Drug Elution, Data, and Decisions

What the data tell us about how to integrate drug-eluting technology into our daily practice.

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The use of drug-eluting technology has been studied and subsequently utilized for the treatment of peripheral vascular disease for over a decade. Specific to the superficial femoral and popliteal arterial segment during this time interval, investigators have conducted many trials for both drug-coated balloons (DCBs) and drug-eluting stents (DES). The Zilver PTX DES (Cook Medical) is the first drug-eluting technology to be approved in the United States. The 5-year data were presented at the VIVA 2014 meeting and demonstrated stable patency with superiority over both percutaneous transluminal angioplasty (PTA) and bare-metal stents (BMS). More recent randomized controlled datasets have been presented for DCBs in the LEVANT 2 and IN.PACT SFA trials. Both trials have demonstrated that safety and 1-year effectiveness of these DCBs are superior to plain old balloon angioplasty. However, durable longer-term results for DCBs are yet to be demonstrated.

Currently, it may not be fully apparent how physicians should incorporate DES and DCBs into their daily interventional practice. To this end, what do the latest well-designed trials tell us about each technology, and more importantly, what do the data suggest about how we should incorporate these devices into our practice? For this discussion, we focus on three pivotal trials and, based on the latest level-1 clinical evidence supplemented by real-world registries, deduce how we should initially implement DCBs and DES into everyday practice. In this article, we do not address the use of stent grafts (which have demonstrated superiority over BMS and equivalency to prosthetic open bypass), atherectomy (which has no randomized datasets but growing registry data), nor open surgical bypass.

ZILVER PTX DATA

The Zilver PTX trial is the largest and only randomized and controlled peripheral endovascular device trial with 5-year follow-up data. There is an abundance of peer-reviewed data demonstrating the safety and effectiveness of this device. Importantly, most of the data are centered around the typical pivotal patency, utilizing a duplex PSVR (peak systolic velocity ratio) of 2.0. For this discussion, we will limit the scope to published or presented 1- and 4-year data for primary patency and target lesion revascularization (TLR).

With respect to 1-year patency, primary Zilver PTX stenting demonstrated statistically significant superiority to optimal PTA, and provisional Zilver PTX stenting

TABLE 1. ZILVER PTX 12-MONTH RESULTS ACROSS TRIALS*

	Zilver PTX RCT (Zilver PTX arm only: United States, Japan, Germany)	Zilver PTX Single-Arm Study (European Union, Korea, Canada)	Zilver PTX Japan PMS (Japan)
Number of patients	236	787	907
PSVR	2.0	2.0	2.4
12-month primary patency	84.4%	82.8%	84.8%
Freedom from TLR at 12 months	91.6%	89.5%	91.4%

**Data adapted from Yokoi Y.[1]*
Abbreviations: PMS, postmarketing surveillance; RCT, randomized controlled trial.

was superior to BMS use.[2] Zilver PTX also demonstrated superior TLR rates when compared to either optimal PTA or when comparing provisional Zilver PTX stenting to the use of BMS.[2]

Additionally, the paclitaxel drug effect of Zilver PTX was sustained through 4 years. Four-year data from the Zilver PTX trial demonstrated a 75% primary patency rate compared to a 57.9% patency rate for patients who underwent provisional BMS placement in the study. This represents a 41% reduction in 4-year restenosis, favoring DES over BMS placement.[3] Furthermore, freedom from TLR was 83.2% for Zilver PTX compared to 69.4% of patients who were treated with standard care (BMS or successful PTA).[3] The data from the Zilver PTX randomized controlled trial are supported by large, single-arm registry studies conducted in Europe and Japan. Dr. Hiroyoshi Yokoi recently presented data from the Japan post-market study with a 12-month freedom from TLR rate of 91.7% (Table 1).[1] The 5-year Zilver PTX data were presented at VIVA 2014, and the results were generally consistent with the 4-year results.

DCB TRIAL RESULTS AT A GLANCE

LEVANT 2 Trial

On October 10, 2014, the US Food and Drug Administration approved the Lutonix paclitaxel DCB (Bard Peripheral Vascular, Inc.) for use in the United States. The primary composite safety endpoint for Lutonix was noninferiority to PTA (Table 2). For the primary effectiveness endpoint, utilizing duplex scan evaluation with a PSVR of 2.5, Lutonix demonstrated superior 12-month patency rates to PTA using Kaplan-Meier estimates (73.5% vs 56.8%). However, when using the VIVA criteria (PSVR = 2.0), which is typical of most pivotal trials for primary patency assessment, there is no significant difference between Lutonix and PTA ($P = 0.13$).[4]

The Lutonix freedom from TLR dataset demonstrated no significant difference with balloon angioplasty alone at 12 months. It should be noted that there were a couple of unique aspects to this trial design that may have affected the TLR result. First, trial prescreening involved assessment of the lesion's response to predilation and excluded patients who did not respond favorably, thereby resulting in PTA patency rates that were much higher than what has been seen in most pivotal trials. Additionally, for the first time, investigators were blinded during follow-up, which may have lowered TLR rates.[4] Despite the lower-than-expected patency rates, Lutonix's results did show a favorable trend over PTA on several endpoints, suggesting that there is a benefit conferred from the paclitaxel coating.

IN.PACT SFA II

On April 5, 2014, Prof. Gunnar Tepe presented the 12-month data from the IN.PACT SFA II trial at the Charing Cross meeting in London (Table 3).[5] This randomized controlled trial compared the In.Pact Admiral DCB (Medtronic, Inc.) to standard PTA, with results suggesting significant patency and clinical benefits when using the In.Pact DCB. Both the 12-month primary patency rates and the 12-month clinically driven TLR rates for In.Pact were superior to PTA. Follow-up was not blinded, but nonetheless, the patency data suggest that there is in fact a significant drug effect with the In.Pact balloon when compared to standard PTA. Although the In.Pact DCB data appear more promising than that of Lutonix, comparing the two trials is fraught with bias, especially as they had different blinding during follow-up. The In.Pact DCB awaits US Food and Drug Administration approval and is presently an investigational devices in the United States. We are eager to learn more about the device datasets as more peer-reviewed information becomes available.

One-year TLR data from the initial 655 patients in the ongoing IN.PACT Global trial were recently presented at the 2014 Transcatheter Therapeutics meeting in Washington, DC. This outside-the-United States, core-lab-adjudicated (core lab patency only for long lesions

TABLE 2. LEVANT II TRIAL DATA FOR LUTONIX

	Lutonix	Control PTA	*P* Value
Primary composite safety endpoint (freedom from perioperative death and 12-month index limb amputation [above and below the ankle], index limb reintervention and index limb-related death)	83.9%	79%	0.005
12-month primary patency (Kaplan-Meier, PSVR = 2.5)	73.5%	56.8%	< 0.001
12-month primary patency (PSVR = 2.0)	53.2%	45%	0.13*
Total TLR at 12 months	12.3%	16.8%	0.208*

**No statistically significant difference.*

TABLE 3. IN.PACT SFA II TRIAL DATA FOR IN.PACT ADMIRAL			
	In.Pact Admiral	**Control PTA**	***P* Value**
Primary safety composite	95.7%	76.6%	< 0.001
12-month primary patency (Kaplan-Meier, PSVR = 2.4)	89.8%	66.8%	< 0.001
Clinically driven TLR at 12 months	97.5%	79.3%	< 0.001

and chronic total occlusions), global DCB registry has a planned enrollment of 1,500 patients. The TLR rate for the 655 patients who were evaluable at the 1-year time point was an impressive 8.7%. This low TLR rate is consistent with the randomized trial and is certainly in line with the impressively low TLR rate seen in the randomized trial.

DATA GAPS AND TRIAL DIFFERENCES BETWEEN DCB AND DES

Before we determine what the data tell us about how to incorporate drug-eluting devices into our practice, there are several gaps between DCB data and DES data that must be acknowledged. The first gap is in long-term follow-up. Although all three of the previously mentioned main trials are planned for 5-year follow-up, only the Zilver PTX DES has long-term results available to support its sustained effectiveness. The Lutonix and In.Pact DCBs have only presented non-peer-reviewed 1-year data. Previous studies, such as the SIROCCO II trial (DES) and the THUNDER trial (DCB), demonstrated continued late lumen loss, and this possibility must be considered when physicians evaluate DCB technology as it becomes more widely available.

There are also critical differences in trial design that must be factored in as we consider how and when to use drug-eluting technology. Perhaps the most important difference between the two DCB trials and the DES trials is that these two DCB trials perform screening via standard PTA. In both LEVANT 2 and IN.PACT SFA II, if the lesion did not respond well to the initial predilatation with balloon angioplasty to provide the investigator a reasonable assurance that the lesion would not require stenting, then that patient was not randomized to the control or treatment arm. Because these patients failed the initial screening angioplasty, they were considered a "screen fail" and were not placed in the study or the final results.

Although in this trial design it makes sense to eliminate confounding variables in order to more easily discern the effectiveness of the drug on the balloon, it significantly distorts the ability to generalize effectiveness endpoints to a wider population. For example, when looking at the IN.PACT trial, the PTA patency at 12 months was 66.8% for all PTA. When looking across several trials, the 12-month patency numbers for PTA tend to be much lower because an initial PTA failure was tracked as failed PTA (Table 4). The process of screening lesions may contribute to the significantly higher standalone patency numbers for DCBs by effectively eliminating suboptimal PTA results that would typically require stenting from the trial. This fact becomes even more apparent when looking at the proportion of severely calcified lesions in the three trials (Table 5).

Although the definition of calcification is variable, the Zilver PTX trial appears to have included significantly more calcified lesions than the DCB trials. If accurate, this is an important point because it is becoming increasingly apparent that calcification may be a significant issue that impacts the overall effectiveness of DCBs in real-world lesions. Fanelli et al noted this limitation of DCBs in the conclusion of a recently peer-reviewed publication.[8] To quote the authors, "Calcium represents a barrier to optimal drug absorption. Circumferential distribution seems to be the most influencing factor with the worst effect noticed in 360° calcium presence."[8] The issue of calcification certainly raises other questions, as well. The reported provisional stenting rate in the two major DCB trials varied but was relatively low. Will these stenting rates hold up in real-world lesions? The IN.PACT Global

TABLE 4. TWELVE-MONTH PATENCY RESULTS FOR PTA*				
	Zilver PTX RCT (PTA arm)	**RESILIENT RCT (PTA arm)**	**Viabahn PMA IDE Study (PTA arm)**	**IN.PACT SFA II RCT (PTA arm)**
12-month primary patency for PTA	32.7%	36.7%	40%	66.8%

**Data adapted from Cook Medical, Laird JA et al, Gore & Associates, and Tepe G.[1,5-7]*
Abbreviations: IDE, investigational device exemption; RCT, randomized controlled trial; PMA, premarket approval.

TABLE 5. SEVERE CALCIFICATION IN DRUG-ELUTING DEVICE TRIALS*

	Zilver PTX RCT	IN.PACT SFA II	LEVANT 2
Severe calcification	37.3%	8.1%	10.4%

**Data adapted from Cook Medical, the Department of Health & Human Services, and Tepe G.[1,4,5]*
Abbreviations: RCT, randomized controlled trial.

trial reported an almost 25% provisional stenting rate for a relatively modest average lesion length of 12 cm. Interventionists can still expect to commonly utilize bail-out stenting for many modest-to-complex lesions, adding to the overall cost of a procedure.

The last significant gap is head-to-head data to directly compare the effectiveness of the two drug-eluting modalities in a variety of lesion types. In order to better understand the relative effectiveness of DCBs and DES in the superficial femoral artery (SFA), a head-to-head comparison of the two technologies is needed. Prof. Dierk Scheinert is conducting the REAL PTX study. This study will randomize patients with femoropopliteal disease to either a DCB or DES. This trial is significant, as it will represent the first direct comparison of DCBs to DES in the SFA and will provide even more insight into when to choose a DCB versus DES for treating SFA disease.

Although the DCB and DES trials give us confidence in the ability of drug-eluting devices to fight intimal hyperplasia, they do not answer every question. In light of the previously mentioned data gaps and the differences in trial designs, what can the data really tell us about how we should incorporate drug-eluting devices into our daily practice? The following sections describe what we believe are the five key considerations when deciding whether to use a DCB or DES to deliver paclitaxel to the SFA (see the *5 Considerations for Choosing a Drug-Eluting Modality* sidebar).

5 CONSIDERATIONS FOR CHOOSING A DRUG-ELUTING MODALITY

1. DES and DCB have demonstrated superiority to their bare counterparts.
2. A significant number of "real-world" SFA lesions require stenting.
3. DCB + BMS has not been shown to equal DES results.
4. The effectiveness of DCBs for calcified lesions is still unknown.
5. Long-term data are essential to fully assess new technologies.

1. DES and DCB Have Demonstrated Superiority to Their Bare Counterparts

Zilver PTX demonstrated superiority to BMS through 5 years. The In.Pact and Lutonix DCBs both demonstrated superior patency to standard PTA balloons through 1 year. All three of these trials were randomized and core lab adjudicated, which should give physicians confidence in choosing these drug-eluting devices over their bare counterparts. In general, the use of technologies that have not demonstrated patency benefit over bare ballooning or stenting should be relegated to niche usage, and high-volume usage of other technologies should be scrutinized.

2. A Significant Number of "Real-World" SFA Lesions Require Stenting

One may favor balloons over stents with the hope of "leaving nothing behind." However, we know that stents are used in 70% of SFA cases in the United States.[9] We expect that stenting (either primary or bailout) will be performed at a rate that correlates with lesion complexity, even with the use of DCBs. Balloons and stents both have a role in treating peripheral artery disease, and as such, physicians will need to generate data to help clearly delineate "optimal therapy." Ultimately, choosing a DCB or DES is heavily influenced by lesion morphology and lesion location, and these lesion factors are unlikely to change when adding a drug to a balloon or stent.

3. DCB + BMS Results Have Not Been Shown to Equal DES Results

Dosing is different for each device, and in the case of DCBs, the use of excipients add another potentially confounding variable. DCB effectiveness may not be a class effect, and each product will need to be evaluated and compared. There are no reliable SFA data that prove that DCB + BMS provides comparable results to a DES alone. In fact, some coronary data suggest that DCB + BMS is not equivalent to DES alone.[10] More research is needed to understand the impact that different drug formulations and delivery methods have on outcomes. Finally, just as 5-year results have been the cornerstone for evaluating surgical therapy, DCBs will now need to demonstrate similar or improved durability to the currently available DES.

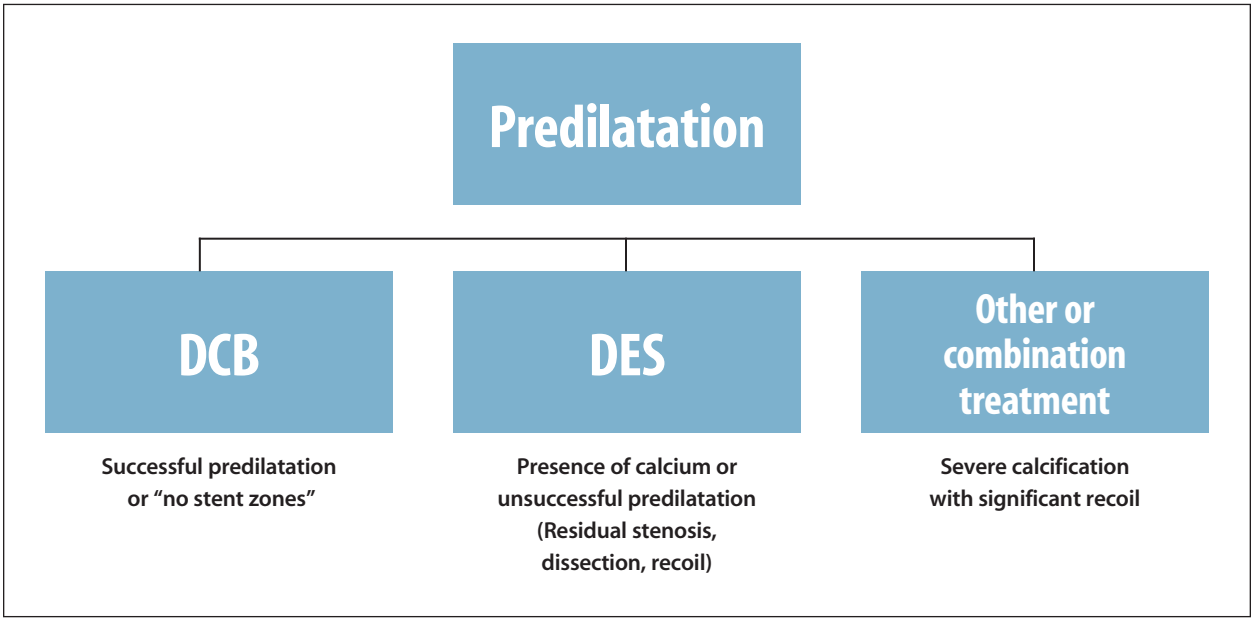

Figure 1. Choosing a drug-eluting modality for SFA lesions.

4. The Effectiveness of DCBs for Calcified Lesions Is Still Unknown

One cannot underestimate the potential significance of this factor when considering a DCB or DES for treating SFA lesions. Further, the work of Fanelli et al should give us pause when considering DCB use for heavily calcified lesions.

5. Long-Term Data Are Essential to Fully Assess New Technologies

Perhaps one of the greatest challenges and most important factors in treating SFA disease is long-term effectiveness. We know that there are several modalities that provide acute success. The real challenge is avoiding restenosis and maintaining long-term patency in the SFA. Zilver PTX has proven long-term effectiveness with few stent fractures and 5 years of level-1 evidence. Although DCBs are promising, they are still early in their level-1 evidence. More time is needed to determine the long-term effectiveness of DCBs, and head-to-head data are needed to determine when to utilize one technology versus another.

CHOOSING A DRUG-ELUTING MODALITY FOR SFA LESIONS IN 2015

Ultimately, recent trials have made it apparent that drug-eluting devices outperform their bare counterparts. However, when incorporating these devices in light of the recent randomized controlled trial results, the remaining gaps in the DCB data, and the differences in drug-eluting device trials, there remains a critical question: How should we incorporate DCBs and DES into everyday practice? We suggest that the approach should be a relatively simple one (Figure 1).

For All Lesions, Predilate First

Whether you are leaning toward using a DCB or DES, perform predilatation with plain old balloon angioplasty in every case. Predilatation is required in the instructions for use for DCBs and is optional and at the discretion of the physician for DES. We also know that vessel preparation can lead to more successful results.

Successful Predilatation May Suggest a "Leave Nothing Behind" Strategy

If the lesion responds well to predilatation (ie, lack of moderate-to-severe calcification, residual stenosis, flow-limiting dissection, or significant recoil), consider using a DCB.

Suboptimal Predilatation Suggests a DES Strategy

If the lesion does not respond well to predilatation due to significant dissection, or if the lesion has moderate-to-severe calcification but can be adequately dilated, choose a DES.

Suboptimal Predilatation With Severe Calcification or Significant Recoil

Whether one should use debulking/scoring technology with spot stenting (particularly with a more crush-resistant woven nitinol stent), with or without DCB or DES

with Zilver PTX is up for debate. Pending actual data, the operator should choose the most appropriate method that will (in their mind) lead to the greatest luminal gain and durability.

All Patients Should Have Aggressive Risk Factor Modification and Medical Therapy

Mild symptoms should not be treated with a device, and a walking program and medical therapy should be considered if doubling the walking for the patient will be adequate. Although drug technology is improving short- and long-term results, all procedures have some risks, and appropriate procedural indications continue to be recognized. ■

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