

DCB in severe Calcium: Core-laboratory analysis and perspectives from the ILLUMINATE trial series

Sean Lyden, MD
Chairman, Department of Vascular Surgery
Cleveland Clinic
Cleveland, Ohio

Disclosure

Speaker name: Sean Lyden MD

.....

I have the following potential conflicts of interest to report:

Consulting Phillips, Endologix, Shockwave, Abbott, BSC, Spectranetics, Medtronic, PQ Bypass

Employment in industry: None

Stockholder of a healthcare company: None

Owner of a healthcare company: None

Other(s) VIVA Physicians Inc 501c3 Board Member

Vascular Calcium: Premise



- Prevalent in elderly patients, diabetics and patients with kidney disease
- More complex PAD lesions are being treated through endovascular techniques
- Calcium is a barrier to optimal dilatation and optimal drug absorption and underestimated by angiography
- Impact of calcium on DCB performance is not fully defined

1. Moe SM, Chen NX. Mechanisms of vascular calcification in chronic kidney disease. *J Am Soc Nephrol.* 2008 Feb;19(2):213-6
2. Bertoni AG, Kramer H, Watson K, Post WS. Diabetes and Clinical and Subclinical CVD. *Glob Heart.* 2016 Sep;11(3):337-342
3. Fanelli F et al. Calcium burden assessment and impact on drug-eluting balloons in peripheral arterial disease. *Cardiovasc Intervent Radiol.* 2014 Aug;37(4):898-907
4. Rocha-Singh KJ, Zeller T, Jaff MR. Peripheral arterial calcification: prevalence, mechanism, detection, and clinical implications. *Catheter Cardiovasc Interv.* 2014 May 1;83(6):E212-20

Bilateral / circumferential distribution = common marker of Calcium severity

Fanelli et al. [1]

DEFINITIVE Ca⁺⁺ [2]

Compliance 360 [3]

PACSS [4]

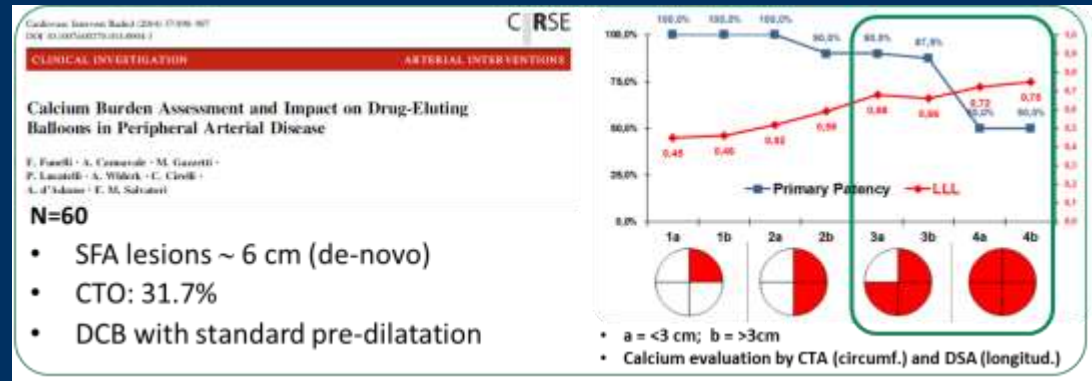
PARC [5]

Fanelli et al. [1]	1a	1b	2a	2b	3a	3b	4a	4b
Circumf.	0-90°	0-90°	90-180°	90-180°	180-270°	180-270°	270-360°	270-360°
Length	<3 cm	>3 cm	<3 cm	>3 cm	<3 cm	>3 cm	<3 cm	>3 cm
DEFINITIVE Ca⁺⁺ [2]					moderate		severe	
Circumf.					one side of vessel		both sides of vessel	
Length					or <1 cm		and >1 cm	
Compliance 360 [3]	0				1		2	
Circumf.	NO calcium		<180° (1 side of vessel)		<180° (1 side of vessel)		≥180° (both sides of vessel)	
Length	NO calcium		<50% of lesion length		≥50% of lesion length		≥180° (both sides of vessel)	
PACSS [4]	0				1		2	
Circumf.	NO calcium		unilateral		unilateral		bilateral	
Length	NO calcium		<5 cm		≥5 cm		bilateral	
PARC [5]	a) intimal calcification; b) medial calcification; c) mixed type				Focal		mild	
Circumf.	<180° (1 side of vessel)		<180° (1 side of vessel)		moderate		severe	
Length	<1/2 of lesion length		>1/2 of lesion length		≥180° (both sides of vessel)		>180° (both sides of vessel)	
					<1/2 of lesion length		>1/2 of lesion length	

1. Fanelli F et al. Calcium burden assessment and impact on drug-eluting balloons in peripheral arterial disease. Cardiovasc Intervent Radiol. 2014 Aug;37(4):898-907
2. Roberts D et al. DEFINITIVE Ca⁺⁺ Investigators. Effective endovascular treatment of calcified femoropopliteal disease with directional atherectomy and distal embolic protection: final results of the DEFINITIVE Ca⁺⁺ trial. Catheter Cardiovasc Interv. 2014 Aug 1;84(2):236-44
3. Dattilo R et al. The COMPLIANCE 360° Trial: a randomized, prospective, multicenter, pilot study comparing acute and long-term results of orbital atherectomy to balloon angioplasty for calcified femoropopliteal disease. J Invasive Cardiol. 2014 Aug;26(8):355-60
4. Rocha-Singh KJ et al. Peripheral arterial calcification: prevalence, mechanism, detection, and clinical implications. Catheter Cardiovasc Interv. 2014 May 1;83(6):E212-20
5. Patel MR et al. Evaluation and treatment of patients with lower extremity peripheral artery disease: consensus definitions from Peripheral Academic Research Consortium (PARC). J Am Coll Cardiol. 2015 Mar 10;65(9):931-41. doi: 10.1016/j.jacc.2014.12.036. Erratum in: J Am Coll Cardiol. 2015 Jun 16;65(23):2578-9

Calcium and DCB

Evidence (in-vivo and ex-vivo) indicates Calcium as potential barrier to optimal drug absorption. Circumferential Calcium strongest contributor



Fanelli F, Cannavale A, Gazzetti M, Lucatelli P, Wlodek A, Cirelli C, d'Adamo A, Salvatori FM. Calcium burden assessment and impact on drug-eluting balloons in peripheral arterial disease. *Cardiovasc Intervent Radiol*. 2014 Aug;37(4):898-907

Tzafirri AR, Garcia-Polite F, Zani B, Stanley J, Muraj B, Knutson J, Kohler R, Markham P, Nikanorov A, Edelman ER. Calcified plaque modification alters local drug delivery in the treatment of peripheral atherosclerosis. *J Control Release*. 2017 Sep 1;264:203-210

Study Purpose



- To assess the impact of severe calcium on 12-month outcomes after DCB treatment
- Post-hoc analysis of a large patient dataset (N=571) treated with Stellarex DCB
- Pooled analysis from 2 prospective studies:
 - ILLUMENATE GLOBAL single-arm, full cohort (N=371) [1]
 - ILLUMENATE PIVOTAL randomized trial, DCB arm (N=200) [2]

1. Schroë H, Holden AH, Goueffic Y, Jansen SJ, Peeters P, Keirse K, Ito W, Vermassen F, Micari A, Blessing E, Jaff MR, Zeller T. Stellarex drug-coated balloon for treatment of femoropopliteal arterial disease-The ILLUMENATE Global Study: 12-Month results from a prospective, multicenter, single-arm study. Catheter Cardiovasc Interv. 2018 Feb 15;91(3):497-504
2. Krishnan P, Faries P, Niazi K, Jain A, Sachar R, Bachinsky WB, Cardenas J, Werner M, Brodmann M, Mustapha JA, Mena-Hurtado C, Jaff MR, Holden AH, Lyden SP. Stellarex Drug-Coated Balloon for Treatment of Femoropopliteal Disease: Twelve-Month Outcomes From the Randomized ILLUMENATE Pivotal and Pharmacokinetic Studies. Circulation. 2017 Sep 19;136(12):1102-1113

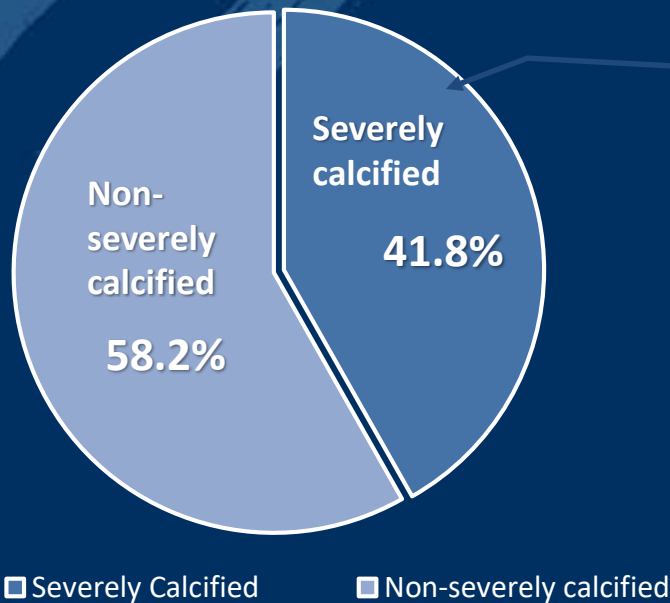
2 ILLUMENATE Trials

2 robust ILLUMENATE Trials with independent (Angiographic and Duplex) core-laboratory and clinical event adjudication

	ILLUMENATE Global	ILLUMENATE Pivotal
N Patients	371	300
N Sites	37	43
Design	Single-arm	RCT
Patient Population	Claudication and rest pain due to fem-pop disease	
Primary Safety Endpoint	Freedom from 30-day device- and procedure-related death and freedom from 12-month target limb major amputation and clinically-driven TLR	
Primary Effectiveness Endpoint	Primary patency at 12 months defined as freedom from restenosis (determined by duplex ultrasound PSVR ≤ 2.5) and freedom from clinically-driven TLR	

Calcium Core-Lab Assessment

Severe calcification: **prospectively** defined as radio opacities noted on **both sides of the arterial wall and extending more than one cm** of length prior to contrast injection or digital subtraction angiography



- **41.8% Ca⁺⁺**
- **87% of Ca⁺⁺ meeting the PACSS Grade 4 definition, bilateral calcification extending $\geq 5\text{cm}$ [1]**

1. Rocha-Singh KJ, Zeller T, Jaff MR. Peripheral arterial calcification: prevalence, mechanism, detection, and clinical implications. Catheter Cardiovasc Interv. 2014 May 1;83(6):E212-20

Baseline Characteristics

	Non-Severely Calcified (N=314)	Severely Calcified (N=242)	p-value
Age (years)	66.7	69.7	<.001
Male	64.0%	71.9%	0.049
Baseline Rutherford-Becker Clinical Category			0.042
2	29.9%	34.7%	
3	62.4%	58.7%	
4	7.0%	3.7%	
5	0.6%	2.9%	
Ankle-Brachial Index	0.72	0.71	0.672
Hypertension	79.9%	90.5%	<.001
Hyperlipidemia	75.2%	87.2%	<.001
Smoking Status			0.634
Never Smoked	16.2%	17.8%	
Previous Or Current Smoker	83.8%	82.2%	
Diabetes	32.2%	48.8%	<.001
Previous Coronary Revascularization	30.3%	47.9%	<.001
Renal Insufficiency	10.5%	11.6%	0.692
Lesion Length (cm)	7.2	8.3	0.007
Reference Vessel Diameter (RVD) (mm)	4.78	4.99	0.004
Total Occlusion	28.2%	25.9%	0.525

Procedural Characteristics

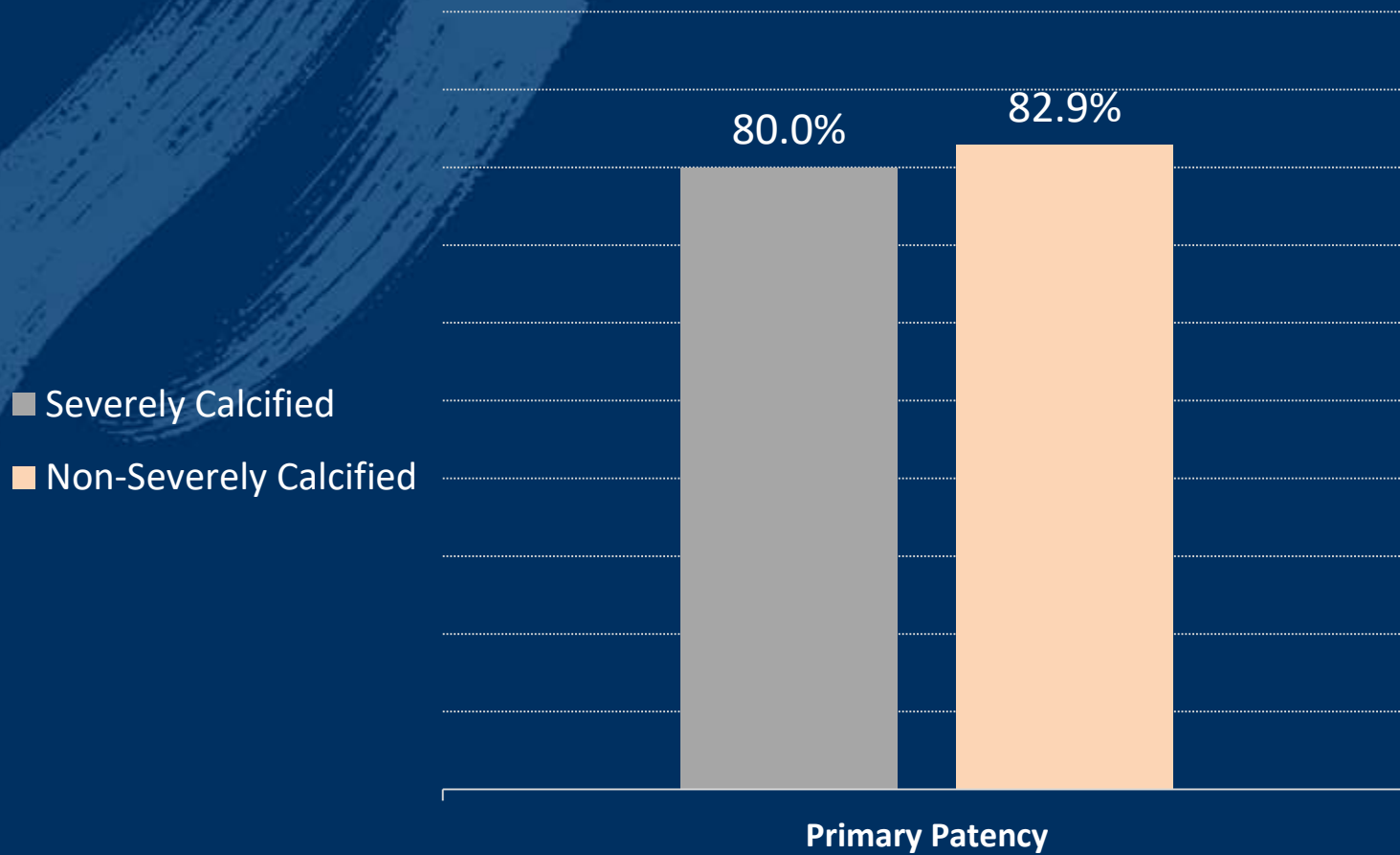
	Non-Severely Calcified (N=314)	Severely Calcified (N=242)	p
Pre-Dilatation	98.9%	98.8%	1
Pre-Dilatation Max Pressure (atm/lesion)	8.8	9.5	0.005
Total Inflation Time (min/lesion)	3.4	3.9	0.005
Dissection Grade > C	20.4%	19.9%	0.885
Post-Dilatation	25.0%	23.9%	0.759
Post-Procedure DS (%)	23.9%	26.4%	0.008
Bailout Stent (per lesion)	13.5%	12.7%	0.787

12-month Outcomes

	Non-Severely Calcified	Severely Calcified	p
Freedom from Primary Safety Event¹	93.0%	93.0%	0.996
12 Month Major Adverse Event²	7.3%	7.8%	0.834
Clinically-Driven TLR	7.0%	7.0%	0.996
All TLR	8.0%	8.3%	0.893

1. Defined as the composite of freedom from device and procedure-related death through 30 days post-procedure and freedom from target limb major amputation and clinically-driven target lesion revascularization (CD-TLR) through 12 months post-procedure
2. Defined as cardiovascular death, target limb major amputation, or clinically-driven target lesion revascularization (CD-TLR).

12-month Primary Patency



Per KM estimate at day 365

Conclusions

- The present study represents a large (N=571), rigorous core-lab adjudicated assessment of the role of calcium in DCB treatment of fem-pop lesions at 1 year
- Severe calcium is confirmed to be more prevalent in patients with diabetes, hypertension, hyperlipidemia, coronary artery disease and renal insufficiency
- Similar 12-month outcomes can be achieved with the Stellarex DCB in severely calcified lesions that are amenable to pre-dilatation

DCB in severe Calcium: Core-laboratory analysis and perspectives from the ILLUMINATE trial series

Sean Lyden, MD
Chairman, Department of Vascular Surgery
Cleveland Clinic
Cleveland, Ohio