Vessel Preparation Has DEFINITIVE LE and DEFINITIVE AR Results Influenced Current Practice?

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

Vessel Prep: What Does It Mean?

Vessel prep is improving the local environment of the vessel prior to leaving something behind, whether that something is a stent or a non-stent anti-proliferative agent

↑ Vessel Compliance and/or Lumen Gain

↑ Drug Transfer and Uptake

Directional Atherectomy achieves lumen gain by reducing plaque burden through debulking

Available Solo Atherectomy Data

Study (* Core Lab)	Type	Patients	Lesions	Dissection (≥Grade D)	BO Stent	30-day MAE	Patency 1-year	Patency >1-year
*DEFINITIVE LE[1]	DA	598 (RCC 1-3) 201 (RCC 4-6)	743 279	2.2% (13/598) 2.5% (5/201)	3.2% (33/1022)	1.0% (6/598) 3.5% (7/201)	78% 71%	?
*DEFINITIVE CA[2]	DA	133	168	0.8% (1/131)	4.1% (7/169)	6.9% (9/131)	NR	?
VISION-IDE[3]	DA	130	130	NR	4.0%	17.6% (6-mo)	NR	?
OASIS[4]	OA	124	201	NR	2.5% (5/201)	3.2% (4/124)	NR	?
COMPLIANCE 360[5]	OA	25	38	NR	5.3% (2/38)	NR	81.2%	?
CALCIUM 360[6]	OA	25	29	3.5% (1/29)	6.9% (2/29)	0%	NR	?
*PATHWAY PVD[7]	RA	172	210	9% (15/172)	7% (14/210)	1.0% (2/172)	61.8%	?
*CELLO[8]	Las	65	65	NR	23.2% (15/65)	0%	54.3%	?
*EXCITE-ISR[9]	Las	169	169	2.4% (≥Grade C)	4.1% (7/169)	5.8% (9/155)	71.1% (6-mo)	?

1. McKinsey J, et al. JACC Cardiovasc Interv 7(8):923-33:2014.
2. Roberts D, et al. Catheter Cardiovasc Interv 84(2):236-44:2014.
3. Schwindt A. Presented at VIVA, Las Vegas 2015.
4. Safian RD, et al. Catheter Cardiovasc Interv 73(3):406-12:2009.
5. Dattilo R, et al. J Invasive Cardiol 26(8):355-60:2014.
6. Shammas NW, et al. J Endovasc Ther 19(4):480-8:2012.
7. Zeller T, et al. J Endovasc Ther 16(6):653-62:2009.
8. Dave R, et al. J Endovasc Ther 16(6):665-75:2009.
9. Dippel EJ, et al. JACC Cardiovasc Interv 8(1 Pt. A):92-101:2015.

DEFINITIVE LE: Trial Overview

DESIGN

- Prospective, multinational, single-arm study
- Clinical events committee (CEC) adjudicated adverse events
- Largest Core Lab[1] adjudicated atherectomy trial

OBJECTIVE

To evaluate the effectiveness of standalone SilverHawk™ and TurboHawk™ Peripheral Plaque Excision Systems for endovascular treatment of peripheral arterial disease in the femoropopliteal and tibioperoneal arteries

PATIENTS

- 800 PATIENTS
- Pre-specified comparison of patients with / without diabetes

SITES

47 total sites in EU and US

1. VasCore DUS Core Laboratory, Boston, MA and SynvaCor Angiographic Core Laboratory, Springfield, IL.

DEFINITIVE LE: Design & Endpoints

800 Patients | 47 Centers

Claudication
598 Patients[1]

Primary Patency by
Duplex US at 12 months

Critical Limb Ischemia
201 Patients

Freedom From Major Unplanned Amputation at 12 months

1. Censored due to informed consent violation.

DEFINITIVE LE: Baseline Lesion Characteristics[1]

	Claudicant n = 598	CLI n = 201	P value	All Patients n = 799
Number of Lesions	743	279	n/a	1022
Mean Length (cm ± SD)	7.5 ± 5.3	7.2 ± 5.5	0.381	7.4 ± 5.3
Baseline Stenosis ± SD	72.7% ± 18.1	75.9% ± 20.0	0.015	73.6% ± 18.7
Occlusions	17.4%	29.9%	<0.001	20.8%
Calcification	37.1%	37.1%	1.000	37.1%
Lesion Location	**Claudicant n = 743 lesions**	**CLI n = 279 lesions**	**P value**	**All Patients n = 1022 lesions**
SFA	72.1%	48.4%	<0.001	65.7%
Popliteal	15.3%	17.2%	0.501	15.9%
Infrapopliteal	12.5%	34.4%	<0.001	18.5%

1. McKinsey, J. F., et al. JACC Cardiovasc Interv 2014;(8): 923-933.

DEFINITIVE LE: Baseline Lesion Characteristics[1]

	Claudicant n = 598	CLI n = 201	P value	All Patients n = 799
Device Success[2]	75.9%	72.1%	0.218	74.9%
Post-device stenosis ±SD	23.9% ± 13.1	25.6% ± 13.8	0.073	24.3% ± 13.3
Adjunctive therapy[3]	38.0%	30.2%	NR	35.3%
Procedure Success[4]	91.3%	83.0%	<0.001	89.1%
Post-adjunctive stenosis ±SD	18.0% ± 11.0	20.9% ± 12.3	0.045	18.6% ± 11.4

Flow-limiting dissections

- 598 (RCC 1-3) = 2.2%
- 201 (RCC 4-6) = 2.5%

- Pre-dilatation: 9%
- Post-dilatation: 33%
- Bail-out stenting: 3%

1. McKinsey, J. F., et al. JACC Cardiovasc Interv 2014;(8): 923-933.
2. Core lab adjudicated device success: ≤30% angiographic residual stenosis after directional atherectomy without adjunctive interventions
3. Core lab adjudicated adjunctive therapy: PTA, stent
4. Core lab adjudicated procedure Success: ≤30% angiographic residual stenosis after directional atherectomy and adjunctive interventions

DEFINITIVE LE: 12-month Primary Patency[1]

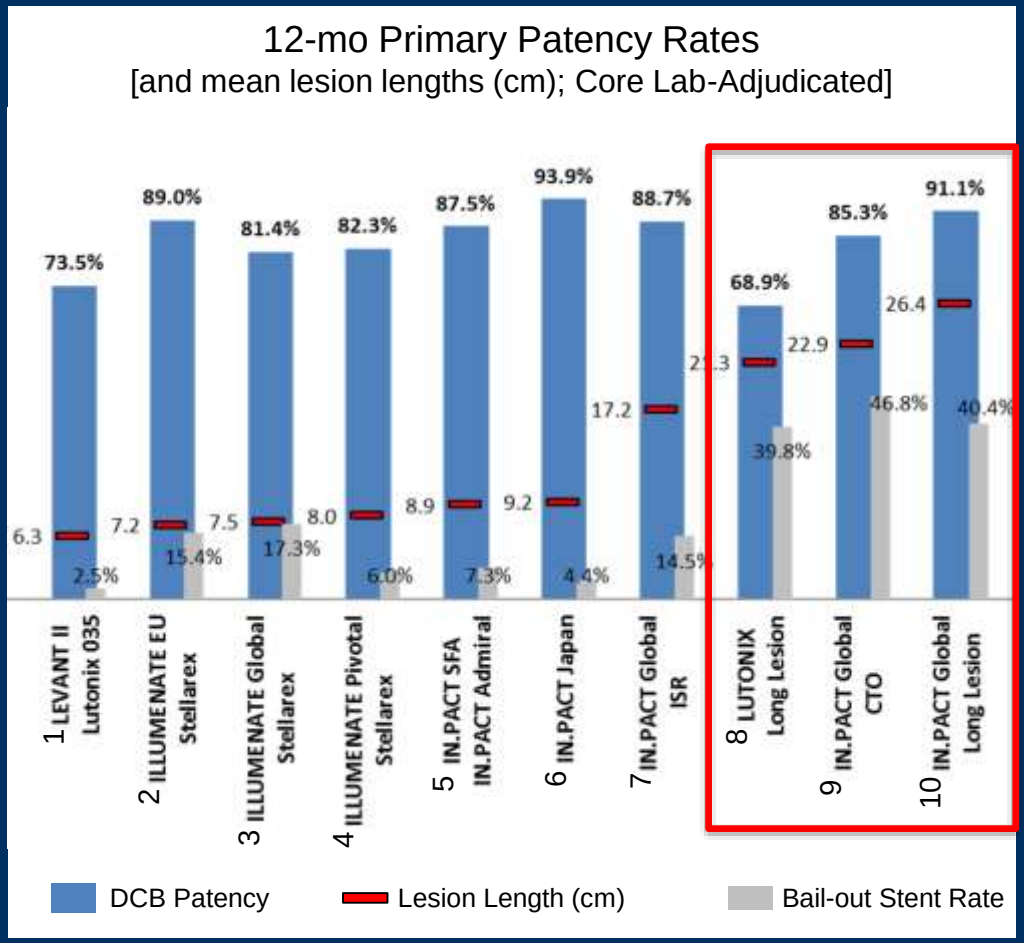
	Lesion Number	Lesion Length (cm)	Primary Patency at 12 months[2]
All Claudicants	743	7.5	78%
All CLI patients	279	7.2	71%

While directional atherectomy demonstrates compelling 12-mo outcomes, adjunctive value may come in the form of low dissection and bail-out stent rates

1. McKinsey, J. F., et al. JACC Cardiovasc Interv 2014;(8): 923-933.
2. Kaplan-Meier estimate of primary patency by duplex ultrasound at 12 months (PSVR ≤2.4 with no clinically-driven reintervention).

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

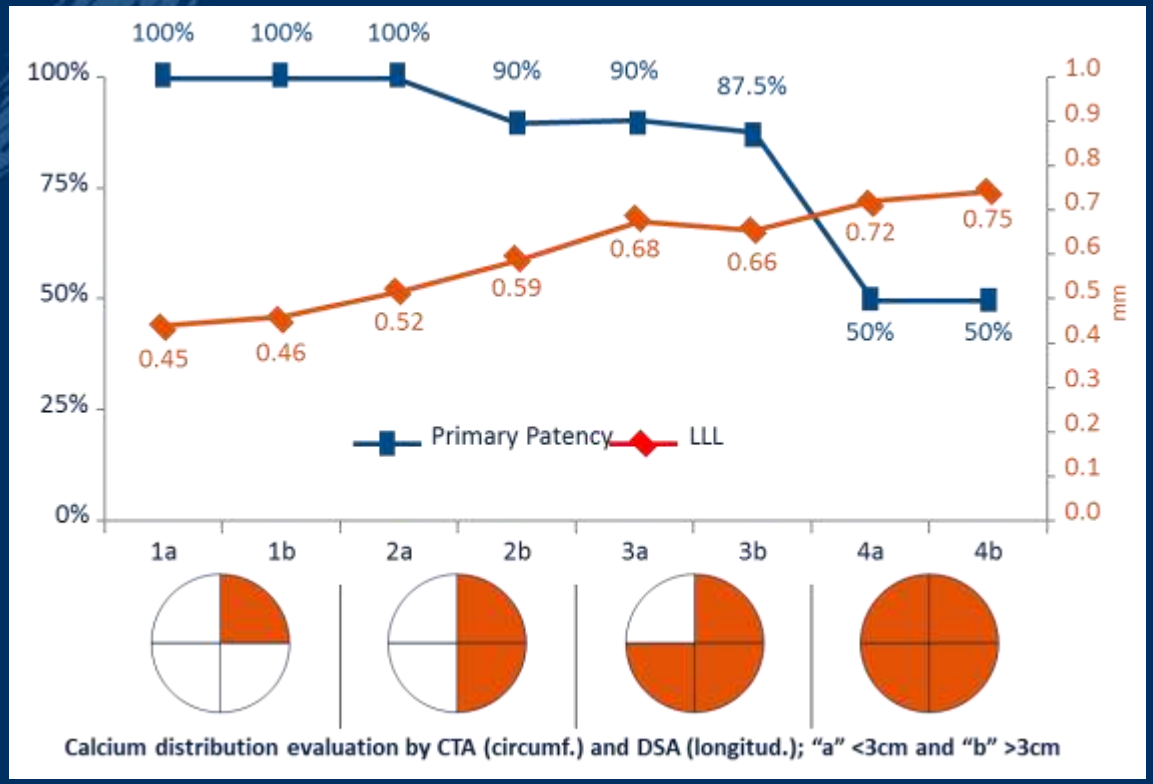


Patient demographics, lesion morphologies, patency definitions, and follow-up vary across trials.

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.

Known Limitations of DCB

- Calcium distribution and severity may affect late lumen loss (LLL) and primary patency
- Calcium may represent a barrier to optimal drug absorption



1. Fanelli F, et al. Cardiovasc Interv Radiol 37:898-907 (2014).

Existing Atherectomy + DCB Data

Few reports – Two single-center studies and one randomized feasibility study

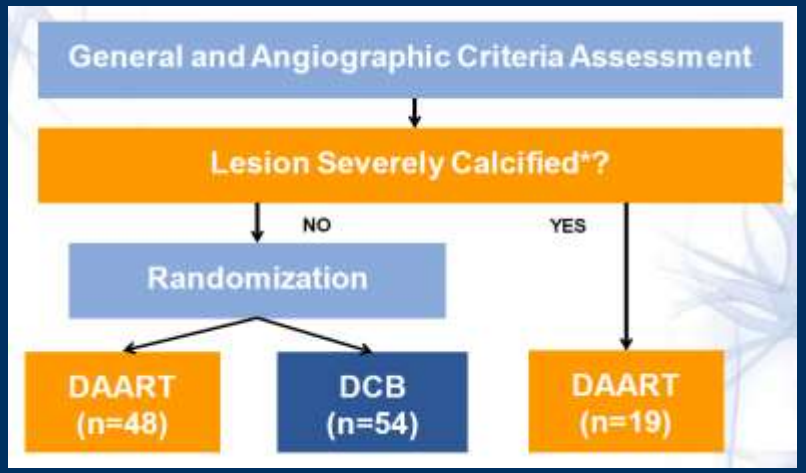
Study (* Core Lab)	Type	Patients	Lesions	Dissection[6]	BO Stent	30-day MAE	Patency 1-year	Patency >1-year
*DEFINITIVE AR[1]	DCB† DAART† DAART-Ca	54 48 19	54 48 19	19% (10/54) 2% (1/48) 0%	3.7% (2/54) 0% 5.3% (1/19)	NR	89.6% 93.4% ---	?
Cioppa[2]	DAART	30	30	6.7% (2/30)	6.7% (2/30)	13% (4/30) (1-year)	90%	?
Stavroulakis[3] (Popliteal)	DAART	21	26	NR	NR	14% (3/21)	95%	90% (18-mo)
Foley[4]	DCB OA+DCB	61 28	99 40	14% (14/99) 13% (5/40)	39% (39/99) 18% (7/40)	NR	81% 77%	?
Stavroulakis[4] (CFA)	DCB DAART	26 21	26 21	31% (8/26) 5% (1/21)	4% (1/26) 5% (1/21)	NR	68% 88%	?

1. Presented by Zeller T, VIVA, Las Vegas, US (2014).
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. Foley TR, et al. Cath Cardiovasc Interv 89:1078-85 (2017).
5. Stavroulakis K, et al. J Endovasc Ther; doi: 10.1177/1526602817748319 (2017).
6. 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[1]

Prospective, multicenter, randomized (DAART v DCB); plus non-randomized DAART arm for severely calcified lesions

- 121 subjects enrolled at 10 sites
- RCC 2-4; lesion lengths 7-15cm [excluding ISR, aneurysmal target sites and multi-lesion limbs]
- Independent CEC, and angiographic and DUS core labs
- Pilot study designed to assess effect of DAART v DCB
  - Not statistically powered
  - Motivated by determining trends that may foster development of future studies



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.

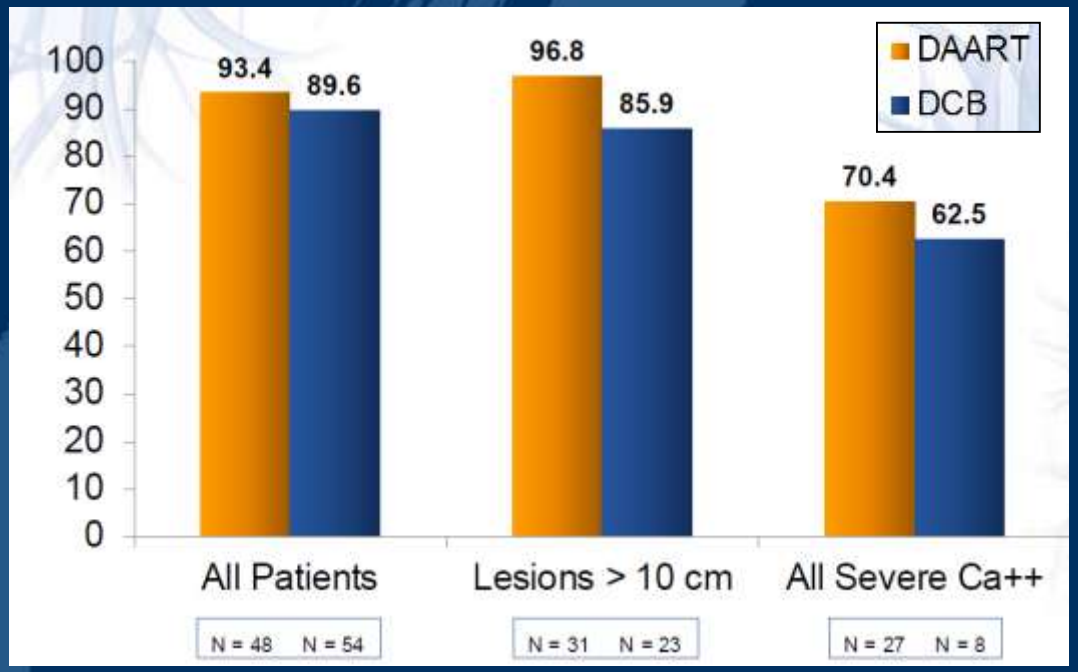
DEFINITIVE AR[1]

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%

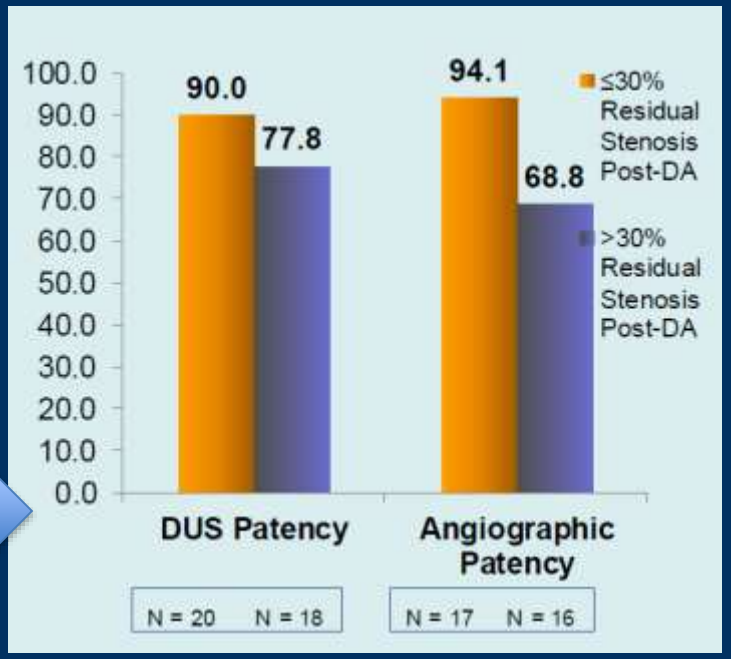
Outcomes	DAART (N= 48)	DCB (N = 54)	*p*-Value (DAART vs. DCB)	DAART Severe Ca++ Arm
Technical Success	89.6%	64.2%	0.004	84.2%
Distal Embolization	6% (3/48)	0% (0/54)	0.101	5.3% (1/19)
No Intervention	1	0		1
Endovascular Intervention	2	0		0
Bail-Out Stent	0% (0/48)	3.7% (2/54)	0.50	5.3% (1/19)
Dissection (flow-limiting, Grade C/D)	2% (1/48)	19% (10/54)	0.01	0% (0/19)
No Intervention	1	6		0
Endovascular Intervention	0	4		0
Perforation	4% (2/48)	0% (0/54)	0.22	0% (0/19)
No Intervention	0	0		0
Endovascular Intervention	2	0		0

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.

DEFINITIVE AR[1]



- Patency rates generally favorable
- Lower residual stenosis trended toward higher patency rates



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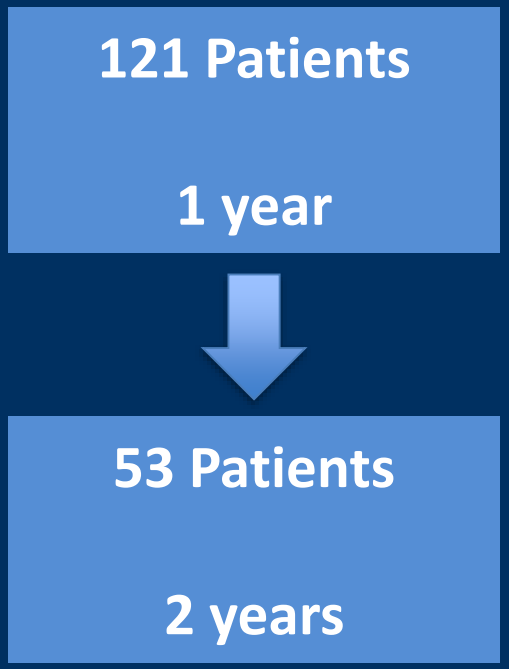
DEFINITIVE AR: 2-year Extension

DEFINTIIVE AR was extended beyond its originally-designed 1-year follow-up to 2 years[1]

Extended endpoints included

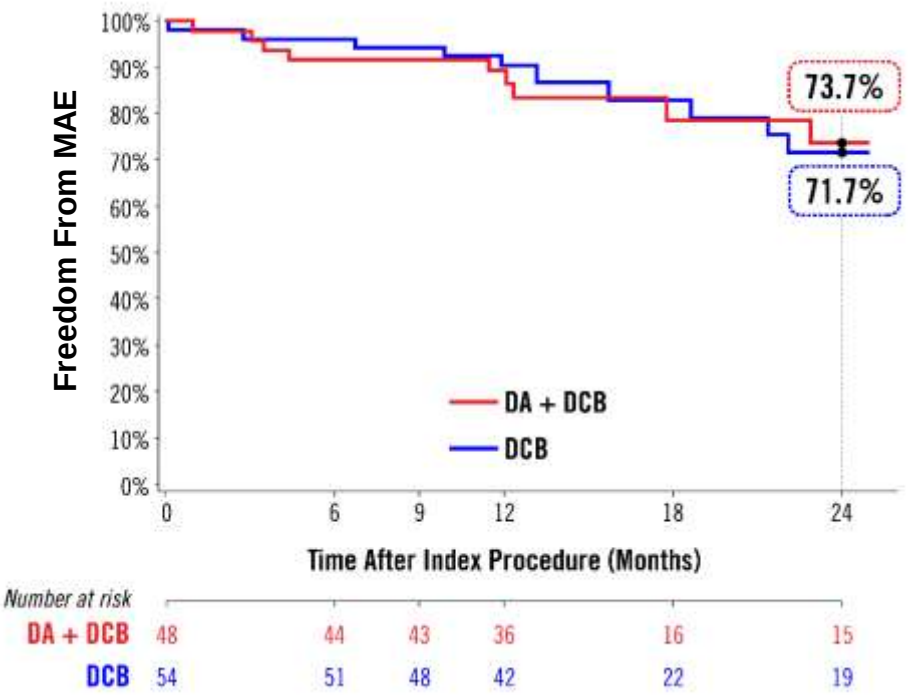
- Major Adverse Event Rate at 2 Years Defined as major unplanned amputation of the treated limb, all-cause mortality or clinically-driven target lesion revascularization.
- Change in WIQ/EQ-5D Score at 2 Years
- Target Lesion Revascularization (TLR) at 2 Years



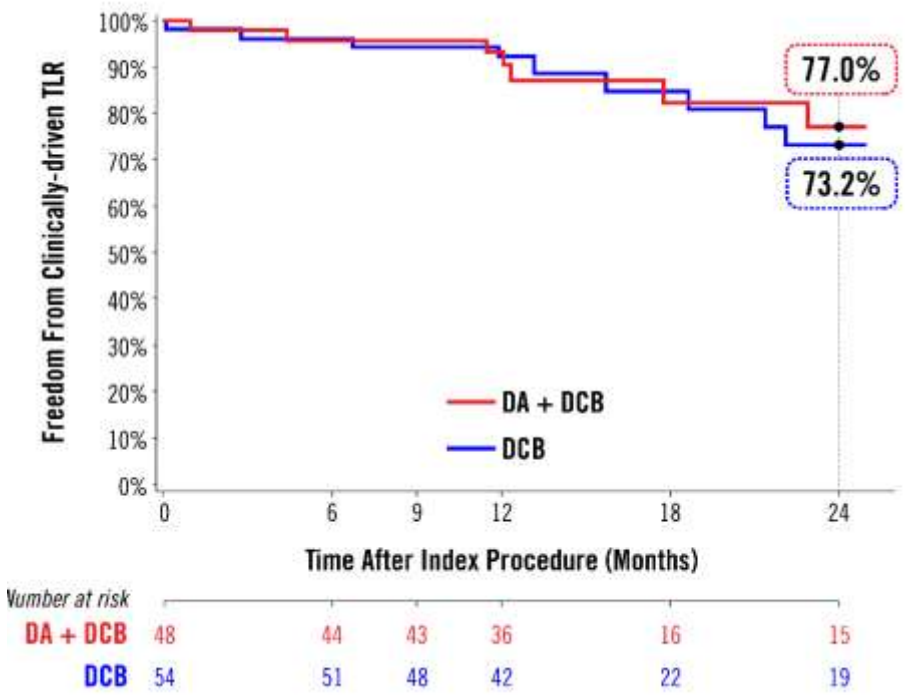
1. Presented by Tepe G, LINC, Leipzig, Germany 2017.

DEFINITIVE AR: 2-year Extension[1]

Freedom from MAE[2]



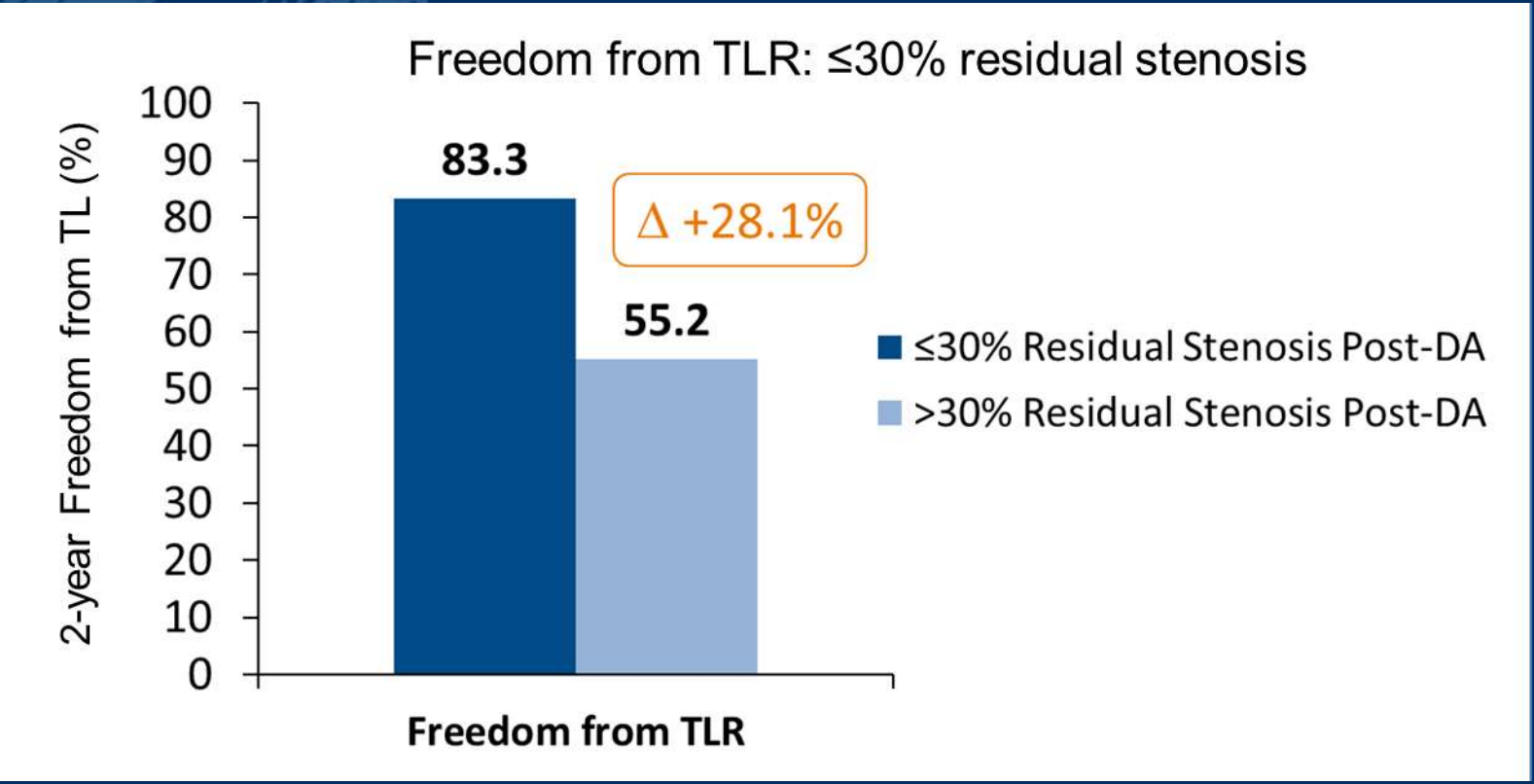
Freedom from Clinically-Driven TLR[3]



1. Presented by Tepe G at LINC, Leipzig, Germany 2017.
2. MAE (Major Adverse Event) defined as major unplanned amputation of the treated limb, all-cause mortality or clinically-driven target lesion revascularization.
3. Clinically-driven TLR (target lesion revascularization) defined as any reintervention or artery bypass graft surgery involving the target lesion in which the subject has a ≥ 70% diameter stenosis (Peak Systolic Velocity Ratio (PSVR) > 3.5 may substitute if a pre-intervention angiogram is not available) and at least two of the following: worsening RCC, worsening WIQ score, or an ABI drop > 0.15 from baseline.

DEFINITIVE AR: 2-year Extension

Impact of lumen gain at 2 years: trend towards lower TLR with ≤30% residual stenosis after DA[1]



1. Presented by Tepe G at LINC, Leipzig, Germany 2017.

Summary

- Vessel preparation is a critical step in enhancing outcomes independent of a drug, a stent, or both being “left behind”
- Directional atherectomy has demonstrated low dissection and bail-out stent rates in the 800-subject DEFINITIVE LE study
- Since calcium may be a potential barrier to DCB effectiveness, atherectomy enhance DCB outcomes by establishing lumen gain and potentially increasing drug uptake
- The promise of atherectomy + DCB for femoropopliteal artery lesions is demonstrated in only a few studies, of which one is a multi-center core lab-adjudicated pilot study
- The marriage of atherectomy and DCB may bring together the best of two worlds – effective plaque modification / debulking paired with sustained drug presence
- While limited data show promise, understanding “what is *optimal vessel prep”* prior to DCB or DES use requires more comprehensive data and longer follow-up

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