Peripheral Atherectomy and Thrombectomy Devices

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

Aetna considers mechanical or laser peripheral atherectomy (atheroablation) medically necessary in members who meet all of the following criteria:

1. Member has symptomatic infrainguinal atherosclerotic arterial occlusive disease caused by atherosclerosis involving the femoral, popliteal, and/or infrapopliteal arteries (limb-threatening ischemia or functionally limiting claudication); and

2. Member can not be treated by standard angioplasty techniques alone, (i.e., balloon angioplasty, etc.); and

3. Either of the following:
   - Member has an eccentric lesion that does not dilate with conventional balloon angioplasty, or
   - Member has vein bypass graft stenosis.

Aetna considers mechanical or laser peripheral atherectomy experimental and investigational for all other indications, including peripheral atherectomy of the renal artery, visceral
artery, abdominal aorta, brachiocephalic trunk and branches, and iliac artery, because its effectiveness for these indications has not been established.

Aetna considers isolated segmental pharmacomechanical thrombolysis (Trellis Peripheral Infusion System) experimental and investigational for treatment of deep venous thromboses, Paget-Schroetter syndrome (also known as venous thoracic outlet syndrome) and other indications because there is inadequate evidence in the peer-reviewed published clinical literature regarding its effectiveness.

Aetna considers the use of FDA-approved drug-eluting balloons medically necessary for the treatment of primary lesion/occlusion of the femoropopliteal arteries.

Aetna considers the use of drug-eluting balloons for in vein grafts and dialysis/vascular accesses, and for the treatment of primary lesion/occlusion of other peripheral arteries experimental and investigational because its long-term effectiveness has not been established.

Aetna considers a drug-eluting balloon for mechanical or laser peripheral atherectomy experimental and investigational for the treatment of in-stent restenosis of peripheral arteries because there is inadequate evidence in the peer-reviewed published clinical literature regarding the effectiveness of this approach.

Aetna considers intravascular shockwave lithotripsy of the anterior tibial, common iliac, external iliac, internal iliac, popliteal, posterior tibial, peroneal arteries, and superficial femoral artery for the treatment of atherosclerosis / calcified peripheral arterial lesions / intermittent claudication experimental and investigational because the effectiveness of this approach has not been established.
See also

CPB 0568 - AngioJet Rheolytic Thrombectomy System
(../500_599/0568.html)

Notes:

The preferred technique for mechanical atherectomy involves the use of the Simpson Atherocath (directional atherectomy). Peripheral atherectomy/atheroablation with other mechanical or rotational devices or rotational aspiration atherectomy devices has not been shown to be effective.

Peripheral laser atherectomy is also known as peripheral laser angioplasty.

Background

Atherectomy was introduced in 1985 to improve upon the limitations of balloon angioplasty, primarily, abrupt reclosure and restenosis. Atherectomy devices cut and remove atherosclerotic plaque from a vessel wall or grind the atheroma into small particles, allowing them to embolize distally. Elastic recoil is reduced after atherectomy because the lumen is widened without stretching of the arterial wall.

Several types of atherectomy devices have been cleared by the U.S. Food and Drug Administration for peripheral use and primary success rates have been favorable with various devices; however, the Simpson Peripheral Atherocath has been the most widely used. This device has a circular cutter that spins at 2,000 rpm inside a metal housing with a window. Balloon inflation on the opposite side of the housing forces the plaque through the window where it is cut by advancing the rotating cutter in the housing. This device is best suited for
short, discrete, eccentric stenosis. The catheters are bulky and stiff to use in the tibial or tortuous vessels. Primary success rate have been 82 to 100 % with few complications.

Data support the use of atherectomy as effective in the peripheral vessels in patients who meet the following criteria: have symptomatic peripheral vascular disease (limb-threatening ischemia or functionally limiting claudication); and cannot be treated by standard angioplasty techniques alone, i.e., balloon angioplasty would be ineffective or is contraindicated; and have an eccentric lesion that does not dilate with conventional balloon angioplasty, or vein bypass graft stenosis.

Until the problem of restenosis can be solved, atherectomy is a reasonable treatment for symptomatic peripheral vascular disease (limb-threatening ischemia or functionally limiting claudication) only when balloon angioplasty may be ineffective or contraindicated.

Zeller et al (2007) reported a safety and efficacy study of the first rotational aspiration atherectomy system (Pathway PV) for the treatment of arterial lesions below the femoral bifurcation. A total of 15 patients (9 men; mean age of 71 +/- 9 years) with Rutherford stage 2 to 5 lower limb ischemia were enrolled at 3 study sites. Target lesions were in the superficial femoral (n = 7, 47 %), popliteal (n = 7, 47 %), and posterior tibial (n = 1, 6 %) arteries. Mean diameter stenosis was 97 % +/- 10 %; mean lesion length was 61 +/- 62 mm (range of 5 to 250). The primary study endpoint was the 30-day serious adverse event (SAE) rate. Interventional success (residual stenosis less than 30 %) was achieved in all lesions (100 %). Stand alone atherectomy was performed in 6 (40 %) patients, adjunctive balloon angioplasty in 7 (47 %), and stenting/endografting in 2 (13 %). The SAE rate at 30 days was 20 % (3/15), including 1 perforation due to an unrecognized displacement of the guidewire (sealed with an endograft), 1 false aneurysm at the puncture site (successful duplex-guided compression therapy),
and 1 dissection in conjunction with a distal embolism (stent implantation and aspiration thrombectomy). Primary patency rates measured by duplex ultrasound at 1 and 6 months were 100% and 73%, respectively; the target lesion revascularization (TLR) rate was 0% after 6 months. The ankle-brachial index increased significantly from 0.54 +/- 0.3 at baseline to 0.89 +/- 0.16, 0.88 +/- 0.19, and 0.81 +/- 0.20 (p < 0.05) at discharge, 1 month, and 6 months, respectively. Mean Rutherford categories were 2.92 +/- 1.19 (range of 1 to 5), 0.64 +/- 1.12 (range of 0 to 1), and 0.83 +/- 1.33 (range of 0 to 3) at the same time points (p < 0.05). The authors concluded that the application of this new atherectomy device was feasible in all cases. The serious adverse event rate was moderate; however, all events were solved during the index procedure. The 0% 6-month TLR rate is promising.

Mahmud et al (2007) noted that over the past decade, percutaneous revascularization therapies for the treatment of patients with peripheral arterial disease (PAD) have evolved tremendously, and a great number of patients can now be offered treatment options that are less invasive than traditional surgical options. With the surgical approach, there is significant symptomatic improvement, but the associated morbidity and mortality preclude its routine use. Although newer percutaneous treatment options are associated with lower procedural complications, the technical advances have outpaced the evaluation of these treatments in adequately designed clinical studies, and therapeutic options are available that may not have been rigorously investigated.

Bunting and Garcia (2007) stated that atherectomy is experiencing increased interest from endovascular specialists as a therapeutic treatment in the peripheral arteries. Long studied in the coronary vasculature, atherectomy has several theoretical advantages that make it uniquely suited for the peripheral circulation. In particular, infra-inguinal PAD experiences physiological stresses and forces that have made traditional percutaneous coronary treatments such as
angioplasty and stenting not as successful. Re-stenosis has been a major problem for angioplasty and stenting alone. The SilverHawk atherectomy device has favorable short-term data but important longer-term data are limited and need further study. Laser atherectomy also has favorable applications in niche patients but the number of studies is limited. Unfortunately, athero-ablative technologies for PAD require more definitive objective data regarding 12-month and longer-term outcomes in order to obtain widespread scientific acceptance.

Biskup et al (2008) noted that an atherectomy device (SilverHawk) had been approved by the Food and Drug Administration, but the results with its use are unclear. These investigators analyzed a series of consecutive patients undergoing atherectomy. They retrospectively reviewed the charts of 35 patients undergoing infra-inguinal (IF) atherectomy in 38 limbs. The Trans-Atlantic Inter-Society Consensus (TASC) classification and Society of Vascular Surgery run-off scores were calculated. Time to event analysis was performed using Kaplan-Meier estimates. Risk factors affecting patency were analyzed with a multi-variate Cox model. Mean patient age was 70 +/- 9.6 years. Indications for intervention were claudication (26 %), rest pain (21 %), and tissue loss (53 %). Femoro-popliteal (FP) atherectomy was performed in 68 % and tibial atherectomy in 32 %. For FP lesions, the TASC distribution was A, 42 %; B, 23 %; C, 4 %; and D, 15 %. The average lesion treatment length was 9.4 +/- 10.6 cm (range of 1 to 40), and the run-off score was 5.1 +/- 3.5. For tibial lesions, the TASC distribution was A, 0 %; B, 17 %; C, 8 %; and D, 75 %. The average lesion treatment length was 9.2 +/- 6.0 cm (range of 2 to 20), with a run-off score of 5.4 +/- 2.4. A total of 39 % of patients had prior IF interventions. Adjunctive angioplasty of the atherectomized lesion was performed in 55 % of cases, stenting in 0 %, and adjunctive therapy for tandem lesions in 39 %. The post-operative ankle-brachial index increased by 0.30 +/- 0.14 and toe pressures increased by 40 +/- 32.4 mm
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Hg. Mean follow-up was 10 +/- 8 months (range of 0.3 to 23). During the studied period, 7 patients required major limb amputation and 5 open surgical re-vascularization. Total primary and secondary patency rates were 66 % and 70 % at 1 year, respectively. Primary and secondary patency rates for FP atherectomy were 68 % and 73 % at 1 year, respectively. The limb salvage rate was 74 % at 6 months. Patients with prior interventions in the atherectomized segment had an almost 10-fold decrease in primary patency. Atherectomy produces acceptable results, similar to those in reported series of conventional balloon angioplasty/stenting. Patients with prior IF interventions had a nearly 10-fold decrease in primary patency. A greater than 6-fold decrease in patency rates was noted in patients who underwent simultaneous inflow or outflow procedures, but this finding did not reach statistical significance (p = 0.082). The authors stated that future studies should focus on cost comparisons with other treatments such as angioplasty and stenting, and prospective randomized trials should be performed to compare these treatment alternatives.

Garcia and Lyden (2009) noted that compared to conventional percutaneous transluminal angioplasty (PTA) and stent implantation for arterial occlusive diseases, atherectomy offers the theoretical advantages of eliminating stretch injury on arterial walls and reducing the, rate of restenosis. Historically, however, neither rotational nor directional atherectomy, whether used alone or with adjunctive PTA, has shown any significant long-term benefit over PTA alone in the coronary or peripheral arteries. However, the SilverHawk Plaque Excision System has produced positive results in single-center prospective registries of patients with FP and IF lesions, with reduced adjunctive PTA, minimal adjunctive stenting, and competitive 6-month and 12-month patency rates. In the observational non-randomized TALON (Treating Peripherals with SilverHawk: Outcomes Collection) registry, freedom from target lesion re-vascularization was 80 % for 87 patients at 12 months. Questions remaining for further research with this device include more accurate determination of an event rate.
for distal embolization, the appropriate use of distal protection, the value of and appropriate circumstances for adjunctive angioplasty, and definitive patency and clinical outcomes.

Indes et al (2010) evaluated the outcomes of atherectomy versus subintimal angioplasty (SIA) in patients with lower extremity arterial occlusive disease. From September 2005 through July 2006, 27 patients (17 women; mean age of 65 years, range of 37 to 85) underwent atherectomy of 46 lesions (11 TASC C/D occlusions) with the SilverHawk device. Results were compared to 67 patients (34 men; mean age of 69 years, range of 46 to 92) undergoing SIA for 67 lower extremity arterial occlusions from July 1999 through June 2004. Technical success in the atherectomy cohort was 100%. In the 11 patients with occlusions, symptoms improved in 10 and worsened in 1, but 9 (82.0%) of the 11 patients required re-intervention, and 8 (72.7%) patients with occlusive lesions re-occluded. Endovascular re-intervention was required to maintain primary patency in only 2 (12.5%) of 16 patients treated for stenotic lesions. At 1 year, the assisted primary patency was 37.7% in the atherectomy group. In the 11 patients with occlusive lesions, the patency rates were 36.8% and 12.3% at 6 and 9 months, respectively, versus 100% and 83.3% at the same time intervals in patients with stenotic lesions. Subintimal angioplasty was technically successful in 56 (83.6%) of 67 occlusions. The assisted primary patency and limb salvage rates of the entire group (intention-to-treat) at 12 and 24 months were 59.2% and 45.0%, respectively, while the assisted primary patency of the 56 technically successful SIAs at 12 and 24 months were 70.7% and 53.8%, respectively. Limb salvage for the entire group (intention-to-treat) was 90.6% and 87.9% at 12 and 24 months, respectively. The authors concluded that atherectomy may yield acceptable primary patency and limb salvage in patients with stenotic lesions. Many of the patients treated for occlusive lesions require re-intervention. Based on patency and limb salvage, SIA appears superior to atherectomy for the treatment of lower extremity occlusive disease.
Sixt and co-workers (2010) reported the acute and long-term outcome of Silverhawk-assisted atherectomy for femoropopliteal lesions. In this prospective study, de novo and re-stenotic lesions of the femoro-popliteal segments were treated with the Silverhawk device. A total of 161 consecutive patients (164 lesions) with PAD Rutherford classes 2 to 5 were included from June 2002 to October 2004 and October 2006 to June 2007 (59% male, mean age of 67 +/- 11 years, range of 40 to 88) and the outcome analyzed according to the TASC II classification. Directional atherectomy alone was performed successfully in 28% (n = 46), adjunctive balloon angioplasty in 65% (n = 107) and stenting in 7% (n = 11). The overall technical success rate was 76% (124/164) and the procedural success rate 95% (154/164). At 12 months primary patency rate was 61% (85/140) and the secondary patency rate was 75% (105/140) in the entire cohort, being less favorable in TASC D compared to TASC A to C lesions (p = 0.034 and p < 0.001, respectively). Furthermore, the re-stenosis rate differed trendwise (p = 0.06) between de novo and re-stenotic lesions. Changes in the ankle-brachial index (ABI) and the Rutherford classes were significantly in favor of TASC A to C lesions compared to TASC D after 12 months (p = 0.004). The event free survival (myocardial infarction, transient ischemic attack, or re-stenosis) was 48% at 12 months and 38.5% at 24 months. Predictor for re-stenosis in the multi-variable analysis was only male gender (p = 0.04). The authors concluded that the results in TASC D lesions are inferior to those in the lesser stages. Directional atherectomy of femoro-popliteal arteries showed a trend to better long-term technical and clinical outcome in de novo lesions compared to re-stenotic lesions.

Mohand and colleagues (2018) stated that peripheral atherectomy has been shown to have technical success in single-arm studies, but clinical advantages over angioplasty and stenting have not been demonstrated, leaving its role unclear. These investigators described patterns of atherectomy use in a real-world U.S. cohort to understand how it is currently being applied. The Vascular Quality Initiative
was queried to identify all patients who underwent peripheral vascular intervention from January 2010 to September 2016. Descriptive statistics were performed to analyze demographics of the patients, co-morbidities, indication, treatment modalities, and lesion characteristics. The intermittent claudication (IC) and critical limb ischemia (CLI) cohorts were analyzed separately. Of 85,605 limbs treated, treatment indication was IC in 51 % (n = 43,506) and CLI in 49 % (n = 42,099). Atherectomy was used in 15 % (n = 13,092) of cases, equivalently for IC (15 %; n = 6,674) and CLI (15 %; n = 6,418). There was regional variation in use of atherectomy, ranging from a low of 0 % in one region to a high of 32 % in another region. During the study period, there was a significant increase in the proportion of cases that used atherectomy (11 % in 2010 versus 18 % in 2016; p < 0.0001). Compared with non-atherectomy cases, those with atherectomy use had higher incidence of prior peripheral vascular intervention (IC, 55 % versus 43 % [p < 0.0001]; CLI, 47 % versus 41 % [p < 0.0001]), greater mean number of arteries treated (IC, 1.8 versus 1.6 [p < 0.0001]; CLI, 2.1 versus 1.7 [p < 0.0001]), and lower proportion of prior leg bypass (IC, 10 % versus 14 % [p < 0.0001]; CLI, 11 % versus 17 % [p < 0.0001]). There was lower incidence of failure to cross the lesion (IC, 1 % versus 4 % [p < 0.0001]; CLI, 4 % versus 7 % [p < 0.0001]); but higher incidence of distal embolization (IC, 1.9 % versus 0.8 % [p < 0.0001]; CLI, 3.0 % versus 1.4 % [p < 0.0001]) and, in the CLI cohort, arterial perforation (1.4 % versus 1.0 %; p = 0.01). The authors concluded that despite a lack of evidence for atherectomy over angioplasty and stenting, its use has increased across the U.S. from 2010 to 2016. It was applied equally to IC and CLI populations, with no identifiable pattern of co-morbidities or lesion characteristics, suggesting that indications were not clearly delineated or agreed on. This study placed impetus on further understanding of the optimal role for atherectomy and its long-term clinical benefit in the management of PAD.
In a retrospective, multi-center study, Loffroy and colleagues (2020) examined the safety and mid-term outcomes of Rotarex S rotational atherectomy plus thrombectomy device (Straub Medical AG, Wangs, Switzerland) with or without adjunctive treatment (e.g., percutaneous transluminal angioplasty, PTA/drug-coated balloon, DCB/stenting) in patients with ISR or occlusion in the iliac and/or infra-inguinal arteries. This trial included patients treated by in-stent percutaneous mechanical debulking (PMD) of the lower limbs with Rotarex S device between January 2013 and November 2018. The cohort consisted of 128 patients (88 men and 40 women), aged 39 to 94 years (mean of 66.7 ± 12 years). All patients presented with cardio-vascular risk factors. Overall, 51.5 % of patients had CLI. The study demonstrated a technical success of 96.9 % in the population with PMD and adjunctive PTA (95/128, 74.2 %) or adjunctive DCB (16/128, 12.5 %) or both (13/128, 10.2 %). At 12-months follow-up, the primary clinical success/patency rate was 92.3 % and the secondary clinical success/patency rate was 91.4 %. Rate of limb salvage was 93.7 %. Overall 32 (25 %) re-interventions were reported with mean time from Rotarex®S treatment to re-intervention of 7.1 ± 8.2 months; TLR was 19.5 % (25/128); 7 (5.5 %) patients developed distal embolism that responded to endovascular treatment. At mean follow-up, MAE observed were death (18/128, 14.1 %), MI (9/128, 7.0 %), stroke (2/128, 1.6 %) and renal failure (3/128, 2.3 %). The authors concluded that re-canalization with Rotarex S rotational atherectomy plus thrombectomy device was a practical choice for arterial ISR/occlusions of the iliac and/or infra-inguinal arteries, regardless of the age of the thrombus, with satisfying TLR. Only adjunctive PTA was often necessary to further improve the re-canalization. These researchers stated that these findings justified further research in the application of the therapy to determine cost/benefit.

The authors stated that this study had several drawbacks. First, this was a non-randomized, retrospective study with a modestly-sized cohort with absence of control group.
Furthermore, these investigators had heterogeneous population with different target vessels (iliac versus SFA versus popliteal artery (PA) versus combined), different stent occlusions like re-stenosis versus occlusion, acute thrombosis versus chronic thrombosis versus combined and the use of different techniques (debulking alone versus debulking + PTA versus debulking + DCB versus combined). They stated that the outcomes need to be confirmed in a larger study or randomized controlled trial (RCT) with longer follow-up.

Jaff et al (2010) analyzed therapeutic strategies, outcomes, and medical cost of treatment among Medicare patients with PAD. Patients who underwent therapy for PAD were identified from a 5% random sample of Medicare beneficiaries from Medicare Standard Analytic Files for the period 1999 to 2005. Clinical outcomes (death, amputation, new clinical symptoms related to PAD) and direct medical costs were examined by chosen re-vascularization options (endovascular, surgical, and combinations). One-year PAD prevalence increased steadily from 8.2% in 1999 to 9.5% in 2005. The risk-adjusted time to first post-treatment clinical outcome was lowest in those treated with PTA or atherectomy and stents (hazard ratio [HR], 0.829; 95% confidence interval [CI]: 0.793 to 0.865; p < 0.001) and stents only (HR, 0.904; 95% CI: 0.848 to 0.963; p = 0.002) compared with PTA alone. The lowest per patient risk-adjusted costs during the quarter of the first observed treatment were associated with "PTA and stents" ($15,197), and stents only ($15,867). Risk-adjusted costs for surgical procedures (bypass and endarterectomy) were $27,021 during the same period. Diabetes was present in 61.7% of the PAD population and was associated with higher risks of clinical events and higher medical costs compared with PAD patients without diabetes. The authors concluded that clinical and economic burden of PAD in the Medicare population is substantial, and the interventions used to treat PAD are associated with differences in clinical and economic outcomes. They stated that prospective cost-effectiveness
analyses should be included in future PAD therapy trials to inform payers and providers of the relative value of available treatment options.

Guidance from the National Institute for Health and Clinical Excellence (NICE, 2011) concluded that “current evidence on the efficacy of percutaneous atherectomy of femoropopliteal arterial lesions with plaque excision devices is inadequate in quality. Evidence on safety is inadequate, specifically with regard to the risk of distal embolisation. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research.” The NICE guidance stated that further research into percutaneous atherectomy of femoropopliteal arterial lesions with plaque excision devices should take the form of well-conducted trials, which should define patient selection, treatment protocols and location and types of arterial lesions treated, and report long-term patency outcomes.

An interventional procedure consultation document on percutaneous laser atherectomy for peripheral arterial disease from the National Institute for Health and Clinical Excellence (2011) concluded: “The evidence on percutaneous laser atherectomy for peripheral arterial disease raises no major safety concerns. Current evidence on its efficacy is inadequate in quantity and quality (in particular, the technical indications for the procedure are not well described in the published literature). Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research.” The consultation document stated that further research should describe the criteria for selection of patients and report clearly whether percutaneous laser atherectomy was used instead of conventional balloon angioplasty (and the reasons for this) or whether balloon angioplasty was attempted but found not to be feasible. In addition, reports should specify whether the procedure was used alone to recanalize arteries or with adjunctive balloon angioplasty and/or stenting. When percutaneous laser
atherectomy is used instead of balloon angioplasty, then studies should compare the outcomes of the two procedures. Reported outcomes should include objective evidence of arterial patency and blood flow in addition to clinical effects. The consultation documents noted that long-term follow-up (2 years and beyond) would be useful.

Guidance from the National Institute for Health and Clinical Excellence (NICE, 2012) on percutaneous laser angioplasty concluded: "Current evidence on the efficacy and safety of percutaneous laser atherectomy as an adjunct to balloon angioplasty (with or without stenting) for peripheral arterial disease is adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance, consent and audit." The guidance stated that patient selection should be carried out by a vascular multidisciplinary team including a vascular surgeon and a vascular interventional radiologist. The guidance stated that the multidisciplinary team should consider carefully whether using percutaneous laser atherectomy as an adjunct to balloon angioplasty (with or without stenting) for peripheral arterial disease is likely to have any benefits over conventional recanalization by balloon angioplasty (with or without stenting) alone. The specialist advisers to NICE listed key efficacy outcomes as an increase in arterial diameter and blood flow, tissue healing, symptom relief, improvement in quality of life, amputation-free survival and reintervention rates. The NICE committee noted that much of the evidence on this procedure is not recent, and that a limited amount of the older evidence described using laser alone for atherectomy but more recent evidence focused on its use as an adjunct to balloon angioplasty (with or without stenting). This more recent evidence and the advice of specialists underpinned the decision to evaluate laser recanalization as an adjunctive procedure. The NICE guidance noted, while the committee considered the evidence adequate to recommend normal arrangements for the use of percutaneous laser atherectomy as an adjunct to balloon angioplasty (with or without stenting),
it remained uncertain about whether its use confers any advantages over balloon angioplasty alone and, if so, in which patients.

The Trellis® Peripheral Infusion System has been developed as a percutaneous mechanical thrombectomy treatment for deep vein thrombosis (DVT) that does not respond adequately to anticoagulant and/or thrombolytic therapy. This system consists of a specially designed catheter that is connected to a handheld motorized control unit. Guided by ultrasonographic images, the Trellis catheter is inserted into an appropriate vein and advanced to the thrombosis. A guidewire is threaded through the clot; next the catheter is advanced into the clot so that the distal end of the catheter passes completely through the clot but the proximal end of the catheter does not enter the clot. At this point in the procedure, balloons in the proximal and distal ends of the catheter are inflated to seal off the section of the vein containing the clot, a thrombolytic agent is injected through the catheter into the clot, and the motor is activated, which causes rotation of a sinusoidally shaped wire that lies between the inflated balloons. The combined action of the thrombolytic agent and rotating wire disrupt the clot, and the disrupted material can be aspirated through the catheter. After clot removal, the balloons are deflated and the catheter is removed. The procedure using the Trellis system has been referred to as isolated segmental pharmacomechanical thrombolysis.

The Trellis Infusion System received FDA 515(k) clearance (K013635) on December 11, 2002. According to the clearance summary, the Trellis Infusion System is intended for controlled and selective infusion of physician-specified fluids, including thrombolytics, into the peripheral vasculature.

The Trellis Plus Infusion System received 510(k) clearance (K021958) on July 3, 2002. The system is intended for controlled and selective infusion of physician-specified fluids, including thrombolytics, into the peripheral vasculature.
The Trellis Reserve Infusion System received 510(k) clearance (K023514) on December 2, 2002. The Trellis Reserve Infusion System is intended for controlled and selective infusion of physician-specified fluids, including thrombolytics, into the peripheral vasculature.

A “Modification to the Trellis Reserve Infusion System” received 510(k) clearance (K032261) on August 22, 2003. According to the clearance summary, the Trellis Reserve Infusion System is intended for controlled and selective infusion of physician-specified fluids, including thrombolytics, into the peripheral vasculature. The Trellis Reserve Infusion System is equivalent to the predicate product, the original Trellis Reserve Infusion System. The indications for use, function, methods of manufacturing, and materials used are substantially equivalent. Bacchus Vascular, Inc. believes the Trellis Reserve Infusion System is substantially equivalent to existing legally marketed devices.

The Trellis-8 Peripheral Infusion System received 510(k) clearance (K050147) on February 3, 2005. According to the clearance summary the Trellis-8 Peripheral Infusion System is intended for controlled and selective infusion of physician specified fluids, including thrombolytics, into the peripheral vasculature.

The Trellis-6 Peripheral Infusion System received 510(k) clearance (K071664) on July 13, 2007. According to the clearance summary the Trellis-6 Peripheral Infusion System is intended for controlled and selective infusion of physician specified fluids, including thrombolytics, into the peripheral vasculature. The system enables the physician to isolate a treatment region, infuse a physician-specified fluid, and disperse the fluid by means of oscillation of a Dispersion Wire. The Isolation/Infusion component is a multi-lumen catheter with two compliant balloons at the distal end and infusion holes located between these balloons. The device also has a central through-lumen that is compatible with a 0.035"
guidewire. The Dispersion Wire provides oscillation when activated. The Dispersion Wire is connected to an integral Oscillation Drive Unit that oscillates the Dispersion Wire within the isolated region to further disperse the infused fluid. If desired by the physician, post procedure aspiration of the isolated area between the occluding balloons may be accomplished through the catheter by using the guidewire lumen.

Papantoniou et al (2013) stated that Paget-Schroetter syndrome (PSS) is a rare form of thoracic outlet syndrome caused by axillo-subclavian vein thrombosis that typically presents in healthy young adults. Prompt therapy, traditionally by means of catheter-directed thrombolysis (CDT) prior to definitive surgery, can prevent the subsequent onset of post-thrombotic syndrome (PTS) and considerable disability. As CDT is associated with major hemorrhage and high overall treatment cost, pharmaco-mechanical thrombectomy (PMT) seems to be an attractive alternative that combines pharmacological thrombolysis with mechanical clot disruption. The Trellis-8 peripheral infusion catheter is an example of such a treatment, which provides topical thrombolysis in an isolated zone. These investigators described the use of the Trellis-8 PMT system in the successful management of 3 patients with PSS.

In a Cochrane review, Wasiak and colleagues (2012) examined the effects of percutaneous transluminal coronary rotational atherectomy (PTCRA) for coronary artery disease in patients with non-complex and complex lesions (e.g., ostial, long or diffuse lesions or those arising from in-stent restenosis) of the coronary arteries. For the original review, these investigators searched the Heart Group Specialised Register; The Cochrane Library to Issue 2, 2001; and MEDLINE, CINAHL, EMBASE and Current Contents to December 2002 and reviewed reference lists for relevant articles. For the current review, they searched the same registries from 2002 to 2012 and reviewed reference lists for
relevant articles. These researchers included randomized and quasi-randomized controlled trials of PTCRA compared with placebo, no treatment or another intervention and excluded cross-over trials. Two review authors independently extracted data and assessed the risk of bias of the studies identified. Data were extracted independently by 2 review authors. They asked authors of trials to provide information when missing data were encountered. Statistical summaries used risk ratios (RR) and weighted mean differences. These researchers included 12 trials enrolling 3,474 patients. The overall risk of bias was unclear for the majority of articles due to a lack of reported data; however, the authors determined that this would be unlikely to impact negatively as most data outcomes were objective (e.g., death versus no death). There was no evidence of the effectiveness in improving patient outcomes of PTCRA in non-complex lesions. In complex lesions, there were no statistically significant differences in re-stenosis rates at 6 months (RR 1.05; 95 % confidence interval (CI): 0.83 to 1.33) and at 1 year (RR 1.21; 95 % CI: 0.95 to 1.55) in those receiving PTCRA with adjunctive balloon angioplasty (PTCA) (PTCRA/PTCA) compared to those receiving PTCA alone. Morphological characteristics distinguishing complex lesions have not been examined in parallel-arm randomized controlled trials. The evidence for the effectiveness of PTCRA in in-stent re-stenosis was unclear. Compared to angioplasty alone, PTCRA/PTCA did not result in a statistically significant increase in the risk of major adverse cardiac events (myocardial infarction (MI), emergency cardiac surgery or death) during the in-hospital period (RR 1.27; 95 % CI: 0.86 to 1.90). Compared to angioplasty, PTCRA was associated with 9 times the risk of an angiographically detectable vascular spasm (RR 9.23; 95 % CI: 4.61 to 18.47), 4 times the risk of perforation (RR 4.28; 95 % CI: 0.92 to 19.83) and about twice the risk of transient vessel occlusions (RR 2.49; 95 % CI: 1.25 to 4.99) while angiographic dissections (RR 0.48; 95 % CI: 0.34 to 0.68) and stents used as a bailout procedure (RR 0.29; 95 % CI: 0.09 to 0.87) were less common. The authors concluded that when conventional PTCA is feasible, PTCRA
appears to confer no additional benefits. There is limited published evidence and no long-term data to support the routine use of PTCRA in in-stent re-stenosis. Compared to angioplasty alone, PTCRA/PTCA did not result in a higher incidence of major adverse cardiac events, but patients were more likely to experience vascular spasm, perforation and transient vessel occlusion. In certain circumstances (e.g. patients ineligible for cardiac surgery, those with architecturally complex lesions, or those with lesions that fail PTCA), PTCRA may achieve satisfactory re-vascularization in subsequent procedures.

An UpToDate review on “Specialized revascularization devices in the management of coronary heart disease” (Cutlip, 2014) states that “Rotational atherectomy summary -- The American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions (ACC/AHA/SCAI) guideline update for PCI concluded that there is no evidence that rotational atherectomy improves late outcomes in lesions that can be safely treated with stenting or angioplasty alone. When rotational atherectomy is being considered, the weight of evidence or opinion was in favor of the efficacy of IVUS for establishing the presence and distribution and coronary calcium. However, in our practices, IVUS is rarely used for this indication”.

In a meta-analysis, Yang and colleagues (2014) evaluated the clinical value of primary stenting for treating PADs in below-the-knee arteries by comparing to PTA. PubMed, ScienceDirect, Embase, and CBM databases were searched for relevant articles. Based on the different types of stents, these researchers divided the primary stent group into the bare metal stent (BMS) group and drug-eluting stent (DES) group. The outcome measures were immediate technical success, freedom from target vessel revascularization (TVR-free) rate and limb salvage. A total of 14 studies (published between 2001 and 2012) satisfying the inclusion criteria were
identified; 3,278 patients and 3,699 limbs constituted the final study population. The technical success rate of PTA was 90.95 % (95 % CI: 86.25 % to 94.15 %). Only 1 study reported a technical failure of 4 % (5/118) in the primary stent group. There were no significant differences in the 1-year primary patency and TVR-free rates between the PTA group and BMS groups (p > 0.05 and p > 0.05), respectively. The pooled estimates of 1-year primary patency and TVR-free rate in DES group were 85.05 % (95 % CI: 79.95 % to 89.02 %) and 90.52 % (95 % CI: 83.68 % to 94.67 %), respectively, which were better than those of the BMS (p < 0.001) and PTA groups (p < 0.001). The pooled estimate of 1-year limb salvage in the PTA, BMS, and DES groups was 88.41 % (95 % CI: 84.53 % to 91.43 %), 94.41 % (95 % CI: 89.52 % to 97.1 %), and 96.81 % (95 % CI: 94.04 % to 98.32 %), respectively. The BMS and DES groups had higher limb salvage rates than the PTA group (p < 0.001 for both comparisons). The rates of severe complications were low both in the PTA and primary stent groups. Although the influence analysis showed rather robust results, the heterogeneity was quite high and they were not adjusted for confounding variables. The authors concluded that primary BMS implantation had no advantage over PTA in reducing restenosis or re-vascularization for infra-popliteal disease; primary DES implantation appeared to be a promising treatment for focal infra-popliteal lesions. (The MeSH terms of this article included balloon).

In a Cochrane review, Chowdhury et al (2014) determined the effect of percutaneous transluminal angioplasty (PTA) compared with PTA with bare metal stenting (BMS) for superficial femoral artery (SFA) stenoses on vessel patency in people with symptomatic (Rutherford categories 1 to 6; Fontaine stages II to IV) lower limb peripheral vascular disease. In addition, these researchers assessed the efficacy of PTA and stenting in improving quality of life, ankle brachial index (ABI) and treadmill walking distance. For this update the Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator searched the Specialised Register (last searched...
August 2013) and the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 6, 2013). Randomized trials of angioplasty alone versus angioplasty with BMS for the treatment of superficial femoral artery stenosis were selected for analysis. Two review authors independently selected suitable trials, assessed trial quality and extracted data. Furthermore, these 2 review authors performed assessments of methodological quality and wrote the final manuscript. The third review author (ADM) cross-checked all stages of the review process. These investigators included 3 new studies in this update, making a total of 11 included trials with 1,387 participants. The average age was 69 years and all trials included men and women. Participants were followed for up to 2 years. There was an improvement in primary duplex patency at 6 and 12 months in participants treated with PTA plus stent over lesions treated with PTA alone (6 months: odds ratio (OR) 2.90, 95% confidence interval (CI): 1.17 to 7.18, p = 0.02, 6 studies, 578 participants; 12 months: OR 1.78, 95% CI: 1.02 to 3.10, p = 0.04, 9 studies, 858 participants). This was lost by 24 months (p = 0.06). There was a significant angiographic patency benefit at 6 months (OR 2.49, 95% CI: 1.49 to 4.17, p = 0.0005, 4 studies, 329 participants) which was lost by 12 months (OR 1.30, 95% CI: 0.84 to 2.00, p = 0.24, 5 studies, 384 participants); ABI and treadmill walking distance showed no improvement at 12 months (p = 0.49 and p = 0.57, respectively) between participants treated with PTA alone or PTA with stent insertion. Three trials (660 participants) reported quality of life, which showed no significant difference between participants treated with PTA alone or PTA with stent insertion at any time interval. Anti-platelet therapy protocols and inclusion criteria regarding affected arteries between trials showed marked heterogeneity. The authors concluded that although there was a short-term gain in primary patency there was no sustained benefit from primary stenting (PS) of lesions of the superficial femoral artery in addition to angioplasty. Moreover, they stated that future trials should focus on quality of life for claudication and limb salvage for critical ischemia.
Antoniou et al (2014) examined if treatment of infra-inguinal arterial occlusive disease with drug-eluting stents (DESs) provided improved outcomes compared with BMSs or PTA alone. Altogether, 136 papers were found using the reported searches, of which 5 provided the best evidence to answer the question. All papers represent either level 1 or 2 evidence. The authors, journal, date, country of publication, patient group studied, study type, relevant outcomes and results of these papers are tabulated. Main outcome measures varied among the studies, and included patency, in-stent restenosis, target lesion revascularization, major adverse events, clinical improvement and limb salvage. Evidence on the comparative efficacy of DESs in femoro-popliteal arterial disease is mainly based on 2 RCTs. Paclitaxel-eluting stents were evaluated in the Zilver PTX trial and demonstrated superior 2-year results to either BMSs or PTA, as indicated/shown by patency (DES versus PTA, 74.8 versus 26.5 %, p < 0.01), clinical benefit (DES versus PTA, P < 0.01) and event-free survival (DES vs PTA, 86.6 vs 77.9%, P = 0.02). However, the SIROCCO trial found that the sirolimus-eluting stent did not exhibit statistically significant differences in 2-year in-stent re-stenosis (22.9 versus 21.1 %) and target lesion re-vascularization (6 versus 13 %) compared with the BMS. Treatment of infra-politeal arterial disease with DESs was related with superior outcomes to those of BMSs, as indicated/shown by patency, freedom from target lesion revascularization and freedom from major adverse events. Furthermore, the ACHILLES trial, the only published trial comparing the infra-popliteal DES with PTA, revealed lower angiographic restenosis (22.4 versus 41.9 %, p = 0.019) and greater vessel patency (75 versus 57.1 %, p = 0.025) in the DES group at 1 year. However, data related to clinical parameters in patients with critical limb ischemia secondary to infra-geniculate arterial disease, such as limb salvage and ulcer healing, are insufficient. The authors concluded that treatment of infra-inguinal arterial disease with DES was safe and appeared to be superior to treatment with
PTA alone or BMS. They stated that the role of DES in sustained improvement in clinical outcome end-points, such as limb salvage, remains to be elucidated.

**Drug-Eluting (Drug-Coated) Balloons for the Treatment of Primary Lesion / Occlusion of Peripheral Arteries**

In a multi-center, randomized non-inferiority trial, Baan and colleagues (2018) evaluated the relative performance of a DEB and a DES in patients with any (bare-metal or drug-eluting stent) ISR. Patients with any ISR were randomly allocated in a 1:1 fashion to treatment with a DEB or a DES. The primary end-point was non-inferiority in terms of in-segment minimal lumen diameter (MLD) at 6-month angiographic follow-up. Secondary end-points included angiographic parameters at 6 months and clinical follow-up up to 12 months. A total of 278 patients, of whom 56 % had DES-ISR, were randomized at 8 sites to treatment with DEB (n = 141) or DES (n = 137). As compared with DEB, DES was associated with larger MLD and lower % stenosis immediately post-procedure (1.84 ± 0.46 versus 1.72 ± 0.35; p = 0.018; and 26 ± 10 % versus 30 ± 10%; p = 0.03). Angiographic follow-up was completed at 196 ± 53 days in 79 % of patients. With respect to the primary end-point of in-segment MLD at 6 months, DEB was non-inferior to DES (DEB 1.71 ± 0.51 mm versus DES 1.74 ± 0.61 mm; p for non-inferiority < 0.0001); TVR at 12-month follow-up was similar in both groups (DES 7.1 % versus DEB 8.8 %; p = 0.65). The authors concluded that in patients with ISR, treatment with DEB was non-inferior compared with DES in terms of 6-month MLD. There were no differences in clinical end-points, including TVR up to 12 months. Therefore, use of a DEB is an attractive therapeutic option for ISR, withholding the need for additional stent implantation. Longer follow-up data are needed to validate these findings.

Beschorner and Zeller (2014) stated that mechanical atherectomy for in-stent restenosis (ISR) appeared to be
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Limited by a low patency rate. This might be due to the mechanical trauma that induces an inflammatory response leading to recurrent ISR. Addition of drug-eluting balloon (DEB) angioplasty could overcome these challenges while preserving the advantages of a better acute result. However, the authors concluded that due to lack of clinical data, combination of atherectomy and DEB remains an experimental procedure for ISR treatment.

The Australian Safety and Efficacy Registry of New Interventional Procedures’ Technology Brief on “Drug-eluting stents and balloons for the treatment of peripheral vascular disease” (2012) considered DEBs to be investigational.

There is Cochrane “protocol” to evaluate the effectiveness of DEBs compared with non-stenting balloon angioplasty in patients with symptomatic lower-limb PAD (Kayssi et al, 2014).

Limpijankit (2015) stated that “Over the past decade, drug-coated balloons (DCBs) have emerged as an exciting new therapeutic option to prevent restenosis in the treatment of peripheral vascular disease …. In this year, 3 major pivotal trials have confirmed the safety and efficacy of paclitaxel-coated balloons in the endovascular treatment of femoropopliteal artery disease. These are the Drug-Coated Balloon Versus Standard Percutaneous Transluminal Angioplasty for the Treatment of Superficial Femoral and/or Popliteal Peripheral Artery Disease (IN.PACT SFA) trial, the Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis 2 (LEVANT 2) trial, and 5-year follow-up of the Local Taxan With Short Time Contact for Reduction of Restenosis in Distal Arteries (THUNDER) trial …. Although the initial findings are encouraging, long-term follow-up will be useful in determining whether the benefit of these new devices is sustained, increased, or attenuated over time. In the LEVANT 2 trial, the primary patency endpoint from the Kaplan-Meier curves seem to drop distinctly in the Lutonix arm after 12 months, while the control arm remained unchanged.
.... although DCBs are generally safe and superior to standard balloon angioplasty, there are many unanswered questions about DCB technology. The results of these trials cannot be generalized to patients not included in these trials. Future studies should be performed in longer lesions, densely calcified lesions, or in-stent restenosis, and consider comparison with bare metal stents and drug-eluting stents. Trials combining DCBs with atherectomy (Atherectomy Followed by a Drug Coated Balloon to Treat Peripheral Arterial Disease [DEFINITIVE AR] trial) are being conducted to clarify if there is an additive effect. Another inconclusive issue is the appropriateness use of these devices. Which patient should be a good candidate for using these DCBs as the first-line therapy instead of standard balloon? In order to justify their broad use, the DCBs must show reduction in repeat revascularization, cost benefit, and improving quality of life. Another concern is the learning curve of how to use the DCBs to ensure proper uptake of the drug and minimize downstream drug loss. This is important to maximize the results of treatment. Post-approval study is also suitable for longer-term follow-up, which is certainly needed to confirm the durability of the benefit.

In a Cochrane review, Bekken et al (2015) examined the effects of PTA versus PS for stenotic and occlusive lesions of the iliac artery. The Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator searched the Specialised Register (last searched April 2015) and Cochrane Register of Studies (CRS) (Issue 3, 2015). The TSC searched trial databases for details of ongoing and unpublished studies. These researchers included all RCTs comparing PTA and primary stenting for iliac artery occlusive disease. They excluded quasi-randomized trials, case reports, case-control or cohort studies. They excluded no studies based on the language of publication. Two authors independently selected suitable trials. JB and HJ independently performed data extraction and trial quality assessment. When there was disagreement, consensus would be reached first by discussion.
among both authors and, if still no consensus could be reached, through consultation with BF. These investigators identified 2 RCTs with a combined total of 397 participants as meeting the selection criteria. One study included mostly stenotic lesions (95%), whereas the second study included only iliac artery occlusions. Both studies were of moderate methodological quality with some risk of bias relating to selective reporting and non-blinding of participants and personnel. The overall quality of evidence was low due to the small number of included studies, the differences in study populations and definitions of the outcome variables. Due to the heterogeneity among these 2 studies it was not possible to pool the data. Percutaneous transluminal angioplasty with selective stenting and primary stenting (PS) resulted in similar improvement in the stage of peripheral arterial occlusive disease according to Rutherford's criteria, resolution of symptoms and signs, improvement of quality of life, technical success of the procedure and patency of the treated vessel. Improvement in walking distance as reported by the patient, measured claudication distance, ulcer healing, major amputation-free survival and delayed complications (greater than 72 hours) were not reported in either of the studies. In 1 trial, PTA of iliac artery occlusions resulted in a significantly higher rate of major complications, especially distal embolization. The other trial showed a significantly higher mean ABI at 2 years in the PTA group (1.0) compared to the mean ABI in the PS group (0.91); mean difference (MD) 0.09 (95% CI: 0.04 to 0.14; p value = 0.001, analysis performed by review authors). However, at other time-points there was no difference. These researchers considered it unlikely that this difference was attributable to the study procedure, and also believed this difference may not be clinically relevant. The authors concluded that there is insufficient evidence to assess the effects of PTA versus PS for stenotic and occlusive lesions of the iliac artery. From 1 study it appeared that PS in iliac artery occlusions may result in lower distal embolization rates. They stated that more studies are needed to come to a firm conclusion.
Furthermore, an UpToDate review on “Percutaneous interventional procedures in the patient with lower extremity claudication” (Zaetta et al, 2016) states that “Drug-eluting balloons -- A number of medical therapies aimed at preventing restenosis after femoral PTA have been tried, but only local delivery of paclitaxel has been shown to improve outcomes. Local delivery of paclitaxel was initially studied in the coronary circulation, but subsequently drug-eluting balloons (e.g., Lutonix, IN.PACT Admiral) have been approved for use in the United States as a means to deliver paclitaxel and have been used in the femoropopliteal segment. Whether the reduced number of interventions that results offsets the additional expense of the drug-coated balloon remains to be determined”.

Herten et al (2016) stated that PAD, particularly critical limb ischemia, is an area with urgent need for optimized therapies because; to-date, vascular interventions often have limited life spans. In spite of initial encouraging technical success after femoro-popliteal percutaneous transluminal angioplasty or stenting, post-procedural re-stenosis remains the major problem. The challenging idea behind the DCB concept is the biological modification of the injury response after balloon dilatation. Anti-proliferative drugs administered via DCBs or drug-eluting stents are able to suppress neointimal hyperplasia, the main cause of re-stenosis. These investigators reviewed the results of DCB treatments of femoro-popliteal and infra-popliteal lesions in comparison to standard angioplasty with uncoated balloons. A systematic literature search was performed in (i) medical journals (i.e., Medline), (ii) international registers for clinical studies (i.e., www.clinicaltrials.gov), and (iii) abstracts of scientific sessions. Several RCTs with follow-up periods of up to 5 years demonstrated the effectiveness of paclitaxel-DCB technology. However, calcified lesions appeared to affect the effectiveness of DCB. Combinations of pre-conditioning methods with DCBs showed promising results. Although the
mechanical abrasion of calcium via atherectomy or laser ablation showed favorable peri-procedural results, the long-term impact on re-stenosis and clinical outcome has to be demonstrated. Major advantages of the DCBs are the rapid delivery of drug at uniform concentrations with a single dose, their effectiveness in areas wherein stents have been contraindicated until now (i.e., bifurcation, ostial lesions), and in leaving no stent scaffold behind. Re-interventions are easier to perform because DCBs leave no metal behind. The authors concluded that various combinations of DCBs with other treatment modalities may prove to be viable options in future; there is still a lack of respectable prospective long-term data to state the long-term superiority of one DCB technology.

Steiner et al (2016) examined patient outcomes following the use of the Lutonix DCB in patients undergoing endovascular intervention in below-the-knee (BTK) arteries. A retrospective chart review identified 248 patients who were treated for symptomatic PAD with the Lutonix DCB between May 2013 and October 2014. A total of 40 patients were lost to follow-up, leaving 208 patients (mean age of 74.1±9.7 years; 138 men) with evaluable data for outcome analysis. The patient cohort suffered from either severe claudication (38.6 %) or CLI (61.4 %) in 220 limbs. Almost 2/3 (140, 63.6 %) of the 220 target lesions were total occlusions, and 37 (17.8 %) of all patients had occlusion of all 3 BTK vessels before intervention. Over a median 9-month follow-up, TLR occurred in 15.9 % of patients with an average time to first re-intervention of 8 months. In total, 39 amputations were performed in 31 limbs. However, 17 of these amputations were pre-planned minor amputations below the ankle; only 9 (4.1 %) major amputations occurred corresponding to 6.6 % of the CLI cohort. Freedom from the composite of death or major amputation was estimated as 92 % and 85 % at 6 and 12 months, respectively, by Kaplan-Meier analysis. In the full cohort, improvement of at least 1 Rutherford category was seen in 130 (59.1 %) limbs after 1 year or at the last follow-up, with 104 (80.0 %) of those limbs showing an improvement of
greater than or equal to 2 categories. The authors concluded that from this single-center experience, the Lutonix DCB showed therapeutic promise in a disease state where new treatment options are needed.

In a prospective, single-center, non-randomized study, Werner et al (2016) evaluated the safety and effectiveness of the Igaki-Tamai biodegradable scaffold after DEB angioplasty in patients with occlusive SFA disease. A total of 20 patients (mean age 66.7 ± 11.6 years; 14 men) with symptomatic de-novo SFA lesions undergoing angioplasty with the In.Pact Admiral paclitaxel-coated balloon and subsequent implantation of the Igaki-Tamai bioresorbable scaffold were included in this study. All patients were claudicants. The average diameter stenosis was 89.7%, and the mean length was 43.6 mm.

Clinical examinations with duplex sonography were performed after 1, 6, 9, and 12 months. The main study outcomes were technical success, re-stenosis, TLR, ABI improvement, and changes in quality of life (QOL) evaluated with the walking impairment questionnaire. Safety was assessed by monitoring the occurrence of AEs. Angioplasty with a paclitaxel-coated balloon was performed in all patients, resulting in an average diameter stenosis of 24%. Subsequent implantation of the Igaki-Tamai scaffold reduced the average diameter stenosis to 3.5%. In the first 6 months, 2 cases of re-stenosis were reported, with no TLRs within that period. However, by the 12-month follow-up in 19 patients, 11 patients had lost in-stent patency. Among these patients, 8 had TLRs, which were the only AEs recorded that were referable to the procedure; QOL assessments showed improvement in the majority of patients.

The authors concluded that the findings of the GAIA-DEB study showed that DEB treatment of the femoral artery prior to the implantation of the biodegradable Igaki-Tamai scaffold was safe; however, the anti-proliferative actions of paclitaxel in the vessel wall were not effective in preventing re-stenosis, which occurred predominantly after 6 months.
Grotti et al (2016) reported the 3-year safety and effectiveness outcomes from the prospective all-comers DEBATE-ISR study of symptomatic diabetic patients with femoro-popliteal ISR undergoing treatment with paclitaxel-eluting balloons compared with historical diabetic controls. From January 2010 to December 2011, a total of 44 consecutive diabetic patients (mean age of 74 ± 11 years; 32 men) were treated with DEBs and enrolled in the study. The control group comprised 42 consecutive diabetic patients (mean age 76 ± 7 years; 23 men) treated with conventional balloon angioplasty (BA) from 2008 to 2009. No significant differences in terms of clinical, angiographic, or procedural characteristics were observed between the study groups; CLI was present in the majority of patients. Tosaka class III ISR was observed in more than 50 % of the patients. Mean lesion length was 132 ± 86 and 137 ± 82 mm in the DEB and BA groups, respectively (p = 0.7). At 3-year follow-up, the rate of TLR was 40 % in the DEB group versus 43 % in the BA group (p = 0.8); Kaplan-Meier analysis showed no significant differences in terms of freedom from TLR. The presence of a Tosaka class III occlusion was associated with a worse outcome in both study groups (OR 3.96, 95 % CI: 1.55 to 10.1, p = 0.004). The authors concluded that using DEBs for femoro-popliteal ISR yielded similar results to BA in terms of TLR at 3-year follow-up. The treatment of more complex ISR lesions was associated with an increased rate of TLR, irrespective of the technology used.

In a Cochrane review, Kayssi et al (2016) evaluated the effectiveness of DEBs compared with uncoated, non-stenting balloon angioplasty in people with symptomatic lower-limb PAD. The authors concluded that based on a meta-analysis of 11 trials with 1,838 participants, there is evidence of an advantage for DEBs compared with uncoated balloon angioplasty in several anatomic end-points (e.g., primary vessel patency [high-quality evidence], binary restenosis rate [moderate-quality evidence], and target lesion revascularization [low-quality evidence] for up to 12 months). On the other hand, there is no evidence of an advantage for
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DEBs in clinical end-points (e.g., amputation, death, or change in ABI, or change in Rutherford category during 12 months’ follow-up). They stated that well-designed randomized trials with long-term follow-up are needed to compare DEBs with uncoated balloon angioplasties adequately for both anatomic and clinical study end-points before the widespread use of this expensive technology can be justified. An editorial (Richards, 2017) noted: "Advances in technology continue relentlessly, but not necessarily for patient benefit? This meta-analysis highlights this problem; 11 trials compared drug eluting angioplasty technology compared to simple angioplasty. Radiological results were better in the short to mid-term but there with no effect on any patient outcomes. Therefore, should the NHS use these devices? On-going NIHR HTA BASIL 2 & BASIL 3 trials are running to compare angioplasty (with or without drug coated balloons to surgical bypass.”

In a prospective, single-arm, multi-center study, Schroeder et al (2015) evaluated the safety and effectiveness of the Stellarex DCB to inhibit re-stenosis in the superficial femoral and/or popliteal artery. This trial enrolled 50 patients with 58 lesions in the first cohort that needed pre-dilatation with an uncoated angioplasty balloon prior to inflation of the DCB. The primary effectiveness end-point was 6-month late lumen loss (LLL). The major secondary end-point was major AE (MAE) rate at 6 months, defined as cardiovascular death, amputation, and/or ischemia-driven TLR. The mean lesion length was 7.2 cm and baseline stenosis was 75.1 %. Calcification was present in 62.1 % of lesions and 12.1 % were occluded. Both end-points met their pre-specified performance goals; at 6 months, the MAE rate was 4 % and the mean LLL was 0.54 mm. The primary patency rate was 89.5 % at 12 months and 80.3 % at 24 months. The freedom from clinically-driven TLR rate, per Kaplan-Meier estimate, was 90.0 % at 12 months and 85.8 % at 24 months. Additionally, there were no amputations or cardiovascular deaths reported through 24 months. The
authors concluded that the Stellarex DCB provided safe and durable clinical outcomes for treatment of femoropopliteal artery disease through 24 months.

The drawbacks of this study included the lack of randomization and small proportion of chronic total occlusions (CTOs; 12.1%). However, all occluded lesions were patent through 24 months, which suggested adequate effectiveness of this DCB in CTOs. These researchers stated that further assessment in complex disease is needed. The study also lacked objective criteria for the exclusion criterion “prohibitive” calcification, which may have left room for investigator bias. They stated that larger studies with robust designs are currently enrolling patients, including 2 RCTs and 1 global registry.

In a prospective, randomized, multi-center, single-blinded trial, Schroeder et al (2017a) evaluated the safety and effectiveness of a next-generation low-dose (2-µg/mm² surface dose of paclitaxel) DCB. Patients were randomized (3:1) to treatment with a low-dose DCB or an uncoated PTA balloon. The primary safety end-point was a composite of freedom from device- and procedure-related death through 30 days after the procedure and freedom from target limb major amputation and clinically driven TLR through 12 months after the procedure. The primary effectiveness end-point was primary patency at 12 months. Patients were randomized to treatment with a DCB (222 patients, 254 lesions) or uncoated PTA balloon (72 patients, 79 lesions) after successful pre-dilatation. Mean lesion length was 7.2 and 7.1 cm, and 19.2 % and 19.0 % of lesions represented total occlusions, respectively. The primary safety end-point was met, and superiority was demonstrated; freedom from a primary safety event was 94.1 % (193 of 205) with DCB and 83.3 % (50 of 60) with PTA, for a difference of 10.8 % (95 % CI: 0.9 % to 23.0 %). The primary effectiveness end-point was met, and superiority of DCB over PTA was achieved (83.9 % [188 of 224] versus 60.6 % [40 of 66]; p < 0.001). Outcomes with DCB were also superior to PTA per the Kaplan-Meier estimate for primary patency (89.0 % versus
65.0 % at 365 days; log-rank p < 0.001) and for rates of clinically driven TLR (5.9 % versus 16.7 %; p = 0.014). The authors concluded that superiority with a low-dose DCB for femoropopliteal interventions was demonstrated over PTA for both the safety and effectiveness end-points.

This study had several drawbacks. First, although the Clinical Events Committee, Data Safety and Monitoring Board, and core laboratory personnel were blinded to treatment, physicians were not blinded because of the visible coating on the DCB catheter. Secondly, these data cannot be generalized to other DCBs because head-to-head comparative trials have not been completed, and lastly, patients were selected with the use of strict inclusion and exclusion criteria; therefore, generalizability of these data to real-world cases may be limited.

In a prospective, multi-center, pilot study, Schroeder and colleagues (2017b) compared 2-year outcomes in patients treated with or without pre-dilatation prior to DCB angioplasty for symptomatic femoropopliteal lesions. This pilot study was conducted at 3 sites in Germany. It compared claudicants undergoing pre-dilatation with a bare PTA balloon before DCB (pre-dilatation group) with patients undergoing direct DCB (direct DCB group). Patients were followed for 2 years. Outcomes included late lumen loss at 6 months, and ABI, MAE, and primary patency at 2 years. A Clinical Events Committee and core laboratories analyzed AEs and angiographic/duplex images, respectively. Between December 2011 and November 2012, a total of 50 patients were enrolled to the pre-dilatation group (12 % total occlusions) and 28 to the direct DCB group (5 % total occlusions). Follow-up compliance at the 2 year visit was 88 % (n = 44) and 86 % (n = 24), respectively. Late lumen loss at 6 months was lower in the direct DCB group (0.03 ± 0.68 mm versus 0.54 ± 0.97 mm; p = .01); MAE over 2 years occurred in 7 (15 %) patients who underwent pre-dilatation and in 5 (19 %) after direct DCB. Mean ABI at 2 years was 0.94 ± 0.15.
after pre-dilatation and 1.0 ± 0.12 after direct DCB. Over 2 years, primary patency (80.3 % versus 78.2 %; p = 0.55) was not statistically different between the groups. After propensity score adjustments, 2 year findings remained unchanged. The authors concluded that paclitaxel-coated PTA, with or without bare pre-dilatation, was effective over 2 years in symptomatic patients with femoropopliteal stenotic lesions; these findings should be considered preliminary and hypothesis-generating. Moreover, they stated that adequately powered RCTs of direct DCB use with or without pre-dilatation are needed to confirm these preliminary findings.

A major drawback of this study was its non-randomized sequential treatment allocation. Despite the use of propensity score co-variate adjustment, potentially confounding unmeasured variables (e.g., balloon inflation time) may introduce bias. These results may not be generalizable to total occlusions, which represented less than 10 % of lesions. Another main drawback of this pilot study was a small sample size (n = 28 in the DCB group) that was not specifically powered to detect clinically important differences between groups.

Krishnan and associates (2017) noted that DCB are a predominant revascularization therapy for symptomatic femoropopliteal artery disease. Due to differences in excipients, paclitaxel dose and coating morphologies, varying clinical outcomes have been observed with different DCBs. These investigators reported the findings of 2 studies investigating the pharmacokinetic (PK) and clinical outcomes of a new DCB in the treatment of femoropopliteal disease. In the ILLUMENATE Pivotal Study, a total of 300 symptomatic patients (Rutherford class 2 to 4), were randomized to DCB (n = 200) or PTA (n = 100). The primary safety end-point was freedom from device- and procedure-related death through 30 days, and freedom from target limb major amputation and clinically-driven TLR (CD-TLR) through 12-months. The primary effectiveness end-point was primary patency through
12-months. In the ILLUMENATE PK study, paclitaxel plasma concentrations were measured after last DCB deployment and at pre-specified times (1, 4, 24 hours and at 7 and 14 days post-procedure) until no longer detectable. In the Pivotal study, baseline characteristics were similar between groups; 50% had diabetes, 41% were women, mean lesion length was 8.3 cm and 44% were severely calcified. The primary safety endpoint was met (92.1% for DCB versus 83.2% for PTA, p = 0.025 for superiority) and the primary patency rate was significantly higher with DCB (76.3% for DCB versus 57.6% for PTA, p = 0.003). Primary patency per Kaplan Meier estimates at day 365 was 82.3% for DCB versus 70.9% for PTA (p = 0.002). The rate of CD-TLR was significantly lower in the DCB cohort (7.9% versus 16.8%, p = 0.023). Improvements in ABI, Rutherford class, and QOL were comparable, but the PTA cohort needed twice as many revascularizations; PK outcomes showed all patients had detectable paclitaxel levels after DCB deployment that declined within the first hour (54.4 ± 116.9 ng/ml to 1.4 ± 1.0 ng/ml). The authors concluded that the Stellarex DCB demonstrated superior safety and effectiveness as compared to PTA, and plasma levels of paclitaxel fall to low levels within 1 hour.

These investigators noted that although occurring despite randomization, the higher prevalence of re-stenotic lesions in the PTA cohort may impact the study results. They stated that long-term follow-up is needed in determining the extended durability of the intervention. Moreover, they stated that outcomes from this trial cannot be generalized to patients not included in this trial or to other DCBs; future studies should encompass adjunctive therapeutic options as well as optimal medical therapy and exercise.

Wu et al (2017) noted that several prospective controlled studies have evaluated the safety and effectiveness of drug-coated balloon angioplasty (DCBA) versus standard plain old balloon angioplasty (POBA) for femoropopliteal ISR.
researchers performed a meta-analysis of prospective controlled trials to pool the results of these trials and obtain more reliable conclusions. Prospective controlled trials comparing DCBA versus POBA were searched through PubMed, Embase, the Cochrane Central Register of Controlled Trials, ISI Web of Knowledge, and relevant websites without language or publication date restrictions. The keywords were “drug-eluting balloon”, “angioplasty”, “femoropopliteal” and “in-stent restenosis”. They selected recurrent ISR, freedom from CD-TLR, clinical improvement, ABI, and MAEs as the outcomes of this meta-analysis. Based on the inclusion criteria, these investigators identified 3 prospective clinical trials. The 1-year outcomes of DCBA and POBA were as follows: recurrent ISR (34.8 % versus 73.1 %, respectively; OR, 0.18; 95 % CI: 0.10 to 0.32, Z = 5.56, p < 0.00001), freedom from CD-TLR (82.2 % versus 54.1 %, respectively; OR, 4.20; 95 % CI: 2.05 to 8.61, Z = 3.92, p < 0.0001), clinical improvement (76.2 % versus 55.7 %, respectively; OR, 2.58; 95 % CI: 1.41 to 4.72, Z = 3.07, p = 0.002), ABI (MD, -0.04; 95 % CI: -0.13 to 0.04, Z = 1.01, p = 0.31), and MAEs (11.0 % versus 18.3 %, respectively; OR, 0.54; 95 % CI: 0.25 to 1.15, Z = 1.60, p = 0.002). The authors concluded that for femoropopliteal ISR, DCBA was associated with superior efficacy outcomes compared with POBA, with the same safety outcome after a 1-year follow-up. Moreover, they stated that multi-center and large-scale prospective controlled trials comparing DCBA with other endovascular strategies are needed to further evaluate the safety and effectiveness profiles of DCBA in the treatment of femoropopliteal ISR.

Andrassy et al (2017) stated that despite a constantly expanding spectrum of therapeutic options for lower limb artery disease, there is not yet a well-defined consensus on the specific type of endovascular treatment that is best suited. Clinical data on patients with femoropopliteal disease treated with DCBs have not been elaborated sufficiently, especially in the case of ISR. These researchers performed a systematic search of the medical databases (PubMed). Keywords such
as "drug-coated balloons" (DCB), "drug-eluting balloons", "in- stent restenosis", "de novo stenosis", "angioplasty", "superficial femoral artery", "popliteal artery", "above the knee", "below the knee", "peripheral artery disease" (PAD) have been used. Furthermore, data from reviews, original contributions regarding RCTs, observational studies, registries and single-center experiences have been included. Many trials have shown superiority for DCB- over PTA-treatment alone in TASC IIA and TASC IIB femoropopliteal lesions. However, the currently available DCB systems are different in terms of efficacy and long-term outcomes depending on their mechanical and pharmacological features. Moreover, angiographic characteristics of femoropopliteal lesions classified by Tosaka seem to influence subsequent outcomes of DCB treatment. The authors concluded that there is still lack of reliable prospective long-term data regarding DCB technology.

In a meta-analysis, Candy et al (2017) reviewed all available literature to evaluate outcome of patients treated with DEBs compared with PTA through measuring the rate of TLR. These researchers performed an electronic search of the Medline, Scopus, Embase, Web of Science, and Cochrane Library databases. Articles reporting RCTs that compared treatment with DEBs versus PTA were selected for inclusion. A meta-analysis was performed by pooling data on rates of TLR, binary restenosis (BR), and LLL. The 10 included articles comprised a sample size of 1,292 patients. Meta-analysis demonstrated the rate of TLR in DEB-treated patients was significantly lower compared with patients treated with PTA at 6 months (OR, 0.24; 95 % CI: 0.11 to 0.53; p = 0.0004), 12 months (OR, 0.28; 95 % CI: 0.13 to 0.62; p = 0.002), and 24 months (OR, 0.25; 95 % CI: 0.10 to 0.61; p = 0.002). Decreased LLL and BR was demonstrated at 6 months in patients treated with DEBs compared with patients treated with PTA (MD, -0.74; 95 % CI: -0.97 to -0.51; p = 0.00001; OR, 0.34; 95 % CI: 0.23 to 0.49; p = 0.00001). The authors concluded that the findings of this meta-analysis
demonstrated that treatment with DEBs compared with PTA resulted in reduced rates of re-intervention in patients with PAD. Moreover, they stated that comparison of DEBs to other emerging treatments to determine which method results in the lowest re-intervention rates and in the greatest improvement in QOL should be the focus of future trials.

In a systematic review and meta-analysis, Zhang et al (2017) evaluated the current available studies investigating outcomes of DEB and DES in the treatment of infrapopliteal artery disease. Multiple databases were systematically searched to identify studies investigating the outcomes of DEB and DES in the treatment of patients with infrapopliteal artery disease. The quality of studies was assessed by Cochrane Collaboration method. The demographic data, risk factors, outcomes, and anti-platelet strategy were extracted. A total of 9 studies were identified with 707 and 606 patients in DEB/DES and standard PTA/BMS group, respectively. The risk of TLR (OR = 0.38, 95 % CI: 0.23 to 0.63, p < 0.01), re-stenosis rate (OR = 0.30, 95 % CI: 0.18 to 0.50, p < 0.01), and amputation rate (OR = 0.49, 95 % CI: 0.29 to 0.83, p < 0.01) significantly decreased in the DES group. The overall survival (OR = 0.86, 95% CI: 0.56-1.32, P = .50) was similar in DES and standard PTA/BMS group; TLR (OR = 0.59, 95% CI: 0.32-1.09, P = .09), restenosis rate (OR = 0.49, 95% CI: 0.11-2.14, P = .35), amputation rate (OR = 1.32, 95 % CI: 0.51 to 3.40, p = 0.57), and overall survival (OR = 1.40, 95 % CI: 0.72 to 2.71, p = 0.32) were similar in DEB and standard PTA group. The authors concluded that the findings of this meta-analysis suggested that compared with standard PTA/BMS, DES may decrease the risk of CD-TLR, re-stenosis rate, and amputation rate without any impact on mortality. However, DEB has no obvious advantage in the treatment of infrapopliteal disease. Moreover, they stated that due to the limitations of this study, more RCTs, especially those for DEB, are needed.
Jongsma et al (2017) evaluated the effects of DEB angioplasty versus uncoated balloon (UCB) angioplasty to rescue infrainguinal autologous bypass grafts at risk (BAR). The study included all consecutive patients treated endovascularly for BAR from December 1, 2012, to July 31, 2015. As of April 1, 2014, the primary treatment of BAR was changed from UCBs to DEBs. Patients treated with DEBs were prospectively recorded in a database and retrospectively analyzed. Patients treated with UCBs were retrospectively collected from a historical cohort with a similar inclusion period length as the DEB cohort. The follow-up scheme did not differ between the 2 groups. The primary end-point was the combined end-point of freedom from recurrent stenosis or bypass occlusion; secondary end-points were primary assisted patency, secondary patency, technical success, major amputation, and mortality. A total of 21 patients were treated in the DEB group and 18 were treated in the UCB group. The 2 groups were evenly distributed in demographics, bypass, treatment, and lesion characteristics. No statistically significant differences were found in the combined end-point of freedom from recurrent stenosis and the occlusion rate after 1 year between the UCB group (77.8 %) and the DEB group (80.0 %; p = 0.76). After 1 year, the primary assisted patency rate was 88.2 % in the UCB group versus 95.2 % in the DEB group (p = 0.47), and the secondary patency rate was 94.1 % in the UCB group versus 95.2 % in the DEB group (p = 0.91). During follow-up, re-stenosis developed in 4 patients (22.2 %) in the UCB group and in 4 patients (19.0 %) in the DEB group (p = 9.80); 1 bypass (5.6 %) in the UCB group and 1 bypass (4.8 %) in the DEB group occluded during follow-up (p = 0.884). The authors concluded that DEBs and UCBs performed equally in the treatment of significant stenosis in infrainguinal autologous bypasses with regard to freedom from re-stenosis or bypass occlusion, primary assisted patency, and secondary patency at 1 year. These investigators suggested using a less expensive UCB in the treatment of BAR.
The National Institute for Health and Care Excellence (NICE, 2016) evaluated the Lutonix drug-coated balloon for peripheral arterial disease. The Lutonix DCB is a paclitaxel-coated percutaneous transluminal angioplasty (PTA) catheter that is indicated for treating peripheral arterial disease (PAD). The briefing found that the key points from the evidence are from 2 randomized trials (citing LEVANT studies I and II; n=101 and 476) comparing the Lutonix DCB with standard angioplasty using non-coated balloons in patients with symptomatic femoropopliteal PAD. The Lutonix DCB showed significantly lower late lumen loss rates at 6 months post-procedure with a similar complication rate to standard balloon angioplasty. Two non-comparative, retrospective case series (citing Steiner et al. 2016 and Micari et al. 2016) indicate that the Lutonix DCB is a potentially viable treatment for below-the-knee PAD, with acceptable outcomes and safety rates. The briefing noted, however, that key uncertainties around the evidence are that the primary outcome of the 2 randomized studies is late lumen loss. This is considered to be a technical outcome so its clinical impact is unclear. The additional clinical evidence comprises retrospective non-comparative case series (n = 246 and n = 55).

An earlier assessment of drug-eluting balloons and stents for peripheral arterial disease by the Swedish Regional Health Technology Assessment Centre (HTA-centrum) (Falkenberg, et al., 2015) reached the following conclusions: "Despite almost 3,000 studied patients, no positive effects on patient-related outcomes have consistently been observed with drug eluting stents or balloons in the treatment of atherosclerotic disease of the lower extremities, compared with uncoated stents or balloons. Mortality rate within 12 months was reported to be between zero and 18 %, probably mainly related to the underlying general atherosclerotic disease. Commonly encountered SAEs are mortality, amputations, pseudo aneurysms and thrombosis. For patients with intermittent claudication (P1) due to below the knee lesions, it is uncertain whether there is little or no difference regarding
mortality, restenosis or symptom severity with DES (sirolimus) compared with BMS. Very low certainty of evidence (GRADE +000). In patients with critical ischemia (P2) and lesions below the knee, DES (everolimus) may reduce restenosis compared with BMS. In the same patient group, DEB with paclitaxel compared with UCB may slightly reduce symptom severity (Rutherford score). Low certainty of evidence (GRADE ++00). Importantly, for patients with critical ischemia below the knee, in one RCT comparing DEB (paclitaxel) with UCB (ref), a significant increase in amputation rate (not reported in the RCT) was detected in the DEB group when all amputated patients from the study flowchart were included in the analysis. There was also a non-significant but numerically higher mortality in the DEB (paclitaxel) group compared with the UCB group. In a mixed population (P3) (i.e. intermittent claudication or critical ischemia patients) with lesions above the knee, DES (paclitaxel) compared with BMS may reduce restenosis. DES (sirolimus) compared with BMS in lesions below the knee, may reduce restenosis and may slightly reduce symptom severity. In the mixed population, with lesions above and/or below the knee, restenosis may be reduced with DEB (paclitaxel) compared with UCB. In all cases low certainty of evidence (GRADE ++00). In the studied patient populations (P1-P3), the effect estimates for all other studied outcomes were uncertain, non-significant or inconclusive. Very low-, or low certainty of evidence (GRADE +000 or ++00)."

Bajraktari and co-workers (2016) performed a meta-analysis to evaluate the clinical efficiency and safety of DEB compared with DES in patients with drug-eluting stent restenosis (DES-ISR). A systematic search was conducted and all RCTs and observational studies that compared DEB with DES in patients with DES-ISR were included. The primary outcome measure -- major adverse cardiovascular events (MACE) -- as well as individual events such as TLR, stent thrombosis (ST), MI, cardiac death (CD) and all-cause mortality, were analyzed. A total of 3 RCTs and 4 observational studies were included with a total of 2,052 patients. MACE (RR = 1.00, 95 % CI: 0.68 to
1.46, p = 0.99), TLR (RR = 1.15 [CI: 0.79 to 1.68], p = 0.44),
ST (RR = 0.37 [0.10 to 1.34], p = 0.13), MI (RR = 0.97 [0.49 to
1.91], p = 0.93) and CD (RR = 0.73 [0.22 to 2.45], p = 0.61)
were not different between patients treated with DEB and with
DES. However, all-cause mortality was lower in patients
treated with DEB (RR = 0.45 [0.23 to 0.87, p = 0.019) and in
particular when compared to only 1st generation DES (RR
0.33 [0.15 to 0.74], p = 0.007). There was no statistical
evidence for publication bias. The authors concluded that the
results of this meta-analysis showed that DEB and DES had
similar efficacy and safety for the treatment of DES-ISR.

Basavarajaiah and colleagues (2016) compared DEBs versus
2nd-generation DES in the treatment of DES-ISR. These
researchers evaluated all procedures between 2009 and 2011,
involving DES-ISR that were treated either with DEB or 2nd­
generation DES. The measured end-points during the follow­
up period were CD, target-vessel MI, TLR, TVR, and MACE
defined as composite of cardiac-death, TV-MI, and TVR. A
total of 247 patients (302 lesions) with DES-ISR were treated
with either DEB (81 patients; 104 lesions) or 2nd-generation
DES (166 patients; 198 lesions). The mean age of patients
was 66.1 ± 9.4 years. There were higher numbers of patients
with diabetes in the DEB group (DEB 47 % versus DES 33 %;
p = 0.03). The mean length of DEB was significantly longer
than the DES (35.4 versus 19.8 mm; p < 0.001). During the 12­
month follow-up, there were no significant differences in the
MACE rates (12.3 % versus 8.4 %; p = 0.3) and TLR rates (9.9
% versus 7.8 %; p = 0.6) between DEB and DES,
respectively. On the multivariate analysis, use of DEB or DES
was not the predictor of MACE (HR: 0.84, 95 % CI: 0.46 to
1.85; p = 0.6). There were no cases of definite or probable
stent thrombosis in either group. The authors concluded that
there were no significant differences in the clinical outcomes
between DEB and 2nd-generation DES in the treatment of
DES-ISR. They stated that these results should encourage
operators to consider DEB in the treatment of DES-ISR, which
offers certain advantages over DES.
Wang and associates (2017) evaluated the efficacy of DEB with DES in patients with ISR. Electronic databases were searched for RCTs and observational cohort studies which reported the clinical outcomes of using DEB comparing with DES implantation in patients with ISR. Clinical endpoints such as MACE, death, and MI were assessed. A total of 5 RCTs and 5 observational cohort studies with 962 patients in the DEB group and 908 patients in the DES group met inclusion criteria. There was no significant difference between DEB and DES in major clinical outcomes, such as MACE (OR 1.01; 95% CI: 0.64 to 1.58; p = 0.97; I² = 0%), all-cause death (OR 1.04; 95% CI: 0.54 to 1.98; p = 0.91; I² = 0%), cardiovascular death (OR 1.44; 95% CI: 0.57 to 3.65; p = 0.44; I² = 0%), stent thrombosis (OR 0.61; 95% CI: 0.16 to 2.33; p = 0.47; I² = 0%), and MI (OR 1.02; 95% CI: 0.53 to 1.94; p = 0.96; I² = 0%). DEB was associated with a significant increase in TLR (OR 1.54; 95% CI: 1.10 to 2.15; p = 0.01; I² = 57%). The authors concluded that treatment of ISR using DEB led to comparable clinical outcomes with DES implantation.

Milnerowicz and colleagues (2019) analyzed the long-term outcomes of a hybrid therapeutic approach combining rotational atherectomy with drug-coated balloon (DCB) angioplasty in patients with total in-stent occlusion in the iliac and/or infra-inguinal arteries. Between April 2014 and June 2017, a total of 74 consecutive patients (mean age of 66.7 ± 9.7 years; 49 men) with total occlusion of a previously implanted stent underwent endovascular re-canalization using the Rotarex system and DCB angioplasty; 50% (n = 37) of the patients had CLI, and 41% (n = 30) of the procedures were performed in emergency. Mean lesion length was 22 ± 15 cm. Overall procedure success was achieved in 73 (98.6%) patients; 6 (8.1%) CLI patients developed distal embolism that responded to thrombolysis; 3 (4.1%) dissections did not require treatment, while 1 (1.4%) perforation necessitated stent-graft implantation. In all, 33 (44.6%) patients had an additional stent implanted, mainly due to a sub-optimal outcome (n = 28) or complications (n = 5 including the stent-
graft). The re-stenosis rate assessed by Duplex ultrasound (US) at 12 months was 20.5% (15/73); 4 (5.5%) patients underwent TLR. Recurrent re-stenosis was more frequent in patients with Rutherford category 5 ischemia ($p = 0.005$), in emergency procedures ($p = 0.021$), after extensive procedures involving 3 independent vessel segments ($p = 0.016$), and if a complication arose during the procedure ($p < 0.001$). In multivariate analysis, only occurrence of a procedural complication was an independent predictor of recurrent restenosis at 1 year ($OR\ 63.3,\ 95\ %\ CI: \ 5.7\ to\ 701.5$). The authors concluded that these findings implied that rotational atherectomy and DCB angioplasty may provide satisfactory outcomes in the treatment of total in-stent occlusion, with a satisfactory recurrent re-stenosis rate at 12 months.

Scheinert and colleagues (2014) examined the safety and efficacy of the Lutonix drug-coated balloon (DCB) coated with 2 μg/mm² paclitaxel and a polysorbate/sorbitol carrier for treatment of femoro-popliteal lesions. Subjects at 9 centers with Rutherford class 2 to 5 femoro-popliteal lesions were randomized between June 2009 and December 2009 to treatment with Lutonix DCB ($n = 49$) versus uncoated balloons (control group [$n = 52$]), stratified by whether balloon-only treatment ($n = 75$) or stenting ($n = 26$) was intended. The primary end-point was angiographic late lumen loss at 6 months; secondary outcomes included adjudicated SAEs (death, amputation, target lesion thrombosis, re-intervention), functional outcomes, and pharmacokinetics. Demographic, peripheral vascular disease, and lesion characteristics were matched, with mean lesion length of 8.1 +/- 3.8 cm and 42% total occlusions. At 6 months, late lumen loss was 58% lower for the Lutonix DCB group (0.46 +/- 1.13 mm) than for the control group (1.09 +/- 1.07 mm; $p = 0.016$). Composite 24-month SAEs were 39% for the DCB group, including 15 TLR, 1 amputation, and 4 deaths versus 46% for uncoated balloon group, with 20 TLR, 1 thrombosis, and 5 deaths. Pharmacokinetics showed bi-exponential decay with peak concentration (Cmax) of 59 ng/ml and total observed exposure
(AUC(all)) of 73 ng h/ml. For successful DCB deployment excluding 8 malfunctions, 6-month late lumen loss was 0.39 mm and the 24-month TLR rate was 24%. The authors concluded that treatment of femoro-popliteal lesions with the low-dose Lutonix DCB reduced late lumen loss with safety comparable to that of control angioplasty.

The authors stated that this study had several drawbacks. LEVANT I was a single-blind study. Although angiographic entry and stratification criteria were operator-determined prior to randomization, potential post-randomization procedural and follow-up bias cannot be precluded for unblinded operators. Only limited balloon sizes were available, and the protocol-mandated angiograms at 6 months may have confounded clinical follow-up. The study was limited by small sample size for evaluating binary outcomes such as clinical events or patency. Runoff was not compared between the 2 study groups. An unexpected limitation to the study was the balloon deployment malfunctions, with poorer late outcomes in the subgroup with failed deployment that diluted the ITT analysis. Despite the clear failure of drug delivery in this subset of subjects, safety and primary end-point treatment effect were still evident on an intention-to-treat (ITT) basis.

Rosenfield and associates (2015) stated that the treatment of PAD with percutaneous transluminal angioplasty is limited by the occurrence of vessel recoil and restenosis. Drug-coated angioplasty balloons deliver anti-proliferative agents directly to the artery, potentially improving vessel patency by reducing restenosis. In a single-blind, randomized trial conducted at 54 sites, these researchers assigned, in a 2:1 ratio, 476 patients with symptomatic intermittent claudication or ischemic pain while at rest and angiographically significant atherosclerotic lesions to angioplasty with a paclitaxel-coated balloon or to standard angioplasty. The primary efficacy end-point was primary patency of the target lesion at 12 months (defined as freedom from binary restenosis or from the need for TLR). The primary safety end-point was a composite of freedom from
peri-operative death from any cause and freedom at 12 months from limb-related death (i.e., death from a medical complication related to a limb), amputation, and re-intervention. The 2 groups were well matched at baseline; 42.9% of the patients had diabetes, and 34.7% were current smokers. At 12 months, the rate of primary patency among patients who had undergone angioplasty with the drug-coated balloon was superior to that among patients who had undergone conventional angioplasty (65.2% versus 52.6%, p = 0.02). The proportion of patients free from primary safety events was 83.9% with the drug-coated balloon and 79.0% with standard angioplasty (p = 0.005 for non-inferiority). There were no significant between-group differences in functional outcomes or in the rates of death, amputation, thrombosis, or re-intervention. The authors concluded that among patients with symptomatic femoro-popliteal PAD, percutaneous transluminal angioplasty with a paclitaxel-coated balloon resulted in a rate of primary patency at 12 months that was higher than the rate with angioplasty with a standard balloon. The drug-coated balloon was non-inferior to the standard balloon with respect to safety. Moreover, these researchers stated that this trial did not provide definitive guidance concerning the potential role of this paclitaxel-coated balloon in clinical practice. They stated that although the findings were encouraging, long-term follow-up studies are needed in examining if the benefit of this intervention is sustained, increased, or attenuated over time. In addition, further studies may compare the drug-coated balloon with other therapeutic options, such as atherectomy or stenting with bare-metal stents or drug-eluting stents.

The authors stated that this study had several drawbacks. Although the trial was designed to have the power to detect a difference in the primary end-point of patency at 12 months, it was not designed to have the power to assess differences in functional end-points or QOL measures. Determinants of these outcomes may not be specific to the study lesion; changes may be due to progression of PAD in other arterial
segments or to co-existing conditions that are known to limit physical function rather than to a difference in the device used to treat a specific lesion. In addition, although the patients, core laboratory staff, and clinicians performing the follow-up assessments were unaware of the study-group assignments, the physicians performing the index procedures could not be unaware of the assignments because of the different characteristics of the 2 types of angioplasty balloons.

In a prospective, multi-center study, Thieme and co-workers (2017) examined the safety, clinical benefit, and outcomes of the Lutonix 035 DCB in a heterogeneous, real-world patient population at 12 and 24 months. This trial enrolled 691 patients in 38 centers from 10 countries treated with the Lutonix 035 DCB in femoro-popliteal lesions. The primary safety end-point was freedom from a composite of target vessel restenosis, major index limb amputation, and device- or procedure-related death at 30 days. The primary effectiveness end-point was freedom from target lesion restenosis at 12 months; secondary end-points were acute device and procedural success and clinically assessed primary patency. Freedom at 30 days from the composite safety end-point was 99.4 %. Freedom from target lesion restenosis was 93.4 %/89.3 % for the overall population, 93.2 %/88.2 % for long lesions up to 500 mm, and 90.7 %/84.6 % for ISR at 12/24 months. Clinically assessed primary patency by Kaplan-Meier estimates was 85.4 %/75.6 % at 12/24 months. More than 76 % of patients showed improvement of at least 1 Rutherford category. The authors concluded that the Global SFA Registry 24-month outcomes confirmed the Lutonix 035 DCB was a safe and effective long-term therapeutic option in real-world patients with PAD with superficial femoral artery lesions, also in long lesions and ISR.

The authors stated that this study had several drawbacks. The trial was a prospective, multi-center, single-arm registry, and did not include a comparison control group. Rather, reference to past clinical experience was used as a point of comparison.
Physicians enrolled patients for whom they believed the therapy would be appropriate, and the decision to enroll was not based on randomization or sequential patient identification. The study included patients observed in typical real-world clinical practice with a commercially available product used consistent with established European instructions for use (IFU). The intent of this study was to evaluate the DCB outcomes in standard of care practice. Reporting the TLR outcomes were real-world results and were not adjusted by core laboratory review.

Casserly (2017) stated that percutaneous treatment of atherosclerotic disease in the femoro-popliteal (FP) segment remains one of the most challenging subsets for endovascular operators. The experience of unacceptably high restenosis rates with POBA and nitinol self-expanding stents (SES) generated considerable interest in a variety of atherectomy technologies as a complement or replacement for angioplasty/stenting over the past 10 years. However, it has become clear that these technologies suffer from the same problem of high restenosis rates. In addition, application of atherectomy technologies was generally expensive, introduced greater technical challenges in performing the procedure, leading to a greater degree of variability in outcome based on operator experience and skill level, and probably increased the risk of distal embolization during treatment, necessitating the use of embolic protection devices. More recently, the pendulum has swung back toward the use of angioplasty and stents with the availability of DCB and a DES system with proven superiority over POBA and non–drug-eluting SES, respectively. The author noted that currently, there are 2 FDA-approved DCB systems available for clinical use in the FP segment. Each system was tested in pivotal randomized trials (LEVANT II [Moxy Drug Coated Balloon versus Standard Balloon Angioplasty for the Treatment of Femoropopliteal Arteries] and IN.PACT SFA [Randomized Trial of IN.PACT Admiral Drug Coated Balloon versus Standard PTA for the Treatment of SFA and Proximal Popliteal Arterial Disease]).
trials) comparing DEB with POBA. Moving forward, there is a need to perform a head-to-head comparison between the 2 DCB systems to examine if the superior patency rates reported for the DCB arm of the IN.PACT SFA trial (using the IN.PACT Admiral DCB [Medtronic, Santa Rosa, CA]) reflected a real difference or was due to differences in patient population and/or lesion type, or trial design. This may help to move the field forward by examining if the dose of paclitaxel and the excipient used can have a significant clinical impact on restenosis rates. The author concluded that it must be accepted that DCB therapy will always suffer from the major Achilles heel of not being able to deal with the issue of elastic recoil or development of flow-limiting dissections following angioplasty. In addition, it would be naive to think that DCB therapy will reliably prevent restenosis in the most severe lesion types that are encountered in the FP artery. Although DCB therapy is a welcome addition to the options for re-vascularization in the FP segment, there is a long way to go before endovascular therapy that includes DCB angioplasty can rival the patency rates of surgical bypass. It is hard not to feel that an inert biodegradable metal scaffold combined with an anti-proliferative agent still offers the best chance of achieving this goal. Unfortunately, the many failures to-date for non-biodegradable DES in the FP segment have hampered investment and investigation, and may continue to do so for some time.

Kayssi and colleagues (2019) noted that stents are placed in the femoro-popliteal arteries for numerous reasons, such as atherosclerotic disease, the need for dissection, and perforation of the arteries, and can become stenosed with the passage of time. When a stent develops a flow-limiting stenosis, this process is known as "ISR". It is thought that ISR is caused by a process known as "intimal hyperplasia" rather than by the progression of atherosclerotic disease. Management of ISR may include performing balloon angioplasty, deploying another stent within the stenosed stent to force it open, and creating a bypass to deliver blood around
the stent. The role of drug-eluting technologies, such as DEBs, in the management of ISR is unclear. Drug-eluting balloons might function by coating the inside of stenosed stents with cytotoxic chemicals such as paclitaxel and by inhibiting the hyperplastic processes responsible for ISR. It is important to perform this systematic review to evaluate the efficacy of DEB because of the potential for increased expenses associated with DEBs over uncoated balloon angioplasty, also known as POBA. In a Cochrane review, these researchers examined the safety and efficacy of DEBs compared with uncoated balloon angioplasty in people with ISR of the femoro-popliteal arteries as assessed by criteria such as amputation-free survival, vessel patency, TLR, binary restenosis rate, and death. They defined "ISR" as 50% or greater narrowing of a previously stented vessel by Duplex US or angiography. The Cochrane Vascular Information Specialist searched the Cochrane Vascular Specialized Register, CENTRAL, MEDLINE, Embase, and CINAHL databases and the World Health Organization International Clinical Trials Registry Platform and ClinicalTrials.gov trials registers to November 28, 2017. Review authors also undertook reference checking to identify additional studies. These researchers included all RCTs that compared DEBs versus uncoated balloon angioplasty for treatment of ISR in the femoro-popliteal arteries. Two review authors independently selected appropriate trials and performed data extraction, assessment of trial quality, and data analysis. The senior review author adjudicated any disagreements. A total of 3 trials that randomized a combined total of 263 participants met the review inclusion criteria. All 3 trials examined the treatment of symptomatic ISR within the femoro-popliteal arteries. These trials were performed in Germany and Austria and used paclitaxel as the agent in the DEBs; 2 of the 3 trials were industry-sponsored. Two companies manufactured the DEBs (Eurocor, Bonn, Germany; Medtronic, Fridley, MN). The trials examined both anatomical and clinical endpoints. These investigators noted heterogeneity in the frequency of bailout stenting deployment between studies as well as in the dosage...
of paclitaxel applied by the DEBs. Using GRADE assessment criteria, they determined that the certainty of evidence presented was very low for the outcomes of amputation, TLR, binary restenosis, death, and improvement of one or more Rutherford categories. Most participants were followed-up to 12 months, but 1 trial followed participants for up to 24 months. Trial results showed no difference in the incidence of amputation between DEBs and uncoated balloon angioplasty.

DEBs showed better outcomes for up to 24 months for TLR (OR 0.05, 95% CI: 0.00 to 0.92 at 6 months; OR 0.24, 95% CI: 0.08 to 0.70 at 24 months) and at 6 and 12 months for binary restenosis (OR 0.28, 95% CI: 0.14 to 0.56 at 6 months; OR 0.34, 95% CI: 0.15 to 0.76 at 12 months). Participants treated with DEBs also showed improvement of one or more Rutherford categories at 6 and 12 months (OR 1.81, 95% CI: 1.02 to 3.21 at 6 months; OR 2.08, 95% CI: 1.13 to 3.83 at 12 months). Data showed no clear differences in death between DEBs and uncoated balloon angioplasty. Data were insufficient for subgroup or sensitivity analyses to be conducted. The authors concluded that based on a meta-analysis of 3 trials with 263 participants, evidence suggested an advantage for DEBs compared with uncoated balloon angioplasty for anatomical end-points such as TLR and binary restenosis, and for one clinical end-point - improvement in Rutherford category post-intervention for up to 24 months.

However, the certainty of evidence for all these outcomes was very low due to the small number of included studies and participants and the high risk of bias in study design. These researchers stated that adequately powered and carefully constructed RCTs are needed to examine the role of drug-eluting technologies in the management of ISR.

Medicines and Healthcare products Regulatory Agency (MHRA, 2019) provided the following recommendations for ongoing use of paclitaxel DCBs and implantable DESs in the treatment of patients with PAD:
• Do not use paclitaxel DCBs or DESs in the routine treatment of patients with intermittent claudication until further notice, as the potential mortality risk generally out-weighs the benefits.

• In patients with critical limb ischemia, management should follow NICE guideline CG 147 (2018), which recommends angioplasty or bypass surgery, with consideration of bare metal stents only where there is complete aorto-iliac occlusion.

• Use of paclitaxel DCBs and DESs in patients with critical limb ischemia remains an appropriate option in selected cases, where the benefits may out-weigh the risks. This is because these patients generally have a higher risk of irreversible ischemic damage resulting from restenosis, such as limb loss, and a lower life expectancy.

Drugs-Eluting Balloon for Vein Grafts and Dialysis / Vascular Accesses

Bjorkman and colleagues (2017) analyzed outcomes of the first experiences with DEBs in native arteries, vein grafts, and vascular accesses. The study was also a pilot for the authors’ future prospective, randomized, and controlled studies regarding the use of DEBs in the treatment of the stenosis in bypass vein graft and dialysis access. A total of 93 consecutive patients were retrospectively analyzed and 81 were included in the study. Inclusion criteria included at least 1 previous percutaneous angioplasty to the same lesion.

Patients were divided into 3 groups according to the anatomical site of the lesion: (i) native lower limb artery, (ii) vein bypass graft, or (iii) vascular access. Time from the previous percutaneous angioplasty to the DEB was compared to the time from the DEB to end-point in the same patient. End-points included any new re-vascularization of the target lesion, major amputation, or new vascular access. The median time from the DEB to end-point was significantly longer than the median time from the preceding percutaneous angioplasty to DEB in all 3 groups. This difference was
clearest in native arteries and vein grafts, whereas the difference was smaller from the beginning and disappeared over time in the vascular access group. No significant differences were seen between the groups with regard to smoking, antiplatelet regime, diabetes, Rutherford classification, or sex. The authors concluded that although the setup of this study had several limitations, the results suggested that there could be benefit from DEBs in peripheral lesions. Moreover, they stated that very little data have been published on the use of DEBs in vein grafts and vascular accesses, and randomized and controlled prospective studies are needed to further investigate this field.

Trerotola and colleagues (2018) noted that re-stenosis remains a problem in hemodialysis access interventions. Paclitaxel-coated balloons have shown promise in reducing access-related re-stenosis in small trials. The primary hypotheses for this multi-center trial were superior effectiveness at 180 days and non-inferior safety at 30 days of a drug-coated balloon compared with conventional angioplasty for treatment of dysfunctional arterio-venous (AV) fistulae. This randomized trial enrolled 285 patients with dysfunctional AV fistulae at 23 centers. Grafts, central venous stenoses, thrombosed fistulas, and immature fistulas were excluded. All patients received angioplasty of the lesion responsible for access dysfunction. After successful angioplasty (less than or equal to 30 % residual stenosis), lesions were treated with either a paclitaxel-coated balloon or an uncoated control balloon of similar design to the drug-coated balloon. Access function during follow-up was determined per centers’ usual protocols; re-intervention was clinically driven. The primary efficacy outcome assessment was carried out at 6 months, and the safety assessment was done within 30 days of the procedure. Pre-specified secondary end-points included assessment of post-intervention target lesion primary patency and access circuit primary patency at 6 months. The 180-day end-point was not met with target lesion primary patency (71 % ± 4 % for the drug-coated balloon and 63 % ± 4 % for
control; p = 0.06), representing a difference of 8% ± 6% (95%
Ci: -3% to 20%). Access circuit primary patency did not
differ between groups. Interventions to maintain target lesion
patency were fewer for the drug-coated balloon at 6 months
(0.31 versus 0.44 per patient; p = 0.03). The primary safety
non-inferiority end-point was met and did not differ between
groups (p = 0.002). The authors concluded paclitaxel-coated
balloon used after successful angioplasty in AV fistulas
stenosis was not shown to be superior to a standard balloon
using a strict 180-day definition of the 6-month end-point.
Fewer interventions were needed in the drug-coated balloon
group to maintain target lesion patency. The drug-coated
balloon was as safe as the standard balloon.

Trerotola and associates (2020) presented final, 2-year results
of a randomized trial comparing paclitaxel-coated versus
uncoated balloon angioplasty following vessel preparation with
ultra-high-pressure PTA hemodialysis AV fistulae. Twenty-
three sites enrolled 285 subjects with dysfunctional AV fistulae
located in the arm. Before 1:1 randomization, successful
vessel preparation was achieved (full waist effacement, less
than 30% residual stenosis). Follow-up was clinically driven
except for a 6-month office visit; 96 of 141 subjects in the
DCB-arm and 111 of 144 in the control-arm completed the
study. Target lesion primary patency (TLPP) rates for the DCB
and control groups were 58% ± 4 versus 46% ± 4 (p = 0.02)
at 9 months, 44% ± 5 versus 36% ± 4 (p = 0.04) at 12
months, 34% ± 5 versus 28% ± 4 (p = 0.06) at 18 months,
and 27% ± 4 versus 24% ± 4 (p = 0.09) at 24 months,
respectively. Mean time to TLPP event for subjects with an
event was longer for DCBs (322 versus 207 days; p < 0.0001).
Fewer interventions were needed to maintain target lesion
patency in the DCB group at 9 months (p = 0.02) but not at 12
(p = 0.08), 18 (p = 0.13), or 24 months (p = 0.19). The non-
inferiority safety target was met at all intervals (p < 0.01).
Mortality did not differ between groups (p = 0.27). Post-hoc
analyses showed equivalent DCB effect in all subgroups. The
authors concluded that the use of a DCB after adequate
vessel preparation in patent, dysfunctional arm AV fistulae resulted in an improved patency trend over control at 9 months and not at other time-points over the 2-year study, as well as significantly reduced interventions to maintain TLP and a significant prolongation of time to next intervention at the target lesion. Subset analysis did not reveal any specific factors suggesting more targeted application of the DCB. These investigators believed that these findings are an important step forward in the development of novel therapies that improve the QOL of patients undergoing hemodialysis. They hope the further introduction of other such therapies, as well as the analysis of more patients treated with DCBs, will result in a future precision-based approach to AV fistulae stenosis.

The authors stated that this study had several drawbacks. The investigative team performing the PTA could not be blinded to device, which could theoretically have affected outcomes even though the rest of the study team, patients, dialysis unit, core laboratory, data safety monitoring board, and clinical events committee were all blinded. Performance of a second “sham” PTA in the control-arm was considered by the study designers to be necessary to match the treatment and control groups, but this may have improved results in the control-arm and biased the study against the DCB. Likewise, insisting on optimal PTA-based vessel preparation may have biased the study in favor of the control-arm. Access surveillance methodology and thresholds for fistula imaging were not study-directed, such that clinically driven repeat intervention thresholds may have varied between study centers. Certain factors such as antiplatelet use were not controlled for in the study, and flow measurement was not consistently performed (or required) as part of the study. The latter might have given more objective referrals for clinically driven repeat intervention. Duration of DCB inflation was lengthened during the study in light of emerging data from DCB studies in arterial disease, and, although the subset analysis did not show any significant differences between shorter and longer inflations, use of the
longer inflation time throughout the study could conceivably have influenced the results. As with any large trial over a long period of time, the data were incomplete for some subjects.

Intravascular Shockwave Lithotripsy of the Peripheral Arteries for the Treatment of Atherosclerosis / Calcified Lower Extremity Arterial Lesions / Intermittent Claudication

Giannopoulos and Armstrong (2019) noted that femoro-popliteal lesions account for a significant proportion of endovascular interventions for peripheral artery disease (PAD). These investigators reviewed the literature on the application of newly approved devices in the treatment of atherosclerotic lesions at this segment. New drug-coating technologies provide sustained drug-eluting over time and better scaffolds are more resistant to the increased biomechanical stress at the femoro-popliteal segment. Thus, the newer drug-eluting stents (i.e., Eluvia), nitinol interwoven stents (i.e., Supera), and drug-coated balloons (i.e., Stellarex) are associated with improved pharmacokinetic profiles and promising primary patency rates. A major predictor of technical failure and re-stenosis is the calcification of the target vessel. Recently, intravascular lithotripsy of calcified lesions at the femoro-popliteal segment with the Shockwave balloon was introduced as a feasible therapeutic option for these complex lesions. The authors also described the Tack Endovascular System, the first-of-its-type, for the repair of post-angioplasty dissections. These researchers concluded that the use of innovative stent designs and novel drug-coating, the application of adjunctive intravascular lithotripsy and the combined use of new devices treating complications, might improve the overall outcomes of angioplasty, thereby promising favorable outcomes even for more complex lesions.
Furthermore, UpToDate reviews on “Overview of lower extremity peripheral artery disease” (Berger and Davies, 2020) and “Management of claudication due to peripheral artery disease” (Davies, 2020) do not mention intravascular shockwave lithotripsy as a therapeutic option.

Holden (2019) noted that the endovascular management of complex lower limb arterial occlusive disease is generally associated with poorer acute results, a higher incidence of provisional stenting and subsequent re-stenosis compared to more simple arterial lesions. Even more challenging results can be expected when 2 complex features are combined such as chronic total occlusion (CTO) and severe calcification. Intravascular lithotripsy (IVL) with the Shockwave system has recently been examined as a familiar angioplasty-balloon-based but effective technique for the management of arterial calcification. In the DISRUPT PAD clinical trials, excellent acute results were obtained in moderate-to-severely calcified femoro-popliteal lesions, including a group of patients with CTOs. The incidence of provisional stenting was very low, despite the lesion complexity. There was a high incidence of subsequent re-stenosis, suggesting an anti-restenotic therapy with drug-coated balloon (DCB) is a necessary adjunct. This is being currently evaluated in the DISRUPT PAD III randomized trial. There has also been positive experience in calcified tibial artery CTOs in the DISRUPT BTK trial and further clinical experience is currently being accumulated.

Adams and colleagues (2020) examined the performance of peripheral IVL in a real-world setting during endovascular treatment of multi-level calcified PAD. The Disrupt PAD III Observational Study was a prospective, non-randomized, multi-center, single-arm, observational study evaluating the acute safety and effectiveness of the Shockwave Peripheral IVL System for the treatment of calcified, stenotic lower limb arteries. Patients were eligible if they had claudication or chronic limb-threatening ischemia and moderate or severe arterial calcification. Between November 2017 and August...
2018, a total of 200 patients (mean age of 72.5 ± 8.7 years; 148 men) were enrolled across 18 sites and followed through hospital discharge. In the 220 target lesions, IVL was more commonly used in combination with other balloon-based technologies (53.8 %) and less often with concomitant atherectomy or stenting (19.8 % and 29.9 %, respectively). There was a 3.4-mm average acute gain at the end of procedure; the final mean residual stenosis was 23.6 %. Angiographic complications were rare, with only 2 type D dissections and a single perforation following DCB inflation (unrelated to the IVL procedure). There was no abrupt closure, distal embolization, no re-flow, or thrombotic event. The authors concluded that the use of peripheral IVL to treat severely calcified, stenotic PAD in a real-world study demonstrated low residual stenosis, high acute gain, and a low rate of complications despite the complexity of disease. It should be noted that this was industry-sponsored study.

The authors stated that this study had several drawbacks. First, the Disrupt PAD III Observational Study was a single-arm study without a control group, therefore, no definitive comparisons could be made to other interventions regarding safety and effectiveness. While the purpose of the observational study was to examine acute outcomes following IVL treatment in the real-world setting, the Disrupt PAD III RCT will directly assess safety and effectiveness outcomes in IVL plus DCB compared with balloon angioplasty (BA) plus DCB. Second, by design, only acute procedure results were reported in this study. The PAD III RCT will follow subjects through 2 years, which will provide data on the longer-term safety and effectiveness of IVL. Third, the infra-popliteal lesions treated in this cohort were too few to analyze. During early enrollment in the observational study, there was limited commercial availability of the S4 IVL catheter sized for use in infra-popliteal lesions. Thus, data availability was limited for this lesion subset. However, the PAD III Observational Study has recently been expanded to 1,500 subjects with a minimum of
200 patients treated with the S4 IVL catheter. This allowance should ensure a robust infra-popliteal lesion cohort for evaluation.

Armstrong et al (2020) examined the safety and efficacy of peripheral IVL during endovascular treatment of iliac arterial PAD. The Disrupt PAD III Observational Study was a prospective, non-randomized, multi-center, single-arm study that examined the “real-world” safety and effectiveness of the Shockwave Peripheral IVL System for the treatment of de novo calcified lesions in the peripheral arteries, with a goal of treating 1,500 patients. This was an analysis of consecutive patients enrolled for treatment of an iliac artery, a specified sub-group, with at least moderate calcification and a minimum length of 20 mm. Between December 2017 and July 2019, a total of 118 patients with a total of 200 lesions were enrolled across 20 sites -- 101 patients were treated primarily for claudication or CLI, while 17 patients were treated to optimize the iliac vasculature for large-bore access. All 118 patients had successful IVL catheter delivery. The average reference vessel diameter was 7.3 mm ± 1.9 mm, with an average diameter stenosis of 83.1 % ± 13.4 % and an average lesion length of 58.3 mm ± 57.6 mm. Severe calcification was present in 82.0 % of overall cases. Stent placement was performed in 72.9 % of the overall cases. As expected, the access group received less adjunctive therapies including stents (41.2 %, p < 0.001). Angiographic complications were minimal with no flow-limiting dissections and a final mean residual stenosis of 12.0 % ± 12.1 % with no differences between the groups. The authors concluded that acute results with IVL in calcified iliac lesions suggested that it is a safe and effective option for calcified, stenotic iliac disease.

Lazar and Morrissey (2020) stated that as associated co-morbidities have transformed over time, the evaluation and management of PAD have evolved as well. New classification systems have been created to better understand the severity of a patient's condition and the risk of amputation. These
classifications include the Wound, Ischemia, and Foot Infection
(WIfI) and Global Anatomic Staging System (GLASS)
classification systems. Through the use of these systems, a
patient's disease can be appropriately staged and managed
with medical, endovascular, or surgical therapies or a
combination of these. Endovascular therapies specifically
have grown with the explosion of new technologies. There are
numerous options for patients with disease amenable to
endovascular therapy. Among other new technologies
currently under investigation is the Shockwave Lithoplasty
System (Shockwave Medical, Fremont, CA), which adapts
technology used in the treatment of renal calculi. This
technology uses a catheter-guided balloon that produces
powerful acoustic shockwaves to disrupt plaque while reducing
vessel wall injury. The technology is being studied in the
DISRUPT PAD III clinical trial. The authors concluded that a
number of available technologies have been discussed and
many others are on the horizon. They stated that although
some devices have demonstrated superiority, it is clear that
significant research and clinical trials are needed to determine
the specific utility and effectiveness of each device.

Madhavan and co-workers (2020) performed an individual
patient-level data (IPD) pooled analysis of available studies to
examine the safety and efficacy of IVL in the treatment of
PAD. These researchers pooled IPD, including baseline and
procedural variables, from 5 prospective studies that examined
IVL in the treatment of patients with extensive peripheral artery
calcification. Final post-procedural percent diameter stenosis
(%DS) and procedural angiographic complications were
evaluated by independent core laboratory. Efficacy end-points
were analyzed using linear mixed effects models and safety
end-points were tabulated overall and by vascular bed.
Among 336 patients who underwent endovascular re-
vascularization with use of IVL, there was a significant
reduction between pre-procedural and final %DS of 55.1 % (95
% CI: 53.3 to 57.0 %, p < 0.0001). Core-laboratory assessed
lesion-level complications, including flow-limiting dissections
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(Types D-F), vessel perforation, distal embolization, thrombus, abrupt closure, and no re-flow, occurred in 4/328 (1.22 %) of treated lesions. The authors concluded that the present IPD of 5 prospective studies, marking the largest analysis to date evaluating the use of IVL in significantly calcified PAD lesions, demonstrated this treatment strategy to be both safe and effective. Moreover, these researchers stated that these findings support the need for prospective, randomized trials comparing IVL to non-IVL approaches for the treatment of PAD, such as the ongoing DISRUPT PAD III RCT; further studies are needed to determine optimal treatment strategies for PAD in this vulnerable patient population.

The authors stated that this study had several drawbacks. The trials included in this analysis were single-arm studies with no comparators, and so these investigators were unable to effectively compare the safety and efficacy of IVL with other endovascular PAD treatment devices. It was also important to note that a proportion of patients received adjunctive device therapy (approximately 12 % received atherectomy), and so isolating the benefits of IVL in this specific patient subset was challenging. However, these researchers performed separate analyses to evaluate improvements in vascular dimensions and safety profiles in patients who received stand-alone IVL therapy with IVL and other adjunctive treatments and found no differences in final %DS or procedural complication rates between these groups. Given the varying dimensions of the vascular beds included in this analysis, there is a need for improved end-points and parameters that have applicability in these different therapeutic settings. The authors presented net gain index as one potential measure of efficacy, which may allow for assessment and comparison of procedural success across different vascular territories. To fully understand the comparative effectiveness of these therapies, head-to-head trials ideally with the use of intravascular imaging would need to be carried out to better understand mechanisms of action. Given the limited number of patients available to study in each of the described key clinical subgroups (including a limited
number of patients with chronic limb-threatening ischemia), larger cohorts will need to be studied to verify these observations. Lastly, discharge and follow-up clinical assessment and outcomes data were not systematically collected in several of the studies included in this analysis, making it challenging to draw robust conclusions regarding the long-term risks and benefits of treatment with IVL, with or without other calcium modification therapies; future studies should aim to address these limitations.

Furthermore, an UpToDate review on “Endovascular techniques for lower extremity revascularization” (Dosluoglu, 2020) does not mention intravascular shockwave lithotripsy as a management / therapeutic option.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CPT codes covered if selection criteria are met:</td>
</tr>
<tr>
<td></td>
<td><strong>Intravascular shockwave lithotripsy - no specific code</strong></td>
</tr>
<tr>
<td>37225</td>
<td>Revascularization, endovascular, open or percutaneous, femoral, popliteal artery(s), unilateral; with atherectomy, includes angioplasty within the same vessel, when performed</td>
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<tr>
<td>37227</td>
<td>Revascularization, endovascular, open or percutaneous, femoral, popliteal artery(s), unilateral; with transluminal stent placement(s) and atherectomy, includes angioplasty within the same vessel, when performed</td>
</tr>
<tr>
<td></td>
<td>CPT codes not covered for indications listed in the CPB:</td>
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<tr>
<td>Code</td>
<td>Code Description</td>
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<td>--------</td>
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</tr>
<tr>
<td>0234T</td>
<td>Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; renal artery</td>
</tr>
<tr>
<td>0235T</td>
<td>visceral artery (except renal), each vessel</td>
</tr>
<tr>
<td>0236T</td>
<td>abdominal aorta</td>
</tr>
<tr>
<td>0237T</td>
<td>brachiocephalic trunk and branches, each vessel</td>
</tr>
<tr>
<td>0238T</td>
<td>iliac artery, each vessel</td>
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Other CPT codes related to the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>32096</td>
<td>Thoracotomy, with diagnostic biopsy(ies) of lung infiltrate(s) (eg, wedge, incisional), unilateral</td>
</tr>
<tr>
<td>35511</td>
<td>Bypass graft, with vein; subclavian-subclavian</td>
</tr>
<tr>
<td>35512</td>
<td>subclavian-brachial</td>
</tr>
<tr>
<td>35516</td>
<td>subclavian-axillary</td>
</tr>
<tr>
<td>35518</td>
<td>axillary- axillary</td>
</tr>
<tr>
<td>35521</td>
<td>axillary-femoral</td>
</tr>
<tr>
<td>35525</td>
<td>brachial- brachial</td>
</tr>
<tr>
<td>35533</td>
<td>axillary-femoral- femoral</td>
</tr>
<tr>
<td>35537</td>
<td>aortoiliac</td>
</tr>
<tr>
<td>35538</td>
<td>aortobi-iliac</td>
</tr>
<tr>
<td>35539</td>
<td>aortofemoral</td>
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<tr>
<td>35540</td>
<td>aortobifemoral</td>
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<tr>
<td>35556</td>
<td>femoral-popliteal</td>
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<tr>
<td>35558</td>
<td>femoral-femoral</td>
</tr>
<tr>
<td>35563</td>
<td>ilioiliac</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
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<tr>
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<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>35565</td>
<td>iliofemoral</td>
</tr>
<tr>
<td>35566</td>
<td>femoral-anterior tibial, posterior tibial, peroneal artery or other distal vessels</td>
</tr>
<tr>
<td>35570</td>
<td>tibial-tibial, peroneal-tibial, or tibial/peroneal trunk-tibial</td>
</tr>
<tr>
<td>35571</td>
<td>popliteal-tibial, -peroneal artery or other distal vessels</td>
</tr>
<tr>
<td>35583</td>
<td>In-situ vein bypass; femoral-popliteal</td>
</tr>
<tr>
<td>35585</td>
<td>femoral-anterior tibial, posterior tibial, or peroneal artery</td>
</tr>
<tr>
<td>35587</td>
<td>popliteal-tibial, peroneal</td>
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<tr>
<td>35637</td>
<td>Bypass graft, with other than vein; aortoiliac</td>
</tr>
<tr>
<td>35638</td>
<td>aortobi-iliac</td>
</tr>
<tr>
<td>37211 -</td>
<td>Transcatheter therapy, arterial or venous infusion for thrombolysis</td>
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<td>37214</td>
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<td>37220 -</td>
<td>Revascularization, endovascular, open or percutaneous; iliac artery</td>
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<td>femoral, popliteal artery(s)</td>
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<tr>
<td>37226</td>
<td></td>
</tr>
<tr>
<td>37228 -</td>
<td>tibial, peroneal artery</td>
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HCPCS codes covered if selection criteria are met:

- C2623    | Catheter, transluminal angioplasty, drug-coated, non-laser                       |

HCPCS codes not covered for indications listed in the CPB:
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<tr>
<th>Code</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>C9764</td>
<td>Revascularization, endovascular, open or percutaneous, any vessel(s); with intravascular lithotripsy, includes angioplasty within the same vessel(s), when performed</td>
</tr>
<tr>
<td>C9765</td>
<td>with intravascular lithotripsy, and transluminal stent placement(s), includes angioplasty within the same vessel(s), when performed</td>
</tr>
<tr>
<td>C9766</td>
<td>with intravascular lithotripsy and atherectomy, includes angioplasty within the same vessel(s), when performed</td>
</tr>
<tr>
<td>C9767</td>
<td>with intravascular lithotripsy and transluminal stent placement(s), and atherectomy, includes angioplasty within the same vessel(s), when performed</td>
</tr>
</tbody>
</table>

**ICD-10 codes covered if selection criteria are met:**

- I70.0 - Atherosclerosis
- I70.92
- I74.3 Embolism and thrombosis of arteries of the lower extremities

**ICD-10 codes not covered for indications listed in the CPB (not all inclusive):**

- I70.201 - Unspecified atherosclerosis of native arteries of extremities
- I70.209
- I70.211 - Atherosclerosis of native arteries of extremities with intermittent claudication
- I70.219
- I73.9 Peripheral vascular disease, unspecified

**Isolated segmental pharmacomechanical thrombolysis (Trellis Peripheral Infusion System):**

No specific code

**ICD-10 codes not covered for indications listed in the CPB (not all inclusive):**
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I74.4</td>
<td>Embolism and thrombosis of arteries of extremities, unspecified [Occlusion of peripheral arteries]</td>
</tr>
<tr>
<td>I82.401</td>
<td>Acute embolism and thrombosis of deep veins of lower extremity</td>
</tr>
<tr>
<td>I82.4Z9</td>
<td>Acute embolism and thrombosis of other specified veins [Paget-Schroetter syndrome]</td>
</tr>
<tr>
<td>I82.890</td>
<td>Acute embolism and thrombosis of other specified veins [Paget-Schroetter syndrome]</td>
</tr>
</tbody>
</table>

The above policy is based on the following references:


Peripheral Atherectomy and Thrombectomy Devices


48. Parrella A, Mundy L. SilverHawk Peripheral Plaque Excision System: Percutaneous peripheral atherectomy for patients with peripheral vascular
Peripheral Atherectomy and Thrombectomy Devices - Medical Clinical Policy Bulletin...


Trellis Peripheral Infusion System


2. Goshima K. Primary (spontaneous) upper extremity deep vein thrombosis. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed January 2014.


**Drug-Eluting (Drug-Coated) Balloons for the Treatment of Primary Lesion / Occlusion of Peripheral Arteries**


Gothenburg, Sweden: The Regional Health Technology Assessment Centre (HTA-centrum); 2015.


33. Zaetta JM, Mohler ER III, Baum RA. Percutaneous interventional procedures in the patient with lower extremity claudication. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed January 2016.

AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0295 Peripheral Arteries

There are no amendments for Medicaid.

www.aetnabetterhealth.com/pennsylvania

revised 10/08/2020