

# Newly FDA-approved paclitaxel devices for lower extremity and dialysis and the regulatory implications

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# Disclosures:

In the past 12 months, my spouse or myself have engaged in financial relationships as follows:

- **Advisory Board:** Boston Scientific, Medtronic
- **Consultant:** Penumbra, Neptune Medical
- **Clinical Events Committee/DSMB:** INTACT Vascular, Shockwave, Trireme, Thrombolex, Magneto
- **Speakers Bureau:** Abbott Vascular
- **Research Support**
  - Philips Healthcare, Spectranetics, Terumo, Boston Scientific, INARI, Penumbra, Ethicon, Walk Vascular
- **Equity Shareholder:** Truvic, Summa

# Background

- In 2018, three Paclitaxel Coated Balloons (DCB) and two Paclitaxel eluting stents (DES) had received FDA approval for the endovascular treatment of obstructive disease in the Superficial Femoral and Popliteal Arteries
- These approvals were based on uniform superiority in prospective, independently adjudicated randomized trials demonstrating improved primary patency and freedom from clinically driven target lesion revascularization (CD-TLR) as compared to control
- As Vascular Specialists, we had entered the anti-proliferative era in peripheral intervention that coronary intervention had moved to almost 15 years prior.
- Last approval prior to meta-analysis Sept 2018 (Eluvia)

# Then in December 2018

SYSTEMATIC REVIEW AND META-ANALYSIS



## Risk of Death Following Application of Paclitaxel-Coated Balloons and Stents in the Femoropopliteal Artery of the Leg: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Konstantinos Katsanos, MD, PhD, MSc, EBIR; Stavros Spiliopoulos, MD, PhD; Panagiotis Kitrou, MD, PhD; Miltiadis Krokidis, MD, PhD; Dimitrios Karnabatidis, MD, PhD

**Background**—Several randomized controlled trials (RCTs) have already shown that paclitaxel-coated balloons and stents significantly reduce the rates of vessel restenosis and target lesion revascularization after lower extremity

**Conclusions**—There is increased risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery of the lower limbs. Further investigations are urgently warranted.

# This Brought The Vascular Community To A Standstill

- There were physician and industry townhalls in Europe, Asia and recently in Washington DC with the FDA and CMS
- Hospitals shut down orders and usage
- There was tremendous interest and a vocal concerned response from the global medical device community and the medical community in general
- Usage in the USA went from 50% penetrance down to 15% usage in less than 2 months

At first

January 2019

- “The FDA believes that the benefits continue to outweigh the risks for approved paclitaxel coated balloons and paclitaxel eluting stents when used according to the IFU”

# Then .....March 2019

- We have now conducted a preliminary analysis of long-term follow-up data (up to five years in some studies) of the pivotal premarket randomized trials for paclitaxel-coated products indicated for PAD. While the analyses are ongoing, our preliminary review of this data has identified a potentially concerning signal of increased long-term mortality in study subjects treated with paclitaxel-coated products compared to patients treated with uncoated devices.
- Of the three trials with 5-year follow-up data, each showed higher mortality in subjects treated with paclitaxel-coated products than subjects treated with uncoated devices. In total, among the 975 subjects in these 3 trials, there was an approximately 50% increased risk of mortality in subjects treated with paclitaxel-coated devices versus those treated with control devices (20.1% versus 13.4% crude risk of death at 5 years).

# August 2019 ...after the FDA panel

- **RECOMMENDATIONS**

- Based on the FDA's review of available data and the Advisory Panel conclusions, we recommend that health care providers consider the following recommendations:
- Continue diligent monitoring of patients who have been treated with paclitaxel-coated balloons and paclitaxel-eluting stents.
- When making treatment recommendations, and as part of the informed consent process, consider that **THERE MAY BE AN INCREASED RATE OF LONG-TERM MORTALITY** in patients treated with paclitaxel-coated balloons and paclitaxel-eluting stents.
- **DISCUSS THE RISKS AND BENEFITS OF ALL AVAILABLE PAD TREATMENT OPTIONS WITH YOUR PATIENTS.** For many patients, alternative treatment options to paclitaxel-coated balloons and paclitaxel-eluting stents provide a more favorable benefit-risk profile based on currently available information.
- **FOR INDIVIDUAL PATIENTS JUDGED TO BE AT PARTICULARLY HIGH RISK FOR RESTENOSIS AND REPEAT FEMOROPOPLITEAL INTERVENTIONS, CLINICIANS MAY DETERMINE THAT THE BENEFITS OF USING A PACLITAXEL-COATED DEVICE OUTWEIGH THE RISK OF LATE MORTALITY.**
- In discussing treatment options, physicians should explore their patients' expectations, concerns and treatment preferences.
- Ensure patients receive optimal medical therapy for PAD and other cardiovascular risk factors as well as guidance on healthy lifestyles including weight control, smoking cessation, and exercise.

# Recent FDA Approvals

- InPact AV
- Approved November 2019

- Ranger DCB
- Approved November 2020

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Drug-Coated Balloons for Dysfunctional Dialysis Arteriovenous Fistulas

Robert A. Lookstein, M.D., M.H.C.D.L., Hiroaki Haruguchi, M.D.,  
Kenneth Ouriel, M.D., M.B.A., Ido Weinberg, M.D., Lanyu Lei, Ph.D.,  
Stephanie Cihlar, B.S., and Andrew Holden, M.B., Ch.B.,  
for the IN.PACT AV Access Investigators\*



ESC

European Society  
of Cardiology

European Heart Journal (2020) 41, 2541–2552  
doi:10.1093/eurheartj/ehaa049

FASTTRACK CLINICAL RESEARCH

Vascular medicine

## COMPARE: prospective, randomized, non-inferiority trial of high- vs. low-dose paclitaxel drug-coated balloons for femoropopliteal interventions

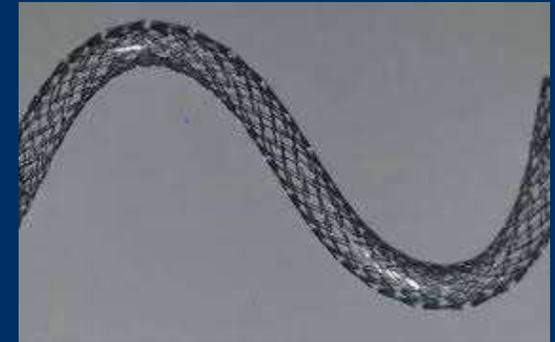
Sabine Steiner<sup>1</sup>, Andrej Schmidt<sup>1</sup>, Thomas Zeller<sup>2</sup>, Gunnar Tepe<sup>3</sup>,  
Marcus Thieme<sup>4</sup>, Lars Maiwald<sup>5</sup>, Henrik Schröder<sup>6</sup>, Wulf Euringer<sup>7</sup>,  
Matthias Ulrich<sup>8</sup>, Klaus Brechtel<sup>9</sup>, Steffen Brucks<sup>10</sup>, Erwin Blessing<sup>11</sup>,  
Johannes Schuster<sup>12</sup>, Ralf Langhoff<sup>13</sup>, Sebastian Schellong<sup>14</sup>,  
Norbert Weiss<sup>15</sup>, and Dierk Scheinert<sup>1\*</sup>

# Remaining Peripheral Paclitaxel Devices currently under investigation

- SURMODICS



- SAVAL



- STELLAREX BTK



- CHOCOLATE TOUCH



- LUTONIX BTK

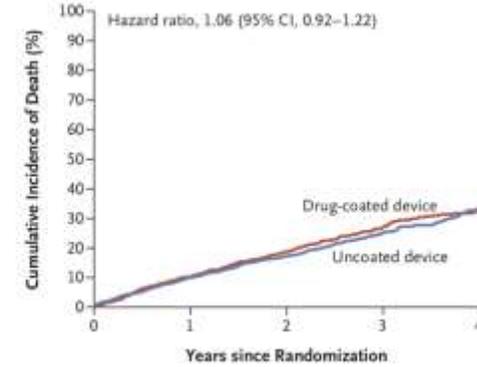


ORIGINAL ARTICLE

## Mortality with Paclitaxel-Coated Devices in Peripheral Artery Disease

J. Nordanstig, S. James, Manne Andersson, Mattias Andersson, P. Danielsson, P. Gillgren, M. Delle, J. Engström, T. Fransson, M. Hamoud, A. Hilbertson, P. Johansson, L. Karlsson, B. Kragsterman, H. Lindgren, K. Ludwigs, S. Mellander, N. Nyman, H. Renlund, B. Sigvant, P. Skoog, J. Starck, G. Tegler, A. Toivola, M. Truedson, C.-M. Wahlgren, J. Wallinder, A. Öjersjö, and M. Falkenberg

A Overall Population



# Drug-Coated Devices for Peripheral Arterial Disease

Andrew Farb, M.D., Misti Malone, Ph.D., and William H. Maisel, M.D., M.P.H.

- The results of the SWEDEPAD interim analysis provide important and reassuring information on PCDs used to treat femoro- popliteal disease.
- **THESE NEWER ANALYSES, THOUGH COMFORTING, ARE LIMITED BY THE DURATION OF FOLLOW-UP.** For example, in SWEDEPAD, fewer than 300 patients have been followed for 4 years. In contrast, 1090 participants were available for analysis at 5 years in the FDA's meta- analysis of the pivotal RCTs of the approved paclitaxel-coated devices. This gap underscores the importance of continued patient follow-up for ongoing randomized trials.
- The FDA will continue to work with investigators, medical professional societies, and the device industry to facilitate data development and to communi- cate with the public as new in- formation becomes available.

# In Summary

- We are in a different regulatory environment regarding paclitaxel based devices for peripheral lesions
- All IDE studies will now require 5 year clinical follow up to assess for any late safety concerns
- New Devices are being approved but there is heightened focus on full patient compliance with follow up protocols especially regarding vital status and safety events in the mid to late term.
- The FDA is attempting to give all the PTX data a fresh look with more randomized data becoming available including SWEDEPAD and VOYAGER among others.