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

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ABSTRACT

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 been 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. 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 uncoated balloon) 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. (J Vasc Surg 2017;■:1-6.)

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 comparing drug-eluting balloons (DEBs) with UCB angioplasty, with provisional or primary stenting, have been published. DEBs are associated with an 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—the randomized trial of IN.PACT Admiral DEB vs standard percutaneous transluminal angioplasty for the treatment of superficial femoral

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The Dutch Endovascular Alliance foundation, Rotterdam, The Netherlands, is the sponsor of the FOREST trial. The Dutch Endovascular Alliance is an independent research foundation.

Dutch Trial registration: NTR5797.

Author conflict of interest: none.

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The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

0741-5214

http://dx.doi.org/10.1016/j.jvs.2017.05.098

artery (SFA) and proximal popliteal arterial disease (IN.PACT SFA) and the 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 angioplasty (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 drug-eluting stent (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 been proven to be superior to UCB angioplasty. Although the results after primary stenting with a DES in the femoropopliteal arteries are 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 whereby 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, then DEB angioplasty may be the favorable technique because stent limitations will be restricted.

METHODS

The randomized comparison of femoropopliteal artery DEBs and DESs (FOREST) trial is a multicenter, single-blind, noninferiority, 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, the Antonius Hospital, Sneek, 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).

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 one symptomatic de novo atherosclerotic stenosis or occlusion in the SFA 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 one patent tibial runoff vessel	
Reference artery diameter between 4 and 7 mm	
All lesion lengths	
Successful passage with a guidewire	
Dutch language comprehension	

SFA, Superficial femoral artery.

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 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.

The Zilver PTX DES 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 on deployment. After deployment, the stent is designed to impart an outward radial force on the inner lumen of the vessel, establishing patency in the stented region. The stent is preloaded in a