Table 1a and 1b. In both study groups, patients abstaining from alcohol were significantly older than patients consuming alcohol. Furthermore, significantly more men and more former or current smokers were among the alcohol users in the femoral as well as the carotid group. In the carotid study population, more patients abstaining from alcohol reported a history of coronary artery disease. All shown differences between patients abstaining from alcohol and patients consuming alcohol were linear dose-dependent. In the femoral cohort we observed 35 major cardiovascular events and in the carotid cohort 86 major cardiovascular events during follow-up.

Plaque characteristics in relation to alcohol consumption for both study groups are presented in Table 2. Plaques of the femoral study population revealed larger lipid

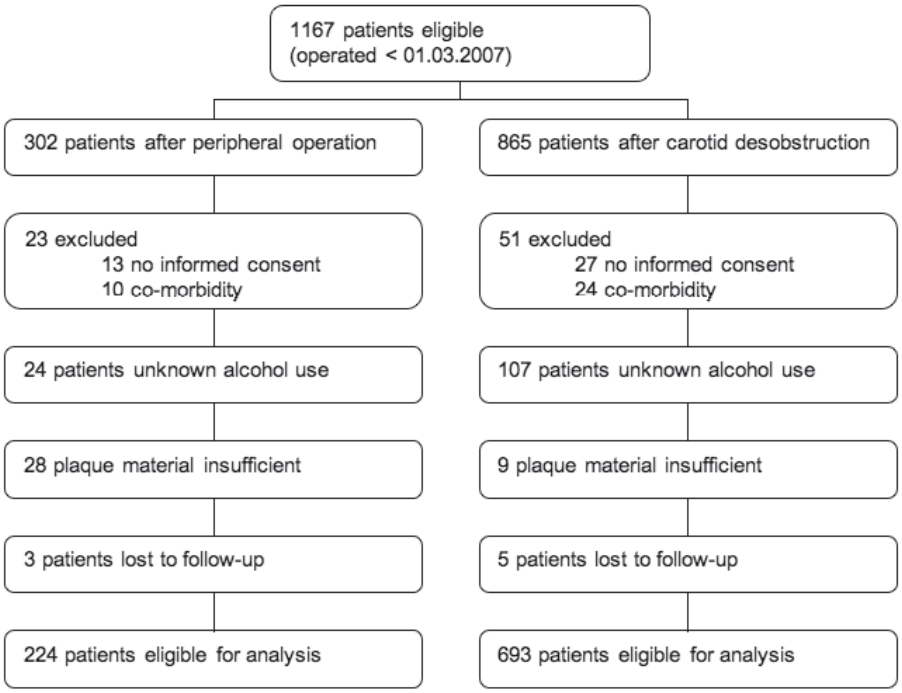




**Figure 1.** Enrollment of patients

cores and more macrophage infiltration in patients abstaining from alcohol than in patients consuming alcohol, with a dose-response relationship: 47% of the plaques in the no alcohol group had a lipid core larger than 10% versus 28% for the 1-10 U/wk group and 19% for the >10 U/wk group (p = 0.002). In the no alcohol group 33% of the plaques showed moderate or heavy macrophage infiltration versus 26% in the 1-10 U/wk group and 17% for >10 U/wk group (p = 0.033). In the carotid study population, such a relationship was not observed. Multivariable analyses did not show materially different results in terms of statistical significance or magnitude of the associations.

Patients in the femoral group who abstained from alcohol had significantly more major cardiovascular events than those who consumed alcohol after a mean follow-up of 25 months. The Kaplan-Meier estimate of event rate after 3 years of follow-up was 35% for no alcohol and 21% for 1-10 U/wk, whereas only 10% of the >10 U/wk group had sustained a major cardiovascular event (univariate p = 0.010, Figure 2a). The Kaplan-Meier estimate of event rate after 3 years of follow-up in the carotid group was 11% for no alcohol, 15% for 1-10 U/wk, and 17% for >10 U/wk (univariate p =

| | None (n=45) | 1-10 U/wk (n=86) | >10 U/wk (n=93) | P value |
|---|---|---|---|---|
| **Age, mean (range), y** | 69 (48-81) | 65 (44-87) | 65 (48-84) | .004 |
| **Sex** | | | | |
| Female | 17 (37.8) | 25 (29.1) | 13 (14.0) | .001 |
| Male | 28 (62.2) | 61 (70.9) | 80 (86.0) | |
| **Body mass index†, mean (SD)** | 26 (3.6) | 26 (3.4) | 25 (3.8) | .364 |
| **Current smoker** | 19 (43.2) | 29 (33.7) | 32 (34.4) | .441 |
| **History of smoking‡** | 41 (93.2) | 82 (95.3) | 92 (100) | .019 |
| **Diabetes** | 9 (20.5) | 19 (22.1) | 28 (30.8) | .133 |
| **Hypertension** | 32 (71.1) | 58 (67.4) | 63 (67.7) | .758 |
| **Hypercholesterolemia** | 33 (75.0) | 59 (71.1) | 64 (68.8) | .473 |
| **History of coronary artery disease** | 21 (46.7) | 32 (37.2) | 33 (35.5) | .268 |
| **History of cerebrovascular disease** | 22 (48.9) | 24 (27.9) | 33 (35.5) | .373 |
| **History of peripheral vascular disease** | 43 (95.6) | 82 (95.3) | 89 (95.7) | .944 |
| **Indication for operation** | | | | |
| Rutherford category 3 | 33 (73.7) | 68 (79.1) | 67 (72.0) | .423 |
| Rutherford category 4 | 10 (22.2) | 12 (14.0) | 15 (16.1) | |
| Rutherford category 5 | 2 (4.4) | 6 (7.0) | 11 (11.8) | |
| **Ankle-Brachial Index§, mean (SD)** | 0.60 (0.16) | 0.58 (0.17) | 0.59 (0.19) | .520 |
| **HDLǁ, mean (SD)** | 1.08 (0.40) | 1.05 (0.29) | 1.16 (0.46) | .692 |
| **LDLǁ, mean (SD)** | 2.76 (0.98) | 2.52 (0.88) | 2.56 (0.97) | .799 |
| **Statin use** | 37 (82.2) | 63 (73.3) | 69 (74.2) | .433 |
| **Aspirin use** | 36 (80.0) | 69 (80.2) | 75 (80.6) | .923 |
| **Oral anticoagulant use** | 12 (26.7) | 22 (25.6) | 21 (22.6) | .559 |
| **Duration of alcohol use, mean (range), y** | | 44 (19-63) | 48 (7-61) | .036 |
| **Duration of abstention, mean (range), y** | 16 (10-38) | | | |



**Table 1a.** Clinical Characteristics of the Femoral Study Population in Relation to Alcohol Consumption*

0.618, Figure 2b). Adjustment for imbalance in baseline characteristics by use of Cox hazard regression analysis did not alter these results.

The Kaplan-Meier estimate for cardiovascular death rate in the femoral group was 20% for no alcohol, 14% for 1-10 U/wk, and 3% for >10 U/wk at 3 years of follow-up (univariate p = 0.036). Total mortality in the femoral cohort (n = 24) was 25%, 16% and 3% respectively (univariate p = 0.007). In the carotid group, no significant difference was noted in the cardiovascular death rate: 7% for no alcohol, 5% for 1-10 U/wk, and 3% for >10 U/wk (univariate p = 0.235). Total mortality in the carotid cohort (n = 44) was 10%, 7% and 5% respectively (univariate p = 0.281). The event rate for all cardiovascular events by Kaplan-Meier life table analysis in the femoral group was 70% for no alcohol, 57% for 1-10 U/wk, and 53% for >10 U/wk (univariate p = 0.182), and in the carotid group, 21% for no alcohol, 26% for 1-10 U/wk, and 29% for >10 U/wk (univariate p = 0.343).

| | None (n=210) | 1-10 U/wk (n=304) | >10 U/wk (n=186) | P value |
|---|---|---|---|---|
| **Age, mean (range), y** | 68 (37-88) | 67 (43-90) | 65 (44-89) | < .001 |
| **Sex** | | | | |
| Female | 100 (48.1) | 75 (24.9) | 28 (15.2) | < .001 |
| Male | 108 (51.9) | 226 (75.1) | 156 (84.8) | |
| **Body mass index†, mean (SD)** | 27 (3.9) | 26 (3.8) | 27 (3.4) | .186 |
| **Current smoker** | 58 (28.3) | 70 (23.3) | 54 (29.5) | .853 |
| **History of smoking‡** | 154 (75.1) | 270 (90.9) | 168 (91.8) | < .001 |
| **Diabetes** | 48 (23.6) | 65 (21.8) | 36 (20.2) | .420 |
| **Hypertension** | 150 (73.5) | 214 (72.3) | 143 (78.6) | .283 |
| **Hypercholesterolemia** | 130 (65.0) | 191 (65.9) | 127 (70.6) | .261 |
| **History of coronary artery disease** | 76 (36.5) | 100 (33.2) | 46 (25.0) | .016 |
| **History of cerebrovascular disease** | 204 (98.1) | 299 (99.3) | 180 (97.8) | .902 |
| **History of peripheral vascular disease** | 46 (22.1) | 88 (29.2) | 38 (20.7) | .840 |
| **Duplex stenosis** | | | | |
| 50-64% | 5 (2.4) | 11 (3.7) | 6 (3.3) | .561 |
| 65-89% | 83 (40.5) | 130 (43.3) | 79 (43.9) | |
| 90-100% | 117 (57.1) | 159 (53.0 | 95 (52.8) | |
| **HDL‖, mean (SD)** | 1.12 (0.33) | 1.15 (0.35) | 1.22 (0.41) | .197 |
| **LDL‖, mean (SD)** | 2.79 (0.93) | 2.88 (1.04) | 2.89 (1.05) | .808 |
| **Statin use** | 153 (75.7) | 221 (74.9) | 138 (76.7) | .850 |
| **Aspirin use** | 182 (90.5) | 253 (85.8) | 164 (91.1) | .945 |
| **Oral anticoagulant use** | 32 (15.9) | 41 (13.9) | 19 (10.6) | .131 |
| **Duration of alcohol use, mean (range), y** | | 49 (8-73) | 48 (18-72) | .043 |
| **Duration of abstention, mean (range), y** | 15 (10-55) | | | |



**Table 1b.** Clinical Characteristics of the Carotid Study Population in Relation to Alcohol Consumption*

**Footnote Table 1a and 1b**

* Numbers are presented as No. (%) unless otherwise indicated

† Calculated as weight in kilograms divided by height in meters squared

‡ Including current smoking

§ Calculated as blood pressure at ankle level divided by blood pressure at arm level (mmHg)

‖ Expressed in mmol/L

In the femoral group, with 35 events, univariate analysis showed that age was associated with an increased risk for major cardiovascular events, with a hazard ratio of 1.04 per year of age (95% CI 1.00-1.08; p = 0.039). Other baseline characteristics were not significantly associated with an altered risk for cardiovascular events.
In multivariate Cox hazard regression analysis, with adjustments for age, gender, smoking, diabetes and body mass index, only alcohol consumption remained independently associated with a decreased risk for major cardiovascular events, with a hazard ratio of 0.52 (95% CI 0.33-0.81; p = 0.004, Table 3).

Alcohol use is associated with atherosclerotic plaque composition and with a reduced cardiovascular event risk in patients with peripheral arterial occlusive disease, but not in patients with cerebrovascular disease.

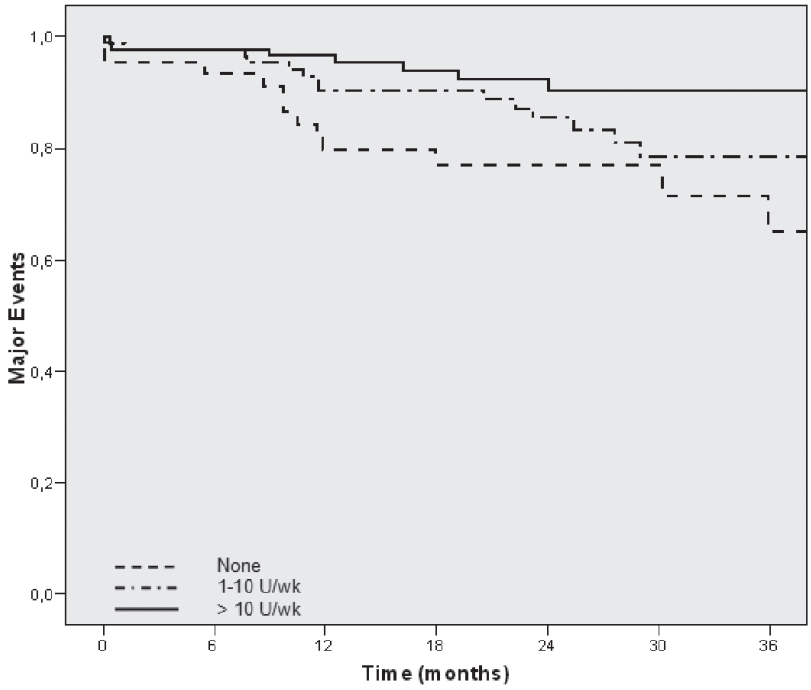




**Figure 2a.** Kaplan-Meier survival estimate comparing amount of alcohol consumption with regard to major cardiovascular events in the femoral study population (p = 0.010)

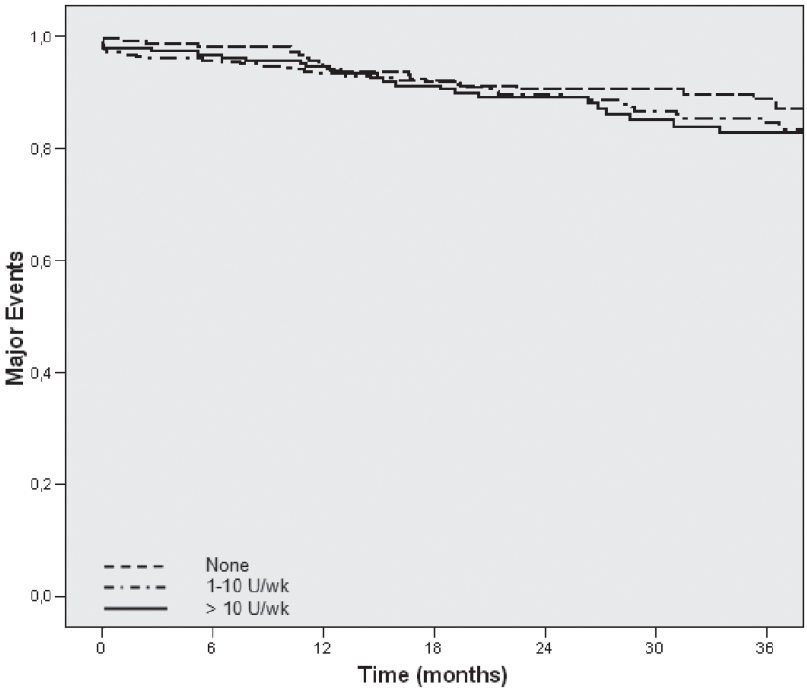




**Figure 2b.** Kaplan-Meier survival estimate comparing amount of alcohol consumption with regard to major cardiovascular events in the carotid study population (p = 0.618)

| | Femoral | | | | Carotid | | | |
|---|---|---|---|---|---|---|---|---|
| | Alcohol consumption | | | | Alcohol consumption | | | |
| Plaque characteristic | None (n=45) | 1-10 U/wk (n=86) | >10 U/wk (n=93) | P value | None (n=210) | 1-10 U/wk (n=304) | >10 U/wk (n=186) | P value |
| **Lipid core** | | | | | | | | |
| Lipid core < 10% | 24 (53.3) | 62 (72.1) | 75 (80.6) | .002 | 46 (22.1) | 64 (21.3) | 31 (16.8) | .208 |
| Lipid core > 10% | 21 (46.7) | 24 (27.9) | 19 (19.4) | | 162 (77.9) | 237 (78.7) | 153 (83.2) | |
| **Intraplaque thrombus** | | | | | | | | |
| No thrombus | 9 (20.0) | 30 (34.9) | 24 (25.8) | .909 | 61 (29.3) | 79 (26.2) | 56 (30.4) | .854 |
| Thrombus | 36 (80.0) | 56 (65.1) | 69 (74.2) | | 147 (70.7) | 222 (73.8) | 128 (69.6) | |
| **Calcifications** | | | | | | | | |
| None or minor | 13 (28.9) | 36 (41.9) | 22 (23.7) | .162 | 82 (39.4) | 137 (45.7) | 69 (37.5) | .781 |
| Moderate or heavy | 32 (71.1) | 50 (58.1) | 71 (76.3) | | 126 (60.6) | 163 (54.3) | 115 (62.5) | |
| **Collagen** | | | | | | | | |
| None or minor | 6 (14.0) | 7 (8.3) | 13 (14.6) | .600 | 39 (18.8) | 52 (17.4) | 33 (17.9) | .802 |
| Moderate or heavy | 37 (86.0) | 77 (91.7) | 76 (85.4) | | 168 (81.2) | 247 (82.6) | 151 (82.1) | |
| **Smooth muscle cell infiltration** | | | | | | | | |
| None or minor | 9 (20.0) | 19 (22.1) | 22 (23.9) | .604 | 58 (28.0) | 78 (26.0) | 61 (33.5) | .264 |
| Moderate or heavy | 36 (80.0) | 67 (77.9) | 70 (76.1) | | 149 (72.0) | 222 (74.0) | 121 (66.5) | |
| **Macrophage infiltration** | | | | | | | | |
| None or minor | 30 (66.7) | 62 (73.8) | 76 (82.6) | .033 | 81 (39.1) | 116 (39.1) | 67 (36.4) | .594 |
| Moderate or heavy | 15 (33.3) | 22 (26.2) | 16 (17.4) | | 126 (60.9) | 181 (60.9) | 117 (63.6) | |

**Table 2.** Plaque Characteristics Versus Alcohol Consumption in the Femoral and Carotid Group*

**Footnote Table 2.**

* Categoric data are presented as No. (%) unless otherwise indicated

| | Hazard Ratio (95% CI) | P value |
|---|---|---|
| **Sex** | 1.18 (0.53-2.65) | .683 |
| **Age** | 1.03 (0.99-1.07) | .126 |
| **Alcohol** | 0.52 (0.33-0.81) | .004 |

**Table 3.** Multivariate Cox Hazard Regression Analysis for the Femoral Study Population Regarding Major Cardiovascular Events

**Footnote Table 3.**

Abbrevation: CI, confidence interval

# Discussion

This study describes the effects of alcohol consumption in relation to plaque characteristics on the occurrence of future cardiovascular events in patients operated on for peripheral arterial occlusive disease and in patients operated on for cerebrovascular disease. Our results suggest a protective, dose-related effect of alcohol consumption on major cardiovascular events and death risk in patients with peripheral arterial occlusive disease. For patients with cerebrovascular disease, such a relationship could not be observed. Remarkably, the atherosclerotic plaques of patients in the femoral group who abstained from alcohol contained more inflammation and larger lipid cores, which are characteristics of vulnerable plaques. A linear relation was distinguished between histologic markers for plaque stability and alcohol consumption. Again, in the carotid group, such a difference could not be observed.



Our results are in concordance with previous studies where alcohol has consistently been associated with a decreased risk of clinical manifestations of atherosclerosis. The effects of alcohol on high-density lipoprotein cholesterol, fibrinogen, thrombogenicity, and insulin sensitivity have been confirmed in randomized trials. These proven anti-atherosclerotic effects of alcohol suggest that the observed inverse association between alcohol use and cardiovascular events is causal.[16-21] Plaque size and intima-media thickness have been studied in relation to alcohol consumption. In most of these previous studies, however, no correlation was observed between alcohol consumption and the atherosclerotic plaque burden.[19, 28-32] In addition, calcification of coronary and aortic plaques determined by computed tomography scan was not

Alcohol use is associated with atherosclerotic plaque composition and with a reduced cardiovascular event risk in patients with peripheral arterial occlusive disease, but not in patients with cerebrovascular disease.

associated with alcohol consumption.[33-35] A possible explanation for the difference in observed effects of alcohol consumption on atherosclerotic disease in our study might be that we studied clinical end points and histologic characteristics of atherosclerotic disease, whereas these imaging studies focused on the quantitative measures of atherosclerotic disease. Our observed inverse association between histologic characteristics of vulnerable plaques and alcohol consumption suggests that not plaque amount—but plaque composition—is influenced by the use of alcohol.

Previous studies have demonstrated that symptomatic cerebrovascular disease is related to plaques with a large lipid core and heavy macrophage infiltration.[36,37] Why alcohol is associated with stability of femoral plaques and not with characteristics of carotid plaques remains to be investigated. An explanation could be that peripheral arterial interventions are generally initiated in a more advanced stage of atherosclerosis than cerebrovascular disease, with a worse prognosis. Patients presenting with chronic critical limb ischemia have a 20% mortality in the first year after presentation, whereas the mortality rate for patients with cerebrovascular disease is 27% at 6 years of follow-up.[24,38] This is supported by the fact that the event rate was much lower in the carotid cohort for both the primary and secondary endpoints. Alcohol might influence the stabilization process during aging of the atherosclerotic plaque. We have no data yet to support this. Our results are consistent with recent literature, as in a study by Andersen et al. alcohol consumption did not affect survival in patients suffering from stroke.[39]



Our study has several potential limitations. Although multivariate analysis was used to test many possible confounders, we cannot exclude the possibility of unknown residual confounders. Nonetheless, a beneficiary effect of alcohol has also been demonstrated in experimental trials.[16,17,20,40] We relied on self-reported alcohol consumption. It is difficult to exclude a healthy effect bias, because healthy individuals are more likely to engage in social drinking. However, unhealthy participants might be under-reporting, suggesting that protective effects could occur at even higher intake levels than currently assumed.[26] We did not asses alcohol consumption during the follow-up period of 3 years. Theoretically, changes in drinking habits might have occurred between the carotid and femoral group during follow-up. However, we feel this is very unlikely, because all patients routinely received the same advice regarding alcohol moderation. Furthermore, for change in alcohol consumption to explain the finding, this change needs to be related to risk of death and needs to have occurred predominantly in the femoral group. Moreover, at baseline we assessed changes in drinking behavior in the past, and there were no differences between groups (data not shown).

Careful interpretation of the data is warranted. Alcohol consumption also has poten-

tial health risks. Alcohol is causally related to cancers of the oral cavity, esophagus, larynx, breast, colon, and liver, and also to hypertension, liver cirrhosis, chronic pancreatitis, injuries and violence, and cardiomyopathy and arrhythmias.[41,42] In this perspective, abstainers should not be encouraged to consume alcohol, and patients consuming moderate amounts of alcohol should not be encouraged to abstain.

## Conclusions

This study shows an inverse relationship between alcohol use and cardiovascular events in patients who undergo endarterectomy for peripheral arterial occlusive disease, but not in patients after endarterectomy for cerebrovascular disease. This is the first study to show that a lower risk for adverse events in patients with peripheral arterial occlusive disease who consume alcohol is accompanied by differences in plaque composition. In the femoral arteries, alcohol abstainers revealed more atheromatous and inflammatory plaque characteristics, known attributes of unstable plaques.



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**Alcohol use is associated with atherosclerotic plaque composition and with a reduced cardiovascular event risk in patients with peripheral arterial occlusive disease, but not in patients with cerebrovascular disease.**

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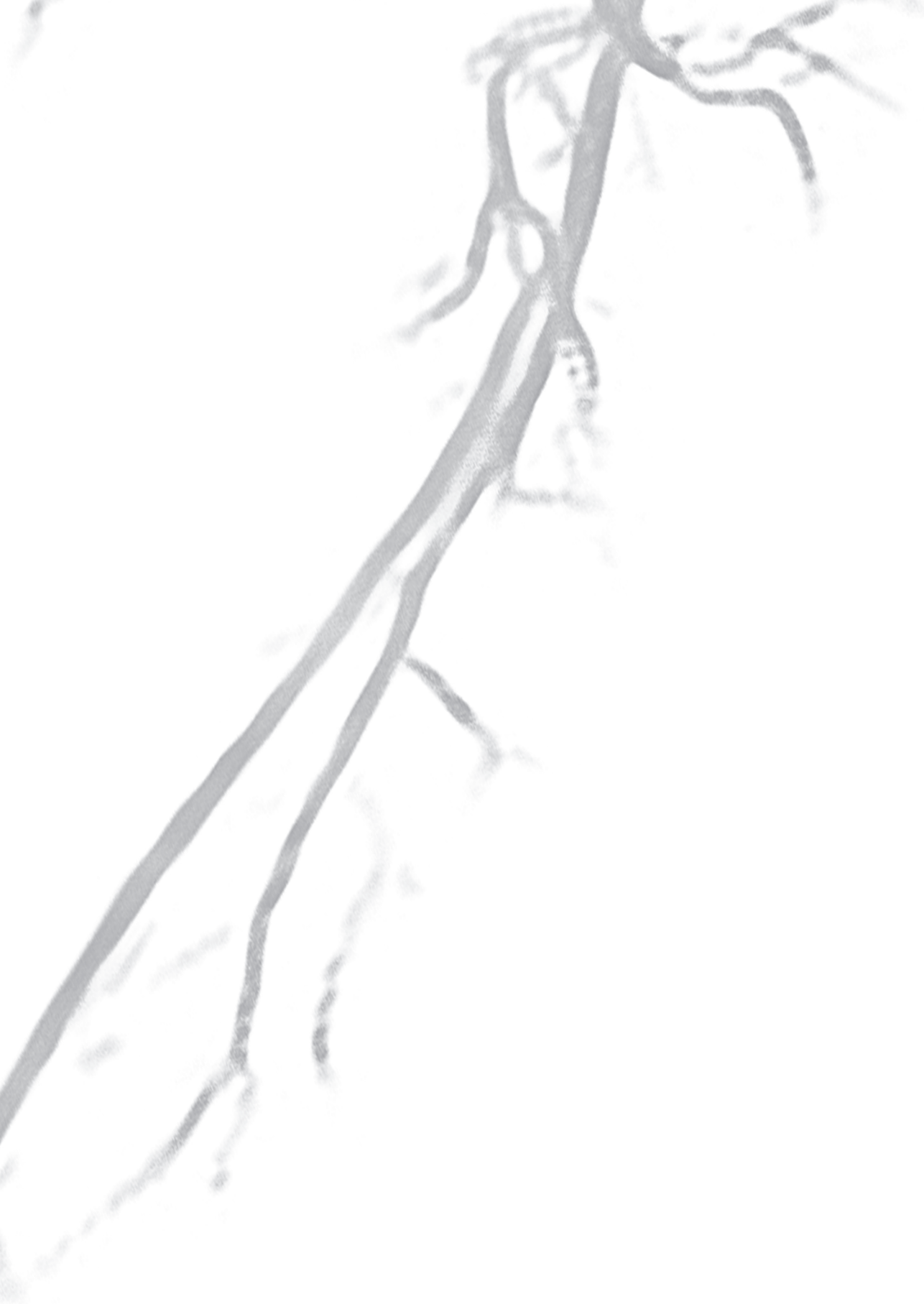

# 7

WJM Derksen, SS Gisbertz, WE Hellings, A Vink, DPV de Kleijn, JPPM de Vries, FL Moll, G Pasterkamp

# Predictive risk factors for restenosis after remote superficial femoral artery endarterectomy

Submitted

# Abstract


## Objective

Restenosis following remote superficial femoral artery endarterectomy (RSFAE) remains a challenging problem. Determinants predicting failure are lacking. This study investigated patient characteristics with predictive value for restenosis during the first year after RSFAE.

## Design

Prospective cohort study.

## Materials and methods

Ninety patients post-RSFAE were studied for the occurrence of restenosis in the first 12 months postoperatively. At baseline, clinical parameters were recorded. Vessel size was measured on the basis of plaque perimeter in the culprit lesion and lumen diameter on peroperative digital subtraction angiography.

## Results

In 57 patients (63%) a restenotic lesion was diagnosed within 12 months following surgery. Patients with longer time interval between start of ischemic walking complaints and RSFAE revealed a significantly higher incidence of restenosis (Hazard Ratio [HR] = 1.27 [1.05-1.52] per 4 years). Small plaque perimeter and small SFA diameter on angiography, were significantly associated with restenosis (HR = 0.54 [0.34-0.88] per 10mm and HR = 0.46 [0.27-0.78] per 1.5mm, respectively). In multivariate analysis, age, duration of ischemic walking complaints and lumen diameter were independently associated with increased risk of restenosis after RSFAE.

## Conclusion

This study provides evidence that age, vessel size, and duration of ischemic walking complaints before RSFAE are predictive values for restenosis after RSFAE.

# Introduction

Remote superficial femoral artery endarterectomy (RSFAE) is established as a minimaly invasive treatment option for long occlusions, defined as TransAtlantic Inter-Society Consensus [TASC] C and D lesions of the superficial femoral artery (SFA).[1] RSFAE has comparable primary assisted and secondary patency rates to prosthetic supragenicular bypass surgery.[2] Besides, hospital stay is shorter and consequences of possible reobstructions are less severe in patients treated with RSFAE.[2, 3]

A drawback of RSFAE is the restenosis rate in the first year postoperatively caused by neointimal hyperplasia, with more than 80% of all restenoses occuring in the first year after surgery. Restenosis within the first year has been associated with a higher risk for occlusion. The restenotic lesions are equally distributed in the endarterectomized SFA, including the distal part of the SFA with the stented transection zone.[4]

Determinants predicting failure after RSFAE are lacking. General risk factors for cardiovascular disease are not successful in discriminating the risk for restenosis. The extent and severity of the treated lesion and technical considerations are determinants of failure after percutaneous interventions or bypass surgery.[5] However, these clinical characteristics have not yet been proven to be of value for predicting restenosis after RSFAE. The objective of this study was to investigate patient characteristics that have a predictive value for restenosis during the first year after RSFAE.



# Materials and methods

## Study population

All patients in the current study were included in the Athero-Express Biobank; an ongoing vascular biobank with a longitudinal study design that has been described previously.[6] Dissected femoral plaques, obtained by endarterectomy in two participating Dutch teaching hospitals, are collected and examinded histopathologically. In addition, clinical baseline characteristics of all included patients are obtained. The medical ethics boards of both participating hospitals approved the study, and all patients provided written informed consent.[6]

Ninety consecutive patients who underwent RSFAE between February 2003 and October 2007 were selected. All patients underwent unilateral RSFAE with or without an additional open endarterectomy of the common femoral artery. All patients presented with intermittent claudication, critical ischemia or tissue loss (Rutherford category 3-5)[1] due to long-segment occlusion (TASC C and D lesions)[1] of the SFA.

At baseline, clinical preoperative, perioperative and postoperative parameters were obtained from the Athero-Express medical database. Missing data were obtained from medical files or referral letters. The preoperative evaluation included a magnetic resonance angiography (MRA).

## RSFAE Technique

This minimally invasive debulking technique has been described previously.[8,9] In summary, the SFA is exposed through a small groin incision. After heparinization, the proximal SFA is clamped, and a longitudinal arteriotomy is made in the proximal SFA. The intima core is dissected, between the lamina elastica interna and the circular fibers of the media, using the Vollmar dissector (Vollmar Dissector, Aesculap®, San Francisco, CA, USA), until it reaches the distal limit of the atheroma in the SFA. The Vollmar dissector is then exchanged for the Moll ringcutter (Mollring Cutter®, LeMaître Vascutek, San Jose, CA, USA). This device can transect and remove the entire desobstructed intimal core, all under fluoroscopic guidance. After the SFA is debulked, the distal transaction zone is secured by a stent and a completion angiography is performed to check the patency of the SFA and outflow arteries.



## Atherosclerotic plaque

The excised plaques were directly transferred to the laboratory, processed, and examined as described previously.[6] The atherosclerotic lesions were dissected into 5-mm segments, and the segment with the greatest plaque area was defined as the culprit lesion. This segment was fixed in formaldehyde 4%, decalcified for 1 week in ethylenediaminetetraacetic acid, and embedded in paraffin. Segments adjacent to the culprit lesion were snapfrozen in liquid nitrogen and stored at -80 C for future analysis.[6]

## Arterial size

Cross-sections of the elastin von Gieson staining of the harvested atherosclerotic plaques were captured by digital image microscopy (AnalySiS version 3.2, Soft Imaging GmbH, Munster, Germany), and the perimeter of the plaque was measured in each cross-section by tracing the internal elastic lamina (Figure 1). Because the studied femoral atherosclerotic plaques are dissected between the internal elastic lamina and the circular fibers of the media, we assumed that the perimeter of the dissected

atherosclerotic plaque (the perimeter of the internal elastic lamina) is a measure of preoperative artery size.

The diameter of the arterial lumen was also measured on angiography performed at the end of the procedure as a measure for residual lumen size. The lumen diameter was measured at 3 standardized levels: 1, 3 and 5 cm proximal of the stent in the distal SFA. The measurement outcomes at the 3 sites were averaged. An interventional radiologist supervised the execution of all angiographic measurements.

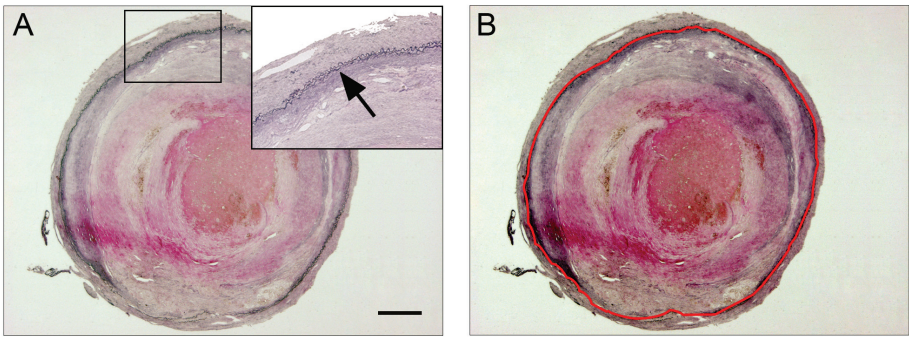


**Figure 1.** Measurement of the perimeter of the plaque in the culprit lesion of the occluded superficial femoral artery.

A: Elastin van Gieson staining of the atherosclerotic plaque. Inlay: magnification of the marked area showing the internal elastic lamina in black (arrow). Bar = 1 mm. B: Measurement of the perimeter of plaque by tracing the internal elastic lamina (in red) using digital image microscopy.

## Follow-up

Restenosis after initially successful RSFAE most often occurs in the first year postoperatively. These restenotic lesions have to be treated at an early stage to maintain patency whether symptomatic or not.[7] Follow-up, including duplex ultrasound scanning, was scheduled at 3, 6 and 12 months and annually thereafter. A peak systolic velocity ratio > 2.5 was considered to reflect a stenosis > 50%.[8] Additional MRA may be performed in case of restenosis at the preference of the treating vascular surgeon.

## Data analysis

Statistical analysis was performed with SPSS version 15.0 software (SPSS Inc, Chicago, IL, USA). In univariate analysis, the association between baseline data and restenosis was tested for significance with the Cox regression analysis. Hazard ratios (HR) were calculated. The 95% confidence intervals (CI) not containing 1 or values

of P < 0.05 were considered statistically significant. To test independency of the univariate variables, multivariate Cox regression analysis (with backward exclusion of nonsignificant variables using likelihood ratio test) was performed. Variables showing an association with restenosis (P < 0.1) in univariate analysis were included in the multivariate analysis. Furthermore, age, sex, and operation indication were always included in the multivariate analysis models.

# Results

The study included 90 consecutive patients (74% men) undergoing unilateral RSFAE between February 2003 and October 2007. The baseline patient characteristics are summarized in Table 1. Mean patient age was 67 years. In 72 patients (80%) Rutherford category 3 was the indication for operation. Median duration of ischemic walking complaints due to SFA occlusion before surgery was 56 months (range: 4-303 months).



A restenotic lesion was diagnosed in 57 patients (63%) within 12 months after RSFAE, including one patient with an early restenosis (< 30 days). Of the 57 patients with restenosis, 47 (82%) were symptomatic. 34 patients (72%) had claudication complaints (Rutherford category 2 or 3). 8 (17%) presented with critical leg ischemia (Rutherford category 4), and 3 (6%) had tissue loss (Rutherford category 5). In addition, 2 patients (4%) were readmitted with acute critical leg ischemia.

In univariate analysis, gender was associated with restenosis. A restenotic lesion was found in 19 of 23 women (83%) and in 38 of 67 men (57%) within 12 months (p = 0.001). The other baseline characteristics and peroperative results, as presented in Tables 1 and 2, did not influence the restenosis rate significantly.

Patients with longer time interval between the start of ischemic complaints and RSFAE revealed higher incidence of restenosis. Median duration of ischemic walking complaints before surgery was 65 months (range, 3-303 months) for patients with restenosis and 28 months (range, 3-248 months) in patients without restenosis (Figure 2). Risk of restenosis increased with 30% (HR 1.27 [95% CI 1.05-1.52]) per 4 years of ischemic walking complaints (p = 0.012; Table 1).

Histopathologic analysis of the excised atherosclerotic plaques revealed that all femoral arteries were totally occluded at the time of RSFAE and the atherosclerotic plaque was dissected between intima and media as a circular core (Figure 1).
A small perimeter of the plaque was significantly associated with restenosis. Median

plaque perimeters were 16.9 +/- 4.9 mm in patients with restenosis and 20.2 +/- 4.7 mm in those without restenosis (p = 0.01; Table 2). Patients with a plaque perimeter smaller than the median (< 17.6 mm) had a significantly higher risk of restenosis than patients with a larger perimeter (Figure 3). The risk of restenosis decreased by 46% per 10 mm increase of plaque perimeter (HR 0.54 [95% CI 0.34-0.88]; p = 0.01).

Consistent with the results of the plaque perimeter, median diameters of the SFA lumen, as measured on perioperative angiography, were significantly smaller in patients with restenosis (5.6 mm) compared with patients without restenosis (6.4 mm; Table 2). The risk of restenosis decreases by 54% per 1.5 mm increase of lumen diameter as measured on the perioperative angiography (HR 0.46 [95% CI 0.27-0.78]; p = 0.004).

## Multivariate analysis

Because sex, time interval between ischemic complaints and RSFAE, plaque perimeter, and lumen diameter on peroperative angiography were associated with 1-year restenosis, these variables were consequently entered in multivariate Cox hazard regression analysis. Age and operation indication (Rutherford category) were always included in the multivariate analysis models. In multivariate analysis, age (HR 1.61 [95% CI: 1.03-2.53]; p = 0.04), duration of ischemic walking complaints (HR 1.29 [95% CI: 1.03-1.62]; p = 0.03), and lumen diameter (HR 0.37 [95% CI: 0.19-0.72]; p < 0.01) were independently associated with increased risk of restenosis after RSFAE (Table 3).

| Characteristics | All patients (n=90) | | Restenosis (n=57) | | No restenosis (n=33) | | Hazard ratio[b] (95% CI) | p-value[b] |
|---|---|---|---|---|---|---|---|---|
| **Age, mean (range), years** | 67 | (50-84) | 67 | (50-83) | 67 | (52-84) | 1.18(0.85-1.65) | 0.33 |
| **Sex** | | | | | | | | |
| Male | 67 | (74) | 38 | (67) | 29 | (88) | 0.39(0.22-0.69) | 0.001* |
| Female | 23 | (26) | 19 | (33) | 4 | (12) | - | |
| **Current smoker** | 39 | (43) | 23 | (40) | 16 | (50) | 0.76 (0.45-1.30) | 0.32 |
| **Hypertension** | 59 | (66) | 38 | (67) | 21 | (64) | 0.99(0.99-1.01) | 0.62 |
| **Diabetes Mellitus** | 27 | (30) | 17 | (30) | 10 | (30) | 1.51(0.84-2.73) | 0.17 |
| **Hypercholesterolemia** | 63 | (70) | 42 | (74) | 21 | (64) | 1.40(0.77-2.52) | 0.27 |
| **Body mass index, mean (range)** | 26 | (3.1) | 26 | (21-35) | 27 | (17-32) | 0.98(0.90-1.08) | 0.73 |
| **Clinical presentation**[c] | | | | | | | | |
| Rutherford class III | 72 | (80) | 50 | (88) | 22 | (67) | 2.46(0.34-17.92) | 0.38 |
| Rutherford class IV | 12 | (13) | 6 | (11) | 6 | (18) | 1.99(0.24-16.66) | 0.53 |
| Rutherford class V | 6 | (7) | 1 | (1) | 5 | (15) | reference | |
| **Duration of ischemic walking complaints, median (range), months** | 56 | (4-303) | 65 | (3-303) | 28 | (3-248) | 1.27(1.05-1.52) | 0.01* |
| **Patent runoff arteries** | | | | | | | | |
| 1 artery | 9 | (10) | 6 | (11) | 3 | (10) | 1.43 (0.59-3.48) | 0.44 |
| 2 arteries | 32 | (36) | 23 | (40) | 9 | (29) | 1.46 (0.84-2.53) | 0.19 |
| 3 arteries | 47 | (52) | 28 | (49) | 19 | (61) | reference | |
| Missing | 2 | (2) | 0 | (0) | 2 | (6) | | |

**Table 1.** Clinical Characteristicsa

aData are presented as No.(%) unless otherwise indicated

bCox regression analysis

cComparison of Rutherford class II-III and Rutherford class IV vs. reference

*P < 0.05

| Characteristics | All patients (n=90) | | Restenosis (n=57) | | No restenosis (n=33) | | Hazard ratio[a] (95% CI) | p-value[a] |
|---|---|---|---|---|---|---|---|---|
| **Operation time, mean (range), minutes** | 124 | (70-190) | 121 | (70-187) | 129 | (70-190) | 0.80 (0.62-1.05) | 0.10 |
| **Blood loss, mean (range), ml** | 246 | (50-1200) | 228 | (50-500) | 280 | (50-1200) | 0.68 (0.43-1.07) | 0.96 |
| **Length of dissected intima core, median (SD), cm** | 27 | (5.6) | 25 | (6) | 28 | (4) | 0.97 (0.92-1.02) | 0.24 |
| **Lumen diameter on peri-operative angiography, median (SD), mm** | 5.7 | (1.0) | 5.6 | (0.9) | 6.4 | (1.0) | 0.46 (0.27-0.78) | 0.004* |
| **Perimeter of the plaque, median (SD), mm** | 17.6 | (5.1) | 16.9 | (4.9) | 20.2 | (4.7) | 0.54 (0.34-0.88) | 0.01* |

**Table 2.** Peroperative results

[a]Cox regression analysis

| Characteristics | Hazard ratio (95% CI) | p-value |
|---|---|---|
| **Age, per 10 years** | 1.61 (1.03-2.53) | 0.04* |
| **Sex** | | |
| Male | - | ns |
| Female | - | |
| **Clinical presentation** | | |
| Rutherford class II-III | - | ns |
| Rutherford class IV | - | |
| Rutherford class V-VI | - | |
| **Duration of ischemic walking complaints, per 4 years** | 1.29 (1.03-1.62) | 0.03* |
| **Perimeter of the plaque, per 10mm** | - | ns |
| **Lumen diameter, per 1.5mm** | 0.37 (0.19-0.72) | < 0.01* |

**Table 3.** Multivariate Cox Regression Analysis[a]

Abbreviations: CI, confidence interval; ns, not significant (removed from the multivariate model based on likelyhood ratio)

[a] Cox regression analysis with backward exclusion of non-significant variables using likelihood ratio test

* $P < 0.05$

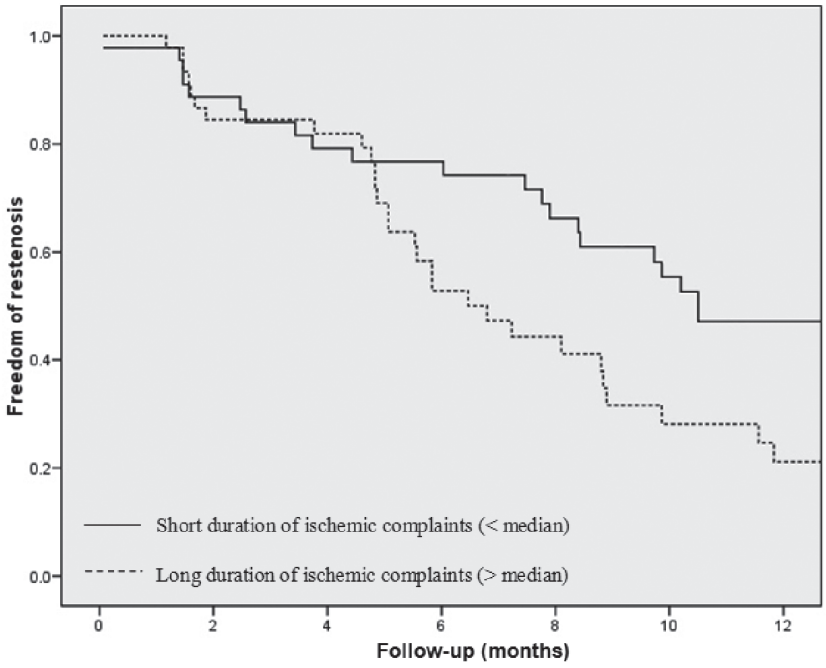




**Figure 2.** Restenosis in relation to duration of ischemic walking complaints

Patients with longer duration of ischemic walking complaints (> median) due to superficial femoral artery occlusion revealed a significantly ($p = 0.01$) higher incidence of restenosis in the first 12 months postoperatively than patients with shorter duration of ischemic walking complaints (< median).

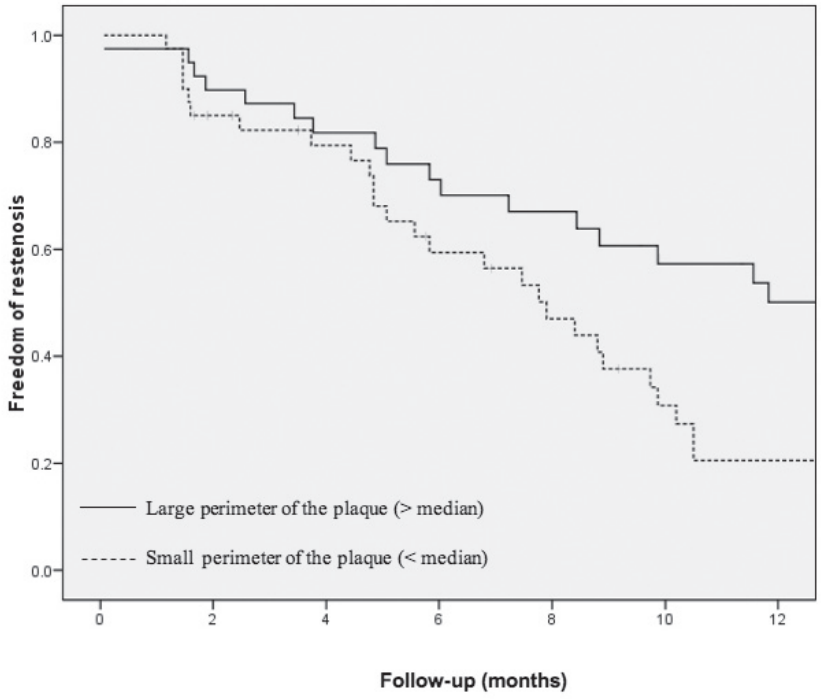




**Figure 3.** Restenosis in relation to plaque perimeter

Patients with a smaller perimeter of the plaque (< median) revealed significantly (p = 0.01) higher incidence of restenosis in the first 12 months postoperatively than patients with a larger perimeter of the plaque (> median).

# Discussion

Restenosis is a drawback in the first year after RSFAE; thus far, predictive clinical variables for restenosis are not available. This study shows that SFA diameter, age, and interval between occurrence of ischemic walking complaints and the RSFAE procedure are predictive for restenosis after RSFAE. These findings may have an effect in clinical practice. RSFAE should be reconsidered in older patients, in patients with a long history of ischemic complaints, and in patients with small SFA diameter. Follow-up and treatment of restenosis may need to be more aggressive for these subgroups.

In research considering peripheral arterial disease, little is known about arterial size in relation to restenosis, although, a recent study of bypass surgery showed an increase of graft restenosis as graft diameter diminished.[9] In cardiology, vessel size is well established as an important determinant of an adverse outcome after revascularization.[10-12] It is biologically plausible that a reduction in luminal diameter by a constant amount of neointimal hyperplasia results in a proportionally higher-grade of restenosis in small compared with large vessels. Revascularization results in arterial injury, initiating a proliferative vascular cascade that causes smooth muscle cell proliferation and migration resulting in neointimal hyperplasia.[13] The amount of neointimal hyperplasia is largely independent of vessel size, and thus late luminal loss, an angiographic measure of neointimal hyperplasia, is similar across a wide range of vessel diameters.[12] Accordingly, small vessels are more prone to restenosis than larger vessels because they are less able to accommodate neointimal tissue without compromising blood flow.[13]



This study found gender was not an independent predictive variable for restenosis, although in univariate analysis women showed significant more restenosis than men. Published reports indicate gender differences in the risk of restenosis can be explained by the physical size of the patient. Although coronary artery diameter is highly related to body size, women have smaller coronary arteries than men after accounting for differences in body size. These findings further support the hypothesis that smaller coronary arteries explain higher perioperative mortality with coronary artery bypass grafting and poorer outcomes with other treatments for coronary disease in women and smaller people.[10, 14, 15]

We can only speculate about the predictive value of the duration of ischemic walking complaints due to SFA occlusion for restenosis. In most cases, the SFA is occluded for a long period and will be fibrous. Fibrous plaques have previously been associated with arterial shrinkage resulting in smaller vessel size.[16, 17] Our results sug-

gest that longer occlusion time and subsequent arterial fibrotic shrinkage may result in a smaller residual lumen after intervention which makes the artery more prone to develop restenosis.

This study may have important implications for the care and treatment of patients with arterial obstructive disease in the SFA. Structured exercise and medical treatment are the initial approach to the treatment of intermittent claudication. Failure to respond to this would lead to limb revascularization.[1] Accordingly, almost all patients undergo operations after a long period of ischemic complaints. The median duration of ischemic walking complaints in our study was 56 months before surgery. As was explained, a likely assumption is that the occluded fibrous femoral artery will shrink over time. Subsequently, patients with longer duration of ischemic complaints will have smaller arteries with a higher restenosis rate. Therefore, our findings lead to a recommendation of a more aggressive treatment strategy in a subgroup of patients. The major challenge however, is to identify the subgroup of patients who would benefit from this aggressive treatment; consequently, a longitudinal study is required to support this concept.

Known factors influencing outcomes after percutaneous intervention include the extent of the disease, use of a stent, amount of calcification, and runoff below the knee.[5, 18-20] Factors influencing the outcome of bypass surgery focus on the quality of the bypass (graft diameter, graft length and type of bypass) instead of the extent and severity of the lesion.[5, 9] Similar to percutaneous interventions, bypass surgery for tissue loss has worse outcomes compared with bypass for claudication.[21, 22] The reason for this is not fully understood and is not simply explained by inflow and outflow levels, because distal origin grafts as well as pedal bypass grafts have durable results.[5, 23]



In this study, runoff, TASC classification and operation indication were not associated with restenosis after RSFAE. It is notable that recent reports concerning RSFAE also show no relation between these variables and restenosis.[2, 24]

Our study has several potential limitations. Our data are prospectively obtained but are retrospectively analyzed. Findings of this study have to be confirmed in a larger randomized study. Our findings are based on a relatively small patient group, and confirmation in a larger cohort is required.

This study is the first study to provide clinical characteristics that are predictive for RSFAE restenosis in the first year. Clinicians should reconsider RSFAE in older patients, patients with a longer history of ischemic complaints and in patients with small SFA diameter. Follow-up and treatment of restenosis may need to be more aggressive for these subgroups.

# Conclusion

This study provides evidence that age, vessel size, and duration of ischemic walking complaints before RSFAE are predictive values for restenosis after RSFAE.

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# 8 General discussion and summary

## Peripheral arterial disease

The prevalence of peripheral arterial occlusive disease in the general population is approximately 3-10%, increasing to 15-20% in persons over 70 years of age.[1] This chronic disease is therefore an increasing concern in an aging population. Atherosclerosis is a generalized condition, hence, patients presenting with a symptomatic lesion, are likely to have other manifestations of vascular disease. Peripheral arterial disease, coronary artery disease and cerebrovascular disease commonly occur together. For women in the Netherlands, cardiovascular disease is still the main cause of death, and, in the Dutch population accounts for 40.129 deaths last year, 30% of all cause mortality.[2] Besides, once diagnosed with peripheral arterial disease, prognosis is poor. Patients presenting with chronic critical limb ischemia suffer from 25% mortality in the first year after presentation due to fatal cardiovascular events.[3] The superficial femoral artery (SFA) is most commonly affected, 70% of patients with peripheral arterial disease present with an obstructive lesion in this artery, with a preference for the adductor canal hiatus.[4,5]

## Remote superficial femoral artery endarterectomy

These are all reasons for continuous development of new (surgical) techniques,

cardiovascular risk factor identification and modification and improvement of prevention strategies. One such new SFA desobstruction technique is the minimal invasive remote superficial femoral artery endarterectomy (RSFAE), which preserves the native artery in its continuity. This technique is especially applicable for long (>20 cm) occlusions of the SFA (Trans-Atlantic Inter-Society Consensus[1] [TASC] C and D lesions), where other minimal invasive techniques such as percutaneous transluminal angioplasty (PTA) fail. A main concern following this procedure remains the significant early (< 1 year) restenosis rate, caused by neointimal hyperplasia.

## Aim of this thesis

This thesis focuses on determinants for successful RSFAE and defines its role in the spectrum of treatment options for long-segment chronic SFA occlusive disease.

## Summary and future perspectives

**Chapter 2** reviews current treatment modalities for peripheral arterial disease caused by SFA obstruction. Supportive and preventive medical treatment options, risk factor modification as well as interventional strategies, endovascular and surgical, are described. Moreover, a view to future perspectives is provided, with fields for improvement and implications for future research. The conclusion focuses on restorative interventions and systemic and local drug therapy to suppress neointimal hyperplasia

and prevent restenosis.

Previous retrospective trials and cohort studies have shown promising patency rates for RSFAE. A recent systematic review showed a primary patency rate of 60%, 57% and 35% at 1, 2 and 5 years of follow-up respectively.[6] However, no randomised trials have been performed so far comparing RSFAE with the most established surgical procedure; the supragenicular bypass.

In **chapter 3** and **chapter 4** we compared the patency rates of RSFAE and supragenicular bypass surgery (venous and polytetrafluoroethylene [PTFE]) in the treatment of SFA occlusive disease in a multicentre randomised trial. Both patients with intermittent claudication (Rutherford category 3) and critical limb ischemia or tissue loss (Rutherford category 4 and 5) were included. In 4 Dutch hospitals 116 patients were randomised to RSFAE or supragenicular venous bypass surgery. When the saphenous vein was not available or not suitable (< 3 mm), a PTFE graft was constructed. In **chapter 3** short-term results are presented. The primary patency rate after 1-year follow-up was 61% for RSFAE and 73% for the combined bypass group (p = 0.094). Assisted primary patency rates were 73% and 75%, respectively (p = 0.698). Secondary patency was 79% for both groups (p = 0.953). For venous (n = 25) and prosthetic grafts (n = 30) at 1 year follow up, primary patency was 89% and 63% respectively, compared to 63% for RSFAE (p = 0.086). Median hospital stay was significantly shorter following endarterectomy: 4 days versus 6 days (p = 0.004). Postoperative complications did not differ significantly between groups. It was concluded that RSFAE is a minimally invasive option in the treatment of TASC C and D lesions of the SFA, with shorter admittance and comparable assisted primary and secondary patency rates to bypass. The venous bypass is superior to both RSFAE and PTFE bypass surgery, but only 45% of patients had a sufficient saphenous vein available.



In **chapter 4** the follow-up has been prolonged to a median of 37 months. This includes 20% mortality in the bypass group and 13% mortality in the endarterectomy group (p = 0.317). Primary patency after 3-years follow-up was 47% for RSFAE and 60% for the combined bypass group (p = 0.107). Assisted primary patency was 63% and 69% respectively (p = 0.406). Secondary patency was 69% versus 73% (p = 0.541). Subdividing between venous and prosthetic grafts compared to RSFAE shows a primary patency of 65% and 56% (p = 0.143), an assisted primary patency of 84% and 56% (p = 0.052) and a secondary patency of 89% and 59% (p = 0.046) respectively at 3-years follow-up. Limb salvage was 97% after RSFAE and 95% after bypass surgery (p = 0.564). The medium-term results support the conclusion that RSFAE is a true alternative for surgical repair of TASC C and D SFA obstructions, with comparable assisted primary and secondary patency rates to bypass surgery at 3 years follow-up, with superior results for the venous bypass. If the saphenous vein is not applicable,

RSFAE should be considered because it is less invasive and prosthetic graft material can be avoided. For the future, long-term results of the REVAS trial can be expected in 2 years. These trial results will definitely establish RSFAE in the spectrum of treatment options for long-segment SFA occlusive disease.

Despite aggressive treatment of recurrent stenoses, the reobstruction rate following RSFAE caused by neointimal hyperplasia remains considerable. Other strategies are to be developed to avoid early restenosis and improve patency. In **chapter 5** we addressed this issue. In a pilot study including 17 patients the desobstructed SFA was concomitantly treated with cryoplasty. Cryoplasty is thought to provoke apoptosis in arterial smooth muscle cells rather than necrosis, preventing migration and proliferation of smooth muscle cells, and thus reducing neointimal hyperplasia.[7] Debulking of the intima core during RSFAE seems the optimal preliminary treatment to maximize the effect of cryoplasty. Dissection on the level of the internal elastic lamina leaves the proliferative cells of the media bare and possibly more sensitive to the apoptotic effect of supercooling and therefore reduces the stimulus for cellular migration and proliferation into the vessel lumen. The primary patency rate at 1-year follow-up was 74%, compared to 61% in our previous trial. Moreover, in eight patients the use of a stent at the distal transection zone could be ommited; cryoplasty alone proofed to be sufficient in securing the transection zone. There were no perioperative adverse events. It was concluded that although these results are promising, they need confirmation in a larger, preferably randomised trial. Moreover, future research should focus on alternative methods to oppose neointimal hyperplasia, such as the development of drug eluting stents and concomitant treatment of the desobstructed SFA with Paclitaxel coated balloons. For PTA promising results have been described[8] and perhaps results will improve after surgically debulking the SFA, equivalent to cryoplasty. In addition, systemic medical treatment might offer an additive effect on maintaining patency. Dual antiplatelet therapy consisting of clopidogrel and acetylsalicylic acid has been shown to improve outcome in patients after endovascular treatment for femoropopliteal occlusions compared with acetylsalicylic acid alone.[9] After RSFAE, a large thrombogenic surface remains, and therefore these patients might benefit even more from this medical strategy. Cilostazol may have additional advantages over other platelet inhibitors. It has been demonstrated to inhibit neointimal formation by improving endothelial function and induction of apoptosis in smooth muscle cells.[10] Future studies should analyse whether these strategies are of additional value for patients after RSFAE.

Moderate alcohol consumption has been consistently associated with a lower risk for myocardial infarction, stroke, peripheral arterial occlusive disease, and type 2 diabetes.[11-15] Atherosclerosis is a generalized condition with a segmental distribu-

tion. It is well established, that atherosclerotic plaques which contain more inflammation (e.g. presence of macrophages) and larger lipid cores, are related to unstable coronary syndromes and symptomatic cerebrovascular disease.[16,17] Whether patients with clinical presentation of peripheral arterial or cerebrovascular disease would benefit from the effects of alcohol and whether alcohol is associated with atherosclerotic plaque composition remains unknown. In **chapter 6** we analysed the association between alcohol intake, cardiovascular events, and atherosclerotic plaque characteristics in patients undergoing femoral or carotid endarterectomy. The atherosclerotic plaques of 224 patients following femoral endarterectomy and 693 patients following carotid endarterectomy were evaluated for the presence of collagen, calcifications, smooth muscle cells, macrophages, fat, and intraplaque thrombus. Clinical parameters, including alcohol consumption habits, were recorded at baseline. The primary endpoint was a composite endpoint "major cardiovascular event" and included cardiovascular and cerebrovascular death, myocardial infarction, coronary artery bypass grafting, coronary angioplasty, and stroke. After mean follow-up of 25 months patients in the femoral group who abstained from alcohol had significantly more major cardiovascular events than those who consumed alcohol. The Kaplan-Meier estimate of event rate after 3 years of follow-up was 35% for no alcohol and 21% for 1-10 U/wk, whereas only 10% of the >10 U/wk group had sustained a major cardiovascular event ($p = 0.010$). In the carotid cohort the event rate did not differ significantly: 11% for no alcohol, 15% for 1-10 U/wk, and 17% for >10 U/wk ($p = 0.618$). Plaques of the femoral study population revealed larger lipid cores and more macrophage infiltration in patients abstaining from alcohol than in patients consuming alcohol, with a dose-response relationship: 47% of the plaques in the no alcohol group had a lipid core larger than 10% versus 28% for the 1-10 U/wk group and 19% for the >10 U/wk group ($p = 0.002$). In the no alcohol group 33% of the plaques showed moderate or heavy macrophage infiltration versus 26% in the 1-10 U/wk group and 17% for >10 U/wk group ($p = 0.033$). In the carotid study population, such a relationship was not observed. In multivariate Cox hazard regression analysis only alcohol consumption remained independently associated with a decreased risk for major cardiovascular events, with a hazard ratio of 0.52 (95% CI 0.33-0.81; $p = 0.004$). It was concluded that this study shows an inverse relationship between alcohol use and major cardiovascular events after endarterectomy for peripheral arterial occlusive disease, accompanied by a more stable plaque phenotype. However, no such relationship could be observed for patients with cerebrovascular disease. An explanation could be that peripheral arterial interventions are generally initiated in a more advanced stage of atherosclerosis than cerebrovascular disease, with a worse prognosis. Patients presenting with chronic critical limb ischemia have a 20% mortality in the first year

after presentation, whereas the mortality rate for patients with cerebrovascular disease is 27% at 6 years of follow-up.[1,18] This is supported by the fact that the event rate was much lower in the carotid cohort. Alcohol might influence the stabilization process during aging of the atherosclerotic plaque. This of course, remains to be investigated in future trials.

In our search for improvement of patency rates following RSFAE it is important to identify determinants predicting failure. **In chapter 7** patient characteristics with predictive value for restenosis during the first year following RSFAE were investigated. Ninety patients post-RSFAE were included and studied for the occurrence of restenosis in the first 12 months postoperatively. At baseline, clinical parameters were recorded. Vessel size was measured on the basis of plaque perimeter in the culprit lesion on cross-sections of the harvested plaque, and lumen diameter on peroperative digital subtraction angiography. In 57 patients (63%) a restenotic lesion was diagnosed within 12 months following surgery. Patients with longer time interval between start of ischemic walking complaints and RSFAE revealed a significantly higher incidence of restenosis (Hazard Ratio [HR] 1.27 [95% confidence interval [CI] 1.05-1.52] per 4 years; p = 0.012). Small plaque perimeter and small SFA diameter on angiography were significantly associated with restenosis (HR 0.54 [95% CI 0.34-0.88] per 10 mm; p = 0.010 and HR 0.46 [95% CI 0.27-0.78] per 1.5 mm; p = 0.004, respectively). In multivariate analysis, age (HR 1.61 [95% CI: 1.03-2.53]; p = 0.040), duration of time interval between start of ischemic walking complaints and RSFAE (HR 1.29 [95% CI: 1.03-1.62]; p = 0.030) and lumen diameter (HR 0.37 [95% CI: 0.19-0.72]; p < 0.010) were independently associated with increased risk of restenosis after RSFAE. It was concluded that age, vessel size, and time interval between start of ischemic walking complaints and RSFAE are predictive values for restenosis following RSFAE. Older age is a known risk factor for restenosis following carotid endarterectomy, in contrast, following peripheral bypass surgery, younger age has been associated with restenosis.[19,20] This trial is the first to describe older age as a risk factor for restenose following RSFAE. Smaller graft size in peripheral bypass surgery as well as smaller coronary artery size in coronary angioplasty are known determinants of adverse outcome after revascularisation.[20] These results are consistent with our trial results. Eventually, duration of ischemic complaints as a risk factor has not been described before. Structured exercise and medical treatment are the initial approach to the treatment of intermittent claudication. This strategy leads to delayed surgical treatment. The median duration of ischemic walking complaints before surgery was 56 months. We assume, as has been demonstrated before, that the occluded femoral artery becomes fibrous and will shrink over time.[21] Subsequently, patients with longer duration of ischemic complaints will have smaller and fibrous arteries with a higher

restenosis rate, although, in multivariate analysis, duration of ischemic complaints was independently associated with restenosis. In addition, it has been demonstrated that dissection of a lipid-poor plaque, with none or minor macrophage infiltration, is associated with increased risk of future restenosis following carotid endarterectomy.[22] Whether these results apply to patients with peripheral arterial disease is subject of investigation. Future research should focus on atherosclerotic plaque composition in relation to restenosis following RSFAE in patients with peripheral arterial disease.

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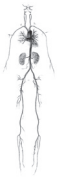
# 9



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# Nederlandse samenvatting

## Perifeer vaatlijden

De prevalentie van perifeer vaatlijden in de algemene populatie is ongeveer 3-10%, en neemt toe tot 15-20% bij patiënten ouder dan 70 jaar.[1] Deze chronische ziekte is derhalve een toenemend probleem in een vergrijzende populatie. Atherosclerose is een gegeneraliseerde conditie, daarom hebben patiënten die zich presenteren met een symptomatische laesie zeer waarschijnlijk ook andere manifestaties van hart- en vaatziekten. Perifeer vaatlijden, coronair vaatlijden, en cerebrovasculair vaatlijden komen vaak samen voor. Voor Nederlandse vrouwen is cardiovasculaire ziekte nog steeds de belangrijkste doodsoorzaak, en afgelopen jaar verantwoordelijk voor 40.129 doden in de Nederlandse samenleving; 30% van de totale mortaliteit.[2] Daarnaast is de prognose somber wanneer perifeer vaatlijden eenmaal is gediagnosticeerd. Patiënten met kritieke ischaemie hebben een mortaliteit van 25% ten gevolge van fatale cardiovasculaire incidenten in het eerste jaar na presentatie.[3] De arteria femoralis superficialis (AFS) is het meest frequent aangedaan; 70% van de patiënten met perifeer vaatlijden hebben een obstructieve laesie in deze arterie, met een voorkeur voor de hiatus canalis adductorii.[4,5]



## Remote endarteriëctomie van de arteria femoralis superficialis

Dit zijn redenen voor voortdurende ontwikkeling van nieuwe (chirurgische) technieken, het identificeren en modificeren van cardiovasculaire risicofactoren, en het verbeteren van preventie strategieën. De minimaal invasieve remote endarteriëctomie (RE) is één zo'n nieuwe techniek, waarbij de AFS wordt gedesobstrueerd, en de natieve arterie derhalve in zijn continuïteit wordt gepreserveerd. Deze techniek is vooral geschikt voor lange (> 20 cm) occlusies van de AFS (Trans-Atlantic Inter-Society Consensus[1] [TASC] C and D laesies), waar andere minimaal invasieve technieken, zoals percutane transluminale angioplastiek (PTA), falen. De aanzienlijke mate van vroege (< 1 jaar) restenose na deze procedure, veroorzaakt door neointima hyperplasie, blijft echter een belangrijk probleem.

## Doel van dit proefschrift

Dit proefschrift richt zich op determinanten voor succesvolle RE en definieert de rol van RE in het spectrum van behandelingsmogelijkheden voor chronische lange occlusies van de AFS.

## Samenvatting en toekomst perspectieven

In **hoofdstuk 2** worden de huidige behandelingsmodaliteiten voor perifeer vaatlijden op basis van een AFS obstructie weergegeven. Ondersteunende en preventieve medicamenteuze behandelopties, modificatie van risicofactoren alsmede endovasculaire en chirurgische interventiestrategieën worden beschreven. Bovendien worden toekomst perspectieven verschaft, met suggesties voor toekomstig wetenschappelijk onderzoek en aspecten voor verbetering. De conclusie richt zich op restoratieve interventies en systemische en locale medicamenteuze therapie om neointima hyperplasie te onderdrukken en zo restenose te voorkomen.

Eerdere retrospectieve studies en cohort onderzoeken hebben veelbelovende patency percentages laten zien voor RE. Een recente systematische review liet een primaire patency van 60%, 57% en 35% zien na respectievelijk 1, 2 en 5 jaar follow-up.[6] Er zijn echter nog geen gerandomiseerde studies verricht welke RE vergelijken met de meest gangbare chirurgische procedure; de supragenuale bypass. In **hoofdstuk 3** en **hoofdstuk 4** wordt de patency vergeleken van RE en supragenuale bypass chirurgie (veneus en polytetrafluoroethylene [PTFE]) voor AFS occlusies, in een multicenter gerandomiseerd onderzoek. Zowel patiënten met claudicatio intermittens (Rutherford categorie 3) als patiënten met kritische ischaemie en gangreen (Rutherford categorie 4 en 5) werden geïncludeerd. In 4 Nederlandse ziekenhuizen werden 116 patiënten gerandomiseerd tussen RE of supragenuale veneuze bypass chirurgie. Indien de vena saphena magna niet aanwezig of niet geschikt (< 3 mm) was, werd een PTFE bypass geconstrueerd. In **hoofdstuk 3** worden de korte termijn resultaten gepresenteerd. De primaire patency na 1 jaar follow-up was 61% voor RE en 73% voor de gecombineerde bypass groep (p = 0.094). De geassisteerde primaire patency was respectievelijk 73% en 75% (p = 0.698). De secundaire patency was 79% in beide groepen (p = 0.953). Voor veneuze (n = 25) en kunststof (n = 30) bypasses was de primaire patency respectievelijk 89% en 63%, vergeleken met 63% voor RE (p = 0.086). De mediane opnameduur was significant korter na RE: 4 versus 6 dagen (p = 0.004). De postoperatieve complicaties verschilden niet significant tussen beide groepen. Er werd geconcludeerd dat RE een minimaal invasieve optie is om TASC C en D laesies van de AFS te behandelen, met een kortere opnameduur en vergelijkbare geassisteerde primaire en secundaire patency percentages als bypass chirurgie. De veneuze bypass is superieur zowel ten opzichte van RE als de kunststof bypass, maar slechts 45% van de patiënten had een geschikte of aanwezige vena saphena magna.

In **hoofdstuk 4** is de follow-up verlengd tot mediaan 37 maanden. Dit is inclusief 20% mortaliteit in de bypass groep en 13% mortaliteit in de RE groep (p = 0.317). De primaire patency na 3 jaar follow-up was 47% voor RE en 60% voor de gecombineer-

de bypass groep (p = 0.107). De geassisteerde primaire patency was respectievelijk 63% en 69% (p = 0.406). De secundaire patency was 69% versus 73% (p = 0.541). Een onderverdeling tussen veneuze en kunststof bypasses in vergelijking met RE toont respectievelijk een primaire patency van 65% en 56% (p = 0.143), een geassisteerde primaire patency van 84% en 56% (p = 0.052) en een secundaire patency van 89% en 59% (p = 0.046) na 3 jaar follow-up. Limb salvage was 97% na RE en 95% na bypass chirurgie (p = 0.564). De middenlange termijn resultaten ondersteunen de conclusie dat RE een waar alternatief is voor chirurgisch herstel van TASC C en D AFS obstructies, met een vergelijkbare geassisteerde primaire en secundaire patency als bypass chirurgie na 3 jaar follow-up, met superieure resultaten voor de veneuze bypass. Als de vena saphena magna niet toepasbaar is zou RE overwogen moeten worden, omdat het minder invasief is en implantatie van kunststof materiaal vermeden kan worden. Voor de toekomst: de lange termijn resultaten van de REVAS studie kunnen over 2 jaar worden verwacht. Deze studie resultaten zullen RE definitief vestigen in het spectrum van behandelopties voor lange occlusies van de AFS.

Ondanks agressieve behandeling van restenosen blijft het reocclusie percentage na RE ten gevolge van neointima hyperplasie aanzienlijk. Er moeten andere strategieen worden ontwikkelt om vroege restenose te voorkomen en daarmee de patency te verbeteren. In **hoofdstuk 5** wordt deze kwestie behandeld. In een pilot studie waarbij 17 patiënten werden geïncludeerd, werd de gedesobstrueerde AFS aansluitend behandeld met cryoplastiek. Cryoplastiek veroorzaakt apoptose in plaats van necrose in arteriële gladde spiercellen, waardoor migratie en proliferatie van gladde spiercellen wordt voorkomen, en zo neointima hyperplasie wordt gereduceerd.[7] Debulking door het verwijderen van de intima kern tijdens RE lijkt de optimale voorbereiding om het effect van cryoplastiek te maximaliseren. Dissectie op het niveau van de lamina elastica interna legt de proliferatieve cellen van de media bloot en mogelijk ontvankelijker voor het apoptotische effect van bevriezing, waardoor de stimulus voor celmigratie en celproliferatie in het arterielumen wordt verminderd. De primaire patency na 1 jaar follow-up was 74%, vergeleken met 61% in onze eerdere studie zonder aanvullende cryoplastiek. Bovendien kon in 8 patiënten een stent op de distale transectiezone worden vermeden; cryoplastiek alleen bewees voldoende te zijn om de overgangszone te zekeren. Er waren geen perioperatieve complicaties. Er werd geconcludeerd dat ondanks dat deze resultaten veelbelovend zijn, ze bevestigd moeten worden in een groter, bij voorkeur gerandomiseerd onderzoek. Toekomstig onderzoek zou zich bovendien moeten richten op alternatieve methoden om neointima hyerplasie te voorkomen, zoals de ontwikkeling van drug eluting stents en aanvullende behandeling van de gedesobstrueerde AFS met Paclitaxel gecoate ballonnen. Er zijn goede resultaten beschreven voor PTA in combinatie met Paclitaxel[8] en wellicht zullen de resultaten

verbeteren wanneer chirurgische debulking van de AFS heeft plaats gevonden, analoog aan cryoplastiek. Daarnaast heeft systemische medicamenteuze behandeling wellicht een additief effect om de patency te handhaven. Van duale thrombocytenaggregatieremmende therapie bestaande uit clopidogrel en acetylsalicylzuur is aangetoond dat het de uitkomst verbeterd bij patiënten na endovasculaire behandeling van femoropopliteale occlusies ten opzichte van monotherapie met acetylsalicylzuur.[9] Na RE resteert een groot thrombogeen oppervlak, en daarom heeft deze patiëntengroep wellicht meer baat bij deze medicamenteuze strategie. Cilostazol heeft wellicht aanvullende waarde ten opzichte van andere thrombocytenaggregatieremmers. Van cilostazol is aangetoond dat het de neointima vorming remt doordat het de endotheelfunctie verbeterd en apoptose induceert in gladde spiercellen[10] Toekomstig onderzoek zou de aanvullende waarde van deze geopperde strategieën voor RE patiënten moeten onderzoeken.

Gematigd alcoholgebruik wordt consequent geassocieerd met een lager risico op myocardinfarct, herseninfarct, perifeer vaatlijden en diabetes mellitus type 2.[11-15] Atherosclerose is een gegeneraliseerde aandoening, met een segmentale distributie. Het is bekend dat atherosclerotische plaques met meer inflammatie (zoals de aanwezigheid van macrofagen) en een grotere vetkern, zijn gerelateerd aan instabiele coronaire syndromen en symptomatische cerebrovasculaire ziekte.[16,17] Of patiënten met perifeer of cerebrovasculair vaatlijden baat hebben bij alcohol gebruik en of alcohol is geassocieerd met de samenstelling van atherosclerotische plaques is onbekend. In **hoofdstuk 6** werd de relatie tussen alcoholgebruik, cardiovasculaire incidenten en atherosclerotische plaque karakteristieken onderzocht in patiënten na femoralis of carotis endarteriëctomie. De atherosclerotische plaques van 224 patiënten na femoralis endarteriëctomie en van 693 patiënten na carotis endarteriëctomie werden onderzocht op de aanwezigheid van collageen, calcificaties, gladde spiercellen, macrofagen, vet en intraplaque thrombus. Preoperatief werden klinische parameters, waaronder alcohol consumptie gewoontes, geregistreerd. Het primaire eindpunt was een samengesteld eindpunt “majeur cardiovasculair incident” en omvatte cardiovasculair en cerebrovasculair overlijden, myocardinfarct, coronair arterie bypass grafting, percutane transluminale coronair angioplastiek en herseninfarct. Na een gemiddelde follow-up van 25 maanden hadden patiënten in de femoralis groep die zich onthielden van alcohol significant meer majeure cardiovasculaire incidenten dan patiënten die alcohol gebruikten. De Kaplan-Meier raming van het incident percentage na 3 jaar follow-up was 35% in de geen alcohol groep, 21% voor de 1-10 E/wk groep, terwijl slechts 10% van de > 10 E/wk groep een majeur cardiovasculair incident doormaakte ($p = 0.010$). In de carotis groep was het incident percentage niet significant verschillend tussen de 3 groepen: 11% voor geen alcohol, 15% voor 1-10 E/wk en 17% voor

> 10 E/wk (p = 0.618). De plaques van patiënten in de femoralis studie populatie die zich onthielden van alcohol consumptie lieten significant grotere vetkernen zien en significant meer infiltratie van macrofagen dan de plaques van patiënten die alcohol gebruikten, in een lineair verband: 47% van de plaques in de geen alcohol groep had een vetkern > 10% versus 28% voor de 1-10 E/wk groep en 19% voor de >10 E/wk group (p = 0.002). In de geen alcohol groep had 33% van de plaques matige tot forse infiltratie van macrofagen versus 26% in de 1-10 E/wk groep en 17% voor de >10 E/wk groep (p = 0.033). In de carotis studie populatie werd deze relatie niet waargenomen. In multivariate Cox hazard regressie analyse bleef alleen alcohol consumptie onafhankelijk geassocieerd met een verminderd risico op majeure cardiovasculaire incidenten, met een hazard ratio van 0.52 (95% CI 0.33-0.81; p = 0.004). Er werd geconcludeerd dat deze studie een omgekeerde lineaire relatie laat zien tussen alcohol gebruik en majeure cardiovasculaire incidenten na endarteriëctomie voor perifeer vaatlijden, gepaard gaande met een stabieler plaque phenotype. Voor cerebrovasculair vaatlijden echter, kon deze relatie niet worden aangetoond. Een mogelijke verklaring is dat patiënten met perifeer vaatlijden vaak in een verder gevorderd stadium van atherosclerose worden geopereerd, dan patiënten met cerebrovasculair vaatlijden. Ook hebben patiënten met perifeer vaatlijden een slechtere prognose dan patiënten met cerebrovasculair vaatlijden. Patiënten met chronische kritieke ischaemie hebben een mortaliteit van 20% in het eerste jaar na presentatie, terwijl patiënten met cerebrovasculair vaatlijden een mortaliteit van 27% hebben na 6 jaar follow-up.[1,18] Dit wordt ondersteund door het feit dat het incident percentage veel lager was in de carotis groep. Alcohol beïnvloed wellicht het stabilisatieproces tijdens het verouderen van de atherosclerotische plaque. Dit echter, blijft onderwerp van onderzoek in toekomstige studies.



Om de patency na RE te kunnen verbeteren, zullen we determinanten moeten identificeren die falen kunnen voorspellen. In **hoofdstuk 7** worden patiëntenkarakteristieken onderzocht die een voorspellende waarde voor restenose na RE hebben in het eerste postoperatieve jaar. Er werden 90 patiënten geïncludeerd die RE van de AFS hadden ondergaan. Zij werden onderzocht op het voorkomen van een restenose de eerste 12 maanden postoperatief. Bij inclusie werden klinische parameters genoteerd. Vaatgrootte werd gemeten aan de hand van plaque omtrek ter hoogte van de ernstigste laesie op dwarsdoorsneden van de geoogste plaque en aan de hand van lumendiameter op peroperatief verrichte digitale substractie angiografie. Bij 57 patiënten (63%) werd in de eerste 12 postoperatieve maanden een restenose gediagnosticeerd. Patiënten met een langer tijdsinterval tussen het ontstaan van de klachten en RE hadden een hogere incidentie van restenose (Hazard Ratio [HR] 1.27 [95% confidence interval [CI] 1.05-1.52] per 4 jaar; p = 0.012). Kleine plaque

omtrek en kleine AFS lumen diameter op angiografie waren significant geassocieerd met restenose (respectievelijk HR 0.54 [95% CI 0.34-0.88] per 10 mm; p = 0.010 en HR 0.46 [95% CI 0.27-0.78] per 1.5 mm; p = 0.004). In multivariate analyse waren leeftijd (HR 1.61 [95% CI: 1.03-2.53]; p = 0.040), klachten duur (HR 1.29 [95% CI: 1.03-1.62]; p = 0.030) en lumen diameter (HR 0.37 [95% CI: 0.19-0.72]; p < 0.010) onafhankelijk geassocieerd met een verhoogd risico voor restenose na RE. Er werd geconcludeerd dat leeftijd, vaatgrootte, en klachtenduur voorspellende waarde hebben voor het ontstaan van restenose na RE. Hogere leeftijd is een bekende risicofactor voor restenose na carotis endarteriëctomie, in tegenstelling tot restenose na perifere bypass chirurgie, waar juist jongere leeftijd is geassocieerd met restenose.[19,20] Dit is de eerste studie die hogere leeftijd beschrijft als een risicofactor voor restenose na RE. Zowel kleinere bypass diameter in perifere bypass chirurgie als kleiner coronair arterie lumen in coronair angioplastiek zijn bekende determinanten van ongunstige uitkomst na revascularisatie.[20] Deze resultaten zijn consistent met onze studie resultaten. Tenslotte, klachtenduur als een risicofactor voor restenose is niet eerder beschreven. De primaire benadering van de behandeling van claudicatio intermittens is gestructureerde looptherapie en medicamenteuze behandeling. Deze strategie leid tot een vertraagde chirurgische behandeling. In onze studie was de mediane klachtenduur tot operatie 56 maanden. Wij nemen aan, zoals ook eerder is aangetoond, dat de geoccludeerde arteria femoralis fibreus wordt, en krimpt met de tijd.[21] Dientengevolge zouden patiënten met een langere klachtenduur, kleinere en meer fibreuze arteriën hebben, en derhalve een hoger restenose percentage. Hoewel, in multivariate analyse, klachtenduur onafhankelijk geassocieerd was met restenose. Daarnaast is aangtoond dat dissectie van een vet-arme plaque, met weinig tot geen infiltratie van macrofagen, geassocieerd is met een verhoogd risico op restenose na carotis endarteriëctomie.[22] Of deze resultaten toepasbaar zijn op patiënten met perifeer vaatlijden blijft onderwerp van studie. Toekomstig onderzoek zou zich moeten richten op de samenstelling van atherosclerotische plaques in relatie tot restenose na RE in patiënten met perifeer vaatlijden.

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# Review committee

## Prof.dr. IHM Borel Rinkes

Department of Surgery
University Medical Center Utrecht
Utrecht, the Netherlands

## Prof.dr. ML Bots

Julius Center for Health Sciences and Primary Care
University Medical Center Utrecht
Utrecht, the Netherlands

## Prof.dr. HJM Verhagen

Department of Vascular Surgery
Erasmus Medical Center
Rotterdam, the Netherlands



## Prof.dr. FEG Vermassen

Department of Vascular Surgery
Ghent University Hospital
Ghent, Belgium

## Prof.dr. FLJ Visseren

Department of Vascular Medicine
University Medical Center Utrecht
Utrecht, the Netherlands

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1. Predictive risk factors for restenosis after remote superficial femoral artery endarterectomy. Derksen WJ, Gisbertz SS, Hellings WE, Vink A, de Kleijn DP, Moll FL, de Vries JP, Pasterkamp G. Submitted.

2. Remote endarterectomy versus supragenicular bypass surgery for long occlusions of the superficial femoral artery: medium-term results of a randomized controlled trial. [The REVAS trial]. Gisbertz SS, de Borst GJ, Hoedt MT, Ho G, Overtoom TTh, Moll FL, de Vries JP. Submitted.

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# Curriculum Vitae

Suzanne Sarah Gisbertz werd op 29 april 1974 geboren te Breda. Hier volgde zij met veel plezier het lager en middelbaar onderwijs aan de Rudolf Steiner school om in 1993 in Zeist eveneens aan de vrije school haar VWO diploma te behalen. In dat zelfde jaar begon zij de studie Geneeskunde aan de Universiteit van Amsterdam. Haar eerste wetenschappelijke schreden werden gezet als student onderzoeker in het AMC te Amsterdam, onder leiding van Dr. JW van Sandick en Prof. dr. H Obertop. In 1998 onderbrak ze haar studie voor een periode van 1 jaar voor een reis door Azië, waar ze werkte als scubaduikgids bij verschillende duikscholen in Thailand en Indonesië. Na het behalen van het Artsexamen in 2002 werkte ze 18 maanden als assistent geneeskunde niet in opleiding op de afdeling Heelkunde van het OLVG te Amsterdam (hoofd Dr. NJM Out). Op 1 januari 2004 begon zij haar opleiding tot algemeen chirurg in het St Antonius Ziekenhuis te Nieuwegein (opleider Dr. PMNYH Go). Hier startte ze met het onderzoek resulterend in dit proefschrift. Het academische deel van haar opleiding vond plaats in UMC Utrecht in de periode 2007-2008 (opleider Prof.dr. IHM Borel Rinkes). In 2008 keerde zij terug in het St Antonius ziekenhuis te Nieuwegein waar ze op 31 december 2009 chirurg zal worden. Op 1 januari 2010 zal zij beginnen als chirurg in vervolgopleiding tot gastro-intestinaal chirurg in het VU Medisch Centrum te Amsterdam (vervolgopleider Prof.dr. MA Cuesta).