Chapter 8
Vessel Preparation with Longitudinal and Controlled-Depth Micro-Incisions

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Peripheral artery disease (PAD) involving the lower extremities is an increasingly prevalent problem. It is estimated that worldwide more than >200 million people have PAD [1]. The standard practice for endovascular treatment of peripheral artery disease is percutaneous transluminal angioplasty (PTA), including plain balloon (POBA) and drug-coated balloons (DCB). The safety and efficacy of PTA compared to surgical revascularizations have been established [2]. PTA is intended to increase luminal gain in the obstructed vessel. Although PTA and DCB are primary therapies, there is risk of uncontrolled dissections, including those that are flow-limiting. Severe dissections can require bailout stenting and have subsequent negative effects on long-term clinical outcomes, including restenosis and the need for future reinterventions [3]. The FLEX Vessel Prep (FLEX VP) System (VentureMed Group, Minneapolis, MN) is a proprietary technology that enables for controlled and predictable plaque modification in long, complex lesions of varying morphology. The FLEX VP System is designed to create longitudinal, controlled-depth, circumferential micro-incisions along the entire length of a lesion that reduce the number and severity of dissections and other complications often seen with other vessel preparation devices. These controlled-depth micro-incisions help reduce the circumferential tension along the entire length of stenoses, improving vessel compliance that enables enhanced luminal gain at lower balloon inflation pressures.

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The Clinical Benefit of Reducing Dissections

PTA remains the primary intervention to treat peripheral arterial stenoses [4]. Balloon dilatation can result in uncontrolled dissections that separate the intima from the media of a vessel wall and/or cause injury to the adventitia [5, 6]. The acute vessel damage may range from a superficial plaque disruption to deep, flow-limiting dissections. Dissections are a clinical concern as dissection-induced damage to smooth muscle tissue increases the risk of stenosis due to induction of an inflammatory response, leukocyte recruitment, platelet activation, thrombosis, and neointimal hyperplasia [7–12].

Dissections have been reported across a wide range of superficial femoral artery (SFA) and popliteal angioplasties (7–84%) [13–18]. However, the reported occurrence and severity of dissection may be underestimated as data from clinical studies that utilize independent core lab review tend to report significantly higher extent and severity of dissections as compared to the dissection data reported from non-adjudicated clinical studies [19]. It has also been noted that intravascular imaging methods such as intravascular ultrasound (IVUS) or optical coherence tomography (OCT) allow for more precise identification of arterial dissections, as compared to conventional angiography, with a comparative analysis demonstrating that IVUS identified four to six times more dissections than angiography [20]. High-grade dissections post balloon angioplasty correlate with reduced patency and increased target lesion revascularization (TLR) [14, 20]. Mild-to-moderate-grade dissections also may be associated with lower patency and higher TLR rates (National Heart, Lung, and Blood Institute [NHLBI] Classification of Dissection) [4]. PTA-induced dissections have been identified as a contributing factor in acute procedure complications, such as bailout stenting, long-term clinical outcomes such as reduced patency, acute occlusions, thrombus formation, in-stent restenosis, and an increased need for future target lesion revascularization (TLR) [4, 14, 16, 20–24]. Minimizing dissection rate and severity are key to successful endovascular procedures.

Plaque morphology and lesion length play a key role in the severity of dissections after angioplasty. It is widely accepted that calcification is a more challenging lesion morphology to treat and often results in higher rates of severe dissections [16, 25–28]. In a study involving IVUS in coronary and peripheral arteries to assess dissections and calcium burden of the lesion, it was noted that 87% of dissections showed calcium deposits on the same side of the vessel wall as the dissection [25]. Unfortunately, our understanding of calcification's contribution to dissection rates during endovascular procedures is limited because severely calcified lesions that are associated with higher rates of dissections are routinely excluded as part of trial criteria [4, 28]. In addition, lesion length was found as independent predictor of severe dissection rate [14, 21].

Often dissections are treated with adjunctive therapies, such as stenting, to maximize luminal gain and improve flow dynamics. Another commonly used technique to treat dissections is prolonged balloon inflation. Contributing factors such as the location, depth, and magnitude of dissections determine the treatment algorithm. Minor

dissections (Type A or B) may not require further treatment, while more severe (Types C through F) dissections may require a bailout stent. A retrospective analysis of the incidence of post-PTA dissections found an occurrence of 84% [14]. Lesions with Type C–F dissections had a 34% TLR at 6 months, as compared to a 14% TLR for Type A and B dissections or patients with zero dissections identified in the same study [14].

The THUNDER study evaluated the safety and efficacy of a paclitaxel-coated balloon and reported that lesions with Type A and B dissections had statistically similar rates of TLR at 6 months as lesions with Types C through E (33% and 44%, respectively). At 24 months, the TLR rates increased to 43% for Type A and B dissections and to 78% for Type C through E dissections [17]. The prevalence of dissections identified via angiography has been reported to be between 50 and 85% following balloon angioplasty in the SFA [14]. POBA complication rates have been reported to be as high as 30%, including high rates of uncontrolled dissections with higher rates observed in longer lesions with likelihood that angiographically identified dissections are under-reported [20, 29–32].

Current Methods for Vessel Preparation

Although PTA remains the most common endovascular intervention, the dissections that occur remain uncontrolled and have the potential to impact the patient's long-term outcomes. Advances in vessel preparation prior to PTA show promise in reducing the risk of severe dissections and long-term adverse consequences. Numerous technologies have been developed to modify the plaque prior to endovascular treatments in order to improve therapeutic response and reduce procedural complications. Additionally, vessel preparation and plaque modification may potentially facilitate the delivery of anti-restenotic drugs across the arterial wall [33, 34]. Current technologies include specialty angioplasty balloons, atherectomy, and intravascular lithotripsy.

Specialty Angioplasty Balloons

Specialty angioplasty balloons include additional features that modify plaque by focal force, static cutting, or scoring. These balloon-based scoring devices utilize the combination of external wires or atherotomes and balloon dilatation to attempt to create controlled dissections by exerting focal force to the lesion [32]. However, limitations of these devices include fixed scoring elements, application of symmetrical focal force even when lesions are asymmetrical, potential requirement for overlapping dilatations, and risk for injury to healthy tissue due to dilatation of more normal vessel segments. A pivotal trial for evaluating intervention of a specialty scoring balloon in 245 patients with SFA/PA lesions reported dissection and stent rates of 26% and 32%, respectively [35].

Atherectomy

Atherectomy is intended to provide lumen gain by removing (debulking) the plaque through cutting, shaving, grinding, or vaporizing. The four current types of atherectomy technologies are directional, rotational, orbital, and laser. Atherectomy has reported advantages in shorter lesions, severely calcified lesions, and longer non-occlusive lesions [36, 37]. However, limitations to atherectomy include the inability to control depth of plaque removal, risk of vessel perforations during debulking, damage to the media and adventitia, and risk of embolization [38–40]. Dissection rates related to atherectomy range from 2 to 17% [41–43]. In addition to clinical risks, atherectomy may both increase procedure times and require the use of additional procedural resources related to training, capital equipment, extra time with fluoroscopy, additional ancillary products like filter devices, and inventory of multiple size single-use devices [36].

Intravascular Lithotripsy (IVL)

IVL is intended to achieve plaque modification in calcified lesions by using sonic pressure waves to create microfractures or microfissures [22, 44]. IVL relies on energy absorption by calcium and thus may have suboptimal impact on lesions with mixed morphology and/or light calcification. Furthermore, the current device is limited to 300 pulses with longer lesions requiring overlapping treatments for complete coverage. Based on its design, IVL may be best suited for shorter, severely calcified lesions with circumferential calcium deposition [45].

Creating Longitudinal Micro-Incisions to Modify Plaque with Fewer Complications

The FLEX VP System is a novel approach to vessel preparation and plaque modification that uses proprietary non-balloon technology to create multiple, longitudinal, controlled-depth micro-incisions across the entire lesion length (Fig. 8.1). These circumferential controlled-depth micro-incisions are an integral part of the design that reduce the number and severity of dissections and other complications (Fig. 8.2). The FLEX VP System is indicated for use with PTA catheters to facilitate dilation of stenoses in the femoral and popliteal arteries and treatment of obstructive lesions of native or synthetic arteriovenous dialysis fistulae. The device is also indicated for the treatment of in-stent restenosis (ISR) of balloon-expandable and self-expanding stents in the peripheral vasculature. The FLEX VP is designed for mixed morphology lesions with a range of characteristics (e.g., long, calcified).

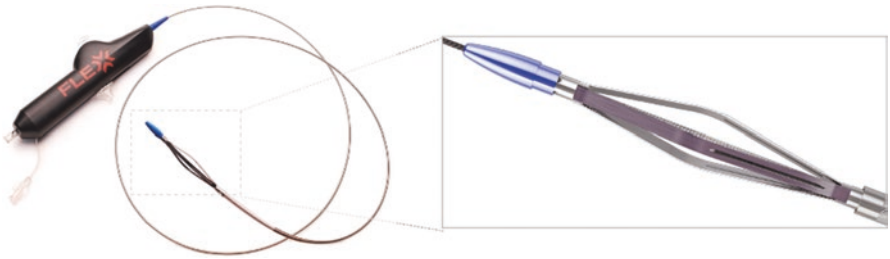

Fig. 8.1 FLEX Vessel Prep System product overview

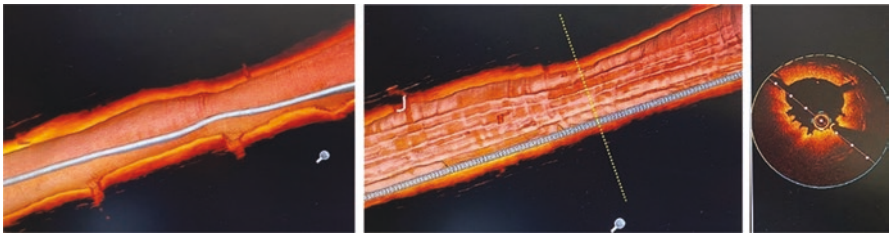

Fig. 8.2 Longitudinal optical coherence tomography reconstruction pre- (left) and post-FLEX VP (center, right) in a porcine model of superficial femoral artery in-stent restenosis demonstrating the micro-incisions (longitudinal view, center; cross-sectional view, right)

The FLEX VP is an over-the-wire sheathed catheter with a three-strut treatment element at the distal tip. It is compatible with a 6-French sheath and 0.014 in or 0.018 in guidewire and is available in two working lengths (40 cm or 120 cm). The proximal portion of each treatment element strut includes a 0.010 in height micro-surgical blade. Once the device is advanced past the lesion, the treatment element (TE) is deployed and expanded, and the catheter is drawn back, allowing the micro-surgical blades on the proximal end of each TE strut to independently engage in the lesion and create three parallel, circumferential continuous micro-incisions, with a consistent depth, along the entire length of the lesion. After the first pass, the TE is re-sheathed and advanced again through the lesion, rotated approximately 30 degrees before the treatment element is re-deployed and the retrograde pullback described above is repeated. This process is repeated based on the patient's disease characteristics. For example, a procedure with 4 passes of the device prepares the artery by performing 12 longitudinal micro-incisions in the lesions (as illustrated in Fig. 8.2 center and right panels). Additional features that benefit the clinician and adoption into current clinical practice include a braided shaft that is engineered to facilitate tracking the pullback performance; an atraumatic tip, with a 2 mm crossing profile that provides trackability and a low risk of perforation; a radiopaque marker band that facilitates placement of the FLEX VP System to treat any length lesion; and a single size that applies to most complex, mixed morphology lesions by self-sizing to the lumen diameter.

Clinical Data in Peripheral Arterial Disease

Clinical data has reported consistent outcome with FLEX VP treatment across long complex lesions [20, 46]. In over 700 peripheral arterial disease patients, average luminal gain following FLEX VP alone was 20–30% with average balloon opening pressure <5 atm and provisional stent rate of <20% in lesions with average length ranging from 136 to 245 mm (see Table 8.1 for study summary details).

Collectively, these data indicate that FLEX VP is effective in a broad range of PAD lesion lengths across real-world plaque morphologies, improves vessel compliance, is associated with reduced rate/grade/severity of dissections, and creates luminal gain without perforations or embolization.

Mechanism of Action

The longitudinal micro-incisions created by FLEX VP are key to the technology's mechanism of action in several ways. First, the treatment element struts are designed to independently "flex" (adaptively expand and compress) to the contour of the vessel wall morphology (Fig. 8.3). This is in contrast with other vessel preparation or plaque modification technologies that utilize concentric expansion of angioplasty balloons to apply focal force to the vessel wall. The independent, dynamic action of

Table 8.1 Summary of clinical studies

Subset	Patient (N)	Average lesion length (mm)	Lumen gain (%)	Balloon opening pressure (atm)	Provisional stent use (%)
Jobst retrospective study [47]	123	245 ± 102	22.4 ± 16[a]	4.8 ± 1.4[a]	17 (12)
BELONG feasibility study [48]	63	196 ± 127	N/A	N/A	11 (16.9)
iDissection study [20]	15[b]	63.6 ± 32.5	17	N/A	6 (40)
Acute outcomes [46]	255[c]	133.4 ± 87.5[d]	25.2 ± 16.4[a]	4.2 ± 1.5[a]	49 (19.2)
Post-market surveillance summary[e]	523[e]	136 ± 96[f]	31 ± 20%[a]	4.5 ± 1.6[a]	103 (19%)

[a] Subset analysis
[b] Patients also enrolled in Intact Vascular study
[c] Initial 255 patients of Post-Market Surveillance Study
[d] $N = 252$
[e] Data on file; $N = 538$ lesions in 523 patients
[f] $N = 531$

the protective struts of the FLEX VP System enables precise, controlled-depth micro-incisions that self-size to the lesion during the retrograde pullback. The FLEX VP is also indicated for ISR which can be difficult to treat due to the limitations of other vessel prep devices inside a stent (Fig. 8.4).

Minimizing disruption to the elastic lamina during vessel prep reduces the damage to the media and adventitia and associated risk of an inflammatory response leading to lower rates of restenosis [7–12]. FLEX VP evaluated in cadaveric tissue demonstrates minimal disruption to the elastic lamina while offering continuous engagement along the treated lesion (Figs. 8.5 and 8.6).

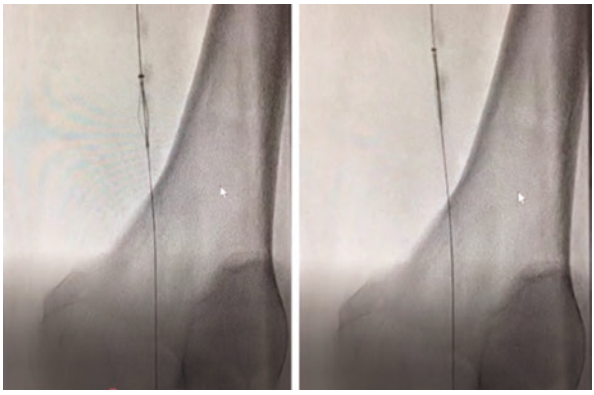

Fig. 8.3 FLEX VP treatment element shown expanded in a non-stenotic segment of the vessel (left) and FLEX VP treatment element self-sized and engaged in stenosis (right)

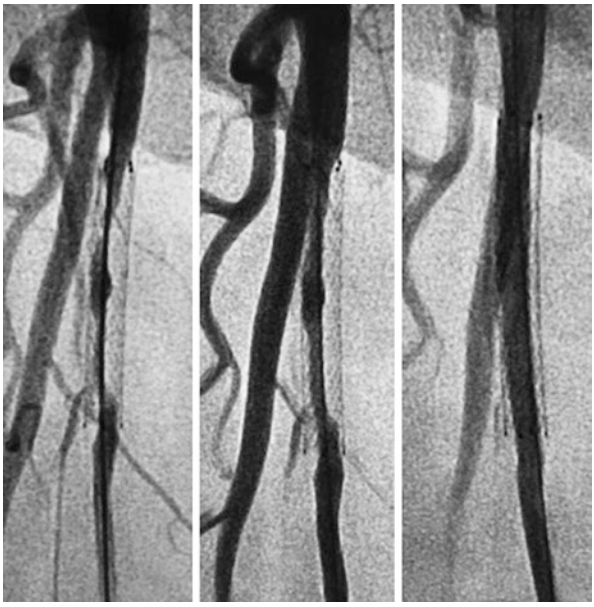

Fig. 8.4 Angiography images of in-stent restenosis in the SFA at baseline ISR (left), post-FLEX VP recanalization (middle), and final result post-DCB (right)

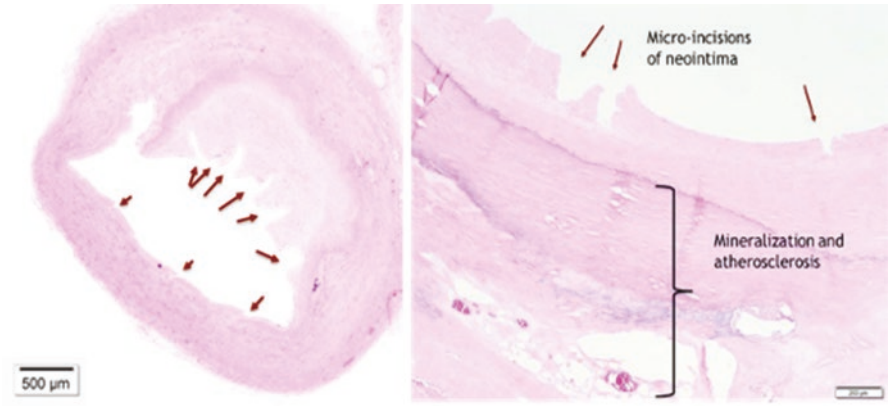

Fig. 8.5 Histology (hematoxylin and eosin stain; H&E) in a tibial cadaveric lesion with an asymmetrical neointima with partial luminal occlusion (left) and a calcified cadaveric SFA lesion (right) post-FLEX VP. Arrows indicate micro-incisions created by FLEX VP used to treat cadaveric popliteal stenosis. Micro-incision depth is equivalent to the blade height (0.25 mm)

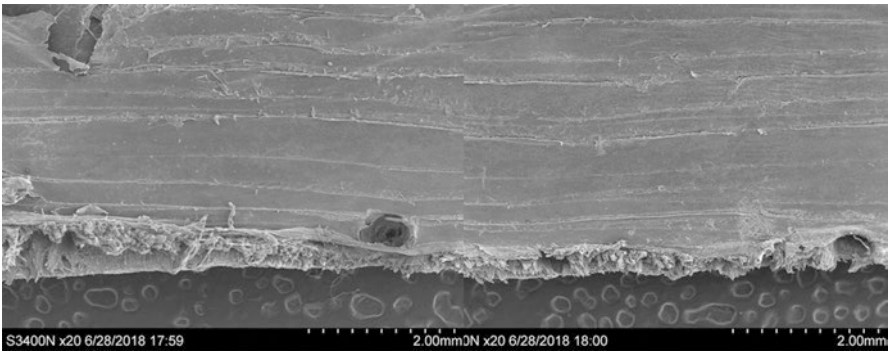

Fig. 8.6 Scanning electron microscopy (SEM) image of a cadaveric SFA treated with FLEX VP. Longitudinal lines (left to right) demonstrate consistent and parallel FLEX VP micro-incision engagement along the entire length of the lesion

Next, the circumferential placement and controlled depth of the micro-incisions improve vessel compliance and enable even lumen gain and controlled expansion of the artery during PTA or DCB. Figure 8.7 provides an optical coherence tomography (OCT) cross-sectional image of pre- and post-different vessel preparation technologies tested in an ISR porcine lesion. Vessel prep technology tested included scoring PTA, direction atherectomy, and FLEX VP. Note the lack of circumferential engagement in alternative technologies as compared to FLEX VP, which demonstrates a consistent circumferential engagement (Fig. 8.8).

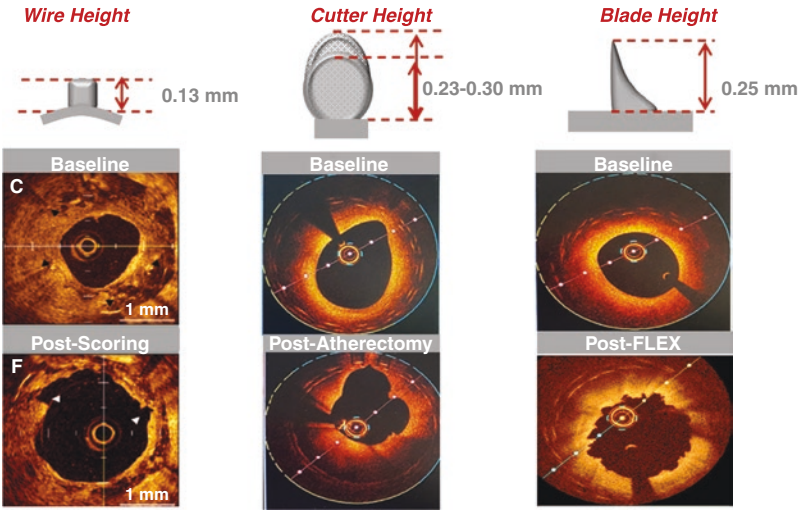

Fig. 8.7 OCT cross section of pre- (baseline, top image) and post- (bottom images) application of different vessel preparation technologies tested in an ISR porcine lesion. Vessel prep technology tested included wire-wrapped balloon scoring PTA directional atherectomy and FLEX VP

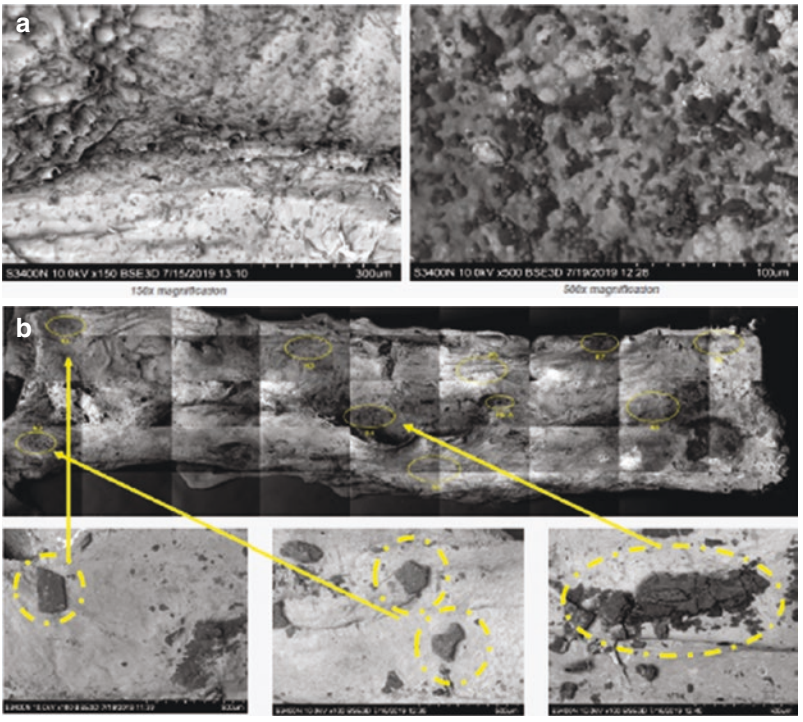

Fig. 8.8 Confirmation of drug deposition along FLEX VP micro-incisions. (**a**) Sirolimus drug microspheres deposited in the FLEX micro-incisions after DCB treatment in cadaveric lesions. (**b**) Shards of paclitaxel from a drug-coated balloon treating a cadaveric lesion post-FLEX VP

FLEX VP Micro-Incisions May Facilitate Drug Delivery

In addition to improving vessel compliance, FLEX VP micro-incisions potentially facilitate the diffusion of anti-restenotic drugs to the target lesions from drug-coated or drug-eluting technologies. SEM evaluation in human cadaver studies confirms the deposition of both sirolimus and paclitaxel anti-restenotic drugs into FLEX VP micro-incisions (Fig. 8.8).

A retrospective clinical study evaluating 12-month outcomes of patients with de novo SFA/PA lesions treated with FLEX VP prior to a DCB reported freedom from TLR rates (>93%) that were comparable to freedom from TLR rates reported for DCBs with published superior performance characteristics [49, 50]. Thus, these encouraging early patency results suggest that vessel preparation with circumferential, controlled-depth, continuous micro-incisions may facilitate DCB drug delivery [33, 34]. Results from this retrospective observational study are currently being investigated in the BELONG prospective study (NCT03721939).

Future Directions

In conclusion, the FLEX VP System provides safe plaque modification and vessel preparation via consistent circumferential controlled-depth micro-incisions in complex, mixed morphology PAD lesions. FLEX VP is currently indicated for use with PTA catheters to facilitate dilation of stenoses in the femoral and popliteal arteries and treatment of obstructive lesions of native or synthetic arteriovenous dialysis fistulae. In addition, FLEX VP is indicated for ISR treatment of balloon-expandable and self-expanding stents in the peripheral vasculature. Future directions include seeking expanded indications to include below-the-knee lesions. Other new indications being evaluated include venous, iliac, and coronary applications.

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