Drug-Eluting in Long Segment and Calcified Disease

- Current Status and Role for Atherectomy for Vessel Preparation

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Case: 65 year-old male, Lt. leg

Case Rt. leg

Filter

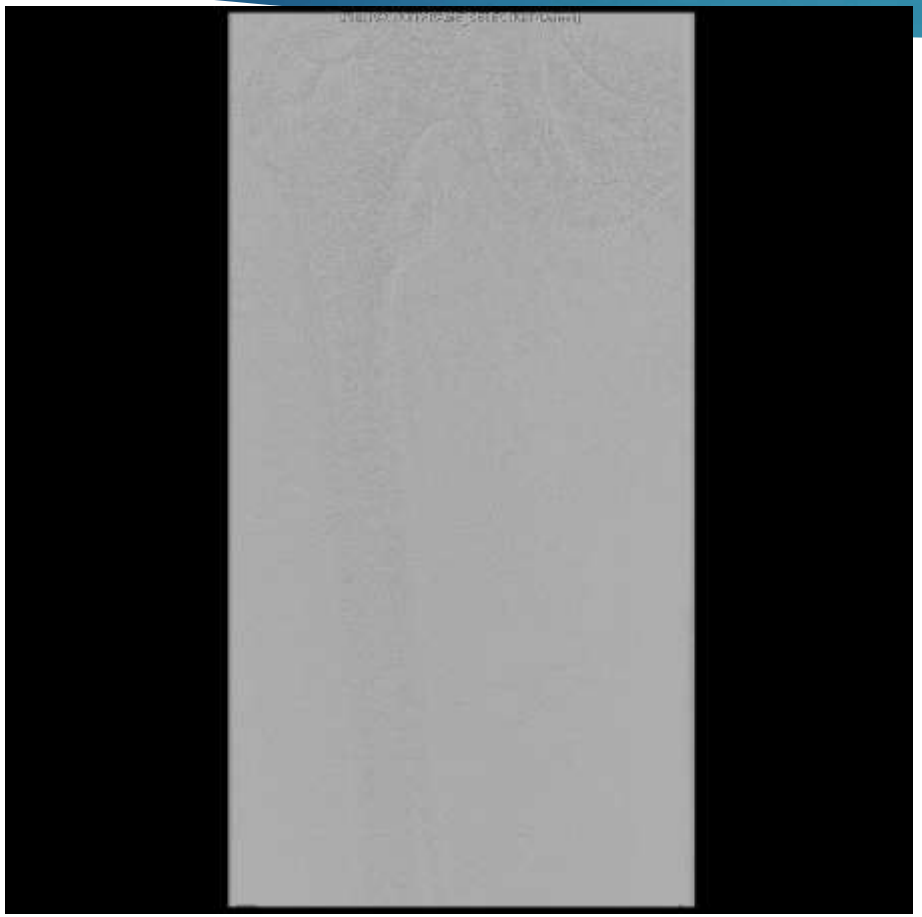
Case

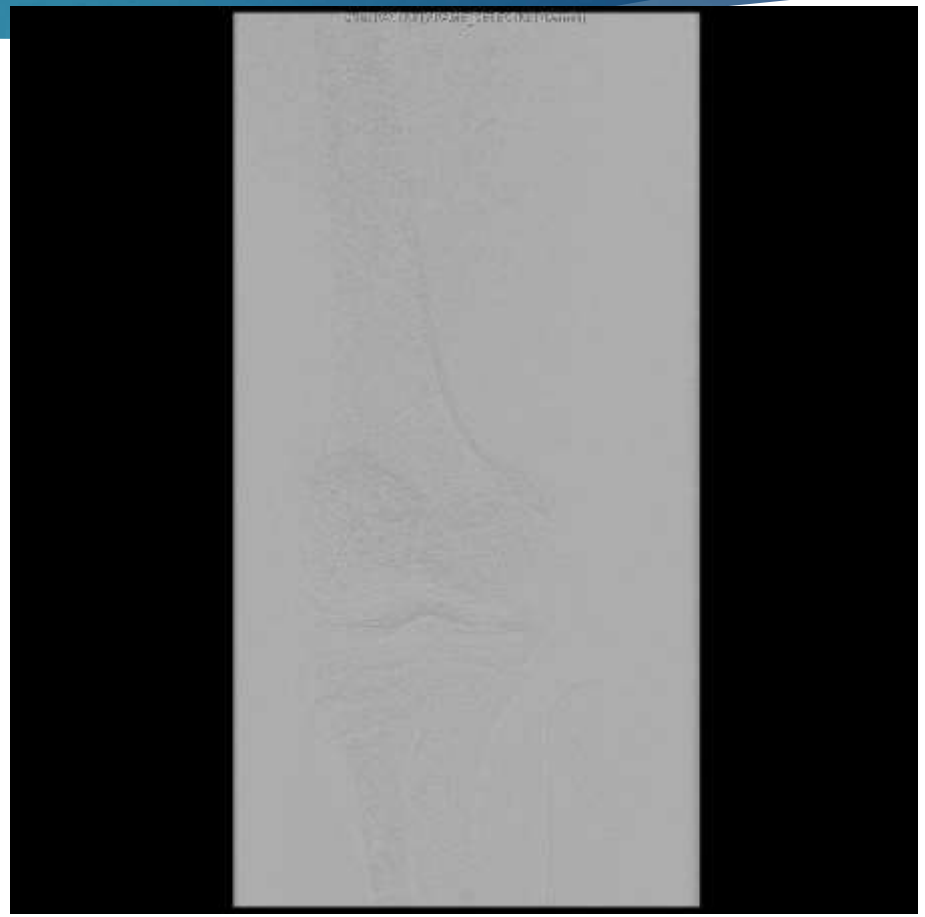
Case

NC balloon

Lutonix #3

Case





DCB: Basic and Complement

1. **PRE-DILATATION**
   - Required for all lesions prior to DCB procedure
   - Size - Diameter: 1 mm less than RVD
   - Size - Length: should not be greater than planned DCB length

For adequate drug delivery, predilation or lesion preparation might be most important!
Plaque burden is excessive and may limit effective drug delivery.

Especially, high likelihood from suboptimal simple PTA results,
such as long, total occlusion and calcification…

We need more things to do…

- Minimum length as necessary to fully treat the residual stenosis or dissection

Perspective of DCB

Benefits

- More uniform drug delivery than drug-eluting stents
- Native vessel maintained
- Reduced requirement for DAPT (if stents are avoided)
- Re-interventions are less challenging than in-stent-restenosis

Limitations

- Procedural effectiveness, same as POBA
  - Recoil
  - Calcium
  - Dissections
  - Lesion length (?)
- Increasing bail-out stent rate with increasing lesion length

PTA in Calcific Lesions

FLOW LIMITING DISSECTION

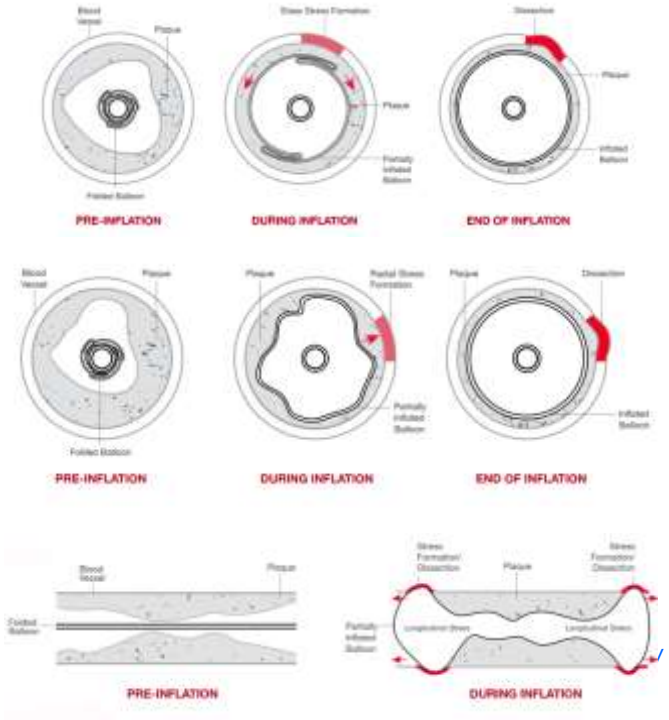
With conventional balloons, inflation can result in a vessel trauma—which often leads to dissection.

There are three primary reasons when this occurs:

Torsional Stress (*Twisting*)

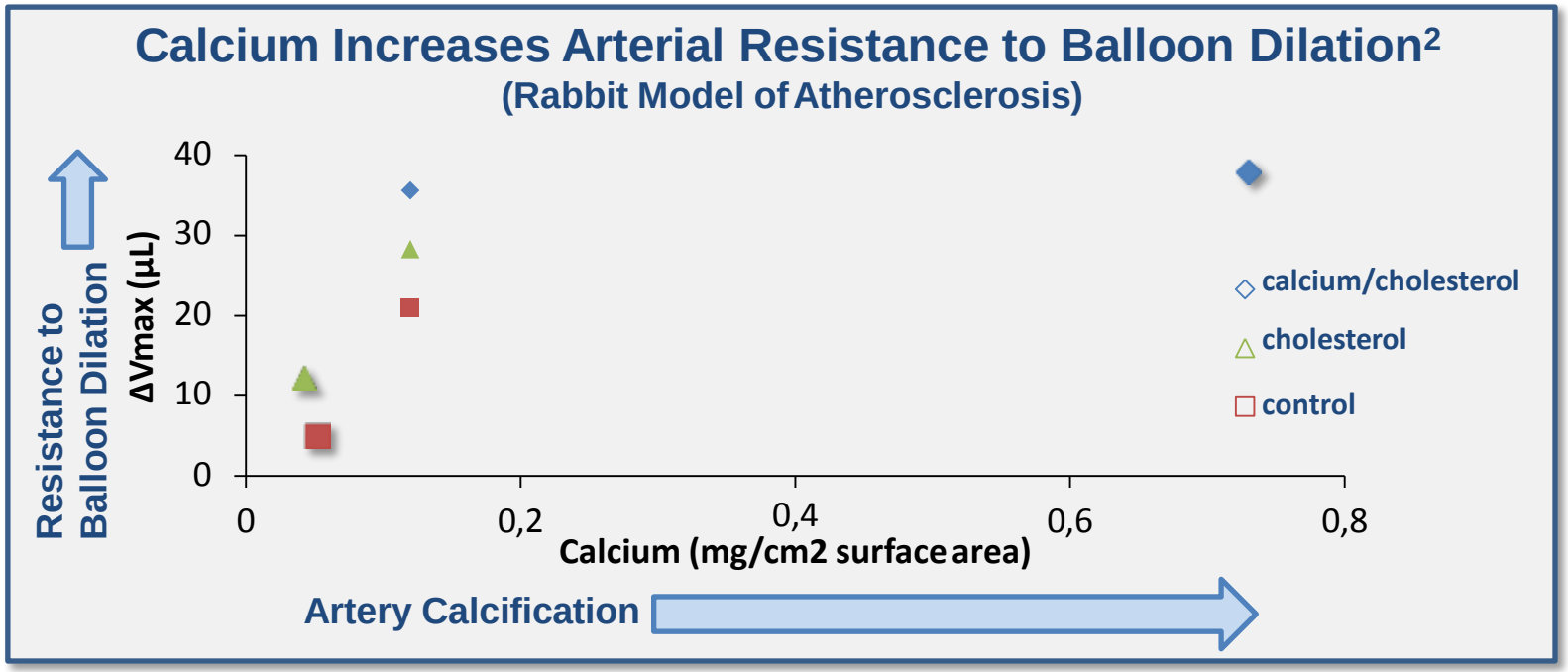
Radial Stress (*Expanding*)

Longitudinal Stress (*Elongating*)



Why Should We Remove Calcium?

- Calcium is present in peripheral lesions[1]
- Presence of calcium necessitates greater balloon pressures[2,3]
- Plaques with associated calcium have increased dissection rates after angioplasty[5]
- Calcium may influence drug-coated balloon efficacy[4] and stent expansion

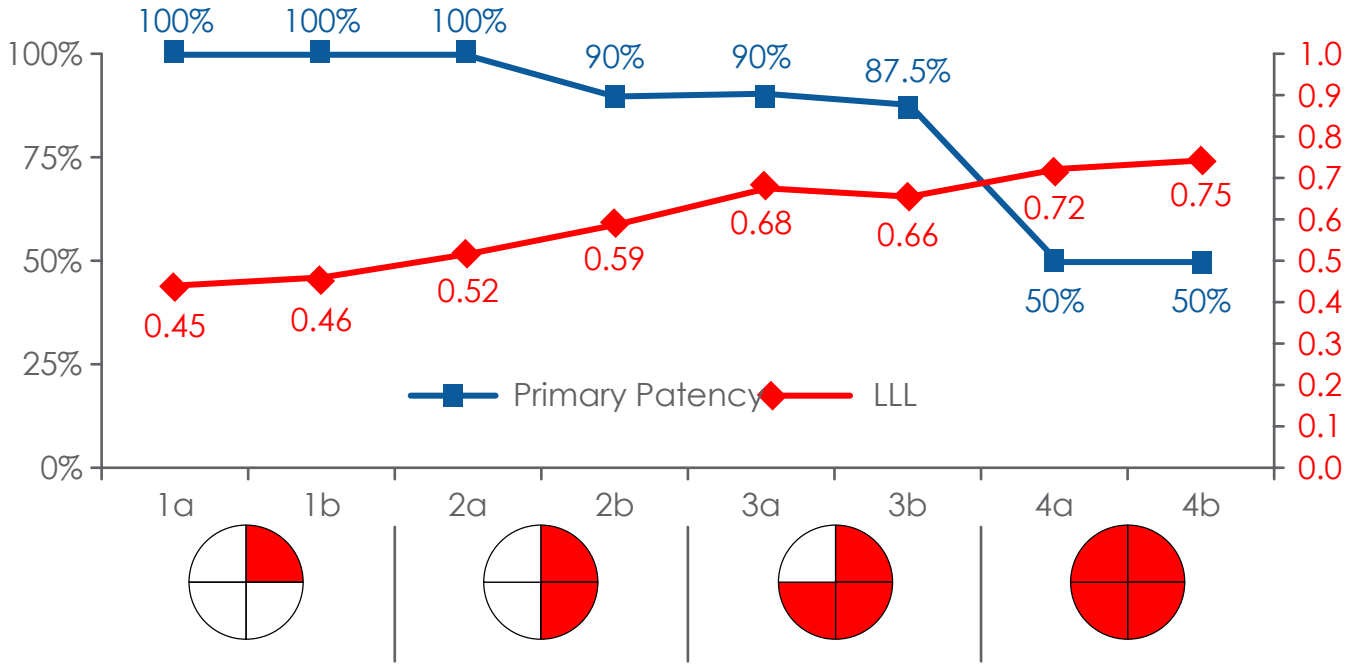


1. Bishop, et al. Ann Vasc Surg. 2008;22:799-805.
2. Demer. Circulation. 1991;83:2083-2093.
3. Makam. J Invasive Cardiol. 2013;25(2):85-8.
4. Fanelli F, et al. Cardiovasc Intervent Radiol. 2014 ;37(4):898-907.
5. Fitzgerald, et al. Circulation. 1992;86(1):64-70.

DCB and Calcium

- IN.PACT DCB and Calcium Prospective Study (n=60)

12 month Results



Calcium distribution evaluation by CTA (circumf.) and DSA (longitud.)

- Calcium distribution and severity affect LLL and primary patency.
- Ca^{++} represents a barrier to optimal drug absorption and a source for acute and subacute vessel recoil.

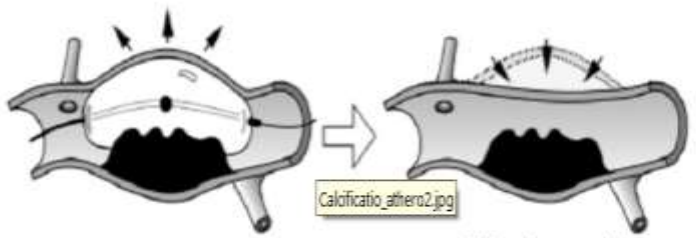
Fanelli F, et al.
Fanelli J Endovas Ther 2012;19:571-580

Cardiovasc Intervent Radiol, 37: 898-907 (2014).

Clinical Limitations & Unmet Needs

Calcium Limits Vessel Expansion

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



Fully inflated balloon

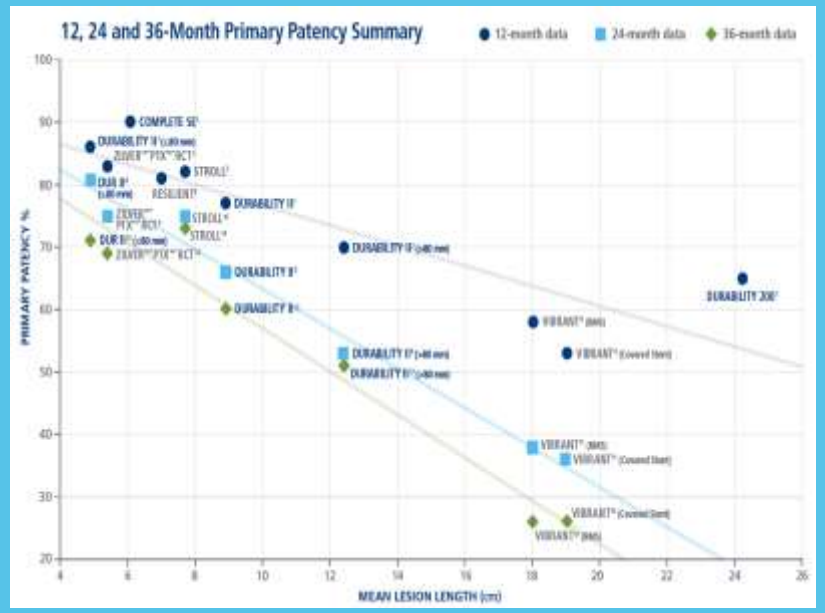
Elastic recoil
Residual, high-grade stenosis

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

Longer Lesion Length



Increased lesion length is an independent predictor of decreased patency.

[1]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)

Challenge of Long lesions

- Significant progress had been made in the endovascular treatment of long lesions, but, still, siginificantly associated with poor prognosis.

- Atherectomy for long lesions
  - •Limited data
    - Relatively low patency
    - Significant procedural time/radiation
    - Significant risk of embolization
- Atherectomy and DCB
  - Not yet defined but good data on mid range lesions in some reports

All lesions need to lesion preparation before DCB ?

- When and Why of Pre-dilatation before DCB: Lessons from ILLUMENATE FIH

1. To analyze ILLUMENATE FIH (Stellarex DCB) study 2-year results with and without pre-dilatation

2. To discuss the role of pre-dilatation and optimal PTA.

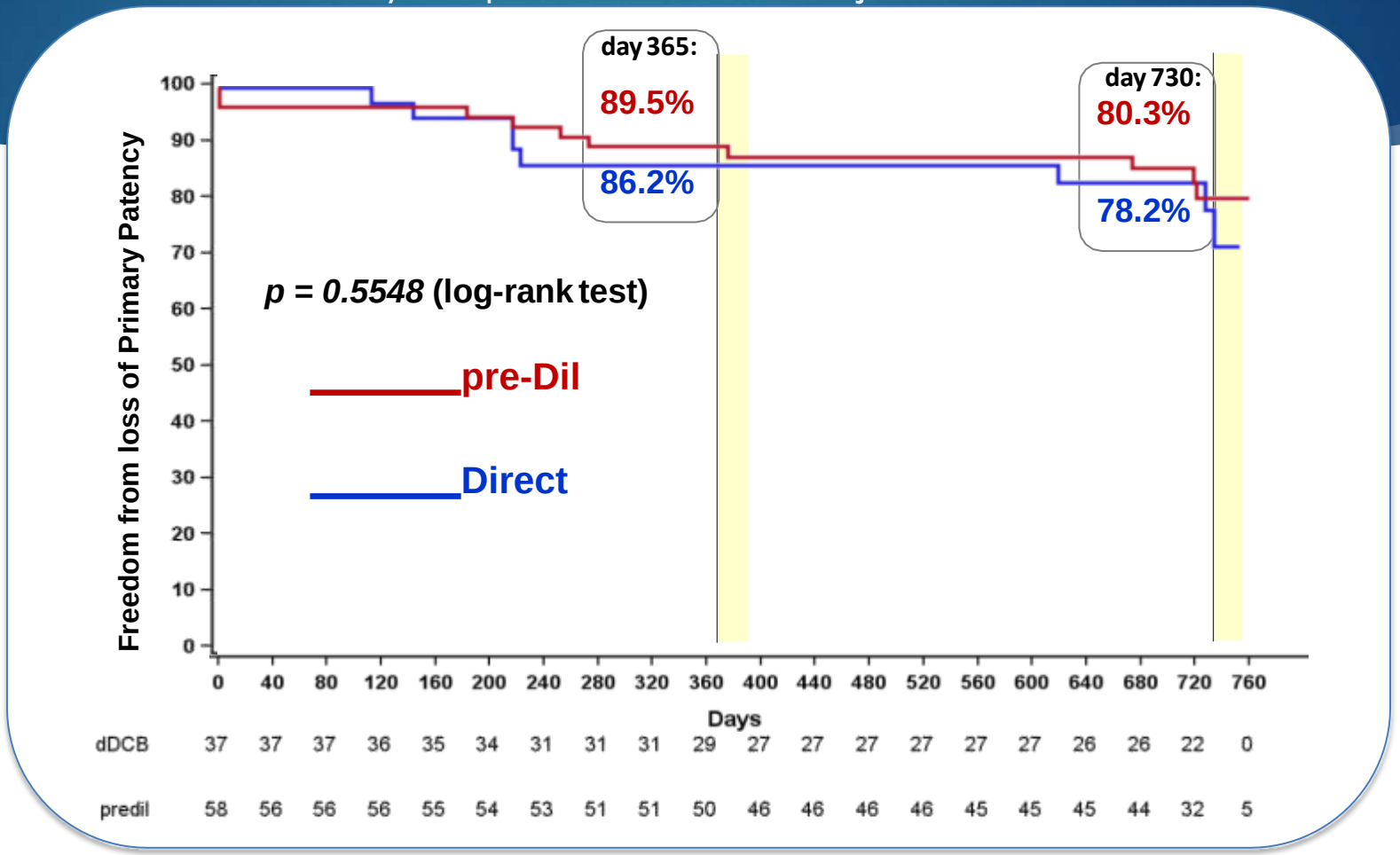
ILLUMENATE FIH - Overview

80-patient, prospective, multi-center Trial

	pre-Dil	Direct	*p*
Lesion (N)	58	37	
Proximal Popliteal	5.2% (3/58)	10.8% (4/37)	*0.4255*
Lesion length (mm)	72.1±46.7 (58		
RVD (mm)	5.2±0.9 (58)		
% Diameter Stenosis	75.1±17.0 (58		
MLD (mm)	1.3±1.0 (58)		
Total Occlusions	12.1% (7/58)		
Severe Calcium	13.8% (8/58)		
Run Off Vessels: 0	1.7% (1/58)		
1	19.0% (11/58)	45.9% (17/37)	*0.0930*
2	39.7% (23/58)	48.6% (18/37)	
3	39.7% (23/58)		

	pre-Dil	Direct	*p*
Pre-Dilatation	100%	0%	
N DCB per lesion	1.5	1.5	
Mean inflation time	data non collected	2.2 min/ DCB	
post-Dilatation	12.1% (7/58)	35.1% (13/37)	*0.0100*
Adjunctive Stenting	5.2% (3/58)	8.1% (3/37)	*0.6749*
Device Success [1]	96.6% (56/58)	89.2% (33/37)	*0.2040*
Lesion Success [2]	100% (58/58)	100% (37/37)	

2-year Primary Patency (pre-Dil vs Direct cohorts)
by Duplex Corelab Adjudication



Primary Patency defined as freedom from Duplex derived restenosis (PSVR < 2.5) and clinically driven TLR

Primary Patency survival estimates at upper bound of follow up windows for 1 and 2 years:

- pre-dil cohort: 87.9% at 395-day and 80.3% at 760-day
- direct cohort: 86.2% at 395-day and 71.7% at 750-day (last observed follow up)

ILLUMENATE FIH-Conclusions

- Predilation is not mandatory to enhance efficacy but higher risk : mismatch

- No significant difference noted between pre-Dilatation and Direct Cohorts

  (mean lesion length: 70 mm)

  - Data suggests pre-dilatation in simple lesions may be optional
  - Pre-dilatation reduces need for post-dilatation and stenting
  - May be highly recomended in presence of ca++ and in total occlusions

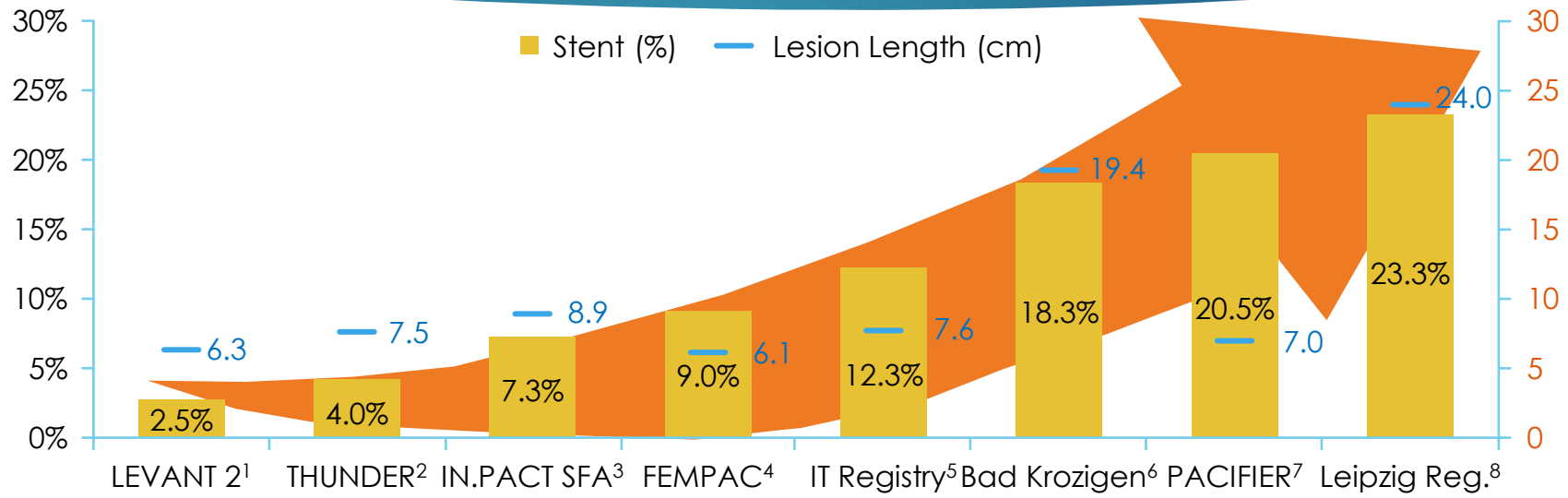
LEVANT II DCB: Predictor of patency

- Balloon transit time (< 30 seconds)
- Balloon inflation pressure (> 7 atm)
- Balloon inflation time (≥ 120 seconds)
- Final % diameter stenosis (<20%)

SCAFFOLDS STILL NEEDED, LIKELY AT RATES PROPORTIONAL TO LESION COMPLEXITY

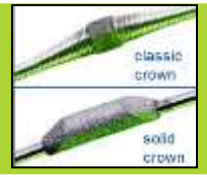
DCB AND PROVISIONAL STENTING

Provisional stent rates in DCB trials trend with lesion length



1. Rosenfield K TCT 2013; 2. Tepe G et al. *N Engl J Med*. 2008; 3. Tepe CX 2014; 4. Werk M et al. *Circulation*. 2008; 5. Micari A et al. *J Am Coll Cardiol Intv*. 2012; 6. Zeller T CX 2013 oral presentation; 7. Werk et al. *Circ Cardiovasc Interv*. 2012; 8. Schmidt A LINC 2013 oral presentation

Atherectomy Devices

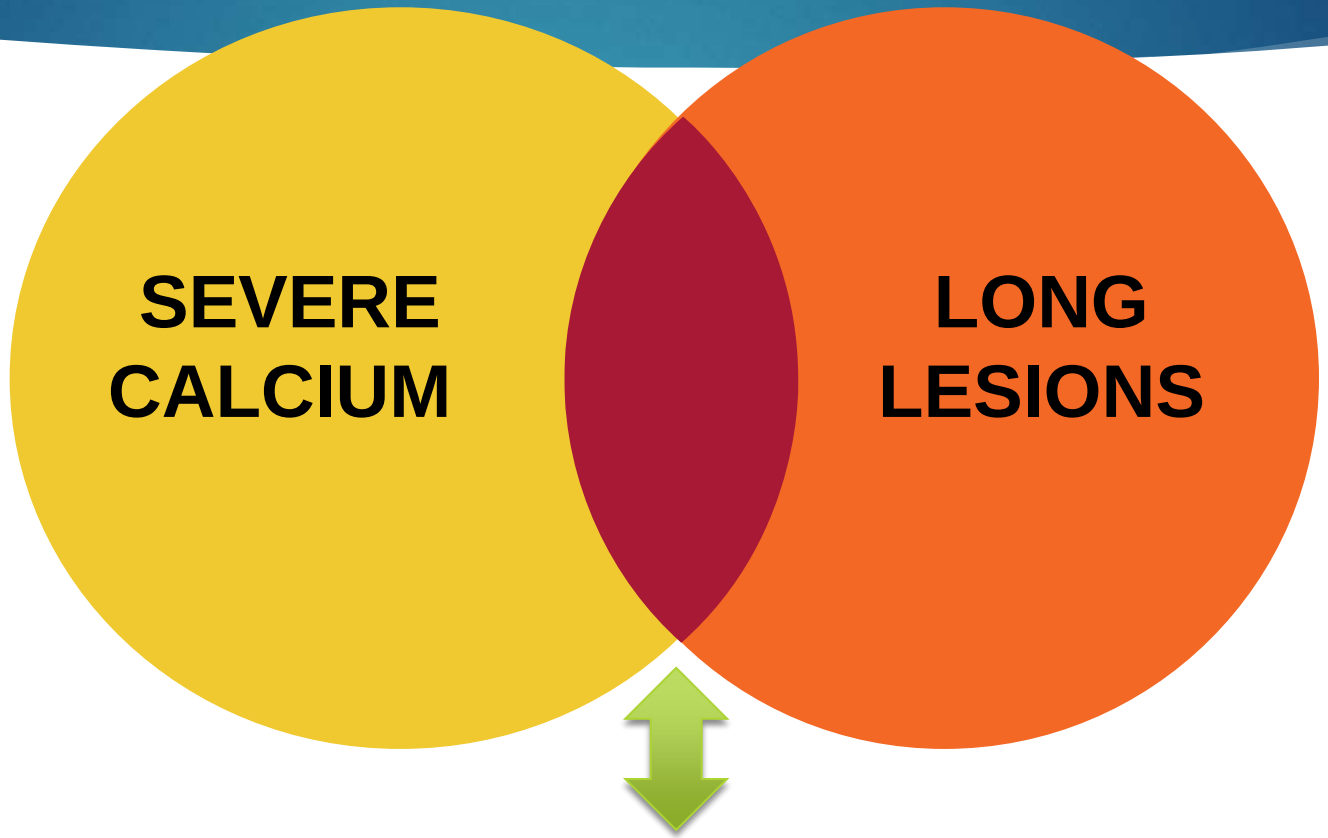
	Jetstream™ Atherectomy System (Boston Scientific)	Peripheral Rotablator™ Rotational Atherectomy System (Boston Scientific)	Diamondback 360™, Stealth 360™ Atherectomy System (Cardiovascular Systems, Inc)	SilverHawk™, TurboHawk™ Plaque Excision System (Covidien)	Turbo-Elite™ Laser Atherectomy Catheter (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.

Atherectomy

- Lesion Charcteristics
  - calcium
  - in-stent restenosis
  - chronic total occlusion
  - soft plaque
  - thrombus (thrombectomy)
- Procedural goals
  - avoid or minimize stenting
  - vessel preparation for drug penetration
  - modify vessel compliance
  - efficacy in calcified and long lesions
  - leaving no residual stenosis > 30%

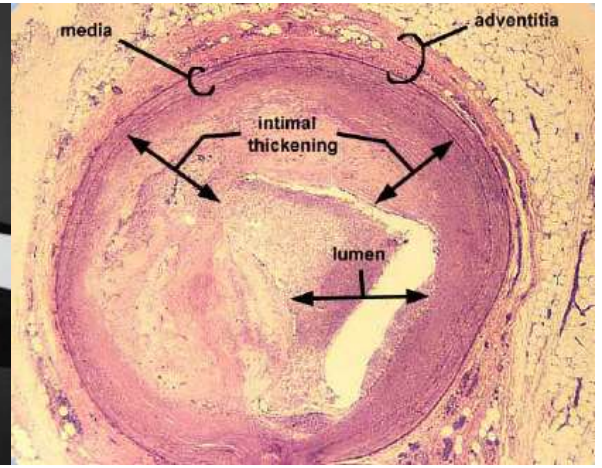
Defining 'Challenging' SFA Lesions



DAART= Directional Atherectomy + Anti-Restenotic Therapy: An Emerging Paradigm

DAART =
Directional Atherectomy + Anti-Restenotic Therapy

- Mechanically re-canalize the vessel without overstretch
- Remove perfusion barrier (improve penetration of drug into the media/adventia)
- Reduce the likelihood of bail-out stenting and preserve the native vessel



DEFINITIVE AR

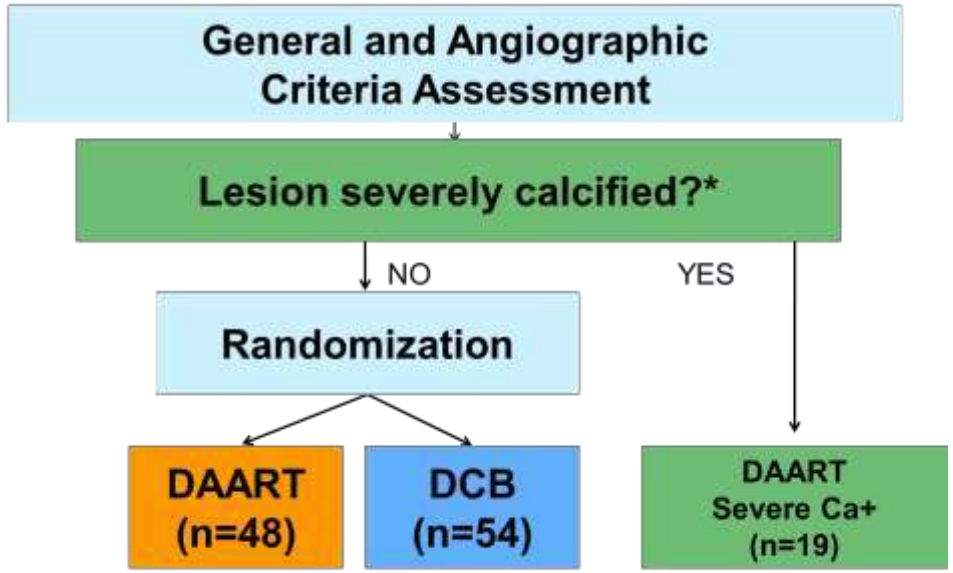
Pilot study to detect trends in treatment differences between groups and designed to assess the effect of treating lesions with DA followed by DCB (DAART)

INCLUSION CRITERIA

- RCC 2-4
- ≥ 70% stenosis of SFA and/or popliteal artery
- **Lesion Length 7-15cm**
- Reference Vessel ≥ 4mm and ≤ 7mm

EXCLUSION CRITERIA

- In-stent restenosis
- Aneurysmal target vessel
- Multiple lesions in target limb that require treatment



1. Zeller T, et al. Presentation at VIVA 2014, Late-breaking Clinical Trials, Tuesday, November 4, 2014.

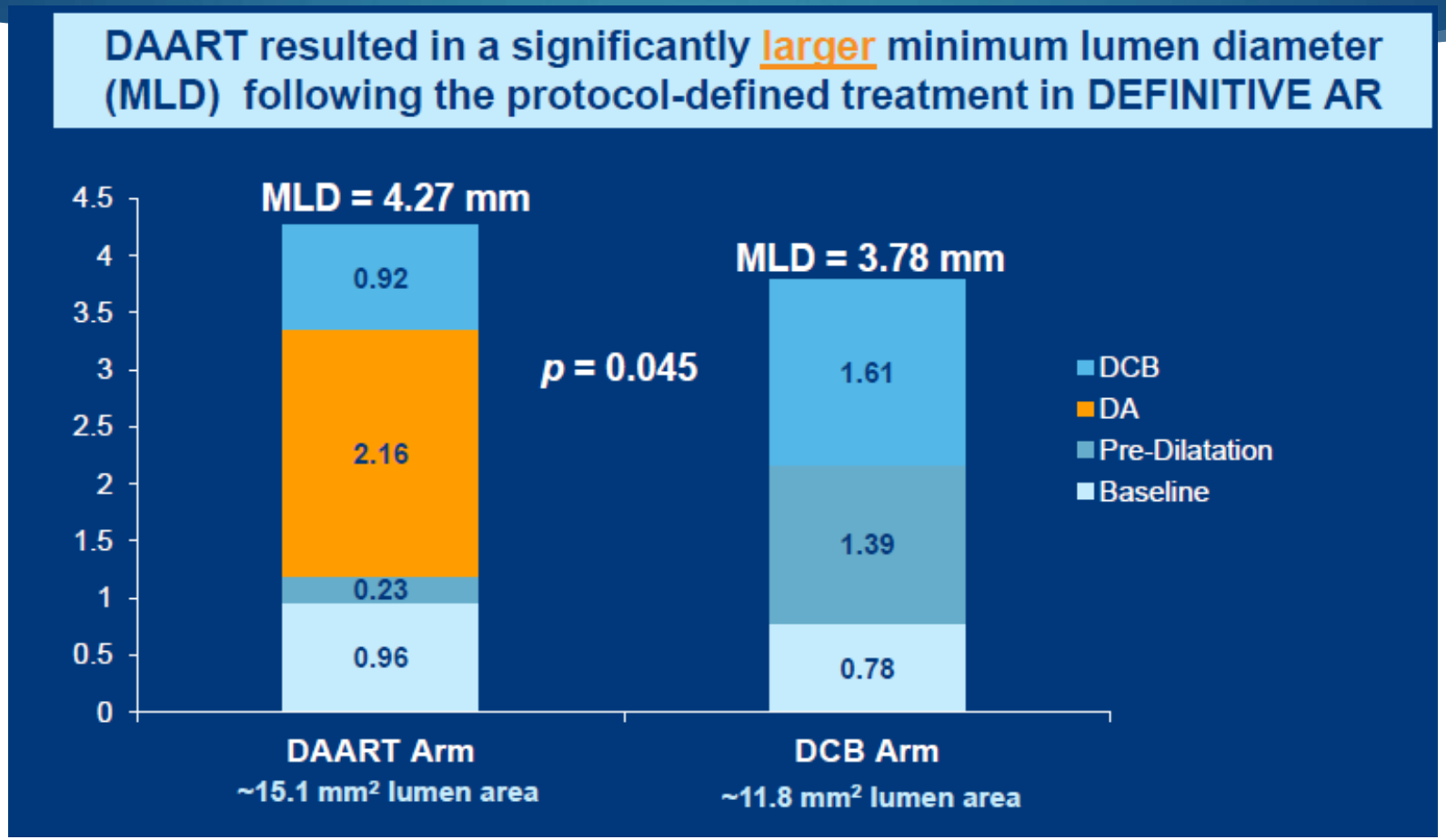
DEFINITIVE AR

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	89.8%

* *p*-value for DAART and DCB groups

Impact of lumen gain with DAART

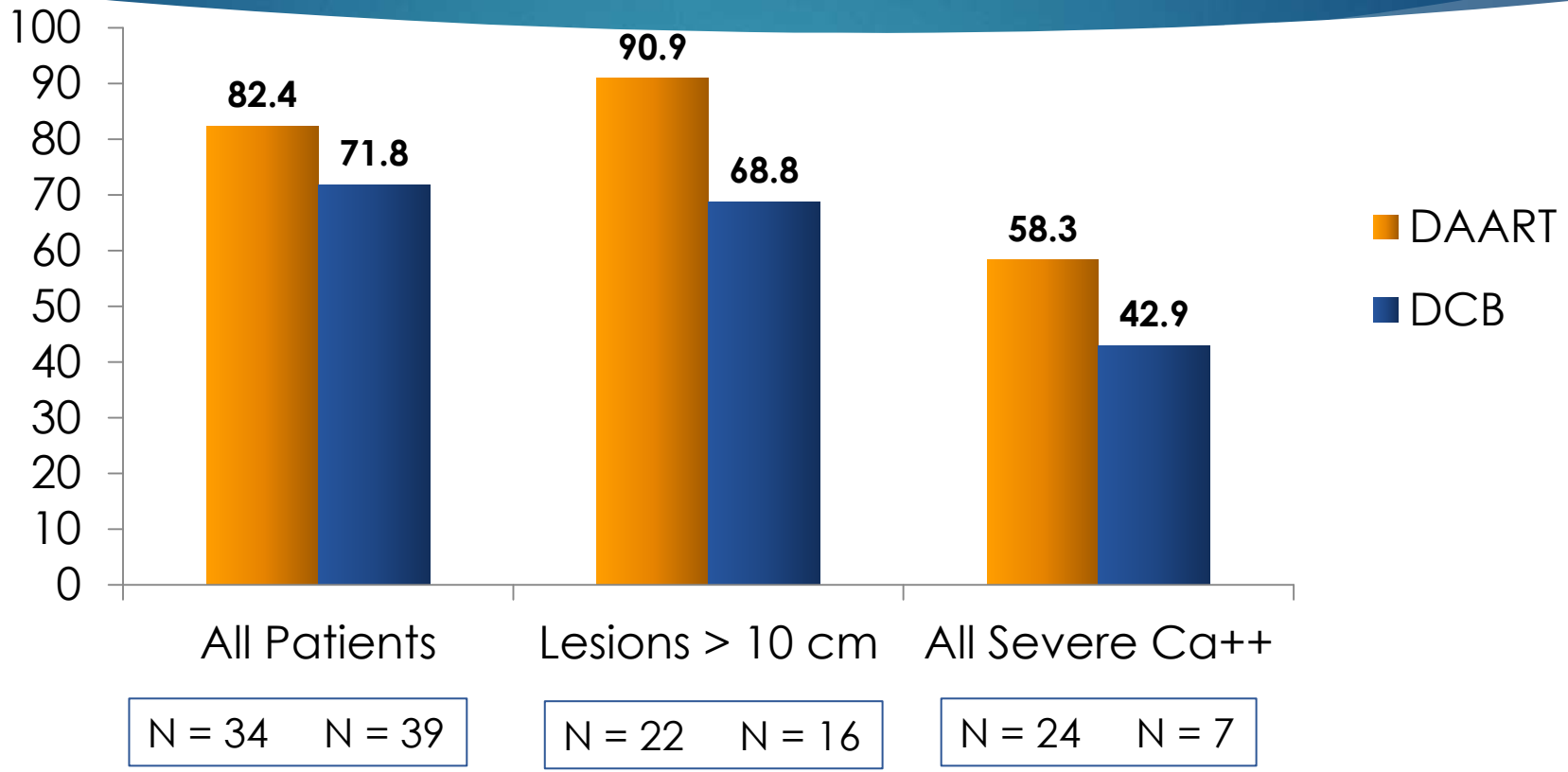
Reaffirms the value of luminal gain achieved by DA



Results for all patients who returned for angiographic follow-up

Angiographic patency at 12 Months

Potential Advantage Emerging in Long and Severely Calcified Lesions



Results for all patients who returned for angiographic follow-up

DAART

- Prospective, single center study to characterize conjunctive DAART use in severely calcified lesions

Procedural characteristics (n = 30)

- **mean lesion length: 115 mm**
- total occlusion: 13.3%
- provisional stenting rate: 6.7%
- all cases: < 30% residual stenosis

12-month results

- primary patency: 90%
- TLR: 10%
- limb salvage: 100% (12 CLI patients)

Cioppa, et al. Cardiovasc Revasc Med 13:219---23:2012

Upcoming ***REALITY*** Study

Questions to be Explored:

- Clinical safety/effectiveness of DA *"vessel preparation"* prior to DCB use in *long* (8-25 cm), *severely calcified* SFA lesions in up to 250 RC 2-4 claudicants in the US and Germany (13 sites).

  -- Duplex core lab to assess 12 mo. patency
  -- Angiographic core lab to assess technical success after DA and DCB; adjudicate dissection grade and provisional stenting
  -- PACSS Calcium grading scale to be validated

REALITY
Sponsored by VIVA

Atherectomy in the era of DCB?

- Plaque modification using atherectomy and calcium removal pre-intervention may improve early and long term results by
  - reducing the incidence of ballon induced dissection
  - optimizing drug delivery of DCB
  - Improving stent expansion, luminal gain, and drug delivery of stent platforms

- Pilot studies of conjunctive directional atherectomy with DCB use are suggestive of potential improvement of long term patency of long and calcified lesion, if adequate debulking (< 30% residual stenosis) was achieved after atherectomy treatment.

- More data is needed…

Atherectomy in the era of DCB?

- DCB's have dramatically changed the SFA landscape.
- A "leave nothing behind" strategy appears to be the current trend for SFA therapy.

- RCT data compel discussion and treatment strategies
  - ***Vessel prep remains a key element of benefit for drug-eluting technologies***
  - Calcium and long lesion remain a principal disruptor for DCB
  - ***REALITY trial can show answer***

Thank you for your attention