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Rethinking DAPT Duration with Smarter DES: Personalized vs. Generalized Strategy

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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, Abbott Vascular, Bayer, Sanofi Aventis
Consulting	Abbott Vascular, Bayer
Advisory Board	Abbott Vascular, AstraZeneca, Bayer

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What Makes a Smart DES a Better DES?

Thinning the struts

BIOFLOW V RCT
(N=1,334)
BP O-SES vs. DP-EES
1-Y TLF 5.9% vs 9.2%
P=0.03

Yes

Bioabsorption of the polymer

EVOLVE II
(N=1,684)
BP-EES vs. Pt-Cr EES
4-Y ST 0.4% vs 0.9%
P=0.19

Maybe

Elimination of the polymer

LEADERS-FREE
(N=2,432)
DCS vs. BMS
1-Y MACE 9.4% vs 12.9%
P=0.005

Sometimes

Elimination of the stent

ABSORB III
(N=2,008)
BRS vs. EES
3-Y TLF 13.4% vs 10.4%
P=0.06

Not Yet

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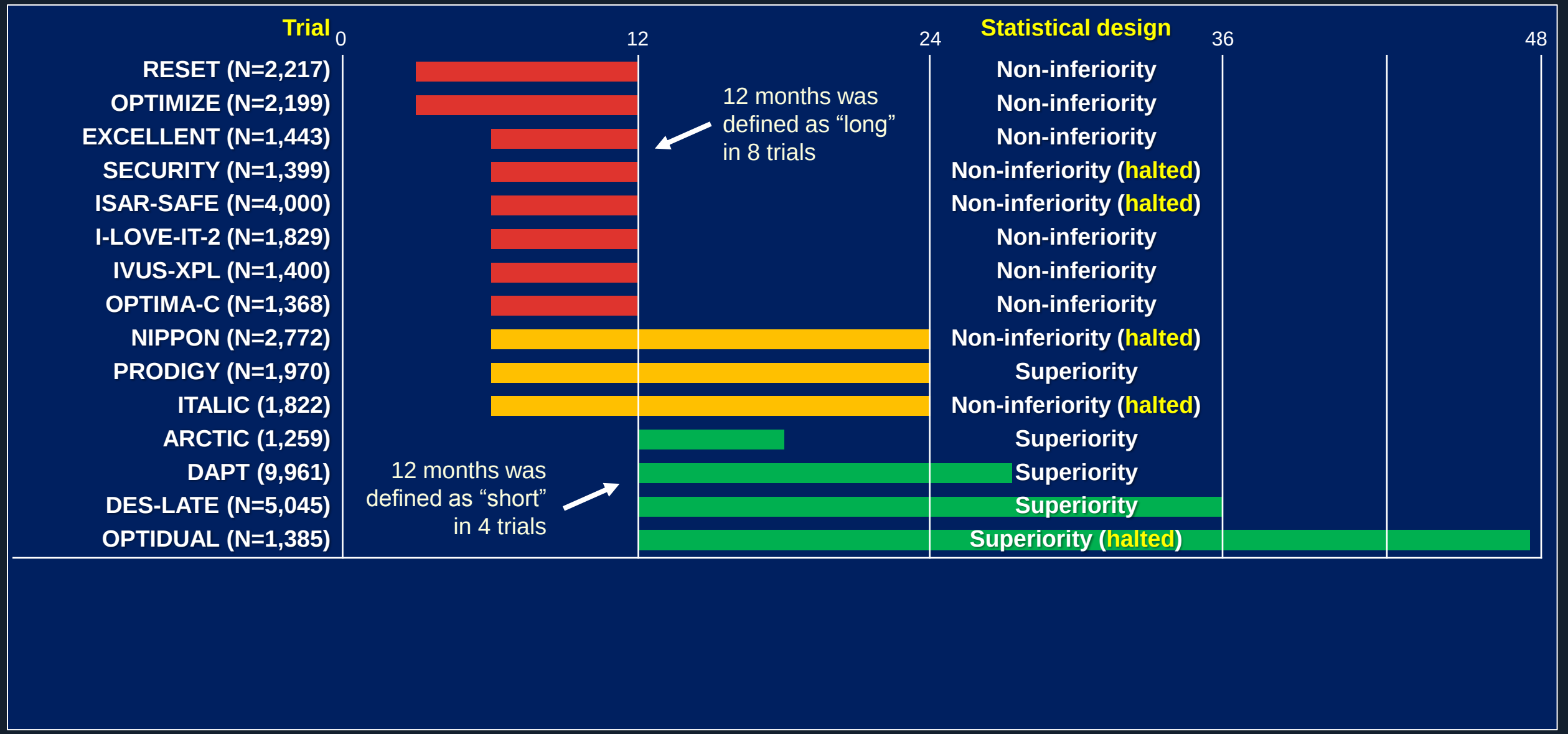
Kandzari DE, et al. Lancet. 2017;390:1843-1852; Lee Jobe R. ACC 2018
Urban P, et al. N Engl J Med. 2015;373:2038-47; Kereiakes D, et al. J Am Coll Cardiol. 2017;70:2852-2862

DAPT Duration: 15 PCI Trials, ~40,000 pts Randomized



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Bittl JA, et al. Eurointervention 2018;13:1864-1868

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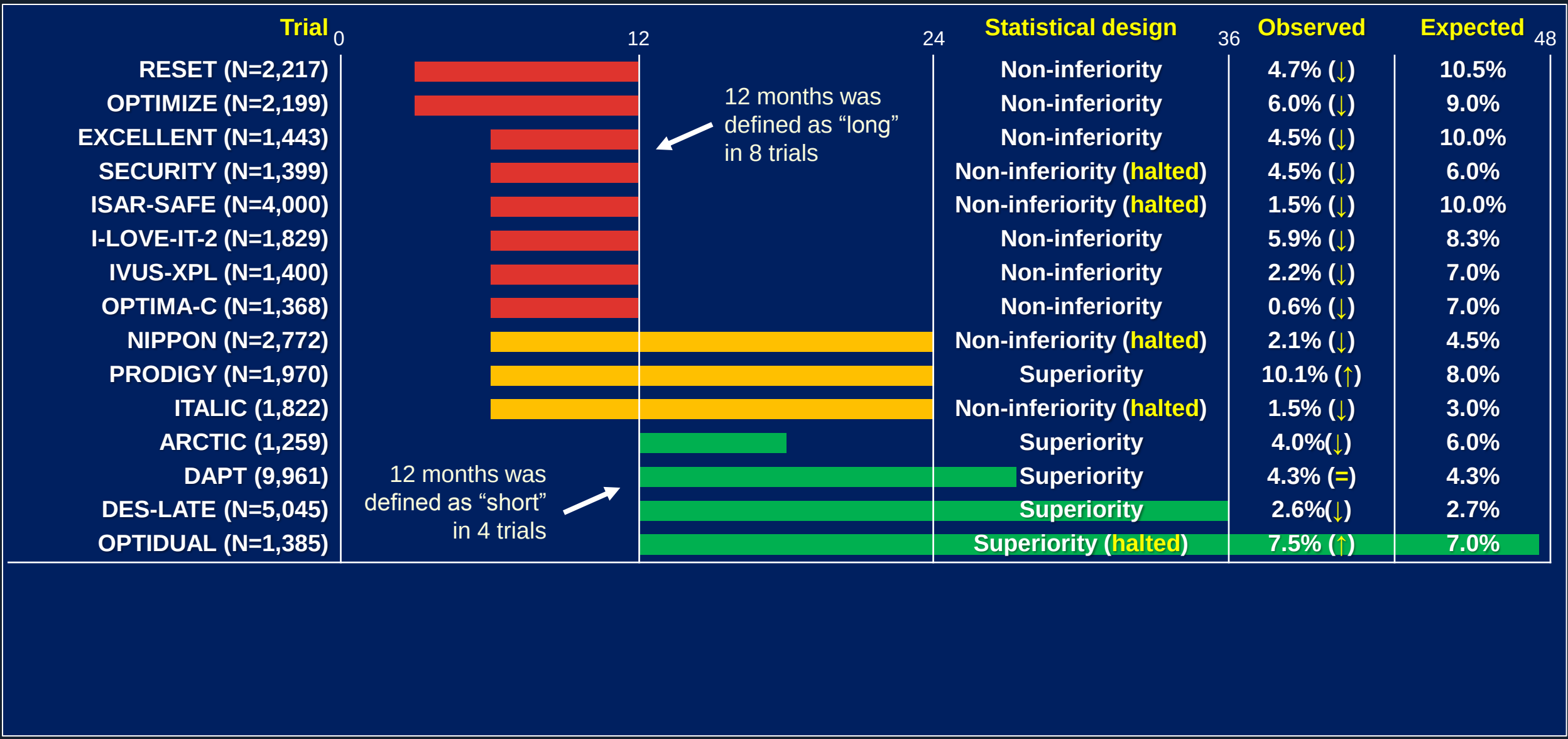

Trial	Statistical design	Observed	Expected
RESET (N=2,217)	Non-inferiority	4.7% (↓)	10.5%
OPTIMIZE (N=2,199)	Non-inferiority	6.0% (↓)	9.0%
EXCELLENT (N=1,443)	Non-inferiority	4.5% (↓)	10.0%
SECURITY (N=1,399)	Non-inferiority (halted)	4.5% (↓)	6.0%
ISAR-SAFE (N=4,000)	Non-inferiority (halted)	1.5% (↓)	10.0%
I-LOVE-IT-2 (N=1,829)	Non-inferiority	5.9% (↓)	8.3%
IVUS-XPL (N=1,400)	Non-inferiority	2.2% (↓)	7.0%
OPTIMA-C (N=1,368)	Non-inferiority	0.6% (↓)	7.0%
NIPPON (N=2,772)	Non-inferiority (halted)	2.1% (↓)	4.5%
PRODIGY (N=1,970)	Superiority	10.1% (↑)	8.0%
ITALIC (1,822)	Non-inferiority (halted)	1.5% (↓)	3.0%
ARCTIC (1,259)	Superiority	4.0%(↓)	6.0%
DAPT (9,961)	Superiority	4.3% (=)	4.3%
DES-LATE (N=5,045)	Superiority	2.6%(↓)	2.7%
OPTIDUAL (N=1,385)	Superiority (halted)	7.5% (↑)	7.0%

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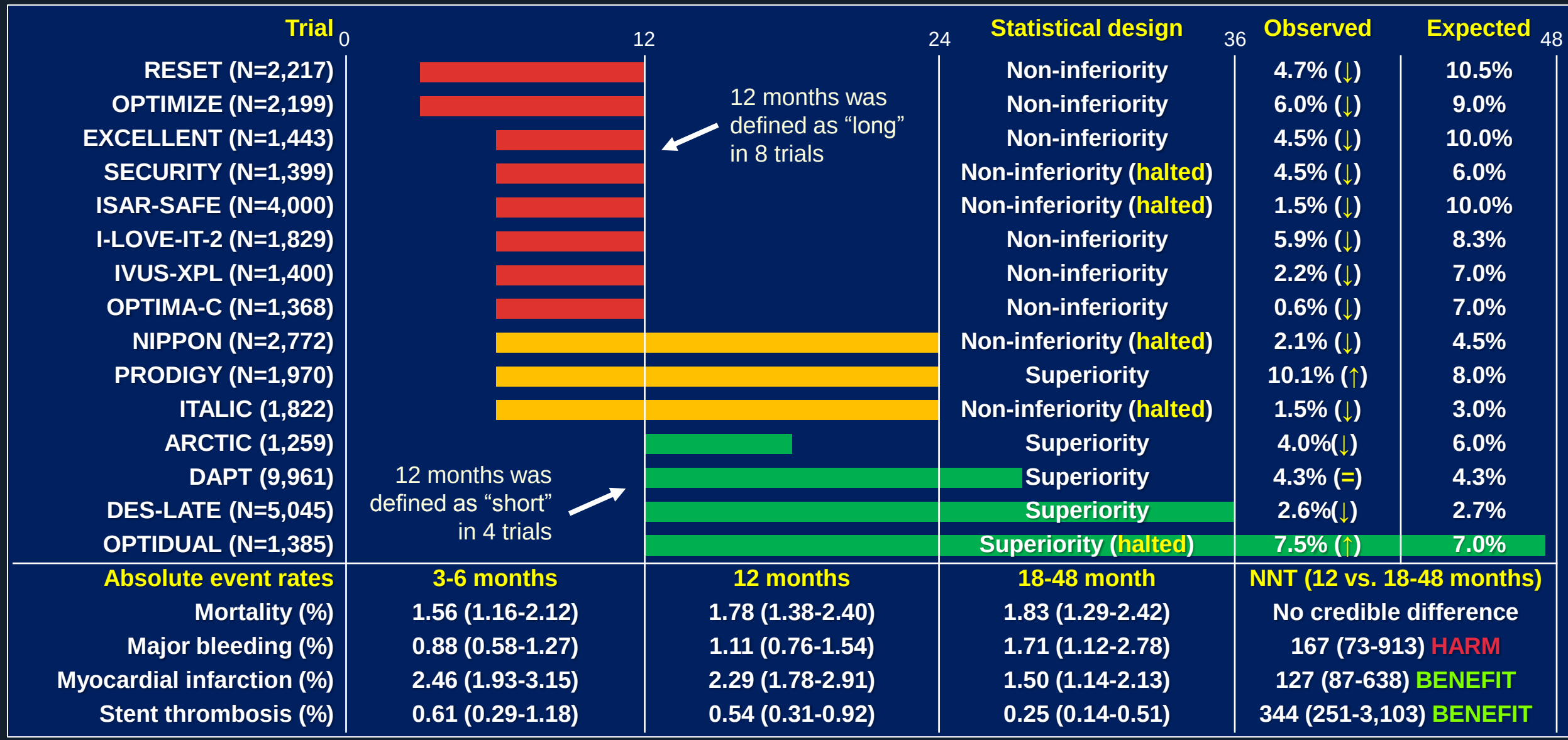

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Absolute event rates	3-6 months	12 months	18-48 month	NNT (12 vs. 18-48 months)
Mortality (%)	1.56 (1.16-2.12)	1.78 (1.38-2.40)	1.83 (1.29-2.42)	No credible difference
Major bleeding (%)	0.88 (0.58-1.27)	1.11 (0.76-1.54)	1.71 (1.12-2.78)	167 (73-913) HARM
Myocardial infarction (%)	2.46 (1.93-3.15)	2.29 (1.78-2.91)	1.50 (1.14-2.13)	127 (87-638) BENEFIT
Stent thrombosis (%)	0.61 (0.29-1.18)	0.54 (0.31-0.92)	0.25 (0.14-0.51)	344 (251-3,103) BENEFIT

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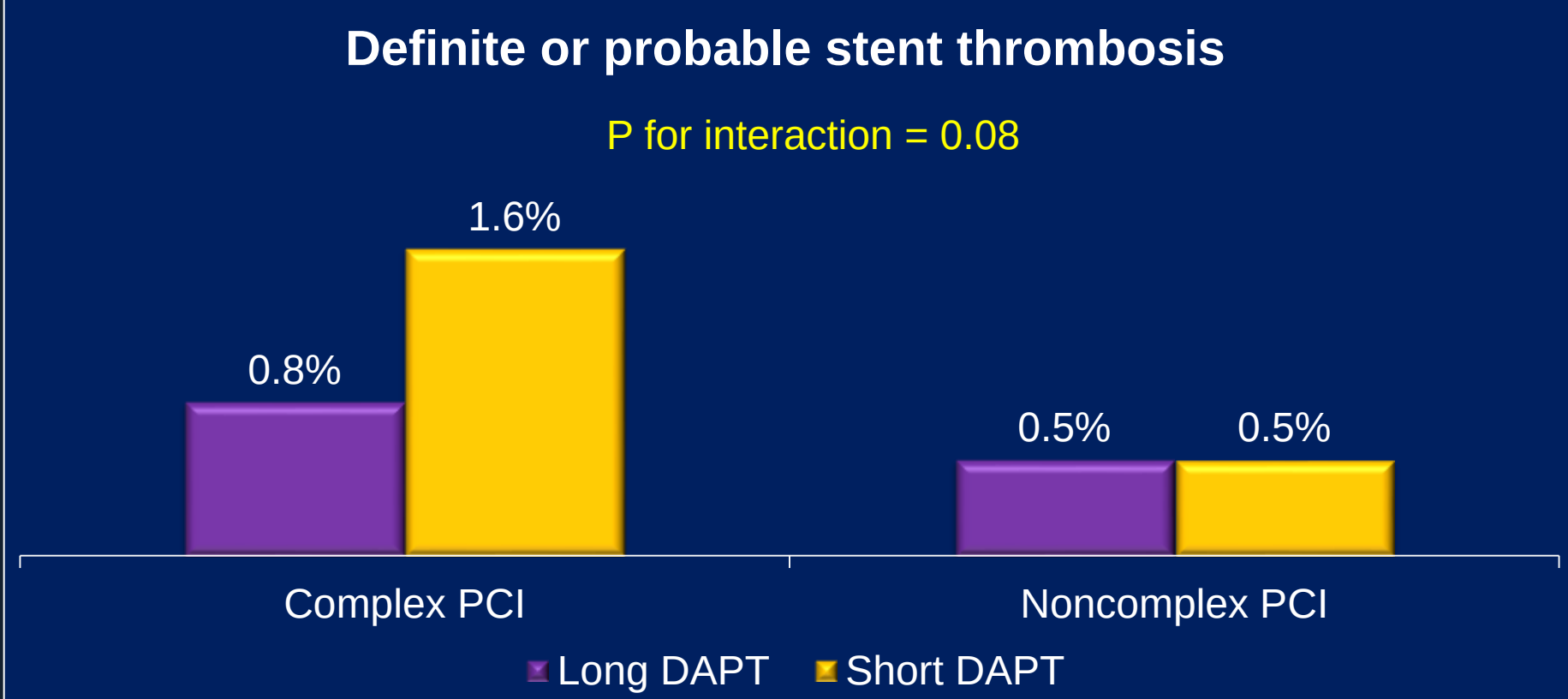
Bittl JA, et al. Eurointervention 2018;13:1864-1868

Short vs. Long DAPT By PCI Complexity

Patient-level meta-analysis of 9,577 patients from 6 trials of DAPT duration after PCI (SECURITY, OPTIMIZE, ITALIC, EXCELLENT, RESET and PRODIGY)



63% ↓ ST with longer DAPT in complex PCI (p_{int}=0.08)

81% ↑ Bleeding with longer DAPT in complex PCI (p=0.96)

Complex PCI was defined as having at least 1 of the following features: 3 vessels treated, ≥3 stents implanted, ≥3 lesions treated, bifurcation with 2 stents implanted, total stent length >60 mm, or chronic total occlusion

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Giustino G, et al. J Am Coll Cardiol. 2016;68:1851-1864

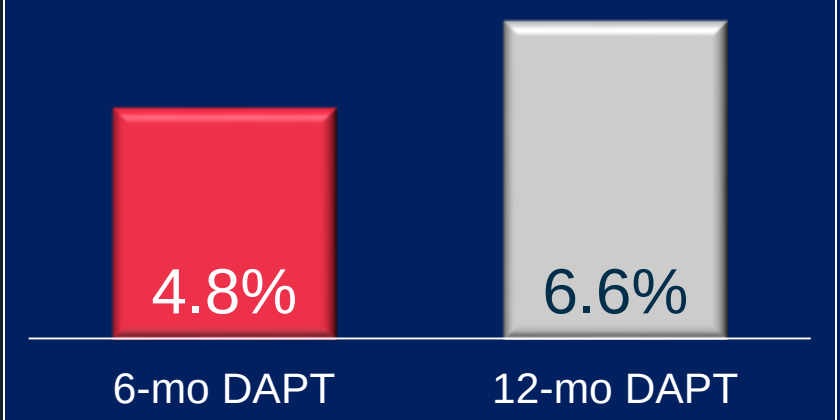
DAPT Duration: 3 ACS Trials, ~5,000 pts Randomized

DAPT STEMI

870 STEMI patients with uneventful 6-mo DAPT

Death, MI, Revascularization, Stroke and Major Bleeding at 18 months

P for noninferiority = 0.004
P for superiority = 0.26

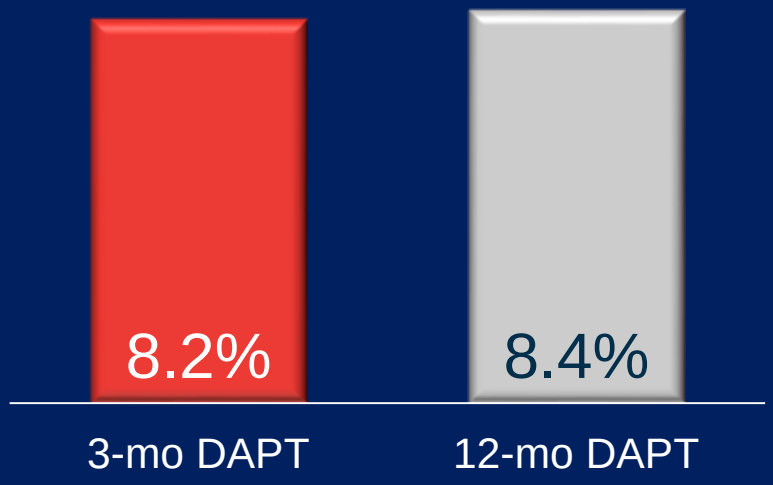


REDUCE

1,496 patients with ACS undergoing PCI

Death, MI, ST, stroke, TVR or BARC 2-5 bleeding at 12 months

P for noninferiority<0.001

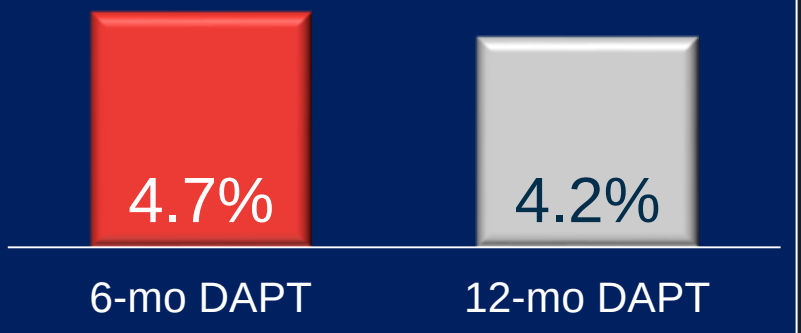


SMART-DATE NEW!

2,719 patients with ACS undergoing PCI

Death, MI, CVA at 18 months

P for noninferiority = 0.027
P for superiority = 0.51



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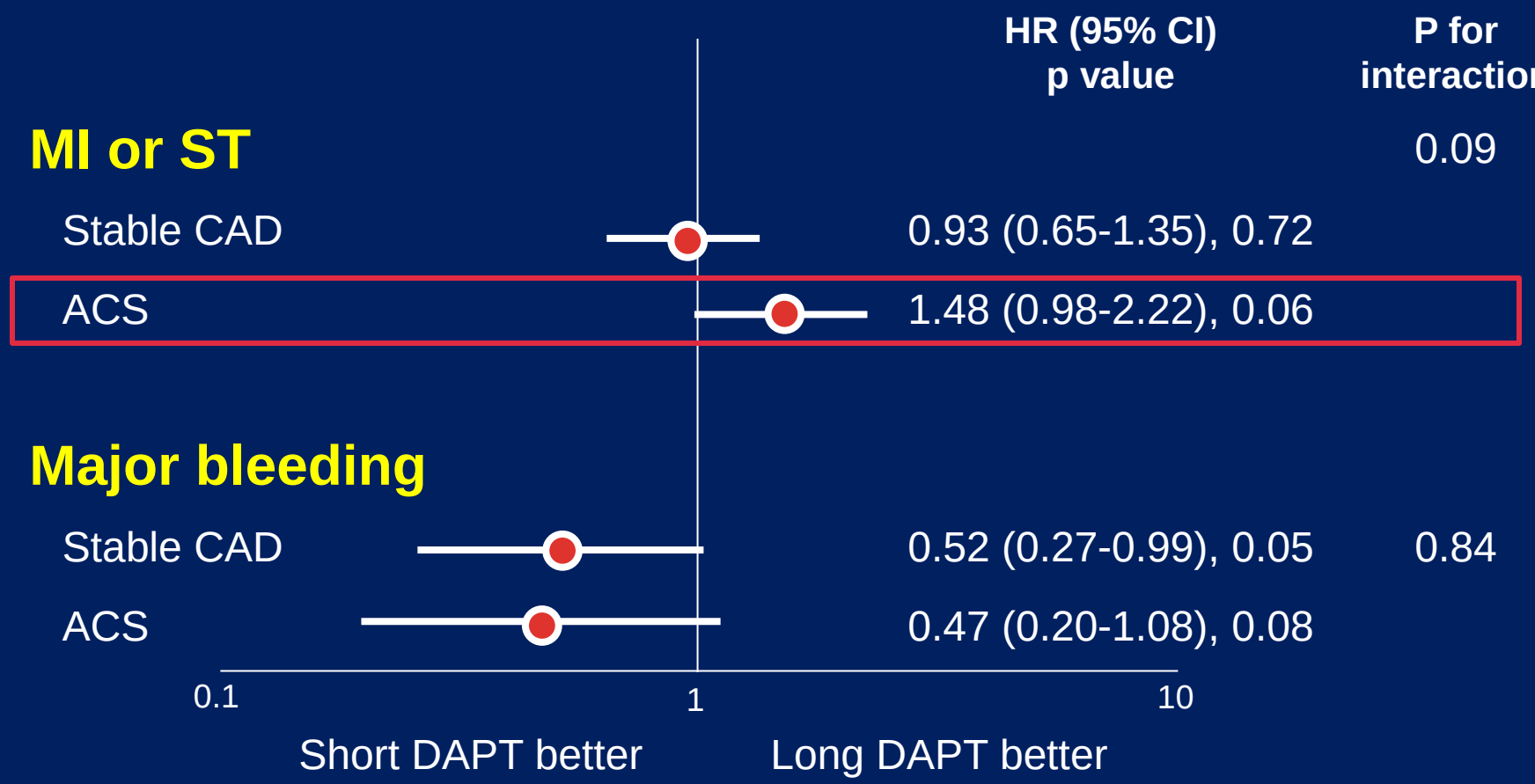
Kedhi E, presented at TCT 2017, Denver; Suryapranata H, presented at TCT 2017, Denver
Hahn JY et al. Lancet. 2018;391:1274-1284

Short vs. Long DAPT By ACS Status

Patient-level meta-analysis of 11,473 patients with stable CAD or low-risk ACS from 6 randomized clinical trials comparing 3-6 months DAPT vs. ≥1-year DAPT



48% ↑ MI or ST with shortened DAPT in ACS (*p*=0.06)

53% ↓ Bleeding with shortened DAPT in ACS (*p*=0.08)

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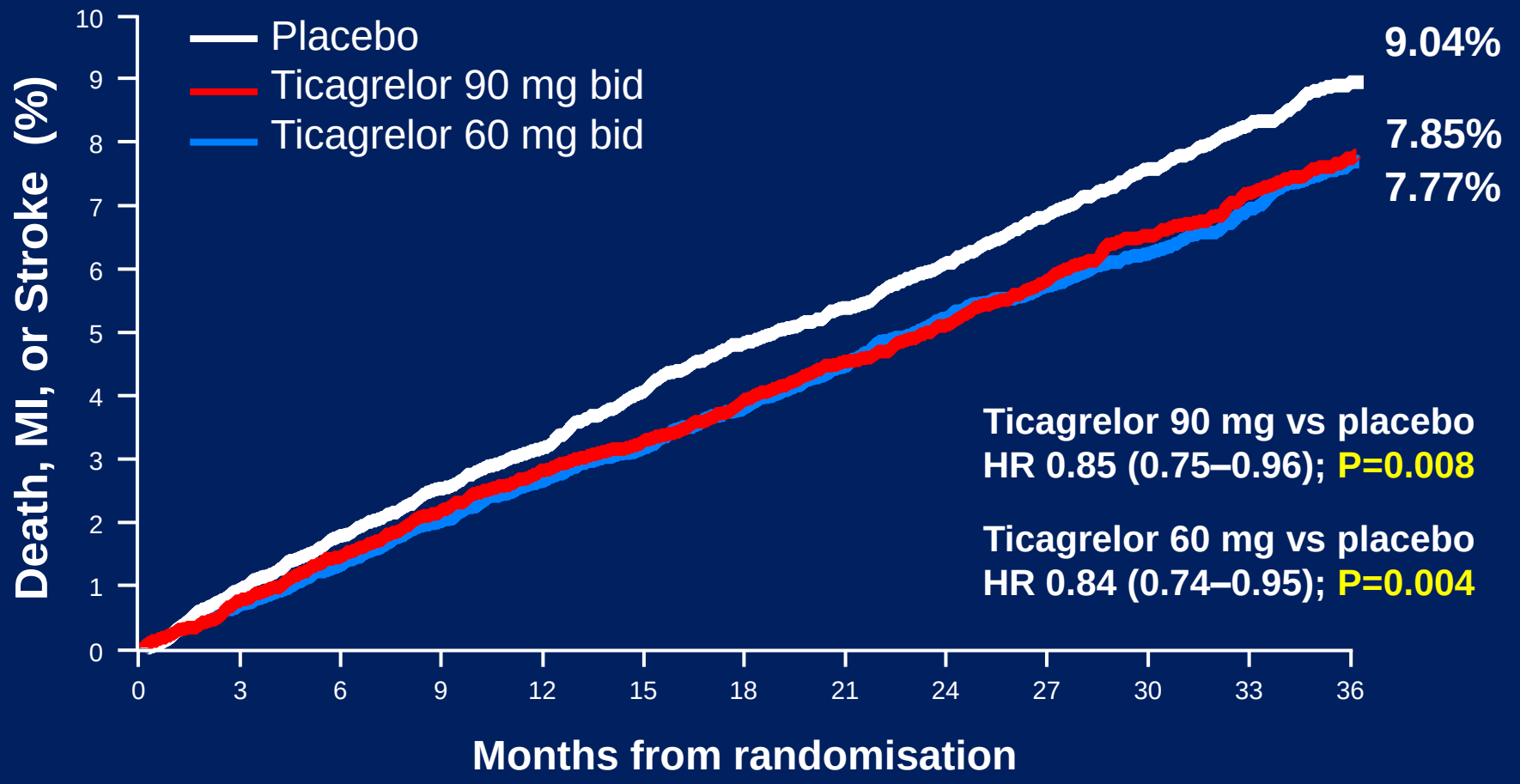
Palmerini T, et al. Eur Heart J. 2017;38:1034-1043

Extended DAPT in Patients with Prior MI

PEGASUS TIMI 54: 21,162 pts with MI 1-3 years prior + ≥1 high-risk factor treated with aspirin and randomized to ticagrelor 60 mg qd, ticagrelor 90 mg qd, or placebo



16% ↓ D/MI/Stroke with prolonged DAPT in prior MI (*p*=0.004)

132% ↑ Bleeding with prolonged DAPT in prior MI (*p*<0.001)

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Bonaca MP, et al. N Engl J Med 2015;372:1791-800

DAPT Duration: Factors to Be Weighed

PCI with DES

High bleeding risk	Low ischemic risk	Interm. ischemic risk	High ischemic risk
▸ Clinically significant bleeding on DAPT ▸ Bleeding diathesis ▸ Prior bleeding ▸ Female gender ▸ Elderly ▸ Liver disease ▸ Chronic renal dysfunction ▸ Anemia or thrombocytopenia ▸ Chronic anticoagulation therapy ▸ Diabetes ▸ Second generation DES	▸ Stable CAD ▸ Troponin negative ACS ▸ Single vessel disease ▸ Simple stenting (single, short, large stent)	▸ Troponin positive ACS	▸ High-risk ACS ▸ Recurrent ischemic events on DAPT ▸ Peripheral vascular disease ▸ Prior MI ▸ Diabetes ▸ Chronic renal dysfunction ▸ Complex/multivessel CAD ▸ Stent related factors (multiple stents, overlapping stents, long stents, small-sized stents, double stents in bifurcations) ▸ First-generation DES or BRS
Favors 3 or 6-month DAPT		**Favors 1-year DAPT**	**Favors >1-year DAPT**

When assessing ischemic risk, clinical presentation (ACS vs stable CAD) and disease/PCI complexity are two of the most important factors to consider

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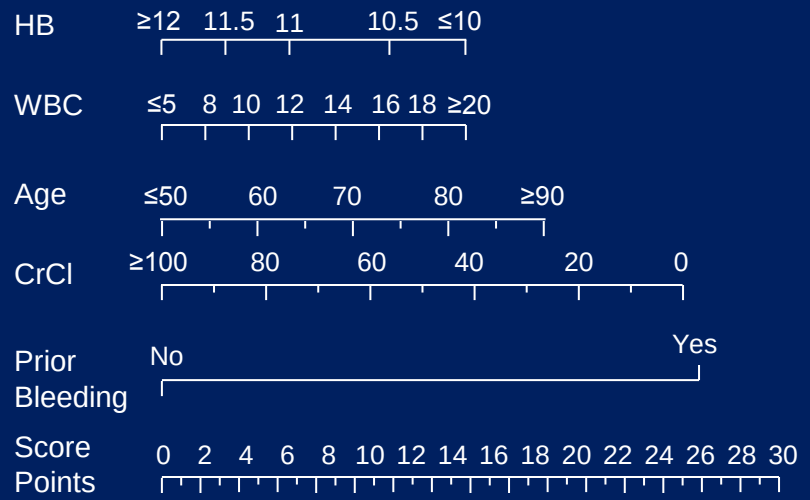
Palmerini T and Stone GW. Eur Heart J 2016;37:353-64

Risk Scores for DAPT Duration Decision-Making

	PRECISE-DAPT score	DAPT score	
Time of use	At the time of coronary stenting	After 12 months of uneventful DAPT	
DAPT duration strategies assessed	Short DAPT (3-6 months) vs. Standard/long DAPT (12-24 months)	Short DAPT (12 months) vs. Long DAPT (30 months)	
Score calculation		Age ≥75 65 yo <75 <65 Cigarette smoking Diabetes mellitus MI at presentation Prior PCI or prior MI Paclitaxel-eluting stent Stent diameter <3 mm CHF or LVEF <30% Vein graft stent	 -2 pt 1 pt 0 pt +1 pt +1 pt +1 pt +1 pt +1 pt +1 pt +1 pt +2 pt +2 pt
Score range	0 to 100 points	-2 to 10 points	
Decision making cut-off suggested	Score ≥25 → Short DAPT Score <25 → Standard/Long DAPT	Score ≥2 → Long DAPT Score <2 → Short DAPT	
Calculator	www.precisedaptscore.com	www.daptstudy.org	

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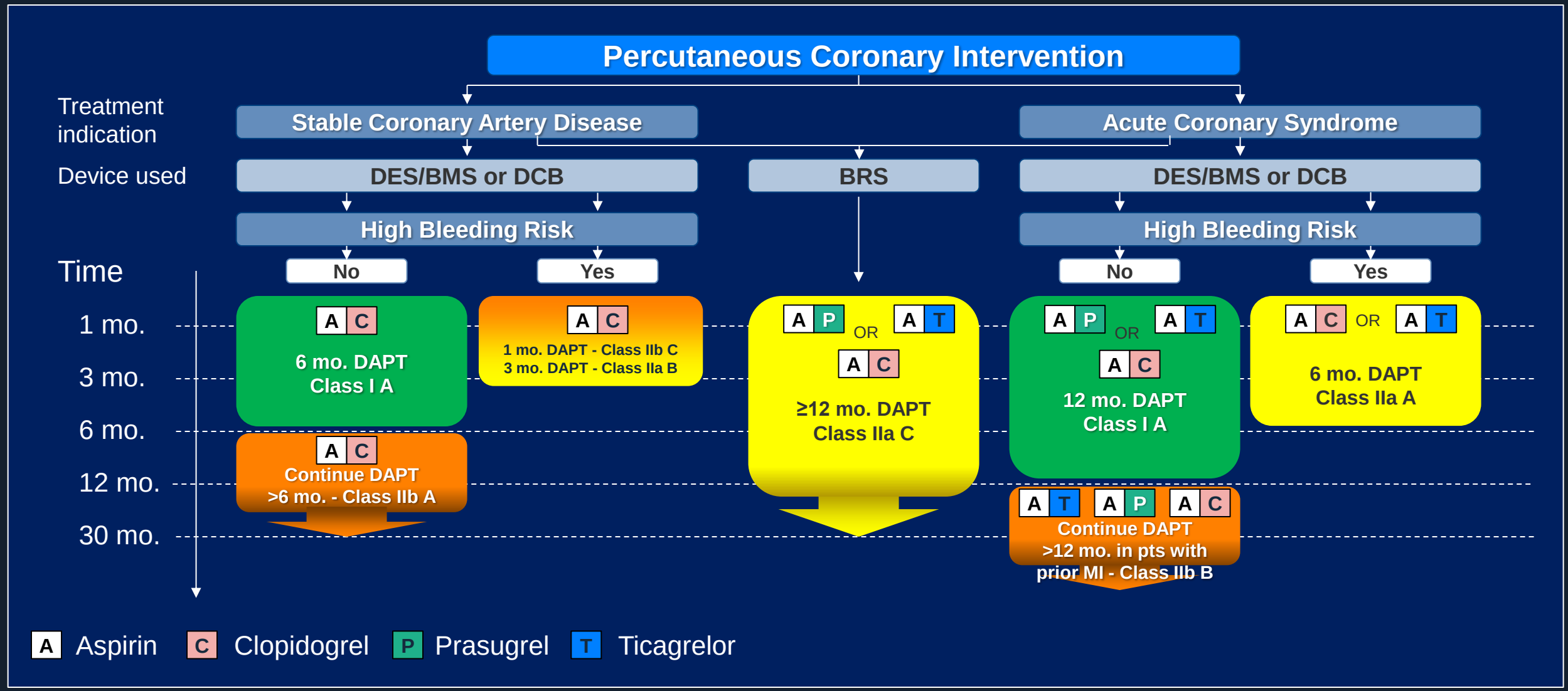
Valgimigli M, et al. Eur Heart J. 2018;39:213-260

DAPT Duration in Patients Treated with PCI (±ACS)



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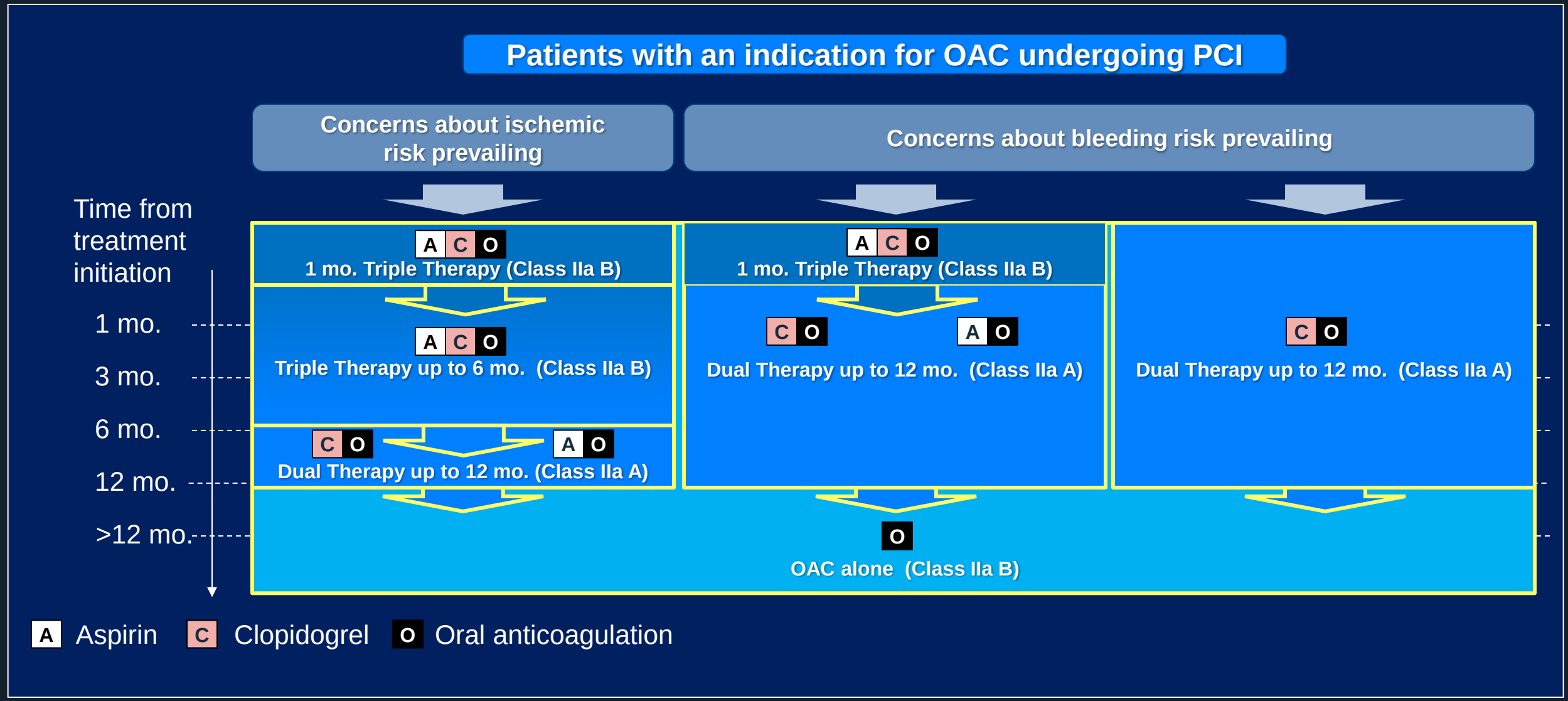
Valgimigli M, et al. Eur Heart J. 2018;39:213-260

Antithrombotic Therapy in OAC Pts undergoing PCI



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Valgimigli M, et al. Eur Heart J. 2018;39:213-260

What Next? Trials of Short DAPT

	Xience (DP-EES)	Synergy (BP-EES)	Onyx (DP-ZES)
Existing data	▶ Retrospective analysis of Xience data ▶ STOPDAPT	▶ Retrospective analysis of Synergy data ▶ SENIOR	▶ Retrospective analysis of Onyx data ▶ STEMI DAPT
IFU Language (CE Mark)	The decision to interrupt or discontinue DAPT is the responsibility of the treating physician, taking into consideration the individual patient's condition. In case an unanticipated interruption or discontinuation of DAPT is required any time after **one month** following XIENCE coronary stent implantation, two-year data from the XIENCE coronary clinical trials show low stent thrombosis rates and **no observed increased risk for stent thrombosis**	In selected higher risk patients where the physician determines that the risks outweigh the benefits of continued DAPT, it may be **reasonable to interrupt or discontinue therapy after 1 month** based on low stent thrombosis rates and no observed increased risk for stent thrombosis as shown in the current literature. Patients who require premature discontinuation of antiplatelet therapy should be monitored closely and have their antiplatelet therapy restarted as soon as possible per the discretion of their treating physicians.	One year data from the RESOLUE Clinical Program indicates **low stent thrombosis rates for those that interrupted or discontinued DAPT at any time after one month**. While physicians should adhere to current ESC or ACC/AHA/SCAI Guidelines for PCI, patients who interrupt or discontinue DAPT medication one month or more after stent implantation are considered at low risk and showed no increased risk for stent thrombosis
Ongoing studies	▶ STOPDAPT-2 ▶ XIENCE 28 ▶ XIENCE 90	▶ POEM ▶ EVOLVE Short DAPT	▶ ONYX ONE

What Next? Trials of Aspirin-Free Strategies

Trial Name	Population	Intervention	Control	Outcome	Expected
GLOBAL LEADERS (NCT01813435)	16,000 all-comers DES-PCI patients after 1 mo DAPT	Ticagrelor monotherapy	DAPT, followed by ASA	Death or MI at 24 mo from PCI	Q3 2018
SMART-CHOICE (NCT02079194)	3,000 all-comers DES-PCI patients after 3 mo DAPT	Clopidogrel or ticagrelor monotherapy	DAPT	D/CVA/MI at 12 mo from PCI	Q3 2018
SMART-CHOICE II (NCT03119012)	1,520 BRS-PCI patients after 12 mo DAPT	Clopidogrel or ticagrelor monotherapy	DAPT	D/CVA/MI at 36 mo from PCI	Q3 2018
TWILIGHT (NCT02270242)	9,000 high-risk DES-PCI patients after 3 mo DAPT	Ticagrelor monotherapy	DAPT	BARC 2-5 at 15 mo from PCI	Q2 2019
MASTER-DAPT (NCT03023020)	4,300 HBR DES-PCI patients after 1 mo DAPT	$P2Y_{12}$ inhibitor monotherapy	DAPT, followed by ASA	NACE, MACCE, Bleeding at 12 mo from PCI	Q1 2020
STOPDAPT-2 (NCT02619760)	3,000 all-comers DES-PCI patients after 1 mo DAPT	Clopidogrel monotherapy	DAPT, followed by ASA	CD/MI/ST/S or Bleed at 60 mo from PCI	Q1 2023

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Capodanno D, et al. Nat Rev Cardiol 2018 [In press]

Duration of DAPT in 2018: Closing Remarks

- RCTs can only elucidate broad principles and scoring systems only consider a small number of risk factors for bleeding or ischemic risk. No single DAPT recommendation applies to every patient.
- The fine details of DAPT duration in the era of smarter DES must be personalized:
  - In low- risk patients, a minimum DAPT duration of 6 months may be sufficient to prevent early and largely stent-related thrombotic events. However, prolonging >6 months in patients who tolerate DAPT is not unreasonable.
  - Patients who undergo stenting in the context of ACS should receive DAPT for at least 12 months. In selected patients at higher risk (e.g. those with prior MI), extension of DAPT beyond 12 months entails a trade-off between increased bleeding and reduced ischemic events.
  - In patients at high risk of bleeding, halving of DAPT duration to 1-3 months (stable CAD) and 6 months (ACS) may be justifiable.

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