Lutonix™ 014 Drug Coated Balloon PTA Catheter for Treatment of Below-the-Knee (BTK) Arteries

February 17, 2021

BD

Circulatory System Devices Panel

Introduction

George Papandreou, PhD

Vice President and Scientific Advisor

BD, Peripheral Intervention

Lutonix DCB: Safe Treatment Option for Patients with Critical Limb Ischemia (CLI)

- Debilitating, ultimately life-threatening disease
- Limited treatment options require frequent, early reinterventions
- Lutonix DCB delivers patency, results in meaningful benefits to patients
  - Longer time to reintervention
  - Reduced number of interventions

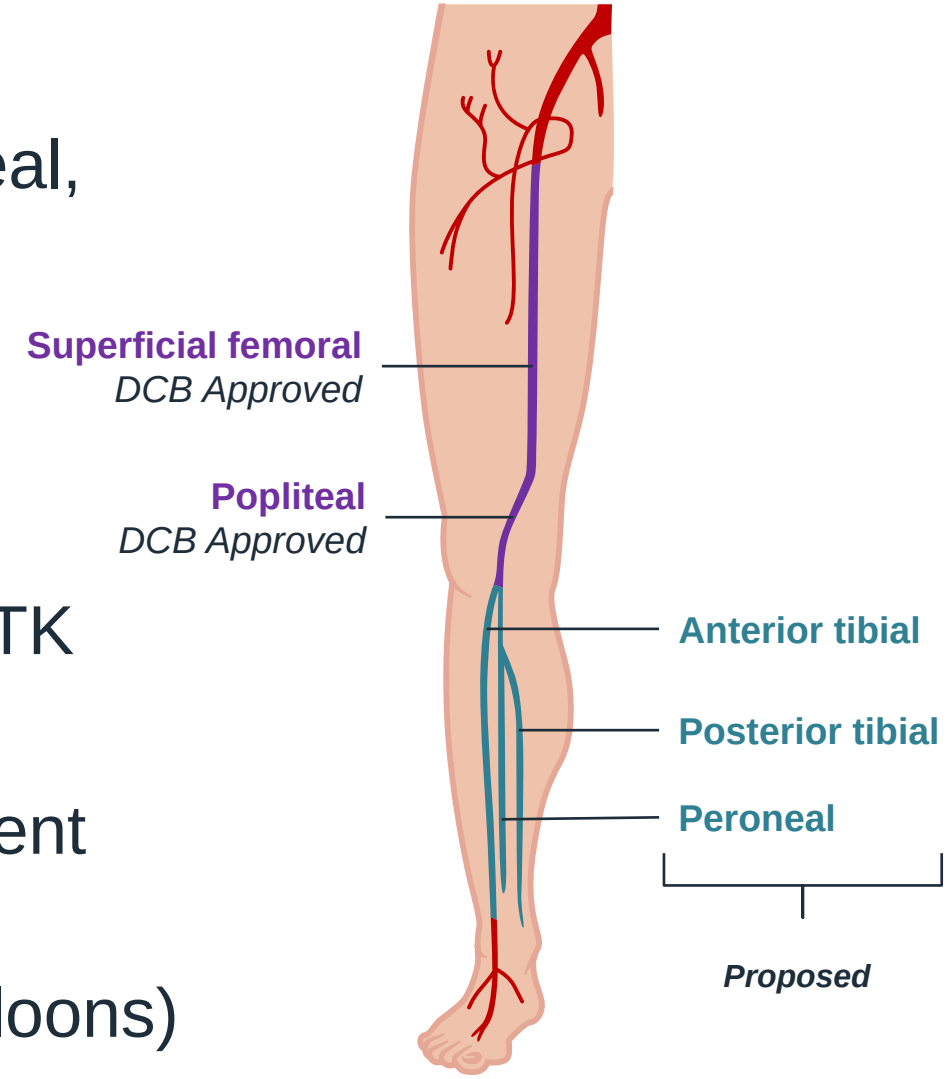
Most Severe Form of Peripheral Arterial Disease, Blockage Below-the-Knee (BTK)

- Significant restriction of blood flow to lower leg and foot
- Severe pain in feet or toes, even when sitting still
- No cure for CLI, patients will need repeated interventions

Can a drug-coated balloon provide a safe and more consistent treatment to improve blood flow below the knee?

Paclitaxel-Coated Balloons Used in Other Vascular Beds

- Lutonix DCB approved for use in SFA, popliteal, and AV fistulae
- Lutonix DCB for BTK approved outside the US since 2013, no safety signals
- Seeking approval in US for BTK
  - Biologic plausibility for effectiveness in BTK
- Lutonix BTK study results
  - Achieved 10.5% effectiveness improvement through 6 months
  - Non-inferior to standard of care (PTA balloons)



Proposed Indication

Original

Proposed indication is for ~~percutaneous transluminal angioplasty, after appropriate vessel preparation, of~~ obstructive de novo or non-stented restenotic lesions in native popliteal, tibial, and peroneal arteries up to 320 mm in length and 2.0 to 4.0 mm in diameter.

From FDA

Proposed indication is for patients with critical limb ischemia who have obstructive de novo or non-stented restenotic lesions in native popliteal, tibial, and peroneal arteries up to 320 mm in length and 2.0 to 4.0 mm in diameter.

Combination of Cleared Device + Paclitaxel
Uniquely Designed to Reach, Treat BTK Arteries

- Same formulation as Lutonix DCB indicated for treatment of **larger** diameter vessels ***above*** the knee
- BTK vessels are narrower, typically between 2-3 mm diameter
- Smaller diameter balloons, low-profile guidewires, longer catheter
  - Paclitaxel coating on Ultraverse™ PTA catheter

Lutonix DCB Procedure Opens Up Blocked Vessels BTK

- Mechanically dilates vessel when balloon is inflated, like PTA
- Delivers paclitaxel to decrease incidence of restenosis
- With Lutonix paclitaxel-coated balloon
  - Observed no mortality signal during IDE evaluation period

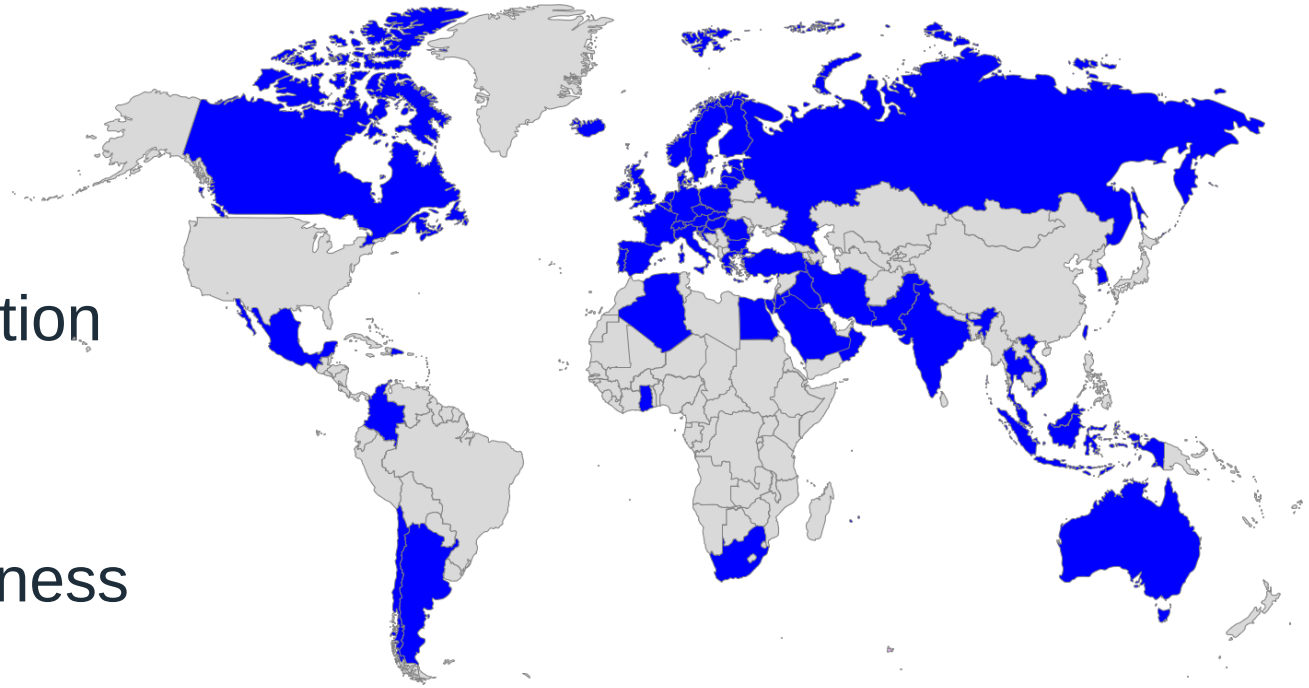
Interim Analysis: No Significant Difference in Incidence of Death with Paclitaxel-Coated Devices

- Large, prospective, randomized study
- Conclusion: No significant difference between groups in incidence of death during 1 to 4 years follow-up
  - Paclitaxel-coated devices: 33.4%
  - Uncoated devices: 33.1%

Nordanstig, 2020

Lutonix DCB BTK Commercially Available for Treatment of CLI in > 40 Countries

- CE Mark granted in 2013
- Approvals followed in
  - Australia, Canada, Mexico, and Singapore
- > 54,000 devices sold in this indication
- Lutonix DCB BTK global registry outside of US
  - Evaluated safety and effectiveness in real-world setting



Requesting Expert Panel's Assessment on Lutonix DCB BTK

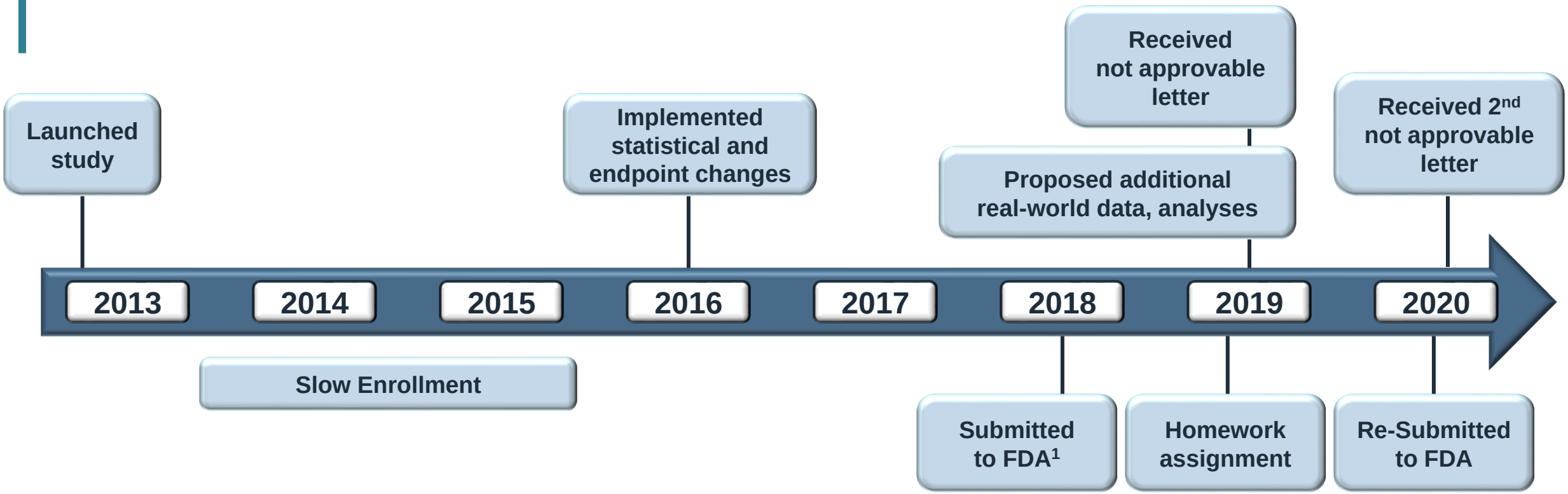
Clinical interpretation of results

Statistical interpretation of data

RCT to Compare Performance of Lutonix DCB to Standard PTA for Treatment of BTK Stenosis

- First to design, run US IDE trial in this population
  - Disease notoriously hard to treat
- Required protocol changes
- Prior to unblinding and with FDA knowledge, revised protocol to speed enrollment, improve efficiency
- New learnings about aggressive nature of CLI, critical time period for evaluating treatment effectiveness
  - Changed primary endpoint from 12 to 6 months

Regulatory Timeline to Today's Panel Meeting



Requested panel meeting to gain expert input on clinical meaningfulness of magnitude and duration of benefit

1. Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications

Totality of Safety and Effectiveness Data Supports Approval

Need for improved options to treat serious, life-threatening disease

Met primary safety endpoint – durable results out to three years

10.5% incremental effectiveness improvement at 6 months
Benefits of balloon angioplasty + ancillary benefits of paclitaxel

Increased time to first reintervention + Decreased number of reinterventions at 6 months

Supportive effectiveness and safety results in real-world data

Agenda

Unmet Need	**Jihad Mustapha, MD** Assistant Professor of Medicine, Michigan State University President & CEO, Director of Endovascular Interventions Advanced Cardiac & Vascular Centers for Amputation Prevention
Study Design	**Patrick Geraghty, MD** Washington University School of Medicine in St. Louis Department of Surgery
Safety and Effectiveness	**Marianne Brodmann, MD** Head, Clinical Division of Angiology Medical University of Graz, Austria
Benefit Risk and Conclusion	**JD Meler, MD** Clinical Professor, Texas A&M Health Science Center Vice President, Medical Affairs BD Peripheral Intervention

Additional Experts

Gary M. Ansel, MD
OhioHealth, Vascular Institute
Clinical Assistant Professor, University of Toledo

Chris Mullin, MS
Director, Product Development Strategy
NAMSA

John Kirby, MD
Acute & Critical Care Surgeon
Washington University School of Medicine
Surgical and Wound Care Clinic

Kenneth Ouriel, MD
Chief Executive Officer
Syntactx

Unmet Need for Patients with CLI

Jihad Mustapha, MD

Assistant Professor of Medicine, Michigan State University

President & CEO, Director of Endovascular Interventions

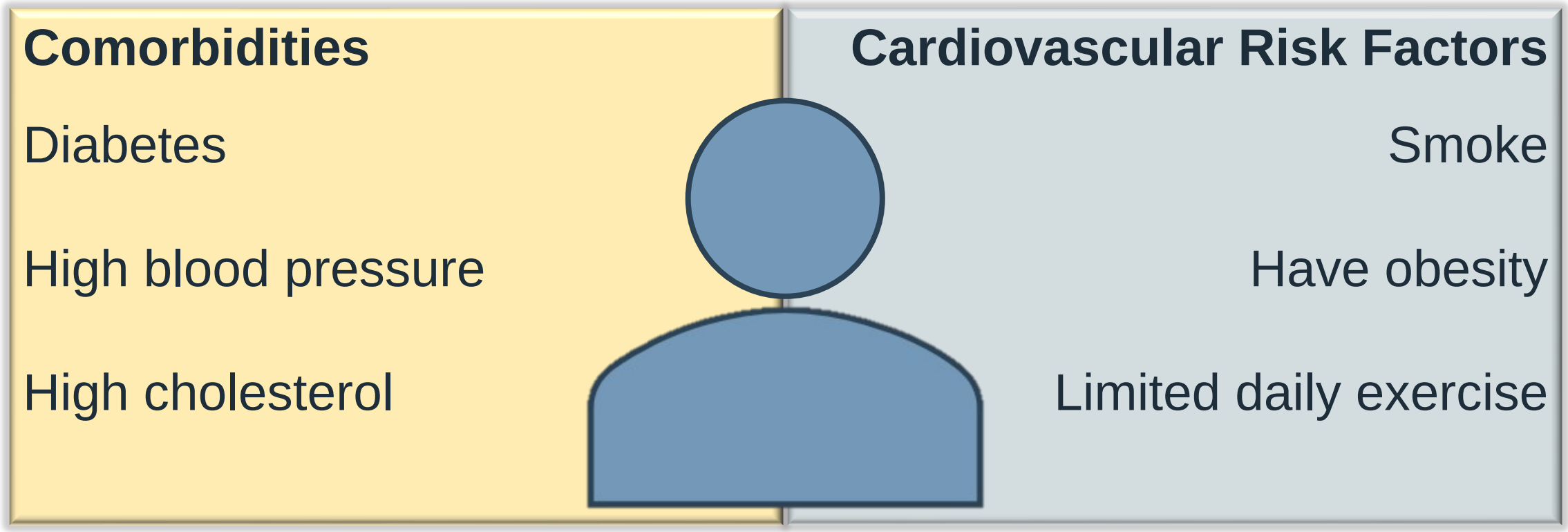
Advanced Cardiac & Vascular Centers for Amputation Prevention

CLI: Aggressive, Debilitating Disease Affecting ~3.4 Million in US

- Manifestation of severe atherosclerosis
- End-stage symptom of this relentless, progressive peripheral artery disease (PAD)
- Arteries BTK become occluded, restricting blood flow to lower leg, foot
- Patients feel extreme pain, even at rest
- Untreated CLI can lead to tissue loss, gangrene, amputations, death

Yost, 2017

Older Patients with Multiple, Serious Comorbidities



Complex patients dealing with a serious disease

High Rates of Mortality

- Risk of mortality upon diagnosis[1]
  - 24% at 1 year
  - 60% over 5 years
- Higher than 5-year mortality rate for patients with most cancers, including breast, colon and prostate[2]

1. Mustapha, 2018; 2. ACS Statistics Center, 2018

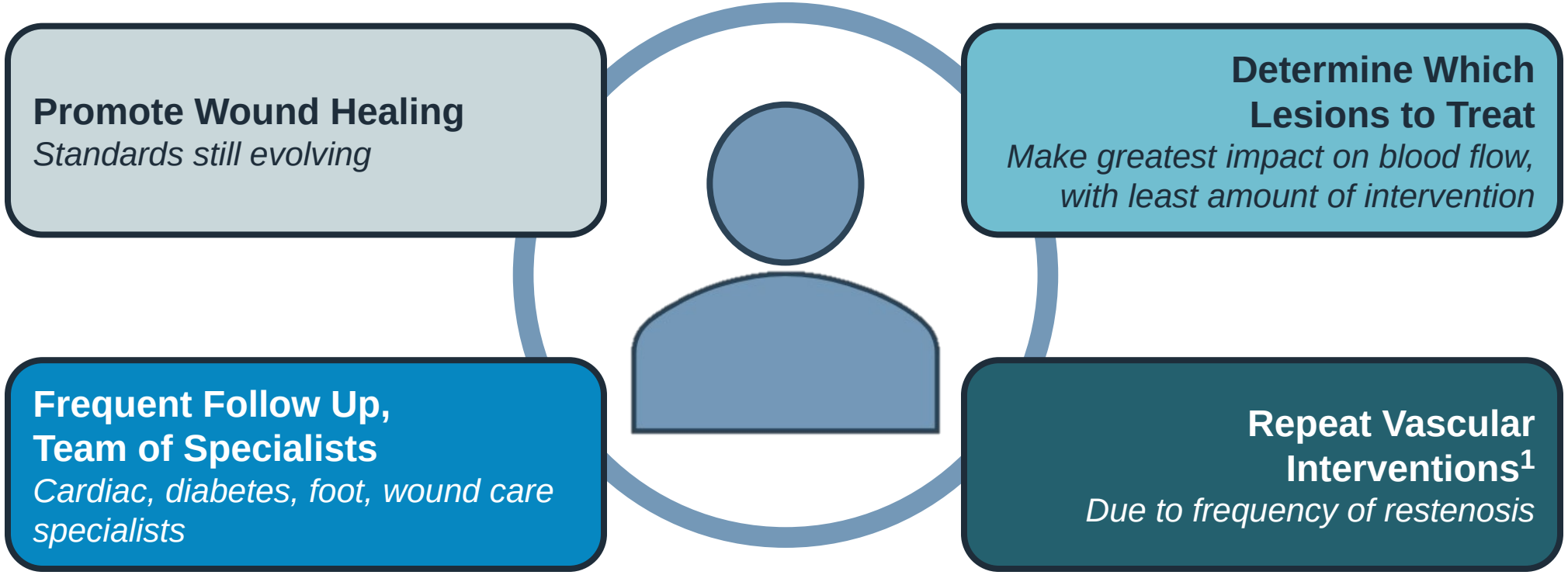
Need for Prompt Revascularization

- Guidelines recommend urgent referral to vascular specialist
- Interventions for CLI
  - Purpose
  - Considerations
  - Options

Gerhard-Herman, 2016; Conte, 2019

Purpose of Vascular Intervention: Restore Patency by Opening Vessels

- Improve blood flow below the knee, preserve limb
- Multiple factors to fully address complex disease



1. Conte, 2013

Pace of Intervention and Number of Reinterventions Important

- Prompt revascularization after diagnosis is critical
  - ***Extend*** time before reintervention
  - ***Reduce*** number of interventions
- Longer period before reintervention limits impact on quality of life[1,2]
- Fewer interventions = reduction of risks from another procedure
  - Decision to reintervene is not taken lightly

1. Corriere, 2017; 2. Pisa, 2012

Arteries Below-the-Knee are Complex

- BTK lesions longer, have total occlusions, more difficult to treat than above the knee
- Vessels smaller, more prone to restenosis, heavier calcification

Lorbeer, 2018

Limited Options for Treating BTK Lesions

- Most CLI patients have many comorbid conditions
  - Open surgery may be less favorable option
- Prioritize endovascular over open surgery
  - Lower procedural risks, lower morbidity and mortality[1]

1. Kinlay, 2016

PTA is Only On-Label Endovascular Option

- No drug-coated technologies for BTK
- Off-label use of Drug Eluting Stents (DES) and DCB
  - DES designed for short lesions
  - DCB sized for larger vessels
- Borrow drug-coated technology in attempt to achieve patency effect BTK
  - Need multiple DES for longer BTK lesions
  - Smallest diameter DCB twice as large as BTK arteries

Poor Prognosis and Few Options to Provide Sustained Care Patients Need

- Patients have markedly reduced life expectancy, about 2 years[1]
  - Additional intervention-free time would be a benefit
- Need additional treatments specifically designed for BTK
  - Reestablish patency
  - Delay reintervention
  - Limit number of interventions

1. Soga, 2014

Study Design

Patrick Geraghty, MD

Washington University School of Medicine in St. Louis

Department of Surgery

First US Trial to Study Effectiveness of Paclitaxel-Coated Balloons Below-the-Knee

- Prospective, multicenter, randomized, single blind study
- Randomized 2:1 – DCB to standard PTA
- 462 patients enrolled at 51 centers in 4 different regions
  - 62% from US
  - 29% from Europe and Canada
  - 9% from Japan

Study Oversight to Measure Effectiveness and Protect Patient Safety

- Two blinded Core Labs
  - Angiographic: reviewed images of vessels and inflow
  - Duplex Ultrasound (DUS): determined target vessel patency and assessed blood flow to foot
    - Used qualitative measure – flow or no flow through segment
- CEC adjudicated stroke, MACE, target limb-related events, TLR, and device- and/or procedure-related adverse events
- DMC assessed overall patient safety

Rutherford Category Used to Classify Patients' Clinical Symptoms at Enrollment

Category	Clinical Description
0	Asymptomatic
1	Mild claudication
2	Moderate claudication
3*	Severe claudication
4	Ischemic rest pain
5	Minor tissue loss – nonhealing ulcer, focal gangrene with diffuse pedal ischemia
6	Major tissue loss – extending above transmetatarsal level, frank gangrene

* Added to protocol in Dec 2015 with intent to increase enrollment

Key Inclusion Criteria

- Rutherford Category 3–5
- Cumulative lesion length ≤ 320 mm
- Target vessel diameter 2–4 mm and able to be treated with available device sizes
- Target vessel reconstitutes at or above ankle with inline flow to at least one patent (< 50%) infra-malleolar outflow vessel
- Arterial stenosis (≥ 70%) below tibial plateau & above tibiotalar joint
- Appropriate for angioplasty per operator visual assessment
- Patent inflow artery from aorta to target lesion free from significant (≥ 50%) stenosis

Key Exclusion Criteria

- Ischemic ulceration extending > 4 cm proximal to digit-metatarsal skin crease (target limb)
- Neurotrophic ulcer or heel pressure ulcer or ulcer potentially involving calcaneus (target limb)
- Gangrene extending proximal to digit-metatarsal skin crease (target limb)
- Planned or prior major amputation
- Acute limb ischemia, in-stent restenosis, or presence of thrombus (target lesion)

Primary Safety Endpoint Assessed Per Patient

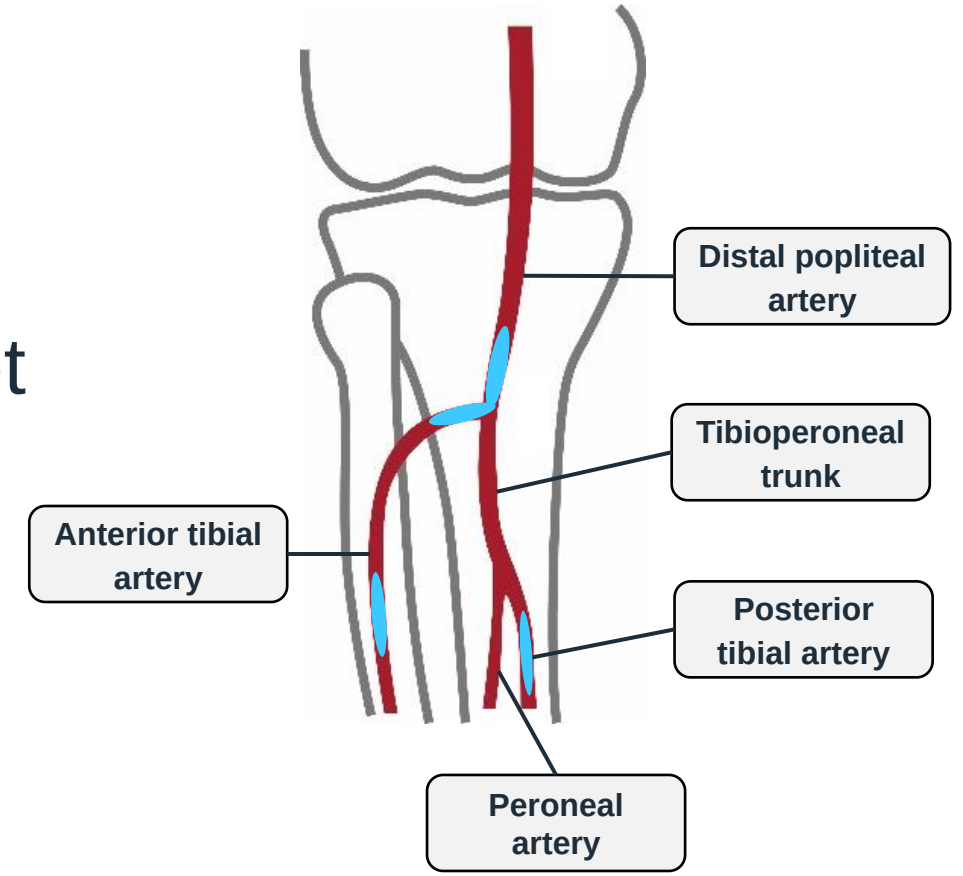
- Freedom from MALE (major adverse limb event) + POD (all-cause peri-operative death) at 30 days
  - Freedom from composite of all-cause death, above-ankle amputation or major reintervention of index limb
- Non-inferiority assessment
  - $p < 0.025$

Composite Primary Effectiveness Endpoint Assessed at 6 Months

- **Freedom from** 1) Major Amputation; 2) Target Vessel Occlusion; 3) Clinically-Driven Target Lesion Revascularization (CD-TLR)
- CD-TLR defined as revascularization at target lesion due to:
  - Worsening of Rutherford Category of index limb, or
  - Stagnant or worsening wound healing, or
  - New or recurrent wound in index limb
- All TLR performed only with POBA, not DCB
- Assumed 15% drop-out rate for primary effectiveness endpoint
  - SAP included analyses to address impact of missing data

Effectiveness Endpoint Assessed Per Arterial Pathway

- Establish straight-line flow to terminal branches of peroneal or inframalleolar outflow arteries
- Pathway is entire flow path where target lesion is treated
- Protocol permitted treatment of parallel tibial arteries



Impact of Trial Design and Conduct on Results

- Components of effectiveness endpoint selected to capture patency and effect of improved patency on limb salvage
- Certain aspects of threatened limb known to predict higher risk of amputation
  - Risks partially independent of revascularization
- To avoid confounding the assessment of clinical effectiveness
  - Excluded patients with advanced wounds
    - Diminished expected rates of major amputation
- Patients with loss of primary patency underwent prompt re-intervention
  - No expected differences in wound healing or major amputation rates

Composite effectiveness endpoint primarily driven by patency

Primary Effectiveness Endpoint Changed from 12 to 6 Months

- VIVA[1] meeting in 2016
  - Supported use of 6-month endpoint to better reflect importance of critical early months after initial treatment
  - Early loss of patency has a greater predictive effect for limb loss than later loss of patency
- Median time to reintervention is 3-4 months after index procedure[2,3]
- Primary effectiveness endpoint guidance in trials evaluating BTK devices[4]
  - 6-month endpoint now standard
  - 12-months is important

1. VIVA = Vascular Interventional Advances; 2. Lin, 2019; 3. Meloni, 2018
4. VDM, 2020: “FDA Recommended Endpoints for Critical Limb Ischemia Trials”

Added Proximal Segment Co-Primary Endpoint Based on Peer-Reviewed Literature

- Literature showed:
  - Tibial arteries prone to early recoil[1]
  - Distal aspects of tibial arteries have more medial calcification[2,3]
    - Segments respond differently to angioplasty
- DCB effectiveness hypothesized to be less favorable in distal tibial segments

1. Baumann, 2014; 2. Mustapha, 2017; 3. Bishop, 2008

Study Planned for Strong Type I Error Control

Protocol Revision	p-value Threshold	Planned Statistical Rationale
Original protocol	0.025	Preserve study type I error rate at traditional one-sided 0.025 level
Revision 9/10	0.017	Trial changed to adaptive sample size / adjusted for interim analyses
Revision 12	0.0085	Adjusted for two analyses of primary endpoint Assumed independence between all pathways and proximal segment

Study Planned for Strong Type I Error Control (Continued)

- 95% of total pathways classified as proximal
  - Co-primary analyses essentially the same
  - High amount of overlap rendered the two analyses highly correlated
  - Adjusted p-value of 0.0085 likely conservative
- Enrollment terminated prior to reaching final sample size, without crossing a boundary for predictive success
  - Resulted in underpowered study

Approach to Blinding Minimized Bias in Study

- Investigator not blinded
  - Reintervention determined based on patient's clinical symptoms, prior to performing DUS and angiography
  - Minimized occurrence of non-clinically-driven TLR
  - Reinterventions adjudicated by blinded CEC
- No protocol changes made based on study results
  - Study changes based on external considerations

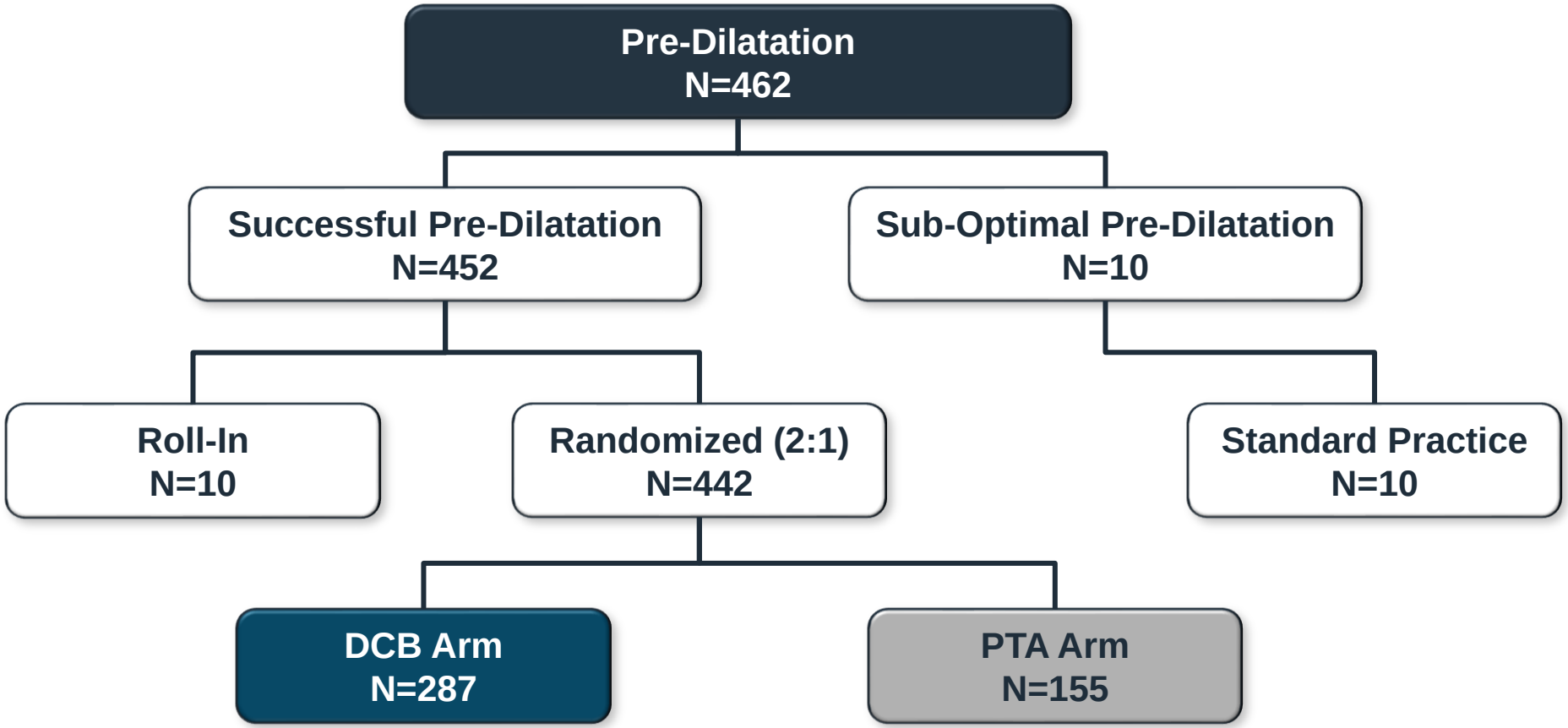
Key Secondary Endpoints

- Amputation-Free Survival
- Primary Effectiveness Endpoint at 36 months
- Freedom from CD-TLR
- Cumulative TLR
- Wound Healing
- Quality of Life
- Change in Rutherford Category

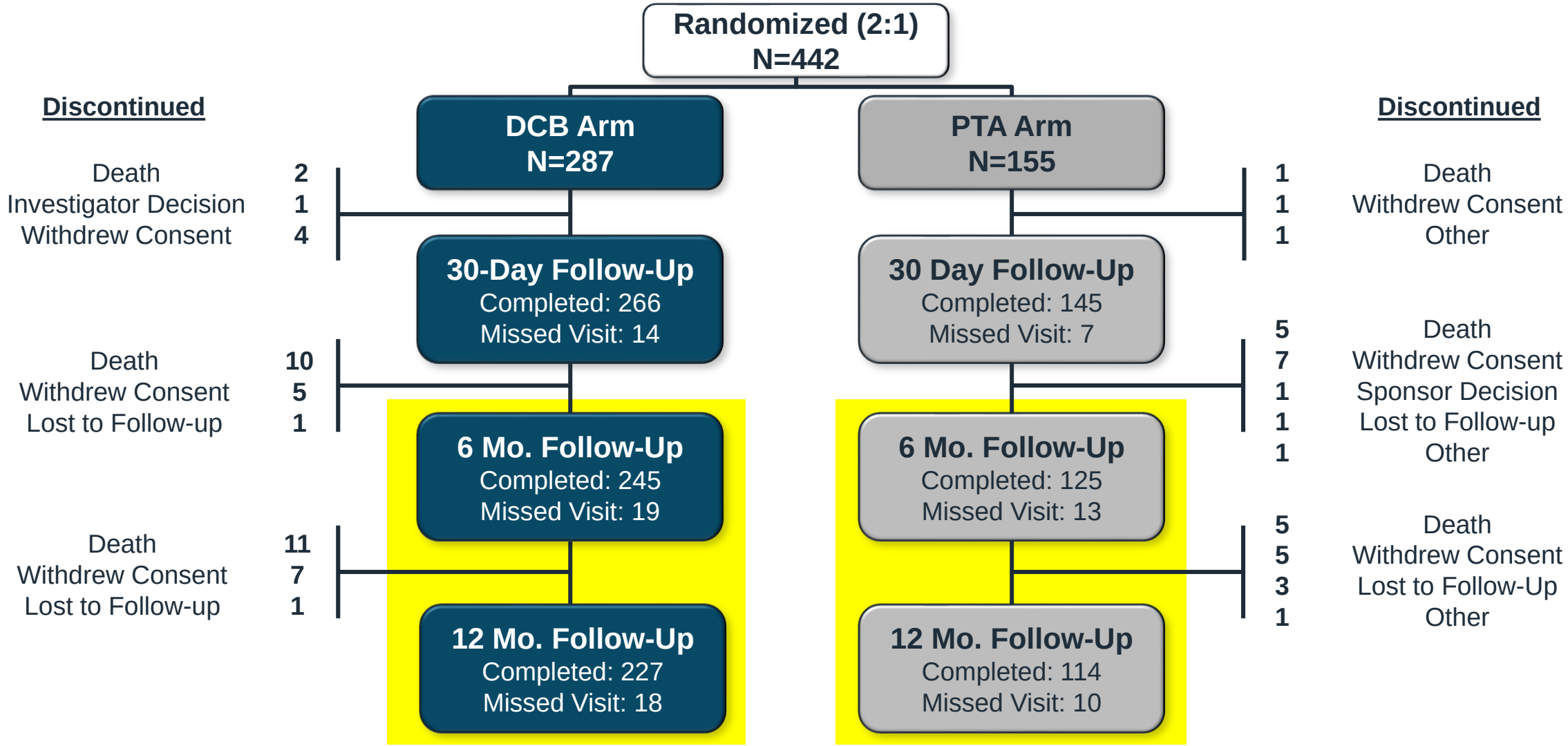
Study not powered to detect differences in Secondary Endpoints

Patient Enrollment

Pre-Dilatation Screening Prior to Randomization



Patient Disposition Through 12 Months



Demographics, Risk Factors Representative of CLI Population: Older, Multiple Comorbidities

Demographic Characteristic		DCB Patients N=287	PTA Patients N=155
Age (years), mean ± SD		73 ± 9.7	73 ± 9.6
Sex, male		70%	67%
BMI		28.4 ± 6.3	28.0 ± 5.7
Rutherford category	3	9%	10%
	4	35%	34%
	5	56%	56%
Comorbidities / medical history			
Smoker current / former		15% / 44%	12% / 45%
Hypertension		92%	96%
Dyslipidemia		78%	75%
Diabetes (Type 2)		71%	68%
Previous peripheral intervention		54%	54%

A Trend of Longer Lesions and More Calcification in DCB Arm

Lesion Characteristic		DCB Patients N=287	PTA Patients N=155
Lesion morphology	Lesion length (mm), mean ± SD[1]	112 ± 93	95 ± 85
	Baseline stenosis (%), mean ± SD	87% ± 15	85% ± 15
	Calcification (any)	60%	54%
	Severe calcification	15%	13%
	Occlusion or re-occlusion	38%	36%
Lesion pathway locations	Popliteal artery	10%	9%
	Tibioperoneal trunk	28%	31%
	Anterior tibial artery	41%	36%
	Posterior tibial artery	24%	27%
	Peroneal artery	24%	25%

1. Nominal p-value=0.03

Safety and Effectiveness Results

Marianne Brodmann, MD

Head, Clinical Division of Angiology

Medical University of Graz, Austria

Safety Results

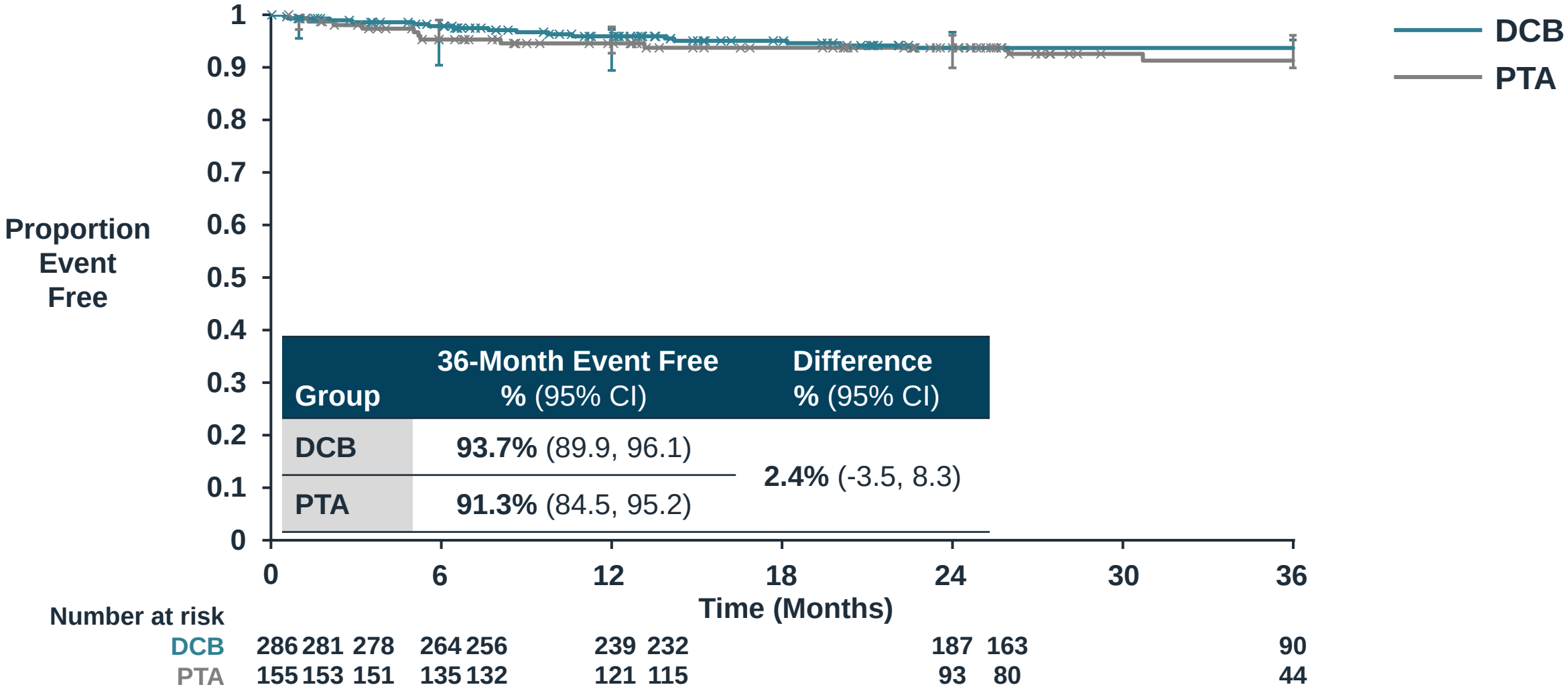
- Data demonstrate Lutonix DCB is as safe as PTA for patients with CLI
- IDE met primary safety endpoint
- Results durable out to 3 years, no increased risk for mortality

Lutonix DCB Met Primary Safety Endpoint

	DCB Patients N=287 n (%) (95% CI)[1]	PTA Patients N=155 n (%) (95% CI)[1]	Difference in Response (95% CI)[2]	p-value[3]
Free from primary safety event at 30 days	**284 (99.3%)** (97.5, 99.9)	**154 (99.4%)** (96.5, 100.0)	**-0.1%** (-3.9, 3.8)	**< 0.0001**
Primary safety events ≤ Day 30, n (%)[4]				
Death	**1 (0.4%)**	**1 (0.6%)**		
Above ankle amputation	**0 (0%)**	**0 (0%)**		
Major re-intervention	**1 (0.4%)**	**0 (0%)**		

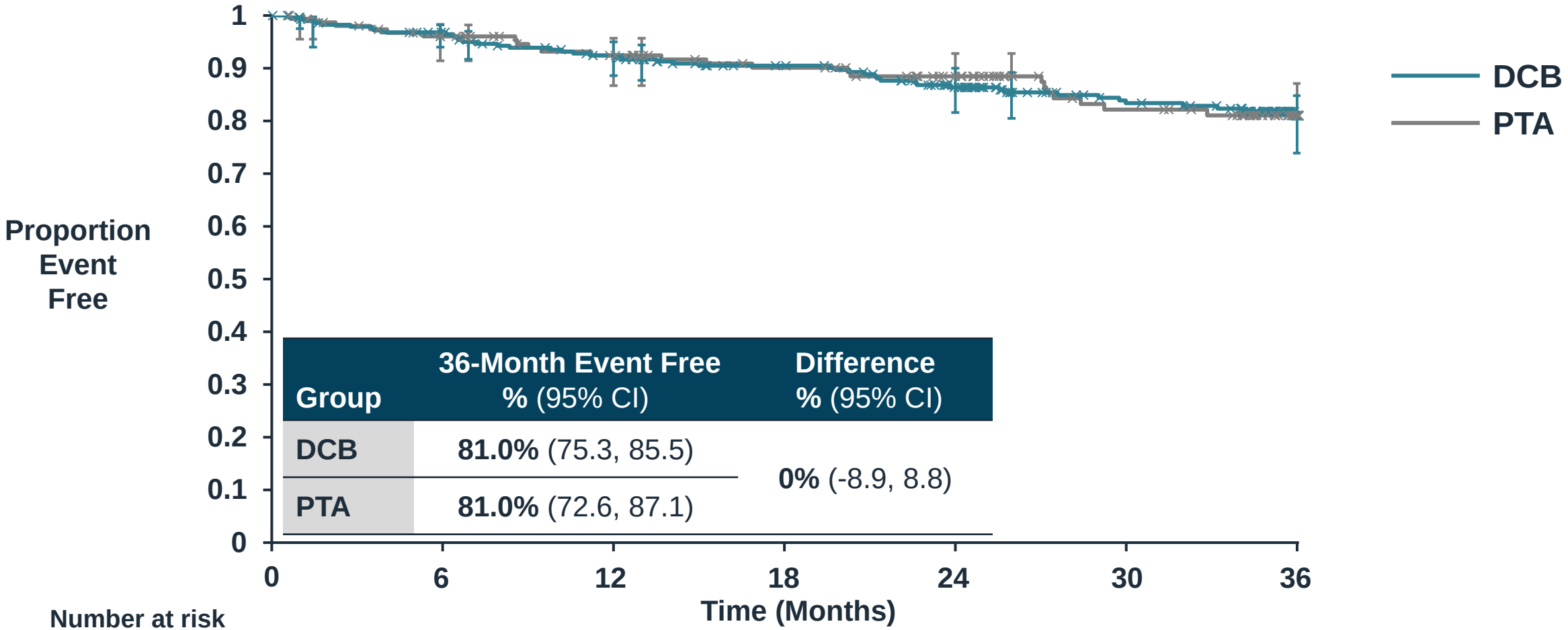
1. 95% CI based exact binomial distribution
2. 95% CI is estimated by Farrington-Manning Test
3. p-value for non-inferiority margin of 12%
4. Patients may fail primary safety due to more than one cause

Freedom from Primary Safety Events Through 36 Months



Per patient analysis

No Difference in Mortality Between Arms at 36 Months



Group	36-Month Event Free % (95% CI)	Difference % (95% CI)
DCB	**81.0%** (75.3, 85.5)	**0%** (-8.9, 8.8)
PTA	**81.0%** (72.6, 87.1)	

Number at risk

DCB	286	282	279	269	261	247	240	199	175	96
PTA	155	153	152	141	137	127	121	100	87	47

Per patient analysis

MACE Rates Similar Between Treatment Arms

Visit	DCB Patients N=287 Response Rate	(95% CI)	PTA Patients N=155 Response Rate	(95% CI)	Difference (95% CI)
30 Days	**3.1% (9/286)**	(1.4, 5.9)	**1.3% (2/155)**	(0.2, 4.6)	**1.9%** (-0.8, 4.5)
6 Months	**7.9% (22/280)**	(5.0, 11.7)	**6.0% (9/150)**	(2.8, 11.1)	**1.9%** (-3.1, 6.8)
12 Months	**11.1% (30/270)**	(7.6, 15.5)	**10.0% (14/140)**	(5.6, 16.2)	**1.1%** (-5.1, 7.3)
24 Months	**18.8% (47/250)**	(14.2, 24.2)	**15.2% (19/125)**	(9.4, 22.7)	**3.6%** (-4.3, 11.5)
36 Months	**27.5% (56/204)**	(21.5, 34.1)	**26.3% (25/95)**	(17.8, 36.4)	**1.1%** (-9.6, 11.9)

Corrected values from Panel Pack; FDA has not reviewed this data in full

Similar Freedom From Major Amputation Rates Between DCB and PTA

Visit	DCB Patients N=287 Response Rate	(95% CI)	PTA Patients N=155 Response Rate	(95% CI)	Difference (95% CI)
30 Days	**100% (286/286)**	(98.7, 100.0)	**99.4% (154/155)**	(96.5, 100.0)	**0.6%** (-0.6, 1.9)
6 Months	**98.5% (267/271)**	(96.3, 99.6)	**97.9% (142/145)**	(94.1, 99.6)	**0.6%** (-2.1, 3.3)
12 Months	**97.2% (244/251)**	(94.3, 98.9)	**97.7% (127/130)**	(93.4, 99.5)	**-0.5%** (-3.8, 2.8)
24 Months	**94.9% (204/215)**	(91.0, 97.4)	**94.5% (103/109)**	(88.4, 98.0)	**0.4%** (-4.8, 5.6)
36 Months	**93.1% (148/159)**	(88.0, 96.5)	**90.5% (67/74)**	(81.5, 96.1)	**2.5%** (-5.2, 10.3)

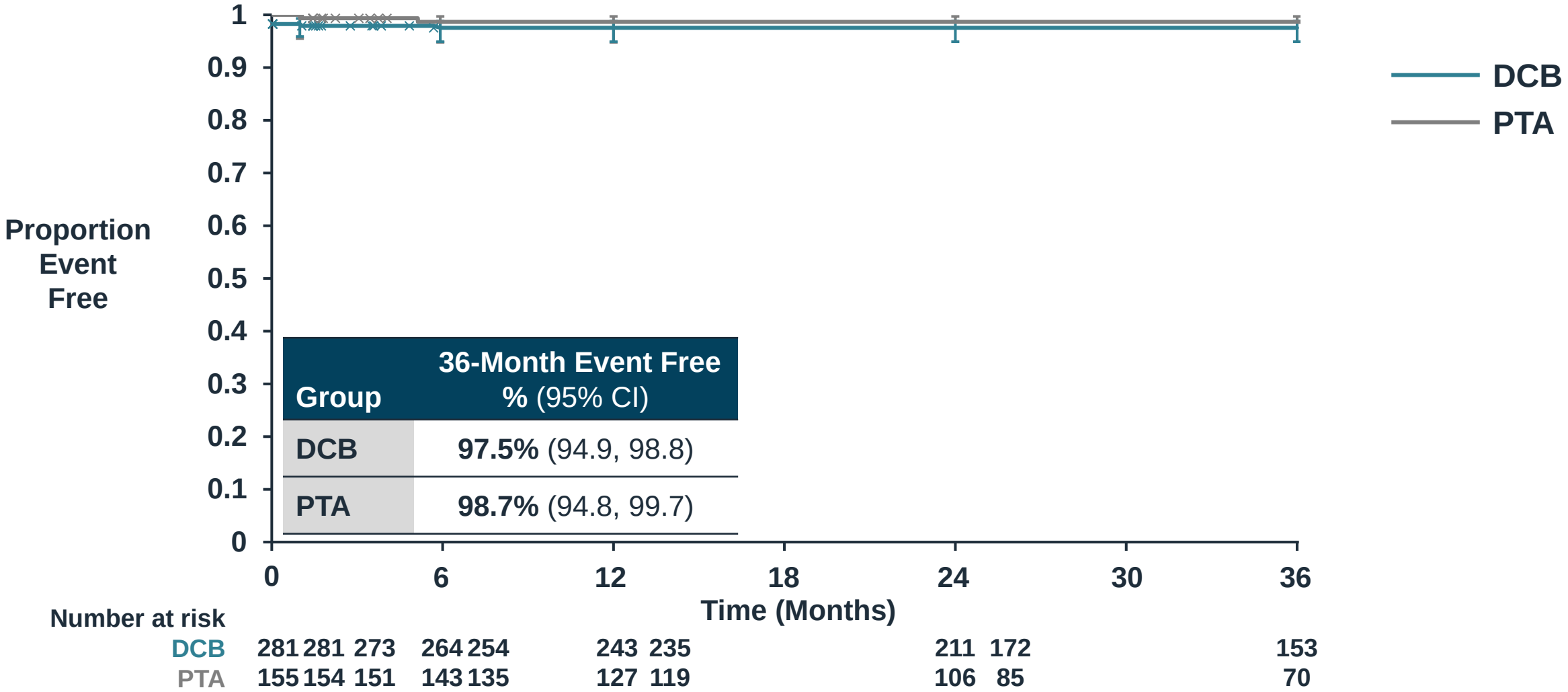
Per patient analysis

Similar Rates of SAEs Between Arms Through 12 Months

MedDRA Preferred Term	DCB Patients N=287	PTA Patients N=155
At least one SAE	199 (69%)	101 (65%)
Peripheral arterial occlusive disease	37 (13%)	11 (7%)
Peripheral artery stenosis	33 (12%)	22 (14%)
Peripheral artery restenosis	39 (14%)	29 (19%)
Peripheral arterial reocclusion	23 (8%)	7 (5%)
Wound	11 (4%)	4 (3%)
Osteomyelitis	18 (6%)	12 (8%)
Gangrene	15 (5%)	9 (6%)
Cellulitis	10 (4%)	2 (1%)
Pneumonia	7 (2%)	6 (4%)
Cardiac failure congestive	11 (4%)	6 (4%)
Skin ulcer	10 (4%)	6 (4%)

Table includes SAE rates for preferred terms > 3%

High Rates of Freedom from Embolization



Group	36-Month Event Free % (95% CI)
DCB	**97.5%** (94.9, 98.8)
PTA	**98.7%** (94.8, 99.7)

Per patient analysis

Effectiveness Results

- DCB showed incremental improvement over PTA at 6 months
- DCB patients had 73.7 more days before first TLR and fewer reinterventions through 6 months

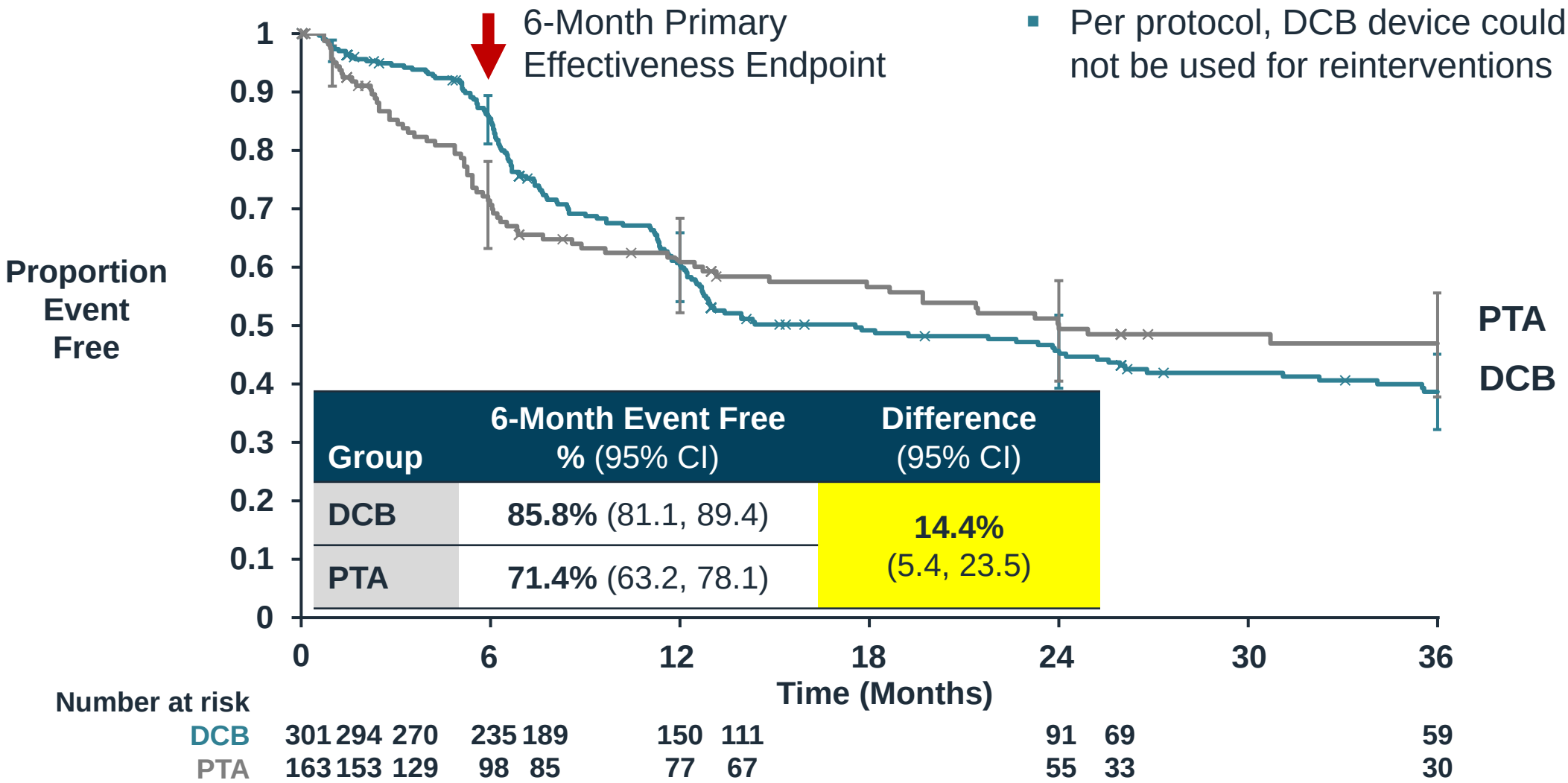
10.5% Improvement Over PTA in Primary Effectiveness Endpoint

	DCB N=323	PTA N=184	% Difference (95% CI)	p-value
Composite endpoint at 6 months[1], % (95% CI)	**74.7%** (69.1, 79.8)	**64.2%** (55.6, 72.2)	**10.5%** (0.3, 18.8)	**0.022**
Composite endpoint failure events[2], n (%)				
Major amputation[3]	**4 (1.4%)**	**3 (1.9%)**		
Primary patency failure[1]	**65 (24.2%)**	**46 (33.6%)**		
▪ CD-TLR[1,4]	28 (10.4%)	30 (21.9%)		
▪ Occlusion without TLR[5]	37 (13.8%)	16 (11.7%)		

- P-value of 0.0085 needed for significance

1. Values represent pathways; 2. Patients may fail primary effectiveness due to more than one cause; 3. Values represent patients
4. TLR failure is a component of primary patency failure; 5. Analysis not reviewed by FDA

Meaningful Difference in Kaplan-Meier Plot of Primary Effectiveness at 6 Months

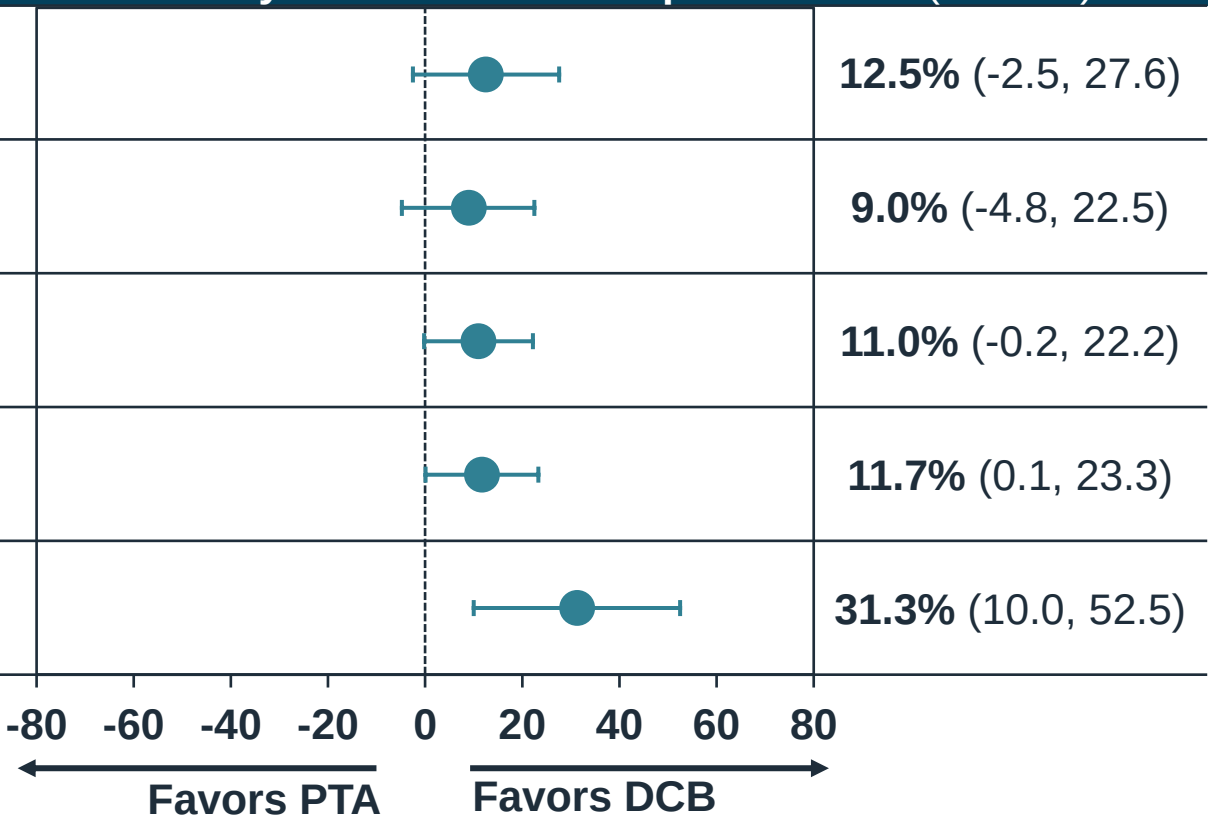


Group	6-Month Event Free % (95% CI)	Difference (95% CI)
DCB	**85.8%** (81.1, 89.4)	**14.4%** (5.4, 23.5)
PTA	**71.4%** (63.2, 78.1)	

Per pathway analysis; confidence intervals based on nominal levels and not adjusted for multiple comparisons

Results Favor DCB in Patients With Complex Baseline Factors, Supports Generalizability

Patient Baseline Factor	DCB Response Rate N=269 n/N	PTA Response Rate N=137 n/N	% Difference (95% CI)
Rutherford category 4	87/104	32/45	**12.5%** (-2.5, 27.6)
Rutherford category 5	87/136	44/80	**9.0%** (-4.8, 22.5)
Prior intervention	150/200	64/100	**11.0%** (-0.2, 22.2)
Diabetes	138/192	59/98	**11.7%** (0.1, 23.3)
Lesion length > 200 mm	42/65	9/27	**31.3%** (10.0, 52.5)

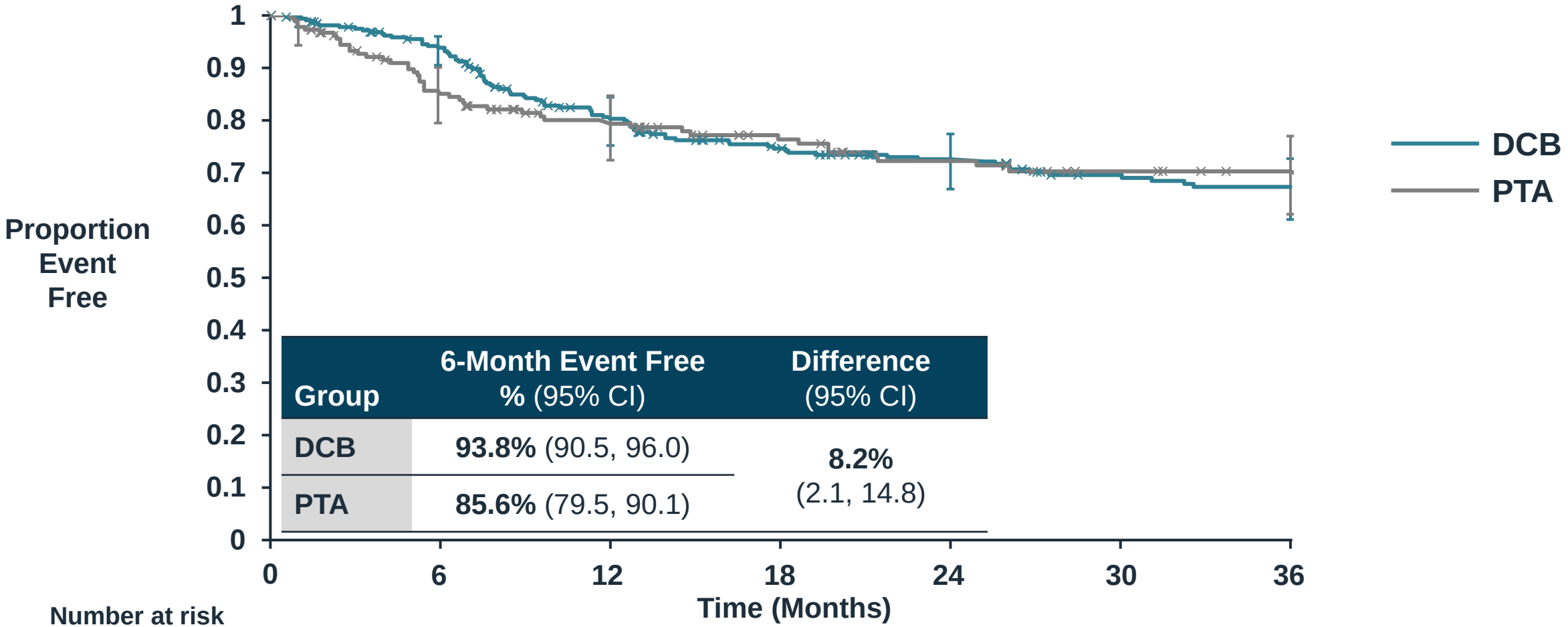


Per pathway analysis
Confidence intervals based on nominal levels and not adjusted for multiple comparisons

Secondary Endpoints Not Powered to Show Difference; Improvement Seen in Both Arms

Secondary Endpoints	
Wound healing	▪ Patients with large wounds excluded ▪ No plan to assess small differences in small wounds ▪ Confounded by variables such as diabetes and wound management procedures, patient compliance
Rutherford category	▪ Imprecise measure of disparate symptoms
Quality of life	▪ No difference between arms, consistent with literature

Clinically-Driven TLR Shows Benefit for Lutonix DCB at 6 Months



Group	6-Month Event Free % (95% CI)	Difference (95% CI)
DCB	**93.8%** (90.5, 96.0)	**8.2%** (2.1, 14.8)
PTA	**85.6%** (79.5, 90.1)	

Per pathway analysis; confidence intervals based on nominal levels and not adjusted for multiple comparisons

DCB Arm had More Time Before First Target Lesion Revascularization

		DCB Pathways N=323	PTA Pathways N=184	Difference (95% CI)
Days to first TLR[1]	Mean (SD) (95% CI)	**339.9 (236.4)** (289.9, 390.0)	**266.3 (246)** (194.1, 338.5)	**73.7** (-12.0, 159.3)
	Median	**257.5**	**165.0**	**92.5**

		DCB Patients N=287		PTA Patients N=155	
	Timepoint	Cumulative TLRs	TLR / Patient Year	Cumulative TLRs	TLR / Patient Year
Cumulative CD-TLRs and CD-TLRs per patient year[2]	1 month	5	0.14	6	0.32
	6 months	36	0.24	36	0.42
	12 months	101	0.35	53	0.35
	24 months	151	0.29	71	0.26
	36 months	170	0.27	75	0.23

1. Estimate is calculated for those with TLR, confidence interval not adjusted for multiple comparisons; 2. Includes recurrent TLRs

Angiograms at Reinterventions: Assessment of Investigator Bias

Core Lab Angiographic Assessment at CD-TLR (Through 6 Months)*	DCB N=24	PTA N=28
Angiographic stenosis, % ± SD	86% ± 20%	92% ± 13%
Angiographic occlusions, % (n)	50% (12)	64% (18)

- Core laboratory blinded to treatment arm when assessing angiograms at reintervention
- If investigator bias present, would expect less severely stenotic lesions in PTA arm at time of revascularization
- Analysis shows lesions similar in severity in DCB and PTA (2:1 randomization)

*** Among 28 DCB and 30 PTA total CD-TLRs through 6 months, 4 and 2 were not evaluated by the core lab, respectively. Angiographic stenosis and occlusion data not submitted to FDA and analysis not previously reviewed by FDA.**

Additional Data

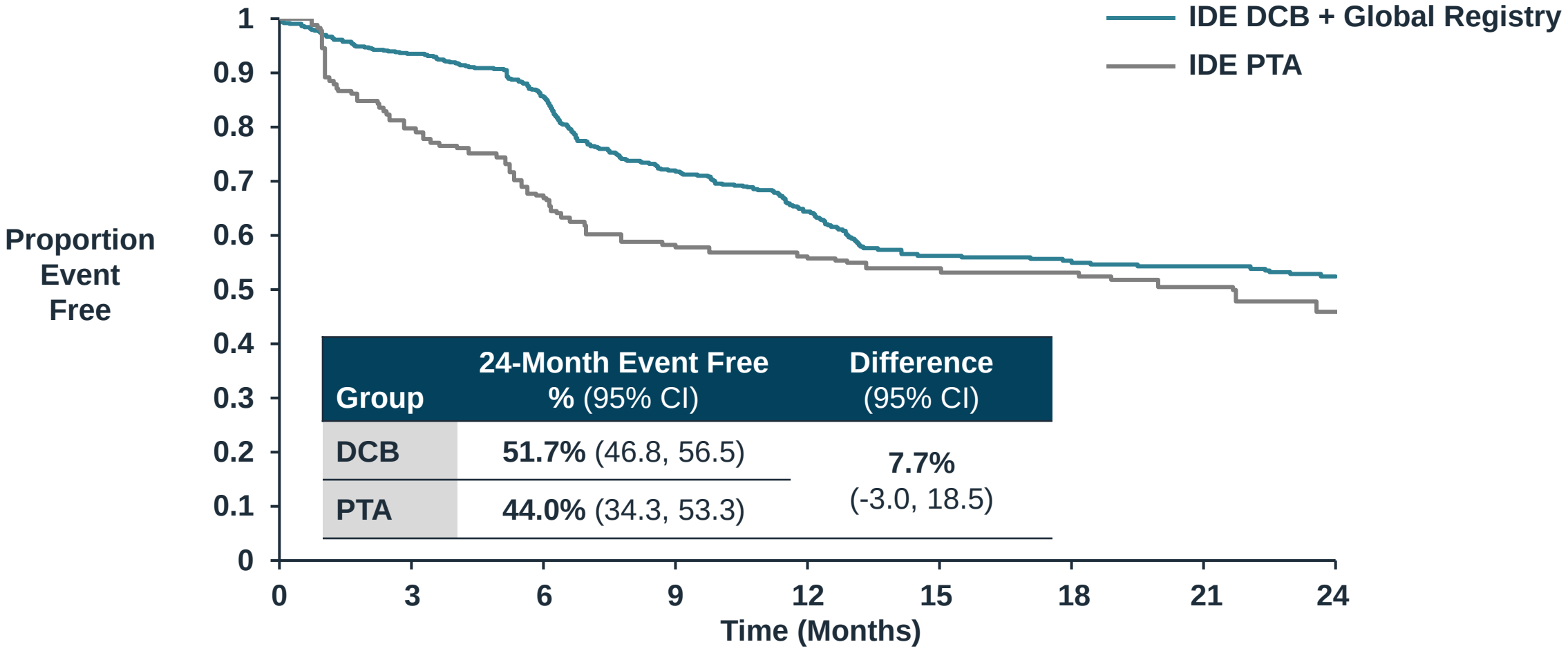
Lutonix BTK Global Registry

- Multicenter, single arm, real-world registry
- 371 patients enrolled from 26 sites in 11 countries
- Objective: to provide supportive information on DCB
- 98% met primary safety endpoint
  - Freedom from all-cause death, above ankle amputation or major reintervention at 30 days
- 90% met primary effectiveness endpoint
  - Freedom from CD-TLR at 6 months

Additional Global Registry Analyses to Add Power to IDE DCB Cohort

- Pooled results of Global Registry with IDE trial
  - Used propensity adjustment
- Compared to IDE PTA arm
- Adds power to 6-month endpoint
- Stabilizes effect beyond 6 months

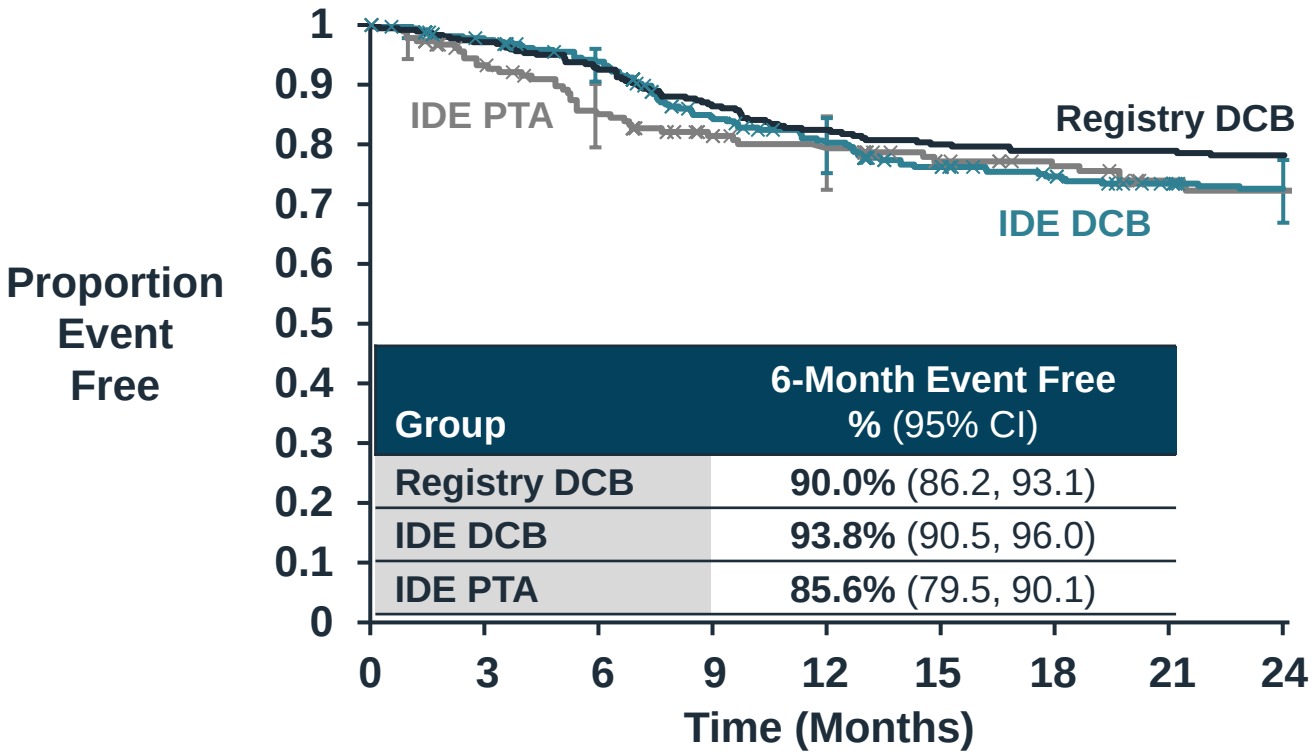
Global Registry Data Support Effectiveness of Lutonix IDE



Group	24-Month Event Free % (95% CI)	Difference (95% CI)
DCB	**51.7%** (46.8, 56.5)	**7.7%** (-3.0, 18.5)
PTA	**44.0%** (34.3, 53.3)	

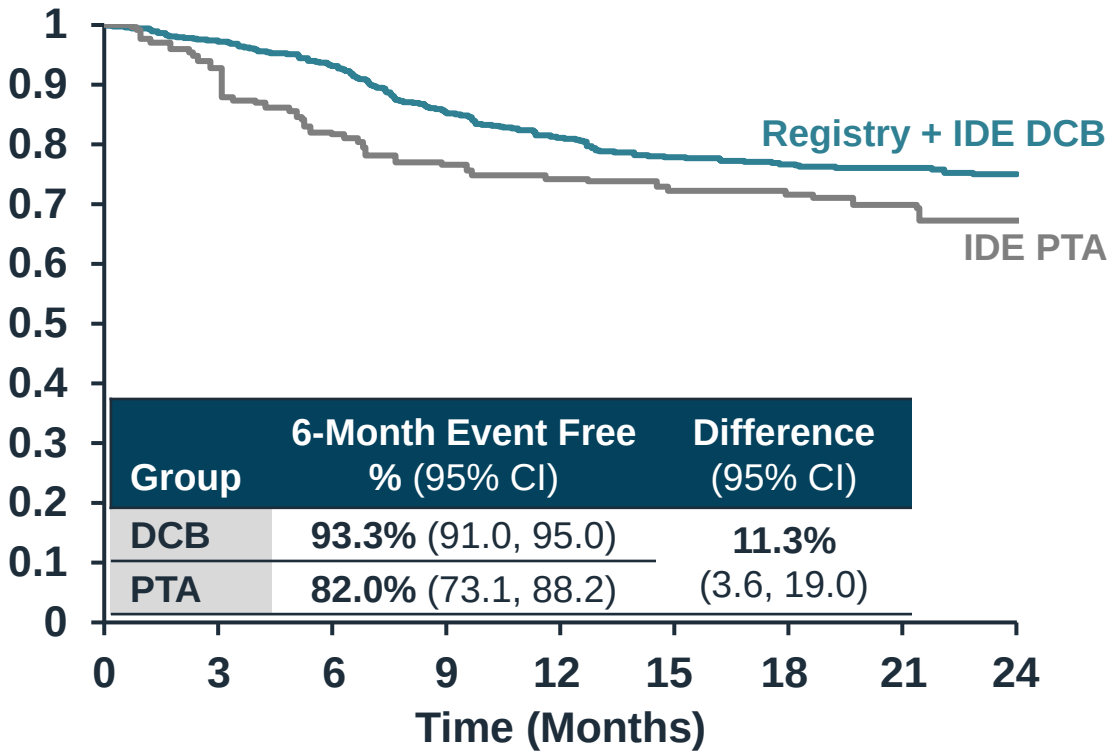
CEC-Adjudicated CD-TLR Shows Improved Benefit for DCB Patients

Global Registry DCB and IDE DCB and PTA Freedom From CD-TLR



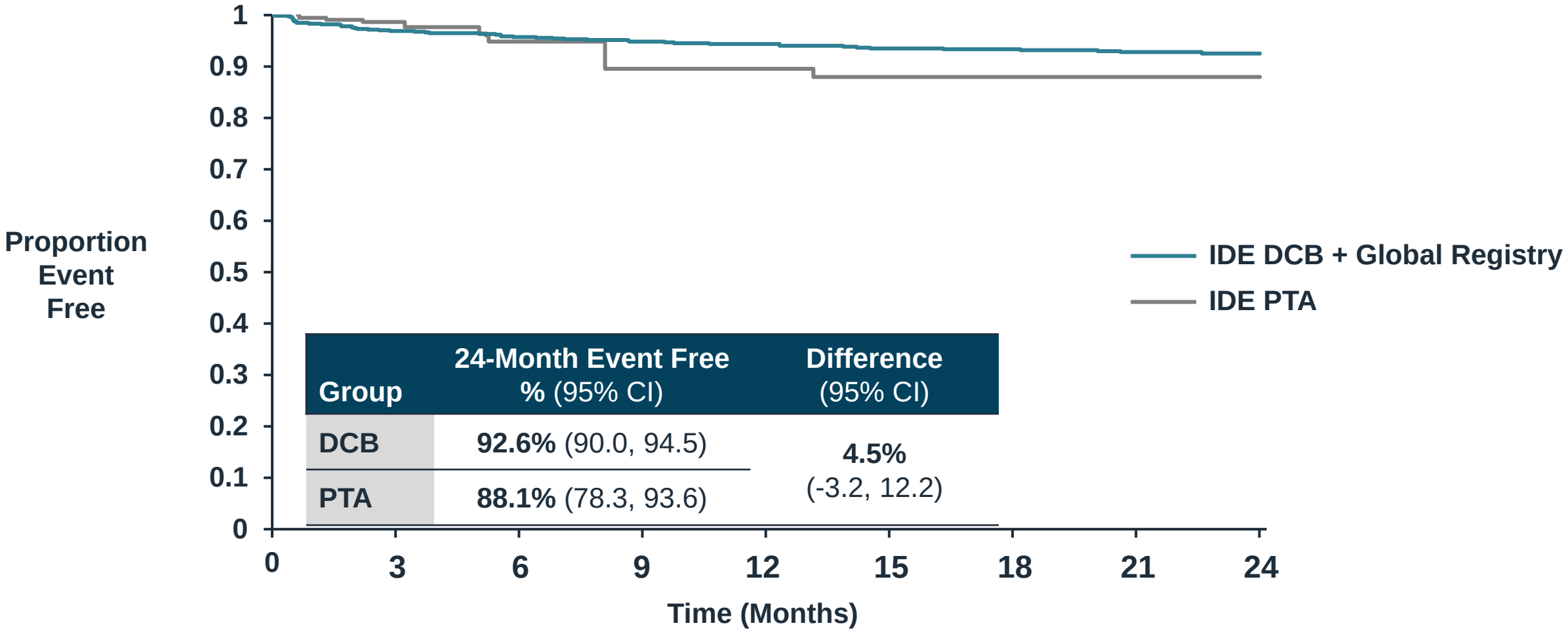
Group	6-Month Event Free % (95% CI)
Registry DCB	**90.0%** (86.2, 93.1)
IDE DCB	**93.8%** (90.5, 96.0)
IDE PTA	**85.6%** (79.5, 90.1)

Propensity Adjusted Global BTK Registry + IDE DCB vs PTA



Group	6-Month Event Free % (95% CI)	Difference (95% CI)
DCB	**93.3%** (91.0, 95.0)	**11.3%** (3.6, 19.0)
PTA	**82.0%** (73.1, 88.2)	

Global Registry Data Support Safety of Lutonix IDE



Group	24-Month Event Free % (95% CI)	Difference (95% CI)
DCB	**92.6%** (90.0, 94.5)	**4.5%** (-3.2, 12.2)
PTA	**88.1%** (78.3, 93.6)	

Additional Analyses Performed

Analysis	N	Results
Vascular Quality Initiative (VQI)	**167 DCB** **397 PTA**	▪ Propensity adjusted ▪ No difference in safety ▪ Effectiveness slightly favored DCB at 6 months ▪ No crossover in effectiveness at 12 months
Japanese HD study	**19 DCB** **17 PTA**	▪ No safety events in DCB arm, 1 in PTA arm ▪ Composite of limb salvage and primary patency through 6 months ▪ 70% in DCB vs 39% in PTA arm

Supportive literature published on Lutonix DCB BTK patients	**21–208 DCB**	▪ Reported freedom from TLR:
		  ▪ 78% at 6 months[1]
		  ▪ 84% at 9 months[2]
		  ▪ 84% at just over 1 year[3]

1. Micari, 2016, 2. Steiner, 2016, 3. Palena, 2018

Totality of Data Supports Lutonix DCB is Safe, Provides Meaningful Benefit to Patients

Lutonix DCB for BTK provides important option for treating Critical Limb Ischemia

Favorable safety profile

- Similar rates for primary endpoint, MACE, mortality and amputation-free survival to 36 months

10.5% incremental benefit over PTA

- Likelihood of patency benefit through 6 months
- p-value = 0.022

Delaying and reducing reinterventions

- Additional 73.7 days before first TLR – 340 days for DCB vs 266 for PTA
- Half as many TLRs through 6 months for DCB

Benefit-Risk Profile and Conclusion

JD Meler, MD

Clinical Professor, Texas A&M Health Science Center

Vice President Medical Affairs

BD, Peripheral Intervention

Relentlessly Progressive Disease; Need to Intervene, Restore Vessel Patency

- Managing disease requires regular check ups, lifestyle changes, and vascular interventions
- Collective effort to
  - Prevent complications of CLI
  - Control pace of progression
  - Disrupt cascade of tissue loss

Deficiencies with Current Treatment Options for Patients with CLI

- Analysis of long-term outcomes among revascularization approaches[1]
  - Poor outcomes for all treatment groups
  - High mortality and major amputation rates

Lutonix DCB BTK presents opportunity to use existing technology to improve care CLI patients need and deserve

1. Mustapha, 2019

Meaningful Benefits for Patients Outweigh Potential Risks

Benefits

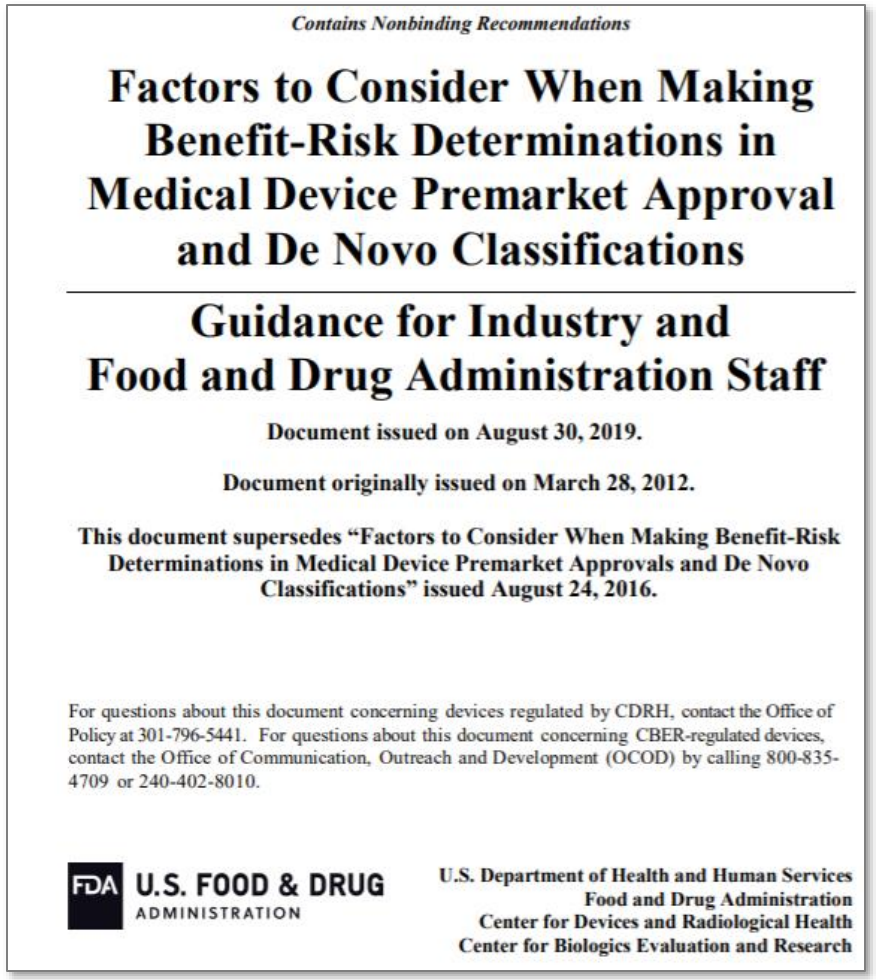
- Effectiveness favored DCB through 6 months
  - Appropriate interval given aggressive nature of CLI
- Patients faced fewer interventions than with PTA
- Longer period of intervention-free time, > 2 months
- Additional treatment for patients who have few options, shortened life expectancy, comorbidities

Risks

- Same procedural risks as other angioplasty procedures
- Addition of drug did not induce related safety events in trial

Advances care for patients with urgent, unmet need with existing technology used to treat restenosis, re-occlusion

Review FDA Guidance



Contains Nonbinding Recommendations

Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications

Guidance for Industry and Food and Drug Administration Staff

Document issued on August 30, 2019.

Document originally issued on March 28, 2012.

This document supersedes "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approvals and De Novo Classifications" issued August 24, 2016.

For questions about this document concerning devices regulated by CDRH, contact the Office of Policy at 301-796-5441. For questions about this document concerning CBER-regulated devices, contact the Office of Communication, Outreach and Development (OCOD) by calling 800-835-4709 or 240-402-8010.

FDA U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

- Factors supported rationale for Lutonix DCB submission

Evidence Provides Reasonable Assurance of Positive Benefit-Risk, Per FDA Guidance

FDA Guidance	Lutonix DCB Study Results
"The device fills an unmet medical need or niche for more effective treatment of life-threatening or irreversibly debilitating human disease/conditions"	▪ CLI is an irreversibly debilitating disease ▪ No drug-coated technologies available for BTK vessels, creates gap in treatment options
"[What are] the adverse events (AEs) or outcomes related to the device itself?"	▪ No increased risk from device compared to PTA ▪ MACE rate: Low and similar in both treatment groups, through 36 months
"Benefit should be considered based on the assessment of the data, <u>whether or not the results are statistically significant</u>"	▪ 10.5% benefit for DCB over PTA in primary effectiveness endpoint, p-value 0.022
"Favorable change in at least 1 clinical assessment that is equal to or greater than seen in the control group"	▪ Meaningful difference with reduced reintervention rate at 6 months, and additional 73.7 days to first reintervention

Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications

Evidence to Support Approval of Lutonix DCB BTK with Data Reviewed Today

- Shown to be safe
- Offers incremental improvement
- Study included patients with typical CLI characteristics
- Committed to long-term, post-market evaluation

Important, additional treatment option for patients with CLI

Lutonix™ 014 Drug Coated Balloon PTA Catheter for Treatment of Below-the-Knee (BTK) Arteries

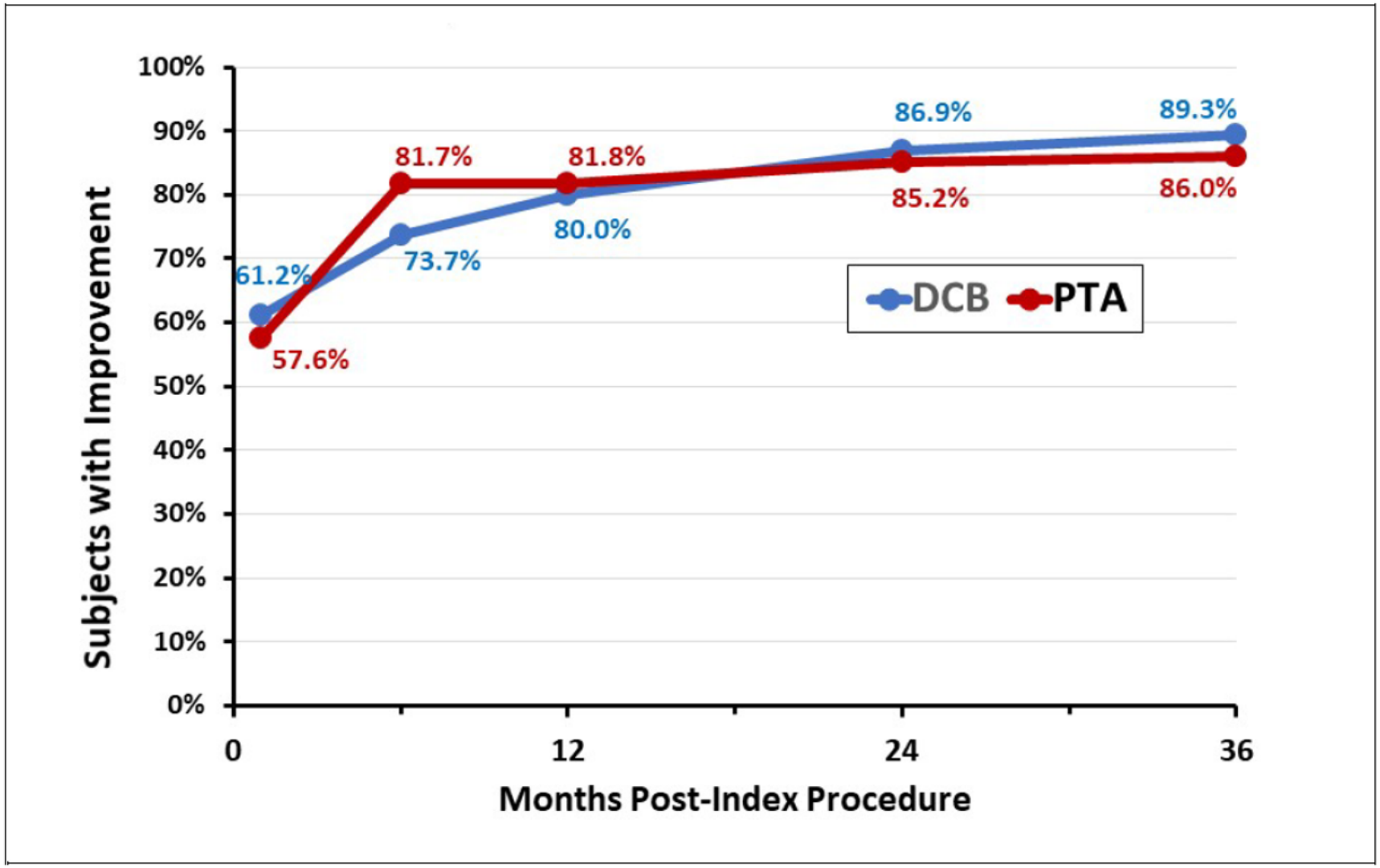
February 17, 2021

BD

Circulatory System Devices Panel

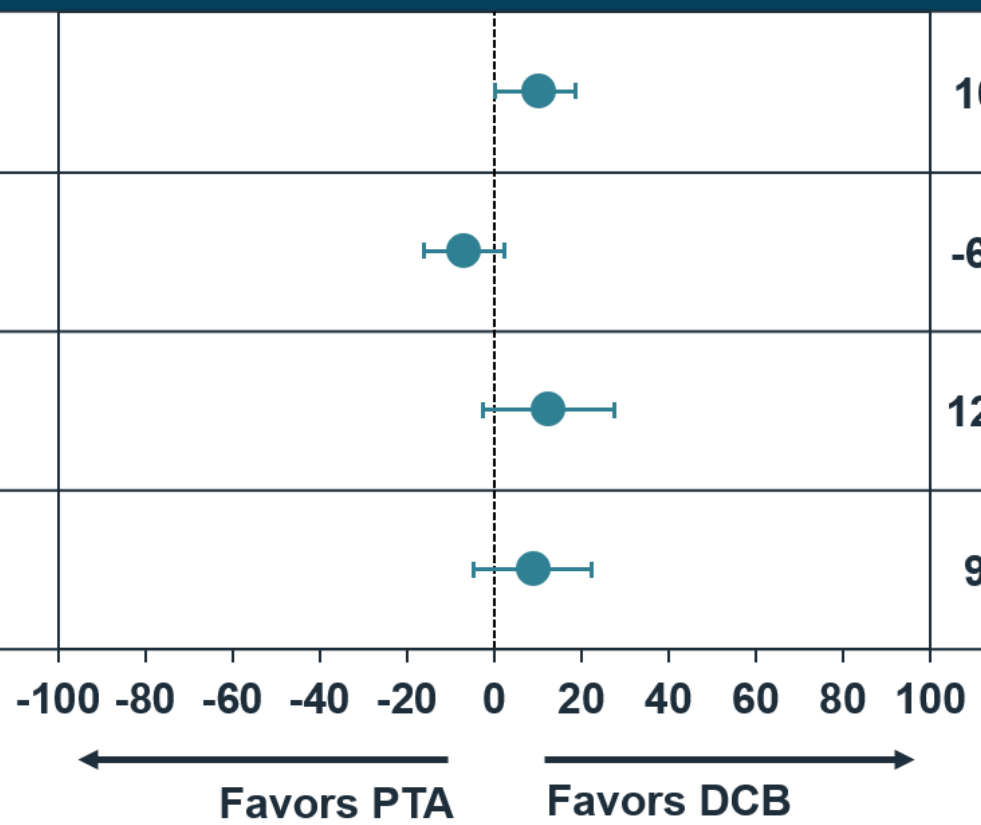
Additional Slides Shown

Figure 9-8. Improvement in Rutherford Category through 36 Months



No Significant Variation in Primary Effectiveness by Rutherford Category

	DCB Pathways N=269 n/N	PTA Pathways N=137 n/N	% Difference (95% CI)	Interaction p-value
Primary effectiveness endpoint	201/269	88/137	**10.5%** (0.3, 18.8)	
Rutherford category 3	27/29	12/12	**-6.9%** (-16.1, 2.3)	
Rutherford category 4	87/104	32/45	**12.5%** (-2.5, 27.6)	**0.781**
Rutherford category 5	87/136	44/80	**9.0%** (-4.6, 22.5)	



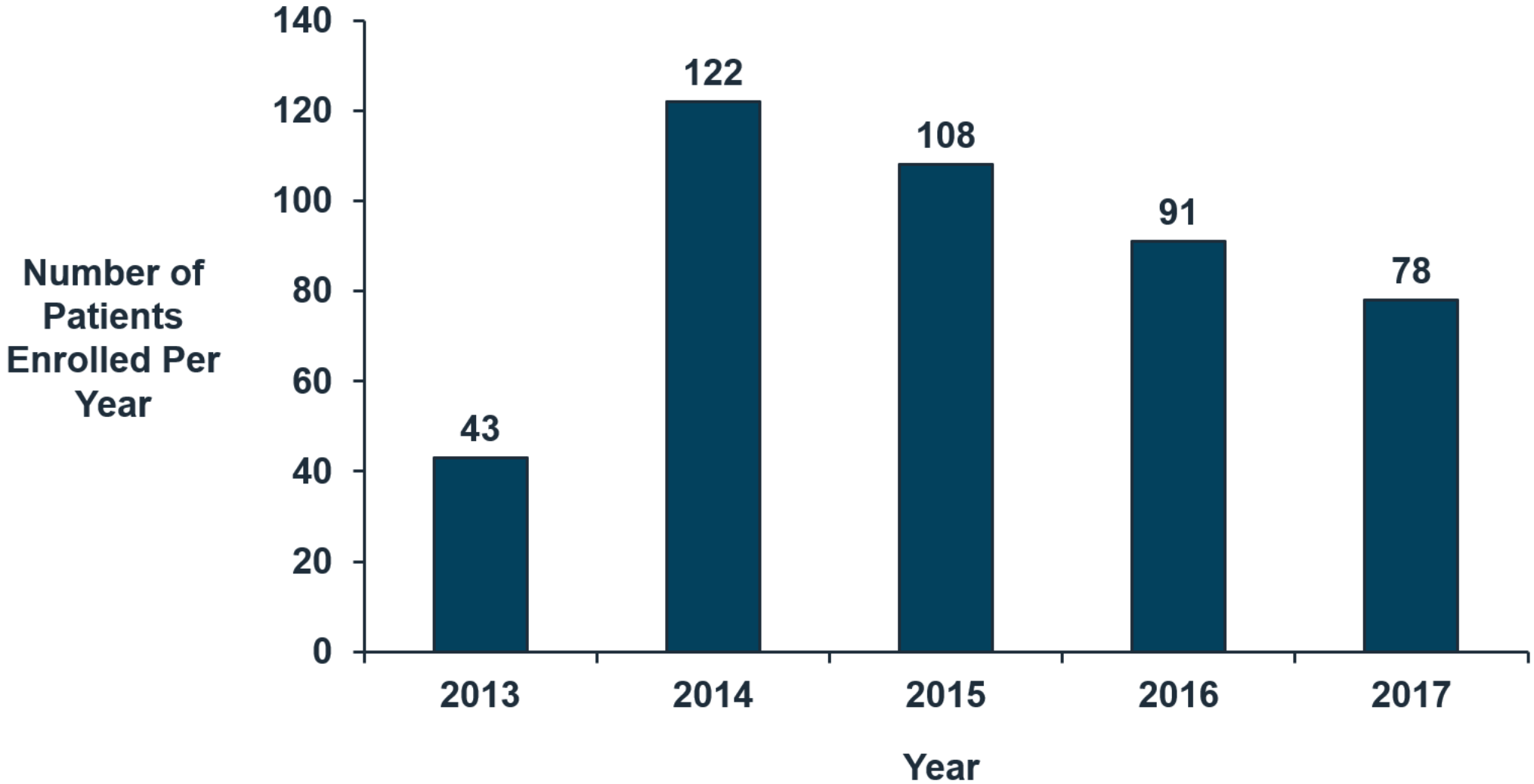
ABI and TBI: Improvement in Both Groups

ABI	Baseline	30 days	6 Months	12 Months	24 Months	36 Months
DCB	0.81 ± 0.40	1.05 ± 0.32	0.97 ± 0.34	0.92 ± 0.35	0.94 ± 0.33	0.94 ± 0.33
PTA	0.83 ± 0.39	1.11 ± 0.37	0.99 ± 0.40	0.96 ± 0.32	0.99 ± 0.30	0.95 ± 0.33

TBI	Baseline	30 days	6 Months	12 Months	24 Months	36 Months
DCB	0.35 ± 0.24	0.57 ± 0.23	0.52 ± 0.26	0.50 ± 0.22	0.49 ± 0.24	0.48 ± 0.20
PTA	0.39 ± 0.26	0.51 ± 0.24	0.49 ± 0.26	0.43 ± 0.21	0.50 ± 0.27	0.52 ± 0.23

All values are means ± SD

Patient Enrollment by Year



*Trial started in June 2013

Overlap of Failure Events for Primary Effectiveness Endpoint

	DCB Pathways N=269	PTA Pathways N=137
Free from primary effectiveness failure (≤ 210 days), n (%) (95% CI)	**201 (74.7%)** (69.1%, 79.8%)	**88 (64.2%)** (55.6%, 72.2%)
Composite endpoint failures (failed pathways ≤ 210 days)	**68**	**49**
Patients with major amputation	**4**	**3**
Pathways with CD-TLR	**28**	**30**
Pathways with lost primary patency*	**65**	**46**

**Primary Patency can be lost from occlusion or CD-TLR; overlaps with CD-TLR row*

Data/analysis not previously submitted to, or reviewed by, FDA.

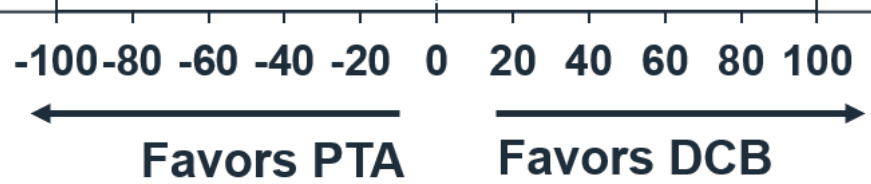
Unique Patterns of Effectiveness Failure

	DCB Pathways N=269	PTA Pathways N=137
Pathways with primary effectiveness failure (≤ 210 days)	68/269 (25.3%)	49/137 (35.8%)
Unique patterns of failure (≤ 210 days)		
Major amputation alone	3 (1.1%)	3 (2.2%)
CD-TLR alone	22 (8.2%)	25 (18.2%)
DUS occlusion alone	37 (13.8%)	16 (11.7%)
CD-TLR and major amputation	1 (0.4%)	0 (0.0%)
CD-TLR and DUS occlusion	5 (1.9%)	5 (3.6%)

Data/analysis not previously submitted to, or reviewed by, FDA.

No Evidence of Variation by Lesion Location

		DCB N=269 n/N	PTA N=137 n/N	Primary Effectiveness Endpoint	% Difference (95% CI)	Interaction p-value
Lesion Location	Tibioperoneal Trunk alone	24/24	14/16		**12.5%** (-3.7, 28.7)	NA
	Anterior Tibial alone	72/98	28/42		**6.8%** (-9.9, 23.5)	
	Posterior Tibial alone	25/45	13/27		**7.4%** (-16.4, 31.2)	
	Peroneal alone	26/35	9/16		**18.0%** (-10.3, 46.3)	



Inflation Times and Atmosphere Pressure in DCB and PTA

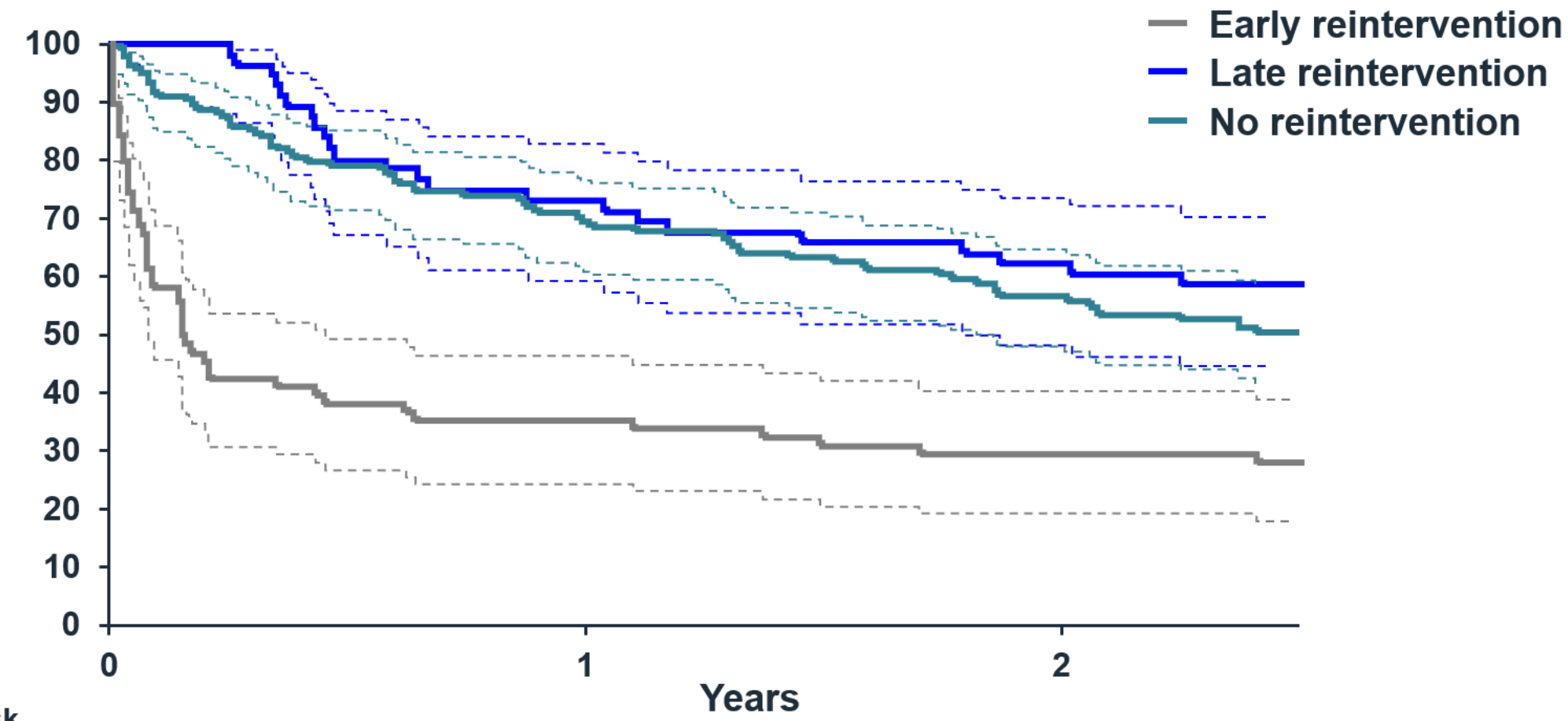
	DCB Devices N=647	PTA Devices N=234
Maximum Balloon Pressure (atm)		
Mean (SD)	8.71 (3.06)	8.63 (2.81)
Maximum Balloon Diameter (mm)		
Mean (SD)	2.9 (0.53)	2.9 (0.56)
Device Inflation Time (sec)		
Mean (SD)	141.6 (53.93)	123.9 (70.55)

> 91% Concordance

CEC Assessment of Clinically Driven Status	Site		
	Yes	No	Total
Yes	160 (89.9%)	11 (6.2%)	171
No	4 (2.2%)	3 (1.7%)	7
Total	164	14	178

For the primary analysis, CEC identified events were used, not the site classification.

Early Reintervention is Associated with Lower Amputation-Free Survival



No. at risk			
Early	70	25	20
Late	56	41	35
None	135	96	75

Klaphake, 2018

Summary of all TLRs, Site vs CEC Assessment of Clinically Driven Event Status - PTA

CEC Assessment of Clinically Driven Status	Site		
	Yes	No	Total
Yes	48 (90.6%)	1 (1.9%)	49
No	2 (3.8%)	2 (3.8%)	4
Total	50	3	

For the primary analysis, CEC identified events were used, not the site classification.

Summary of all TLRs, Site vs CEC Assessment of Clinically Driven Event Status - DCB

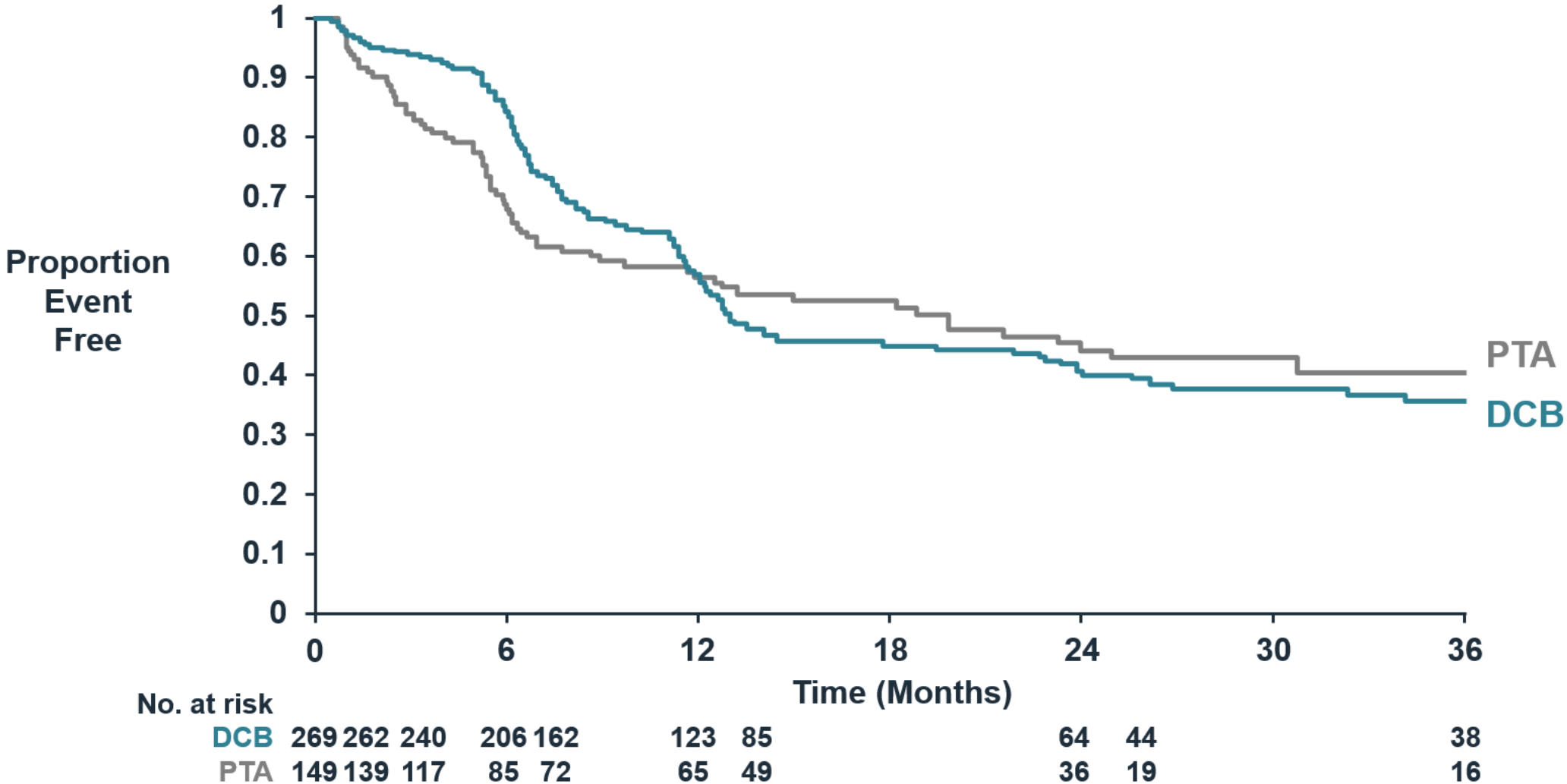
CEC Assessment of Clinically Driven Status	Yes	No	Total
Yes	112 (89.6%)	10 (8.0%)	122
No	2 (1.6%)	1 (0.8%)	3
Total	114	11	

For the primary analysis, CEC identified events were used, not the site classification.

Baseline Rutherford Category in IDE and Global Registry Studies

Baseline Rutherford Category	IDE DCB Patients N=287	IDE PTA Patients N=155	Global Registry Patients N=371
3	26 (9.1%)	16 (10.3%)	89 (24.1%)
4	100 (34.8%)	52 (33.5%)	39 (10.5%)
5	161 (56.1%)	87 (56.1%)	242 (65.4%)

Kaplan-Meier of Primary Effectiveness Endpoint in Rutherford 4 and 5 Patients



95% CIs/p-value not adjusted for multiple comparisons. Data/analysis not previously submitted to, or reviewed by, FDA.

Types of TLR Re-Interventions (1 of 2)

	DCB TLR	PTA TLR
All interventions by type to 30 days, n/N (%)		
Atherectomy	1 (11.1%)	0 (0.0%)
Laser	1 (11.1%)	0 (0.0%)
PTA	5 (55.6%)	5 (100.0%)
Stent	2 (22.2%)	0 (0.0%)
All interventions by type to 6 months, n/N (%)		
Atherectomy	8 (16.7%)	4 (8.5%)
Bypass graft	1 (2.1%)	0 (0.0%)
Laser	1 (2.1%)	1 (2.1%)
PTA	30 (62.5%)	35 (74.5%)
Stent	8 (16.7%)	5 (10.6%)
Thrombectomy/thrombolysis	0 (0.0%)	2 (4.3%)
All interventions by type to 12 months, n/N (%)		
Atherectomy	22 (18.2%)	6 (9.2%)
Bypass graft	2 (1.7%)	0 (0.0%)
Laser	2 (1.7%)	1 (1.5%)
PTA	83 (68.6%)	46 (70.8%)
Stent	11 (9.1%)	9 (13.8%)
Thrombectomy/thrombolysis	1 (0.8%)	3 (4.6%)

Types of TLR Re-Interventions (2 of 2)

	DCB TLR	PTA TLR
All interventions by type to 24 months, n/N (%)		
Atherectomy	29 (16.0%)	10 (11.8%)
Bypass graft	3 (1.7%)	0 (0.0%)
Laser	6 (3.3%)	1 (1.2%)
PTA	126 (69.6%)	61 (71.8%)
Stent	12 (6.6%)	10 (11.8%)
Thrombectomy/thrombolysis	5 (2.8%)	3 (3.5%)
All interventions by type to 36 months, n/N (%)		
Atherectomy	32 (15.9%)	11 (12.4%)
Bypass graft	3 (1.5%)	0 (0.0%)
Laser	6 (3.0%)	1 (1.1%)
PTA	142 (70.6%)	64 (71.9%)
Stent	12 (6.0%)	10 (11.2%)
Thrombectomy/thrombolysis	6 (3.0%)	3 (3.4%)

Risk stratification based on Wound, Ischemia, and foot Infection (WIfI)

	Ischemia - 0				Ischemia – 1				Ischemia – 2				Ischemia – 3			
W-0	VL	VL	L	M	VL	L	M	H	L	L	M	H	L	M	M	H
W-1	VL	VL	L	M	VL	L	M	H	L	M	H	H	M	M	H	H
W-2	L	L	M	H	M	M	H	H	M	H	H	H	H	H	H	H
W-3	M	M	H	H	H	H	H	H	H	H	H	H	H	H	H	H
	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3

	Ischemia - 0				Ischemia – 1				Ischemia – 2				Ischemia – 3			
W-0	VL	VL	VL	VL	VL	L	L	M	L	L	M	M	M	H	H	H
W-1	VL	VL	VL	VL	L	M	M	M	M	H	H	H	H	H	H	H
W-2	VL	VL	VL	VL	M	M	H	H	H	H	H	H	H	H	H	H
W-3	VL	VL	VL	VL	M	M	M	H	H	H	H	H	H	H	H	H
	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3

fI = Foot Infection, I = Ischemia, W = Wound

VL = Very Low, clinical stage 1

L = Low, clinical stage 2

M = Moderate, clinical stage 3

H = High, clinical stage 4

Missing Data Over Time

Missing Endpoint Status	30 Days		6 Months		12 Months		24 Months		36 Months	
	DCB	PTA	DCB	PTA	DCB	PTA	DCB	PTA	DCB	PTA
n/N	29/323	28/184	54/323	47/184	72/323	52/184	95/323	61/184	113/323	84/184
%	9.0%	15.2%	16.7%	25.5%	22.2%	28.2%	29.4%	33.2%	35.0%	45.7%

Per pathway analysis

Multiple Imputation Model Results

- Imputation model used key demographic, target lesion, and procedural characteristics to model missing outcomes
- 2 analyses performed
  - 1 combining treatment groups
  - 1 separate by treatment group

	DCB N=323	PTA N=184	Difference (95% CI)
Multiple imputation model			
Imputation combining treatment groups	**74.2%**	**66.3%**	**7.9%** (-1.6, 16.0)
Imputation separate by treatment groups	**73.8%**	**63.8%**	**10.0%** (0.4, 18.5)

Treatment Groups Remained on Antiplatelet Therapy

Medication	Treatment	Baseline	30 Days	6 Months	12 Months	24 Months	36 Months
Aspirin	DCB	202 (74.8%)	250 (89.6%)	220 (87.3%)	186 (80.5%)	138 (75.8%)	99 (72.3%)
	PTA	106 (72.1%)	129 (86.0%)	109 (81.3%)	82 (73.9%)	68 (72.3%)	48 (76.2%)
Cilostazol (pletal)	DCB	18 (6.7%)	19 (6.8%)	15 (6.0%)	13 (5.6%)	7 (3.8%)	4 (2.9%)
	PTA	9 (6.1%)	12 (8.0%)	9 (6.7%)	6 (5.4%)	3 (3.2%)	4 (6.3%)
Clopidogrel	DCB	129 (47.8%)	224 (80.3%)	184 (73.0%)	137 (59.3%)	103 (56.6%)	66 (48.2%)
	PTA	75 (51.0%)	124 (82.7%)	103 (76.9%)	70 (63.1%)	52 (55.3%)	31 (49.2%)
Coumadin	DCB	0 (0%)	8 (2.8%)	7 (2.4%)	9 (3.1%)	8 (2.8%)	5 (1.7%)
	PTA	0 (0%)	9 (5.8%)	7 (4.5%)	8 (5.2%)	8 (5.2%)	3 (1.9%)
DAPT	DCB	125 (46.3%)	219 (78.5%)	182 (72.2%)	134 (58.0%)	95 (52.2%)	63 (46.0%)
	PTA	68 (46.3%)	114 (76.0%)	89 (66.4%)	60 (54.1%)	46 (48.9%)	30 (47.6%)
Other - Antiplatelet	DCB	20 (7.4%)	23 (8.2%)	21 (8.3%)	21 (9.1%)	20 (11.0%)	17 (12.4%)
	PTA	13 (8.8%)	14 (9.3%)	9 (6.7%)	10 (9.0%)	9 (9.6%)	7 (11.1%)
Prasugrel	DCB	1 (0.4%)	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	PTA	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Ticagrelor	DCB	5 (1.9%)	7 (2.5%)	7 (2.8%)	6 (2.6%)	5 (2.7%)	2 (1.5%)
	PTA	0 (0%)	2 (1.3%)	1 (0.7%)	1 (0.9%)	1 (1.1%)	0 (0%)
Ticlopidine	DCB	1 (0.4%)	2 (0.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	PTA	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)