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IN.PACT™ Admiral™ DCB: Safety and Effectiveness in Treating Complex Lesions

Weighing the risks and benefits when treating complex lesions in the femoropopliteal vascular bed.

By Gary M. Ansel, MD, FACC

I am pleased to encore and update the lesion length and patency scatter plot from when it was first published in November 2018. Because the treatment considerations have become more complex, I hope that this updated scatter plot helps in the treatment planning of symptomatic femoropopliteal artery disease.

CURRENT CLINICAL DATA FOR COMPLEX LESIONS

As physicians, we have all seen summary graphics similar to Figure 1. It is still pertinent that comparing patency rates across multiple trials is fraught with limitations due to variations in populations, lesions, study protocols, definitions, follow-up, and various types of inherent biases. Especially in light of the concerns raised with respect to a late mortality signal in patients with peripheral artery disease who are treated with paclitaxel-coated devices in the femoropopliteal artery,[1] this figure offers us insight into the overall clinical patency and repeat intervention data of core laboratory–adjudicated femoropopliteal studies of FDA class 3 devices and their respective control arms. Since the modest beginning of Figure 1's data points more than 10 years ago, the landscape has certainly evolved; but, a few particular trends have become apparent and seem to persist. This article highlights and discusses each of these trends, and it has been updated with the most current available data, including results from the Real PTX trial, the IMPERIAL Long Lesion substudy, and Viabahn Japan.

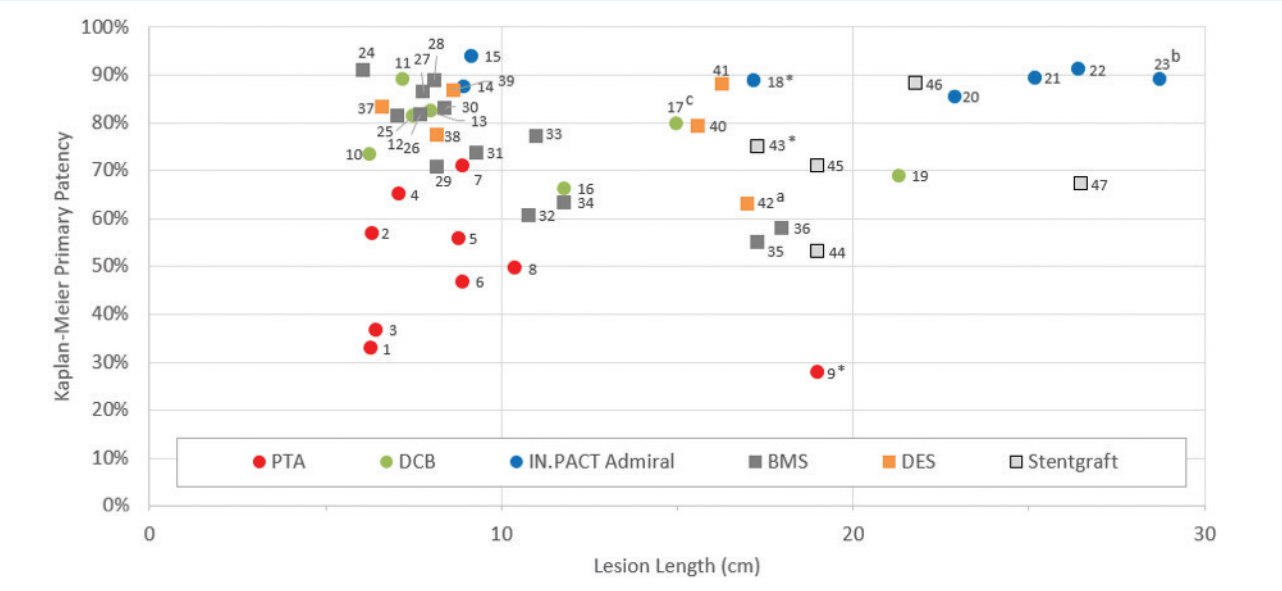
DATA EXIST MOSTLY FOR LESIONS ≤ 10 CM

We still see a majority of data clustered toward shorter lesions. As you might expect, these lesions range from approximately 5 to 12 cm and typically comprise what most operators define as the simple disease process often encountered in investigational device exemption studies that device manufacturers are required to perform to gain FDA approval (Figure 1; data points 1-8, 10-16, 23-39). However, these lesions are typically uncommon in many of our clinical practices and attempting to extrapolate these data sets to longer, more complex lesion types is a challenge. For what most of us would describe as more moderate lesion lengths (15–20 cm), we are still limited to five studies consisting of the prespecified in-stent restenosis (ISR) cohort of IN.PACT Global (Figure 1; 18); the randomized ISR cohorts treated with either percutaneous transluminal angioplasty (PTA) or heparin-bound stent graft of the RELINE study (Figure 1; 9, 43); the cohorts of heparin-bound stent graft and non-bound stent graft randomized against their bare-metal stent (BMS) control arms of VIASTAR (Figure 1; 35, 45) and VIBRANT (Figure 1; 36, 44), respectively; and the ZEPHYR single-arm Japan postmarket approval study of a drug-eluting stent (DES) (Figure 1; 42). The more complex lesion data sets (ie, those with lesions longer than 20 cm) continue to be sparse, with outcomes reported from five drug-coated balloon (DCB) cohorts from three studies and a single peripheral stent graft study (Figure 1; 19-23, 47). The message here is that although many of us practice in the domain beyond 15 cm, the vast majority of adjudicated outcomes come from data sets that are significantly shorter than this range.

CONVENTIONAL PTA PATENCY CLUSTERS TOWARD LOW END

For the previous gold standard of PTA, we see the outcomes clustering toward the low patency end of

Figure 1. Core lab–adjudicated 12-month primary patency by Kaplan-Meier estimate of FDA-approved class 3 devices and their control arms.



Qualitative comparison for illustration purposes only. Not meant for head-to-head comparison.

Data Point	Cohort	Patency Definition
1	Zilver PTX RCT: PTA arm[2]	PSVR < 2.0 or < 50% stenosis
2	LEVANT II RCT: PTA arm[3]	PSVR < 2.5 and freedom from TLR
3	RESILIENT RCT: PTA arm[4]	PSVR < 2.5 and freedom from TLR
4	ILLUMENATE EU RCT: PTA arm[5]	PSVR ≤ 2.5 and freedom from TLR
5	IN.PACT SFA RCT: PTA arm[6]	PSVR ≤ 2.4 and freedom from CD-TLR
6	IN.PACT Japan RCT: PTA arm[7]	PSVR ≤ 2.4 and freedom from CD-TLR
7	ILLUMENATE Pivotal RCT: PTA arm[8]	PSVR ≤ 2.5 and freedom from TLR
8	SFA ISR IDE RCT: PTA arm[9]	Freedom from restenosis and CD-TLR
9	RELINE RCT: PTA arm[10]	PSVR < 2.5 and freedom from TLR
10	LEVANT II RCT: Lutonix 035 DCB arm[3]	PSVR < 2.5 and freedom from TLR
11	ILLUMENATE EU RCT: Stellarex DCB arm[5]	PSVR ≤ 2.5 and freedom from TLR
12	ILLUMENATE Global: Stellarex DCB[11]	PSVR ≤ 2.5 and freedom from TLR
13	ILLUMENATE Pivotal RCT: Stellarex DCB arm[8]	PSVR ≤ 2.5 and freedom from TLR
14	IN.PACT SFA RCT: IN.PACT Admiral DCB arm[6]	PSVR ≤ 2.4 and freedom from CD-TLR
15	IN.PACT Japan RCT: IN.PACT Admiral DCB arm[7]	PSVR ≤ 2.4 and freedom from CD-TLR
16	SFA ISR IDE RCT: Lutonix 035 DCB arm[9]	Freedom from restenosis and CD-TLR
17	REAL PTX - DCB arm[12]	Binary restenosis: PSVR > 2.4 and freedom from CD-TLR
18	IN.PACT Global - ISR: IN.PACT Admiral DCB[13]	PSVR ≤ 2.4 and freedom from TLR
19	Lutonix Long Lesion: Lutonix 035 DCB[9]	Freedom from restenosis and CD-TLR
20	IN.PACT Global - CTO: IN.PACT Admiral DCB[14]	PSVR ≤ 2.4 and freedom from CD-TLR
21	SFA-Long Study: IN.PACT Admiral DCB[15]	Freedom from >50% restenosis and CD-TLR
22	IN.PACT Global - Long Lesion: IN.PACT Admiral DCB[16]	PSVR ≤ 2.4 and freedom from CD-TLR
23	IN.PACT Global - Complex Lesion post-hoc subset: IN.PACT Admiral DCB[6]	PSVR ≤ 2.4 and freedom from CD-TLR
24	Complete SE SFA - Complete SE Stent[17]	PSVR < 2.0 and freedom from revascularization
25	RESILIENT RCT: LifeStent stent arm[4]	PSVR < 2.5 and freedom from TLR
26	STROLL: SMART stent[18]	PSVR < 2.5 / 50% diameter stenosis and freedom from TLR
27	SUPERB: Supera stent[19]	PSVR ≤ 2.0 and freedom from TLR
28	SIROCCO RCT: SMART stent arm[20]	≤ 50% stenosis by angiography
29	BioFlex 1: Astron and Pulsar stents[21]	PSVR ≤ 2.4 and freedom from CD-TLR
30	OSPREY: Misago stent[22]	PSVR < 2.5 and freedom from TLR
31	SUPERNOVA: Innova stent[23]	PSVR < 2.4 and freedom from TLR
32	TIGRIS RCT: Tigris stent arm[24]	PSVR ≤ 2.5 and freedom from TLR
33	DURABILITY II: Protégé EverFlex stent[25]	PSVR < 2.0 and freedom from CD-TLR
34	TIGRIS RCT: LifeStent stent arm[24]	PSVR ≤ 2.5 and freedom from TLR
35	VIASTAR RCT: BMS arm[26]	PSVR ≤ 2.5 or < 50% stenosis
36	VIBRANT RCT: BMS arm[27]	PSVR < 2.5 and freedom from TLR
37	Zilver PTX RCT: Zilver PTX DES arm[2]	PSVR < 2.0 or < 50% stenosis
38	IMPERIAL RCT: Zilver PTX DES arm[28]	PSVR ≤ 2.4 and FF CD-TLR
39	IMPERIAL RCT: Eluvia DES arm[28]	PSVR ≤ 2.4 and FF CD-TLR
40	REAL PTX - DES arm[12]	Binary restenosis: PSVR > 2.4 and freedom from CD-TLR
41	IMPERIAL Long Lesion: Eluvia DES[29]	PSVR ≤ 2.4 and FF CD-TLR
42	ZEPHYR: Zilver PTX DES[30]	PSVR ≤ 2.4 or < 50% stenosis
43	RELINE RCT: Viabahn heparin-bonded stent-graft arm[10]	PSVR < 2.5 and freedom from TLR
44	VIBRANT RCT: Viabahn stent-graft arm[27]	PSVR < 2.5 and freedom TLR
45	VIASTAR RCT: Viabahn heparin-bonded stent-graft arm[26]	PSVR ≤ 2.5 or < 50% stenosis
46	Viabahn Japan[31]	PSVR < 2.5 and FF TLR
47	Viabahn-25 cm: Viabahn heparin-bonded stent-graft[32]	PSVR ≤ 2.5 and freedom from TLR

*In-stent restenosis studies.
[a]Subset analysis of previously reported data. IN.PACT Global Complex Lesion cohort consists of 227 patients enrolled in the three IN.PACT Global prespecified imaging cohorts (long lesion, CTO, and in-stent restenosis) exhibiting lesion lengths > 18 cm.
[b]Patency is reported using proportion rates in the ZEPHYR study.
[c]A mix of DCBs were used in the REAL PTX study.
Abbreviations: BMS, bare-metal stent; CD-TLR, clinically driven target lesion revascularization; CTO, chronic total occlusion; DCB, drug-coated balloon; DES, drug-eluting stent; PSVR, peak systolic velocity ratio; PTA, percutaneous transluminal angioplasty; RCT, randomized controlled trial; SFA, superficial femoral artery.

the shorter lesions. Although a variation certainly exists within the PTA cohorts, we have to keep in mind that the study protocols, endpoint definitions, and technical practices have evolved during the decade of performing these studies. For instance, compare the two control arms of the Zilver PTX and RESILIENT randomized trials, which posted PTA patency rates of 32.8% and 36.7%, respectively (Figure 1; 1, 3), in lesions of approximately 6.5 cm, against a contemporary DCB control arm such as the ILLUMENATE Pivotal trial control patency rate of 70.9% (Figure 1; 7). In doing so, we see how factors such as randomization after various definitions of successful predilatation and sustained balloon inflation complicate comparisons across studies. Despite this variability, PTA clearly occupies the low end of the patency spectrum, and this treatment has all but been supplanted in randomized trials by advancing technology.

PRIMARY PATENCY IS INVERSELY PROPORTIONAL TO LESION LENGTH

It is evident that there is a declining patency rate associated with the increasing complexity of a lesion, often based on long lesion length. This underscores the pitfall of extrapolating data captured in short-lesion approval studies to our own practices, where much more complex and longer lesions are commonplace. Less is known about length-dependent performance of DESs given the lack of available core lab–controlled data. The core lab–adjudicated ZEPHYR DES study reports positive 12-month outcomes in a challenging population exhibiting a mean lesion length of 17 cm (Figure 1; 42), as do those in the IMPERIAL Long Lesion study with a mean lesion length of 16.3 cm (Figure 1; 41). These add to the experience of shorter-lesion DES cohorts studied as part of the Zilver PTX and IMPERIAL trials (Figure 1; 37-39).

Diverging from independently adjudicated patency outcomes, both the all-comers Japan Zilver PTX postmarket surveillance study and a single-center retrospective analysis demonstrate patency consistent with outcomes observed in the shorter-lesion randomized controlled trials (RCTs), despite reported mean lesion lengths of 14.7 and 24.2 cm, respectively.[33,34] Importantly, further analysis of noncore lab–adjudicated data from Phillips et al did discern higher patency in DES-treated lesions ≤ 20 cm compared with those > 20 cm, the latter of which also exhibited a higher proportion of occlusions.[34] This once again suggests a length-dependency effect on patency for very long lesions treated with DESs.[34] However, as stent length increases, the discussion of stent fracture cannot be totally ignored. Consider 12-month outcomes of two cohorts employing the same stent: the RESILIENT study's BMS arm reported a fracture rate of 3.1% for lesions averaging 7.1 cm (Figure 1; 25) compared with a fracture rate of 27.1% for lesions averaging 11.8 cm in the TIGRIS study BMS arm (Figure 1; 34). Despite being a well-known phenomenon, the consequences of lesion length and fracture are not fully understood or consistent between stent designs.[35]

IN.PACT GLOBAL PRESPECIFIED IMAGING COHORTS BUCK THE TREND IN LESION LENGTH

There are few adjudicated data that exist for treatment of lesion lengths > 20 cm; the only data available is composed of five DCB cohorts from three studies (Figure 1; 19-23) and a single heparin-bound stent graft study (Figure 1; 45). Historically, studies in this range came late in the evolution of these data. Zeller et al[32] reported the outcomes associated with the 25-cm heparin-bound stent graft in lesions averaging 26.5 cm (Figure 1; 45), interestingly with non–length-dependent patency rates similar to those reported in the RELINE and VIASTAR studies (Figure 1; 43, 45). For the DCB cohorts, the Lutonix Long Lesion study reported a mean lesion length of 21.3 cm (Figure 1; 19); the chronic total occlusion and long lesion prespecified imaging cohorts of the IN.PACT Global study posted mean lesion lengths of 22.8 and 26.4 cm, respectively (Figure 1; 20, 22); and the SFA-Long study performed by Micari et al[15] averaged 25.2 cm lesion lengths (Figure 1; 21). Importantly, when considering the IN.PACT™ Admiral™ DCB (Medtronic) cohorts, the patency definition is identical across the two RCTs and the three prespecified imaging cohorts of IN.PACT Global, therefore facilitating patency comparisons across cohorts and underscoring the consistency in patency beyond 20-cm lesions, despite variation in study populations and lesion morphologies. However, it is also worth highlighting that these long-lesion DCB studies are not without significant provisional stent usage; in three of these four cohorts, provisional stent rates of approximately ≥ 40% were reported (Figure 1; 19, 20, 22). The one exception to this trend of provisional stenting is reported by the SFA-Long study, which demonstrated similar patency results while only resorting to provisional stenting in 10.5% of lesions (Figure 1; 21).

The IN.PACT Admiral DCB results of lesion lengths up to 53 cm were obtained from a post hoc analysis performed on all core lab–adjudicated IN.PACT Global patients who exhibited lesions ≥ 18 cm, including patients with ISR (Figure 1; 23). The outcomes are consistent with the other IN.PACT Admiral DCB trends demonstrated in Figure 1, and 96 (42.5%) of 227 patients received provisional stenting of various lengths. Importantly, this observation indicates that using a DCB with stents led to patency similar to the simpler lesions treated with DCBs alone.

CONCLUSION

From the simple, single-digit lesion lengths to the truly long lesions, we certainly have more insight today than 10 years ago. We are all left with our own interpretation of these data, but a few trends are evident: (1) PTA is at the low end of the performance range; (2) length-dependent patency is a consistent observation for PTA and BMSs; and (3) DCBs and, if needed, provisional stent optimization may yield consistent patency with apparently less lesion length dependence. Of course, the data continue to evolve, and we hope it will not take us another 10 years to identify new trends, possibly aided by the evolution of lesion preparation with new specialty balloon technologies, atherectomy, and yet-to-be-developed devices that may be used prior to DCBs. ■

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Disclosures: Consulting or advisory board for Medtronic, Boston Scientific Corporation, Abbott Vascular, Surmodics, Philips, CR Bard, and Cook Medical.

The IN.PACT™ Admiral™ drug-coated PTA balloon catheter: Brief Statement
Indications for Use

- The IN.PACT Admiral Paclitaxel-coated PTA balloon catheter is indicated for percutaneous transluminal angioplasty, after appropriate vessel preparation, of de novo, restenotic, or in-stent restenotic lesions with lengths up to 360 mm in superficial femoral or popliteal arteries with reference vessel diameters of 4-7 mm.

Contraindications

The IN.PACT Admiral DCB is contraindicated for use in:

- Coronary arteries, renal arteries, and supra-aortic/cerebrovascular arteries
- Patients who cannot receive recommended antiplatelet and/or anticoagulant therapy
- Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the delivery system
- Patients with known allergies or sensitivities to paclitaxel
- Women who are breastfeeding, pregnant or are intending to become pregnant or men intending to father children. It is unknown whether paclitaxel will be excreted in human milk and whether there is a potential for adverse reaction in nursing infants from paclitaxel exposure.

Warnings

- Use the product prior to the Use-by Date specified on the package.
- Contents are supplied sterile. Do not use the product if the inner packaging is damaged or opened.
- Do not use air or any gaseous medium to inflate the balloon. Use only the recommended inflation medium (equal parts contrast medium and saline solution).
- Do not move the guidewire during inflation of the IN.PACT Admiral DCB.
- Do not exceed the rated burst pressure (RBP). The RBP (14 atm [1419 kPa]) is based on the results of in vitro testing. Use of pressures higher than RBP may result in a ruptured balloon with possible intimal damage and dissection.
- The safety and effectiveness of using multiple IN.PACT Admiral DCBs with a total drug dosage exceeding 34,854 µg of paclitaxel in a patient has not been clinically evaluated.

Precautions

- This product should only be used by physicians trained in percutaneous transluminal angioplasty (PTA).
- This product is designed for single patient use only. Do not reuse, reprocess, or resterilize this product. Reuse, reprocessing, or resterilization may compromise the structural integrity of the device and/or create a risk of contamination of the device, which could result in patient injury, illness, or death.
- Assess risks and benefits before treating patients with a history of severe reaction to contrast agents.
- The safety and effectiveness of the IN.PACT Admiral DCB used in conjunction with other drug-eluting stents or drug-coated balloons in the same procedure or following treatment failure has not been evaluated.
- The extent of the patient's exposure to the drug coating is directly related to the number of balloons used. Refer to the Instructions for Use (IFU) for details regarding the use of multiple balloons and paclitaxel content.
- The use of this product carries the risks associated with percutaneous transluminal angioplasty, including thrombosis, vascular complications, and/or bleeding events
- Vessel preparation using only pre-dilatation was studied in the clinical study. Other methods of vessel preparation, such as atherectomy, have not been studied clinically with IN.PACT Admiral DCB.
- This product is not intended for the expansion or delivery of a stent.

Potential Adverse Effects

- The potential adverse effects (e.g. complications) associated with the use of the device are: abrupt vessel closure; access site pain; allergic reaction to contrast medium, antiplatelet therapy, or catheter system components (materials, drugs, and excipients); amputation/loss of limb; arrhythmias; arterial aneurysm; arterial thrombosis; arteriovenous (AV) fistula; death; dissection; embolization; fever; hematoma; hemorrhage; hypotension/hypertension; inflammation; ischemia or infarction of tissue/organ; local infection at access site; local or distal embolic events; perforation or rupture of the artery; pseudoaneurysm; renal insufficiency or failure; restenosis of the dilated artery; sepsis or systemic infection; shock; stroke; systemic embolization; vessel spasms or recoil; vessel trauma which requires surgical repair.
- Potential complications of peripheral balloon catheterization include, but are not limited to the following: balloon rupture; detachment of a component of the balloon and/or catheter system; failure of the balloon to perform as intended; failure to cross the lesion.
- Although systemic effects are not anticipated, potential adverse events that may be unique to the paclitaxel drug coating include, but are not limited to: allergic/immunologic reaction; alopecia; anemia; gastrointestinal symptoms; hematologic dyscrasia (including leucopenia, neutropenia, thrombocytopenia); hepatic enzyme changes; histologic changes in vessel wall, including inflammation, cellular damage, or necrosis; myalgia/arthralgia; myelosuppression; peripheral neuropathy.
- Refer to the Physician's Desk Reference for more information on the potential adverse effects observed with paclitaxel. There may be other potential adverse effects that are unforeseen at this time.
- Please reference appropriate product Instructions for Use for a detailed list of indications, warnings, precautions and potential adverse effects. This content is available electronically atwww.manuals.medtronic.com.

CAUTION: Federal (USA) law restricts this device to sale by or on the order of a physician.