XIENCE Safety: Review of XIENCE DAPT Clinical Evidence and Clinical Program

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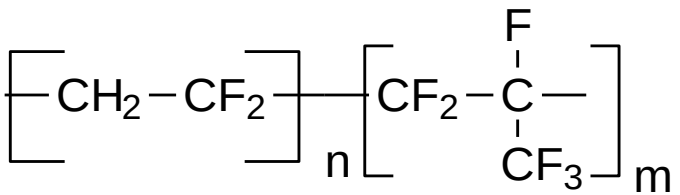
Disclosures

- None

Xience Drug Matrix: Fluorinated Copolymer

- Ultra-pure random copolymer composed of (VDF) and (HFP) monomers
- Used in cardiovascular, neurological and ophthalmic sutures
- VDF-HFP ratio allows for optimization of coating elasticity (from elastomeric properties - avoids cracking or splitting during stent expansion) and toughness (from high crystallinity – doesn't crack or peel during stent delivery)
- Durable C-C backbone and covalent C-F bonds provide excellent stability and high biocompatibility

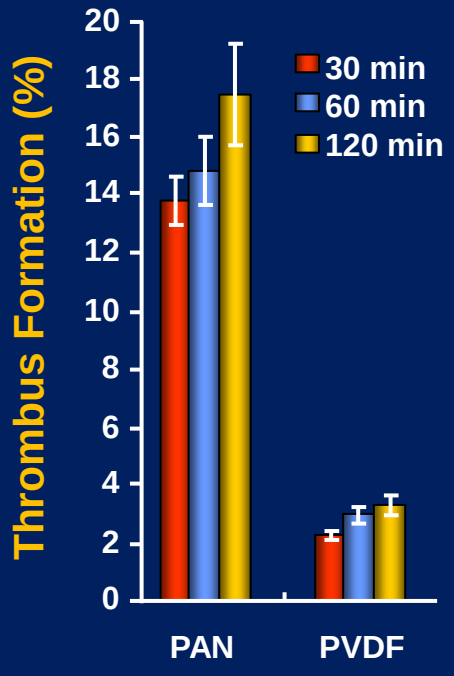


VDF **HFP**

VDF = vinylidene fluoride
HFP = hexafluoropropylene

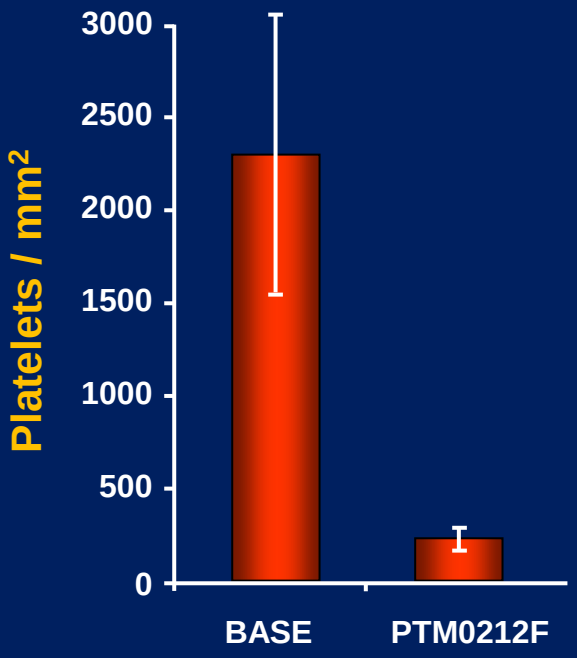
The Concept of Fluoropassivation

Fluoropolymer coated surfaces are platelet and thromboresistant in blood-contact applications



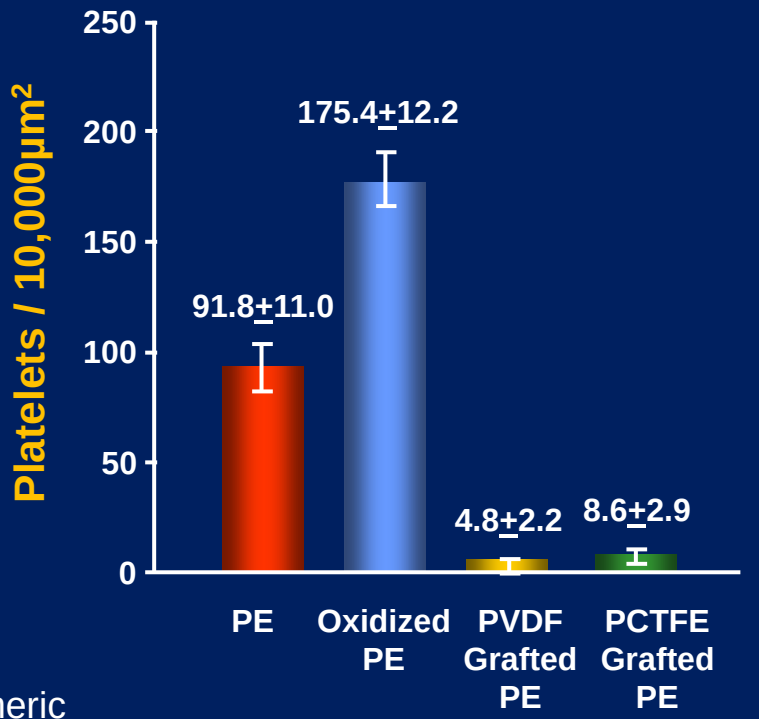
Thrombus formation ratio of PAN/PVDF blend membranes after 30, 60 and 120 min incubation (n=3)

Ting-Yu Liu et al. Polym. Adv. Technol. 2005;16:413–419



Platelet adhesion onto polymeric surfaces after 15 min exposure to blood at 150 rpm (37° C); Platelet count measured using ^{51}Cr method

Massa TM et al. J Biomed Materials Research Part A DOI 10.1002/jbm.a



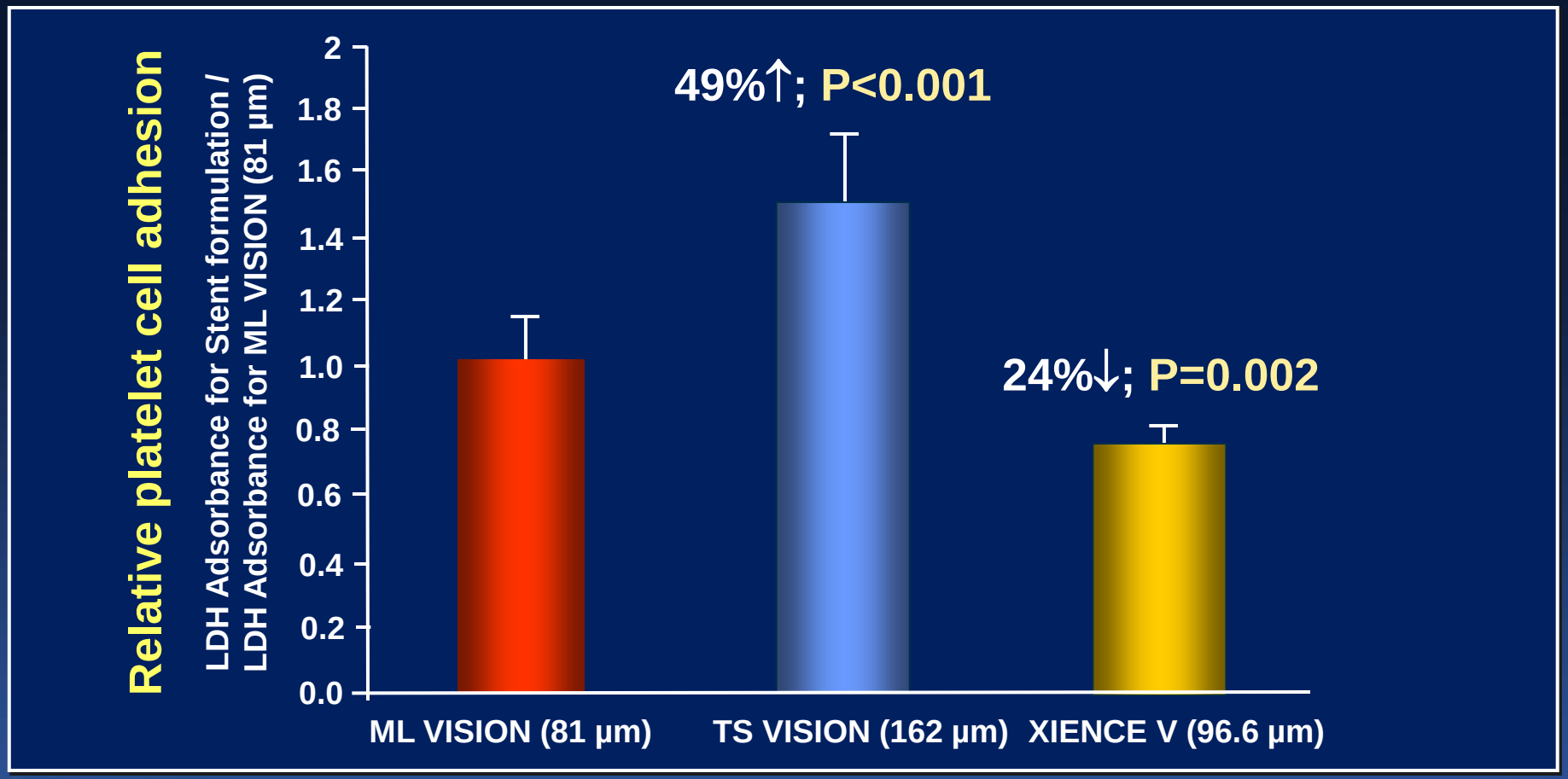
Platelet adhesion density of PE and various modified PEs

Jui-Che Lin et al. J Biomater Sci Polymer. 2000;11:701–714

Stent Thrombosis is Affected by Stent Design, Deployment and Polymer

Impact of strut thickness and Xience V polymer coating

In vitro pulsatile Chandler loop model with porcine blood



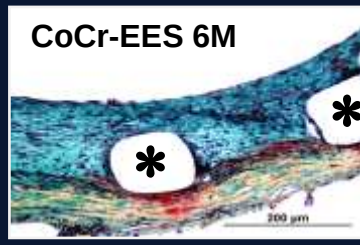
Kolandaivelu K et al. Circulation 2011;123:1400-1409

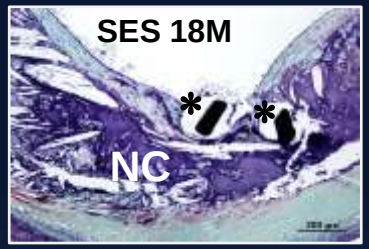
204 lesions (SES=73; PES=85; CoCr-EES=46) from 149 autopsy cases with implant duration >30 days and ≤3 years

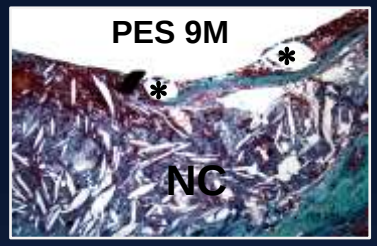
Greater strut coverage with less inflammation, less fibrin deposition, and less late and very late stent thrombosis – but similar rates of neoatherosclerosis and fracture-related adverse pathological events

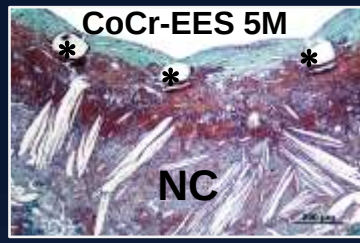
DES for Stable CAD

DES for ACS



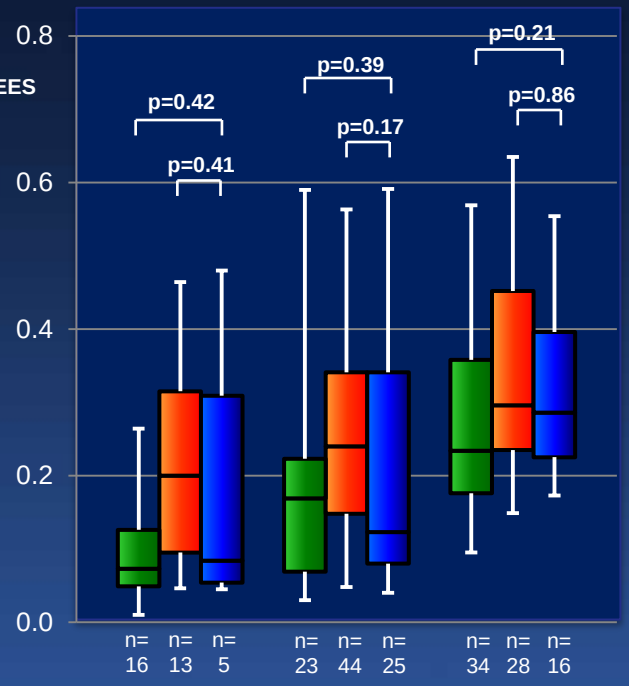






SES PES CoCr-EES

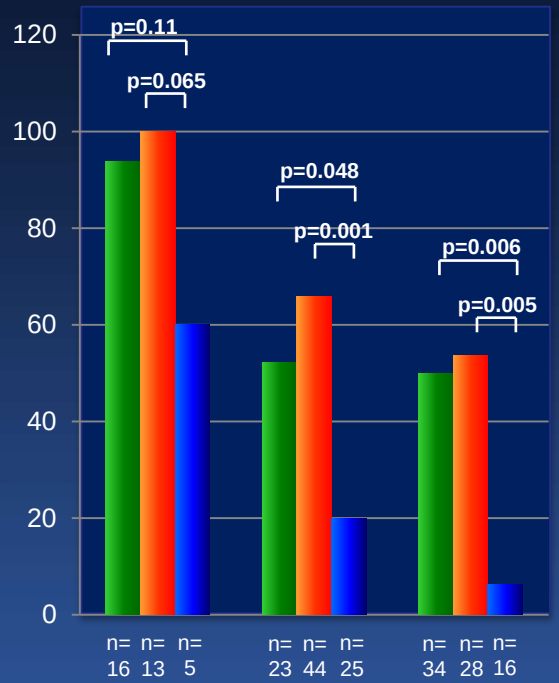
Maximum Neointimal Thickness (mm)



Equivalent efficacy in reducing neointima compared to 1st gen DES

SES PES CoCr-EES

Prevalence of DES with >30% Uncovered Struts (%)



Increased safety with regards to strut coverage compared to 1st gen DES.

Otsuka et al. Circulation 2014;129:211-23

Cardiovascular Research Foundation — A Passion for Innovation

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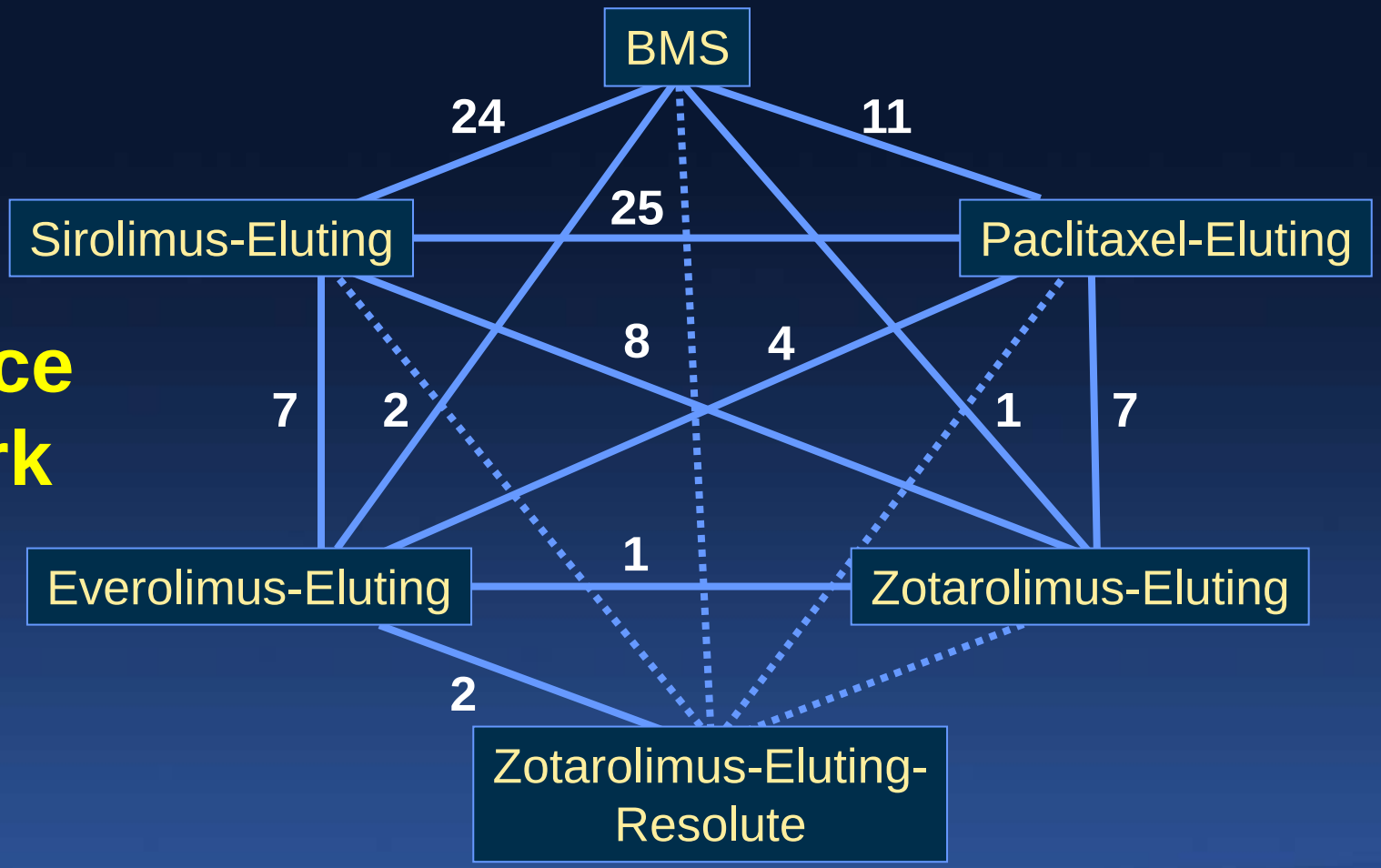
Network Meta-analysis

Endpoints: Death, MI, ST, TVR early (<1 yr) and late

77 RCTs, 57,138 pts, 117,762 pt-yrs of FU

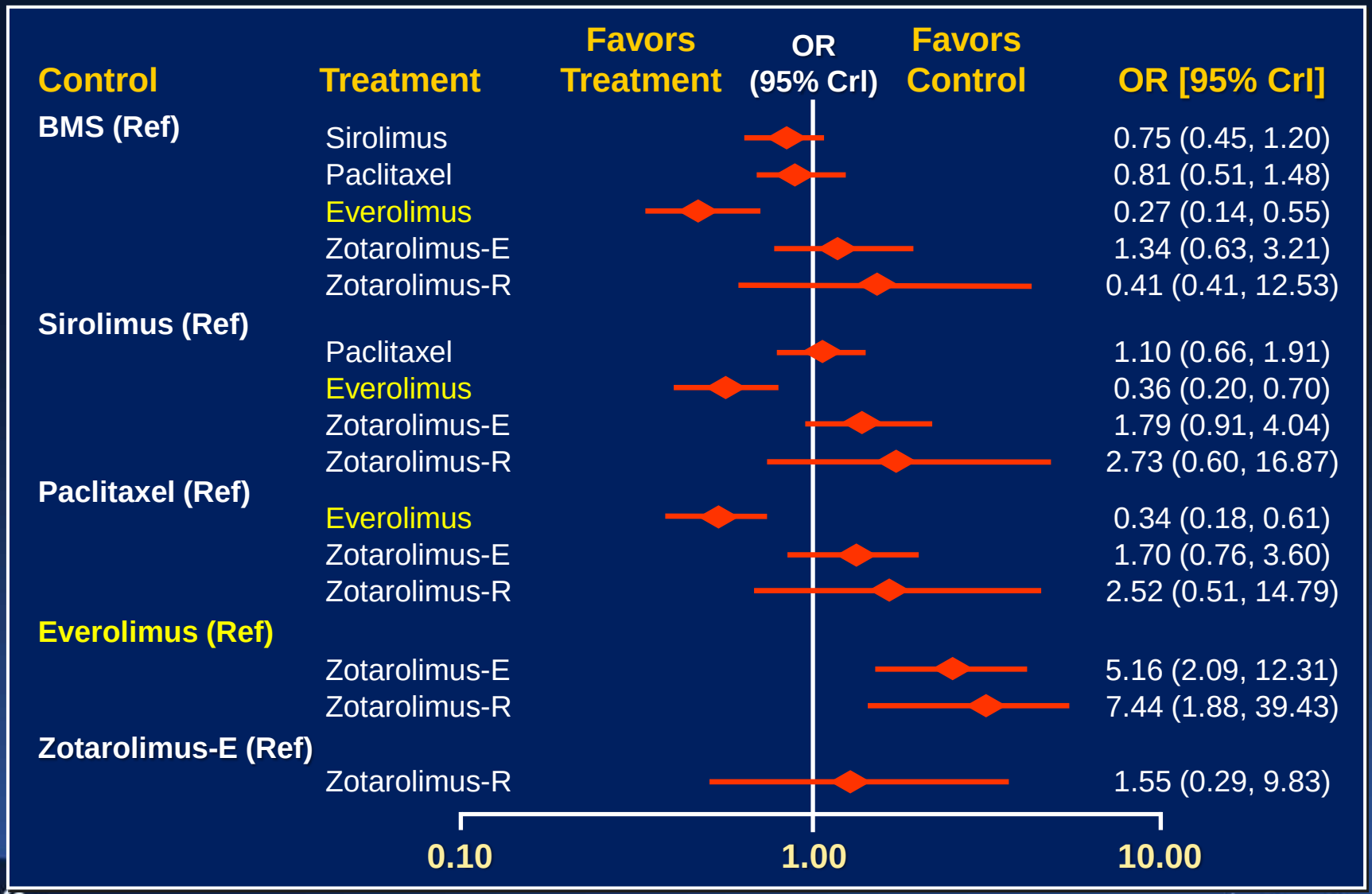
Evidence network



Bangalore S et al. *Circulation* 2012;125:2873-91

Network Meta-analysis: 1-year Definite ST

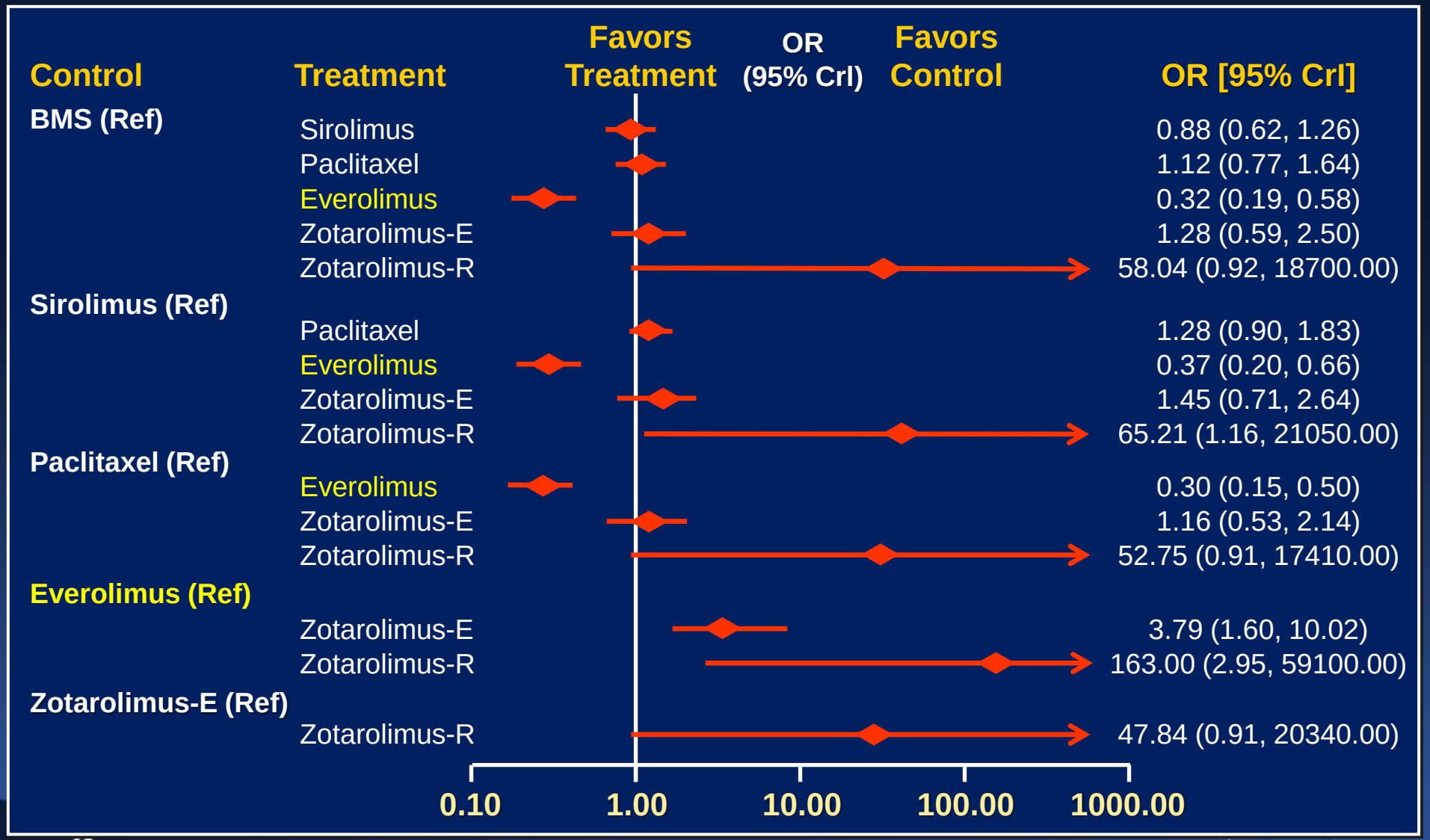
77 RCTs, 57,138 pts, 117,762 pt-yrs of FU



Bangalore S et al. *Circulation* 2012;125:2873-91

Network Meta-analysis: Long-term Definite ST

77 RCTs, 57,138 pts, 117,762 pt-yrs of FU

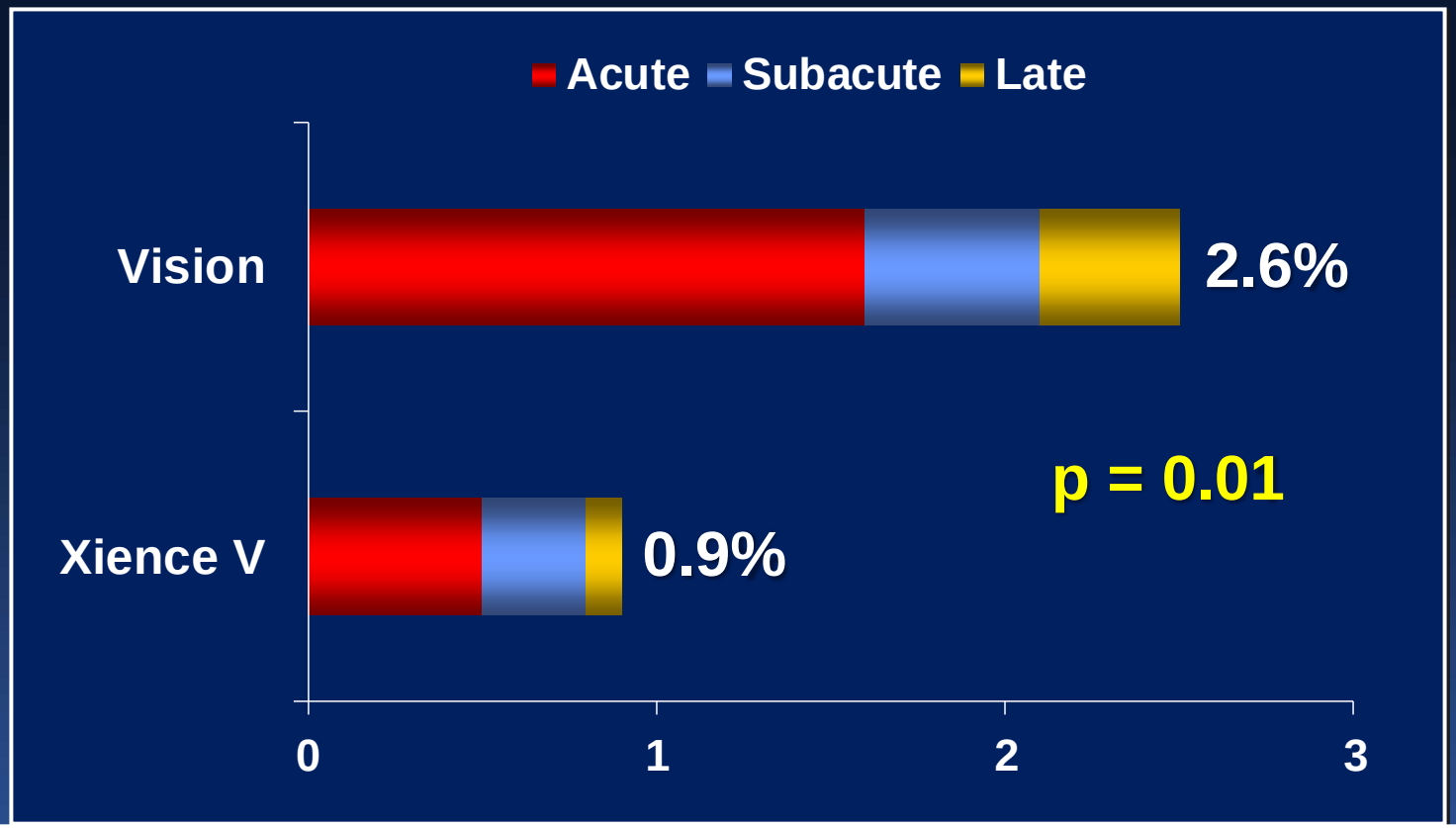


Bangalore S et al. *Circulation* 2012;125:2873-91

EXAMINATION Trial

1504 pts with STEMI undergoing PCI within 48° (85% primary PCI within 12°) were randomized to Xience V EES vs. Vision BMS

Stent thrombosis (Def/prob) within 1 year



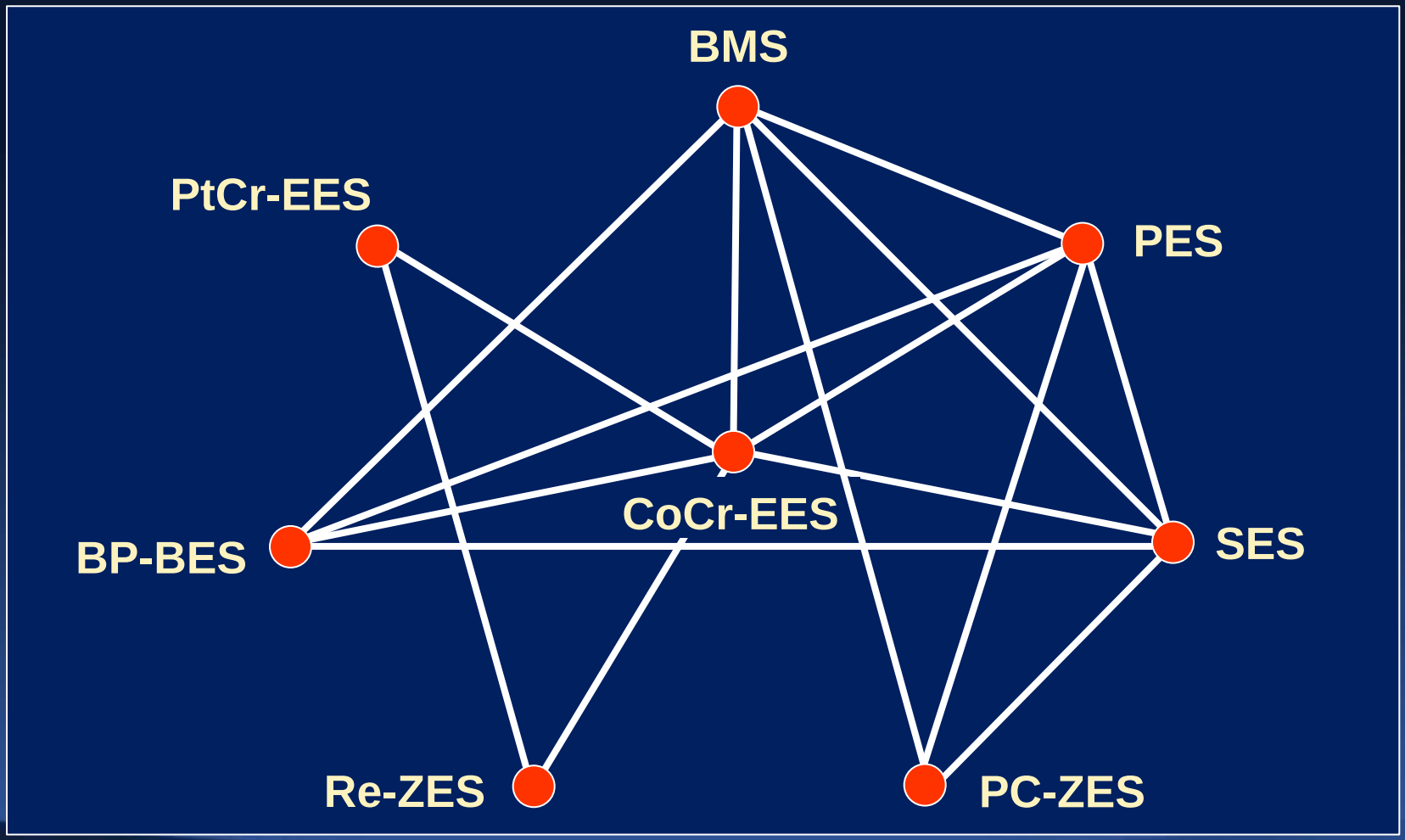
Definite ST was reduced with Xience V from 1.9% to 0.5%, p=0.01

Sabate M et al. Lancet 2012;380:1482-90

Bioabsorbable Polymer-based DES

Meta-analysis of 89 RCTs, 84,590 pts

Evidence Network

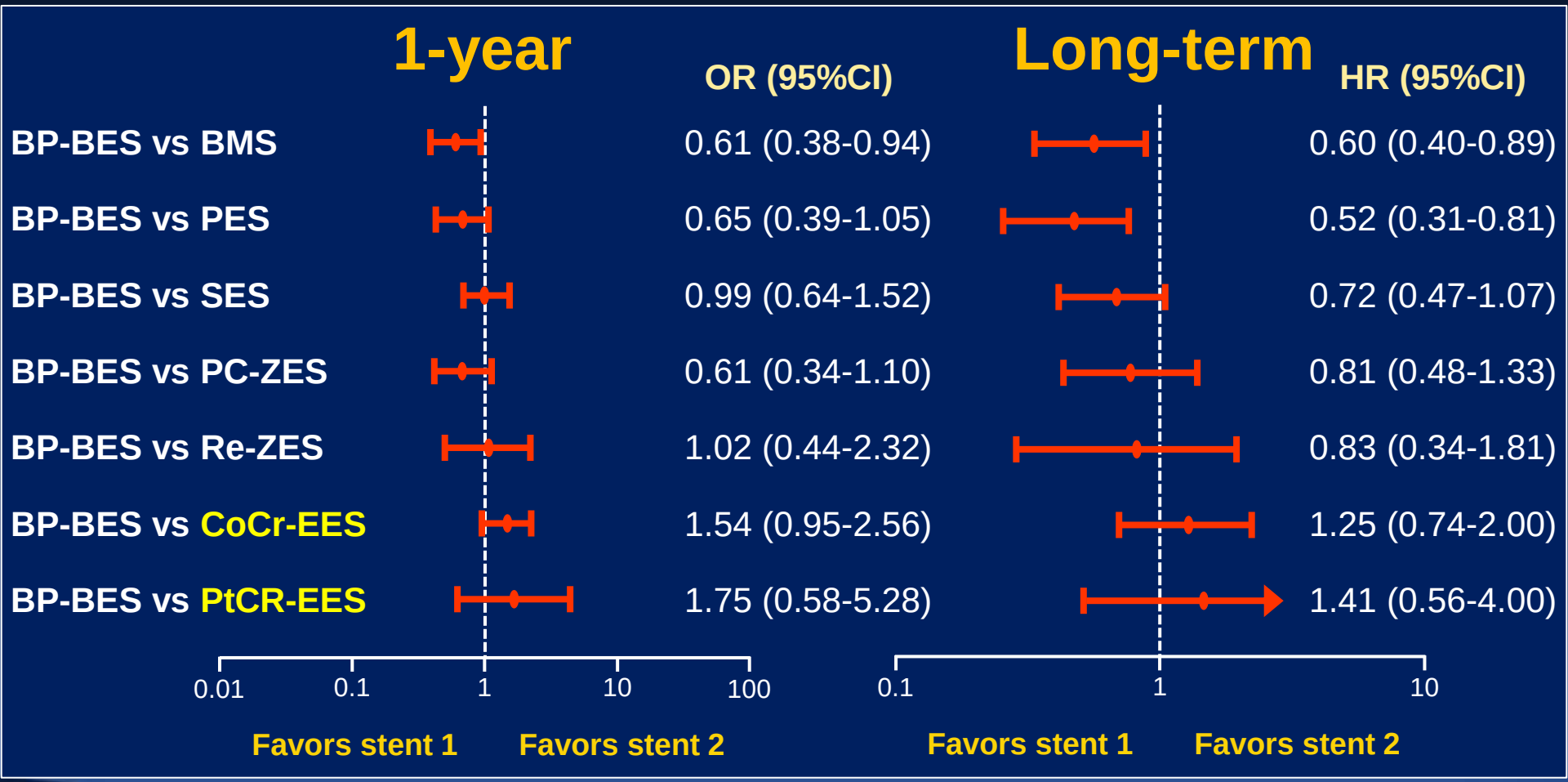


Palmerini T et al. *JACC* 2014;63:299-307

Bioabsorbable Polymer-based DES

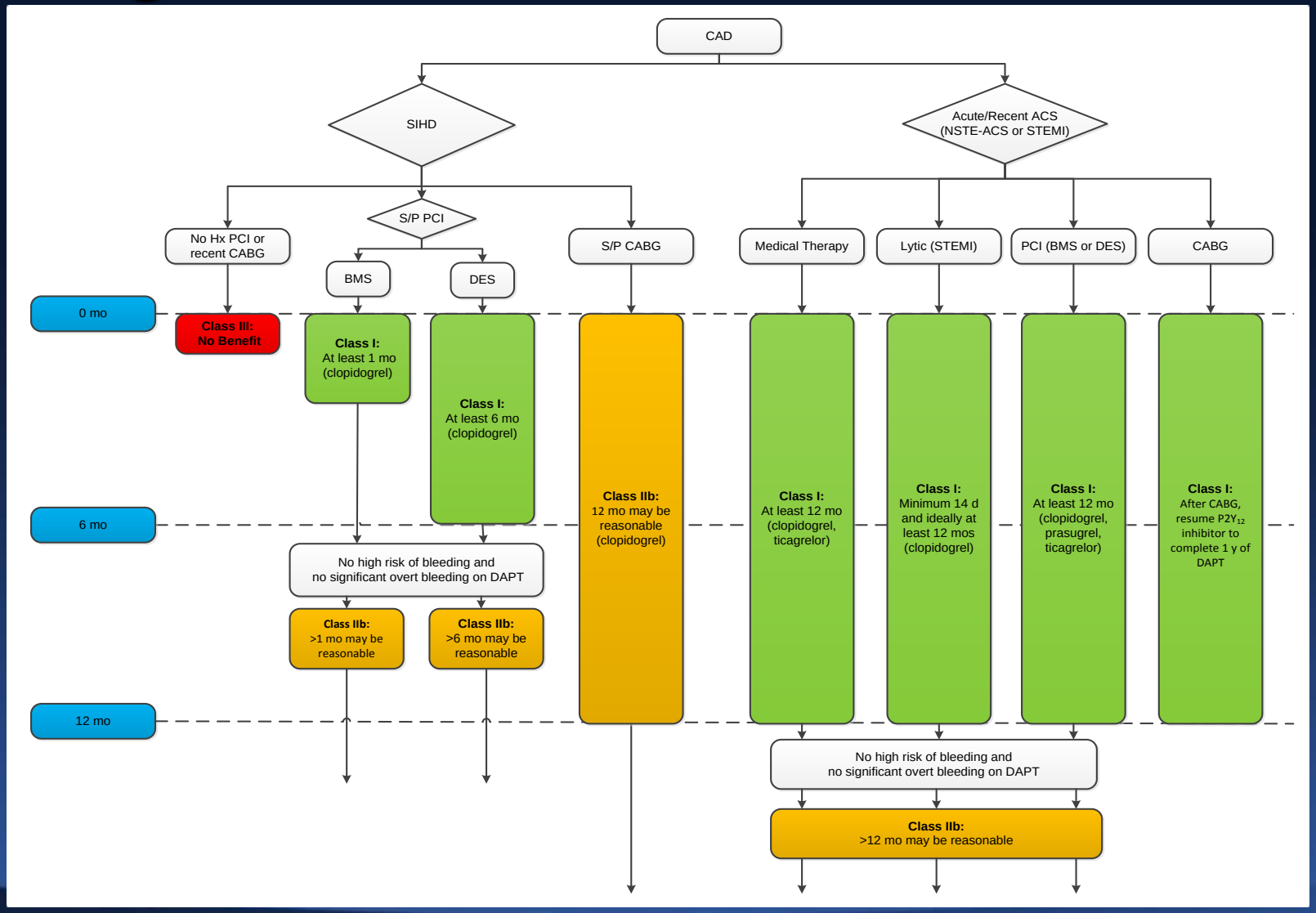
Meta-analysis of 89 RCTs, 84,590 pts

Stent Thrombosis



Palmerini T et al. *JACC* 2014;63:299-307

2016 ACC/AHA Guidelines: Updated Algorithm for DAPT Duration in CAD



Levine GN et al. J Am Coll Cardiol. 2016;68:1082-115

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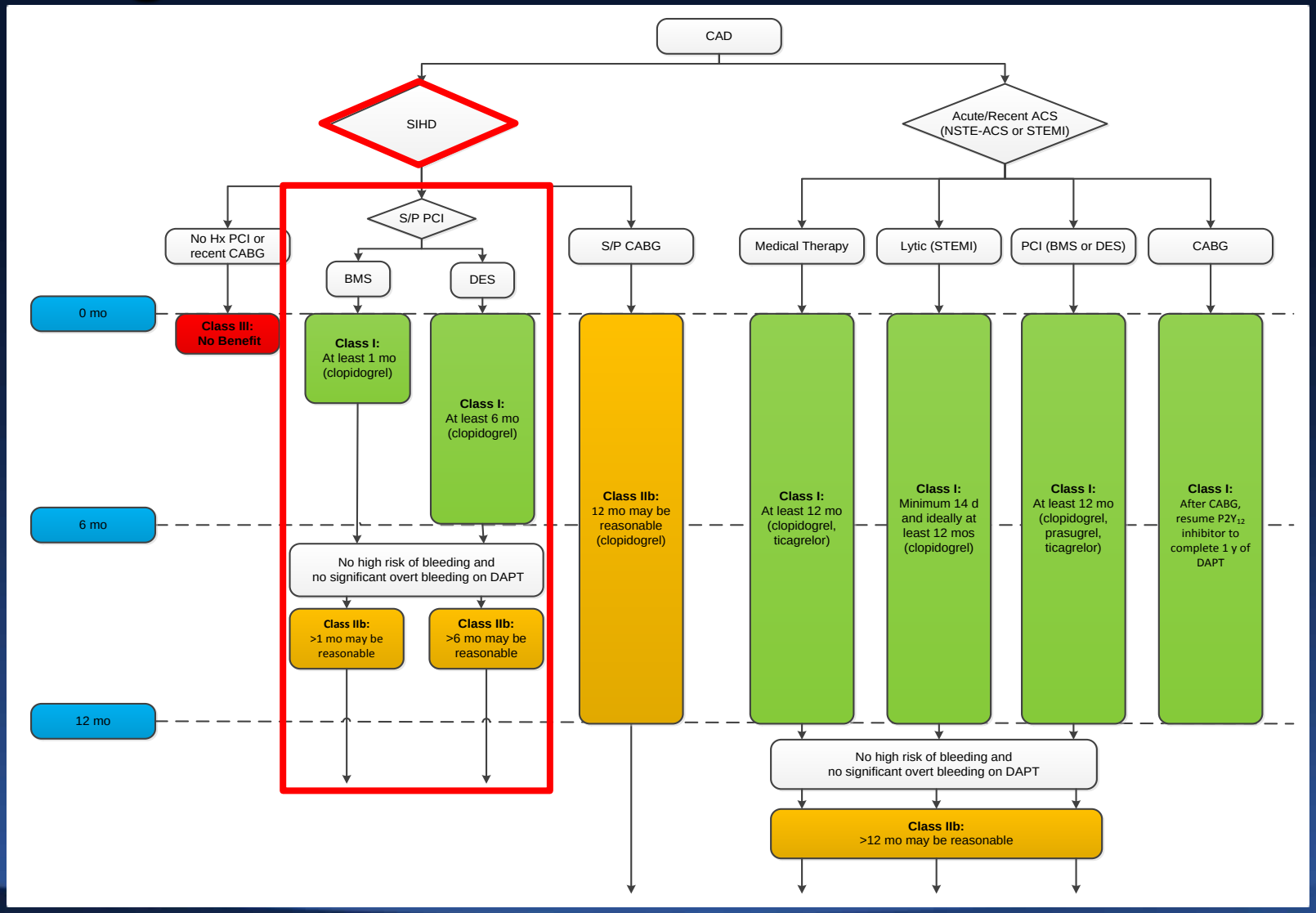

Levine GN et al. J Am Coll Cardiol. 2016;68:1082-115

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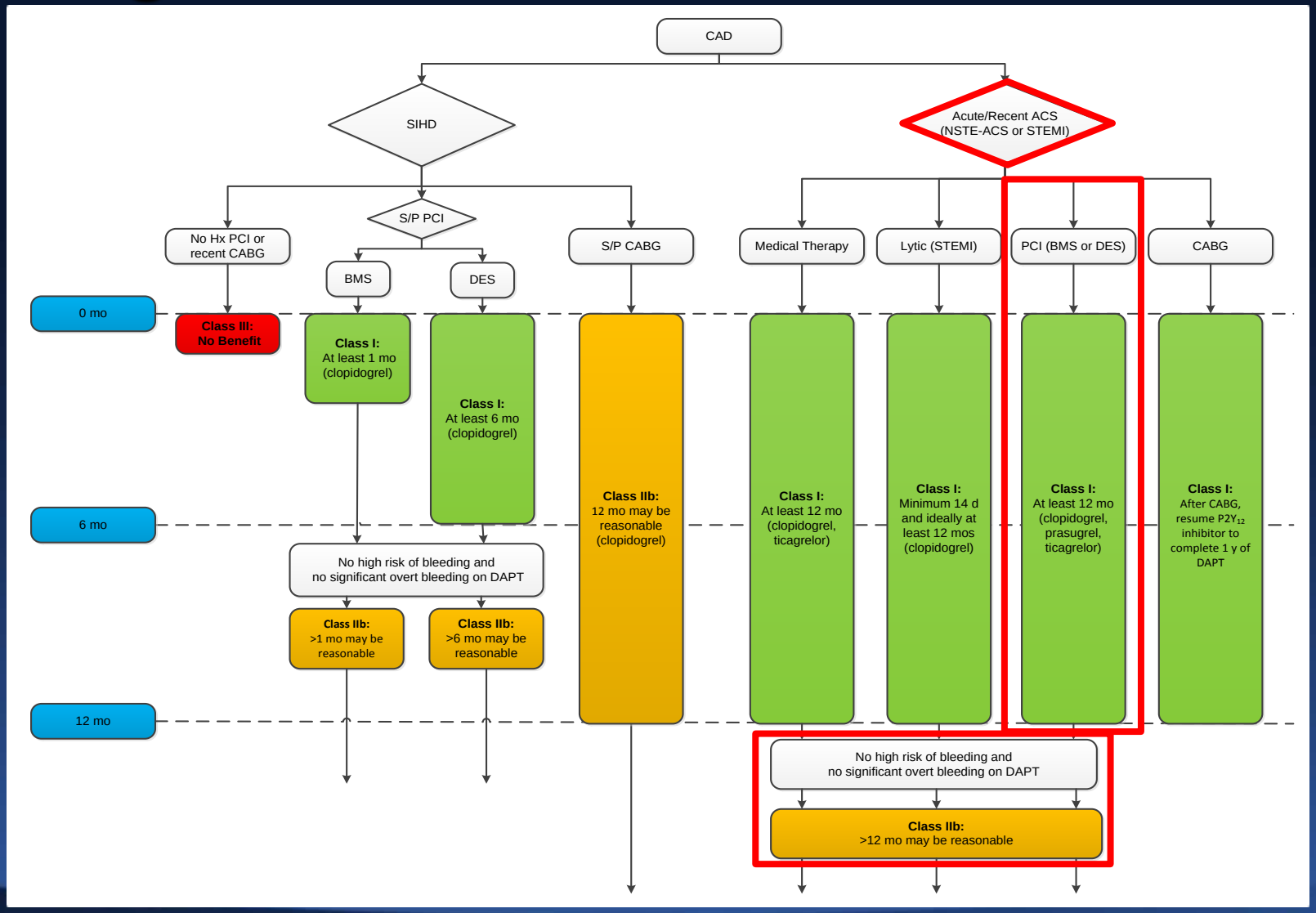
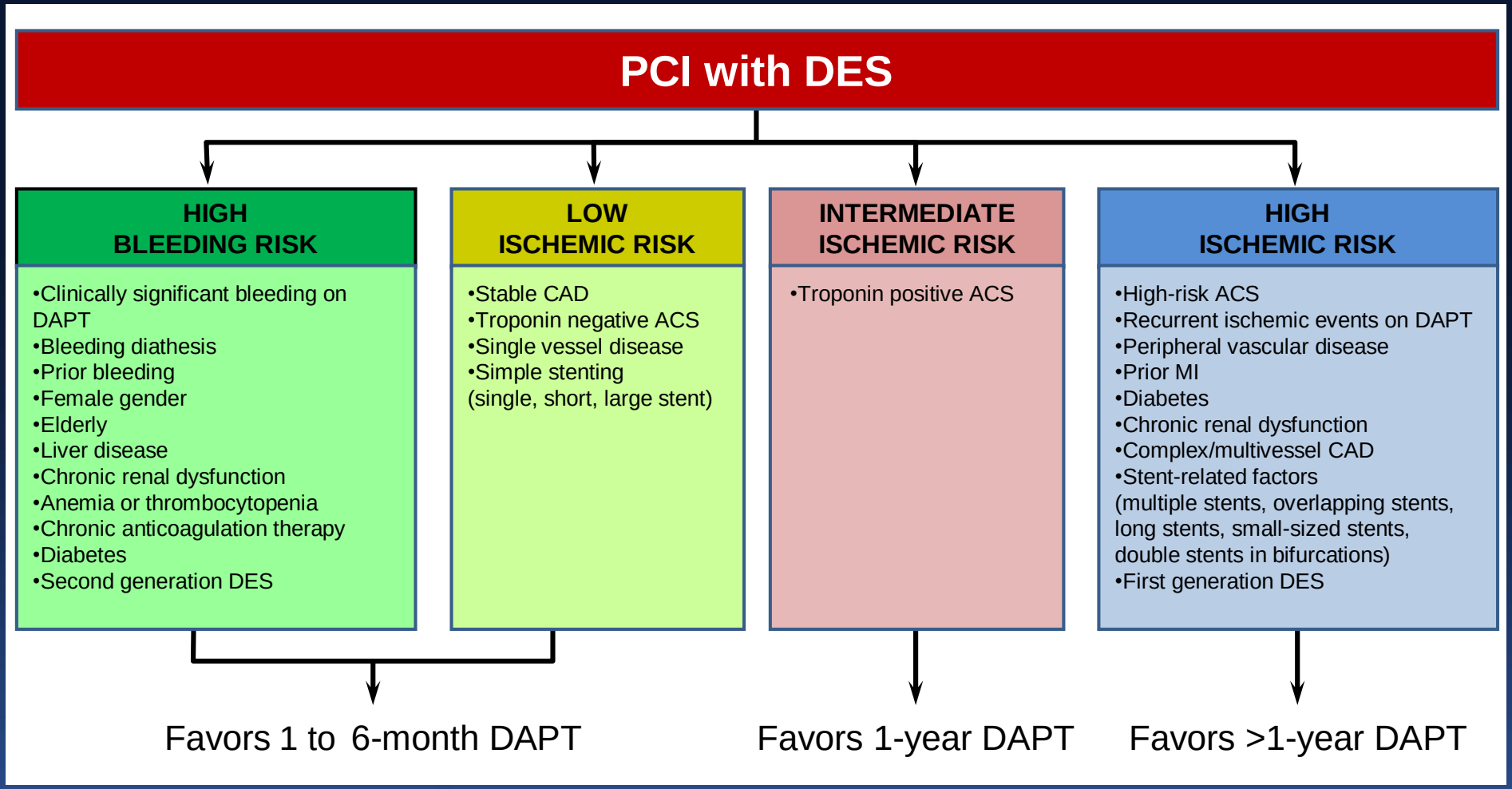


Levine GN et al. J Am Coll Cardiol. 2016;68:1082-115

DAPT Duration: Factors to be weighed



When assessing ischemic and bleeding risk, clinical presentation (ACS vs SIHD), age, disease/PCI complexity and stent type are important factors to consider

Palmerini T and Stone GW. Eur Heart J 2016;37:353-64

Patient Flow and Stent Thrombosis Through 2 Years

Généreux P et al.
Circ CV Interv 2015

SPIRIT II, III, IV, V, Women, V USA, V India

13,259 total pts

2,040 pts (15.4%) without complete DAPT data (11 ST events, 0.54%)

Analysis population

11,219 pts (84.6%) with complete DAPT data through 2 years (2-year complete follow-up rate 94.3%)

85 ST events in 83 pts (0.74%) through 2 years

45 ST events occurred in 44 pts with no DAPT interruption from day 1 through 2 yrs

45 events occurred "On" DAPT*

40 ST events occurred in 39 pts with some DAPT interruption from day 1 though 2 yrs

23 events occurred "On" DAPT

17 events occurred "Off" DAPT

►68/85 ST events (80.0%) occurred "On" DAPT

*One patient did not receive loading lose and was off DAPT at ST event (day 0) but started day 1 and never interrupted through 730 days.

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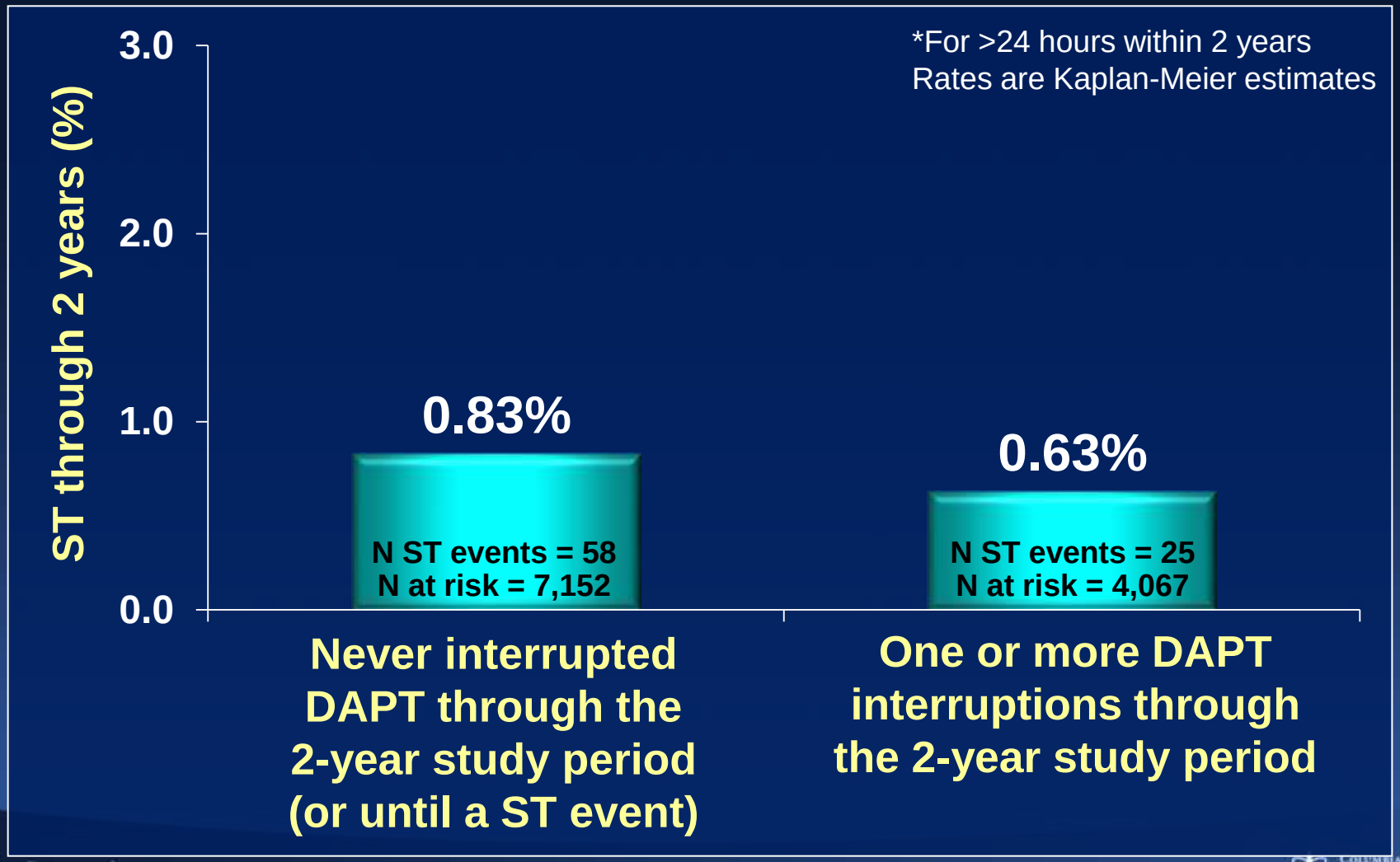
Timing of First DAPT Interruption

4,080/11,219 (36.4%) XIENCE V pts interrupted DAPT one or more times during the 2-year follow-up period

Timing of the first DAPT interruption	
Between 0-1 months:	520 (4.6%)
Between 1-3 months:	151 (1.4%)
Between 3-6 months:	301 (2.7%)
Between 6-12 months:	1,273 (11.4%)
Between 12-24 months:	1,835 (16.4%)

Stent Thrombosis in Patients With and Without DAPT Interruption* Through 2 Years

N = 11,219 Xience V pts



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Généreux P et al. Circ Cardiovasc Interv 2015

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Stent Thrombosis in Patients With and Without DAPT Interruption* Through 2 Years

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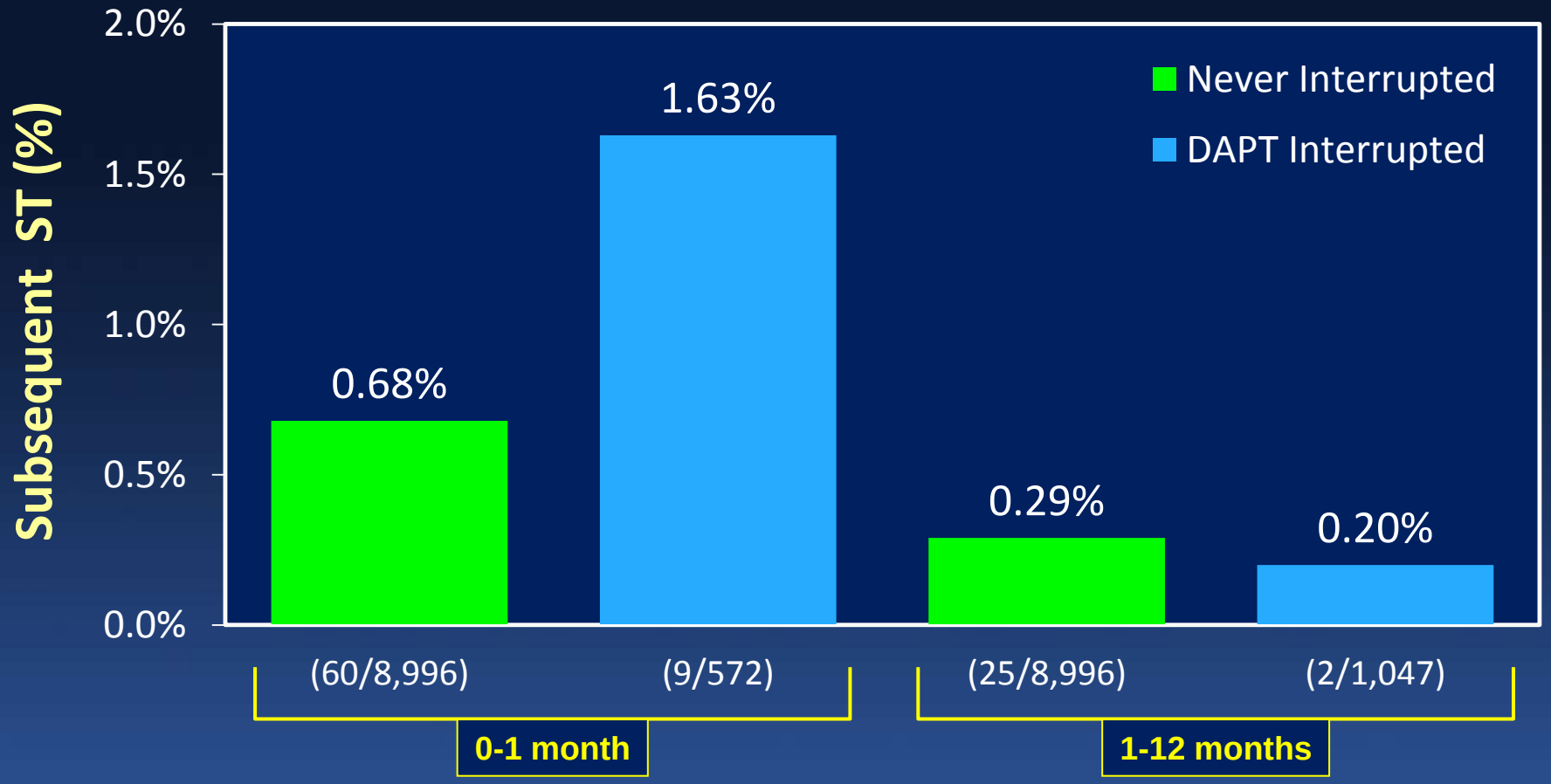

Timing of first DAPT interruption and stent thrombosis through 12 months

*For >24h within 2 yrs
Rates are KM estimates

Généreux P et al. Circ Cardiovasc Interv 2015

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Stent Thrombosis According to the Timing of Permanent DAPT Interruption*

Stent thrombosis through the entire 2-year follow-up period:	ST, % No DAPT interruption except possibly after ST	ST, % Permanent DAPT discontinuation in this interval*	HR [95% CI]	P Value
Between 0 and 1 mos	0.83% (58) (N at risk = 7,152)	4.95% (11) (N at risk = 229)	6.13 [3.22, 11.68]	<0.0001
Between 1 and 3 mos	0.83% (58) (N at risk = 7,152)	2.78% (2) (N at risk = 76)	3.38 [0.82, 13.82]	0.07
Between 3 and 6 mos	0.83% (58) (N at risk = 7,152)	0.78% (1) (N at risk = 146)	0.85 [0.12, 6.13]	0.87
Between 6 and 12 mos	0.83% (58) (N at risk = 7,152)	0.45% (4) (N at risk = 934)	0.52 [0.19, 1.43]	0.20
Between 12 and 24 mos	0.83% (58) (N at risk = 7,152)	0.16% (3) (N at risk = 1,925)	0.19 [0.06, 0.60]	0.002
Between 0 and 24 mos	0.83% (58) (N at risk = 7,152)	0.64% (21) (N at risk = 3,310)	0.77 [0.47, 1.27]	0.30

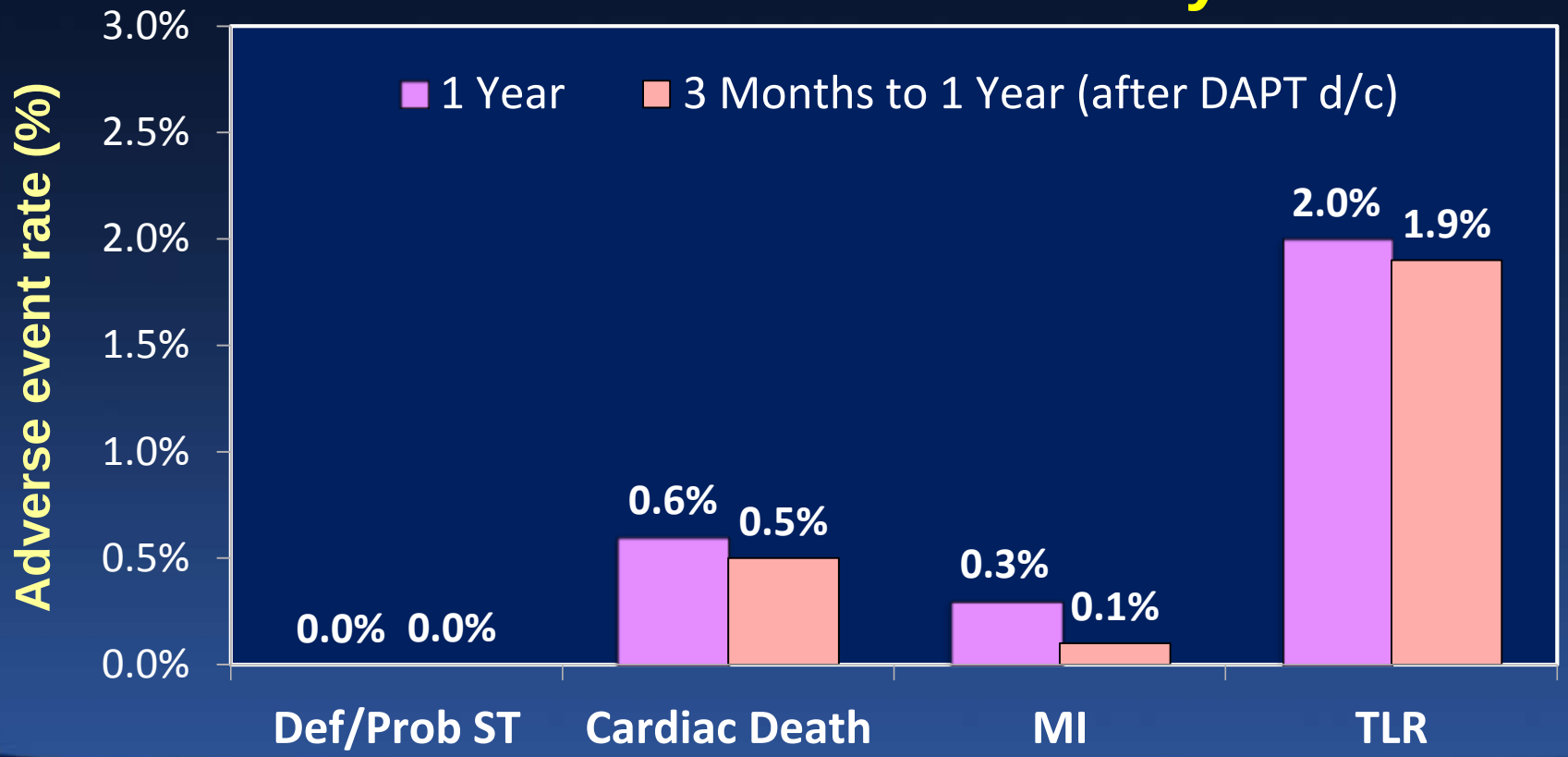
* Or until the time of a ST

STOPDAPT Study: 3-Month DAPT After XIENCE (n=1,525 at 58 Japanese sites)

39.6% diabetes, 31.6% ACS (13.3% STEMI), 1.4 stents/pt, 33 mm stent length

Thienopyridine was discontinued within 4 months in 1,444 pts (94.7%)

Event rates within 1 year



Natsuaki M et al. Cardiovasc Interv and Ther 2015

XIENCE 90: High-bleeding risk pts

2000 pts at ~100 US sites

High bleeding risk (one or more of the following):

- Age ≥ 75 years
- Chronic oral anticoagulation therapy
- History of major bleeding
- Thrombocytopenia or coagulation disorder
- Anemia
- History of stroke
- Chronic kidney disease

Key exclusion criteria: STEMI; LVEF <30%; LM; total occlusion; graft; ISR, thrombus containing lesion; judged by physician as inappropriate for discontinuation from P2Y12 inhibitor use at 3 months

1-year follow-up

Primary endpoint: All-cause death or MI between 3 and 12 months in pts who are event-free and compliant with DAPT at 3 months, powered for noninferiority against a propensity-adjusted historical control group treated with standard DAPT

XIENCE 28: High-bleeding risk pts

800 pts at ~50 EU and Asian sites

High bleeding risk (one or more of the following):

- Age ≥ 75 years
- Chronic oral anticoagulation therapy
- History of major bleeding
- Thrombocytopenia or coagulation disorder
- Anemia
- History of stroke
- Chronic kidney disease

Key exclusion criteria: STEMI; LVEF <30%; LM; total occlusion; graft; ISR, thrombus containing lesion; judged by physician as inappropriate for discontinuation from P2Y12 inhibitor use at 3 months

1-year follow-up

Primary endpoint: All-cause death, MI, ST, stroke or major bleeding between 1 and 6 months in pts who are event-free and compliant with DAPT at 1 month, powered for noninferiority against a propensity-adjusted historical control group Rx w/standard DAPT

Conclusions: Safety of Early DAPT Discontinuation After Xience Stent Implantation

- Fluoropolymer-coated EES have been associated with the lowest ST rates of all DES, and with lower ST than BMS
- Available data suggest that DAPT discontinuation in EES-treated pts is safe after 3 months
- Large-scale single-arm studies are ongoing to determine the safety of discontinuing DAPT after 90 days and 28 days in high-bleeding risk patients treated with Xience EES