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Peripheral arterial disease:

Understanding the challenges in the treatment of peripheral atherosclerosis

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Contents

1. Abbreviations

BMS: Bare metal stent

CERAB: Covered Endovascular Reconstruction of Aortic Bifurcation

CFA: Common femoral artery

CKD: Chronic kidney disease

CLTI: Chronic Limb threatening ischemia

CTO: Chronic total occlusion

DAART: Directional atherectomy with anti-restenotic therapy

DCB: Drug coated balloon

DES: Drug eluting stent

CS: Covered stent

IVUS: Intravascular ultrasound

OCT: Optical coherence tomography

MACCE: Major adverse cardiovascular and cerebral events

PAD: Peripheral arterial disease

POBA: Plain old balloon angioplasty

RCT: Randomized control trial

SFA: Superficial femoral artery

TASC: TransAtlantic Inter-Society Consensus

TLR: Target lesion revascularization

WIfI: Wound ischemia foot infection

2. List of publications

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3. Introduction

Peripheral Arterial Disease (PAD) affects more than 200 million people worldwide (Conte, J Vasc Surg 2019) PAD is associated with lifestyle limiting intermittent claudication, or Chronic Limb Threatening Ischemia (CLTI) and is the leading cause of non-traumatic amputation of the lower extremities (Conte, J Vasc Surg 2019, Dua Tech Vasc Interv Radiol. 2016, Morley, Br J Med 2018) Improvements in the diagnosis and treatment of PAD have led to an increasing number of revascularizations and especially of endovascular procedures. As new and increasingly sophisticated devices are developed, the medical community needs to understand how to incorporate these technologies into the everyday practice, and how to choose between novel and already established methods.

Historically, plain old balloon angioplasty (POBA) has been considered the treatment of choice for infrainguinal atherosclerosis, while permanent scaffolds were used selectively in case of flow limiting dissections or significant recoil (Adam, Lancet 2005). However, the risk for neointimal hyperplasia, restenosis, and consequently of clinical failure after POBA with bailout stenting is rather high (Dake, Circulation 2016, Laird, Circ Cardiovasc Interv 2010). Thus, novel endovascular strategies have been developed to reduce the rates of reinterventions. Both the 'chemical barrier' of antiproliferative agents and the 'mechanical barrier' of stent grafts have been used to inhibit re-stenosis of the treated vessels. Paclitaxel is the main anti-proliferative agent used for peripheral interventions. It is a lipophilic antineoplastic agent, which can be locally delivered in the arterial wall either with drug coated balloons (DCB) or drug eluting stents (DES) to inhibit neointimal hyperplasia. Several randomized control trials (RCTs) showed improved patency rates in lesions treated by paclitaxel coated devices (Katsanos, J Endovasc Ther 2016). Although RCTs are the most scientifically rigorous clinical study design, patients included in these trials were highly selected, and carried a different atherosclerotic burden compared to 'real-world-patients' (Lottes, Am Heart J. 2021, Ansel, J Endovasc Ther 2018). Accordingly, the performance of novel endovascular devices should be evaluated in the framework of pragmatic cohorts.

Regarding open repair, encouraging long term patency- and amputation-free survival rates are observed after bypass grafting, especially in cases of autogenous vein conduits (Conte, J Vasc

Surg 2013, Twine, Cohrane 2010, Johnson, J Vasc Surg 2000). Nevertheless, recovery following percutaneous revascularization is faster, and the minimally invasive nature of endovascular therapy significantly reduces the periprocedural morbidity (Conte, J Vasc Surg 2019) On the other hand, the durability of endovascular reconstructions on the long run is unclear. Unfortunately, the Bypass Versus Angioplasty for Severe Ischemia of the Leg (BASIL) trial remains the only RCT comparing the performance of surgical and endovascular therapy in this field, leading to a relevant gap of updated data (Adam, Lancet 2005).

In the first part of this study overview, we identified independent risk factors for mortality, morbidity, and limb loss in patients with lower limb atherosclerosis. In the second part, the performance of endovascular therapy was assessed in a 'real world' setting and especially in patients that are usually excluded from randomized trials. In the final part of this analysis, the outcomes of endovascular treatment were compared to open repair in a pragmatic setting of patients with CLTI and acute lower limb ischemia.

4. Identification of risk factors for morbidity, mortality, and limb loss in patients undergoing revascularization for peripheral arterial disease

4.1. Secondary prevention with statin therapy

Although revascularization is the cornerstone of CLTI management, secondary prevention following surgical and endovascular repair is crucial for the reduction of cardiovascular morbidity and mortality. Nevertheless, current recommendations regarding lipid lowering treatment are extrapolated from other high-risk populations for cardiovascular events and there is a lack of CLTI-dedicated trials. In a retrospective explorative study of the CRITISCH data we evaluated the impact of statin therapy on the outcomes of CLTI patients following revascularization. For the purposes of this analysis, patients were divided into two groups based on statin use. Treatment crossovers and non- adherent patients were excluded from analysis. The primary composite end point of this study was the amputation-free survival. Major adverse cardiovascular and cerebral events (MACCEs), time to death, and time to major amputation were additionally evaluated. A statin therapy throughout the study period was administrated in 445 individuals (37%), 371 (31%) patients received no statins, and 384 subjects were excluded (non-compliance/treatment crossovers). Patients on statins had a lower hazard for amputation-free-survival (HR, 0.45; 95% CI, 0.34-0.63; P < 0.001), death (HR, 0.40; 95% CI, 0.24-0.66; P < 0.001) and lower risk for MACCE (OR: 0.41; 95% CI, 0.23-0.69; P= 0.001). However, statin therapy did not reduce the risk for major amputation (HR, 1.02; 95% CI, 0.67-1.56; P= 0.922). Statin effect was consistent among diabetics (HR, 0.47; 95% CI, 0.31-0.70; P < 0.001), patients with CKD (HR, 0.53; 95% CI, 0.32-0.87; P= 0.012), and older individuals (HR, 0.40; 95% CI, 0.26-0.60; P < 0.001). Statin therapy was also associated with improved outcomes in patients with (HR, 0.64; 95% CI, 0.41- 0.99; P= 0.049) and without antiplatelet medication (HR, 0.26; 95% CI, 0.12-0.57; P= 0.001) and after both endovascular procedures (HR, 0.51; 95% CI, 0.34-0.76; P= .001) and bypass grafting (HR, 0.38; 95% CI, 0.21-0.68; P= .001). These findings suggest that statin therapy in CLTI patients is associated with increased amputation free survival and lower rates of mortality and MACCEs regardless of the applied treatment strategy. However, patients on statins did not have any benefit from the lipid lowering therapy in terms of reduced

amputation rates. An alarming observation of this analysis is that only 37% of the patients received a statin therapy throughout the entire study period (Stavroulakis, J Vasc Surg 2017).

4.2. The Wound, Ischemia, foot Infection (WIfI) classification system

The Society for Vascular Surgery Lower Extremity Guidelines Committee developed the Wound, Ischemia, foot Infection (WIfI) classification system as a clinical tool to predict the risk for amputation in CLTI patients. Although, previous published series have already evaluated its prognostic value, these cohorts were rather heterogeneous. In a single-center study we evaluated the prognostic value of the WIfI classification system in nondiabetic CLTI patients who underwent endovascular revascularization. All patients were classified according to their (W) wound status, (I) severity of ischemia, and (fI) extent of foot infection to four classes: very low risk, low risk, moderate risk, and high risk. The amputation-free survival at 12 months in the very low-risk, low-risk, moderate risk, and very high-risk groups was 87%, 81%, 81%, and 62% respectively (P= .106). A statistically significant difference was observed between the very low-risk and high-risk group (hazard ratio, 3.4; 95% confidence interval, 1.1-10.3; P= .029). A similar finding was observed for the 12-months overall survival between the very low-risk and the high-risk groups (87%, 84%, 81%, 65%; P= .166). The amputation rate during the follow-up time was 0%, 2% (n=6), 3% (n=5), and 12% (n= 9) for the very low-risk, low-risk, moderate-risk, and very high-risk groups, respectively (P= .033). In this context, this analysis confirmed the prognostic value of the WIfI classification regarding major amputation in this CLTI subgroup of nondiabetic patients treated by percutaneous procedures (Beropoulis, J Vasc Surg 2016).

4.3. Chronic kidney disease as risk factor for CLTI patients

Chronic renal function impairment is a common finding among patients with PAD. The German VASC study enrolled patients with symptomatic lower extremity atherosclerosis, who underwent revascularization in 31 high-volume centers in Germany. The main goal of this registry was to quantify to which extent real-world treatment follow guideline recommendations. Among a total of 6449 procedures, 4468 (69%) were endovascular, 1086 (17%) were common-/deep femoral endarterectomy and 895 (14%) bypass grafting. Although the data analysis is ongoing, an interesting finding of this study was that CKD was found in

22.1% of the included patients and 2.5% (95% CI:2.1–2.9) had end-stage renal disease (Kotov, VASA 2021).

The impact of non-dialysis dependent CKD on the in-hospital outcomes of patients with CLTI was evaluated in the framework of the CRITISCH registry. The primary endpoint was the occurrence of major amputation or death during hospital stay. Secondary endpoints were major adverse cardiovascular events (including myocardial infarction and/ or stroke and/or death) and hemodynamic failure of the arterial reconstruction. A logistic regression analysis showed an increased early risk for amputation and/or death (OR=1.92, 95% CI: 1.09-3.40), death (OR=5.53, 95% CI: 1.92-15.90) and hemodynamic failure (OR=1.80, 95% CI: 1.19-2.72) among patients with renal function impairment. Additionally, CKD was associated with a higher risk for cardiovascular events (OR=1.82, 95% CI: 0.99-3.36) but not for limb loss (OR=1.05, 95% CI: 0.49-2.22) (Gkremoutis, J Cardiovascular Surg (Torino) 2021).

A second analysis evaluated the impact of end-stage renal disease on the early outcomes of patients with CLTI. The study cohort was divided into two groups, namely patients on hemodialysis (n = 102) and patients with normal renal function (n = 674; glomerular filtration rate >60/mL/min/1.73 m^2). The selected treatment option in dialysis patients was endovascular in 64% (n=65), bypass grafting in 13% (n=13), common femoral artery endarterectomy in 11% (n=11), and conservative treatment in 13% (n=13). In patients with normal renal function, endovascular therapy was applied in 48% (n=326), bypass surgery in 27% (n=185), endarterectomy of the groin vessels in 13% (n=86), and conservative therapy in 11% (n=77). For dialysis patients, a statically significant risk for the composite endpoint of amputation and/or death (OR, 2.62; 95% CI, 1.19-5.79; P [.017), amputation (OR, 3.14; 95% CI, 1.35-7.31; P=0.008), and hemodynamic failure (OR, 2.19; 95% CI, 1.19-4.04; P=0.012) was observed. These findings suggest that endovascular therapy is generally considered as the most favorable treatment option in end stage renal disease CLTI individuals. Furthermore, patients on hemodialysis have an increased risk for amputation and hemodynamic failure compared to patients with normal renal function (Meyer, J Vasc Surg 2016).

The 2 years results of the same cohort revealed an increased risk for cardiovascular morbidity and mortality among hemodialysis patients. Patients with end-stage renal disease showed inferior results at 2 years in terms of amputation free survival (dialysis, 35.4%; non-dialysis,

67.2%; P < .001). Similarly, mortality- (dialysis, 55.0%; non-dialysis 20.7%; P < .001) and major amputation rates (dialysis, 24.5%; non-dialysis, 15.8%; P= .029) were significantly higher for patients on hemodialysis. The choice of therapeutic approach did not influence the incidence of the investigated end points. Cox regression analysis indicated that end stage renal disease subjects carry a twofold increased hazard of death or major amputation (hazard ratio, 2.27; 95% confidence interval, 1.67-3.10; P < .001). This analysis showed an inferior amputation-free-survival and overall survival among patients on hemodialysis. Cardiovascular comorbidities were without significant impact on outcome parameters, whereas choice of treatment modality in dialysis patients did not influence outcomes of the patients. Consequently, decision-making as to the choice of a therapeutic approach in these patients should notably account for the individual's lesion characteristics and vascular disease (Meyer, J Vasc Surg 2018).

5. Endovascular treatment of peripheral arterial disease

5.1. Crossing strategies for peripheral occlusive disease

Successful crossing is essential for the minimally invasive treatment of peripheral atherosclerosis. Although, current research focuses on the evaluation of novel endovascular modalities after successful crossing, little is known regarding the technical success and complication rates of access and crossing strategies. Transfemoral access with primary wire-catheter crossing remains the gold standard for peripheral vascular interventions. However, retrograde popliteal-/ tibial- or upper extremity access can be alternatively used in complex procedures or in case of a hostile femoral access.

In a retrospective analysis of 300 femoropopliteal chronic total occlusions (CTOs) we identified risk factors for crossing failure in patients who underwent peripheral interventions via transfemoral access (Bernandini, J Endovasc Ther 2022). A primary catheter-wire approach was applied in all patients. The majority (n=183, 61%) presented with calf claudication, 34 patients (n= 34, 11%) with ischemic rest pain, 77 patients (26%) had minor tissue loss and 6 subjects (2%) foot gangrene. The mean lesion length was 180 mm [interquartile range (IQR) 100-260 mm] and the median CTO length was 100 mm (IQR 50-210 mm). A successful crossing through a transfemoral access was feasible in 210 patients and consequently the primary crossing success was 70%. The use of re-entry devices in 28 patients (9%) or of a combined antegrade-retrograde crossing strategy in 34 patients (11%) led to an assisted crossing success of 89% (n=267). A higher risk for primary crossing failure was observed in calcified lesions (OR: 4.20, 95% CI: 1.71 to 10.30, p=0.0017) and especially in arteries with circumferential calcification (>180^0) (OR: 2.53, 95% CI 1.32 to 4.86, p=0.0053). The morphology of the proximal and distal cap of the CTO also influenced the success of the procedure as a higher technical failure was observed in patients with CTOP (Chronic Total Occlusion Crossing Approach Based on Plaque Cap Morphology) class III or IV (OR: 1.9, 95% CI 1.4 to 2.6). Finally, the presence of proximal occlusion of the superficial femoral artery (SFA) (OR: 3.52, 95% CI 1.68 to 7.39, p=0.0009), or the distal popliteal artery (OR 4.06, 95% CI 1.52 to 10.84, p=0.0051) increased the risk of antegrade crossing failure. This analysis revealed that the morphology of a lesion, the calcification burden and the localization of the CTO are independent risk factors for

unsuccessful transfemoral crossing. However, adjunctive crossing strategies either with re-entry devices or retrograde approach improved the success rate of the procedure and enabled the recanalization of almost 90% of all femoropopliteal CTOs.

In an additional analysis, we retrospectively evaluated the safety and efficacy a of a primary transbrachial approach among 201 patients, who underwent iliac interventions. The primary technical success defined as successful crossing and treatment via a single upper extremity access was 81%. The overall procedural success rate with a combination of transbrachial and transfemoral access amounted to 92%. Local hematomas (n=9, 4%) were the main local complication of the brachial puncture, followed by pseudoaneurysms (n=8, 4%), late brachial artery bleeding (n=4, 2%), brachial artery occlusion (n=2, 1%), and puncture site infection (n=2, 1%). No transient or permanent nerve injury was identified. The stroke/transient ischemic attack rate was 2% (n=4). A single patient died due to acute coronary syndrome leading to a mortality rate of 0.5%. Female gender was associate with a higher incidence of access site complications (hazard ratio 6.7, 95% confidence interval 2.7 to 15, $p<0.001$), whereas the size of the sheath did not influence the incidence of local complications ($p=0.22$). This study showed that a transbrachial approach enables the endovascular treatment of most iliac artery lesions, although an adjunctive transfemoral access might be required. Nevertheless, an alarming high incidence of access site complications and ischemic cerebral events limited the performance of a primary transbrachial approach (Stavroulakis, J Endovasc Ther 2016).

Finally, in a multicenter, interdisciplinary registry, we evaluated the safety and efficacy of retrograde popliteal and tibial access in 1516 peripheral interventions after failed primary transfemoral crossing. The mean lesion length was 240 mm and most lesions where either moderate (n= 415, 27.6%) or severely calcified (n=615, 40.9%). The successful retrograde puncture- and recanalization success rates were 99% and 93%, respectively and severe calcification was identified as an independent predictor of recanalization failure. The incidence of local complications in the retrograde access site was very low (n= 48, 3.1%), mainly including non–hemodynamic-relevant arteriovenous fistulas or local hematomas. Interestingly, a failed retrograde approach was associated with a higher risk for major amputation (8.5% versus 1.5%; $P < 0.001$). This study showed that retrograde tibial and popliteal access can be safely and effectively used after transfemoral crossing failure (Korosoglou, J Am Coll Cardiol Int 2022).

5.2. The use of permanent scaffolds for peripheral atherosclerotic lesions:

The introduction of flexible nitinol bare-metal stents (BMSs) was essential to overcome the problems of early elastic recoil, residual stenosis, and flow-limiting dissections after POBA. Self-expanding BMSs demonstrated a significant benefit over POBA in terms of improved patency. Nevertheless, there is a paucity of data concerning the outcomes of this modality on the long run. In a retrospective analysis we evaluated the 7 years performance of primary BMS treatment in 89 patients with femoropopliteal PAD (Stavroulakis, J Vasc Surg 2016). The prevalence of CLTI was 34% (n = 30), a TASC II C/D lesion was observed in 31 patients (35%). CTOs were present in 49 patients (55%), and the mean lesion length was 116 ± 33 mm. The primary patency at 1, 3, 5, and 7 years was 73%, 64%, 47%, and 33%, respectively. At 7 years, the secondary patency rate was 67%, the freedom from target lesion revascularization (TLR) was 47%, and the amputation free survival was 73%. A lower amputation-free-survival was observed in diabetics (hazard ratio [HR], 2.6; 95% confidence interval [CI], 1.08-6.28; P= 0.03), whereas popliteal artery involvement was identified as independent risk factor for secondary interventions (HR, 2.07; 95% CI, 1.05-4.06; P= 0.04) and TLR (HR, 1.99; 95% CI, 1.03-3.83; P= .04). CLTI increased the risk for surgical conversion after stent occlusion (HR, 5.46; 95% CI, 2.44-12.17; P < 0.001). This study showed that the primary BMS deployment for femoropopliteal disease is associated with acceptable clinical outcomes at 7 years but also with an increased risk for re-interventions and surgical conversion.

In a further analysis we evaluated the impact of gender on the outcomes of primary BMS deployment in patients with femoropopliteal PAD. Given that females are underrepresented in most studies, data regarding the sex related differences following endovascular procedures is scarce. In a retrospective evaluation of 517 patients (333 men and 184 women; mean age 70.6 years) female gender was associated with a higher prevalence of CLTI at baseline, poorer secondary patency, and increased risk for restenosis. However, both genders showed comparable 5-year primary patency- (64.3% men vs. 58.1% women, p=0.11) limb salvage- (p=0.83) and survival- rates (83.3% and 82.6% for men and women, respectively; p=0.63) (Stavroulakis, J Endovasc Ther 2015).

In accordance with the coronary field, the relative high number of secondary procedures following the use of BMSs, led to the development of paclitaxel coated drug eluting stents (DES) to reduce the need for re-interventions. Paclitaxel interrupts the cell cycle, by activating apoptosis, and consequently inhibits the proliferation and migration of smooth muscle cells from the adventitial to the intimal layer. Theoretically, DES combine the excellent acute luminal gain of a permanent scaffold with the long-term anti-restenotic effect of paclitaxel elution. The first generation of polymer-free DES showed promising outcomes in short non-calcified lesions, however, a higher risk for clinical failure and reintervention was observed among challenging patients (Bosiers, J Cardiovasc Surg (Torino) 2013, Davaine, Eur J Vasc Endovasc Surg 2015). A second generation of polymer-based DES (Eluvia, Boston Scientific, Marlborough, Massachusetts) was developed, to achieve a sustained and controlled release of paclitaxel over the first 12 months after stent deployment. In our analysis we assessed the safety and efficacy of the new generation fluoropolymer-based DES in complex femoropopliteal lesions.

In the initial cohort we evaluated the performance of the device in 62 patients treated between March 2016 and March 2017 (Bisdas, J Am Coll Cardiol Int 2018) The mean lesion length was 20 cm, and 79% of the lesions (n= 49) were CTOs. Moderate or severe calcification was observed in 42% of the patients (n= 26). Both the Kaplan-Meier estimate of primary patency and freedom from target lesion revascularization was 87%. The amputation-free survival was 100% for patients with claudication (n= 32 [52%]) and 87% in patients with CLTI (n= 30, 48%) (HR: 6.3; 95% CI: 1.25 to 31.54; p= 0.052). A very interesting finding of this study was that an aneurysmal degeneration of the treated arterial segment was found (mean diameter 14 mm) in 5 patients (8%).

In a second extended cohort we reported the 2 years outcomes of the same stent platform in 130 patients (137 lesions) with femoropopliteal atherosclerosis (Stavroulakis, J Am Coll Cardiol Int 2021). The majority were claudicants (n = 90, 69%), while the mean lesion length was comparable with the initial cohort and amounted to 194 ± 108 mm. Furthermore, 74% of the lesions (n = 101) were CTOs, and 72% (n = 99) were calcified. At 24 months, the primary patency was 71%, whereas both the secondary patency rate and freedom from TLR amounted to 80%. Overall survival was 85%, freedom from major amputation was 98% and freedom from surgical conversion was 89%. The rate of vessel wall degeneration was 20% and higher than initially

observed (n=27). However, this finding was neither associated with an increased risk for loss of patency nor for reintervention and the pathophysiology of this phenomenon remains unclear.

Covered stents (CS) were also introduced as an alternative to BMS to improve the outcomes of permanent scaffolds in the peripheral vasculature. The mechanical barrier of stent grafts prevents the development of in-stent restenosis and might reduce the need for secondary interventions. Although CS are commonly used for aortic reconstructions, there is a lack of multicenter trials showing a benefit from the use of stent grafts over BMS in this vascular bed. The COBRA registry was a multicenter European study, which evaluated the performance of the Covered Endovascular Reconstruction of Aortic Bifurcation (CERAB) technique over BMS revascularization in 252 patients with aorto-iliac PAD (134 males, 53%; mean age: 65 +/- 10 years; 102 with a bare metal and 150 with a covered aortic stent). Severe calcification was observed in > 65% of patients, 70% presented with a TASC II D lesion, 32% had an aortic and 46% an iliac CTO. At 17 months, both the mortality- (BMS 14% vs. CS 7%, HR 0.97, 95% CI 0.42 e 2.26, p= .94, log rank test) and the TLR- (11% vs. 10%, HR= 1.98, 95% CI 0.89- 4.43, p= 0.095) rates were comparable between the two groups. In a multivariable model, the use of an aortic stent graft as standalone therapy did not influence the incidence of TLR, however, the concomitant use of aortic and iliac CSs was associated with improved freedom from TLR. In this context the combination of covered aortic and iliac stents seems to offer a benefit over BMS reconstructions in terms of reduced need for reinterventions for aortoiliac PAD. Nonetheless, both treatment strategies showed promising mid-term results and excellent safety profile (Saratzis, Eur J Vasc Endovasc Surg 2022).

5.3. The `leave nothing approach` for femoropopliteal disease

Despite the added benefit from permanent scaffolds in the treatment for peripheral arterial lesions, the development of in-stent-restenosis is not neglectable. Thus, the introduction of paclitaxel coated balloons has led to a paradigm shift from primary scaffolding to a “leave nothing behind” or “leave less behind” approach. Although several RCTs showed a benefit from the use of drug coated balloons (DCBs), lesions included in these studies were predominantly short, and not severely calcified. In this context, the findings of these trials cannot always be extrapolated in everyday practice.

The In.Pact Global registry aimed to evaluate the performance of the IN.PACT Admiral DCB (Medtronic, Dublin, Ireland) in a pragmatic cohort of patients with femoropopliteal PAD. The study was conducted at 64 international sites and enrolled 1535 patients. The mean lesion length was 12.09±9.54 cm; 18% of the patients had in-stent restenosis, 35.5% CTOs, and 68.7% were calcified. At 36 months the Kaplan-Meier estimate of freedom from TLR was 76.9%, the all-cause mortality rate amounted to 11.6% and the major target limb amputation rate was 1.0%. The freedom from TLR through 36 months was significantly lower in patients with CLTI compared with claudicants (67.6% vs 78.0%; p=0.003). Lesions affecting both the SFA, and popliteal artery showed an increased risk for TLR (69.2%) than either isolated SFA (79.7%) or popliteal lesions (76.5%; log- rank p<0.001). Increased lesion length, reference vessel diameter ≤4.5 mm, in-stent restenosis, bilateral disease, CLTI, and hyperlipidemia were associated with increased risk for TLR (Torsello, J Endovasc Ther 2020). Although this study showed a sustained clinical efficacy and low rates of reinterventions at 3 years following DCB angioplasty, the complexity of the lesion increased both the risk for clinical failure and the need for stent deployment. Of note, in the subgroup of patients with CTOs, a scaffold was needed in 48% of the procedures. A major limitation of DCB angioplasty as standalone therapy is the higher risk for dissections and the reduced drug uptake in calcified arteries. Specialty balloons, mechanical debulking or intravascular lithotripsy have been used prior to DCB angioplasty as 'vessel-preparation' techniques. Aim of this approach is to 'prepare` the vessel by removing or modifying the atherosclerotic plaque, increase the drug uptake and minimize the risk for dissections. Despite this theoretical advantage there is limited data regarding the performance of this approach for femoropopliteal disease.

In two studies we evaluated the performance of directional atherectomy with anti-restenotic therapy (DAART) using DCB angioplasty vs DCB angioplasty alone for two 'no-stenting' arterial segments. In the first cohort we analyzed the data of 72 patients, who were treated with either DCB angioplasty as stand-alone therapy (n=31) or with DAART (n=41) for isolated popliteal lesions. Most patients in both groups were claudicants (74% vs 86%, respectively). Vessel calcification (29% vs 29%, respectively), mean lesion length (47 vs 42 mm, respectively), and number of runoff vessels were comparable between the groups. The technical success rate did not differ significantly (84% vs 93%, p=0.24), however, the 12-month primary patency rate was higher in the DAART group (65% vs 82%; hazard ratio 2.64, 95% confidence interval 1.09 to

6.37, p=0.021). There was a non-significant trend in favor of DAART regarding the freedom from TLR (82% vs 94%, p=0.072), however, the secondary patency at 12 months was identical (96% vs 96%). Bailout stenting was more common after DCB angioplasty, nevertheless the difference did not reach a statical significance (16% vs 5% for DAART, p=0.13). The aneurysmal degeneration of the treated segment limited, however, the performance of DAART (7% vs 0% for DCB alone, p=0.25) (Stavroulakis, J Endovasc Ther 2017).

In a second cohort we assessed the performance of DAART and DCB angioplasty in patients with common femoral artery (CFA) disease. Although endovascular techniques significantly evolved, the role of endovascular therapy in the treatment of groin vessels remains controversial. Endovascular treatment, and especially stent therapy, are not favored by many physicians owing to the high mechanical stress exerted on the artery, the potential loss of an access vessel, and the risk of jailing the deep femoral artery. Furthermore, current recommendations suggest against the use of scaffolds for CFA disease (Conte, J Vasc Surg 2019). Although both DCB angioplasty and DAART could be an alternative to open repair in highly selected patients, data concerning the outcomes of "leave nothing behind" strategies for CFA lesions is scarce.

A retrospective analysis of 47 consecutive patients treated by either DCB angioplasty alone (n=26) or DAART (n=21) was conducted. Most patients presented with lifestyle limiting claudication (14 DCB and 15 DAART). The mean lesion length (39±14 mm DCB and 34±16 mm DAART) and the calcification burden (17/26 DCB and 11/21 DAART) were comparable between the groups. At 12-months there was a trend in favor of DAART regarding the primary patency (88% vs 68%) and the freedom from TLR (89% vs 75%), but neither difference was statistically significant. The secondary patency estimate at 12 months was higher in the DAART group (100% vs 81% for DCB, p=0.03). Bailout stenting (1 DCB vs 1 DAART) and complication rates were comparable and more non-flow-limiting dissections were observed in the DCB group (8 vs 1 for DAART, p=0.02). In contrast to our previous observations no aneurysmatic degeneration of the common femoral artery was found. This study showed that vessel preparation with atherectomy prior to DCB angioplasty was associated with a higher estimated 12-month patency, although the difference did not reach statistical significance. Nonetheless, both modalities were associated with acceptable 12-month outcomes. Because of the limited

number of patients in this study, it was difficult to detect more than a trend and this analysis could serve as a basis for future randomized control trials (Stavroulakis, J Endovasc Ther 2018).

Intravascular lithotripsy is an additional vessel preparation tool, that can be used in combination with DCB angioplasty for severely calcified disease. Intravascular lithotripsy is based on the same principles of kidney stone treatment and uses pulsatile sonic waves to fracture intimal and medial calcification. In a single center study, we analyzed the 12 months outcomes of lithotripsy in combination with DCB angioplasty in fifty-five patients (71 lesions) with femoropopliteal disease. In this challenging cohort 56% (n = 31) of the patients presented with CLTI, 47% (n = 26) were diabetics, and 66% (n = 36) had chronic kidney disease (CKD). The median lesion length was 77 mm (interquartile range: 45-136), and 20% (n = 14) of the lesions were CTOs. The technical success after lithotripsy was 87% (n = 62) and the procedural success 97% (n = 69). A flow-limiting dissection was observed in 2 lesions (3%). Both the rates of arterial perforation and distal embolization were 1% (n = 1). A bail-out stent was used in 5 lesions (7%). At 12 months the primary patency was 81%, the freedom from TLR was 92% and the secondary patency 98%. The overall survival was 89% and the freedom from major amputation amounted to 98%. This analysis reviled that the combination of intravascular lithotripsy with DCB is a valid treatment option for heavily calcified disease with and an excellent safety profile and acceptable rate of re-interventions at 12 months (Stavroulakis, J Endovasc Ther 2022).

In overall, these pragmatic cohorts showed that despite the promising results of DCB angioplasty in highly selected patients, the treatment of challenging lesions is associated with high rates of restenosis, clinical failure, and TLR. Vessel preparation techniques might improve the outcomes of DCB angioplasty owing to the increased drug uptake in the vessel wall, the reduced need for bail out stenting and the reduction of flow limiting dissections.

5.4. The use of intraluminal imaging for endovascular procedures

Historically, angiography has been considered the gold standard for vessel sizing and treatment and fluoroscopic guidance remains the basis of endovascular treatment. Angiography has a critical role in determining the periprocedural strategy and the applied treatment option, nevertheless it is a 'luminography' that commonly fails to extrapolate the three-dimensional

structure of the vessel wall. Utilization of intravascular ultrasound (IVUS) and optical coherence tomography (OCT) has been incorporated into diagnostic and treatment algorithms to further characterize and treat the atherosclerotic plaque. In two studies we evaluated the use of IVUS and OCT guidance for peripheral interventions.

In a retrospective analysis of 43 patients who underwent endovascular revascularization for CLTI we compared the estimated diameter of the treated vessels by visual assessment (angiographic imaging) with IVUS guided measurements. Both above- and below-the-knee vessels were analyzed. Regardless the arterial segment, angiography-based measurements were significantly smaller than those obtained from IVUS analysis. The same trend was observed for above and below the knee disease and for both female and male patients (Pliagas, J Inv Card 2020). Given the significance of arterial wall sizing for peripheral interventions, the clinical impact of this finding and the role of IVUS to improve the outcomes of endovascular interventions should be further evaluated in the framework of larger clinical trials.

In an additional analysis we assessed the value of real-time visualization of the arterial wall during atherectomy using an (OCT)-guided directional atherectomy catheter. The real time visualization of the artery allows the identification of the vessel wall structures, which might reduce the risk for deep cuts in the adventitial layer that predispose to perforation of the vessel or aneurysm formation after DCB angioplasty. Thirty-three patients (N.=33, mean age 67±8 years) and 37 lesions were included into our analysis. The median lesion length was 70 mm (IQR: 27-104) and 35% (N.=13) of the lesions were CTOs. Vessel wall calcification was present in 22% (N.=8) of the treated vessels. The 12 months primary patency was 93% and the freedom from TLR at 12 months was 100%. A single target vessel perforation (N.=1, 3%) and 2 peripheral embolizations (N.=2, 5%) were observed. The bailout stenting rate was 3% (N.=1) and the final angiography did not reveal any flow limiting dissection. Like previous studies of fluoroscopic guided atherectomy, an aneurysmatic degeneration of the target vessel was observed in 2 lesions (5%). In this analysis, the use of OCT guided atherectomy in selected patients was associated with very low rates of loss of patency and no need for-reintervention at 12 months, however, perforation and aneurysmatic degeneration of the arterial wall also complicated this modality (Stavroulakis, J Cardiovasc Surg (Torino) 2019).

6. Surgical vs Endovascular treatment for peripheral occlusive disease

Despite the continuous development of endovascular therapy, surgery remains a viable option for patients with peripheral occlusive disease. However, only few trials evaluated the performance of both treatment strategies for PAD/CLTI patients. Furthermore, previous published cohorts did not enroll patients with end-stage renal disease and consecutive individuals and excluded hybrid procedures as therapeutic options. Moreover, during their enrollment period, novel endovascular modalities, such as CS, DCB, DES, and vessel preparation modalities etc, were not available.

The CRITISCH (Registry of First-Line Treatments in Patients With Critical Limb Ischemia) registry was designed to inform the current debate and compare the endovascular approach to bypass grafting for infrainguinal atherosclerosis in CLTI individuals. Between January 2013 and September 2014, 1.200 patients from 27 vascular centers were enrolled. Endovascular therapy was applied to 642 (54%) and bypass surgery to 284 (24%) patients. Adjustment for several confounders by means of multivariate Cox regressions was necessary, because statistically significant differences between the baseline characteristics of the two groups were observed. Patients treated by endovascular means were older and frailer (higher PREVENTIII score), they had more frequently CKD and usually presented with minor tissue loss (Rutherford class 5). On the other hand, bypass grafting was use more frequently in patients who have already undergone one or more previous vascular procedures. The non-inferiority of endovascular therapy versus bypass surgery for amputation-free-survival was confirmed (HR: 0.91; upper bound of 1-sided (1-0.0058), CI: 1.29; p=0.003). An impact of the treatment strategy on time until death (HR: 1.14; 95% CI: 0.80 to 1.63; p=0.453), major amputation (HR: 0.86; 95% CI:0.56 to 1.30; p=0.463), and reintervention and/or above-ankle amputation (HR: 0.89; 95% CI: 0.70 to 1.14; p=0.348) was not observed. This study highlights that when physicians are free to individualize their treatment for CLTI patients, both strategies can achieve encouraging outcomes (Bisdas, J Am Coll Cardiol Int 2016).

In a further analysis of the CRITISCH registry we evaluated the outcomes of all currently available therapeutic options for CLTI including CFA endarterectomy, hybrid procedures and conservative treatment. Since a meaningful head-to-head comparison between the modalities

could not be performed due to the heterogeneity of the groups, the event rates of each treatment group were compared with the objective performance goal for amputation free survival (71%) suggested from the Society of Vascular Surgery. This benchmark is based on validated multicenter trial datasets of bypass grafting and was designed to offer a standardized measure for the evaluation of newly introduced endovascular devices. Multivariable regression methods were employed to identify variables that influenced the treatment selection and the major endpoint after each treatment. Treatment options were endovascular revascularization (642, 53.5%), bypass grafting (284, 23.7%), common-/ deep- femoral artery endarterectomy (126, 10.5%) with or without simultaneous peripheral intervention, conservative treatment (118, 9.8%), and primary major amputation (30, 2.5%). The 12-month amputation free survival estimates following endovascular therapy, bypass grafting, common femoral endarterectomy, and conservative treatment were 75%, 72%, 73%, and 72%, respectively. Accordingly, all first-line treatment strategies in the individualized framework of the CRITISCH registry met the suggested objective goal of 71%. Cox regression analysis identified CKD (HR 2.07, 95% CI 1.26 to 3.41, p=0.004), the use of a prosthetic bypass conduit (HR 1.97, 95% CI 1.23 to 3.14, p=0.004), and previous vascular intervention of the index limb (HR 1.52, 95% CI 0.94 to 2.43, p=0.085) as independent risk factors for lower amputation free survival after bypass grafting. CKD (HR 1.47, 95% CI 1.09 to 1.99, p=0.012) and Rutherford class 6 (HR 1.81, 95% CI 1.30 to 2.52, p<0.001) compromised the performance of endovascular revascularization. Although the 5 treatment groups could not be directly compared to each other and no suggestion can be made regarding one treatment option over the other, the outcomes of this study highlight that physician can achieve encouraging outcomes with all first-line therapies when they are free to individualize their therapy for CLTI individuals (Stavroulakis, J Endovasc Ther 2018).

CKD is one of the major parameters influencing a physician's decision-making process and is an important determinant of a patient's prognosis regardless the applied treatment option. Although previous published data analyzed the impact of end-stage-renal disease on CLTI individuals, patients with non-dialysis dependent CKD are underrepresented in interventional studies. Thus, we evaluated the performance of endovascular therapy vs bypass grafting in CLTI patients with non-dialysis-dependent renal impairment. For this analysis, only 337 patients from the CRITISCH registry with non-dialysis-dependent renal disease treated by either bypass surgery (n=86; median 78 years, 48 men) or endovascular therapy (n=251; median age 80 years, 135 men) were evaluated. The Cox regression analysis revealed a significantly greater hazard

of amputation or death after surgery (HR 1.78, 95% CI 1.05 to 3.03, p=0.028). Additionally, a higher hazard for major amputation and mortality was shown for bypass grafting, but the differences were not significant (Amputation: HR 1.66, 95% CI 0.78 to 3.53, p=0.188; Survival: HR 1.41, 95% CI 0.80 to 2.47, p=0.348). The absence of runoff vessels (HR 1.73, 95% CI 1.15 to 2.60, p=0.008) was associated with a decreased amputation free survival. The risk for major amputation was significantly higher in males (HR 2.21, 95% CI 1.10 to 4.45, p=0.027), in patients without patent runoff vessels (HR 1.95, 95% CI 0.96 to 3.95, p=0.065), and after myocardial infarction during the last 6 months (HR 3.74, 95% CI 1.23 to 11.35, p=0.020). Death was more likely in patients without runoff vessels (HR 1.76, 95% CI 1.11 to 2.80, p=0.016) and those with a higher PREVENT risk score (HR 1.73, 95% CI 1.03 to 2.91, p=0.038). In overall, the results of this study suggest a benefit in terms of improved amputation free survival from percutaneous revascularization in this fragile group of patients. However, this study was not designed to report on the long-term impact of the selected treatment option on the renal function (Stavroulakis, J Endovasc Ther 2020).

In an additional cohort we evaluated the performance of surgery, hybrid treatment and endovascular therapy in patients with acute limb ischemia and active neoplastic disease. A multicenter, interdisciplinary, retrospective registry collected data from 139 patients (mean age 72.3±12.4 years; 73 men) treated in 7 European centers between July 2007 and February 2019. The primary underlying malignancy was lung cancer. Endovascular treatment was applied in 41 patients (29%), surgery (bypass grafting/embolectomy) in 70 (51%), and hybrid therapy in 28 (20%). Endovascular therapy showed an improved 12-month amputation free survival compared to both surgery (HR 2.27, 95% CI 1.20 to 4.28, p=0.002) and hybrid treatment (HR 2.14, 95% CI 1.09 to 4.18, p=0.008). An increased risk for mortality was observed after surgery (HR 2.50, 95% CI 1.19 to 5.53, p=0.003) and hybrid revascularization (HR 3.10, 95% CI 1.45 to 6.65, p<0.001) compared to percutaneous revascularization. At 12 months, the amputation free time was similar between the 3 groups (endovascular vs surgery: HR 1.52, 95% CI 0.51 to 4.53, p=0.45 and endovascular vs hybrid: HR 1.21, 95% CI 0.36 to 4.11, p=0.73). The 12-month reintervention free time also did not differ significantly between the 3 treatment options (endovascular vs surgery: HR 1.10, 95% CI 0.49 to 2.46, p=0.79 and endovascular vs hybrid: HR 0.51, 95% CI 0.22 to 1.17, p=0.19). Surgery and/or hybrid treatment increased the risk for the major amputation and/or death (HR 1.76, 95% CI 1.05 to 2.05, p=0.03), whereas Rutherford class I ischemia (HR 0.12, 95% CI 0.02 to 0.90, p=0.04) and previous vascular interventions on

the index limb (HR 0.55, 95% CI 0.32 to 0.97, p=0.04) showed a protective effect. This analysis showed improved amputation free survival after endovascular treatment of ALI in the setting of malignancy, with comparable limb salvage and reintervention rates among the 3 treatment groups. A significant survival benefit was observed after endovascular treatment (Argyriou, J Endovasc Ther 2021).

7. Discussion:

The clinical and socioeconomic impact of lower extremity atherosclerosis

Since the outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 or COVID-19), the term pandemic has suddenly become part of our everyday life. According to the dictionary of epidemiology, pandemic is in an epidemic occurring worldwide or over a very wide area, crossing international boundaries and usually affecting a large number of patients (Porta, Miquel, ed. (2008). Dictionary of Epidemiology). Nevertheless, the word pandemic was not unknown in the field of vascular medicine. It is estimated that in 2015, 236 million people aged 25 years and older were living with PAD globally, while in western societies the incidence of CLTI varies between 500 and 1000 per 1 million persons every year (Song, Lancet Glob Health. 2019, Norgen, JVS 2007). As a comparison, 34 million people were living with HIV at the end of 2011, and the global burden of ischemic heart disease in 2019 was 197 million (Hirsch Lancet 2013, Roth J Am Coll Cardiol. 2020). Of note, the numbers of PAD cases and PAD related deaths have risen consistently between 1990 and 2019 resulting in a 2-fold increase within the last thirty years (Hirsch, Lancet 2013). Therefore, there is no doubt that lower extremity atherosclerosis is an ongoing pandemic and a global health problem.

The socioeconomic effect of PAD is also not neglectable. The last decades a significant increase of the disability-adjusted life years was observed, especially among men in Eastern Europe and Africa (Hirsch, Lancet 2013). In Germany, the total costs for the inpatient care of individuals with symptomatic lower limb atherosclerosis increased more than 21% in a period of two years (Malyar, Eur Heart J. 2013). Furthermore, PAD is an important risk factor for diabetes-related foot ulcerations and tissue loss, a dramatic condition with increased mortality and high medical cost (Criqui, Circulation 2021). In a retrospective analysis of Medicare data, the mean cost of in-hospital treatment for PAD patients in the year before major amputation was $22,405 (Goodney, JAMA Surg. 2014). Notably, a primary major amputation (above the ankle) for patients with CLTI is associated with higher costs, shorter survival and a higher risk for subsequent major amputation compared to any revascularization strategy (Mustapha, J Am Heart Assoc. 2018)

PAD as a coronary heart disease equivalent

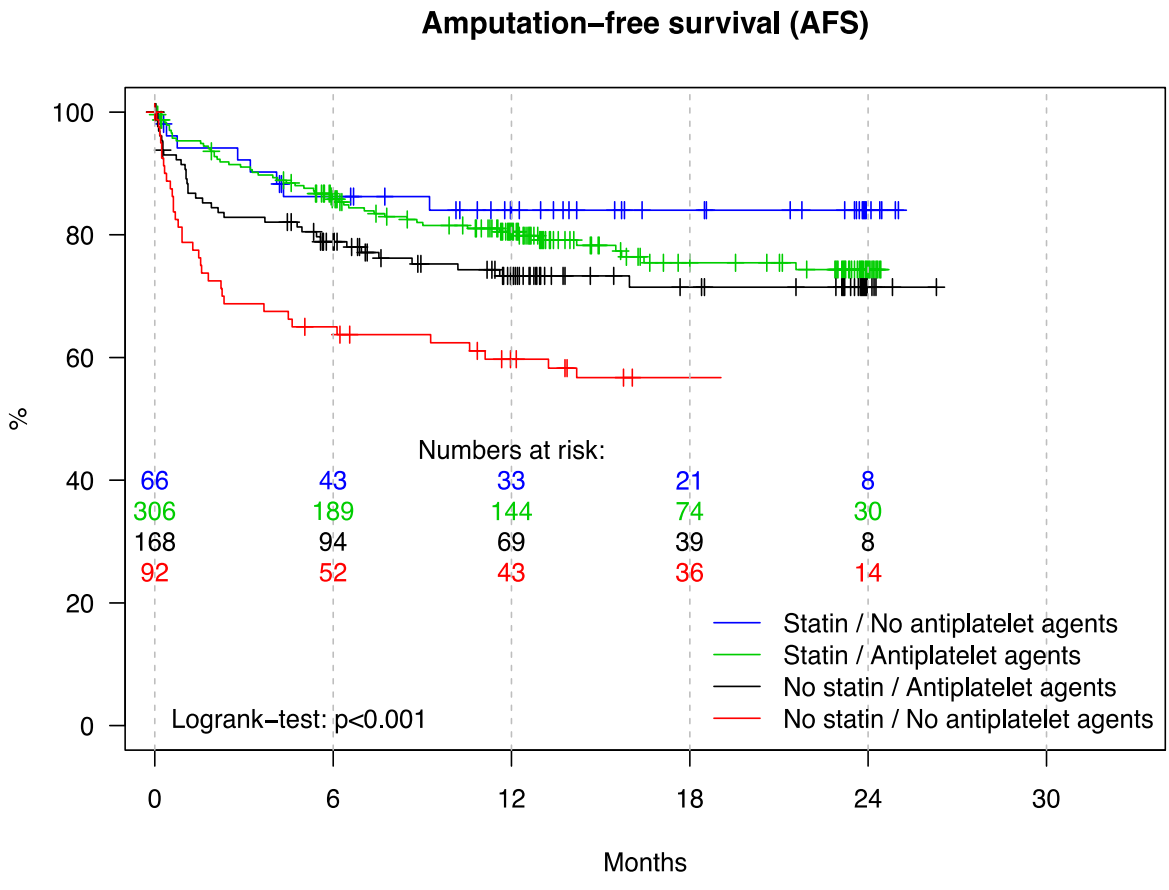
Lower limb atherosclerosis is the third leading cause of atherosclerotic morbidity following ischemic heart disease and stroke and has been historically considered a coronary heart disease risk equivalent (Criqui, Circulation 2021, Subheral, Eur J Prev Cardiol. 2015)The latter suggests that PAD confers a long-term risk to patients similar to established heart disease. An analysis, however, of 113,772 patients from 28danish registry data showed that individuals with symptomatic peripheral atherosclerosis have higher long-term risks of total and cardiovascular mortality than patients with previous acute coronary syndrome (Subheral, Eur J Prev Cardiol. 2015). Moreover, a study of 1,121,359 cases from the Japanese nationwide databases revealed a significant heterogeneity in terms of predisposing risk factors between patients with PAD and coronary heart disease. PAD individuals were older and had more frequent diabetes mellitus and end-stage renal disease on dialysis indicating a higher risk profile among patients with lower limb disease (Takahara, Cardiovasc Diabetol. 2019).

There is growing evidence that adherence to guidelines recommendations improved the natural history of PAD even among patients treated by conservatively (Armstrong, J Am Heart Assoc. 2014, Benoit, J Vasc Surg. 2012). Although, patients with PAD have significantly less chance of receiving an appropriate medical therapy than individuals with coronary disease, there has been an improvement over the years regarding the secondary prevention (Subherwal, Circulation 2012, Søgaard Circulation 2021). Søgaard et al examined the temporal changes in the use of aspirin, clopidogrel, and statins among patients undergoing revascularization between 2000 and 2016. The cumulative incidence of medication use increased during the study period with a parallel reduction of the 1-year major adverse events (Søgaard, Circulation 2021). Data from the CRITISCH registry showed that patients receiving both antiplatelet therapy and statins had an improved amputation-free-survival and a reduced risk for major cardiac and cerebrovascular events, however only a minority of patients were on statins throughout the study period (figure 1) (Stavroulakis, J Vasc Surg 2017).

Despite, however, its increasing prevalence, socioeconomic and clinical impact, PAD remains an underrecognized and undertreated condition (Conte, J Vasc Surg 2019, Criqui, Circulation 2021, Roth J Am Coll Cardiol. 2020). The lack of awareness both between physicians and the

society is an important determinant for the patient's prognosis. A recent systematic review showed that when patients are asked to classify the severity of peripheral atherosclerosis, PAD is considered an innocent condition by 25%, relatively serious by 61%, and very serious by 5%. The same study also showed an inadequate understanding of risk factors, consequences, and management of PAD among healthcare professionals (Bridgwood, Vasc Med. 2020). There is general belief that a lower limb disease cannot be fatal, whereas coronary heart disease has been recognized as a leading cause of sudden cardiac death. Additionally, PAD is considered a 'discomfort' and not a disabling condition, while stroke is established as the main cause of disability (Criqui, Circulation 2021). Accordingly, strategies to educate healthcare professionals and patients and increase the awareness of PAD are crucial for the future healthcare politics.

Figure 1: The effect of 'best-medical-treatment' on the amputation-free-survival of patients with chronic limb threatening ischemia: Insights from the CRITISCH registry. Stavroulakis et al. J Vasc Surg. 2017 Nov;66(5):1534-1542



The evolution of endovascular therapy

In 1997 Frank Veith in his presidential address as newly selected president of the Society of Vascular Surgery predicted that in the upcoming years 40% to 70% of vascular surgery operations will be replaced with less-invasive endovascular procedures (Veith, J Vasc Surg. 1997). Indeed, endovascular therapy rapidly evolved during the last decades and is currently considered the first line treatment option for most patients with peripheral atherosclerosis. In the CRITISCH registry more than 50% of the enrolled patients were treated by endovascular means, while a percutaneous treatment was used in 69% of the patients included into the German VASC study (Bisdas, JACC Cardiovasc Interv. 2016, Kotov, VASA 2021).

The minimally invasive nature of percutaneous procedures might offer a benefit for this frail group of patients. Furthermore, the continuous development of endovascular techniques enables the treatment of lesions previously considered particularly challenging for endovascular revascularization. In the BASIL trial 20% of the procedures in the angioplasty group were deemed immediate technical failure because of a crossing failure (Bradbury, J Vasc Surg. 2010). On the contrary, our analysis revealed that currently most peripheral lesions can be crossed. Although, a transfemoral crossing might fail in challenging lesions, the utilization of a retrograde crossing techniques or the use of re-entry devices might increase the crossing success rates up to 93% (Bernandini JEVT 2022, Korosoglou JACC Cardiovasc Interv 2022). Additionally, the TASC II consensus document, published in 2007, indicated a primary endovascular treatment mainly in short, non-calcified lesions (Norgen, J Vasc Surg 2007). Ten years later the common position document of the European Society of Cardiology and the European Society of Vascular Surgery suggested the use of percutaneous revascularization in femoropopliteal lesions up to 25 cm (Aboyans, Eur Heart J. 2018). This swift, in the clinical practice recommendations, mainly mirrors the improved results of endovascular therapy in complex lesions following the introduction of novel sophisticated devices. The TASC II document considered a 20 cm femoropopliteal occlusion or an isolated popliteal occlusion as a contraindication for endovascular therapy (Norgen, J Vasc Surg 2007). However, two studies from our group showed promising outcomes in long lesions and popliteal artery occlusions with the use of paclitaxel coated stents and atherectomy in combination with DCB angioplasty respectively (Bisdas, JACC Cardiovasc Interv 2018, Stavroulakis JACC Cardiovasc Interv 2021).

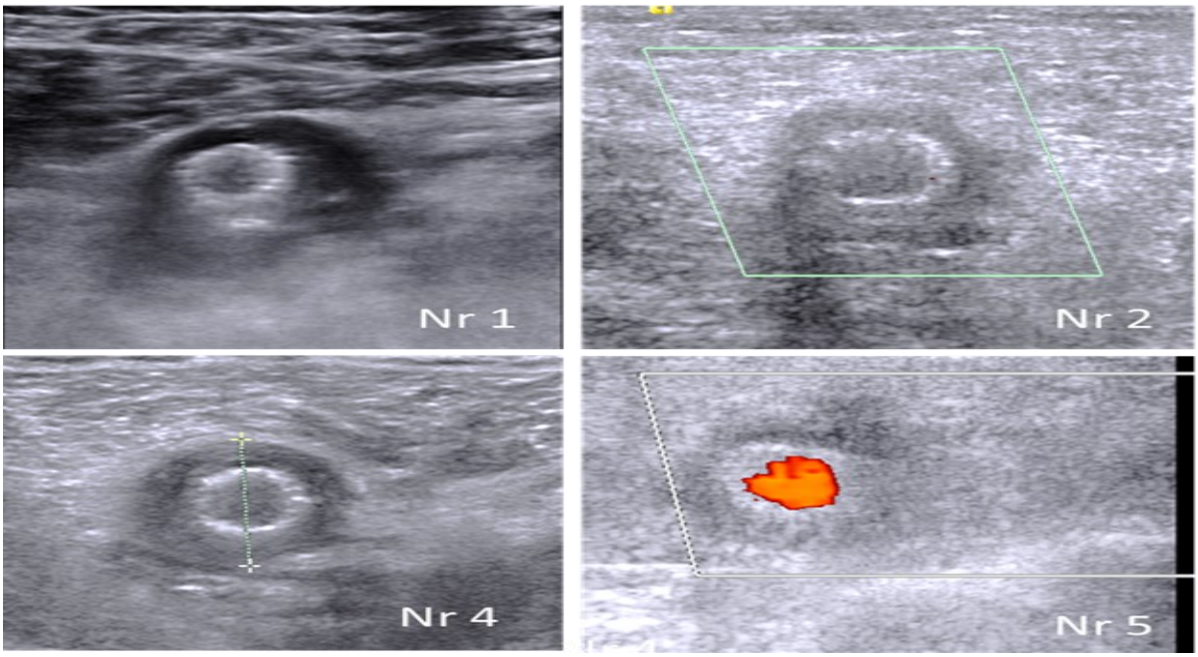
The lack of high-quality evidence is one of the main criticisms of percutaneous procedures. Sardar et al, evaluated the strength of evidence of the American Heart Association/American College of Cardiology clinical recommendations on endovascular and surgical treatment for PAD. Only 27% of the recommendations regarding endovascular therapy were class I and 18% had a level of evidence A (Sardar, Circ Cardiovasc Interv. 2019). The authors concluded that most recommendations were moderate to weak, that can be useful/effective/beneficial (class IIa) or may be considered (class IIb), whereas the majority of recommendations were based on levels of evidence B and C which are considered moderate (Lee, Circ Cardiovasc Interv. 2019).

The inclusion of highly selected patients with significant less comorbidity than 'real-world' individuals is a major limitation of many trials in the peripheral field. An analysis of the IN.PACT Global registry showed that only 20% of the patients that were included into this study, would be eligible for randomization in the IN.PACT SFA randomized trial. Patients that did not meet the inclusion criteria of the randomized trial had longer and more calcified lesions, had more frequently popliteal artery involvement, bilateral disease, and in-stent restenosis (Ansel, J Endovasc Ther. 2018). Additionally, the overall 2 years mortality after Eluvia deployment in our analysis was 15% and much higher than the 7.1% for Eluvia and the 8.3% for Zilver PTX DES observed in the IMPERIAL randomized control trial (Stavroulakis JACC Cardiovasc Interv 2021, Müller-Hülsbeck Cardiovasc Intervent Radiol. 2021). This finding mainly highlights the different atherosclerotic burden and risk profile of the two cohorts. Accordingly, there is a true need for large scale studies evaluating the performance of novel endovascular modalities in 'real-world' patients.

The durability of endovascular therapy is probably the Achilles heel of minimally invasive procedures. The risk for restenosis and accordingly for re-intervention depends on the nature of the disease and the applied treatment strategy. The presence of calcified disease, chronic occlusions, long lesions, and in-stent-stenosis increase the risk for restenosis, while the use of POBA is associated with the poorest performance on the long-run (Giannopoulos, Cardiovasc Revasc Med. 2021). The chemical/pharmacological barrier of paclitaxel, the mechanical barrier of permanent scaffolds and the use of several 'vessel-preparation' devises has been suggested to address the problem of restenosis in challenging lesions.

Although, paclitaxel is the main agent used to inhibit re-stenosis after endovascular treatment, there is a growing concern regarding the safety of the antiproliferative drug. In December 2018 a study-level metanalysis of 28 randomized trials with 4663 patients questioned the safety of paclitaxel for peripheral interventions. Katsanos et al reported an increased risk for all-cause mortality, which manifests ≥ 2 years after the use of DCB or DES (Katsanos, J Am Heart Assoc. 2018). Following the initial publication, the Food and Drug Administration (FDA) performed its own meta-analysis showing that paclitaxel-coated devices increased the mortality risk three years after the index procedure (Dan, Am Heart J. 2020). Moreover, an individual patient data meta-analysis published from the Vascular InterVentional Advances (VIVA) physicians found an absolute 4.6% risk for mortality after PTX exposure (Rocha-Singh, Circulation 2020). Nevertheless, registry data could not confirm this finding and more recently the interim analysis of the randomized registry-based SWEDEPAD trial did not reveal any difference between paclitaxel coated and uncoated devices (Secemsky, JAMA Cardiol. 2019, Freisinger, Eur Heart J. 2020, Donas Cardiovasc Intervent Radiol. 2020, Nordanstig N Engl J Med. 2020). In this context, the current body of evidence suggests that paclitaxel might increase the mortality in low atherosclerotic risk patients, but it does not influence the prognosis of 'real-world' patients. Besides the late mortality signal the use of the anti-restenotic agent is related with distal embolization of microparticles of paclitaxel and a local toxic effect on the vessel wall. A systematic review and meta-analysis of 21 randomized controlled trials found an increased risk for major amputation following DCB angioplasty (Katsanos, Eur J Vasc Endovasc Surg. 2022). The pathophysiology of this finding remains unclear, however, a distal embolization with microparticles might compromise the run-off of the affected extremity, impair the wound healing and lead to major adverse limb events. Regarding the local toxicity of paclitaxel observed from our group after DES deployment and DAART treatment, this did not increase the rates of clinical adverse events, loss of patency or re-intervention (figure 2).

Figure 2: Vessel wall degeneration following drug eluting stent deployment

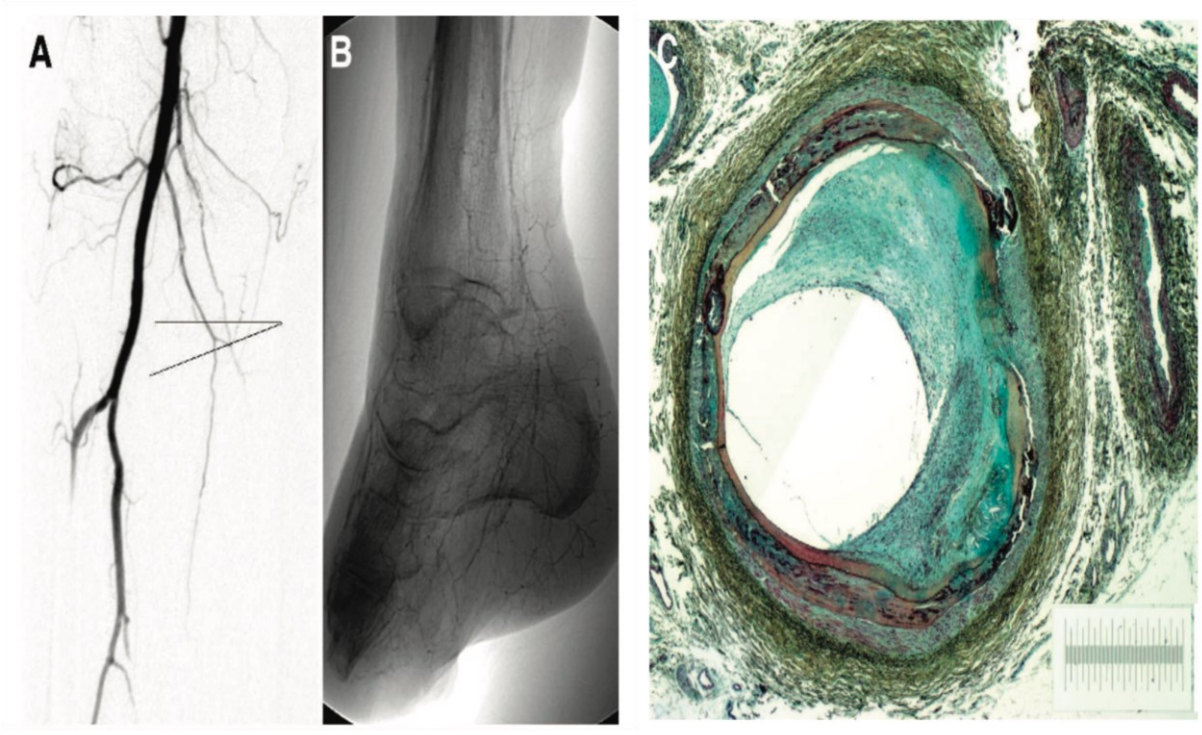


Given the ongoing discussion about the safety of paclitaxel, there is an increasing interest on alternative antiproliferative agents for the femoropopliteal segment. The DANCE (Dexamethasone to the Adventitia to Enhance Clinical Efficacy After Femoropopliteal Revascularization) trial evaluated the local delivery of dexamethasone in the vessel wall to inhibit restenosis. The study included 262 patients with femoropopliteal disease with rather short (<9 cm) and non-severely calcified lesions. The primary patency at 12 months amounted to 78.4%, while 10% of the patients underwent a TLR in the first year after the index procedure (Razavi, JACC Cardiovasc Interv. 2018). Moreover, the ongoing SIRONA randomized control trial will assess the performance of sirolimus coated balloons for femoropopliteal disease (Teichgräber, Trials 2021). Of note, sirolimus was used as anti-restenotic therapy in the SIROCCO trial, which was the first study that evaluated the use of DES for femoropopliteal lesions. The sirolimus coated DES did not show any clinical or radiological benefit over the uncoated devices (Duda, J Vasc Interv Radiol. 2005). Although currently there is not sufficient evidence to support the use of these agents for above the knee disease in the clinical practice, limus coated stents are used predominantly for below the knee disease (Scheinert, J Am Coll Cardiol. 2012).

Finally, an important development that might influence the further refinement of endovascular therapy is the use of advanced imaging for peripheral interventions. Since the first successful

endovascular limb salvage procedure performed from Andreas Grüntzig in 1974, percutaneous therapies are performed under fluoroscopic guidance (Barton, Front Cardiovasc Med. 2014). However, angiography is a luminography that frequent underestimates the extent of atherosclerosis. A histopathological analysis of 69 patients that underwent major amputation, revealed a significant atherosclerotic burden even in angiographically ‘‘normal appearing’’ vessels (figure 3) (Kashyap, J Endovasc Ther. 2008). Additionally, conventional angiography underappreciates the presence and severity of post-intervention dissections (Shammas, J Endovasc Ther. 2020). The use of intraluminal imaging might better assess the diameter of the target vessels, provide information regarding the nature of the atherosclerotic plaque and detect postinterventional dissections compared to angiography. A study of Medicare beneficiaries aged 65 years or older who underwent lower limb revascularization found a 32% reduction in major adverse limb events, such as amputations, over a median 425 days of follow-up (Secemsky, (TCT) 2021). The randomized Contribution of Optical Coherence Tomography in the Endovascular Treatment of Femoral Occlusions (TOCAF) trial will evaluate the use of OCT guidance for the treatment of TASC II C and D femoropopliteal lesions and will provide evidence regarding the potential use of intraluminal imaging in the peripheral field (Dubosq, Ann Vasc Surg. 2021).

Figure 3: Angiographic imaging of a patent popliteal artery (A, B). Histopathological evaluation of the same arterial segment (C) revealing significant atheroma and circumferential calcification. Kashyap VS et al. JEVT 2008 Feb;15(1):117-25.



Developing a treatment algorithm for patients with symptomatic PAD

The lack of commonly accepted reporting standards and treatment algorithms is one of the main challenges that physicians face in their clinical practice. The continues introduction of novel endovascular devices made the treatment of complex lesions possible but on the same time complicated the decision-making process. Furthermore, different endovascular modalities share the same indications, for instance lithotripsy and atherectomy for calcified disease.

Several factors might influence the development of an endovascular treatment algorithm. The characteristics of the lesions, the clinical status, and the comorbidity of the patient are the main parameters that should be taken into consideration in everyday practice. A long calcified stenotic lesion in a young claudicant with patent tibial vessels should be preferably treated by a 'leave-nothing-behind' approach. On the contrary, a long femoral occlusion in an older individual with critical limb ischemia can be treated with a permanent scaffold, given that the

goal of the intervention is to establish an optimal perfusion to the foot. Additionally, the theoretical risk for the development of in-stent-restenosis is secondary because of the poor prognosis of CLTI patients. Moreover, atherectomy should not be preferred in patients with compromised run-off, as a distal embolization might be difficult to treat and lead to a major amputation. Likewise, in patients with CKD repeated angiograms and excessive administration of contrast medium should be avoided, thus endovascular debulking might not be the first treatment option. On the other hand, an in-stent-restenosis might be better treated with a primary debulking or stent graft placement because of the 'malignant' nature of neo-intimal atherosclerosis. Anyhow, there is a need for 'head-to-head' comparisons, especially for endovascular modalities that have similar indications. Unfortunately, endovascular treatment algorithms differ significantly among the institutions, are based on the institutional experience, the skills of the treating physicians and the local reimbursement policies and far less on an evidence-based approach.

In the 'endovascular first' era, surgery remains a valuable option for many patients with peripheral atherosclerosis. Nevertheless, it is unclear in which cases a 'surgery-first' approach should be recommended. The BASIL trial showed similar clinical outcomes for the overall cohort, but in patients with a life expectancy of more than 2 years a primary bypass grafting approach was beneficial. A very important result of the BASIL trial was that patients that underwent secondary surgical procedures after endovascular therapy had a poorer prognosis compared to individuals underwent a primary bypass grafting (Adam, Lancet 2005). The CRITISCH registry revealed the same trend for patients treated by surgical bypass (Stavroulakis, J Endovasc Ther. 2018). This might be explained either through a rapid progress of the underlying atherosclerosis among those patients, or from a negative effect from the primary endovascular revascularization. Conway et al, showed that when a femoropopliteal stent occludes, 22% of the patients lose the original bypass target. Chronic obstructive pulmonary disease (p=0.007), CKD (p=0.026), popliteal artery stenting (p=0.001), and the below-knee popliteal artery as an optimal bypass target (p=0.026) were associated with increased risk for loss of bypass target following stent occlusion (Conway, J Endovasc Ther. 2015).

Although, it remains difficult to assess the life expectancy of a CLTI patient, a bypass first approach should be considered in younger patients with acceptable peri-operative risk and an

available vein conduit. Nevertheless, vein mapping and excessive preprocedural workout should be performed in every CLTI patient even if a primary endovascular strategy is indicated. As percutaneous procedures for CLTI cases still curry a relatively high risk for complications and technical failure, the treating physician should be aware of the vein availability and adjust their treatment strategy accordingly. Beyond comorbidity and vein availability, the lesion's characteristics also influence the treatment algorithm. Primary open repair remains the standard of care for common femoral artery atherosclerosis. Main reasons are the high technical success and the durability of CFA endarterectomy, while no endovascular modality can match the long-term outcomes of surgery in this anatomical region (Stavroulakis, J Endovasc Ther. 2018, Saratzis Br J Surg. 2021, Ballota, Surgery. 2010). Additionally, the endovascular treatment of long calcified occlusions or of lesions involving the tibial trifurcation can be very demanding, and a primary surgical approach is meaningful if the perioperative risk is acceptable. Patient selection is of paramount importance as very-high risk individuals such as CKD patients or patients with active neoplastic disease might benefit from a primary endovascular approach (Stavroulakis J Endovasc Ther 2020, Argyriou J Endovasc Ther 2021).

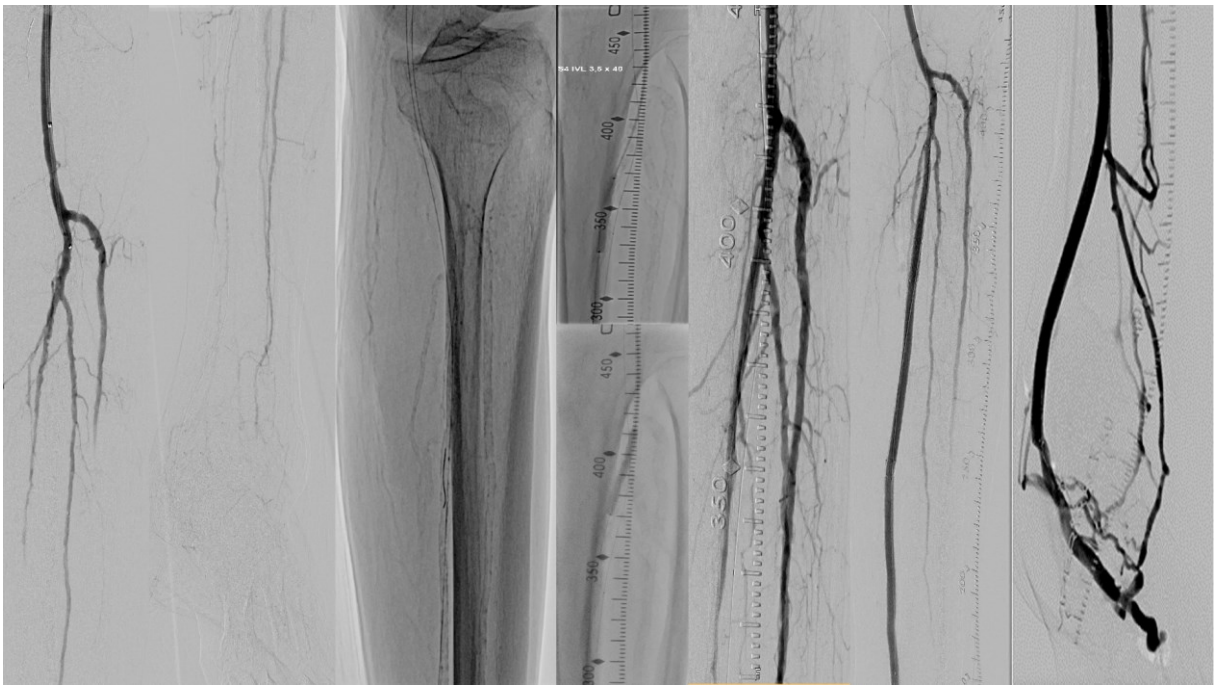
Hybrid revascularization and conservative therapy are two more therapeutic options that should be incorporated in a modern PAD treatment algorithm. CFA endarterectomy or bypass grafting can be offered simultaneously with endovascular treatment of the inflow or outflow vessels. Although CFA endarterectomy in combination with endovascular therapy is a standardized procedure, the endovascular treatment of the outflow vessels following a bypass grafting is less described (Stavroulakis J Endovasc Ther 2018). This approach might be particularly helpful if a vein conduit is unavailable to avoid a below the knee bypass or in cases of compromised tibial outflow. Additionally, in patients with prosthetic bypass occlusion endovascular therapy can be applied after conventional thrombectomy for the treatment of distal anastomosis stenosis. A hybrid approach might be also a helpful bailout option. A stent deployment can be used for the treatment of dissections following conventional thrombectomy or remote endarterectomy. A recent evaluation of the Vascular Quality Initiative database revealed that hybrid treatment increased from 6.1% in 2010 to 32% in 2017 (P = 0.03). Interestingly, after propensity matching, hybrid treatment was associated with a significant reduction of the risk for myocardial infarction (1.9% vs 5.7%; P = 0.005) and renal complications (2.1% vs 6.7%; P = 0.003), and higher rate of discharge to home (90.8% vs 81.4%;

P < .001) compared with bypass grafting (Fareydooni, J Vasc Surg. 2020). Anyhow, because of the inhomogeneous nature of these procedures a long-term analysis is very difficult.

Until recently conservative treatment was considered the primary treatment option for patients with lifestyle limiting claudication (Aboyans, Eur Heart J. 2018). Although, revascularization is the cornerstone of CLTI treatment, there is growing evidence that conservative treatment can be an acceptable strategy for critical limb ischemia as well (Conte J Vasc Surg 2019). In the CRITISCH registry, the conservative approach reached the suggested objective performance goal for amputation free survival and had similar amputation and survival rates as primary revascularization (Stavroulakis, J Endovasc Ther). Benoit et al, showed that the continuous improvement in medical therapy changed the natural history of unreconstructable CLTI (Benoit, J Vasc Surg. 2012). A small retrospective cohort study, which evaluated the performance of invasive (revascularization within 6 weeks), deferred invasive (revascularization after 6 weeks), or permanently conservative treatment showed also comparable outcomes among the three groups (Santema, Eur J Vasc Endovasc Surg. 2017). These findings do not support that a primary conservative treatment should be offered in all CLTI patients, but that a conservative approach does not necessarily increase the risk for limb loss or mortality. Our analysis revealed that the WIfI class of the CLTI patient is an important prognostic factor for the fate of the affected limb (Beropoulis, J Vasc Surg 2016). Accordingly, and based on the current global guidelines, a conservative treatment should be suggested in patients with a very low and low WIfI score (Conte, J Vasc Surg 2019).

Finally, although limb salvage is one of the main goals of CTLI treatment a major amputation may be selectively offered as primary treatment strategy. In most patients the benefits of revascularization outweigh the risks, as a major amputation is associated with excessive trauma, morbidity, and mortality (Mustapha, J Am Heart Assoc. 2018). A non-ambulatory status, a limited life-expectancy (palliative care) or a high WIfI score with unreconstructable disease or severe comorbidity might indicate a major amputation as primary option. Of note, the evolution of PAD treatment offers alternative solutions for high-risk patients that were previously considered no-option or unreconstructable (figure 4) (Clair, Semin Vasc Surg. 2021). Thus, a major amputation should be offered from an interdisciplinary team in a CLTI center when all other options are either exhausted or carry a significant risk for the patient.

Figure 4: Deep vein arterialization in a ‘no-option’ patient with ‘desert-foot’, rest pain and minor tissue loss.



Future perspectives and research areas for PAD

Two ongoing trials will evaluate the efficacy of open and endovascular repair for CLTI, whereas a further study will prove the theoretical benefit of paclitaxel coated devices over conventional endovascular modalities. The Best Endovascular vs Best Surgical Therapy in Patients with Critical Limb Ischemia (BEST-CLI) trial is a prospective, multicenter, interdisciplinary randomized controlled trial designed to compare the clinical outcomes, cost-effectiveness, and quality of life following endovascular and surgical therapy in 2100 CLTI patients. The study enrolled patients mainly in North America. All currently available surgical and endovascular treatment options could be used and the choice of best therapy within the assigned treatment arm was at the discretion of the treating physician (Farber, J Vasc Surg. 2019). The British Bypass vs. Angioplasty in Severe Ischaemia of the Leg - 2 Trial (BASIL II) will randomize patients to 'vein bypass first' or 'best endovascular treatment first' for CLTI due to infra-popliteal disease. A subgroup analysis will be performed for patients with diabetes, CKD, and rest pain (Popplewell, Trials 2016). Both trials will have a significant impact on the treatment of CLTI patients, given the developments in this field since the publication of the initial BASIL trial 20 years ago. The

Swedish Drug-elution Trial in Peripheral Arterial Disease (SWEDEPAD) randomized registry will test the hypothesis that drug coated technology is superior to conventional endovascular treatment in a pragmatic cohort of patients (ClinicalTrials.gov Identifier: NCT02051088). The trial consists of 2 separate parallel studies, SWEDEPAD 1 for patients with claudication and SWEDEPAD 2 for CLTI individuals. This study is the first prospective, large scale, non-industry sponsored trial assessing paclitaxel coated devices. The initial analysis of this study was recently published and showed similar mortality rates between coated and uncoated devices (Nordastig, N Engl J Med. 2020).

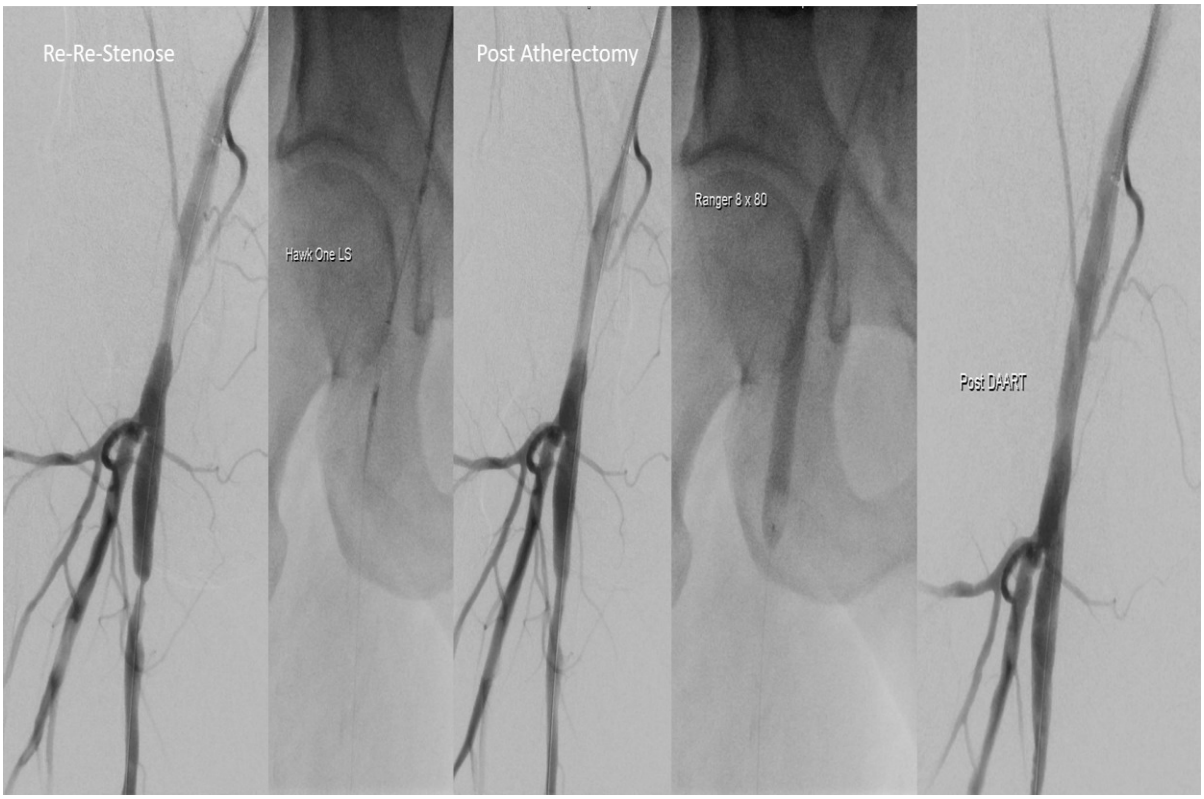
Common femoral atherosclerosis shows some similarities with the left main coronary disease. Like left main stenosis, surgical treatment is considered the standard of care, nonetheless there is a growing interest for percutaneous procedures (Mohr, Lancet. 2013). The PESTO-AFC study will randomize 306 participants to CFA endarterectomy or atherectomy in combination with DCB angioplasty (ClinicalTrials.gov Identifier: NCT02517827). Additionally, the SUPERSURG trial will compare the outcomes of the Supera interwoven stent (Abbott Medical, Illinois, USA) with surgery for CFA disease (NCT04349657). The exclusion of patients from both studies with severe medical comorbidities, advanced disease (Rutherford class 5 and 6) and complex lesions will limit their clinical relevance. There is no doubt that specific subgroups of patients with CFA disease might benefit from a minimally invasive approach, namely patients with restenosis after endarterectomy or bypass grafting, or individuals with severe obesity and/or comorbidity (figure 5). However, these subgroups are excluded from these trials and there is limited data to suggest that an endovascular approach is beneficial (Saratzis, Br J Surg. 2021). Although, a pragmatic non-industry sponsored, randomized 'Best Endovascular vs Best Surgical Therapy' trial would be essential for this anatomical region, this till now not planed.

Acute limb ischemia is a further clinical entity of the peripheral field that is not adequately examined. The last randomized trials were performed 30 years ago and mainly compared catheter directed thrombolysis with open repair (Björk, Eur J Vasc Endovasc Surg. 2020). Nowadays, endovascular thrombectomy devices allow not only the direct reperfusion of the limb but also the treatment of patients that were previously considered a contraindication for lysis. Our retrospective analysis showed an improved amputation free survival among patients with acute ischemia and active neoplastic disease, a subgroup that is not adequately evaluated

(Argyriou, J Endovasc Ther 2021). Unfortunately, published recommendations are based on retrospective studies or trials that do not represent the current standard of care (Björk, Eur J Vasc Endovasc Surg. 2020). In this context, a large-scale randomized trial is a true clinical need.

Finally, the development of commonly accepted reporting standards and clinical endpoints is of paramount important for future PAD studies. A standard classification of vascular calcium burden or lesion's length is still missing, and the definitions used vary significant among published studies and consensus documents (Stavroulakis, J Cardiovasc Surg (Torino) 2019). Furthermore, CLTI studies used till now the composite endpoint of major amputation and/or death as primary endpoint and did not evaluate other functional outcomes like wound healing or time to wound healing (Conte, J Vasc Surg 2019). Moreover, in specific subgroups of patients the assessment of not limb-related endpoints is necessary. In CKD patients, for instance, the progress of the renal impairment and the risk for acute kidney injury following open and endovascular repair remains unknown.

Figure 5: Directional atherectomy and drug coated balloon angioplasty for re-re-stenosis of the common femoral artery



Conclusions

Lower extremity atherosclerosis is an ongoing pandemic with significant clinical and socioeconomic impact. Endovascular treatment evolved rapidly and currently represents the first line treatment strategy for most patients with intermittent claudication and critical limb ischemia. The minimally invasive nature of the procedure offers a short-term benefit over surgery for frail individuals. Nonetheless, the durability of endovascular repair is questionable. Thus, young patients with acceptable perioperative risk would benefit from a primary open repair. Hybrid procedures, conservative treatment and primary amputation are further therapeutic options that should be offered to PAD/CLTI patients based on their clinical status, comorbidity, and lesions characteristics. The lack of large-scale studies, of high-quality evidence and commonly accepted reporting standards negatively influence the evidence approach of peripheral atherosclerosis.

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