Morning Roundtable Forum - Antithrombotic Therapy: Finding the "Sweet-Spot"

DAPT After BRS Implantation: The Longer the Better?

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Disclosure Statement of Financial Interest

Within the past 12 months, I, **Davide Capodanno**, have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial relationship	Company
• **Speakers' honoraria**	AstraZeneca, Daiichi Sankyo, Sanofi Aventis
• **Consulting**	Abbott Vascular (VHD branch)
• **Advisory Board**	AstraZeneca

Trials of DAPT Duration After PCI

15 studies, ~40,000 patients randomized

	Study	Journal	Patients	Hypothesis	Result
Trials of short DAPT	RESET	JACC 2012	N=2,117	3 months noninferior to 12 months	
	OPTIMIZE	JAMA 2013	N=2,199	3 months noninferior to 12 months	
	SECURITY	JACC 2016	N=1,399	6 months noninferior to 12 months (stopped)	
	ISAR SAFE	EHJ 2015	N=4,000	6 months noninferior to 12 months (stopped)	
	I-LOVE-IT 2	CIRC CV 2016	N=1,829	6 months noninferior to 12 months	
	OPTIMA-C	TCTAP 2015	N=1,368	6 months noninferior to 12 months	
	EXCELLENT	Circulation 2015	N=1,443	6 months noninferior to 12 months	
	IVUS XPL	JACC: CI 2016	N=1,400	6 months comparable to 12 months	
Trials of long DAPT	NIPPON	ESC 2016	N=2,772	6 months noninferior to 18 months (stopped)	
	ITALIC	JACC 2015	N=1,822	6 months noninferior to 24 months (stopped)	
	PRODIGY	Circulation 2012	N=1,970	24 months more effective than 6 months	
	ARCTIC	Lancet 2014	N=1,259	≥18 months more effective than 12 months	
	DAPT	NEJM 2014	N=9,961	30 months more effective than 12 months	
	DES LATE	Circulation 2014	N=5,045	36 months superior to 12 months	
	OPTIDUAL	EHJ 2015	N=1,385	48 months superior to 12 months (stopped)	

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Meta-analysis of DAPT Duration after DES

A Systematic Review for the 2016 ACC/AHA Guideline Focused Update on DAPT

	12 mo vs 3-6 mo (N=12,078 pts, 5 RCTs)
Mortality	1.17 (95% CI 0.85-1.63)
Myocardial infarction	0.87 (95% CI 0.65-1.18)
Stent thrombosis	0.87 (95% CI 0.49-1.55)
Major bleeding	1.65 (95% CI 0.97-2.82)

Bittl JA, et al. Circulation. 2016;134:156-78

Meta-analysis of DAPT Duration after DES

A Systematic Review for the 2016 ACC/AHA Guideline Focused Update on DAPT

	12 mo vs 3-6 mo (N=12,078 pts, 5 RCTs)	**18-48 mo vs 6-12 mo** (N=20,973 pts, 6 RCTs)
Mortality	1.17 (95% CI 0.85-1.63)	1.14 (95% CI 0.92-1.42)
Myocardial infarction	0.87 (95% CI 0.65-1.18)	0.67 (95% CI 0.47-0.95)
Stent thrombosis	0.87 (95% CI 0.49-1.55)	0.42 (95% CI 0.24-0.74)
Major bleeding	1.65 (95% CI 0.97-2.82)	1.58 (95% CI 1.20-2.09)

Bittl JA, et al. Circulation. 2016;134:156-78

DAPT Duration in Clinical Guidelines

Population	ACCF/AHA/SCAI 2016	ESC 2014
Acute Coronary Syndrome (BMS or DES)	At least 12 months (Class I-BR) Shorter (Class IIb-C-LD) or longer (Class IIb-A^{SR}) durations may be considered	Maximum of 12 months (Class I-A) Shorter or longer durations may be considered (Class IIb-A)
Stable Ischemia and BMS	At least 1 month (Class I-A) >1 month if no HBR (Class IIb-A)	At least 1 month (Class I-A)
Stable Ischemia and DES	At least 6 months (Class I-B-NR) >6 months if no HBR (Class IIb-A) HBR: 3 months (Class IIb-C-LD)	6 months (Class I-B)
Secondary Prevention	Prior MI (1-3 yrs), no HBR: May be reasonable (Class IIb-A)	Selected patients at high ischemic risk

Amsterdam EA, et al. 2014 AHA/ACC Guideline for Management of NSTE-ACS. JACC 2014;64:e139-228. Montalescot G, et al. 2013 ESC Guidelines on Management of Stable CAD. EHJ 2013;34:2949-3003. Levine GN, et al. 2011 ACCF/AHA/SCAI Guidelines for PCI. JACC 2011;58:e44-122. Smith SC Jr, et al. 2011 AHA/ACCF Secondary Prevention Guidelines. JACC 2011;58:2342-46. Levine GN, et al. 2016 ACC/AHA Guidelines for DAPT. JACC AOP. Roffi M, et al. 2015 ESC Guidelines for Management of ACS. EHJ 2015 (Online Aug 29, 2015). Windecker S, et al. 2014 ESC/EACTS Guidelines on Myocardial Revascularization. EHJ 2014;35:3541-619.

Current Landscape of CE-Marked BRS

ABSORB GT1

Bioresorbable vascular scaffold (BVS)

PLLA, everolimus-eluting

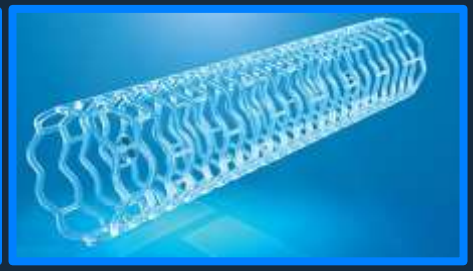
Strut thickness 150 μm, coat thickness 3 μm/side

Full mass loss at approximately 3 years

CE mark in October 2011

DESsolve

Bioresorbable coronary scaffold (BCS)



PLLA, novolimus-eluting

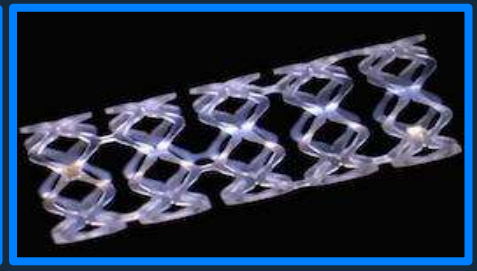
Strut thickness 150 μm, coat thickness <3 μm/side

Full mass loss at approximately 1 year

CE mark in May 2014

ART

Pure bioresorbable scaffold (PBS)



PDLLA, drug-free

Strut thickness 170 μm, uncoated

Full mass loss at approximately 1 year

CE mark in May 2015

Magmaris

Resorbable magnesium scaffold (BCS)

Mg, sirolimus-eluting

Strut thickness 150 μm, coat thickness 8 μm/side

Full mass loss at approximately 1 year

CE mark in June 2016

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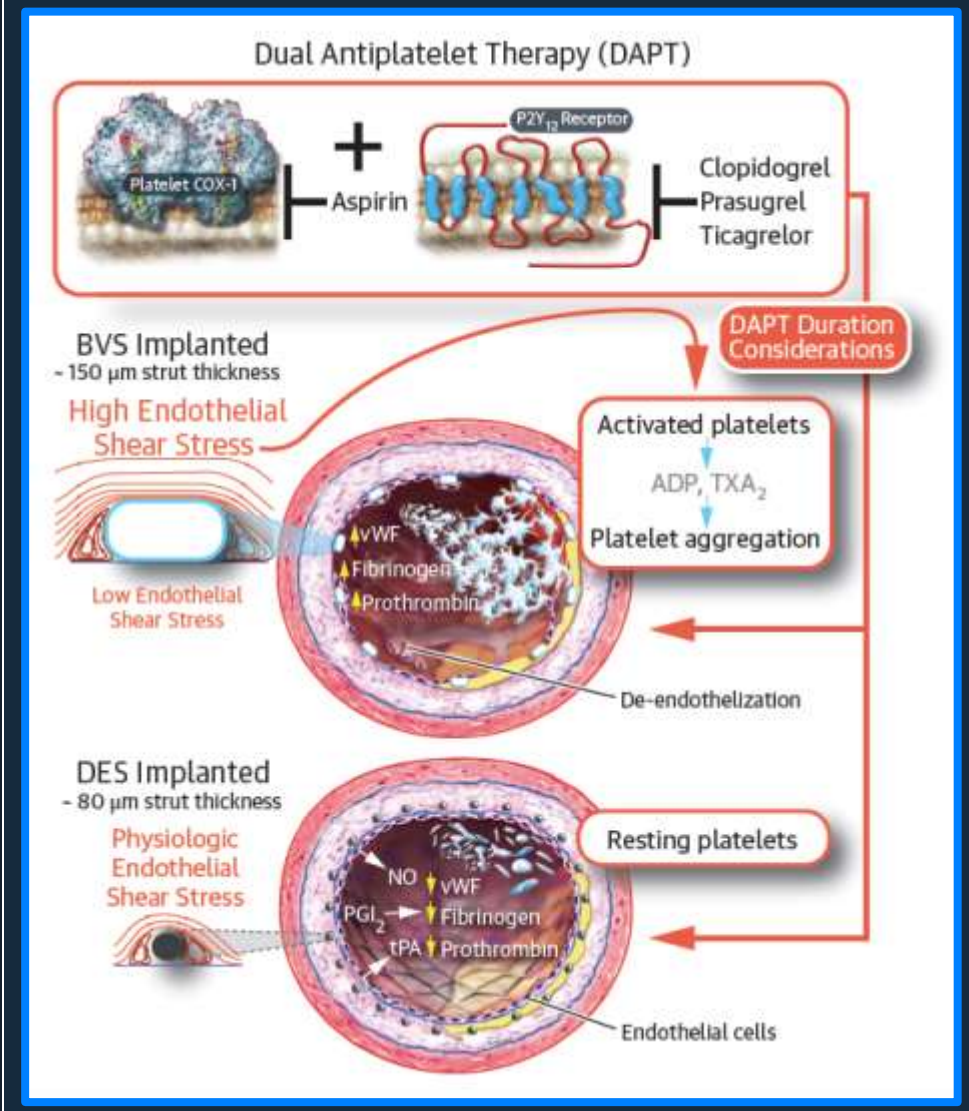
Strut Thickness and Thrombogenicity



Bioresorbable scaffolds

① Thick, rectangular struts

② High endothelial shear stress (ESS) on top of struts

③ Recirculation zones with low ESS downstream of the strut

④ Platelet activation

Everolimus-eluting stents

① Thin, circular struts

② Physiologic ESS

③ Platelet quiescence on top of struts

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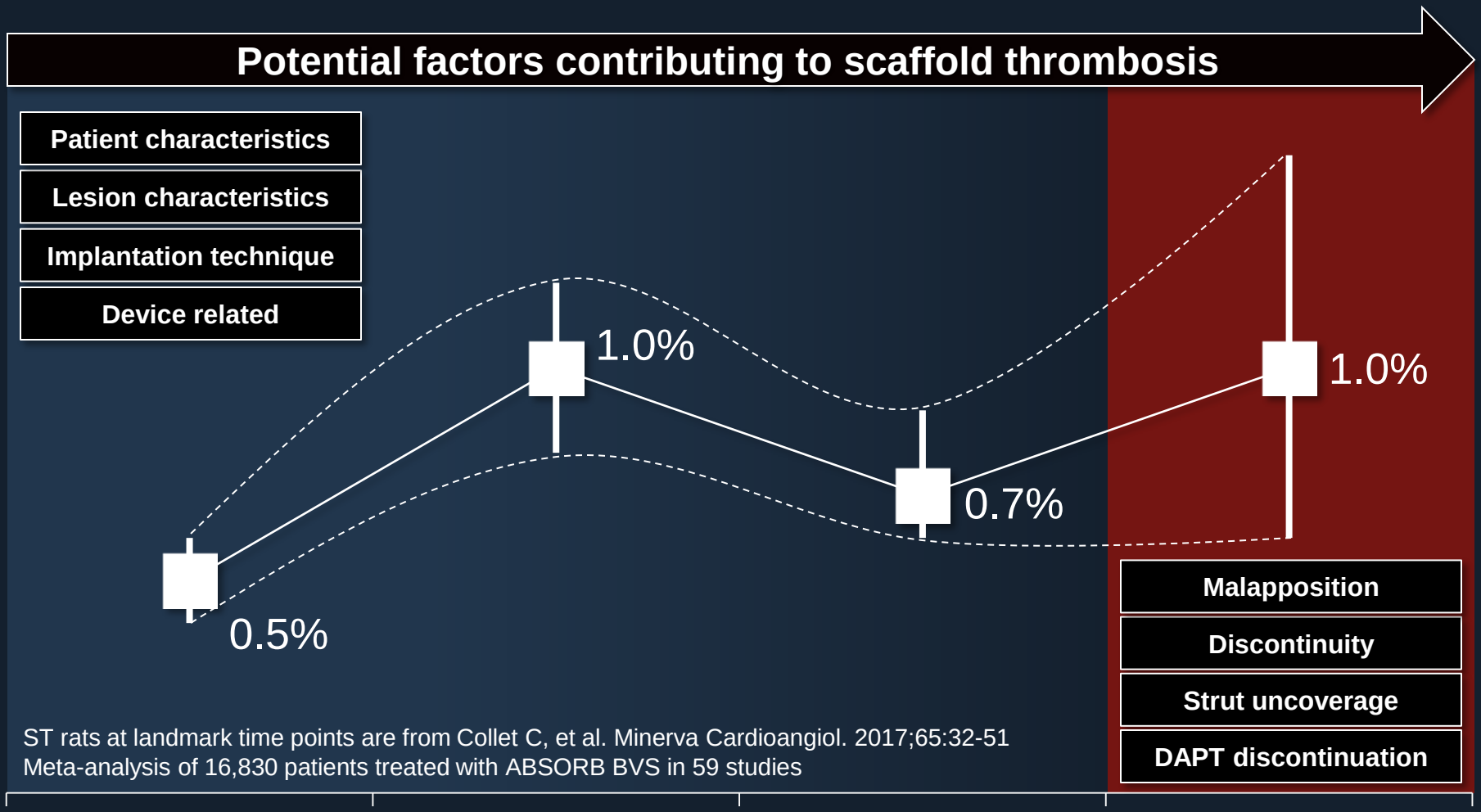
Capodanno D, Angiolillo DJ. J Am Coll Cardiol Intv 2017;10:425–37

BVS Thrombosis at Landmark Time Points



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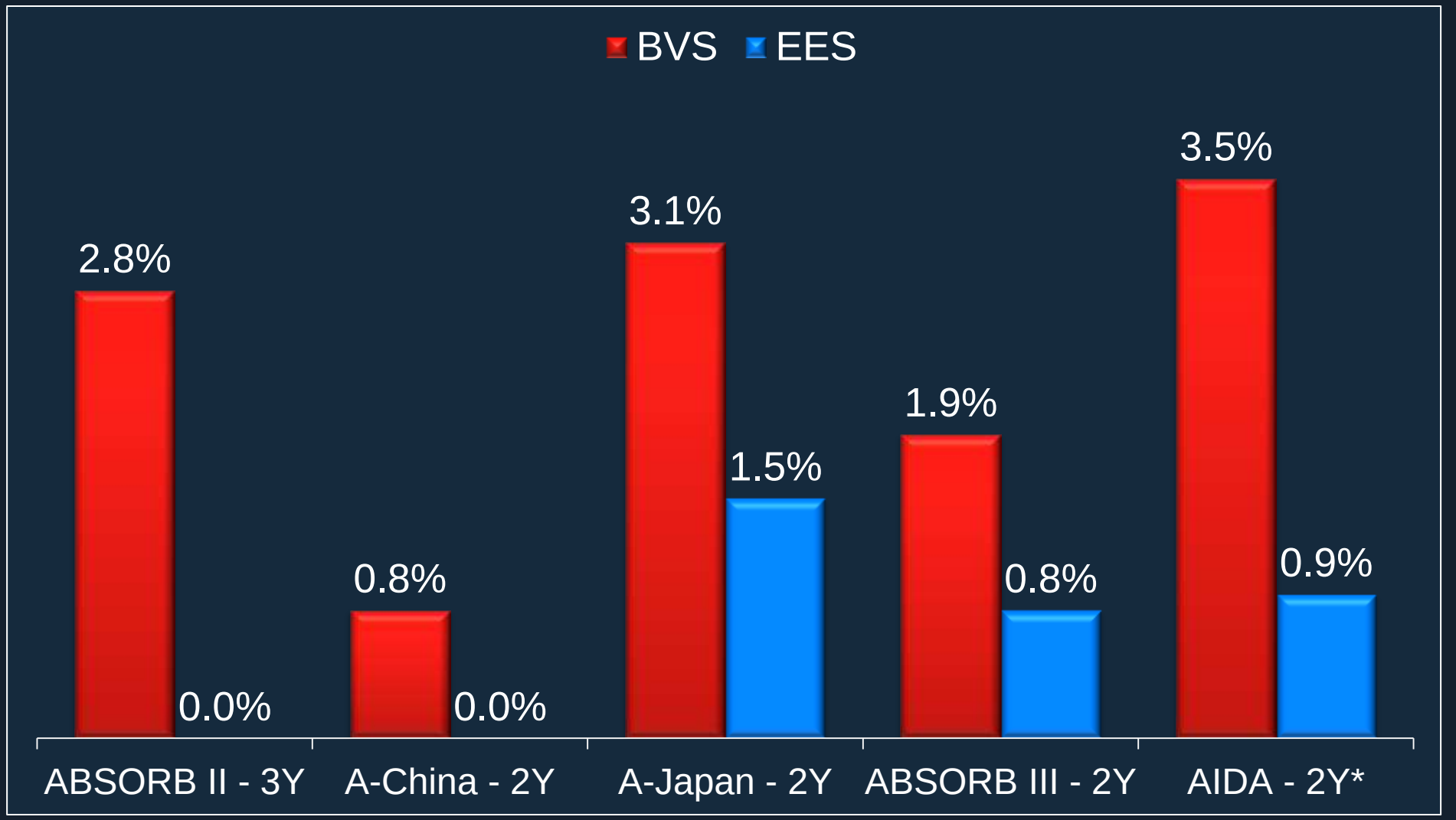
BVS vs. EES Thrombosis (Absolute Risks)

Definite or probable thrombosis from 0 to 2-3 yrs in ABSORB RCTs



*Follow up of AIDA is incomplete (median 707 days)

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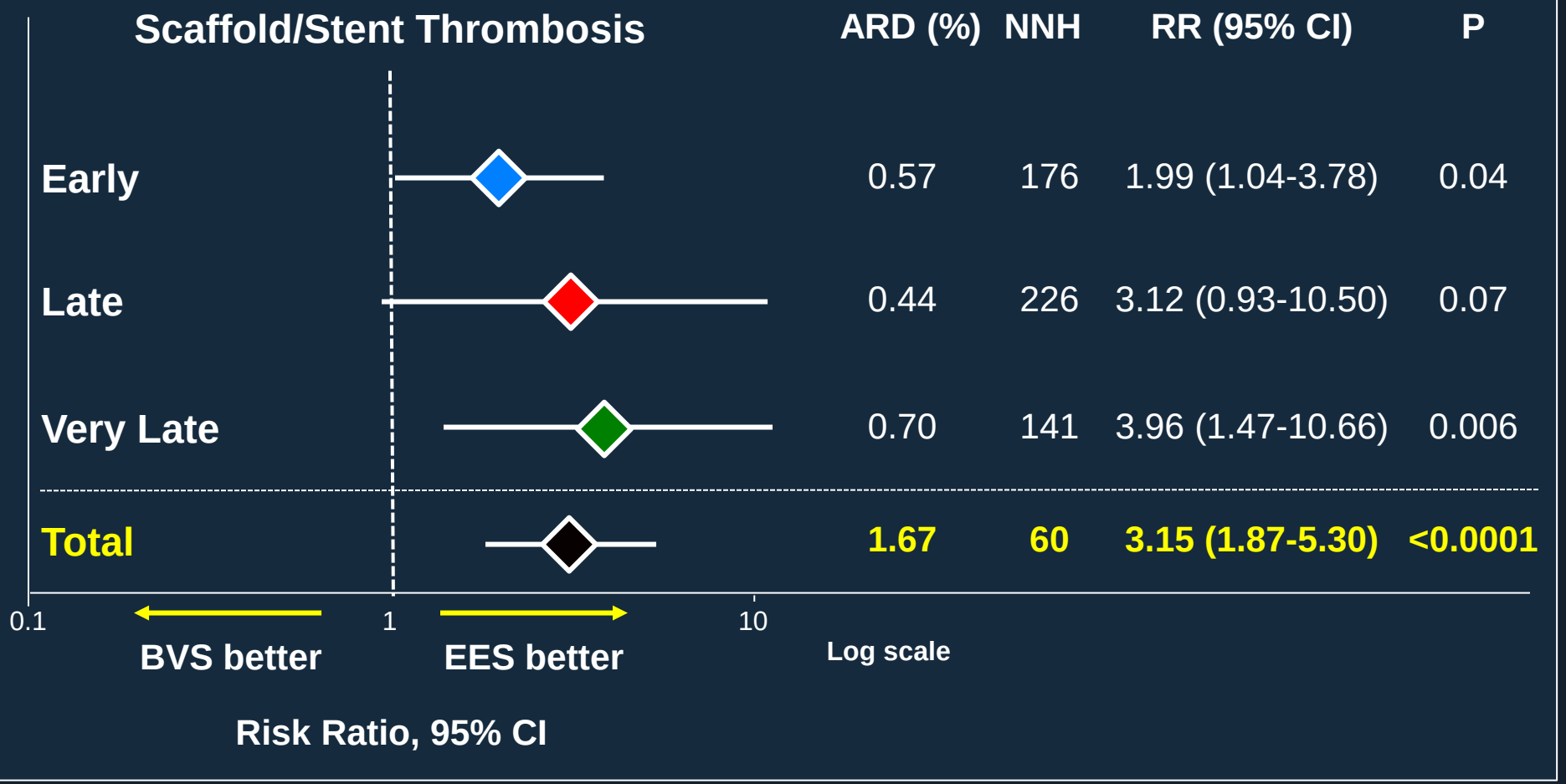
BVS vs. EES Thrombosis (Relative Risk)

Meta-analysis of 5,584 patients from 7 RCTs (ABSORB II, ABSORB China, ABSORB Japan, ABSORB III, EVERBIO II, TROFI II, AIDA)



Sorrentino S, et al. J Am Coll Cardiol 2017 [ePub ahead of print]

Putative Causes of Scaffold Thrombosis

Patient-related factors		Smoking	DAPT discontinuation
		Diabetes mellitus	Resistance to antiplatelets
		Renal failure	Thrombocytosis
		Poor ventricular function	Malignancy
		Acute coronary syndrome	Surgical procedures
Lesion-related factors		Diffuse disease	Saphenous vein graft
		Small vessel disease	Thrombus containing lesion
		Bifurcation lesion	Inflow or outflow tandem lesions
		Chronic total occlusion	Ostial lesions
Operator-related factors		Inadequate expansion or sizing	Deployment in necrotic core
		Incomplete apposition	Residual edge dissection
Device-related factors		Hypersensitivity or inflammation	Late-acquired malapposition
		Delayed or incomplete healing	Intraluminal dismantling
		Thick-strut design	Neoatherosclerosis

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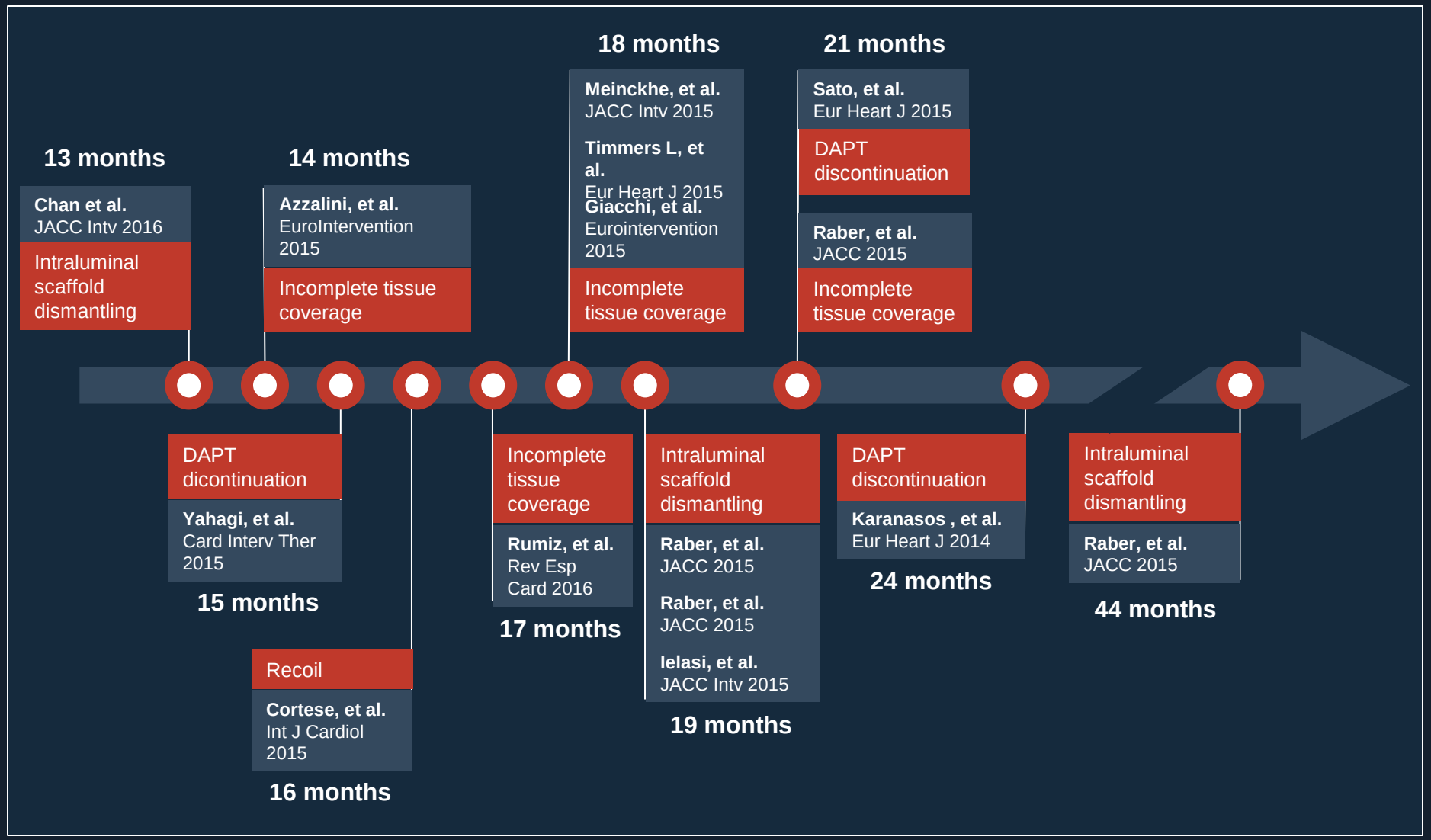
Capodanno D, et al. EuroIntervention. 2015;11 Suppl V:V181-4

Causes of Very Late Scaffold Thrombosis



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Mechanisms Associated with LST and VLST and their Relation to Implantation Technique

Correctable	Uncertain	Not correctable
Malapposition	Late discontinuity	Peri-strut low intensity area
Incomplete lesion coverage	Late recoil	Neoatherosclerosis
Underexpansion	Restenosis	
Acute disruption		
Overlap		
Acute recoil		
Uncovered struts		
Bifurcation		

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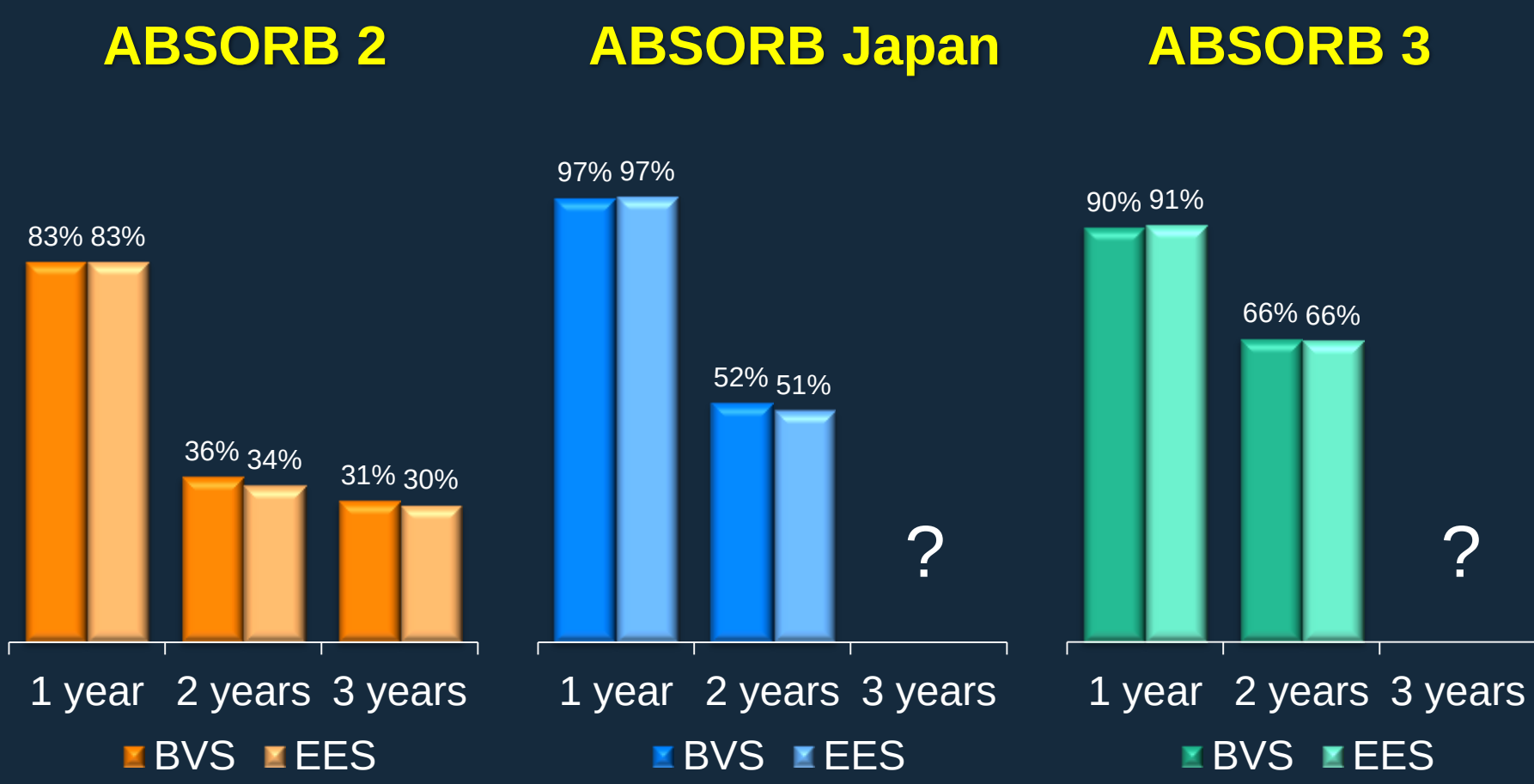
Yamaji K, et al. EuroIntervention 2017;12:1684-1687

DAPT Status in Landmark BVS Trials



Serruys PW, et al. Lancet. 2016;388:2479-2491
Onuma Y, et al. EuroIntervention. 2016;12:1090-1101
Ellis SG, et al. ACC 2017. Washington DC

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Independent Correlates of 0-12 Month Scaffold Thrombosis

105 ST cases matched with 210 controls from 14 high-quality RCTs or registries

	Odds ratio	P value
Model 1		
Off DAPT	3.47	**0.006**
No Post Dilatation ≥1.1	2.29	**0.022**
RVD <2.40	2.12	**0.036**
Model 2		
MLD <1.85 mm	3.07	**0.004**
Off DAPT	2.49	0.053

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Ellis SG. ACC 2017, Washington DC

DAPT Status in VLST And No VLST Cases from ABSORB II

	No VLST	VLST
DAPT at 3 years without discontinuation	63	0
DAPT at 3 years with discontinuation	266	**6**

p = 0.599

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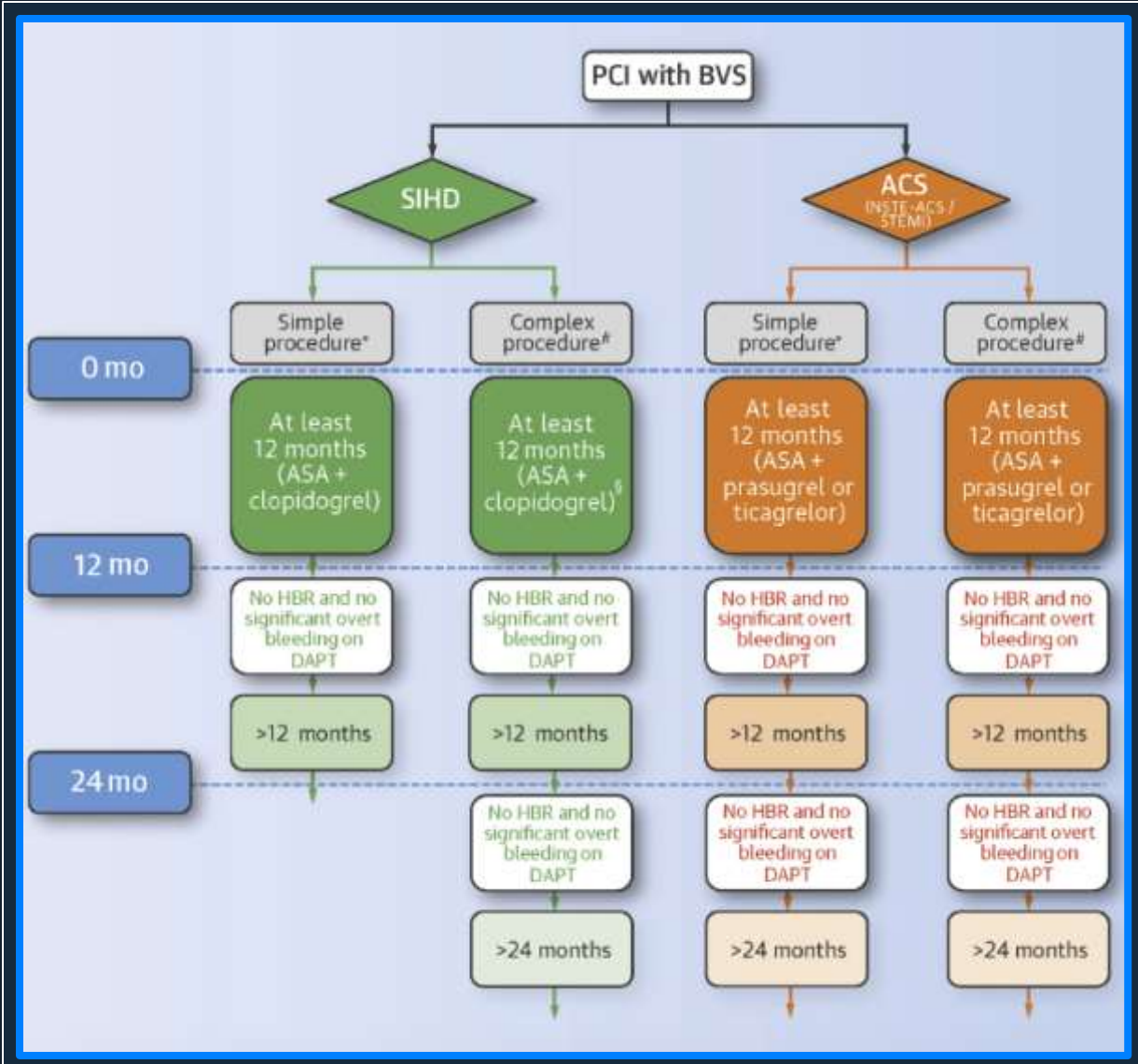
Serruys PW, et al. Lancet. 2016;388:2479-2491

DAPT duration After BVS Implantation



* Simple procedures include 1 BVS implanted in ACC/AHA A/B_1 lesions.

Complex procedures include 1 BVS implanted in ACC/AHA B_2/C lesions, >1 BVS implanted on lesions of any ACC/AHA type, or any other unfavorable clinical, angiographic and procedural characteristics.

§ Considerations on the use of aspirin in combination with prasugrel or ticagrelor for the initial 30 days, followed by switch to aspirin and clopidogrel, may prevail based on the individual risks of ischemia and bleeding.

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Risk Scores for DAPT Duration

Score	Number of variables	Development cohort (patients, design)	Setting	Predicted outcome(s)	Validation cohort(s) (patients, c-statistic)
DAPT	5 clinical, 3 procedural	N=11,648, multicentre randomized clinical trial	PCI patients on DAPT who were event-free for 12 months	Ischemia and bleeding between 12 and 30 months after PCI	N=8,136, 0.64 for both ischemia and bleeding
PARIS	Coronary thrombosis risk score: 6 clinical Major bleeding risk score: 6 clinical	N=4,190 patients, multicentre registry	PCI patients on DAPT	Ischemia and bleeding at 24 months after PCI	N=8,665, 0.65 for ischemia and 0.64 for bleeding
PRECISE-DAPT	5 clinical	N=14,963, pooled analysis of randomized clinical trials	PCI patients on DAPT	Bleeding at 12 months after PCI	N=8,595, 0.70 N=6,172, 0.66

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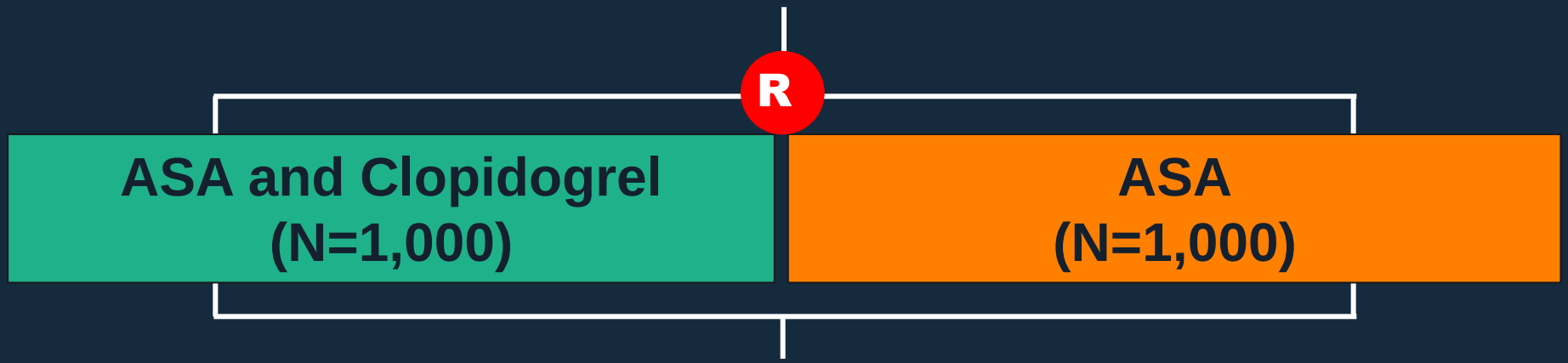
Capodanno D, Angiolillo DJ. Lancet. 2017;389:987-989

BVS LATE - Study design

2,000 pts at 12-18 months from BVS implantation

No history of death, serious MI, stroke, repeat revascularization, or major bleeding

Randomize 1:1



1-year follow-up (Expected Q1 2020)

Primary endpoint: Death, MI, or stroke

Secondary endpoints: Death, MI, Stroke, TVR, TLR, ST, Bleeding

NCT02939872

Closing Remarks

① Strut thickness and thrombosis of current-generation BRS approximate those of first-generation DES. Therefore, the guideline recommended approach to 6-mo DAPT after second-generation DES does not apply to BRS.

② BVS promise to cancel long-term device thrombosis but the rate of this complication is still ~1% between 1 and 2 years and 4-fold increased compared with EES, generally as a consequence of regional suboptimal flow conditions and delayed healing in some patients.

③ As such, DAPT should be empirically maintained long-term after implantation of first-generation BVS, with an option to prolong up to 24 months and beyond in selected patients and lesions if no bleeding issues arise in the meanwhile.

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