Critical Limb Ischemia

Prognostic Factors and Endovascular Strategies

Marlon Spreen

Promotiereeks HagaZiekenhuis

Het HagaZiekenhuis van Den Haag is trots op medewerkers die fundamentele bijdragen leveren aan de wetenschap en stimuleert hen daartoe. Om die reden biedt het HagaZiekenhuis promovendi de mogelijkheid hun dissertatie te publiceren in een speciale Haga uitgave, die onderdeel is van de promotiereeks van het HagaZiekenhuis. Daarnaast kunnen promovendi in het wetenschapsmagazine HagaScoop van het ziekenhuis aan het woord komen over hun promotieonderzoek.

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Critical Limb Ischemia
Prognostic Factors and Endovascular Strategies

– Kritieke Ischemie –
Prognostische Factoren en Endovasculaire Strategieën
(Met een samenvatting in het Nederlands)

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Chapter 1

Introduction

1 Introduction

Critical Limb Ischemia

Peripheral artery disease (PAD) is defined by the presence of atherosclerotic stenoses or occlusions in major arteries, which is most common in the lower limb.[1] The Rutherford classification, ranging from 0 to 6, is used to grade the severity of these chronic arterial occlusive lesions.[2] Patients with category 0 are asymptomatic. Rutherford category 1, 2, and 3 are defined as mild, moderate, and severe intermittent claudication. The end stage of PAD, critical limb ischemia (CLI), results in insufficient oxygen delivery not meeting metabolic tissue demands, causing chronic ischemic rest pain and/or ischemic skin lesions, i.e. ulcers or gangrene.[1,3,4] Patients with CLI are classified as Rutherford category 4, 5, or 6, when they suffer from ischemic rest pain, minor, or major tissue loss, respectively.[2] The incidence of CLI is estimated at 500 to 1000 new cases per million inhabitants per year in the western world.[1] Important risk factors in CLI are advanced age, smoking, and diabetes.[1,3,5] Since the atherosclerotic burden in CLI is not just in the lower extremities but rather systemic, CLI patients have high (cardiovascular) mortality rates, with reported 1-year mortality rates as high as 40%.[1,3,6-8] Limb prognosis is poor as well; 25 to 30% of patients will have had a major amputation one year after presentation.[1,3] These distressing morbidity and mortality rates even exceed several malignancies.[4] However, a recent meta-analysis reported encouraging results of improved amputation-free survival (AFS) and mortality rates in patients with CLI without revascularization options over the past two decades.[9]

Treatment Options in Infrapopliteal Critical Limb Ischemia

Treatment options in CLI comprise medical treatment strategies, recanalization strategies, and cell therapy strategies.[1,8,10,11]

Medical treatment mainly consists of reduction of traditional atherosclerotic risk factors, consisting of smoking cessation, weight reduction in patients with a body mass index >25, tight control of hypertension and in particular of diabetes mellitus (DM), lipid control, and antiplatelet therapy Specific pharmaceutical agents with proven efficacy in CLI are yet lacking.[8]

Recanalization strategies aim at symptom relief and preventing major amputation by restoring unobstructed blood flow into the foot, which can be achieved by either surgical or endovascular techniques.[10,12] In below-the-knee lesions, surgical techniques were traditionally recommended for more severe and complex anatomic disease, provided that the patient's perioperative risk is appropriate and a conduit available.[10]

In recent years endovascular therapy of CLI has become the primary strategy, as it was shown that bypass-surgery-first and balloon-angioplasty-first strategy yielded broadly similar outcomes concerning amputation-free survival and surgery proved to be more expensive in the short-term. However, in this trial patients were included with infrainguinal rather than isolated infrapopliteal disease.[10,13] Regarding infrapopliteal arterial disease it is shown that although the patency of infrapopliteal percutaneous transluminal angioplasty (PTA) and bail out bare metal stenting (BMS), the current reference endovascular treatment, may be less than of bypass surgery, limb salvage rates are equivalent for at least mid-term outcome.[14-18] Furthermore, newer endovascular technologies, such as patency-enhancing drug coated devices, or different access sites, are increasingly studied.[8,10]

Our group designed the **PADI** (Percutaneous transluminal Angioplasty versus Drug-eluting stents for Infrapopliteal lesions) trial to investigate whether drug-eluting stents (DES) would reduce restenosis in infrapopliteal lesions in patients with CLI, would reduce major amputation rate, and would improve amputation-free survival.[19] DES are considered a possible solution to restenosis by reducing neointimal hyperplasia. Their superior performance has already been proved in coronary arteries, which are similar in size compared with infrapopliteal arteries.[20,21]

Cell therapy strategies supporting angiogenesis and neovascularization have been studied in patients with non-revascularizable disease, the so-called no-option CLI. Thus far, insufficient evidence of efficacy of these strategies exists. A meta-analysis of randomized-controlled trials showed diverging results of cell-based therapies regarding major amputation and AFS.[22]

Risk Factors and Predictors in Critical Limb Ischemia

As mentioned above, diabetes mellitus (DM) is an important risk factor in CLI, besides increasing age and smoking.[1,5] PAD progresses more rapidly in patients with DM and the risk of developing CLI is four times higher than in patients without DM.[1,23] The extensive comorbidity and high mortality in CLI patients hampers the inclusion of large groups of patients with adequate follow-up, which limits the possibilities of scientific evaluation. Consequently, CLI patients with and without DM are typically reported as one group and high-quality, prospective data comparing the two groups are lacking.[24]

It is because of the poor prognosis of CLI that risk stratification is important to enable clinicians to offer individual patients the most appropriate treatment. Currently, three validated prediction models exist regarding outcomes in CLI: the BASIL survival prediction model designed to predict death at 6, 12, and

24 months[25], the FINNVASC risk-scoring method for prediction of 30-day postoperative outcome after infrainguinal surgical revascularization[26], and the PREVENT III model for prediction of AFS at one year follow-up[27]. Validation of these models showed comparable and moderate performance of the chosen endpoints, with a slightly better performance of the BASIL survival prediction model.[28] A major disadvantage of this latter model is however the inclusion of the Bollinger score[29], a time consuming method to assess the severity and extent of arterial disease which requires angiographic data.[25] Furthermore, AFS is considered the most important clinical outcome parameter in CLI, since it incorporates the hard outcomes of both amputation and mortality.[1,9]

Outline of this Thesis

The primary objective of this thesis was to investigate the performance and applicability of DES for the treatment of infrapopliteal lesions in patients with CLI compared with the current reference treatment, both at short- en midterm as well as at long-term follow-up. The first part of this thesis uses data from the **PADI** trial to meet this objective. In **Chapter 2**, we report on the short- and mid-term results after DES placement, compared with percutaneous transluminal angioplasty with bailout bare metal stenting (PTA±BMS) in patients with CLI due to infrapopliteal lesions. **Chapter 3** shows the long-term results of the **PADI** trial up to 5 years after treatment.

The second part focuses on the prognostic factors of CLI. The data of the **PADI** trial were pooled with these of the **JUVENTAS** trial on patient level. The **JUVENTAS** (reJUVenating ENdothelial progenitor cells via Transcutaneous intra-Arterial Supplementation) trial was initiated to determine whether repetitive intra-arterial infusion of bone marrow mononuclear cells would reduce amputation rates in patients with non-revascularizable CLI.[30] By pooling the two patient cohorts a study population could be selected with comparable, infrapopliteal CLI. For **Chapter 4**, we examined the comorbidity of DM as a risk factor for major amputation and death in CLI patients. In **Chapter 5**, the prognostic value of the ankle-brachial index (ABI) regarding CLI outcomes is discussed and a modified version of the PREVENT III prediction model for the prediction of AFS at 1 and 2 years is proposed.

Chapter 6 reports on the treatment of CLI using a transpopliteal approach in selected patients with inaccessible groins.

We provide a synopsis in **Chapter 7** and conclude this thesis in **Chapter 8** by discussing the major findings and future perspectives in relation to the current state of knowledge.

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Chapter 2

Percutaneous transluminal angioplasty and drug-eluting stents for infrapopliteal lesions in critical limb ischemia (PADI) trial

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2 Percutaneous transluminal angioplasty and drug-eluting stents for infrapopliteal lesions in critical limb ischemia (PADI) trial

ABSTRACT

Background

Endovascular infrapopliteal treatment of patients with critical limb ischemia using percutaneous transluminal angioplasty (PTA) and bail-out bare metal stenting (BMS) is hampered by restenosis. In interventional cardiology, drug-eluting stents (DES) have shown better patency rates and are standard practice nowadays. An investigator-initiated, multi-center, randomized trial was conducted to assess whether DES also improve patency and clinical outcome of infrapopliteal lesions.

Methods & Results

Adults with critical limb ischemia (Rutherford category ≥ 4) and infrapopliteal lesions were randomized to receive PTA±BMS or DES with paclitaxel. Primary endpoint was 6-month primary binary patency of treated lesions, defined as ≤ 50% stenosis on Computed Tomography Angiography. Stenosis > 50%, re-treatment, major amputation and critical limb ischemia-related death were regarded as treatment failure. Severity of failure was assessed with an ordinal score, ranging from vessel stenosis through occlusion to the clinical failures. Seventy-four limbs (73 patients) were treated with DES and 66 limbs (64 patients) received PTA±BMS. Six-month patency rates were 48.0% for DES and 35.1% for PTA±BMS (*P*=0.096) in the modified-intention-to-treat and 51.9% and 35.1% (*P*=0.037) in the per-protocol analysis. The ordinal score showed significantly worse treatment failure for PTA±BMS versus DES (*P*=0.041). The observed major amputation rate remained lower in the DES group until 2 years post-treatment, with a trend towards significance (*P*=0.066). Less minor amputations occurred after DES until 6 months post-treatment (*P*=0.03).

Conclusions

In patients with critical limb ischemia caused by infrapopliteal lesions, DES provide better 6-month patency rates and less amputations after 6 and 12 months compared with PTA±BMS.

INTRODUCTION

Critical limb ischemia (CLI) manifests with chronic ischemic rest pain, tissue loss, or both. At present, the incidence of CLI, the final stage of peripheral arterial disease, in the Western world is ≈ 500 to 1000 cases per 1 million inhabitants every year.[1] Major risk factors in the development of CLI are diabetes mellitus, increased age, and smoking.[1,2] With an ageing Western population and an increasing prevalence of diabetes mellitus, the burden of CLI and its costs are likely to increase in the near future.[3] Preventing major amputation is of particular concern in the treatment of CLI as amputation is associated with a high peri-procedural morbidity and mortality and functional outcome is often poor.[4]

To avoid amputation and relieve pain, revascularization techniques attempt to restore unobstructed arterial blood flow into the affected foot.[1,5,6] The selected method of revascularization, either endovascular or surgical, depends on the local anatomical situation, condition of the patient, estimated risk, and expected patency of the reconstruction.[1,5]

Although the patency of infrapopliteal percutaneous transluminal angioplasty (PTA) and bail-out bare metal stenting (BMS), the current standard endovascular treatment, may be less than of bypass surgery, limb salvage rates are equivalent for at least middle-term outcome.[3,5,7-11] The major advantage of endovascular treatment is the lower peri-procedural morbidity and mortality, which is of particular concern in typical patients with CLI, that is older and fragile patients with systemic atherosclerosis and diabetes mellitus who are at high risk for cardiovascular events.[1]

Vascular restenosis, caused by intimal hyperplasia due to vessel injury during PTA, remains the main limitation of infrapopliteal PTA and BMS with clinical relapse and re-interventions.[7,8,10-13] Drug-eluting stents (DES) are considered a possible solution to the problem of restenosis by reducing neointimal hyperplasia, after promising results in coronary arteries.[12] There is a limited number of randomized studies concerning the use of DES in infrapopliteal arteries to date and these studies either included patients with intermittent claudication (≤ 68%)[13-15] or had limited follow-up (12-months angiography available in 46% of patients)[16].

The PTA and Drug-eluting Stents for Infrapopliteal Lesions in critical limb ischemia (**PADI**) trial, an investigator-initiated multicenter randomized study, was conducted to determine whether DES reduce restenosis and occlusion in infrapopliteal arteries in patients with CLI and may thus decrease amputation. In this trial 6-month patency rates and clinical outcomes at 6 and 12 months after endovascular treatment of infrapopliteal lesions in CLI are compared using either paclitaxel-eluting DES or PTA with bail out BMS.

METHODS

Study Design and Study Population

The **PADI** trial is an investigator-initiated, multicenter, randomized, controlled, non-blinded, double-arm study, conducted in three major vascular centers in The Netherlands. The protocol was approved by the medical ethical boards of the participating centers and all enrolled patients gave written informed consent. The trial was registered at http://www.clinicaltrials.gov (identifier NCT00471289). Adult patients were eligible for enrolment if they have CLI (defined as Rutherford category ≥ 4[17]) caused by infrapopliteal lesions.

Lesions were considered for inclusion if there was >50% luminal loss, lesion length of ≤ 90 mm, and reference vessel diameter 2 to 6 mm, estimated by pre-treatment imaging.[18] Inflow had to be unobstructed, possibly after revascularization in the femoropopliteal segment during the same session. Outflow distal to target lesions should consist of ≥1 crural vessel with expected unobstructed runoff until the level of the ankle joint.

Detailed inclusion and exclusion criteria are available in Supplemental table I in the Supplementary Material.

Randomization and Masking

After target lesions were successfully crossed with a guidewire, patient's limbs were randomly allocated to one of the two treatment strategies, PTA±BMS or DES. The attending radiological technician opened the sealed, opaque envelope containing a computer-generated random sequence on a 1:1 basis. Randomization was per limb and stratified in blocks per center. The block size (N=4) was known only to the statistician. Patients, operators, and investigators were not blinded to treatment assignment.

Study Procedures

Endovascular procedures were mainly performed by an antegrade approach using 6F sheaths. In case of failure, a contralateral retrograde transfemoral approach was used. Lesions were crossed under fluoroscopic guidance with the combination of a catheter and guidewire according to the choice of the operator, usually transluminally. Subintimal routes were used when transluminal recanalization failed.

After randomization, patients were treated according to one of the two treatment strategies.

In the DES arm, target lesions were treated with balloon expandable paclitaxel-eluting stainless steel coronary stents (TAXUS Liberté; Boston Scientific, Natick, MA). Paclitaxel, an extract derived from the Taxus brevifolia (Pacific Yew) tree, inhibits smooth muscle cell proliferation by affecting mitosis.[12] If necessary, according to the operator, mainly in cases of occlusion, lesions were predilated. The premounted DES was advanced over the guidewire and deployed at the site of the target lesion, according to the manufacturer's manual. The full length of lesions was covered, if necessary with overlapping stents. A maximum of three stents was allowed with a 3 to 5 mm overlap.
Patients in the PTA±BMS arm received PTA according to the normal practice of the operator. A balloon with a diameter matching the target vessel was advanced over the guidewire and inflated at the target lesion site. Average inflation time was 1 minute. If bail out stenting was required caused by post-PTA occlusion or flow-limiting dissection, only nondrug-eluting BMS were allowed.
A maximum of three lesions per limb were included. When a patient was included for both limbs, each limb was randomized separately.
After the procedure, the access site was closed with a sealing device or with manual compression.
During the procedure, 5000 international units of heparin were administered intra-arterially. Post-procedure all patients were prescribed 100 mg of carbasalate calcium daily indefinitely and 75 mg of clopidogrel daily (with 300 mg loading dose) orally for ≥ 6 months.

Follow-up
Patient assessments were planned before intervention, at discharge, after 3, 6, and 12 months and annually until 5 years. Assessments included medical history, physical examination including severity scoring of limb ischemia according to the Rutherford classification[17], ankle-brachial index, toe pressure, and duplex sonography of the treated limb. Computed Tomography Angiography (CTA) of the pelvis and lower extremities was performed at 6 months follow-up. Patency of treated sites on CTA was scored independently by 2 board- certified interventional radiologists (JMM and HO), who were unaware of the treatment. The degree of restenosis was scored from 0 to 50.0%, 50.0 to 99.9%, or occluded. In case of discordance, lesions were reassessed simultaneously to reach consensus.

Study End Points

Primary endpoint of the **PADI** trial was primary binary patency per treated lesion at 6 months, defined as ≤ 50% loss of luminal diameter on CTA without re-intervention in interim. If CTA was not available but digital subtraction angiography or duplex sonography was available, patency of treated sites was scored by those techniques. Loss of >50% of luminal diameter on CT, treatment in interim by means of infrapopliteal bypass or endovascular re-intervention, major amputation, and death related to CLI were considered as treatment failure. An ordinal score was used to grade the severity of treatment failure from vessel restenosis, through vessel occlusion to treatment in interim, major amputation, or CLI-related death.

Additional secondary endpoints were ischemic categorization of the treated leg by means of Rutherford classification, minor and major amputation (at or below versus above ankle level, respectively) of the trial leg, and peri-procedural (within 30 days) complications, serious adverse events, and death.

Statistical Analysis

On the bases of published data, a patency rate of 50% was assumed in the PTA±BMS arm at 6 months.[19] The study was designed to have a power of 80% to detect an elevation of the patency rate by DES to 75% with a two-sided $P < 0.05$. Taking into account a 15% loss to follow-up rate, the required sample rate had to be ≥ 136 patients.[18]

To evaluate difference in primary endpoint between PTA±BMS and DES, logistic regression with adjustment for multiple lesions within one limb was applied, assuming compound symmetry of the covariance matrix. For the ordinal composite endpoint a weighted χ^2-test was used, with weights equal to the inverse number of lesions per limb. Limbs in patients included for both limbs were considered independent for the analysis.

The observed rate of amputation, death, and the combined endpoint amputation or death was estimated with the Kaplan-Meier method. Patients were censored at end of follow-up. Differences between the treatment strategies were assessed with the log-rank test. Differences in mean Rutherford category were analyzed with t-test.

All endpoints were evaluated in the modified-intention-to-treat (MITT) analysis, excluding patients who did not fulfill all inclusion criteria or complete follow-up and who had incorrectly been included. Furthermore, patients who had died because of causes unrelated to CLI were censored. In addition, all endpoints were repeated in the per-protocol (PP) analysis considering analyses per lesion, in which only lesions were included which were technically treated according to randomization.

In the PTA±BMS arm all lesions were treated according to protocol and included in PP-analysis. Twenty-two lesions in the DES arm were treated with PTA only and excluded from PP-analysis. Eight lesions were located near a joint, five lesions at a bifurcation, technical failure precluded stenting in one lesion, and in eight lesions only PTA was performed because of operator preference.
Analyses were performed in SPSS version 21 and SAS System 9.3 for Windows by BEH and MIS.

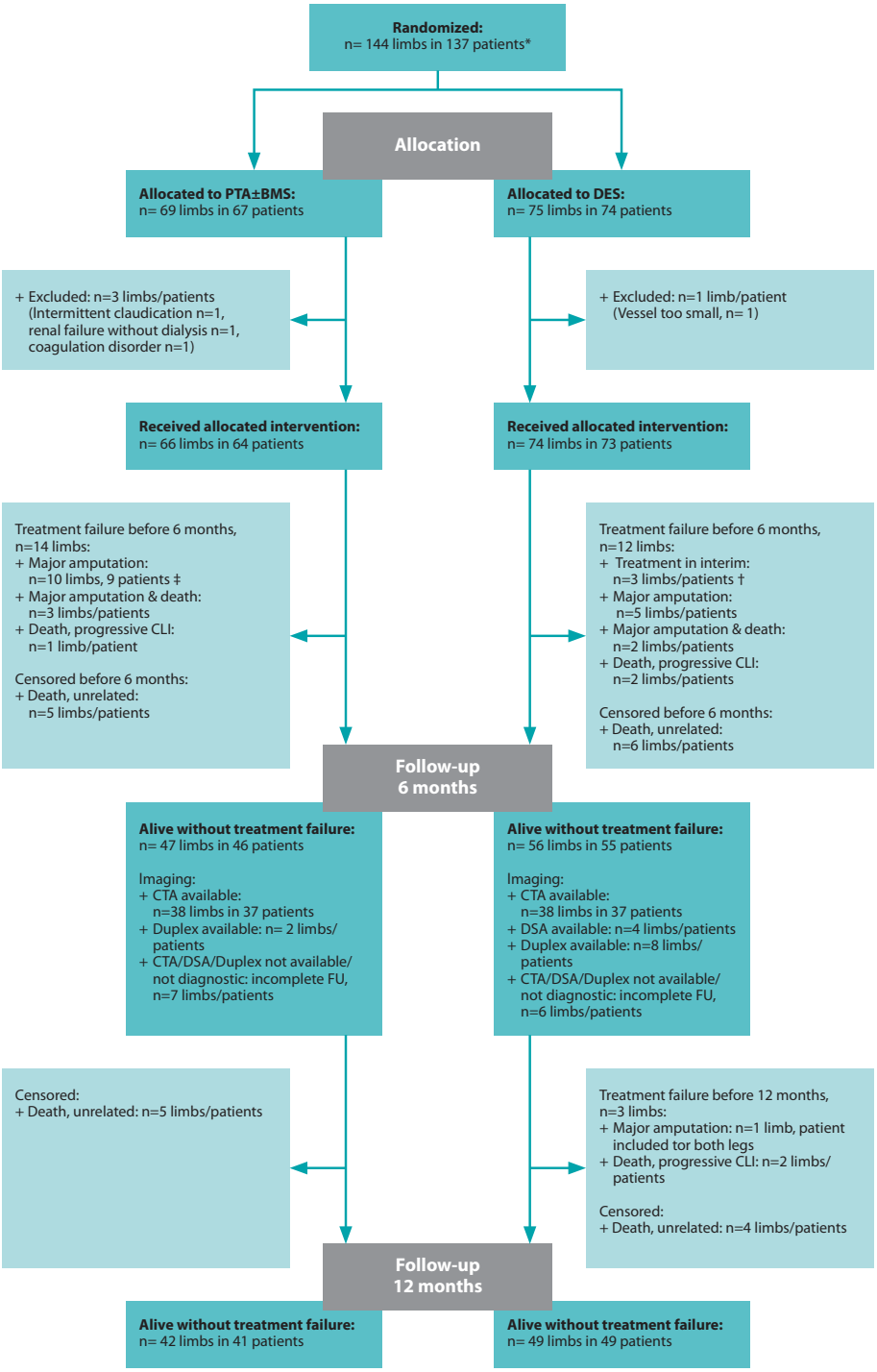
RESULTS

Patient and Lesion Characteristics

From October 2007 through February 2013, 75 limbs in 74 patients were randomly assigned to DES and 69 limbs in 67 patients to PTA±BMS (figure 1).
In the DES arm, one patient (one limb) and in the PTA arm three patients (three limbs) were excluded from the MITT-analysis.
Both arms had similar baseline characteristics (table 1). Diabetes mellitus was a common co-morbidity. The overall mean baseline Rutherford category was 5.1, with a range of 4 to 6.
Almost all limbs showed extensive peripheral arterial disease; 93.9% of limbs in the PTA±BMS arm and 98.6% in the DES-arm were classified as category D, according to the TransAtlantic Inter-Society Consensus (table 2).[20] Ninety-one lesions were treated in the PTA±BMS arm and 121 lesions in the DES arm, an average of 1.4 and 1.6 lesions per limb, respectively. Lesion characteristics were similar in both arms (table 2). Residual stenosis after treatment was significantly less in the DES than in the PTA±BMS arm (3.2% versus 10.7%, *P*=0.002).
An average of 1.8 stents was implanted per limb randomized for DES.
In the PTA±BMS arm, a mean of 0.3 bail out BMS were placed per limb.

Figure 1. Flow chart, modified-intention-to-treat population

BMS indicates bare metal stent; CLI, critical limb ischemia; CTA, computed tomographic angiography; DES, drug-eluting stent; DSA, digital subtraction angiograpy; FU, follow-up; and PTA, percutaneous transluminal angioplasty. *Four patients included for 2 limbs with 1 limb in each arm. †One of these patients died before 1 year FU. ‡Two of these patients died before 1 year FU.


Randomized:
n= 144 limbs in 137 patients*
Allocation
Allocated to PTA±BMS:
n= 69 limbs in 67 patients
Allocated to DES:
n= 75 limbs in 74 patients
+ Excluded: n=3 limbs/patients (Intermittent claudication n=1, renal failure without dialysis n=1, coagulation disorder n=1)
+ Excluded: n=1 limb/patient (Vessel too small, n= 1)
Received allocated intervention:
n= 66 limbs in 64 patients
Received allocated intervention:
n= 74 limbs in 73 patients
Treatment failure before 6 months, n=14 limbs:
+ Major amputation: n=10 limbs, 9 patients ‡
+ Major amputation & death: n=3 limbs/patients
+ Death, progressive CLI: n=1 limb/patient
Censored before 6 months:
+ Death, unrelated: n=5 limbs/patients
Treatment failure before 6 months, n=12 limbs:
+ Treatment in interim: n=3 limbs/patients †
+ Major amputation: n=5 limbs/patients
+ Major amputation & death: n=2 limbs/patients
+ Death, progressive CLI: n=2 limbs/patients
Censored before 6 months:
+ Death, unrelated: n=6 limbs/patients
Follow-up 6 months
Alive without treatment failure:
n= 47 limbs in 46 patients
Imaging:
+ CTA available: n=38 limbs in 37 patients
+ Duplex available: n= 2 limbs/patients
+ CTA/DSA/Duplex not available/not diagnostic: incomplete FU, n=7 limbs/patients
Alive without treatment failure:
n= 56 limbs in 55 patients
Imaging:
+ CTA available: n=38 limbs in 37 patients
+ DSA available: n=4 limbs/patients
+ Duplex available: n=8 limbs/patients
+ CTA/DSA/Duplex not available/not diagnostic: incomplete FU, n=6 limbs/patients
Censored:
+ Death, unrelated: n=5 limbs/patients
Treatment failure before 12 months, n=3 limbs:
+ Major amputation: n=1 limb, patient included tor both legs
+ Death, progressive CLI: n=2 limbs/patients
Censored:
+ Death, unrelated: n=4 limbs/patients
Follow-up 12 months
Alive without treatment failure:
n= 42 limbs in 41 patients
Alive without treatment failure:
n= 49 limbs in 49 patients

		PTA±BMS	DES
		N=64 patients	N=73 patients
		N=66 limbs	N=74 limbs
Mean age, y (SD)		72.9 (11.9)	74.2 (12.1)
Men		47 (73.4)	49 (67.1)
Smoking status	Ex-smoker	12 (18.8)	18 (24.7)
	Current smoker	17 (26.6)	16 (21.9)
Diabetes mellitus		43 (67.2)	44 (60.3)
Previous stroke or transient ischemic attack		13 (20.3)	12 (16.4)
Coronary disease		25 (39.1)	27 (37.0)
Venous and pulmonary thromboembolic disease		6 (9.4)	8 (11.0)
Impaired renal function (eGFR <45 mL/min/1.73m^2)		22 (34.4)	15 (20.5)
Chronic obstructive pulmonary disease		9 (14.1)	8 (11.0)
Previous malignancy		6 (9.4)	8 (11.0)
On anticoagulation medication		58 (90.6)	67 (91.8)
Rutherford category *	4	8 (12.1)	10 (13.5)
	5	46 (69.7)	48 (64.9)
	6	12 (18.2)	16 (21.6)
Increased/decreased ABI*	<0.4	4 (6.1)	5 (6.8)
	0.4-0.7	18 (27.3)	25 (33.8)
	0.7-0.9	9 (13.6)	13 (17.6)
	>1.4 / immeasurable	9 (13.6)	13 (17.6)
Decreased toe pressure*, mmg Hg	< 40 mmHg	15 (22.7)	21 (28.4)
	40-50 mmHg	7 (10.6)	4 (5.4)
	immeasurable	9 (13.6)	11 (14.9)

Table 1. Baseline characteristics

Data are number (%) unless stated otherwise. ABI indicates ankle brachial index; BMS, bare metal stent; DES, drug-eluting stent; eGFR, estimated glomerular filtration rate; and PTA, percutaneous transluminal angioplasty.

*Per index limb.

	PTA±BMS	DES
	N=66 limbs	N=74 limbs
	N=91 lesions	N=121 lesions
TASC *		
B	1 (1.5)	0 (0)
C	3 (4.5)	1 (1.4)
D	62 (93.9)	73 (98.6)
No. of treated infrapopliteal arteries	1.3 (0.6)	1.4 (0.6)
Lesion length, mm	23.1±21.8	21.1±19.3
Vessel diameter, mm	2.9±0.6	2.9±0.7
Preprocedure % stenosis	83.1±16.7	83.2±15.3
Postprocedure % stenosis	10.7±20.7	3.2±9.6
Postprocedure vessel runoff distal of lesion *		
≤50% stenosis	84 (92.3)	115 (95.0)
>50% stenosis	1 (1.1)	3 (2.5)
Occluded	6 (6.6)	3 (2.5)
Lesion location *		
Infragenual popliteal artery	5 (5.5)	6 (5.0)
Tibioperoneal trunk	20 (22.0)	21 (17.4)
Tibioperoneal trunk & peroneal artery	1 (1.1)	1 (0.8)
Anterior tibial artery	27 (29.7)	35 (28.9)
Posterior tibial artery	12 (13.2)	31 (25.6)
Peroneal artery	26 (28.6)	27 (22.3)
No. of limbs treated with (bail-out) stents	14 (21.2)	74 (100)
Stents implanted per limb	0.3±0.7	1.8±0.8

Table 2. Lesion characteristics

Values are mean or % ± SD unless stated otherwise. BMS indicates bare metal stent; DES, drug-eluting stent; PTA, percutaneous transluminal angioplasty; and TASC, TransAtlantic Inter-Society Consensus. *N (%).

End Points

The MITT-analysis showed a 6-month patency rate of 48.0% in the DES arm versus 35.1% in the PTA±BMS arm (*P*=0.096). In the PP analysis, this difference was statistically significant; 51.9% in the DES arm and 35.1% in the PTA±BMS arm (*P*=0.037; table 3).

Lesions in the DES arm showed a more favorable composite clinical and morphological outcome than those in the PTA arm after 6 months in both the MITT (*P*=0.041) and PP analysis (*P*=0.009) (table 3).

	PTA±BMS	DES	*P* Value
	N=54 limbs*	**N=62 limbs***	
MITT-analysis	**N=77 lesions***	**N=98 lesions***	
Lesions with preserved patency	27 (35.1)	47 (48.0)	0.096†
Ordinal score:			0.041‡
≤50% stenotic	27 (35.1)	47 (48.0)	
>50% stenotic	23 (29.9)	15 (15.3)	
Occluded	7 (9.1)	19 (19.4)	
Amputation/CLI related death/treatment in interim	20 (26.0)	17 (17.3)	
PP analysis	**N=77 lesions***	**N=81 lesions***	
Lesions with preserved patency	27 (35.1)	42 (51.9)	0.037†
Ordinal score:			0.009‡
≤50% stenotic	27 (35.1)	42 (51.9)	
>50% stenotic	23 (29.9)	8 (9.9)	
Occluded	7 (9.1)	17 (21.0)	
Amputation/CLI related death/treatment in interim	20 (26.0)	14 (17.3)	

Table 3. Primary End Point Per Lesion After 6 Months, MITT and PP analysis

Values are N (%). BMS indicates bare metal stent; CLI, critical limb ischemia; DES, drug-eluting stent; MITT, modified-intention-to-treat; PP, per protocol; and PTA, percutaneous transluminal angioplasty. *Numbers are no. of limbs/lesions with available, diagnostic imaging and those with treatment failure. Limbs/lesions in patients deceased because of unrelated causes were censored. †*P* value adjusted for multiple lesions per patient. ‡*p* value weighted by number of lesions per patient.

During the first 6 months after treatment, there were seven major amputations of the index limb (9.8%; 95% CI 2.9-16.7%) in the DES arm, versus 13 (20.5%; 95% CI, 10.5%-30.5%) in the PTA±BMS arm (*P*=0.10; table 4). After 1 year was 11.4% (95% CI, 4.0%-18.8%) in the DES arm and 20.5% (95% CI, 10.5%-30.5%) in the PTA±BMS arm. The Kaplan-Meier curves during the 2-year follow-up period diverged after 2 months in advantage of DES (*P*=0.066; figure 2).

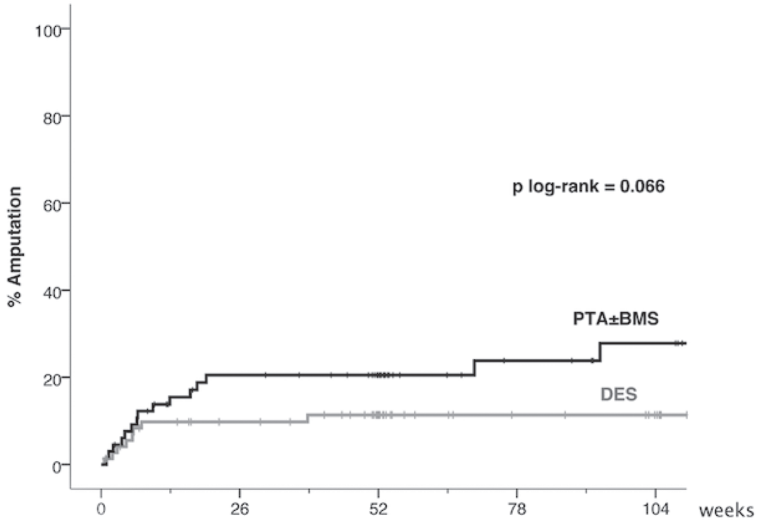
	0-6 months		0-12 months		
	N	**% (95% CI)**	**N**	**% (95% CI)**	***P* value***
Major amputation					0.066
PTA±BMS (N=66 limbs)	13	20.5 (10.5-30.5)	13	20.5 (10.5-30.5)	
DES (N=74 limbs)	7	9.8 (2.9-16.7)	8	11.4 (4.0-18.8)	
Death					0.52
PTA±BMS (N=64 patients)	9	14.1 (5.7-22.5)	16	25.1 (14.5-35.7)	
DES (N=73 patients)	10	13.7 (5.9-21.5)	17	23.3 (14.1-33.1)	
Major amputation or death					0.15
PTA±BMS (N=66 limbs)	19	28.8 (20.4-37.2)	24	36.4 (25.8-47.0)	
DES (N=74 limbs)	15	20.1 (12.3-27.9)	23	31.1 (20.5-41.7)	

Table 4. Clinical outcomes after 6 and 12 months

BMS indicates bare metal stent; CI, confidence interval; DES, drug-eluting stent; and PTA, percutaneous transluminal angioplasty. * Overall log-rank test.

Significantly less minor amputations occurred in the DES arm during the first 6 months after treatment (*P*=0.03), but not during the second 6 months interval (table 5).

During the first post-treatment year, 17 patients in the DES arm and 16 patients in the PTA±BMS arm died, corresponding to a survival rate of 76.7% (95% CI, 66.9%-85.9%) versus 74.9% (95% CI, 64.3%-85.5%), respectively (table 4). The Kaplan-Meier curves of survival and death or amputation until 2 years follow-up showed no significant difference between the treatment arms (*P*=0.52 and 0.15, respectively; figure 3 and 4).
Three patients (4.1%) in the DES arm underwent re-treatment of the affected leg within 6 months follow-up, against none in the PTA±BMS arm (*P*=0.098).



numbers (limbs) at risk

DES	74	59	47	32	28
PTA±BMS	66	47	38	22	18

Figure 2. Kaplan–Meier curves representing the estimated 2-year cumulative incidence rates of major amputation per limb after PTA±BMS and DES

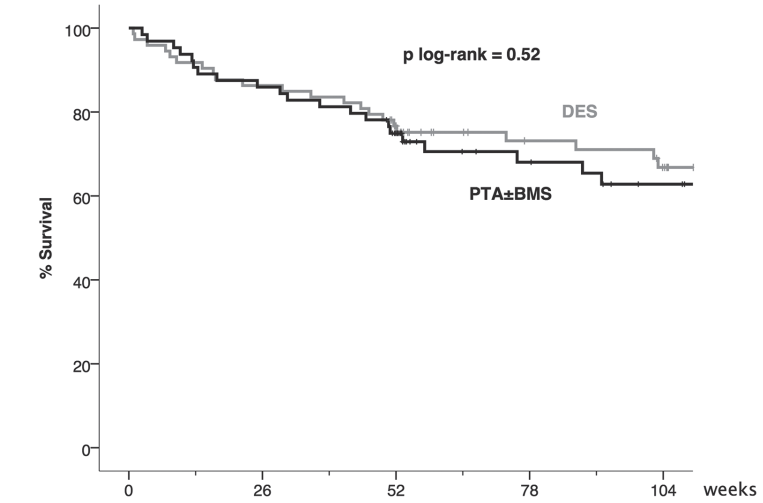
BMS indicates bare metal stent; DES, drug-eluting stent; and PTA, percutaneous transluminal angioplasty.

		PTA±BMS	DES	*P* value*
0-6 months		**N=66 limbs**	**N=74 limbs**	0.03
	Toes	14 (21.2)	5 (6.8)	
	Forefoot	2 (3.0)	5 (6.8)	
6-12 months		**N=42 limbs†**	**N=51 limbs†**	0.69
	Toes	2 (4.8)	4 (7.8)	

Table 5. Worst Minor Amputations

Values are N(%). BMS indicates bare metal stent; DES, drug-eluting stent; and PTA, percutaneous transluminal angioplasty. *Likelihood Ratio test. †In 5 limbs, data on minor amputations are missing.

The mean Rutherford category,[17] ankle-brachial index, and toe pressure after 6 and 12 months improved significantly in the survivors of both groups compared with baseline ($P \leq 0.005$; figure 5-7; Supplemental table II).
These improvements were comparable in both groups.

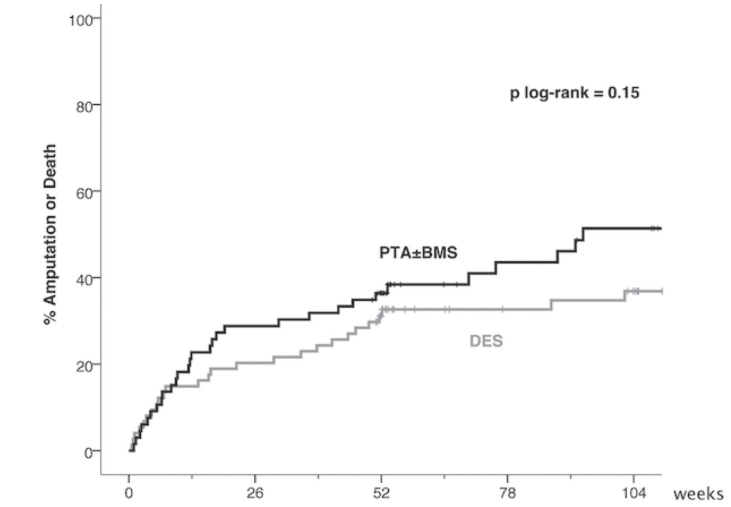


numbers (patients) at risk

DES	73	63	52	35	30
PTA±BMS	64	55	44	27	21

Figure 3. Kaplan–Meier curves representing the estimated 2-year cumulative incidence rates of survival per patient after PTA±BMS and DES

BMS indicates bare metal stent; DES, drug-eluting stent; and PTA, percutaneous transluminal angioplasty.



numbers (limbs) at risk

DES	74	59	47	32	28
PTA±BMS	66	47	38	22	18

Figure 4. Kaplan–Meier curves representing the estimated 2-year cumulative incidence rates of major amputation or death per limb after PTA±BMS and DES

BMS indicates bare metal stent; DES, drug-eluting stent; and PTA, percutaneous transluminal angioplasty.

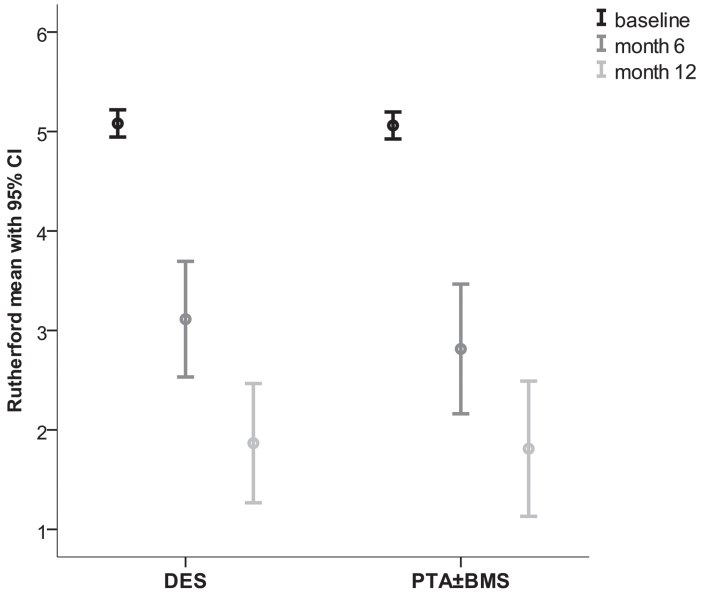


Figure 5. Mean Rutherford categories at baseline, 6 and 12 months

BMS indicates bare metal stent; DES, drug-eluting stent; and PTA, percutaneous transluminal angioplasty.

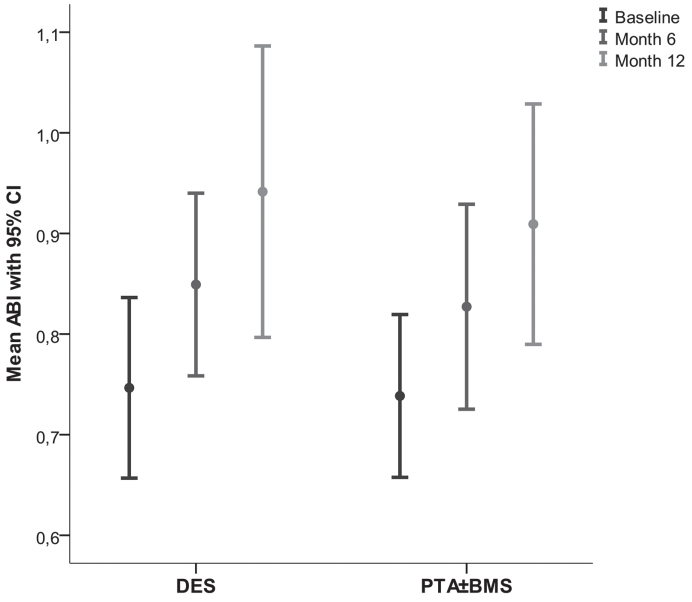


Figure 6. Mean ankle brachial index at baseline, 6 and 12 months

BMS indicates bare metal stent; DES, drug-eluting stent; and PTA, percutaneous transluminal angioplasty.

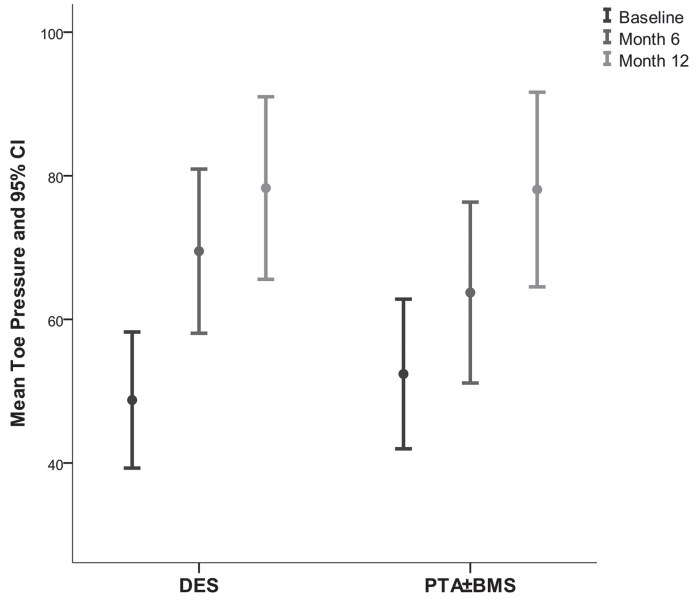


Figure 7. Mean toe pressure at baseline, 6 and 12 months

BMS indicates bare metal stent; DES, drug-eluting stent; and PTA, percutaneous transluminal angioplasty.

Complications and Adverse Events

Interim analysis for safety reasons at 6 weeks follow-up of the first 40 patients showed an acute thrombosis rate of 5% in both arms. The incidence of peri-procedural complications, complications during treatment admission, and late complications did not differ significantly between the two arms, neither did the number of serious adverse events. A table with complications and serious adverse events is available in Supplemental table III.

DISCUSSION

Our study shows that paclitaxel-eluting DES provide higher patency rates at 6 months in infrapopliteal stenotic or occluded lesions in patients with CLI when compared with the current reference treatment, PTA±BMS.[5] Treatment failure was observed significantly more often in the latter group and was more severe, as is shown by the composite results. Such a composite endpoint better reflects the overall performance of DES compared with PTA±BMS because it combines the results of the morphological, local, and general clinical situation in patients.

This is the first study that demonstrates a difference in limb amputation rate using DES in CLI. The Kaplan-Meier curves of major amputations diverge at 2 months post-treatment with a trend towards significance at 2 years. In addition, there were less minor amputations.
Survival was comparable in both groups. The majority of deaths was not related to progression of limb ischemia, which can be explained by the fact that 25% of patients presenting with CLI are known to die within a year of onset of the symptoms, often caused by coronary heart disease.[1,2,21,22]
Surviving non-amputated patients showed improved Rutherford categories during follow-up. The decrease of Rutherford categories from 4 to 6 to stages 3 and 2 after 6 and 12 months follow up show that all these patients actually benefit from their medical care.

In interventional cardiology, DES were developed to decrease in-stent neointimal hyperplasia, which mainly occurs until 6 months postprocedural.[12,23,24] Nowadays, DES are standard treatment in coronary lesions because several meta-analyses proved their superior performance on restenosis and ischemia-driven repeat revascularization rates in comparison with BMS.[25]
Given these positive results of DES in coronary arteries, expectations arose that these stents might be efficacious in the similarly sized infrapopliteal arteries, what is supported by the results of our study. A recent meta-analysis of three randomized controlled trials to assess the efficacy of DES for the management of infrapopliteal arterial disease reported a significantly higher primary patency rate for DES compared with PTA or BMS at 1 year.[26] There was no difference in major amputation rates; however, this is probably because of the fact that the individual studies included patients with intermittent claudication,[13,14] in whom amputations are rare, or had follow-up in less than half of the cases.[16] We observed a lower major amputation rate in the DES group, with a trend towards significance. Furthermore, our study demonstrates that DES reduce minor amputations.
In a CLI population, major amputation is a serious threat.[1,3] The severity and extensiveness of vascular disease in our patients are further reflected by the lower patency rates than anticipated in the sample size calculations. The patency and re-intervention rates in our study are lower compared with studies that include patients with intermittent claudication.[13,14]
Till now, the experience with infrapopliteal paclitaxel-eluting stents is confined to small non-randomized series that often included the use of various DES.[27-31] Although some authors report higher infrapopliteal patency rates of sirolimus-eluting than paclitaxel-eluting stents, there are no randomized studies regarding this issue.[13-16,26-29,32]

Considering our relatively low complication rate, revascularization by means of endovascular techniques seems a justifiable treatment strategy in patients with CLI, who are in general elderly with substantial co-morbidities and therefore less suitable for surgery.

Our study has some limitations. Not all of our patients showed decreased ankle-brachial index and toe pressures, thereby not strictly meeting the hemodynamic criteria for CLI.[1] This is probably because of the fact that >63% of our patients have diabetes mellitus, in whom Ankle-Brachial Index values are known to be relatively elevated.[1] Toe pressures have been thought to represent a more reliable parameter in CLI but a recent study has failed to confirm this. Optimal cut-off values remain to be established in diagnosing CLI.[33] We think that the overall clinical picture of patients presenting with rest pain or tissue loss, and excluding patients with intermittent claudication, is the most important factor in properly selecting patients who need revascularization.
In 8 limbs, randomized for DES, 8 additional lesions were treated with PTA only, after treating the main lesion with DES. As a result, there is a difference between the primary endpoint in the MITT-analysis and additional PP-analysis.
Our primary endpoint was scored by means of CTA instead of digital subtraction angiography. CTA has been reported as an adequate tool for the assessment of arterial obstructions despite the fact that calcifications may hinder the assessment of stenosis rate.[34] Because there were no lesions excluded from treatment in either group in our study because of severe calcifications, it is unlikely that treatment results have been influenced by unequal distribution of calcified lesions. In addition, digital subtraction angiography was considered too invasive and burdening for our elder and vulnerable study population.
In those cases when the index limb had been amputated or the patient had died because of progressive ischemia before 6 months follow-up, lesions were scored as treatment failures. In these cases, amputation or related death may also have been related to progression of disease elsewhere in the arteries supporting the affected limb. Patients who died because of unrelated causes were censored. Because these numbers of deceased patients are almost equal in both groups and consistent with previously reported high mortality rates among patients with CLI, it is unlikely that this has caused any bias.
In 13 patients, imaging at 6 months follow-up is not available. Patients with lower limb ischemia show high rates of loss to follow-up and low survival rates in longitudinal studies.[1,16] Despite this challenging population, clinical follow-up was obtained in all our patients.

Finally, because this study is an investigator-initiated study, financial means were insufficient to provide patency analysis by means of a core laboratory. This was solved by assessing patency analysis independently by two board certified interventional radiologists.

CONCLUSION

In patients with CLI caused by infrapopliteal lesions, a treatment strategy with DES should be considered because they are associated with better patency and less amputations when compared with PTA±BMS, which is the current standard endovascular treatment.

Acknowledgments
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Disclosures
Dr Van Overhagen has received speakers fees from Cordis Corporation, Fremont, CA; Cook Medical, Bloomington, IN; and AngioDynamics, Latham, NY. The above are unrelated to the submitted work. The other authors report no conflicts.

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SUPPLEMENTARY MATERIAL

Inclusion criteria
■ Age > 18 years.
■ If female patient with child-bearing potential, patient may not be pregnant at the study entry and must utilize reliable birth control for the duration of her participation in the study.
■ Patient is willing and able to comply with the specified follow-up evaluation.
■ Critical limb ischemia, defined as Rutherford category 4 (ischemic rest pain), 5 (minor tissue loss), or 6 (major tissue loss).
■ Stenosis (>50% luminal loss) or occlusion of an infrapopliteal artery, including the tibiofibular trunk, the anterior tibial artery, the posterior tibial artery, and the peroneal artery.
■ Target lesion length ≤90 mm.
■ Artery to be treated with a diameter ≥2 mm and ≤6 mm.
■ Patent common iliac, external iliac, superficial femoral and popliteal artery on the ipsilateral side prior to randomization, possibly after treatment during the same session.
■ At least 1 patent crural (anterior tibial, posterior tibial, or peroneal) artery with expected unobstructed runoff to ankle level after treatment.

Supplemental table IA. Inclusion criteria

Exclusion criteria
■ Acute limb ischemia.
■ Previous amputation of affected limb at or above ankle level.
■ Subacute limb ischemia which requires thrombolysis as first treatment modality.
■ Active bleeding or bleeding diathesis.
■ Recent (≤3 months) hemorrhagic stroke or any other CNS abnormality with increased risk of hemorrhage, such as intracranial neoplasm, arteriovenous malformation, intracranial aneurysm, or aneurysm repair.
■ Gastrointestinal or genitourinary bleeding of clinical significance within the previous 6 weeks before treatment.
■ Aneurysm in common femoral, superficial femoral, or popliteal artery on the ipsilateral side.
■ Surgical revascularization involving the same limb within 30 days prior to the index procedure or planned surgical revascularization of the same limb within 30 days of the index procedure.
■ Previous implanted stent at the index site.
■ Life expectancy of less than 6 months or other factors making clinical follow-up difficult.
■ Known allergy to acetylsalicylic acid (aspirin), clopidogrel, heparin, or paclitaxel.
■ Known allergy to contrast media.
■ Known heparin-induced thrombocytopenia (HIT type 2).
■ Patient unable or unwilling to tolerate anticoagulant, anti-platelet therapy or contrast media.
■ Creatinine clearance <20 mL/minute (as derived from Cockroft-Gault formula).
■ Severely calcified lesions with expected resistance to stenting.
■ Poor inflow due to ipsilateral stenoses or occlusions of the iliac or femoropopliteal arteries that cannot be treated during the same session.
■ Significant vessel tortuosity or other parameters prohibiting access to the lesions and/or delivery of the stent.
■ Patients without (expected) distal runoff to the index site.

Supplemental table IB. Exclusion criteria

		PTA±BMS	DES	*P* value *
Rutherford category				
		N=43 limbs	**N=53 limbs**	
	Month 6	2.81 (0.32)	3.11 (0.29)	0.49
		N=37 limbs	**N=45 limbs**	
	Month 12	1.81 (0.34)	1.87 (0.30)	0.90
Ankle brachial index				
		N=32 limbs	**N=39 limbs**	
	Month 6	0.83 (0.05)	0.85 (0.04)	0.74
		N=26 limbs	**N=33 limbs**	
	Month 12	0.91 (0.06)	0.94 (0.07)	0.74
Toe pressure (mmHg)				
		N=34 limbs	**N=40 limbs**	
	Month 6	63.7 (6.2)	69.5 (5.7)	0.49
		N=24 limbs	**N=31 limbs**	
	Month 12	78.1 (6.6)	78.3 (6.2)	0.98

Supplemental table II. Mean Rutherford score, ankle brachial index and toe pressure at 6 and 12 months post treatment

Values are mean (standard error). BMS indicates bare metal stent; DES, drug-eluting stent; and PTA, percutaneous transluminal angioplasty. * T-test.

	PTA±BMS	DES	*P* value*
	N=66 limbs	N=74 limbs	
Periprocedural complications †			
Hematoma	8 (12.1)	7 (9.5)	0.61
Material dysfunction	0	3 (4.1)	0.10
Acute thrombosis	4 (6.1)	5 (6.8)	0.87
Distal emboli	3 (4.5)	4 (5.4)	0.82
Pseudo aneurysm	0	1 (1.4)	0.34
Complications until 12 months			
Acute thrombosis	1 (1.5)	0	0.29
Wound infection	3 (4.5)	8 (10.8)	0.17
Serious adverse events			
Gastrointestinal bleeding	3 (4.5)	2 (2.7)	0.56
Ischemic cerebral event	1 (1.5)	2 (2.7)	0.63
Cerebral hemorrhage	2 (3.0)	0	0.13
Pneumonia	1 (1.5)	3 (4.1)	0.37
Decubitus	1 (1.5)	0	0.29
Cardiac disease	1 (1.5)	5 (6.8)	0.13
Renal failure	2 (3.0)	1 (1.4)	0.49
Non CLI related infection	4 (6.1)	2 (2.7)	0.33

Supplemental table III. Complications and Serious Adverse Events

Values are number (%). BMS indicates bare metal stent; CLI, critical limb ischemia, DES, drug-eluting stent; and PTA, percutaneous transluminal angioplasty. * χ^2 test. †<30 days post procedural.

Chapter 3

Long-term follow-up of PADI trial: Percutaneous transluminal angioplasty versus drug-eluting stents for infrapopliteal lesions in critical limb ischemia

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Submitted.

3 Long-term follow-up of PADI trial: Percutaneous transluminal angioplasty versus drug-eluting stents for infrapopliteal lesions in critical limb ischemia

ABSTRACT

Background

More favorable clinical outcomes after treatment of infrapopliteal lesions with drug-eluting stents (DES) compared with percutaneous transluminal angioplasty with bailout bare metal stenting (PTA±BMS) have been reported in patients with critical limb ischemia (CLI) until mid-term follow-up. In the present study, the long-term results of the treatment of infrapopliteal lesions with DES are presented.

Methods & Results

Adults with CLI (Rutherford category ≥ 4) and infrapopliteal lesions were randomized to receive PTA±BMS or DES with paclitaxel. Long-term follow-up consisted of annual assessments up to 5 years post-treatment, or until a clinical endpoint was reached. Clinical endpoints were major amputation (above ankle level) or infrapopliteal surgical or endovascular re-intervention, and death. Preserved primary patency (≤50% restenosis) of treated lesions was an additional morphological endpoint, assessed by duplex sonography.

Seventy-four limbs (73 patients) were treated with DES and 66 limbs (64 patients) received PTA±BMS. The estimated 5-year major amputation rate was lower in the DES arm (DES: 19.3% vs. PTA±BMS: 34.0%; $P = 0.091$). The 5-year amputation-free survival and event-free survival (survival free from major amputation or re-intervention) rates were significantly higher in the DES arm (DES: 31.8%; PTA±BMS: 20.4%; $P = 0.043$; and DES: 26.2%; PTA±BMS: 15.3%; $P = 0.041$, respectively). Survival rates were comparable. The limited available morphologic results show higher preserved patency rates after DES than after PTA±BMS at 1, 3, and 4 years follow-up.

Conclusions

Both clinical and morphologic long-term results after treatment of infrapopliteal lesions in patients with critical limb ischemia are improved with DES when compared with PTA±BMS.

INTRODUCTION

Critical limb ischemia (CLI) manifests with chronic ischemic rest pain, tissue loss of the limb, or both. At present, the incidence of this final stage of peripheral arterial disease (PAD) is estimated at 500-1000 cases per 1 million inhabitants every year in the western world.[1] Major risk factors in the development of CLI are diabetes mellitus, smoking, and an increasing age.[1,2] With an ageing Western population and an increasing prevalence of diabetes, the burden of CLI and its costs are likely to increase.[3]

The main goal in the treatment of CLI is to prevent major amputation. This mutilating procedure is associated with high peri-procedural morbidity and mortality and functional outcome after amputation is often poor.[4]

Restoration of unobstructed pulsatile blood flow to the foot is imperative to relieve symptoms and to prevent amputation. Revascularization can be achieved by means of either endovascular or surgical techniques.[1,3,5,6] In case of CLI due to infrapopliteal lesions, percutaneous transluminal angioplasty (PTA) with bailout bare metal stenting (BMS) is nowadays probably still the most used endovascular technique. Drug-eluting stents (DES) in infrapopliteal lesions have demonstrated lower restenosis rates than either PTA or BMS in several randomized clinical trials but only few of these studies also reported improved clinical results such as lower amputation rates.[7-12] The reason for this may be the study design[7], the small number of patients[8,9], or the inclusion of subjects with intermittent claudication and therefore not at risk of major amputation.[8-11] In addition, only one study so far has reported long term clinical result.[13]

The **PADI** trial was designed to compare the performance of paclitaxel-eluting DES with PTA±BMS of infrapopliteal lesions, in a population consisting solely out of CLI patients.[14] Short and mid-term results of this study have been published elsewhere and showed more favorable clinical outcomes after DES compared with PTA±BMS, with less major amputations after DES with a trend towards significance until 2 years follow-up and significantly less minor amputations during the first 6 months of follow-up.[12] This paper presents the outcomes of the long-term follow-up of this multicenter randomized controlled trial.

METHODS

Study Design, Population and Procedures

The purpose of the **PADI** trial (Percutaneous transluminal Angioplasty versus Drug-eluting stents for Infrapopliteal lesions) was to assess the performance of paclitaxel-eluting DES compared with PTA±BMS in infrapopliteal lesions causing CLI. Patients were enrolled between October 2007 and February 2013 in three major vascular centers in the Netherlands. Adults with a Rutherford category[15] ≥ 4 due to infrapopliteal lesions, as assessed with pre-treatment imaging, were randomly allocated to one of the two treatment arms. Randomization was per limb. When a patient was included for both limbs, each limb was randomized separately. A maximum of three lesions per limb could be included, with each of these lesions allocated to the same treatment arm. In the DES arm, target lesions were treated with paclitaxel-eluting stainless steel coronary stents (TAXUS Liberté; Boston Scientific, Natick, MA). Patients in the PTA±BMS arm received PTA with optional bailout stenting using non-drug-eluting BMS. All patients were treated with carbasalate calcium (100 mg daily, indefinitely) and clopidogrel (loading dose of 300 mg directly after the procedure followed by 75 mg daily for at least 6 months). Details of study design and short and mid-term results have been reported previously.[12,14] The trial was registered at ClinicalTrials.gov with the identifier NCT00471289.

Long-term Follow-up and Endpoints

Long-term follow-up existed of annual patient assessments until 5 years after inclusion, or until a clinical endpoint was reached. Assessments consisted of medical history, physical examination, and duplex sonography of the treated limb. When patients were not willing or able to visit the hospital, passive follow-up was obtained by contacting the patients or their general practitioner by phone or by retrieving data from the hospital electronic medical records. Survival was recorded of patients who underwent a major amputation or infrapopliteal surgical or endovascular re-treatment of the target limb. Causes of death were registered as CLI related or unrelated whenever known.

Clinical endpoints of the long-term follow-up registry of the **PADI** trial were major amputation (above ankle level) of the treated limb or infrapopliteal surgical or endovascular re-intervention attempted on the treated limb, and death, during the entire observation period. Preserved primary patency of treated lesions was an additional morphological endpoint of the long-term follow-up. This endpoint was assessed by duplex sonography, defined as ≤50% restenosis (peak systolic velocity (PSV) ratio ≤2.5). An ordinal score was used to grade the severity of

treatment failure from 'vessel restenosis' (>50% stenosis, PSV ratio >2.5), to 'vessel occlusion', to clinical failures 'treatment in interim, major amputation, or CLI related death'.

Statistical Analysis

Categorical variables were compared with the use of the two-sided χ^2 test, ordinal variables with the Mann Whitney test, and continuous variables were compared with the two-sided Student t test. The observed rate of major amputation per limb and survival rate per patient were estimated with the Kaplan-Meier method. Additionally, estimated amputation-free survival (defined as survival free from major amputation of the index limb) and event-free survival rates (defined as survival free from major amputation or re-intervention of the index limb) were analyzed with this same method. Limbs/patients were censored at end of follow-up. For the analyses regarding the endpoints per lesion a weighted χ^2 was used, with weights equal to the inverse number of lesions per limb. Limbs in patients included for both limbs were considered independent for the analysis.
All primary and secondary endpoints were evaluated in the modified-intention-to-treat (MITT) analysis, excluding patients who did not fulfill all inclusion criteria or patients who had incorrectly been included.
A two-sided *P* value ≤0.05 was considered to indicate statistical significance.
Analyses were performed in SPSS version 23 for Mac.

RESULTS

Baseline Characteristics and Short-term Outcomes

From October 2007 through February 2013, 75 limbs in 74 patients were randomly assigned to the DES arm and 69 limbs in 67 patients to the PTA±BMS arm (figure 1). In the DES arm one patient (one limb) and in the PTA arm three patients (three limbs) were excluded from the MITT-analysis. Ninety-one lesions were treated in the PTA±BMS arm and 121 lesions in the DES arm, an average of 1.4 and 1.6 lesions per limb, respectively.
The comparable baseline characteristics as well as the short-term outcomes have been published elsewhere.[12]

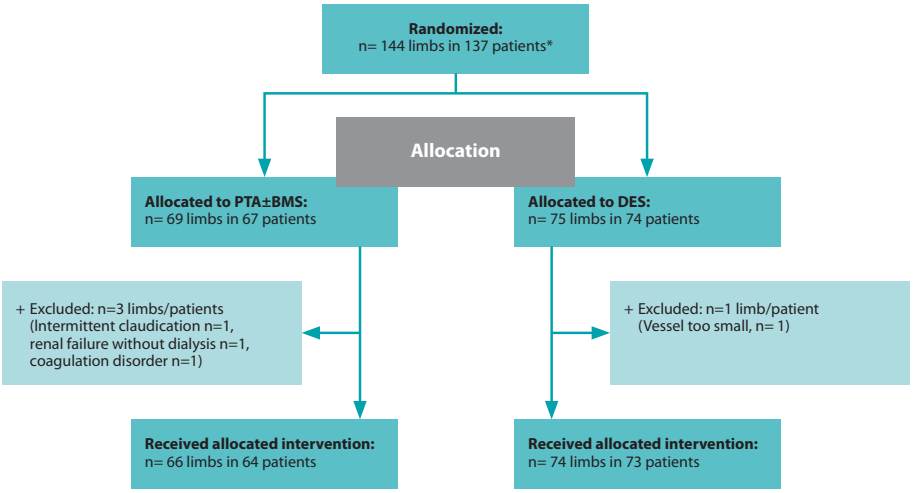


Figure 1. Flow diagram of inclusion

BMS indicates bare metal stent; DES, drug-eluting stent; and PTA, percutaneous transluminal angioplasty.

*4 patients included for two limbs with one limb in each arm.

Long-term Clinical Outcomes

Patients were followed for a mean duration of 163.8 weeks (SD 107.1 weeks), equivalent to 430 patient-years of observation.

Figure 2 graphically shows the outcome per limb at 1, 2, 3, 4 and 5 years post-treatment (the exact numbers can be found in the online supplemental table I). At all of these observation moments the percentage of preserved limbs was higher in the DES arm than in the PTA±BMS arm. However, these outcomes did not differ significantly.

The estimated major amputation rate was lower in the DES arm than in the PTA±BMS arm (19.3% versus 34.0% after 5 years, respectively), with a trend towards significance ($P = 0.091$) (table 1 en figure 3A). The amputation-free survival (AFS) rate and event-free survival rate were significantly higher in the DES arm than in the PTA±BMS arm (31.8% versus 20.4% at 5 years follow-up respectively, $P = 0.043$; and 26.2% versus 15.3%, $P = 0.041$), as is shown in table 1 and figures 3B and 3C. Survival rates were comparable (table 1 and figure 3D).

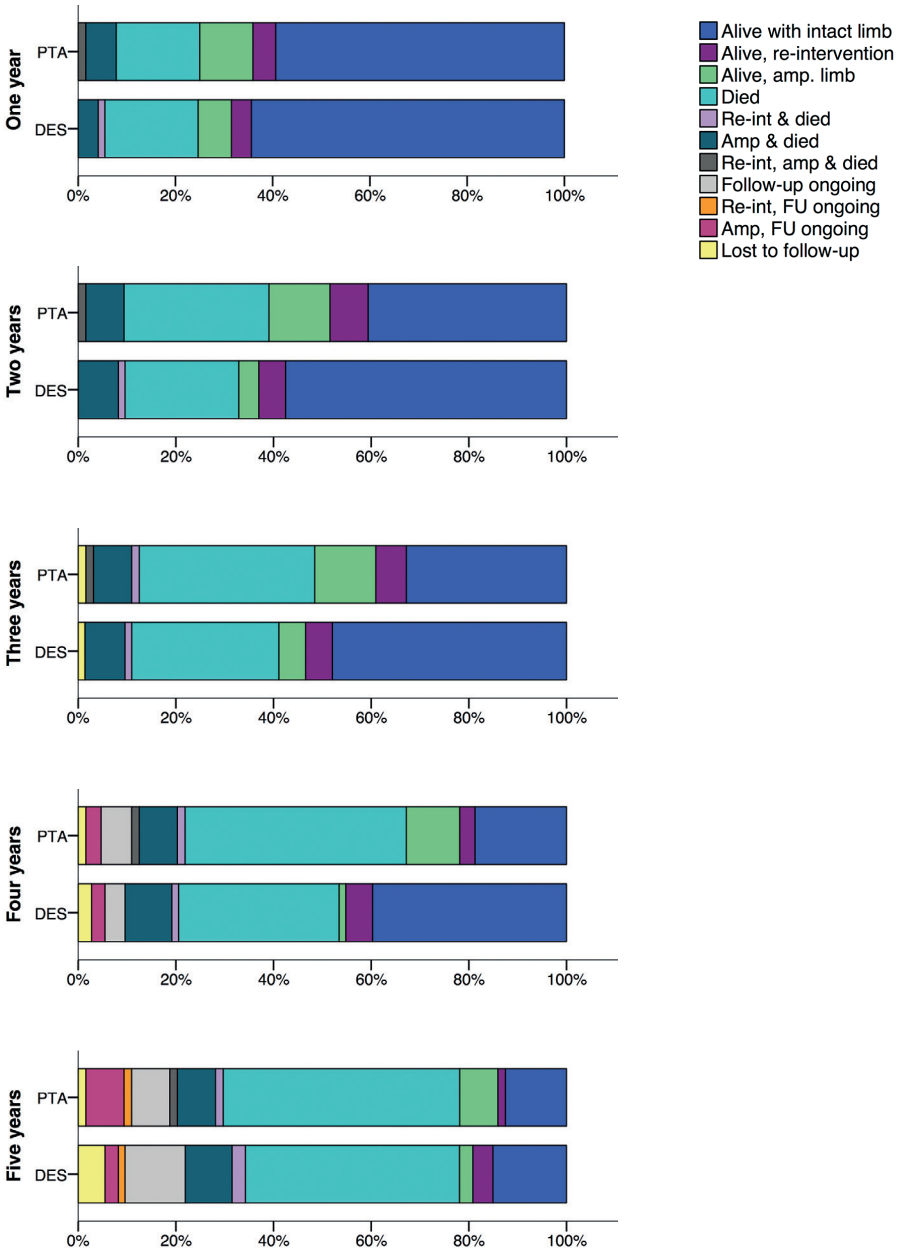


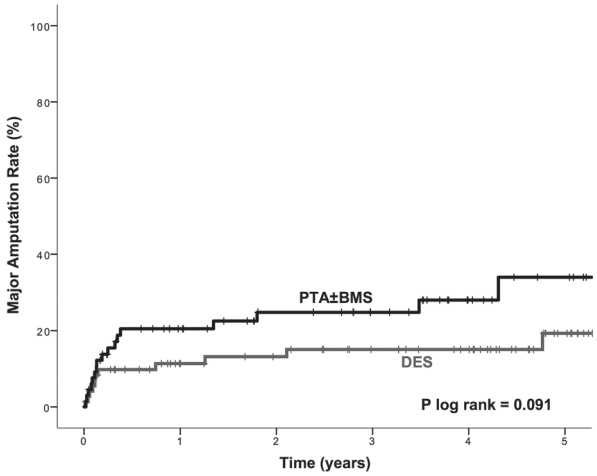
Figure 2. Outcome at 1, 2, 3, 4 and 5 years follow-up, per patient

Amp indicates amputated; DES, drug-eluting stent; FU, follow-up; PTA, percutaneous transluminal angioplasty; and re-int, re-intervention.

	PTA±BMS (66 limbs, 64 patients)		DES (74 limbs, 73 patients)		*P* value*
	N	% (95% CI)	N	% (95% CI)	
Major amputation rate per limb					
0-6 months	13	20.5 (10.5-30.5)	7	9.8 (2.9-16.7)	
0-1 year	13	20.5 (10.5-30.5)	8	11.4 (4.0-18.8)	
0-2 years	15	24.8 (13.6-36.0)	9	13.2 (5.2-21.2)	
0-3 years	15	24.8 (13.6-36.0)	10	15.1 (6.5-23.7)	
0-4 years	16	28.0 (15.8-40.2)	10	15.1 (6.5-23.7)	
0-5 years	17	34.0 (18.1-49.9)	11	19.3 (7.7-30.9)	0.091
Major amputation/death rate per patient					
0-6 months	18	28.1 (17.1-39.1)	15	20.5 (11.3-29.7)	
0-1 year	23	35.9 (24.1-47.7)	23	31.5 (20.9-42.1)	
0-2 years	33	51.6 (39.4-63.8)	27	37.0 (25.8-48.2)	
0-3 years	39	60.9 (48.9-72.9)	33	45.2 (33.8-56.6)	
0-4 years	46	73.5 (62.3-84.7)	35	48.3 (36.7-59.9)	
0-5 years	49	79.6 (69.0-90.2)	45	68.2 (56.0-80.4)	0.043
Event rate per patient					
0-6 months	20	31.2 (19.8-42.6)	17	23.3 (13.7-32.9)	
0-1 year	26	40.6 (28.6-52.6)	26	35.6 (24.6-46.6)	
0-2 years	38	59.4 (47.4-71.4)	31	42.5 (31.1-53.9)	
0-3 years	43	67.2 (55.6-78.8)	37	50.7 (39.1-62.3)	
0-4 years	50	79.0 (68.8-89.2)	39	53.8 (42.2-65.4)	
0-5 years	53	84.7 (75.5-93.9)	49	73.8 (62.2-85.4)	0.041
Survival rate per patient					
0-6 months	54	84.4 (75.6-93.2)	63	86.3 (78.5-94.1)	
0-1 year	48	75.0 (64.4-85.6)	55	75.3 (65.5-85.1)	
0-2 years	39	60.9 (48.9-72.9)	49	67.1 (56.3-77.9)	
0-3 years	33	53.1 (40.9-65.3)	43	60.3 (49.1-71.5)	
0-4 years	21	41.8 (29.3-54.3)	34	55.5 (43.9-67.1)	
0-5 years	13	37.0 (24.3-49.7)	17	37.7 (25.2-50.2)	0.45

Table 1. Estimated major amputation rate, major amputation/death rate, event rate, and survival rate

CI indicates confidence interval; PTA, percutaneous transluminal angioplasty; BMS, bare metal stent; and DES, drug-eluting stent. * Overall log-rank test.

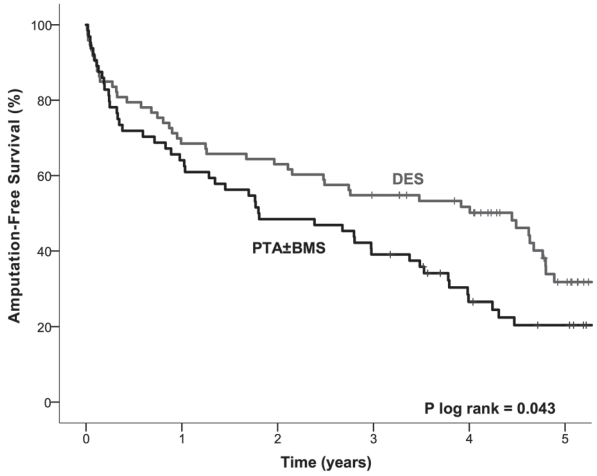


numbers at risk

DES	74	51	46	39	33	14
PTA±BMS	66	42	32	26	15	9

Figure 3A. Kaplan–Meier curves representing the estimated 5-year cumulative incidence rates of major amputation per limb after PTA±BMS and DES

PTA indicates percutaneous transluminal angioplasty; BMS, bare metal stent; and DES, drug-eluting stent.

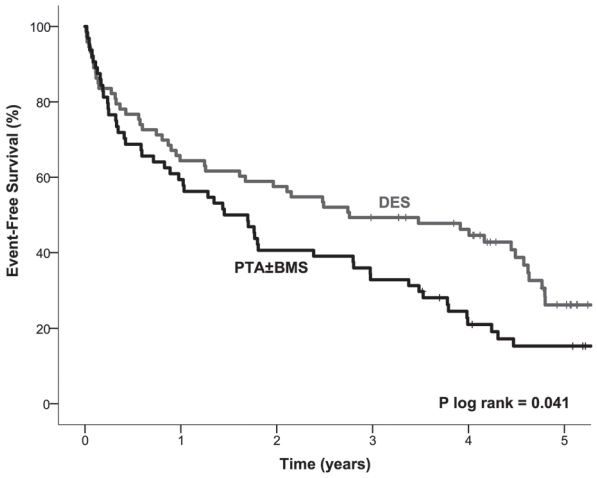


numbers at risk

DES	73	50	46	39	33	14
PTA±BMS	64	41	31	25	14	9

Figure 3B. Kaplan–Meier curves representing the estimated 5-year cumulative incidence rates of amputation-free survival per patient after PTA±BMS and DES

PTA indicates percutaneous transluminal angioplasty; BMS, bare metal stent; and DES, drug-eluting stent.

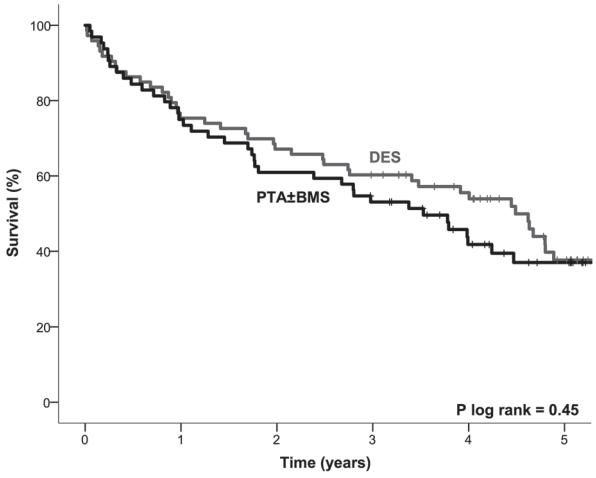


numbers at risk

DES	73	47	42	35	29	11
PTA±BMS	64	38	26	21	12	8

Figure 3C. Kaplan–Meier curves representing the estimated 5-year cumulative incidence rates of event-free survival per patient after PTA±BMS and DES

PTA indicates percutaneous transluminal angioplasty; BMS, bare metal stent; and DES, drug-eluting stent.



numbers at risk

DES	73	55	49	43	34	17
PTA±BMS	64	48	39	33	21	13

Figure 3D. Kaplan–Meier curves representing the estimated 5-year cumulative incidence rates of survival per patient after PTA±BMS and DES

PTA indicates percutaneous transluminal angioplasty; BMS, bare metal stent; and DES, drug-eluting stent.

Long-term Patency Rates

Table 2 shows the results of the MITT-analysis of the patency rates of the treated lesions, as assessed on duplex sonography. These results of duplex sonography are available in a limited percentage of limbs. Many patients were unable to visit the hospital and during follow-up a substantial percentage of patients died due to unrelated or unknown causes. The number of limbs without imaging is comparable in both groups.

Despite the limited number of lesions still available for follow-up, the percentages of lesions with preserved primary patency were significantly higher in the DES arm than in the PTA±BMS arm at 1, 3, and 4 years follow-up. After 2 and 5 years the percentages of lesions with preserved patency were also higher in the DES group, but these differences did not reach statistical significance. The ordinal scores showed significantly more favorable outcomes in the DES group at 1 year follow-up.

MITT-analysis	PTA±BMS	DES	*P* value‡
	N=71 lesions*	N=90 lesions*	
Lesions with preserved patency	30 (42.3)	59 (65.6)	0.007
Ordinal score:			0.021
≤50% stenotic	30 (42.3)	59 (65.6)	
>50% stenotic	12 (16.9)	2 (2.2)	
Occluded	6 (8.5)	5 (5.6)	
Amputation/CLI related death/treatment in interim	23 (32.4)	24 (26.7)	

Table 2A. Patency per lesion, at 1-year follow-up (duplex)

Values are n (%). BMS indicates bare metal stent; DES, drug-eluting stent; MITT, modified-intention-to-treat; and PTA, percutaneous transluminal angioplasty. *Numbers are numbers of limbs/lesions with available, diagnostic imaging and those with treatment failure. Unavailable imaging: 9 limbs in PTA±BMS, 8 limbs in DES. Limbs/lesions in patients deceased due to unrelated causes were censored (10 limbs in PTA±BMS, 10 limbs in DES). ‡*P* value weighted by number of lesions per patient.

MITT-analysis	PTA±BMS	DES	*P* value‡
	N=45 lesions*	N=48 lesions*	
Lesions with preserved patency	11 (24.4)	15 (31.3)	0.25
Ordinal score:		0.64	0.021
≤50% stenotic	11 (24.4)	15 (31.3)	
>50% stenotic	4 (8.9)	2 (4.2)	
Occluded	2 (4.4)	4 (8.3)	
Amputation/CLI related death/treatment in interim	28 (62.2)	27 (56.3)	

Table 2B. Patency per lesion, at 2-years follow-up (duplex)

Values are N (%). BMS indicates bare metal stent; DES, drug-eluting stent; MITT, modified-intention-to-treat; and PTA, percutaneous transluminal angioplasty. *Numbers are numbers of limbs/lesions with available, diagnostic imaging and those with treatment failure. Unavailable imaging: 19 limbs in PTA±BMS, 29 limbs in DES. Limbs/lesions in patients deceased due to unrelated causes were censored (18 limbs in PTA±BMS, 14 limbs in DES). ‡*P* value weighted by number of lesions per patient.

MITT-analysis	PTA±BMS	DES	*P* value‡
	N=39 lesions*	N=53 lesions*	
Lesions with preserved patency	8 (20.5)	20 (37.7)	0.036
Ordinal score:			0.18
≤50% stenotic	8 (20.5)	20 (37.7)	
>50% stenotic	2 (5.1)	2 (3.8)	
Occluded	1 (2.6)	2 (3.8)	
Amputation/CLI related death/treatment in interim	28 (71.8)	29 (54.7)	

Table 2C. Patency per lesion, at 3-years follow-up (duplex)

Values are N (%). BMS indicates bare metal stent; DES, drug-eluting stent; MITT, modified-intention-to-treat; and PTA, percutaneous transluminal angioplasty. *Numbers are numbers of limbs/lesions with available, diagnostic imaging and those with treatment failure. Unavailable imaging: 19 limbs in PTA±BMS, 22 limbs in DES. Limbs/lesions in patients deceased due to unrelated causes were censored (22 limbs in PTA±BMS, 19 limbs in DES). ‡*P* value weighted by number of lesions per patient.

MITT-analysis	PTA±BMS	DES	*P* value‡
	N=37 lesions*	N=46 lesions*	
Lesions with preserved patency	5 (13.5)	15 (32.6)	0.031
Ordinal score:			0.08
≤50% stenotic	5 (13.5)	15 (32.6)	
>50% stenotic	2 (5.4)	0	
Occluded	0	2 (4.3)	
Amputation/CLI related death/treatment in interim	30 (81.1)	29 (63.0)	

Table 2D. Patency per lesion, at 4-years follow-up (duplex)

Values are N (%). BMS indicates bare metal stent; DES, drug-eluting stent; MITT, modified-intention-to-treat; and PTA, percutaneous transluminal angioplasty. *Numbers are numbers of limbs/lesions with available, diagnostic imaging and those with treatment failure. Unavailable imaging: 11 limbs in PTA±BMS, 21 limbs in DES. Limbs/lesions in patients deceased due to unrelated causes were censored (27 limbs in PTA±BMS, 21 limbs in DES). Follow-up still ongoing: in 6 limbs in PTA±BMS, in 5 limbs in DES. ‡*P* value weighted by number of lesions per patient.

MITT-analysis	PTA±BMS	DES	*P* value‡
	N=35 lesions*	N=43 lesions*	
Lesions with preserved patency	3 (8.6)	5 (11.6)	0.67
Ordinal score:			0.52
≤50% stenotic	3 (8.6)	5 (11.6)	
>50% stenotic	1 (2.9)	0	
Occluded	0	2 (4.7)	
Amputation/CLI related death/treatment in interim	31 (88.6)	36 (83.7)	

Table 2E. Patency per lesion at 5-years follow-up (duplex)

Values are N (%). BMS indicates bare metal stent; DES, drug-eluting stent; MITT, modified-intention-to-treat; and PTA, percutaneous transluminal angioplasty. *Numbers are numbers of limbs/lesions with available, diagnostic imaging and those with treatment failure. Unavailable imaging: 7 limbs in PTA±BMS, 12 limbs in DES. Limbs/lesions in patients deceased due to unrelated causes were censored (30 limbs in PTA±BMS, 28 limbs in DES). Follow-up still ongoing: in 11 limbs in PTA±BMS, in 12 limbs in DES. ‡*P* value weighted by number of lesions per patient.

DISCUSSION

Our long-term results show that up to 5 years after endovascular treatment of infrapopliteal lesions in CLI patients the amputation-free survival and event-free survival rates are significantly higher in patients treated with paclitaxel-eluting DES compared with PTA±BMS. When considering the major amputation rate or survival rate separately, both are more favorable in the DES group, with a trend towards significance regarding major amputation rate.
Morphological follow-up of the treated infrapopliteal lesions in a limited number of patients shows that at 1-, 3- and 4-year follow-up, the percentage of lesions with preserved binary patency is significantly higher in the DES than in the PTA±BMS group.

Few studies thus far have studied the long-term (>1 year) follow-up of patients with CLI due to infrapopliteal lesions that were treated with DES. The published meta-analyses considering the endovascular treatment of lesions below-the-knee with DES versus either PTA or BMS evaluated the available outcomes until 1 year post-treatment only.[16-20] Of the individual randomized controlled trials reporting on DES for the treatment of infrapopliteal lesions[7-11], only the YUKON trial evaluated the long-term results[13]. The mean follow-up period of this trial, in which non-polymer sirolimus-eluting stents (SES) were compared with BMS, was 1,016 days, a few months shorter than our follow-up period (1,285 days). Reported event-free survival rates (defined as freedom from target limb amputation, target vessel revascularization, myocardial infarction, and death) were 65.8% and 44.6% (P =0.02) and amputation rates were 2.6% and 12.2% (P =0.06) for the SES and BMS group, respectively. Furthermore, the authors found a significantly stronger improvement in Rutherford category in the SES group.[13] A prospective non-randomized registry investigated the 3-year angiographic and clinical outcomes after infrapopliteal revascularization with angioplasty and bail-out SES or BMS in patients with CLI. The SES group showed significantly better primary patency and reduced binary restenosis rates, and better repeat intervention-free survival (HR 2.56, P =0.006; 77.6% in SES group and 70.3% in BMS group, P =0.049).[21]

Our results show that the long-term prognosis of CLI patients nowadays remains poor, with estimated AFS and event-free survival rates after 5 years in our study population of 20.4% and 15.3% in the PTA±BMS group and 31.8% and 26.2% in the DES group, respectively. In the above mentioned studies regarding long-term follow-up after infrapopliteal DES placement, the reported event-free survival (with a slightly different definition compared with our definition) and repeat

intervention-free survival rates are higher. This can be explained by the difference in patient characteristics; not even half of the patients included in the YUKON trial suffered from CLI[13] and a larger percentage of patients included in the non-randomized registry suffered from rest pain[21]. Clinical event rates in patients with claudication are reported to be very low[1,16] and patients with tissue loss have a much higher amputation rate than those with rest pain.[22]

The estimated survival rates of our cohort are very poor in both groups (5-year survival 37.0% in the PTA±BMS group and 37.7% in the DES group). Reported 1-year and 5-year mortality rates in CLI patients are as high as 40% and 40 to 70%, respectively, pointing out the systemic character of the atherosclerotic disease in these patients, who in majority also suffer from coronary and cerebrovascular disease.[1,23-26] These mortality rates even exceed those of several malignancies.[27] A more recent meta-analysis evaluated the 1-year AFS and mortality rates in CLI patients without revascularization options and reported significant improvement of these outcomes over the past two decades.[28] The most recent trial included in this meta-analysis reported a 1-year mortality rate of 19.8% (95% confidence interval 11.6-31.7%)[29], which in fact is in line with our 1-year survival rates. Insufficient data are available in the literature to determine whether this improvement, which has been suggested to be the result of improved secondary prevention, is also occurring on the long term.[26,28]

DES used in this study were balloon-expandable coronary DES, with limited length only suited to treat lesions up to 90 mm. Infrapopliteal disease in CLI patients, especially in those with diabetes mellitus, is known to consist of long and diffuse lesions.[30,31] The fact that the concept of DES seems to be effective below the knee in order to reduce restenosis warrants the development of long self-expandable DES.

The major strength of the present study is the long follow-up period up to 5 years post-treatment, with very few patients lost to follow-up. Furthermore, we included only CLI patients, who are actually at risk of clinical events. Unfortunately, during the 5 years of follow-up a substantial number of patients were physically unable to visit the hospital for evaluation by the vascular surgeon and duplex sonography of the treated limb. Therefore, we could present major clinical endpoints, such as major amputation, reinterventions, and survival, for all patients and the primary patency rates for a subgroup only.

Another limitation is that we did not test the cost-effectiveness of DES, which in fact is important to evaluate, as drug-eluting devices are costly. Additional to the already existing evidence of the superior performance of DES in infrapopliteal lesions, its cost-effectiveness should be derived in the future.

CONCLUSION

This RCT shows that long-term amputation-free survival and event-free survival in patients with critical limb ischemia due to infrapopliteal lesions is more favorable after treatment with DES as compared with the conventional endovascular strategy of PTA with bail-out BMS. The limited available morphological results also show higher preserved patency rates after DES than after PTA with bail-out BMS. Given the feasibility of DES for infrapopliteal lesions, proven not only at short- and mid-term, but also at long-term, one should consider treatment with DES in patients with CLI due to lesions below the knee.

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SUPPLEMENTARY MATERIAL

Status after 1 year	PTA±BMS (N=64)	DES (N=73)
Alive without amputation or re-intervention	38 (59.4)	47 (64,4)
Major amputation	7 (10.9)	5 (6.8)
Re-intervention	3 (4.7)	3 (4.1)
Amputation and death	4 (6.3)	3 (4.1)
Re-intervention and death	0	1 (1.4)
Re-intervention, amputation and death	1 (1.6)	0
Death	11 (17.2)	14 (19.2)

Supplemental table I-A. Outcome at 1 year follow-up, per patient

$P = 0.78$ (χ^2).

BMS indicates bare metal stent; DES, drug-eluting stent; and PTA, percutaneous transluminal angioplasty. Values are N (%).

Status after 2 years	PTA±BMS (N=64)	DES (N=73)
Alive without amputation or re-intervention	26 (40.6)	42 (57.5)
Major amputation	8 (12.5)	3 (4.1)
Re-intervention	5 (7.8)	4 (5.5)
Amputation and death	5 (7.8)	6 (8.2)
Re-intervention and death	0	1 (1.4)
Re-intervention, amputation and death	1 (1.6)	0
Death	19 (29.7)	17 (23.3)

Supplemental table I-B. Outcome at 2 years follow-up, per patient

$P = 0.25$ (χ^2)

BMS indicates bare metal stent; DES, drug-eluting stent; and PTA, percutaneous transluminal angioplasty. Values are N (%).

Status after 3 years	PTA±BMS (N=64)	DES (N=73)
Alive without amputation or re-intervention	21 (32.8)	35 (47.9)
Major amputation	8 (12.5)	4 (5.5)
Re-intervention	4 (6.3)	4 (5.5)
Amputation and death	5 (7.8)	6 (8.2)
Re-intervention and death	1 (1.6)	1 (1.4)
Re-intervention, amputation and death	1 (1.6)	0
Death	23 (35.9)	22 (30.1)
Lost to follow-up	1 (1.6)	1 (1.4)

Supplemental table I-C. Outcome at 3 years follow-up, per patient

$P = 0.61$ (χ^2)

BMS indicates bare metal stent; DES, drug-eluting stent; and PTA, percutaneous transluminal angioplasty. Values are N (%).

Status after 4 years	PTA±BMS (N=64)	DES (N=73)
Alive without amputation or re-intervention	12 (18.8)	29 (39.7)
Major amputation	7 (10.9)	1 (1.4)
Re-intervention	2 (3.1)	4 (5.5)
Amputation and death	5 (7.8)	7 (9.6)
Re-intervention and death	1 (1.6)	1 (1.4)
Re-intervention, amputation and death	1 (1.6)	0
Death	29 (45.3)	24 (32.9)
Lost to follow-up	1 (1.6)	2 (2.7)
Follow-up ongoing	4 (6.3)	3 (4.1)
Amputation, follow-up ongoing	2 (3.1)	2 (2.7)

Supplemental table I-D. Outcome at 4 years follow-up, per patient

P=0.12 (χ^2)

BMS indicates bare metal stent; DES, drug-eluting stent; and PTA, percutaneous transluminal angioplasty. Values are N (%).

Status after 5 years	PTA±BMS (N=64)	DES (N=73)
Alive without amputation or re-intervention	8 (12.5)	11 (15.1)
Major amputation	5 (7.8)	2 (2.7)
Re-intervention	1 (1.6)	3 (4.1)
Amputation and death	5 (7.8)	7 (9.6)
Re-intervention and death	1 (1.6)	2 (2.7)
Re-intervention, amputation and death	1 (1.6)	0
Death	31 (48.4)	32 (43.8)
Lost to follow-up	1 (1.6)	4 (5.5)
Follow-up ongoing	5 (7.8)	9 (12.3)
Re-intervention, follow-up ongoing	1 (1.6)	1 (1.4)
Amputation, follow-up ongoing	5 (7.8)	2 (2.7)

Supplemental table I-E. Outcome at 5 years follow-up, per patient

P =0.63 (χ^2)

BMS indicates bare metal stent; DES, drug-eluting stent; and PTA, percutaneous transluminal angioplasty. Values are N (%).

Chapter 4

Diabetes mellitus is associated with decreased limb survival in patients with critical limb ischemia

Pooled data from two randomized controlled trials

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4 Diabetes mellitus is associated with decreased limb survival in patients with critical limb ischemia

Pooled data from two randomized controlled trials

ABSTRACT

Objective

Although never assessed prospectively, diabetes mellitus (DM) is assumed to negatively affect the outcomes of critical limb ischemia (CLI). DM was highly prevalent in two recently conducted randomized controlled trials in CLI patients, the **PADI** (Percutaneous Transluminal Balloon Angioplasty (PTA) and Drug-eluting Stents for Infrapopliteal Lesions in critical limb ischemia) and **JUVENTAS** (Rejuvenating Endothelial Progenitor Cells via Transcutaneous Intra-Arterial Supplementation) trials. To determine the implications of DM in a population of patients with infrapopliteal CLI, clinical outcomes were compared in patients with and without DM.

Research Design and Methods

Individual data from patients with CLI (Rutherford category ≥ 4) were pooled. Patients were considered to have DM when this diagnosis was reported in the hospital electronic medical records. Rates of major amputation (above ankle level) and major events (major amputation or death) were compared between CLI patients with and without DM. Hazard ratios (HRs) were calculated.

Results

Of a total of 281 patients, DM was present in 49,1%. The major amputation rate at 5 years of follow-up was higher in patients with DM than in patients without DM (34.1% vs. 20.4%, $P = 0.015$). The major event and death rate did not differ. The unadjusted HR of DM for the major amputation risk was 1.87 (95% CI 1.12-3.12). Model factors with significant HRs in the multivariate analysis were baseline Rutherford category (HR 1.95; 95% CI 1.24-3.06) and ankle-brachial index (ABI) >1.4 (HR 2.78; 95% CI 1.37-5.64).

Conclusions

CLI patients with DM are at significantly higher risk of major amputation than CLI patients without DM. This increased risk is associated with a higher prevalence of baseline ABI>1.4 and more severe ischemia at initial presentation in patients with DM.

4 Diabetes mellitus is associated with decreased limb survival in patients with critical limb ischemia: Pooled data from two randomized controlled trials

INTRODUCTION

Critical limb ischemia (CLI) is the most severe form of peripheral artery disease (PAD) and imposes an increasing burden on health care. The current incidence is substantial, with 500-1,000 new cases per 1 million inhabitants every year in Western Europe and North America.[1,2] Moreover, with a 6-month major amputation rate of 10 to 40% and a 1-year mortality rate of 25% in CLI patients who are not able to be revascularized, its poor prognosis is striking.[1-3]

One of the main goals in the treatment of CLI is to prevent major amputation, because a lower leg amputation in these patients is a high-risk procedure with a 30-day mortality of ±10% and less than 30% of surviving patients are ambulatory outdoors at 17 months of follow-up.[4] Identifying those patients who are at particularly high risk of major amputation is important to improve clinical decision-making and to select the most appropriate therapy for each patient. PAD progresses more rapidly in patients with diabetes mellitus (DM).[5] The risk of developing CLI is four-times higher in patients with DM than in patients without DM.[1] PAD in patients with DM is often accompanied by peripheral neuropathy with sensory dysfunction, which is thought to contribute to the development of foot ulcers and progressive tissue loss in patients with CLI.[6] Although CLI in patients with diabetes is often assumed to have a worse prognosis, this has not been proven prospectively in populations consisting exclusively of CLI patients. In studies that focus on CLI, patients with and without DM are usually reported as one group.[7] Because CLI patients are typically elderly, vulnerable, and fragile patients who are at high risk for cardiovascular events[1], CLI study populations are often small, which limits subgroup analyses and separate reporting of results for patients with and without DM.

The **PADI** (Percutaneous Transluminal Balloon Angioplasty (PTA) and Drug-eluting Stents for Infrapopliteal Lesions in critical limb ischemia) and **JUVENTAS** (Rejuvenating Endothelial Progenitor Cells via Transcutaneous Intra-Arterial Supplementation) trials investigated different treatment strategies in patients with CLI.[8,9] DM was a common comorbidity in both studies. Our study pooled data from these two studies with the aim of determining whether the prognosis regarding major amputation and major events differs between CLI patients with and without DM.

RESEARCH DESIGN AND METHODS

PADI Trial

Study Design, Population, and Procedures

Between October 2007 and February 2013, 137 patients with 144 limbs were enrolled in the **PADI** trial, an investigator-initiated, multicenter, randomized controlled, nonblinded, double-arm study.

Adult patients with CLI (defined as Rutherford category[10] ≥4) caused by infrapopliteal lesions were eligible for enrolment. Major exclusion criteria were (sub)acute limb ischemia, increased risk of bleeding, and estimated glomerular filtration rate (eGFR) <20 mL/min/1.73 m^2. Treatment with paclitaxel-eluting coronary stents (TAXUS Liberté; Boston Scientific, Natick, MA) was compared with percutaneous transluminal angioplasty with optional bail-out bare-metal stents. The rationale of this study, detailed inclusion and exclusion criteria, and study procedures have been reported previously.[11]

Follow-up and End Points

Patient assessments were planned before intervention, at discharge, after 3, 6, and 12 months, and annually until 5 years or until a major end point (major amputation or death) was reached. No patients were lost to follow-up until 12 months after inclusion. Long-term follow-up until 5 years is still ongoing. Follow-up of patients who underwent a major amputation was obtained by phone assessments or using data from patient medical records.

The primary end point of the **PADI** trial was the 6-month primary binary patency of treated lesions, defined as ≤50% stenosis on computed tomography angiography. Secondary end points were Rutherford classification[10], minor (below ankle level) and major amputation (above ankle level) of the trial leg, and periprocedural (within 30 days) complications, serious adverse events, and death. Short-term results have been published previously.[12] The trial was registered at ClinicalTrials.gov with the identifier NCT00471289.

JUVENTAS Trial

Study Design, Population, and Procedures

The **JUVENTAS** trial is a single-center, double-blind placebo-controlled randomized controlled trial that investigated the effects of repetitive infusion of bone marrow mononuclear cells into the common femoral artery.[9] The cohort included 160 patients (160 limbs). Inclusion criteria consisted of severe infrapopliteal PAD, defined as class IIB to IV in the Fontaine classification[1],

that was not amenable for conventional revascularization. Major exclusion criteria were factors that diminished life expectancy and/or precluded follow-up. The intervention consisted of three intra-arterial infusions of autologous bone marrow mononuclear cells. Patients in the placebo group received an autologous peripheral blood infusion designed to mimic the cell therapy product.

Follow-up and End Points
Primary outcome was major amputation (amputation through or above the ankle joint) or death at 6 months. Secondary outcomes were amputation at 2 months and during the entire observation period, as well as changes in Fontaine/Rutherford classification, minor amputations, ulcer size, ankle-brachial index (ABI), and quality of life.[8] Results have been published elsewhere.[8] No patients were lost to follow-up in the primary trial period of 6 months. Follow-up was extended until a maximum 5 years for this additional analysis, using patient medical records or by contacting patients by phone. The trial was registered at ClinicalTrials.gov under number NCT00371371.

Patient Selection
Data of the **PADI** and **JUVENTAS** trials were pooled on a patient level. We selected patients with CLI (i.e., Rutherford category 4/Fontaine stage III, or Rutherford category 5 or 6/Fontaine IV). Four patients were included in both trials; they were included in the analysis only once, with the longest available follow-up period. Selected **PADI** and **JUVENTAS** patients were analyzed according to the presence of DM. Subjects were classified as having DM when this diagnosis was reported in the hospital electronic medical records. All subjects in this study with DM were treated with blood glucose-lowering medication (oral hypoglycemic medications, insulin, and/or other noninjectable therapies); none were on diet or lifestyle modification alone.

Outcomes
Baseline characteristics, presence of ulcers at baseline and after 6 months of follow-up, major amputation, and major event rates until 5 years after treatment were compared between patients with and without DM. Major amputation was defined as amputation above the ankle level. A major event was defined as a major amputation or death. In addition, survival rates were analyzed separately for patients with and without a major amputation.

Statistical Analysis

Categorical variables were compared with the use of the two-sided χ^2 test, ordinal variables with the Mann-Whitney test, and continuous variables with the two-sided Student t test. A two-sided *P* value ≤0.05 was considered to indicate statistical significance. Missing data at inclusion were <5% for any parameter. In case of missing data, data points were imputed by multiple regression. The observed amputation and major event rates were estimated with the Kaplan-Meier method. Patients were censored at end of follow-up. Hazard ratios (HRs) of DM for the risk of major amputation were calculated with Cox proportional hazards regression models. A full model adjusted for age, smoking, history of stroke, history of coronary artery disease, previous treatment for PAD, impaired renal function (eGFR < 30 mL/min/1.73 m^2), Rutherford category at baseline, and categorized ABI at baseline of <0.7, 0.7-1.4, and >1.4 (including immeasurable ABI owing to incompressible vessels) was created for the multivariate analysis. Missing ABIs as a covariate for this model were imputed. We also performed backward reduction of model factors. The best performing model was based on the lowest Akaike information criterion. Potential interactions between variables were analyzed. The proportional hazards assumptions for all presented Cox models were evaluated by plotting Schoenfeld residuals. Stratification according to randomization was used to correct for the effects of treatment in the Kaplan-Meier analyses and Cox proportional hazards regression analyses. Analyses were performed in SPSS 22 software and R 3.1.0 software.

RESULTS

Patient Characteristics

Of the **PADI** trial, 133 patients (97.1%) fulfilled all inclusion criteria and were selected for this pooled analysis[12]; of whom 84 patients (63.2%) had DM. Of the **JUVENTAS** cohort, 152 patients (95.0%) were selected, of whom 57 patients (37.5%) had DM. Four patients were included in both trials; thus, 281 subjects were selected. Table 1 reports the baseline characteristics.

		Patients without DM	Patients with DM	*P* value*
		N=143 patients	N=138 patients	
Mean age in years (SD)		67.9 (15.0)	70.9 (11.3)	NS†
Male sex		94 (65.7)	99 (71.7)	NS
Smoking status				0.000
	Ex-smoker	62 (43.4)	54 (39.1)	
	Current smoker	48 (33.6)	24 (17.4)	
Previous stroke or TIA		14 (9.8)	33 (23.9)	0.002
Coronary disease		47 (32.9)	62 (44.9)	0.038
Impaired renal function §		15 (10.5)	19 (13.8)	NS
Renal disease requiring dialysis		8 (5.6)	9 (6.5)	NS
On anticoagulation medication		136 (95.1)	129 (93.5)	NS
History of PAD		107 (74.8)	102 (73.9)	NS
Rutherford category				
	Mean (SD)	4.8 (0.6)	5.0 (0.6)	0.002‡
	Median (min-max)	5 (4-6)	5 (4-6)	
Ankle-brachial index				
	Mean (SD)	0.57 (0.30)	0.70 (0.35)	0.003†
	<0.7	97 (67.8)	55 (39.9)	0.000
	0.7-0.9	18 (12.6)	31 (22.5)	
	0.9-1.2	15 (10.5)	27 (19.6)	
	1.2-1.4	3 (2.1)	2 (1.4)	
	>1.4/ immeasurable	10 (7.0)	23 (16.7)	

Table 1. Baseline characteristics, according to diabetes state

Data are N (%) unless stated otherwise. Missing ABIs were imputed. TIA, transient ischemic attack. *By χ^2 test, unless stated otherwise; † By t test; ‡By Mann-Whitney test; §Determined by eGFR <30mL/min/1.73 m^2

Overall, 138 patients (49.1%) had DM. Significantly more patients with DM than those without DM had a history of stroke or transient ischemic attack and coronary artery disease. Significantly more patients without DM were current smokers or had smoked in the past.
Patients with DM showed a significantly higher Rutherford category at baseline. More patients without DM had an ABI <0.7, whereas a larger proportion of patients with DM showed an ABI between 0.7 and 1.4, or an ABI>1.4 ($P < 0.001$). Supplementary Table I reports the baseline characteristics separately for patients with and without diabetes in the **PADI** and **JUVENTAS** cohorts.

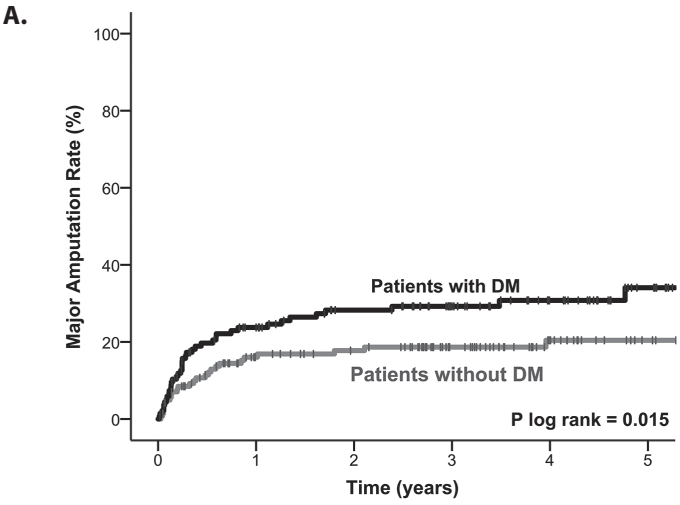
End Points

Patients were monitored for a median duration of 142.5 weeks, equivalent to 767 patient-years of observation. The mean follow-up time of surviving patients with DM was 184.5 (SD 92.8) weeks and of surviving patients without DM was 197.6 (SD 112.6) weeks.
Table 2 reports the significantly higher rate of major amputations in patients with DM compared with patients without DM, with an estimated rate of 34.1% of the former undergoing a major amputation during 5 years of follow-up versus 20.4% of the latter ($P = 0.015$). This is also graphically shown by the Kaplan-Meier curves of the estimated cumulative incidence rates of major amputation (Fig. 1A). Most of the major amputations in both groups were performed in the first 6 months after randomization.
The major event rate (major amputation or death) and death rate did not differ significantly between patients with or without DM (Table 2 and Fig. 1B).
Figure 1C shows that survival is significantly decreased in patients after amputation ($P = 0.006$). This poor survival after major amputation is comparable in patients with and without DM ($P = 0.63$) (Supplementary Fig. I). The survival of patients without a major amputation did not differ between patients with and without DM ($P = 0.99$) (Supplementary Fig. II).
Both at baseline and at 6 months of follow-up, ulcers were present in a significantly larger percentage of patients with DM ($P = 0.043$ and $P = 0.002$, respectively) (Supplementary Table II).
The unadjusted HR of DM for the risk of major amputation was 1.87 (95% CI 1.12-3.12; $P = 0.017$) (Table 3). The multivariate analysis with all factors included and with stratification by randomization showed a HR of DM of 1.59 (95% CI 0.91-2.78; $P = 0.11$). The model factors with significant HRs in the multivariate analysis were Rutherford category at baseline (HR 2.03; 95% CI 1.28-3.21; $P = 0.003$) and a baseline ABI >1.4 (HR 2.62; 95% CI 1.23-5.57; $P = 0.012$).

	Patients without DM		Patients with DM		*P* value*
	N= 143 patients		N= 138 patients		
Major Amputation	**N**	**% (95% CI)**	**N**	**% (95% CI)**	
0-6 months	16	11.4 (6.1-16.7)	26	19.7 (12.8-26.6)	
0-12 months	22	16.0 (9.9-22.1)	31	23.8 (16.5-31.1)	
0-24 months	24	17.8 (11.3-24.3)	36	28.3 (20.5-36.1)	
0-36 months	25	18.7 (12.0-25.4)	37	29.2 (21.2-37.2)	
0-48 months	26	20.4 (13.1-27.7)	38	30.8 (22.4-39.2)	
0-60 months	26	20.4 (13.1-27.7)	39	34.1 (23.9-44.3)	0.015
Death	**N**	**% (95% CI)**	**N**	**% (95% CI)**	
0-6 months	11	8.0 (3.5-12.5)	17	12.8 (7.1-18.5)	
0-12 months	24	17.9 (11.4-24.4)	25	19.2 (12.3-26.1)	
0-24 months	34	25.6 (18.2-33.0)	41	32.0 (24.0-40.0)	
0-36 months	41	31.3 (23.3-39.3)	48	38.1 (29.5-46.7)	
0-48 months	45	36.1 (27.3-44.9)	52	43.0 (33.8-52.2)	
0-60 months	53	48.0 (37.6-58.4)	59	55.7 (44.7-66.7)	0.78
Amputation/Death	**N**	**% (95% CI)**	**N**	**% (95% CI)**	
0-6 months	25	17.5 (11.2-23.8)	38	27.5 (20.1-34.9)	
0-12 months	42	29.4 (22.0-36.8)	47	34.1 (26.3-41.9)	
0-24 months	51	35.7 (27.9-43.5)	62	45.0 (36.8-53.2)	
0-36 months	59	41.7 (33.5-49.9)	70	51.2 (42.8-59.6)	
0-48 months	63	46.3 (37.7-54.9)	74	55.6 (47.0-64.2)	
0-60 months	69	54.4 (44.8-64.0)	82	68.7 (58.7-78.7)	0.19

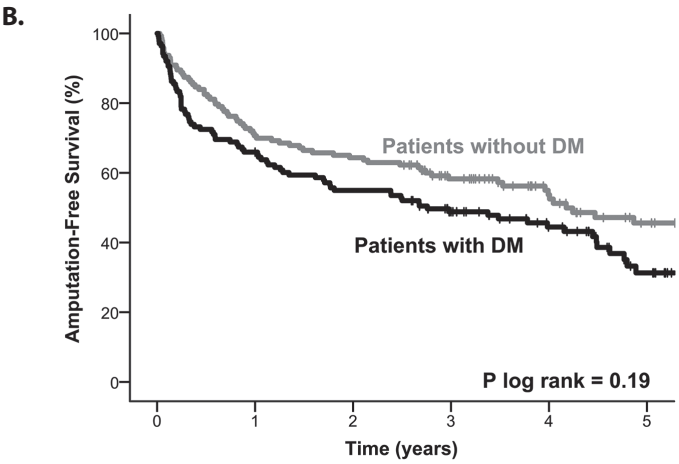
Table 2. Cumulative proportion experiencing amputation/death categorized by diabetes

*Overall log-rank test, stratified by randomization



numbers at risk

DM +	138	90	75	54	36	16
DM -	143	101	92	66	43	28



numbers at risk

DM +	138	90	75	54	36	16
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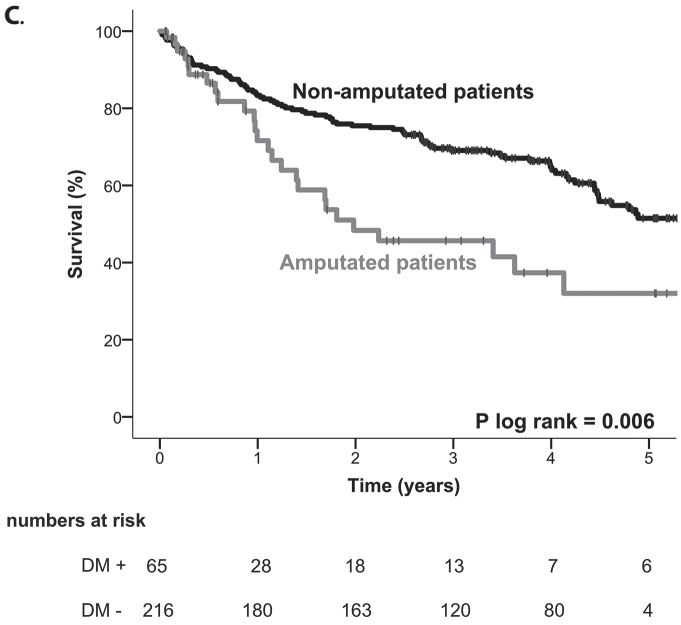

Figure 1. Kaplan-Meier curves representing the estimated cumulative incidence rates of major amputation (A) and amputation-free survival (B) per patient for patients with and without DM, and survival in amputated and nonamputated patients (C)

Multivariate analysis with the inclusion of DM, baseline Rutherford category, and baseline ABI category yielded the best performing model with the lowest Akaike information criterion. In this model, the HR of DM was 1.56 (95% CI 0.92-2.65; $P = 0.10$), of baseline Rutherford category was 1.95 (95% CI 1.24-3.06; $P = 0.004$), and of baseline ABI>1.4 was 2.78 (95% CI 1.37-5.64; $P = 0.005$).

Variables at baseline	Hazard Ratio	95% CI	*P* value*
Univariate analysis			
Diabetes mellitus	1.87	1.12-3.12	0.017
Multivariate analysis			
Age	1.01	0.99-1.03	0.29
Diabetes mellitus	1.59	0.91-2.78	0.11
Stroke	0.88	0.45-1.70	0.70
Coronary disease	1.02	0.59-1.75	0.95
PAD	1.47	0.73-2.95	0.28
Former smoker	0.91	0.45-1.81	0.78
Current smoker	1.39	0.65-2.98	0.40
eGFR < 30	1.59	0.81-3.13	0.18
Rutherford category	2.03	1.28-3.21	0.003
ABI<0.7	1.26	0.68-2.32	0.46
ABI>1.4	2.62	1.23-5.57	0.012
Multivariate analysis, best performing model			
Diabetes mellitus	1.56	0.92-2.65	0.10
Rutherford category	1.95	1.24-3.06	0.004
ABI<0.7	1.32	0.73-2.41	0.36
ABI>1.4	2.78	1.37-5.64	0.005

Table 3. Results of Cox proportional hazards regression analysis of variables for prediction of major amputation

ABI indicates ankle-brachial index; PAD, peripheral arterial disease; CI, confidence interval; eGFR < 30, estimated glomerular filtration rate < 30 ml/min/1.73m^2.

*Stratified by randomization.

CONCLUSIONS

Our data show that a significantly larger percentage of CLI patients with DM require a major amputation within 5 years compared with CLI patients without DM. Patients in our cohorts with CLI and DM had an almost 20% risk to undergo major amputation in the first 6 months after inclusion versus 10% in patients without DM. Within 5 years, the estimated major amputation rate is one of three in patients with DM versus one of five in patients without DM. Survival is poor after major amputation, both for patients with and without DM.

Higher baseline Rutherford category and ABI>1.4 were significant predictors of major amputation, which may suggest that merely these manifestations of DM are more important for the outcome of CLI than the disease itself. Both factors are more common in patients with DM.

In addition, compared with patients without DM, significantly more patients with DM had a history of stroke, transient ischemic attack, and coronary artery disease, indicating more extensive vascular disease.

The association between DM and the development of PAD has been described previously but is not well known.[1] The course of PAD in patients with DM is more aggressive compared with patients without DM, with the former group being at higher risk of developing CLI.[1,13] The fate of a patient's ischemic leg related to the presence or absence of concomitant DM is less well studied.[7] To our knowledge, this study is the first that has prospectively proven in a true CLI population that DM is associated with lower limb survival in patients with CLI, by comparing 138 CLI patients with DM and 143 CLI patients without DM from two prospective randomized trials. Our results are supported by a previous retrospective population-based cohort study showing a lower amputation-free survival after leg bypass surgery in CLI patients with DM than in CLI patients without DM.[14]

The higher mean Rutherford category at baseline in the subgroup with DM in the current study may relate to the high prevalence of concomitant peripheral neuropathy in these patients. Because pain perception is blunted in case of neuropathy, patients are not aware of the development of an ischemic ulcer or gangrene. Consequently, the presentation of CLI in patients with DM is usually at a later stage with more severe lesions.[6] This is supported by our finding that ulcers are more prevalent at baseline and at 6 months of follow-up in patients with DM.

An ABI>1.4 is probably related to medial artery calcification (MAC), leading to poorly compressible, stiffened arteries. MAC is more often seen in patients with DM and end-stage renal disease.[15-18] Several studies have reported an association between an elevated ABI and amputation.[18-20]

Our data confirm that an ABI>1.4 is strongly associated with a higher risk of amputation in patients with DM. Arterial wall stiffness caused by MAC is associated with reduced arterial flow volume in the lower extremities of patients with DM.[21] In these patients, besides recanalization, treatment should be considered for the stiff and calcified vessel wall, although options in this field thus far are limited. It has been suggested that nitrogen-containing bisphosphonates might limit cardiovascular calcification.[22] An association of high dietary menaquinone (vitamin K2) intake with reduced coronary calcification has been reported.[23] Chelation therapy with disodium EDTA has also been proposed to treat vascular calcifications, but proof of efficacy thus far is insufficient.[24]

It is recommended that in case of a high or immeasurable ABI, additional non-invasive diagnostic testing, such as toe systolic pressures, pulse volume recordings, transcutaneous oxygen measurements, or vascular imaging (e.g., duplex ultrasound) should be performed to detect coexisting stenotic or occlusive arterial disease.[1,15] A high or immeasurable ABI in a population with DM with a clinical suspicion of CLI requires a careful diagnostic process and treatment strategy to avoid amputation. Our study underscores the limited value of the ABI in the assessment of PAD in DM, because almost half of our patients with DM and CLI had baseline ABI values between 0.7 and 1.4.[25]

Amputation-free survival was lower in patients with DM than in patients without DM at all times at follow-up, but this difference did not reach statistical significance. The difference in amputation-free survival rate is mostly attributable to the higher amputation rate in patients with DM, because the death rate in patients with DM is comparable with that in patients without DM.
Survival was significantly lower in patients after a major amputation during follow-up. This is analogous to a previously conducted study that reported a survival rate after major amputation of only 55% at 3 years of follow-up[4] and illustrates the poor prognosis of patients after major amputation. The diminished survival after major amputation did not differ between patients with and without DM, but these subgroups were considered too small for further subanalysis. Two retrospective cohort studies did find significantly lower survival rates in patients with DM than in patients without DM during follow-up after minor and major lower extremity amputations.[26,27] Because neither of these studies analyzed the indications for amputation, whether these patients are comparable with the current study population with severe CLI cannot be determined.

Some limitations of this study need to be considered. Subjects were classified as having DM based on the hospital electronic medical records. All of these subjects were using blood glucose-lowering medication (oral hypoglycemic medications, insulin, and/or other noninjectable therapies). It is possible that some subjects in the group without DM might actually have had early, undiagnosed DM, which could have increased the chance of a false-negative but not of a false-positive observation. Our findings are therefore only applicable to patients with DM that requires blood glucose-lowering medication.

Because the study population consisted of two patient cohorts from randomized controlled trials designed to test interventions in CLI, potential heterogeneity exists because of treatment effects. To forestall this limitation, we have stratified by randomization in the Kaplan-Meier survival and Cox regression analyses to correct for effects of different treatment strategies. We also ascertained that there were no statistical interactions between the treatment arm and the presence of DM. We corrected for differences in baseline characteristics, by apply multivariate Cox regression analyses.

Some exclusion criteria were applied in the **PADI** and **JUVENTAS** trials, and therefore, our findings may not be extrapolated to every CLI patient. The **PADI** trial excluded patients with non-treatable iliac or femoropopliteal lesions, which may have resulted in a lower risk of major amputation in the study subjects. The same may be applied to the exclusion criterion of the **PADI** trial of a diminished renal function (eGFR<20 mL/min/1.73 m^2).

Patients included in the **JUVENTAS** trial had CLI caused by severe PAD that could not be revascularized. The risk of major amputation in these patients is supposedly higher than in patients with CLI who can be treated with surgical or endovascular recanalization.

However, we stress that this study focuses on CLI, and because of the inclusion and exclusion criteria, a study population could be selected with comparable infrapopliteal CLI, which is the unique and major strength of our study.

Finally, infection is known to increase the risk of major amputation[1,28]; however, data regarding the presence of concomitant infection in some patients with ulcers and necrosis are lacking.

In conclusion, CLI patients with DM have significantly more prevalent cardiovascular comorbidity and are at a substantially higher risk of major amputation compared with patients with CLI without DM. The higher amputation risk is associated with a higher proportion of patients with DM with ABI>1.4 at baseline and a more advanced clinical stage at presentation. Future research should indicate whether treatment strategies aimed at these factors could reduce the amputation rate in patients with DM.

Author Contributions

M.I.S. participated in data collection, researched data, wrote the manuscript, and takes overall responsibility. H.G. participated in data collection, researched data, and wrote the manuscript. M.T. reviewed/edited the manuscript. R.W.S. participated in data collection and researched data. M.C.V. reviewed/edited the manuscript. R.G.S.E. participated in data collection. J.P.P.M. participated in data collection and reviewed/edited the manuscript. W.P.Th.M.M. participated in data analysis, wrote/edited the manuscript, and takes overall responsibility. H.O. participated in data collection, data analysis, wrote/edited the manuscript, and takes overall responsibility.

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Guarantor's Statement

Marlon Spreen, Hans van Overhagen and Willem Mali are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of Interest

The authors have no conflicts of interest to disclose.

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JUVENTAS Study Group

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SUPPLEMENTARY MATERIAL

	PADI		JUVENTAS	
	Patients without DM	Patients with DM	Patients without DM	Patients with DM
	N=49 patients	N=82 patients	N=94 patients	N=56 patients
Mean age in years (SD)	76.4 (11.8)	73.0 (11.3)	63.5 (14.7)	67.7 (10.8)
Male sex	32 (65.3)	59 (72.0)	62 (66.0)	40 (71.4)
Smoking status				
Ex-smoker	12 (24.5)	17 (20.7)	50 (53.2)	37 (66.1)
Current smoker	13 (26.5)	18 (22.0)	35 (37.2)	6 (10.7)
Previous stroke or TIA	7 (14.3)	17 (20.7)	7 (7.4)	16 (28.6)
Coronary disease	16 (32.7)	33 (40.2)	31 (33.0)	29 (51.8)
Impaired renal function (eGFR<30)	7 (14.3)	12 (14.6)	8 (8.5)	7 (12.5)
On dialysis	5 (10.2)	8 (9.8)	3 (3.2)	1 (1.8)
Anticoagulation medication	44 (89.9)	75 (91.5)	92 (97.9)	54 (96.4)
History of PAD	26 (53.1)	55 (67.1)	81 (86.2)	47 (83.9)
Rutherford category				
Mean (SD)	5.1 (0.6)	5.1 (0.6)	4.6 (0.6)	4.9 (0.5)
Median (min-max)	5 (4-6)	5 (4-6)	5 (4-6)	5 (4-6)
Ankle brachial index*				
<0.7	29 (59.2)	25 (30.5)	68 (72.3)	30 (53.6)
0.7-1.4	17 (34.7)	41 (50.0)	19 (20.2)	19 (33.9)
>1.4/ immeasurable	3 (6.1)	16 (19.5)	7 (7.4)	7 (12.5)

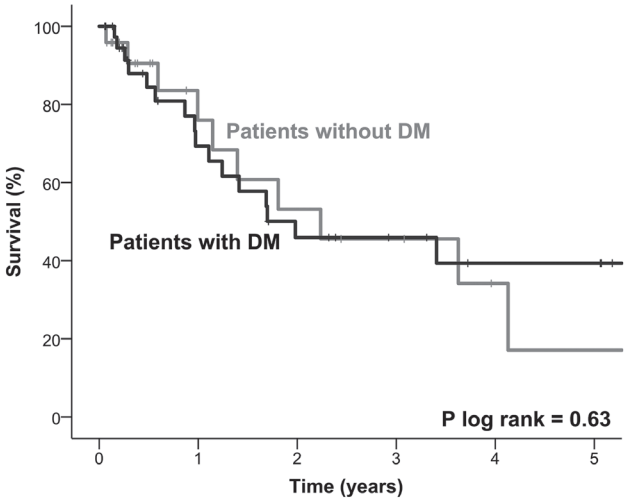
Supplemental table I. Baseline characteristics, according to cohort and separately for patients with and without DM

Data are N (%) unless stated otherwise. *Missing ankle brachial indices were imputed. DM indicates diabetes mellitus; eGFR, estimated glomerular filtration rate (in mL/min/1.73 m^2); PAD, peripheral artery disease; SD, standard deviation; and TIA, transient ischemic attack.

Ulcers	Patients without DM	Patients with DM	*P* value*
Baseline	**N=143 limbs**	**N=138 limbs**	
	84 (58.7)	97 (70.3)	0.043
6 months	**N=112 limbs**	**N=95 limbs**	
	31 (27.7)	46 (48.4)	0.002

Supplemental table II. Ulcers in patients with and without DM

Values are N (%). DM indicates diabetes mellitus.* χ^2 test.

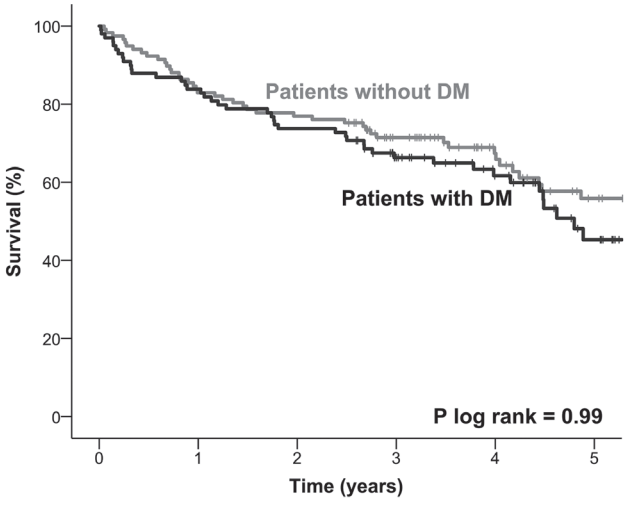


numbers at risk

DM +	39	18	11	8	5	5
DM -	26	10	7	5	2	1

Supplemental figure I. Kaplan-Meier curves representing the estimated cumulative incidence rates of survival following major amputation in patients with and without DM

DM indicates diabetes mellitus.



numbers at risk

DM +	99	83	73	54	36	16
DM -	117	97	90	66	44	29

Supplemental figure II. Kaplan-Meier curves representing the estimated cumulative incidence rates of survival in non-amputated patients with and without DM

DM indicates diabetes mellitus.

Chapter 5

High and immeasurable ankle–brachial index as predictor of poor amputation-free survival in patients with critical limb ischemia

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On behalf of **PADI** and **JUVENTAS** Study Groups

Submitted.

5 High and immeasurable ankle–brachial index as predictor of poor amputation-free survival in patients with critical limb ischemia

ABSTRACT

Background

Previous studies have investigated the prognostic value of the ankle-brachial index (ABI) for (cardiovascular) events in high-risk patients. Its value in critical limb ischemia (CLI) is less well studied. In the current study, the prognostic value of the ankle-brachial index (ABI) is assessed regarding major amputation and survival in patients with CLI and proven arterial obstructive disease below the knee.

Methods & Results

Data from two recently conducted trials in CLI patients, the **PADI** and **JUVENTAS** trials, were pooled. Adult patients with CLI (Rutherford category ≥ 4) and proven arterial obstructive disease were allocated according to baseline ABI to the low (<0.7), intermediate (0.7-1.4), or high (>1.4)/immeasurable ABI subgroup. Major amputation and amputation-free survival (AFS) rates were compared. Hazard ratios (HRs) for the risk of major amputation and amputation/death were calculated. To quantify the effect of inclusion of high/immeasurable ABI in the existing PREVENT III prediction model, the net reclassification improvement (NRI) was derived.

Of 260 patients at baseline, 146 patients (56.2%) had a low, 81 patients (31.2%) an intermediate and 33 patients (12.7%) a high/immeasurable ABI. Patients with high/immeasurable ABI showed higher 5-year major amputation (52.1%) and lower 5-year AFS (5.0%) rates than the intermediate (25.5% and 41.6%, respectively) and low ABI patients (23.5% and 46.9%, respectively) (both $P<0.001$). This same trend was observed in subgroup analysis of diabetics and non-diabetics. Adjusted HR of high/immeasurable ABI for major amputation/ death risk was 2.93 (95% confidence interval (CI) 1.67-5.13) (both $P<0.001$). Adding the risk factor high ABI to the PREVENT III model yielded an NRI of 0.38 (95%CI 0.20-0.56; $P<0.0001$).

Conclusions

A high/immeasurable ABI in patients with CLI and proven arterial obstructive disease below the knee is an independent risk factor of major amputation and poor AFS, both in diabetics and non-diabetics. Incorporating high/immeasurable ABI in the PREVENT III prediction model improves its performance significantly.

INTRODUCTION

Critical limb ischemia (CLI) is the final stage of peripheral arterial disease (PAD).[1,2] Although the prognosis with respect to limb salvage and survival in CLI patients is reported to have improved over the years, probably due to better medical therapy and secondary prevention, CLI still poses a substantial burden on patients and health care.[3,4] More than 20% of patients presenting with CLI will have undergone a major amputation one year later.[1,5] In addition, CLI patients are at very high risk for cardiovascular events, including myocardial infarction and death.[6]

Patients with PAD and diabetes mellitus (DM) have a higher risk of developing CLI than non-diabetic patients.[1,7] In a recent prospective, pooled study, it was shown that the prognosis of CLI regarding major amputation is worse in patients with DM compared with patients without DM. An elevated or immeasurable ankle-brachial index (ABI) proved to be an independent predictor of major amputation.[8] In these cases the ABI is artificially elevated because higher cuff pressures are needed to compress the stiffened artery. In severe cases arteries may be completely incompressible, resulting in an immeasurable ABI.[9-14]
Previous studies have investigated the prognostic value of the ABI for cardiovascular events and mortality in high-risk populations.[15-20] Its prognostic value in established CLI is less well studied. None of the three existing externally validated prediction models that focus on CLI patients have incorporated the ABI[21-24] and only the PREVENT III model reports on amputation-free survival (AFS), the most relevant clinical outcome parameter in CLI.[1,3,21]

In the current study, the prognostic value of the ABI regarding the most important clinical outcomes of CLI, major amputation and amputation-free survival, is assessed by comparing different ABI categories in a cohort of patients with CLI and arterial obstructive disease below the knee, as assessed by pre-treatment imaging. An additional aim was to determine whether incorporating the ABI in the existing PREVENT III prediction model would improve its performance in this population.

METHODS & MATERIALS

The individual patient data were collected from two recent randomized controlled trials, the **PADI** trial[25,26] and the **JUVENTAS** trial[27,28], conducted in patients with CLI and infrapopliteal arterial obstructive disease. These trials are described in short below.

PADI Trial

Study design, Population and Procedures

The **PADI** trial (Percutaneous transluminal Angioplasty versus Drug-eluting stents for Infrapopliteal lesions) is an investigator-initiated, multi-center, randomized controlled, open label, double-arm study, in which the use of drug-eluting stents (DES) are compared with percutaneous transluminal angioplasty (PTA) with bail-out bare metal stents (BMS) in patients with CLI due to infrapopliteal lesions. One hundred thirty-seven patients (144 limbs) were included. In the DES arm, target lesions were treated with paclitaxel-eluting stainless steel coronary stents (TAXUS Liberté; Boston Scientific, Natick, MA). Patients in the PTA±BMS arm received PTA with optional bail-out stenting using non-drug-eluting coronary bare metal stents (BMS).[25]

Follow-up and End Points

Patient assessments were planned before intervention, at discharge, after 3, 6, and 12 months and annually until 5 years or until a major end point (major amputation or death) was reached. Follow-up of patients who underwent a major amputation was obtained by means of assessments by phone, or using data from patient medical records. No patients were lost to follow-up until 12 months after inclusion.

Primary end point of the **PADI** trial was 6-month primary binary patency of treated lesions, defined as ≤50% stenosis on Computed Tomography Angiography (CTA). Secondary end points were Rutherford classification[29], minor and major amputation (below and above ankle level, respectively) of the trial leg, and peri-procedural (within 30 days) complications, serious adverse events, and death. Short-term results have been published elsewhere.[26]

The trial was registered at ClinicalTrials.gov with the identifier NCT00471289.

JUVENTAS Trial

Study design, Population and Procedures

The **JUVENTAS** trial is a single-center, double-blind placebo-controlled randomized controlled trial, in which the effects of repetitive infusion of bone marrow mono-nuclear cells (BMMNCs) into the common femoral artery were investigated.[27] One hundred sixty patients (160 limbs) were included. Inclusion criteria consisted of severe infra-popliteal PAD, defined as class IIB to IV in the Fontaine Classification[1] that was not amenable for conventional revascularization. Major exclusion criteria were factors that diminished life expectancy and/or precluded follow-up.

The intervention consisted of three intra-arterial infusions of autologous BMMNCs. Placebo patients received an autologous peripheral blood infusion, designed to mimic the cell therapy product.

Follow-up and End Points

Primary outcome was major amputation (amputation through or above the ankle joint) or death at 6 months. Secondary outcomes were amputation at 2 months and during the entire observation period, as well as changes in Fontaine/Rutherford classification, minor amputations, ulcer size, ankle-brachial index (ABI), and Quality of Life. Results have been published elsewhere.28 No patients were lost to follow-up in the primary trial period of 6 months. Follow-up was extended until maximum 5 years for this additional analysis, using patient medical records or by contacting patients by phone.

The trial was registered at ClinicalTrials.gov under number NCT00371371.

Patient Selection

Patients were selected who suffered from CLI (i.e. Rutherford category 4 / Fontaine stage III, or Rutherford category 5 or 6 / Fontaine IV[1,29]). Subjects without an ABI measurement at baseline were excluded from the analysis (n=21 patients). Four patients were included in both trials; they were included in the analysis only once, with the longest available follow-up period.

Selected patients were analyzed according to their ABI at baseline.

Three different categories regarding baseline ABI were distinguished: a low ABI (<0.7[1]); an intermediate ABI (0.7 to 1.4); and a high/immeasurable ABI (>1.4[10] or incompressible vessels). No full consensus exists regarding the cutoff value in the lower ABI spectrum. We chose 0.7 a priori, as it is known that in case of ABI<0.7 PAD patients have a two-fold elevated risk of developing CLI.[1] Additionally, we repeated all analyses using a different cutoff for low ABI (<0.5).

The ABI value was determined by taking the highest pressure of the dorsalis pedis and posterior tibial arteries, divided by the highest ipsilateral or contralateral brachial arterial systolic pressure. In general, a single pressure measurement of each limb vessel was performed. The ABI was considered immeasurable when inflation of the blood pressure cuff to a pressure of >250 mmHg was insufficient to compress the anterior (just proximal of the dorsalis pedis artery) and posterior tibial arteries. Measurements were performed in accredited vascular laboratories.

Outcomes

Baseline characteristics were compared in the three different ABI subgroups and the major amputation and major event rates were calculated until 5 years after inclusion for each baseline ABI category. Major amputation was defined as amputation through or above the ankle joint, and a major event as either major amputation or death. Amputation-free survival (AFS) was defined as survival free of major amputation.

We performed additional subgroup analyses in patients with and without diabetes mellitus (DM) regarding AFS rates.

Unadjusted and adjusted hazard ratios (HRs) were calculated for the risk of major amputation and major event. The prognostic value of the ABI as continuous variable and of high/immeasurable ABI as binary variable for prediction of AFS at 1 and 2 years was evaluated.

Statistical Analysis

Categorical variables were compared using the two-sided χ^2 test, ordinal variables using the Kruskal-Wallis test, and continuous variables using analysis of variance (ANOVA). A two-sided *p*-value ≤0.05 was considered to indicate statistical significance. Missing data at inclusion were ≤5% for any parameter.

The observed rate of amputations and major events was estimated with the Kaplan-Meier method. To correct for the effects of treatment and trial differences subjects were stratified according to randomization in the two arms of each trial. Patients were censored at the end of follow-up.

HRs of either a high baseline ABI as well as a low baseline ABI for the risk of major amputation and for the risk of major event were calculated with Cox proportional hazards regression models, stratified by randomization. A full model adjusting for age, smoking, history of PAD, history of stroke, history of coronary artery disease, history of diabetes, impaired renal function (estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m^2; stage 4 or 5 according to the K/DOQI (Kidney Disease Outcomes Quality Initiative) 2002 classification of chronic kidney disease[30]), use of anticoagulant medication, Rutherford category[29] at baseline, and categorized ABI at baseline (<0.7;

0.7-1.4; >1.4/immeasurable) was created for the multivariate analysis. Additionally, backward reduction of model factors was performed. The best performing model was based on lowest Akaike information criterion (AIC). To validate the cut-off points in ABI, a restricted cubic spline was fit to the Cox regression model to evaluate the form of the relation between continuous outcomes and the risk of events.
For prediction models, multivariate logistic regression analysis was used to evaluate the effect of different factors on the cumulative odds of experiencing an event in a given time period.
Discriminative potential of various models was assessed by Receiver Operating Characteristic (ROC) curves, and summarized by C-statistic. The effect of in- and exclusion of model factors was evaluated by calculating the continuous Net Reclassification Improvement (NRI) of various models. We present the continuous NRI instead of category-based NRI, since this former NRI is considered the most objective and prudent to use when no established categories exist.[31]
Analyses were performed in SPSS version 23 for Mac and R version 3.1.0 independently by two operators (M.I.S. and H.G.).

RESULTS

Patient Characteristics

One hundred thirty-three of 137 patients (97.1%) of the **PADI** trial fulfilled all inclusion criteria and were selected for this pooled analysis. One hundred fifty-two of 160 patients (95.0%) were selected from the **JUVENTAS** cohort. Four patients were included in both trials. In 21 patients (7.5%) a baseline ABI was missing; these patients were excluded. Accordingly, a total of 260 patients were selected.
The majority, 146 patients (56.2%), had a low ABI at baseline (table 1). Thirty-three patients (12.7%) had a high/immeasurable ABI. The remaining 81 patients (31.2%) showed an intermediate ABI.
The prevalence of diabetes, a history of stroke or TIA, history of coronary disease, and impaired renal function (table 1) differed significantly between the three groups, with the highest percentages in the high/immeasurable ABI group.
All patients in the high ABI group already received anticoagulation medication (anti-platelet therapy, acenocoumarol, or phenprocoumon); this percentage was significantly lower in the other two groups. Furthermore, patients in the high/immeasurable ABI group showed the highest mean Rutherford category at baseline.

	Low ABI	Intermediate ABI	High ABI
	N=146 patients	N=81 patients	N=33 patients
Mean age in years (SD)	68.4 (14.1)	70.5 (13.6)	70.3 (9.7)
Male sex	93 (63.7)	58 (71.6)	26 (78.8)
Smoking status			
Ex-smoker	64 (43.8)	35 (43.2)	13 (39.4)
Current smoker	43 (29.5)	18 (22.2)	5 (15.2)
Diabetes mellitus	53 (35.6)	48 (59.3)	23 (69.7)*
Previous stroke or TIA	21 (14.4)	10 (12.3)	12 (36.4)*
Coronary disease	47 (32.2)	33 (40.7)	23 (69.7)*
Impaired renal function §	15 (10.3)	7 (8.6)	9 (27.3)*
Renal disease requiring dialysis	8 (5.5)	3 (3.7)	4 (12.1)
On anticoagulation medication	141 (96.6)	73 (90.1)	33 (100)*
History of PAD	116 (79.5)	53 (65.4)	26 (78.8)
Rutherford category (mean (SD))	4.7 (0.6)	5.0 (0.6)	5.2 (0.5)¶

Table 1. Baseline characteristics, categorized according to baseline ABI

Numbers are N (%), unless stated otherwise. ABI indicates ankle-brachial index; PAD, peripheral arterial disease; SD, standard deviation; TIA, transient ischemic attack. * χ^2 test, P<0.05. § Estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m^2. ¶Kruskal-Wallis test, P<0.001. Low ABI: <0.7; intermediate ABI: 0.7-1.4; high ABI: >1.4/immeasurable.

Major Amputation and Major Event Rates

In table 2 the cumulative proportion of patients experiencing major amputations and major events is shown, separately for the three ABI categories. The majority of major amputations was performed in the first 12 months after inclusion in patients with a low and high/immeasurable ABI. Overall, a significantly higher proportion of patients in the high/immeasurable ABI group was amputated in comparison with the other two groups; 52.1% after 5 years in the former group against 23.5% in the low ABI group and 25.5% in the intermediate ABI group (P<0.001) (table 2, supplemental figure I). After 5 years follow-up, the vast majority of patients in the high/immeasurable ABI group had suffered from a major amputation or had died (95.0%, table 2). In the low and intermediate ABI group these percentages were 53.1% and 58.4%, respectively (P <0.001) (table 2, supplemental figure II).

	Low ABI N=146 patients		Intermediate ABI N=81 patients		High ABI N=33 patients	
Amputation*	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
0-6 months	22	15.2 (9.3-21.1)	6	7.8 (1.7-13.9)	10	34.1 (16.9-51.3)
0-1 year	28	19.5 (13.0-26.0)	6	7.8 (1.7-13.9)	13	46.1 (27.3-64.9)
0-2 years	32	22.6 (15.7-29.5)	8	11.0 (3.7-18.3)	14	52.1 (32.1-72.1)
0-3 years	33	23.5 (16.4-30.6)	9	12.7 (4.9-20.5)	14	52.1 (32.1-72.1)
0-4 years	33	23.5 (16.4-30.6)	11	18.8 (7.8-29.8)	14	52.1 (32.1-72.1)
0-5 years	33	23.5 (16.4-30.6)	12	25.5 (9.2-41.8)	14	52.1 (32.1-72.1)
Major event*	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
0-6 months	28	19.2 (12.7-25.7)	15	18.5 (10.1-26.9)	15	45.5 (28.4-62.6)
0-1 year	40	27.4 (20.1-34.7)	20	24.7 (15.3-34.1)	21	63.6 (47.1-80.1)
0-2 years	52	35.6 (27.8-43.4)	27	33.3 (23.1-43.5)	25	76.9 (62.2-91.6)
0-3 years	58	39.9 (31.9-47.9)	34	42.5 (31.5-53.5)	26	80.2 (66.3-94.1)
0-4 years	61	42.9 (34.7-51.1)	37	48.8 (37.0-60.6)	26	80.2 (66.3-94.1)
0-5 years	69	53.1 (43.7-62.5)	40	58.4 (44.5-72.3)	29	95.0 (86.0-100)

Table 2. Cumulative proportion experiencing amputation/death categorized by baseline ABI

CI indicates confidence interval; major event, major amputation or death. Low ABI: <0.7; intermediate ABI: 0.7-1.4; high ABI: >1.4/immeasurable. *Overall *P* value, stratified according to randomization: <0.001.

Supplemental figure III shows the AFS rates of patients with high/immeasurable ABI, separately for patients with and without DM. Patients with high/immeasurable ABI without DM had a significantly lower AFS than patients with DM, with AFS rates after one year of 0.0% versus 52.2% (*P*=0.035), respectively. Patients with DM and a high/immeasurable baseline ABI showed significantly lower AFS rates when compared with patients with DM and intermediate and low ABI (supplemental figure IV, *P*=0.046). This difference in AFS rate according to the three ABI categories was even more outspoken in the subgroup of patients without DM (supplemental figure V, *P*<0.001).

Regression Analysis of Major Amputations and Major Events

Table 3 shows the results of the cox regression analysis, both in a univariate and multivariate fashion. The univariate analysis showed an association between a high/immeasurable ABI and amputation (HR 4.07; 95%CI 1.87-8.88; *P*<0.001). No association was detected between a low ABI at baseline and major amputation. In the multivariate analysis of the risk of major amputation with all model factors included and with stratification by randomization, an HR of 3.56 (95%CI 1.51-8.36; *P*=0.004) was observed for high/immeasurable baseline ABI. The only other factor significantly associated with major amputation was Rutherford category at baseline (HR 2.24; 95%CI 1.37-3.67; *P*=0.001).

Variables at baseline	Hazard Ratio	95% CI	*P* value*
Univariate analysis			
Low ABI	1.45	0.74-2.85	0.28
High ABI	4.07	1.87-8.88	<0.001
Multivariate analysis			
Age	1.01	0.99-1.04	0.23
Male gender	1.09	0.58-2.04	0.79
Diabetes mellitus	1.54	0.85-2.80	0.15
History of PAD	1.43	0.68-2.99	0.35
Impaired renal function§	1.48	0.71-3.06	0.30
Stroke	0.74	0.36-1.52	0.41
Coronary disease	1.11	0.61-2.00	0.74
Former smoker	0.73	0.34-1.58	0.42
Current smoker	1.25	0.55-2.88	0.60
On anticoagulants	0.89	0.20-3.97	0.88
Rutherford category	2.24	1.37-3.67	0.001
Low ABI	1.81	0.89-3.69	0.10
High ABI	3.56	1.51-8.36	0.004
Multivariate analysis, best performing model			
Diabetes	1.53	0.88-2.67	0.14
Rutherford category	2.09	1.31-3.34	0.002
Low ABI	1.85	0.94-3.67	0.08
High ABI	3.66	1.68-8.01	0.001

Table 3. Cox regression analysis of major amputation

ABI indicates ankle-brachial index, low, <0.7; high, >1.4/immeasurable; PAD, peripheral arterial disease; CI, confidence interval. *Stratified by randomization. §Estimated glomerular filtration rate < 30 ml/min/1.73m^2.

The best performing model for the risk of major amputation was with the inclusion of DM, baseline Rutherford category, and baseline ABI category. In this model the hazard ratio of diabetes was 1.53 (95%CI 0.88-2.67; *P*=0.14), of baseline Rutherford category 2.09 (95%CI 1.31-3.34; *P*=0.002), of low ABI 1.85 (95%CI 0.94-3.67, *P*=0.08) and of high/immeasurable ABI 3.66 (95% CI 1.68-8.01; *P*=0.001) (table 3). High/immeasurable ABI was also associated with a higher risk of major events, with HRs of 2.95 (95%CI 1.82-4.78, *P*<0.001) in the univariate analysis and 2.93 (95%CI 1.67-5.13, *P*<0.001) in the multivariate analysis with all model factors included. Other significant predicting factors were age and Rutherford category at baseline (table 4). No significant HRs were found for DM and impaired renal function.

Variables at baseline	Hazard Ratio	95% CI	*P* value*
Univariate analysis			
Low ABI	1.03	0.69-1.53	0.89
High ABI	2.95	1.82-4.78	<0.001
Multivariate analysis			
Age	1.04	1.02-1.06	<0.001
Male gender	1.00	0.66-1.53	0.98
Diabetes mellitus	1.00	0.69-1.45	0.99
History of PAD	1.12	0.73-1.72	0.61
Impaired renal function§	1.37	0.85-2.21	0.20
Stroke	1.26	0.81-1.95	0.31
Coronary disease	1.46	0.99-2.15	0.06
Former smoker	1.14	0.70-1.87	0.59
Current smoker	1.44	0.84-2.46	0.19
On anticoagulants	0.64	0.31-1.33	0.23
Rutherford category	1.52	1.10-2.09	0.01
Low ABI	1.16	0.75-1.78	0.51
High ABI	2.93	1.67-5.13	<0.001
Multivariate analysis, best performing model			
Age	1.04	1.02-1.05	<0.001
Coronary disease	1.53	1.07-2.18	0.02
Rutherford category	1.50	1.10-2.03	0.009
Low ABI	1.18	0.79-1.77	0.42
High ABI	3.02	1.84-4.96	<0.001

Table 4. Cox regression analysis of major event

ABI indicates ankle-brachial index, low <0.7; high >1.4/immeasurable; PAD, peripheral arterial disease; CI, confidence interval. *Stratified by randomization. §Estimated glomerular filtration rate < 30 ml/min/1.73m^2.

The best performing model describing the risk of major amputation or death included the model factors age, history of coronary disease, baseline Rutherford category, and baseline ABI. In this model a high/immeasurable ABI proved to be the most strongly associated with major outcomes, with a HR of 2.73 (95%CI 1.61-4.63, *P*<0.001).

Figure 1A depicts the relationship between ABI as continuous variable and the relative HR for major amputation. It is shown that in particular higher ABIs (>1.0) and to a lesser degree lower ABIs (<0.5) are associated with an increased risk of major amputation. Patients with immeasurable ABI values are plotted separately and have a HR of 3.76 (95% CI 1.65-8.56; *P*<0.002).

A J-shaped relationship between ABI and the risk for major events exists (figure 1B), patients with an immeasurable ABI have a HR of 3.10 (95% CI 1.88-5.10; *P*<0.001).
Repetition of all analyses with a different cutoff for low ABI (<0.5) yielded comparable results.

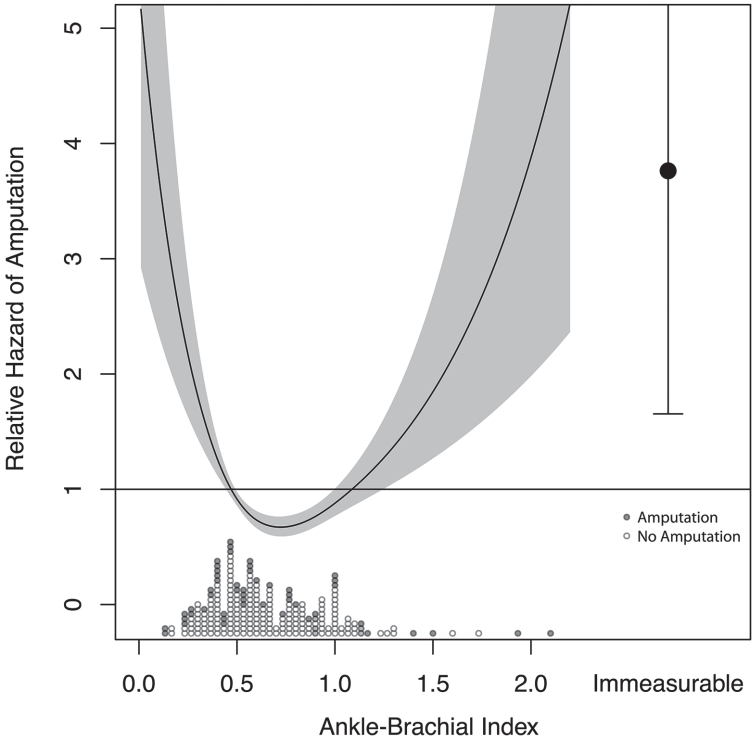

Figure 1A. Baseline ankle-brachial index and relative hazard ratios of major amputation

Relative HR of immeasurable ABI (plotted separately): 3.76 (95% CI 1.65-8.56; *P*<0.002).

ABI indicates ankle-brachial index; CI, confidence interval; HR, hazard ratio.

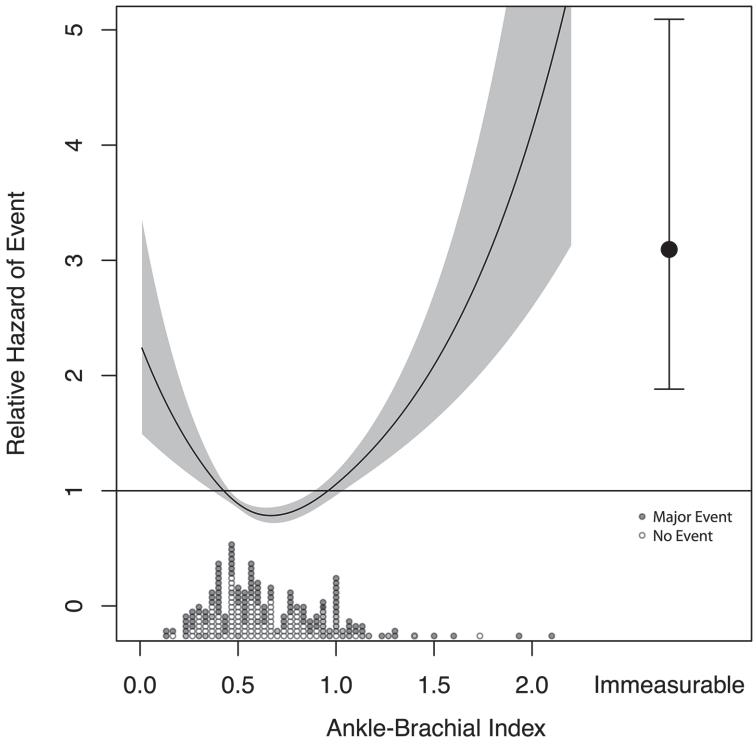

Figure 1B. Baseline ankle-brachial index and relative hazard ratios of major event (major amputation or death)

Relative HR of immeasurable ABI (separately plotted): 3.10 (95% CI 1.88-5.10; *P*<0.001).

ABI indicates ankle-brachial index; CI, confidence interval; HR, hazard ratio.

C-index and NRI of ABI in Addition to Current Models

We evaluated whether ABI would prove useful as an independent risk factor for risk-stratification in CLI patients. The C-statistics of baseline ABI expressed as continuous linear variable for predicting a major event at 1 and 2 years follow-up are 56.2% (95%CI 47.8-64.5, *P*=0.15) and 57.4% (95%CI 49.9-65.0%; *P*=0.05), respectively. If the J-shape of the relationship between ABI and risk of events is taken into account, the C-statistics are 58.28% (95% CI, 49.9-66.6%, *P*=0.052) and 60.0% (95% CI 52.25-67.77%; *P*=0.011) for 1 and 2 years, respectively. As reference we used the Prevent III model, a frequently used model that creates a weighted risk score on the basis of a history of advanced coronary artery disease (CAD) (1 point), advanced age (>75 years) (2 points), hematocrit (HT) ≤30% (2 points), the presence of tissue loss (3 points), and history of dialysis (4 points).[21] In the combined two cohorts of the present study, the Prevent III score had C-statistics of 64.51% (95%CI 57.5-71.5%, *P*<0.00001) and 69.6% (95% CI 63.2%-76.0%, *P*<0.001) for major events at 1 and 2 years, which is slightly higher than in other cohorts.[24,32]

A re-examination of the relative weights of the risk factors in Prevent III by multivariate logistic regression yielded similar weights (OR≈2 for age, CAD, and HT; OR≈2-3 for tissue loss) with the exception of dialysis history, which showed lower ORs in our cohorts (OR=1.5-1.7).
We next evaluated the additive value of a high/immeasurable ABI as binary variable to predict major events at 1 and 2 years. In multivariate logistic regression, high/immeasurable ABI proved an independent risk factor for major events (OR=3.85 for 1-year AFS, *P*=0.0012; OR=4.28, for 2-year AFS, *P*=0.001, supplemental table I) in addition to the Prevent III parameters. To reduce the model to a simplified score, we assigned 4 points to a high/immeasurable ABI, and maintained the scoring of the Prevent III model factors. The modified score had C-statistics of 68.5% (95%CI=61.6-75.4%) and 72.4% (95% CI 66.2-78.7%) for major event prediction at 1 and 2 years follow-up, respectively. The Net Reclassification Improvement (NRI) of the modified score in comparison to the Prevent III score was 0.45 (95%CI 0.23-0.66, *P*<0.0001) and 0.38 (95%CI 0.20-0.56, *P*<0.001) for 1- and 2-year prediction, respectively.

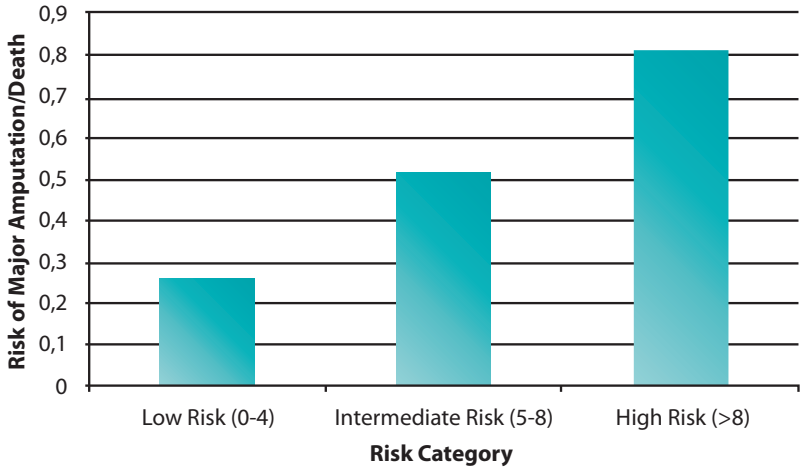

Figure 2. Two-year risk of major amputation or death for each risk category in the modified PREVENT III Risk Score

The risk score range of this modified model was stratified into three distinct risk categories; low risk, intermediate risk, and high risk (figure 2). Patients with a score of 0 to 4 points have a 26.1% risk, patients with a score of 5 to 8 points a 51.5% risk, and patients with a score>8 points a 90.0% risk of major amputation or death after 2 years.

DISCUSSION

The principal findings of the current study are that in patients with CLI and proven atherosclerotic arterial obstructive disease below the knee a high or immeasurable ABI at baseline is a significant and independent predictor of major amputation and a poor AFS. The observed association between ABI and major events is J-shaped, with very high ABI being a comparatively greater risk factor than very low ABI. Ninety-five percent of patients with a high/immeasurable ABI underwent a major amputation or died within 5 years. The incorporation of the risk factor high/immeasurable ABI leads to a significantly improved performance of the PREVENT III prediction model regarding 1-year and 2-year AFS in patients with CLI.

The strength of the current cohort of CLI patients is that the whole range of ABI values is present in subjects with arterial obstructive disease below the knee pointing at atherosclerosis, proven by pretreatment imaging. This enabled comparison of outcomes in patients with poorly or non-compressible and stiffened arteries (high/immeasurable ABI) with the outcomes in patients with compressible vessel walls (low and intermediate ABI), providing new insight in the deleterious effect of vascular stiffness.

The primary limitation of this study is that the study population consisted of two different patient cohorts, obtained from two intervention studies with mutually exclusive inclusion criteria. The homogeneity of the population could therefore be questioned. To forestall this limitation and to correct for effects of treatment, a conservative approach is applied by stratifying by randomization in the Kaplan-Meier survival and Cox regression analyses.
Nevertheless, an inclusion bias may be assumed, favoring patients with progressive disease in whom interventions are indicated. The absolute rates of major events are therefore probably higher than in a general CLI population, which is generally beneficial for the performance of the presented prediction models. We for instance observed, that the Prevent III model showed a higher C-statistic in our cohort than in the original study and in external validation cohorts.[24,32] We presume however that the relative contribution of risk factors, in particular the value of a high/immeasurable ABI, is likely to be generalizable to other populations.

While ABI has been studied as a risk factor and diagnostic parameter for incident cardiovascular disease[15-20], little is known about the prognostic value of ABI in established CLI. Contrary to intuition, studies have suggested that high ABI, rather than low ABI is a greater risk factor in advanced disease.[11-13]
Our results suggest a J-shaped association between ABI and decreased AFS, with a worse outcome in the high/immeasurable ABI group than in the low ABI group. This is line with the findings of a recent cohort study in subjects with suspected or confirmed PAD showing an elevated ABI to be a significantly better independent predictor of all-cause mortality than a normal or reduced ABI.[33] The adjusted HR of dying in the high ABI group (≥1.4, including non-compressible vessels) was 2.0-fold higher than in patients with normal ABI (1.0-1.3) and 1.3-fold higher than in those with ABI≤0.9.[33] Several other studies have investigated the relation between ABI and cardiovascular events and mortality, however often not specifically in a CLI population. These studies showed that an elevated ABI >1.4 or incompressible vessels should be considered as a risk factor for cardiovascular events and mortality.[9,12,33-36]

Although a high ABI is known to be associated with DM and end-stage renal disease[9], the higher risk of major amputation and diminished AFS in patients with a high/immeasurable ABI is not restricted to patients with DM or impaired renal function. In fact, non-diabetic patients in the high/immeasurable ABI group had even lower AFS rates than patients with DM. A cohort study in 229 CLI patients showed an ABI>1.3 to be associated with higher risk of major amputation in non-diabetic patients without renal insufficiency.[37] A significant relationship between high ABI (>1.4) and mortality among non-diabetic individuals has been reported as well.[35] Thus, the clinical use of a high/immeasurable ABI is not limited to patients with diabetes or renal function loss.

The PREVENT III model was designed to predict AFS at 1-year follow-up in patients with CLI.[21] A low ABI (defined as <0.3) was not incorporated in this model, since this was not a statistically significant risk factor of AFS, consistent with our findings regarding low ABI. A high ABI was not analyzed as a possible predictive factor.[21] Adding high/immeasurable ABI to the PREVENT III prediction model leads to a significantly better performing model in our cohort of CLI patients for the prediction of AFS at 1 and 2 years follow-up in our cohort of CLI patients, suitable for clinical use. In this modified PREVENT III model a high/immeasurable ABI is the best predicting factor with a higher OR than the PREVENT III model factors age>75 years, advanced coronary disease, hematocrit≤30%, tissue loss, and dialysis-dependency.[21]

A high/immeasurable ABI represents poorly compressible or incompressible arteries in the lower extremities. The precise etiology of this increased stiffness is unknown, but it is thought that medial arterial calcifications (MAC) play an important role.[9,10,14,33] There is increasing evidence from laboratory, autopsy, and epidemiological studies that MAC is a manifestation of an independent and separate age-associated pathophysiologic pathway different from atherosclerosis.[38-40] The current results imply that vascular stiffness has a local effect on the lower leg leading to high amputation rates. It has been suggested that stiffness due to MAC prevents compensatory positive arterial remodeling related to atherosclerosis when both diseases coincide, leading to substantial aggravation of the latter.[39] This coexistence of MAC and atherosclerotic disease is not uncommon with reported rates of 56 to 80%.[9,11,41]
In addition, stiffness probably has a systemic effect leading to high comorbidity and low AFS. Whether this systemic effect is caused by the stiff peripheral vasculature, or is due to a local stiffness in the coronary and cerebral vessels is as yet unknown. Further studies are needed to clarify the exact mechanisms and consequences of high/immeasurable ABI.

In conclusion, a high/immeasurable ABI in patients with CLI and proven atherosclerotic obstructive disease is an independent predictor for the risk of major amputation and poor AFS. This increased risk is observed both in patients with and without DM. Incorporating high ABI in the PREVENT III prediction model leads to a significantly better performing modified PREVENT III prediction model suitable and simple to use in clinical practice to identify patients who are at high risk of poor AFS. Clinicians should actively search for a high/immeasurable ABI.

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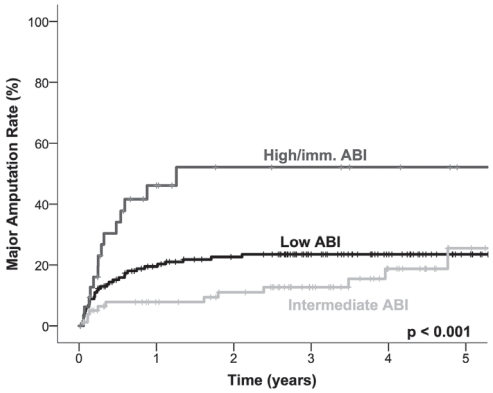
SUPPLEMENTARY MATERIAL



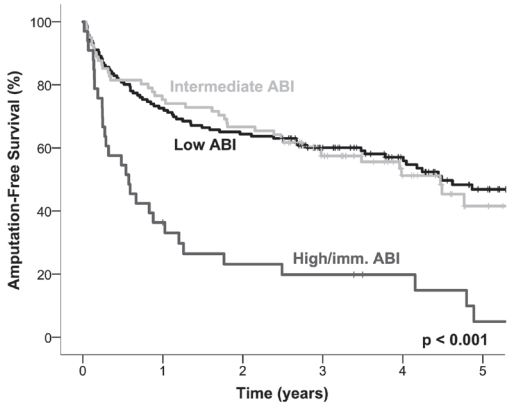
numbers at risk

Low ABI	146	106	94	70	49	31
Interm. ABI	81	61	54	39	22	9
High/imm. ABI	33	12	7	6	4	1

Supplemental figure I. Kaplan-Meier curves representing the estimated cumulative incidence rates of major amputation per patient according to baseline ankle-brachial index

ABI indicates ankle-brachial index; low, <0.7, intermediate, 0.7-1.4, high/imm, >1.4 or immeasurable.

Overall *P* value stratified according to randomization.



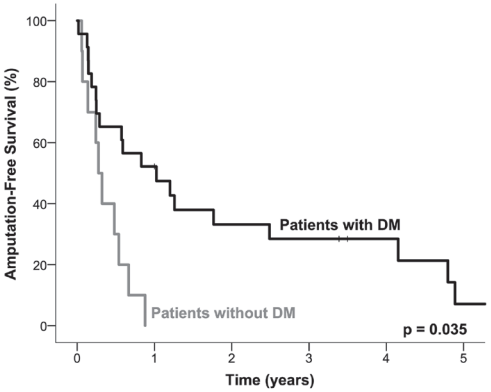
numbers at risk

Low ABI	146	106	94	70	49	31
Interm. ABI	81	61	54	39	22	9
High/imm. ABI	33	12	7	6	4	1

Supplemental figure II. Kaplan-Meier curves representing the estimated cumulative incidence rates of amputation-free survival per patient according to baseline ankle-brachial index

ABI indicates ankle-brachial index; low, <0.7, intermediate, 0.7-1.4, high/imm, >1.4 or immeasurable.

Overall *P* value stratified according to randomization.

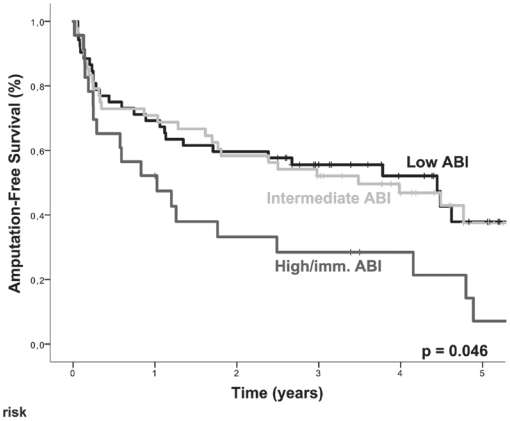


numbers at risk

DM +	23	12	7	6	4	1
DM -	10	0	0	0	0	0

Supplemental figure III. Amputation-free survival in patients with and without DM and with high (>1.4) or immeasurable ankle-brachial index

DM indicates diabetes mellitus. Overall *P* value stratified according to randomization.



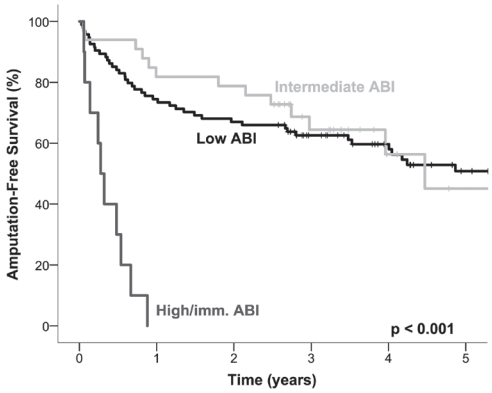
numbers at risk

Low ABI	52	36	31	22	14	7
Interm. ABI	48	34	28	24	16	6
High/imm. ABI	23	12	7	6	4	1

Supplemental figure IV. Amputation-free survival in patients with diabetes mellitus according to ABI at baseline

ABI indicates ankle-brachial index; low, <0.7, intermediate, 0.7-1.4, high/imm, >1.4 or immeasurable.

Overall *P* value stratified according to randomization.



numbers at risk

Low ABI	94	70	63	48	35	24
Interm. ABI	33	27	26	15	6	3
High/imm. ABI	10	0	0	0	0	0

Supplemental figure V. Amputation-free survival in patients without diabetes mellitus according to ABI at baseline

ABI indicates ankle-brachial index; low, <0.7, intermediate, 0.7-1.4, high/imm, >1.4 or immeasurable.

Overall *P* value stratified according to randomization.

Variables	One-year follow-up		Two-year follow-up	
	Odds Ratio	*P* value	Odds Ratio	*P* value
Age>75 years	1.76	<0.05	2.38	0.002
CAD	1.49	0.18	1.83	0.037
Hematocrit≤30%	1.38	0.54	1.81	0.28
Tissue loss	1.77	0.11	2.33	0.015
Dialysis	1.43	0.53	1.53	0.47
High ABI	3.85	0.001	4.28	0.001

Supplemental table I. Odds Ratios of PREVENT III model factors and high ABI for major events at 1 and 2 years follow-up

CAD indicates coronary artery disease; high ABI, ankle-brachial index >1.4 or immeasurable.

Chapter 6

Transpopliteal stenting of femoral occlusions in patients with critical limb ischemia using a 4 French system

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6 Transpopliteal stenting of femoral occlusions in patients with critical limb ischemia using a 4 French system

ABSTRACT

Purpose

In many patients with critical limb ischemia (CLI), transfemoral endovascular recanalization is the preferred treatment. Transpopliteal treatment may be used in patients with inaccessible groins. This retrospective study regards transpopliteal stenting of superficial femoral artery (SFA) occlusions using a 4F system.

Materials and Methods

Eleven patients (4 male and 7 female [mean age of 77 years]) underwent 12 attempts of transpopliteal recanalization of long SFA occlusions (Trans-Atlantic InterSociety Consensus B through D). All patients had CLI (Rutherford 4 to 6) and were non-operable due to poor general condition. Indications for transpopliteal access were proximal/flush SFA occlusions (N=5), failure of antegrade recanalization (N=4), infected femoral-femoral crossover bypass (N=2), and occlusion of both the native SFA and the femoral-popliteal bypass (N=1). The popliteal artery was punctured under ultrasound guidance. Occlusions were recanalized subintimally, and 4F compatible stents were implanted.

Results

Technical success rate (<30% residual stenosis) was achieved in 83% of cases. In two patients, stent dislocation occurred while the sheath was removed. One arteriovenous fistula was successfully treated with additional stenting. During 6-month follow-up, there were no major amputations, and three patients died from non-related causes. Fifty percent of patients alive after 6 months improved to Rutherford score ≤3. The duplex restenosis (>50%) rate at six months was 50%.

Conclusions

Transpopliteal primary stenting of complex SFA lesions in CLI for a temporary bypass is now technically feasible using a 4F system. Technical results are promising. Clinical results after 6 months are acceptable, when taking into consideration that this approach may be the last option for limb salvage.

6 Transpopliteal stenting of femoral occlusions in patients with critical limb ischemia using a 4 French system

INTRODUCTION

The superficial femoral artery (SFA) is the most commonly affected vessel in peripheral arterial disease.[1] Estimated 1-year amputation rate and mortality rate in patients presenting with chronic critical limb ischemia (CLI), the most serious form of peripheral arterial disease, are approximately 30 and 25%, respectively.[2] To restore unobstructed arterial blood flow to the foot, treatment strategies are either bypass surgery or endovascular revascularization. However, many patients with CLI and long lesions are elderly with multiple comorbidities and therefore are poor surgical candidates. Endovascular revascularization may be an effective and less invasive alternative to avoid amputation.

The antegrade transfemoral approach by way of the common femoral artery (CFA) is most commonly performed. However, if the groin is inaccessible or when an antegrade approach has failed, retrograde transpopliteal access may be an option.[3] At present, reported results from this transpopliteal approach mainly consider balloon dilatation with provisional stenting in case of significant restenosis or flow-limiting dissections.[4-13] However, a meta-analysis by Muradin et al. showed improved 3-year patency rates after stent implantation in the treatment of femoropopliteal arterial occlusions and in patients with CLI compared with Percutaneous Transluminal Angiography (PTA) alone.[14]

Thus, when a 4F stent platform recently became available, we assumed that transpopliteal primary stenting of femoral occlusions could be a useful option for patients with CLI and an inaccessible groin. We report our initial experiences with this technique, which is the first study considering primary stenting of SFA occlusions using a retrograde transpopliteal approach by means of a 4F system in patients with CLI.

MATERIALS AND METHODS

Patient Selection

All consecutive patients with critical limb ischemia (Rutherford 4 to 6[15]) who underwent endovascular treatment of femoral occlusions by a transpopliteal approach in 2011 and 2012 were retrospectively included.

Procedures and Follow-up

Retrograde ipsilateral puncture with a 21G needle of the popliteal artery (PA) in the popliteal fossa was performed under ultrasound guidance. Ultrasound not only facilitates puncture of the deeply located and, in the case of SFA occlusion,

poorly pulsating PA, it also avoids accidental puncture of the more superficially located popliteal vein. A 4F radial sheath (Cordis, Johnson & Johnson, Bridgewater, NJ, USA) was introduced after confirmation of a successful puncture. The target lesion was traversed with a 4F multipurpose angiographic (MPA) or vertebral catheter and 0.035-inch hydrophilic guide wire (Terumo, Tokyo, Japan). In this series of long occlusions, generally the subintimal recanalization, using standard techniques, turned out to be successful. After re-entering the true lumen, the guide wire was exchanged for a 0.018 inch V18 guide wire (Boston Scientific, Natick, MA, USA). The lesion was pre-dilatated with a 5-mm Passeo-18 PTA balloon (Biotronik AG, Bülach, Switzerland). The appropriate stent size was selected after reviewing the patient's baseline angiogram, with a requirement that the diameter of the stent was 1-2 mm larger than the reference vessel diameter. Self-expandable nitinol Pulsar-18 stents (Biotronik AG, Bülach, Switzerland) were inserted through the sheath in the PA, with sizes ranging from 5.0 x 170 mm to 6.0 x 200 mm. In case of multiple stents we aimed for a stent overlap of 10 mm. Subsequently, the stent was post-dilatated with a 5-to 6-mm Passeo-18 PTA balloon. Completion angiography was performed to assess the technical result at the end of the procedure. Manual compression was applied to the access site until hemostasis was obtained. During the procedure, 5,000 U of heparin were administered intra-arterially.

Follow-up was performed by means of clinical evaluation (i.e., Rutherford category[15], major / minor amputation, survival) and duplex sonography at 6 months after the procedure. Clinical records, laboratory tests, and duplex examinations of all patients were examined retrospectively. In cases where additional data were required, patients were contacted for an additional follow-up visit.

Demographics, symptoms (by means of Rutherford classification), existing comorbidities, anticoagulation medication, and risk factors for atherosclerosis were identified for all patients. Indications for transpopliteal access were evaluated. Target lesions were classified according to the Trans-Atlantic Inter-Society Consensus (TASC) II document.[2]

Study End Points

Technical success rate, which was defined as a patent SFA with <30% residual stenosis, was recorded. In addition, the periprocedural complications (adverse events related to the treated limb or index procedure that required the patient to be hospitalized, prolonged hospitalization, necessitated intervention, or were fatal) were evaluated.

The primary end point was amputation-free survival, which was defined as freedom from major (i.e. above the ankle) amputation of the index limb. Patency of the treated lesion according to duplex sonography and the follow-up Rutherford category were secondary end points. The treated lesion was considered patent if the peak systolic velocity ratio (PSVR) was ≤2.5 on duplex sonography.

RESULTS

Patient Population

During a 24-months period, 11 patients (4 male and 7 female [mean age 77 years]) were treated by way of a transpopliteal approach for long femoral occlusive lesions (TASC B through D[2]) in 12 limbs. All patients had CLI and were considered unsuitable for surgery due to their poor general condition. Table 1 lists the patient characteristics.

Treated Lesions

Indications for transpopliteal access were flush or proximal occlusion of the SFA in five, failure of antegrade recanalization in four, and infected femoral-femoral crossover bypass in two limbs. One patient could not be treated antegradely because of an occlusion of both the native SFA and the femoral-popliteal bypass. Technical success rate was achieved in 10 of 12 limbs. Figure 1 shows the angiographic images of a successfully recanalized SFA occlusion.

In one patient, it was not possible to re-enter the true lumen. In two patients, complications occurred while removing the sheath. In one patient, during sheath removal, the stent was removed completely resulting in direct re-occlusion of the treated vessel. In the other patient, the stent was partially dislocated and elongated, and protruded from the PA. The vascular surgeon cut off the protruding segment of the stent, and 1 day after surgery the stented SFA was patent on duplex examination.

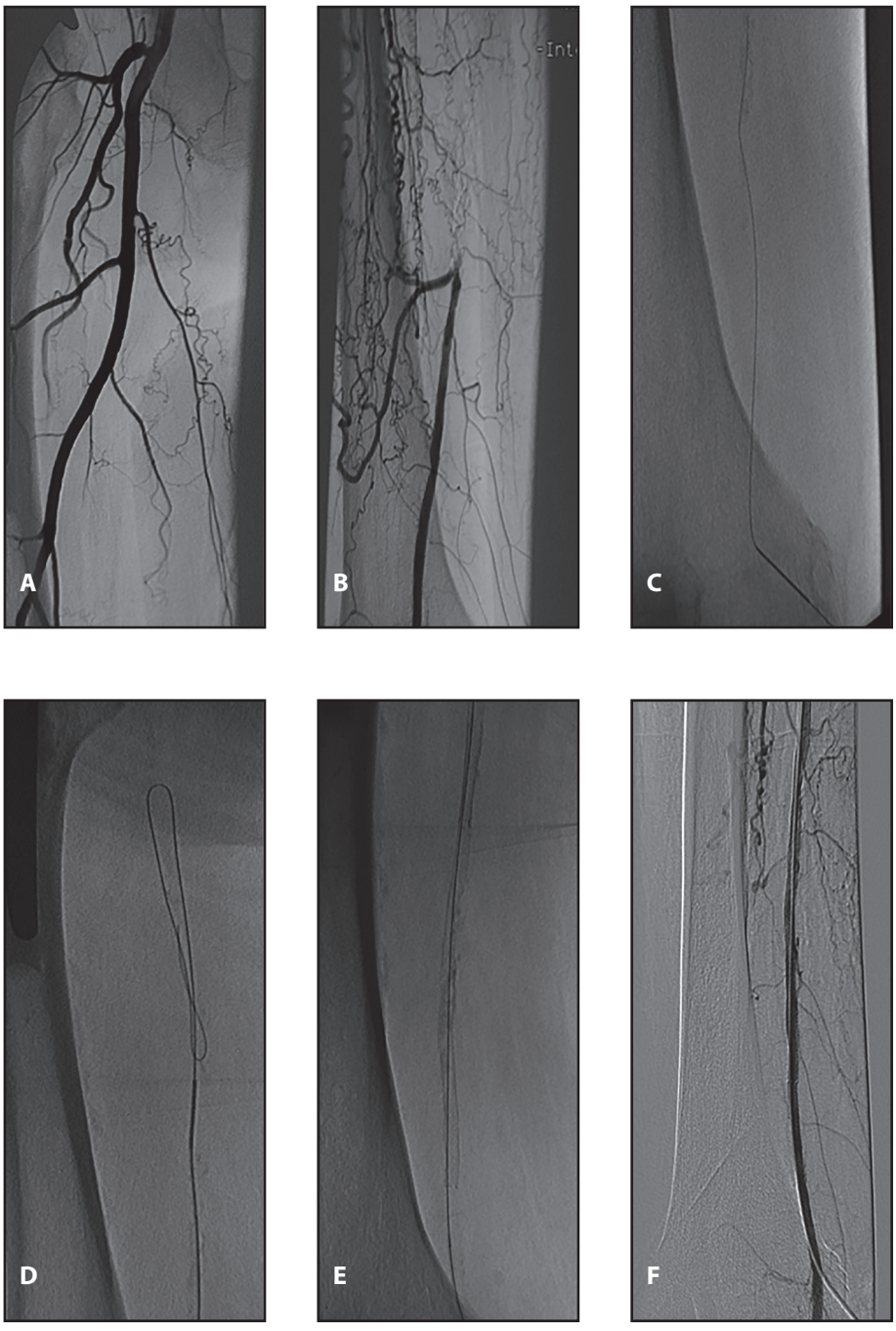

Figure 1. Angiographic images.

A) Flushocclusion of SFA, patent deep femoral artery. **B)** Patent distal SFA and supragenual PA. **C)** Transpopliteal access. **D)** Subintimal recanalization of SFA. **E)** Stenting of SFA. **F)** Postprocedural patent SFA.

There was one puncture-related complication (supragenual popliteal arteriovenous fistula [AVF]), which was successfully treated with additional stenting through the contralateral groin.
Nine out of 10 successfully treated patients received antithrombotic medication after the intervention (clopidogrel 75 mg/day [N=1], aspirin 100mg/day [N=2], combination of clopidogrel and aspirin [N=4], and oral anticoagulants [N=2]).
Table 2 lists lesion characteristics and technical outcomes.

Variables	N
Patients	11
Male sex	4 (36%)
Age (mean, years)	77 (range 49-91)
Body mass index (mean, kg/m^2)	26.3 (range 20.7-32.0)
Risk factors / comorbidity	
Diabetes	7 (64%)
Smoker	6 (55%)
Hypertension	10 (91%)
Hypercholesterolemia	5 (45%)
Coronary artery disease	2 (18%)
Renal insufficiency	1 (9%)
eGFR (mean, ml/min/1.73m^2)	71 (17-119)
On anti-thrombotic medication	10 (91%)
Treated limbs	12
Rutherford category, pre-procedural	
Rutherford 4	3 (25%)
Rutherford 5	5 (42%)
Rutherford 6	4 (33%)

Table 1. Baseline patient characteristics

Variables	N
Treated lesions	12
Occlusions	12 (100%)
Indications for transpopliteal access	
Flush/proximal SFA occlusion	5 (42%)
Failure of antegrade recanalization	4 (33%)
Infected fem-fem crossover	2 (17%)
Occlusion of native SFA &fem-pop	1 (8%)
TASC II classification*	
B	1 (8%)
C	2 (17%)
D	9 (75%)
Technical success rate	10 (83%)
Stents implanted per lesion, mean (range	2.1 (1-3)
Periprocedural complication rate	3 (25%)

Table 2. Lesion characteristics and outcomes

*TASC: Trans-Atlantic Inter-Society Consensus2

eGFR: estimated glomerular filtration rate

Follow-Up

Eight of 11 patients were alive without major amputations at 6 months.
Two patients (included for three limbs) died from pneumonia after 12 days.
One patient died 5 months after the intervention, from cardiac disease. Regarding his peripheral arterial disease, this patient was asymptomatic until his death.
Four of eight patients alive after 6 months improved to Rutherford category <3.
The other patients still had CLI (Figure 2).

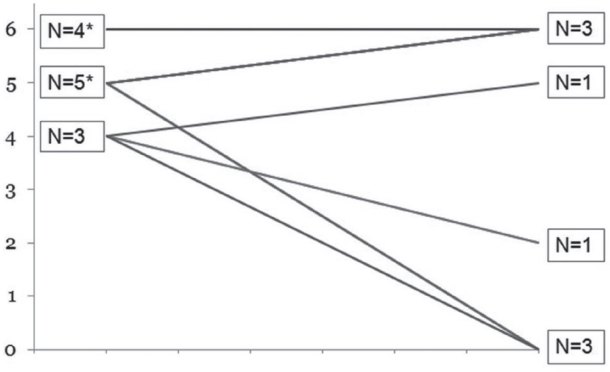

Figure 2. Rutherford score before intervention and at 6 months follow-up.

* Three patients (included for four limbs) died before 6 months post-procedural.

On duplex, restenosis (PSVR >2.5) was observed in half (four of eight) of the successfully treated limbs in patients alive after 6 months. Three of these patients still had CLI (Rutherford 5 or 6[15]), and one patient was asymptomatic.
Table 3 lists the clinical outcome after 6 months.

Outcome	N
Survival	8/11 (73%)
(Re)stenosis / occlusion	4/8 (50%)
Major amputation*	0 (0%)
Minor amputation†	1/8 (13%)
Rutherford category	
Rutherford 0	3/8 (38%)
Rutherford 2	1/8 (13%)
Rutherford 5	1/8 (13%)
Rutherford 6	3/8 (38%)

Table 3. Clinical outcome at 6-months follow-up

* Major amputation: above the ankle

† Minor amputation: distal to the ankle joint

DISCUSSION

The main purpose of CLI treatment is to prevent amputation by providing unobstructed arterial blood flow to the foot, either by bypass surgery or endovascular treatment. A significant number of patients with CLI are considered ineligible for bypass surgery due to their advanced age, existing comorbidities, or the lack of an adequate vein. In endovascular treatment, a complicating factor may be an inaccessible groin or failed recanalization using a traditional femoral approach. Transpopliteal access may be an alternative method for limb salvage in these cases.
In a meta-analysis, Muradin et al. showed that for femoropopliteal occlusions and for patients with CLI, stent implantation improves 3-year patency rates compared with balloon dilation alone.[14] A more recent meta-analysis concluded that primary stenting using nitinol stents yields a lower binary restenosis rate after 6 months compared with PTA with optional stenting.[16] Therefore we postulated that with the recent introduction of a 4F compatible, self-expanding stent (Biotronik AG, Bülach, Switzerland), primary stent implantation in SFA occlusions using a transpopliteal access could be technically feasible with better results than with PTA alone in patients with CLI and an inaccessible groin.

Until recently, only small non-randomized case studies regarding transpopliteal PTA have been published.[3-13] In some cases, transpopliteal stent implantation was used as a bail-out in the presence of suboptimal PTA results.[5-7] To our knowledge, our article is the first to report on the results of primary stenting of SFA occlusions using a transpopliteal approach through a 4F sheath.

The low profile of the 4F Biotronik system enables transpopliteal stenting regarding the limited diameter of the PA compared with the CFA. Therefore, even in case of stenting, only one access site is needed. In addition, primary stenting of SFA flush occlusions using a transpopliteal approach has other advantages compared with a transfemoral approach. With the antegrade approach, exact stent placement is precarious because of the limited segment in which the proximal end of the stent may land. Obviously, it is important to stent the SFA occlusion, but too proximal delivery and protrusion through the vessel wall of the CFA should be avoided. When using retrograde transpopliteal access, the proximal CFA segment in which the stent may land is not limited. The origin of the deep femoral artery will incidentally be covered. This occurred in six of our patients without affecting patency. Covering of the deep femoral artery may also occur with the antegrade common femoral approach.
In addition, transpopliteal access is well tolerated by patients lying in a prone position or on their side. The popliteal fossa is less sensitive than the groin, and patients feel less threatened by this approach.

Our initial experience shows that the results of transpopliteal stenting of SFA occlusions are promising with a primary technical success rate of 83%.
Two complications (one of which resulted in a technical failure) were caused by the fact that the 4F sheath of the radial access set we initially used does not have a radiopaque marker. Therefore, the distal end of the stent was accidentally deployed in the sheath in two patients. When this happens in larger sheaths, the sheath can usually be removed without dislocating the stent. Although removing the 4F sheath, however, the stent stretched and dislocated. In one of these two patients the stent was removed completely, resulting in reocclusion of the vessel. In the other patient, the stent dislocated and protruded from the PA. The vascular surgeon was requested to cut off the protruding part of the stent by means of a limited arteriotomy. The patency of the stented segment could thus be preserved. After these technical issues, we began to exchange the 4F sheath for a 4F sheath with a radiopaque marker after successful recanalization of the SFA. Hereafter, stent dislocations have no longer occurred.

Our technical success rate of transpopliteal recanalization is consistent with those reported in the literature ranging from 81 to 100%.[5-10,12] None of these studies has considered primary stenting using a transpopliteal approach, probably due to the fact that until recently, stent placement required a 6F or 5F sheath into the PA.

Concerns about transpopliteal approach are often related to the limited size of the artery and the possibility of puncture-induced complications, in particular the risk of causing an AVF.8,11,13 Using ultrasound, we only encountered one puncture-related complication in our series, which is consistent with the study of Yilmaz in 2005 who showed a low puncture-related complication rate of only 4.3% in 234 ultrasound-guided popliteal punctures. The investigators did report that the use of large (6-7F) sheaths was associated with significant longer hemostasis times than with using small-sized 4F sheaths.[11]

Little has been published about the patency rates of retrograde transpopliteal recanalizations of SFA lesions. Results are mainly from the retrospective studies. Tønnesen et al., the first to describe PTA of SFA lesions using a retrograde transpopliteal approach, reported a cumulative patency of 43% at 1 year using increased ankle index and a lower Fontaine classification as an indication for patency.[3]
A prospective study regarding the results of PTA of femoral occlusions in patients with claudication using either a femoral or a popliteal catheterization technique, was published by Matsi et al.[4] Survival analysis with the Kaplan-Meier method revealed a 3-year patency rate of 55% for all treated limbs.
Yilmaz et al. performed transpopliteal percutaneous intentional extraluminal recanalization of 39 long SFA lesions in patients mainly with claudication, including PTA in 33 patients and PTA and stenting in 6 patients.[7] A 62% patency rate was reported at 1 year on color Doppler ultrasound (CDU).
A restenosis rate of 54.9% in 51 patients at 12 months after retrograde transpopliteal recanalization of chronic SFA occlusions was reported by Noory et al.[9] In this study balloon angioplasty was performed in all cases with provisional stenting in 40 cases (71.4%). Whether the stents were deployed from an antegrade approach or a retrograde transpopliteal approach is not reported.
Much better results, based on the results of 24 transpopliteal retrograde subintimal recanalizations with provisional stenting of iliofemoral stenoses and occlusions, was reported by Brountzos with a primary patency rate at 6 months of 86.4% on CDU.[6]

The study by Ye et al. (N=19 patients) showed a primary patency at 6 months of 84.2% after angioplasty of SFA and/or PA occlusions by means of a rendez-vous procedure using antegrade femoral and retrograde popliteal access in patients with severe claudication or CLI.[5]

Our own results show a 50% restenosis or reocclusion rate after 6 months, which is somewhat less favorable than the previously reported results. However, patients included in this study all had CLI and SFA occlusions, whereas in most published studies patients were less seriously affected and mainly had claudication. In our present case, transpopliteal revascularization was the only option left to avoid amputation. Using this technique as a last resort, we were able to avoid major amputation in all patients and obtained clinical improvement in half of them.

Due to the retrospective nature of our study, there are some limitations. In such studies, selection bias may occur. In addition, the collected data will be less accurate than they may have been in case of prospective series.

In conclusion, the transpopliteal approach can be an alternative in patients with CLI who are unsuitable for bypass surgery and in whom the traditional antegrade transfemoral endovascular treatment is not possible or was unsuccessful. Our small study shows that transpopliteal primary stenting of complex SFA lesions is now technically feasible using a 4F system. Technical results are promising after initial problems. Patency after 6 months seems acceptable when taking into consideration that this approach may be the only option left for limb salvage. Long-term follow-up must be determined.

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Chapter 7

Synopsis

7 Synopsis

Critical limb ischemia (CLI) is the final stage of peripheral arterial disease (PAD). Endovascular infrapopliteal treatment of patients with CLI using percutaneous transluminal angioplasty (PTA) and bail-out bare metal stenting (BMS) is hampered by restenosis. In interventional cardiology, drug-eluting stents (DES) have shown better patency rates and are standard practice nowadays. The **PADI** (Percutaneous transluminal Angioplasty and Drug-eluting Stents for Infrapopliteal lesions in critical limb ischemia) trial was conducted to assess whether DES also improve patency and clinical outcome of infrapopliteal lesions.

In **Chapter 2** the short- and mid-term results of this investigator-initiated, multi-center, randomized trial are presented. Adults with CLI (Rutherford category[1] ≥ 4) and infrapopliteal lesions were randomized to receive PTA±BMS or DES with paclitaxel. Primary endpoint was 6-month primary binary patency of treated lesions, defined as ≤ 50% stenosis on Computed Tomography Angiography. Stenosis > 50%, re-treatment, major amputation (above ankle level), and CLI-related death were regarded as treatment failure. Severity of failure was assessed with an ordinal score, ranging from vessel stenosis, through occlusion, to the clinical failures. Seventy-four limbs (73 patients) were treated with DES and 66 limbs (64 patients) received PTA±BMS. Six-month patency rates were 48.0% for DES and 35.1% for PTA±BMS (P=0.096) in the modified-intention-to-treat and 51.9% and 35.1% (P=0.037) in the per-protocol analysis. In the latter analysis, lesions that were randomized for DES but were treated with PTA only were excluded. The ordinal score showed significantly more severe treatment failures for PTA±BMS versus DES (P=0.041). The observed major amputation rate remained lower in the DES group until 2 years post-treatment, with a trend towards significance (P=0.066). Less minor amputations (below ankle level) occurred after DES until 6 months post-treatment (P=0.03). In conclusion, DES provide better 6-month patency rates and less amputations up to 2 years post-treatment compared with PTA±BMS in patients with CLI due to infrapopliteal lesions.

Chapter 3 reports on the long-term follow-up of the **PADI** trial. Long-term follow-up consisted of annual assessments up to 5 years post-treatment, or until a clinical endpoint was reached. Clinical endpoints were major amputation (above ankle level), or infrapopliteal surgical or endovascular re-intervention attempted on the treated limb, and death. Preserved primary patency (≤ 50% restenosis) of treated lesions was an additional morphological endpoint, assessed by duplex sonography. The estimated major amputation rate was lower in the DES arm than in the PTA±BMS arm (19.3% vs. 34.0% after 5 years, respectively, P=0.091).

The 5-year amputation-free survival and event-free survival (events are defined as re-intervention, major amputation, or death) rates were significantly higher in the DES arm (DES: 31.8% versus PTA±BMS: 20.4%; *P*=0.043; and DES: 26.2% versus PTA±BMS: 15.3%; *P*=0.041, respectively). Survival rates were comparable. The limited available morphologic results show higher preserved patency rates after DES than after PTA±BMS at 1, 3, and 4 years follow-up. So treatment of infrapopliteal lesions in CLI patients with DES yields also at long-term more favourable clinical and morphologic results than with PTA±BMS.

In **Chapter 4** the implications of diabetes mellitus (DM) for the prognosis in CLI patients with infrapopliteal arterial disease are discussed. DM supposedly negatively affects the outcomes of CLI, but this has not been proven in prospective studies thus far. DM was highly prevalent in the **PADI** trial and as well in the **JUVENTAS** (reJUVenating ENdothelial progenitor cells via Transcutaneous intra-Arterial Supplementation) trial, a randomized controlled trial conducted in equivalent CLI patients. Data of the two trials were pooled on patient level. Patients were considered to have DM when this diagnosis was reported in the hospital electronic medical records. Rates of major amputation and major events (major amputation or death) were compared between CLI patients with and without DM. Hazard ratios (HRs) were calculated.
Of a total of 281 patients, DM was present in 49,1%. The major amputation rate at 5 years of follow-up was higher in patients with DM than in patients without DM (34.1% versus 20.4%, *P*=0.015). The major event and death rates did not differ. The unadjusted hazard ratio (HR) of DM for the major amputation risk was 1.87 (95% confidence interval (CI) 1.12-3.12). Model factors with significant HRs in the multivariate analysis were baseline Rutherford category (HR 1.95; 95% CI 1.24-3.06) and ankle-brachial index (ABI) >1.4 (HR 2.78; 95% CI 1.37-5.64). CLI patients with DM are thus at significantly higher risk of major amputation than CLI patients without DM. This increased risk is associated with a higher prevalence of baseline ABI>1.4 and more severe ischemia at initial presentation in patients with DM.

For **Chapter 5** the prognostic value of the ABI regarding major amputation and survival in patients with CLI and proven arterial obstructive disease below the knee was investigated. The pooled patient data from the **PADI** and **JUVENTAS** trials were used for this objective. Subjects of whom a baseline ABI was registered were allocated according to baseline ABI to the low (<0.7), intermediate (0.7-1.4), or high (>1.4)/immeasurable ABI subgroup. Major amputation and amputation-free survival rates were compared. HRs for the risk of major amputation and major event (major amputation or death) were calculated. To quantify the effect of inclusion of high/immeasurable ABI in the existing PREVENT III risk score[2] for predicting amputation-

free survival at 1 and 2 years, the net reclassification improvement (NRI) was derived. Of 260 patients, 146 patients (56.2%) had a low ABI, 81 patients (31.2%) had an intermediate ABI and 33 patients (12.7%) had a high/immeasurable ABI at baseline. Patients with a high/immeasurable ABI showed a significantly higher major amputation rate (52.1%) and lower amputation-free survival rate (5.0%) at 5 years of follow-up than those with an intermediate (25.5% and 41.6%, respectively) and low ABI (23.5% and 46.9%, respectively) (both $P<0.001$). Unadjusted and adjusted HRs of high/immeasurable ABI for the major event risk were 2.95 (95% CI 1.82-4.78) and 2.93 (95%CI 1.67-5.13) (both $P<0.001$). Adding the risk factor high/immeasurable ABI to the PREVENT III model yielded an NRI of 0.45 (95%CI 0.23-0.66, $P<0.0001$) and 0.38 (95%CI 0.20-0.56; $P<0.0001$) for amputation-free survival prediction at 1 and 2 years, respectively. In conclusion, a high/immeasurable ABI in patients with CLI and proven arterial obstructive disease below the knee is an independent risk factor of major amputation and of poor amputation-free survival. Incorporating high/immeasurable ABI in the PREVENT III prediction model significantly improves its performance.

Chapter 6 reports on a different access site in patients with CLI and inaccessible groins. In a retrospective study stenting of superficial femoral artery (SFA) occlusions using a transpopliteal approach and a 4 French system is evaluated. Eleven patients (4 male and 7 female [mean age of 77 years]) underwent 12 attempts of transpopliteal recanalization of long SFA occlusions (Trans-Atlantic InterSociety Consensus[3] type B - D lesions). All patients had CLI (Rutherford category[1] 4 to 6) and were non-operable due to poor general condition. Indications for transpopliteal access were proximal/flush SFA occlusions (n=5), failure of antegrade recanalization (n=4), infected femoral-femoral crossover bypass (n=2), and occlusion of both the native SFA and the femoral-popliteal bypass (n=1). The popliteal artery was punctured under ultrasound guidance. Occlusions were recanalized subintimally, and 4 French compatible stents were implanted.
Technical success rate (defined as < 30% residual stenosis) was achieved in 83% of cases. In two patients, stent dislocation occurred while the sheath was removed. One arteriovenous fistula was successfully treated with additional stenting. During follow-up of 6 months, there were no major amputations, and three patients died due to non-related causes. Fifty percent of patients alive after 6 months improved to Rutherford category[1] ≤ 3. The duplex restenosis (> 50%) rate at 6 months was 50%. Thus, transpopliteal primary stenting of complex SFA lesions in CLI for a temporary bypass is technically feasible using a 4 French system. Clinical results after 6 months are acceptable, when taking into consideration that this approach may be the last option for limb salvage.

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Chapter 8

General discussion

8 General discussion

Due to its poor prognosis both for limb and for life, critical limb ischemia (CLI) represents a substantial burden for patients and health care.[1,2] Since medical treatment is not very effective and new cell therapies have been disappointing, recanalization of the occluded vessels in the leg remains the most important therapy.[1-3] For lesions above as well as below the knee, endovascular therapy has become the recommended recanalization strategy replacing vascular surgery in the last decade.[1,4,5] In this thesis, it was investigated whether drug-eluting stents (DES) improve results compared to standard endovascular treatment, i.e. percutaneous transluminal angioplasty with bail-out bare metal stenting (PTA±BMS). Since the outcome of CLI patients is poor[2,6-10], it was assessed which factors determine this poor prognosis and whether it is possible to predict which patients are at greatest risk.

Drug-Eluting Stents

In case of endovascular treatment of infrapopliteal disease causing CLI, this thesis shows that treatment with drug-eluting stents (DES) is superior in comparison with percutaneous transluminal angioplasty with bail-out bare metal stenting (PTA±BMS), the reference treatment. At mid-term follow-up DES show significantly improved patency rates, less minor amputations, and a lower major amputation rate with a trend towards significance, and, at long-term follow-up, significantly improved amputation-free and event-free survival.[11,12] It is important to make a distinction between technical results and clinical results.[13] Most studies investigate whether DES cause less restenosis at follow-up, while few investigate whether amputation rates decrease.[14]

Investigating the local technical effect of DES is possible by assessing local patency following treatment. Since vessel patency is not the only factor determining limb salvage, randomized controlled trials (RCTs) with amputation-free survival as outcome remain important.[6,15] However, in nearly all observational studies and RCTs regarding infrapopliteal CLI, CLI patients are mixed with claudicants[14,16-19], who have a very low chance of amputation, making these studies underpowered for amputation as primary outcome.[13] Furthermore, the technical outcome in patients with claudication could be quite different from CLI patients as the underlying disease process differs. These considerations have to be kept in mind when considering results of these trials. The effectiveness of DES placement in infrapopliteal arteries has been shown in other randomized trials.[16-22] Superior mid-term patency rates after DES are reported compared with BMS[16,18,20-22], PTA[19,21], and drug-eluting balloons (DEB)[17].

Some studies found superior clinical endpoints in DES as well, such as a larger decline in Rutherford classification[18,20], and improved long-term amputation-free and event-free survival rates[20].
The available meta-analyses regarding the endovascular treatment of infrapopliteal disease in patients with CLI yielded lower restenosis grades and reduced target lesion revascularization rates after DES compared with PTA[14,23,24] and BMS[14,23-26] until 1 year post-treatment. Two of these studies reported more favorable clinical outcomes after DES, with improvement of Rutherford category, wound healing, overall event-free survival[23], and reduced risk of amputation[24]. Overall, DES are a promising technique for infrapopliteal arterial disease in patients with CLI, with evidence of superior anti-restenotic effects. The clinical outcomes after DES seem to be superior as well, although the evidence supporting this is inconsistent. The limited evidence of improved clinical outcomes seems at least partially caused by the low to moderate quality of the conducted randomized trials[14], with the inclusion of a limited number of patients[16,17], and/or the inclusion of patients with intermittent claudication[16-19].
A limitation of the balloon-expandable DES (TAXUS Liberté; Boston Scientific, Natick, MA) investigated in the **PADI** trial, is its maximum length of 32 mm. Infrapopliteal arterial disease is often diffuse with long lesions, especially in diabetic patients[27,28], and therefore less suitable for balloon expandable stents. Future technical developments might provide a solution for this problem, with long and flexible self-expandable DES.
Other endovascular techniques have been introduced for the treatment of lesions below the knee, but, unlike DES, no other technique has shown to be a meaningful improvement compared with current state-of-the-art treatment. Drug-eluting balloons (DEB) did not prove superior performance for infrapopliteal lesions. Although some studies found more favorable patency rates and lower restenosis rates in comparison with PTA[29,30], the last conducted randomized trial did not show a difference in the primary efficacy endpoint of late lumen loss[31]. Furthermore, this latter trial found a trend of higher amputation rates in the DEB group (DEB: 8.8%; PTA: 3.6%; P=0.08).[31] The reason for this may have been distal embolization of coating material or medication.
Other new endovascular technologies, such as devices with cutting balloons, laser, or cryoplasty, did not find superior performance when compared with conventional endovascular techniques, but have only been evaluated in non-randomized series thus far.[32-34] In addition, different access sites, such as the transpopliteal approach in our retrospective study, or crossing techniques are developing techniques in the field of endovascular treatment and have mostly been reported in retrospective series.[35,36]

Prognostic Factors in Critical Limb Ischemia

Patients with CLI are at high risk of major amputation, and death.[7] The prognosis of CLI is in fact as poor as some malignancies, or even worse.[8] Consensus guidelines and reviews traditionally report that at one-year follow-up 25 to 30% of CLI patients will have undergone a major amputation and 20 to 25% of patients will have died.[6-8] Long-term amputation-free survival (AFS) after 5.5 years has been reported to be as low as 55%.[4] The prognosis of CLI is, however, reported to have improved over the last decades.[15,37] A review examining the AFS in CLI patients without revascularization options found significantly increased AFS and declined mortality from 1995 to 2010.[15] The most recent trial included in this review reported a one-year AFS of 67% in CLI patients unsuitable for revascularization.[38] The long-term results of the **PADI** trial nevertheless underline that the prognosis of CLI is still very poor with 5-year AFS from 20.4% to 31.8%. Identifying prognostic factors that determine poor outcome can help to identify the patients at highest risk, to understand the disease process and enable to improve clinical decision-making and offer individual patients the most appropriate treatment. Several prediction models have been proposed. The BASIL survival prediction model was designed to predict death at 6, 12, and 24 months in CLI patients and identified tissue loss, body mass index, creatinine, Bollinger score[39], age, smoking, coronary artery disease, and ankle pressure as predictive factors.[40] Risk factors included in the FINNVASC risk-scoring method for 30-day postoperative outcome prediction after infra-inguinal surgical revascularization are diabetes mellitus (DM), foot gangrene, coronary artery disease, and urgent operation.[41] The PREVENT III model incorporated the risk factors dialysis, tissue loss, age over 75 years, and coronary artery disease for one-year AFS prediction.[42] Analysis of CLI outcomes in the pooled **JUVENTAS**[43,44] and **PADI** cohorts showed that DM is associated with decreased AFS. This is attributable to the higher prevalence of high/immeasurable ankle-brachial index (ABI) and higher Rutherford category at baseline, as multivariate regression analysis showed these factors to be significant predictors. It is evident that the severity of CLI is prognostic for its outcome and likewise included in abovementioned prediction models.[40-42] The prognostic value of a high/immeasurable ABI for CLI is however poorly studied and previously not as clearly revealed as in our study. A high/immeasurable ABI represents poorly compressible or incompressible arteries in the lower extremities, which is supposedly caused by medial arterial calcification (MAC). The ABI is artificially elevated because higher cuff pressures are needed to compress the stiffened artery in the lower limb. In some cases cuff pressures are even insufficiently high to do so, resulting in an immeasurable ABI.[45-50]

The etiology of MAC has not yet been fully untangled, but increasing evidence suggests that its age-associated pathophysiology differs from that of atherosclerosis and it is not merely a manifestation of the latter phenomenon.[51-53] MAC is associated with increasing age, DM, and renal disease.[45-47,51] The **PADI** and **JUVENTAS** study populations all had obstructive atherosclerotic arterial disease below the knee, proven by pre-treatment imaging.[12,44] This enabled the evaluation of the effect of increased vessel wall stiffness, reflected by the ABI. The stiffness of the vessel wall was the most important predictor, not only of limb loss but also of declined AFS. Obstructive atherosclerotic disease only, with a normally compressible, elastic vessel wall and thus a low ABI, showed a relatively better limb outcome, as well as better AFS. On the other hand, patients with obstructive atherosclerotic disease and a stiff vessel wall, reflected by high/immeasurable ABI, had a very poor prognosis regarding AFS. Apparently, the stiff vessel wall either aggravates atherosclerosis or is itself responsible for the poor AFS. MAC is thought to prevent compensatory positive arterial remodeling associated with atherosclerosis, and so to consequently aggravate the atherosclerotic process.[51] Furthermore, invasion of the intima in the final stage of MAC can increase the risk of thrombo-embolic events. Arteriolar MAC may disturb auto regulation and impair peripheral tissue perfusion.[51] We presume that, in our patient population, patients with a low ABI had obstructive atherosclerotic disease only, while patients with a high or immeasurable ABI had atherosclerotic disease and a concomitant disease, leading to a stiff vessel wall and poor outcome.

In our study, patients with a high/immeasurable ABI also had comprehensive cardiovascular comorbidity at baseline, significantly different from patients with a low ABI, and a much lower AFS at follow-up, pointing at a higher death rate. This is particularly caused by (cardio)vascular events due to arterial disease in other vascular territories.[6,7] Fifty to 75% of CLI patients have concomitant cerebrovascular disease and about 20% have coronary artery disease.[7] This difference in observed disease in other vascular territories between patients with low and high/immeasurable ABI suggests a systemic effect of stiff vessel walls. It can only be speculated how this stiffness leads to vascular diseases. It could be that, when the aorta is stiffened, an increased pulse wave velocity develops which can cause severe chronic damage to the heart, brain, and kidneys resulting in heart failure, chronic cerebrovascular diseases such as vascular dementia, and renal failure, respectively. Another explanation could be that when the vascular stiffness is extended into these vascular territories, it might interfere with atherosclerosis in a similar way as in the legs by preventing the compensatory positive remodeling.

Obstructive atherosclerotic disease and increased stiffness of the vessel wall could be the targets for therapy in the future. Treatment of obstructive atherosclerotic disease by secondary prevention is of utmost importance. This consists of smoking cessation, weight reduction in patients with a body mass index of over 25, tight control of hypertension and in particular of DM, lipid control, and antiplatelet therapy.[2,6,54]

How to treat patients with a stiff vessel wall is as yet unclear. Secondary prevention and treatment of concomitant associated diseases is recommended in patients with MAC, in particular of DM, and chronic kidney disease-mineral and bone disorder.[51] Therapies such as nitrogen-containing bisphosphonates[55], high dietary menaquinone (vitamin K2)[56], or chelation therapy with disodium EDTA[57], have been reported to reduce cardiovascular calcifications, but these strategies are not specifically targeted at MAC nor has their efficacy been proved. Hypertension is closely linked to MAC, as hypertension is a calcification promoting stressor. Additionally, MAC may contribute to the development of hypertension by decreasing the elasticity of the media.[58] Blood pressure reduction possibly relieves the calcification stress.[58] Patients with a high/immeasurable ABI may therefore benefit from blood pressure lowering medication.

Future Directions

Since atherosclerotic obstructive disease and stiff arterial vessel walls both probably play a very important role in the morbidity and mortality of patients with CLI, research efforts should be targeted at these afflictions. That should be done with improved medical and endovascular therapies.

Medical therapies should not only focus on atherosclerotic disease, but also on vascular stiffness and medication influencing this process. Certain modern antihypertensive medication that affects the vessel wall instead of causing vasodilation, such as calcium channel blockers and endothelin-1 antagonists, should be tested for their effects in CLI patients. Also bisphosphonates and vitamin K2 should be investigated. These latter therapies have been reported to reduce cardiovascular calcifications.[55,56]

As mentioned earlier, endovascular techniques should be improved, by having longer and flexible drug-eluting stents available for the lower leg arteries. These new approaches should be investigated in clinical trials. Well-conducted studies in the field of CLI providing high-level evidence are as yet sparse. There are several reasons for this; the (public) awareness regarding CLI is less than for e.g. coronary artery disease and both the inclusion as well as the follow-up in CLI patients is challenging. Furthermore, the care for these patients is fragmented, making it difficult to coordinate research.

Additionally, the rate of events may be declining[15], which requires the inclusion of even more patients in order to have enough power to detect differences in event rate. Future trials should include CLI patients only and no claudicants. Relevant endpoints for CLI patients are clinical endpoints considering life and limb, which are preferred above surrogate radiological endpoints such as primary patency or late lumen loss.[13,14] Yet, when MAC is the therapeutic target, vascular calcification as seen on CT could be a proxy endpoint. The most relevant endpoint when considering treatment strategies in CLI however is AFS.[13]
Furthermore, in order to obtain generalizable results, it is important to employ a generally accepted definition of CLI, which includes both hemodynamic criteria as well as clinical staging criteria.[59]

Trials should be different for patients with a low ABI and patients with a high/immeasurable ABI.
In trials with patients with a low ABI, the focus should be on recanalization and secondary prevention of atherosclerosis. In patients with a high/immeasurable ABI, medication directed against MAC should be added. Since certainly for this latter group the number of events is high, a relatively small number of included patients will suffice. Furthermore, since comorbidity is abundant in this group, these patients should get diagnostic studies such as a whole body CT for assessment of MAC in all vascular territories with a CTA of the head, heart and legs to assess atherosclerotic disease.
To make substantial progress in the treatment of CLI patients, a national CLI collaboration should be established which collects all clinical data of CLI patients in a registry and coordinates the clinical trials. This collaboration should consist of vascular surgeons, interventional radiologists, specialists in vascular medicine, nephrologists, cardiologists, diabetologists, and neurologists.

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Chapter 9

Appendices

9

NEDERLANDSE SAMENVATTING

Kritieke ischemie (KI) is het eindstadium van perifeer arterieel vaatlijden. De huidige standaard endovasculaire behandeling van patiënten met KI ten gevolge van infrapopliteale laesies, te weten percutane transluminale angioplastiek (PTA) en bail-out bare metal stents (BMS), wordt beperkt door restenosering. Drug-eluting stents (DES) geven een medicijn af dat deze restenosering tegengaat. In de interventiecardiologie is het nut van deze stents reeds bewezen en worden deze standaard geplaatst in de coronairen. De **PADI** (Percutaneous transluminal Angioplasty and Drug-eluting stents for Infrapopliteal lesions in critical limb ischemia) studie is opgezet om te beoordelen of DES ook bij infrapopliteale laesies de doorgankelijkheid verbeteren en hiermee bijdragen aan een beter klinisch resultaat.

In hoofdstuk 2 van dit proefschrift worden de korte en middellange termijn resultaten van deze multicenter, gerandomiseerde trial uiteengezet. Volwassen patiënten met KI (Rutherford categorie ≥ 4) en infrapopliteale laesies werden gerandomiseerd voor behandeling met PTA±BMS of DES met paclitaxel. Het primaire eindpunt van de studie was primaire binaire doorgankelijkheid van de behandelde laesies na 6 maanden, gedefinieerd als ≤50% stenose, gescoord met behulp van Computer Tomografie Angiografie. Indien er sprake was van stenose >50%, occlusie, re-interventie, major amputatie (boven enkelniveau) en overlijden ten gevolge van KI na 6 maanden werd dit beschouwd als falen van de behandeling. De ernst van dit falen werd gescoord middels een ordinale score, waarbij stenose als minst ernstig en de klinische eindpunten als meest ernstige vorm van falen zijn aangemerkt. Occlusie zit qua ernst tussen beide eindpunten in. Drieënzeventig patiënten (74 benen) zijn behandeld met DES en 64 patiënten (66 benen) met PTA±BMS. 48,0% van de laesies behandeld met DES en 35,1% in de PTA±BMS-groep waren 6 maanden na inclusie doorgankelijk ($P = 0,096$) in de gemodificeerde intention-to-treat-analyse. Een klein deel van de voor DES gerandomiseerde laesies bleken alleen met PTA te zijn behandeld. In de per-protocol-analyse zijn deze laesies geëxcludeerd. In deze additionele analyse was het percentage in de DES-groep met behouden doorgankelijkheid na 6 maanden 51,9% versus de genoemde 35,1% in de PTA±BMS-groep ($P = 0,037$). De ordinale score leverde significant slechtere uitkomsten op in de PTA±BMS-groep, met een groter percentage met een klinische eindpunt re-interventie, major amputatie of overlijden ten gevolge van KI ($P = 0,041$). Het percentage major amputaties

was lager in de DES-groep tot 2 jaar na de behandeling, met een trend naar significantie (*P* = 0,066). De DES-groep onderging minder minor amputaties (onder enkelniveau) tot 6 maanden na de behandeling (*P* = 0,03). Samenvattend leiden DES tot een verbeterde doorgankelijkheid 6 maanden na de behandeling in vergelijking met de standaard behandeling PTA±BMS bij patiënten met KI ten gevolge van infrapopliteale laesies. Tevens vinden er minder amputaties plaats tot 2 jaar na de behandeling.

Hoofdstuk 3 behandelt de lange-termijn follow-up van de **PADI** studie. De follow-up bestond uit jaarlijkse controles tot maximaal 5 jaar na de behandeling, of tot een klinisch eindpunt was bereikt. Klinische eindpunten waren: major amputatie (boven enkelniveau), infrapopliteale chirurgische of endovasculaire re-interventies van het geïncludeerde been en overlijden. Een behouden primaire doorgankelijkheid (≤ 50% restenose) van de behandelde laesies, geëvalueerd middels duplex echografie, was een additioneel morfologisch eindpunt. Het geschatte percentage van major amputaties tot 5 jaar na de behandeling was lager in de DES-groep (19,3%) dan in de PTA±BMS-groep (34,0%), *P* = 0,091. Het geschatte aantal gevallen van 5-jaars amputatie-vrije overleving (1) en event-vrije overleving (2), gedefinieerd als overleving zonder het ondergaan van een major amputatie of re-interventie, waren significant groter in de DES-groep – respectievelijk DES: 31,8% versus PTA±BMS: 20,4%; *P* = 0,043 (1); en DES: 26,2% versus PTA±BMS: 15,3%; *P* = 0,041 (2). In een beperkt aantal patiënten zijn de morfologische resultaten van de behandelde laesies geëvalueerd door middel van duplex echografie. Bij 1, 3 en 4 jaar follow-up was het percentage laesies met behouden doorgankelijkheid significant groter in de DES- dan in de PTA±BMS-groep. De behandeling van infrapopliteale laesies in KI patiënten met DES leiden derhalve ook op de lange termijn (tot 5 jaar na behandeling) tot gunstiger klinische en morfologische resultaten ten opzichte van PTA±BMS.

In hoofdstuk 4 worden de implicaties van diabetes mellitus (DM) voor de prognose van KI patiënten met arterieel vaatlijden in het onderbeen behandeld. Er bestaan aanwijzingen dat DM een negatieve invloed heeft op de uitkomst van KI, maar dit is tot dusver niet aangetoond in prospectieve studies. Opvallend is dat DM een veel voorkomende comorbiditeit was in de **PADI** studie. Ook in de **JUVENTAS** (Rejuvenating Endothelial Progenitor Cells via Transcutaneous Intra-Arterial Supplementation) studie, een gerandomiseerde, geblindeerde trial onder KI patiënten, zijn veel diabeten geïncludeerd. In deze trial zijn de klinische effecten van herhaalde intra-arteriële infusie van beenmergcellen bestudeerd.

Data van deze twee onderzoeken werden gepooled op patiëntniveau. Patiënten werden hierbij beschouwd als diabeet indien deze diagnose werd vermeld in het elektronische patiënten dossier. De percentages van major amputaties en major events (major amputatie of overlijden) werden vergeleken tussen KI patiënten met en zonder DM. Middels regressie-analyse werd het risico op major amputatie en op major events in beide groepen geanalyseerd.
49,1% van de in totaal 281 geïncludeerde patiënten was gediagnosticeerd met DM. Het geschatte percentage van major amputaties na 5 jaar follow-up was significant hoger bij patiënten met DM dan bij patiënten zonder DM – 34,1% versus 20,4% respectievelijk, *P* = 0,015. De major event- en overlevingspercentages waren vergelijkbaar in beide groepen. De univariate hazard ratio (HR) van DM voor het risico op major amputatie was 1,87 (met een 95%-betrouwbaarheidsinterval (BI) van 1,12-3,12). Risicofactoren met significante HR's in de multivariate analyse waren baseline Rutherford categorie (HR 1,95; 95% BI 1,24-3,06) en enkel-arm index (ABI) >1,4 (HR 2,78; 95% BI 1,37-5,64).
KI patiënten met DM hebben aldus een aanzienlijk hoger risico op major amputatie dan KI patiënten zonder DM. Dit verhoogde risico wordt verklaard door een hogere prevalentie van ABI > 1,4 en ernstiger ischemie bij presentatie onder diabeten.

In hoofdstuk 5 wordt de prognostische waarde van de ABI onderzocht ten aanzien van major amputatie en overleving bij patiënten met KI en bewezen arteriële obstructieve ziekte in het onderbeen. Hiervoor werden de gepoolde patiëntendata van de **PADI** en **JUVENTAS** studies gebruikt, waarbij patiënten van wie er een baseline ABI geregistreerd was geïncludeerd zijn. Drie subgroepen werden vergeleken; de lage (<0,7) ABI subgroep, de intermediaire (0,7-1,4) ABI subgroep, en de hoge (>1,4) / onmeetbare ABI subgroep. De klinische uitkomsten major amputatie en amputatie-vrije overleving zijn geanalyseerd, middels Kaplan Meier en Cox regressie-analyse. Om het effect te analyseren van de inclusie van de risicofactor hoge/onmeetbare ABI in het bestaande PREVENT III predictiemodel voor het voorspellen van amputatie-vrije overleving na 1 en 2 jaar is de Net Reclassification Improvement (NRI) berekend.
Van een totaal van 260 patiënten hadden 146 patiënten (56,2%) een lage ABI, 81 patiënten (31,2%) hadden een intermediaire ABI en 33 patiënten (12,7%) hadden een hoge/onmeetbare ABI bij presentatie. Patiënten met een hoge/onmeetbare ABI toonden een significant hogere major amputatie rate (52,1%) en lagere amputatie-vrije overleving (5,0%) bij 5 jaar follow-up, dan de patiënten met een intermediaire (respectievelijk 25,5% en 41,6%) en lage ABI (respectievelijk 23,5% en 46,9%) (beide *P* <0,001).

Univariate en multivariate HR's van hoge/onmeetbare ABI voor major amputatie of overlijden waren 2.95 (95% BI 1,82-4,78) en 2,93 (95% BI 1,67-5,13) (beide *P* <0,001). Het toevoegen van de risicofactor hoge/onmeetbare ABI aan het PREVENT III predictie model resulteerde in een NRI van 0,45 (95% BI 0,23-0,66; *P* <0,0001) en 0,38 (95% BI 0,20-0,56; *P* <0,0001) voor de predictie van amputatie-vrije overleving na respectievelijk 1 en 2 jaar. Concluderend is een hoge/onmeetbare ABI bij patiënten met KI en bewezen infrapopliteale arteriële obstructieve ziekte een onafhankelijke en significante risicofactor voor zowel major amputatie als amputatie-vrije overleving. Incorporeren van de risicofactor hoge/onmeetbare ABI in de PREVENT III score leidt tot een verbetering van het voorspellende vermogen van dit predictiemodel.

In hoofdstuk 6 wordt een retrospectieve studie naar een transpopliteale benadering met behulp van een '4 French' systeem bij patiënten met KI en ontoegankelijke liezen besproken. Elf patiënten (4 mannen en 7 vrouwen met een gemiddelde leeftijd van 77 jaar) ondergingen 12 pogingen van transpopliteale rekanalisaties van lange occlusies in de arteria femoralis superficialis (Trans-Atlantic Intersociety Consensus type B-D laesies). Alle patiënten hadden KI (Rutherford categorie 4-6) en waren niet-operabel gezien hun uitgebreide comorbiditeit. Indicaties voor een transpopliteale benadering waren: proximale/flush SFA occlusies (N = 5), het falen van antegrade rekanalisatie (N = 4), geïnfecteerde femorale-femorale crossover bypass (N = 2) en occlusie van zowel de natieve arteria femoralis superficialis als van de femorale-popliteale bypass (N = 1). De arteria poplitea werd echogeleid aangeprikt, waarna de occlusies subintimaal gerekanaliseerd werden met behulp van 4 French-compatibele stents. Technisch succes (gedefinieerd als <30% reststenose) werd bereikt in 83% van de gevallen. Bij twee patiënten disloceerde de stent bij het verwijderen van de sheath. Eén arterioveneuze fistel werd opgeheven door middel van een extra stentplaatsing. Geen van de patiënten onderging een major amputatie. Drie patiënten overleden aan niet-gerelateerde ziekten. Bij 50% van de overlevende patiënten was er na 6 maanden sprake van een verbetering in Rutherford categorie (≤3). Zes maanden na inclusie was bij 50% van de patiënten de AFS gerestenoseerd (>50% restenose).
Primair stenten van complexe laesies in de arteria femoralis superficialis in KI patienten is technisch mogelijk met behulp van een 4 French systeem middels een transpopliteale benadering. Klinische resultaten na 6 maanden zijn aanvaardbaar, waarbij aangetekend dient te worden dat deze benadering de laatste optie voor het behoud van het been kan zijn.

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CURRICULUM VITAE

Marlon Irene Spreen was born on 19 December 1983 in Haarlem, the Netherlands. She graduated with honors from Atheneum College Hageveld in 2002. That same year, she started Medical School at the VU University in Amsterdam to receive the Master of Science degree in 2006. Before starting internships, she completed an additional Master's program in Policy and Organization of Health Care in 2007. As part of this program, she did an internship at the CPB Netherlands Bureau for Economic Policy Analysis, and wrote a CPB document regarding a cost-benefit analysis of the smoking ban for the Dutch hotel and catering industry. Next, she fulfilled her medical internships in Amsterdam and surroundings, as well as in Surinam, to obtain her Medical Degree in 2009.

Marlon started her Radiology Residency in the Haga Teaching Hospital in The Hague in 2010. As part of her training, she worked in the Academic Medical Center in Amsterdam during a year. In 2016, she was registered as a Radiologist and started a fellowship in Abdominal Radiology in the Haga Teaching Hospital and the Leiden University Medical Center in Leiden.

From 2012, Marlon is involved in the **PADI** trial, a randomized controlled trial regarding percutaneous transluminal angioplasty versus drug-eluting stents for infrapopliteal lesions in critical limb ischemia, under supervision of Prof. Dr. W.P.Th.M. Mali and Dr. H. van Overhagen. This research has resulted in the current thesis.