ACC.17
66th Annual Scientific Session & Expo

Critical Limb Ischemia

Endovascular Revascularization For CLI: Current & Future Therapies

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FRI • SAT • SUN
MARCH 17 – 19, 2017

Endovascular Revascularization for CLI
Current and Future Therapies: *Outline*

- Present ‘Good News’
- Multidimensional approach to endovascular revascularization in CLI
- Focus on relevant recent evidence

In science consensus is irrelevant. What is relevant is reproducible success….

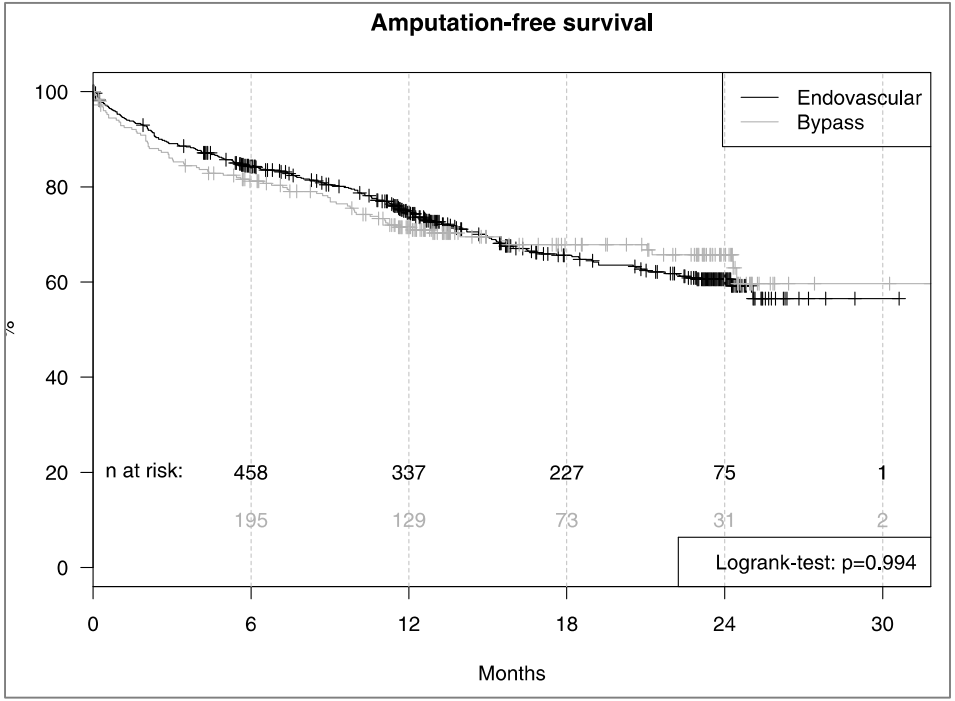
Mark Twain

Clinical & Anatomic Features of PAD in CLI

- DM, CKD, CAD
- Wound, ulcer, infection
- Multi-level, long CTOs, restenotic lesions (ISR)
- Extensive & diffuse below-the knee PAD (pedal arch)
- Calcification

Endovascular First vs. Surgery in CLI

Interim Analysis of the CRITISCH Registry



- 1200 patients, 2013-14
- Prospective registry
- Endo=54%, bypass=24%
- Median f/u=12 months
- AFS:
  - Endo=75%
  - Bypass=72%
  - NI of endo met
- No impact of treatment strategy on:
  - Time to death, amputation or reintervention

Bisdas et al. J Am Coll Cardiol Intv 2016;9:2557–65

Routine SFA Intervention: Real-world Registries

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	INPACT GLOBAL (n=655)[1]	LUTONIX GLOBAL (N=691)[2]	XLPAD (n=3,253)[3]
Mean age in years	69.2±10.2	68.3±9.8	66.1±9.8
Female	33%	32%	20%
Diabetes mellitus	41%	40%	56%
≥Rutherford 3	58%	70%	86%
CLI	15%	9%	40%
Mean lesion length	122.3±95.9 mm	101.0±84.0 mm	100.7±24.9 mm
CTO	36%	31%	42%
ISR	21%		13.5%
Calcification	70% (severe=10%)	34%	57% (Heavy)
Popliteal artery	29%	30%	12%

[1]Laird et al. J Am Coll Cardiol. 2015 Dec 1;66(21):2329-38; [2]Unpublished; [3]Banerjee et al. J Invasive Cardiol. 2015 Jan;27(1):14-8 (updated); www.XLPAD.org

Non-BEST CLI On-going Clinical trials

BASIL-2 – infra-popliteal (IP) SLI (600)

- Vein Bypass *first* (n = 300)
- Best Endovascular Treatment *first* (n = 300)

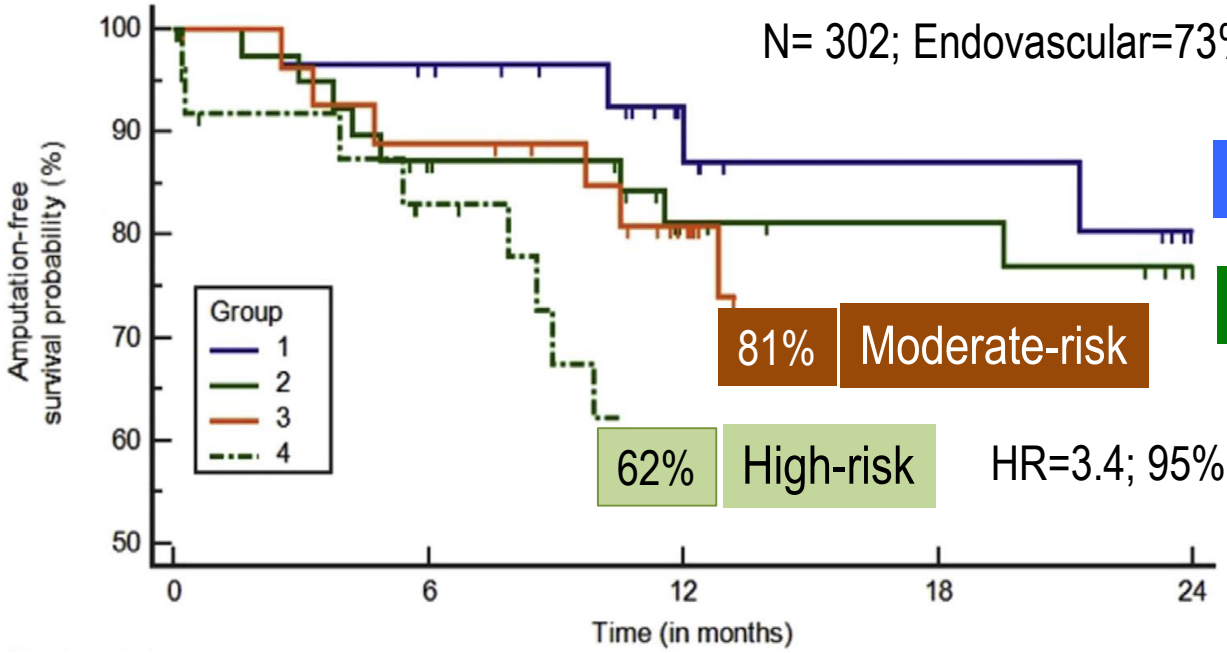
BASIL-3 – femoro-popliteal (FP) SLI (846)

- PBA *+/- BMS* (n = 282)
- DCB *+/- BMS* (n = 282)
- DES (n = 282)

Follow-up 24-60 months
Amputation free survival
Overall Survival
Clinical end-points

Quality of revascularisation
Quality of life
Functional status
Health economic

WIFI Outcomes Following Endovascular Revascularization in Non-diabetic CLI



N= 302; Endovascular=73%; Non-diabetic=58%

87% Very low-risk

81% Low-risk

81% Moderate-risk

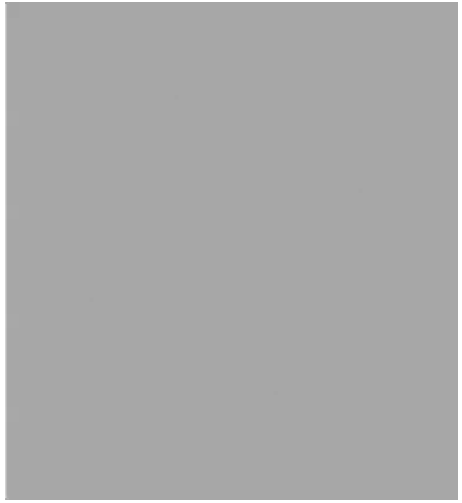
62% High-risk

HR=3.4; 95% CIL1.1-10.3; p=0.029

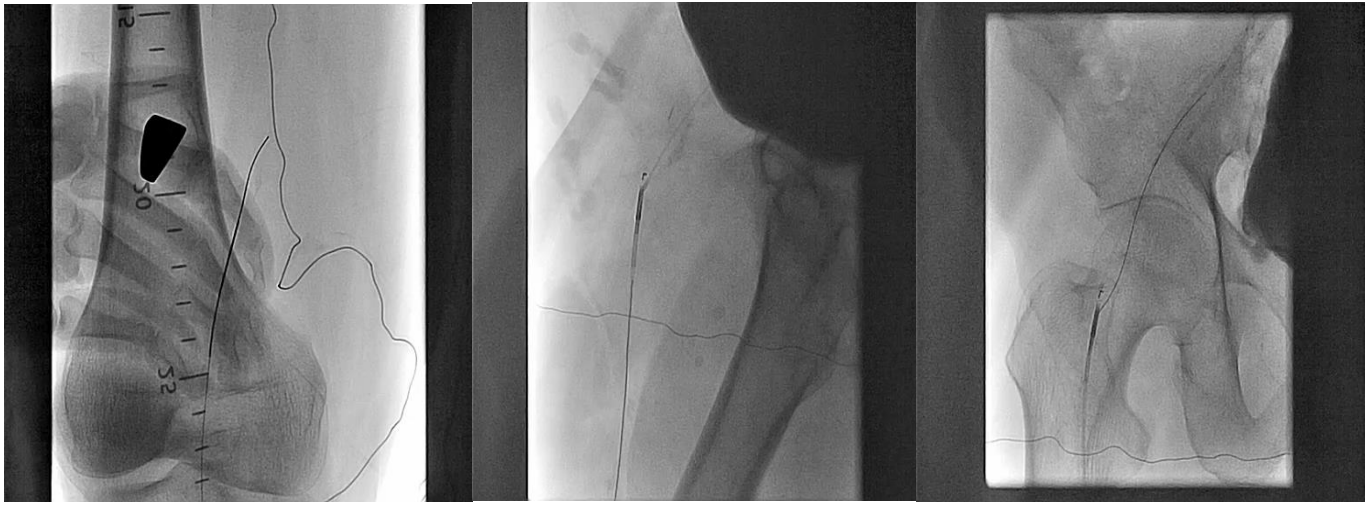
Beropoulis et al. J Vasc Surg 2016;64:95-103

A Case for Planned CLI Intervention:

Avoid Adhoc 'Poke & Hope Approach'

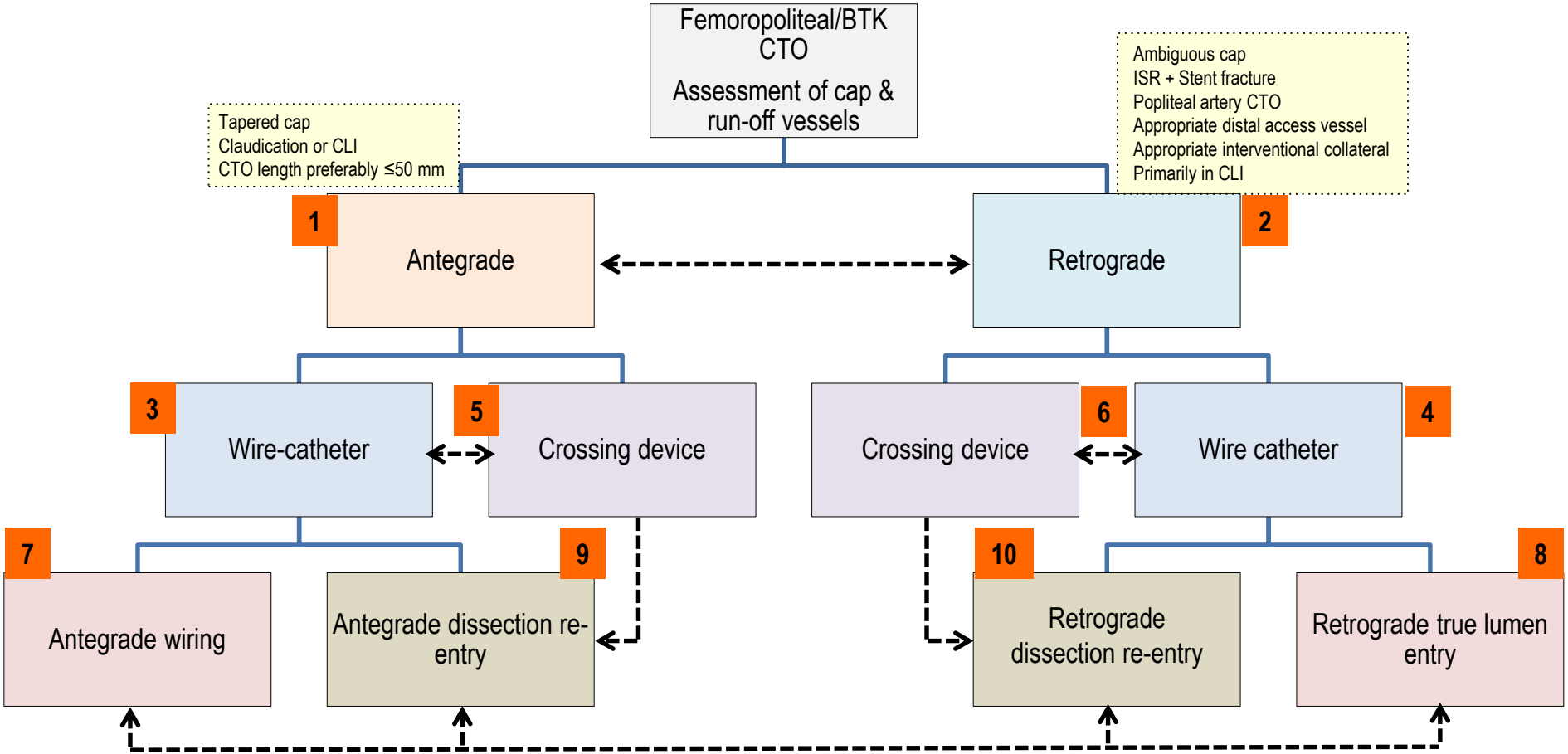


Mid SFA TASC A Lesion



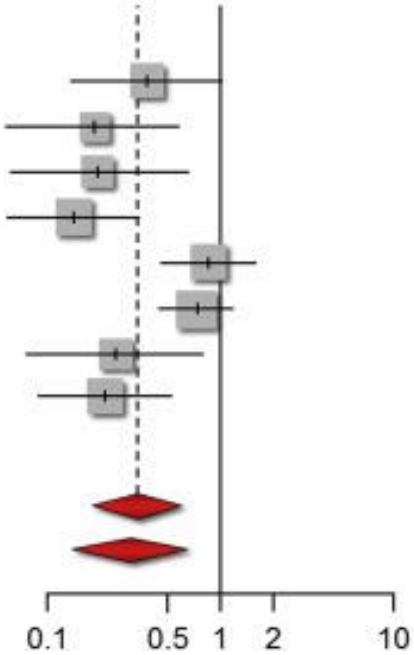
Long (>200 mm) SFA CTO with heavy calcification crossed subintimally via retrograde approach

Hybrid Algorithm For Crossing Femoropopliteal/BTK CTO



Banerjee et al. Practical Approach to FP CTO; Springer; Feb 2017 (XLPAD Registry; www.xlpad.org). Adapted from: Brilakis et al. JAAC Card. Interv. 2014

DCB Reduces FP-TLR Compared with PTA



	DCB Events	DCB Total	PB Events	PB Total	RR [95% CI]	Weight	Z Value	p Value
Biolux P-I	4	25	10	24	0.38 [0.14, 1.06]	11.6%	-1.848	0.065
FAIR	3	47	16	44	0.18 [0.06, 0.59]	10.3%	-2.864	0.004
FemPac	3	45	14	42	0.20 [0.06, 0.65]	10.2%	-2.687	0.007
IN.PACT SFA	6	207	22	107	0.14 [0.06, 0.34]	12.9%	-4.404	<0.001
LEVANT I	13	45	14	42	0.87 [0.46, 1.62]	15.3%	-0.447	0.655
LEVANT 2	35	285	24	143	0.73 [0.45, 1.18]	16.8%	-1.278	0.201
PACIFIER	3	42	12	43	0.26 [0.08, 0.84]	10.1%	-2.242	0.025
THUNDER	5	48	26	54	0.22 [0.09, 0.52]	12.9%	-3.341	0.001
Frequentist	**72**	**744**	**138**	**499**	**0.33 [0.19, 0.57]**	**100%**	**-3.997**	**<0.001**
Bayesian					**0.30 [0.14, 0.58]***			

Q=22.85, p=0.002, τ^2=0.405, I^2=69.4%

DCB compared with PB produced a 67% RR reduction in 12-month TLR

DCB: drug-coated balloon

JACC: Cardiovascular Interventions, Volume 9, Issue 16, 2016, 1731–1742

BTK DCB Application: Completed & On-going Trials

INPACT DEEP	**12m: CD-TLR:** DCB (9.2%) vs. PTA (13%); p=0.291	**6m Death:** DCB (17.7%) vs. PTA (15.8%); p=0.021 (n.i); ↑**Amp. rate**
Lutonix DCB Versus Standard Balloon Angioplasty for Treatment of BTK Arteries (NCT01870401)		
IN.PACT BTK Randomized Study to Assess Safety and Efficacy of IN.PACT 014 vs. PTA (NCT02963649)		

J Am Coll Cardiol. 2014

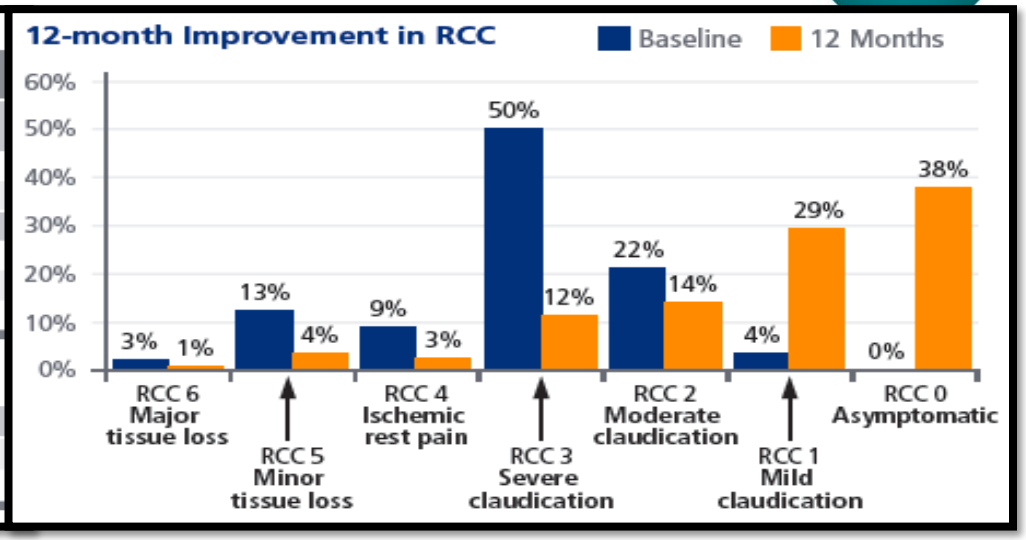
No Stent Approach: Definitive LE

Stent-like Patency at 12 Months in Claudicants

	Mean Lesion Length (cm)	Primary Patency (PSVR < 2.4)
All Claudicants (n = 743 lesions)	7.5	78%
Diabetic (n = 345 lesions)	7.6	77%
Non-Diabetic (n = 398 lesions)	7.4	78%
By Vessel		
SFA (n = 536 lesions)	8.1	75%
Popliteal (n = 114 lesions)	6.0	77%
Infrapopliteal (n = 93 lesions)	5.5	90%

12 Month Results in CLI Patients

All CLI (n = 201)	
Freedom from Amputation	95%
Primary Patency (PSVR ≤ 2.4)	71%

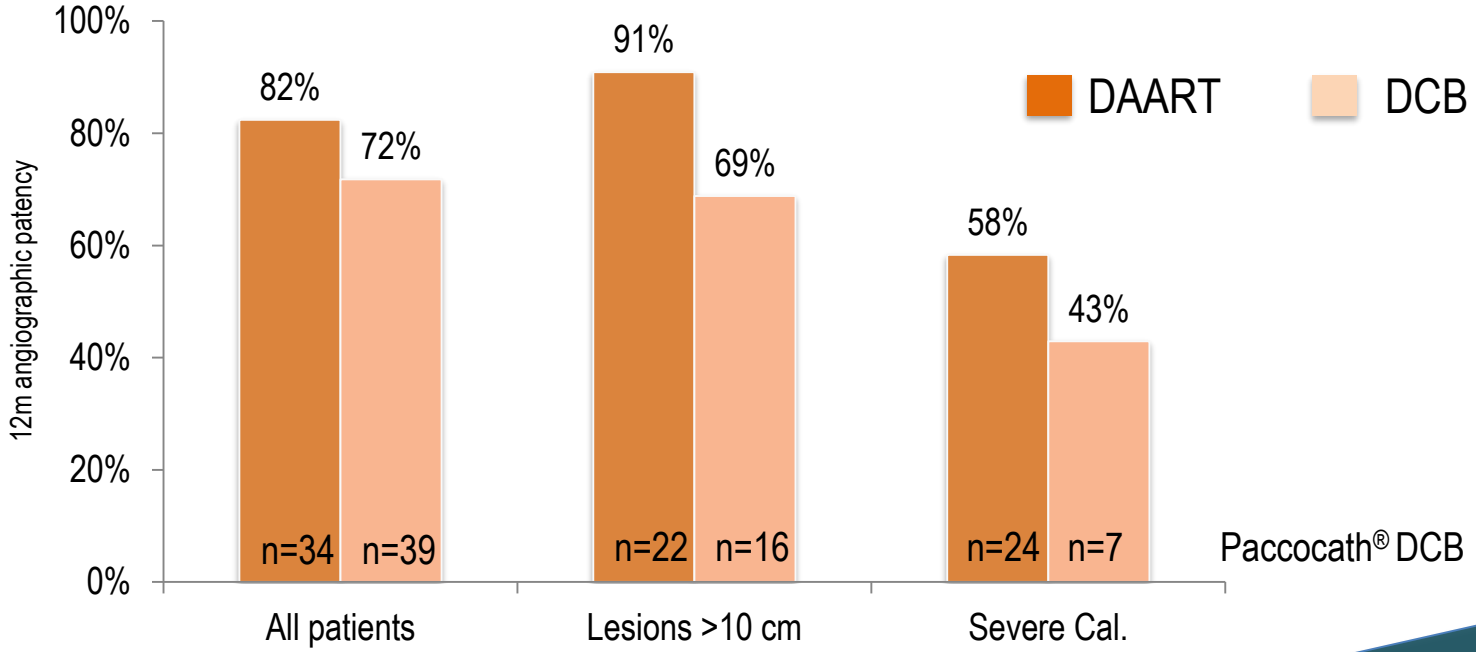


n=800; 47 U.S.& European centers; length <20 cm; ref. vessel= 1.5 to 7.0 mm
Mean lesion length= 7.5 cm; CTO: claudicants= 17%; CLI= 30%; SFA= 66%

JACC Cardiovasc Interv. 2014 Aug;7(8):923-33

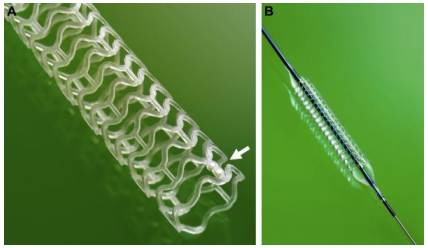
DAART: Directional Atherectomy & Anti-Restenotic Therapy

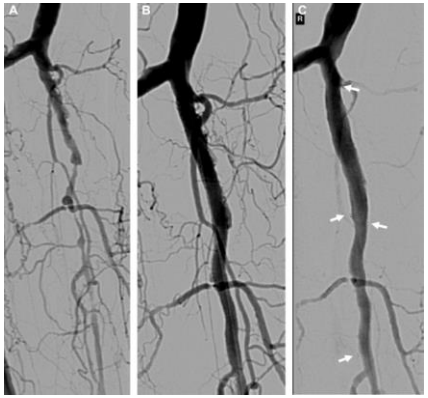
DEFINITIVE AR Pilot RCT: 12m Angiographic Patency

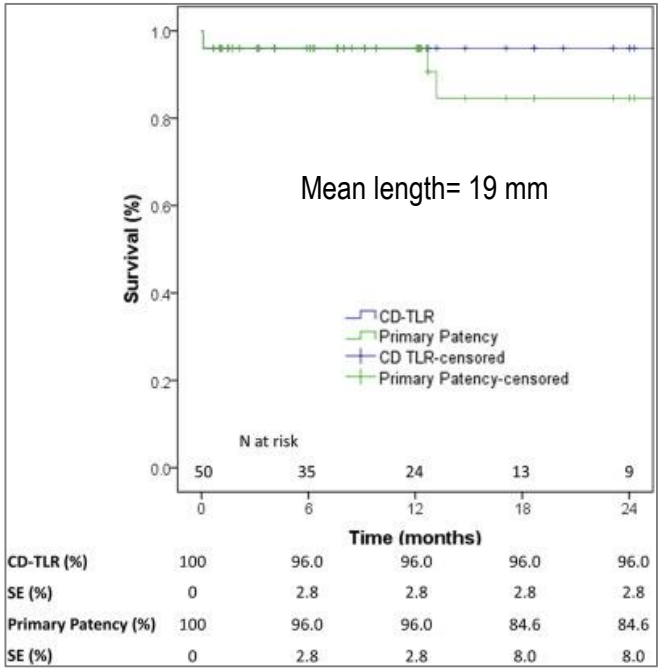


Langhoff et al. VIVA 2014

Absorb Everolimus-Eluting Bioresorbable Vascular Scaffold in BTK Arteries







CD-TLR (%)	100	96.0	96.0	96.0	96.0
SE (%)	0	2.8	2.8	2.8	2.8
Primary Patency (%)	100	96.0	96.0	84.6	84.6
SE (%)	0	2.8	2.8	8.0	8.0

Features	N; %
RC3	32%
RC5	53%
Scaffolds	50
Mean no. scaffolds	1.35
TP trunk, AT, PT	18, 11, 9
Tech. success	100%
Scaffold thrombosis	4%, 2.6%

Patients=33, Limbs=38; Binary restenosis=6%; KM PP= 96% (12m), 85% (24m)

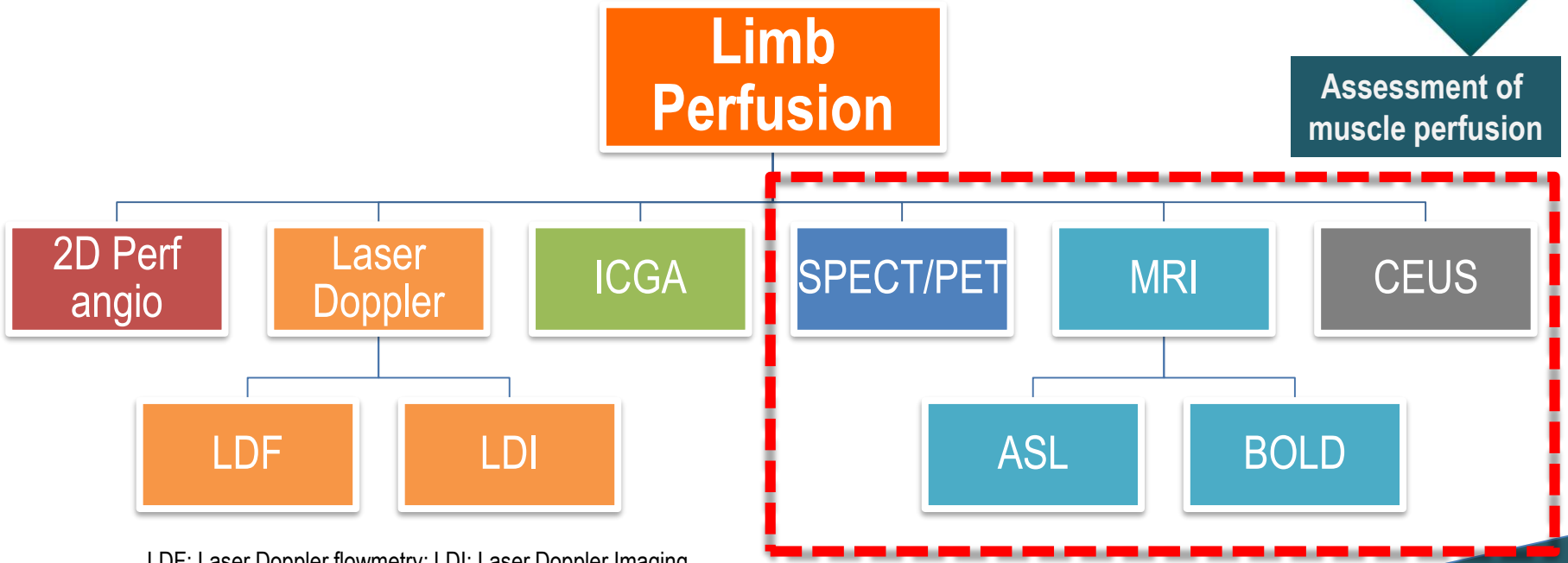
Varcoe et al. JACC: Cardiovascular Interventions August 2016

No Revasc. Options: *Gene & Cell Therapy in CLI*

Agent	Description	Results
Hepatocyte Growth Factor (HGF); ATVB 2011;31:713-720	IM injection of HGF plasmid	↓Rest pain, ↑ABI @6m;
Fibroblast Growth Factor (FGF); Mol Ther. 2008;16:972-978	TALISMAN 201 (n=107): IM injection of FGF plasmid	No change in ABI or TBI; ↑AFS @ 12m: 48% vs. 72%
Fibroblast Growth Factor (FGF); Lancet. 2011;377:1929-1937	TAMARIS (n=525): IM injection of FGF plasmid	No difference in AFS
Hypoxia Inducible Factor-1 Alpha (HIF1alpha); Proc Natl Acad Sci.;106:18769-18774	Absence of oxygen generates HIF-1. Activated HIF-1 induces the production of other proangiogenic cytokines, including VEGF; mobilize **CD34 progenitor cells**	

54 clinical trials: ~50% equivocal or negative

Tissue Perfusion in the Lower Limb:
What are your options?



LDF: Laser Doppler flowmetry; LDI: Laser Doppler Imaging
ICGA: Indocyanine green fluorescent angiography: PET: Positron Emission Tomography
MRA: Magnetic resonance angiography; ASL: Arterial spin labeling; BOLD: Blood oxygen level dependent
CEUS: Contrast enhanced ultrasound

Bajwa et al. Circ. Card. Imaging 2014; 7: 836-843

Perfusion Imaging to Optimize Endovascular Therapy in CLI: '*Wound Blush*'

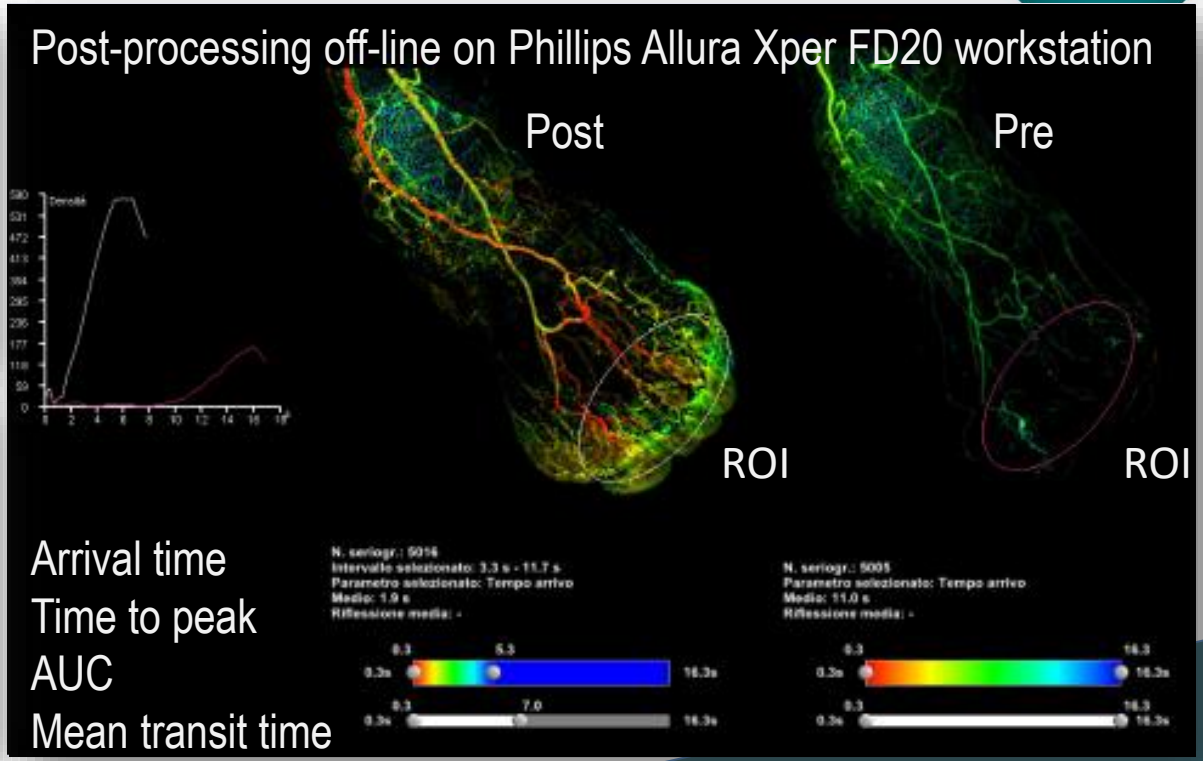
- Contrast opacification of the vessels around the wound in DSA immediately after EVT via catheter in the popliteal artery
- Presence of wound blush after EVT is associated with higher skin perfusion pressure & higher rates of limb salvage
- **Limb salvage rates at 3years:**
  - Wound blush positive (WB –ve): 96.4%
  - Wound blush negative (WB +ve): 56.8%

  } p<0.001
- Limitations:
  - Patient compliance with instructions, contrast load
  - Only successful interventions included

J Vasc Surg 2012
JACC 2017

Perfusion Imaging to Optimize EVT in CLI:

2D Perfusion Angiography

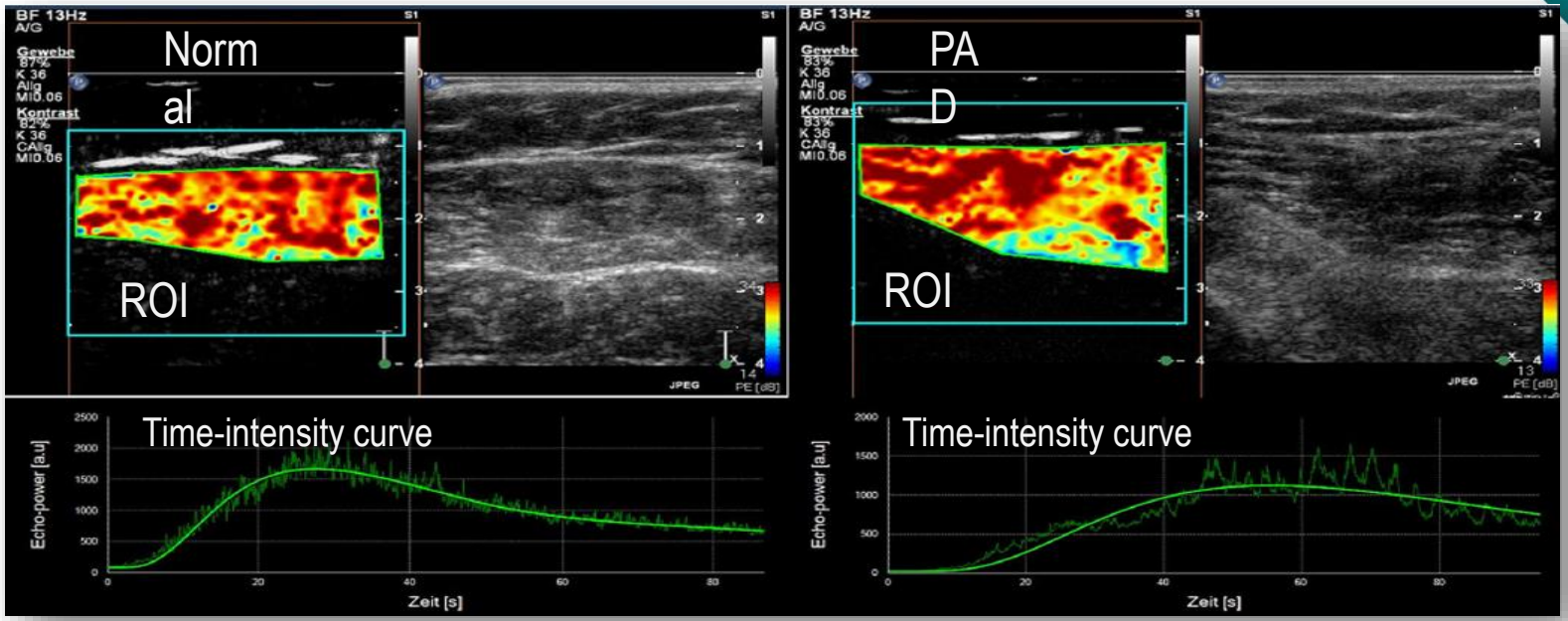


DSA; 12cc contrast (1:1) 3ml/s; 3 images/s

Manzi. EVT May 2015

Perfusion Imaging to Optimize EVT in CLI:

Contrast Enhanced Ultrasound (CEUS)

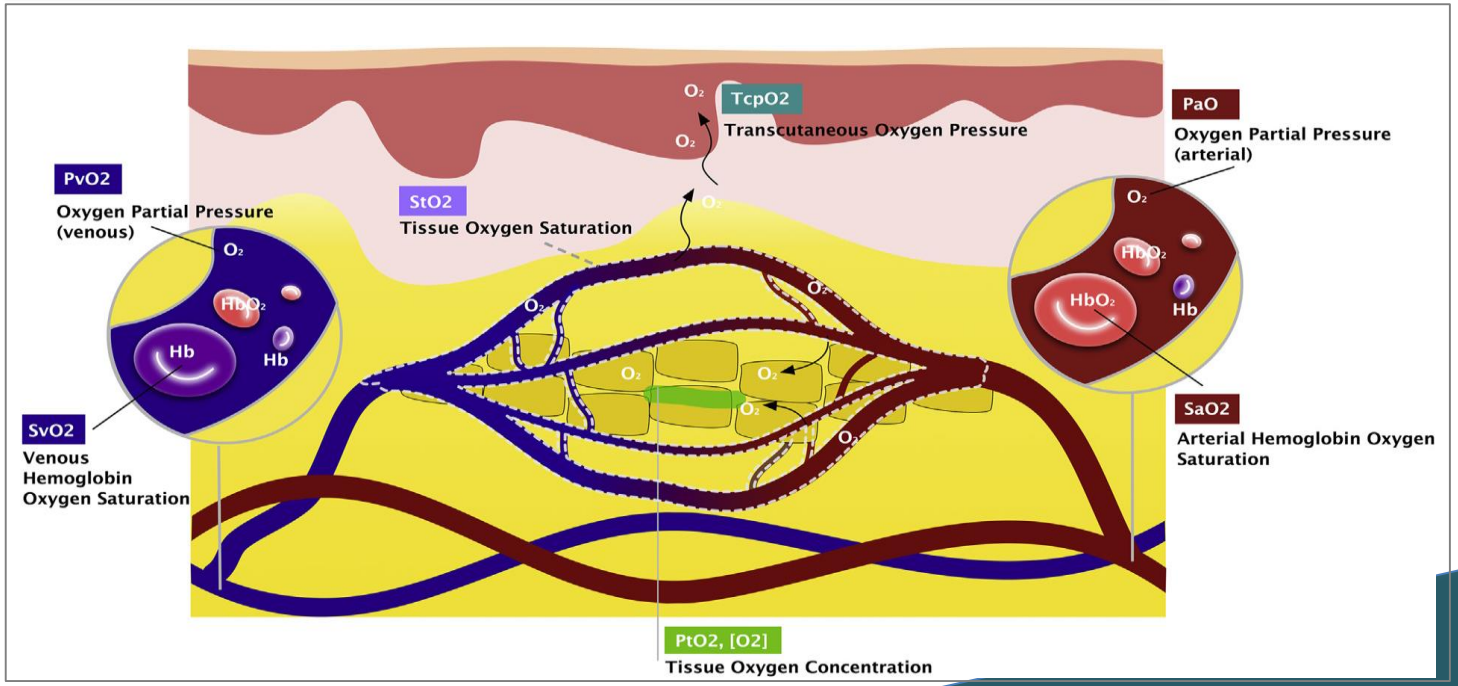


Time-intensity-curves of a ROI within the skeletal muscle after bolus injection of the US contrast shows a steeper slope of wash-in-curve in combination with a shorter time-to-peak in the healthy volunteer

Cardiovasc Diagnosis and Therapy. 2014

The First-in-Man "Si Se Puede" Study for the use of micro-oxygen sensors (MOXYs) to determine dynamic relative oxygen indices in the feet of patients with limb-threatening ischemia during endovascular therapy

Miguel F. Montero-Baker, MD,[a,b] Kit Yee Au-Yeung, PhD,[c] Natalie A. Wisniewski, PhD,[d] Soya Gamsey, PhD,[d] Luis Morelli-Alvarez, MD,[e] Joseph L. Mills Sr, MD,[a] Marianella Campos, MD,[e] and Kristen L. Helton, PhD,[c] *Tucson, Ariz; South San Francisco, Calif; and San José, Costa Rica*

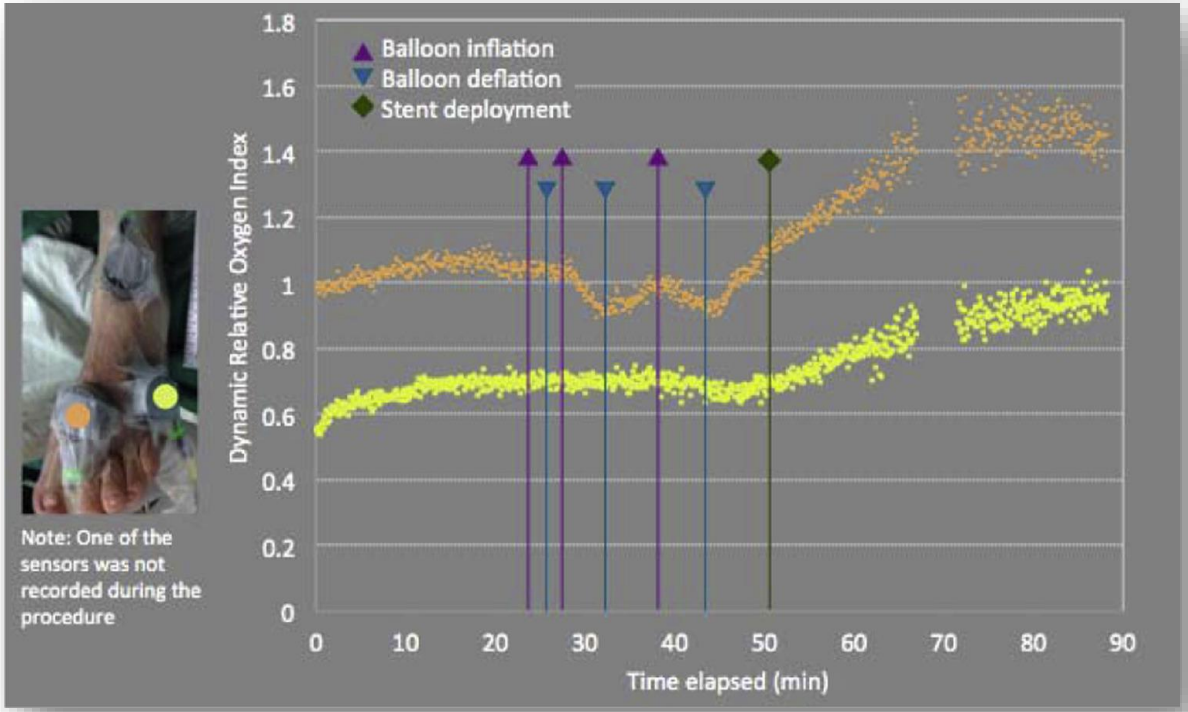


Injectable microsensors that measure O_2 directly from the interstitial space in the subcutis

Hydrogel with Pd-metalloporphyrin
Measures: Pd-phosphroescent lifetime decay proportional to tissue oxygen concentration

J Vasc Surg 2014; 60: 548-549

Micro-Oxygen Sensors (MOXYs) to Determine Dynamic Relative Oxygen Indices in the Foot

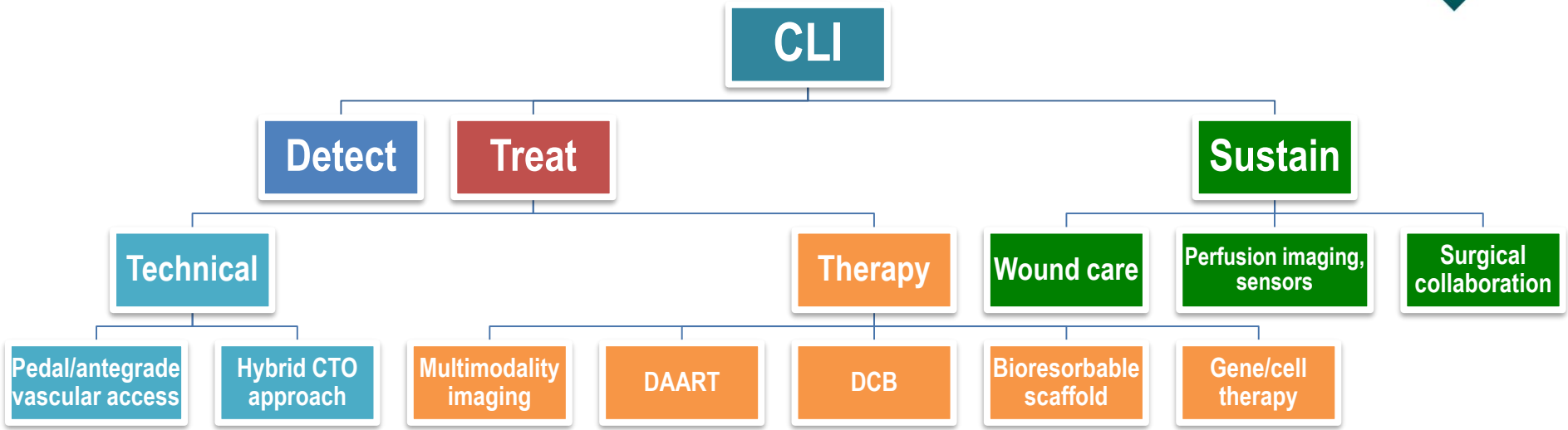


- Microsensors injected prior to EVT measure O_2 directly from the interstitial space in the subcutis
- Acquisition of signal via surface detectors
- Provide 'live' tissue oxygenation levels during the procedure
- FIM: n=10; 98.6% signal detection for up to 28 days

Journal of Vascular Surgery 2014; 60: 548-549

Endovascular Approach to CLI

Take-home message: CLI 'Life-cycle'



CLI centers of excellence & management networks

DAART: Directional Atherectomy and Anti-Restenotic Therapy