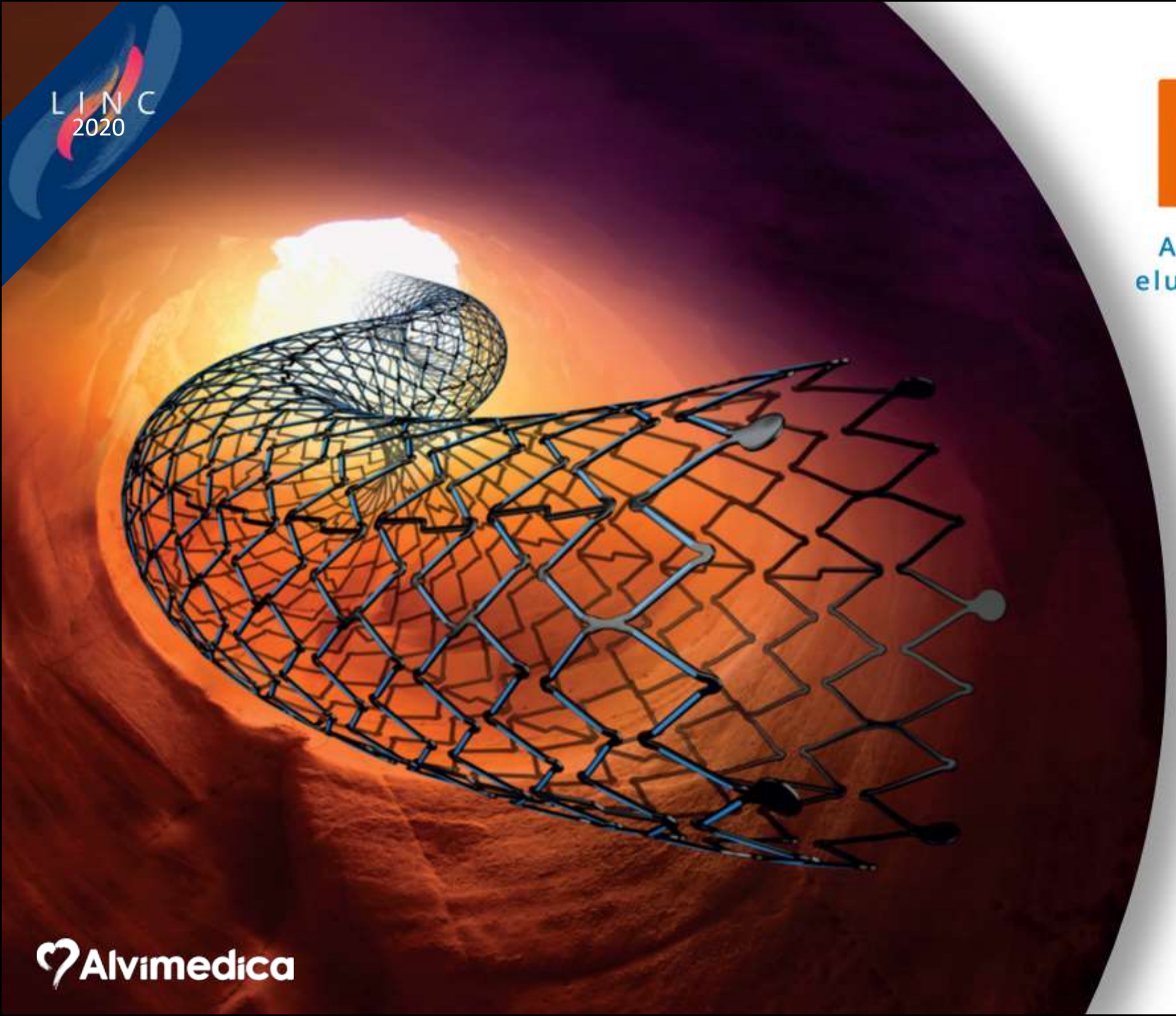
LINC 2020



NiTiDES

Amphilimus™(Sirolimus + Fatty Acid) eluting Peripheral Self-Expanding stent

Why, when and where: the DES role in SFA treatment

Prof. S. Müller-Hülsbeck

Alvimedica

Disclosure

Speaker name:

Stefan Müller-Hülsbeck.....

I have the following potential conflicts of interest to report:

- [X] **Consulting:** Terumo, Boston Scientific, Eurocor Tech, Alvimedica
- [ ] Employment in industry
- [ ] Stockholder of a healthcare company
- [ ] Owner of a healthcare company
- [ ] Other(s)

- [ ] I do not have any potential conflict of interest

Today's DES role in SFA treatment

- Drug added value in Drug Eluting Technologies
- DES main position in SFA lesion treatment
- Currently available DES technologies
- The Paclitaxel issue and devices drug dose released
- Expected DES features for the near future
- Conclusions

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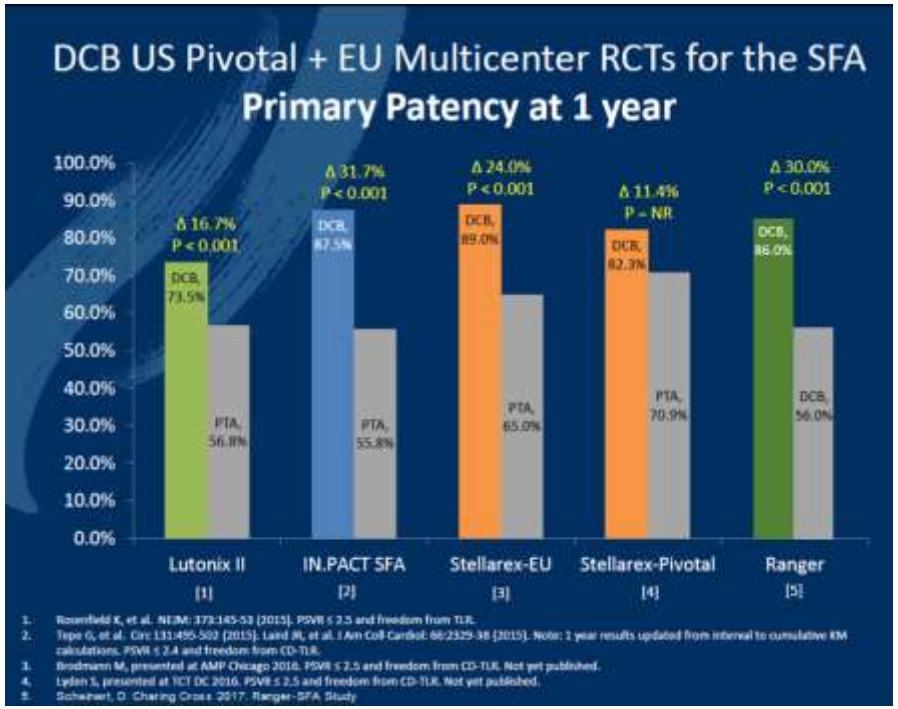
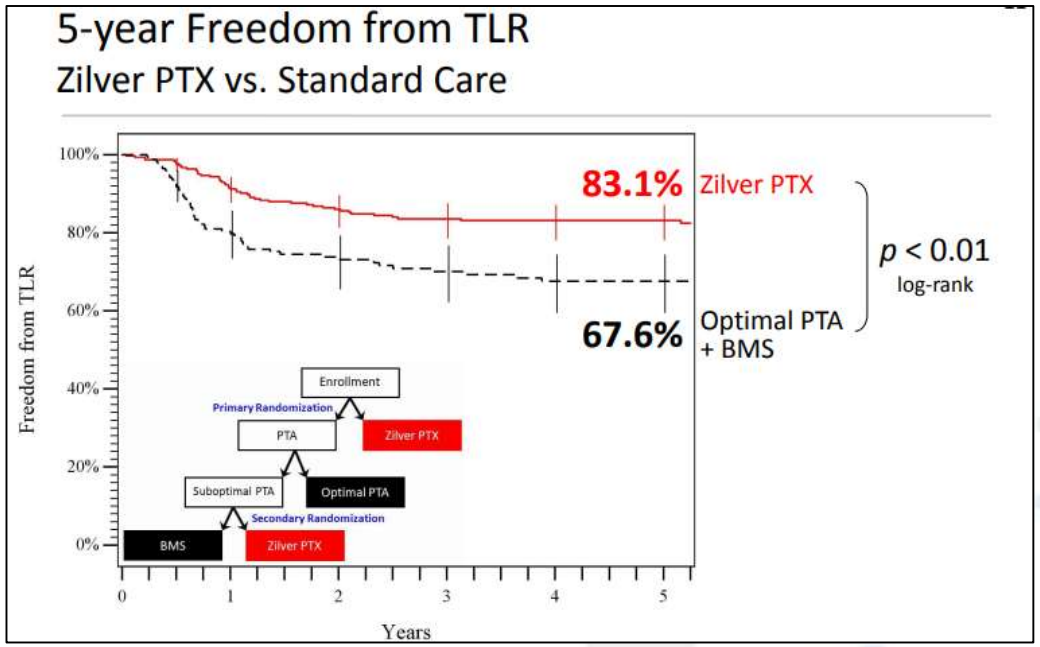
Drug added value in Drug Eluting Technologies

- The added value provided by a Drug, eluted from a Balloon or from a Stent, has been an increased device effectiveness over time.



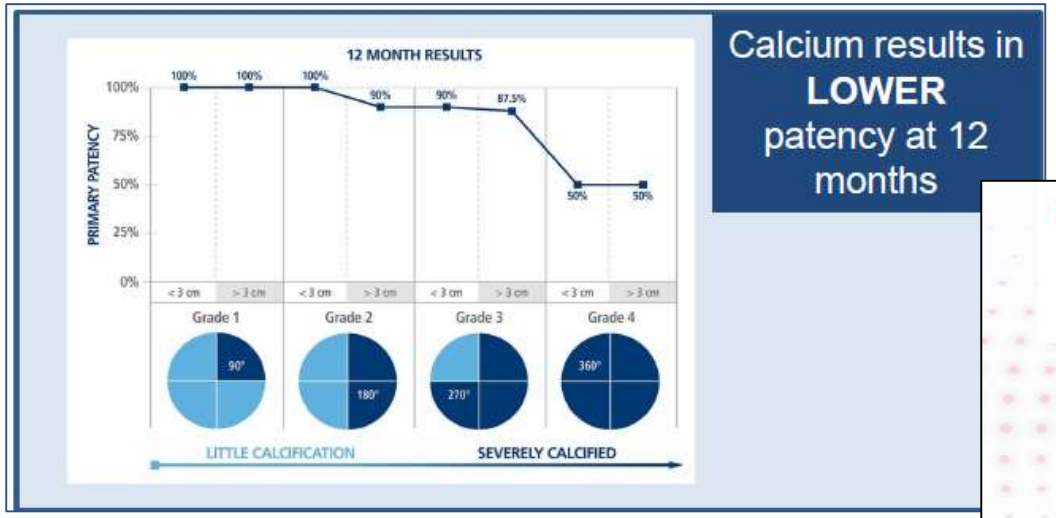


Circulation. 2016;133:1472-1483

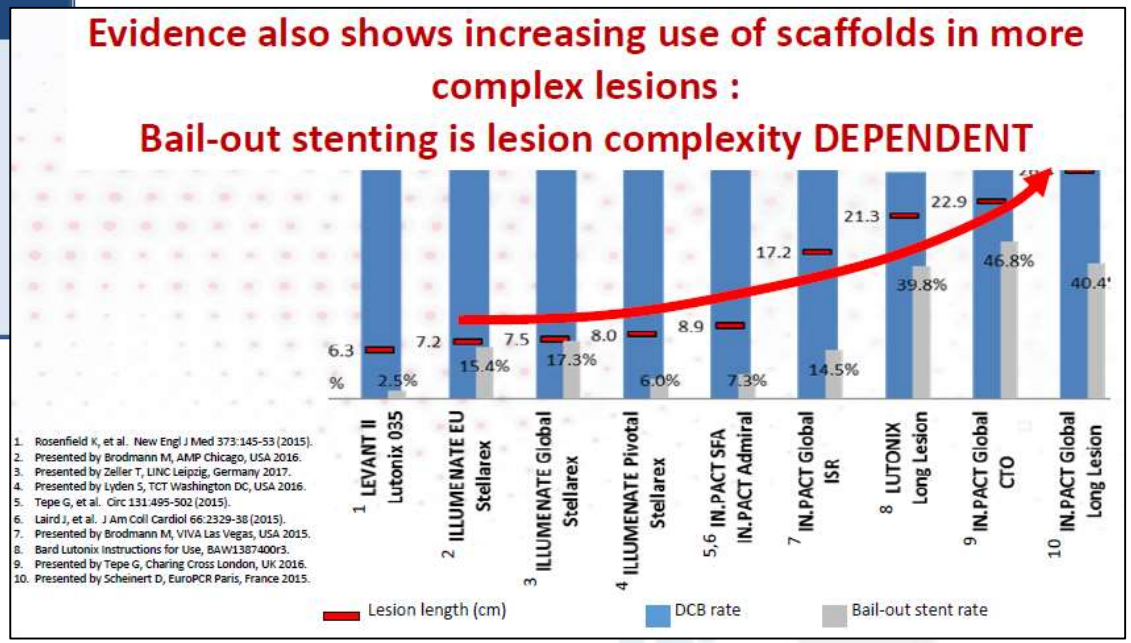
- Although both DCB and DES have provided better outcomes vs respective comparators without drug, some considerations have to be made for both devices.

DCB & DES limitations

- DCB: its efficacy is reduced by higher calcium content, and "DCB use only strategy" is less feasible when lesion complexity is higher.



Cardiovasc. Intervent. Radiol. 2014;37(4):898-907



- DES: Popliteal p2 stenting provides mechanical challenges to the device that may interfere with the procedural outcome in the mid-long term.

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Indications for SX stenting:

- Lesions with calcium content or very complex lesions (lesions needing stenting to maximize MLD)
- Flow limiting dissections or high vessel elastic recoiling

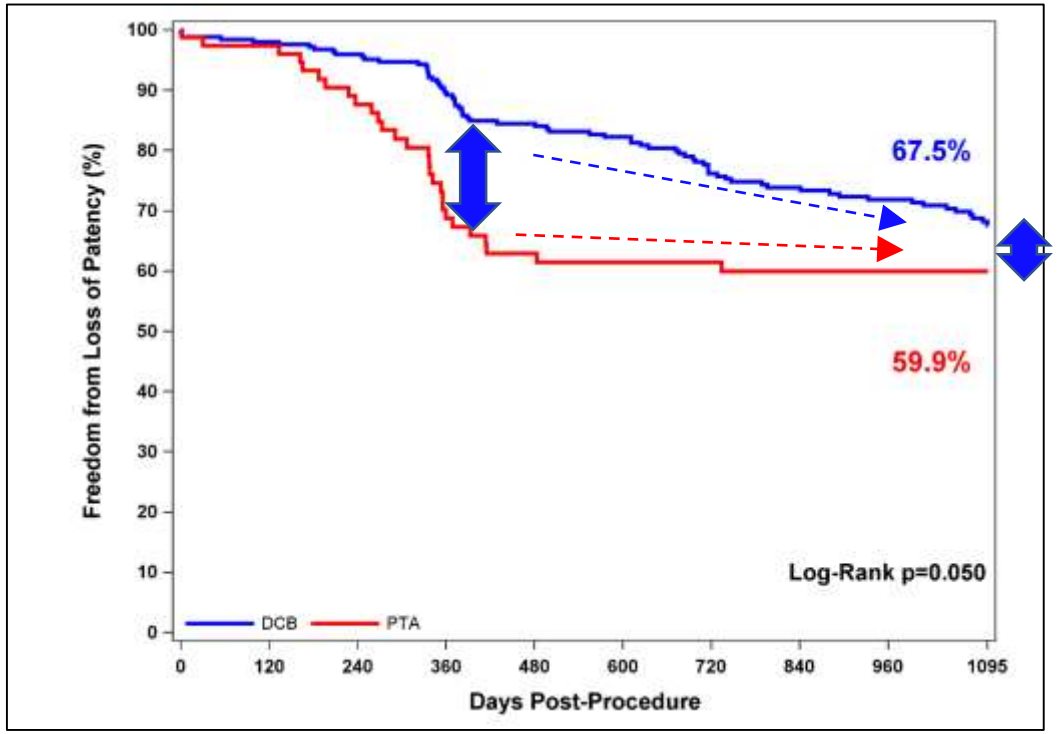
Indications for SX DES:

- “All the above” + “lesions at high restenosis risk”

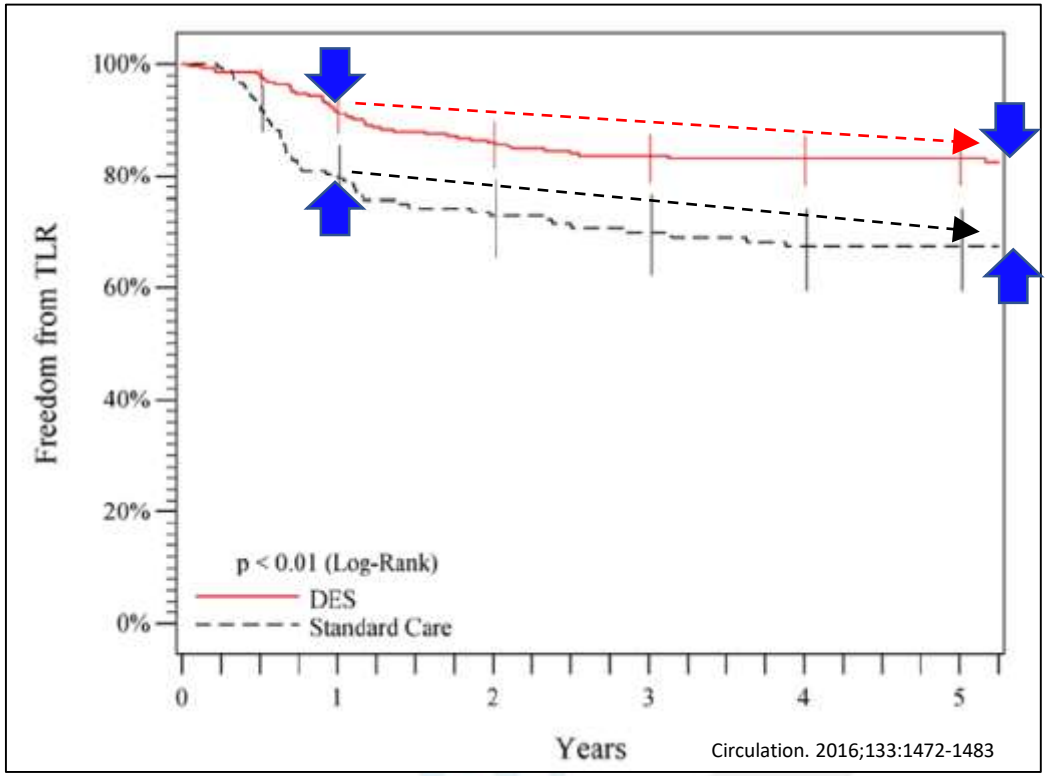
DES main position in SFA lesion treatment

While DCB efficacy benefits over PTA seem to slowly vanish with the time passing, this is not what has been seen for DES efficacy benefits over optimal PTA

3years results of the ILLUMENATE EU RCT (Stellarex DCB vs PTA)



5years results of the ZILVER PTX RCT (ZILVER PTX DES vs PTA)



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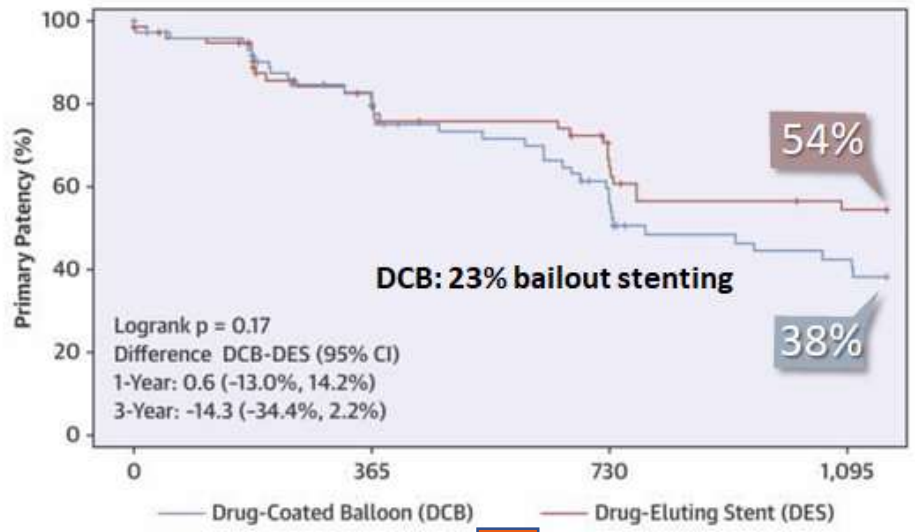
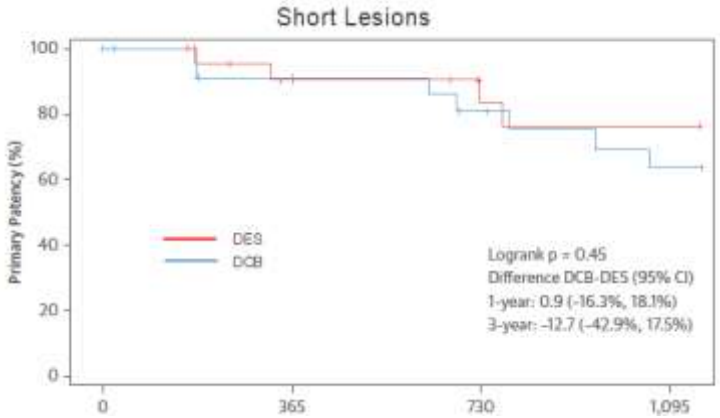
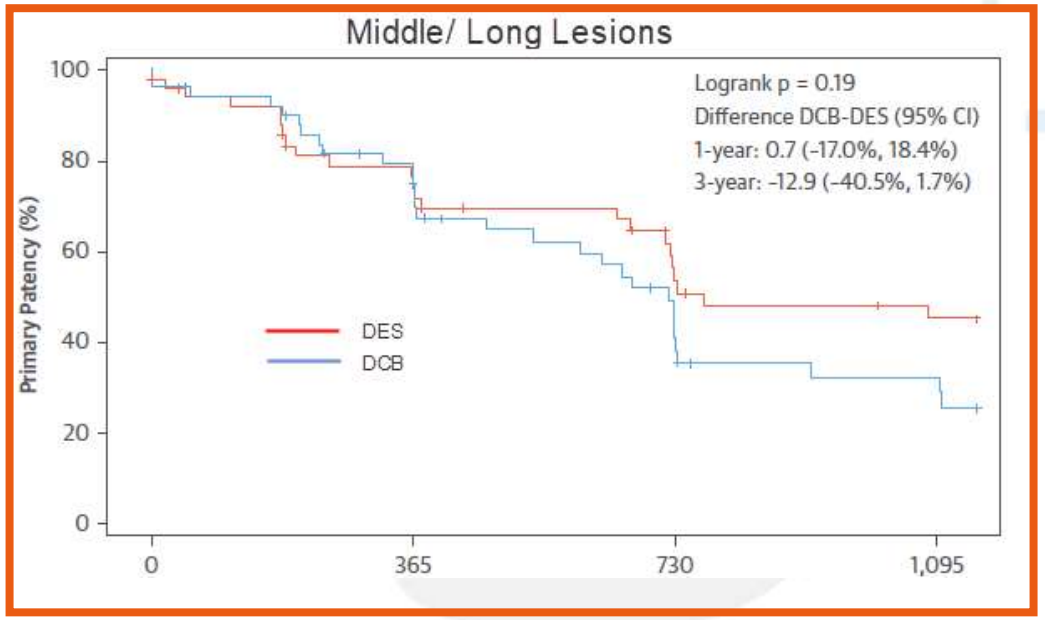
DES main position in SFA lesion treatment

- Recently published studies* show that medium/ complex lesions (where Ca2+/ recoiling/ dissection… are more often present) may benefit from DES over DCB to reduce restenosis.





REAL PTX study:
Zilver® PTX® vs. In.Pact Admiral/ In.Pact Pacific/ Lutonix



* REAL PTX study - Bausback et al. JACC 7 3/ 6/ 2 0 1 9

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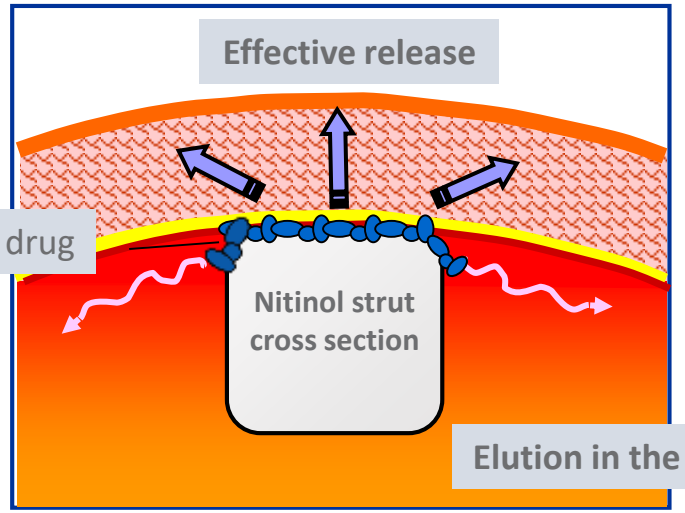
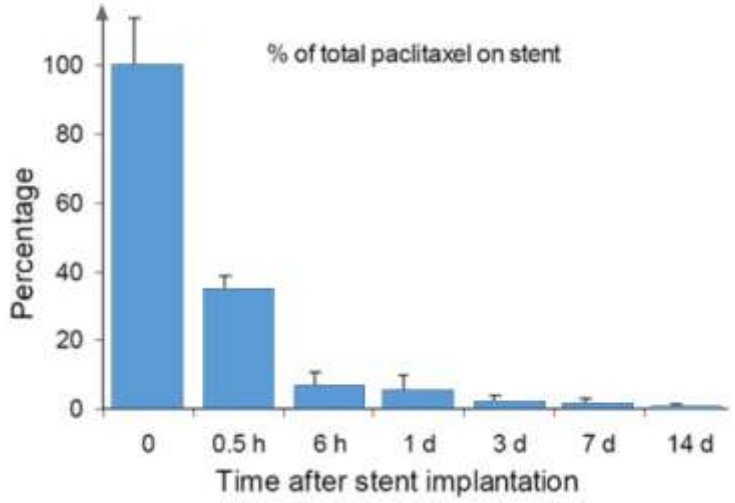
Currently available DES on the market

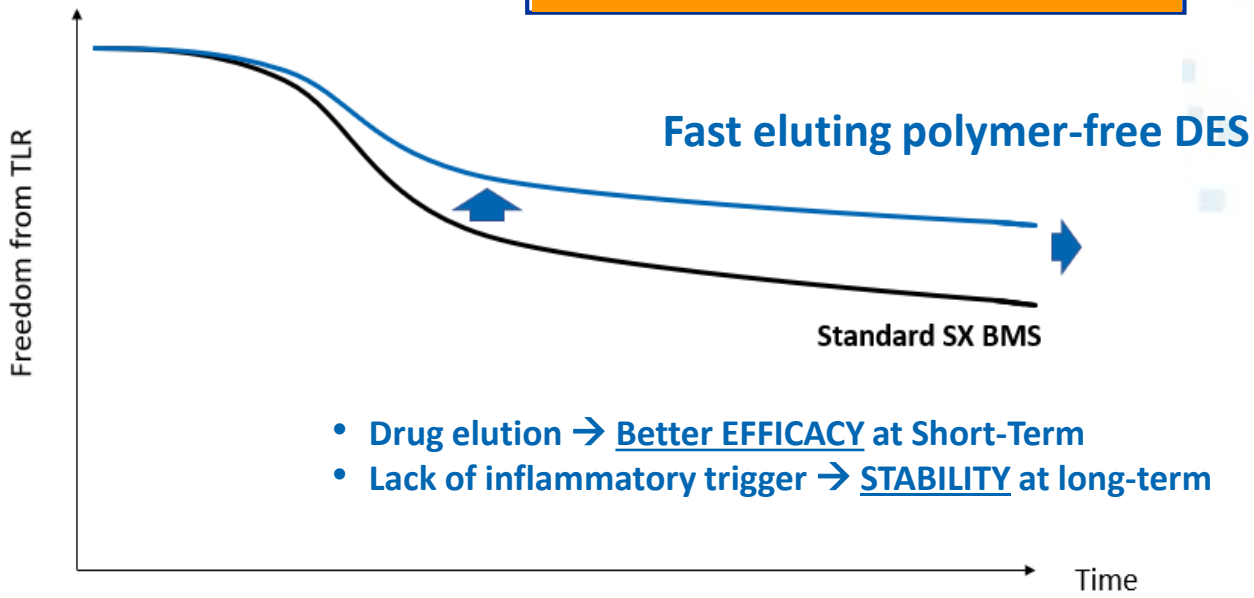
Zilver PTX (Cook) provides a "polymer-free fast elution approach" to deliver the drug from a Self-Expanding nitinol platform.

Crystals of pure drug are deposited on the bare Nitinol stent surface and quickly released:

- Drug = PACLITAXEL (cytotoxic)
- Release = Polymer-free fast drug elution (days)







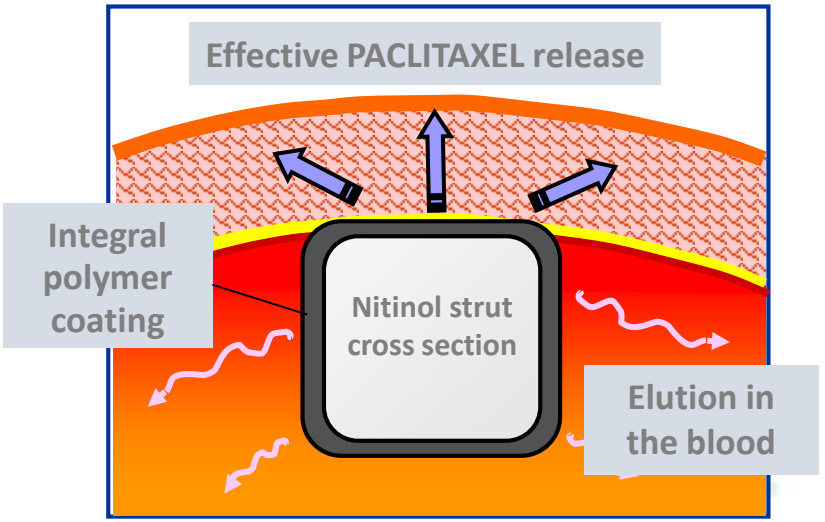
- Drug elution → Better EFFICACY at Short-Term
- Lack of inflammatory trigger → STABILITY at long-term

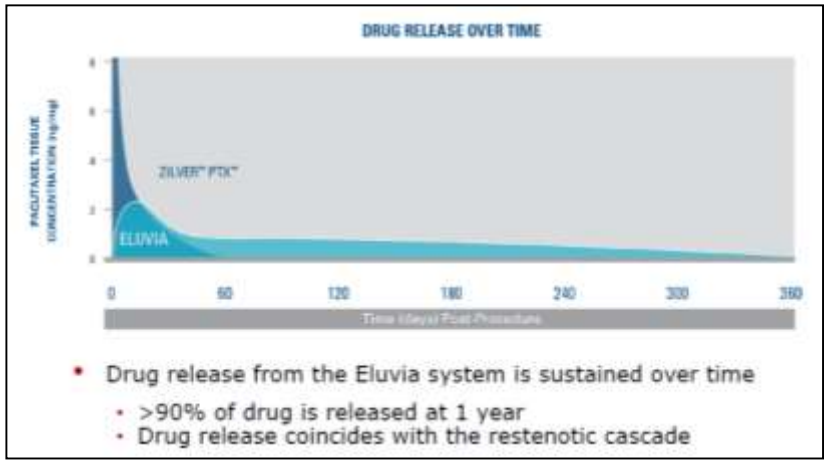
Currently available DES on the market

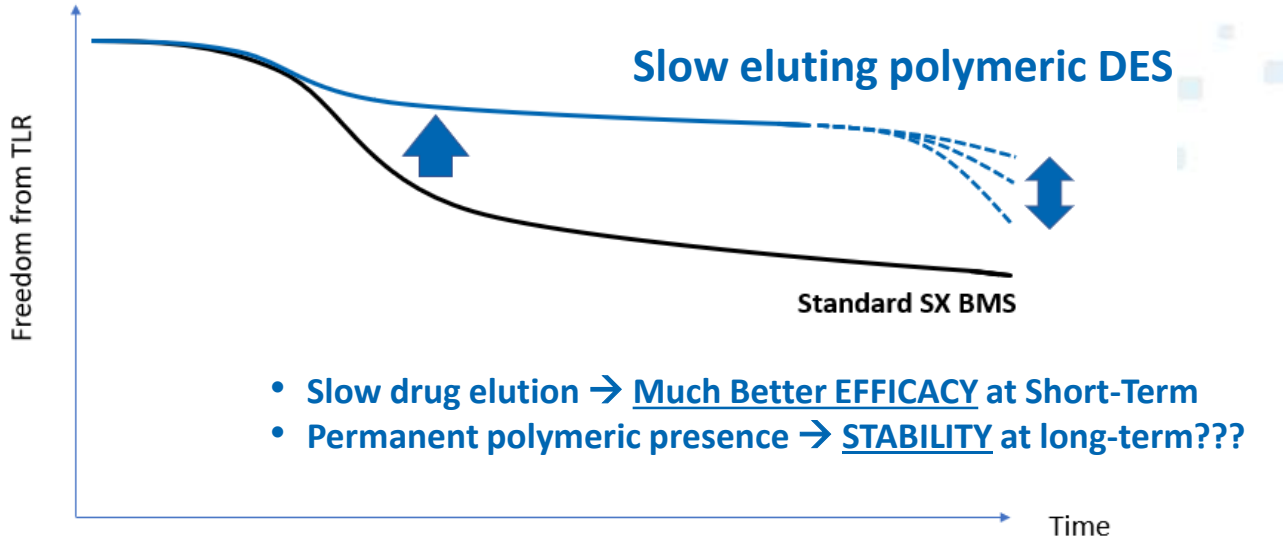
Eluvia (Boston Sc.) provides a "slow release approach" utilizing a durable polymer to deliver drug from a Self-Exp nitinol platform.

Pure drug is deposited within a permanent polymeric matrix:

- Drug = PACLITAXEL (cytotoxic)
- Release = Durable polymeric slow drug elution (1y)



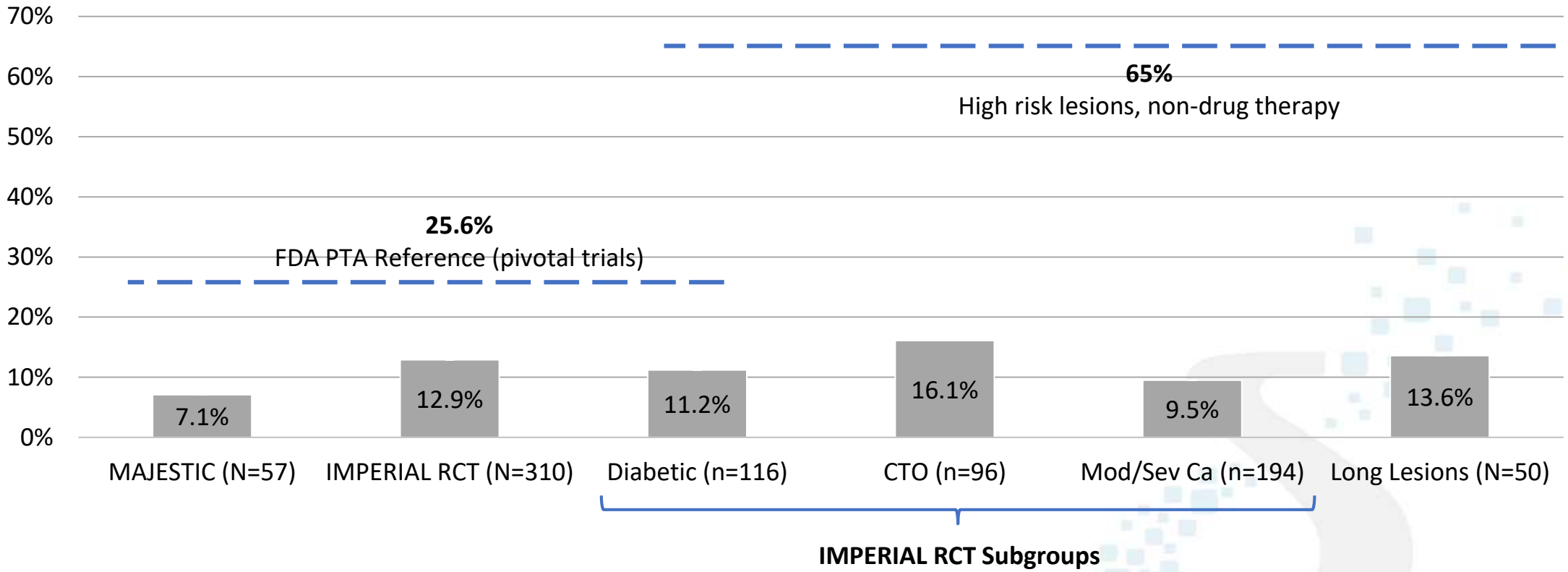




IMPERIAL - TLR @ 2 Years: Slower drug elution provides higher efficacy

Eluvia™ 12.9% vs. **Zilver® PTX® 20.5%** (p=0.0472)

Consistent clinical benefit with Eluvia DES in all high-risk subgroups



BSC Data on File. As-treated ELUVIA patients. FDA PTA reference based on FDA Executive Summary (median of PTA arms). High-risk reference: Wu TY, et al. ScientificWorldJournal. 2013;2013:247102. Abbreviations: Ca, calcification; CTO, chronic total occlusion; RCT, randomized controlled trial; TLR, target lesion revascularization.

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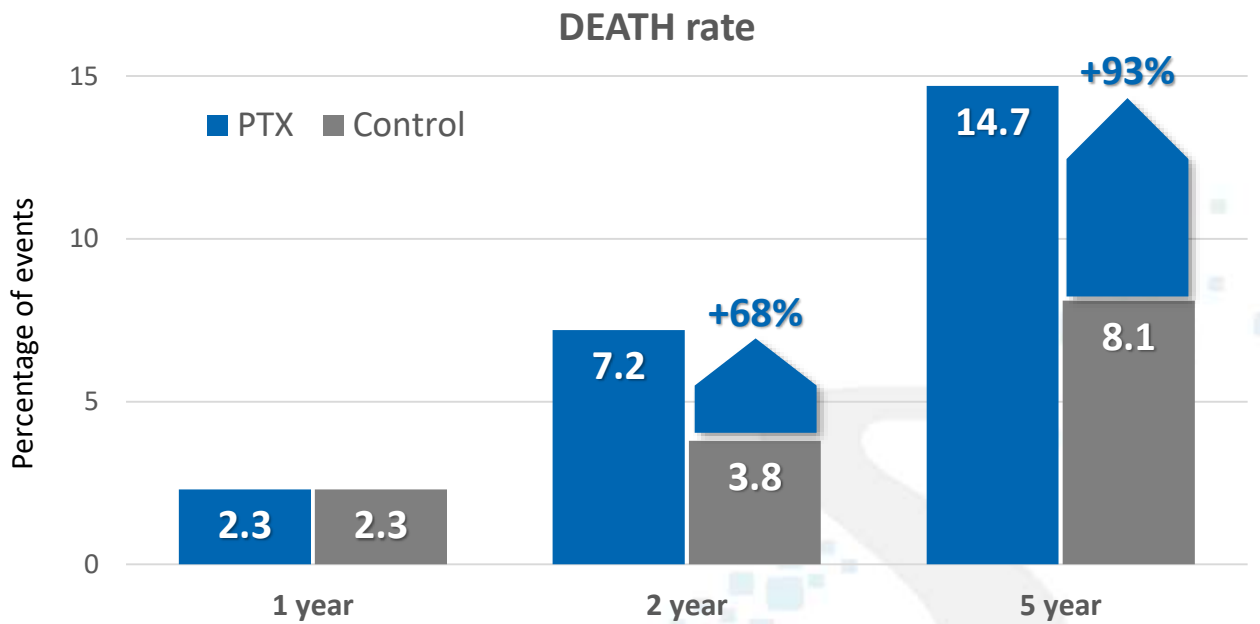
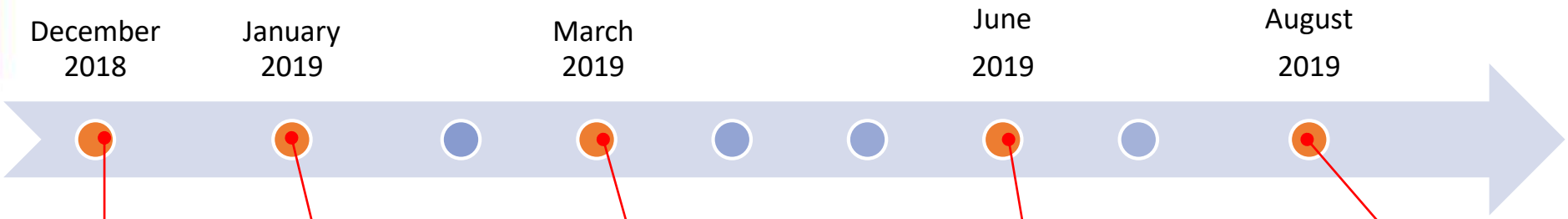
December 2018: Katsanos meta analysis

Dr. Katsanos presented a meta-analysis of the 28 most important and rigorous randomized controlled trials done with DCB (27) and DES (1 - Cook) in femoro-popliteal lesions.

While both patients treated with the PTX and control devices showed equivalent all-cause mortality at 1 year, a high change (worsening) occurred beyond that time point (2 & 5 years) only for the patients where the drug eluting devices were used.



Analysis on mortality for Paclitaxel-Containing Devices: Key Events



Meta-analysis by Katsanos et al. published in J Am Heart Assoc

FDA Letter to Health Care Providers #1

- **VIVA Vascular Leaders Forum Convened**
- **FDA Letter to Health Care Providers #2**

FDA Advisory Committee meeting of the Circulatory System Devices Panel

BfArM Letter to Health Care Providers in Germany (equal to FDA Letter #2)

FDA Letter to Health Care Providers #3

... accompanied by society recommendations and scientific publications

Predictors of 2y mortality in Majestic & Imperial trials

List of predictors for Eluvia/Zilver PTX pts included into Majestic & Imperial trials

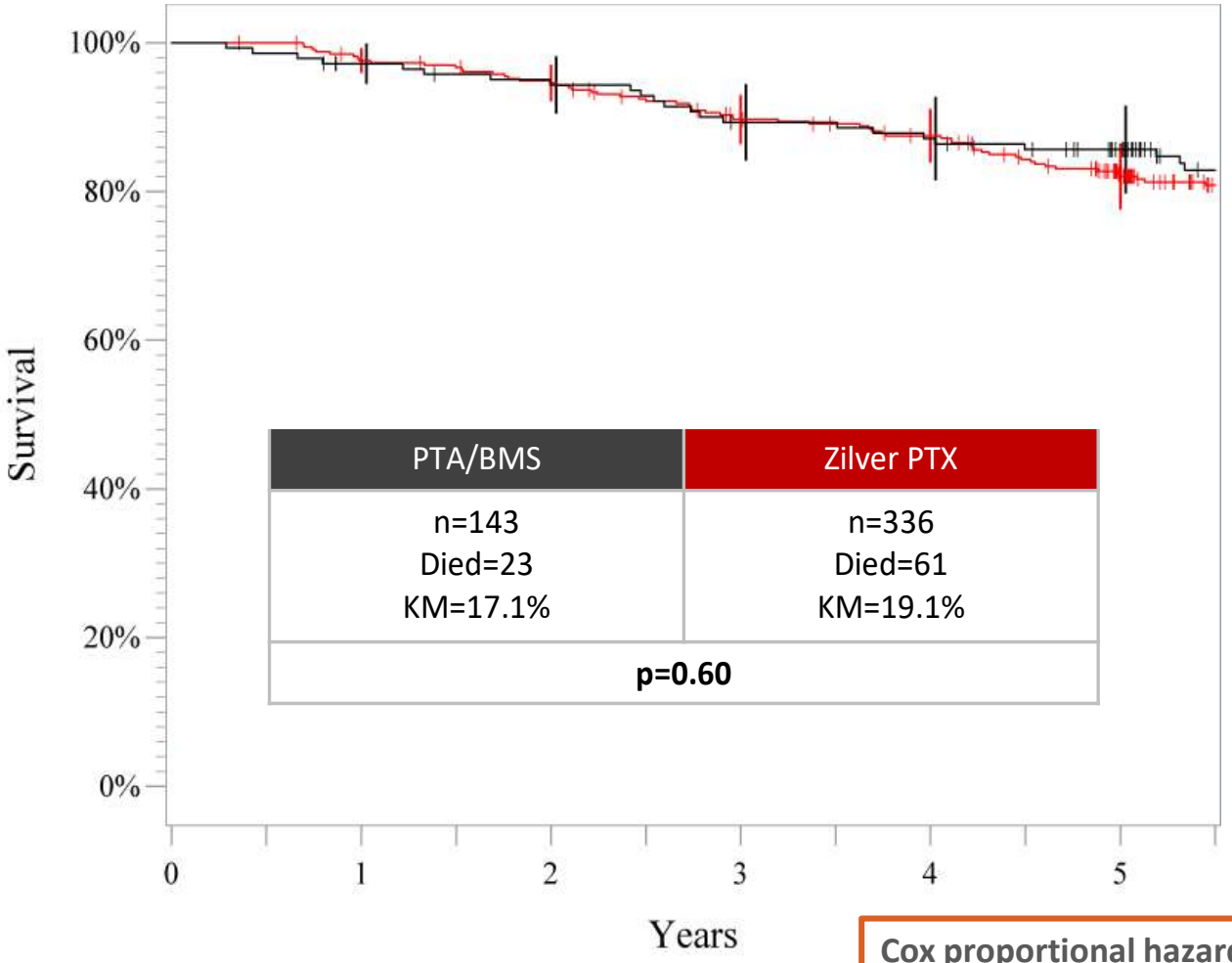
Multivariable Model with Dose Variable (N=540 Eluvia & Zilver PTX)

	Coefficient	Standard Error	Odds Ratio (95% CI)	P-value
PTX Dose (100µg)	0.04	0.04	1.04 (0.96 , 1.00)	0.3543
Diabetes	1.12	0.36	3.07 (1.52 , 6.20)	0.0018
Age /year	0.06	0.02	1.06 (1.02 , 1.10)	0.0029

- **Diabetes and Age resulted significant predictors**, typical for PAD patients
- **Paclitaxel didn't result a significant predictor**

Significant comorbidities in pts with PAD are not fully accounted for in the meta-analyses

RCT Actual Treatment with ZilverPTX



- 5-year vital status for 94% of patients
- All patients analyzed by actual treatment
- No mortality signal

Cox proportional hazard models revealed that age, tissue loss, and congestive heart failure were significantly associated with mortality in the RCT

Dake MD, Ansel GM, Bosiers M, Holden A, Iida O, Jaff MR, Lottes AE, O'Leary EE, Saunders AT, Schermerhorn M, Yokoi H, Zeller T. Paclitaxel-Coated Zilver PTX Drug-Eluting Stent Treatment Does Not Result in Increased Long-Term All-Cause Mortality Compared to Uncoated Devices. Cardiovasc Intervent Radiol. 2020 Jan;43(1):8-19.

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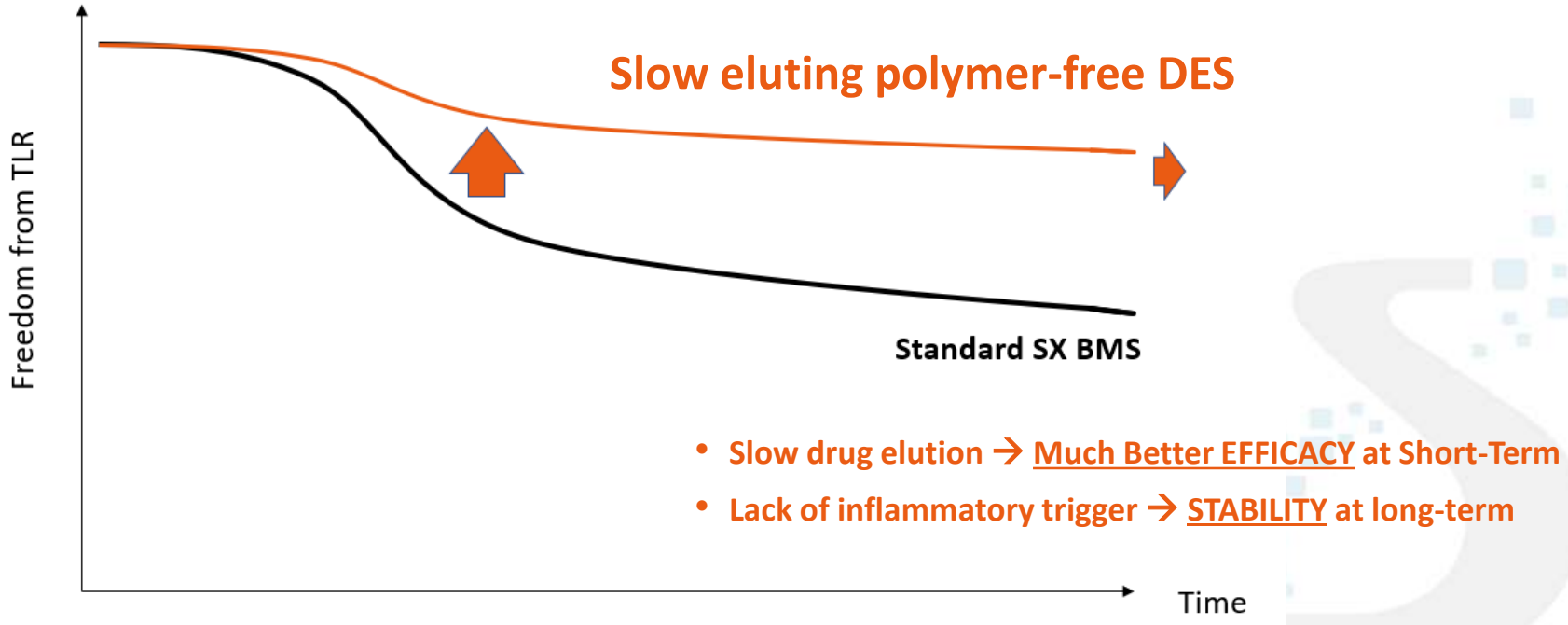
Expected DES features for the near future

- Controlled drug elution for maximized DES efficacy in the short-medium term.
- Release of a non-Cytotoxic drug to avoid possible long term safety issues
- SX BMS platform without any inflammatory trigger which could elicit long-term restenotic events (polymer-free platform?)



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Conclusions

- DES, in selected patient populations, provide better reduction in both primary patency & TLR compared with DCB;
- Current DES slowly releasing Paclitaxel - Eluvia™ - demonstrated superior patency and reduced TLR rates compared to DES fast releasing Paclitaxel - Zilver® PTX®;
- Paclitaxel didn't result being a significant predictor of mortality for both DES (Eluvia™ and Zilver® PTX®) at 2 years, and its efficacy benefits seem to outweigh the theoretical and currently uncertain higher risk of death;
- The availability of an alternative DES - able to slowly elute a non-cytotoxic drug which result in equivalent efficacy - is warranted, as it's worth to invest in innovative research in order to improve patient's clinical outcome.


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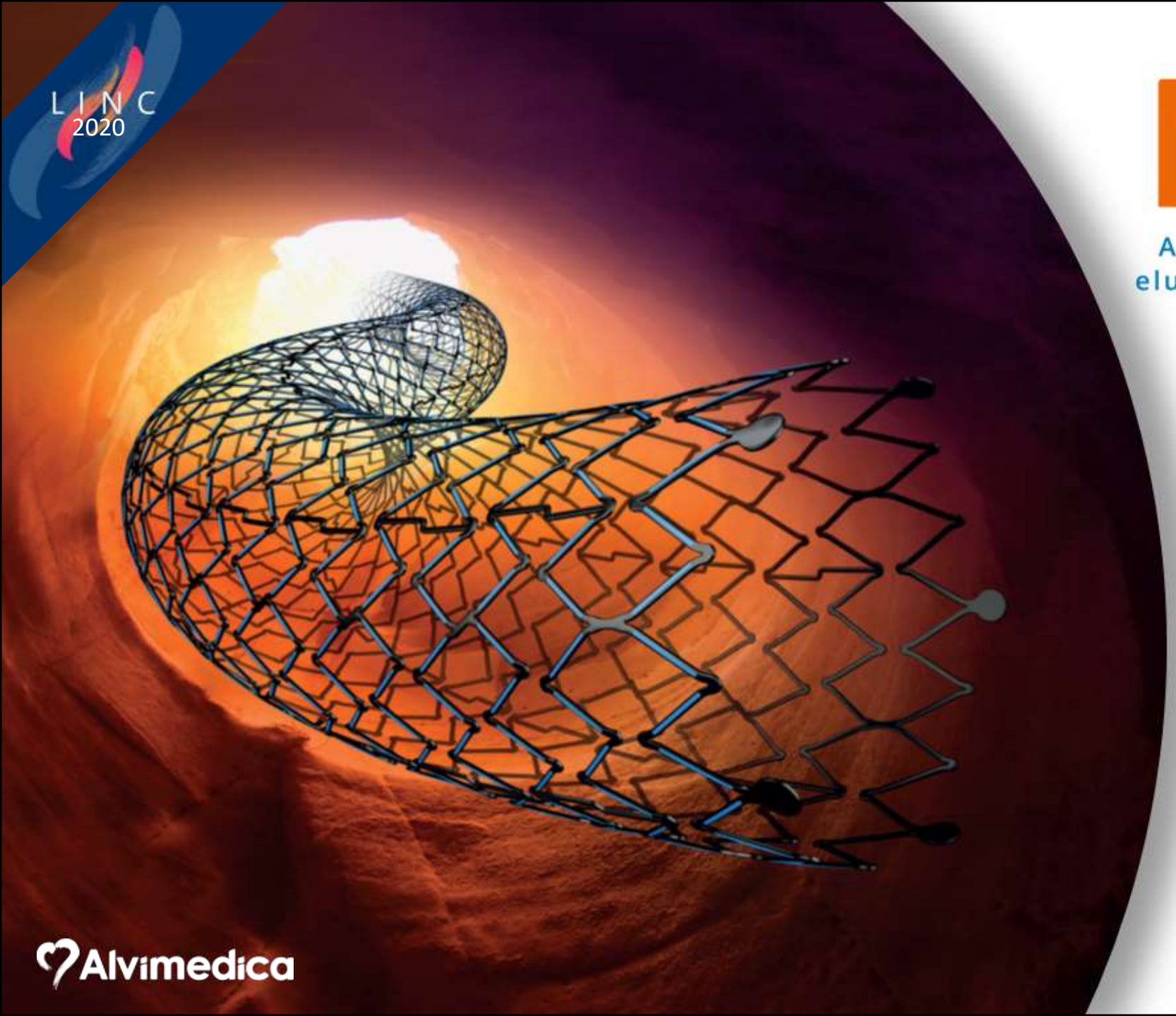

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