TCT 2018
FDA Town Hall Meeting Part 2: Hot Topics

DCB for BTK: Clinical Challenges and Lessons Learned

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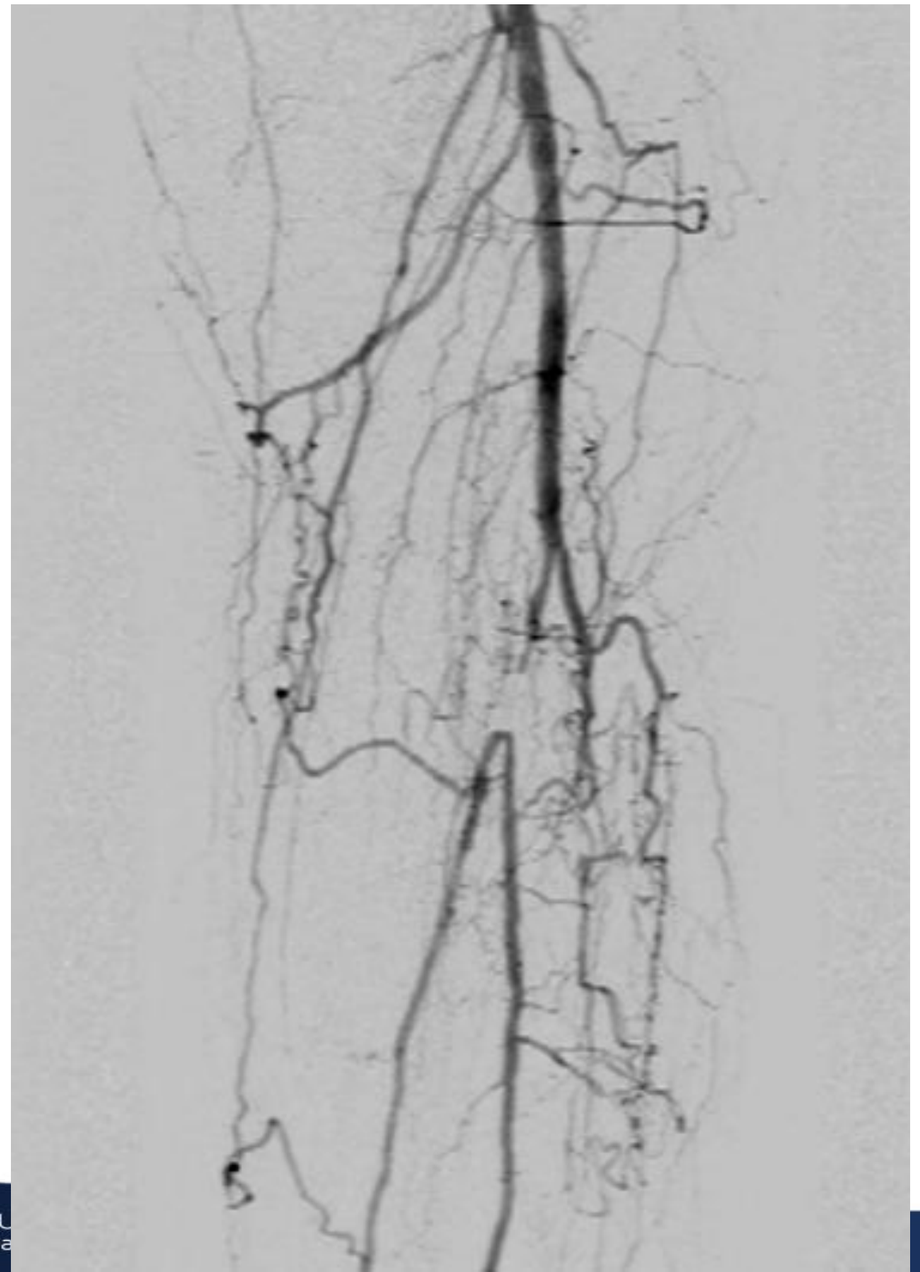
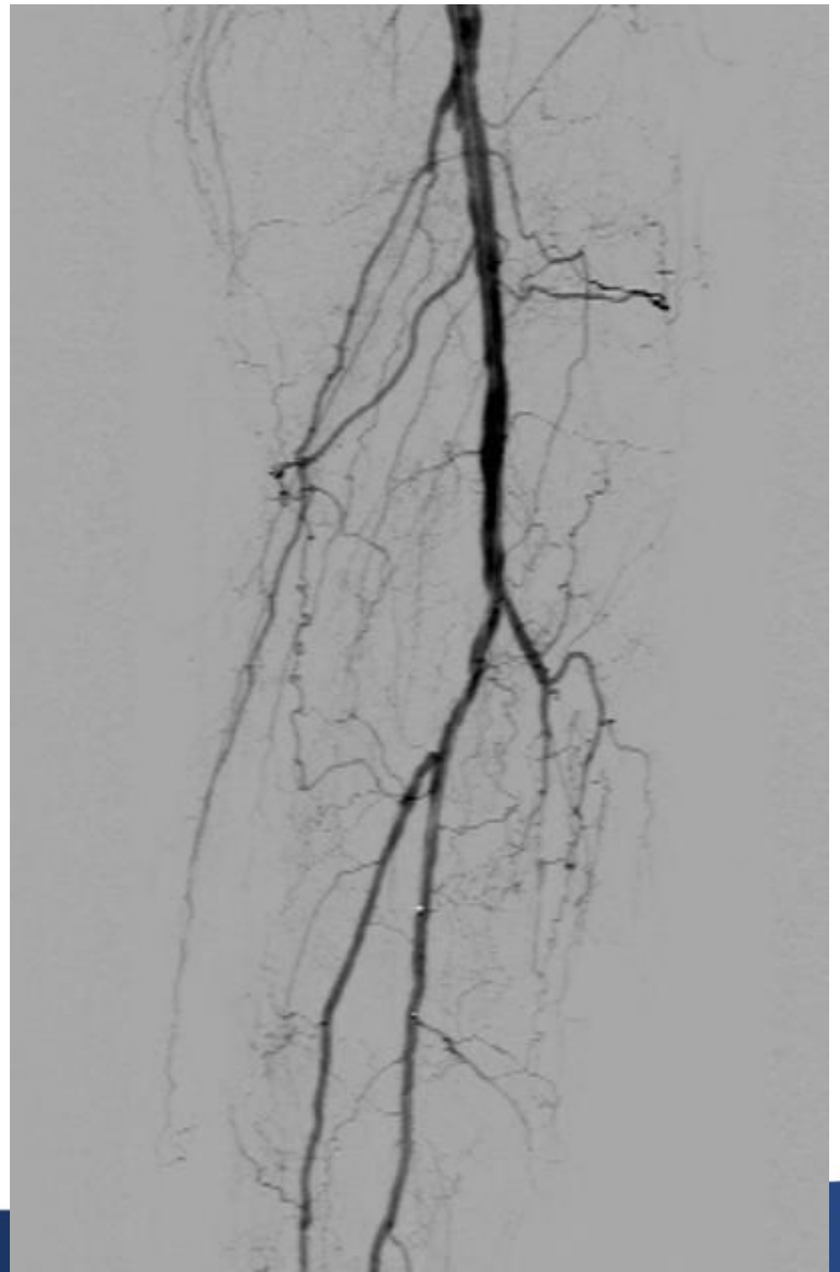
Disclosure Statement of Financial Interest

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

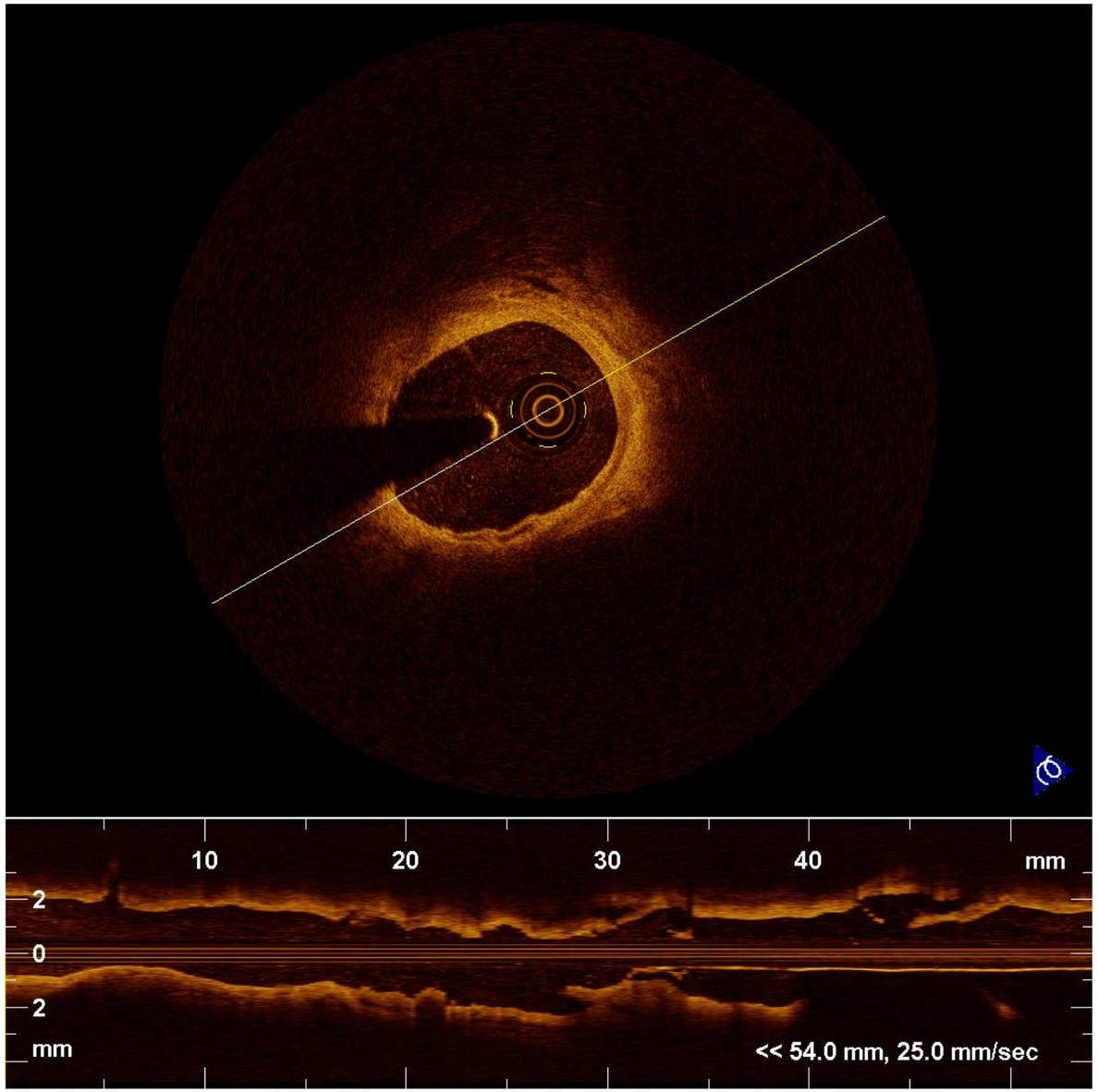
Affiliation/Financial Relationship	Company
• ***Research Support***	• **Shockwave Medical, TriReme Medical, Surmodics, Silk Road Medical, NIH**
• ***Consulting Fees/Honoraria***	• **Terumo, Asahi, Heartflow, Merril Lifesciences**
• ***Advisory Board***	• **Abbott, Medtronic, Boston Scientific, CSI, Philips**

Short Segment Occlusion in CLI





Short Segment Occlusion in CLI



Courtesy: Sahil A. Parikh, MD

BTK Clinical Challenges

- Smaller Vessels
- Vast majority of BTK cases involve Calcium
  - Large # of CTOs
- Diabetic patients
- Vessel Tortuosity
- LONG lesions
- Distal Embolization is a big concern
- Compared to other vascular beds, there is a paucity of labeled devices for this anatomic region.

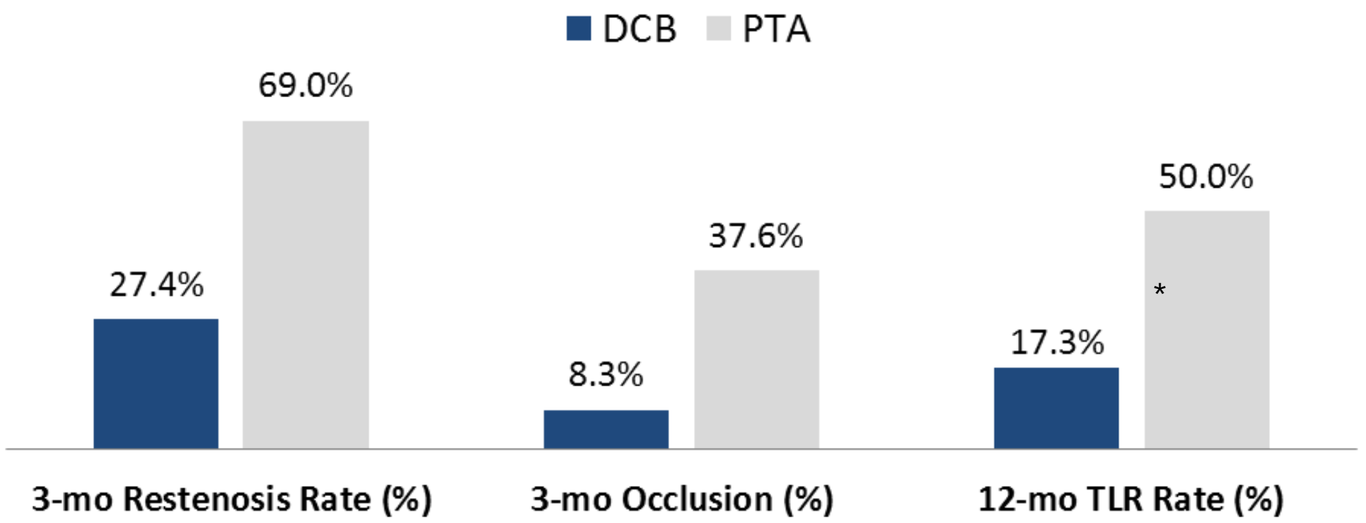
BTK revascularization technologies

- Plain Balloon Angioplasty
- Atherectomy
- Scoring/Focal Force Angioplasty
- Bare Metal Stent
- Drug Eluting Stent --> coronary DES (so far)
- Drug Coated Balloon

Leipzig Registry - Promising

Leipzig Registry[1]

- Single-center
- N = 104 (73% Diabetics)
- 17.3cm mean lesion length
- IN.PACT Amphirion (Medtronic)
  - Compared here with same group's PTA results[2]

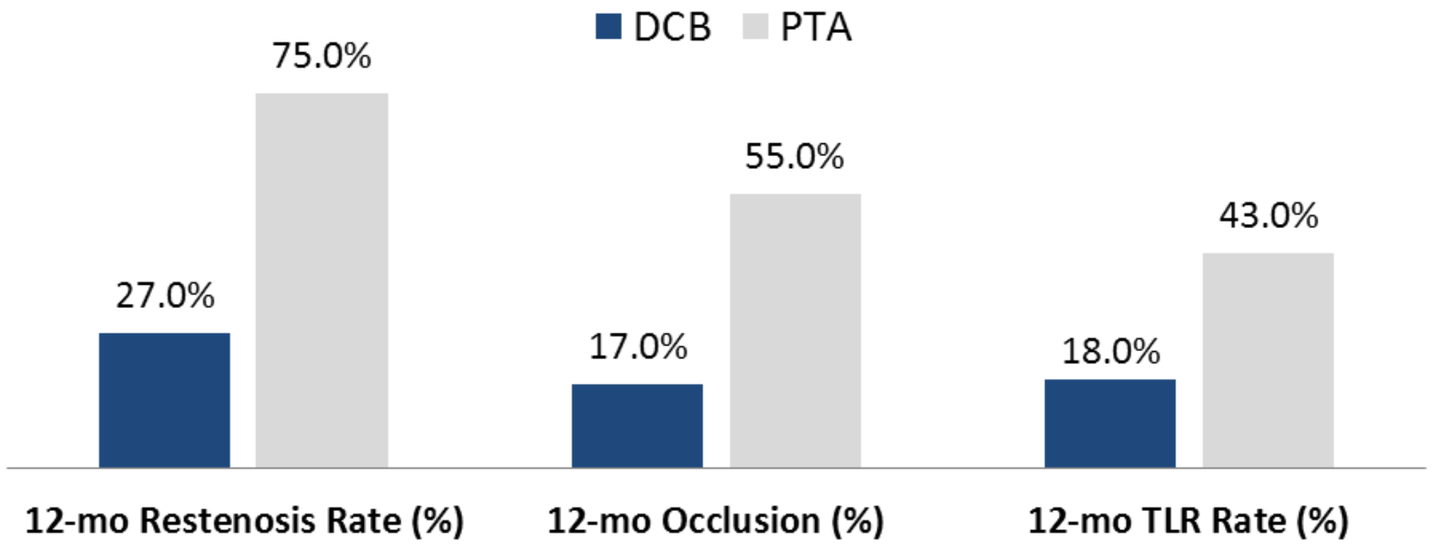


1. Schmidt A, et al. J Am Coll Cardiol 2011;58:1105-1109.
2. Schmidt A, et al. Catheter Cardiovasc Interv 2010;76:1047-1054.

Debate BTK Promising

DEBATE-BTK (Liistro, et al.)[1]

- Single-center, randomized (1:1 v PTA)
- N = 132, 100% diabetics
- 12.9cm mean lesion length (DCB arm), 77.5% CTO
- IN.PACT Amphirion (Medtronic) v PTA



1. Liistro F, et al. Circ 2013;128:615-621.

Drug-Eluting Balloon in Peripheral Intervention for Below the Knee Angioplasty Evaluation (DEBATE-BTK)

A Randomized Trial in Diabetic Patients With Critical Limb Ischemia

Francesco Liistro, MD; Italo Porto, MD PhD; Paolo Angioli, MD; Simone Grotti, MD; Lucia Ricci, MD; Kenneth Ducci, MD; Giovanni Falsini, MD; Giorgio Ventoruzzo, MD; Filippo Turini, MD; Guido Bellandi, MD; Leonardo Bolognese, MD

Table 2. Procedural and Angiographic Characteristics

	DEB	PTA	*P* Value
Lesions, n	80	78	
Vessel location, n (%)			
ATA	37 (46.3)	32 (41.0)	
PT	13 (16.3)	18 (23.1)	
PA	14 (17.5)	21 (26.9)	0.5
TPT	16 (20.0)	7 (9.0)	
Complete vessel occlusion, n (%)	62 (77.5)	64 (82.1)	0.5
Lesion length, mm	129±83	131±79	0.9
Severe calcification, n (%)	20 (25.0)	22 (28.2)	0.5
RVD, mm	2.91±0.27	2.87±0.29	0.7
MLD, mm	0.06±0.14	0.05±0.14	0.6
DS, %	97.2±7.7	97.1±8.0	0.9
Predilatation, n (%)	80 (100.0)	…	
Subintimal recanalization, n (%)	17 (21.3)	17 (21.8)	0.8
Antegrade recanalization, n (%)	78 (97.5)	75 (96.2)	0.7
Retrograde recanalization, n (%)	2 (2.5)	3 (3.8)	0.7
Balloon inflation time, s	142±38	140±50	0.5
Balloon diameter, mm	2.90±0.39	2.85±0.36	0.4
Balloon length, mm	148±83	140±79	0.5
Bailout stenting, n (%)	1 (1.3)	1 (1.3)	0.9
Technical success, n (%)	80 (100)	78 (100)	1
Procedural success, n (%)	65 (100)	67 (100)	1

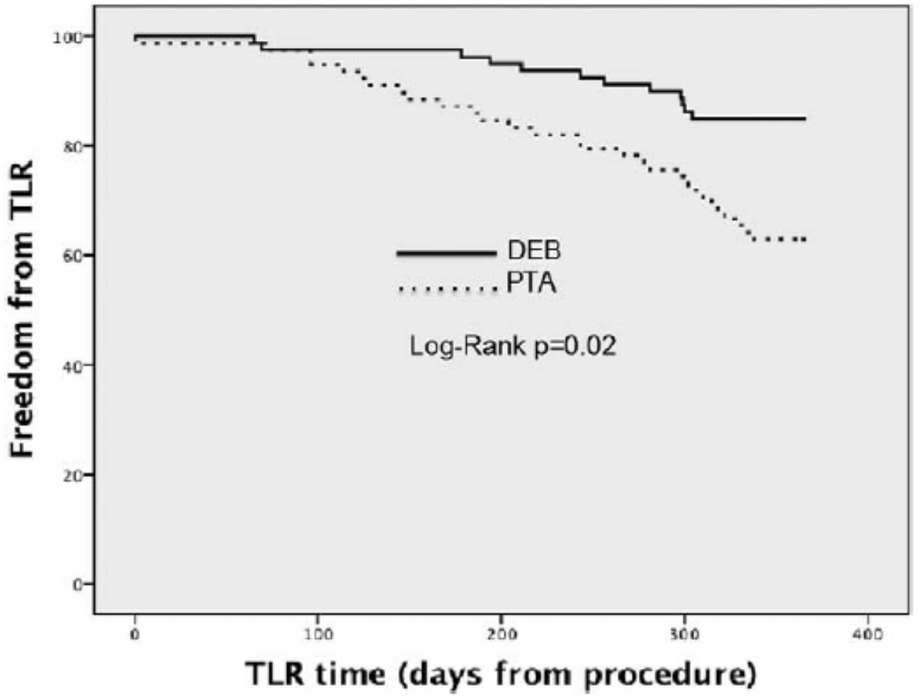
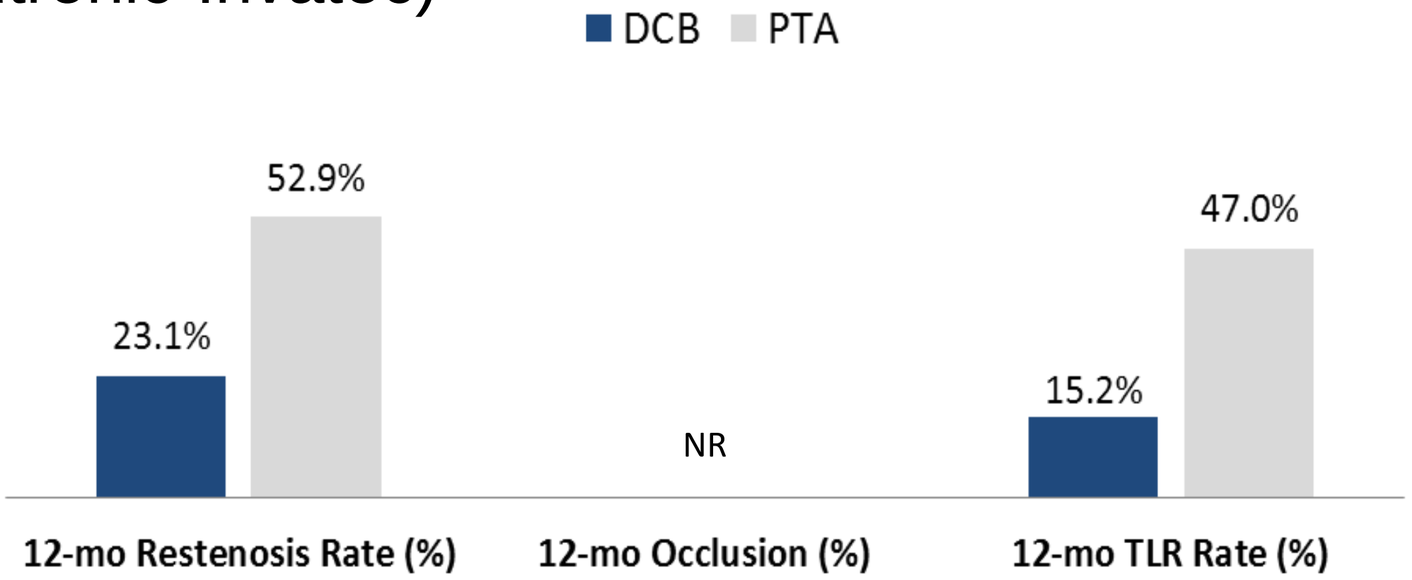


Figure 2. Kaplan–Meier analysis for survival free from target lesion revascularization (TLR) in both study groups. DEB indicates drug-eluting balloon; and PTA, percutaneous transluminal angioplasty.

Debellum – Still Promising

DEBELLUM (Fanelli, et al.)[1]

- Single-center, randomized (1:1 v PTA)
- N = 30 (BTK cohort)
- 7.5cm mean lesion length, 40% CTO (BTK cohort)
- IN.PACT Admiral [SFA] and IN.PACT Amphirion [BTK] (Medtronic-Invatec)



1. Fanelli F, et al. J Cardiovasc Surg 2014;55: 207-216. NR = not reported.

Drug-Eluting Balloon Versus Standard Balloon Angioplasty for Infrapopliteal Arterial Revascularization in Critical Limb Ischemia

12-Month Results From the IN.PACT DEEP Randomized Trial

Thomas Zeller, MD,* Iris Baumgartner, MD,† Dierk Scheinert, MD,‡ Marianne Brodmann, MD,§ Marc Bosiers, MD,‖ Antonio Micari, MD, PhD,¶ Patrick Peeters, MD, PhD,# Frank Vermassen, MD, PhD,** Mario Landini, MS,†† David B. Snead, PhD,†† K. Craig Kent, MD,‡‡ Krishna J. Rocha-Singh, MD,§§ IN.PACT DEEP Trial Investigators

JACC 2014

Prospective Randomized Independently adjudicated and Monitored trial of infrapopliteal therapy for critical limb ischemia

N=358 2:1 DCB v PTA

TABLE 3 Baseline Angiographic and Procedural Characteristics (ITT Population)

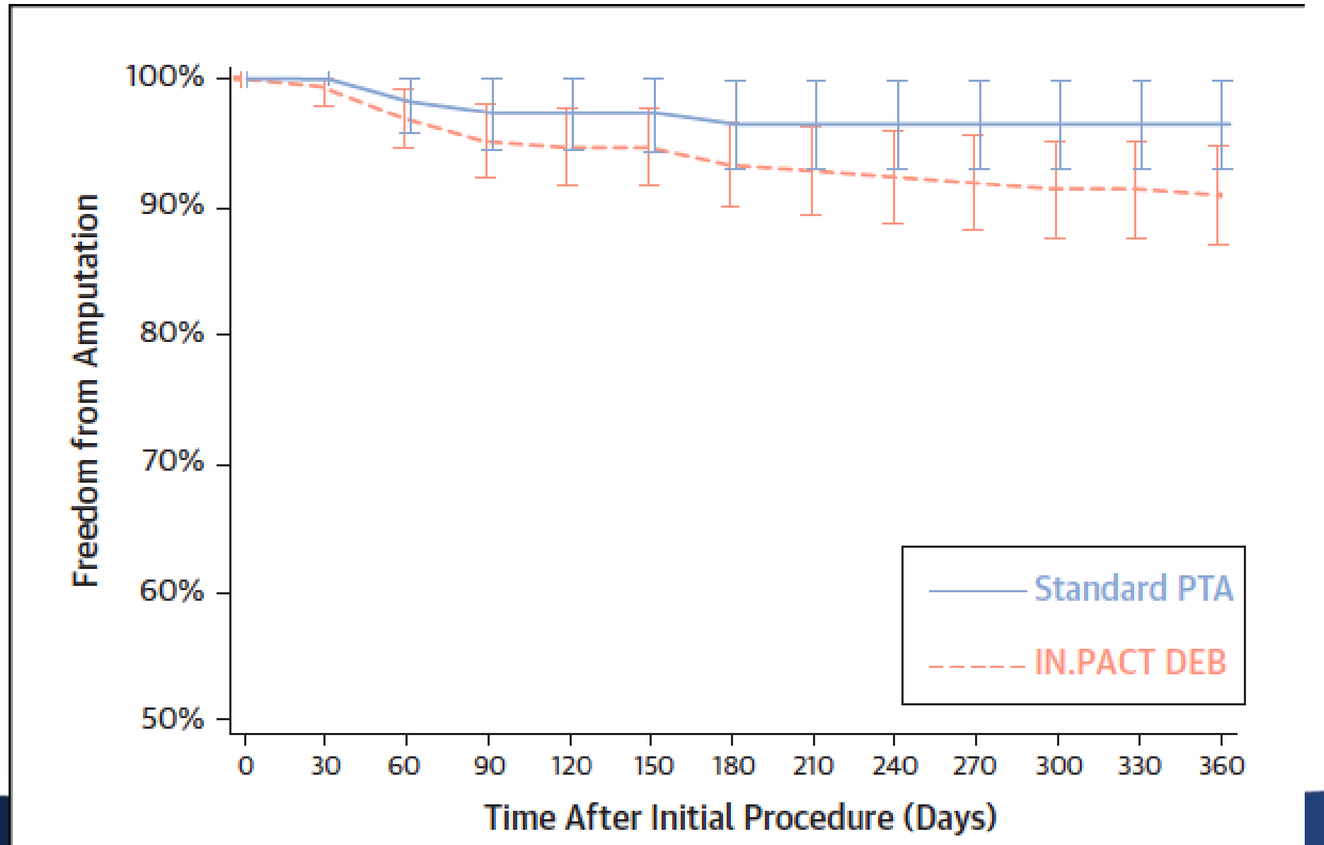
	IA-DEB	PTA	p Value
Lesion length, cm	10.15 ± 9.10	12.86 ± 9.46	0.002
Lesion length in angiography cohort, cm	5.91 ± 4.17	7.97 ± 7.46	0.060
Reference vessel diameter, mm	2.46 ± 0.69	2.41 ± 0.56	0.304
Total occlusions	38.6 (135/350)	45.9 (83/181)	0.114
Restenotic lesions	6.7 (24/359)	3.7 (7/189)	0.176
Severe calcium	13.7 (48/350)	10.5 (19/181)	0.336
% Diameter stenosis (pre-procedure)	83.9 ± 16.9	86.6 ± 15.7	0.078
% Diameter stenosis (post-procedure)	25.6 ± 14.8	28.0 ± 13.0	0.066

Real World Enrollment with Real World lesions being treated

JACC 2014

TABLE 4 12-Month Efficacy Endpoints

	IA-DEB	PTA	p Value
Late lumen loss,* mm	0.605 ± 0.775	0.616 ± 0.781	0.950
Binary restenosis*	41.0 (25/61)	35.5 (11/31)	0.609
Occlusion rate	11.5 (7/61)	16.1 (5/31)	0.531
Longitudinal restenosis†	62.7 ± 56.2	93.2 ± 60.8	0.167
Clinically driven TLR (AFS subjects)	9.2 (18/196)	13.1 (14/107)	0.291
Clinically driven TLR (all ITT subjects)	11.9 (27/226)	13.5 (15/111)	0.682



Paclitaxel-Coated Balloon in Infrapopliteal Arteries

12-Month Results From the BIOLUX P-II Randomized Trial (BIOTRONIK'S-First in Man study of the Passeo-18 LUX drug releasing PTA Balloon Catheter vs. the uncoated Passeo-18 PTA balloon catheter in subjects requiring revascularization of infrapopliteal arteries)

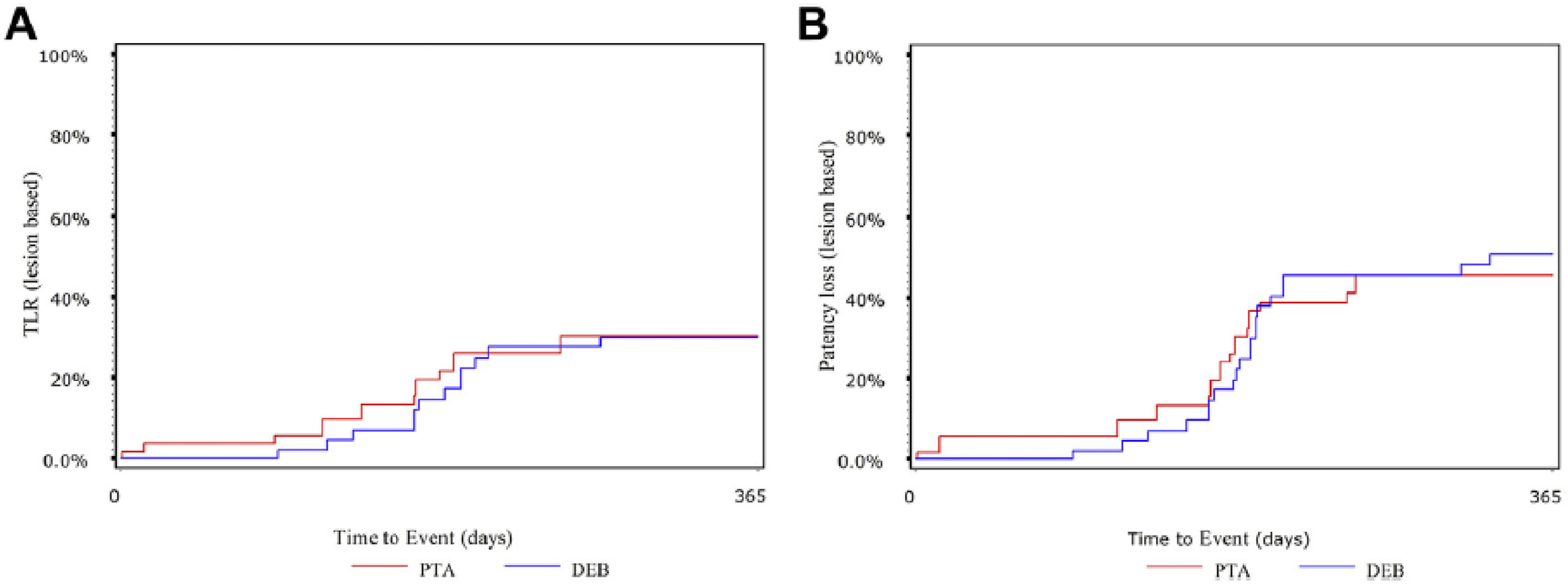
Thomas Zeller, MD,* Ulrich Beschorner, MD,† Ernst Pilger, MD,‡ Marc Bosiers, MD,§ Koen Deloose, MD,§ Patrick Peeters, MD,‖ Dierk Scheinert, MD, PhD,¶ Karl-Ludwig Schulte, MD, PhD,# Aljoscha Rastan, MD,* Marianne Brodmann, MD, PhD‡

JACC CI 2015

Lesion location			
Anterior tibial artery	24 (48.0)	25 (46.3)	
Posterior tibial artery	11 (22.0)	12 (22.2)	0.693
Peroneal artery	7 (14.0)	11 (20.4)	
Tibioperoneal trunk	5 (10.0)	2 (3.7)	
Other	3 (6.0)	4 (7.4)	
Calcification†			–
None	19 (55.9)	31 (81.6)	0.018
Mild	6 (17.6)	4 (10.5)	0.501
Moderate	1 (2.9)	0 (0.0)	0.472
Moderate/severe	3 (8.8)	1 (2.6)	0.338
Severe	5 (4.7)	2 (5.3)	0.243
Moderate to severe	9 (26.5)	3 (7.9)	0.056
Thrombus present	0 (0.0)	0 (0.0)	>0.999
Treated lesion length, mm	113.1 ± 88.1, 24–351	115.0 ± 86.9, 39–295	0.960
MLD, mm	0.63 ± 0.63, 0.0–1.78	0.62 ± 0.53, 0.0–1.64	0.986
RVD, mm	2.28 ± 0.54, 1.40–4.02	2.19 ± 0.57, 1.21–3.93	0.246
Stenosis pre-procedure	72.5 ± 25.4, 31–100	72.1± 23.2, 30–100	0.936

N=72
1:1 DCB v PTA

FIGURE 2 Course of Target Lesion Revascularization and Patency Loss Per Kaplan-Meier Estimates



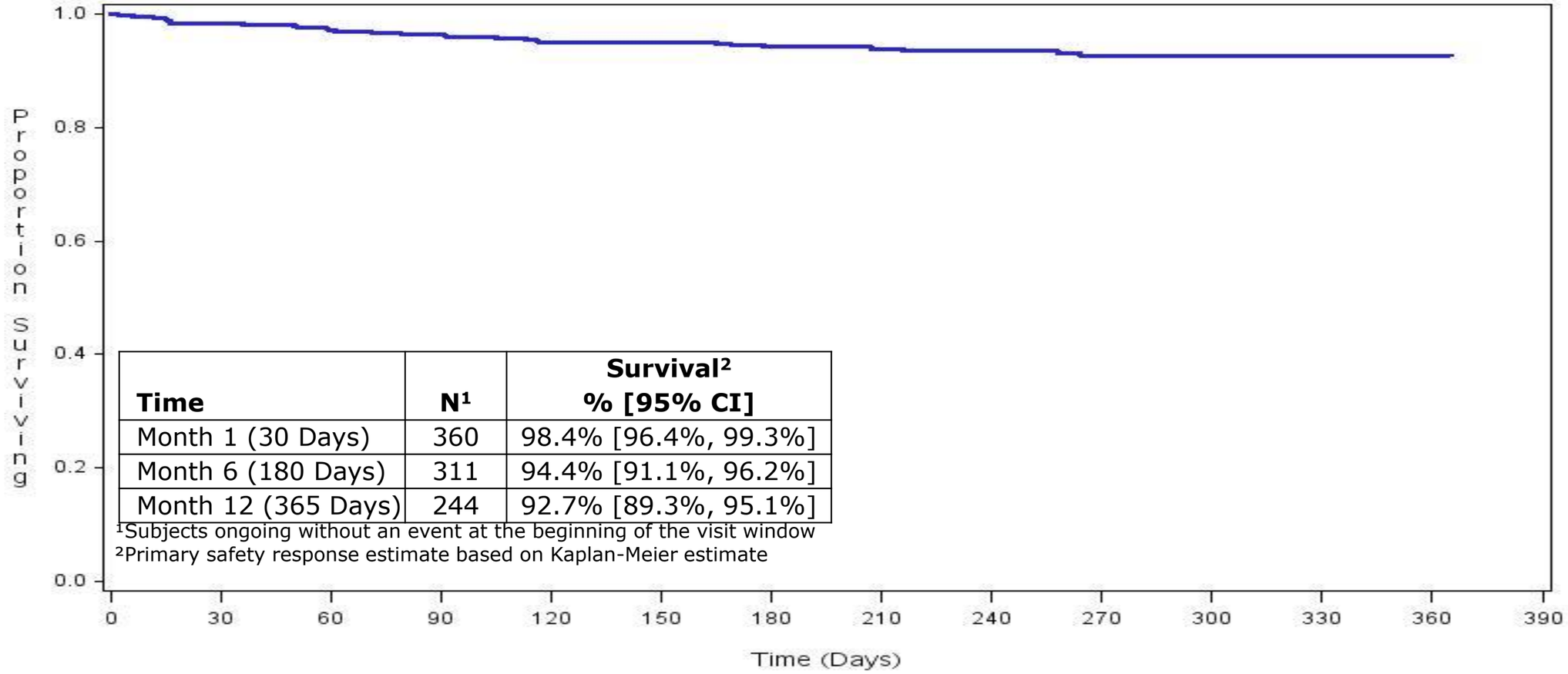
JACC CI 2015

Ongoing BTK DCB Studies

- Lutonix BTK RCT: prospective, multicenter, randomized (NCT01870401)[1]
  - Target enrollment = 1,000 subjects
  - Primary endpoints
    - FF BTK MALE + POD at 30d
    - Limb salvage at 6m
    - Primary patency at 6m
  - Target completion = September 2019
- Lutonix BTK Registry: prospective, multicenter, non-randomized (NCT02554266)[2]
  - Target enrollment = 500 subjects[3]
  - Primary endpoints
    - Freedom from death, above-knee amputation, or major reintervention at 30d
    - CD-TLR at 6m
  - Target completion = October 2019
- IN.PACT Admiral 014 BTK RCT: prospective, multicenter, randomized (NCT02963649)[4]
  - Target enrollment = 60 subjects (13 enrolled)
  - Primary endpoint defined as late lumen loss at 9m
  - Target completion = June 2020

1. Clinicaltrials.gov NCT01870401: FF BTK MALE + POD, freedom from below-the-knee major adverse limb event and perioperative death.
2. Clinicaltrials.gov NCT02554266: major reintervention defined as new bypass graft, jump/interposition graft revision, or thrombectomy/thrombolysis, of the index limb involving a below-the-knee artery.
3. Presented by Lichtenberg MKW, LINC Leipzig, Germany 2017.
4. Clinicaltrials.gov NCT02963649.

Lutonix Registry: Freedom from Primary Safety Events



Time	N[1]	Survival[2] % [95% CI]
Month 1 (30 Days)	360	98.4% [96.4%, 99.3%]
Month 6 (180 Days)	311	94.4% [91.1%, 96.2%]
Month 12 (365 Days)	244	92.7% [89.3%, 95.1%]

[1]Subjects ongoing without an event at the beginning of the visit window
[2]Primary safety response estimate based on Kaplan-Meier estimate

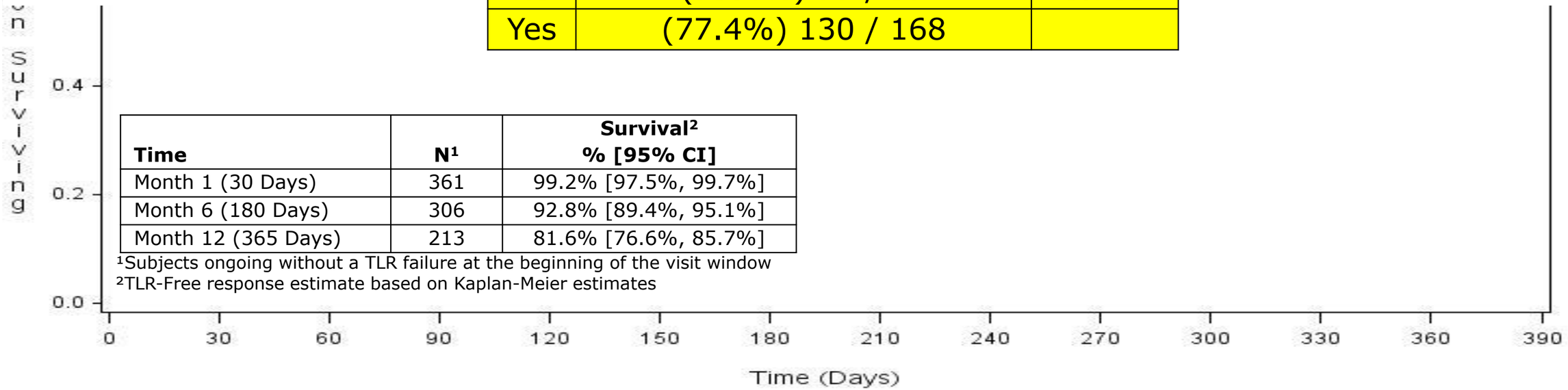
Freedom at 30-Days from the composite of all-cause death, above-ankle amputation or major re-intervention, i.e., new bypass graft, jump/interposition graft revision, or thrombectomy/thrombolysis of the index limb involving a below-the-knee artery.

Interim data, site reported, subject to change - For Investigational Use Only in the U.S.A

Courtesy: M. Lichtenberg

Freedom from TLR

Diabetics – 12 Month TLR Free		
No	(79.4%) 77 / 97	0.705
Yes	(77.4%) 130 / 168	



Time	N[1]	Survival[2] % [95% CI]
Month 1 (30 Days)	361	99.2% [97.5%, 99.7%]
Month 6 (180 Days)	306	92.8% [89.4%, 95.1%]
Month 12 (365 Days)	213	81.6% [76.6%, 85.7%]

[1]Subjects ongoing without a TLR failure at the beginning of the visit window
[2]TLR-Free response estimate based on Kaplan-Meier estimates

Interim data, site reported, subject to change - For Investigational Use Only in the U.S.A

Courtesy: M. Lichtenberg

12 Months Conclusions

- Only BTK Registry Multi Center On-going Study
- Freedom from Re-intervention For Distal Embolization - 99.7%
- Freedom from TLR - 81.6%
- Low Amputation Rate - 5.4%
- 61% Improvement by ≥3 Rutherford Classifications
- Diabetics - No Difference in Freedom From TLR at 6 Months

Courtesy: M. Lichtenberg

Interim data, site reported, subject to change - For Investigational Use Only in the U.S.A

Lutonix® 014 Drug Coated Balloon IDE BTK Trial

OBJECTIVE	To demonstrate the superior efficacy and non-inferior safety of the Lutonix DCB by direct comparison to standard PTA catheter for treatment of stenosis or occlusion of below-the-knee arteries.
STUDY DESIGN	Prospective, Multicenter, Single Blind, Randomized, Safety and Efficacy
STUDY DEVICE	Lutonix® 0.014" OTW Drug Coated PTA Dilatation Catheter (Lutonix DCB Catheter)
RANDOMIZATION	2:1 Lutonix DCB to standard PTA
PRIMARY ENDPOINTS	Safety at 30 days Limb salvage & primary patency at 6 months
NUMBER OF SUBJECTS/SITES	442 randomized subjects at 49 global sites
FOLLOW-UP	Clinical: 1, 6, 12, 24, and 36 Months Duplex Ultrasound (DUS): 1, 6,12, 24, & 36 months

Interim data, site reported, subject to change - For Investigational Use Only in the U.S.

Courtesy: J. Mustapha

Primary Endpoints

SAFETY

Freedom from Major Adverse Limb Events (MALE) & All-Cause Perioperative Death (POD) at 30 Days

★ Amputation (above ankle)

★ Major re-intervention

- **New bypass graft**
- **Jump/Interposition graft revision**
- **Thrombectomy/Thrombolysis**

EFFICACY

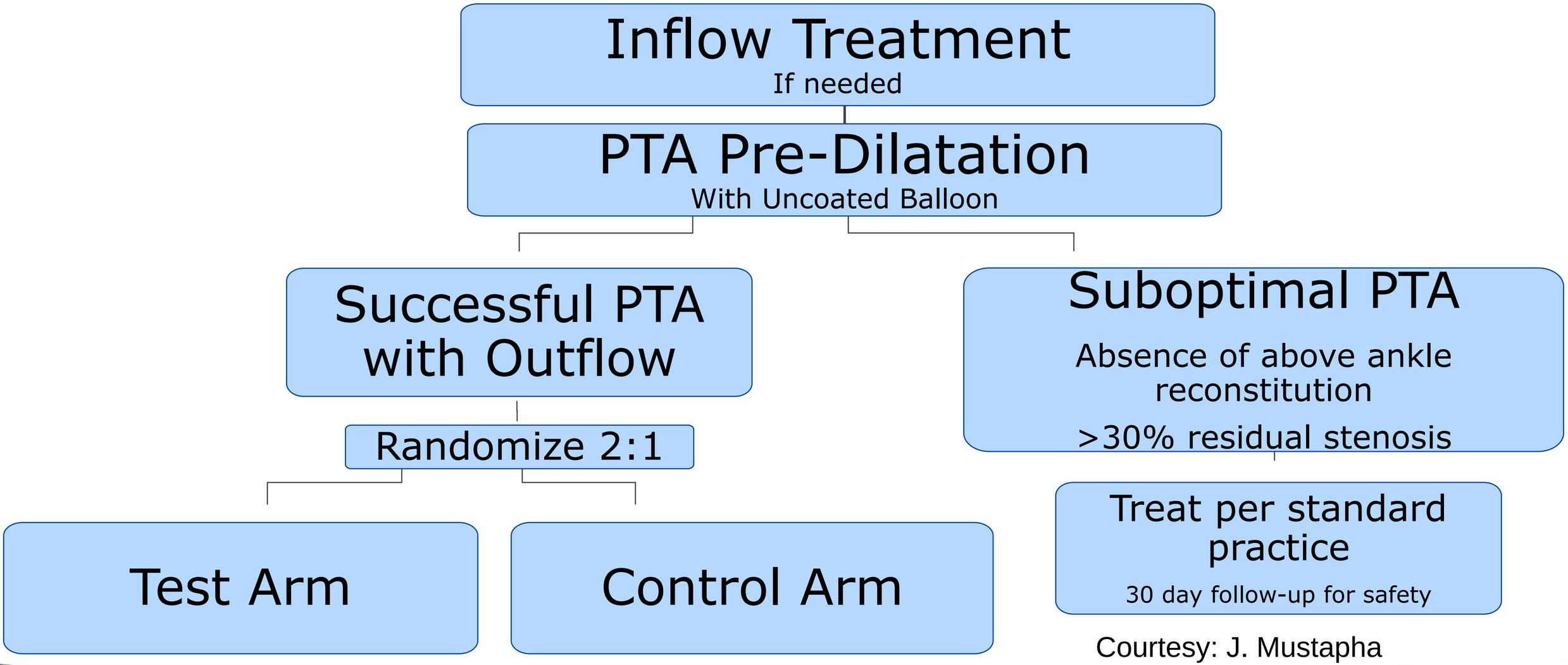
Composite of Limb Salvage and Primary Patency at 6 Months

Defined as freedom from the composite of above ankle amputation, target vessel occlusion, and clinically-driven target lesion re-intervention. ★

Interim data, site reported, subject to change - For Investigational Use Only in the U.S.

Courtesy: J. Mustapha

Study Flowchart



Courtesy: J. Mustapha

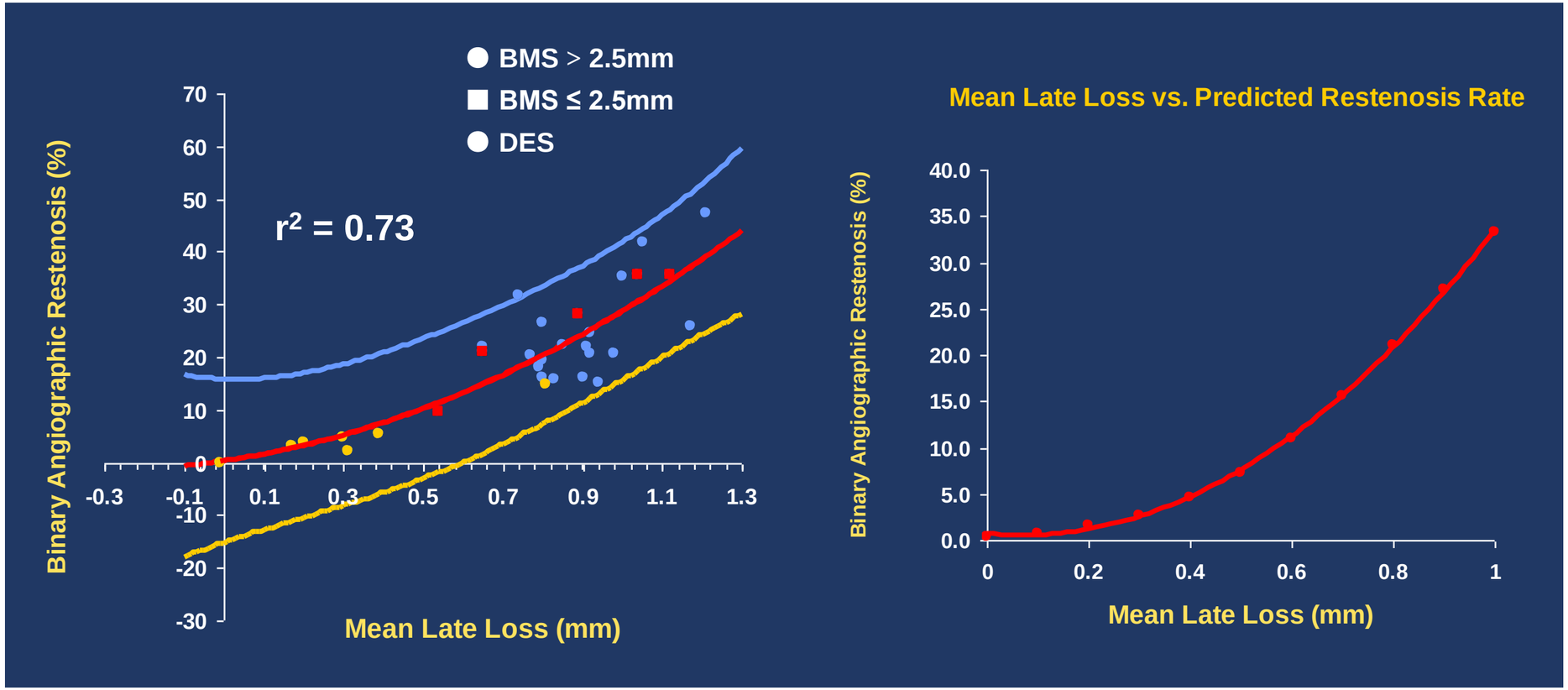
Current Status of Lutonix 014 BTK IDE Study

- 49 Active Global Sites (30 US, 13 Europe/Canada, 5 Japan, 1 Australia)
- 442 Randomized Subjects (Completed Enrollment)
- 17 subjects with a Major Amputation (3.8%)
- The Data Monitoring Committee (DMC) has met 16 times and unanimously recommended continuation of the study with no modifications.

Courtesy: J. Mustapha

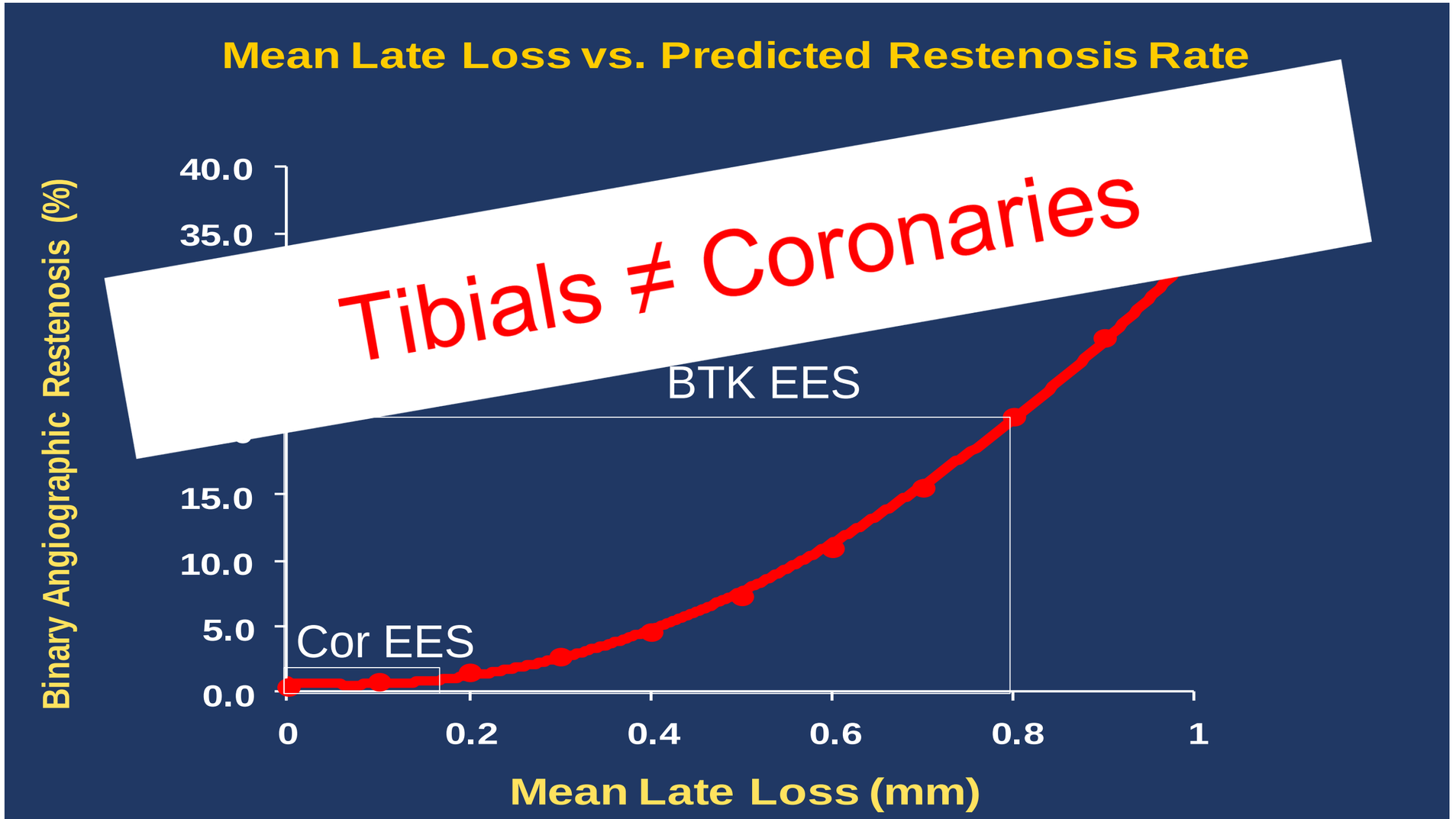
Interim data, site reported, subject to change - For Investigational Use Only in the U.S.

Late Loss Predicts Restenosis Rate for Coronary DES



Nearly linear relationship between late loss and binary restenosis.

Late Loss Predicts Restenosis Rate for Coronary DES but the setpoints for BTK DES are different!



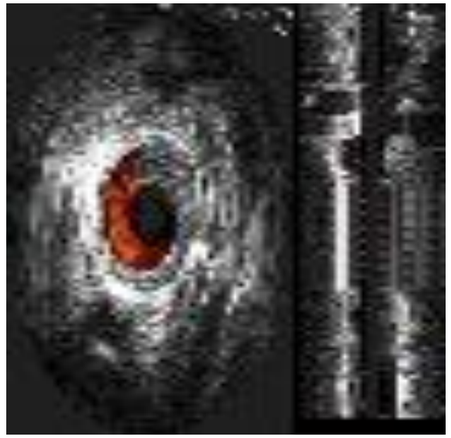
Adapted from Mauri et al. *Circulation*. 2005:111:3435-3442.

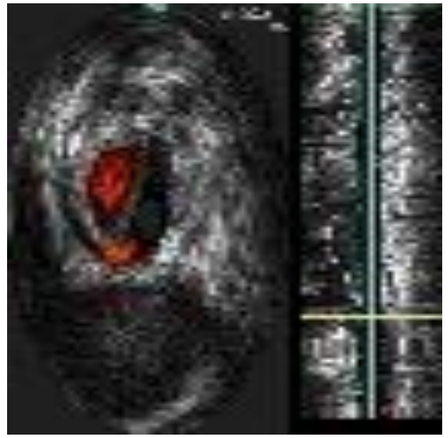
Spirit III, Stone GW, et al. JAMA 2008

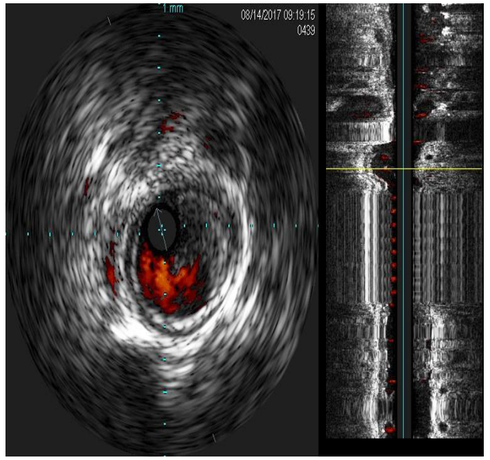
Destiny, Bosiers, et al. JVS 2012

What Are We Missing?

- Calcium is a problem
  - More of it in the tibials
  - Different location
- Are we planning appropriately
  - Vessel sizing
    - Should we be using QVA or Doppler?
    - Intravascular ultrasound
- Appropriate end-points
- Do we have the right drug?







In summary

- Drug Coated Balloons have failed to demonstrate clinical benefit despite improved angiographic outcomes in BTK lesions
- Ongoing large RCT should help better elucidate the potential value (or lack of value) for DCB
- Possible changes in the drug, dose or vessel prep could influence clinical outcomes
- Drug eluting balloon expandable stents have several randomized trials showing clinical benefit
- Drug eluting self expanding stents are being studied in a rigorous RCT