Randomized trial of Legflow® Paclitaxel eluting balloon (LPEB) with stentplacement vs. standard PTA with stentplacement for the treatment of intermediate (>5 cm and < 15 cm) and long (>15 cm) lesions of the superficial femoral artery (SFA). The RAPID trial.

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Outline:
Multi-center, randomized controlled trial of SFA balloon angioplasty using the Legflow® Paclitaxel Eluting Balloon (Cardionovum Sp.z.o.o., Warsaw, Poland) with additional stenting, using the Supera® stent (intervention arm) vs. standard non-coated balloon angioplasty with additional stenting, using the same (Supera®) stent (control arm). Two-years follow up will comprise both clinical and angiographic parameters.

Index

1 List of general abbreviations and relevant definitions

ABR	ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)
AE	Adverse Event
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
DSMB	Data Safety Monitoring Board
EU	European Union
GCP	Good Clinical Practice
IC	Informed Consent
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
(S)AE	(Serious) Adverse Event
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
WBP	Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met mensen

2 List of study-specific abbreviations and relevant definitions

ABI	Ankle-brachial index. Defined as the ratio between the highest systolic pressure in both brachial arteries and the highest systolic pressure in the crural arteries. In patients without CLI, this is repeated after the standardized treadmill test, termed 'ABI in rest' and 'ABI after exercise'.
Absence of binary restenosis	Absence of hemodynamically significant obstruction (see definition) after endovascular intervention.
ACT	Absolute claudication time. Defined as the time (in minutes and seconds) after initiation of the treadmill test when the patient cannot walk any further due to severe (ischemic) claudication pain.
SFA	Superficial femoral artery
CLI	Critical limb ischemia (Rutherford category 4, 5 or 6)
COT	Claudication onset time. Defined as the time (in minutes and seconds) after initiation of the treadmill test when patient first experiences symptoms of claudication.
Crural level	Proximal limit: Origin of anterior tibial artery. Including foot arteries
DSA	Digital subtraction angiography
DUS	Duplex ultrasonography
Femoro-popliteal level	Proximal limit: Deep circumflex iliac artery, inguinal ligament. Distal limit: Origin of anterior tibial artery.
Hemodynamically significant obstruction	Hemodynamic significance can be assessed using the following measurement techniques (in hierarchical order): Per-procedural: - Intra-arterial mean translesional pressure gradient >10 mmHg at rest or during pharmacological dilatation of the arterial bed (by papaverin, tolazolin, nitroglycerine etc.), as assessed by means of two simultaneous measurements using two pressure channels proximally and distally to the lesion - Intra-arterial DSA, in 2 imaging planes with at least 30 degrees difference in rotation, indicating ≥50% diameter stenosis or ≥75% area stenosis by quantitative vessel analysis software (PIE medical)

	Pre-procedurally and follow-up: - CT-angiography or MR-angiography indicating ≥50% diameter stenosis or ≥75% area stenosis - DUS indicating ≥50% diameter stenosis as defined by a peak systolic velocity index >2.4 (Defined as the ratio of intra-stenotic peak systolic velocity to pre-stenotic peak systolic velocity)
IC	Intermittent Claudication
PAOD	Peripheral arterial occlusive disease
Primary sustained clinical improvement	Improvement by at least one Rutherford category, except for those with actual tissue loss (category 5 and 6), who must at least improve to the level of IC (category 3), without the need for TLR, in surviving patients with preserved limb.
Secondary sustained clinical improvement	Improvement by at least one Rutherford category, except for those with actual tissue loss (category 5 and 6), who must at least improve to the level of IC (category 3), including the need for TLR, in surviving patients with preserved limb.
Standardized treadmill test	Patients are required to walk with 3.2 km/h at a 12% grade for a maximum of 5 minutes on a treadmill. Claudication onset time (COT) and absolute claudication time (ACT) are determined in minutes and seconds.
Technical success	Successful access and deployment of the device and ≤30% diameter residual stenosis after revascularization, as measured by DSA, in 2 imaging planes with at least 30 degrees difference in rotation, using quantitative vessel analysis software (PIE medical, MaastrichtEindhoven, The Netherlands)
TER	Target-extremity revascularization
TLR	Target-lesion revascularization

3 Summary

Rationale: Atherosclerotic lesions in the superficial femoral artery may cause intermittent claudication and critical limb ischemia, leading to serious complications such as tissue loss, amputation and even death. Revascularization relieves symptoms and might prevent these complications. Over the last decade, endovascular repair has become the preferred treatment for femoral arterial obstructive disease. No definitive consensus has emerged concerning the best endovascular strategy, for example if balloon angioplasty or stenting is superior. However, literature is most supportive of balloon angioplasty with stenting in longer segment lesions in the SFA. Paclitaxel covered balloons have been found to reduce neo-intimal hyperplasia, and reduce restenosis.[1,2] Recently, the Legflow® Paclitaxel eluting balloon (Cardionovum Sp.z.o.o., Warsaw, Poland) has been introduced. This Paclitaxel eluting balloon is covered with Shellac, to obtain an equally distributed tissue concentration of Paclitaxel, reaching an optimal dosis at a short inflation time of 30 seconds because of a high delivery dose. This results in reduced neo-intimal growth, and reduces the risk of local and systemic complications.[2,3] In porcine models Paclitaxel/Shellac coated balloons show a higher tissue concentration over time than other Paclitaxel balloons, requiring a shorter inflation time for optimal tissue concentrations.[3] However, no randomized controlled trials have been performed on this specific balloon in the superficial femoral artery. We hypothesize that the Legflow PEB balloon in combination with Nitinol stents will lead to significantly less hemodynamically significant restenosis when compared to conventional uncovered balloons combined with Nitinol stents in treatment of intermediate ($\geq$5 cm and < 15 cm) and long ($\geq$ 15 cm) SFA lesions.

Hypothesis: The use of PDEB will reduce the restenosis rate of treated SFA lesions compared to conventional PTA with stent.

Objectives: The primary objective is to assess the difference in absence of binary restenosis rate of endovascular treatment of intermediate and long lesions of the superficial femoral artery with the Legflow® PEB and nitinol stent, when compared to uncoated conventional balloon angioplasty and nitinol stent after a 2-year follow-up.

The secondary objectives are to asses the clinical success, hemodynamic success, reocclusion rate, target lesion revascularization rate, major amputation rate, complication rate, mortality rate and cost-effectiveness of endovascular treatment of intermediate and long lesions of the superficial femoral artery with the Legflow® PEB and nitinol stents, when compared to conventional balloon angioplasty and nitinol stent.

Study design: A randomized, controlled, patient-blind, multi-center trial

Study population: Human patients aged over 18 years, with symptomatic atherosclerotic intermediate or long segment obstructions of the superficial femoral artery, Rutherford category 2-6.

Intervention: The intervention group will undergo endovascular dilatation of intermediate and long lesions of the SFA with the LegFlow® Paclitaxel eluting balloon followed by placement of a nitinol

selfexpandable stent (Supera®, IDEV inc., Webster TX). The control group will undergo endovascular dilatation of the SFA with standard PTA followed by placement of the same Supera® stent.

Main study parameters/endpoints: The primary endpoints are absence of binary restenosis rate,. Secondary endpoints are reocclusion rate and target-lesion revascularization rate, clinical success, hemodynamic success, major amputation rate, complication rate, mortality rate and cost-effectiveness. Main study parameters are age, gender, relevant co-morbidity, and several disease and procedure related parameters.

Sample size: Based on the present literature, a two-year restenosis rate of 45% in the standard group may be expected, and a two-year restenosis rate of 20% in the LegFlow® PEB group.[1,2] Based on a two-tail test with an alpha error level of 0.05 and a beta error level of 0.2, and an anticipated loss to follow-up of 10% a sample size of 88 patients per group, for a total of 176 patients will be needed. This calculation was performed with the online program of DSS Research (http://www.dssresearch.com/toolkit/sscalc/size.asp).

Nature and extent of the burden and risks associated with participation and benefit: All devices, guidewires and catheters have CE-approval (1434-MDD-32/2011). Participating patients will need to make five study-related hospital visits, which is standard for this type of treatment. Five non-invasive duplex-ultrasound (DUS) studies and five non-invasive ABI measurements with treadmill test will be performed, as well as non-invasive toe pressure measurements (TcpO2). When compared to the standard pre-procedural imaging and follow-up imaging, patients do not need to make extra hospital visits. When treadmill test and DUS show possible asymptomatic significant restenosis >75%, or symptomatic restenosis >50% patients will receive additional digital subtraction angiography and (re)intervention. This is routine in daily vascular practice. Furthermore, patients will be asked to fill out a 13-item questionnaire at every follow-up moment. The Shellac used on the catheter is recognized as safe by the FDA (E904). Recently, the use of the DIOR 2 balloon (also covered with Shellac and used in the cardiac field) for in-stent stenosis, and restenosis of small cardiac vessels was safe at one year. TLR of the treated stenoses in this study was 12%.[4]

4. Introduction

4.1 Background

Peripheral Arterial Occlusive Disease (PAOD) is a disease defined as reduced arterial blood flow to the lower extremities due to atherosclerotic arterial lesions and is diagnosed by an ankle-brachial of less than 0.9. It may lead to intermittent claudication (IC) or, with progression of the disease, critical limb ischemia (CLI). Only one out of every four to five patients with PAOD will be symptomatic.[5] The most common clinical manifestation of PAOD is intermittent claudication involving the pelvis, upper thigh and lower limb. It is defined as ischemic pain occurring during exercise, which is quickly relieved with rest (Fontaine II, Rutherford 1 to 3). CLI is a more severe presentation of PAOD, defined as ischemic rest pain (Fontaine III, Rutherford 4) or ischemic skin lesions, either ulcers or gangrene (Fontaine IV, Rutherford 5 and 6, respectively).[5] Patients presenting with CLI usually have multisegmental disease with involvement of the infra-inguinal arteries.[6] Ten to twenty percent of patients with IC will progress to CLI in the course of their disease. [7-9] Most important risk factors for progression of PAOD into CLI are age, tobacco use and diabetes mellitus.[10]

4.2 Epidemiology

Newman et al. described the prevalence of PAOD (asymptomatic and symptomatic) in the general population.[11] They found a prevalence of 13.4% in those over 65 years of age, rising to 21.6% in those over 75 years of age. The German ABI study showed a prevalence of 19.8% in men over 65, and 16.8% in women over 65.[12] The exact overall incidence of PAOD is not known, but the Framingham Study showed an incidence of IC of 26/10,000 in men and 12/10,000 in women.[13] More than 50% of all PAOD cases involve the SFA and popliteal artery.[10]

4.3 Endovascular treatment

The first one to perform SFA angioplasty with sequential dilators was Charles Dotter in 1964.[14] In 1974 a catheter-mounted inflatable balloon that could fit over a guidewire was developed by Andreas Grüntzig, significantly improving the technique.[15] Finally, in 1985, the first intraluminal stent was developed by Julio Palmaz, further improving the results of endovascular treatment.[16]

Due to ongoing improvements in materials and techniques over the past decades, endovascular techniques for femoropoplitial obstructions have been advocated in complex and long-segment SFA lesions.

4.4 Define guidelines

In 2008 Diehm and coworkers reported standardized definitions for reports concerning peripheral endovascular revascularization trials.[17] Until then, anatomical characteristics of SFA lesions were mainly classified by the Trans Atlantic Inter-Society Consensus on the Management of Peripheral Arterial Disease (TASC II). The current TASC guidelines were published in 2007 and treatment of

choice is endovascular in type A lesions, whereas it is the preferable treatment in B and C lesions. In TASC D lesions surgery is the advised treatment of choice.[5] However, during the last four years there has been a marked shift towards endovascular treatment even in TASC D SFA lesions. The initial technical and clinical success rate of PTA of femoropopliteal artery stenoses in all series exceeds 95% (range 98%–100%, standard error 1.0%).[18]

One of the drawbacks of the current TASC classification is the lack of inclusion of baseline anatomic characteristics of the target (in this trial the SFA) lesion itself and that it combines femoropopliteal lesions as well as below the knee lesions within the same nomenclature. Therefore, the TASC classification, although commonly utilized, may not be ideal, and the use of a more complete anatomical description of the SFA lesions has been advised by the Define group, which is used in this protocol.

Anatomic definition of the SFA: Origin starts directly below the origin of the deep femoral artery and it ends upon exiting the adductor canal of Hunter; angiographic approximation: crossing of the SFA over the medial cortex of the femur when viewed in an anterior-posterior projection.

Lesion length: Focal lesions: < 1 cm

Short lesions: >1 cm and < 5 cm

Intermediate lesions: $\geq$ 5 cm and < 15 cm

Long lesions: $\geq$ 15 cm

In case of vessel occlusion within a stenosed segment, both the length of the stenosed segment and the length of the occluded segment should be reported.

4.5 Paclitaxel DEB and stent or conventional PTA and stent for superficial femoral artery lesions

In the THUNDER trial 154 patient were randomly assigned to treatment with conventional uncoated balloons, balloons coated with Paclitaxel, or uncoated balloons with Paclitaxel dissolved in the contrast medium. Late lumen loss was significantly lower in the patients treated with Paclitaxel coated balloons compared to either the Paclitaxel solution or control groups. The rate of revascularization was also significantly lower in the Paclitaxel coated balloon group at 6 months.[1] Comparable results were seen in the FemPac trial.[2]

Several studies have been published describing the results of Paclitaxel covered balloons in PAOD of the SFA. These are shown in table 1.

Author, year	Type of study	N	TLR	
Werk, 2008	Randomized controlled trial	48 coated 52 uncoated	6 month : 7% 6 month: 33%	
Tepe, 2008	Randomized controlled trial	48 coated 52 Uncoated	6 month: 6%, 6 month: 37% **Patency**	2 year: 15% 2 year: 52%
Vroegindewij, 1997	Randomized controlled trial	24 Stent	1year: 69%	
Zdanowski	Randomized controlled trial	15 Stent	1year:50%	
Cejna	Randomized controlled trial	77stent	1 year:77%	
Krankenberg 2007	Randomized controlled trial	132 stent	1year 68%	

Table 1. **Results of studies reporting on the results of Paclitaxel coated balloon angioplasty**

As shown in table 1, TLR rates of coated balloons are excellent. However, only few studies have been performed, and most with short-term follow-up or underpowered to draw any firm conclusion.

This current **RAPID** trial compares the LegFlow® balloon in combination with placement of a nitinol Supera stent versus uncoated balloon angioplasty with placement of a nitinol Supera stent in intermediate and long SFA lesions. The Legflow balloon is a Drug Eluting Balloon coated with Paclitaxcel and has Shellac as excipient. It is this carrier that distinguishes this balloon from other DEB. Shellac might be superior to other excipients in binding the Paclitaxel to the balloon and will facilitate a fast and effective delivery of Paclitaxel in the arterial wall. In this way lower doses of Paclitaxel are needed and shorter inflation time of the balloon itself is required.[3]

4.5 Rationale of this study

A primary endovascular approach should be attempted in all patients with focal and short (< 5 cm) SFA lesions. When performing endovascular repair, there are many different strategies and balloons to be used, as described above. There is no general consensus on which strategy and type of stent is best for which obstruction in the superficial femoral artery. However, for more advanced disease of the superficial femoral artery, literature is most supportive of direct stenting (intermediate and long lesions) or even open repair (> 15 cm long lesions). A recent innovative technique is the Paclitaxel coated balloon, which might further improve the primary patency of stents in SFA lesions. However, predominantly porcine studies have been published on the use of Paclitaxel eluting balloons prior to the placements of stents.[19, 20] Furthermore only two RCT's are available on the use of Paclitaxel in the SFA, using different excipients. Therefore, the purpose of this study is to compare the LegFlow® Paclitaxel eluting balloon in combination with placement of a self-expandable nitinol stent (Supera®, IDEV, Webster TX) to standard PTA balloon dilatation in combination with placement of the same Supera® stent, in patients with intermediate and long lesions of the SFA.

5. Objectives

5.1 Endpoints/parameters

Definitions of endpoints and parameters are in concordance with the proposed definitions by the Define group, a multidisciplinary team from various specialties involved in PAOD therapies, from Europe and the USA, which has made definitions for more standardized reporting in studies for endovascular treatment of PAOD.[17] There will be a two year follow up for all primary and secondary endpoints.

5.1.1 Primary endpoints

- Absence of binary restenosis rate. Defined as the percentage of limbs with absence of hemodynamically significant obstruction in the target-lesion after endovascular treatment.

5.1.2 Secondary endpoints

- Immediate outcome
    o Procedural success. Defined as the combination of technical success, device success and absence of procedural complications
    o Technical success. Defined as successful vascular access and completion of the endovascular procedure and immediate morphological success with less than 30% residual diameter reduction and <10 mmHg translesion pressure gradient of the treated lesion on completion.
    o Device success. Defined as exact deployment of the device, according to the instructions for use, using the assigned device only.
- Clinical outcome
    o Distribution of Rutherford stages during follow-up as compared to baseline.
    o In patients with IC: Improvement in claudication onset time (COT) and absolute claudicating time (ACT)
    o Improvement in disease-related health status, functioning and quality of life. As defined by the Peripheral Artery Questionnaire (PAQ)
    o Primary sustained clinical success rate. Defined as improvement by at least one Rutherford category, expect for those with actual tissue loss (category 5 and 6), who must at least improve to the level of IC (category 3), in surviving patients, with preserved limb, without the need for TLR.
    o Secondary sustained clinical success rate. Defined as improvement by at least one Rutherford category, expect for those with actual tissue loss (category 5 and 6), who must at least improve to the level of IC (category 3), in surviving patients, with preserved limb, including the need for TLR.
    o Primary sustained resolution of symptoms from PAOD rate. Defined as sustained absence of IC or CLI (Rutherford 0), in surviving patients, with preserved limb, without the need for TLR.

- o Secondary sustained resolution of symptoms from PAOD rate. Defined as sustained absence of IC or CLI (Rutherford 0), in surviving patients, with preserved limb, including the need for TLR.
  - o Clinical deterioration rate. Defined as downgrade of ≥1 category on the Rutherford classification after endovascular treatment (improvements after TLR/TER are not included)
- **-** Hemodynamic outcome
  - o Mean and median ABI during follow-up as compared to baseline
  - o Immediate hemodynamic improvement. Defined as post-procedural increase in ABI of ≥0.10 or to an ABI ≥0.9.
  - o Primary sustained hemodynamic improvement. Defined as sustained increase in ABI of ≥0.10 or to an ABI ≥0.9, in surviving patients, with preserved limb, without the need for TLR.
  - o Secondary sustained hemodynamic improvement. Defined as sustained increase in ABI of ≥0.10 or to an ABI ≥0.9, in surviving patients, with preserved limb, including the need for TLR.
- **-** Target-extremity revascularization (TER) rate. Defined as the rate and frequency of the need for repeated procedures (endovascular or open surgical) due to a problem arising remote from the target-lesion in surviving patients with preserved limb.
- **-** Target-lesion revascularization (TLR) rate. Defined as the rate and frequency of the need for repeated procedures (endovascular or open surgical) due to a problem arising from the target-lesion (+1 cm proximally and distally to include edge phenomena) in surviving patients with preserved limb. This will be reported as a percentage for each reported frequency (for example, 12% with 1 TLR, 4% with 2 TLR etc.)
- **-** Reocclusion rate. Defined as complete occlusion of the initially treated target-lesion.
- **-** Mortality rate. Mortality rate associated with the endovascular procedure (i.e. mortality within 30 days post-procedure or mortality during a hospitalization >30 days due to the procedure) will be reported separately, as well as overall mortality.

  Adverse events
  - o Adverse events (AE). An AE is defined as any untoward medical occurrence in a subject. Potential procedural related adverse events are:
    - ▪ Groin hematoma
    - ▪ Groin infection
    - ▪ Arterial dissection
    - ▪ (Temporary) renal insufficiency
    - ▪ Thrombo-embolic complications
    - ▪ Stent obstruction
    - ▪ Stent migration
    - ▪ Arterial rupture
    - ▪ Allergy to contrast agents
  - o Serious adverse events (SAE). A SAE is an AE that:
    - ▪ leads to death.
    - ▪ results in a life-threatening illness or injury.
    - ▪ results in permanent impairment of a body structure or bodily function.
    - ▪ requires inpatient hospitalization or prolonged hospitalization.

- - results in medical or surgical intervention to prevent permanent impairment to body structure or bodily function.
  - o (Serious) adverse events will be classified in to four categories:
    - Access site complication (access site including distal to the site): Hematoma/bleeding, arterial/venous occlusion/thrombosis, severe vasospasm, intimal injury/dissection, pseudoaneurysm, arteriovenous fistula, vascular perforation or rupture, arterial embolization distal to puncture site.
    - Treatment site complication (treatment site including distal to the site): Hematoma/bleeding, arterial/venous occlusion/thrombosis, severe vasospasm, intimal injury/dissection, pseudoaneurysm, AV fistula, vascular perforation or rupture, arterial embolization distal to treatment site.
    - Organ-specific complication:
      - Neurological: TIA, minor and major stroke, seizure
      - Cardiovascular: Hypotension or hypertension requiring treatment, arrhythmia requiring treatment, myocardial ischemia/infarction, chronic heart failure
      - Respiratory: Profound hypoxia, pulmonary edema, respiratory arrest, pulmonary embolism, pneumothorax.
      - Gastrointestinal: Gastric bleeding, pancreatitis, peritonitis, abscess, perforation of hollow viscus
    - Systemic complication: Allergic/anaphylactic reaction, renal failure, idiosyncratic reaction to drug, fluid/electrolyte imbalance.
- Amputation rate. Divided in minor (below the ankle) and major (above the ankle). Major amputation is sub-divided in below-the-knee, through-knee, and above-the-knee. Planned and unplanned amputations will be reported separately. Planned amputations are defined as amputations that were be planned prior to the revascularization procedure, i.e. when the revascularization procedure is performed to improve the vascularization (and thereby healing potential) of the planned amputation wound.
- Rate of device-specific problems, e.g. stent fracture, stent migration.

5.1.3 Baseline characteristics

- Risk factors and comorbidities:
  - o Age
  - o Gender
  - o Hypertension: Systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, or if the patient is on antihypertensive therapy for the indication of hypertension
  - o Hyperlipidemia: LDL-cholesterol >4.4 mmol/L (>170 mg/dL) or triglycerides >2.0 mmol/L (>177 mg/dL), or if the patient is taking lipid-lowering medication for the indication of hyperlipidemia
  - o Diabetes mellitus: HbA1c> 7% or if the patient consumes oral hypoglycemic agents or uses insulin
  - o Smoking: Current smoking status (active/previous/never), number of pack years, number of years since last smoked.

- o Ischemic heart disease: History of myocardial infarction, angina pectoris, previous percutaneous or surgical coronary revascularization, positive exercise test, anti-anginal therapy
  - o Congestive heart failure: Ejection fraction <40%
  - o Renal insufficiency: e-GFR <60 mL/min/1.73 m^2
  - o Cerebrovascular disease: Known carotid artery disease and history of minor or major stroke or transient ischemic attack (TIA)
- Medication, pre-, peri- and post-procedural, (including dose, frequency and duration of use):
  - o Anticoagulants (Acenocoumarol, Fenprocoumon, unfractioned or low molecular weight heparins, etc.)
  - o Antithrombotic agents (acetylic salicylic acid, clopidrogel, dipyridamol, etc)
  - o Statins or other lipid lowering agents
  - o Beta-blockers
  - o Angiotensin converting enzyme inhibitors
  - o Angiotensin-II receptor antagonists
  - o Insulin and oral hypoglycaemic agents
  - o Medications for the treatment of IC (Pentoxifylline, Buflomedil)
- Baseline anatomic characteristics of the target lesion in the superficial femoral artery:
  - o Involvement of origin/ostium of the SFA.
  - o Length of the SFA lesion, documented in centimeters and classified as follows:
    - ▪ Focal: ≤1 cm
    - ▪ Short: >1 and <5 cm
    - ▪ Intermediate: ≥ 5 and < 15 cm
    - ▪ Long: ≥ 15 cm
    - ▪ In case of vessel occlusion with a stenosed segment, both the length of the stenosed segment and the length of the occluded segment should be reported.
  - o Occlusion or stenosis
  - o In case of stenosis: Percentage of diameter reduction and area reduction on DSA, in 2 imaging planes with at least 30 degrees difference in rotation, as calculated by quantitative vessel analysis software (PIE medical)
  - o Calcification: Semi quantitative distinction between no, moderate, and heavy calcification at the site of the SFA lesion

- Baseline anatomic characteristics of other hemodynamically significant lesions at the aortoiliac level and distal to the target lesion(s):
  - o Arterial segment:
    - ▪ Infra-renal abdominal aorta
    - ▪ External iliac artery
    - ▪ Common femoral artery
    - ▪ Deep femoral artery
    - ▪ Deep femoral artery
    - ▪ Popliteal artery, subdivided into
      - • P1 segment, from Hunter's canal to proximal edge of patella
      - • P2 segment, from proximal part of patella to center of knee joint space

- P3 segment, from center of knee joint space to origin of anterior tibial artery
  - o Lesion length, documented in centimeters and classified as follows:
    - Focal: ≤1 cm
    - Short: >1 and <5 cm
    - Intermediate: ≥ 5 and < 15 cm
    - Long: ≥ 15 cm
  - o Occlusion or stenosis
- Arterial inflow: Impaired inflow is defined as presence of hemodynamically significant obstruction (>50%) in the infrarenal aorta, ipsilateral common and/or external iliac artery and/or aorta.
- Crural outflow: Each of the crural arteries with patency directly to the foot will score 1 point. A patent dorsal and plantar pedal arch will each score 1 point. This will lead to a score of 0 to 5, indicating crural outflow.
- Presence of multilevel disease: Defined as presence of significant obstructive lesions at more than one level in the same limb. (Aortoiliac, femoropopliteal and crural). A maximum of one leg can be included per patient.
- Disease-related health status and quality of life: As defined by the Peripheral artery questionnaire (PAQ)
- Rutherford stage
- Functional status:
  - o In patients with IC: Claudication onset time (COT) and absolute claudication time (ACT) on a standardized treadmill test (3.2 km/h at a 12% grade for a maximum of 5 minutes.)
- Hemodynamic status
  - o In patients with IC: ABI at rest and after standardized treadmill test
  - o In patients with CLI: Systolic ankle pressure and ABI

5.1.4 Procedure related parameters

- Volume of intravenous contrast used
- Radiation time and dosage, as is measured by the fluoroscopy device.
- Amount and type of materials used (guidewires, sheaths, balloons, catheters)
- Time needed for the intervention

6. Patients and methods

6.1 Study design

A randomized, controlled, patient-blind, multi-center trial with a follow-up period of 2 years

6.2 Population

Patients with symptomatic intermediate and long atherosclerotic lesions of the superficial femoral artery presenting at one of the participating hospitals.

6.3 Inclusion criteria

- Age over 18
- Symptomatic, atherosclerotic intermediate ($\geq$5 cm and < 15 cm) and long ($\geq$15 cm) lesions of the superficial femoral artery.
- Rutherford class 2-6
- At least one patent below-the-knee artery with uninterrupted flow to the pedal arch.
- Signed informed consent
- Randomization will be performed after advancement of a guide wire across the target SFA lesion.

6.4 Exclusion criteria

- Life expectancy less than one year.
- Previous endovascular or surgical treatment of the target superficial femoral artery
- Inability to comply with the follow-up schedule.
- Mental disability that hinders the ability to understand and comply with the informed consent.
- Pregnancy or breast-feeding.
- Severe renal failure (e-GFR <30 mL/min/1.73 m^2).
- Known allergy to iodinated contrast agents.
- Contra-indication for anti-coagulation (Aspirin as well as Clopidogrel).
- (Acute) limb ischemia caused by SFA or popliteal artery aneurysmal disease
- Obstruction caused by SFA or popliteal artery dissections

6.5 Sample size calculation

Based on the present literature, a two-year restenosis rate of 45% in the standard group may be expected, and a two-year restenosis rate of 20% in the LegFlow® PEB group.[1,2] Based on a two-tail test with an alpha error level of 0.05 and a beta error level of 0.2, and an anticipated loss to follow-up of 10% a sample size of 88 patients per group, for a total of 176 patients will be needed. This calculation was performed with the online program of DSS Research (http://www.dssresearch.com/toolkit/sscalc/size.asp).

6.6 Number of sites

6 high-volume vascular referral hospitals in The Netherlands. Estimated inclusion period is one year.

6.7 Randomisation, blinding and treatment allocation

Patients will be randomized after having passed the SFA obstruction with a guide wire. Randomization will be performed by block randomization with use of an automated web-based randomization tool. Patients will be blinded for the treatment they receive. When patients are under local or regional anesthesia, a sterile operating theatre napkin will be placed in such a manner that the patient cannot see the procedure and the balloon in particular. The physician will make sure not to mention the type of balloon prior, during or after the procedure. The physician performing the procedure will not be blinded, as this is practically not possible. Post-operative ABI's, duplex-scans and evaluation of clinical improvement will be performed by personnel who are blinded for the type of balloon used.

The indication for breaking the randomization code is the need for open surgical or endovascular re-intervention, if the treating physician feels this is required. The physician will then contact the coordinating physician or one of the principal investigators, who will reveal the type of balloon and document breaking of the randomization code.

6.8 Study procedures

6.8.1 Digital Subtraction Angiography (DSA)

This is a widely used diagnostic technique to visualize peripheral arteries using fluoroscopy. A pre-contrast image is made, after which intra-arterial contrast is given proximal to the area that needs to be visualized. Using digital techniques, the pre-contrast image is subtracted from later images, thereby visualizing the degree of contrast in the arterial lumen, without interference from bony or soft tissue structures. In the participating hospitals, semi-automatic quantitative vessel analysis software by PIE medical will be used to quantify obstruction rates. This software requires two DSA images, in 2 imaging planes with at least 30 degrees difference in clockwise rotation. It then calculates several vessel parameters, such as percentage of area stenosis, lesion length, vessel tortuosity etc.

6.8.2 Duplex Ultrasonography

This is a non-invasive diagnostic technique to estimate stenoses or occlusions in peripheral arteries. It incorporates two elements:

- Grayscale: Uses ultrasound to directly visualize the structure of the vessel. No motion or bloodflow is assessed. In this way, stenosis or occlusion can be directly visualized

- Color-doppler: Uses ultrasound to visualize the flow in the vessel. This is expressed as peak-systolic velocity (PSV), the highest velocity of the blood, during the systolic fase, in cm/sec. In a

stenosis, the PSV will increase. When a stenosis is suspected, the peak-systolic velocity index is calculated. This is defined as the ratio of intra-stenotic PSV to pre-stenotic PSV. A ratio of >2.4 will be defined as a significant stenosis. When the vessel is occluded, no flow will be measured.

All study-related DUS are required to be performed in the vascular lab of the hospital by dedicated laboratory assistants.

6.8.3. ABI measurement

Systolic pressure in both arms is measured, using an automatic blood pressure monitor. The higher of the two will be used. Next, a blood pressure cuff is placed around the patients calf. Using a doppler ultrasound device the dorsal pedal artery and posterior tibial artery are located. The blood pressure cuff is inflated until the doppler signal disappears, and then slowly deflated. The pressure at which a doppler signal reappears is documented for both arteries. The higher of the two is then divided by the systolic pressure in the arm. This is the ABI. When a standardized treadmill test (in patients with IC) is performed, this ABI measurement will be performed prior to the test (ABI in rest) and after completion of the test (ABI after exercise). All study-related ABI measurements are required to be performed in the vascular lab of the hospital by dedicated laboratory assistants.

6.8.4 Standardized treadmill test

Patients are required to walk with 3.2 km/h at a 12% grade for a maximum of 5 minutes on a treadmill. Claudication onset time (COT) will be measured (in minutes and seconds), which is defined as the time after initiation of exercise when the patients first experiences symptoms of claudication, and absolute claudication time (ACT), which is defined as the time after initiation of exercise until the patient cannot continue due to severe claudication pain. Patients with CLI are not required to undergo the standardized treadmill test. All study-related treadmill tests are required to be performed in the core vascular lab of the hospital by dedicated laboratory assistants.

6.8.5. Peripheral artery questionnaire (PAQ)

The PAQ is a 13-item questionnaire designed specifically for patients with PAOD. It covers 7 domains, and assesses these domains over the past 4 weeks. A translated Dutch version has been made, which has been validated.[21-22] Domains can score from 0 to 100 points, with higher scores representing less physical limitation, fewer symptoms, greater treatment satisfaction, or better quality of life. The domains that are tested are:

- Most symptomatic leg

- Physical functioning

- Symptom stability

- Symptom frequency and bothersomeness

- Treatment satisfaction

- Quality of life

- Social functioning

6.9 Follow up schedule

During follow-up, any change in baseline characteristics, complication, adverse events, or newly developed (re)stenosis or (re)occlusion will have to documented as described in chapter 7.1.

6.9.1 Preoperative Imaging

Pre-operative, a Duplex Ultrasound (DUS) will be performed, to document the occlusion or degree of the stenosis in the iliac and common femoral artery. This is mandatory, as this is the modality that will be used during follow-up. Additionally, a CT-angiography (CT-A) or MR- angiography (MR-A) of the entire lower extremity may be performed at the physician's discretion. An ankle brachial index (ABI) will be measured, including a treadmill test in claudicants. These are all part of our regular pre-operative work-up. In most cases, one or more of these investigations will have been performed prior to inclusion. When this has been no longer than 3 months prior to inclusion, the investigation will not have to be repeated for study purposes. All relevant study parameters will be documented and patients will be asked to fill in the PAQ.

6.9.2 Peroperative Imaging

At the end of the procedure, Digital Subtraction Angiography (DSA) will be performed, which will be used to score technical success rate and run-off. Images of the lesions in 2 imaging planes with at least 30 degrees difference in rotation will be saved, so quantitative vessel analysis can be performed at a later moment in the core lab. If open surgical and/or endovascular repair of other arteries of the lower extremity was performed, this will be documented. Any complication that occurred during the procedure will be documented.

In collaboration with the department of experimental cardiology of the Univeristy Medical Centre Utrecht (head: prof. G. Pasterkamp) we will also draw bloodsamples for two reasons: First to sort out if risk factors that should be assessed in blood (lipid profile, glucose) affect the outcome parameters and could be confounding, but secondly also to validate blood derived biomarkers that may help to predict restenosis in peripheral artery disease. In a previous collaboration the investigators detected blood derived biomarkers that influence smooth muscle cell migration and endothelial proliferation. It is unknown if these markers predict restenosis of stent devices in peripheral artery disease.

6.9.3 Follow-up imaging 1 month after the procedure

At 1 month, patients will undergo treadmill test, and ABI, toe pressure, and $TcpO_2$ measurements. Any complication that occurred within the first 30 days will be scored. Patients will be asked to fill in

the PAQ. Furthermore, DUS of the treated SFA will be performed. In case DUS reveals a symptomatic >50% restenosis , or a >75% asymptomatic restenosis additional digital subtraction angiography will be performed with any necessary reintervention.

6.9.4 Follow-up imaging 6, 12 and 24months postprocedural

At 6 and 12 months treadmill test, and ABI, toe pressure and TcpO2 measurements will be performed, as well as a DUS. If DUS shows a >75% restenosis, or a >50% symptomatic restenosis, or is inconclusive, DSA will be performed with any necessary reintervention. Patients will be asked to fill in the PAQ at each follow-up moment.

Below is a table summarizing the study procedures at different moments.

	Pre-procedural	Per-procedural	1 months	6 months	12 months	24 months
Duplex	X		X	X	X	X
ABI with treadmill test	X		X	X	X	X
MRA	X					
DSA		X				
PAQ	X		X	X	X	X
Toe pressures	X	X	X	X	X	X
TcPO2	X	X	X	X	X	X

6.9.5 Unplanned visits

Patients might present at the outpatient clinic or the emergency ward between planned study visits, with (recurrent) symptoms and complaints of PAOD. This will be recorded in the CRF. In this case at least ABI in rest and DUS is mandatory. If DUS shows a stenosis, or is inconclusive, MRA might be performed. In case for need of reintervention DSA will be performed. If a stenosis or occlusion is identified, this will be documented and treated immediately. If this happens within 2 months of a planned study visit, this study visit will be cancelled (in this case, all study procedures will have to be done, such as filling in the PAQ).

6.10 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. This will be recorded in the CRF and the physician is required to notify the PI.

6.11 Replacement of individual subjects after withdrawal

Patients that have been randomized and are withdrawn from the study will not be replaced. They will be considered lost to follow-up and included in the data analysis based on intention-to-treat.

Patients that have been included but are withdrawn prior to randomization will be replaced. This will be documented.

6.12 Follow-up of subjects withdrawn from treatment

Patients that for whatever reason receive a different treatment than randomized, or received no treatment, will be followed-up, and included in the trial, based on intention-to-treat. Patients that are withdrawn from follow-up will be considered lost to follow-up.

6.13 Premature termination of the study

If at any point during the study information becomes available, either from interim analysis of results, or from external sources, that the investigated device poses an increased risk for participating patients, the study will be terminated. Patients will be unblinded for the type of balloon they received. If applicable, they will receive additional treatment or intervention.

7. Treatment of subjects

The aim of the treatment is to obtain a patent superficial femoral artery, with uninterrupted flow to the pedal arch. Therefore not only the SFA will be treated, but if indicated, the aorto-iliac inflow arteries may be treated additionally during the same procedure. However, for randomization of the SFA stenosis or occlusion it is mandatory that the inflow artery is treated successfully (i.e. a residual obstruction <30% or a translesional mean pressure gradient <10mmHg). This strategy corresponds with daily practice. Invasive translesional pressure gradients will be measured to determine lesion characteristics. The SFA lesions will be treated with PTA. Patients will be randomized to either the LegFlow PEB or conventional balloon PTA when the guidewire has successfully passed the SFA lesion. If the common femoral artery (CFA) needs additional treatment, the physician is free to choose a contralateral (cross-over) or ipsilateral (antegrade) technique.

Patients will be treated under local anesthesia in the angiosuite.

Blood withdrawal. Just before the catheterisation when the sheath is inserted we will draw 40 ml of blood in EDTA tubes. 20 ml will be used to obtain plasma for assessment of new biomarkers. 10 ml will be used to obtain exosomes/microparticles from the plasma (source for biomarkers). The last 10 cc will be used for whole blood stimulation for 2 hours. Plasma content changes when blood cells are being stiumlated. We will put the tube for 2 hours at 37 degrees C and then spin it to obtain "stimulated"plasma. All blood samples will be anonomysed and identification will only be possible by using a key that is known to the study coordinator and the responsible MD. Since blood draw will be executed while inserting the sheath we will not need an additional medical intervention. The blood samples are collected by the Laboratory of Experimental Cardiology in the context of the Athero Express Biobank Study which has been approved in the past (study nr. C-01.18).

DSA images are made of the target lesion in at least to planes with a minimum of 30 degrees difference in angulation. A ruler must be placed under the leg to measure the length of the lesion. A full run-off angiogram of the entire leg is made before an attempt is made to cross the target lesion. Subsequently the target lesion is crossed with a guidewire and the intraluminal position distal to the target lesion is confirmed by angiography. A translesional pressure gradient is measured (without and with i.a. vasodilators). A predilatation with an undersized balloon will be performed. This will be followed by PTA with LPEB or uncoated balloon, as randomized. To avoid geographic miss this balloon dilatation has to be performed with a longer balloon compared to the length of the lesion itself. The balloon has to be inflated to at least the nominal and at most 1 bar below the rated burst pressure of the balloon. Inflation time is at least 45 seconds, allowing adequate drug transfer in case of the LPEB. Next an adequately sized stent (maximum 10% oversizing compared to the diameter of the native SFA below the lesion) is implanted according to IFU. Stenting will be performed using the Supera® wire interwoven nitinol stent. Only in cases of stenosis including the origin of the SFA a Smart® stent (Cordis J&J, Bridgewater NJ) has to be implanted. The stent must be longer than the treated lesion, but shorter than the ballon which has been used for predilatation. It is strongly preferred to use one stent to treat the entire SFA lesion. Radiographic single shots must be made during inflation of the balloons, of the implanted stents, and during eventual post-dilatation of the stents. All single shots must be stored. If necessary the stent may be tailored with an additional in-

stent balloon dilatation at the discretion of the interventionalist, using a standard (non-drug eluting) PTA balloon of adequate size.

Finally a complete angiogram of the ipsilateral limb is made. This should include at least 2 views of the treated segment with a minimum of 30 degrees rotational difference and should include run-off images to the pedal arch. A control duplex scan of the target lesion must be performed before discharge.

7.1 Medication

All patients receive Aspirin 100mg daily and Simvastatin 40mg daily, indefinitely, starting at least one week prior to the procedure. During the intervention all patients receive 5000 units of Heparin. After the intervention all patients receive additional Clopidogrel 75mg daily for a period of 3 months. Thereafter, Aspirin will be continued.

8. Investigational product

8.1 Name and description of investigational product

The Legflow Paclitaxel-eluting peripheral balloon catheter (Cardionovum Sp.z.o.o., Warsaw, Poland) is a CE marked (1434-MDD-32/2011) angioplasty balloon, covered with 3.0µg/mm^2 Paclitaxel. The LegFlow covered balloon is available in diameters from 2 to 7mm and balloon lengths from 8 to 200mm. All LegFlow balloons are 0.014-inch guidewire compatible. Available catheter lengths are 80cm and 140 cm.

9. Safety reporting

9.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited medical ethical review committee (METC) if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardize the subjects' health. The investigator will take care that all subjects are kept informed.

9.2 Adverse and serious adverse events

Adverse events are defined as any undesirable experience occurring to a subject during the clinical trial, whether or not considered related to the investigational treatment. All adverse events and

serious adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded using an adverse events form. All SAEs must and will be reported by the responsible investigator through the web portal ToetsingOnline to the accredited METC that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse reactions.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.

9.3 Follow-up of adverse events

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

9.4 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will safeguard the interests of trial participants, assess the safety and efficacy of the interventions during the trial, and monitor the overall conduct of the clinical trial. After inclusion of every 50 patients, the DSMB will perform an interim analysis to assess the safety and efficacy of the intervention (LegFlow PEB). The advice(s) of the DSMB will be notified upon receipt by the sponsor to the METC that approved the protocol. With this notification a statement will be included indicating whether the advice will be followed. A separate 'Charter for the Data Safety Monitoring Board' has been made, which reports on the structure and organization of the DSMB in more detail.

10. Statistical analysis

Patients with IC and CLI will be evaluated separately.

10.1 Descriptive statistics

Descriptive analysis will be performed to compare the general parameters of both groups.

-   Continuous data (age, BMI, length, etc.): Averages with standard deviation (parametric data) or medians with percentiles (non-parametric data) will be calculated.

-   Categorical data (anatomical lesion characteristics, co-morbidities, etc.): Frequencies will be calculated.

10.2 Univariate analysis

Univariate analysis will be performed to test differences in primary and secondary endpoints.

-   Continuous data (improvement in ABI, etc.): Averages with standard deviation (parametric data) or medians with percentiles (non-parametric data) will be calculated. Differences between both groups will be tested using a Student's t-test (parametric data) or a Mann-Whitney U-test (non-parametric data). Differences with a p-value <0.05 will be considered statistically significant.

-   Categorical data (absence of binary restenosis rate, etc.): Frequencies will be calculated and difference between both groups will be tested using both Chi-squared test and Cox proportional hazards model. Differences with a p-value <0.05 will be considered statistically significant.

10.3 Multivariate analysis

For the primary endpoint, a Cox or logistic regression model will be made to investigate the relation between co-variants and the endpoint. Intrinsic variables (age, sex, BMI, etc.), disease-related variables (TASC-type, presence of distal arterial lesions, etc.) and treatment related variables (Type of balloon used, treatment for distal arterial lesions, etc.) that show a p-value <0.5 in univariate analysis will be included in the model.

10.4 Actuarial analysis

Restenosis and amputation free survival will be calculated Kaplan-Meier analysis for univariate analysis, and Cox proportional hazards model for multivariate analysis, and will be expressed as a percentage with a standard error and 95% CIs.

10.5 Interim analysis

Interim analysis will be performed after 6 months follow-up of the first 50 consecutive patients by the DSMB as described in the 'Charter for the Data Safety Management Board'.

10.6 Software

All statistical analysis will be performed with the Statistical Package for the Social Sciences (SPSS) version 16.0 or up (IBM, Armonk, NY, USA).

11. Ethical considerations

11.1 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki (version: October 2008) and in accordance with the Medical Research Involving Human Subjects Act (Dutch: Wet Medisch-wetenschappelijk Onderzoek met mensen; WMO).

11.2 Recruitment and consent

All patients who present at the outpatient clinic or emergency ward with symptomatic PAOD of the superficial femoral artery will be considered possibly eligible for inclusion. The present surgical or radiological resident or staff member will screen the patient for meeting the in- and exclusion criteria. If for whatever reason the physician at this moment does not screen the patient, any other involved physician or one of the investigators may include the patient at a later moment. When the patient meets the in- and exclusion criteria, the physician will then inform the patient of the study, including the risks and burdens as mentioned before and the availability of an independent physician. A written information letter will be presented to the patient to read, this will include contact details of an independent physician. The patient will then be offered the opportunity to ask questions. Patients will be offered 24 hours to consider their decision. When they agree to participate in the study, they will be asked to fill out an informed consent form. Both the information letter and the informed consent form are attached as separate documents to this protocol.

11.3 Benefits and risks assessment

Participating patients will need to make five study-related hospital visits. Four DUS and five ABI measurement with treadmill tests (only in patients with IC) will be performed. When compared to our standard follow-up, patients do not need to make extra hospital visits or undergo non-invasive tests. When DUS shows possible restenosis, patients will receive additional MR-angiography or CT-angiography, followed by DSA if deemed relevant. This is standard procedure for all patients. Patients will also be asked to fill in a 13-item questionnaire five times, which is not a routine procedure. Patients who participate may benefit by being treated with a balloon that may have a lower restenosis rate.

11.4 Compensation for injury

The investigator has a liability insurance, which is in accordance with article 7 subsection 6 of the WMO.

The sponsor (also) has an insurance, which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research

in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1.   € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;

2.   € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;

3.   € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organization for all damage disclosed by scientific research for the Sponsor as 'verrichter' in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study

11.5 Incentives

Participating patients will not receive any incentives or compensation.

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