Maximal Luminal Gain with Directional or Rotational Atherectomy Followed by DCB May Be the Optimal Strategy

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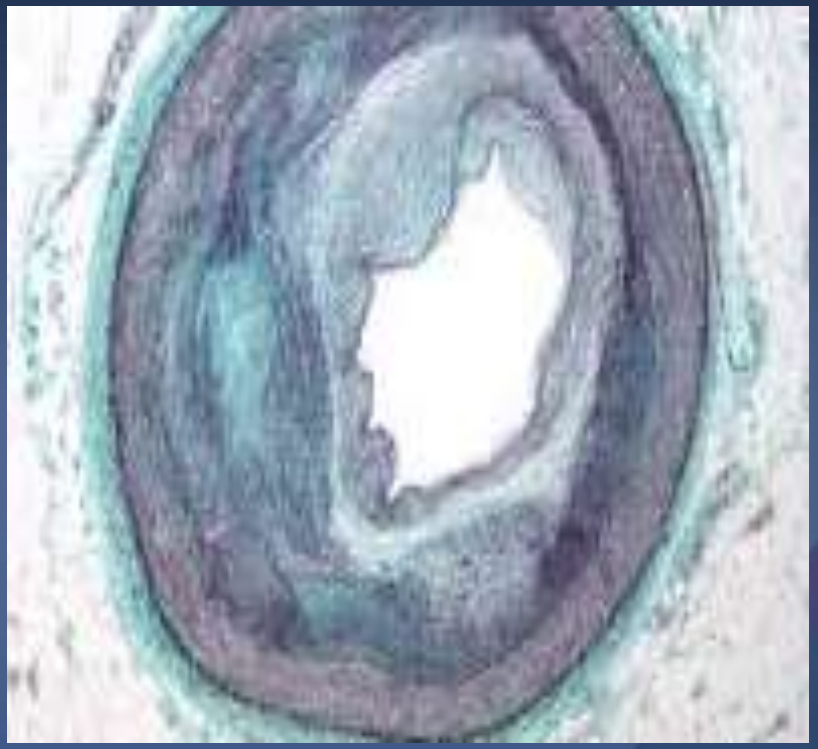
Goals of Treatment of BTK Disease

- Treat CLI
- Improve Wound Healing
- Eliminate or lower the level of amputation

BTK Disease is not the same as ATK Disease

- Smaller Vessels
- More diffuse disease/CTOs
- Less Elastic Vessels/More Recoil
- More Calcification
- Calcium tends to be more medial in location as compared to intraluminal



DCB Experience in BTK
Single Center Studies: Positive

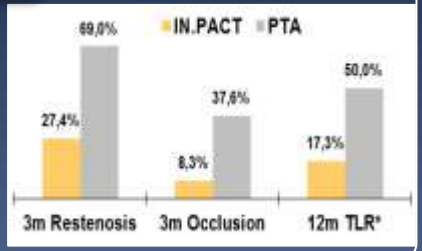
- Steiner et al *(J Endovasc Ther 2016;23:417-23)*
  - 9-M TLR 15.9% & maj amp 6.6% (Lutonix)
- Schmidt et al *(JACC 2011;58:1105-9)*
  - 3-M binary restenosis/reocc 27% (> hist. controls)
- Fanelli F et al *(J Endovasc Ther 2012;19:571)*
- Liistro et al *(Circulation* 2013;128:615-621)
  - Randomized 150 pts using In.Pact Amphirion
  - Restenosis rate of 27% (DCB) v. 74% (POBA)


First Experience With Drug-Eluting Balloons in Infrapopliteal Arteries

IN.PACT Amphirion [1] vs. matched PTA historical cohort [2]:

Single Center Registry

104 Patients
CLI 82.6%
Diabetes 73%
Avg lesion length 17 cm
CTOs 62%



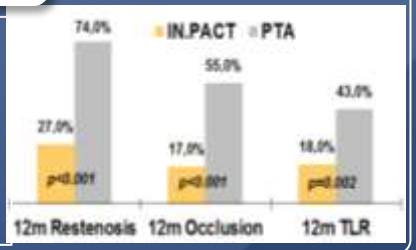

Circulation

IN.PACT Amphirion vs. PTA in patients with CLI and Diabetes

DEBATE BTK 12-month Results:

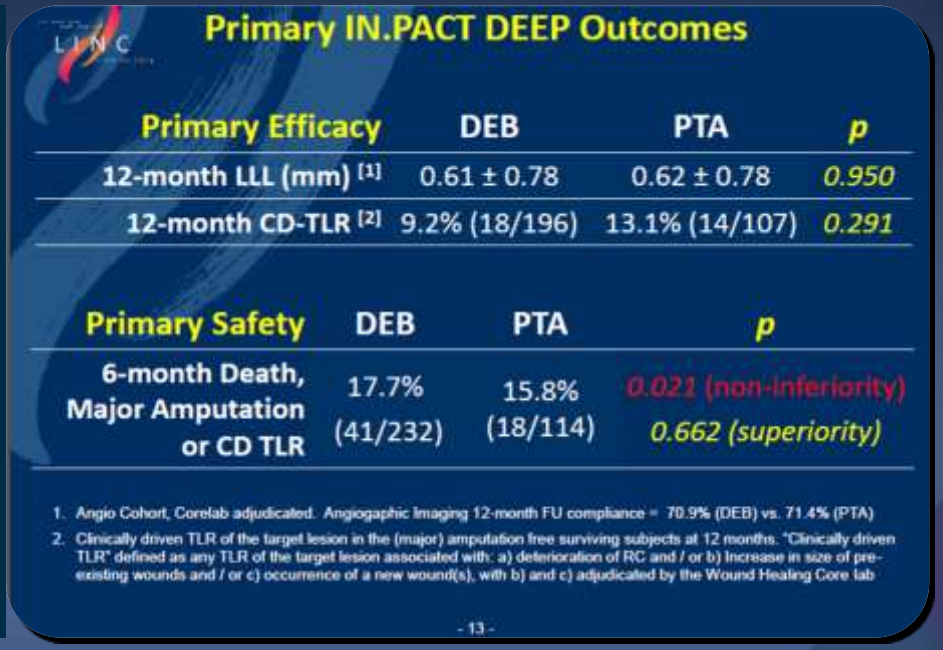
Single Center Randomized Trial

132 Patients
CLI 100%
Diabetes 100%
Avg lesion length ~13 cm
CTOs ~80%



DCB In BTK
Multi- Center Experiences – Failed Trials

- IN.PACT DEEP (*Zeller et al JACC 2014;64:1568-76*)
  - No patency or clinical benefit of Amphirion In.Pact
- Biolux P-II (*Zeller at al JACC 2015;8:1614-22*)
  - Small study showing no patency or clinical benefit to Passeo-18 LUX DEB



Primary IN.PACT DEEP Outcomes

Primary Efficacy	DEB	PTA	p
12-month LLL (mm) [1]	0.61 ± 0.78	0.62 ± 0.78	0.950
12-month CD-TLR [2]	9.2% (18/196)	13.1% (14/107)	0.291

Primary Safety	DEB	PTA	p
6-month Death, Major Amputation or CD TLR	17.7% (41/232)	15.8% (18/114)	0.021 (non-inferiority) 0.662 (superiority)

1. Angio Cohort, Corelab adjudicated. Angiographic Imaging 12-month FU compliance = 70.9% (DEB) vs. 71.4% (PTA)
2. Clinically driven TLR of the target lesion in the (major) amputation free surviving subjects at 12 months. "Clinically driven TLR" defined as any TLR of the target lesion associated with: a) deterioration of RC and / or b) Increase in size of pre-existing wounds and / or c) occurrence of a new wound(s), with b) and c) adjudicated by the Wound Healing Core lab

- 13 -

Possible Reasons for Failed Trials for DCB in BTK

- Drug does not work in BTK lesions
- Insufficient drug dosing in BTK studies
- Improper DCB sizing or insufficient duration of therapy
- PTX delays wound healing
- Loss of drug due to transit time
- Calcification impedes drug delivery
- Recoil effect in small vessels >>>Drug effect
- Heterogeneity of treatment in multi-center studies
  - Procedural differences
  - Differences in post-procedural wound care

Do Drugs Not Work BTK?

Below the Knee DES Studies:

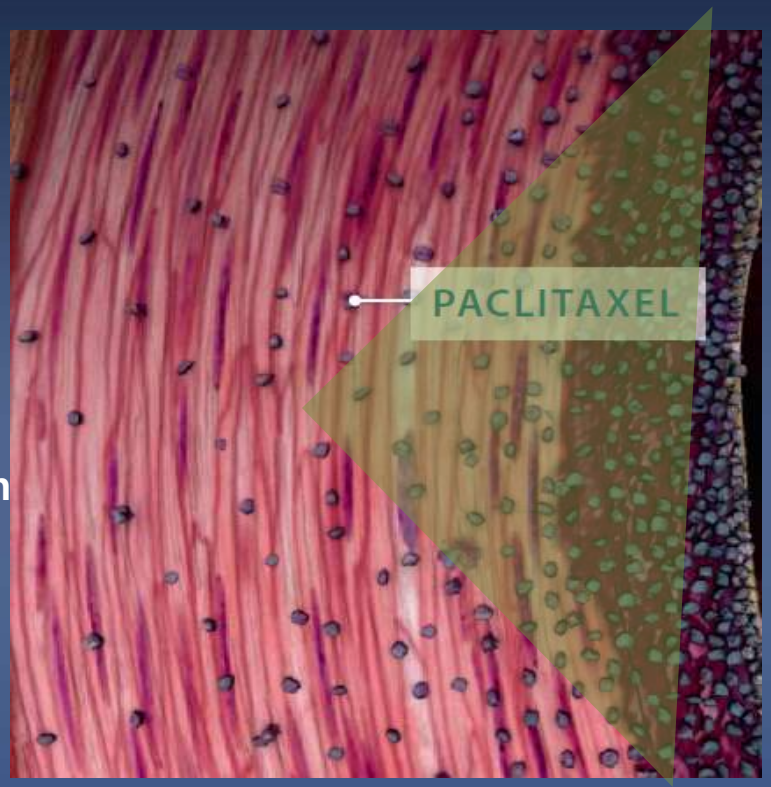
TABLE 2. RANDOMIZED CONTROLLED TRIALS OF BTK DES					
Trials	**Stent/Drug**	**Finish**	**No. of Patients**	**Lesion Length**	**Endpoints**
ACHILLES[15]	Cypher vs PTA (sirolimus)	2010	200	≤ 120 mm	Binary restenosis 19% vs 49% at 1 y
DESTINY[16]	Xience (everolimus) vs MultiLink Vision	2010	140	≤ 40 mm	Primary patency 85% vs 54% at 1 y; TLR 34% vs 9% at 1 y
YUKON-BTK[17]	Yukon DES (sirolimus) vs Yukon BMS	2010	177	≤ 45 mm	Primary patency 81% vs 56% at 1 y
Total			**517**		

15. Scheinert D. Presented at: LINC 2011 Annual Meeting; &Itemid=248. Accessed July 20, 2011. 16.
16. Bosiers M, Deloose K, Peeters P. DESTINY trial: 12-month clinical and angiographic findings. Presented at: LINC 2011 Annual Meeting; January 19, 2011;
17. Zeller T. Presented at: LINC 2011 Annual Meeting. January 19, 2011.

Efficacy

DCB

- 25% of Drug is lost during DCB delivery.
- 25% of Drug is delivered to the vessel wall.
- 25% found on balloon surface after removal.
- 25% embolized



DES

- *Approx.* 80% of Drug is delivered to the vessel wall. (Delivered via sheath)
- Drug stays in the media and adventitia for 56 days.

Primary Endpoint in BTK Studies: Wound Healing
Several Factors at Play

- **Wound related artery revascularization** [1-2]
- **Below the ankle run-off / plantar arch status** [3-4]
- **Wound care type and frequency (surveillance programs)** [5]

Index Vessel Patency is not the only factor associated with wound healing and limb salvage

During Index Procedure: Focus can only be on optimizing procedural outcomes

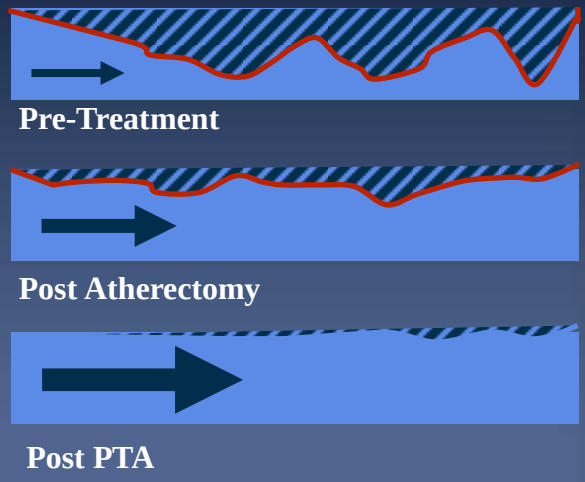
1. Neville et al. Revascularization of a Specific Angiosome for Limb Salvage: Does the Target Artery Matter? Ann Vasc Surg 2009; 23: 367-373
2. Iida O. et al. Importance of the Angiosome Concept for Endovascular Therapy in Patients with Critical Limb Ischemia - Catheterization and Cardiovascular Interventions 75:830–836 (2010)
3. Manzi M, Fusaro M, Ceccacci T, Erente G, Dalla Paola L, Brocco E. Clinical results of below-the knee intervention using pedal-plantar loop technique for the revascularization of foot arteries. J Cardiovasc Surg (Torino). 2009 Jun;50(3):331-7
4. O.Iida et al. Anatomical Predictors of Major Adverse Limb Events after Infrapopliteal Angioplasty for Patients with Critical Limb Ischaemia due to Pure Isolated Infrapopliteal Lesions. European Journal of Vascular and Endovascular Surgery 44 (2012) 318e324
5. Rogers LC, Armstrong DL: Podiatry Care, Chapter 113, Rutherford's Vascular Surgery, 7th Edition, Cronenwett JL, Johnston KW, editors, Elsevier Inc, 2010

Will Atherectomy and DCBs be Synergistic?

Can we get DES-like results without a full metal jacket?

Benefits of Atherectomy for BTK

- Maximize lumen gain
  - Flow increases exponentially as radius increases
- Remove Calcium
  - Improve vessel compliance
  - Lower risk of re-occlusion due to recoil
  - Lower risk of dissection/bailout stenting

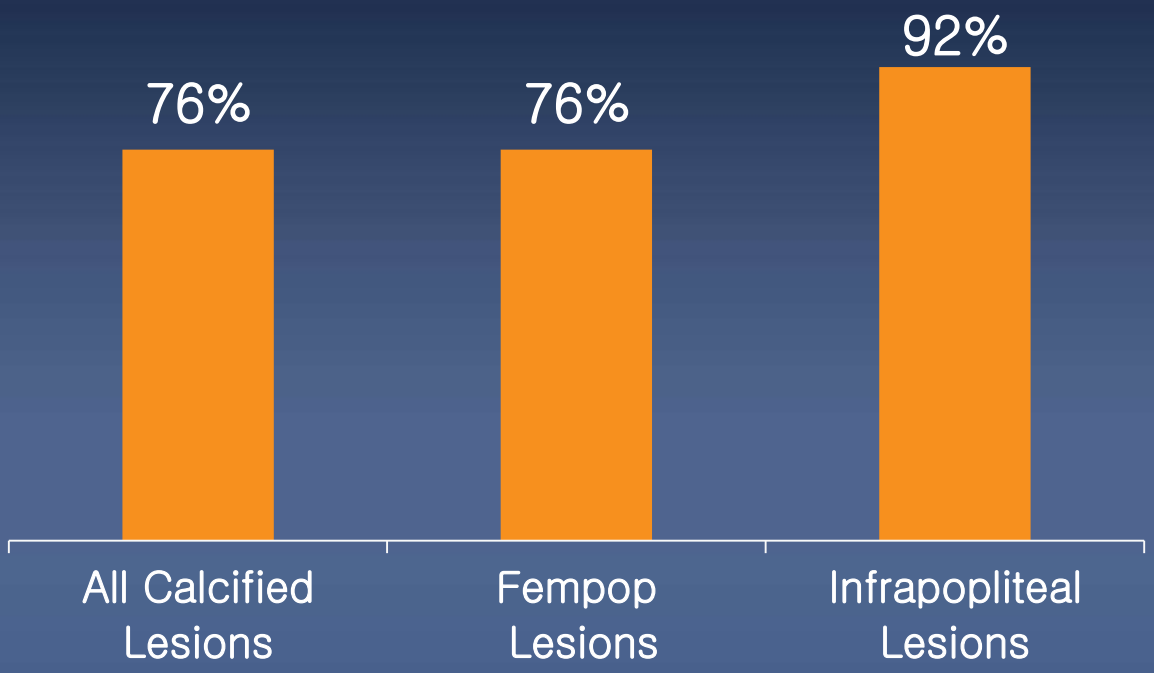


$$Q = \frac{\pi \Pr^4}{8\eta l}$$

Poiseuille's Law

Directional Atherectomy:

12 Month Primary Patency in Calcified Lesions from DEFINITIVE LE



Mean lesion length (cm):	**8.3**	**8.4**	**5.6**
Num. of lesions:	**274**	**262**	**12**

DEF LE CLI Cohort Primary Endpoint:

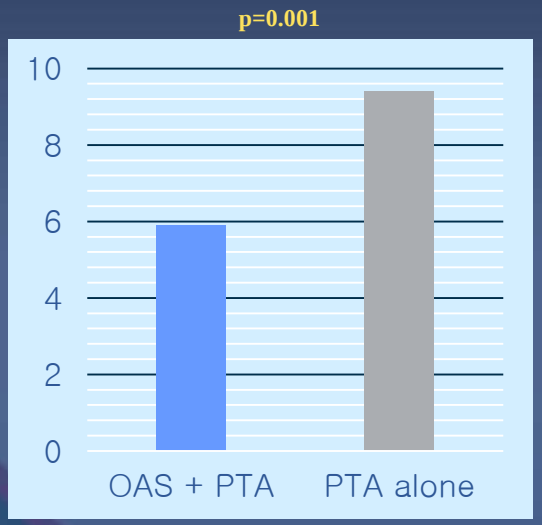
Freedom from Major Amputation at 12 Months

95%

CALCIUM 360° Study

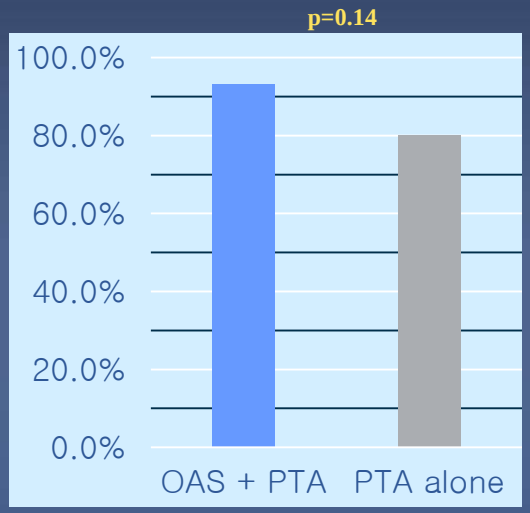
Randomized, prospective, multi-center study comparing OAS + PTA to PTA alone in calcified BTK arteries (tibial: 62.1% vs. 54.3%)

Mean Max Balloon Pressure (atm)



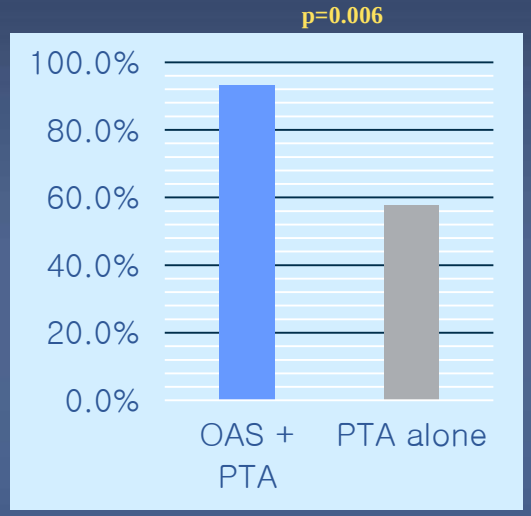
n=27 lesions | n=34 lesions

Freedom From Revascularization at 12 Months



n=15 patients | n=15 patients

Freedom from Major Adverse Events (MAE) at 12 Months

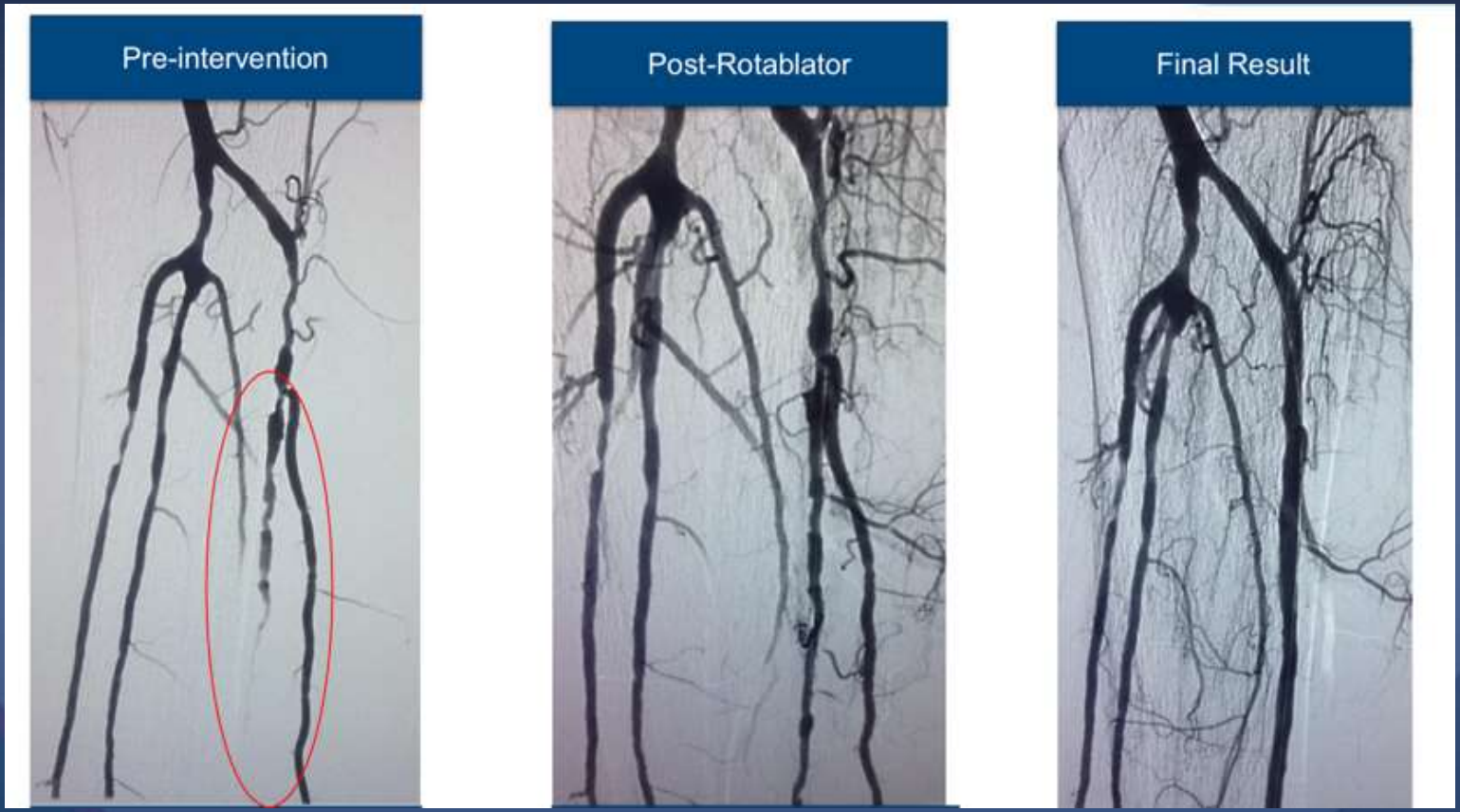


n=15 patients | n=19 patients

Orbital atherectomy provided durable results out to 12 months vs. PTA alone

Shammas NW, et al. *J Endovasc Ther*. 2012;19:480-488.

Anterior Tibial Treated with Jetstream Rotational Atherectomy



Orbital Atherectomy

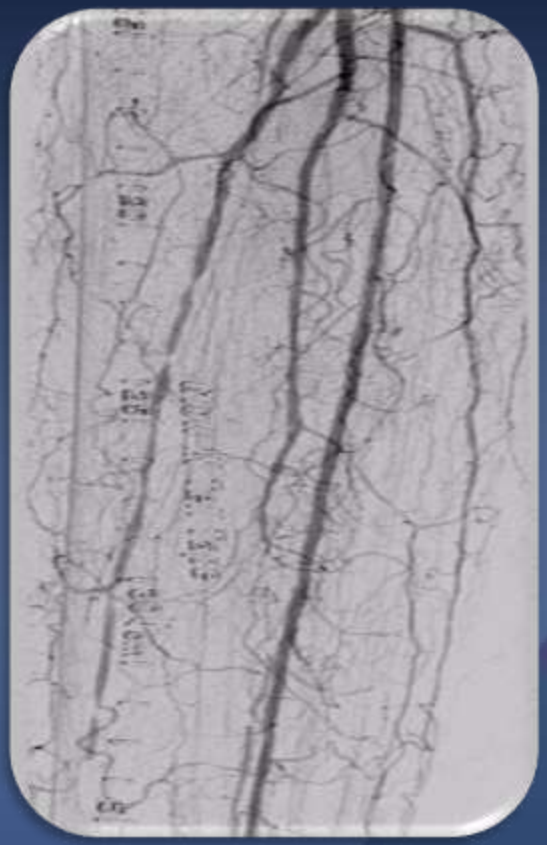
Left Peroneal

- **1.5 Classic Crown Diamondback (multiple passes)**
- **3x80 Armada 018 Balloon (12 atm for 2 min)**

Left AT

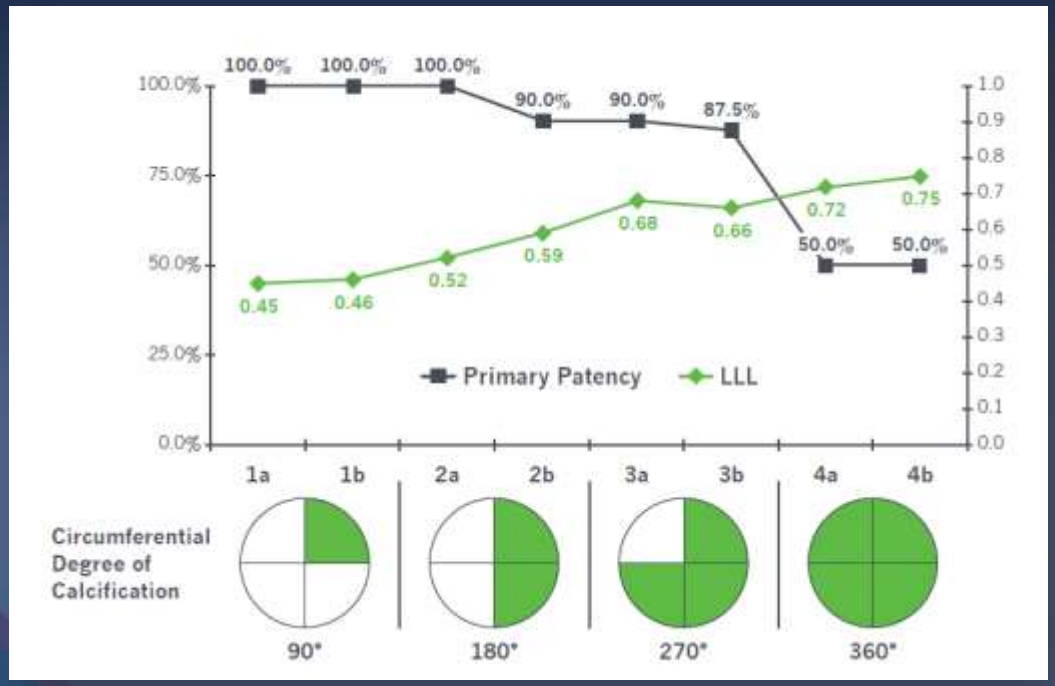
- **1.5 Classic Crown Diamondback (multiple passes)**
- **3.0/2.5x210 NanoCross balloon (4 atm for 2 min)**

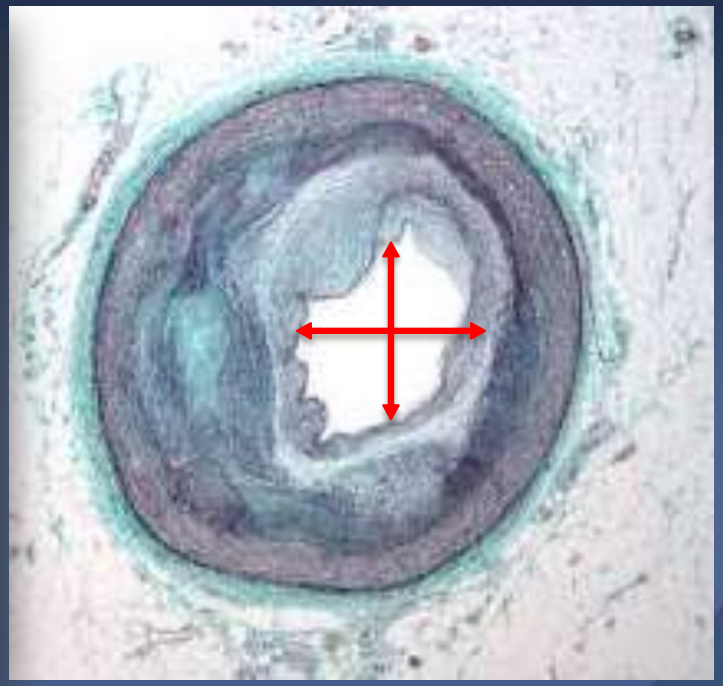
DIRECTIONAL ATHERECTOMY



Runoff to the foot before and after intervention

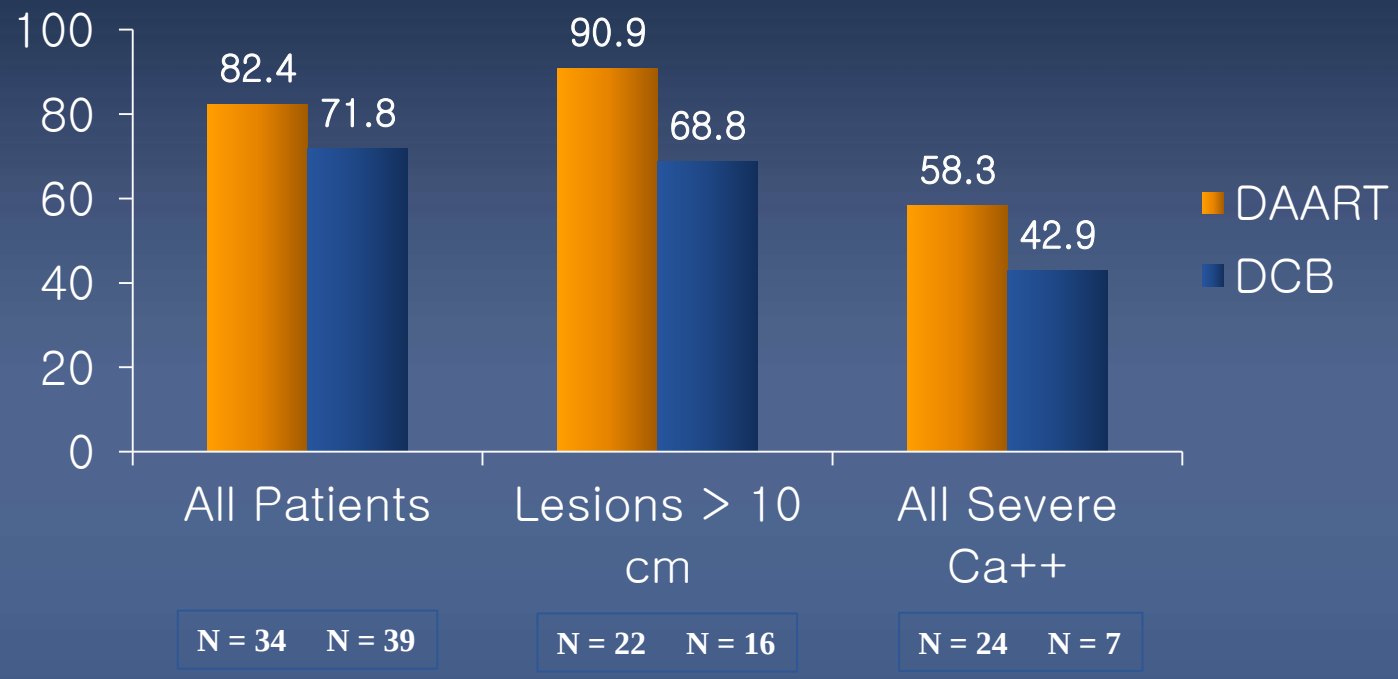
Does Atherectomy Improve DCB Results?



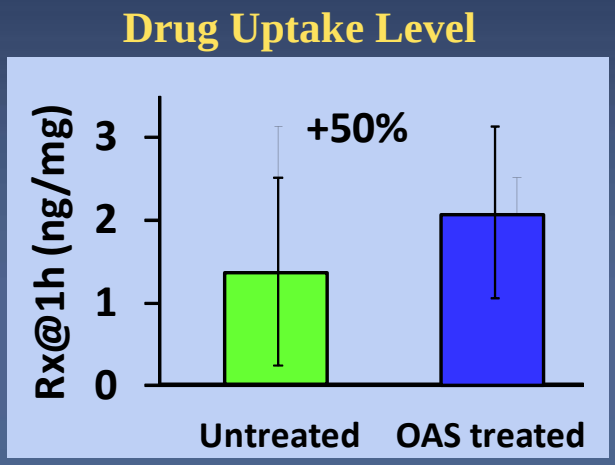


1. Fanelli F et al Cardiovas Interv Radiol 2014
2. Tepe G. ISET 2014

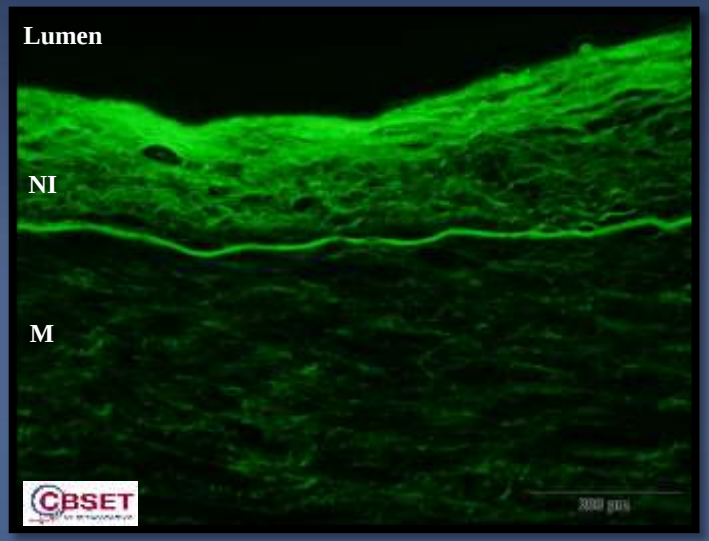
Definitive AR



Improved Drug Delivery After Plaque Modification



Edelman E. EuroPCR 2015



6 X deeper penetration with OAS

Will lumenal gain followed by DCB be the optimal solution for BTK/CLI?

- Limited Data
- Both PTA and Atherectomy increase lumen size, but atherectomy results in a larger lumen, and therefore exponentially more flow
- Atherectomy may also increase drug delivery, therefore more durable results
- Combination of atherectomy + drug may be synergistic and ideal solution for vessel patency

BUT, for wound healing:

- Several other factors involved not related to the index vessel revasc
- Wound care and risk factor control are critically important
- SAFETY??
  - Will atherectomy and DCB increase:
    - Plaque embolization?
    - Drug embolization?

Conclusions

- BTK disease is different and more complex as compared to ATK disease
- Goal of wound healing is not only associated with index vessel revasc
- During the index procedure,
  - Maximizing lumen gain results in an exponential increase in flow
  - Anti-proliferative drug may result in more durable effect
- However, there may be adverse outcomes due to plaque/drug embolization
- More studies are needed evaluate this hypothesis