The Critical Role for DCB in the Treatment of PAD

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Gary M Ansel MD - Disclosures

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  - Venarum
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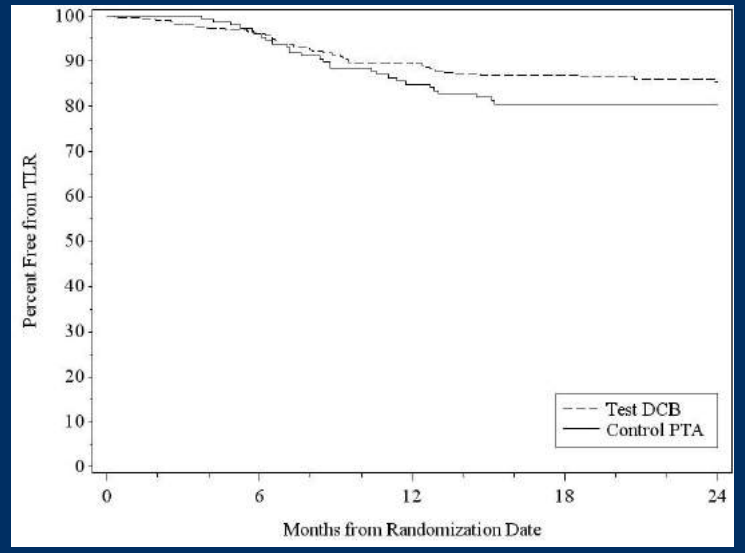
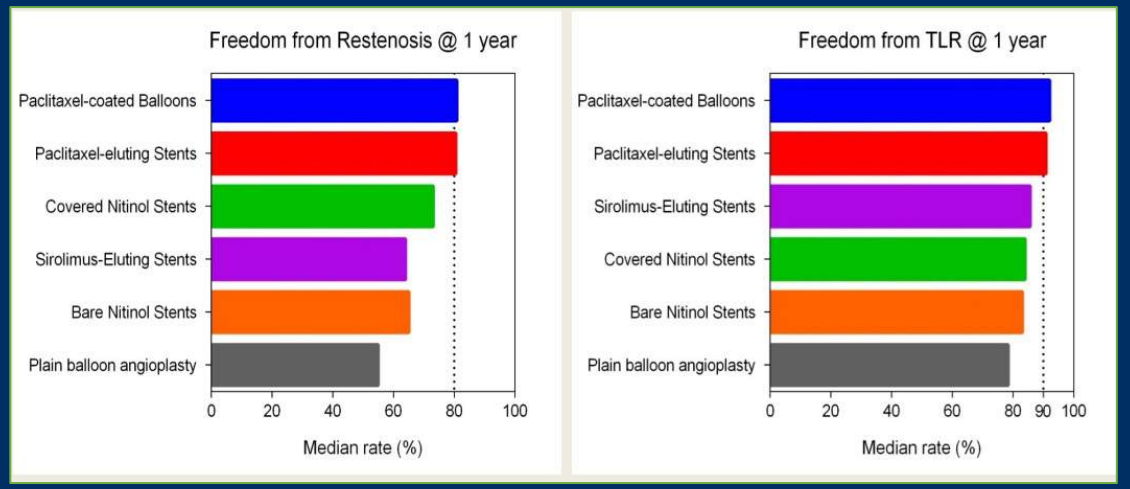
Even From the Beginning The Benefit of Drug Based Devices Was Really Changing Endo Treatment

Levant 2

DCB vs PTA

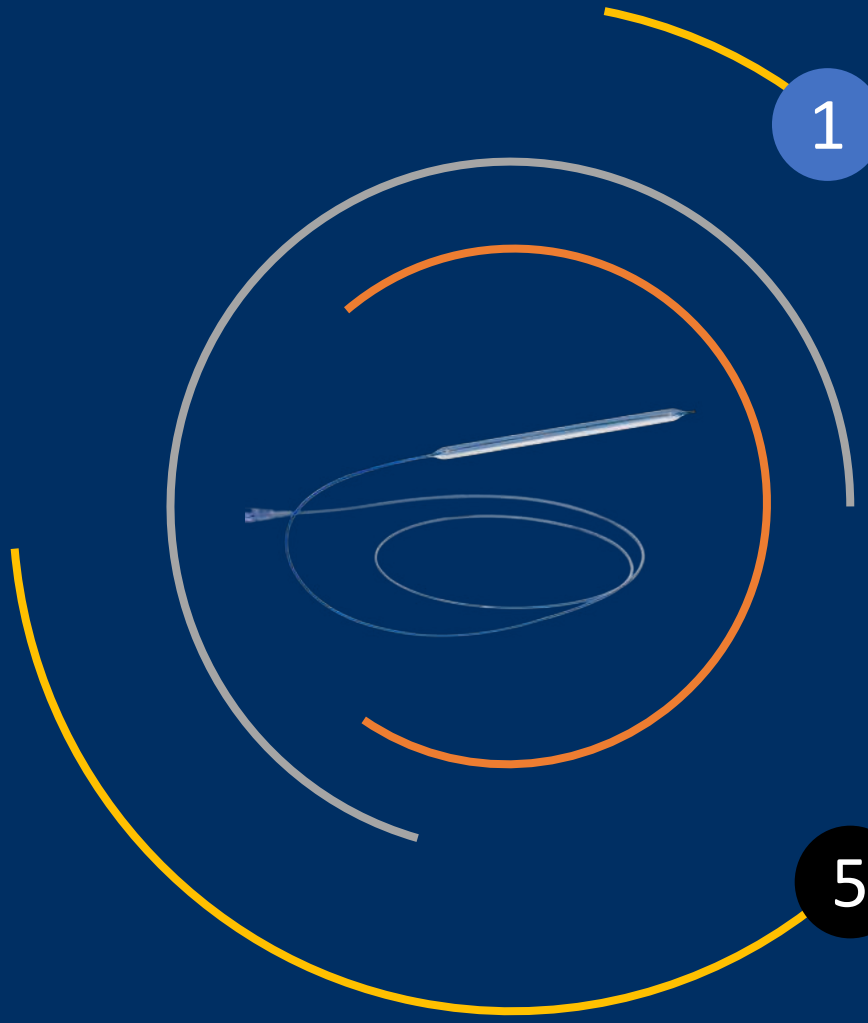


Network meta-analysis of RCTs of endovascular treatment*



*Katsanos et al JVS 2014;59:1123-1133

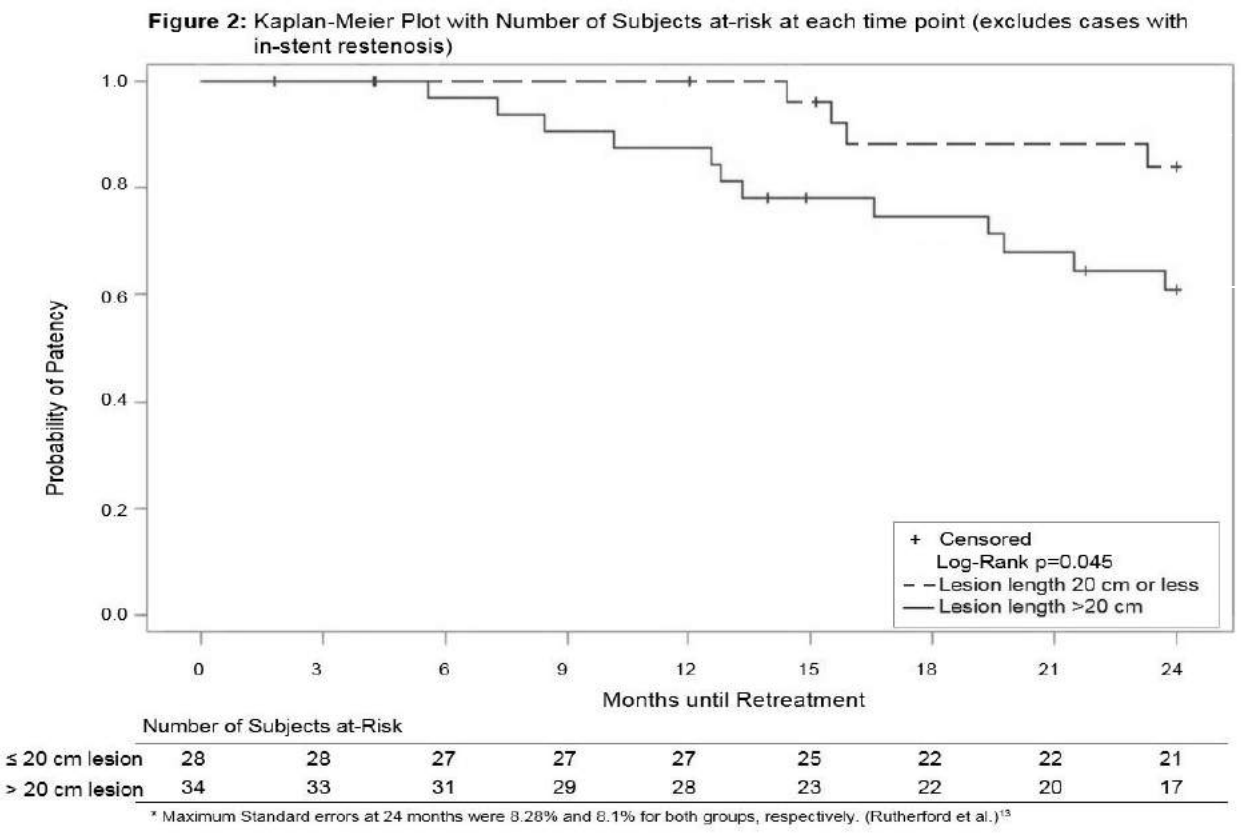
DCBs Enabled the "Leave Nothing Behind Mantra"



1. **Quick procedures**
2. **1-2 min balloon inflations**
3. **Favorable patency rates**
4. **Ability to treat longer lesion lengths**
5. **No concern for stent fractures**

Results of "Full Drug Jacket" Long DES Associated with Declining Patency

KM – Probability of Patency
Lesion length of 20cm or less vs. >20cm



- TLR 12%, lesion length of 20cm or less

-TLR 33%, lesion length of >20cm or less

Phillips, Ansel et al J Endovasc Ther. 2018 25:295-301.

Complex Lesions
The Hurdle for DCBs Due to Stent Usage

	LUTONIX Global	LUTONIX Long lesion	ILLUMENATE Global	IN.PACT Global Full Clinical Cohort	IN.PACT Global Long Lesion	IN.PACT Global CTO
Follow-up	691 subjects Complete follow-up Site-reported	118 Subjects Site-reported	Interim Core Lab-adjudicated	1406 subjects Complete follow-up Core Lab-adjudicated	157 subjects Complete follow-up Core Lab-adjudicated	126 subjects Complete follow-up Core Lab-adjudicated
Key Lesion Characteristics						
Length (cm) CTO (%) Ca++ (%)	10.12 cm 31.2% 50.2%	212 .5 cm 52.1% 88%	7.2 cm 28.3% 62%	12.1 cm 35.5% 68.7%	26.4 cm 60.4% 71.8%	22.9 cm 100.0% 71.2%
Primary Patency FF TLR/CD-TLR	85.4% 94.1%	87.4%	86.5% 93.9%	92.6%	91.1% 94.0%	84.4% 88.2%
Bail-out Stent (%)	25.2%	39.8%	15.0%	25.3%	40.4%	46.8%

Then Along Came the JAHA Article

Noted a delayed mortality in drug-based paclitaxel devices

No signal of etiology

Non patient level data

Unexpected low PTA mortality

FDA concerned and issued a warning letter

Drug based device use plummeted worldwide

VIVA: Vascular Leaders Forum Discussed Paclitaxel Manuscript

Summary Points from VIVA Forum on PTX

- Long hx of PTX use
- Toxicity well described
  - Cytopenias that reverse quickly
  - Short term cardiac (transfusion reaction)
  - Neuro (peripheral neuropathy)
  - Pulmonary
- No increase in any specific mortality found in data
- No Mechanism of action proposed or noted
- Similar signal in non-drug based devices ie BMS
- Dose miscalculated by original paper, no dose response
- Trial design of ITT
- Hx of Cardiac use
  - Stent thrombosis increased
  - No increase in mortality
- Hx of Long-term Breast cancer use
  - No increased mortality with prolonged use in curative breast cancer
  - Recent data: Considered safe in 2nd and 3rd trimester for mother and fetus

- **100 Attendees consisting of global clinicians (vascular and Oncology), society leaders, FDA/CMS personnel, legal and industry representatives**
- **7 sessions over 2 days**
- **Each session includes presentations and a lengthy discussion time**
  - **32 presentations and over 4.5 hours of discussion**
- **COI presented for all physician participants**
- **The two leading moderators had no disclosures with the device industry**
- **FDA felt there was a signal**

VIVA Sponsored Independent Patient Data Set (IPD):ITT

Recovery of LTFU/Vital Status Data: Unexpected continued decrease in RR

Models	Effect* (95% CI)	Lost to Follow-up/Withdrawn: Paclitaxel	Lost to Follow-up/Withdrawn: Control
VIVA original analyses		23%	24%
Primary, intent-to-treat	1.38 (1.06, 1.80)		
As treated, unadjusted	1.36 (1.04, 1.78)		
As treated, adjusted	1.37 (1.04, 1.80)		
Censoring at control crossover to paclitaxel	1.31 (1.00, 1.72)		
Missing data sensitivity / weighted analysis	1.36 (1.05, 1.77)		
Fixed effect two-stage meta-analysis	1.36 (1.05, 1.77)		
Random effects two-stage meta-analysis	1.34 (1.01, 1.78)		
DCB only devices	1.25 (0.92, 1.69)		
Zilver PTX 2nd randomization instead of primary	1.19 (0.89, 1.60)		
Additional analyses			
JAHA original, December 2018 (RR)	1.93 (1.27, 2.93)	NR	NR
JAHA update, Month 2019 (RR)	1.62 (1.20, 2.17)	NR	NR
FDA original, as treated (RR)	1.72 (1.22, 2.38)	25%	23%
FDA update, as treated (RR)	1.57 (1.16, 2.13)	15%	15%
VIVA, additional follow-up #1 (Late May 2019)	1.30 (1.03, 1.63)	15%	16%
VIVA, additional follow-up #2 (August 2019)	1.27 (1.03, 1.58)	9%	10%

* Estimate is hazard ratio (HR) unless indicated otherwise

CI = Confidence interval; DCB: Drug-coated balloon; PTX: Paclitaxel; JAHA = Journal of the American Heart Association; RR = Relative Risk; NR: Not reported

1

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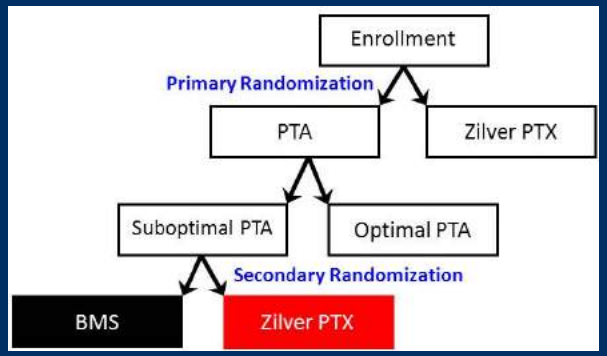
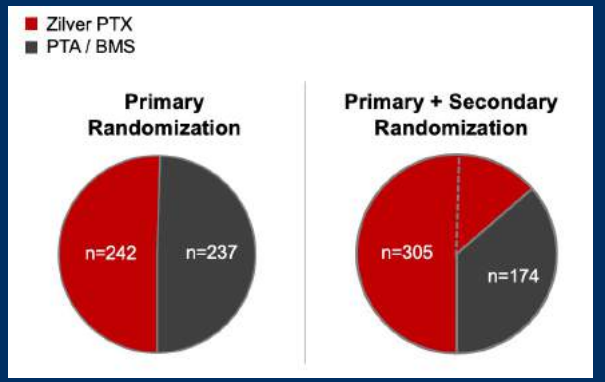




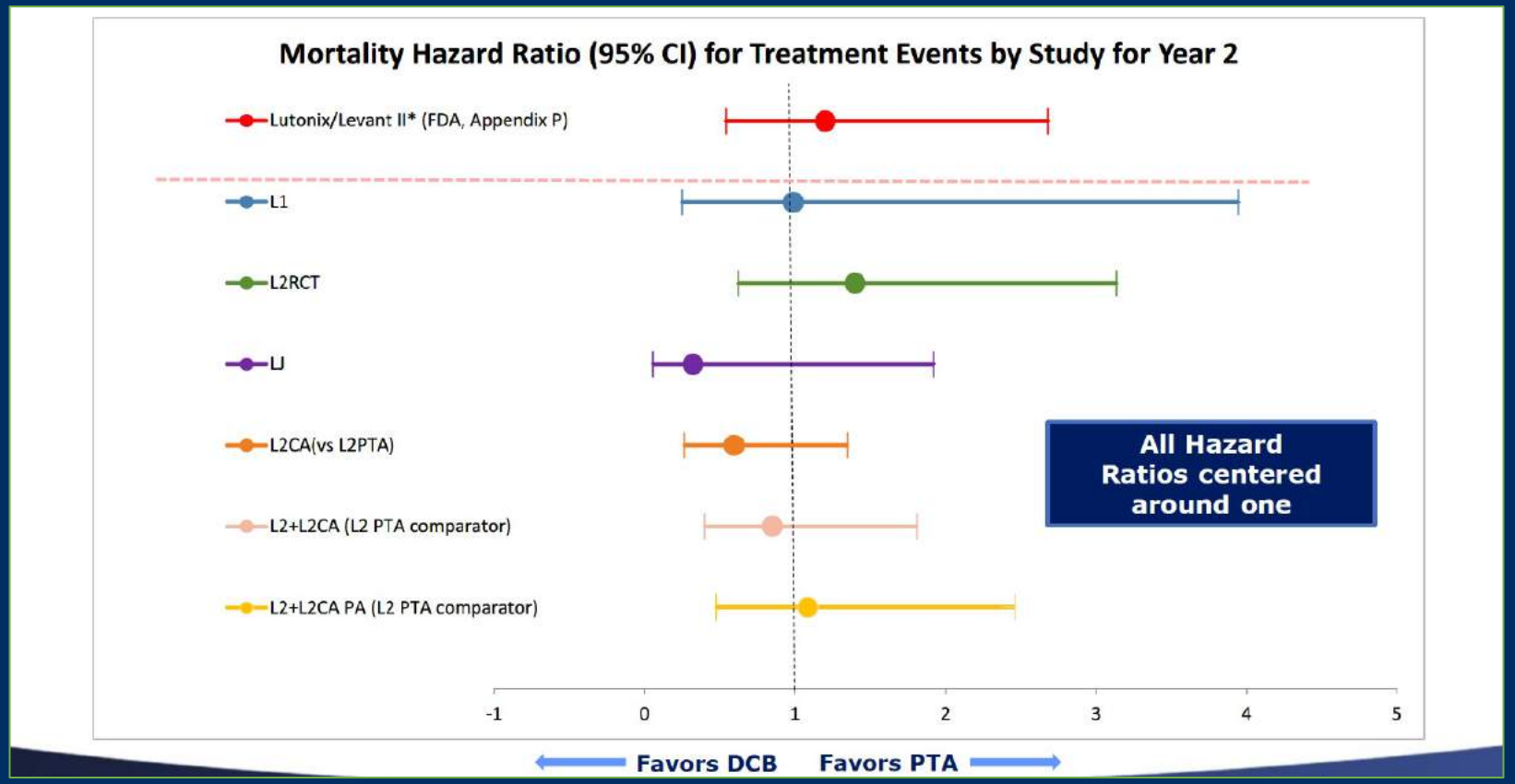
NO DOSE RESPONSE

*** VIVA/NAMSA IPD Meta-Analysis,**

Industry Analysis / Publications

All Without Mortality Signal
(All underpowered)

LEVANT 2 RCT
(Propensity Adjusted)



LEVANT 2 RCT
(Propensity Adjusted)

Multivariable Analysis of Mortality (5 years)

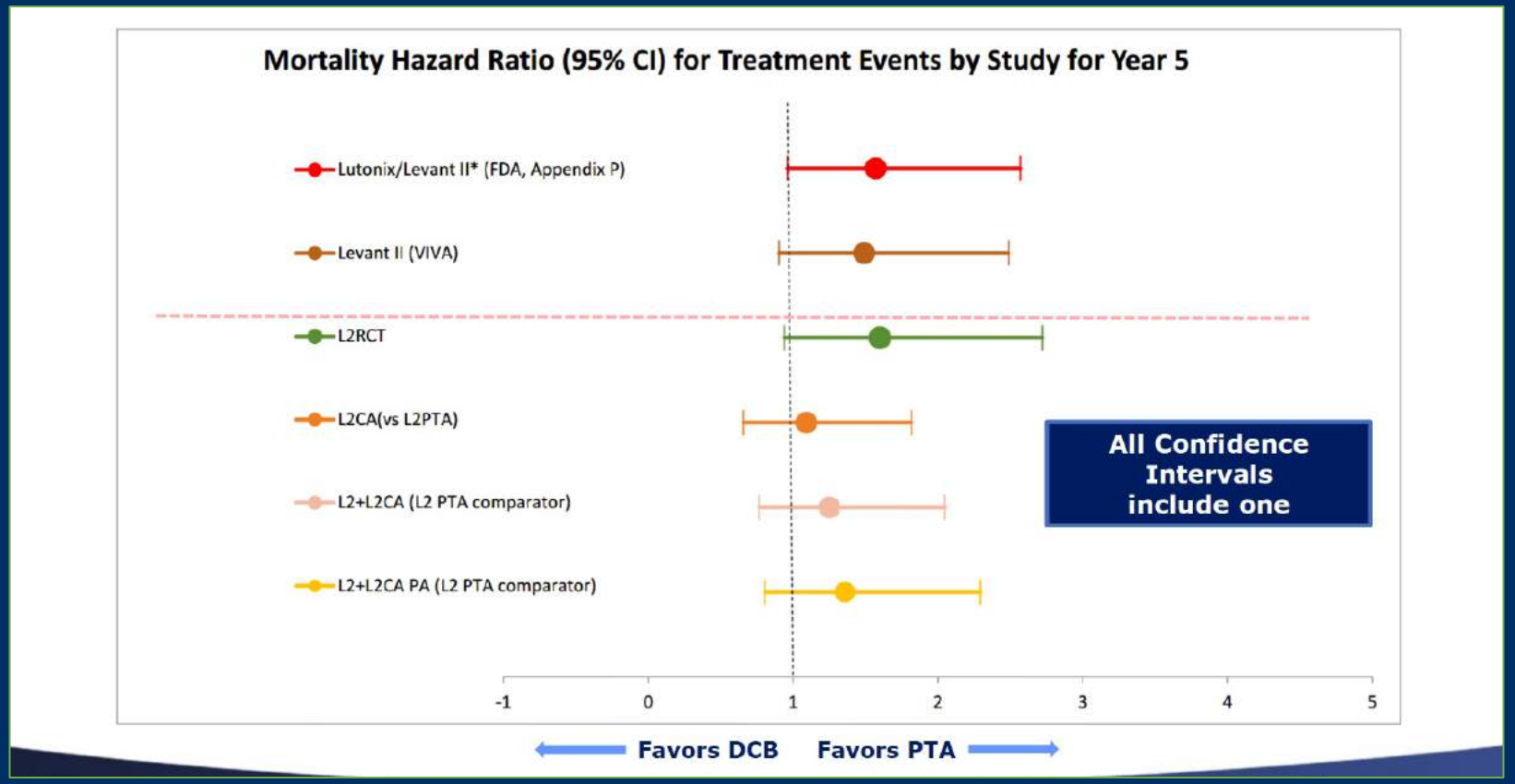
- Performed a propensity-adjusted multivariable analysis of mortality in LEVANT 2 RCT and LEVANT 2 CA
- Variables identified as significant* predictors of mortality irrespective of treatment group (DCB or PTA):

Variable	HR	P-value
Age (per year)	1.03	<0.0001
Rutherford Category	1.7	0.003
Left limb	1.6	0.005
Arrhythmia	1.8	0.011
Angiotensin II Receptor Blockers	0.6	0.02
Diabetes	1.4	0.028
Anticoagulant	2.1	0.029
Prior treatment	1.6	0.03

Treatment (DCB vs. PTA) was not a significant predictor (HR = 1.37, p=0.23)

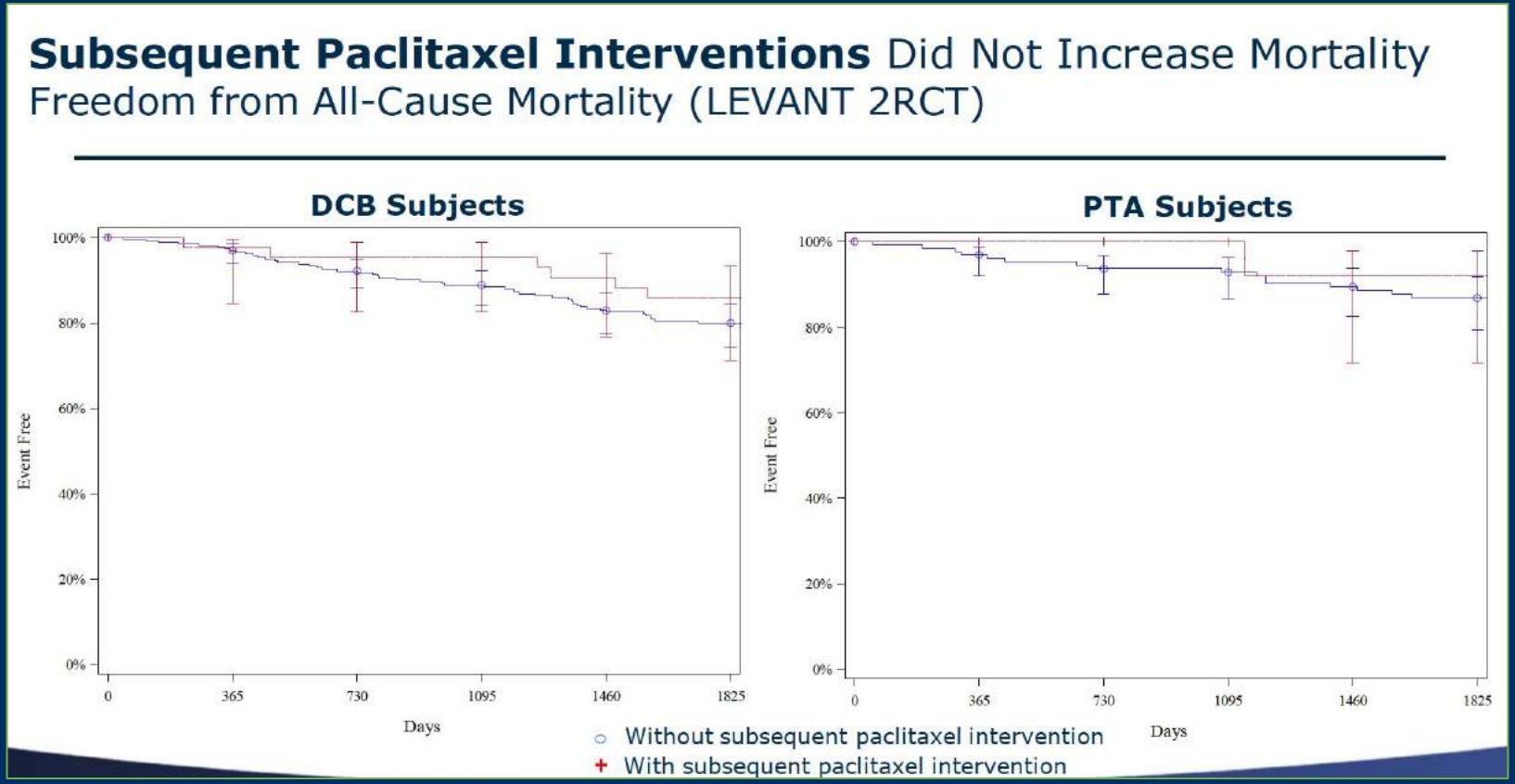
* p<0.05

LEVANT 2 RCT
(Propensity Adjusted)



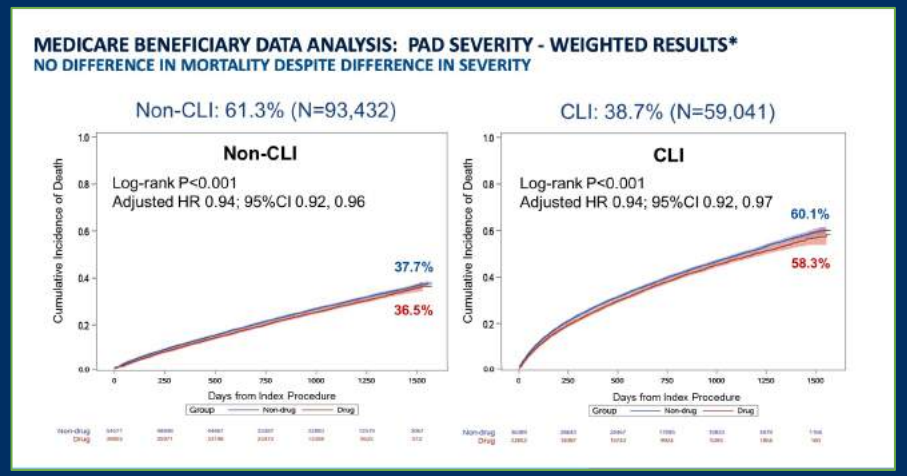
LEVANT 2 RCT
(Propensity Adjusted)

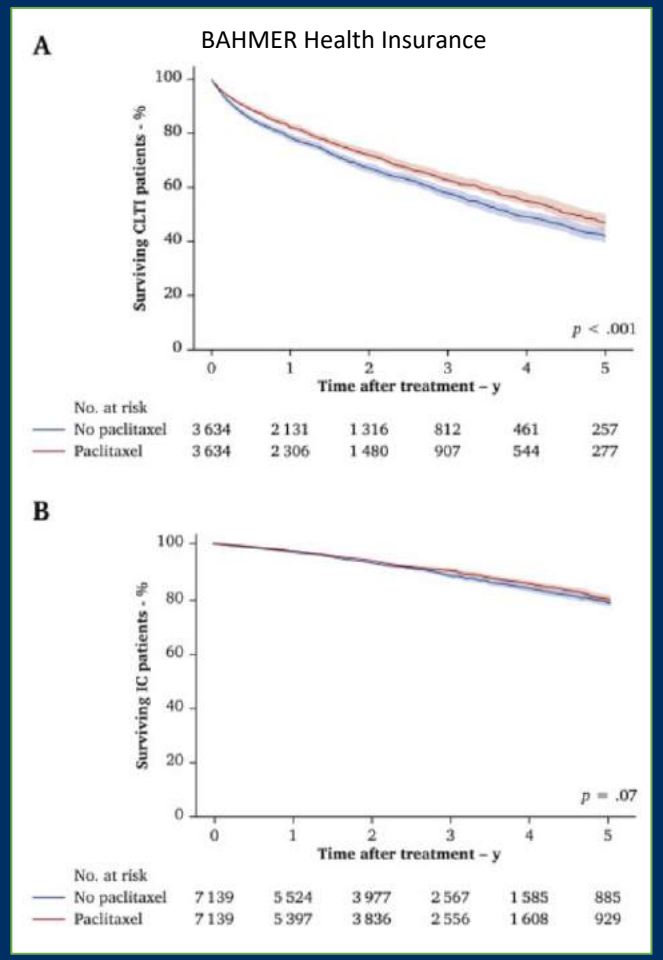
Subsequent Paclitaxel Interventions Did Not Increase Mortality
Freedom from All-Cause Mortality (LEVANT 2RCT)

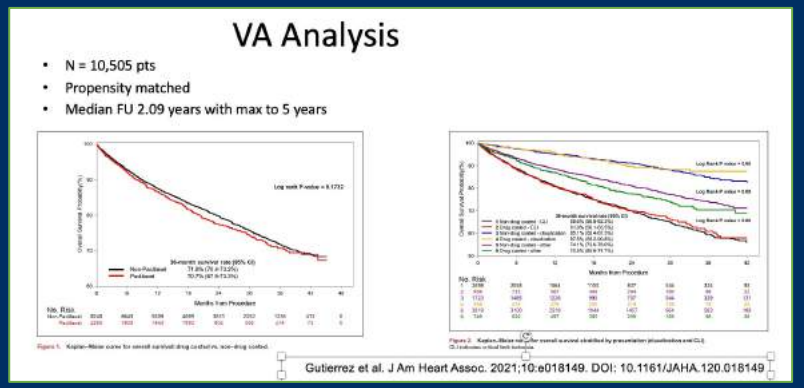


Large Population Based and Propensity Matched Data Sets

(n = > 200,000 no signal of problem CLI or claudicants)





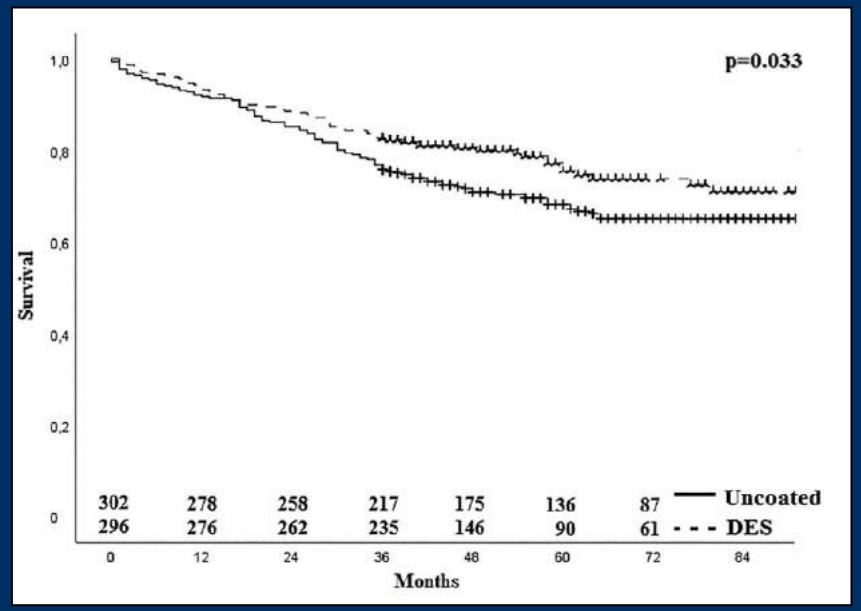


Secemsky EA. FDA Presentation. Washington, DC. June 19, 2019.
Behrendt CA. et al, Eur J Vasc Endovasc Surg. 2020
Gutierrez et al. J. Am Heart Assoc. 2021; 10:e018149. DOI: 10.1161/JAHA. 120.018149
Secemsky, EA. SAFE-PAD Update

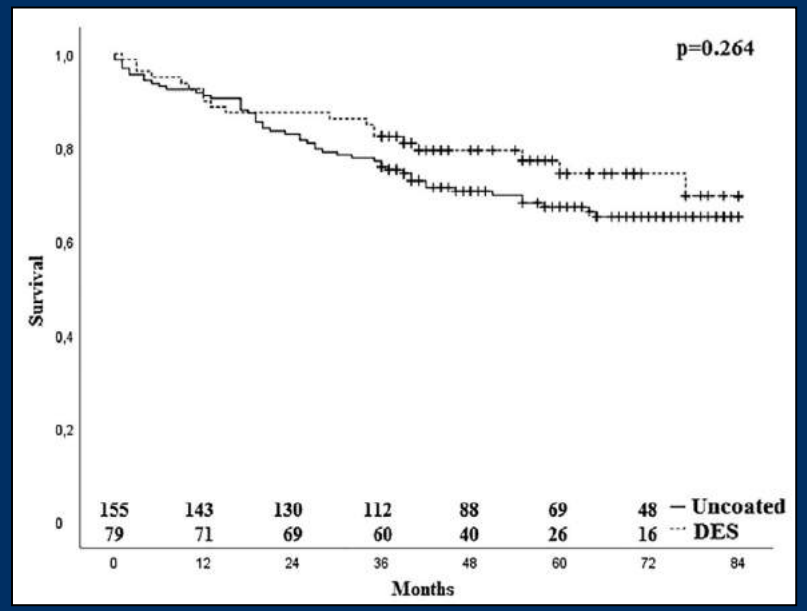
DES Mortality in Clinical Practice: The Zeller Experience

- 599 patients with FP lesions from 2010-2016 with >3 years of follow-up
  - 303 uncoated devices, 296 DES
  - Median follow-up 51.8 months

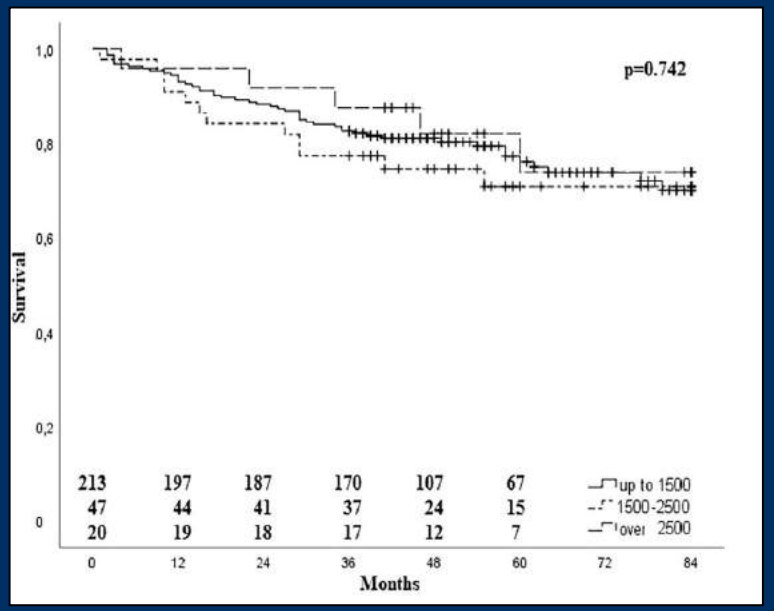
Unmatched Analysis



Matched Analysis



Zilver PTX Dosage Analysis



Bohme T, et al. CCI 2020.

Some Poorly Done Data as Well (JVS)

- Single center, retrospective, nonblinded
- N = 296

Conclusions: Consistent with the meta-analysis of several randomized clinical trials, the use of PES in a real-world setting was associated with a twofold increase in the risk of death. However, these findings were seen only among patients with TASC C and D lesions, who required multiple longer stents and potentially larger paclitaxel dose. There was no advantage in terms of patency in PES vs BMS in this population with extensive disease. Further studies of larger populations are required.

Mathlouthi, (J Vasc Surg 2021;73:548-53.)

Table II. Anatomic and procedural characteristics

Variable	BMS (n = 195 [65.9%])	PES (n = 101 [34.1%])	*P* value
Level of lesion			.4
SFA	155 (79.5)	84 (83.2)	
Popliteal	13 (6.7)	3 (2.9)	
SFA + popliteal	27 (13.8)	14 (13.9)	
TASC II category			.81
A	87 (44.6)	48 (47.5)	
B	62 (31.8)	30 (29.7)	
C	23 (11.8)	14 (13.9)	
D	23 (11.8)	9 (8.9)	
TASC II combined			.87
TASC C/D	46 (23.6)	23 (22.8)	
De novo	172 (88.2)	91 (90.1)	
Restenotic	23 (11.8)	10 (9.9)	
Tibial runoff			.068
0	3 (1.6)	1 (0.99)	
1	54 (27.8)	43 (42.6)	
2	71 (36.6)	33 (32.6)	
3	66 (34)	24 (23.8)	
No. of stents			.002
1	154 (78.9)	63 (62.4)	
>1	41 (21)	38 (37.6)	
Lesion length, cm	9.16 ± 7.6	9.3 ± 6.8	.87

BMS, Bare-metal stent; *PES*, paclitaxel-eluting stent; *SFA*, superficial femoral artery; *TASC*, TransAtlantic Inter-Society Consensus. Categorical variables are presented as number (%). Continuous variables are presented as mean ± standard deviation.

Newer Large Data Set

Voyager-PAD
Analysis of Drug Based Device Usage
(n = 6,564 randomized pts)

- **3.5 year Mortality Results**
- **Unweighted analysis,**
  - **10.2% for DCD**
  - **13.8% for nonDCD**
- **Weighted analysis**
  - **12.1% for DCD**
  - **12.6% for nonDCD**

  (hazard ratio [HR], 0.95; 95% confidence interval [CI], 0.83-1.09; p=0.49)

NEJM 2020 and HESS TCT 2020

Different Agencies Have Different Approaches

FDA

In the *NEJM* Perspectives article, Dr. Farb et al stated, "The results of the SWEDEPAD interim analysis provide important and reassuring information on PCDs used to treat femoropopliteal disease. Furthermore, recent analyses of additional data from nonrandomized studies have not identified an increased mortality risk associated with PCDs." However, the authors cautioned, "These newer analyses, though comforting, are limited by the duration of follow-up."

PMDA

Pharmaceuticals and Medical Devices Agency

This English version is intended to be a reference material for the convenience of users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

(100% follow-up rate) found no difference in mortality at 2.5 years follow-up, and was published in the New England Journal of Medicine[17].

(6) PMDA's evaluation results

Based on the above information, and also considering the deliberations at an Expert Discussion, PMDA believes that based on the research results explained in section (3), there is currently insufficient scientific evidence to justify restricting the use of PTX devices in Japan.

DCB Mortality Risk Summary

- DCB have changed the treatment paradigm of Fempop PAD
- Initial publication of drug devices caused concern but many unanswered questions
- FU publications of high quality and tens of thousands of patients do not support the concern raised
- What will be enough for regulatory relaxation??

Lutonix™ 035 Drug Coated Balloon PTA Catheter

Indications for Use: The LUTONIX™ 035 Drug Coated Balloon PTA catheter is indicated for percutaneous transluminal angioplasty, after appropriate vessel preparation, of de novo, restenotic, or in-stent restenotic lesions up to 300mm in length in native superficial femoral or popliteal arteries with reference vessel diameters of 4-7mm.

Contraindications: · The LUTONIX™ Catheter is contraindicated for use in: Patients who cannot receive recommended anticoagulant therapy. 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 there is a potential for adverse reaction in nursing infants from paclitaxel exposure. Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the delivery system.

Warnings: 1) A signal for increased risk of late mortality has been identified following the use of paclitaxel-coated balloons and paclitaxel eluting stents for femoropopliteal arterial disease beginning approximately 2-3 years post-treatment compared with the use of non-drug coated devices. There is uncertainty regarding the magnitude and mechanism for the increased late mortality risk, including the impact of repeat paclitaxel device exposure. Physicians should discuss this late mortality signal and the benefits and risks of available treatment options with their patients. **2)** Contents supplied STERILE using ethylene oxide (EO) process. Do not use if sterile barrier is damaged or opened prior to intended use. **3)** Do not use if product damage is evident. **4)** The LUTONIX™ Catheter is for use in one patient only; do not reuse in another patient, reprocess or resterilize. Risks of reuse in another patient, reprocessing, or resterilization include: Compromising the structural integrity of the device and/or device failure which, in turn, may result in patient injury, illness or death. Creating a risk of device contamination and/or patient infection or cross-infection, including, but not limited to, the transmission of infectious disease(s) from one patient to another. Contamination of the device may lead to patient injury, illness or death. **5)** Do not exceed the Rated Burst Pressure (RBP) recommended for this device. Balloon rupture may occur if the RBP rating is exceeded. To prevent over-pressurization, use of a pressure monitoring device is recommended. **6)** Use the recommended balloon inflation medium of contrast and sterile saline (≤50% contrast). Never use air or any gaseous medium to inflate the balloon. **7)** This product should not be used in patients with known hypersensitivity to paclitaxel or structurally related compounds. **8)** The safety and effectiveness of the LUTONIX™ Catheter have not been established for treatment in cerebral, carotid, coronary, or renal vasculature. **9)** The safety and effectiveness of using more than four LUTONIX™ drug coated balloons or a maximum drug coating quantity of approximately 15.1 mg paclitaxel in a patient has not been clinically evaluated.

Precautions: 1) The LUTONIX™ Catheter should only be used by physicians trained in percutaneous interventional procedures. **2)** Consideration should be given to the risks and benefits of use in patients with a history of non-controllable allergies to contrast agents.

Potential Adverse Events: Potential adverse events which may be associated with a peripheral balloon dilatation procedure include: •Additional intervention •Allergic reaction to drugs, excipients or contrast medium • Amputation/loss of limb •Aneurysm or pseudoaneurysm •Arrhythmias •Embolization •Hematoma •Hemorrhage, including bleeding at the puncture site •Hypotension/hypertension •Inflammation •Occlusion •Pain or tenderness •Pneumothorax or hemothorax •Sepsis/infection •Shock •Stroke •Thrombosis •Vessel dissection, perforation, rupture, or spasm Although systemic effects are not anticipated, refer to the Physicians' Desk Reference for more information on the potential adverse events observed with paclitaxel.

Potential adverse events, not described in the above source, which may be unique to the paclitaxel drug coating include: •Allergic/immunologic reaction to the drug coating (paclitaxel) •Alopecia •Anemia •Blood product transfusion •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

Please consult product labels and instructions for use for indications, contraindications, hazards, warnings, and precautions.

Thank You!