Atherectomy plus DCB a winning combination?

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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
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• Ownership/Founder	• Innovation Vascular Partners, Consulting
• Intellectual Property Rights	• None
• Other Financial Benefit	• None

Current endovascular data

	Patients (n)	Device	Lesion length (cm)	1 year primary patency (%) (PSVR)
MIMIC	81	PTA	NA	NA
ABSOLUTE	104	Stent	10.2	63 (2.5)
RESILIENT	137	Stent	6.3	81 (2.4)
VIBRANT	76	Stent graft	19.6	53 (2.5)
VIPER	119	Stent graft	19.0	73(2.5)
ZilverPTX	240	DES-SES	5.4	83 (2.0)
THUNDER	54	DCB	7.4	74 (2.4)
LEVANT	50	DCB	8.1	78 (2.5)
IN-PACT	301/220	DCB	8.9	90 (2.4)

Stenting?

- To date the meaningful stenting studies have evaluated 5-6 cm lesions and only 2 studies have tested long lesions closer to 20 cms that we consider “real world” cases
  - Do we honestly believe an 75-80% PP at 12 months is “good enough” to then deal with the permanent prosthesis?
- The gorilla in the room is restenosis
  - In-stent restenosis vs de-novo restenosis
  - Focal vs diffuse
  - Recurrent vs recurrent
- Alternative therapies have been shown to be just as durable and safe as DES/BMS and combination therapy appears very appealing

Why atherectomy?

- In 2012 atherectomy became fashionable again
- We treat patients in a world outside of 5 cm lesions
- There is no finality to treatment with atherectomy
- There is no initial need for an endoprosthesis
- Side-branches are generally preserved with most technologies
- Repeat or other interventions still all possible
- Opportunity for dedicated combination therapy signal is appealing

Definitive LE Design Elements

- **Study Design and Oversight:**
  - Prospective, non-randomized, global study
  - 800 subjects enrolled at 47 centers
  - CEC and Steering Committee oversight and CEC adjudicaiton
  - Angiographic and Duplex core laboratory analyses

- **Inclusion Criteria**
  - RCC 1-6
  - ≥ 50% stenosis
  - Lesion lengths up to 20cm
  - Reference Vessel ≥ 1.5 mm and ≤ 7.0 mm

- **Exclusion Criteria**
  - Severe calcification
  - In-stent restenosis
  - Aneurysmal target vessel

Primary Patency in 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

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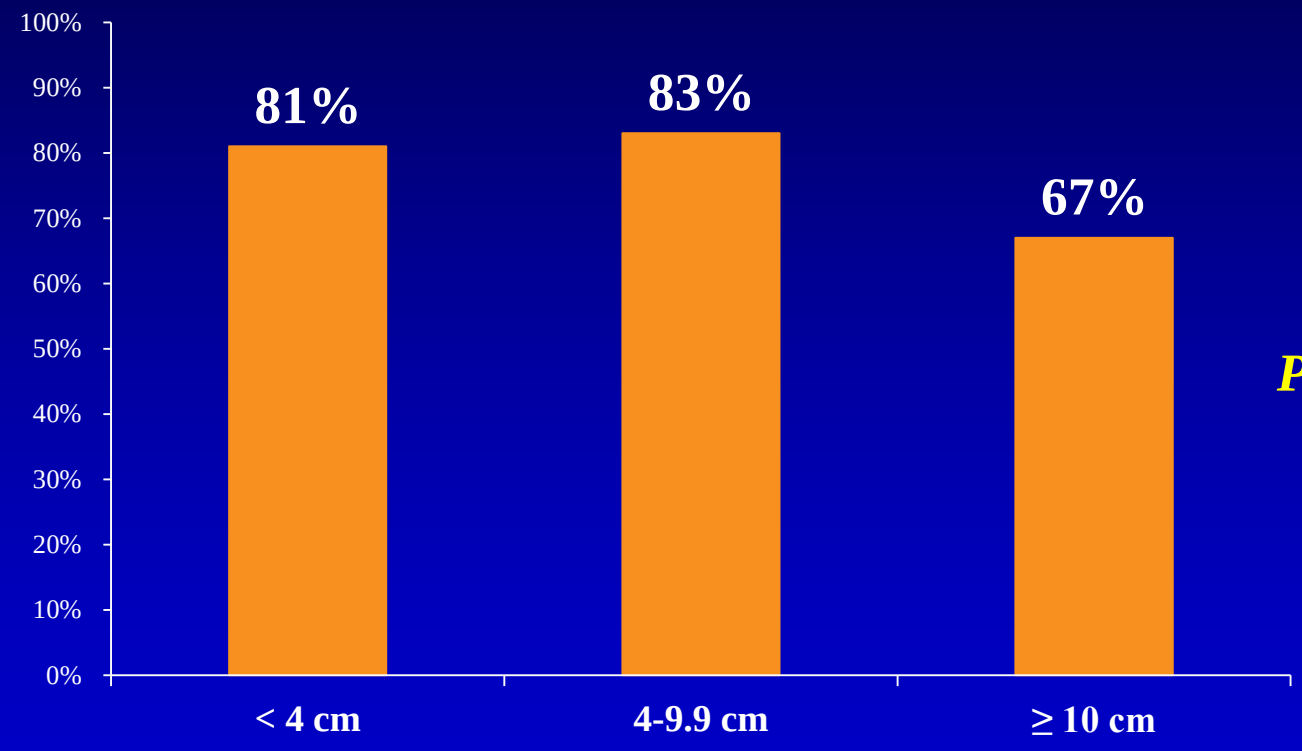
By Lesion Length				
< 4 cm (n=318)	81%	2.2	84%	2.3
4-9.9 cm (n=418)	83%	6.5	62%	6.6
≥ 10 cm (n=283)	67%	14.4	65%	15.1
SFA Only By Lesion Length				
< 4 cm (n=184)	78%	2.3	82%	2.3
4-9.9 cm (n=253)	83%	6.5	60%	6.9
≥ 10 cm (n=232)	65%	14.6	63%	15.5

Effective treatment for myriad of lesion lengths

12 Month Primary Patency Rates from DEFINITIVE LE

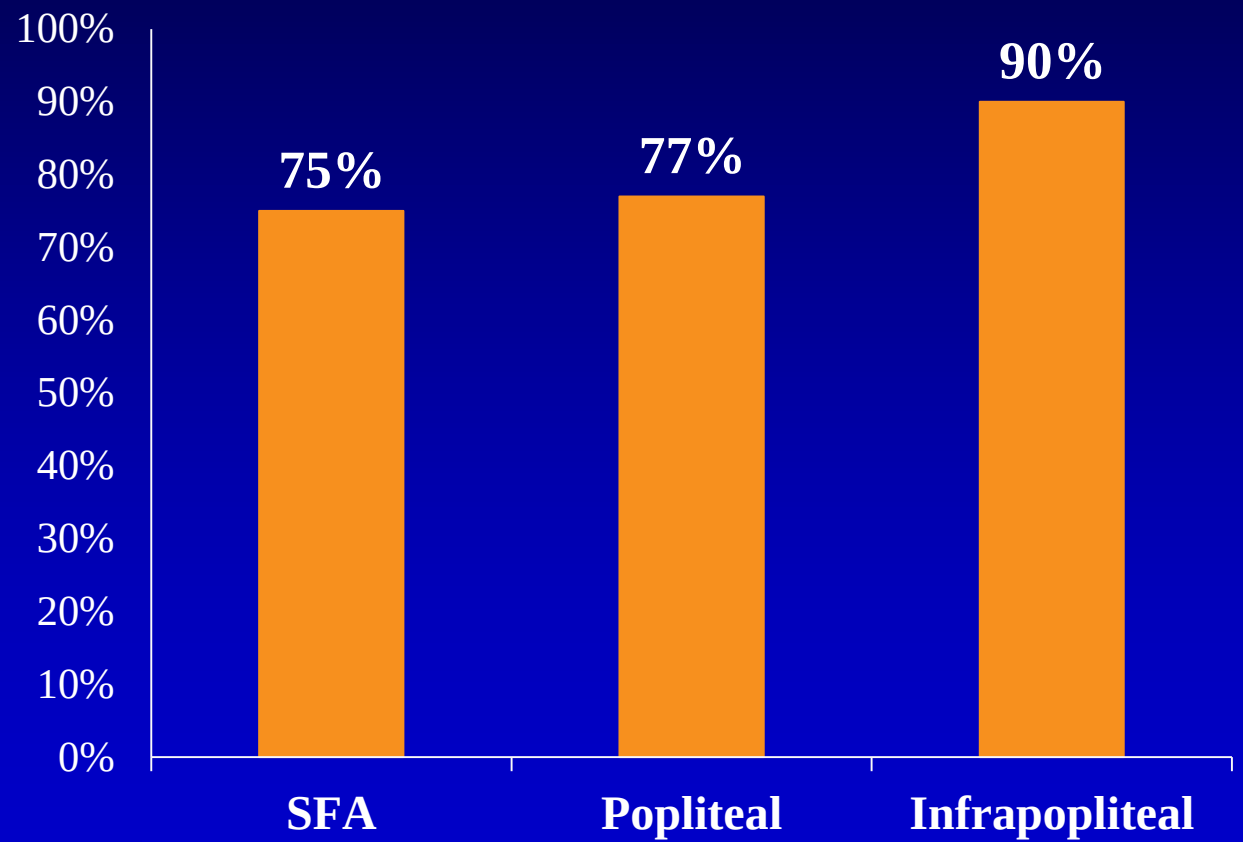


PSVR ≤ 2.4

Mean length :	***2.2 cm***	***6.5 cm***	***14.4 cm***
Number of lesions:	***220***	***307***	***214***

Effective in ATK and BTK

12 Month Primary Patency Rates from DEFINITIVE LE

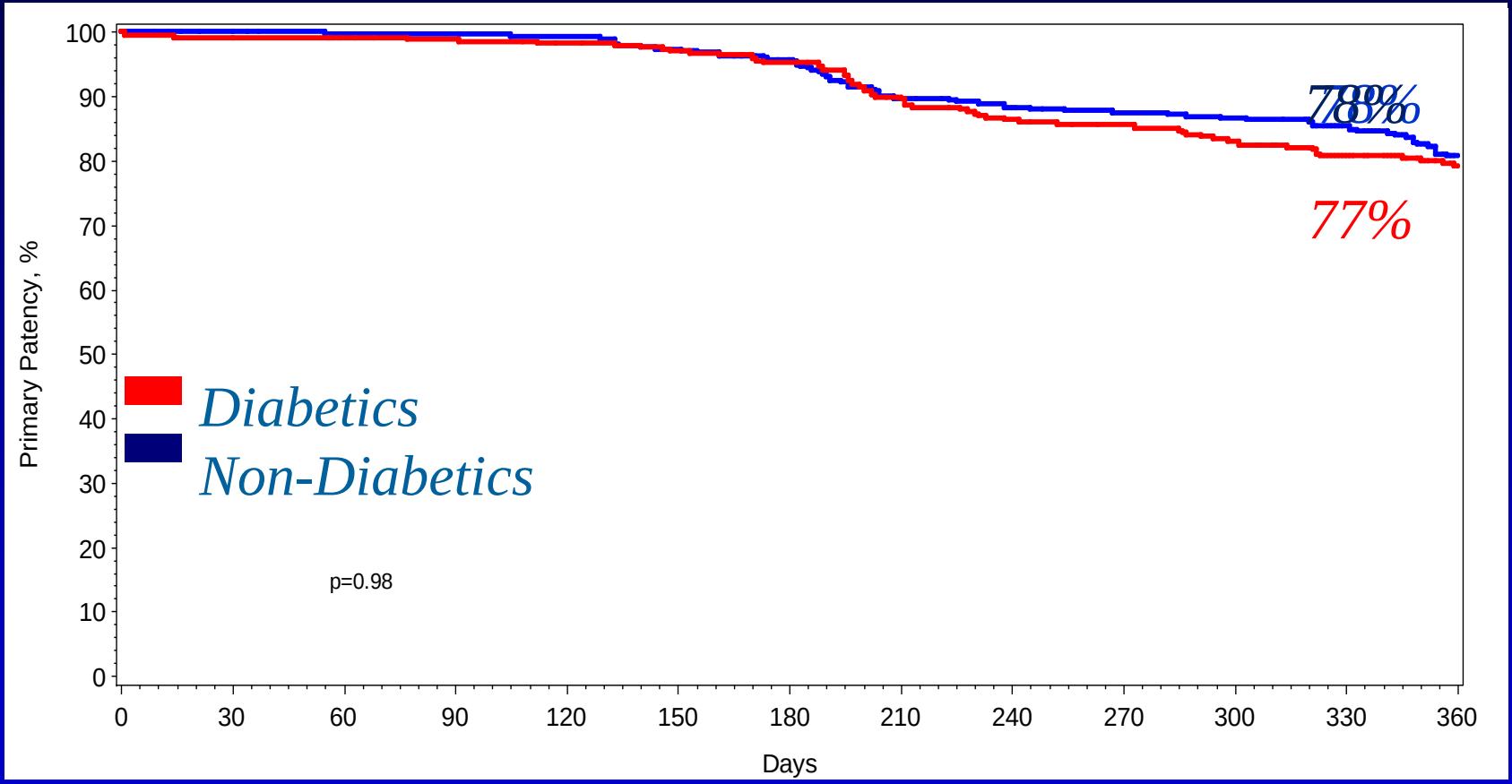


PSVR ≤ 2.4

Mean length :	***8.1 cm***	***6.0 cm***	***5.5 cm***
Number of Lesions:	***536***	***114***	***93***

Primary Patency by Kaplan-Meier

Claudicant Cohort



DEFINITIVE LE Conclusions

- Largest independently-adjudicated study of peripheral atherectomy performed to date

- Directional atherectomy is safe & effective at 12 months
  - Bail out stent rate only 3% in 1100 lesions
  - Effective for short, medium and long lesions in claudicants & CLI patients
    - **83% SFA (4-10cm) in claudicant patients**
    - **78% Infra-popliteal (6.0cm) in CLI patients**
    - **95% Limb Salvage in CLI patients**

- Diabetics perform equally well when treated with directional atherectomy to non-diabetics for claudicants

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

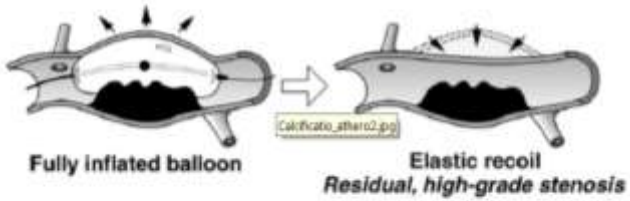
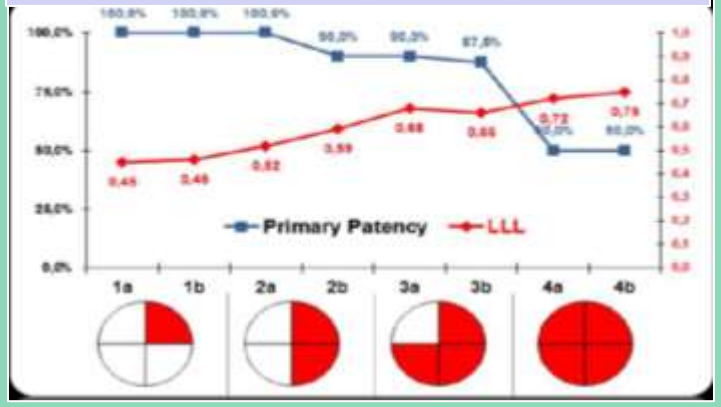


Figure 12.1. Elastic Recoil After PTCA of Calcified Lesions

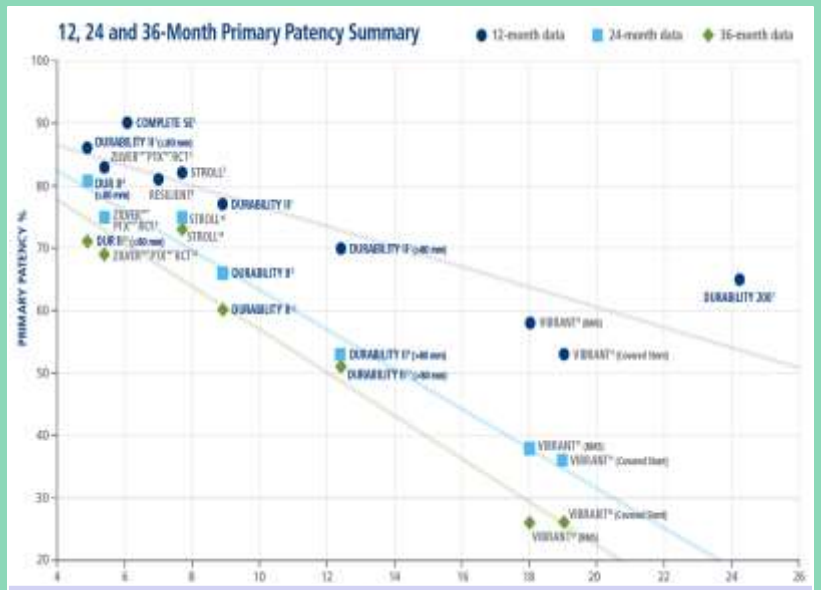
Rather than cracking the hard, calcified atheroma, PTCA causes stretching of the contralateral plaque-free wall segment and ineffective dilatation.

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

Calcium May Limit Drug Effect[2]



Longer Lesion Length



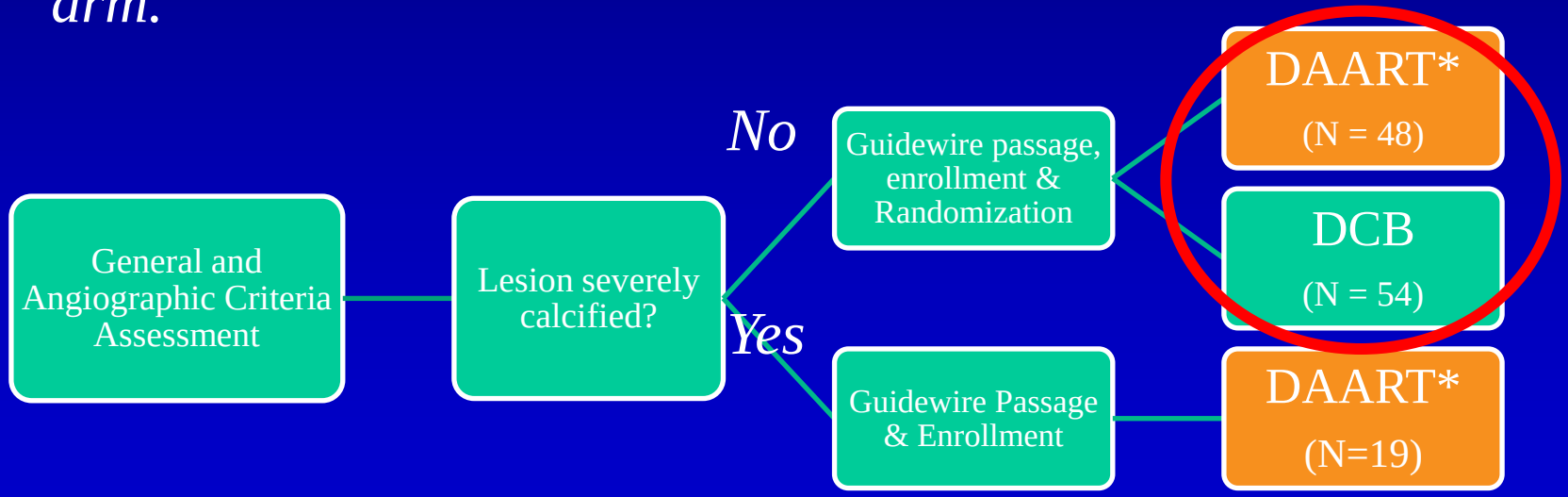
Increased lesion length is an independent predictor of decreased patency[5].

[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 AR Study Design

Purpose: assess and estimate the effect of treating a vessel with directional atherectomy + DCB (DAART) compared to treatment with DCB alone

Registry arm for severely calcified lesions created to limit bail-out stenting (and therefore variables) in randomized arm.



* ***D****irectional* ***A****therectomy +* ***A****nti-****R****estenotic* ***T****herapy*

Baseline Lesion Characteristics

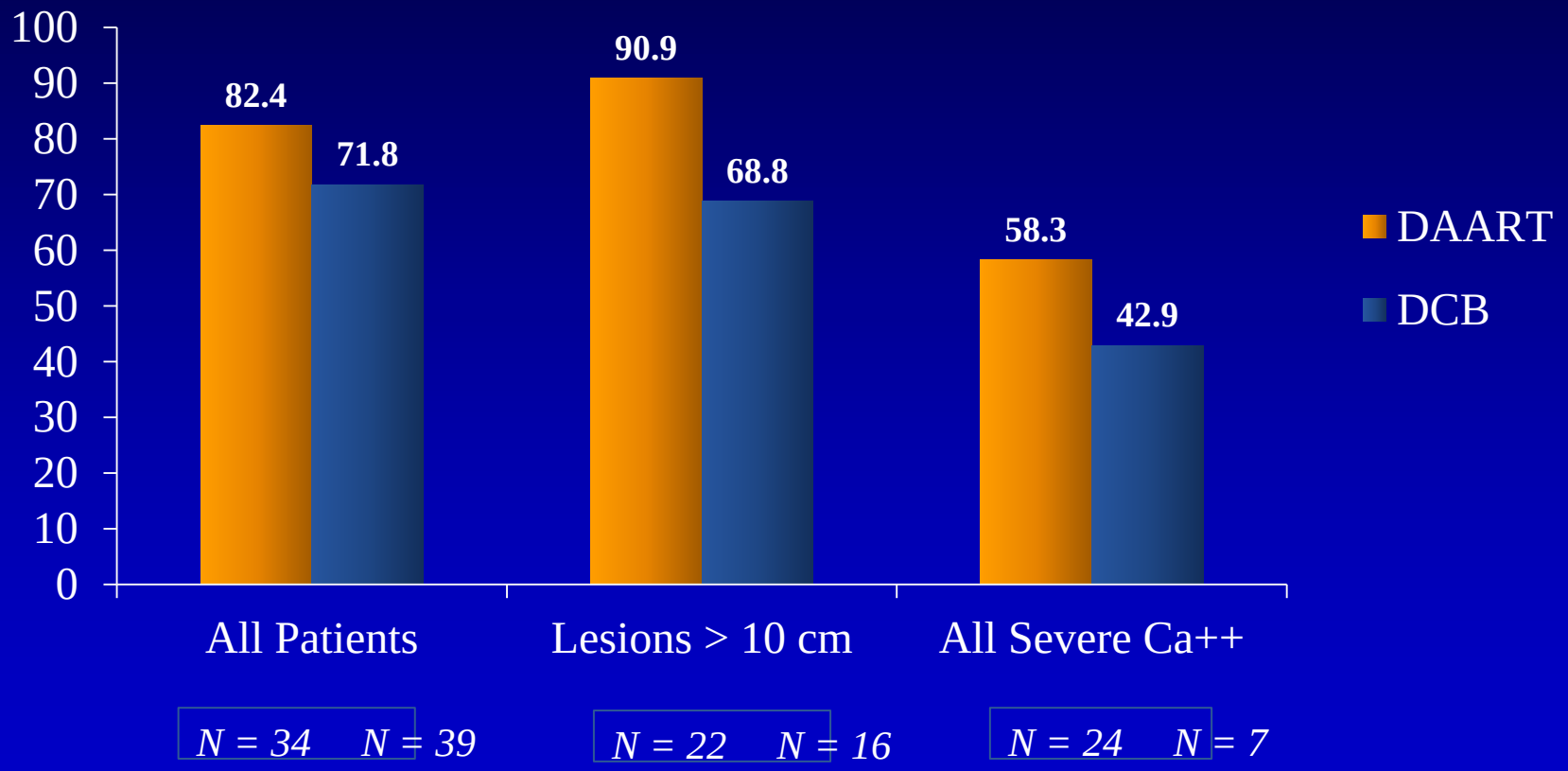
Per Core Lab

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

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

Atherectomy plus DCB

- DEFINITIVE LE proved atherectomy safe & effective at 12 months
  - Effective for short, medium and long lesions in claudicants & CLI patients
- DEFINTIVE AR pilot study demonstrated a signal of additional benefit for combined therapy
  - SFA atherectomy alone 75% to 90% DAART
- No current data regarding BTK application
- Opportunity for re-therapy remains open to the operator and patient if no endoprosthesis is left behind at the index procedure.
- Overall cost benefit needs assessment but remember repeat revascularization for ISRS may not benign and only once