Vessel Preparation: What does it mean and what are the current tools?

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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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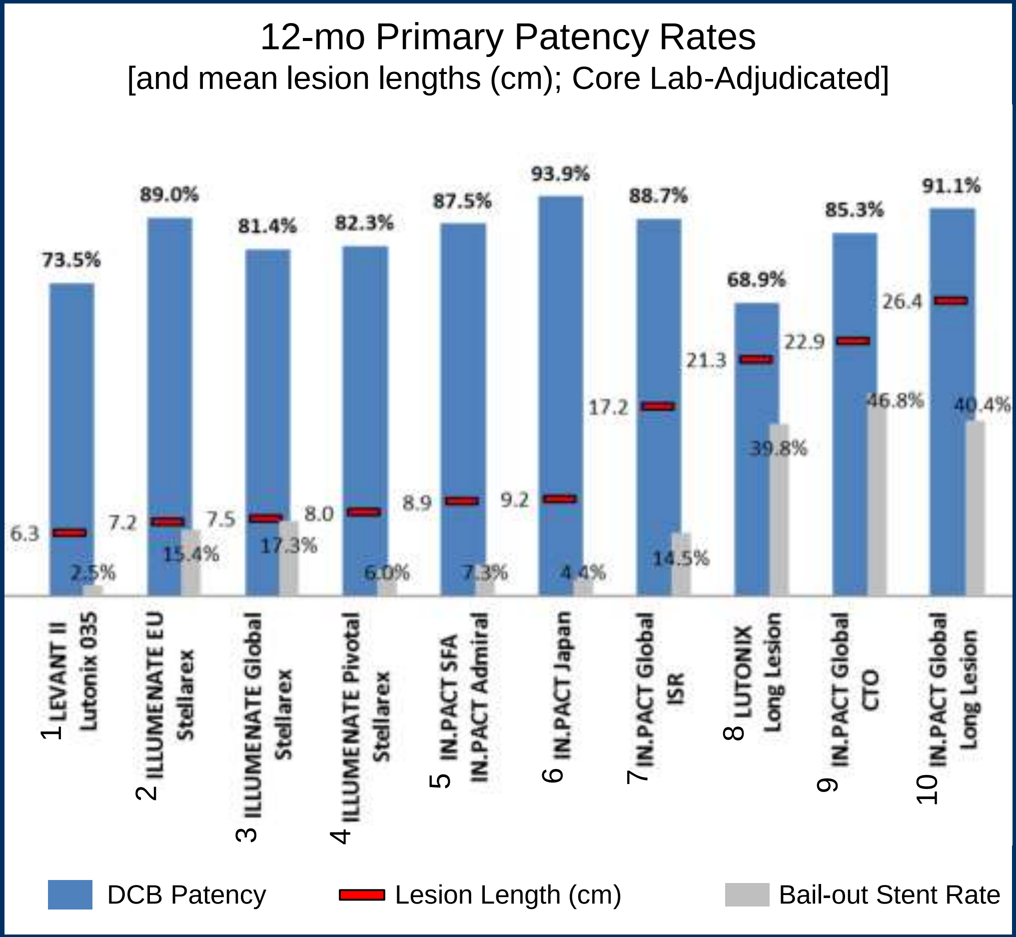
Royalty Income	None
Ownership/Founder	None
Intellectual Property Rights	None
Other Financial Benefit	None

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

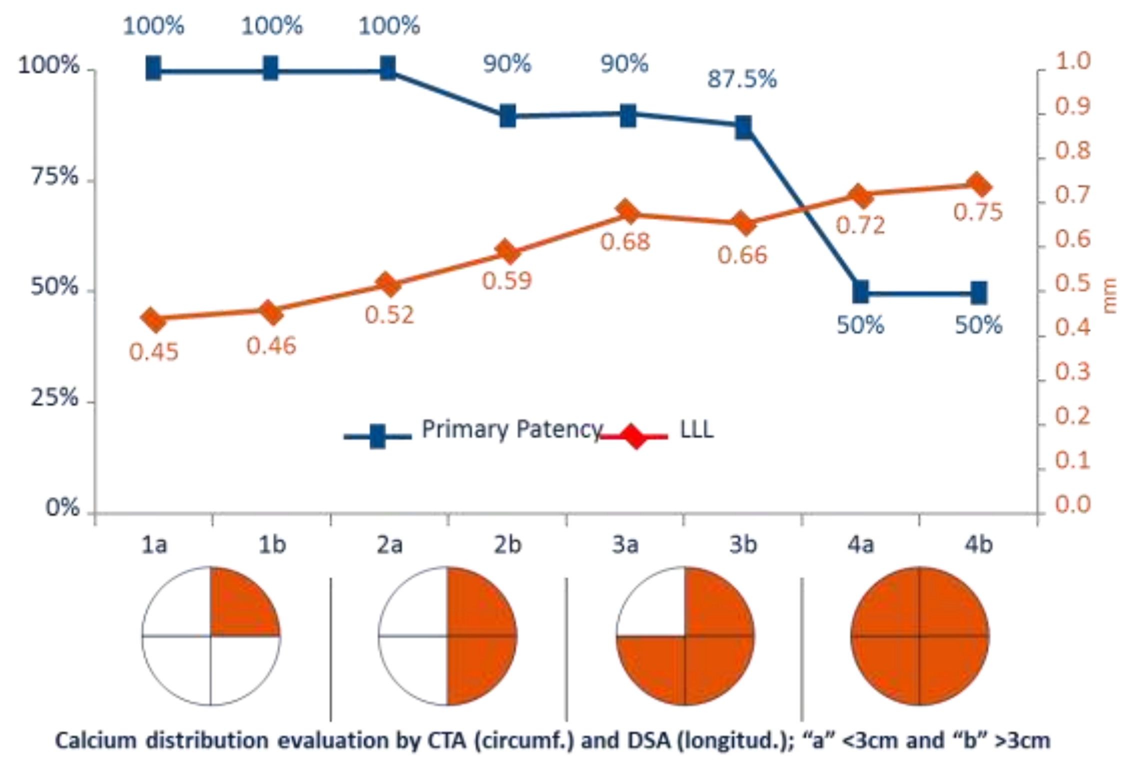


Patient demographics, lesion morphologies, patency definitions, and follow-up vary across trials.

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).

Vessel Prep: What Does It Mean?

- Debulking to increase luminal gain prior to DCB use?[1,2]
- Plaque modification to enhance drug uptake?[3,4]
- Plaque modification to combat flow-limiting dissections?[5]

Honestly…no one knows

1. Zeller T, et al. Circ Cardiovasc Interv 2017;10:e004848.
2. Zeller T, et al. J Endovasc Ther 2004;11:676-85.
3. Tellez A, et al. EuroInterv 2014;10:1002-8.
4. Foley TR, et al. Cath Cardiovasc Interv 2017;89:10078-85.
5. Cioppa A, et al. Cardiovasc Revasc Med 2012;13:219-23.

Tools for Vessel Preparation

Balloons

- Plain Old Balloon Angioplasty
- Cutting Balloons
- Scoring Balloons
- Controlled-inflation Balloon




Atherectomy Devices

- Directional
- Orbital
- Rotational
- Photoablative




Predilation Best Practices

Optimal PTA: Effect of Short vs Long Balloon Inflation Times on the Morphologic Results

- Inflation times of 180s improve immediate infrainguinal PTA results vs. 30s dilations
- Significantly fewer major dissections and a modest reduction of residual stenoses are observed
- Significantly fewer continued interventions (e.g. provisional stenting)

	Inflation Time (sec)		
	30	180	*P*-Value
Major dissection (grades 3 or 4)	16	5	.010
Minor or no dissection (grades 1 and 2)	21	32	.010
Further interventions (Stent, repeat dilatation, dilation with larger diameter)	20	9	.017
Residual stenosis (>30%)	12	5	.097
Complication (embolization, thrombosis)	1	1	-
Mean ankle-brachial index (before, after intervention)	0.66, 0.87	0.65, 0.84	

1. Zorger N, et al. J Vasc Interv Radiol 13:355-9 (2002).

Specialty Balloons

- Specialty balloons aim at modifying/dilating plaque to achieve luminal gain during dilatation and potentially reduce dissections or bail-out stenting
  - In cutting / scoring balloons, blades create fissures in plaque that are intended to facilitate expansion during dilatation
  - In controlled-inflation angioplasty, constraining wire cage is designed to reduce potential dissection points, e.g. ends of balloon (dog-boning) and throughout the contact of the balloon surface with intima
- Very limited data are available describing the use of these devices in conjunction with DCB

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	?
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)	?

It's possible that atherectomy may complement DCB use in real-world lesions by reducing dissection rate and bail-out stenting.

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.

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.

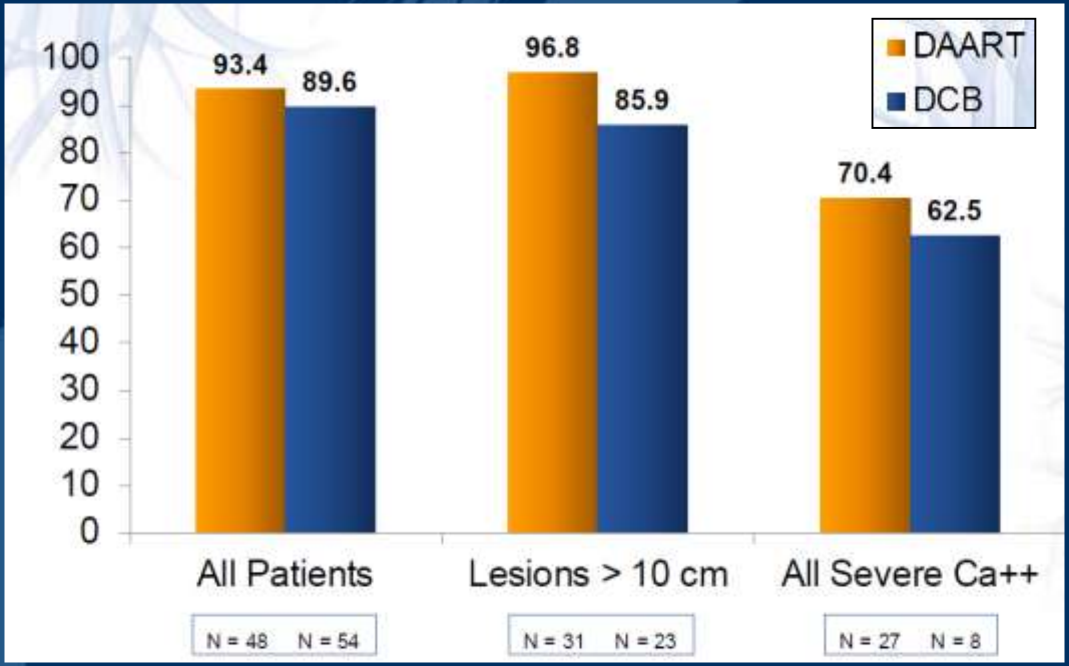
DEFINITIVE AR[1]

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%

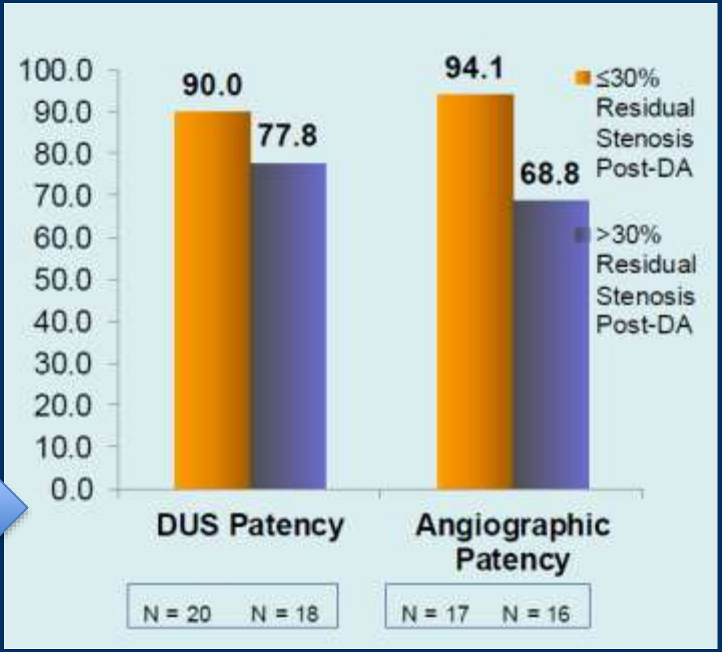
Outcomes	DAART (N= 48)	DCB (N = 54)	*p*-Value (DAART vs. DCB)	DAART Severe Ca++ Arm
Technical Success	89.6%	64.2%	0.004	84.2%
Distal Embolization	6% (3/48)	0% (0/54)	0.101	5.3% (1/19)
No Intervention	1	0		1
Endovascular Intervention	2	0		0
Bail-Out Stent	0% (0/48)	3.7% (2/54)	0.50	5.3% (1/19)
Dissection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

121 Patients

1 year

↓

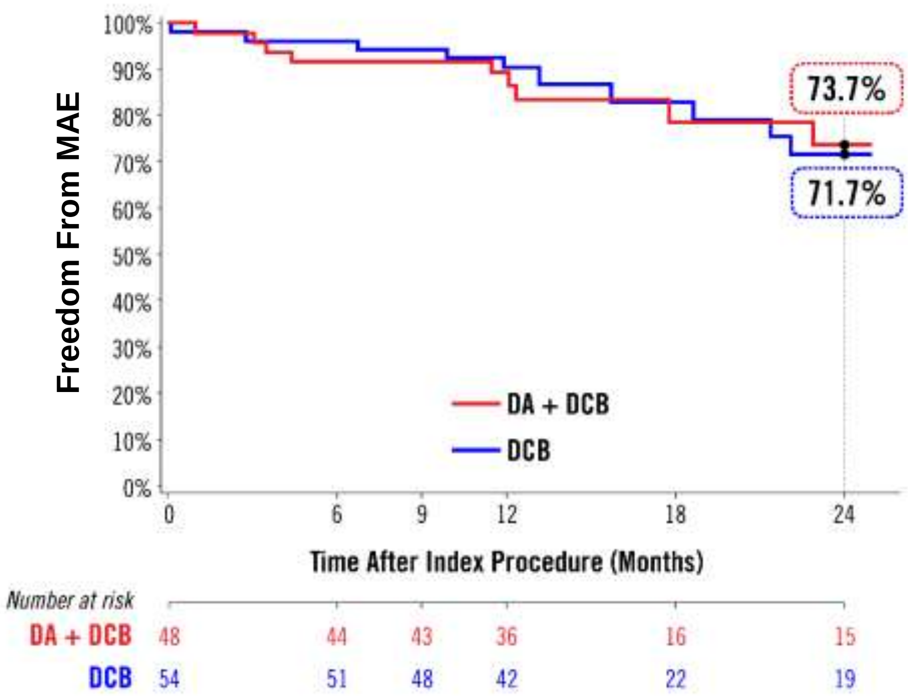
53 Patients

2 years

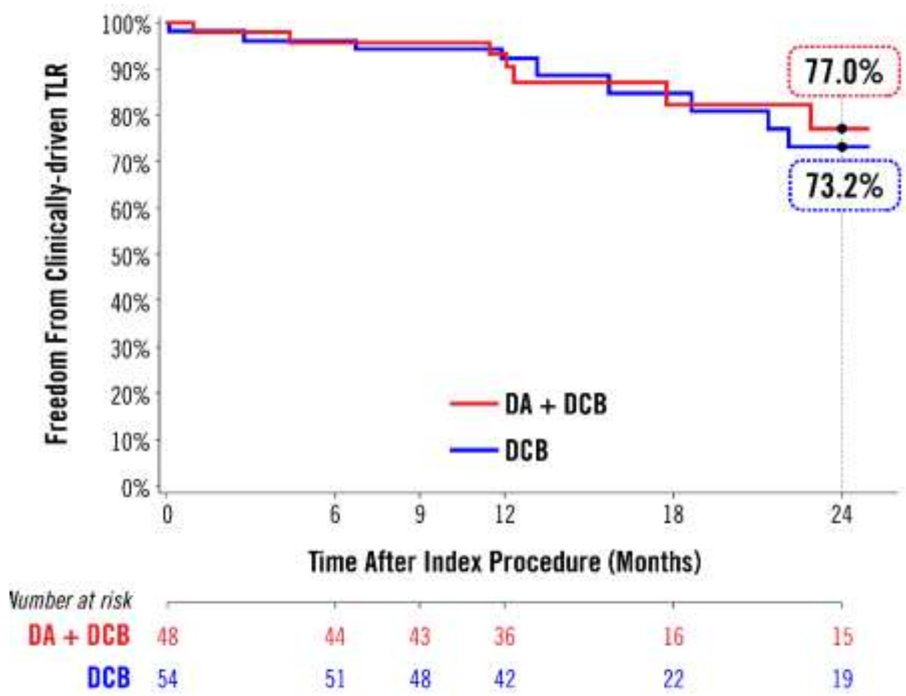
1. Presented by Tepe G, LINC, Leipzig, Germany 2017.

DEFINITIVE AR: 2-year Extension[1]

Freedom from MAE[2]



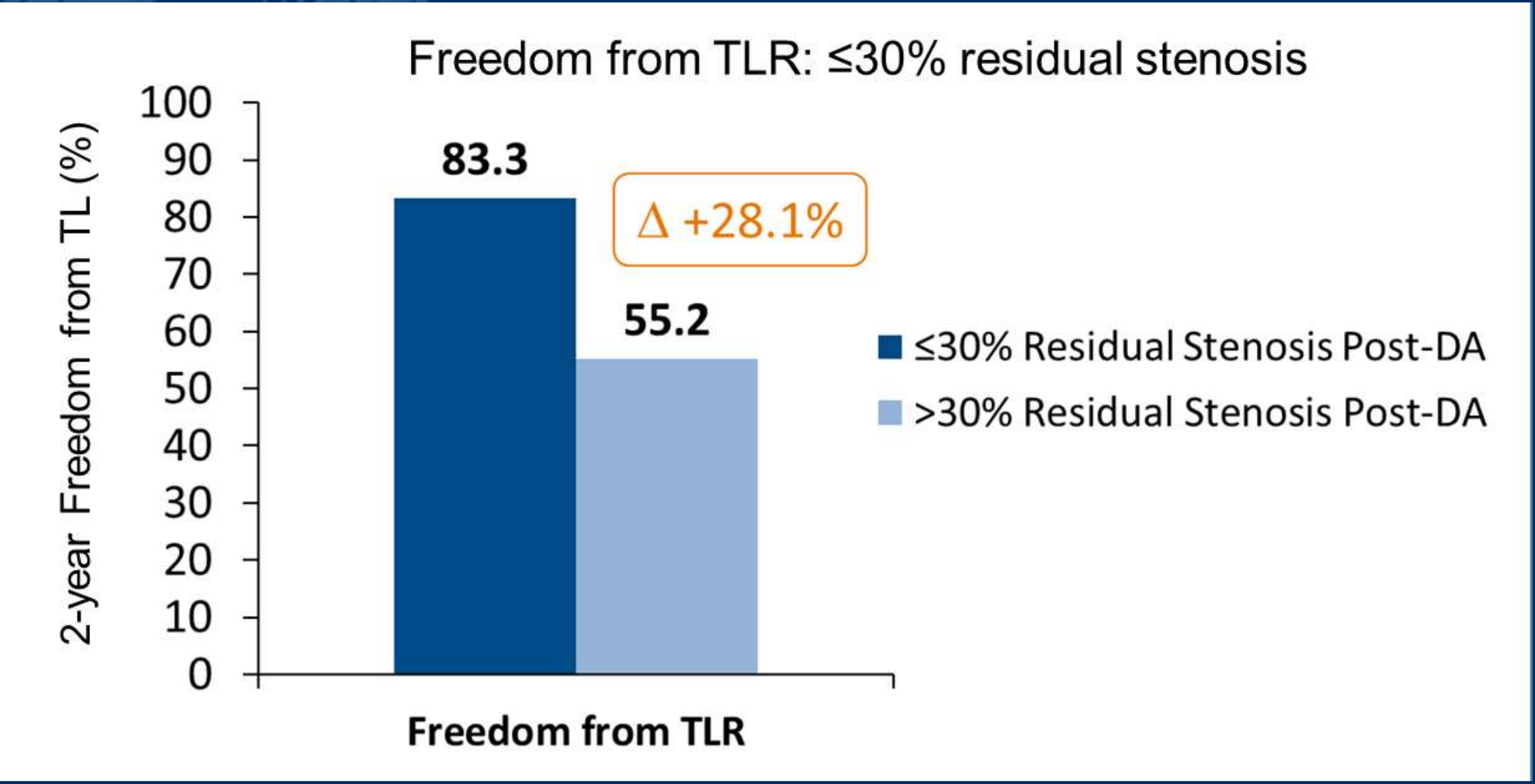
Freedom from Clinically-Driven TLR[3]



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.

Cioppa, et al., DAART Study

Prospective, single-center study to characterize conjunctive DA + DCB use in severely calcified lesions[1]


ELSEVIER

Cardiovascular Revascularization Medicine

Combined treatment of heavy calcified femoro-popliteal lesions using directional atherectomy and a paclitaxel coated balloon: One-year single centre clinical results☆

Angelo Cioppa*, Eugenio Stabile, Grigore Popusoi, Luigi Salemme, Linda Cota, Armando Pucciarelli, Vittorio Ambrosini, Giovanni Sorropago, Tullio Tesorio, Alessia Agresta, Giancarlo Biamino, Paolo Rubino

Procedural Characteristics (*n=30*)

- Mean lesion length: 115mm
- Total occlusion: 13.3% (4)
- < 30% residual stenosis achieved in all cases
- No procedure-related AEs
- Provisional stenting rate: 6.7% (2) [due to flow limiting dissections]

12-mo Results (n=30)

- 1° patency (PSVR<2.5): 90% (27)
- TLR: 10% (3)
- Limb salvage: 100% (12 CLI Pts)

Calcium defined as 1 cm on both sides of lesion

1. Cioppa A, et al. Cardiovasc Revasc Med 13:219-23 (2012).

Foley, et al., OA+DCB Study

Retrospective, single-center study comparing DCB outcomes in subjects treated with or without adjunctive orbital atherectomy (OA)[1]

Procedural Characteristics (n=89)

- 28 patients treated with OA (40 lesions); 61 patients treated with OA+DCB (99 lesions)
- Lesion length: 13.5cm in OA+DCB group and 13.9cm in DCB group
- Scoring balloon utilization was statistically higher and stent placement statistically lower in the OA+DCB cohort versus the DBC-only cohort

Outcomes

- Calcium severity was statistically significantly higher in the OA+DCB group versus the DCB-only group
  - Longer and more circumferential calcium in the combination group
- 12-mo results
  - Freedom from TLR was 82% in both groups
  - Primary patency rate was 77% in OA+DCB and 81% in DCB-alone

1. Foley TR, et al. Cath Cardiovasc Interv 89:1078-85 (2017).

Stavroulakis, et al., CFA Study

Prospective, single-center study to characterize conjunctive DA (SH or PTh) + DCB use in common femoral artery lesions[1]

Procedural Characteristics (n=47)

- Lesion lengths averaged 3.9cm and 3.4cm in the DCB and DAART groups, respectively
- Four occlusion were present in the DAART arm (none in the DCB group)
- Technical success: 88% and 95% in the DCB and DAART groups, respectively
- Bail-out stenting occurred once in each arm (not statistically different)
- Flow-limiting dissection more frequent in the DCB arm versus the DAART arm (8 versus 1, p=0.02)

Follow-up Results (12-mo)

- Primary Patency (PSVR≤2.0 and freedom from TLR or occlusion):
  DCB = 68%
  DAART = 88% (p=0.40)
- 12-mo freedom from TLR:
  DCB = 75%
  DAART = 89% (p=0.98)
- 12-mo Secondary Patency
  DCB = 81%
  DAART = 100% (p=0.03)

1. Stavroulakis K, et al. J Endovasc Ther; doi: 10.1177/1526602817748319 (2017).

Summary

- Vessel preparation is a critical step in enhancing DCB effectiveness
  - Though it remains ill-defined
- The marriage of atherectomy and DCB (effective plaque modification / debulking paired with sustained drug presence) may be a useful union of technologies
- DCBs generally demonstrate high 12-month patency rates, though data at 2 years and beyond are inconsistent
  - Overall, DCB use in increasingly complex and long lesions is associated with increasing provisional stent use
- Calcium is a potential barrier to DCB effectiveness, highlighting the importance of vessel prep
- Atherectomy has demonstrated effectiveness through 12 months, though long-term data remain limited
  - Now with greater data and technologies available
- 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

1. Presented by Zeller T, VIVA Las Vegas 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).

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