DRUG TECHNOLOGY: HOW TO APPLY TO LONG CALCIFIC LESIONS

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PATIENTS WITH CALCIFIED LESIONS

- Untreated population, excluded from most of the clinical trials in the US[1,2]
- Multiple comorbidities[2]
  - Patients with severely calcified peripheral arteries tend to be older with higher prevalence of diabetes, kidney disease, hypertension, and hypercholesterolemia
- Longer treatment time, more resources, longer hospital stay, and higher costs[3,4]

*Peripheral vascular intervention

1. Cioppa A, et al. *Cardiovasc Revasc Med*. 2012;13:219-223.
2. Rocha-Singh KJ, et al. *Catheter Cardiovasc Interv*. 2014;83:E212-220.
3. Meerkin D, et al. *J Invasive Cardiol*. 2002;14:547-551.
4. Parikh K, et al. *Catheter Cardiovasc Interv*. 2013;81:1134-1139

SEVERELY CALCIFIED LESIONS

- Angiography underestimates severity of calcification[1,2]
- Technically challenging[3-6]
  - Respond poorly to angioplasty
    - Vessel recoil after balloon dilatation
    - Flow-limiting dissection related to high inflation pressure
  - Make stent placement difficult
    - Higher stent malapposition rate
    - Higher stent compression and/or fracture rate
- Higher procedural complication rates[3,6,7]
- Insufficient drug penetration with drug-coated balloons and subsequent restenosis[6,8]

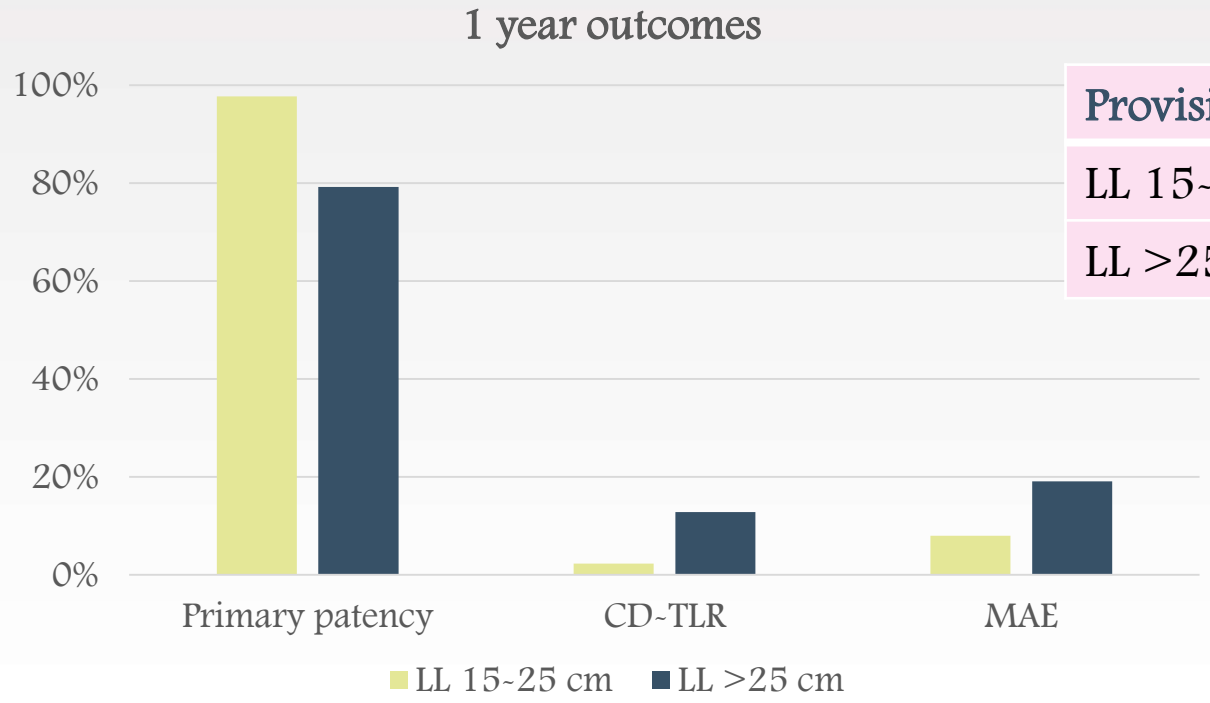
1. Kashyap VS, et al. *J Endovasc Ther*. 2008;15:117-125.
2. Van Lankeren W, et al. *Cardiovasc Intervent Radiol*. 1998;21:367-374.
3. Fitzgerald PJ, et al. *Circulation*. 1992;86:64-70.
4. Henry M, et al. *Tex Heart Inst J*. 2000;27:119-126.
5. Rogers JH and Laird JR. *Circulation*. 2007;116:2072-2085.
6. Cioppa A, et al. *Cardiovasc Revasc Med*. 2012;13:219-223.
7. Mustapha J, et al. *Vasc Dis Manag*. 2013;10:E198-207.
8. Fanelli F, et al. *Cardiovasc Intervent Radiol*. 2014;37:898-907.

DCB vs. DES

- Benefits
  - More uniform drug delivery than DES
  - Native vessel maintained
  - Reduced requirement for DAPT (if stents are avoided)
  - Reinterventions are less challenging than ISR
- Limitations
  - Procedural effectiveness, same as POBA
    - Recoil
    - Calcium
    - Dissections
    - Lesion length (?)
  - Increasing bail-out stent rate with increasing lesion length
    - Increases cost
    - May negatively affect procedural outcomes

Zeller T. Atherectomy and DCB for long and calcified lesions. Presented at CX 2016.

IN.PACT Global Long Lesion Imaging Cohort



Provisional stenting	
LL 15-25 cm	33.3%
LL >25 cm	52.6%

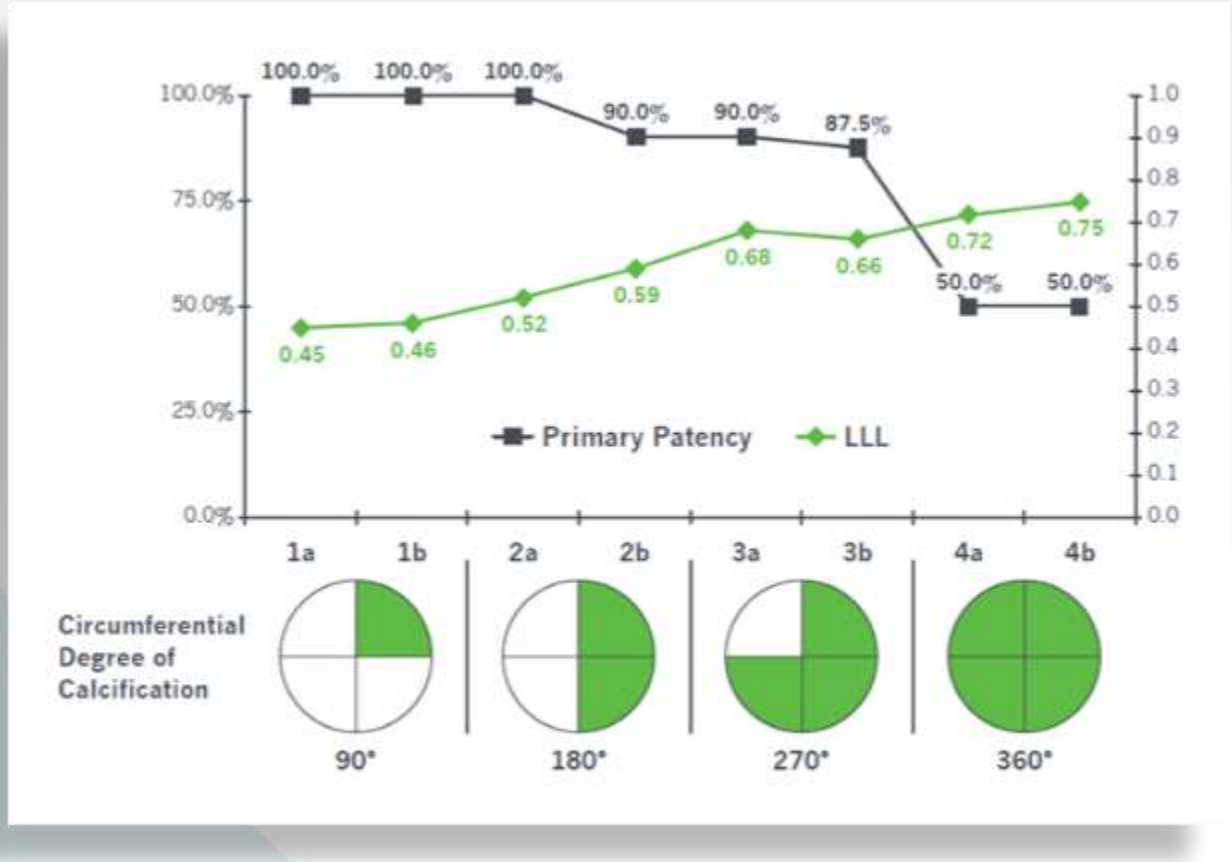
- A higher provisional stent rate in patients with LL >25 cm
- Lower primary patency rate for longer lesions

Scheinert D. IN.PACT Global Study Long Lesion (≥15 cm) Imaging Cohort. Presented at EuroPCR 2015.

LL = lesion length

Calcium is a Barrier of Drug Absorption

- Insufficient drug penetration and subsequent restenosis[1,2]

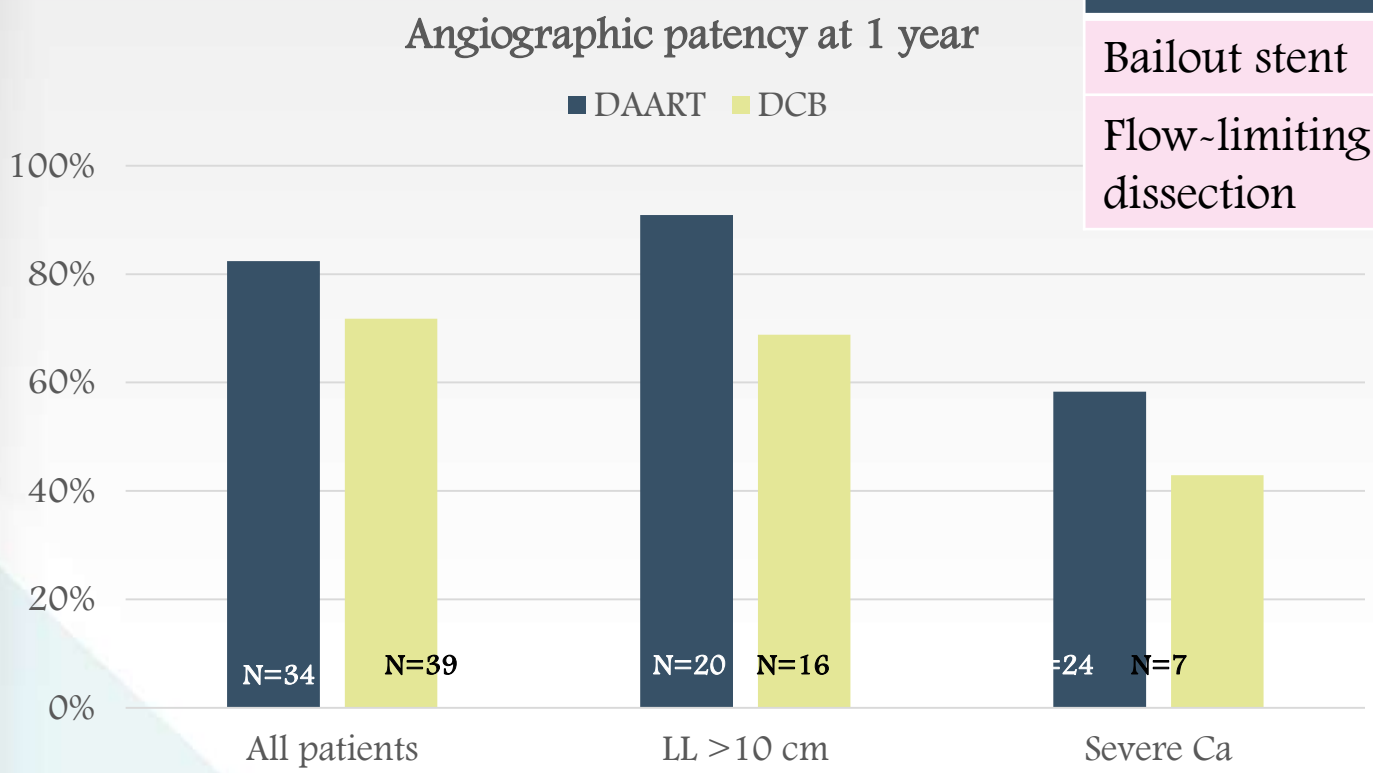


As circumferential calcium increases, the effectiveness of drug-coated balloons decreases.[3]

1. Cioppa A, et al. *Cardiovasc Revasc Med*. 2012;13:219-223.
2. Fanelli F, et al. *Cardiovasc Intervent Radiol*. 2014;37:898-907.
3. Fanelli F, et al. *J Endovasc Ther*. 2012;19:571-580.

DEFINITIVE AR

	DAART	DCB
Bailout stent	0%	3.7%
Flow-limiting dissection	2.0%	19.0%



Zeller T, et al. *Circ Cardiovasc Interv.* 2017;10:e004848.

DIAMONDBACK 360º PERIPHERAL ORBITAL ATHERECTOMY SYSTEM

Electric-Powered Handle

- Simple device set-up
- Optimum torque transfer to the shaft and crown
- Short overall treatment times

Crowns

Micro Crown
Classic Crown
Solid Crown

Saline Pump

- Mounts directly to an I.V. pole
- Bathes shaft and crown to facilitate smooth device operation

Crowns shown are the 1.25 mm Micro Crown, 1.50 mm Classic Crown, and 2.00 mm Solid Crown. Photographs are not to scale and for illustrative purposes only.

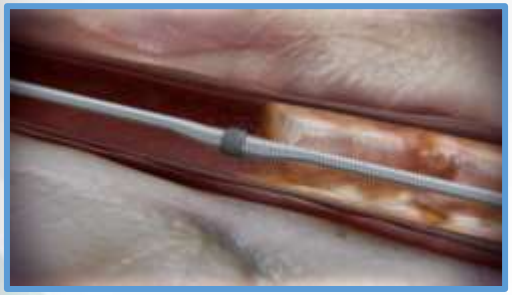
CSI'S MOA FACILITATES COMPLIANCE CHANGE BY MODIFYING BOTH SUPERFICIAL AND DEEP CALCIUM

Centrifugal Force:

- 360° crown contact designed to create a smooth, concentric lumen
- Allows constant blood flow and particulate flushing during orbit

30 µm diamond coating | *eccentric-mounted crown*

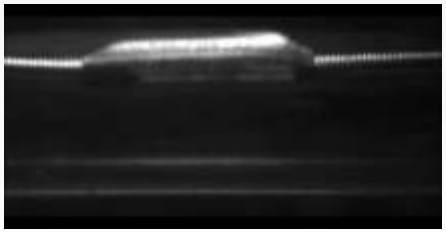
Differential Sanding



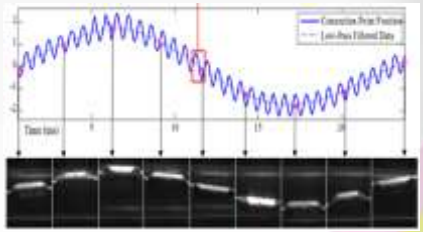
Micro-particulate

- 30 micron diamond coating
- Average particulate size[1] = 2 µm
- Bi-directional sanding of superficial calcium
- Healthy elastic tissue flexes away minimizing damage t o the vessel

Pulsatile Forces



Phantom Popliteal Vessel Model [1]



Motion Analysis

Dual Frequency[2]

- Orbital Frequency: low frequency of the crown orbiting against the vessel wall.
- Rotational Frequency: high frequency corresponding to the crown rotational speed.
- Observed in both crown motion and force.

1. Based on Carbon Block testing.
2. Zheng Y, et al. *Med Eng Phys*. 2016;38:639-647.

EXCELLENT SAFETY PROFILE IN PERIPHERAL CALCIFIED LESIONS CONSISTENTLY LOW ACUTE COMPLICATION RATES

	OASIS[1] n = 201	CONFIRM I Diamondback[2] n = 1146	CONFIRM II Predator[2] n = 1734	CONFIRM III Outflow[2] n = 1886	CALCIUM[3] n = 29	COMPLIANCE[4] n = 38
Mean Max Inflation Pressure (atm)	N/R	5.7	5.4	5.9	5.9	4.0
Bail-out Stent due to complications	2.5%	3.8%*	5.8%*	5.2%*	6.9%	5.3%‡
Perforation	1.5%	0.9%	0.6%	0.7%	0.0%	0.0%
Embolization	0.5%	N/R	2.2%	2.2%	0.0%	2.6%

* Based on reported dissection treatments.
‡ Adjunctive Stenting due to >30% residual stenosis

In real-world patient populations AND the most challenging lesions Orbital Atherectomy demonstrates successful lesion modification while maintaining low rates of procedural ad verse events.

1. Safian RD, et al. *Catheter Cardiovasc Interv*. 2009;73:406-12.
2. Das T, et al. *Catheter Cardiovasc Interv*. 2014;83:115-22. CSI Data on File.
3. Shammas NW, et al. *J Endovasc Ther*. 2012;19:480-8.
4. Dattilo R, et al. *J Invasive Cardiol*. 2014;26:355-60.

CONFIRM SERIES: STUDY DESIGN

CONFIRM I
733 patients/
1,146 lesions

CONFIRM II
1,127 patients/
1,734 lesions

CONFIRM III
1,275 patients/
1,886 lesions

- Prospective, multi-center, acute registries to evaluate t he use of OAS in patients with infra-inguinal PAD
- **Three consecutive prospective registries conducted un der common protocol from 2009 to 2011**
  - **Over 200 US hospitals**
  - **Over 350 physicians**
- Real-world patients
  - No inclusion/exclusion criteria
- Three generations of OAS
  - Diamondback 360º, Predator 360º, Stealth 360º

3,135 patients/4,766 lesions
The **largest PAD real-world patient data set**

Das T, et al. *Catheter Cardiovasc Interv*. 2014;83:115-22.

CONFIRM SERIES
COMMON FEMORAL ARTERY SUB-ANALYSIS

- **Patients** (Patients with both a CFA and SFA lesion location were excluded):

CFA Group	SFA Group
Patients with at least 1 CFA lesion location	*Patients with at least 1 SFA lesion location*
147 patients / 200 lesions	**1,508 patients / 2,367 lesions**

Demographics (by patient)	CFA Group	SFA Group	P-value
Male	61% (90/147)	59% (886/1505)	0.58
Age (years)	70.6 ± 10.3	71.1 ± 10.2	0.56
Smoker	**83%** (116/140)	**80%** (1154/1451)	0.35
Diabetes	**55%** (77/141)	**54%** (806/1487)	0.93
CAD	**63%** (89/142)	**64%** (952/1485)	0.73
Renal disease	33% (48/146)	33% (488/1473)	0.95
Hypertension	**96%** (140/146)	**92%** (1370/1495)	0.07
Hyperlipidemia	**86%** (124/145)	**81%** (1205/1485)	0.20
ABI score	**0.57** ± 0.27	**0.63** ± 0.21	0.16

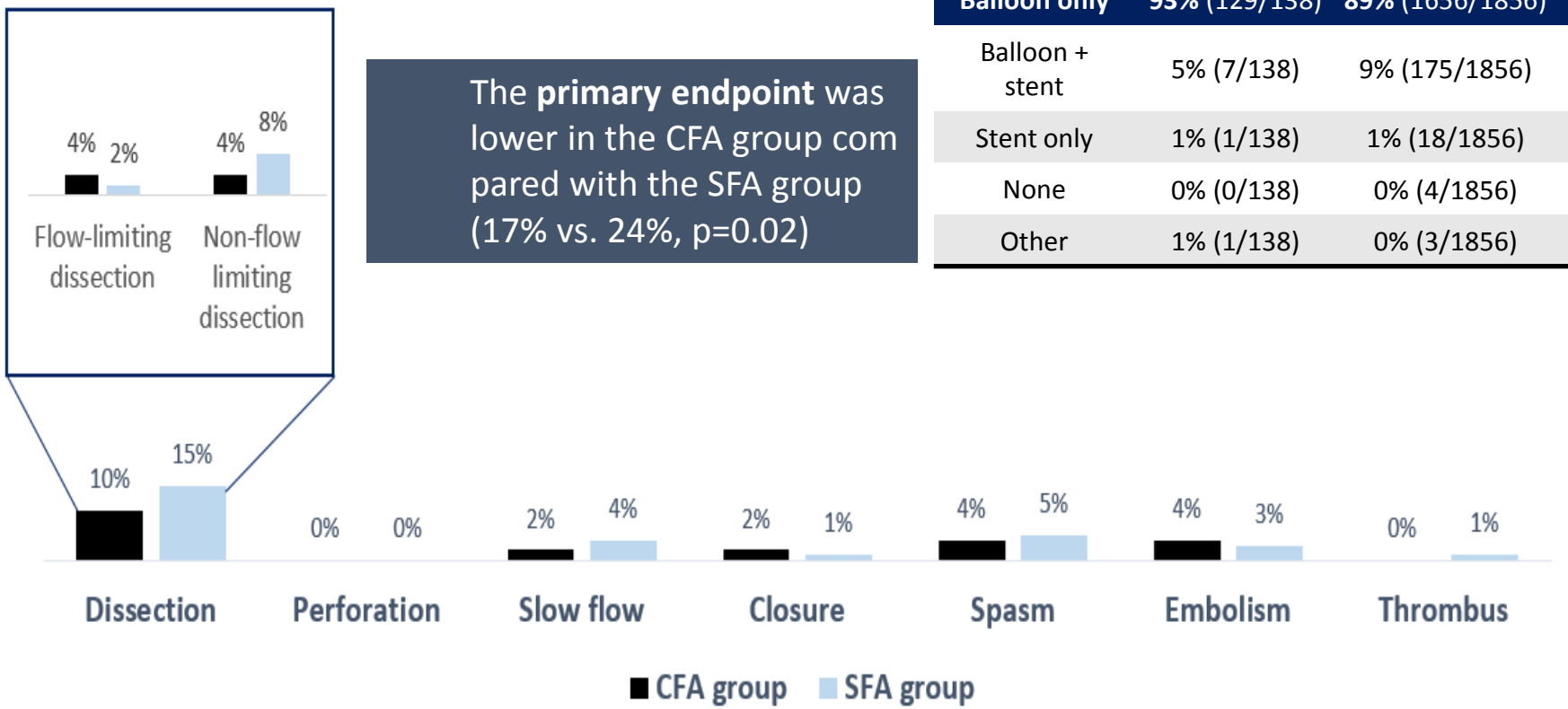
- **Primary endpoint:** angiographic complications (the composite of dissection, perforation, slow flow, closure, spasm, embolism, or thrombus formation)

Lee MS, et al. *Vasc Med*. 2017;22:301-306.

CONFIRM SERIES
COMMON FEMORAL ARTERY SUB-ANALYSIS

Adjunctive therapy (by lesion)	CFA Group	SFA Group	p
Balloon only	**93%** (129/138)	**89%** (1656/1856)	0.12
Balloon + stent	5% (7/138)	9% (175/1856)	0.09
Stent only	1% (1/138)	1% (18/1856)	0.77
None	0% (0/138)	0% (4/1856)	0.59
Other	1% (1/138)	0% (3/1856)	0.15

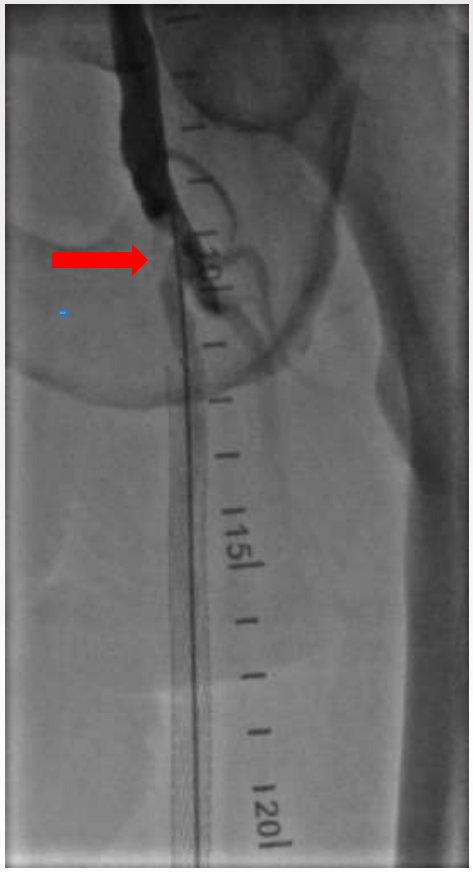
The **primary endpoint** was lower in the CFA group compared with the SFA group (17% vs. 24%, p=0.02)



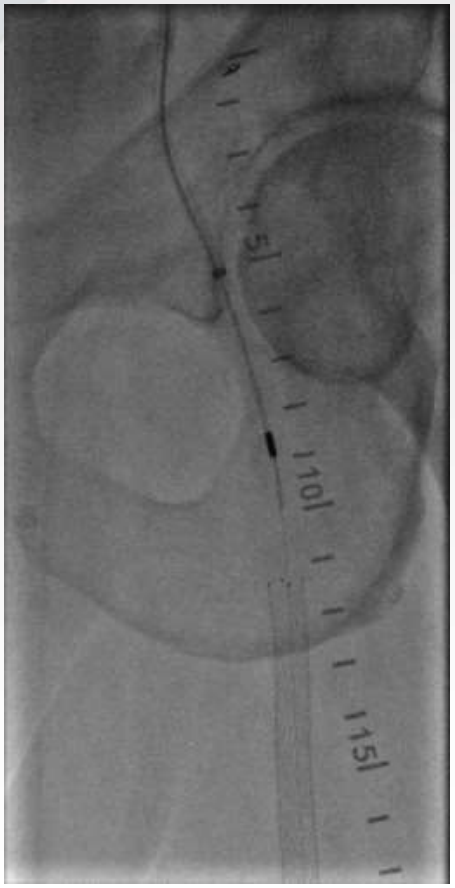
ORBITAL ATHERECTOMY IS A REASONABLE REVASCULARIZATION STRATEGY FOR CALCIFIC CFA DISEASE

Lee MS, et al. *Vasc Med*. 2017;22:301-306.

Calcified Common Femoral Arterial Disease

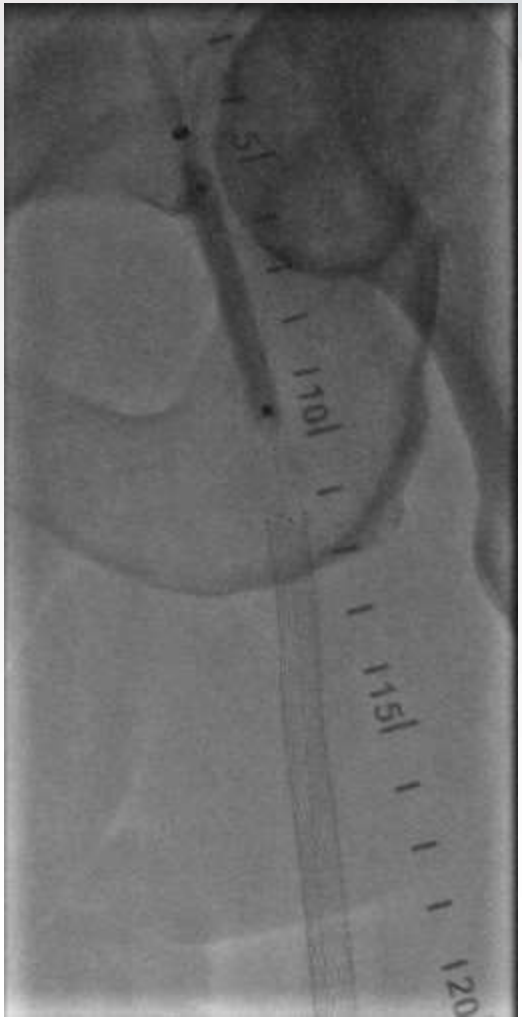


85 y.o. male with lung cancer, severe COPD, with Rutherford class 3 claudication who refused endarterectomy



Orbital atherectomy 1.5 mm crown

6 mm DCB
At 5 atm



CONFIRM SERIES
PROFUNDA FEMORIS ARTERY SUB-ANALYSIS

- **Patients** (Patients with both a PFA and SFA lesion location were excluded):

PFA Group	SFA Group
Patients with at least 1 PFA lesion location	*Patients with at least 1 SFA lesion location*
33 patients / 33 lesions	**1,574 patients / 1,811 lesions**

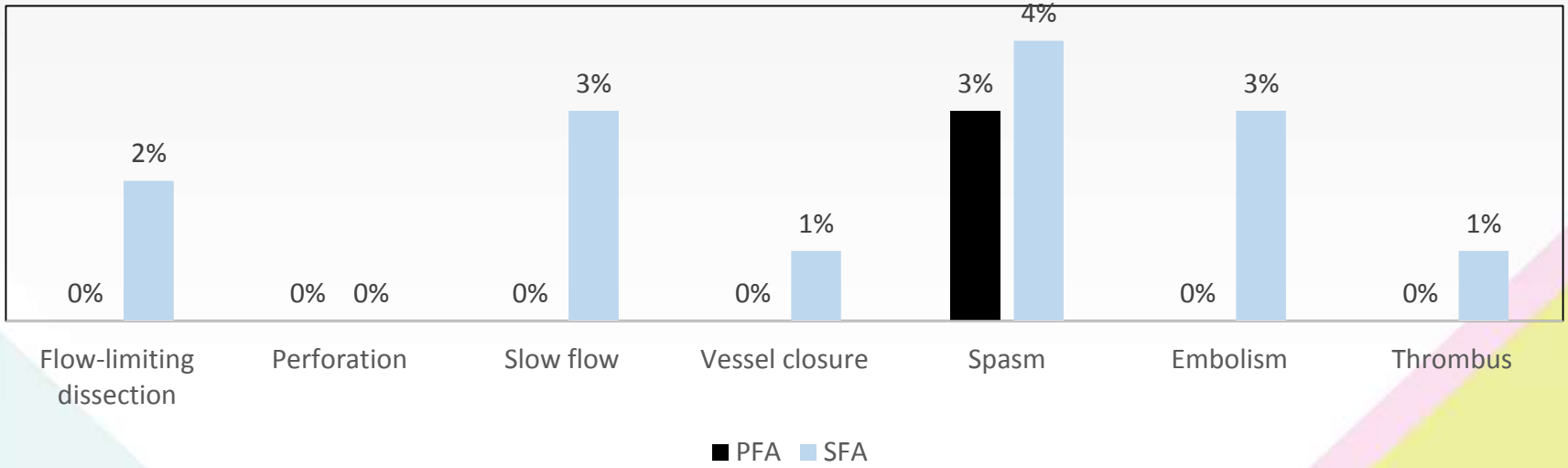
Demographics (by patient)	PFA Group	SFA Group	P-value
Male	73% (24/33)	59% (928/1571)	0.11
Age (years)	72.2 ± 10.3	71.0 ± 10.2	0.53
Current smoker	32% (10/31)	30% (461/1514)	0.83
Diabetes	**45%** (15/33)	**54%** (843/1553)	0.31
CAD	**77%** (24/31)	**65%** (1002/1551)	0.14
Renal disease	42% (14/33)	33% (509/1539)	0.26
Hypertension	**100%** (33/33)	**92%** (1433/1561)	0.09
Hyperlipidemia	**82%** (27/33)	**82%** (1268/1551)	0.99
ABI score	**0.46** ± 0.34	**0.64** ± 0.29	0.12

- **Primary endpoint:** angiographic complications (the composite of flow-limiting dissection, perforation, slow flow, vessel closure, spasm, embolism, or thrombosis)

Lee MS, et al. *J Invasive Cardiol*. 2017 Dec 15. pii: JIC20171215-3. [Epub ahead of print].

CONFIRM SERIES
PROFUNDA FEMORIS ARTERY SUB-ANALYSIS

- **Procedural characteristics and adjunctive therapy**
  - Adjunctive stenting was only performed in the SFA group (10%); no patient in the PFA group underwent stenting
- **Procedural complications**
  - The primary endpoint was low in the PFA group and compared favorably with the SFA group (3% vs. 11%; p=0.14)



ORBITAL ATHERECTOMY OF THE PROFUNDA FEMORIS ARTERY IS FEASIBLE AND SAFE

Lee MS, et al. *J Invasive Cardiol*. 2017 Dec 15. pii: JIC20171215-3. [Epub ahead of print].

Orbital Atherectomy + DCB Study

Single-center study comparing OAS + DCB to DCB alone in calcified femoropopliteal arteries

Lesions	OAS + DCB (N=40)	DCB alone (N=99)	p
Calcification			<0.001
None	0%	19%	
Mild	3%	13%	
Moderate	8%	23%	
Severe	90%	44%	
Ca circumference ≥180	83%	43%	<0.001
Calcium length ≥5 cm	78%	38%	<0.001
Bilateral calcification	83%	43%	<0.001

Lesions	OAS + DCB (N=40)	DCB alone (N=99)	p
Bailout stenting	18%	39%	0.01
Scoring balloon	88%	35%	<0.001
Procedural success	98%	99%	0.8
Embolization	0%	2%	0.4
Dissection	13%	14%	0.8
Perforation	0%	0%	1.0

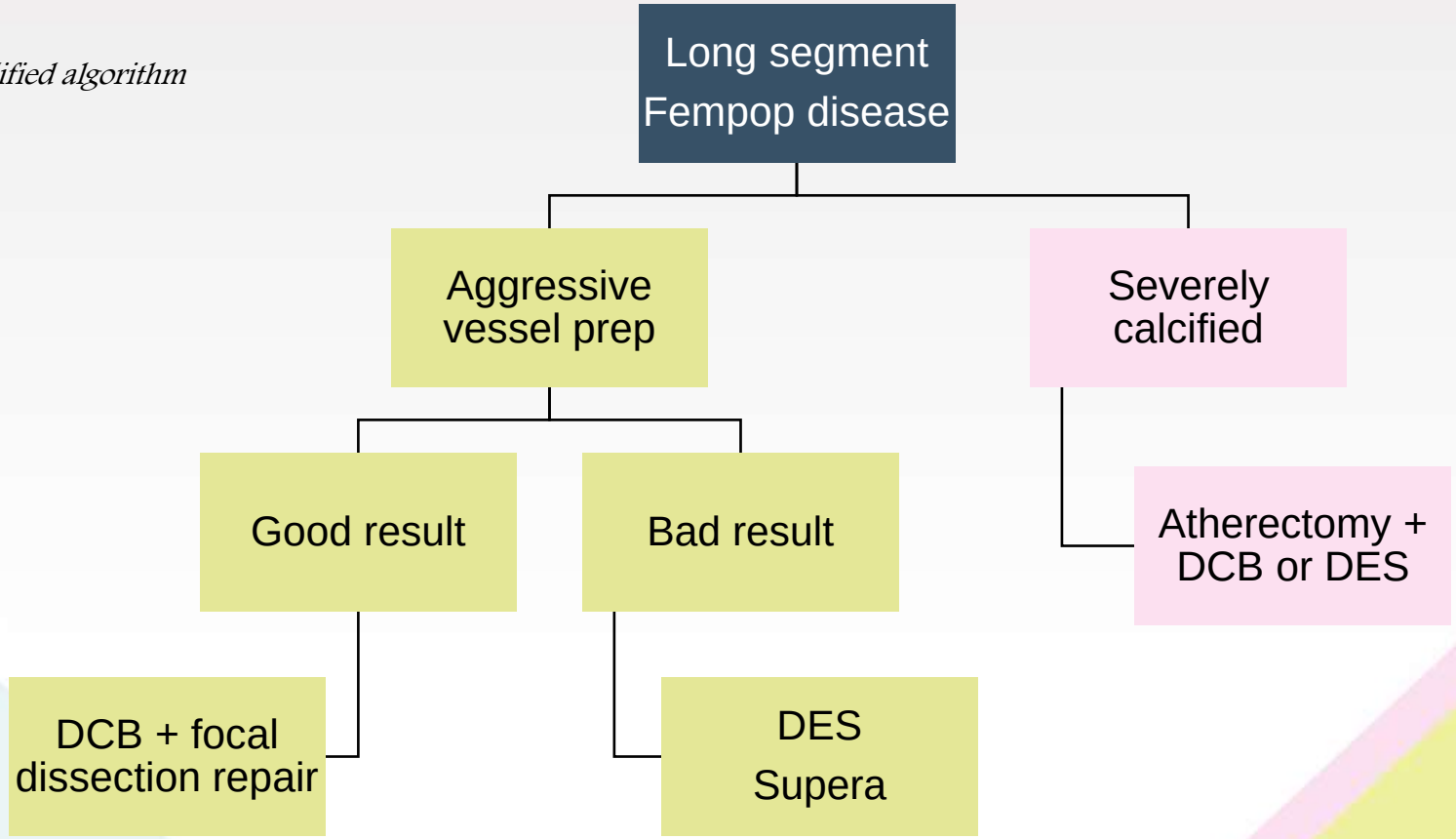
- Freedom from TLR at 1 year was 82% in both groups (p=0.6)
- Primary patency at 1 year was 77% in OAS + DCB vs. 81% in DCB alone (p=0.8)

- OAS was most likely to be used for severely calcified lesions and was associated with less bailout stenting compared to DCB alone
- OAS may enhance the effect of DCBs in calcified femoropopliteal disease

Foley TR, et al. *Catheter Cardiovasc Interv.* 2017;89:1078-1085.

Proposed Algorithm for Long-Lesion Treatment Strategies

Modified algorithm



Schneider P. Progress made in endovascular treatment of long lesions. *Cardiology Today's Intervention*. Nov/Dec 2017. https://www.healio.com/cardiac-vascular-intervention/peripheral/news/print/cardiology-today-intervention/%7B0ee1d1e2-c073-4289-a680-deab5fbeaeeb%7D/progress-made-in-endovascular-treatment-of-long-lesions. Accessed March 26, 2018.

Conclusions

- In general, drug technologies exhibit positive results in long lesions
- Circumferential distribution of calcium represents the main barrier for drug uptake
- Proper lesion preparation can increase the patency rate of DCBs in severely calcified lesions
- Atherectomy devices increase the luminal gain and may also improve drug uptake

John Wooden

“Failing to prepare is preparing to fail.”