Title: RANDOMization Screening for drug coaTed devices in patients undergoing endovascular femorOPopliteal procedures

Short title: The RANDOM-STOP registry

Background and objectives: Various randomized control trials (RCTs) have shown a potential clinical benefit, mostly in terms of vessel / lesion patency, using drug coated devices for patients undergoing endovascular femoropopliteal procedures. Nonetheless, these RCTs enrolled highly selected group of patients, in terms of both clinical and imaging criteria. Thus, their results cannot be fully extrapolated to daily practice of most vascular centers treating all-comers. Additionally, these RCTs do not report on the number of screened / excluded patients. This further complicates their applicability to everyday clinical practice, especially with regards to patients with chronic limb threatening ischemia (CLTI).

This proposed study will retrospectively screen consecutive patients who underwent endovascular procedures between January 2021 and December 2021 (12 months) for femoropopliteal disease and will evaluate the eligibility for randomization for the RCTs of the Food Drug Administration (FDA) approved paclitaxel-coated devices.

Study Design:

Setting: multiple vascular centers across Europe (multicenter study). A retrospective cohort study will be performed.

Patients: Consecutive patients with CLTI or intermittent claudication who underwent endovascular revascularization of the femoropopliteal segment between January 2021-December 2021 (12 months) will be included.

Exclusion Criteria:

- Isolated common femoral / deep femoral artery procedures
- Patients who underwent surgical and hybrid (combined open and endovascular) procedures
- Patients treated conservatively either initially or as a definitive treatment plan, or those who underwent primary major lower limb amputation
- Isolated aortic, iliac or below the knee (crural arteries) procedures
- Interventions performed for femoral or popliteal artery aneurysms
- Patients with acute limb ischemia (symptoms' duration of less than 14 days)
- Patients presenting with vascular trauma.

RCTs that will be evaluated*:

- InPact SFA (InPact Admiral DCB)
- LEVANT II (Lutonix DCB)
- ILLUMENATE (Stellarex DCB)
- Ranger SFA (Ranger DCB)
- EMINENT (Eluvia DES)
- IMPERIAL (Eluvia DES)
- Zilver PTX (Zilver PTX DES)

*If a vessel/plaque modification modality such as atherectomy, intravascular lithotripsy etc. was used, the patient will be additionally screened for the DEFINITIVE AR, DISRUPT PAD III RCTs.

Outcomes:

Primary End Point:

- Exclusion from all the evaluated studies (RCTs)

Secondary End Points

- Inclusion at least into a Single study

- Clinical exclusion
- Radiological exclusion
- 30-day limb salvage (major lower limb amputation)
- 30-day mortality
- 30-day re-intervention (endovascular or open)
- Duration of hospital stay

Analysis

Standard baseline demographics and cardiovascular co-morbidities will be reported using proportions and absolute values. Anatomical characteristics (target lesion site, length, calcification, number of patent tibial arteries), and endovascular modalities used will also be reported using appropriate descriptive statistics (e.g. mean values and standard deviation, proportions, or median values with interquartile range). With regards to the primary endpoint, the number of patients eligible for inclusion in each RCT will be reported as an absolute value and proportion (per RCT). A minimum of five centers will have to take part in the study (from at least five different countries / regions) to ensure generalizability of outcomes. If 30% of patients will be eligible for randomization in any of the RCTs included a total of a minimum of 221 patients will have to be included to be able to estimate the true proportion with 90% power (alpha set at 5%) within a standard deviation of 10%.

References:

1. Laird JR, Schneider PA, Tepe G, Brodmann M, Zeller T, Metzger C, Krishnan P, Scheinert D, Micari A, Cohen DJ, Wang H, Hasenbank MS, Jaff MR; IN.PACT SFA Trial Investigators. Durability of Treatment Effect Using a Drug-Coated Balloon for Femoropopliteal Lesions: 24-Month Results of IN.PACT SFA. J Am Coll Cardiol. 2015 Dec 1;66(21):2329-2338.
2. Schroeder H, Meyer DR, Lux B, Ruecker F, Martorana M, Duda S. Two-year results of a low-dose drug-coated balloon for revascularization of the femoropopliteal artery: outcomes from the ILLUMENATE first-in-human study. Catheter Cardiovasc Interv. 2015 Aug;86(2):278-86.
3. Rosenfield K, Jaff MR, White CJ, Rocha-Singh K, Mena-Hurtado C, Metzger DC, Brodmann M, Pilger E, Zeller T, Krishnan P, Gammon R, Müller-Hülsbeck S, Nehler MR, Benenati JF, Scheinert D; LEVANT 2

   Investigators. Trial of a Paclitaxel-Coated Balloon for Femoropopliteal Artery Disease. N Engl J Med. 2015 Jul 9;373(2):145-53.
4. Sachar R, Soga Y, Ansari MM, Kozuki A, Lopez L, Brodmann M, Schroë H, Ramanath VS, Diaz-Cartelle J, Zeller T; RANGER II SFA Investigators. 1-Year Results From the RANGER II SFA Randomized Trial of the Ranger Drug-Coated Balloon. JACC Cardiovasc Interv. 2021 May 24;14(10):1123-1133.
5. Dake MD, Ansel GM, Jaff MR, Ohki T, Saxon RR, Smouse HB, Zeller T, Roubin GS, Burket MW, Khatib Y, Snyder SA, Ragheb AO, White JK, Machan LS; Zilver PTX Investigators. Paclitaxel-eluting stents show superiority to balloon angioplasty and bare metal stents in femoropopliteal disease: twelve-month Zilver PTX randomized study results. Circ Cardiovasc Interv. 2011 Oct 1;4(5):495-504
6. Gray WA, Keirse K, Soga Y, Benko A, Babaev A, Yokoi Y, Schroeder H, Prem JT, Holden A, Popma J, Jaff MR, Diaz-Cartelle J, Müller-Hülsbeck S; IMPERIAL investigators. A polymer-coated, paclitaxel-eluting stent (Eluvia) versus a polymer-free, paclitaxel-coated stent (Zilver PTX) for endovascular femoropopliteal intervention (IMPERIAL): a randomised, non-inferiority trial. Lancet. 2018 Oct 27;392(10157):1541-1551.
7. Zeller T, Langhoff R, Rocha-Singh KJ, Jaff MR, Blessing E, Amann-Vesti B, Krzanowski M, Peeters P, Scheinert D, Torsello G, Sixt S, Tepe G; DEFINITIVE AR Investigators. Directional Atherectomy Followed by a Paclitaxel-Coated Balloon to Inhibit Restenosis and Maintain Vessel Patency: Twelve-Month Results of the DEFINITIVE AR Study. Circ Cardiovasc Interv. 2017 Sep;10(9):e004848.
8. Tepe G, Brodmann M, Werner M, Bachinsky W, Holden A, Zeller T, Mangalmurti S, Nolte-Ernsting C, Bertolet B, Scheinert D, Gray WA; Disrupt PAD III Investigators. Intravascular Lithotripsy for Peripheral Artery Calcification: 30-Day Outcomes From the Randomized Disrupt PAD III Trial. JACC Cardiovasc Interv. 2021 Jun 28;14(12):1352-1361