Does vessel prep still matter in DCB era?

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Disclosure Statement of Financial Interest

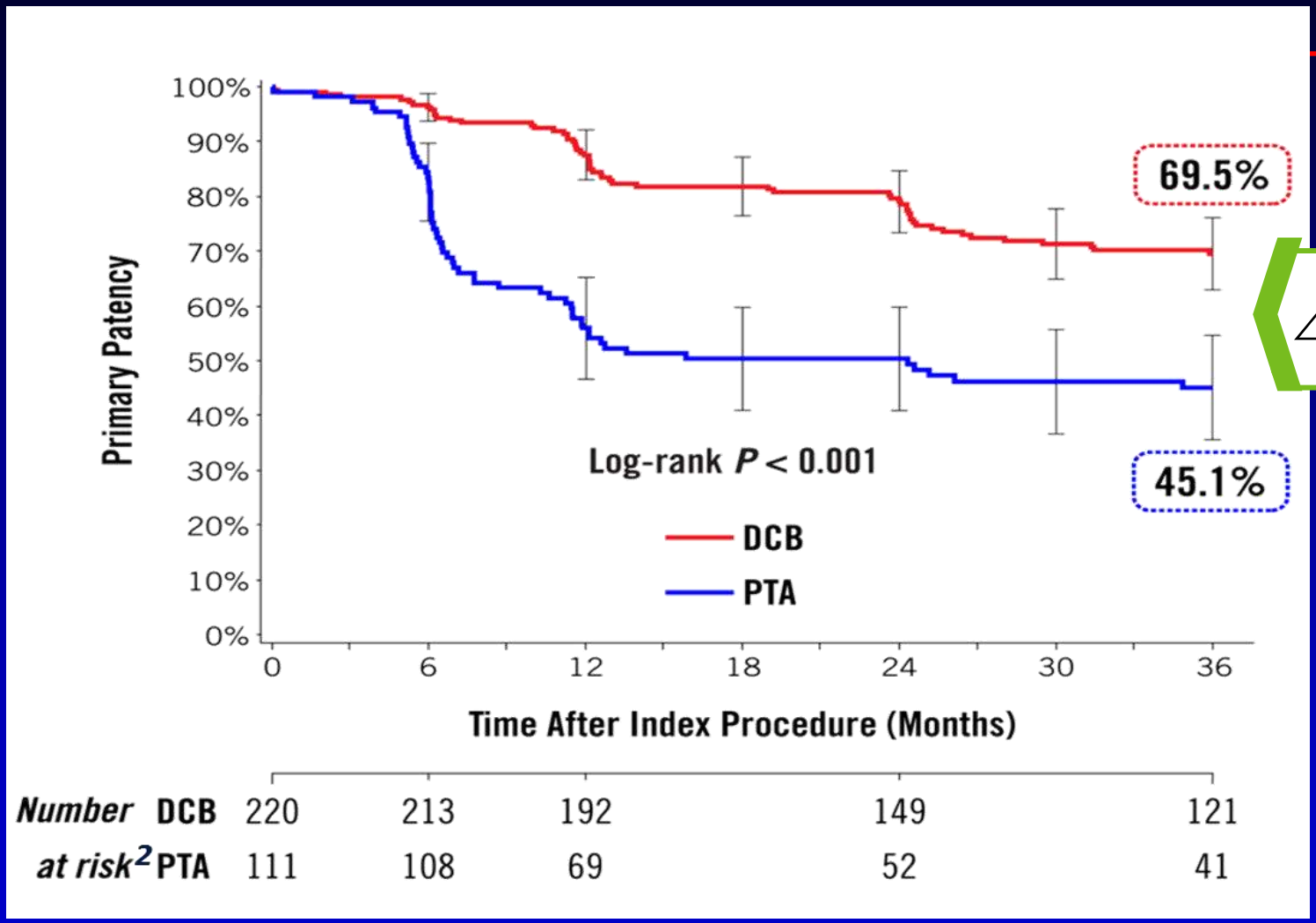
Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

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

What we need to accept

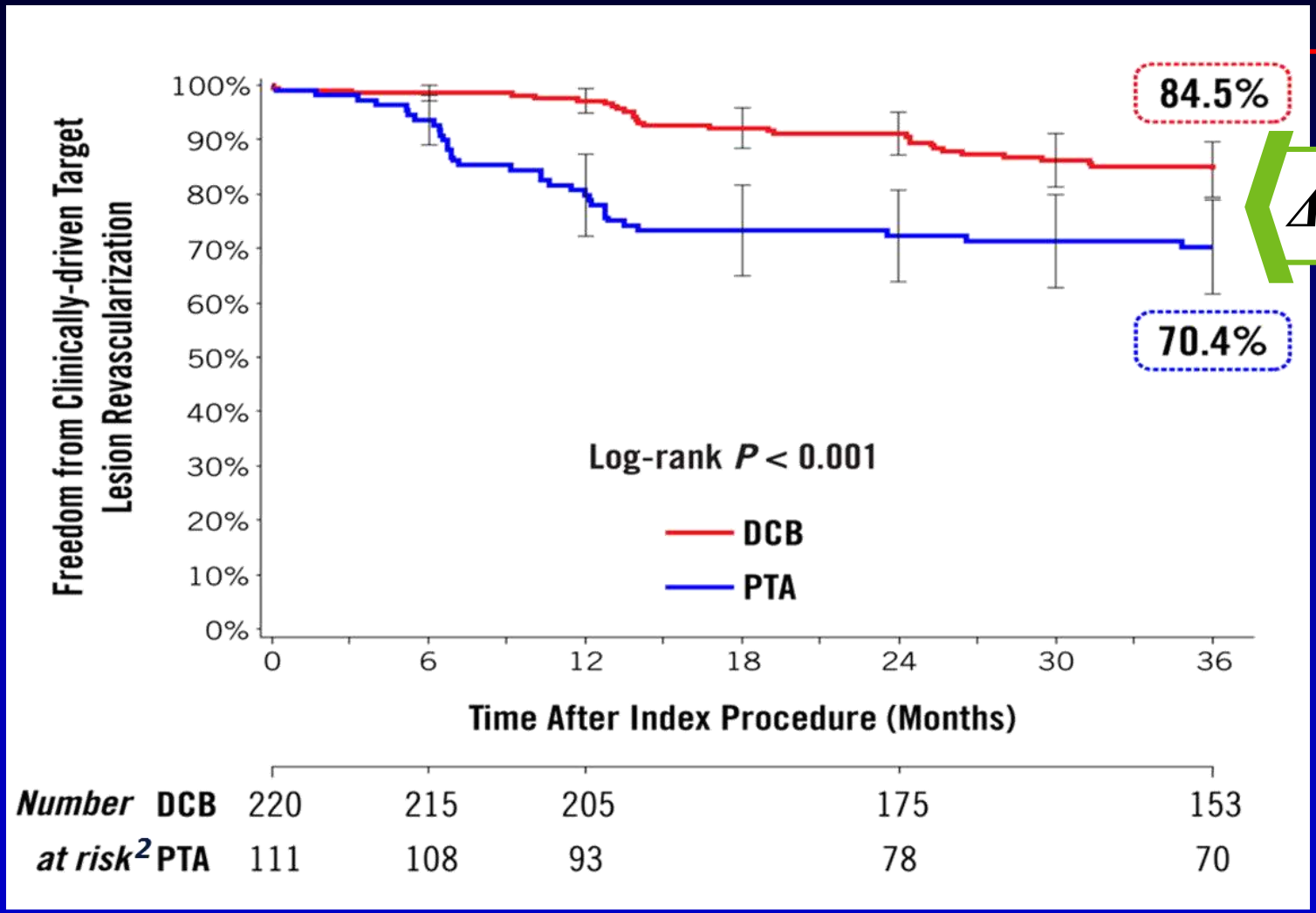
- The SFA landscape is fluid
  - Stenting predominates
  - Leave nothing behind multiple strategies
    - ***Vessel prep remains a key question***
      - ***Definition remains elusive***
        - » ***PTA alone***
        - » ***Debulking strategy***
- Any RCT is unique
  - The registry is not the RCT
- The RCT is not the registry
  - Registry generally does not have the rigor of the RCT
    - Core lab
    - DSMB/CEC
    - Patient population
- Alternative therapies may or may not still be important for lower extremity “leave nothing behind” strategies

IN.PACT SFA Trial:
Primary Patency[1] through 3 Years



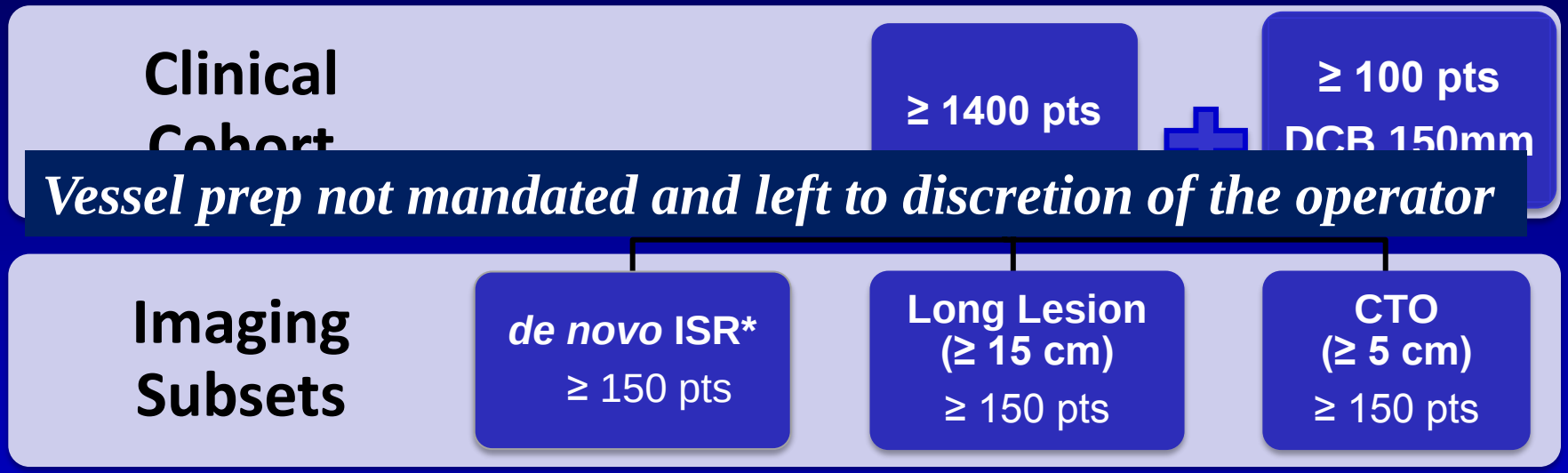
1. Freedom from core laboratory-assessed restenosis (duplex ultrasound PSVR ≤2.4) or clinically-driven target lesion revascularization through 36 months (adjudicated by a Clinical Events Committee blinded to the assigned treatment).
2. Number at risk represents the number of evaluable subjects at the beginning of each 30-day window.

IN.PACT SFA Trial:
Freedom from CD-TLR[1] through 3 Years



1. Clinically-driven TLR adjudicated by an independent Clinical Events Committee, blinded to the assigned treatment based on any re-intervention at the target lesion due to symptoms or drop of ABI of ≥20% or >0.15 when compared to post-procedure baseline ABI.
2. Number at risk represents the number of evaluable subjects at the beginning of each 30-day window.

IN.PACT Global Study Patient Cohorts



1538 patients enrolled

*ISR is not an approved indication in the US

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

Lesion	N=149
Lesion type:	
De Novo	0.0% (0/149)
Non-stented Restenotic	0.0% (0/149)
In-Stent Restenosis	100.0% (149/149)
Lesion Length (cm)	17.17 ± 10.47
Total Occlusions (%)	34.0% (48/141)
Calcification (%)	59.1% (78/132)
Severe Calcification (%)	8.3% (11/132)
RVD (mm)	5.222 ± 0.601
Diameter Stenosis (pre-treatment) (%)	84.8 ± 14.9
Dissections (%): 0	69.1% (103/149)
A-C	26.2% (39/149)
D-F	4.7% (7/149)

Procedural Characteristics	
Device Success [1]	99.6% (282/283)
Procedure Success [2]	99.2% (130/131)
Clinical Success [3]	98.5% (129/131)
Pre-dilatation	64.1% (84/131)
Post-dilatation	26.0% (34/131)
Provisional Stent	14.5% (19/131)

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

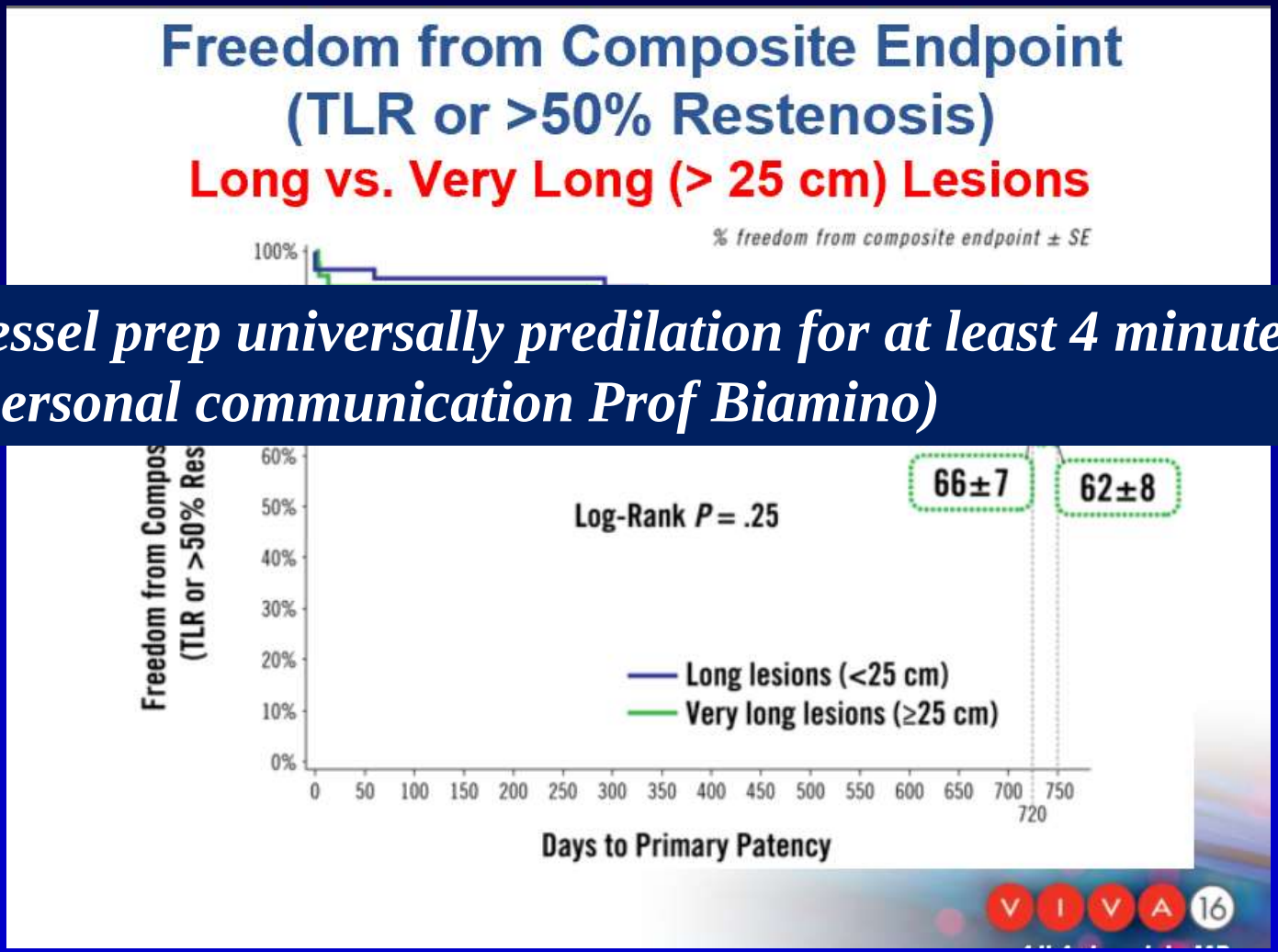
Lesions (N)	164
Lesion Type: de novo restenotic (no ISR) ISR	 83.2% (134/161) 16.8% (27/161) 0.0% (0/161)
Lesion Length	**26.40 ± 8.61 cm**
Total Occlusions	60.4% (99/164)
Calcification Severe	71.8% (117/163) 19.6% (32/163)
RVD (mm)	4.594 ± 0.819
Diameter Stenosis (pre-treatment)	90.9% ± 14.2
Dissections: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

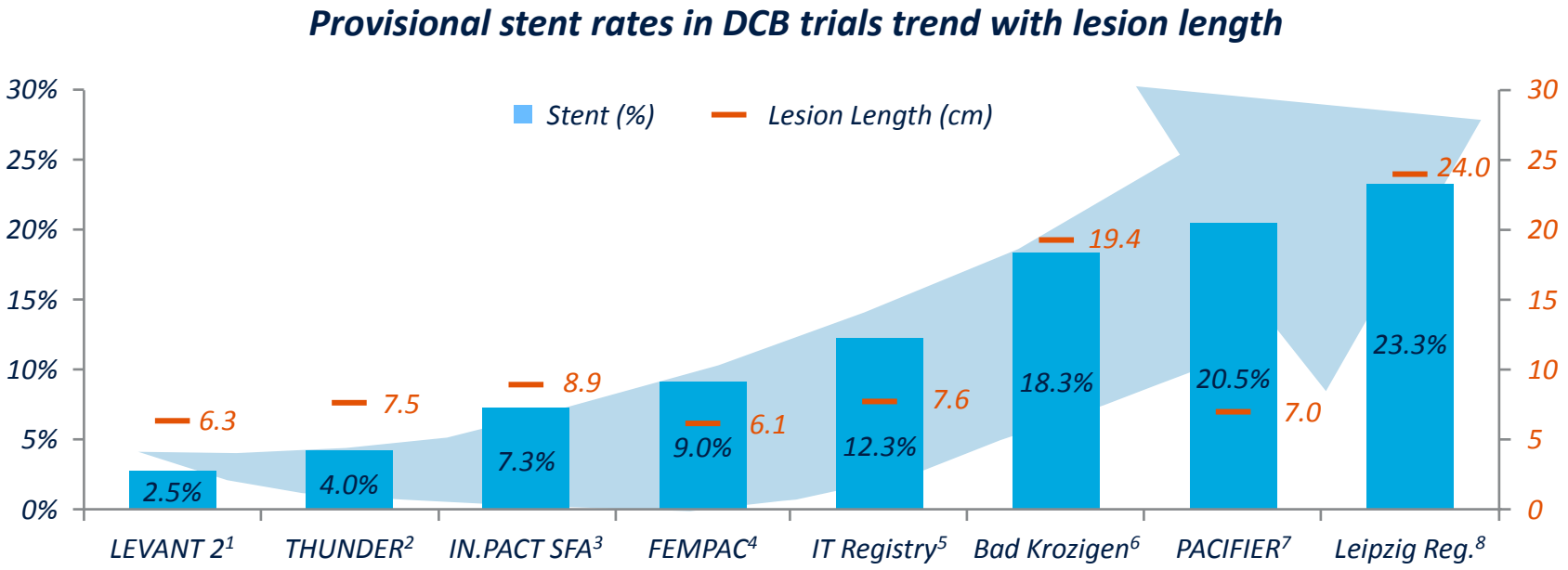
SFA long study



Vessel prep universally predilation for at least 4 minutes (personal communication Prof Biamino)

Micari A Viva 2016 presentation

SCAFFOLDS STILL NEEDED, LIKELY AT RATES PROPORTIONAL TO LESION COMPLEXITY



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

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

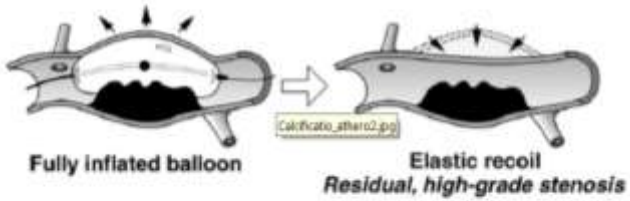
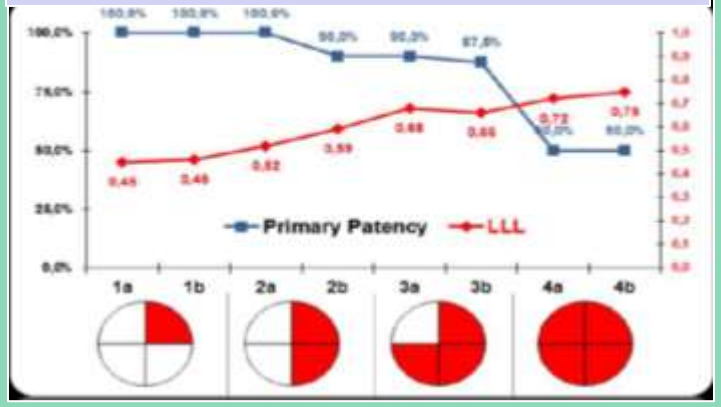


Figure 12.1. Elastic Recoil After PTCA of Calcified Lesions

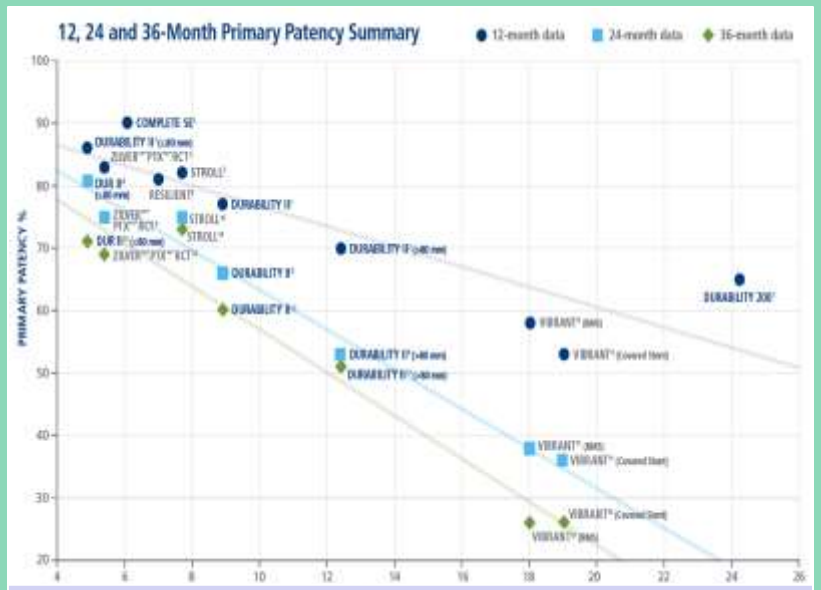
Rather than cracking the hard, calcified atheroma, PTCA causes stretching of the contralateral plaque-free wall segment and ineffective dilatation.

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)

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

Existing Atherectomy + DCB Data

Study (* Core Lab)	Type	Patients	Lesions	Dissection[4]	BO Stent	30-day MAE	1-year	>1-year
*DEFINITIVE AR[1]	DCB† DAART† DAART-Ca	54 48 19	54 48 19	19% (10/54) 2% (1/48) 0%	3.7% (2/54) 0% 5.3% (1/19)	NR	89.6% 93.4% ---	?
Cioppa[2]	DAART	30	30	6.7% (2/30)	6.7% (2/30)	13% (4/30) (1-year)	90%	?
Stavroulakis[3]	DAART	21	26	NR	NR	14% (3/21)	95%	90% (18-mo)

1. *"DEFINITIVE AR: A Pilot Study of Antirestenosis Treatment. 12-month Results: Directional Atherectomy Followed by a Paclitaxel-Coated Balloon to Inhibit Restenosis and Maintain Vessel Patency" presented by Zeller T, VIVA Las Vegas 2014. † Randomized arms included DCB and directional atherectomy plus DCB (DAART). A non-randomized arm, "DAART-Ca", was also enrolled in DEFINITIVE AR, but DUS patency is unavailable for the 19 subjects in this arm.*
2. *Cioppa A, et al. Cardiovasc Revasc Med 13:219-23 (2012).*
3. *Stavroulakis K, et al. J Endovasc Ther 22:847-52 (2015).*
4. *Zeller, et al., defined dissection as ≥ Grade C while Cioppa, et al., defined dissection via chroma-flow involving more than 60% of cross-sectional diameter with blood flow in the false lumen.*

DEFINITIVE AR

BASELINE CLINICAL DATA

BASELINE DEMOGRAPHICS	DAART (N=48)	DCB (N=54)	*P*-VALUE[1]	DAART SEVERE CA++ (N=19)
Age	70.1 ± 9.7	69.0 ± 8.2	0.44	69.7 ± 8.9
Male	64.6%	68.5%	0.68	73.7%
History and Risk Factors				
Angina	4.2%	9.3%	0.44	26.3%
Diabetes	27.1%	35.2%	0.40	26.3%
Hypertension	87.5%	81.5%	0.43	84.2%
Hyperlipidemia	70.8%	68.5%	0.83	73.7%
Renal Insufficiency	12.5%	14.8%	0.78	15.8%
Current/Previous Smoker	50.0%	63.0%	0.23	36.8%

1. p-value for DAART RCT vs. DCB groups

DEFINITIVE AR

LESION CHARACTERISTICS

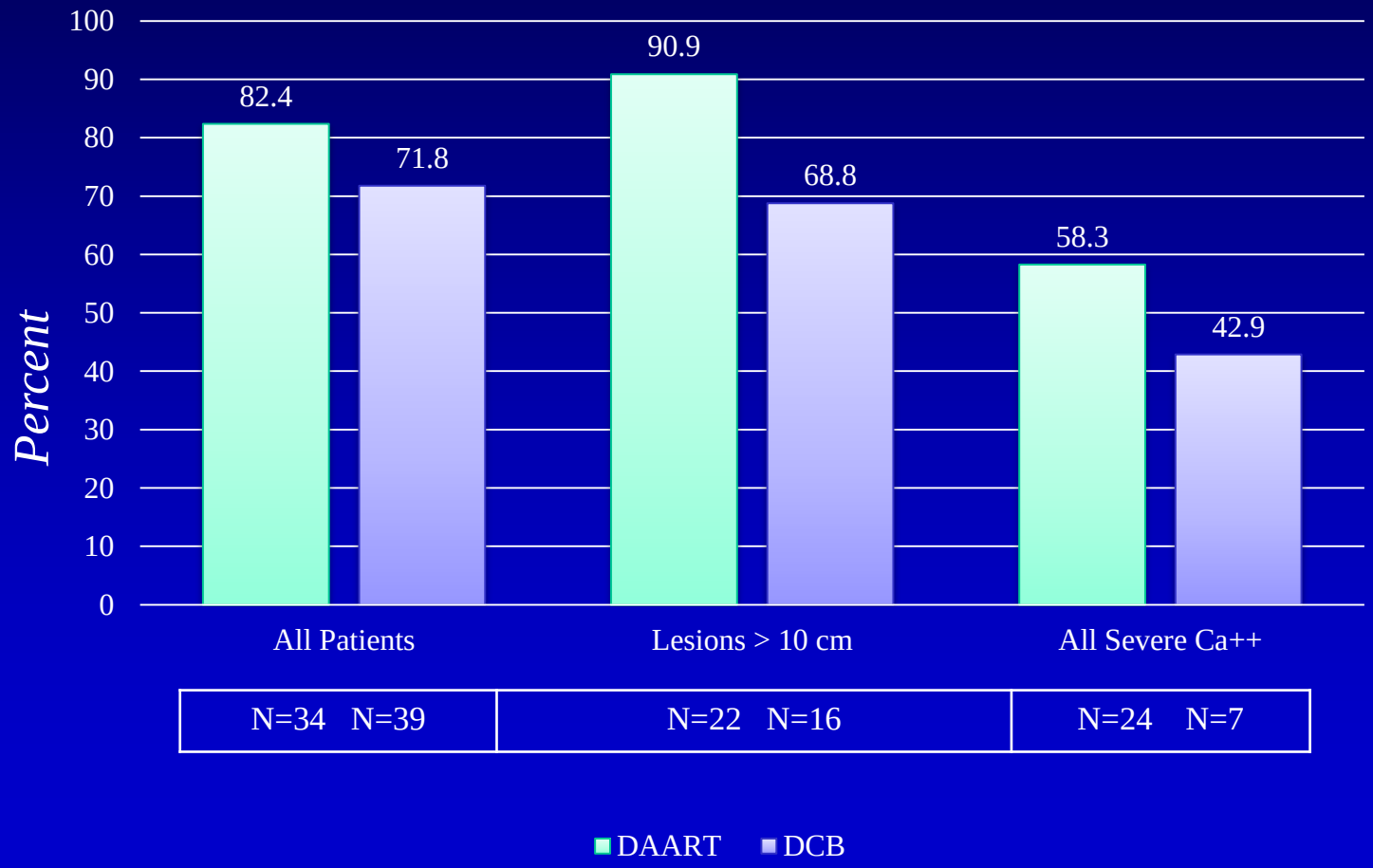
Longer Lesions Treated in DAART Arm

BASELINE CHARACTERISTICS	DAART (N= 48)	DCB (N = 54)	*P*-VALUE[1]	DAART SEVERE CA++ (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%

*1 Per Core Lab * p-value for DAART RCT vs. DCB groups*

DEFINITIVE AR

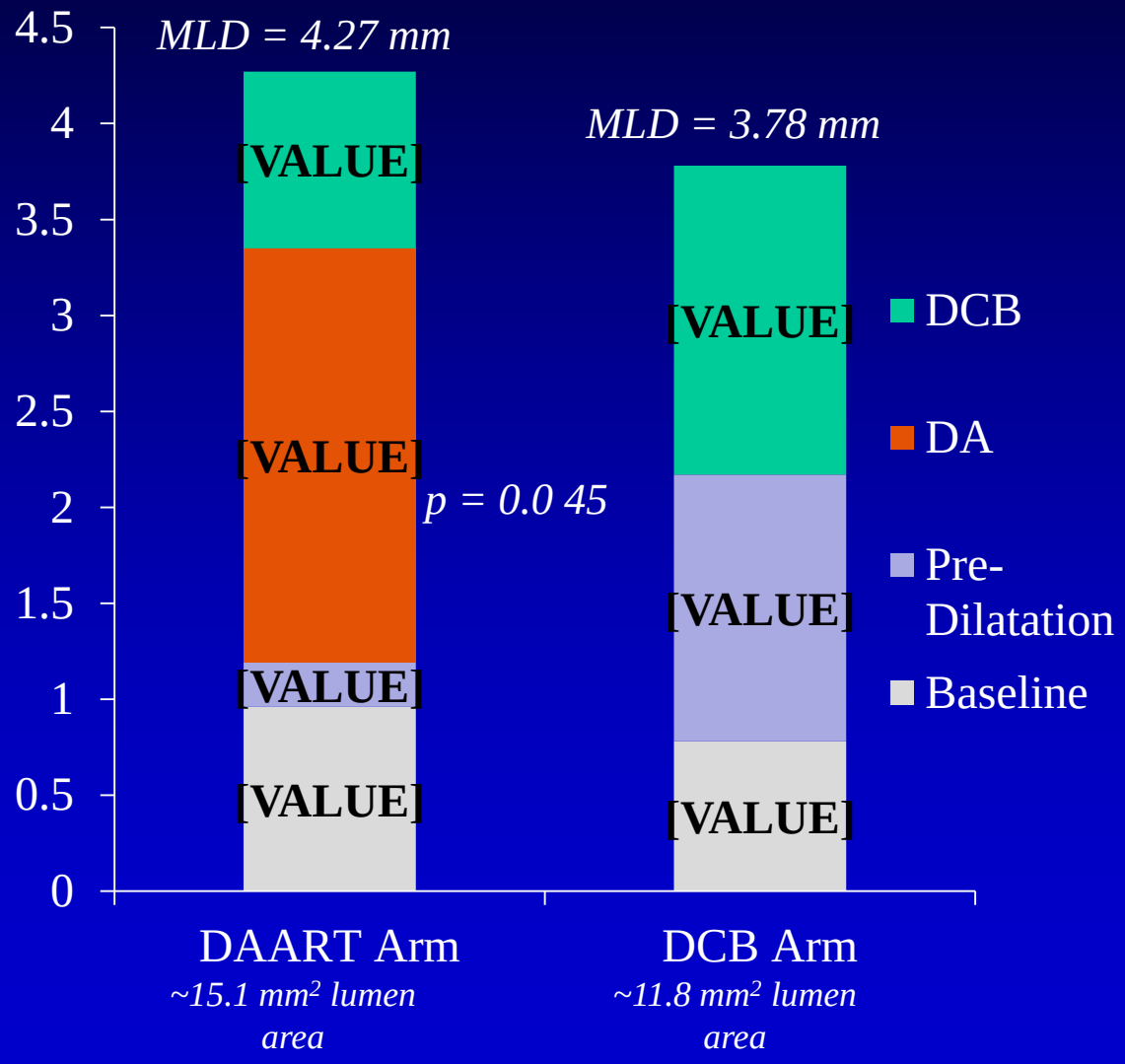
ANGIOGRAPHIC PATENCY



Per Core Lab Assessment. "All Severe Ca++" group includes all patients with severe calcium (including randomized and non-randomized).
Results for all patients who returned for angiographic follow-up.

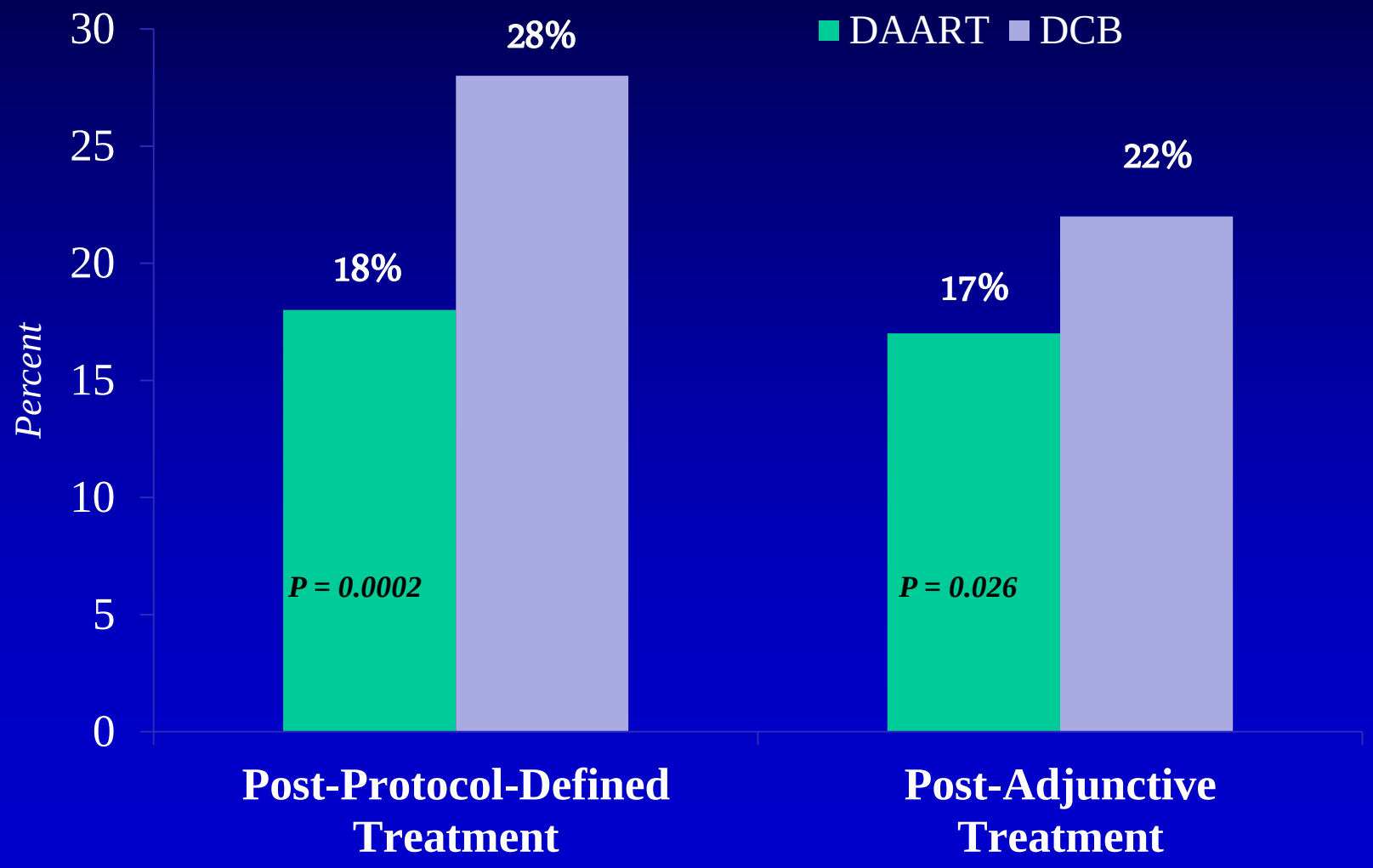
DEFINITIVE AR

GREATER MLD AFTER DAART



DEFINITIVE AR

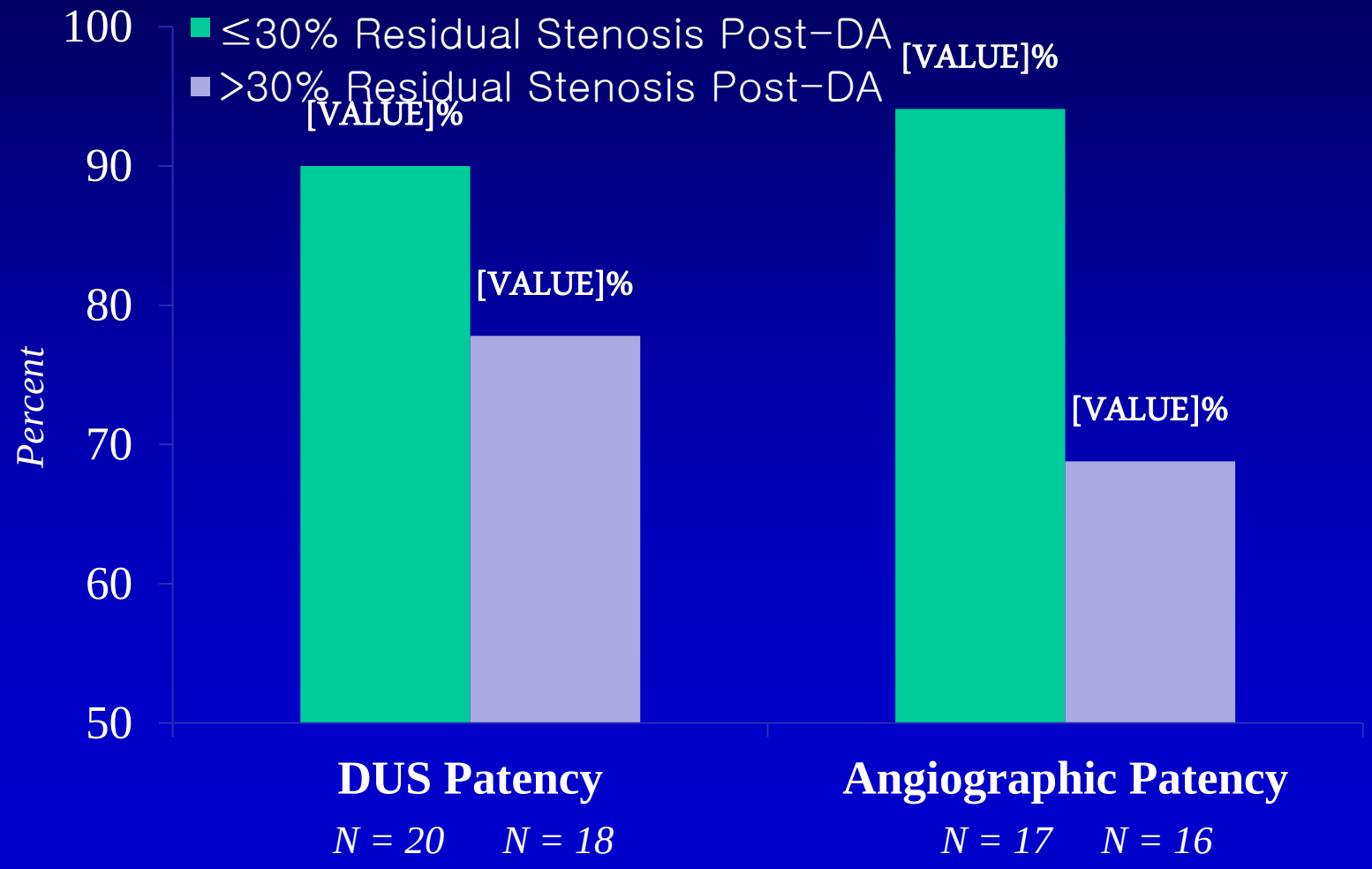
DAART DECREASES RESIDUAL STENOSIS



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

How much is enough?

- Debulking is not the goal of therapy with many atherectomy devices
- Rather, the issue is arterial compliance
- No one study has shown what metric is needed to confirm effective arterial compliance change
  - REALITY may answer this question
- Ultimately, the over use of atherectomy may lead to complications that may be directly attributable or accessory to the complication from DCB

Conclusions

- 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 remains ill-defined is"vessel prep"
  - PTA alone in simple to long lesions may be enough
  - Complex or calcific lesions may require debulking
- 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***
- 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, a debulk strategy may indeed remain a viable technology in the SFA particularly to avoid stent placement