Vascular response of a Polymer-free stent (Zilver PTX) vs. a Polymer-coated, Paclitaxel-eluting stent (Eluvia) in healthy swine femoropopliteal arteries

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Disclaimer

Please refer to the Indications, Safety, and Warnings page for detailed information on implant procedure, indications, contraindications, warnings, precautions, and potential adverse events.

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Disclosure

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Employment in industry: No

Honorarium:

Amgen; Abbott Vascular; Biosensors; Boston Scientific; Celonova; Cook Medical; CSI; Lutonix Bard; Sinomed; Terumo Corporation.

Institutional grant/research support:

R01 HL141425 Leducq Foundation Grant; 480 Biomedical; 4C Medical; 4Tech; Abbott; Accumedical; Amgen; Biosensors; Boston Scientific; Cardiac Implants; Celonova; Claret; Concept Medical; Cook; CSI; DuNing; Edwards; Emboline; Endotronix; Envision Scientific; Lutonix/Bard; Gateway; Lifetech; Limflo; MedAlliance; Medtronic; Mercator; Merill; Microport; Microvention; Mitraalign; Mitra assist; NAMSA; Nanova; Neovasc; NIPRO; Novogate; Occulotech; Orbus Neich; Phenox; Profusa; Protembis; Qool; Recor; Senseonics; Shockwave; Sinomed; Spectranetics; Surmodics; Symic; Vesper; W.L. Gore; Xeltis.

Owner of a healthcare company: No

Stockholder of a healthcare company: No

Background

- Preclinical Studies are designed to demonstrate safety of a product before testing in humans
- Generally consists of looking at treatment site and other organ beds for evidence of toxicity
  - Gross and histological examination
  - Pharmacokinetic levels of drug (systemic plasma levels, local drug levels in tissues and organs)
  - Although safety in the end is a binary decision, there are always limitations because animals aren't humans and almost always young healthy animals are used for Good Laboratory Practice (GLP) studies

We need to show Safety of the Devices (some would say efficacy?)

Animal Studies: Depends on the device to determine what animal model is most appropriate.

Choices are:

- Rabbit
- Pig
- Sheep
- Canine
- Cow
- Horse

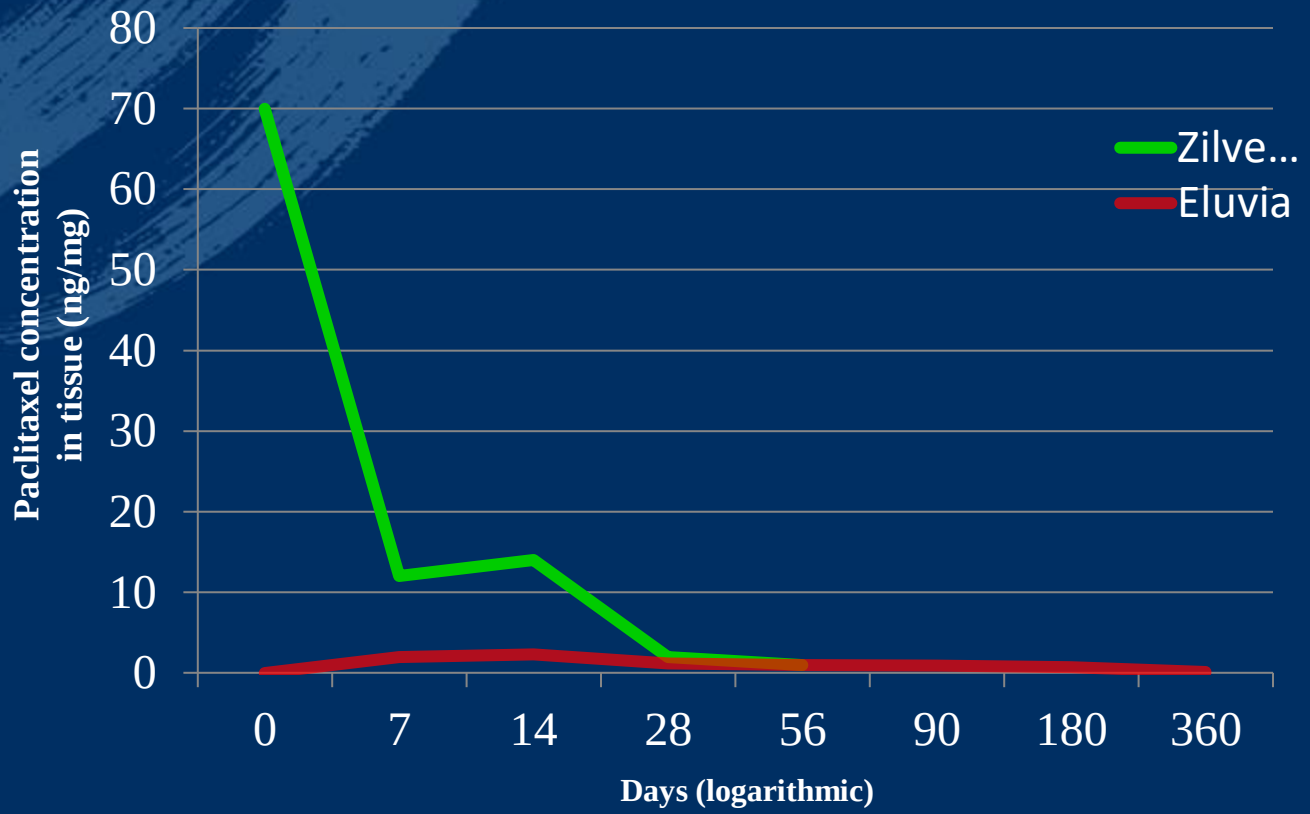
Normal animals are the best and not disease models as they introduce more variability. For peripheral devices, especially >80 mm in length cannot be appropriately assessed in Most of the animal models (pig, sheep or canine) do not have long arteries.

FDA approved DES for PAD: Zilver PTX and Eluvia

Differences in Delivery of Paclitaxel

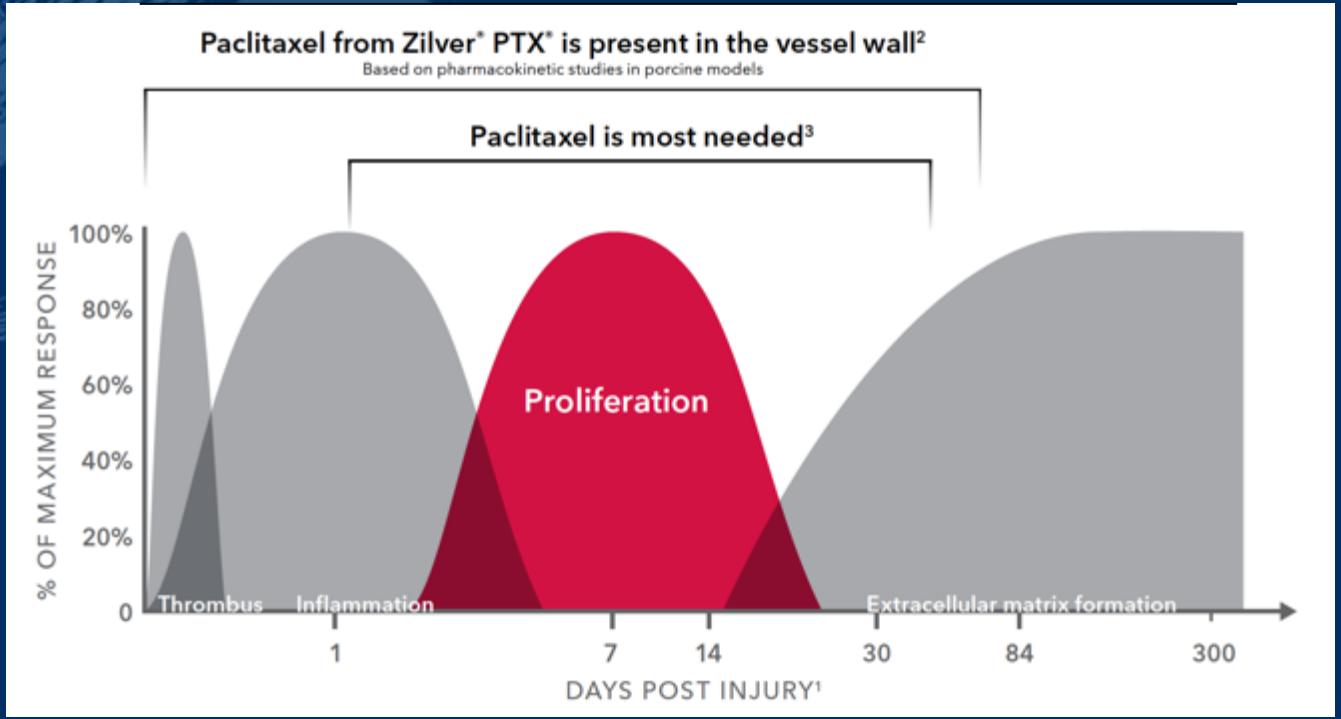
	Zilver PTX	Eluvia
Drug	Paclitaxel	Paclitaxel
Dose	3 µg/mm^2	0.167 µg/mm^2
Polymer use	Polymer-free	Permanent polymer (PVDF-HFP, same as Promus)
Coating method	Extraluminal coating protected from blood exposure 	Conformal coating has chronic exposure to blood 

Paclitaxel concentrations based on pharmacokinetics testing in porcine models



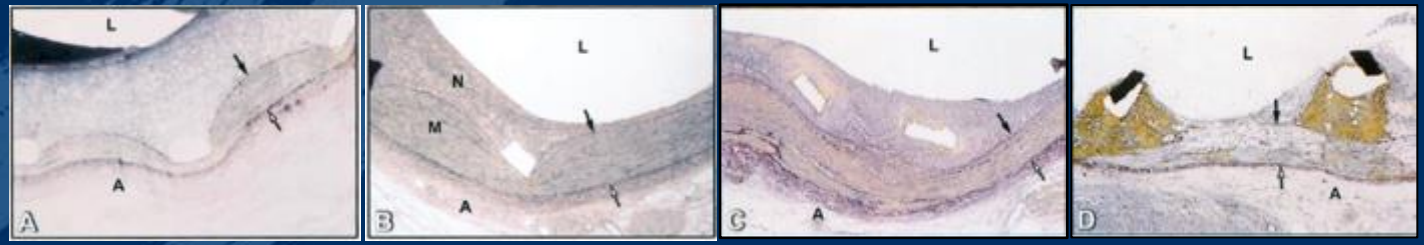
The antiproliferative drug paclitaxel is most needed in the SFA during SMC proliferation but should rapidly go down afterwards

Paclitaxel from Eluvia is present in the vessel wall up to 360 days

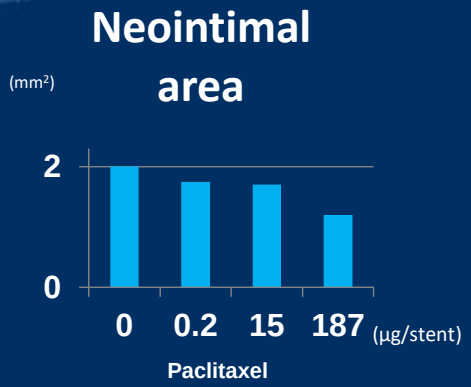


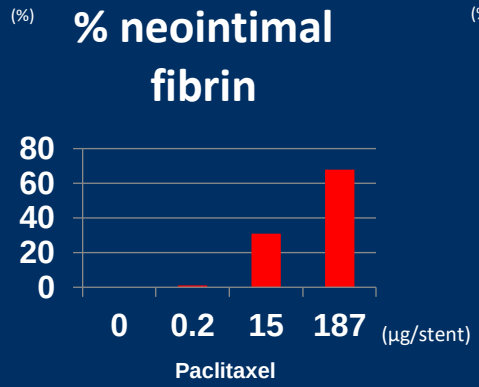
1. Nikol S, *et al. Atherosclerosis.* 1996; 123:17-31.
2. Dake, et. al. Pharmacokinetics paper.
3. Dorothea I. Axel D, Kunert W. *Paclitaxel Inhibits Arterial Smooth Muscle Cell Proliferation and Migration In Vitro and In Vivo Using Local Drug Delivery.* Circulation. March 2018. 2018;96:636-645.

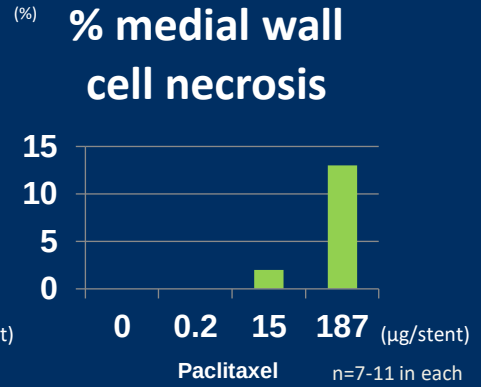
Dose dependent effect and toxicity of paclitaxel eluting stent in porcine coronary artery (28days)



BMS | Paclitaxel 0.2µg/stent | Paclitaxel 15µg/stent | Paclitaxel 187µg/stent







n=7-11 in each

Heldman AW, et al. Circulation. 2001;103:2289-95.

What Histological Markers Indicate Safety and Efficacy?

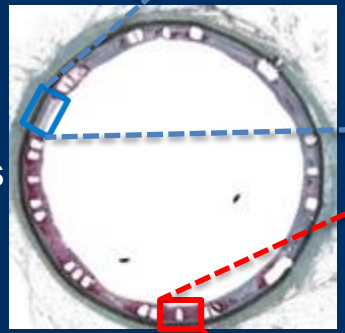
a. Endothelial cell loss

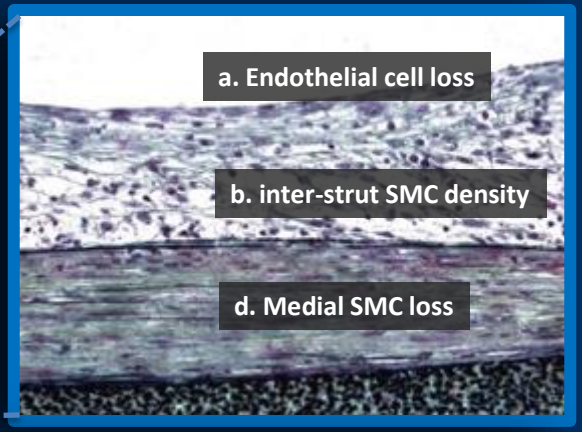
b. Inter-strut SMC density

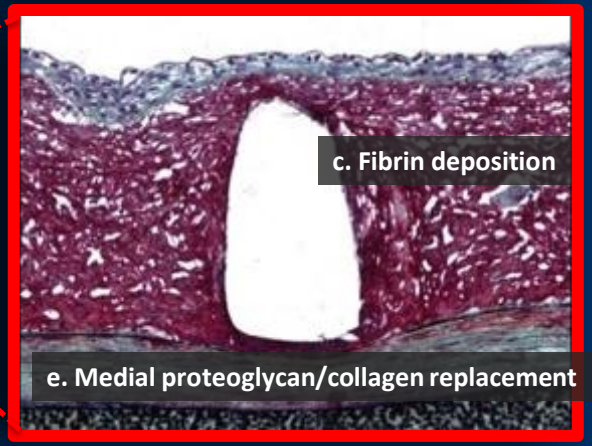
c. Fibrin deposition

d. Medial SMC Loss (Depth and Circumference)

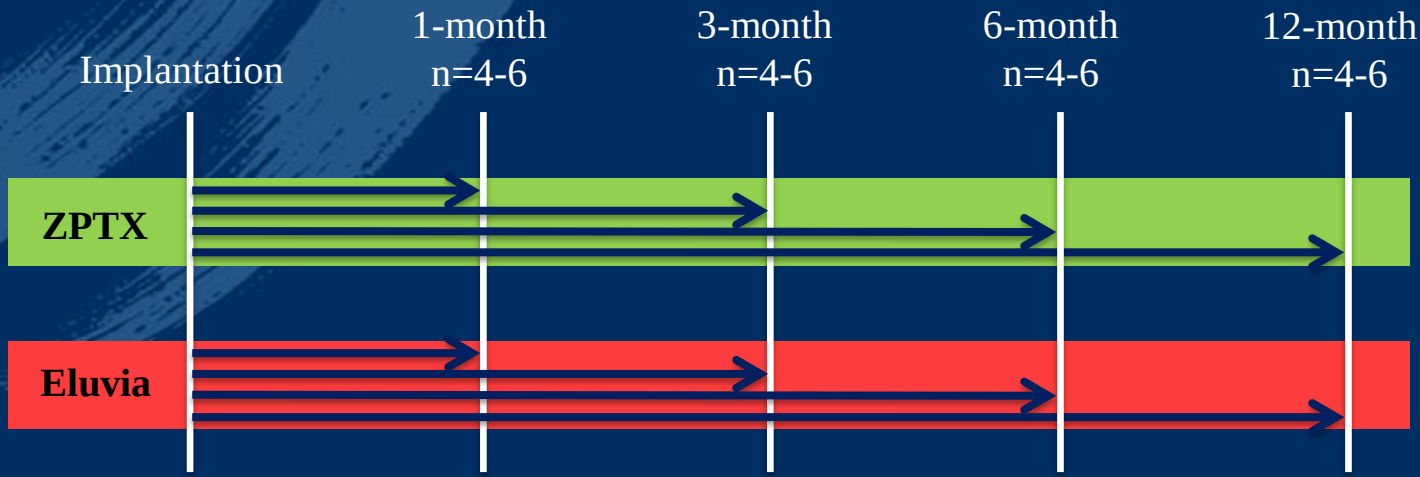
e. Medial Proteoglycan/ Collagen replacement







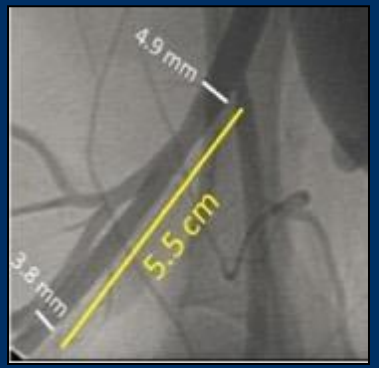
Zilver PTX vs Eluvia stent in porcine femoral artery



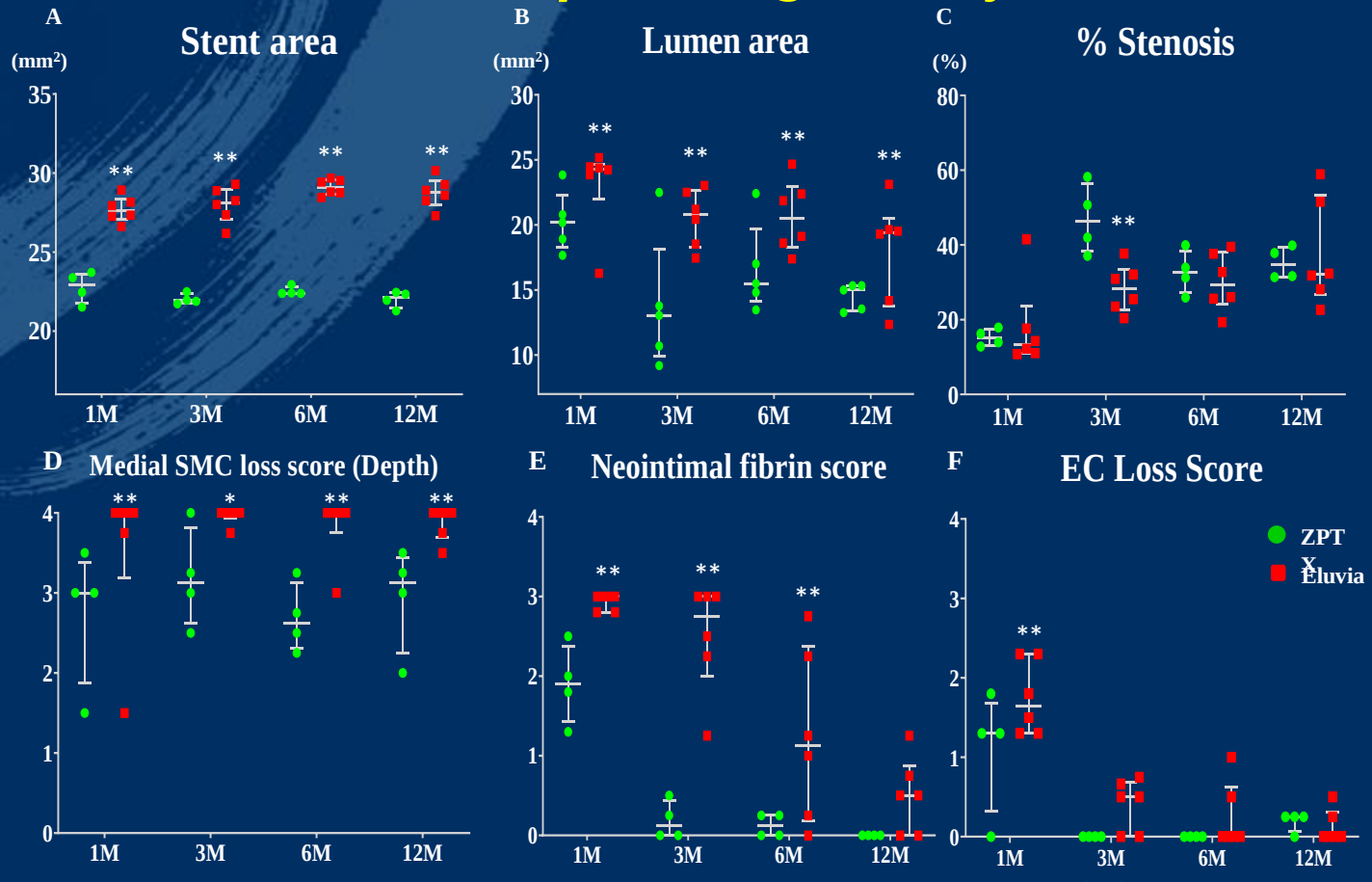
Yucatan Minipig

Devices Used in Study:

- Zilver PTX or Eluvia

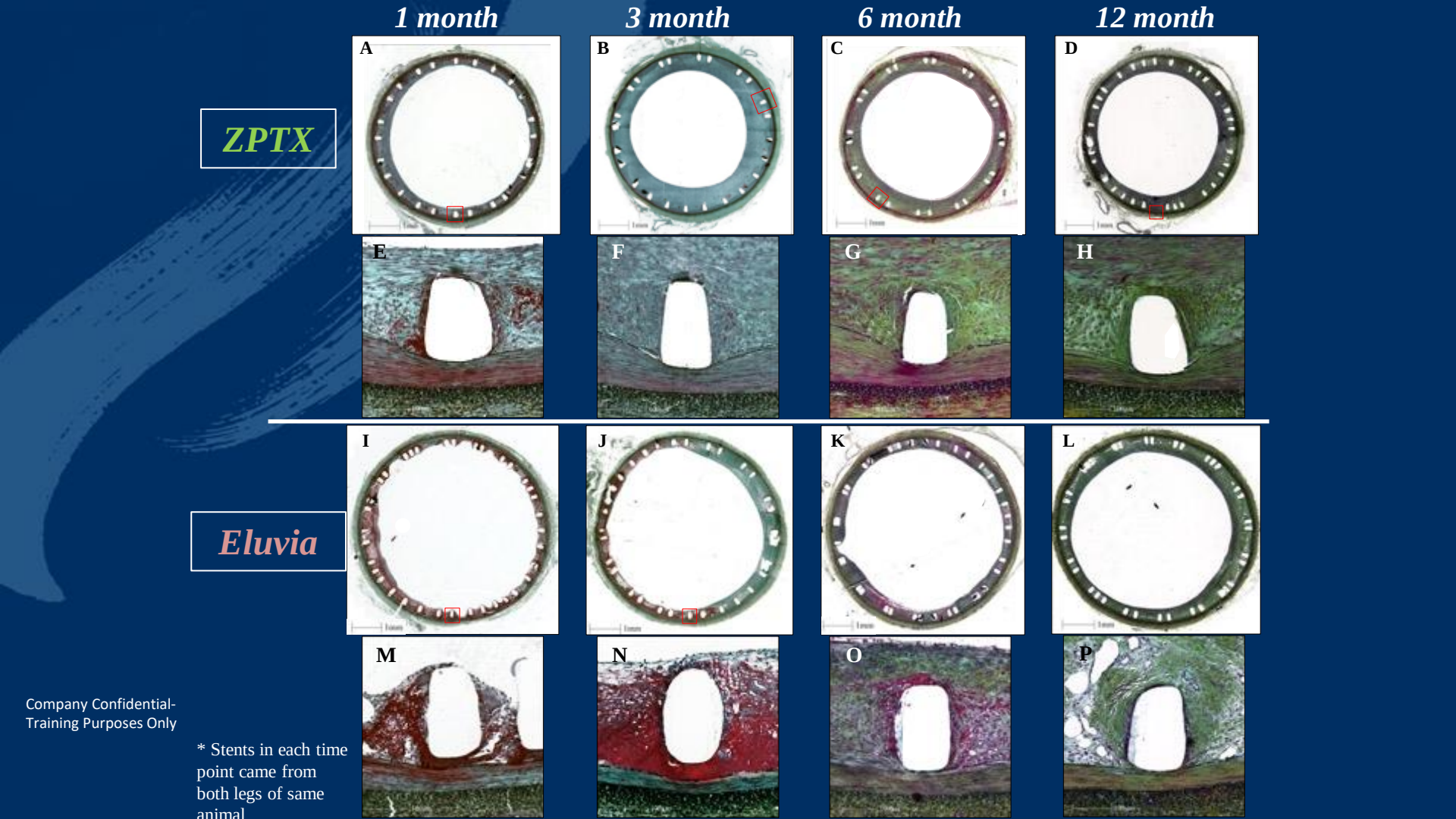


Results of Histologic Analysis



** p<0.01 vs ZPTX (generalized estimating equation (GEE))

Eluvia showed greater expansion and longer drug effect resulting vessel dilatation and delayed healing as compared to ZPTX



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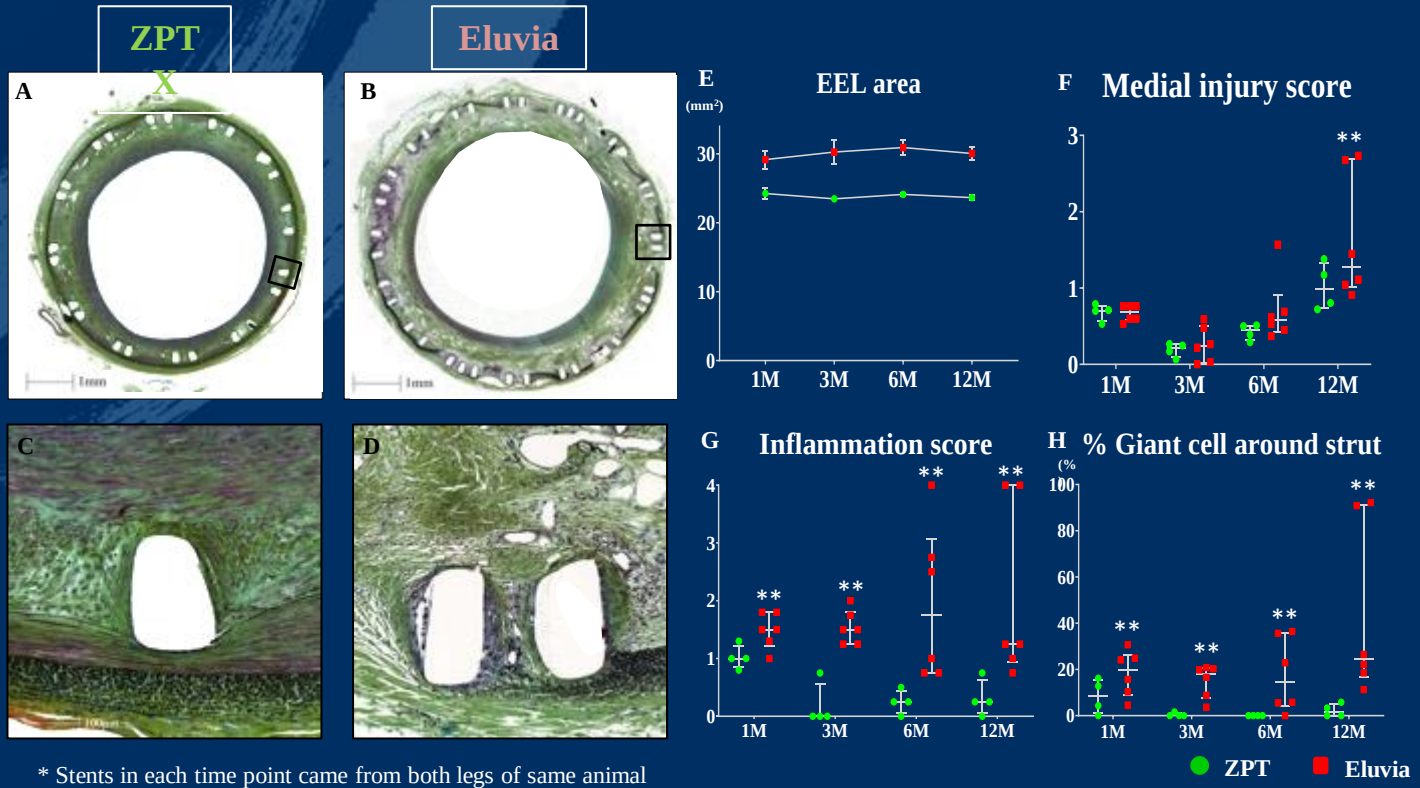
* Stents in each time point came from both legs of same animal

Stent expansion and medial damage of ZPTX vs Eluvia



* Stents in each time point came from both legs of same animal

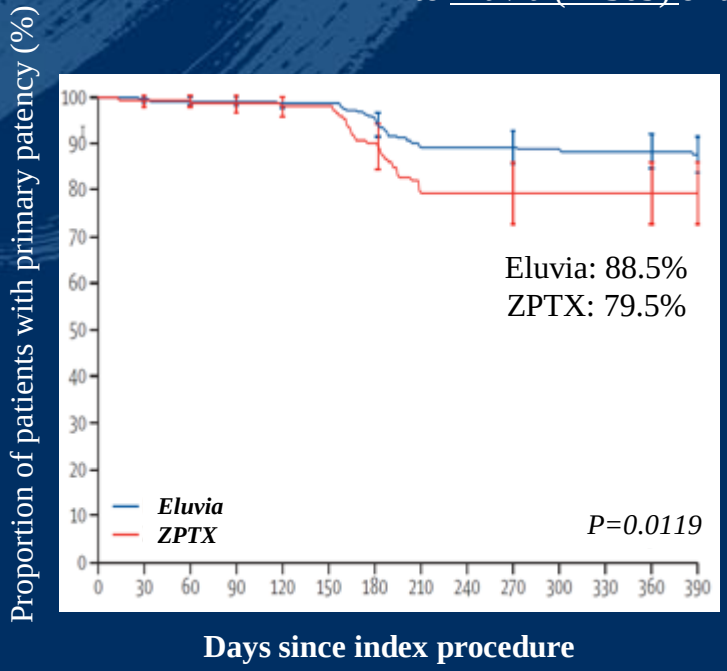
** p<0.01 vs ZPTX (generalized estimating equation (GEE))

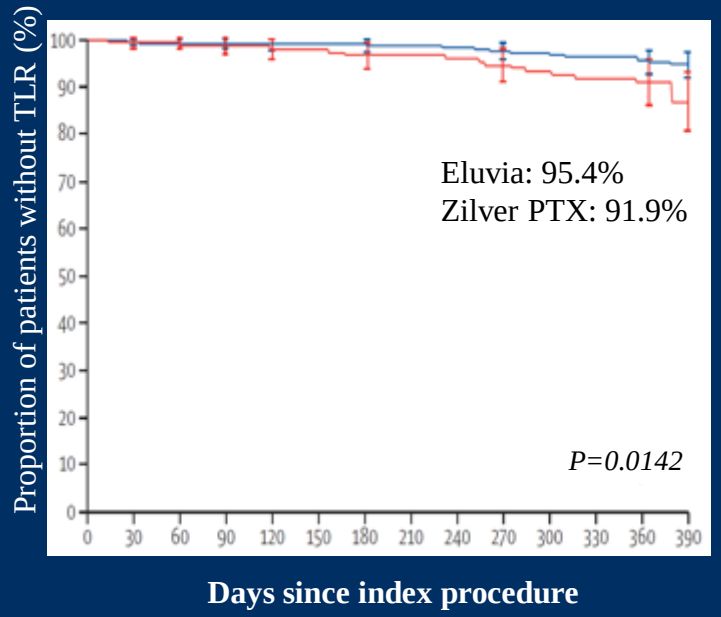
3 Eluvia showed entire circumferential medial disruption (1 in 6M and 2 in 12M).
The contra-lateral ZPTX in these 3 animals did not show any severe medial disruption.

Eluvia which showed greater expanding force and longer drug release effect potentially evoke severe medial disruption.

Eluvia showed better 1-year primary patency and TLR rate than ZPTX in patients who have femoropopliteal PAD with claudication; *IMPERIAL trial (FDA approval study)*

465 patients with atherosclerotic lesions in the femoropopliteal artery were randomly assigned to Eluvia (n=309) or to Zilver PTX (n=156)



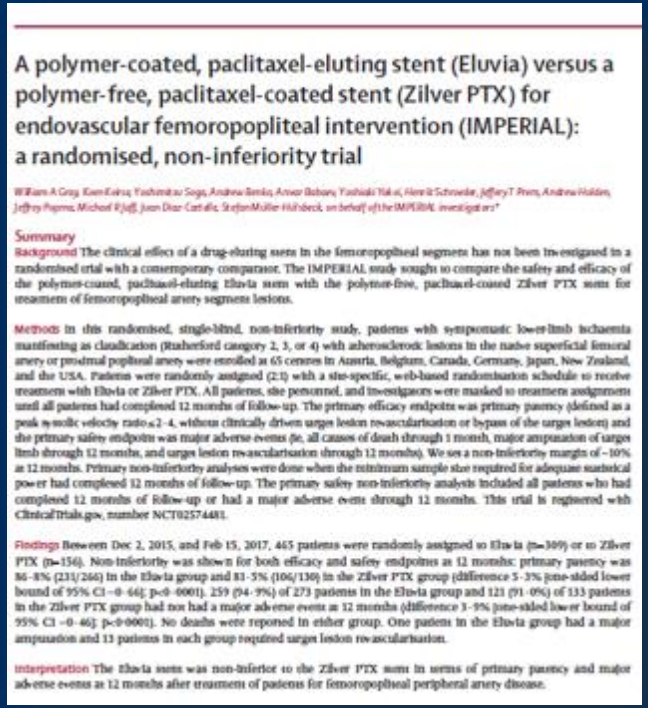


Gray WA, et al. Lancet. 2018;392:1541-1551.

SFA permanent polymer paclitaxel-eluting stents: Potential Signal of harm with greater expansion and long-term paclitaxel exposure?

IMPERIAL RANDOMIZED CONTROL TRIAL

*"…after some cases [of aneurysmal degeneration were] observed in a registry in Germany were reported, personnel at the core laboratory reviewed all available and suitable 1-year duplex ultrasound images and found six cases **(all in the Eluvia group)**."*



A polymer-coated, paclitaxel-eluting stent (Eluvia) versus a polymer-free, paclitaxel-coated stent (Zilver PTX) for endovascular femoropopliteal intervention (IMPERIAL): a randomised, non-inferiority trial

William A Gray, Koen Keirse, Yoshimitsu Soga, Andrew Benko, Anwer Beohon, Yoshiaki Yokoi, Hans U Schroeder, Jeffery T Price, Andrew Holden, Jeffrey Popma, Michael Kipff, Juan Diaz-Cartelle, Stefan Müller-Hülsbeck, on behalf of the IMPERIAL investigators*

Summary

Background The clinical effect of a drug-eluting stent in the femoropopliteal segment has not been investigated in a randomised trial with a contemporary comparator. The IMPERIAL study sought to compare the safety and efficacy of the polymer-coated, paclitaxel-eluting Eluvia stent with the polymer-free, paclitaxel-coated Zilver PTX stent for treatment of femoropopliteal artery segment lesions.

Methods In this randomised, single-blind, non-inferiority study, patients with symptomatic lower-limb ischaemia manifesting as claudication (Rutherford category 2, 3, or 4) with atherosclerotic lesions in the native superficial femoral artery or proximal popliteal artery were enrolled at 65 centres in Australia, Belgium, Canada, Germany, Japan, New Zealand, and the USA. Patients were randomly assigned (2:1) with a site-specific, web-based randomisation schedule to receive treatment with Eluvia or Zilver PTX. All patients, site personnel, and investigators were masked to treatment assignment until all patients had completed 12 months of follow-up. The primary efficacy endpoint was primary patency (defined as a peak systolic velocity ratio ≤2·4, without clinically driven target lesion revascularisation or bypass of the target lesion) and the primary safety endpoint was major adverse events (ie, all causes of death through 1 month, major amputation of target limb through 12 months, and target lesion revascularisation through 12 months). We set a non-inferiority margin of −10% at 12 months. Primary non-inferiority analyses were done when the minimum sample size required for adequate statistical power had completed 12 months of follow-up. The primary safety non-inferiority analysis included all patients who had completed 12 months of follow-up or had a major adverse event through 12 months. This trial is registered with ClinicalTrials.gov, number NCT02574481.

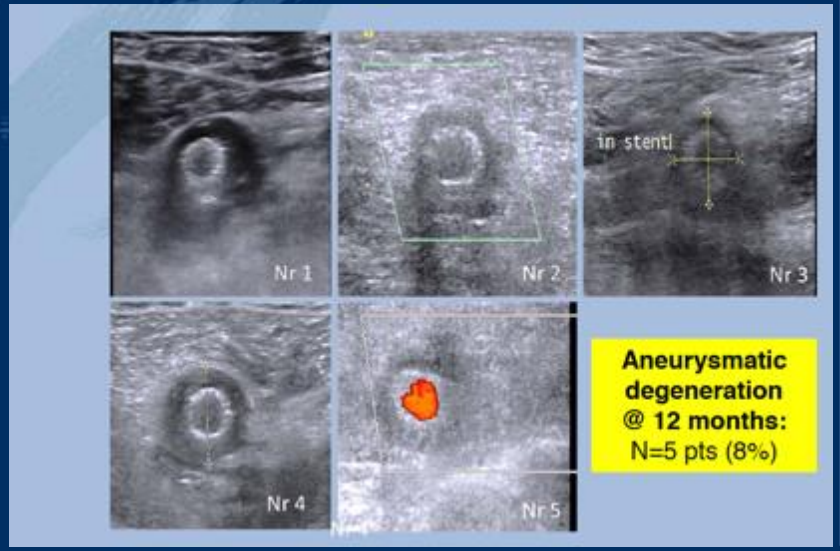
Findings Between Dec 2, 2015, and Feb 15, 2017, 465 patients were randomly assigned to Eluvia (n=309) or to Zilver PTX (n=156). Non-inferiority was shown for both efficacy and safety endpoints at 12 months: primary patency was 86·8% (231/266) in the Eluvia group and 83·5% (106/130) in the Zilver PTX group (difference 3·3% [one-sided lower bound of 95% CI −0·46]; p<0·0001). 259 (94·9%) of 273 patients in the Eluvia group and 121 (91·0%) of 133 patients in the Zilver PTX group had not had a major adverse event at 12 months (difference 3·9% [one-sided lower bound of 95% CI −0·46]; p<0·0001). No deaths were reported in either group. One patient in the Eluvia group had a major amputation and 13 patients in each group required target lesion revascularisation.

Interpretation The Eluvia stent was non-inferior to the Zilver PTX stent in terms of primary patency and major adverse events at 12 months after treatment of patients for femoropopliteal peripheral artery disease.

Gray WA, et al. Lancet. 2018;392:1541-1551.

SFA permanent polymer paclitaxel-eluting stents: Potential Signal of harm with greater expansion and long-term paclitaxel exposure?

Eluvia was implanted in 62 patients with complex femoropopliteal artery disease (CTO 79%, moderate-severe calcification 42%)



1-Year All-Comers Analysis of the Eluvia Drug-Eluting Stent for Long Femoropopliteal Lesions After Suboptimal Angioplasty

Theodosios Bisdas, MD, Efthymios Beropoulis, MD, Angeliki Argyriou, MD, Giovanni Torsello, MD, Konstantinos Stavroulakis, MD

ABSTRACT

OBJECTIVES The aim of this study was to assess the performance of the fluoropolymer-based paclitaxel-eluting stent (PES) in long femoropopliteal lesions.

BACKGROUND The new-generation fluoropolymer-based PES showed promising outcomes in short femoropopliteal lesions. The main feature of the stent is its controlled and sustained paclitaxel release over 12 months. However, the safety and efficacy of this technology in longer femoropopliteal lesions remain unclear.

METHODS Between March 2016 and March 2017, 62 patients were included in this analysis. Indications for fluoropolymer-based PES deployment were insufficient luminal gain or flow-limiting dissection after plain old balloon angioplasty in a femoropopliteal lesion. Primary patency, freedom from target lesion revascularization, amputation-free survival, and paclitaxel-related adverse events were retrospectively analyzed for up to 1 year of follow-up.

RESULTS Lesions were de novo in 84% of patients. Mean lesion length was 20 ± 12 cm, and 79% of the lesions (n = 49) were chronic total occlusions. Moderate or severe calcification was present in 42% of the lesions (n = 26). Stent implantation involved the distal superficial femoral artery and the proximal popliteal artery in 76% (n = 47) and 44% (n = 27) of patients, respectively. The Kaplan-Meier estimate of primary patency and freedom from target lesion revascularization was 87%. Amputation-free survival was 100% for patients with claudication (n = 32 [52%]) and 87% in patients with critical limb ischemia (n = 30 [48%]) (hazard ratio: 6.3, 95% confidence interval: 1.25 to 31.54; p = 0.052). Five aneurysm formations of the treated segments (8%) were thought to be attributable to paclitaxel.

CONCLUSIONS The fluoropolymer-based PES showed promising 1-year clinical and angiographic outcomes in real-world long femoropopliteal lesions. The long-term impact of aneurysm formation remains to be further investigated.

(J Am Coll Cardiol Intv 2018;11:957-66) © 2018 by the American College of Cardiology Foundation.

Bisdas T, et al. JACC Cardiovasc Interv. 2018;11:957-966.

Summary

Our pre-clinical study showed:

- ✓ Stent expansion and obtained lumen area were significantly greater in Eluvia compared with ZPTX at all time points.
- ✓ % stenosis was greater in ZPTX vs Eluvia only at 3M, however, there were no remarkable difference at 6M and 12M.
- ✓ PTX effect upon vascular wall was significantly greater in Eluvia at all time points.
- ✓ Entire circumferential medial layer disruption was observed in Eluvia (3 cases) at 6M (1) and 12M (2) cohort, with normal healing course at contra-lateral ZPTX treated vessels.
- ✓ The distinct characters of ZPTX and Eluvia regarding chronic outward force and drug release profile allow us to understand the results of clinical trials which showed greater patency of Eluvia as compared to ZPTX with higher incidence of aneurysmal formation.

Acknowledgments

CVPath Institute

Atsushi Sakamoto, MD, PhD
Masayuki Mori, MD, PhD
Yu Sato, MD
Rika Kawakami, MD, PhD
Hiroyuki Jinnouchi, MD
Anne Cornelissen, MD
Liang Guo, PhD
Robert Kutyz, MS
Russ Jones
Abebe Atiso, HT
Jinky Beyer
Lila Adams, HT
Frank D Kolodgie, PhD
Renu Virmani, MD

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