How far can we go with DCB's
Is there a role for lithoplasty or atherectomy?

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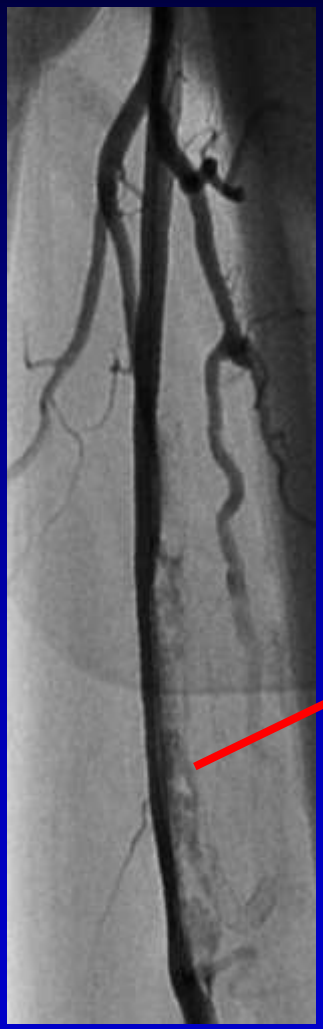
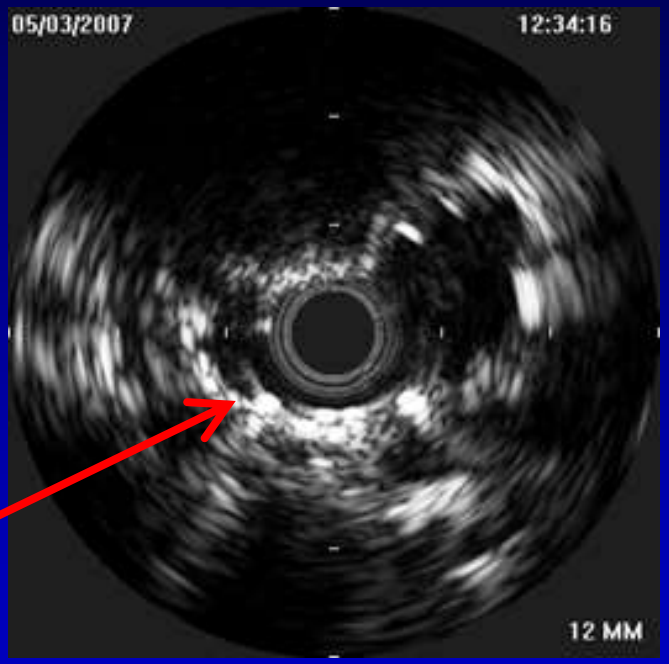
Disclosure Statement of Financial Interest

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
• Intellectual Property Rights	• None
• Other Financial Benefit	• None

Shortcoming of SFA-Stents



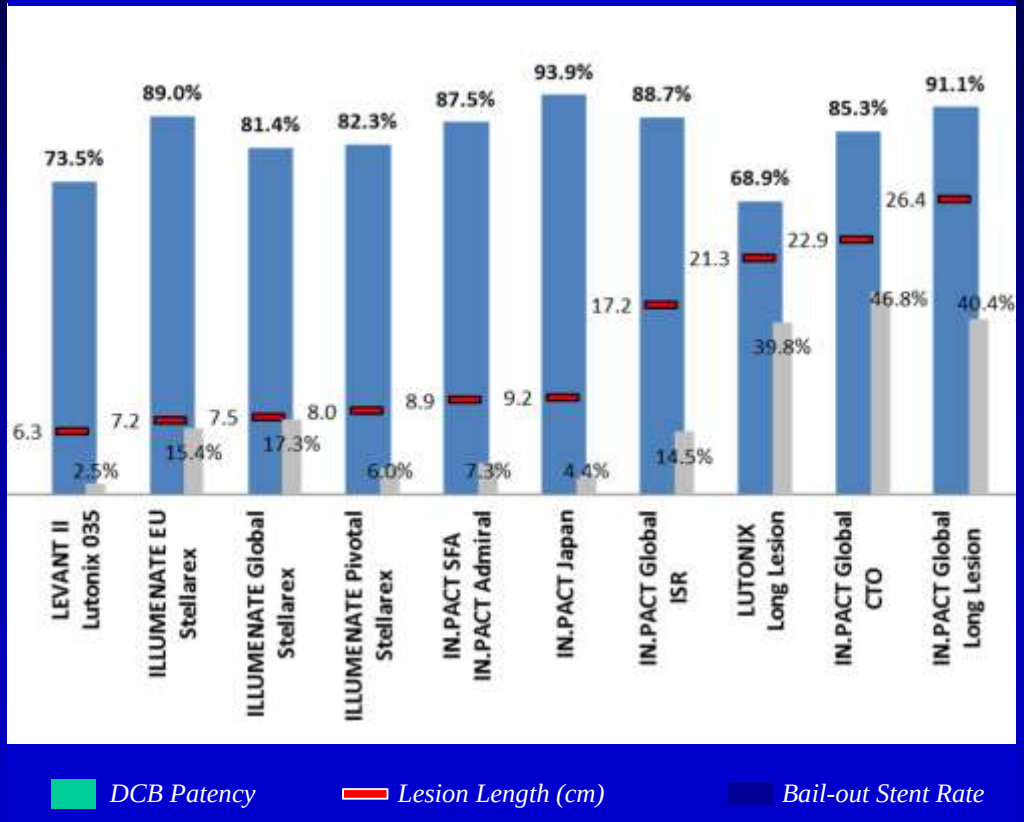


Insufficient radial strength in calcified lesions

DCB Data Synopsis

- DCBs demonstrate safety and effectiveness in RCTs and registries
- DCB use in real-world registries enrolling more complex disease is associated with increased provisional stenting

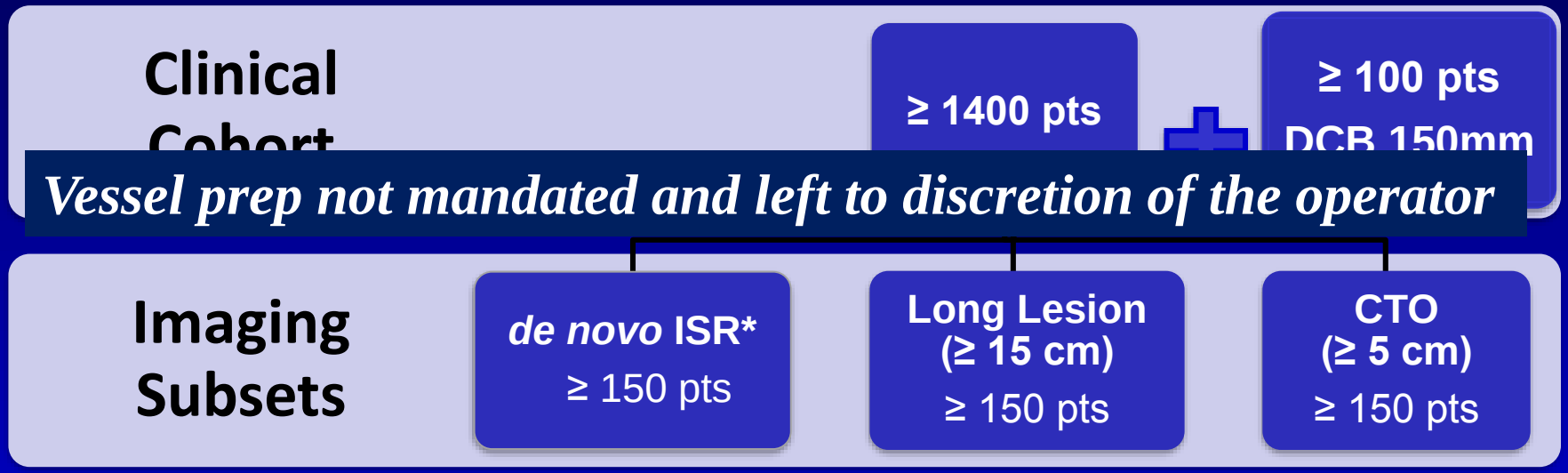
12-mo Primary Patency Rates
[and mean lesion lengths (cm); Core Lab-Adjudicated]



Patient demographics, lesion morphologies, patency definitions, and follow-up vary across trials.

1. Rosenfield K, et al. New Engl J Med 373:145-53 (2015).
2. Presented by Brodmann M, AMP, Chicago, US 2016.
3. Presented by Zeller T, LINC, Leipzig, Germany 2017.
4. Presented by Lyden S, TCT Washington DC, US 2016.
5. IN.PACT™ Admiral Instructions for Use, M052624T001_Rev1F_EN, Figure 10.
6. MDT-2113, IN.PACT *Japan*, presented by Iida O, LINC, Leipzig, Germany 2017.
7. Presented by Brodmann M, VIVA Las Vegas, US 2015. * 14.5% reflects provisional stent rate during DCB treatment of 100% in-stent restenosis cohort.
8. *Lutonix™ 035 Instructions for Use, BAW 1387400r3 Section 10.5.*
9. Presented by Tepe G, Charing Cross London, 2016.
10. Presented by Scheinert D, EuroPCR Paris, 2015.

IN.PACT Global Study Patient Cohorts



1538 patients enrolled

*ISR is not an approved indication in the US

IN.PACT Global Long Lesion Imaging Cohort: Lesion/Procedural Characteristics

Lesions (N)	164
Lesion Type: de novo restenotic (no ISR) ISR	 83.2% (134/161) 16.8% (27/161) 0.0% (0/161)
Lesion Length	**26.40 ± 8.61 cm**
Total Occlusions	60.4% (99/164)
Calcification Severe	71.8% (117/163) 19.6% (32/163)
RVD (mm)	4.594 ± 0.819
Diameter Stenosis (pre-treatment)	90.9% ± 14.2
Dissections: 0	37.9% (61/161)
A-C	47.2% (76/161)
D-F	14.9% (24/161)

Device Success [1]	99.5% (442/444)
Procedure Success [2]	99.4% (155/156)
Clinical Success [3]	99.4% (155/156)
Pre-dilatation	89.8% (141/157)
Post-dilatation	39.1% (61/156)
Provisional Stent - LL 15-25 cm: - LL > 25 cm:	40.4% (63/156) 33.3% (33/99) 52.6% (30/57)

1. *Device success: successful delivery, inflation, deflation and retrieval of the intact study balloon device without burst below the RBP*
2. *Procedure success: residual stenosis of ≤ 50% (non-stented subjects) or ≤ 30% (stented subjects) by core lab (if core lab was not available then the site reported estimate was used)*
3. *Clinical success: procedural success without procedural complications (death, major target limb amputation, thrombosis of the target lesion, or TVR) prior to discharge*

Schienert, D EuroPCR 2015 presentation

- Given that we treat lesions far and away more severe, calcified and longer than any pivotal trial
- We must answer the question is there a need for vessel preparation in anticipation of DCB?
- Critically this answer is elusive given the data

Clinical Limitations & Unmet Needs

Calcium as a Barrier

Calcium Limits Vessel Expansion[1]

Significant difference in vessel compliance leads to overstretch in non-diseased tissue causing dissections, recoil, excessive injury, and poor outcomes

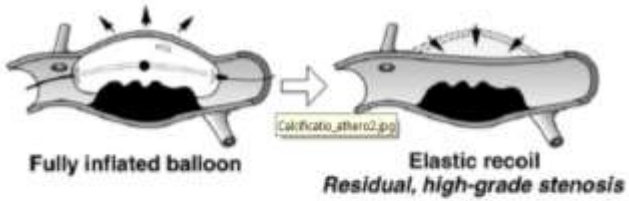
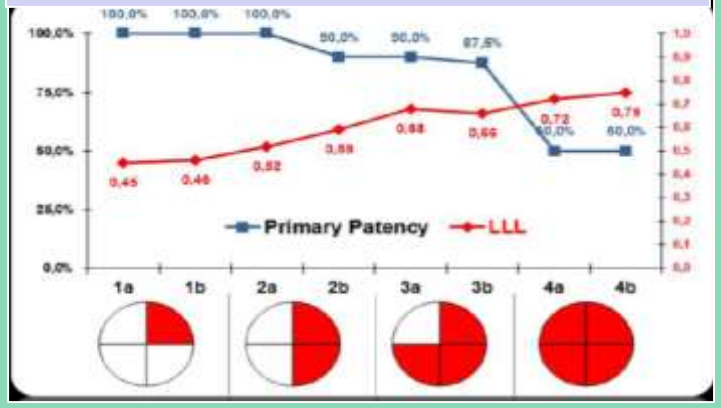


Figure 12.1. Elastic Recoil After PTCA of Calcified Lesions

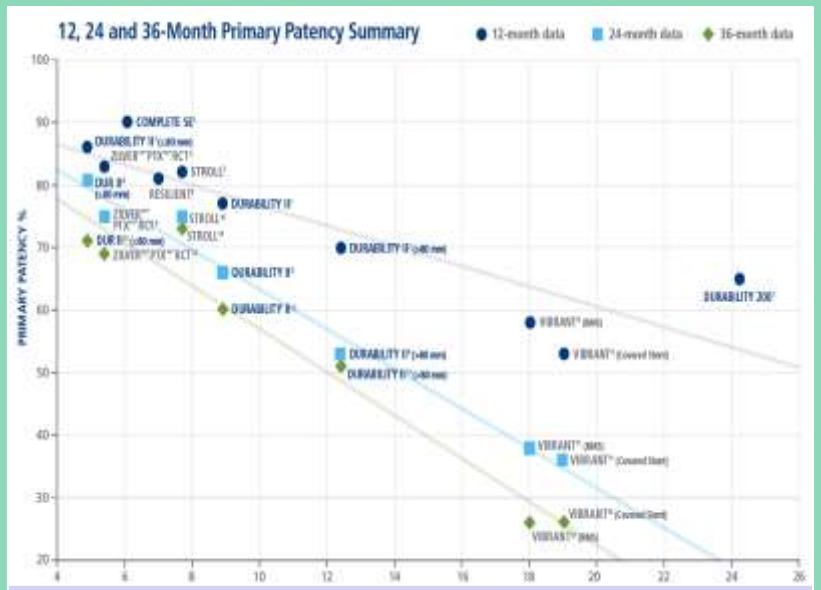
Rather than cracking the hard, calcified atheroma, PTCA causes stretching of the contralateral plaque-free wall segment and ineffective dilatation.

Freed MS, Safian RD; Manual of Interventional Cardiology, Ch. 12, 245-254

Calcium May Limit Drug Effect[2]



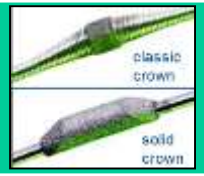
Longer Lesion Length



Increased lesion length is an independent predictor of decreased patency[5].

[1]Freed MS, Manual of Interventional Cardiology, [2]Fanelli DEBELLUM, [3]Laird, CCI, June 2010, [4]SMART Control IFU, [5]Matusumura, DURABILITY IIJVS, July 2013, [6]Davaine, European Journal of Vascular and Endovascular Surgery 44 (2012)

Atherectomy Devices

	Jetstream™ Atherectomy System (Boston Scientific)	Peripheral Rotablator™ Rotational Atherectomy System (Boston Scientific)	Diamondback 360™, Stealth 360™ Atherectomy System (Cardiovascular Systems, Inc)	SilverHawk™, TurboHawk™ Plaque Excision System (Covidien)	Turbo-Elite™ Laser Atherectomy Catheter (Spectranetics)
					
Front-Cutting	✓	✓			N/A
Differential Cutting	✓	✓	✓		N/A
Active Aspiration	✓				
Concentric Lumens	✓	✓			
Lesion Morphology:					
Calcium	✓	✓	✓	✓	✓
Soft/Fibrotic Plaque	✓			✓	✓
Thrombus	✓ (indicated for thrombectomy and atherectomy)				✓

Sources: Endovascular Today Buyer's Guide 2014. JETSTREAM System Brochure, Boston Scientific Website, 2014. Peripheral Rotablator product website, Boston Scientific, 2014. Diamondback 360 product website, CSI, 2014. Covidien website, Directional Atherectomy products, 2014. Turbo-Elite Laser Atherectomy Catheter Instructions for Use, May 2014.

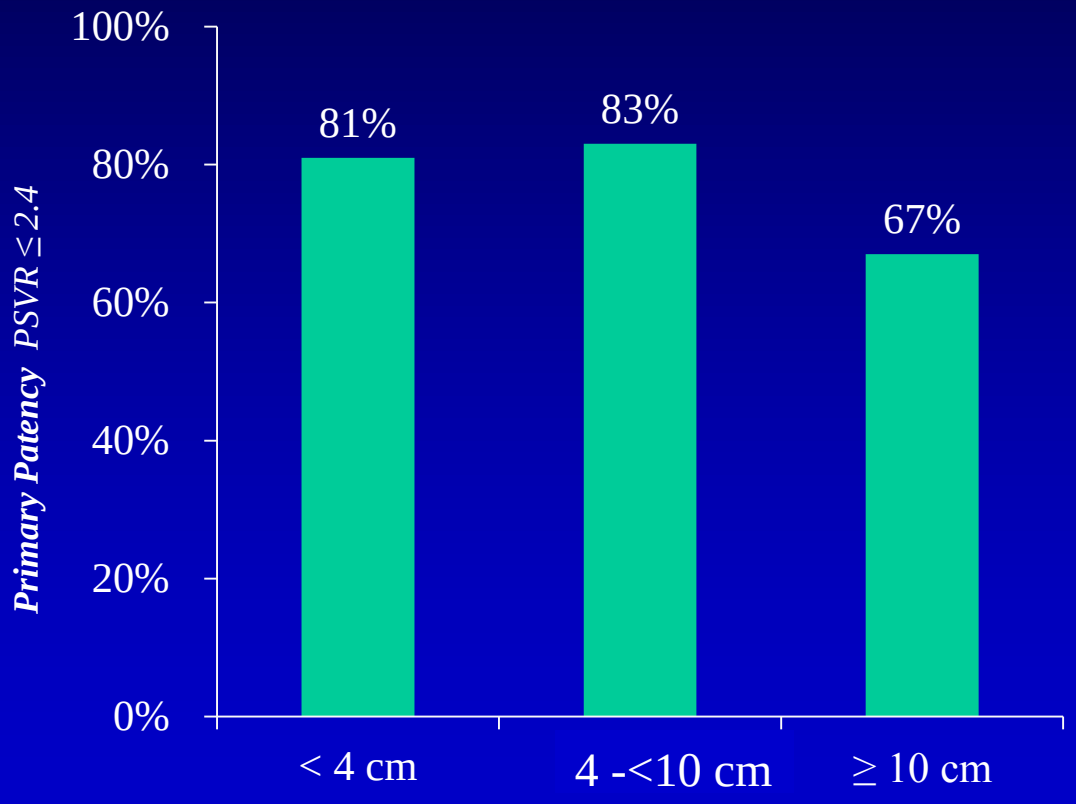
DEFINITIVE LE Subgroups

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

DEFINITIVE LE

PRIMARY PATENCY BY LESION LENGTH

Claudicant Cohort (PSVR ≤ 2.4)

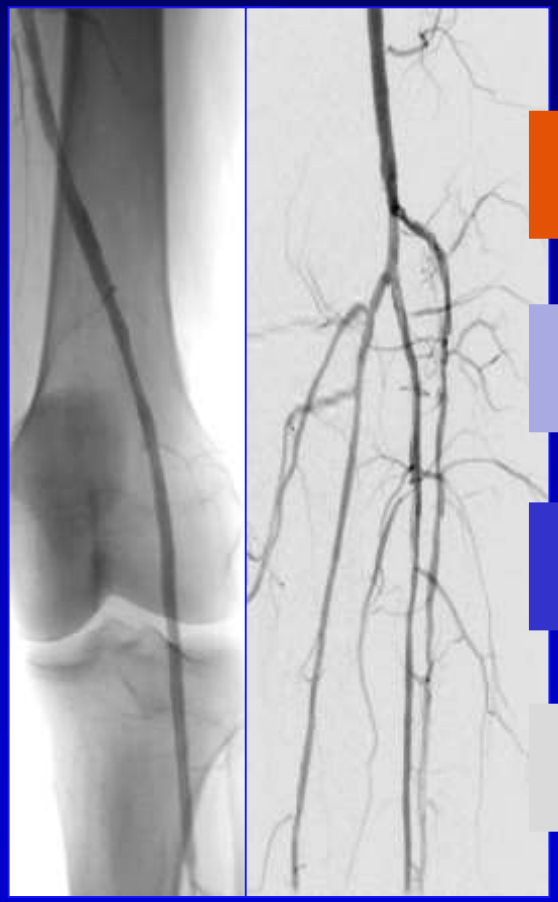


Mean Length:	**2.2 cm**	**6.5 cm**	**14.4 cm**
Number of Lesions:	**220**	**308**	**214**

DEFINITIVE LE

PRIMARY PATENCY AT ONE YEAR

CLI Cohort



PSVR≤ 2.4	*71%*
Lesions	*279*
Mean Lesion Length	*7.2cm*
Mean Baseline Stenosis	*76%*

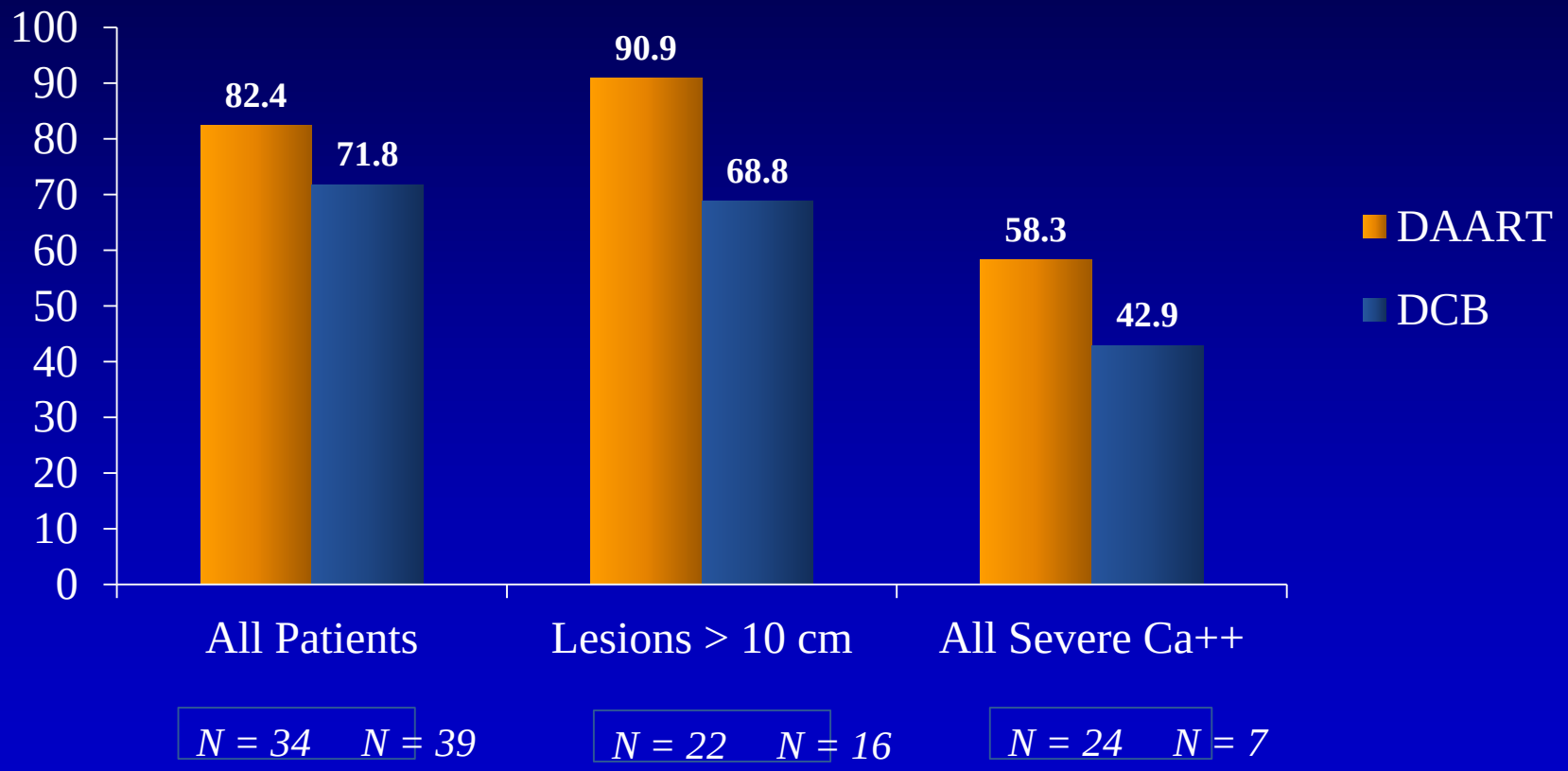
DEFINITIVE AR

Baseline Characteristics	DAART (N= 48)	DCB (N = 54)	*p*-Value*	DAART Severe Ca++ Arm (N=19)
Lesion Length (cm)	11.2	9.7	0.05	11.9
Diameter Stenosis	82%	85%	0.35	88%
Reference vessel diameter (mm)	4.9	4.9	0.48	5.1
Minimum lumen diameter (mm)	1.0	0.8	0.34	0.7
Calcification	70.8%	74.1%	0.82	94.7%
Severe calcification	25.0%	18.5%	0.48	89.5%

* *p*-value for DAART and DCB groups

Key Study Outcome at 12 Months

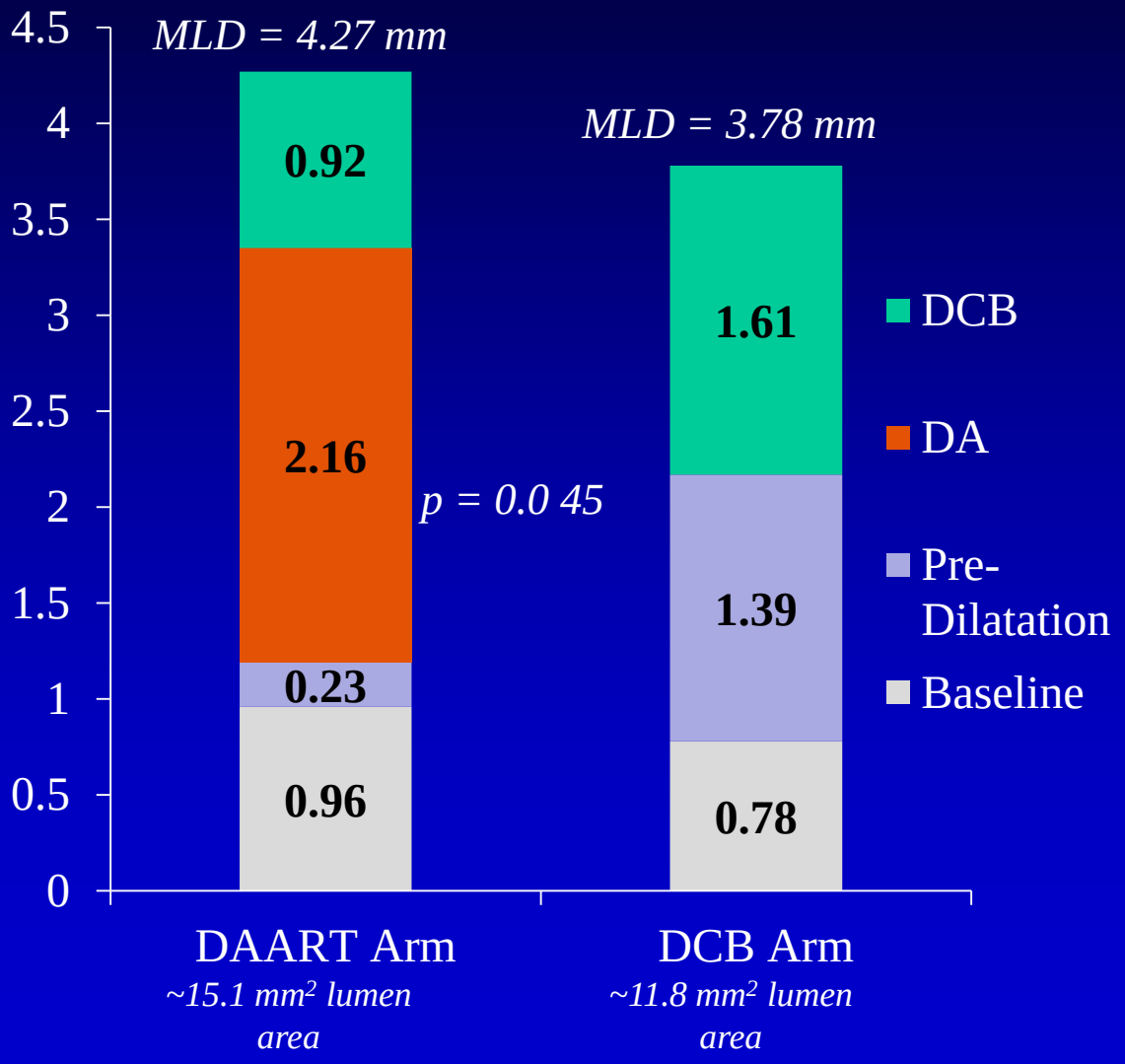
Angiographic Patency shows similar pattern



Results for all patients who returned for angiographic follow-up

DEFINITIVE AR

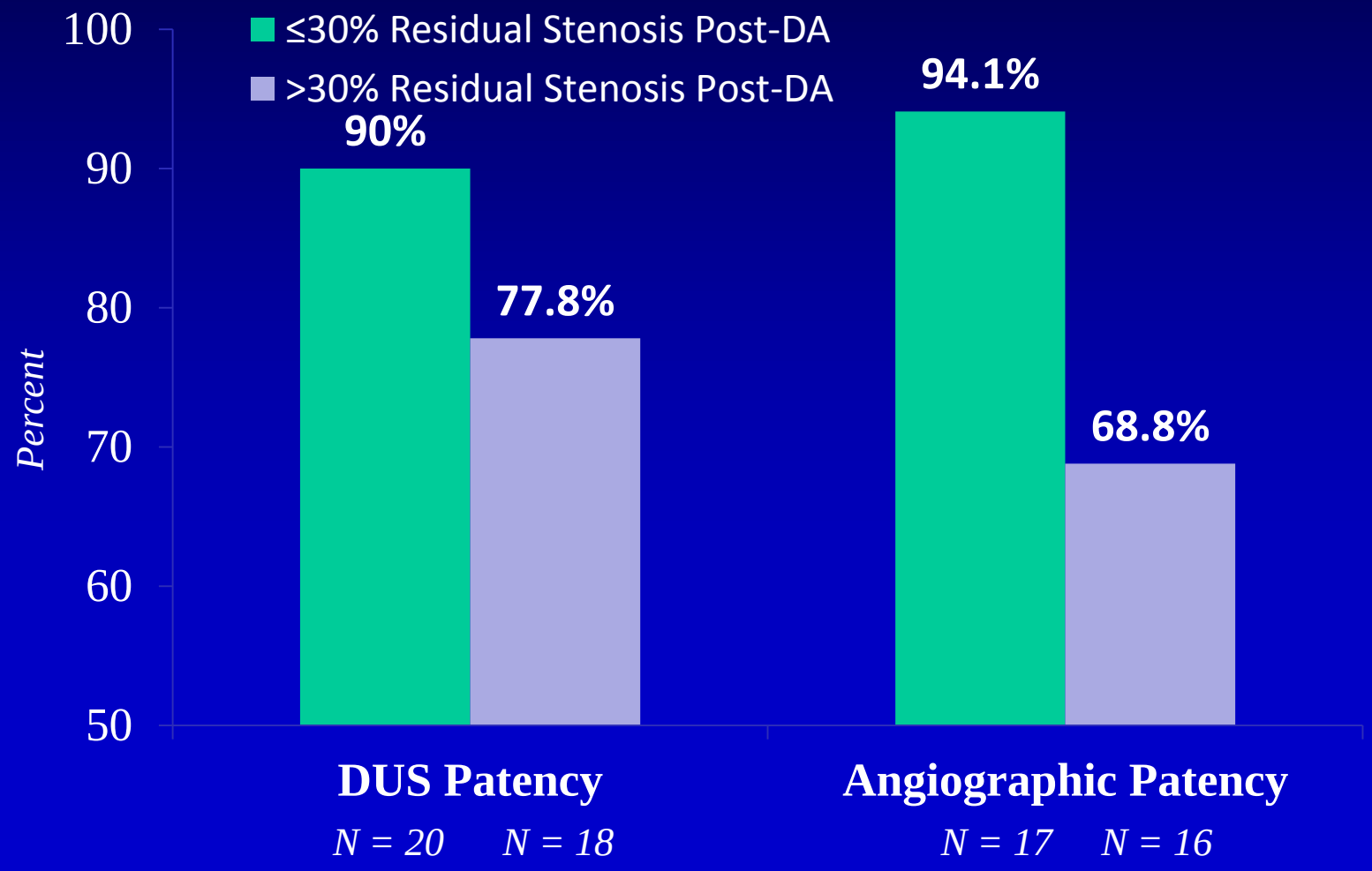
GREATER MLD AFTER DAART



DEFINITIVE AR

IMPACT OF LUMINAL GAIN

DAART ARM: *INCREASED LUMEN GAIN MAY IMPROVE 12-MONTH PATENCY*



What's ahead…*REALITY study*

- International, multi-center, prospective assessment of the safety and effectiveness of combined "vessel preparation" with directional atherectomy (HawkOne® /TurboHawk®) + IN.PACT Admiral® DCB in LONG and SEVERELY calcified FP lesions in 250 patients with RC 2-4 claudication—23 sites (US/Germany)
- Angiographic & Doppler core labs will independently adjudicate PP through 1 year and freedom from CD-TLR through 24 mo
- IVUS, peripheral Ca++ grading, histology sub-studies, WIQ and QoL assessments
- Protocol closed early

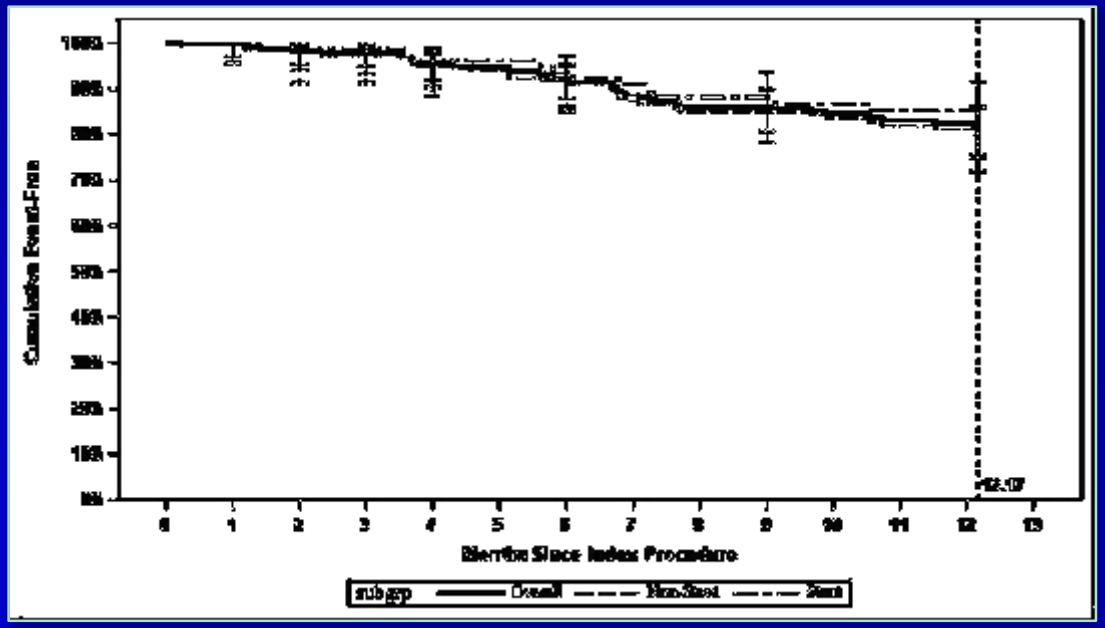
JETSTREAM

- 22.8% overall restenosis rate at 12 months

	Overall Population (N=241)	Non-Stent (N=157)	Stent (N=84)
Binary Stenosis[a], % (n/N)			
30 Days	**2.6% (3/116)**	**3.8% (3/80)**	**0.0% (0/36)**
12 Months	**22.8% (13/57)**	**20.5% (8/39)**	**27.8% (5/18)**

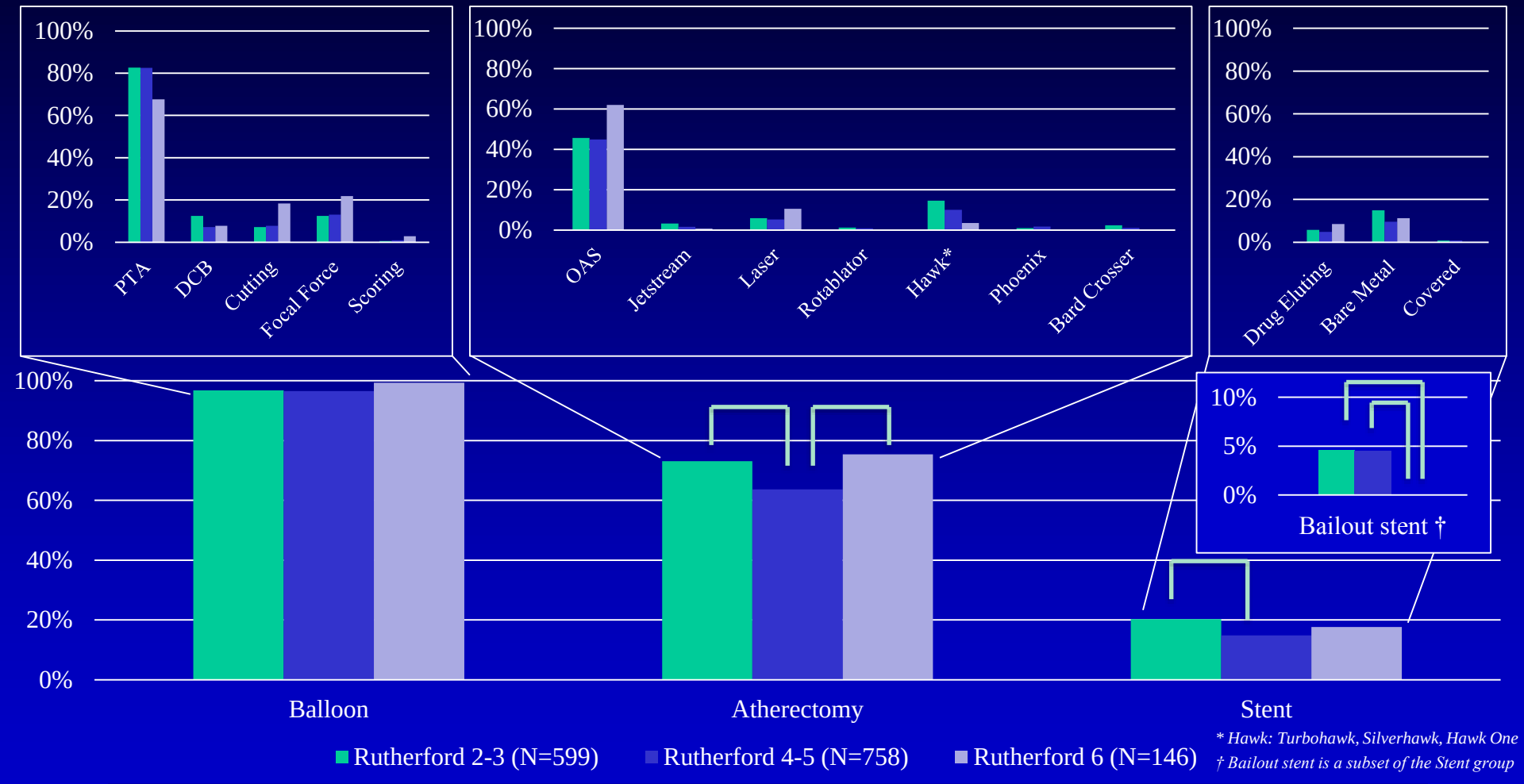
[a]Core lab-assessed DUS-derived PSVR >2.5

Freedom from TVR/TLR through 12 Months



LIBERTY Device Usage by Lesion

Balloon and/or atherectomy were preferred devices with orbital atherectomy (OAS) the most frequently used atherectomy device. RC6 subjects saw significantly higher use of focal force/cutting balloons, OAS, and laser atherectomy. Bailout stenting was significantly less frequent in RC6 compared to either RC2-3 or RC4-5.



** Hawk: Turbohawk, Silverhawk, Hawk One*
† Bailout stent is a subset of the Stent group

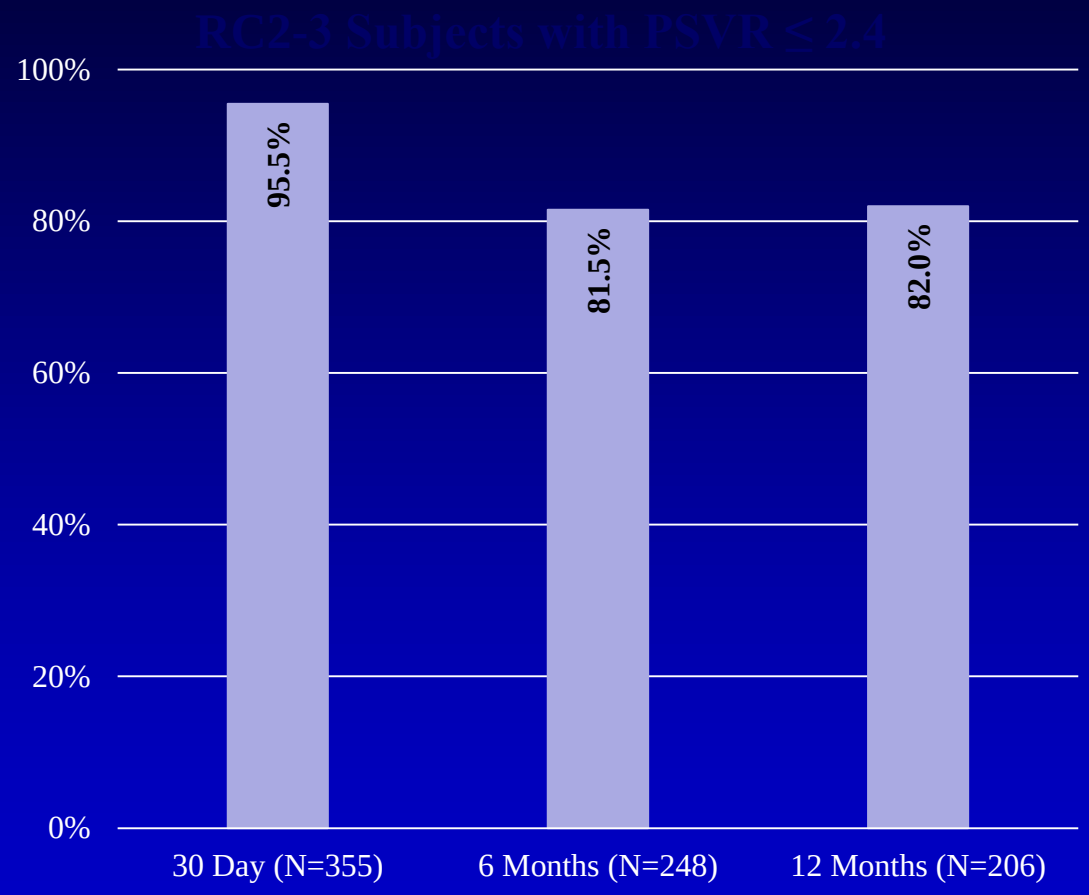
LIBERTY 360: Prospective, observational, multi-center study to evaluate procedural and long-term clinical and economic outcomes of endovascular device interventions in patients with symptomatic lower extremity PAD (N=1,204 Subjects)

Core Lab reported lesions (Lesions with reported values may be less than total number of lesions treated in each arm).
23-May-2017 Data

Comparison between Rutherford categories significant ($p<0.05$)

LIBERTY Duplex Ultrasound (DUS)

High long-term patency rate in RC2-3 subjects.

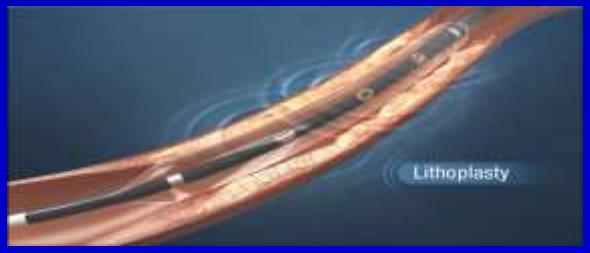


LIBERTY 360: Prospective, observational, multi-center study to evaluate procedural and long-term clinical and economic outcomes of endovascular device interventions in patients with symptomatic lower extremity PAD (N=1,204 Subjects)

VasCore Core Lab Assessed (Patients with reported values may be less than total number of patients enrolled in each arm).
DUS required only for RC2-3 Subjects
At baseline, previous Peripheral Vascular Intervention on target limb in 30% of RC 2-3 subjects
23-May-2017 Data

What about calcification

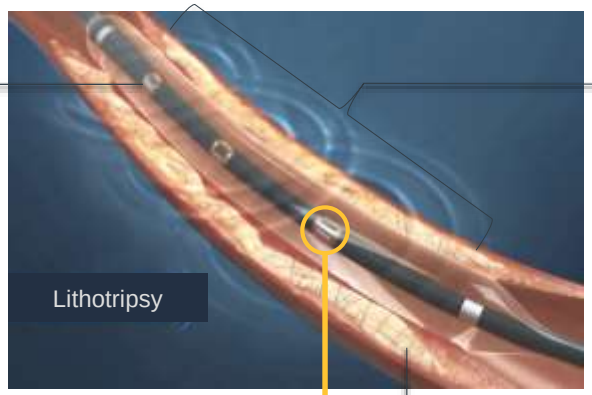
- Shockwave technology (Shockwave Medical)
- 35 patients Europe 30 day safety
- 87% achieved <50% stenosis with lithotripsy alone
- Average stenosis 23% post ShockWave
- PADIII currently enrolling in the US pivotal trial



- Familiar Balloon-based endovascular technique
- “Front-line” balloon strategy (.014”compatible)
- Disrupts both deep & superficial calcium pre dilation
- Normalizes vessel wall compliance
- Ultra-low pressure
- Minimized effect on healthy tissue

How IVL Works: An Overview

1 Integrated Balloon is inflated to a ***ultra-low pressure of 4 atm*** prior to activating emitters to ensure complete vessel wall apposition.



6 Softened vessel then able to be dilated at ***low pressure of 6 atm***, minimizing vessel trauma and complications.

2 ***Emitters*** are the source of the Sonic Pressure Waves emitted at 1 pulse per second for 1 microsecond

5 Sonic Pressure waves ***crack calcium***, softening vessel compliance. Fractured calcium remains inside the vessel wall.

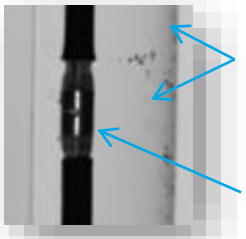
3 ***Sonic Pressure Waves*** are emitted in the shape of a sphere, creating a field effect, thereby addressing calcium around the entire circumference and deep into the vessel wall

4 Sonic Pressure Waves transmit ***~50 atm of instantaneous pressure*** to the site of calcium, but pass through soft tissue

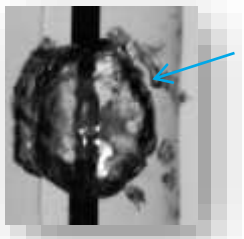
How Shockwave Creates Localized Lithotripsy

High Speed Sonic Pressure Wave Created Safely Inside Integrated Balloon

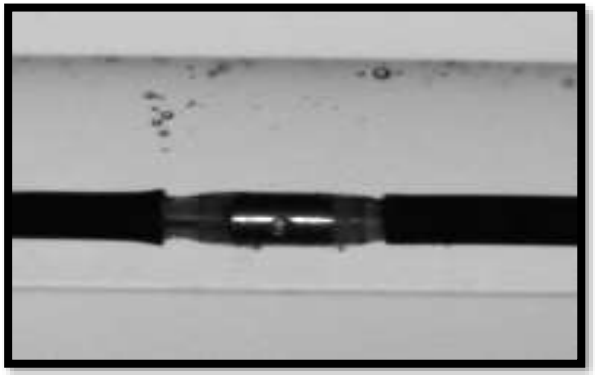
1 **Unfocused lithotripsy energy** is created at the emitters which are contained in a fluid filled coupler



2 Electrical energy is delivered to the emitter, initiating the steam bubble, which expand & collapses – creating **sonic pressure waves**.



***Video*: Actuation of Single Pulse (20µs/frame)**



Does vessel prep still matter?

- DCB's have dramatically changed the SFA landscape
  - Either the data suggests that up-front therapy is beneficial and durable in short and intermediate lesion lengths or that in surrogate fashion work for restenosis
- What we do not know or have not looked at is the head to head with therapy as to lesion length initial DCB or BMS/DES or debulk/DCB in addition to patterns of failure (restenosis) in all
- RCT data compel discussion and treatment strategies
  - ***Vessel prep remains a key element of benefit for many technologies***
  - Calcium remains a principal disruptor for DCB
    - ***REALITY may answer this question***
    - ***DISRUPT may answer this question***
- A "leave nothing behind" strategy appears to be the current trend for SFA therapy though no one group has shown the benefit beyond a modest SFA lesion length
- Currently, vessel prep is an open question that has yet to be clearly defined