Randomized comparison of femoropopliteal artery drug-eluting balloons and drug-eluting stents (FOREST trial): Study protocol for a randomized controlled trial.

Hidde Jongsma, MD[a]

Patricia van Mierlo-van den Broek, M ANP[a]

Farshad Imani, MD[b]

Daniel van den Heuvel, MD, PhD[c]

Jean-Paul P.M. de Vries, MD, PhD[d]

Bram Fioole, MD, PhD[a]

[a]*Department of Vascular Surgery*

[b]*Department of Radiology Maasstad Hospital, Rotterdam, The Netherlands.*

[c]*Department of Radiology*

[d]*Department of Vascular Surgery Sint Antonius Hospital, Nieuwegein, The Netherlands*

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ABSTRACT

Background

The optimal endovascular treatment for femoropopliteal arterial occlusive disease has yet to be assessed. Patency rates after uncoated balloon angioplasty are disappointing. Although stents have better outcomes, they also have limitations. Intra-arterial stenting may lead to stent thrombosis and flow pattern disruption, which may result in stent fracture or in-stent restenosis. In the past decade, drug-eluting balloons (DEBs) and drug-eluting stents (DESs) have been introduced, and both have proven to possess antirestenotic features compared with conventional techniques. The objective of this study is to perform a noninferiority analysis of DEBs with provisional bare-metal stenting and primary stenting with DESs in the treatment of femoropopliteal arterial occlusive disease. If DEB with provisional bare-metal stenting proves to be noninferior to primary stenting with DESs, DEBs may be the favorable technique because the postoperative long-term limitations of stents will be restricted.

Methods

This is a prospective, randomized, controlled, single-blind, multicenter trial. The study population consists of volunteers aged ≥18 years, with chronic, symptomatic peripheral arterial occlusive disease (Rutherford-Baker classification 2 to 5) caused by de novo stenotic or occlusive atherosclerotic lesions of the superficial femoral artery or of the popliteal artery (only segment P1). Subjects will be treated with a DEB and provisional bare-metal stenting (if a stenosis >30% or a flow-limiting dissection persists after prolonged inflation with an UCB) or with primary stenting with a DES. The study will include 254 patients (ratio 1:1). The primary end point is 2-year freedom from binary restenosis, defined as a lumen diameter reduction of <50% assessed by duplex ultrasound imaging (peak systolic velocity ratio <2.5). Secondary end points are technical success, target lesion revascularization, target vessel revascularization, improvement in ankle-brachial index, improvement in Rutherford classification, amputation rate, and mortality rate.

Trial registration: Dutch Trial Register (Trialregister.nl): NTR5797. Registered 1 March 2016.

Keywords: Drug-eluting balloon, drug-eluting stent, superficial femoral artery, peripheral arterial occlusive disease.

INTRODUCTION

Femoropopliteal disease is present in 65% of patients with peripheral arterial disease (PAD).[1] Venous bypass surgery has been the gold standard treatment for femoropopliteal arterial occlusive disease. However, owing to the growth of the frail and aging vascular population and the rapid development of endovascular techniques and improved competence, experienced centers advocate an endovascular-first approach.[2,3] Technical success of endovascular revascularization is high, but long-term patency remains limited. Treatment of femoropopliteal stenosis and occlusions with uncoated balloon (UCB) angioplasty leads to restenosis rates of up to 40% to 60% after 1 year.[4,5] Randomized controlled trials (RCTs) have demonstrated superior patency of bare-metal stents compared with conventional UCB angioplasty in femoropopliteal arteries.[6–8] Stenting, however, has its own limitations because it disrupts the flow pattern, which can lead to stent thrombosis or in-stent restenosis. Moreover, stents may fracture, which is associated with an increased risk of stent occlusion.[9–11]

Drug-eluting techniques have been introduced to improve outcomes of endovascular interventions. Angioplasty balloons and stents have been coated with antiproliferative medication (eg, paclitaxel or everolimus), which reduces intima hyperplasia after treatment and is associated with a decreased restenosis rate and improved patency.[12,13]

Several RCTs of comparing DEB with UCB angioplasty, with provisional or primary stenting have been published. DEBs are associated with improved freedom from binary restenosis rate and a decreased late lumen loss and target lesion revascularization rate.[14] The results of two large RCTs of DEB angioplasty compared with UCB angioplasty in the femoropopliteal artery (Randomized Trial of IN.PACT Admiral Drug Eluting Balloon vs Standard PTA for the Treatment of SFA and Proximal Popliteal Arterial Disease [IN.PACT SFA] trial and Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis [LEVANT 2] trial) were recently published.[15,16] In the LEVANT 2 trial, freedom from binary restenosis after 1 year was significantly better after DEB (65.2% vs 52.6%, P =.02). The results of the IN.PACT SFA trial show similar results after 2 years in the UCB group (53.1%) but even better results in the DEB group (80.2%). The difference in outcome after DEB angioplasty in both trials may possibly be explained by the higher paclitaxel dose in the DEB in the IN.PACT SFA trial (3.5 vs 2 μg/mm^2).[17] In the only high-quality RCT of DES compared with UCB angioplasty in the femoropopliteal artery (Zilver PTX [Cook Medical, Bloomington, Ind] trial), freedom from binary restenosis after 2 years was 74.8% vs 26.5%.[18]

DEBs and DESs have both proven to be superior to UCB angioplasty. Although the results after primary stenting with a DES in the femoropopliteal arteries are very promising, stent limitations, such as stent fracture, stent thrombosis, in-stent restenosis, and the potential limitation to perform future surgical bypass interventions, may advocate techniques where nothing is left behind. Comparing RCTs may be challenging because of differences in

inclusion and exclusion criteria, definitions of end points, and treatment protocols. Up to now, DEBs and DESs in the femoropopliteal arteries have not been compared directly in an RCT. In the current RCT, we intend to compare DEBs and DESs. The available data show that significant differences in patency and freedom from binary restenosis are not likely to be found. Therefore, a noninferiority trial has been designed. If DEB angioplasty with provisional stenting turns out to be noninferior to primary stenting with DESs, than DEB angioplasty may be the favorable technique because stent limitations will be restricted.

METHODS

The Randomized comparison of femoropopliteal artery drug-eluting balloons and drug-eluting stents (FOREST) trial is a multicenter, single-blind, non-inferiority, 1:1, RCT comparing outcomes after treatment of symptomatic femoropopliteal PAD with DEB vs DES. The study hypothesis is that DEB will provide noninferior outcomes compared with DES.

Centers currently participating are the Maasstad Hospital, Rotterdam, and the Sint-Antonius Hospital, Nieuwegein, in The Netherlands. The medical ethics review committee has approved the protocol. Approval is being obtained in two other Dutch vascular centers. The study will be conducted according to the principles of the Declaration of Helsinki (Seoul, October 2008) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

Patients

The first patient was enrolled on September 15, 2016. The study will recruit 254 patients with chronic, symptomatic peripheral arterial occlusive disease in Rutherford-Baker clinical categories 2 to 5, caused by de novo stenotic or occlusive lesions of the superficial femoral artery (SFA) or popliteal artery (only P1 segment), or both. Inclusion and exclusion criteria are provided in Table I.

Study devices

The IN.PACT Admiral paclitaxel-coated percutaneous transluminal angioplasty balloon catheter (Medtronic, Santa Rosa, Calif) is an over-the-wire balloon catheter with a drug-coated balloon at the distal tip. The drug component, referred to as the FreePac drug coating, consists of the drug paclitaxel and the excipient urea. The device component physically dilates the vessel lumen by percutaneous transluminal angioplasty, and the drug is intended to reduce the proliferative response that is associated with restenosis. The balloon is available in diameters of 4 to 7 mm and lengths of 40 to 150 mm.

Table I. Eligibility criteria

Inclusion	*Exclusion*
Age ≥18 years	Life expectancy ≤2 years
Be willing to sign an informed consent form	Recurrent stenosis or occlusion
Rutherford-Baker class 2 to 5	Acute femoropopliteal occlusion
At least 1 symptomatic de novo atherosclerotic stenosis or occlusion in the superficial femoral artery and/or popliteal artery, section P1.	Aspirin, clopidogrel, heparin, or paclitaxel allergy
The lesion should be a stenosis of at least 50% or an occlusion assessed by catheter-guided angiography	Known hypercoagulable state
At least 1 patent tibial runoff vessel	
Reference artery diameter between 4 and 7 mm	
All lesion lengths	
Successful passage with a guidewire	
Dutch language comprehension	

The Zilver PTX DES (Cook medical, Bloomington, Indiana, USA) is a self-expanding stent made of nitinol and coated with the drug paclitaxel. It is a flexible, slotted tube that is designed to provide support while maintaining flexibility in the vessel upon deployment. After deployment, the stent is designed to impart an outward radial force upon the inner lumen of the vessel, establishing patency in the stented region. The stent is preloaded in a 6.0F delivery catheter. Hand loading of the stent is not possible. Stent deployment is controlled by retraction of the handle while the metal cannula is held stationary. The Zilver PTX stent is available in diameters of 4 to 7 mm and lengths of 40 to 140 mm.

Study objectives and end points

The primary objective of this study is to demonstrate that DEB with provisional stenting has noninferior outcomes compared with primary stenting with DES in the endovascular treatment of femoropopliteal stenosis and occlusions in patients with Rutherford-Baker categories 2 to 5 PAD. The primary end point is freedom from binary restenosis after 2 years, defined as a lumen diameter reduction of <50% assessed by duplex ultrasound (DUS) imaging (peak systolic velocity [PSV] ratio <2.5).

Secondary end points are technical success, procedural success, target lesion revascularization, target vessel revascularization, primary patency, changes in the ankle-brachial index (ABI) and Rutherford-Baker categories, amputation, and death and are detailed in Table II.

Sample size calculation and statistical considerations

On the basis of the available literature,[15,18] we expect a 2-year freedom from binary restenosis rate of 80.2% in the DEB group and 74.8% in the DES group. The current trial is designed as a noninferiority trial, and the aim is to demonstrate that the restenosis rate

Table II. Primary and secondary end points

Primary	definition
Freedom from binary restenosis	Absence of hemodynamically significant obstruction in the target lesion after endovascular treatment, defined as a lumen diameter reduction of <50% assessed by duplex ultrasound (DUS) imaging (peak velocity ratio [PVR] <2.5) or on computed tomography angiography.
Secondary	
Technical success	Residual stenosis <30% after treatment assessed by angiography.
Procedural success	Technically successful procedure without complications.
Target lesion revascularization (TLR)	Any secondary intervention of the target lesion to maintain patency
Target vessel revascularization (TVR)	Any secondary intervention of the target vessel to maintain patency.
Primary patency	Freedom from binary restenosis and freedom from TLR during follow-up
Changes in ankle-brachial index (ABI)	Assessed by treadmill test; in patients with critical limb ischemia only a resting ABI will be performed
Changes in the Rutherford-Baker category	Improvement of at least 1 category
Quality of life	Improvement in disease-related health status, functioning, and quality of life, as defined by a Dutch translation of the Peripheral Artery Questionnaire (PAQ)
Major amputation	Above the ankle
Mortality	All-cause

after 2 years is at most 10 percentage points (the noninferiority margin) higher in the DEB arm. The noninferiority of DEB angioplasty is demonstrated if the upper limit of the two-sided 95% confidence interval for the difference (DEB minus DES) in the restenosis rate at 2 years does not exceed +10%. To demonstrate this at a power of 80%, we have calculated that 115 patients are required per arm. To account for a potential 10% rate of loss to follow-up, 127 patients will be randomized per treatment arm.

The primary end point at 2 years will be determined using Kaplan-Meier curves (with Greenwood's standard errors). Noninferiority of DEB angioplasty is shown if the 95% confidence interval for the difference excludes a difference of >10 percentage points in favor of DESs. Demographics and baseline characteristics will be summarized descriptively with mean, median, or percentage.

Study procedure

All symptomatic patients with suspected significant femoropopliteal stenosis and occlusions on DUS, computed tomography angiography (CT-A) or magnetic resonance angiography (MR-A), will be asked to participate in the study by their physician. A treadmill test will be performed in patients with intermittent claudication, and only a resting ABI will be obtained in patients with critical limb ischemia. After informed consent is obtained,

the patient will be planned for angiography. The extent of the femoropopliteal lesion will be assessed by digital subtraction angiography. Only one extremity per patient may be included in the trial. If both legs meet the inclusion criteria, the leg with the most severe complaints will be treated first and will be included in the trial.

Intervention

Patients may be treated under local or general anesthesia. Access will be obtained by a 6F sheath, preferably in the common femoral artery. Antegrade and crossover approaches are both allowed, as are all other additional approaches, including popliteal, tibial, or brachial access. All patients will receive 5000 IU of heparin before the intervention.

A diagnostic angiography of the whole limb must be performed to determine the diameter of the reference vessel, the length and degree of the stenosis, length of the stenosis or occlusion, and the outflow. The diameter of the reference vessel is not only determined by angiography, but also on DUS, computed tomography angiography (CT-A) or magnetic resonance angiography (MR-A), depending on availability. At least one of these imaging modalities will be available next to the diagnostic angiography. A stenosis of >50% is considered significant and meets the inclusion criteria, as well as any occlusion in the SFA or the P1 popliteal artery segment. At least one tibial artery passing the ankle must be present. A stenosis must be imaged in two directions to assess the calcium score.[19] After passage of the femoropopliteal lesion with a wire, the patient will be allocated to treatment with DEB angioplasty with provisional bare-metal stenting, or primary stenting with the DES (Figure 1). Hemodynamically significant lesions in other segments (ie, iliac

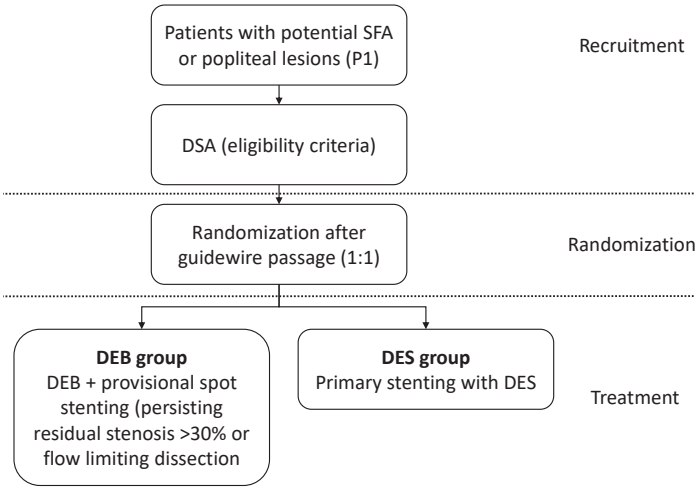

Figure 1. Study overview
SFA = Superficial femoral artery, DSA = Digital subtraction angiography, DEB = Drug-eluting balloon, DES = Drug-eluting stent

or below-the-knee lesion) may be treated to ensure adequate inflow and outflow (including femoral endarterectomy). These lesions may not be treated with DEBs or DESs. All concomitant procedures will be reported and assessed.

Drug-eluting balloon

If the patient is allocated to the DEB group, the lesion will be predilated with an UCB that is 1 mm smaller in diameter than the reference diameter. To avoid geographic miss, treatment with the DEB will start 10 mm proximally from the lesion and end 10 mm distally from the lesion. The diameter of the DEB must be at least the reference diameter and may be slightly oversized (<1 mm). Every DEB must be inflated for at least 3 minutes. If the lesion length exceeds the length of the longest balloon, multiple DEBs must be used to cover the entire lesion. If more than one DEB is used, the balloons must overlap at least 10 mm. If a stenosis >30% or a flow-limiting dissection occurs, prolonged inflation with an UCB must be performed for at least 5 minutes. If a stenosis >30% or a flow-limiting dissection persists after prolonged inflation with an UCB, provisional stenting is allowed. Only a stenosis >30% or flow-limiting dissection may be treated with a self-expandable bare-metal stent (spot stenting). All commercially available self-expandable bare-metal stents are allowed and must be oversized up to a maximum diameter of 1 mm larger than the reference diameter.

Drug-eluting stent

The lesion in a patient allocated to the DES group will be predilated with an UCB. The diameter of the UCB must be similar to the reference diameter of the artery. To avoid geographic miss, treatment with the DES will start 10 mm proximally from the lesion and end 10 mm distally from the lesion. Lesions starting at the origin of the SFA must be treated from the origin of the SFA because the stent may not extend into the common femoral artery. The stents must be oversized up to a diameter 1 mm larger than the reference diameter. If more than one DES is used, the stents must overlap at least 10 mm. Stents are postdilated with an UCB that has a diameter similar to the reference diameter of the artery.

Completion angiography

A completion angiography of the entire limb must be performed. The treated femoropopliteal segment must be imaged in two directions. After the sheath is removed, manual compression and closure devices are both permitted.

Medical therapy

The medical therapy will be similar for all patients. Clopidogrel (75 mg daily after a 300-mg procedural loading dose) and a statin (daily) must have been started at least 24 hours before the therapy and will be continued lifelong, in accordance with Dutch peripheral

artery disease guidelines[20]. Aspirin (100 mg daily) will be administered for 3 months. If patients are already being treated with coumarins, clopidogrel (75 mg daily) will be added for 3 months.

DUS imaging

Color DUS imaging is used to visualize the femoropopliteal artery during follow-up. The PSV ratio is calculated by dividing the PSV at the level of the stenosis by the PSV proximal to the stenosis. A PSV ratio of >2.5 is defined as a significant stenosis. Laboratory technicians from accredited vascular laboratories will perform DUS imaging.

Questionnaire

A Dutch translation of the peripheral artery questionnaire (PAQ) will be used to assess improvement in disease-related health status, functioning, and quality of life.

Randomization, blinding, and treatment allocation

Randomization will be performed using the Castor EDC online registration and randomization program (http://www.castoredc.com). Unstratified randomization will be used. A flowchart of the study procedure is depicted in Figure 1. Patients will be blinded to the treatment they receive. The physician performing the procedure cannot be blinded to the treatment received because there are visible differences in treatment devices. The type of treatment will not be documented in the patient's medical record. Vascular technicians, who are blinded for the type of treatment received, will perform postoperative ABI measurements, DUS imaging, and Rutherford classification scoring. Vascular technicians performing DUS imaging will be able to identify stent placement. However, they will not be aware of whether this is primary DES placement or a provisional bare-metal stent placement after DEB angioplasty. Blinded vascular laboratory technicians will perform color DUS and treadmill tests. An unblinded research team will perform evaluation of these test results.

Follow-up

Patients will visit the outpatient clinic at 1, 6, 12, and 24 months after the procedure. During these visits, a physical examination will be performed and PAQ (Dutch version) will be collected. Before the visits at 6, 12, and 24 months, the ABI with treadmill test will be performed along with DUS imaging of the treated artery. All complications and reinterventions during follow-up will be reported.

Study management

The FOREST trial is a physician-initiated trial. The Dutch Endovascular Alliance (DEALL) foundation is the sponsor of the trial and has the overall responsibility. All protocol

contributors are members of the DEALL foundation. The trial investigators have the final responsibility for scientific conduct and rights to publish the results.

Data collection, management, and analysis

Data will be documented using an online case report form (Castor EDC, Ciwit BV, Amsterdam, The Netherlands). Castor EDC has been audited on good clinical practice compliance by Profess Medical Consultancy and has obtained a good clinical practice compliance certificate. The board of the Maasstad Hospital Rotterdam has approved Castor EDC for collection and storage of data. Only the coordinating and principal investigators will have access to the source data. All data will be handled anonymously. The handling of personal data complies with the Dutch Personal Data Protection Act (in Dutch: De Wet Bescherming Persoonsgegevens, Wbp).

Monitoring and adverse event adjudication

No data safety monitoring board will be appointed while all products used in this trial are indicated and approved for treatment of femoropopliteal vascular disease. The trial investigators review all adverse events, including nonserious adverse events. The study coordinator will report the serious adverse events through a web portal to the medical ethics review committee.

Competing interest

The authors declare that they have no competing interests.

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