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 symptom-atric 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, 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 VIAST AR (Figure 1; 35, 45) and VIBRANT (Figure 1; 36, 44), respectively; and the ZEPHIR 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
Table 1: Overview of patency definitions for various studies.

<table>
<thead>
<tr>
<th>Data Point</th>
<th>Cohort</th>
<th>Patency Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Zilver PTX RCT: PTA arm²</td>
<td>PSVR &lt; 2.0 or &lt; 50% stenosis</td>
</tr>
<tr>
<td>2</td>
<td>LEVANT II RCT: PTA arm³</td>
<td>PSVR &lt; 2.5 and freedom from TLR</td>
</tr>
<tr>
<td>3</td>
<td>RESILIENT RCT: PTA arm³</td>
<td>PSVR ≤ 2.5 and freedom from TLR</td>
</tr>
<tr>
<td>4</td>
<td>IN.PACT SFA RCT: PTA arm⁵</td>
<td>PSVR ≤ 2.4 and freedom from CD-TLR</td>
</tr>
<tr>
<td>5</td>
<td>IN.PACT Japan RCT: PTA arm⁶</td>
<td>PSVR ≤ 2.4 and freedom from CD-TLR</td>
</tr>
<tr>
<td>6</td>
<td>LIMENATE Global: Lutonix 035 DCB arm⁷</td>
<td>PSVR ≤ 2.5 and freedom from TLR</td>
</tr>
<tr>
<td>7</td>
<td>IN.PACT Global - Complex Lesion cohort: IN.PACT Admiral DCB⁸</td>
<td>PSVR ≤ 2.5 and freedom from TLR</td>
</tr>
<tr>
<td>8</td>
<td>IN.PACT Global - Complete SE SFA - Complete SE Stent⁹</td>
<td>Freedom from restenosis and CD-TLR</td>
</tr>
<tr>
<td>9</td>
<td>SIROCCO RCT: Viabahn heparin-bonded stent-graft Arm⁴</td>
<td>PSVR &lt; 2.5 and freedom from TLR</td>
</tr>
</tbody>
</table>

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.

Figures 1-4: Qualitative comparison for illustration purposes only. Not meant for head-to-head comparison.
the shorter lesions. Although a variation certainly exists within the PTA cohorts, we have to keep in mind that the study protocols, end-point definitions, and technical practices have evolved during the decade of performing these studies. For instance, consider 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 ILLUMINATE 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. 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. This one again suggests a length–dependency effect on patency for very long lesions treated with DESS. 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.

**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 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 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 the 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.

5. IN.PACT. Admiral DCB [Instructions for Use - Revision 1G]. Minneapolis, Minnesota: Medtronic; 2018.

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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 266 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-dilation 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, angioplasty 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; hypertension/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 leukopenia, 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 at www.manuals.medtronic.com.

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

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