CONTROVERSES ET ACTUALITÉS EN CHIRURGIE VASCULAIRE

CONTROVERSIES & UPDATES IN VASCULAR SURGERY

JANUARY 25-27 2018

MARRIOTT RIVE GAUCHE & CONFERENCE CENTER, PARIS, FRANCE

DCB level 1 evidence review

Raphaël COSCAS

Vascular Surgery Department

Ambroise Paré Hospital, AP-HP and Paris-Ouest University

Boulogne-Billancourt, France

Disclosure

Speaker name:

Raphael COSCAS

- ■ I have the following potential conflicts of interest to report:
- ■ Consulting: Medtronic, Spectranetics, Terumo
- ☐ Employment in industry
- ☐ Shareholder in a healthcare company
- ☐ Owner of a healthcare company
- ☐ Other(s)
- ☐ I do not have any potential conflict of interest

Evidence	Grade of recommandation
Level 1: **RCT with strong power** **Meta-analysis of RCTs**	Grade A: Established proof
Level 2: RCT with low power Non randomized controlled trials	Grade B: Presumed
Level 3: Case-control studies	Grade C: Low level
Level 4: Comparative studies with major bias Retrospective studies, Case series Transversal or Longitudinal epidemiologic studies	

HAS, French Health Authorities Guidelines 2013

Where are the RCTs with DCBs ?

3 DCBs with large RCTs

	IN.Pact Medtronic	Lutonix Bard	Stellarex Spectranetics
PTX concentration	3,5	2	2
Excipient	Urea	Polysorbate Sorbitol	Polyethylene glycol
PTX type	Crystalline	Hybrid	Hybrid
Balloon state during PTX deposition	Inflated	Inflated	Inflated

The Ideal RCT

Large N / Multicenter

Selected relevant population

Adequate control therapy

Double blind

Blinded duplex and angio corelab

Clinical event committee

Independent data safety monitoring board

External monitoring

Optimal DCB use

Relevant clinical endpoint

3 balloons are supported by high quality RCTs

Similar exclusion criterias

Short lesions < 3-4cm

Rutherford 5, 6

In-stent restenosis

Failure to cross the lesion

Failed PTA

Severe calcification

Medtronic

BARD

Spectranetics

3 balloons are supported by high quality RCTs

	IN.Pact In.Pact SFA	**Lutonix** Levant 2	**Stellarex** Illumenate EU RCT	**Stellarex** Illumenate US Pivotal
N (randomization)	331 (2:1)	476 (3:1)	294 (3:1)	300 (2:1)
Age (y)	67.5 ± 9.5	67.8 ± 4.1	67 ± 9	68 ± 10
Claudicants (%)	91	92	98	96
Lesion Length (cm)	8.9 ± 4.9	6.3 ± 4.1	7.2 ± 5.2	8.0 ± 4.5
Occlusions (%)	26	21	19	19

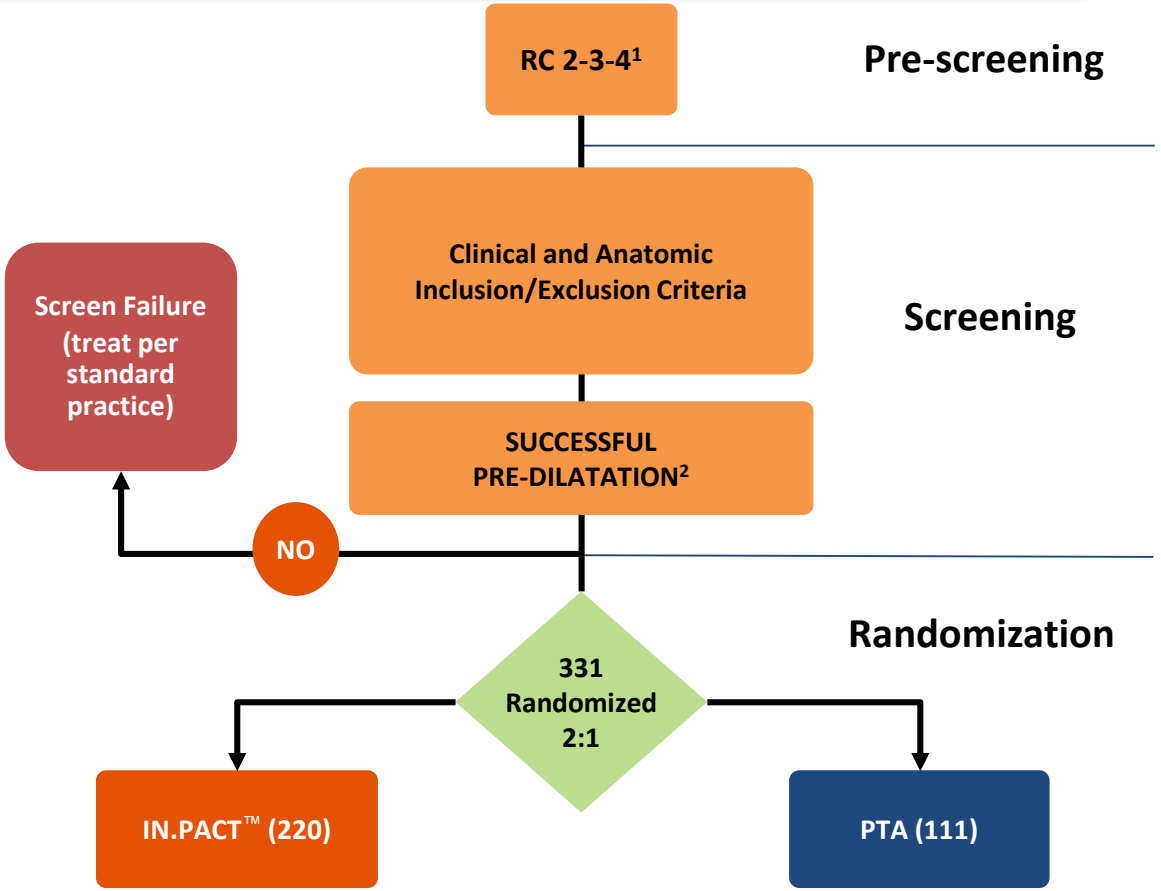
Data from DCB groups

In.Pact SFA trial

IN.PACT SFA I
150 subjects enrolled at 13 EU sites
Sep 2010 - Apr 2011

+

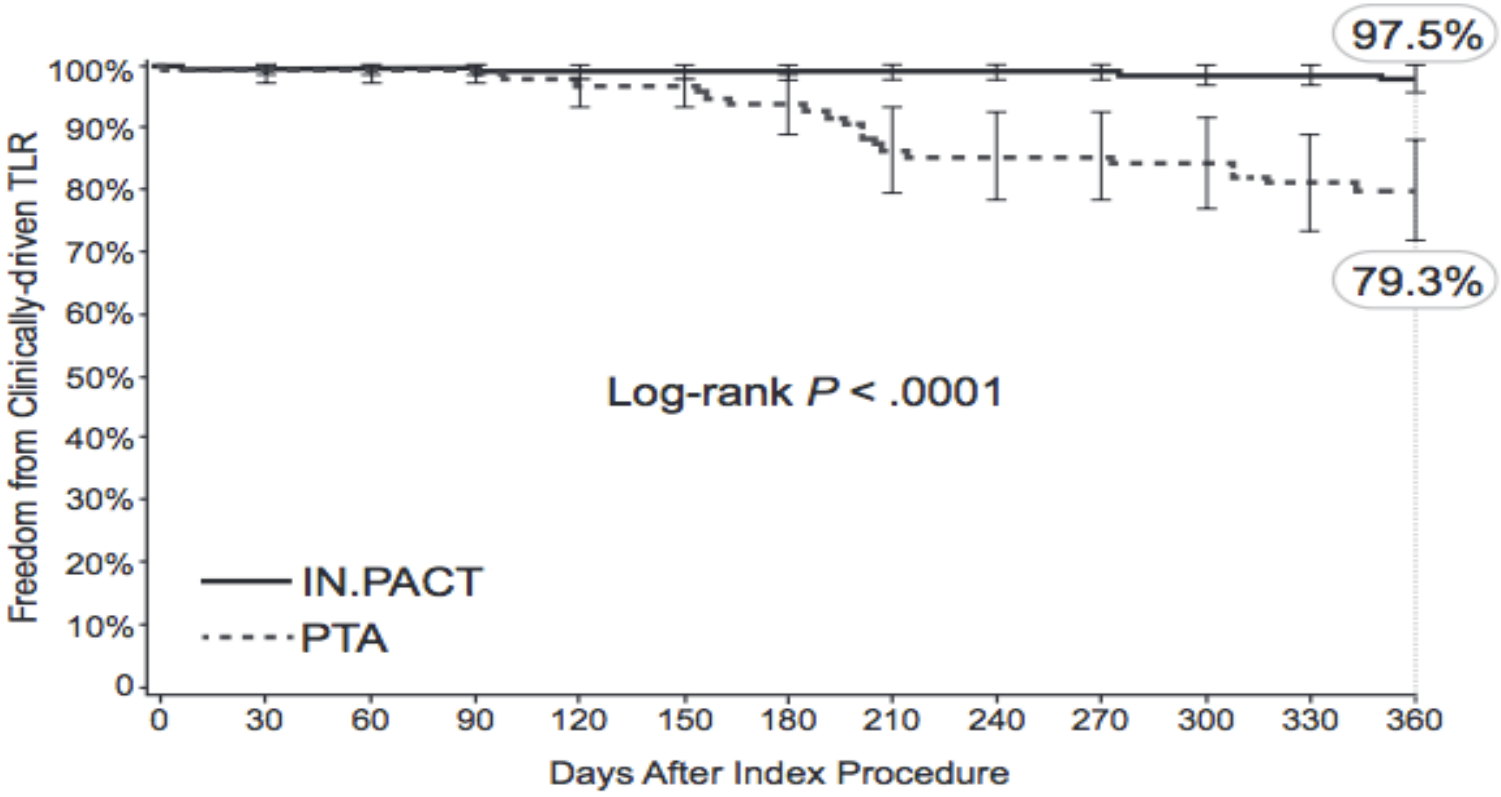
IN.PACT SFA II
181 subjects enrolled at 44 US sites
Apr 2012 - Jan 2013



The patients and the trial sponsor were blinded to the treatment assignments through the completion of all 12-month follow-up evaluations. The independent core laboratories and clinical events committee will remain blinded to the treatment assignments throughout the 60-month follow-up duration. Because of the visual difference between the IN.PACT DCB and standard PTA balloon, treating physicians, research coordinators, and catheterization laboratory staff were not blinded to the treatment assignment. Treating physicians, research coordinators, and catheterization laboratory staff received detailed and specific instructions and training on how to preserve the patients' blinded status.

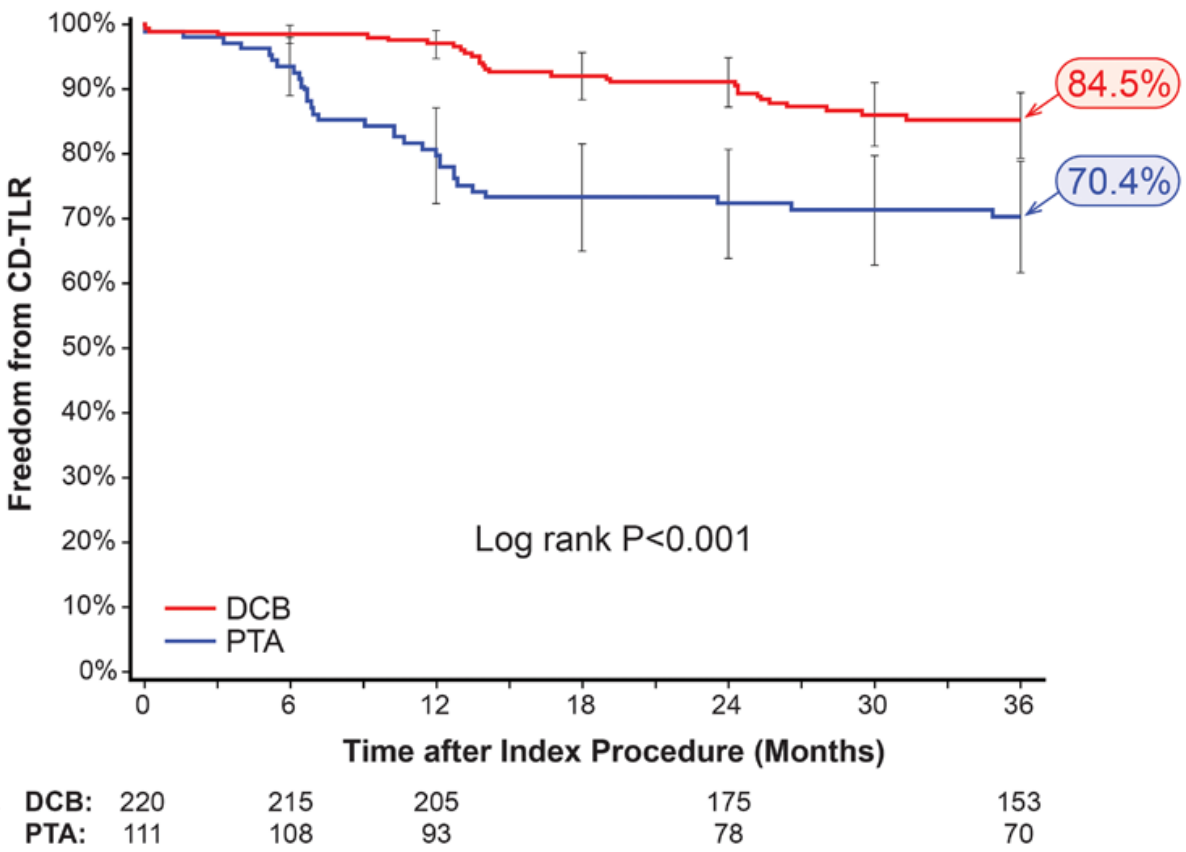
Tepe et al. IN.PACT SFA Trial Investigators, Circulation 2015

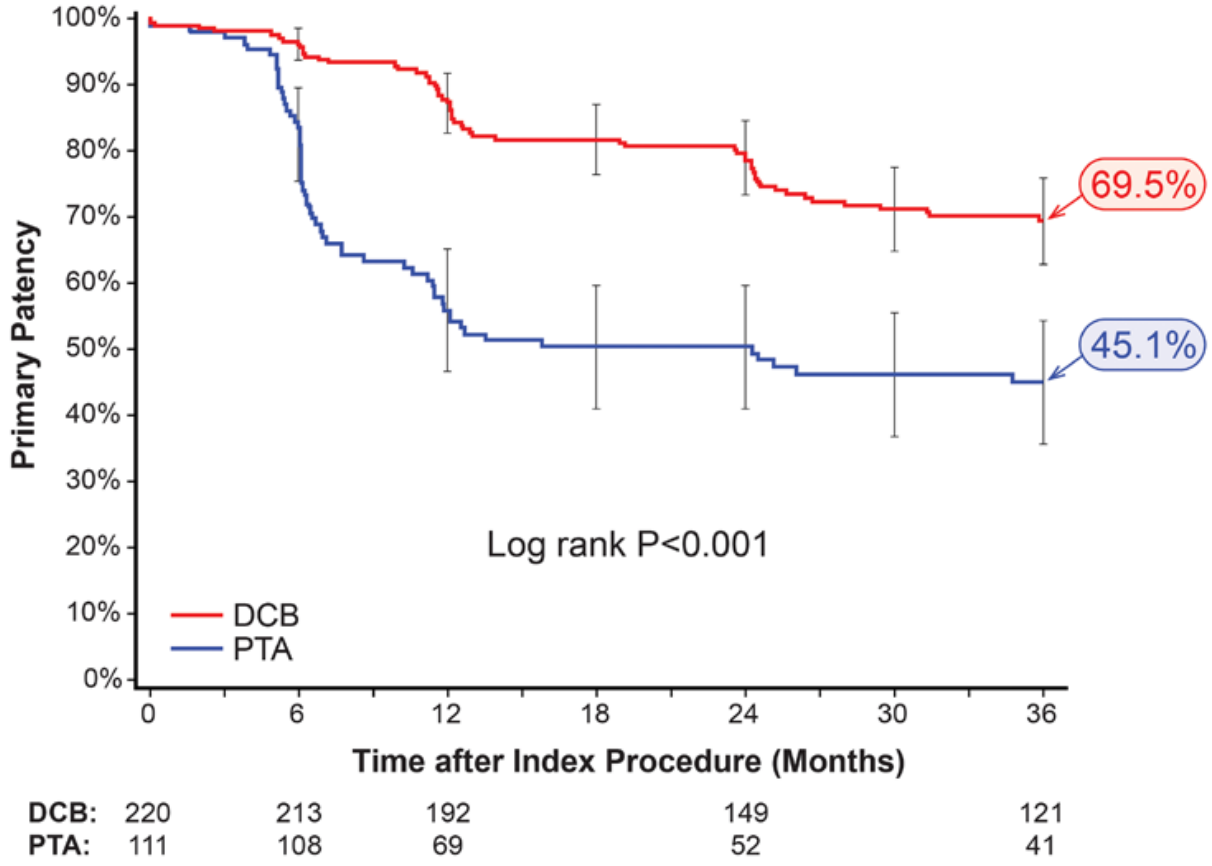
In.Pact SFA at 1 year



Tepe et al. IN.PACT SFA Trial Investigators, Circulation 2015

In.Pact SFA at 3 years





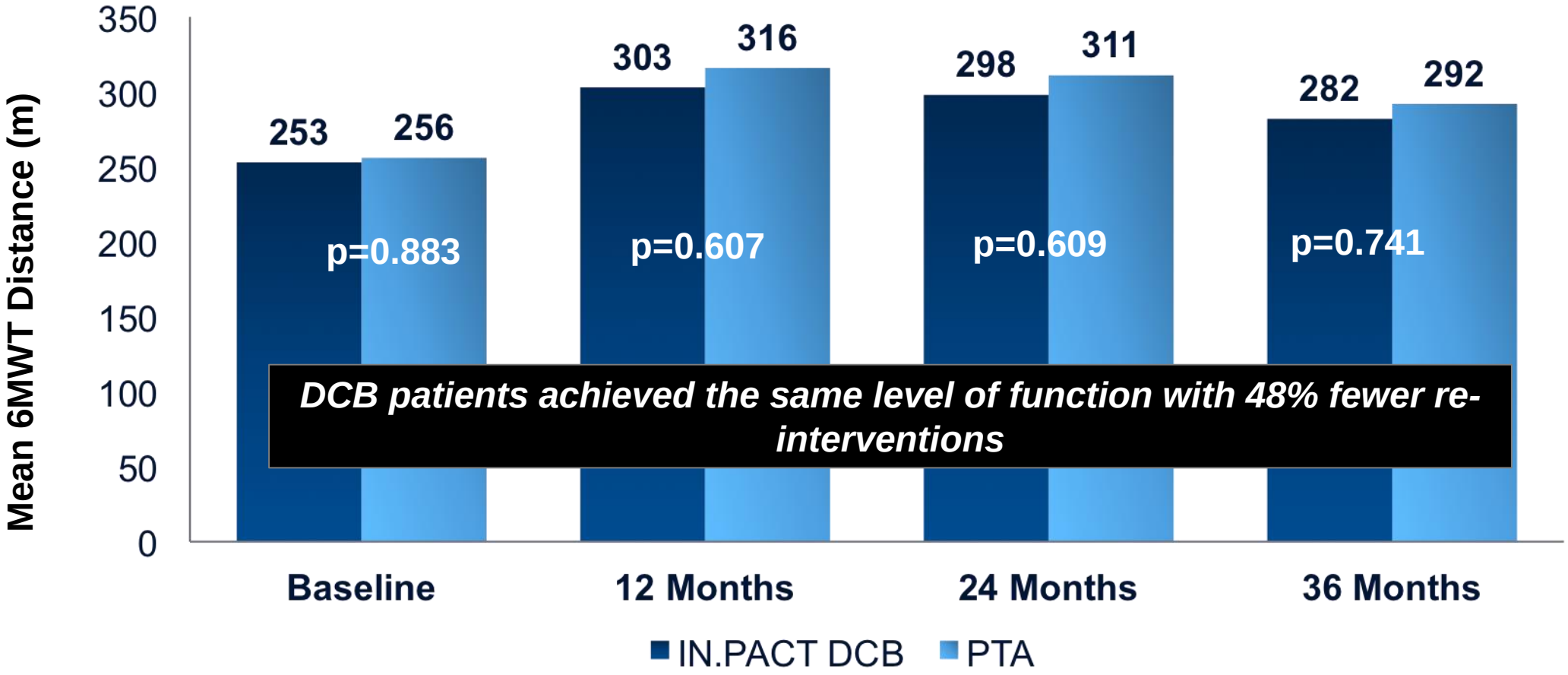
Schneider et al. IN.PACT SFA Trial Investigators, Circ Cardiovasc Interv. 2018

In.Pact SFA at 3 years

	IN.PACT DCB (N=220)	PTA (N=111)	P-value†
Clinically-driven TLR [1]	15.2% (30/197)	31.1% (32/103)	0.002
All TLR [2]	16.2% (32/197)	34.0% (35/103)	< 0.001
Time to First CD-TLR	542.9 ± 278.2	302.9 ± 213.0	< 0.001
Primary Sustained Clinical Improvement[3]	68.7% (114/166)	52.6% (51/97)	0.012
ABI / TBI [4]	0.917 ± 0.231	0.894 ± 0.194	0.429

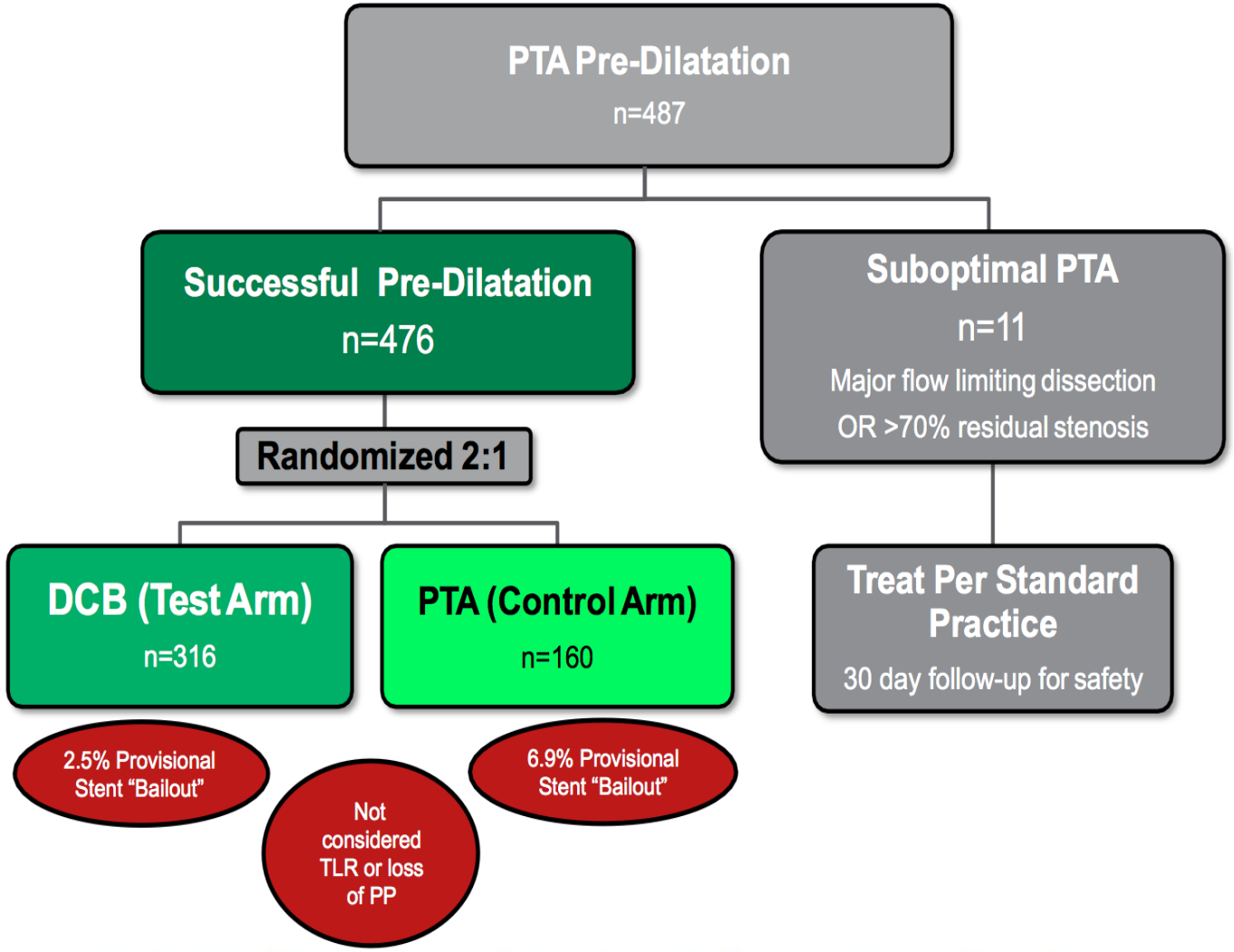
Schneider et al. IN.PACT SFA Trial Investigators, Circ Cardiovasc Interv. 2018

In.Pact SFA at 3 years
6-Minute Walk Test*



*Data collected in IN.PACT SFA II phase only

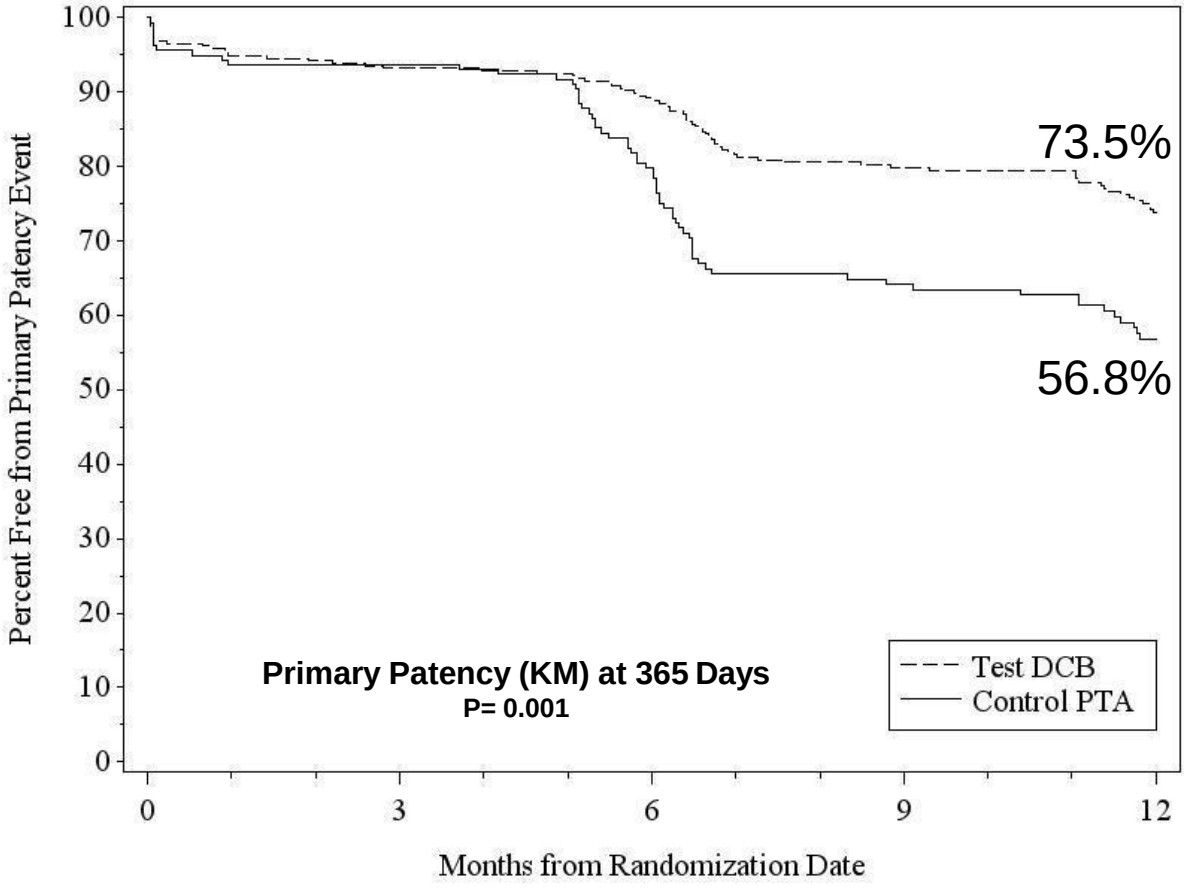
Levant 2 trial

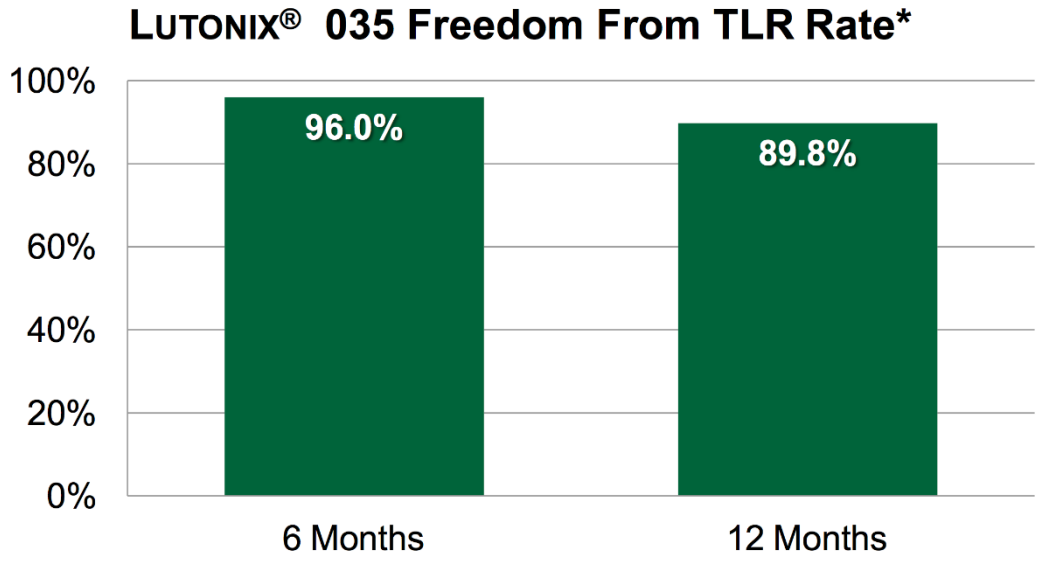


loon; however, according to the study protocol, the patients, investigators who completed follow-up, vascular-laboratory personnel, core laboratory evaluators, and members of the clinical-events committee were unaware of the treatment received. Clinicians were to make treatment decisions subsequent to the initial procedure on the basis of the symptoms of the patients during follow-up, without knowledge of treatment assignment or findings on duplex ultrasonography.

LEVANT II Trial, N Eng J Med 2015

Levant 2 trial



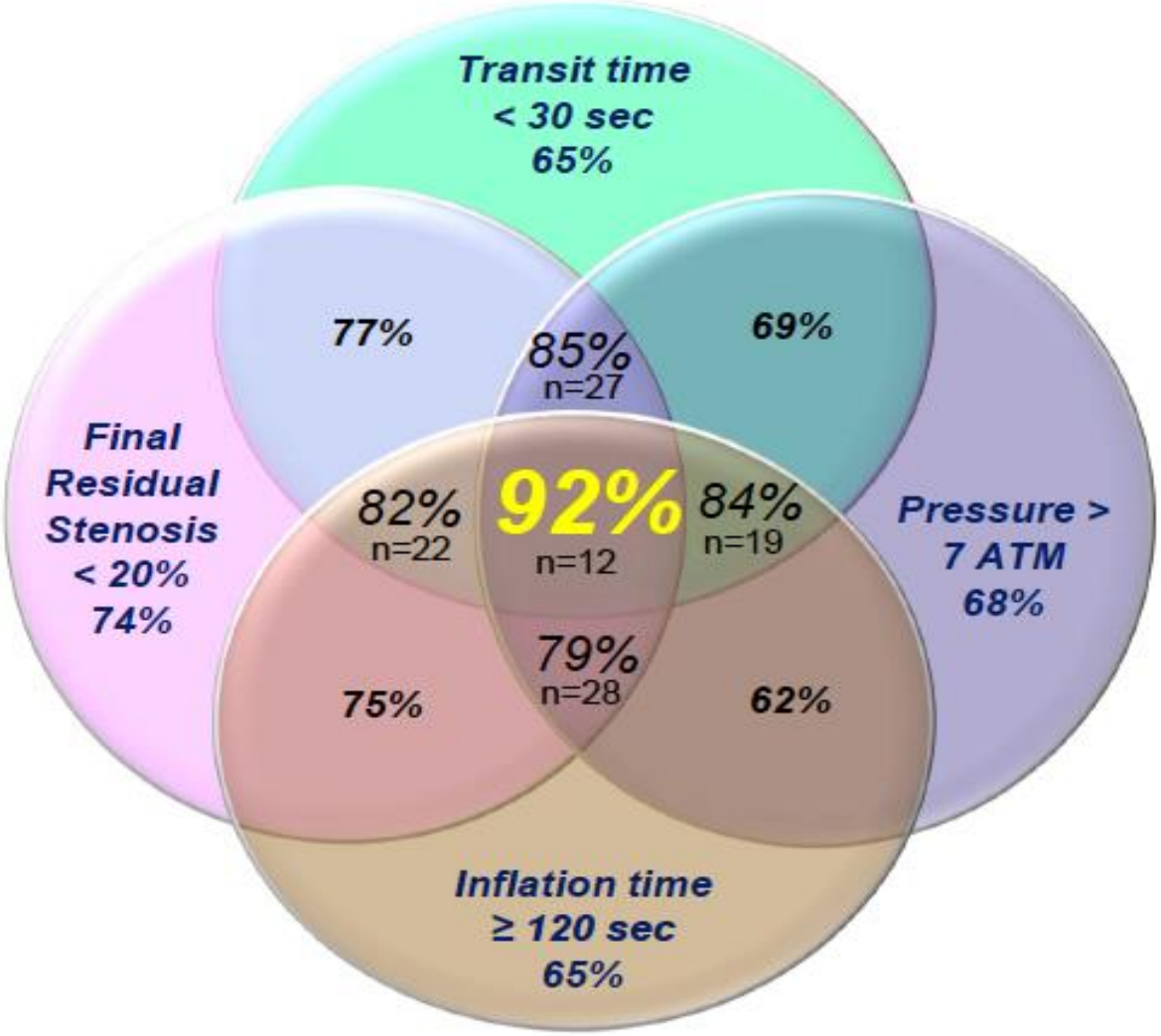


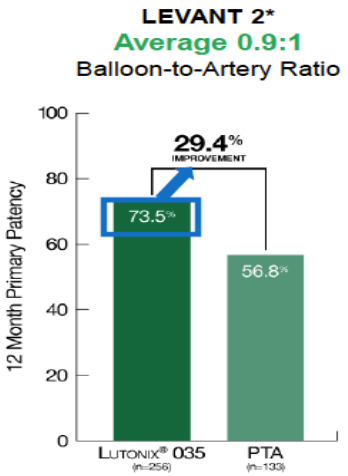
LEVANT II Trial, N Eng J Med 2015

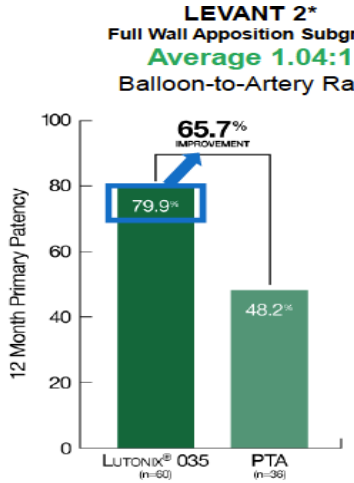
Levant 2 trial

End Point	Drug-Coated Balloon	Standard Angioplasty Balloon	Difference	P Value
	no./total no. (%)		*percentage points (95% CI)*	
Primary end points				
Primary patency at 12 mo†	172/264 (65.2)	71/135 (52.6)	12.6 (2.4 to 22.8)	0.02‡
Restenosis without target-lesion revascularization§	57/92 (62.0)	40/64 (62.5)	−0.5 (−16.0 to 14.9)	—
Target-lesion revascularization§	35/92 (38.0)	24/64 (37.5)	0.5 (−14.9 to 16.0)	—
Safety composite¶	240/286 (83.9)	113/143 (79.0)	4.9 (−2.6 to 12.3)	0.005‖
Perioperative death	0/308	0/155	0**	—
Index-limb amputation	1/286 (0.3)	0/140	0.3 (−0.3 to 1.0)	—
Index-limb reintervention	44/285 (15.4)	30/143 (21.0)	−5.5 (−13.4 to 2.3)	—
Index-limb–related death	0/285	0/140	0	—
Secondary end points				
Total target-lesion revascularization	35/285 (12.3)	24/143 (16.8)	−4.5 (−11.7 to 2.7)	0.21‡
Total target-vessel revascularization	38/285 (13.3)	26/143 (18.2)	−4.8 (−12.3 to 2.6)	0.19
Death	7/290 (2.4)	4/144 (2.8)	−0.4 (−3.6 to 2.8)	0.82
Major amputation	1/286 (0.3)	0/140	0.3 (−0.3 to 1.0)	0.37
Reintervention for thrombosis	1/285 (0.4)	1/140 (0.7)	−0.4 (−1.9 to 1.2)	0.62

Levant 2 trial – The role of the technique

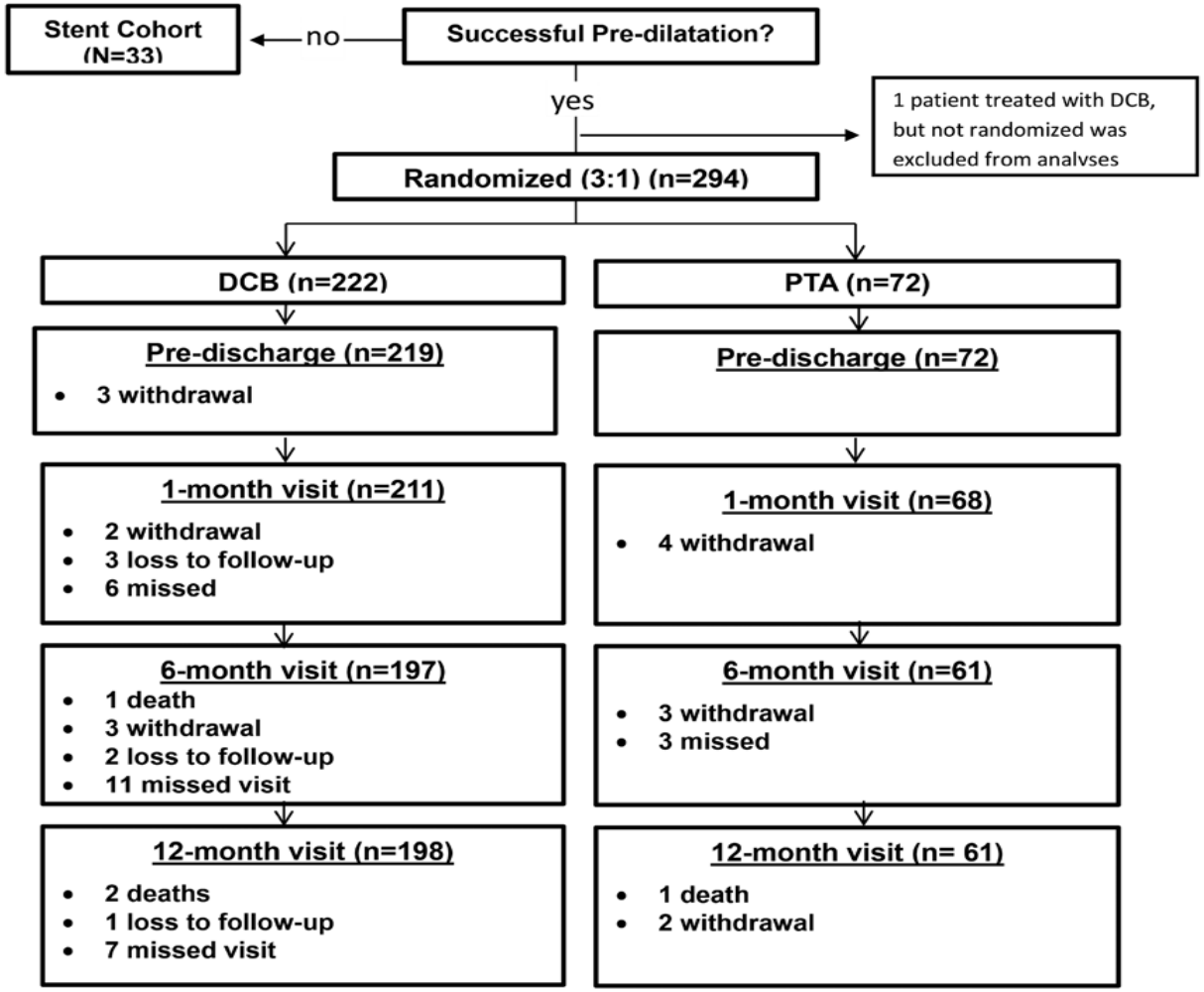






A post-hoc subgroup analysis suggests full wall apposition contributed to improved primary patency at 12 months/

Illumenate EU RCT

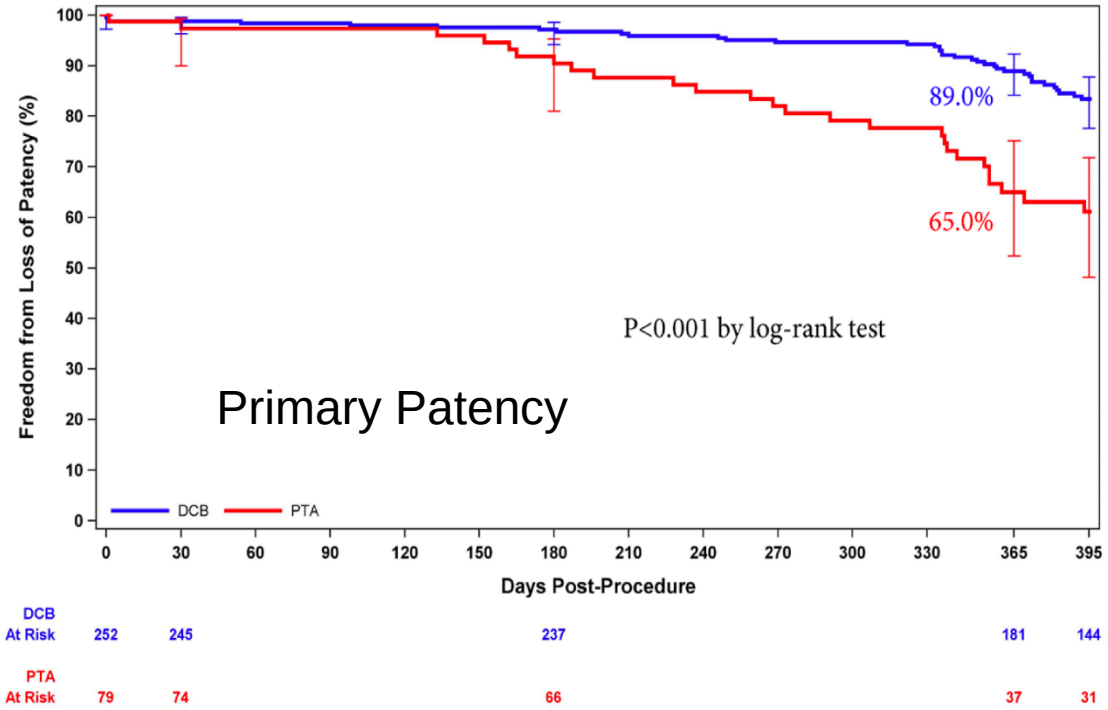


Investigators and research staff at the study centers were not blinded to treatment assignment given visual differences in the study devices. Patients remained blinded to treatment assignment throughout the study.

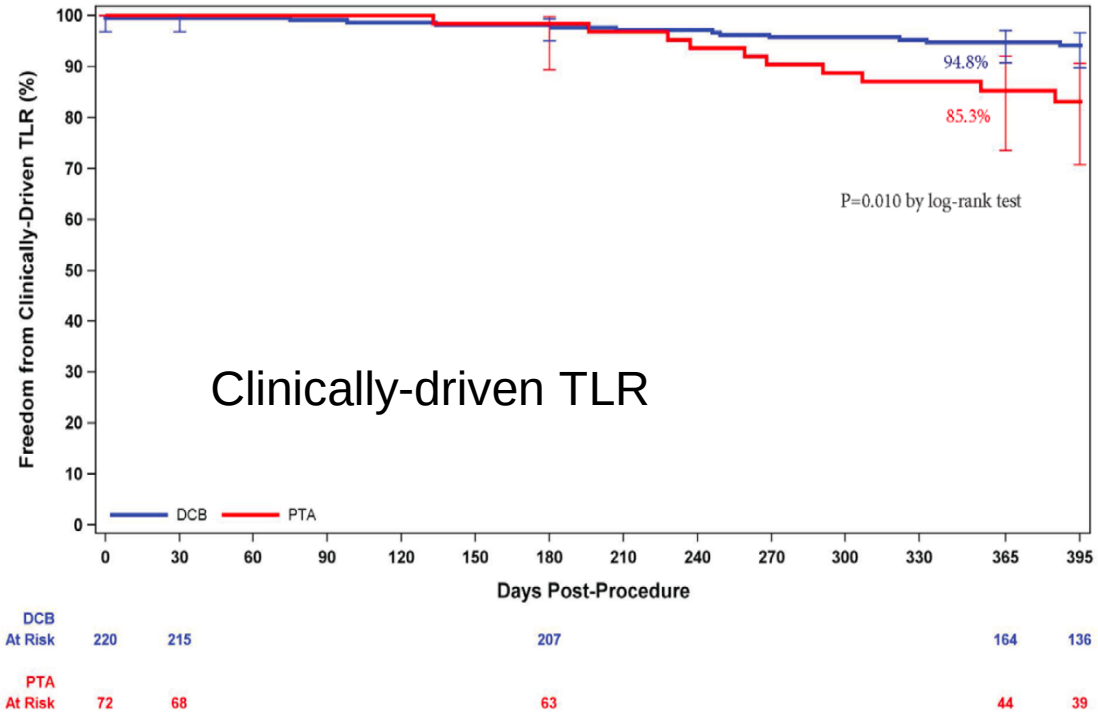
Independent core laboratories analyzed all images, including duplex ultrasound (VasCore, Massachusetts General Hospital, Boston, MA) and angiography (SynvaCor, Springfield, IL). Core laboratory readers remained blinded to treatment assignment. A blinded Clinical Events Committee who did not participate in the study adjudicated all adverse events. An independent Data Safety and Monitoring Board monitored the study for safety. Data were monitored for accuracy with 100% source document verification.

Schroeder H et al. ILLUMENATE EU RCT, Circulation 2017

Illumenate EU RCT at 1 year



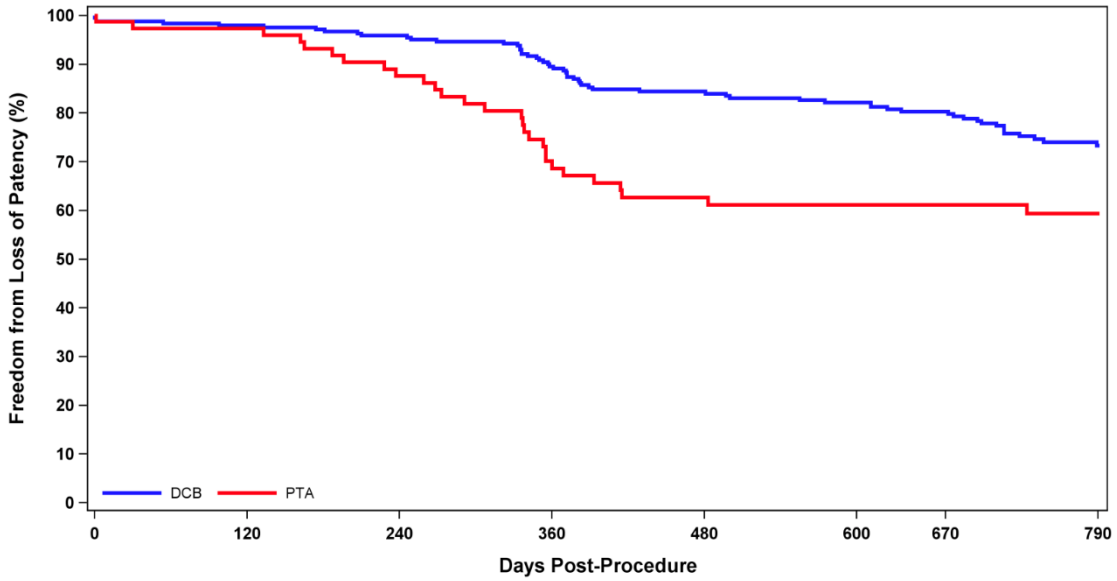
Primary Patency

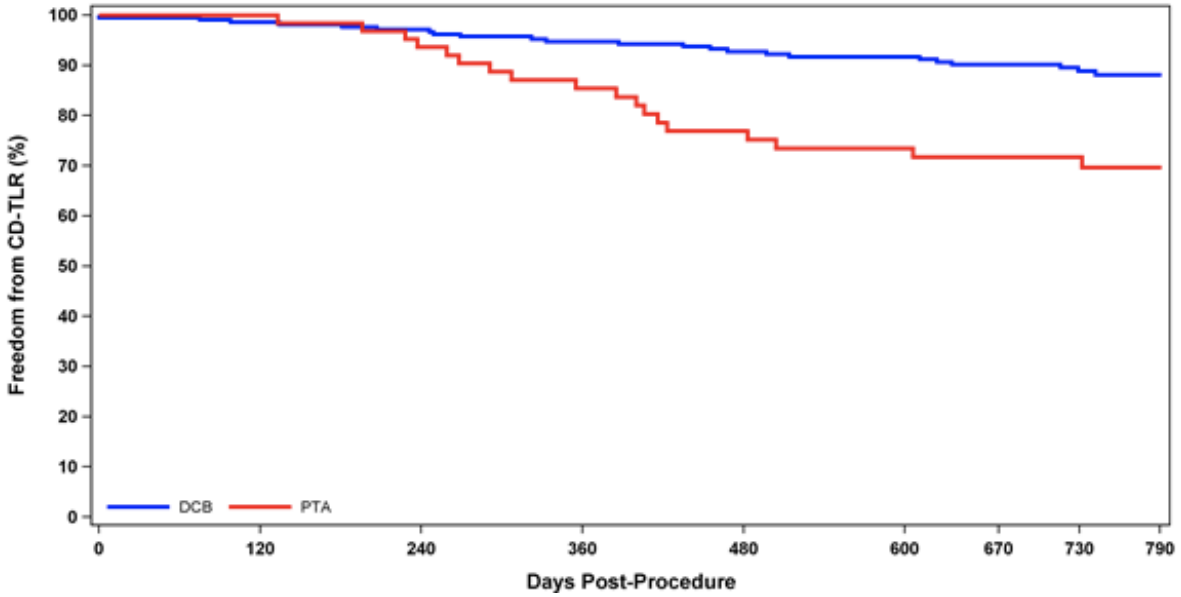


Clinically-driven TLR

Schroeder H et al. ILLUMENATE EU RCT, Circulation 2017

Illumenate EU RCT at 2 years



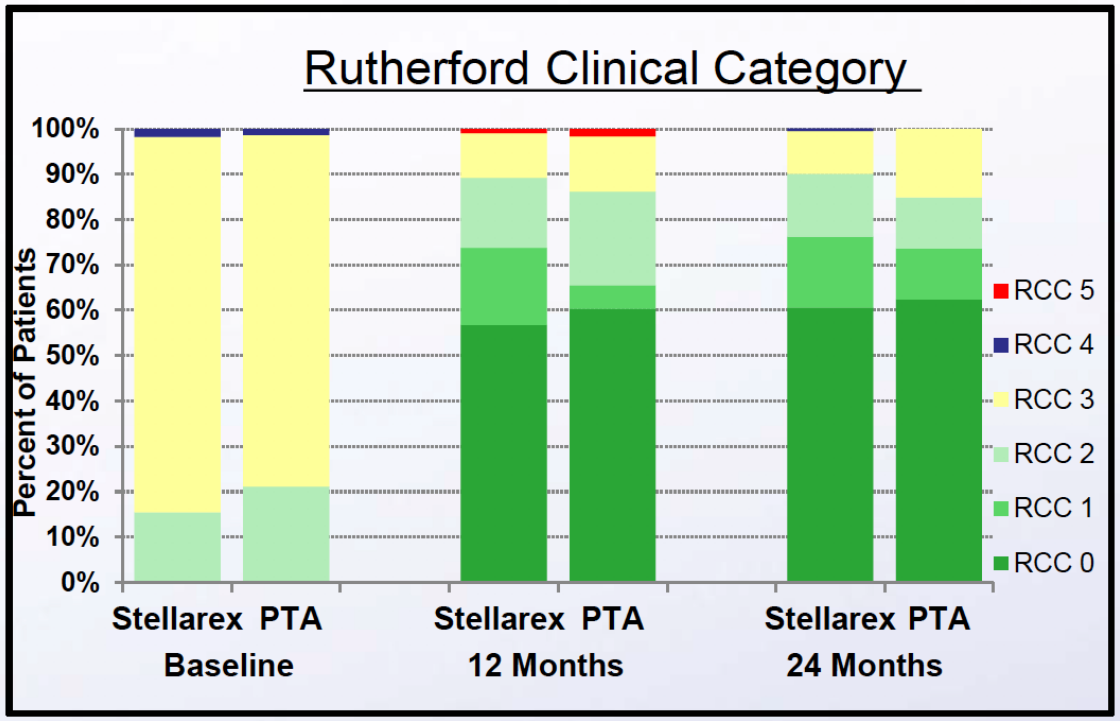


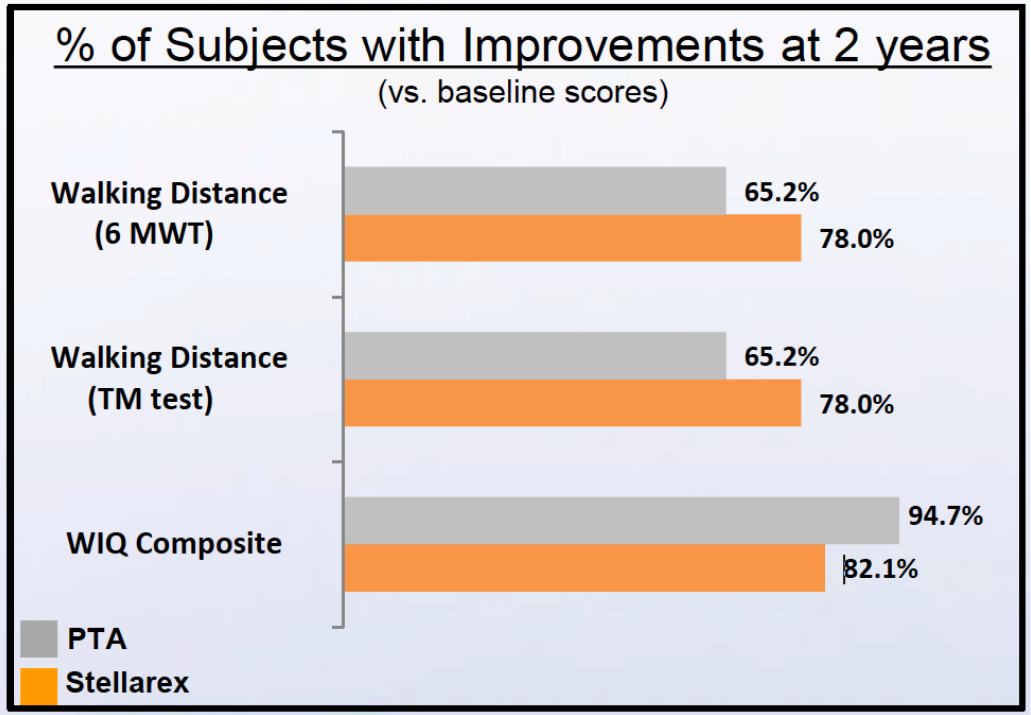
Brodmann et al. ILLUMENATE EU RCT, Oral presentation, Viva 2017

Illumenate EU RCT

Spectranetics

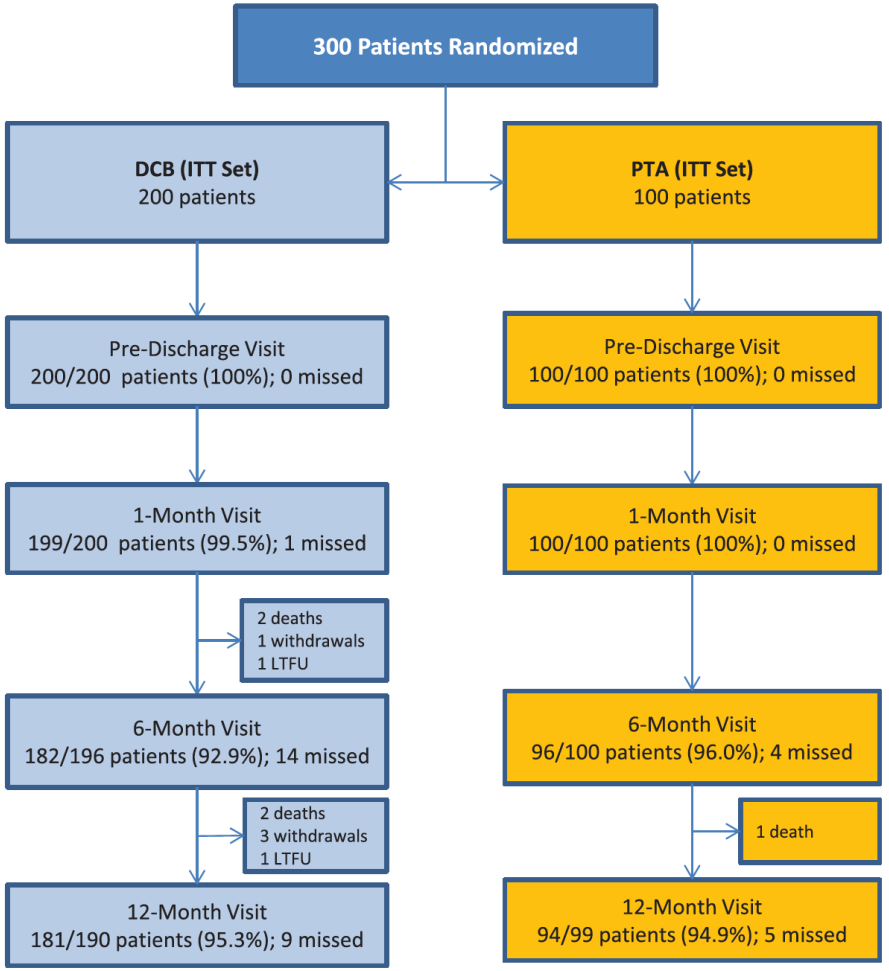
➢The DCB cohort maintained similar outcomes with 60% fewer reinterventions





Brodmann et al. ILLUMENATE EU RCT, Oral presentation, Viva 2017

Illumenate US Pivotal

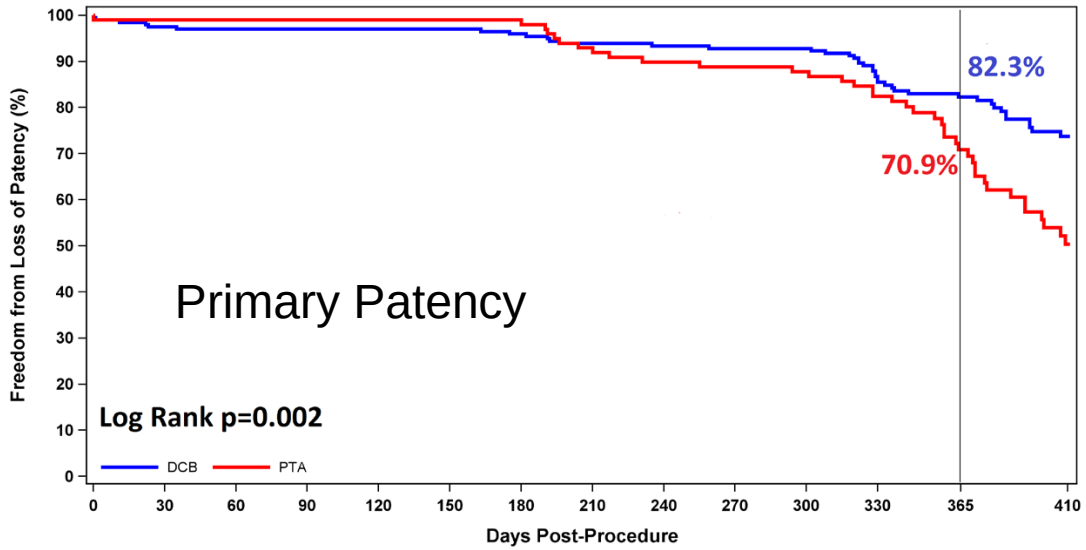


Missed is the number of subjects with a missed visit.
Numerators include both in-window and out-of-window visits; denominators include missed visits.

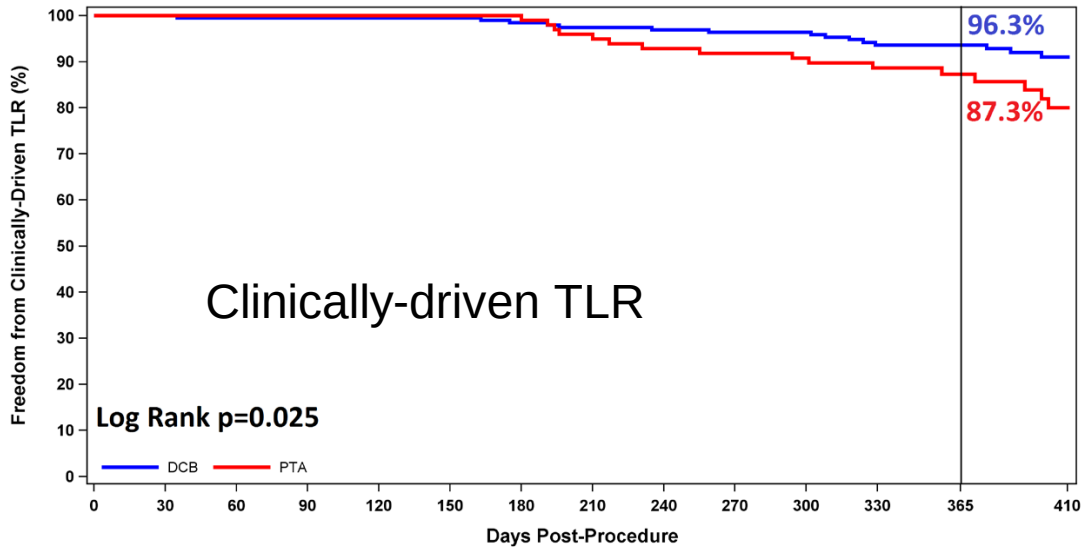
the research team was unable to be blinded because of the visual differences between the DCB and standard balloon angioplasty catheters (uncoated). Research and treatment staff were educated and required to maintain the blinding status to patients. Following the procedure, patients were prescribed clopidogrel or ticlopidine for 30 days and aspirin for the duration of the study. The 1-month follow-up to review adverse events and medication compliance was conducted via office visit or telephone contact. Patients returned for clinical visits at 6 and 12 months, which included clinical assessment, functional status, adverse events, medication compliance, and duplex ultrasound (DUS). Follow-up is ongoing through 5 years.

Krishnan P et al. ILLUMENATE US Pivotal, Circulation 2017

Illumenate US Pivotal



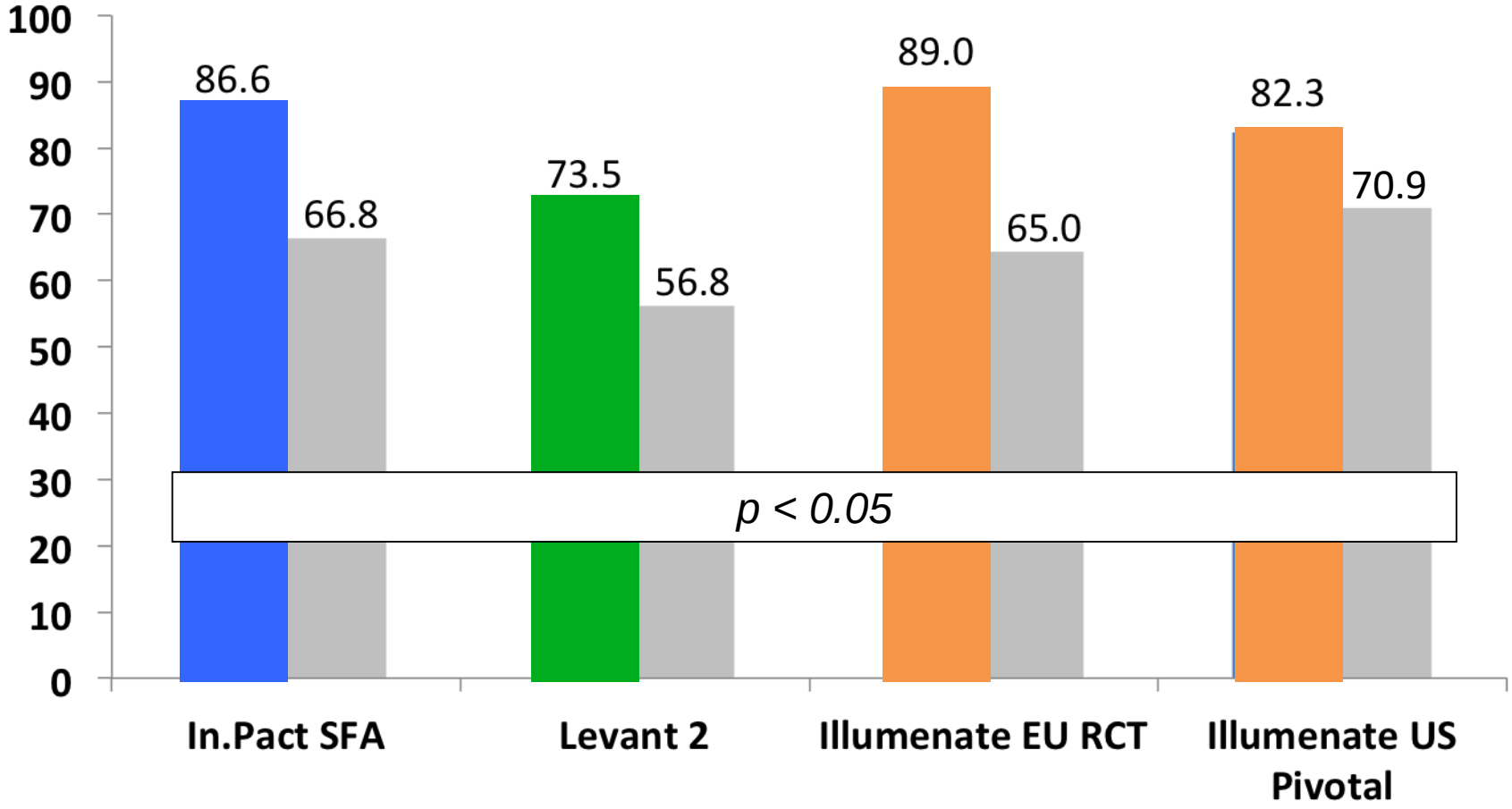
DCB						
At Risk	200	195	186	118	69	
Event	1	5	8	32	42	
Survival (%)	99.5	97.5	96.0	82.3	73.7	
95% CI (%)	[96.5, 99.9]	[94.1, 99.0]	[92.1, 98.0]	[75.8, 87.2]	[65.8, 80.1]	
PTA						
At Risk	100	99	98	51	28	
Event	1	1	2	26	39	
Survival (%)	99.0	99.0	98.0	70.9	50.4	
95% CI (%)	[93.1, 99.9]	[93.1, 99.9]	[92.2, 99.5]	[60.0, 79.3]	[38.2, 61.4]	



DCB						
At Risk	200	200	191	130	83	
Event	0	0	3	12	15	
Survival (%)	100.0	100.0	98.5	93.6	91.0	
95% CI (%)	--	--	[95.3, 99.5]	[89.0, 96.3]	[85.2, 94.6]	
PTA						
At Risk	100	100	99	59	37	
Event	0	0	1	12	16	
Survival (%)	100.0	100.0	99.0	87.3	80.0	
95% CI (%)	--	--	[93.0, 99.9]	[78.6, 92.6]	[68.8, 87.6]	

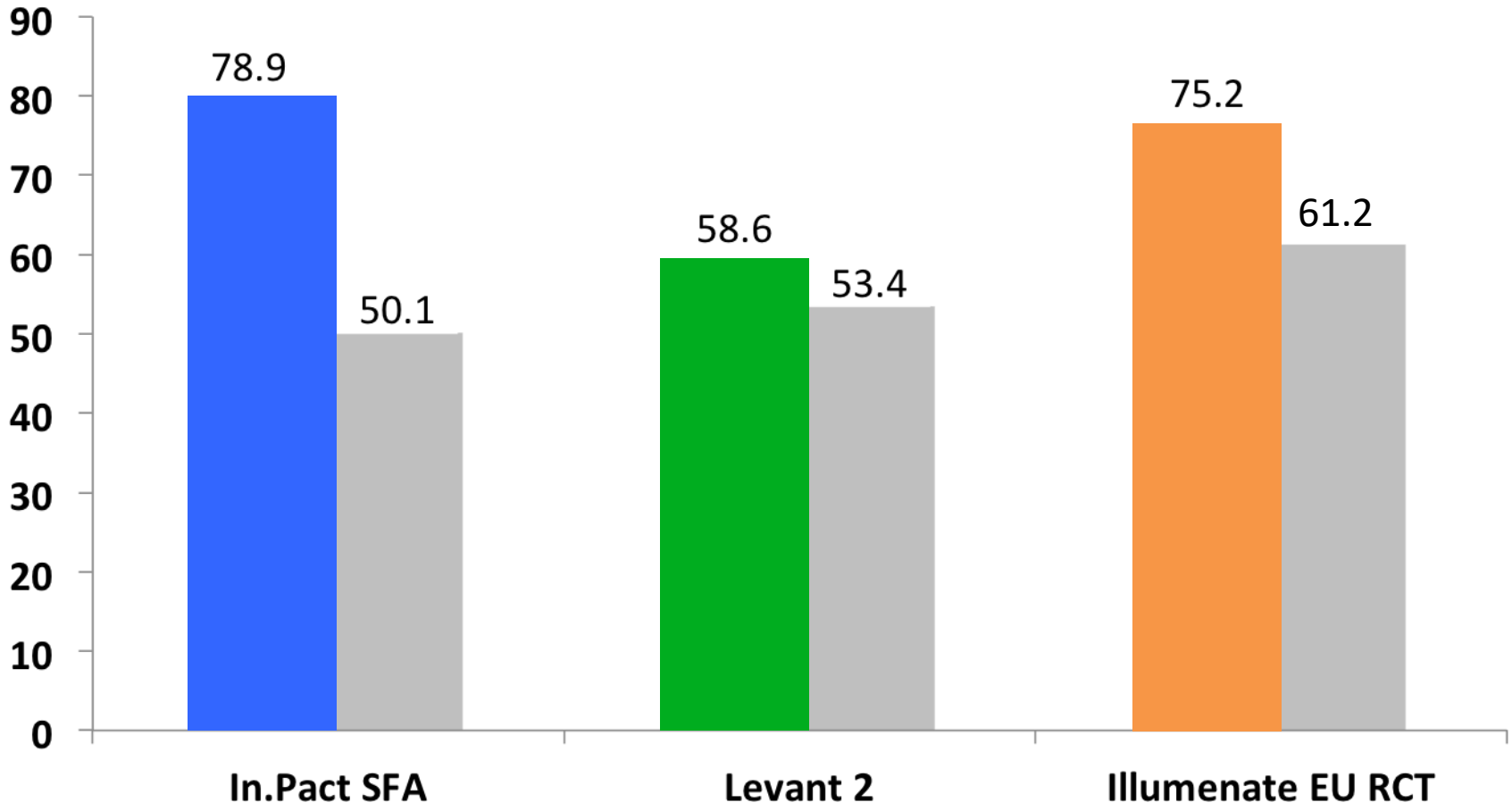
Krishnan P et al. ILLUMENATE US Pivotal, Circulation 2017

Primary patency at 12 m in RCTs (Core lab)



Inspired by slides from K. Keirse

Primary patency at 24 m in RCTs (Core lab)

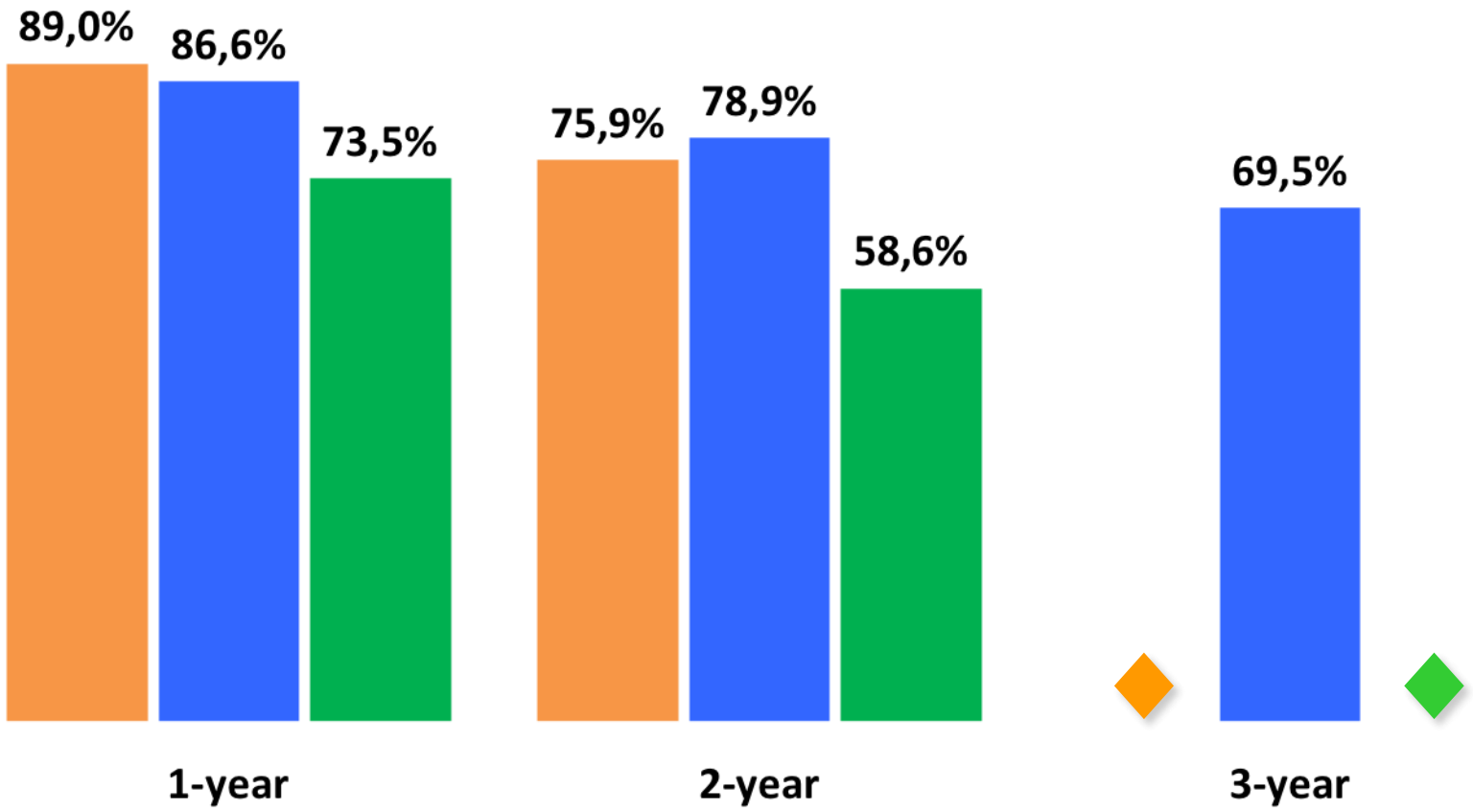


1 M.Brodmann - ILLUMENATE European Randomized Trial: 2-Year Results – oral presentation, VIVA Sep 2017 , Las Vegas

2 Laird JR, Schneider PA, Tepe G, Brodmann M, Zeller T, Metzger C, Krishnan P, Scheinert D, Micari A, Cohen DJ, Wang H, Hasenbank MS, Jaff MR; IN.PACT SFA Trial Investigators. Durability of Treatment Effect Using a Drug-Coated Balloon for Femoropopliteal Lesions: 24-Month Results of IN.PACT SFA. J Am Coll Cardiol. 2015 Dec 1;66(21):2329-38

3 Laurich C, oral presentation at SVS Annual Meeting June 2015, Chicago

Global view of primary patency of DCBs in RCT



Inspired by slides from K. Keirse

Multiple meta-analysis of RCTs favor DCB over POBA

Significant benefits in terms of

TLR at 12 m and 24 m

Primary patency at 6 and 12 m

LLL at 6 m

Katsanos K et al. J Endovasc Ther. 2016

Jongsma H et al. J Vasc Surg. 2016

Giacoppo D et al. JACC Cardiovasc Interv. 2016

Kayssi A et al. Cochrane Database Syst Rev. 2016

DCB in ISR

Study	Patients, n	Age, yrs	Males, %	Diabetes, %	CLI, %	Lesion length, mm	Diameter stenosis, %	ISR class III, %	Bail-out stenting, n (%)*
COPACABANA[19]	88	67.9	59.3	44.5	9.7	114.5	79.4	26.9	N/R
DEBATE ISR[18]	86	75.0	63.7	100	70.8	134.5	92.5	58.0	DCB: 7/44 (15.9%); plain balloon angioplasty: 11/42 (26.2%)
FAIR[9]	119	68.0	61.7	37.5	7.6	81.7	89.5	28.7	DCB: 1/62 (1.6%); plain balloon angioplasty: 4/57 (7.0%)
PACUBA I[10]	74	68.2	58.0	45.0	N/R	178.5	N/R	29.5	DCB: 5/35 (14.2%); plain balloon angioplasty: 2/39 (5.1%)

Overall mean values are reported. *Data are presented as number of events/total number of patients (proportion) for each treatment group. CLI: critical limb ischaemia; DCB: drug-coated balloon; ISR: in-stent restenosis; N/R: not reported. Study acronyms: COPACABANA: Cotavance™ Paclitaxel-Coated Balloon Versus Uncoated Balloon Angioplasty for Treatment of In-stent Restenosis in SFA and Popliteal Arteries; DEBATE ISR: Drug Eluting Balloon in peripherAl inTErvention for In-Stent Restenosis; FAIR: Femoral Artery In-Stent Restenosis; PACUBA I: A Randomised Clinical Trial of PAClitaxel drUg-eluting BAlloon Versus Standard Percutaneous Transluminal Angioplasty to Reduce Restenosis in Patients With In-stent Stenoses in the Superficial Femoral and Proximal Popliteal Artery

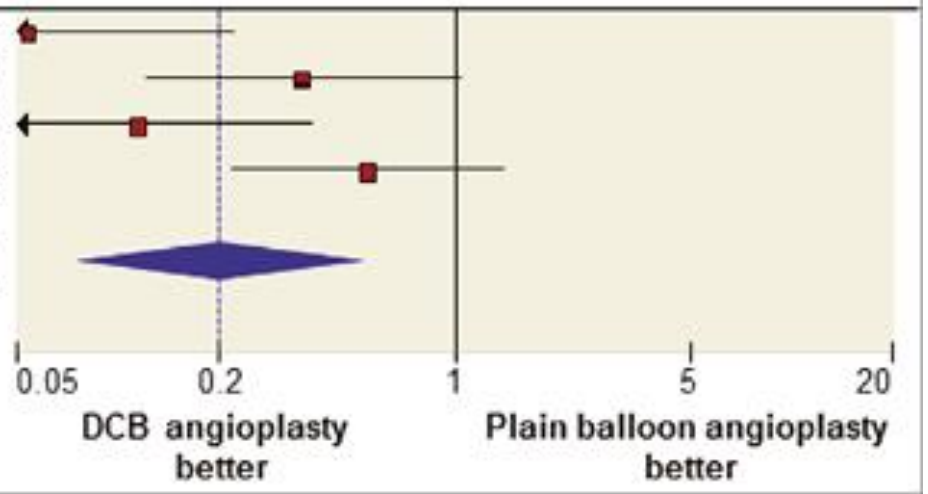
Cassese et al, Eurointervention 2017

DCB in ISR

Target lesion revascularisation

Study	DCB angioplasty Events	Total	Plain balloon angioplasty Events	Total	Weight	Random-effects odds ratio [95% CI]
COPACABANA	3	38	16	26	21.3%	0.05 [0.01, 0.22]
DEBATE ISR	6	44	13	42	26.0%	0.35 [0.12, 1.04]
FAIR	4	50	19	44	24.5%	0.11 [0.04, 0.37]
PACUBA I	12	35	19	39	28.1%	0.55 [0.21, 1.40]
Total	**25**	**167**	**67**	**151**	**100.0%**	**0.20 [0.07, 0.55]**

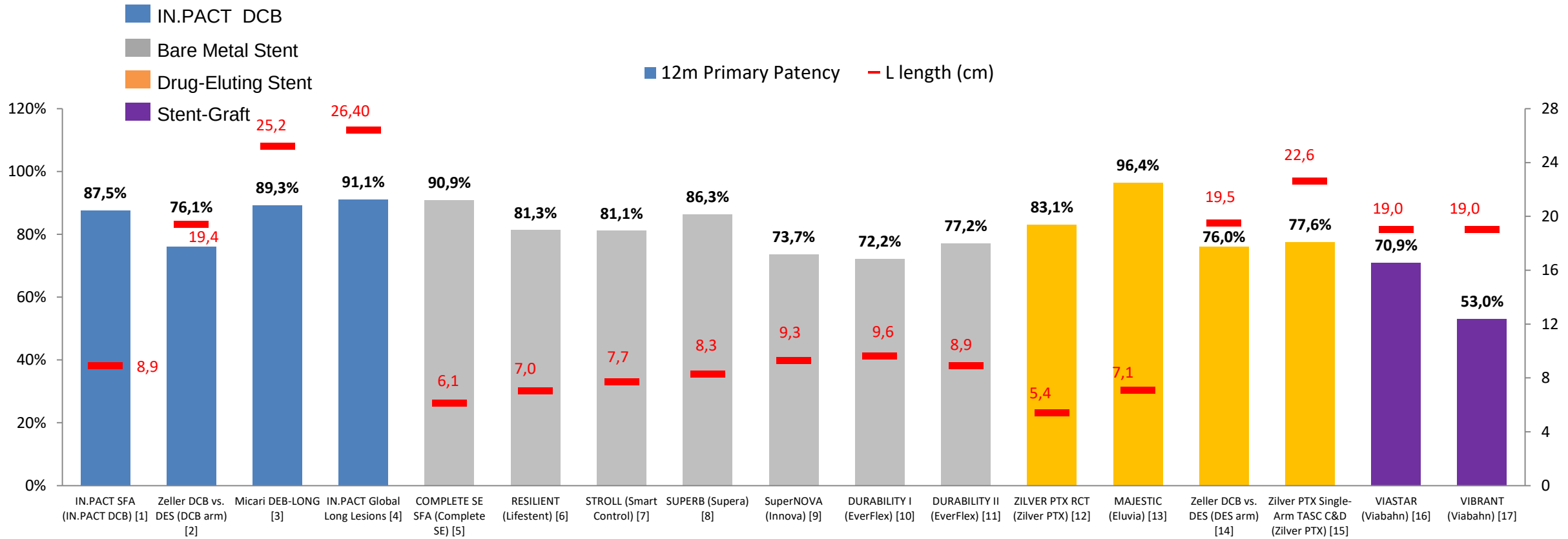
Heterogeneity: $Tau^2 = 0.70$; $Chi^2 = 9.29$, $df = 3$ ($P = 0.03$); $I^2 = 68\%$
Test for overall effect: $Z = 3.12$ ($P = 0.002$)



Cassese et al, Eurointervention 2017

Ott I et al, ISAR-PEBIS study, J Am Heart Assoc. 2017

No RCT comparing DCB with stents



Primary patency rates and mean lesion lengths may be calculated differently, and therefore may not be directly comparable; chart is for illustration only.

[1] Tepe G, et al. Circ 131:495-502 (2015). Laird JR, et al. J Am Coll Cardiol: 66:2329-38 (2015). Note: 1 year results updated from interval to cumulative KM calculations. PSVR ≤ 2.4 and freedom from CD-TLR. [2] Zeller T, et al. JEVT. (3):359-68 (2014). [3] Micari A, et al. JACC Cardiovasc Interv. 9(9):950-6 (2016). [4] Scheinert D. EuroPCR 2015. [5] Complete SE Instructions for Use. [6] Laird J, et al. Circ Cardiovasc Interv 3:267-76 (2010). [7] Gray W, et al. J Vasc Interv Radiol 26:21-28 (2015). [8] Garcia L, et al. Circ Cardiovasc Interv 8(5): e000937 (2015). [9] Innova Instructions for Use (Boston Scientific) [10] Bosiers M, et al. J Endovasc Ther 16:261-9 (2009). [11] Matsumura J, et al. J Vasc Surg 58:73-83 (2013). [12] Dake M, et al. Circ Cardiovasc Interv 4:495-504 (2011); Dake M, et al. JACC 61(24):2417-27 (2013). [13] Müller-Hülsbeck S, et al. J Endovasc Ther. (2016). [14] Zeller T, et al. JEVT. (3):359-68 (2014).[15] Bosiers M, et a. J Cardiovasc Surg (Torino). 54(1):115-22 (2013). [16] Lammer J, et al. Cardiovasc Intervent Radiol 38:25-32 (2015). [17] G. Ansel. VIBRANT interim results presented at VIVA 2009.

Conclusions

- Large RCTs demonstrate the superiority of 3 DCBs over POBA in de novo SFA lesions regarding primary patency at 1 year
- 2 DCBs have sustained superiority at 2 years and 1 DCB remains superior at 3 years
- There is a lack of evidence for DCBs in other locations, in other indications and against other therapies (BMS, DES)

CONTROVERSES ET ACTUALITÉS EN CHIRURGIE VASCULAIRE

CONTROVERSIES & UPDATES IN VASCULAR SURGERY

JANUARY 25-27 2018

MARRIOTT RIVE GAUCHE & CONFERENCE CENTER

PARIS, FRANCE WWW.CACVS.ORG

Hôpitaux Universitaires
Paris Ile-de-France Ouest
RAYMOND POINCARÉ • BERCK
AMBROISE PARÉ • SAINTE PÉRINE

UNIVERSITÉ DE VERSAILLES ST-QUENTIN-EN-YVELINES