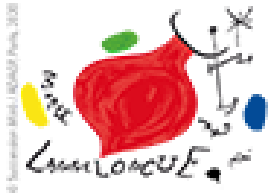
EMINENT and more

Y. Gouëffic, MD, PhD

Department of vascular and endovascular surgery, Groupe Hospitalier Paris Saint Joseph, Paris, France.



GROUPE HOSPITALIER PARIS SAINT JOSEPH

Disclosures

. Gouëffic reports:

Research funding from Abbott, General Electric, Veryan, WL Gore

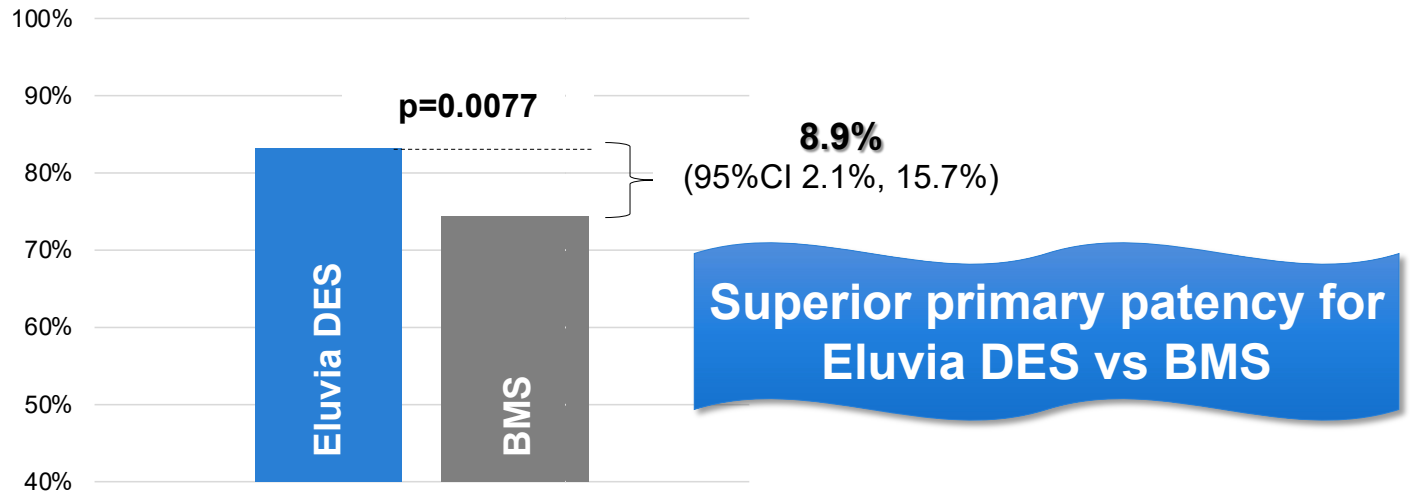
Personal fees and grants from Abbott, Bard, Biotronik, Boston Scientic, Cook, General Electric, Medtronic, Penumbra, Terumo, Veryan, WL Gore (medical advisory board, educational course, speaking)

EMINENT Effectiveness | Primary Patency

Primary Endpoint

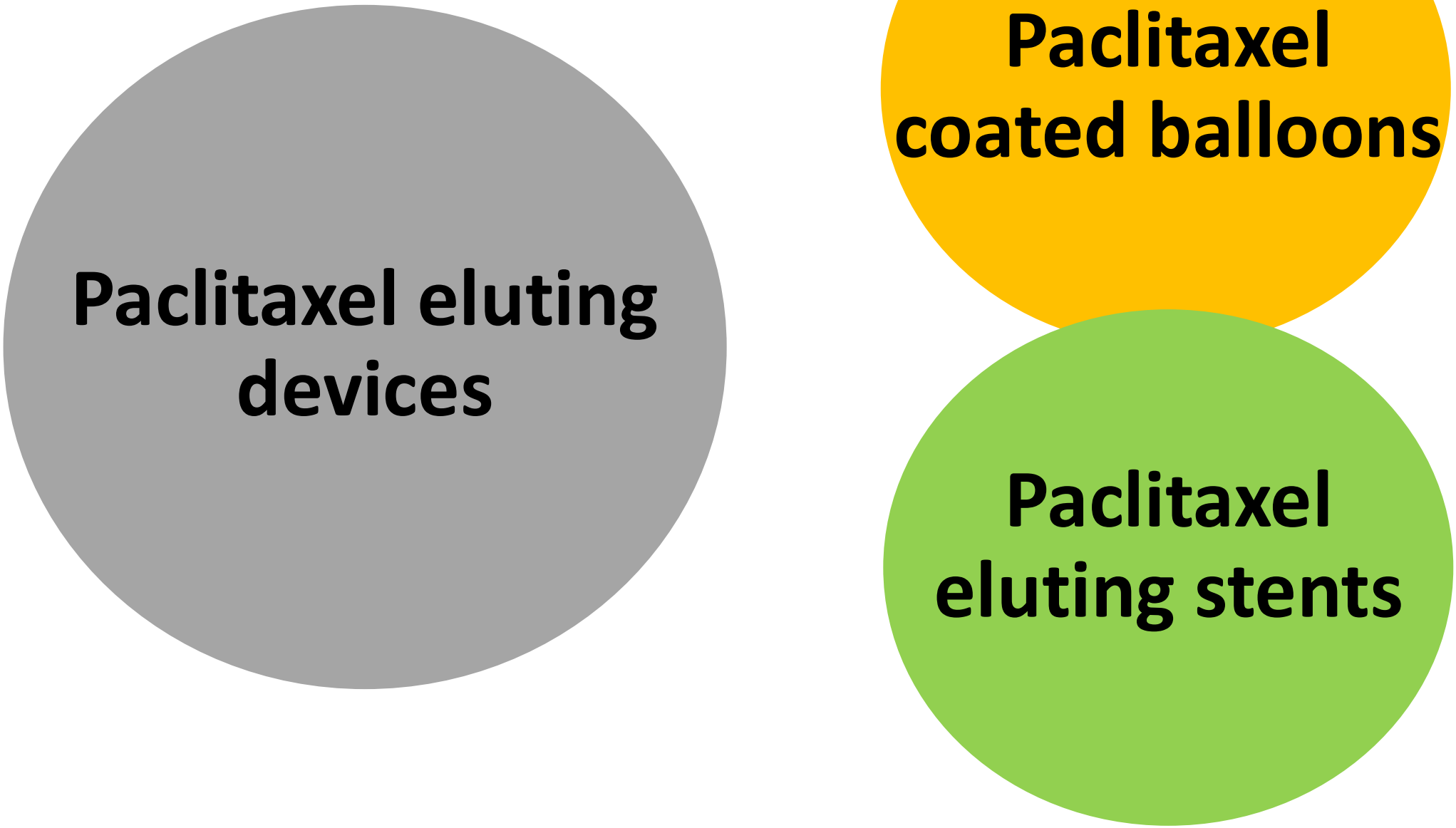
Statistically significantly greater primary patency in patients treated with Eluvia DES vs BMS

83.2% [337/405] vs 74.3% [165/222]; p=0.0077



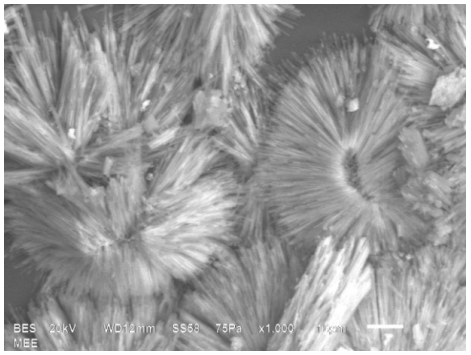
Intention to treat. Primary patency defined as core-lab assessed duplex ultrasound peak systolic velocity ratio (PSVR) ≤ 2.4 at 12 months in the absence of clinically-driven TLR or bypass of the target lesion.

Gouëffic, Circulation, In press

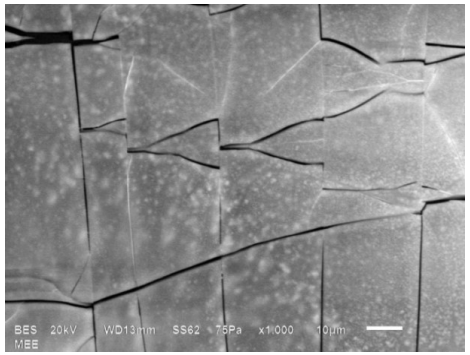

Paclitaxel eluting devices
Paclitaxel coated balloons
Paclitaxel eluting stents

uality and quantity of paclitaxel differ between DES and DCB

Crystalline Coating



Amorphous Coating

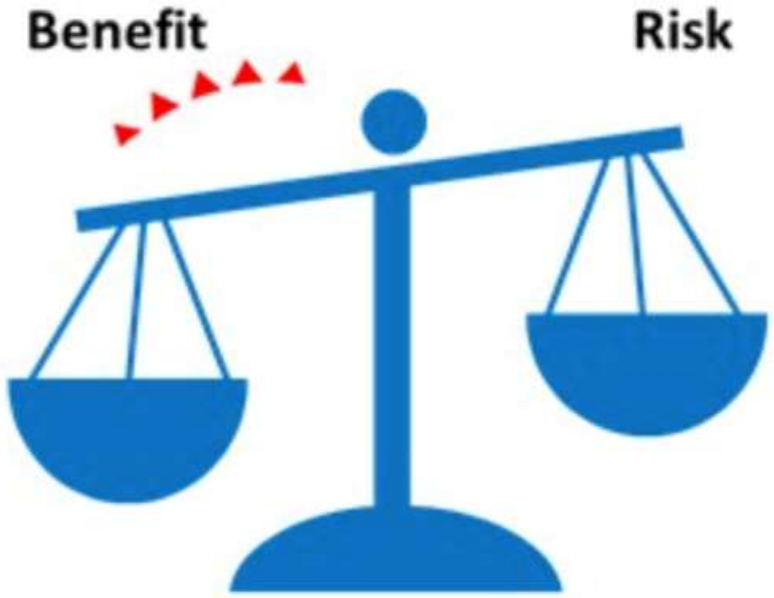


	Drug eluting stent		Drug coating balloons		
	ELUVIA	ZILVER PTX	IN.PACT	Lutonix	Stellarex
Biostable Polymer	✓				
Excipient			✓	✓	✓
Amorphous Coating Morphology	✓	✓			
Paclitaxel Dose Density (µg/mm²)	0.167	3	3.5	2	2
Total Dose (6 mm x 120 mm)	409 µg	1103 µg	8448 µg	4500 µg	4721 µg
Diffusion-Controlled Elution	✓				
Particulate Counts[a] (≥10µm size)	1381	11,928	567,432	210,320	193,968

[a]Simulated use in a tortuous vessel model under clinically relevant flow conditions.
Device sizes for particulates testing: 6mmx120mm stents, 6mmx80mm balloons. BSC Data on file.
Data from ELUVIA, Zilver PTX, Lutonix, Stellarex and IN.PACT DFUs. Abbreviations: DCB, drug-coated balloon; drug-eluting stent.

Benefit and risk before 2018…

Paclitaxel devices showed benefits in term of clinical, morphological, haemodynamic and cost effectiveness endpoints



In 2018: DOUBT ABOUT THE SAFETY

SYSTEMATIC REVIEW AND META-ANALYSIS

American Heart Association | American Stroke Association

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

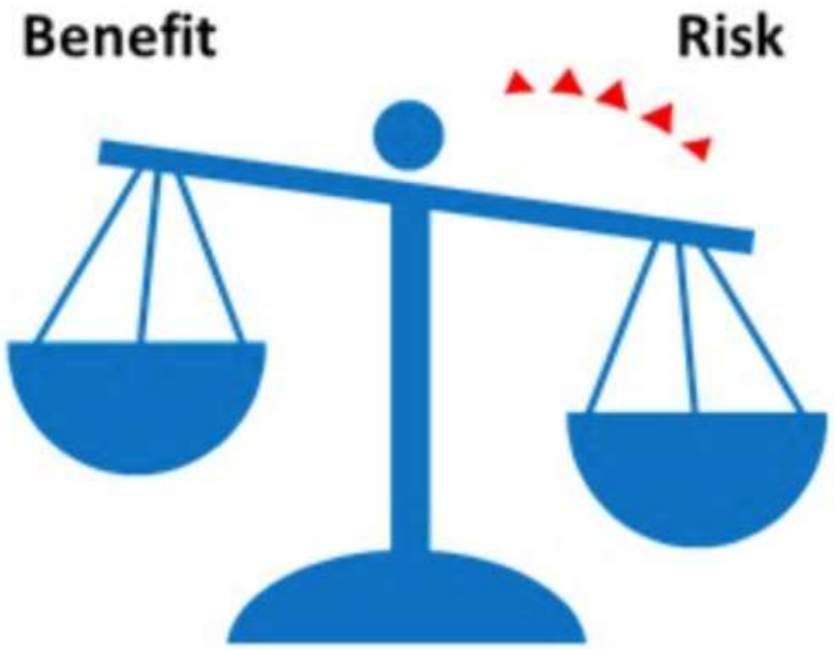
Background—Several randomized controlled trials (RCTs) have already shown that paclitaxel-coated balloons and stents significantly reduce the rates of vessel restenosis and target lesion revascularization after lower extremity interventions.

Methods and Results—A systematic review and meta-analysis of RCTs investigating paclitaxel-coated devices in the femoral and/or popliteal arteries was performed. The primary safety measure was all-cause patient death. Risk ratios and risk differences were pooled with a random effects model. In all, 28 RCTs with 4663 patients (89% intermittent claudication) were analyzed. All-cause patient death at 1 year (28 RCTs with 4432 cases) was similar between paclitaxel-coated devices and control arms (2.3% versus 2.3% crude risk of death; risk ratio, 1.08; 95% CI, 0.72–1.61). All-cause death at 2 years (12 RCTs with 2316 cases) was significantly increased in the case of paclitaxel versus control (7.2% versus 3.8% crude risk of death; risk ratio, 1.68; 95% CI, 1.15–2.47; —number-needed-to-harm, 29 patients [95% CI, 19–59]). All-cause death up to 5 years (3 RCTs with 863 cases) increased further in the case of paclitaxel (14.7% versus 8.1% crude risk of death; risk ratio, 1.93; 95% CI, 1.27–2.93; —number-needed-to-harm, 14 patients [95% CI, 9–32]). Meta-regression showed a significant relationship between exposure to paclitaxel (dose-time product) and absolute risk of death (0.4±0.1% excess risk of death per paclitaxel mg-year; $P<0.001$). Trial sequential analysis excluded false-positive findings with 99% certainty (2-sided α, 1.0%).

Conclusions—There is increased risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal

nclusions – «There is increased risk of death owing application of paclitaxel-coated loons and stents in the femoropopliteal ery of the lower limbs. Further investigations urgently warranted.»

DOI: 10.1161/JAHA.118.011245



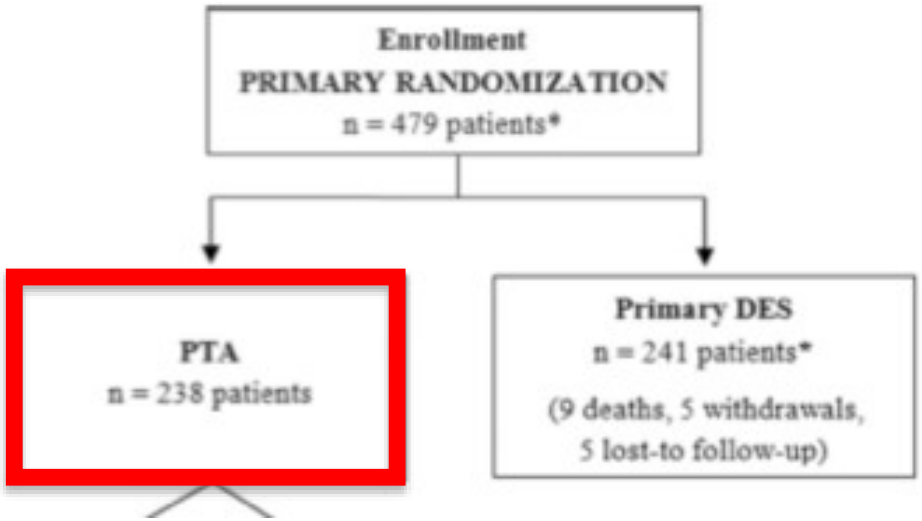
Katsanos, J Am Heart Assoc.,2018

And FEW DATA ABOUT THE BENEFIT of drug eluting stents…

Zilver® PTX® RCT

Zilver PTX vs POBA (n=474)

Designed to compare ZLIVER® PTX® vs uncoated PTA for femoropopliteal lesions

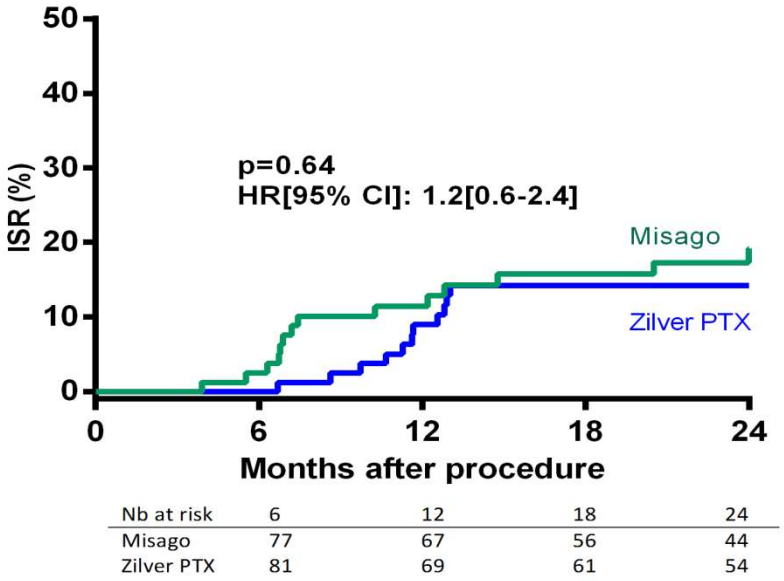


Dake, Circ Cardiovasc Interv. 2011

BATTLE RCT

Zilver PTX vs MISAGO (n=171)

ZILVER® PTX® failed to show superiority in comparison to MISAGO®



Gouëffic, JACC Interv. 2020

And FEW DATA ABOUT THE BENEFIT of drug coated ballons…

RCTs compared DCB with POBA alone

POBA is not the standard of care anymore

No head to head comparison between DCB and BMS

***Leaving nothing behind* is not a RCT but a marketing sentence**

Caradu, J Vasc Surg, 2019

Since 2021, the paradigm has changed

2018: Doubt about paclitaxel device safety is introduced
2021: Accumulated evidence diminishes any doubt

Editor's Choice – Long Term Survival after Revascularisation with Paclitaxel Coated D

The NEW ENGLAND JOURNAL of MEDICINE

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

Mortality Rates After Paclitaxel-Coated Device Use in Patients With Occlusive Femoropopliteal Disease: An Updated Systematic Review and Meta-Analysis of Randomized Controlled Trials

Krystal Dinh, BMed, MTrauma, Alexandra M. Limmer, MBBS, MS, Andy Z. L. Chen, BMed, MD,

First Published June 9, 2021 | Research Article | Find in PubMed | Check for updates

https://doi-org.proxy.insermbiblio.inist.fr/10.1177/15266028211023505

Circulation: Cardi

Revascularization

ORIGINAL ARTICLE

Eric A. Secemsky MD[a,b,c], Harun Kundi MD[a,b], Ido Weinberg MD[c,d], Marc Schermerhon MD[e], Joshua A. Beckman MD[f], Sahil A. Parikh MD[g], Michael Kenneth Rosenfield MD[c,d], and Robert W. Yeh MD[a,b,c]

Mortality After Paclitaxel Coated Balloon Angioplasty and Stenting of Superficial Femo and Popliteal Artery in the Vascular Quality Ini

Daniel J. Bertges, MD; Art Sedrakyan, MD, PhD; Tianyi Sun, MS; Mohammad H. Eslami, MD; Marc Schermerhorn, MD; Philip P. Goodney, MD, MS; Adam W. Beck, MD; Jack L. Cronenwett, MD; Jens Eldrup-Jorgensen, MD

Letter to the Editors

Fragility of the Signal

Yann Gouëffic, MD, PhD[1], Boris Postaire, MD[2], and Brice Leclère, MD, PhD[3]

JOURNAL OF ENDOVASCULAR THERAPY

Journal of Endovascular Therapy 2020, Vol. 27(5) 871–872 © The Author(s) 2020

SAGE

REVIEW ARTICLES

Audra A. Duncan, MD, SECTION EDITOR

Check for updates

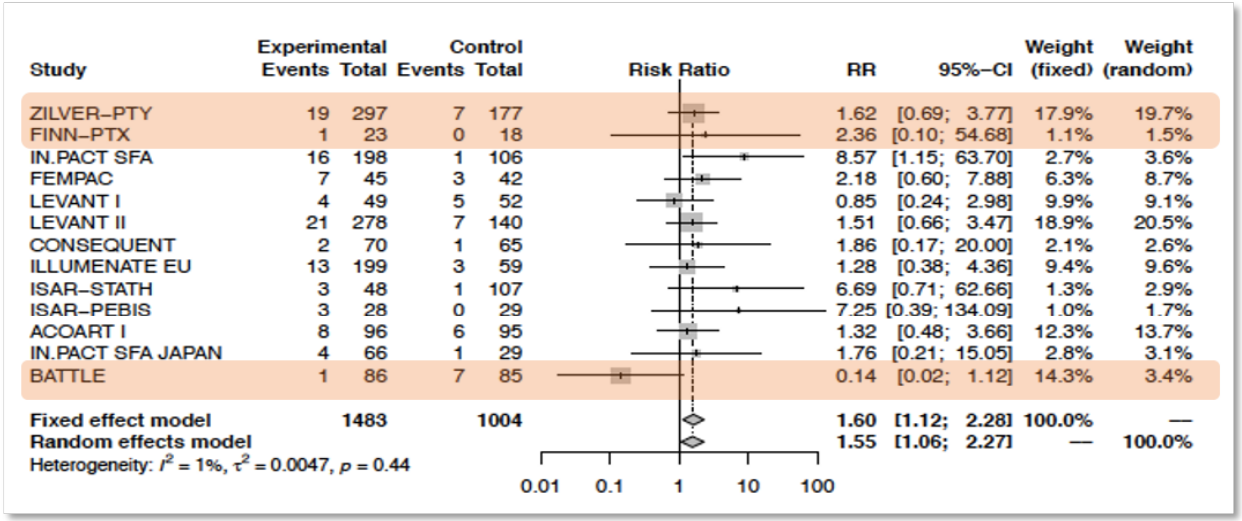
Update on paclitaxel for femoral-popliteal occlusive disease in the 15 months following a summary level meta-analysis demonstrated increased risk of late mortality and dose response to paclitaxel

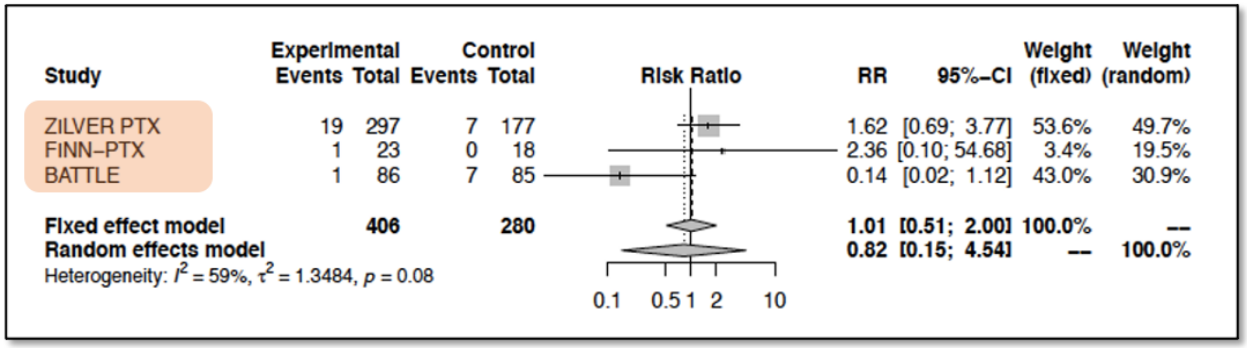
Peter A. Schneider, MD,[a] Ramon L. Varcoe, MBBS, MS, PhD,[b] Eric Secemsky, MD, MSc,[c] Marc Schermerhorn, MD,[d] and Andrew Holden, MBChB,[e] San Francisco, Calif; Sydney, New South Wales, Australia; Boston, Mass; and Auckland, New Zealand

Schneider, J Vasc Surg, 2021; Dinh, J Endovasc Ther, 2021; ,Nordanstig J, NEJM, 2020; Gouëffic, J Endovasc Ther, 2020; Behrendt, Eur J Vasc Endovasc Surg, 2020; Bertges, Cardiovasc Interv, 2020; Freisinger, Eur Heart J, 2019; Katsanos, J Am Heart Assoc, 2018

aclitaxel eluting stents and mortality

Random effects forest plot of all-cause patient death at 2 years updated with BATTLE, 2 years outcomes *(13 RCTs: 10 DCB RCTs (1801 patients) – 3 DES RCTs (686 patients)*





Goueffic, JACC interv, 2019 - Gouëffic, J Endovasc Ther, 2020

VOYAGER PAD RCT

Trial Design

6,564 Patients with Symptomatic Lower Extremity PAD* Undergoing Peripheral Revascularization

ASA 100 daily for all Patients
Clopidogrel at Investigator's Discretion

Randomized 1:1 Double Blind

aban 2.5 mg
ce daily

Stratified by Revascularization Approach (Surgical or Endovascular) and Use of Clopidogrel

Placebo

Follow up Q6 Months, Event Driven, Median f/u 28 Months

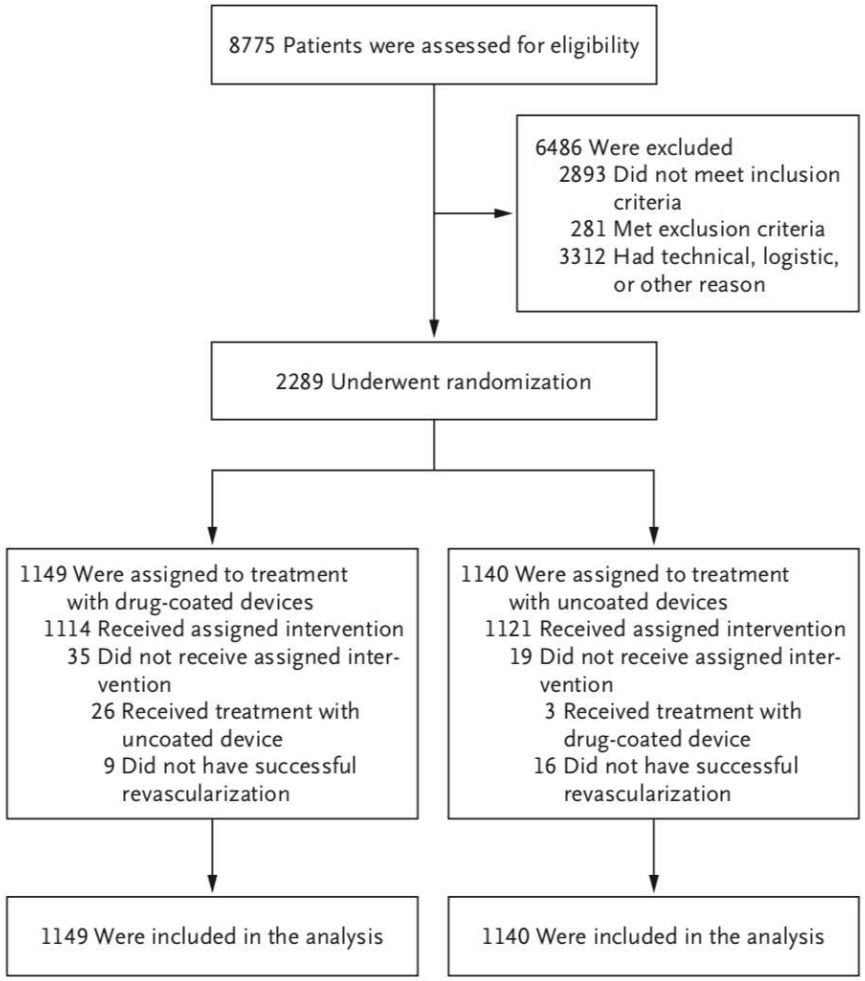
Primary Efficacy Endpoint: Acute limb ischemia, major amputation of vascular etiology, myocardial infarction, ischemic stroke or cardiovascular death

Principal Safety Endpoint: TIMI Major Bleeding

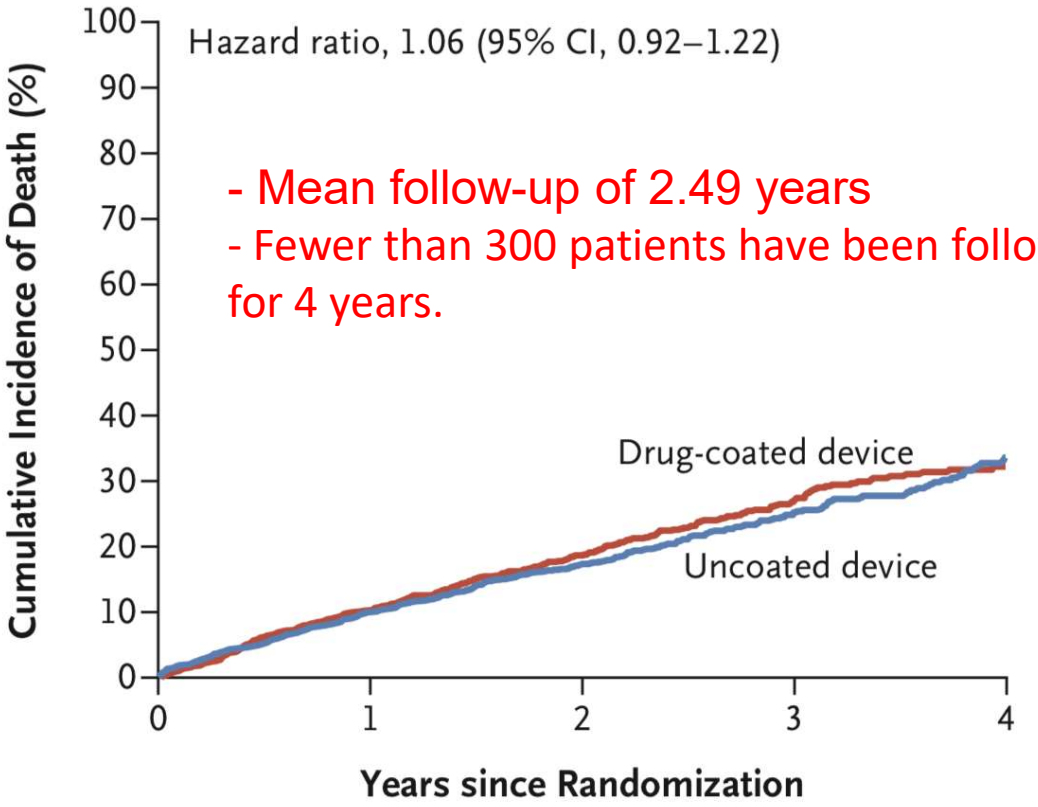
Hess, J Am Coll Cardiol 2021

VEDEPAD RCT

erim analysis of 2289 symptomatic patients from the Swedish Drug Elution Trial in Peripheral Arterial Disease VEDEPAD) trial



Overall population



- Mean follow-up of 2.49 years
- Fewer than 300 patients have been follo for 4 years.

Nordanstig, NEJM, 2020

DA response

The results of the SWEDEPAD interim analysis provide important and eassuring information on PCDs used to treat femoropopliteal disease.

Recent analyses of additional data from nonrandomized studies have ot identified an increased mortality risk associated with PCDs.

The FDA believes that clinical studies of these devices should continue nd should collect long-term mortality data

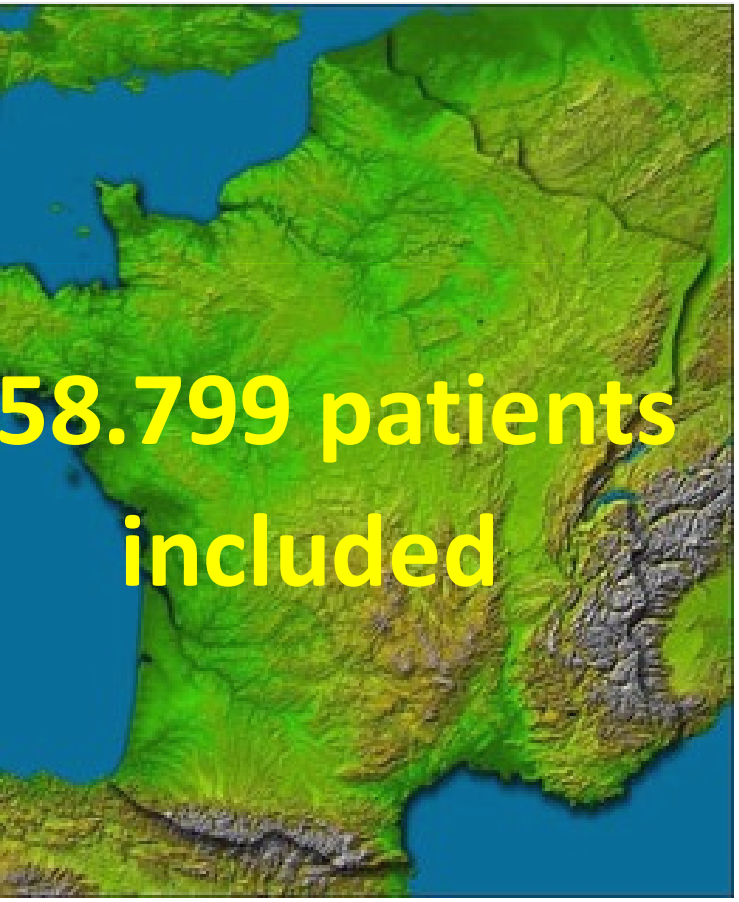
Farb, NEJM, 2021

DETECT survey study

M. Wargny[1], *P.A. Gourraud[1], Y. Gouëffic[3]*

1-Department of clinical data, University hospital of Nantes, France

2- Department of vascular and endovascular surgery, Groupe Hospitalier Paris Saint Joseph, Paris, France



- Source database: Système National des Données de Santé (SNDS) between 2011 and 2019

- Inclusion criteria: patients treated for infra-inguinal lesions, by endovascular repair between 2011 and 201

- Subgroups: POBA – BMS – Zilver PTX – Eluvia – Range Inpact Admiral – Lutonix – Sequent Please – Stellarex – Luminor 35

- Endpoint: mortality at 1, 2 and 5 years of FU (2024)

DETECT survey study

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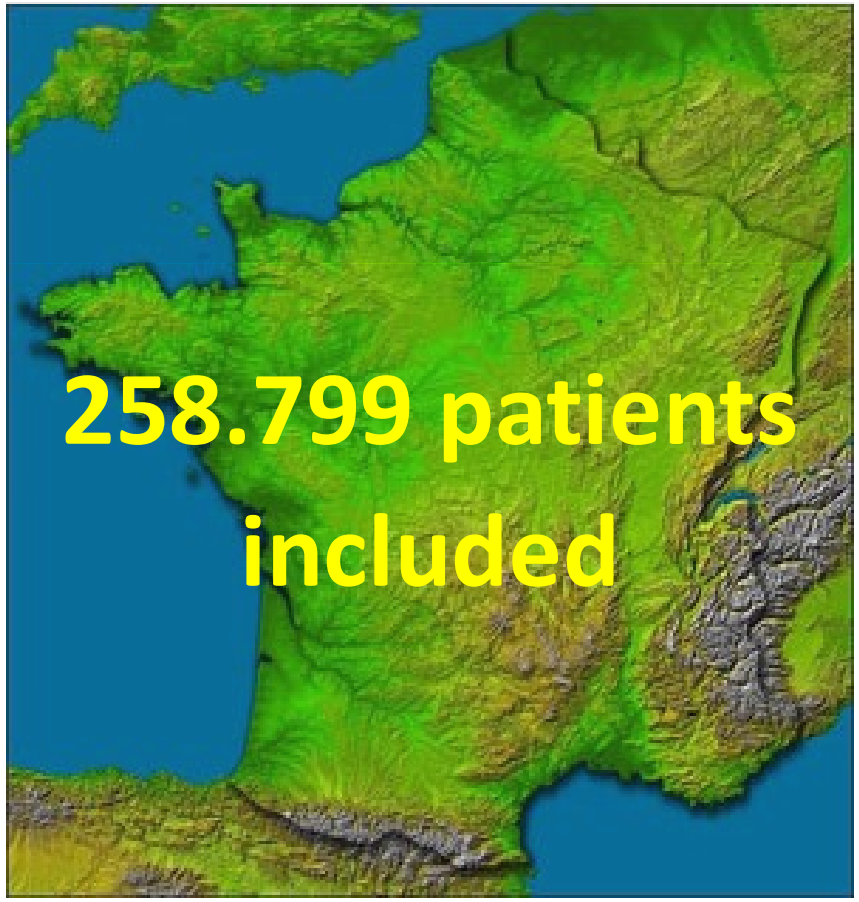
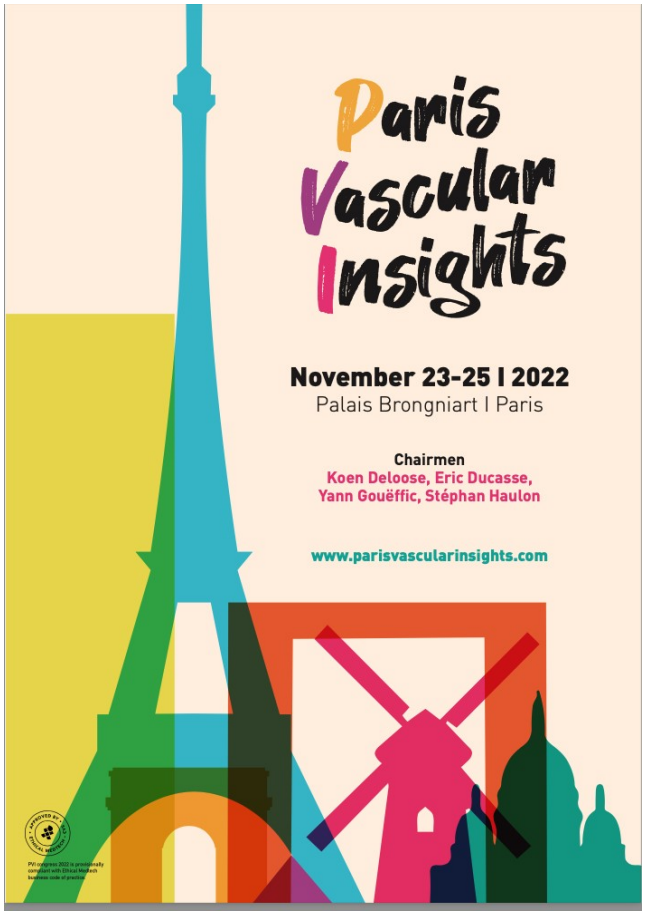




ew benefits of paclitaxel eluting devices

- **REAL PTX (Zilver PTX – DCB) (NCT01728441)**
- **DRASTICO (Zilver PTX – DCB) (NCT01969630)**
- **IMPERIAL (ELUVIA versus ZILVER PTX) (NCT02574481)**
- **EMINENT (ELUVIA versus BMS) (NCT02921230)**

Bausback, JACC, 2019; Liistro, JACC interv, 2019; Gray, Lancet, 2018;
Gouëffic, Circulation, In press

REAL-PTX RCT

lver PTX vs drug coated ballon in native femoropopliteal disease

inicalTrials.gov identifier: NCT01728441

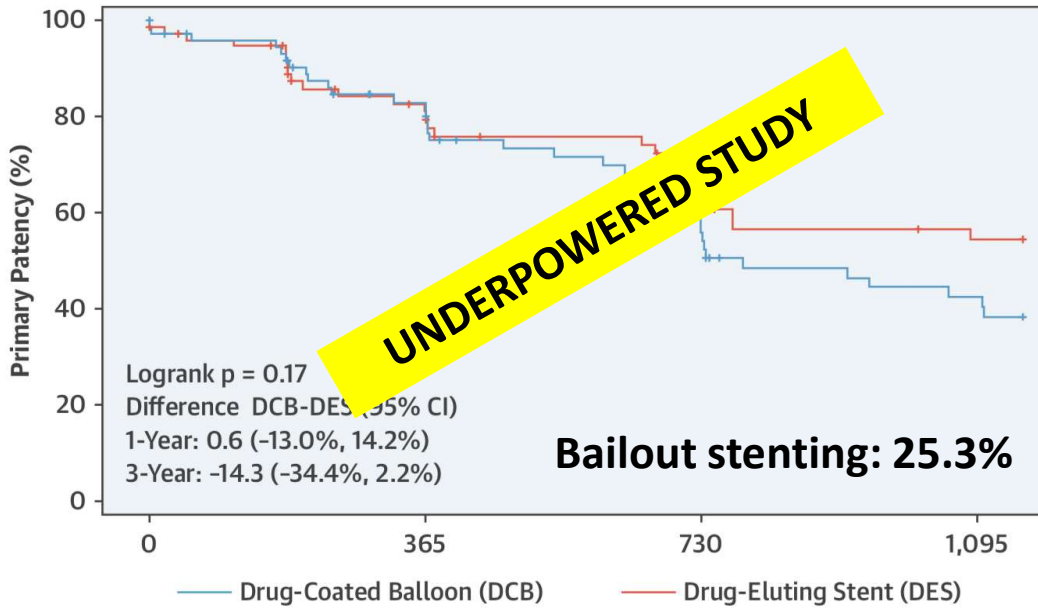
RCT(1:1)

Investigator initiated: PI Prof. D. Scheinert, Germany

N= 150 patients, 75 in each group

Stratification for lesion length for both groups (1:1:1)

Mean lesion length: 152.6 ± 88.2 mm



CONCLUSIONS: *« Patency rates at 12 months suggest comparable effectiveness and safety of DES versus DCB plus bailout stenting in femoropopliteal interventions; a trend in favor of the DES was observed up to 36 months.»*

Bausback, JACC, 2019

DRASTICO

Alloon verSus drug-eluTIng stent for COmplex Femoropopliteal Arterial Lesions
linicalTrials.gov identifier: NCT01969630

Study Design	**RCT (1:1) N=240 lesions** **Superiority (50% reduction in binary restenosis provided by DCB compared with DES)** **High risk population of restenosis**
ntervention	Study arm: **DCB** Control arm: **ZILVER PTX DES**
Primary Endpoint	**12-month binary restenosis rate calculated on DUS as a peak systolic velocity ratio ≥2.4. DUS scans**
nvestigational Centers	Single center
Principal nvestigators	F. Liistro

Liistro, JACC interv, 2019

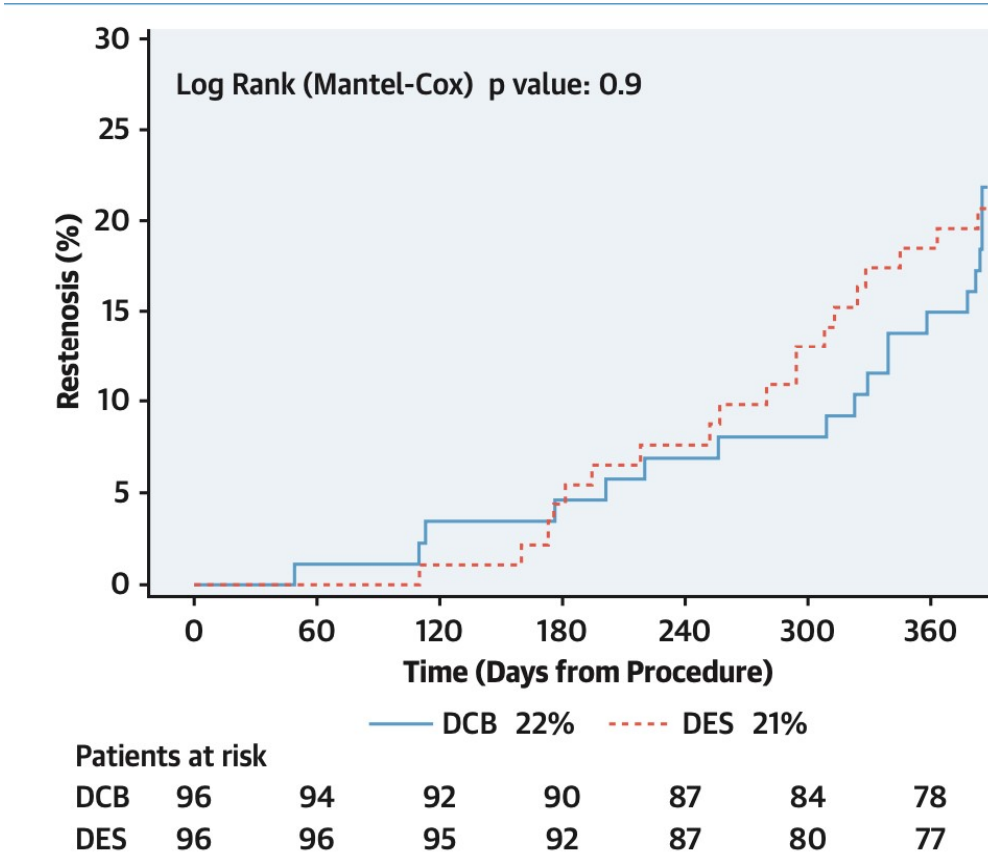
ORASTICO

Alloon verSus drug-eluTIng stent for COmplex Femoropopliteal Arterial Lesions
linicalTrials.gov identifier: NCT01969630

6 patients per group

esion length, mm: 146.3 ±96.4 - 140.7±86.7
Diabetes, %: 68 to 58
CLTI, %: 70.4 to 59.4

DCB was not superior to DES in the treatment of complex FP lesions in a high-risk population, yielding similar rate of restenosis and clinically driven target lesion revascularization.



Liistro, JACC interv, 2019

IMPERIAL Study Overview

Study Design	**RCT (2:1) N=465** **Non inferiority** (effectiveness) – Superiority post-oc analysis **Single-blind** **2 sub-studies**: - *Long Lesion (Eluvia): single arm - lesion length 140 mm-190 mm – N=50* - *Pharmacokinetic (Eluvia): sigle arm – N=13*
Intervention	Study arm: **Eluvia DES** Control arm: **ZILVER PTX DES**
Primary Endpoint	**12-Month Primary Patency**
Investigational Centers	65 study centers: US, Canada, New Zealand, Belgium, Germany, Austria, Japan
Principal Investigators	Global: William A. Gray, MD European: Stefan Müller-Hülsbeck

Primary vessel patency is defined as a binary endpoint and will be determined to be a success when the duplex ultrasound (DUS) Peak Systolic Velocity Ratio (PSVR) is ≤ 2.4 at the 12-month ollow-up visit in the absence of clinically-driven TLR or bypass of the target lesion. All DUS readings assessed by an independent core laboratory.DES, drug-eluting stent; PPA, proximal poplitea artery; RCT, randomized controlled trial; SFA, superficial femoral artery.

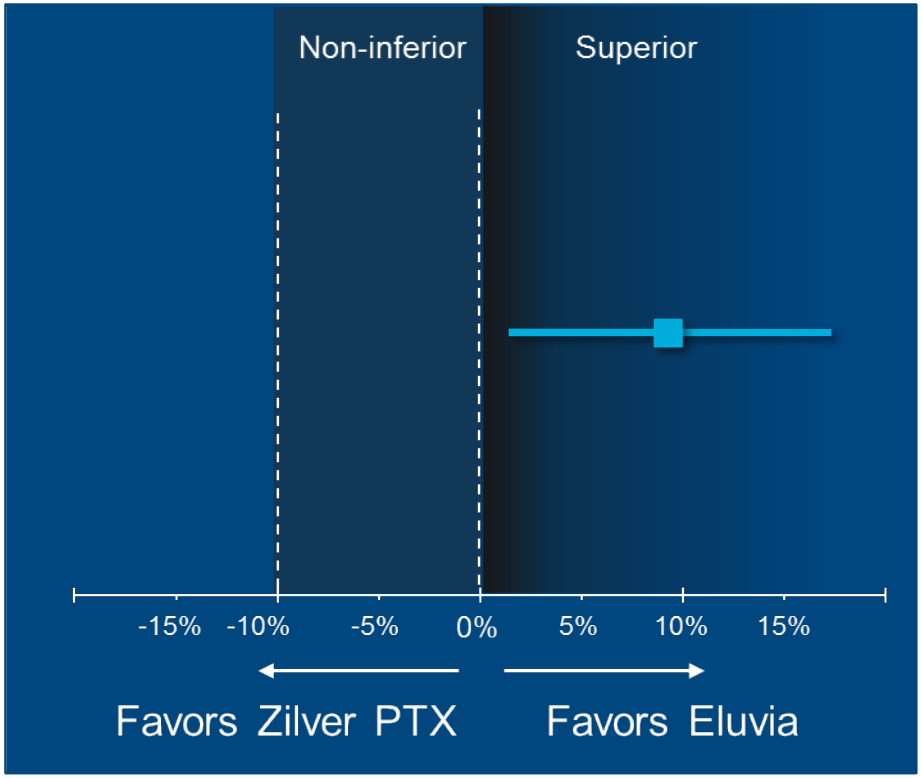
Gray, Lancet, 2018

IMPERIAL- Effectiveness: Primary Patency at 12 Months Pre-specified superiority analysis on primary endpoint

luvia =309)	Zilver PTX (N=156)	Δ (95% CI)	p value
6.8% 3/280)	**77.5%** (110/142)	9.3% (1.4%, 17.3%)	0.0144

Superior primary patency for Eluvia vs Zilver PTX

Treatment Difference for Primary Patency



al: A global randomized controlled multi-center trial with 2:1 randomization of the Eluvia™ Drug-Eluting Stent against Cook Medical's Zilver™ PTX™ Stent, single-blind, non-inferiority design; independent core lab adjudication. Superiority a post hoc analysis that was specified prior to unblinding. 12-Month Primary Patency rate of 86.8% in the Eluvia arm vs. 77.5% in the Zilver PTX arm (p-value = 0.0144). Primary patency defined as duplex ultrasound PSVR ≤2.4, in the linically-driven target lesion revascularization or bypass of the target lesion, as assessed by the DUS core lab.

Gray, Lancet, 2018

EMINENT Study Overview

linicalTrials.gov identifier: NCT02921230

Study Design	**RCT (2:1)** **N=775** **Superiority** (effectiveness) Single-blind	
ntervention	Study arm: **Eluvia DES** Control arm: **Bare nitinol stent**	
Primary Endpoint	**12-Month Primary Patency**	
nvestigational Centers	58 centers in 10 European countries	
Principal nvestigators	Prof. Dr. Yann Gouëffic Groupe Hospitalier Paris St. Joseph, Paris, France	Prof. Dr. Giovanni Torsello Sint-Franziskus-Hospital GmbH, Münster, Germany

Largest industry-sponsored randomized trial of drug-eluting stents for SFA/PPA to date

Primary vessel patency is defined as a binary endpoint and will be determined to be a success when the duplex ultrasound (DUS) Peak Systolic Velocity Ratio (PSVR) is ≤ 2.4 at the 12-month ollow-up visit in the absence of clinically-driven TLR or bypass of the target lesion. All DUS readings assessed by an independent core laboratory. DES, drug-eluting stent; PPA, proximal poplite artery; RCT, randomized controlled trial; SFA, superficial femoral artery.

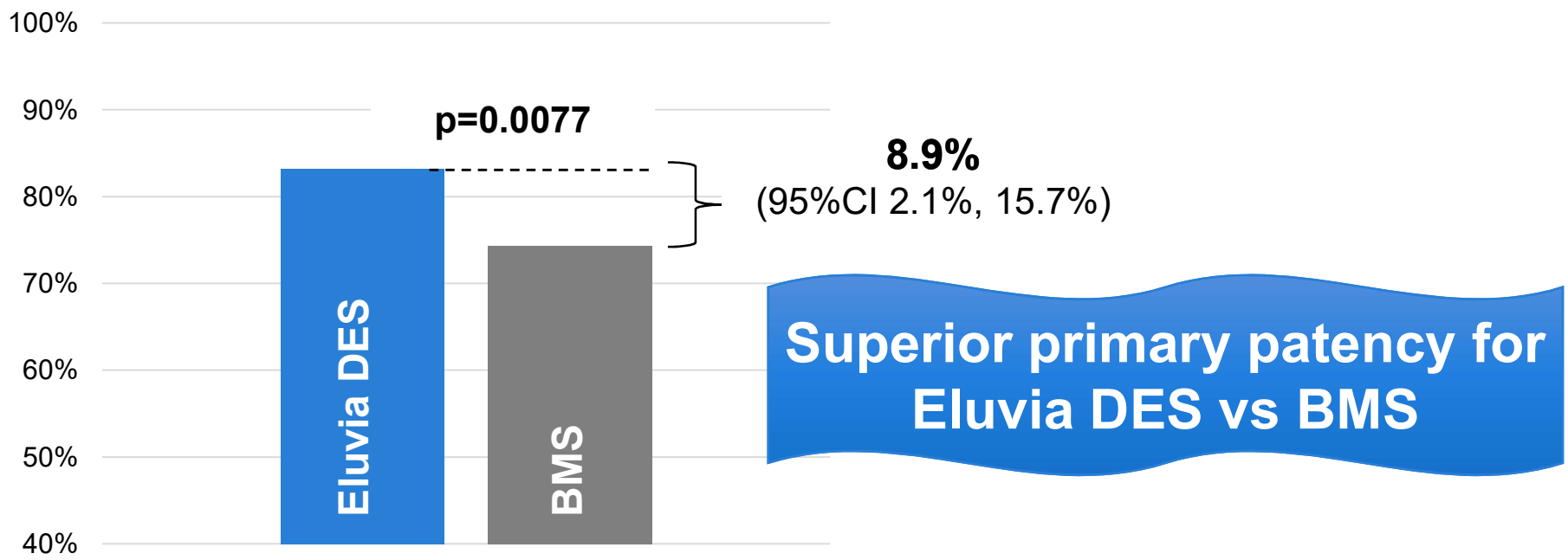
Gouëffic, Circulation, In press

EMINENT Effectiveness | Primary Patency

Primary Endpoint

Statistically significantly greater primary patency in patients treated with Eluvia DES vs BMS

83.2% [337/405] vs 74.3% [165/222]; p=0.0077



Intention to treat. Primary patency defined as core-lab assessed duplex ultrasound peak systolic velocity ratio (PSVR) ≤ 2.4 at 12 months in the absence of clinically-driven TLR or bypass of the target lesion.

Gouëffic, Circulation, In press

ummary

SK

cumulated evidence diminishes any doubt about the paclitaxel safety

NEFIT

Polymer free paclitaxel eluting stent fails to show superiority to BMS

Polymer paclitaxel eluting stent > polymer free paclitaxel eluting stent

Polymer paclitaxel eluting stent > BMS

DCB did not show its superiority or non-inferiority over DES

No head to head comparison exists between DCB and BMS

ke home message

Currently the potential risk is outweigth by the benefit of paclitaxel elutin
levices, in particular polymer paclitaxel eluting stent.

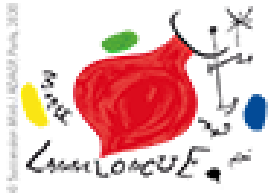
Based on EMINENT and IMPERIAL RCTs, Eluvia DES should be considered a
he stent of choice for treating superficial femoral artery and/or proximal
opliteal artery lesions of intermediate length

Unresolved questions: long lesions, calcifications…

EMINENT and more

Y. Gouëffic, MD, PhD

Department of vascular and endovascular surgery, Groupe Hospitalier Paris Saint Joseph, Paris, France.



GROUPE HOSPITALIER PARIS SAINT JOSEPH