Intravascular Lithotripsy for Peripheral Artery Calcification

The Disrupt PAD III Randomized Controlled Trial
30-day Outcomes

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Faculty Disclosure

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For the 12 months preceding this CME activity, I or my spouse/partner disclose the following types of financial relationships:

- Honoraria received from: None
- Consulted for: Shockwave Medical
- Held common stock in: None
- Research, clinical trial, or drug study funds received from: Shockwave Medical

I will not be discussing products that are investigational or not labeled for use under discussion.

Endovascular Treatment for Calcified PAD

- The presence of calcified PAD*:
  - Restricts arterial compliance
  - Results in poor balloon expansion, dissections and acute procedural failure
  - May impair effectiveness of DCBs by limiting drug uptake
  - Stents to address PTA failure may fracture and complicate future revascularization
- Distal embolization, dissection and perforation remain a concern with atherectomy treatment
- Patients with moderate-severe calcification are often excluded from endovascular treatment trials resulting in little available evidence to provide treatment guidance in this challenging patient population

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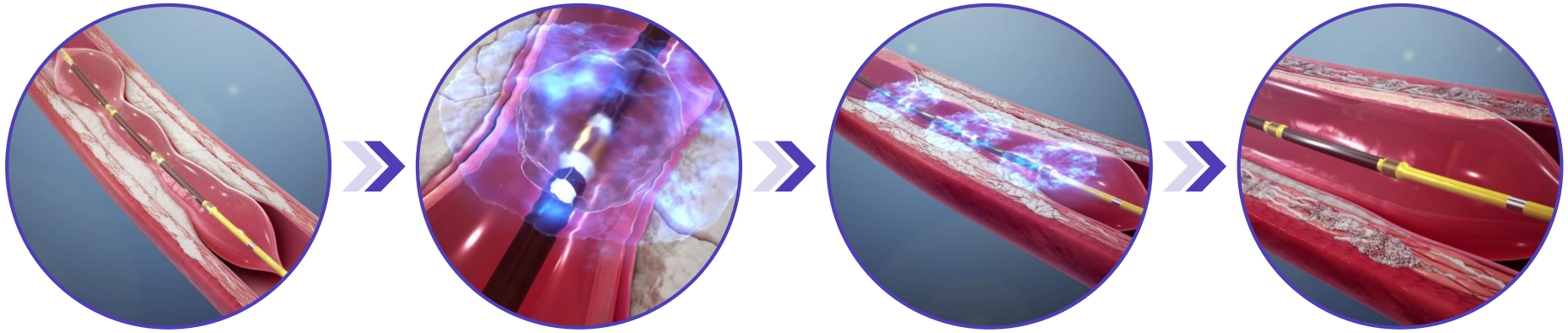
*Rocha-Singh et al., *Catheter Cardiovas Interv* 2014; Tosaka et al, *JACC* 2012; Walker et al., *J. Vasc Surg* 2015

Intravascular Lithotripsy



Deliver catheter and inflate to low pressure

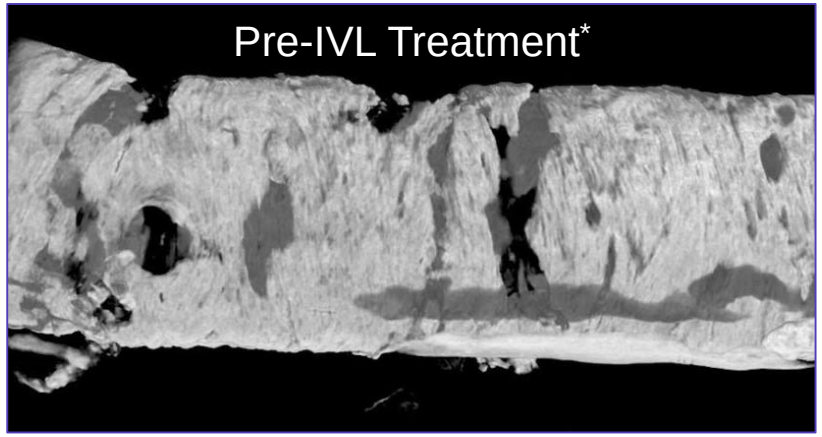
Generate sonic pressure waves using lithotripsy

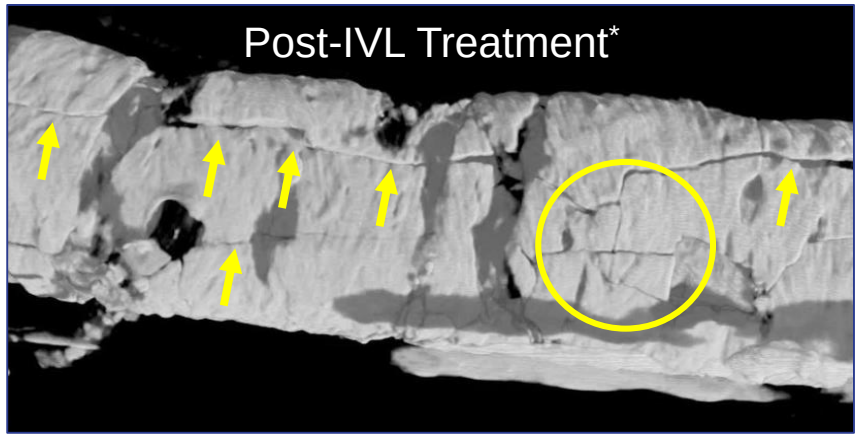
Crack calcium

Safely expand the vessel

IVL

- Delivers 1 pulse/sec at effective pressure of ~50 atm
- At low balloon inflation pressure
- Fractures both superficial and deep calcium





*Micro-CT scan analysis: R. Virmani, CV Path Institute

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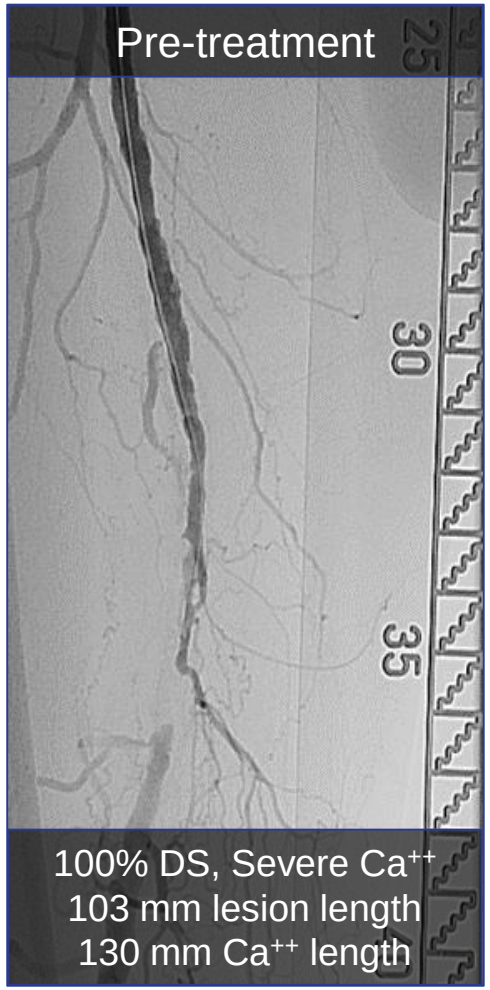
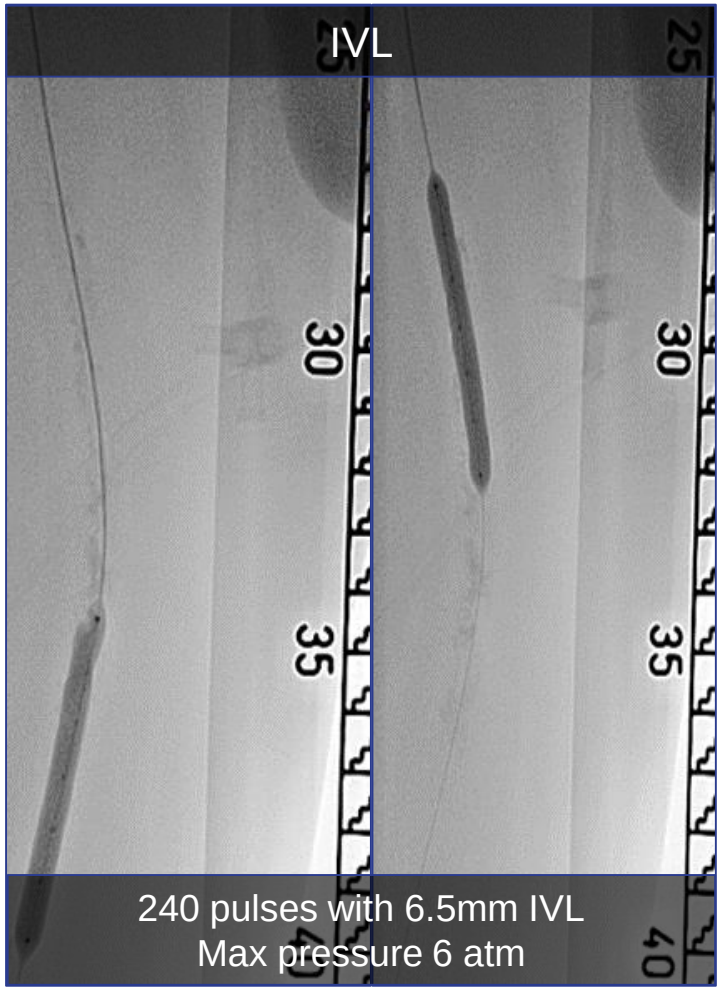
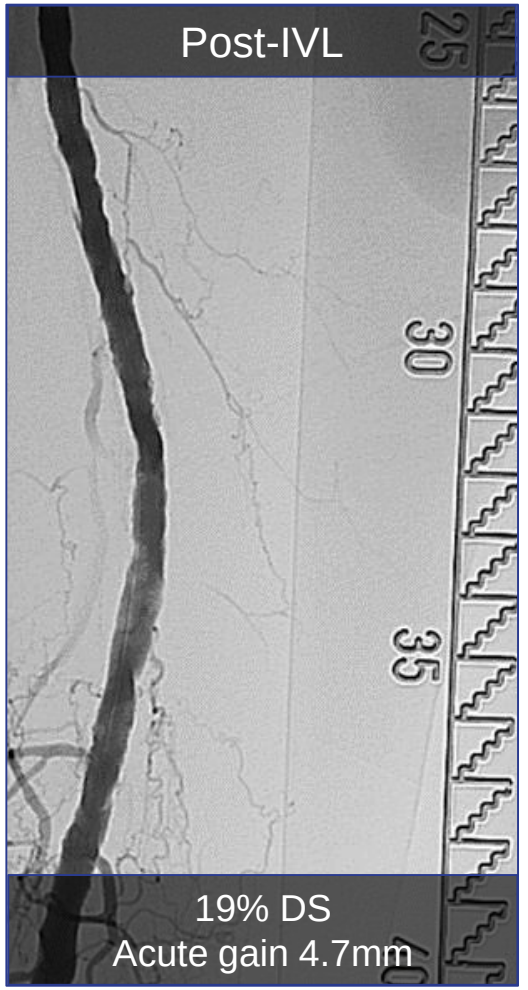
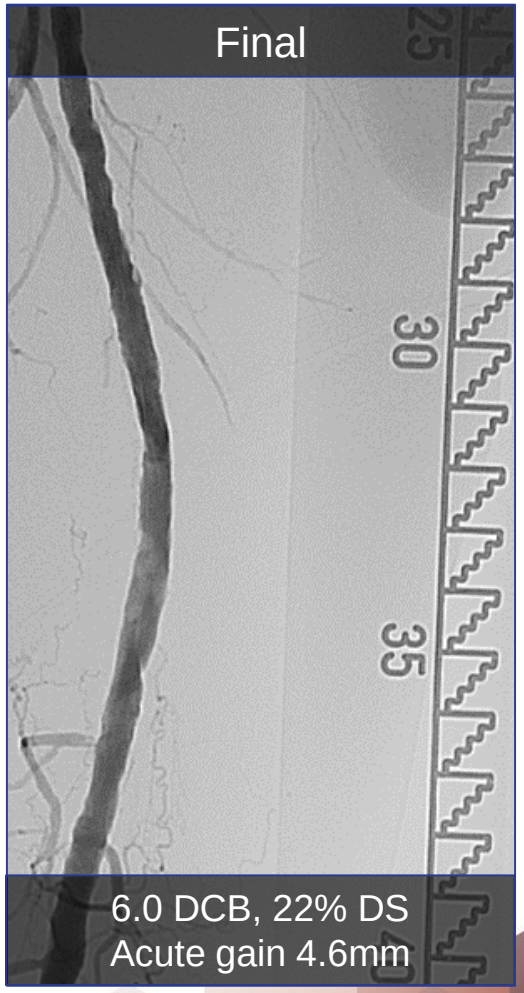
IVL Treatment: Mid-SFA









IVL treatment at low balloon pressure resulted in marked improvement in diameter stenosis with no stent implantation

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Peripheral IVL Clinical Programs

	Disrupt PAD I	Disrupt PAD II	Disrupt BTK	Disrupt PAD III RCT	Disrupt PAD III OS
Status	Enrollment completed	Enrollment completed	Enrollment completed	Enrollment completed	Enrolling
Study design	Single arm, safety & performance	Single arm, safety & effectiveness	Single arm, pilot	RCT, safety & effectiveness	Single arm, observational study
Study conduct*	CEC, ACL	CEC, ACL	ACL	CEC, ACL	ACL
# of patients	35	60	20	306	Up to 1,500
# of sites	3	8	3	45	32
Regions	NZ, EU	NZ, EU	NZ, EU	U.S., NZ, EU	U.S., NZ, EU

*CEC: Independent clinical events committee; ACL: Angiographic core lab

Study Design

Prospective, multicenter, single-blind, randomized controlled trial

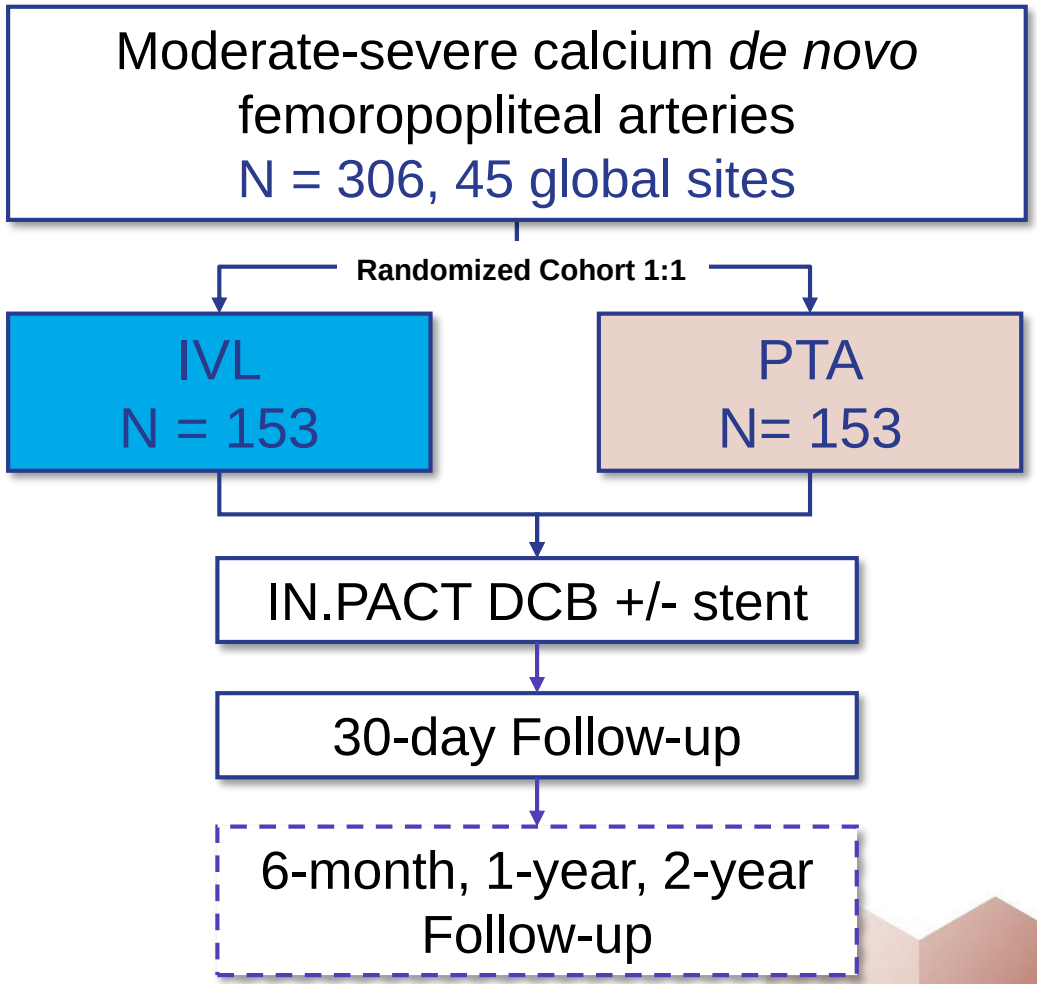
NCT02923193

Objective

Assess the safety and effectiveness of IVL + DCB versus PTA + DCB to treat moderately and severely calcified femoropopliteal arteries

Statistics

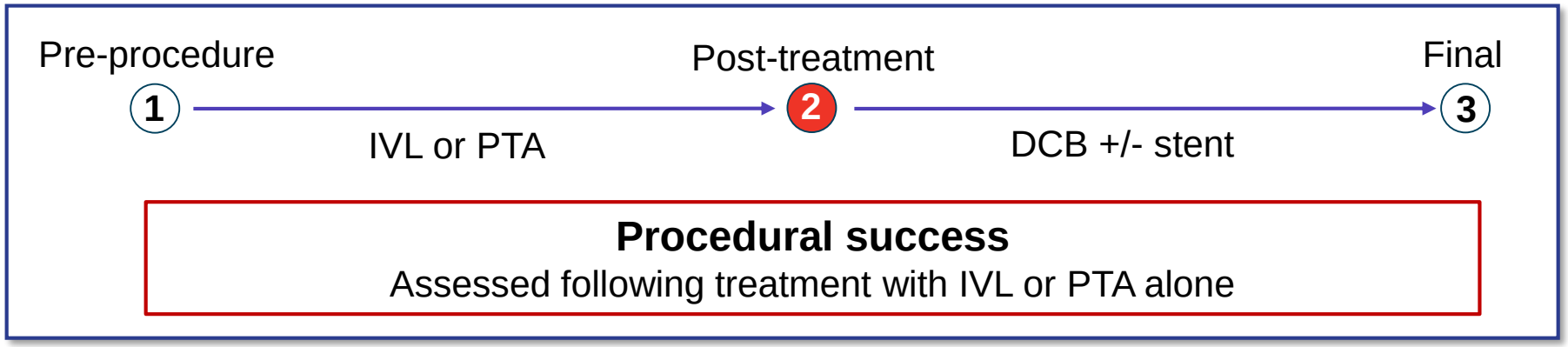
Superiority analysis performed for primary and powered secondary endpoint



Study Endpoints

Primary Endpoint: Procedural success

- Residual stenosis ≤ 30% without flow-limiting dissection (≥ grade D) prior to DCB +/- stenting by angiographic core lab



Secondary Endpoints at 30 days:

- Major Adverse Events*
- CD-TLR
- ABI, RC, WIQ

Powered Secondary Endpoint at 12 months: Primary patency

- Acute PTA failure† requiring a stent at any time during the index procedure will be counted as a loss of primary patency
- Freedom from CD-TLR and freedom from restenosis determined by DUS or angiogram ≥50% stenosis

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*MAE: Need for emergency surgical revascularization of target limb, unplanned target limb major amputation, thrombus or distal emboli requiring intervention to improve flow, perforations that require intervention including bail-out stenting.
†PTA failure defined as residual stenosis ≥50% by visual estimate, or unresolved flow-limiting (≥grade D) dissection, and trans-lesional gradient >10mmHg.

Key Clinical and Angiographic Eligibility Criteria

DISRUPT PAD III

Inclusion

- Rutherford category 2, 3 or 4 of the target limb
- Target lesion is *de novo* SFA or popliteal artery
- Target lesion
  - RVD ≥ 4.0mm and ≤7.0mm
  - Stenosis ≥ 70% by visual estimate
  - Length ≤ 180mm for lesions 70-99% stenosis
  - CTO lesion length ≤ 100mm of the total ≤ 180mm target lesion
- Calcification ≥ moderate defined as presence of fluoroscopic evidence of calcification:
  - On parallel sides of the vessel and
  - Extending >50% of lesion length (if length ≥50mm) or minimum calcification of 20mm (if length <50mm)

Exclusion

- Rutherford category 0, 1, 5 and 6
- Significant stenosis (>50%) or occlusion of inflow tract before target zone not successfully treated
- Planned target limb major amputation
- Renal disease (SCr >2.5 mm/dl) or on dialysis
- In-stent restenosis within 10mm of target zone
- Lesions within 10mm of the ostium of the SFA or anterior tibial artery

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Study Support

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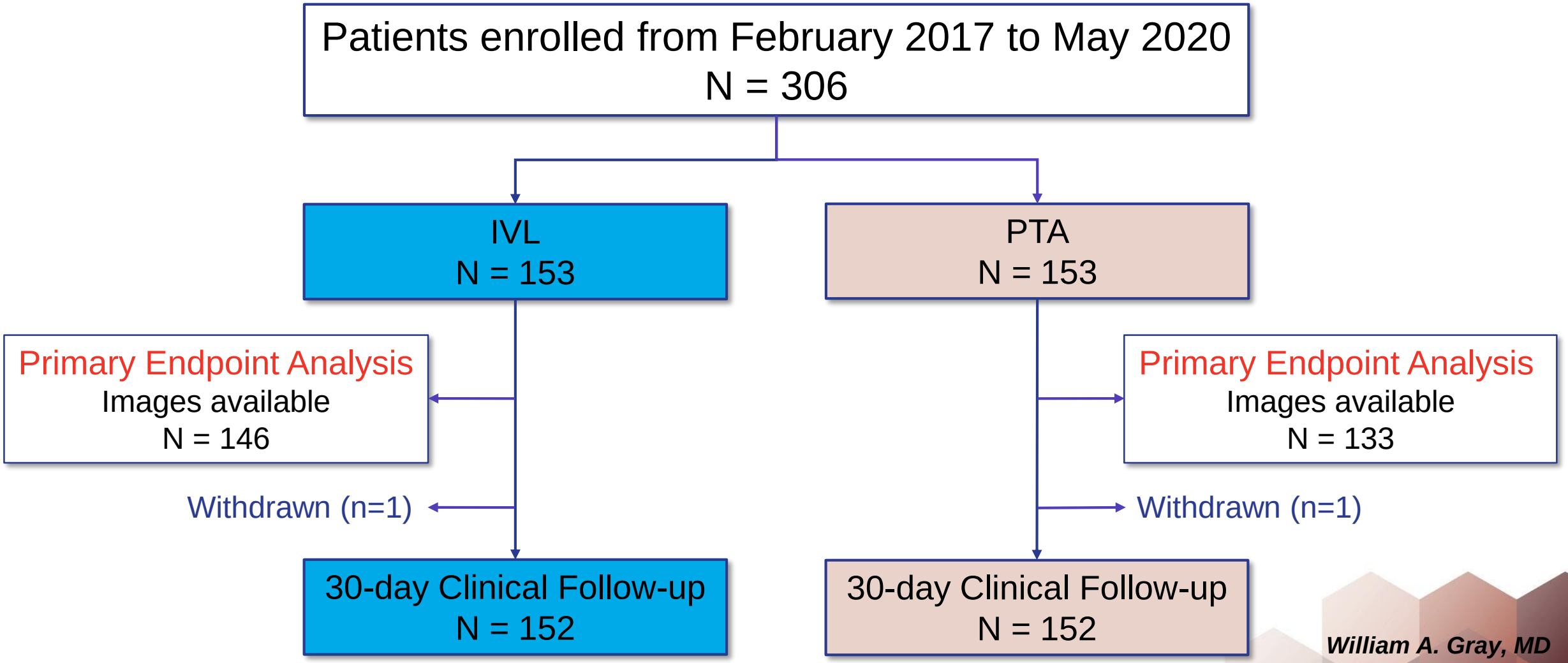
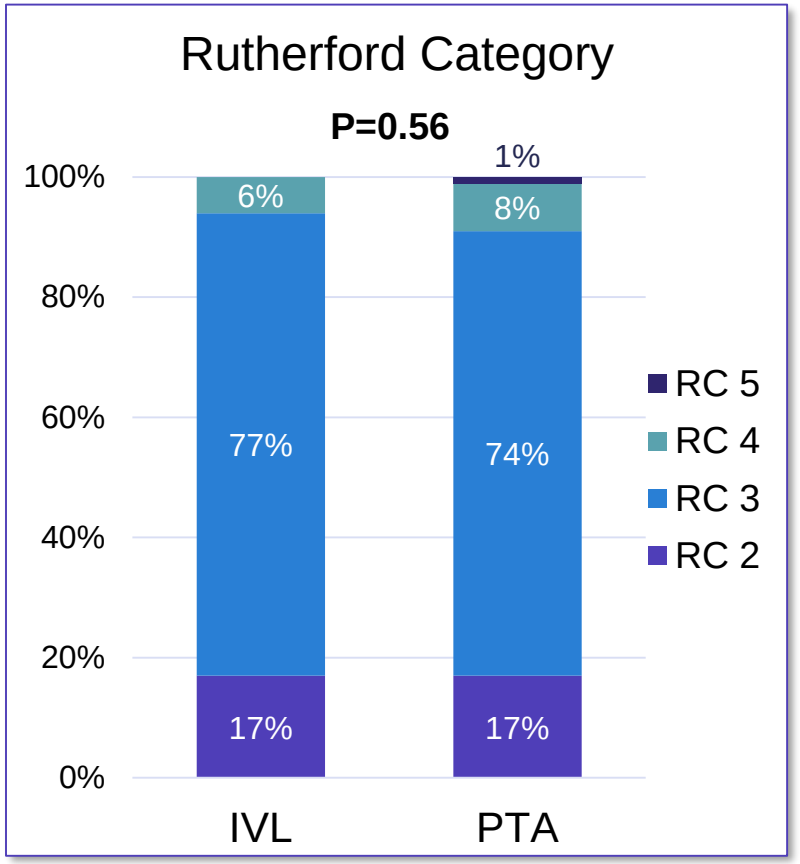
Study Flow


Patients enrolled from February 2017 to May 2020
N = 306
IVL
N = 153
PTA
N = 153
Primary Endpoint Analysis
Images available
N = 146
Primary Endpoint Analysis
Images available
N = 133
Withdrawn (n=1)
Withdrawn (n=1)
30-day Clinical Follow-up
N = 152
30-day Clinical Follow-up
N = 152

Baseline Characteristics

	IVL N=153	PTA N=153	P-value
Age, years	72.2 ± 8.0	71.5 ± 7.7	0.41
Male	69.3%	78.4%	0.07
Hypertension	94.8%	94.1%	0.80
Hyperlipidemia	86.3%	86.3%	0.60
Current smoker	20.3%	28.1%	0.05
Diabetes	41.8%	46.4%	0.72
Myocardial infarction	25.5%	24.2%	0.97
Coronary artery disease	66.7%	58.2%	0.21
Renal insufficiency	24.2%	16.3%	0.13
History of CVA or TIA	12.4%	11.1%	0.85
ABI	0.74 ± 0.20	0.77 ± 0.25	0.25
WIQ – overall	26.0 ± 20.9	26.5 ± 22.0	0.84



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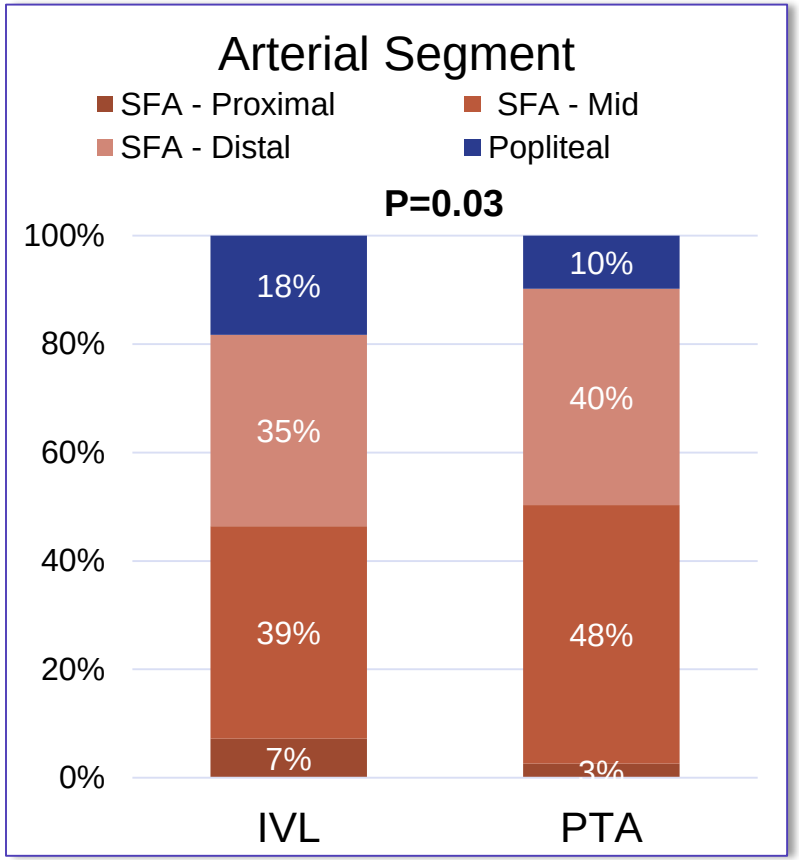
Baseline Lesion Characteristics

Core lab adjudicated

	IVL N=153	PTA N=153	P-value
Reference vessel diameter, mm	5.3 ± 0.8	5.4 ± 0.8	0.68
Minimum lumen diameter, mm	0.81 ± 0.67	0.83 ± 0.76	0.77
Diameter stenosis	85% ± 12%	85% ± 14%	0.76
CTO	26%	31%	0.39
Lesion length, mm	101 ± 41	97 ± 42	0.37
Lesion length >150mm	12%	11%	0.72
Calcified length, mm	129 ± 51	125 ± 48	0.40
Calcification*			0.23
None/Mild	0.7%	0.7%	
Moderate	16.4%	9.8%	
Severe	82.9%	89.5%	
Eccentric	22.4%	17.6%	0.30

*PARC definition of calcium severity



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VIVA 20

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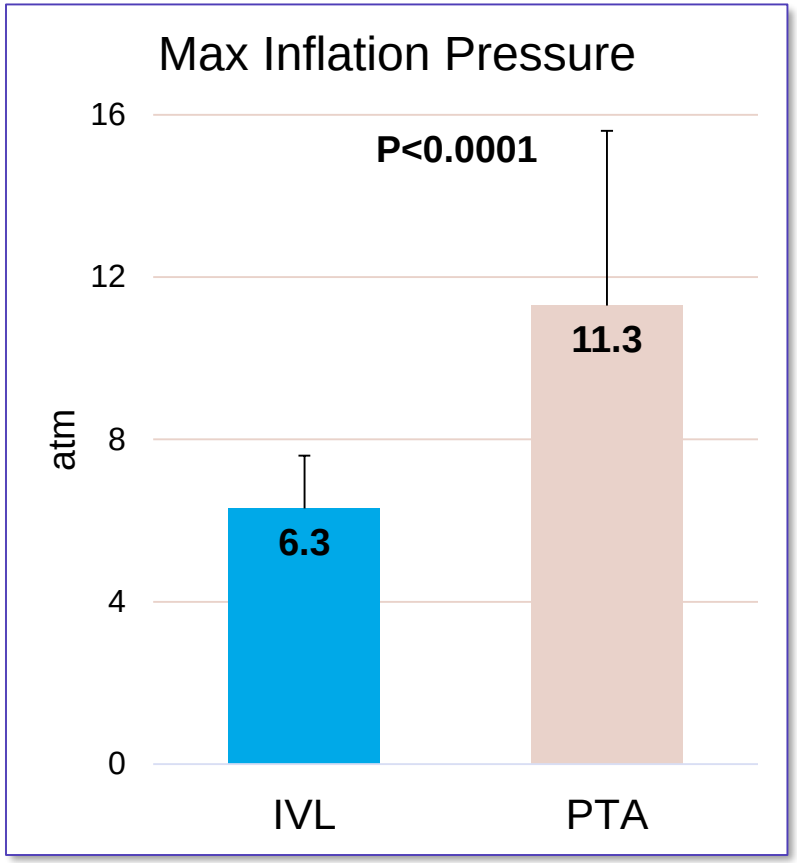
Procedural Characteristics

	IVL N=153	PTA N=153	P-value
Contrast volume, ml	138 ± 73	129 ± 61	0.26
Fluoroscopy time, min	16.6 ± 11.0	13.5 ± 10.1	0.01
Embolic protection used	1.3%	4.6%	0.09
Pre-dilatation	17.6%	15.0%	0.54
Post-dilatation*	5.2%	17.0%	0.001
Stent placed†	4.6%	18.3%	0.0002
Number of treatment balloons	1.6 ± 0.8	1.3 ± 0.6	0.005
Total number of pulses	228 ± 115	---	---

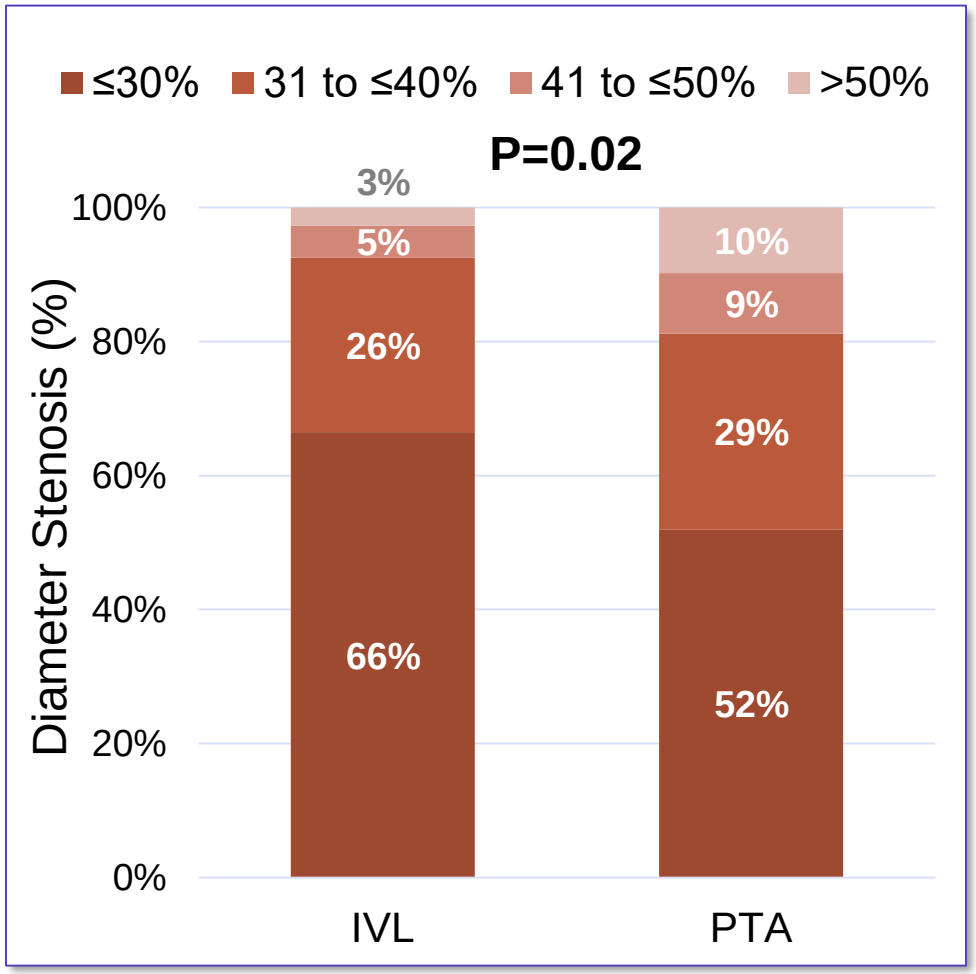


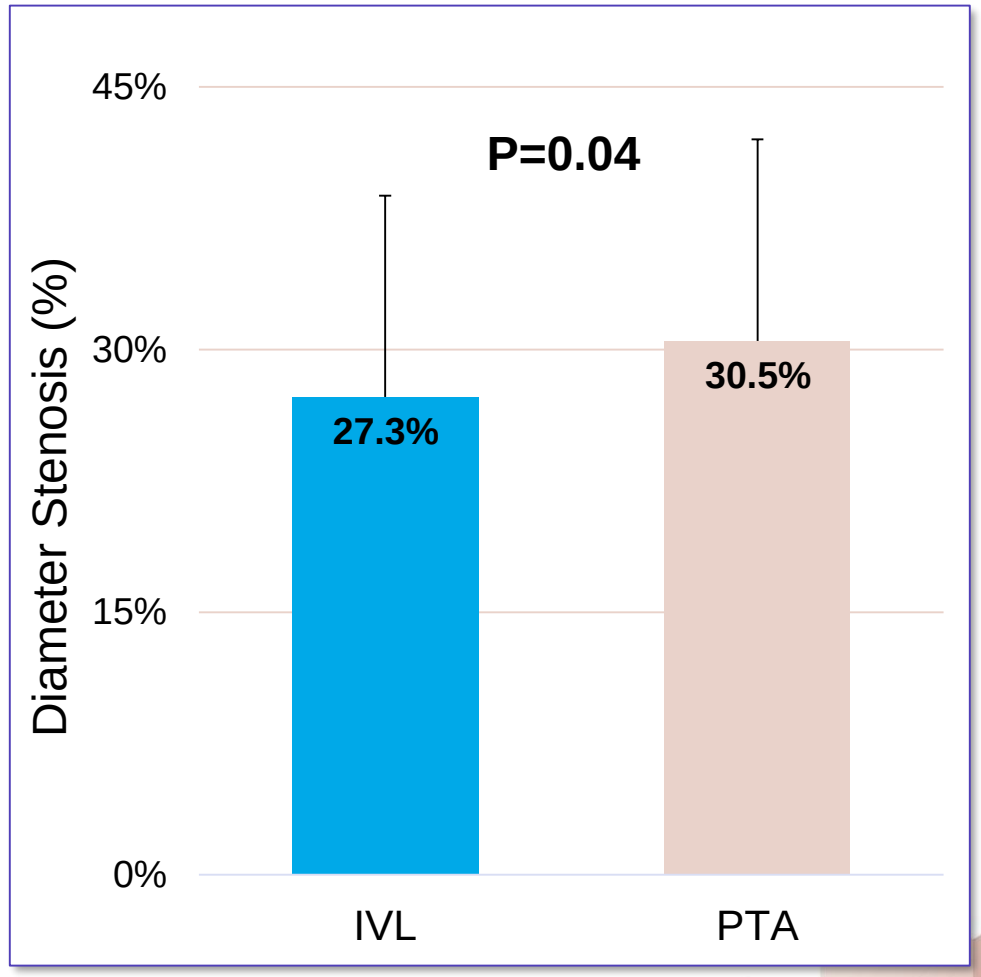
Significantly lower maximum inflation pressure used with a 75% relative risk reduction for stent placement with IVL

*Performed with semi or NC PTA balloon if: RS >30% by visual estimate, or presence of ≥type D dissection and trans-lesional gradient > 10 mmHg
†Provisional stent placed if: RS ≥50% by visual estimate, or unresolved ≥ type D dissection and trans-lesional gradient > 10 mmHg

Post-treatment % Diameter Stenosis

Core lab adjudicated





Significant reduction in post-treatment diameter stenosis in IVL group

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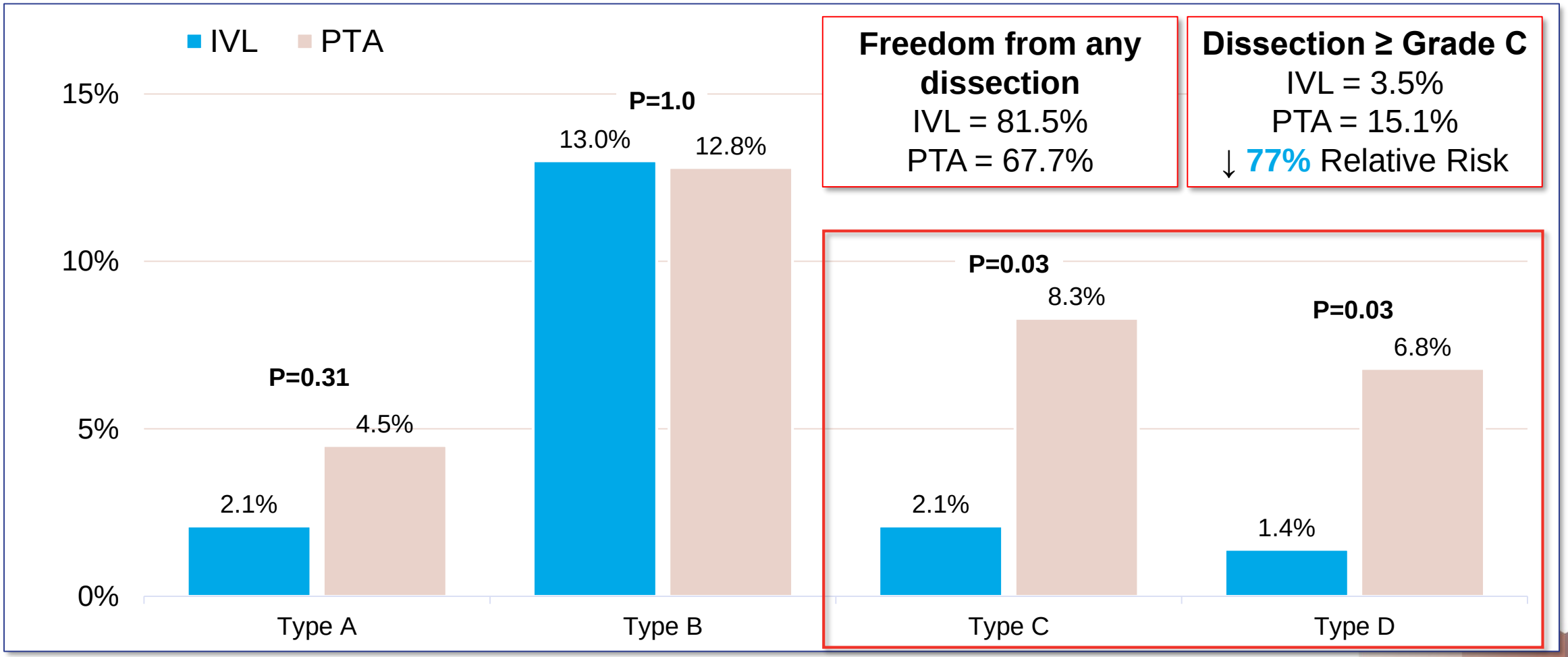
Post-treatment Angiographic Complications

Core lab adjudicated*



Freedom from any dissection
IVL = 81.5%
PTA = 67.7%

Dissection ≥ Grade C
IVL = 3.5%
PTA = 15.1%
↓ **77%** Relative Risk

Significant reduction in the frequency and severity of dissections with IVL

*No occurrence of thrombus, abrupt closure, no-reflow, distal emboli or perforation in both study arms

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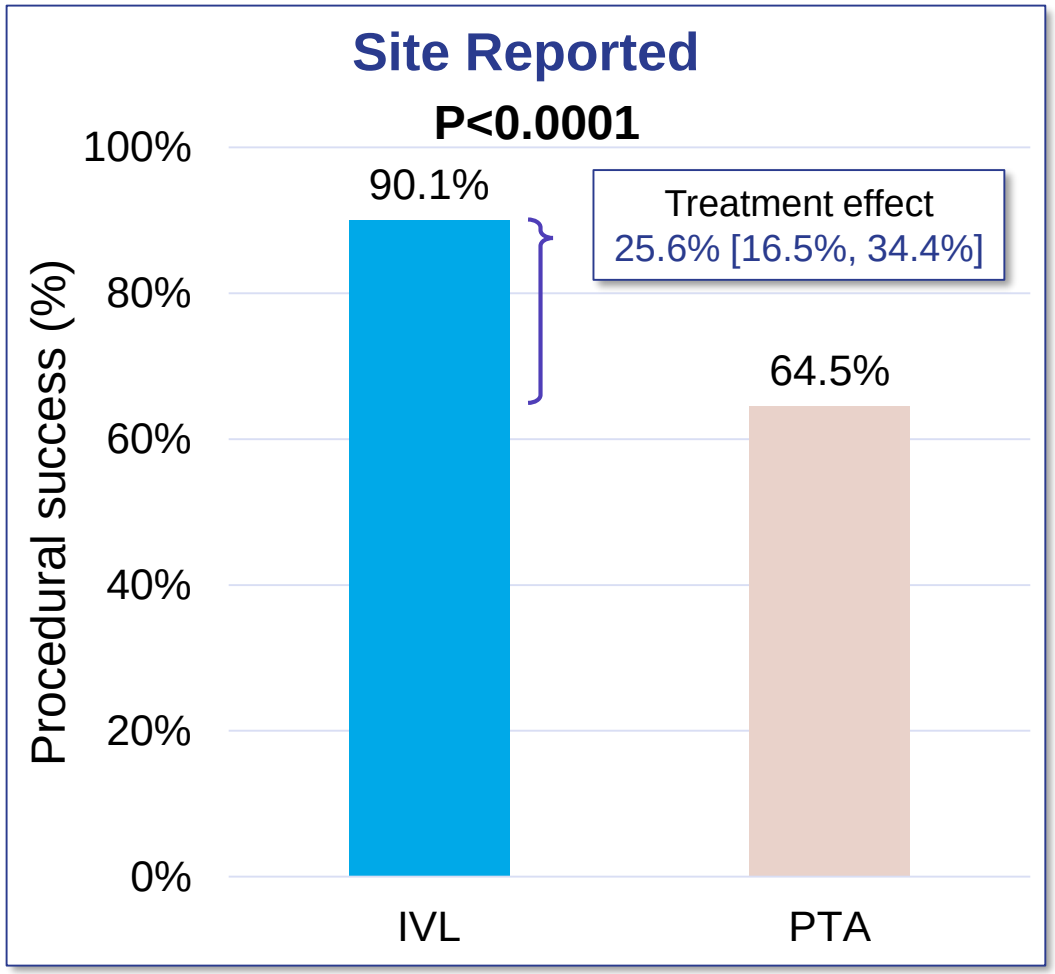
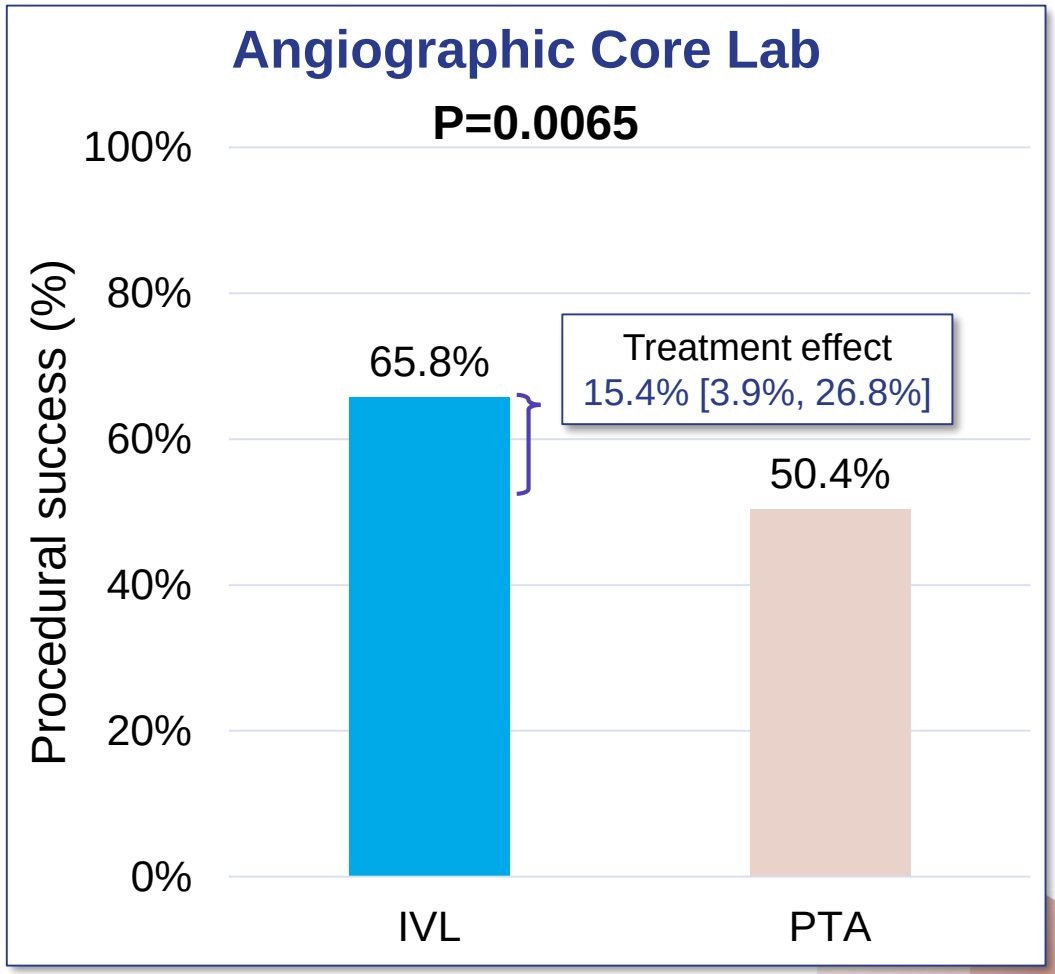
Primary Endpoint

Procedural success: Residual stenosis ≤ 30% without flow-limiting dissection (≥ grade D) prior to DCB +/- stenting by ACL





Superior procedural success with IVL by Site and Core Lab adjudication

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VIVA 20

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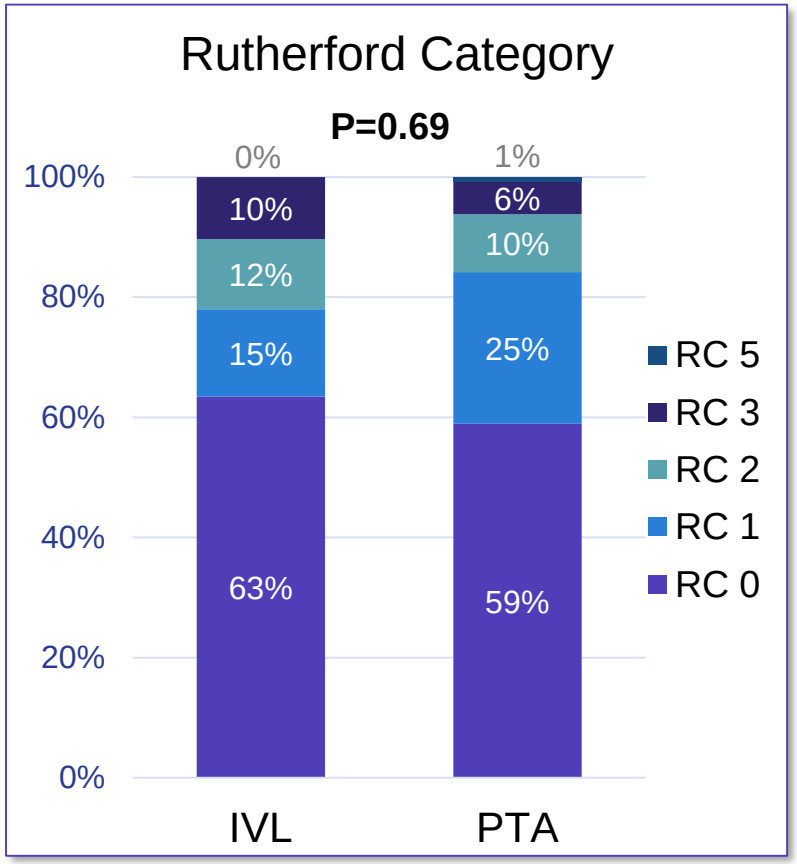
Final Angiographic and Clinical Outcomes

	IVL N=153	PTA N=153	P-value
Final angiographic outcomes*			
Reference vessel diameter, mm	5.4 ± 0.8	5.4 ± 0.8	0.62
Minimum lumen diameter, mm	4.2 ± 0.7	4.3 ± 0.7	0.39
Diameter stenosis	22% ± 8%	21% ± 9%	0.39
Acute gain, mm	3.4 ± 0.8	3.5 ± 0.9	0.63
Dissection			0.47
None	83.9%	77.2%	
Type A/B/C	16.1%	22.8%	
Type D	0.0%	0.0%	
30-day clinical outcomes			
ABI	0.97 ± 0.18	0.99 ± 0.16	0.33
WIQ – overall	51.2 ± 30.3	52.9 ± 31.5	0.64



*Angiographic core lab adjudicated

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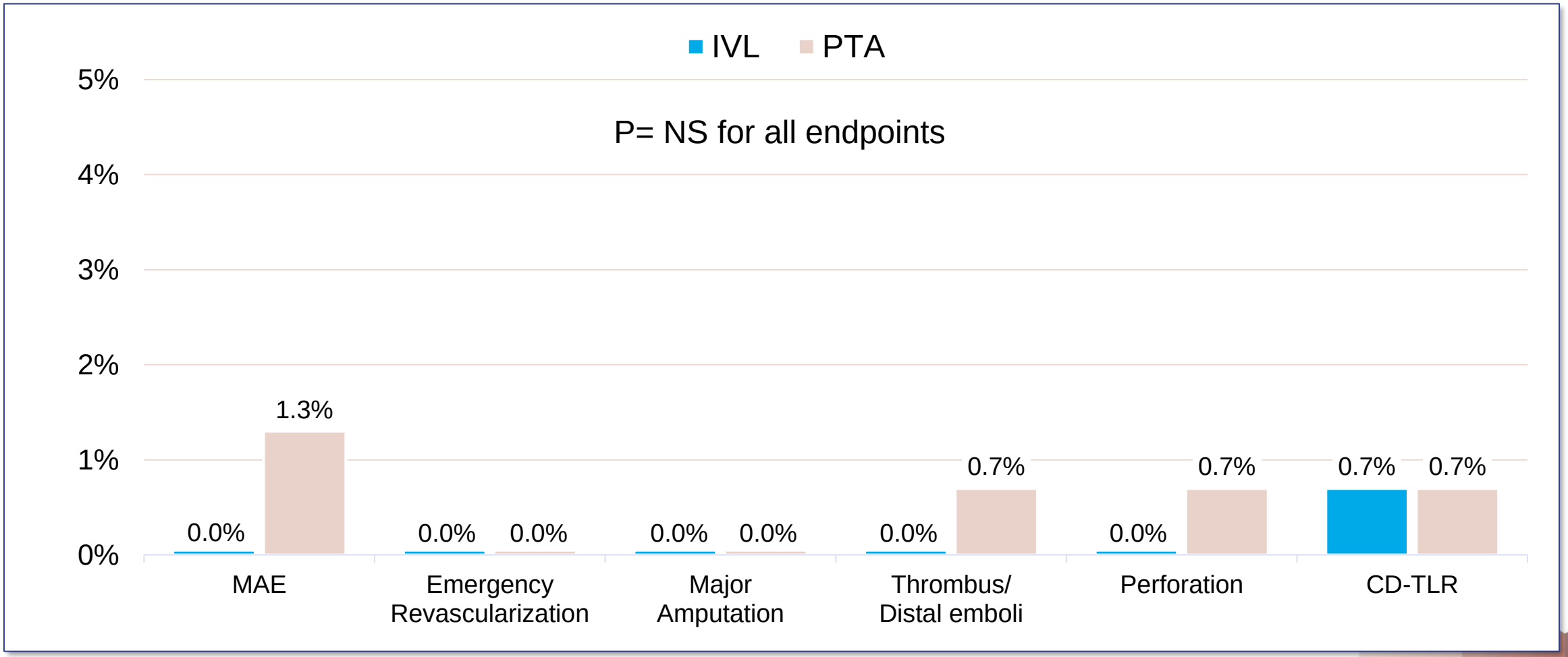
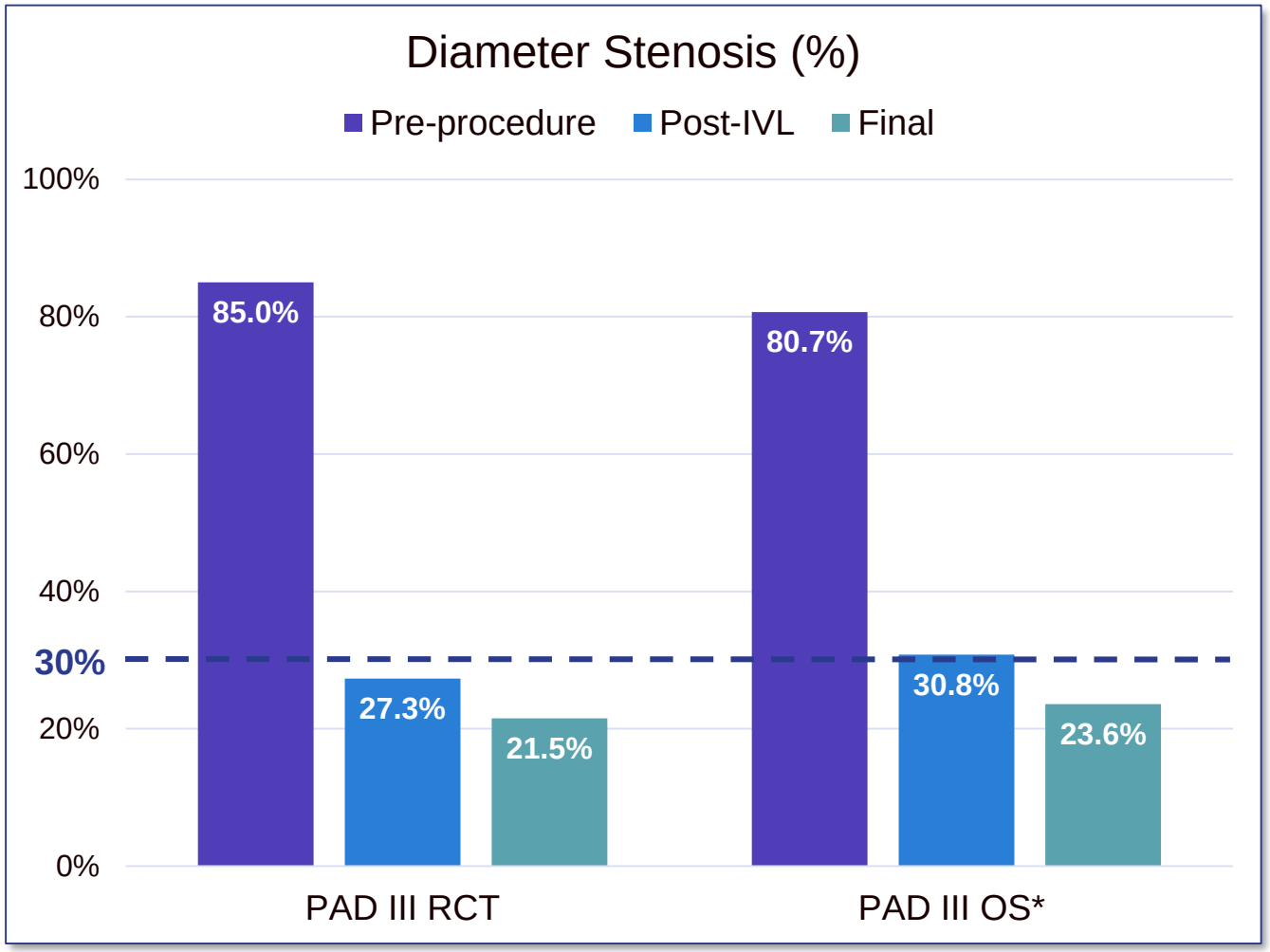
30-Day Safety Endpoints

CEC adjudicated



PAD III Observational Study

Core lab adjudicated



Final Angiographic Complications

	PAD III RCT	PAD III OS*
Dissection (Type D-F)	0%	1.1%
Perforation	0%	0.5%†
Embolization	0%	0%
Thrombus	0%	0%
No reflow	0%	0%
Abrupt closure	0%	0%

†Following DCB inflation; unrelated to IVL

Consistent outcomes from clinical trial to real world environment

*Adams et al., JEVT, 2020;27(3):473-480.

Conclusions

- Disrupt PAD III RCT provides the largest level I evidence for the treatment of heavily calcified femoropopliteal arteries, a cohort often excluded from trials
- IVL was superior to PTA in acute procedural success and demonstrated atraumatic treatment:
  - Reduction in % diameter stenosis prior to DCB or stent placement
  - Lower maximum inflation pressure
  - Reduction in frequency and severity of dissections
  - Lower post-dilatation and stent implantation rate
- RCT outcomes are similar to PAD III registry in multiple vessel beds highlighting the consistency of IVL treatment in complex anatomy
- Powered secondary endpoint of primary patency at 12 months will be analyzed following appropriate follow-up for all enrolled patients