Below the knee DCB
Where are we and what do we know?

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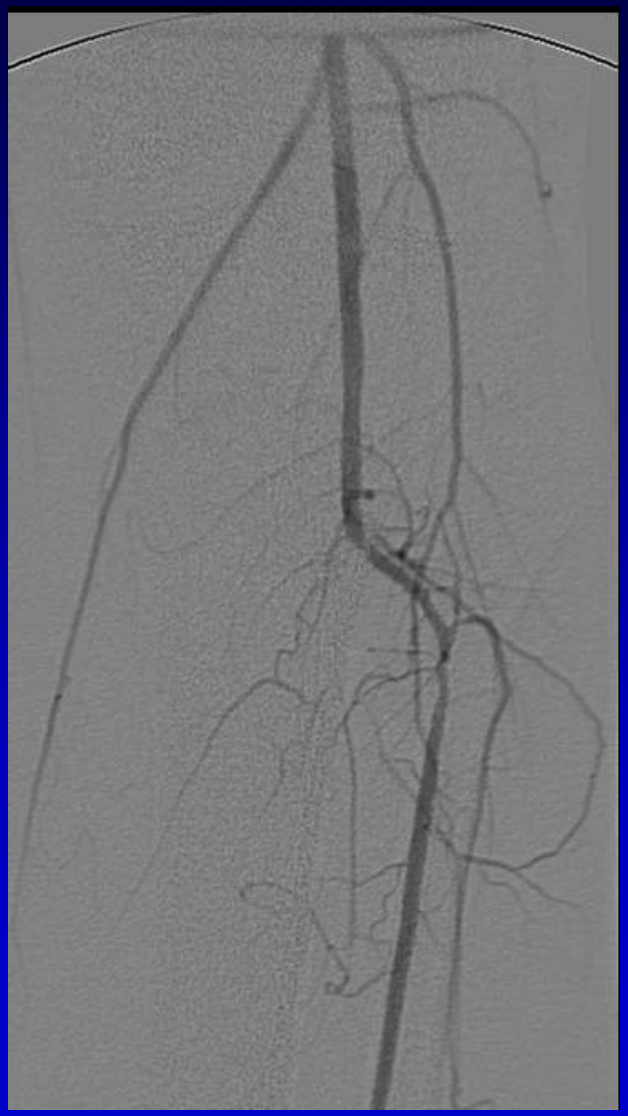
Disclosure Statement of Financial Interest

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

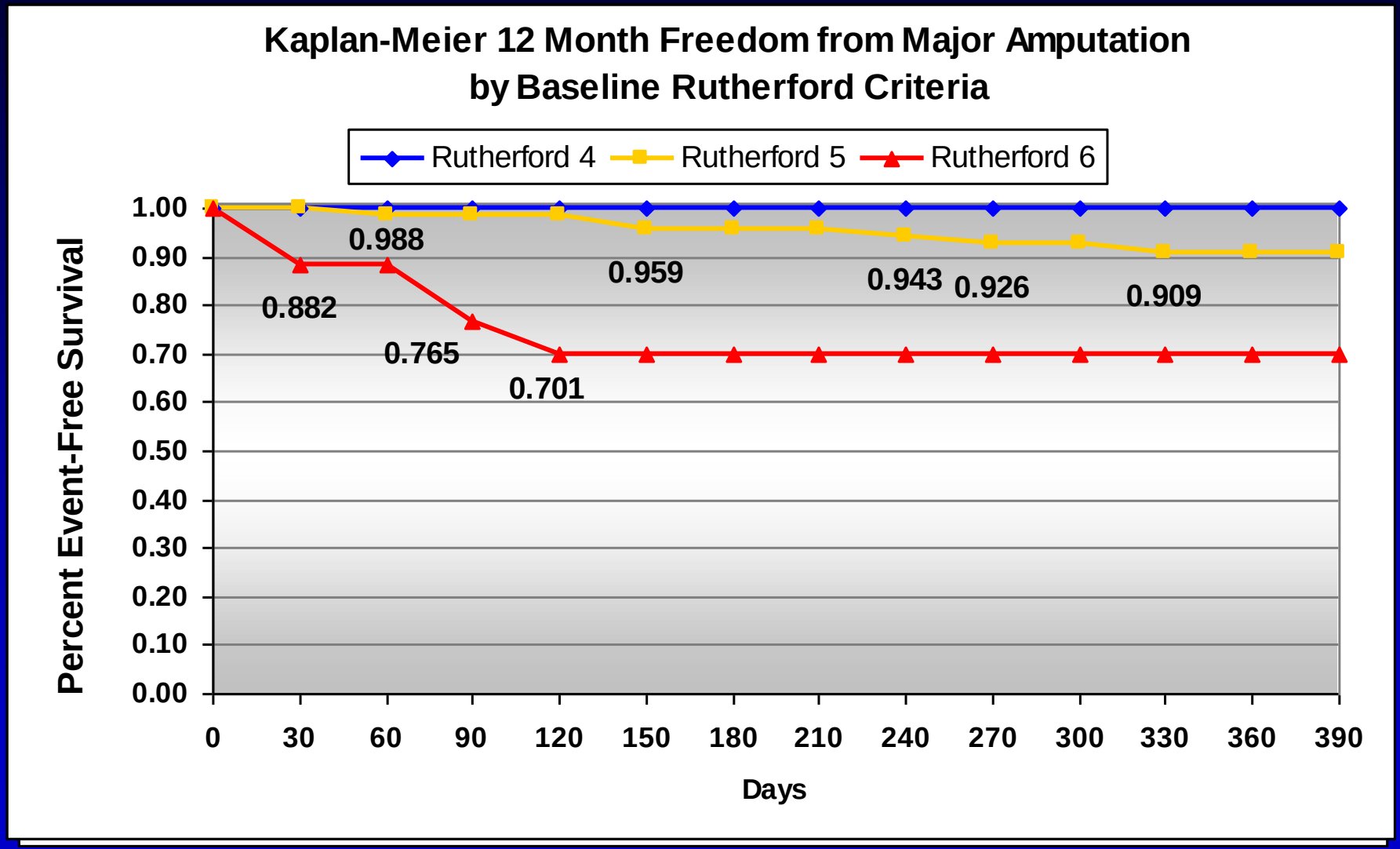
Affiliation/Financial Relationship	Company
• Grant/Research Support	• Abbott, Covidien/Medtronic
• Consulting (non-compensated)	• Covidien/Medtronic, Boston Scientific, Abbott
• Major Stock Shareholder/Equity	• Arsenal, Primacea, TissueGen, CV Ingenuity, Spirox, Scion Cardiovascular, Syntervention, Essential Medical
• Royalty Income	• None
• Ownership/Founder	• Innovation Vascular Partners, Consulting
• Intellectual Property Rights	• None
• Other Financial Benefit	• None

Infra-popliteal revascularization

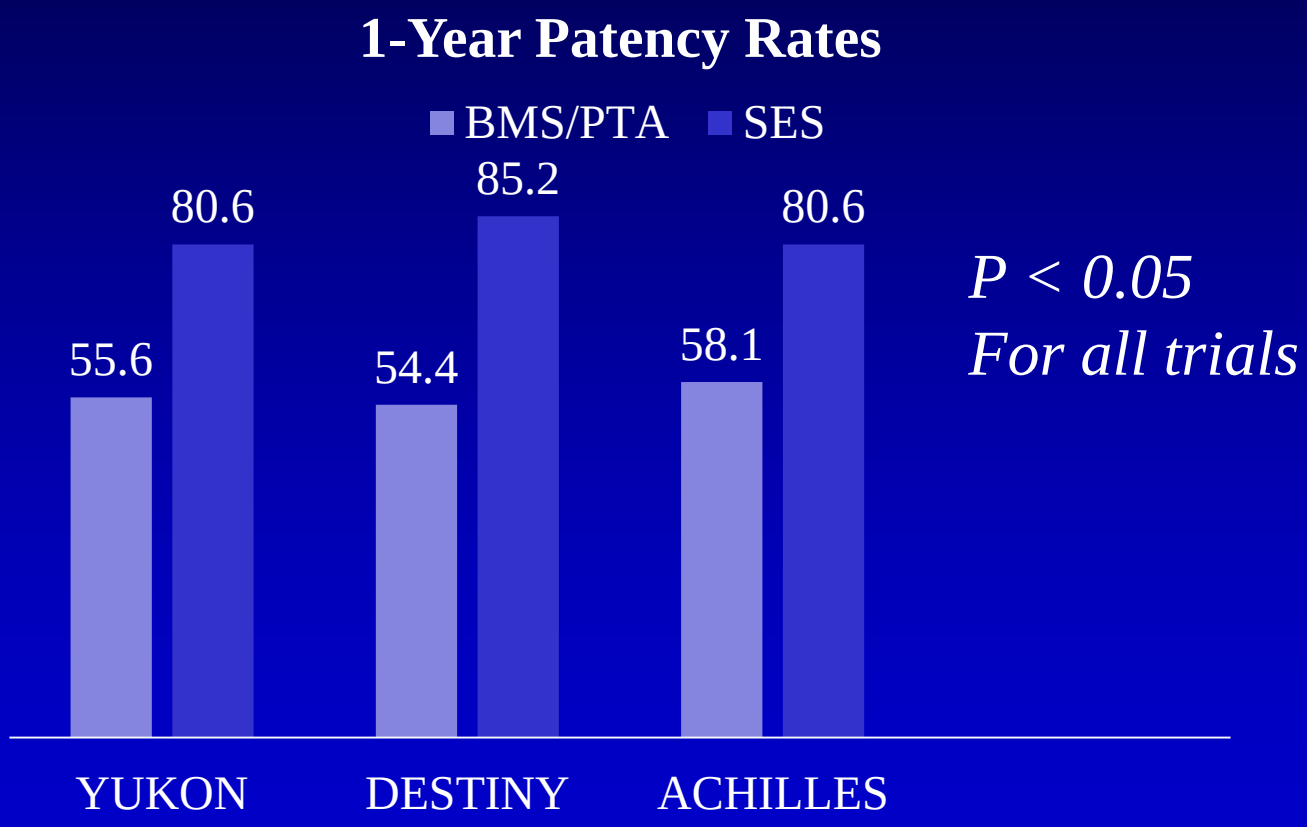
- Short vessel
  - popliteal
- Long vessels
  - tibials
- Generally angled proximally and distally
- Usually calcified
- Total occlusions
- Generally critical limb
  - Outcomes based on AFS



EXCEL TLR


Kaplan-Meier 12 Month Freedom from Major Amputation
by Baseline Rutherford Criteria
Rutherford 4
Rutherford 5
Rutherford 6
Percent Event-Free Survival
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
0.882
0.988
0.765
0.701
0.959
0.943
0.926
0.909
0
30
60
90
120
150
180
210
240
270
300
330
360
390
Days

YUKON, DESTINY & ACHILLES Trials (n=515)
Primary Patency



P < 0.05
For all trials

Rastan et al. EHJ 2011
Scheinert et al. LINC 2011
Bosiers et al. JVS 2011

LIBERTY 360

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-
-
-
  - Angiographic
  - Duplex Ultrasound
  - 6-minute walk test
  - Health economics

LIBERTY 30-day outcomes:

	Rutherford Class		
	R2-3	**R4-5**	**R6**
Freedom from MAE (30-Day)	99.0%	95.7%	90.7%
Major Amputation	100%	98.8%	95.8%
Target Vessel Revascularization (TVR)	99.4%	96.9%	97.9%
Death	99.6%	99.7%	95.9%

Quality of life also improved from baseline across all Rutherford classes.

DEFINITIVE LE

Subgroup	Claudicants (n=743)		CLI (n=279)	
	Patency (PSVR ≤ 2.4)	Lesion Length (cm)	Patency (PSVR ≤ 2.4)	Lesion Length (cm)
All (n=1022)	78%	7.5	71%	7.2
Lesion type				
Stenoses (n=806)	81%	6.7	73%	5.8
Occlusions (n=211)	64%	11.1	66%	10.3
Lesion Location				
SFA (n=671)	75%	8.1	68%	8.6
Popliteal (n=162)	77%	6.0	68%	5.4
Infrapopliteal (n=189)	90%	5.5	78%	6.0
Limb Salvage	95%			

Primary IN.PACT DEEP Outcomes

Primary Efficacy	DEB	PTA	*p*
12-month LLL (mm) [1]	0.61 ± 0.78	0.62 ± 0.78	*0.950*
12-month CD-TLR [2]	9.2% (18/196)	13.1% (14/107)	*0.291*

Primary Safety	DEB	PTA	*p*
6-month Death Major Amputation or CD TLR	17.7% (41/232)	15.8% (18/114)	*0.021* (non-inferiority) *0.662 (superiority)*

1. *Angio Cohort, Corelab adjudicated. Angiogaphic Imaging 12-month FU compliance = 70.9% (DEB) vs. 71.4% (PTA)*
2. *Clinically driven TLR of the target lesion in the (major) amputation free surviving subjects at 12 months. "Clinically driven TLR" defined as any TLR of the target lesion associated with: a) deterioration of RC and / or b) Increase in size of pre-existing wounds and / or c) occurrence of a new wound(s), with b) and c) adjudicated by the Wound Healing Core lab*

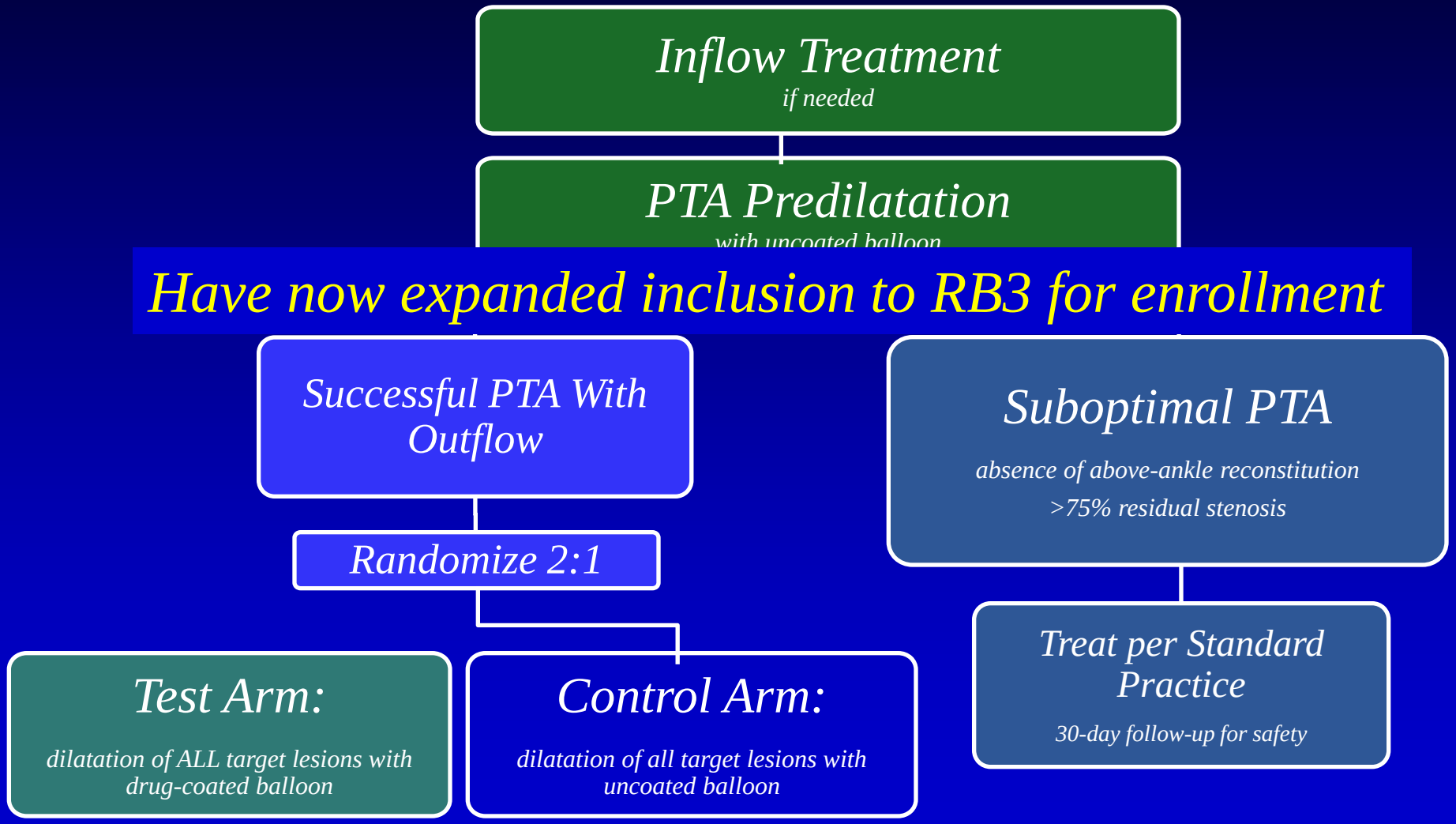
Angio Cohort Outcomes

12-month Outcomes [1]	DEB	PTA	*p*
Mean Lesion Length (mm±SD)	59.1 ± 41.7	79.7 ± 74.6	*0.060*
Binary (50%) Rest. Rate (%)	41.0% (25/61)	35.5% (11/31)	*0.609*
Occlusion Rate (%)	11.5% (7/61)	16.1% (5/31)	*0.531*
Longitudinal Restenosis (%) [2]	62.7 ± 56.2	93.2 ± 60.8	*0.167*

Revalidated Lumen Loss [3]	DEB	PTA	*p*
12-month LLL (mm, mean ± SD)	0.51 ± 0.66	0.60 ± 0.97	*0.654*

1. *Angio Cohort, Corelab adjudicated. Angiogaphic Imaging 12-month FU compliance = 70.9% (DEB) vs. 71.4% (PTA)*
2. *Mean % of stenosis length vs. treated lesion length± SD (Angiographic Cohort, ITT)*
3. *As evaluated by additional angiographic core laboratory (Beth Israel Deconess Medical Center, Boston, MA) to confirm earlier analysis*

LEVANT BTK


Inflow Treatment
if needed
PTA Predilatation
with uncoated balloon
Have now expanded inclusion to RB3 for enrollment
Successful PTA With Outflow
Suboptimal PTA
absence of above-ankle reconstitution
>75% residual stenosis
Randomize 2:1
Treat per Standard Practice
30-day follow-up for safety
Test Arm:
dilatation of ALL target lesions with drug-coated balloon
Control Arm:
dilatation of all target lesions with uncoated balloon

Current Status of Lutonix 014 BTK IDE Study

- *48 Active Sites*
- *382 Randomized Subjects*
  - *287 have completed 6 month follow-up*
  - *222 have completed 12 month follow-up*
- *12 subjects with a Major Amputation (3.2%)*
- *The Data Monitoring Committee (DMC) has met 11 times and unanimously recommended continuation of the study with no modifications.*

Information current as of 03.06.2017

BIOLUX

- RCT 1:1 Paseo DCB to Paseo PTA
  - 72 patients
- Endpoints 30 day, 6 month (angio) and 12 MAE
- 6 month patency DCB 82.9% vs PTA 73.9% (p=NS)

Zeller T, et al JACC Cardio Interv 2015 Oct 8 (12) 1614-22

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

Time-To-Event Estimates of Clinical Outcomes at Follow-Up

365 Days	DEB	PTA	p Value
MAE	13 (41.1)	14 (39.1)	0.957
Death	3 (9.4)	2 (6.0)	0.575
In CLI patients only	2 (8.6)	2 (7.9)	0.917
Amputation target extremity	8 (23.7)	9 (25.7)	0.988
Major	1 (3.3)	2 (5.6)	0.631
In CLI patients only	1 (4.3)	2 (7.1)	0.696
TLR			
Lesion based	12 (30.1)	15 (30.6)	0.805
Subject based	10 (34.9)	10 (30.0)	0.817
Clinically driven	9 (31.3)	9 (26.9)	0.805
TLR, subject based	5 (16.8)	6 (17.5)	0.881
TVR	5 (16.8)	6 (17.5)	0.881
Target lesion thrombosis	0 (0.0)	1 (2.8)	>0.999
Target vessel thrombosis	0 (0.0)	1 (2.8)	>0.999
Patency loss (lesion based)*	7 (17.1)	13 (26.1)	0.298
	20 (50.8)	22 (45.6)	0.908

180 Days
MAE 8 (24.8) 9 (25.0) 0.944
Death 2 (6.1) 1 (2.9) 0.499
In CLI patients only 1 (4.0) 1 (3.7) 0.921
Amputation target extremity 8 (23.7) 7 (19.6) 0.619
Major 1 (3.3) 2 (5.6) 0.631
TLR lesion 6 (14.6) 10 (19.7) 0.460
Subject based 5 (16.8) 6 (17.5) 0.881
TVR 5 (16.8) 6 (17.5) 0.881
Target lesion thrombosis 0 (0.0) 1 (2.8) >0.999
Patency loss (lesion based)* 7 (17.1) 13 (26.1) 0.298

IDEAS

- Small RCT DES vs DCB
- Primary endpoint angio patency at 6 months
- DES PP 28% vs DCB 42%

TABLE 3 Angiographic and Clinical Outcomes: QVA and Outcome Measures at 6 Months (ITT Analysis)

	DES Group	PCB Group	p Value
QVA analysis			
Post-procedure stenosis, %	9.6 ± 2.2	24.8 ± 3.5	<0.0001
6-month vessel stenosis, %	50.6 ± 6.6	54.3 ± 8.1	0.73
Late lumen loss, mm	1.35 ± 0.2	1.15 ± 0.3	0.62
Length of >50% restenosis, cm	3.6 ± 1.5	4.3 ± 1.6	0.16
Outcome measures			
Binary restenosis >50%	7/25 (28)	11/19 (57.9)	0.0457
Positive remodelling, late lumen loss <0 mm	0/25 (0)	3/19 (15.8)	0.07
Target lesion revascularization	2/26 (7.7)	3/22 (13.6)	0.65
Rutherford class at 6 months	1 (1, 2.75)	1 (1, 3.5)	0.87

Values are mean ± SD, n/n (%), or median (interquartile range).

Siablis D, et al JACC Cardio Interv 2014 Sep 7 (9): 1048-56

Future trials

- BSC Ranger BTK
  - FDA approaved IDE Fem-pop study
- Spectranetics Stellarx BTK
- Interest in limus driven therapy

Possible Reasons for Failed Trials for DCB in BTK

- Drug does not work in BTK lesions
- Insufficient drug dosing in BTK studies
- Improper DCB sizing or insufficient duration of therapy
- PTX delays wound healing
- Loss of drug due to transit time
- Calcification impedes drug delivery
- Recoil effect in small vessels >>>Drug effect
- Endpoints have not been validated
- Heterogeneity of treatment in multi-center studies
  - Procedural differences
  - Differences in post-procedural wound care

Areas For Improvement

- Vessel preparation
- Improved balloon platform for optimal drug delivery
- Optimal Drug Dosing
- Optimal Drug Application
  - Crystalline>>Amorphous??
  - Nanoparticles??
- Appropriate trial design
  - Primary Endpoint - Patency vs Wound healing?
  - Patency easier to measure and reflects device performance
  - Wound healing is true desired outcome, but influenced by several factors not related to device being studie=d

What should we choose?

- All interventions afford AFS in short focal lesions
  - BMS primary patency poor
  - Focal DES excellent primary patency compared with BMS
  - Non-stent technologies
    - Directional atherectomy (DEFINITIVE LE) reported outcomes for popliteal and infra-popliteal disease in both claudicants and/or CLI
    - LIBERTY forthcoming
- DCB (IN-Pact DEEP)failed in largest trial for below knee use
  - Principal studies using DCB still may be appealing but given the data?
- Current review of data supports revascularization for infra-popliteal disease though choice is at discretion
  - All DCB BTK data remain mired in the definitions and endpoints
  - Till this is well defined and accepted, seems PTA alone is best option
- Combined therapies for longer lesions seem appealing though currently untested