Optimal Antiplatelet Therapy for HBR Patients and Complex PCI

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Disclosures

Institutional Research Support

- Edwards Lifesciences
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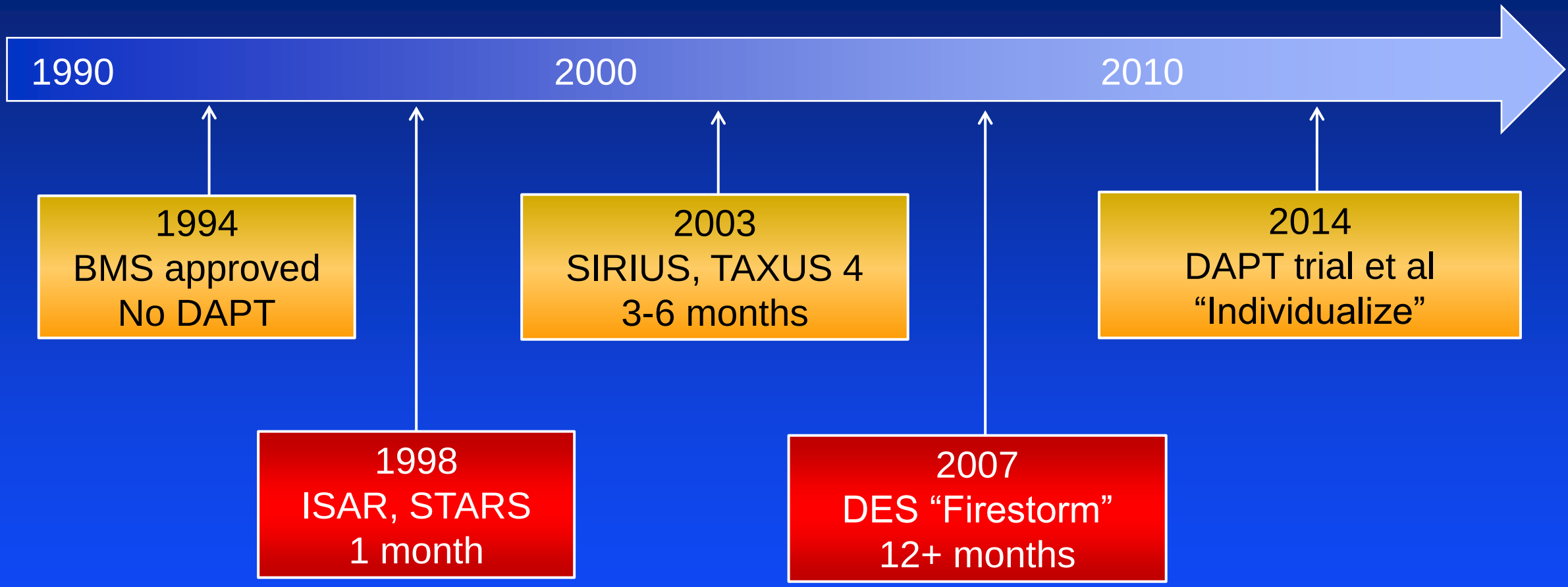
Consulting/Advisory Boards

- Medtronic
- Boston Scientific
- HeartBeam

- Edwards Lifesciences
- Abbott Vascular

History of DAPT after PCI/Stenting



Optimal DAPT in 2024

- Is the DAPT trial still relevant in 2024?
- Optimal DAPT in high bleeding risk (HBR) patients
- Optimal DAPT in complex PCI patients

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Is the DAPT Trial still Relevant in 2024?

Circulation

ORIGINAL RESEARCH ARTICLE

Estimation of DAPT Study Treatment Effects in Contemporary Clinical Practice: Findings From the EXTEND-DAPT Study

Neel M. Butala, MD, MBA; Kamil F. Faridi, MD, MSc; Hector Tamez, MD, MPH; Jordan B. Strom, MD, MSc; Yang Song, MSc; Changyu Shen, PhD; Eric A. Secemsky, MD, MSc; Laura Mauri, MD, MSc; Dean J. Kereiakes, MD; Jeptha P. Curtis, MD; C. Michael Gibson, MD, MS; Robert W. Yeh, MD, MSc

BACKGROUND: Differences in patient characteristics, changes in treatment algorithms, and advances in medical technology could each influence the applicability of older randomized trial results to contemporary clinical practice. The DAPT Study (Dual Antiplatelet Therapy) found that longer-duration DAPT decreased ischemic events at the expense of greater bleeding, but subsequent evolution in stent technology and clinical practice may attenuate the benefit of prolonged DAPT in a contemporary population. We evaluated whether the DAPT Study population is different from a contemporary population of US patients receiving percutaneous coronary intervention and estimated the treatment effect of extended-duration antiplatelet therapy after percutaneous coronary intervention in this more contemporary cohort.

METHODS: We compared the characteristics of drug-eluting stent–treated patients randomly assigned in the DAPT Study to a sample of more contemporary drug-eluting stent–treated patients in the National Cardiovascular Data Registry CathPCI Registry from July 2016 to June 2017. After linking trial and registry data, we used inverse-odds of trial participation weighting to account for patient and procedural characteristics and estimated a contemporary real-world treatment effect of 30 versus 12 months of DAPT after coronary stent procedures.

RESULTS: The US drug-eluting stent–treated trial cohort included 8864 DAPT Study patients, and the registry cohort included 568 540 patients. Compared with the trial population, registry patients had more comorbidities and were more likely to present with myocardial infarction and receive 2nd-generation drug-eluting stents. After reweighting trial results to represent the registry population, there was no longer a significant effect of prolonged DAPT on reducing stent thrombosis (reweighted treatment effect: −0.40 [95% CI, −0.99% to 0.15%]), major adverse cardiac and cerebrovascular events (reweighted treatment effect, −0.52 [95% CI, −2.62% to 1.03%]), or myocardial infarction (reweighted treatment effect, −0.97% [95% CI, −2.75% to 0.18%]), but the increase in bleeding with prolonged DAPT persisted (reweighted treatment effect, 2.42% [95% CI, 0.79% to 3.91%]).

CONCLUSIONS: The differences between the patients and devices used in contemporary clinical practice compared with the DAPT Study were associated with the attenuation of benefits and greater harms attributable to prolonged DAPT duration. These findings limit the applicability of the average treatment effects from the DAPT Study in modern clinical practice.

Key Words: percutaneous coronary intervention ■ platelet aggregation inhibitors ■ pragmatic clinical trials as topic

Editorial, see p 107

- DAPT Study data linked with Cath-PCI Registry data from 2016-17 and "reweighted" to reflect characteristics of contemporary PCI
- Key findings
  - *Benefit of 30-month vs. 12 month DAPT on stent thrombosis, MACCE, and MI attenuated and no longer statistically significant*
  - *Excess risk of bleeding with prolonged DAPT persists*

Butala NM, et al. Circulation. 2022;145:97–106

Why is Prolonged DAPT Less Relevant in 2024?

- Better DES (mostly 1st generation vs. 100% 2nd generation)
- Different pts → more HBR in 2024
- Better P2Y12 inhibition → many contemporary studies use ticagrelor
- Different strategies after DAPT discontinuation (ASA vs. P2Y12 inhibitor monotherapy)

DAPT score still separates patients with net benefit vs. net harm

Butala NM, et al. Circulation. 2022;145:97–106

Optimal DAPT in 2024

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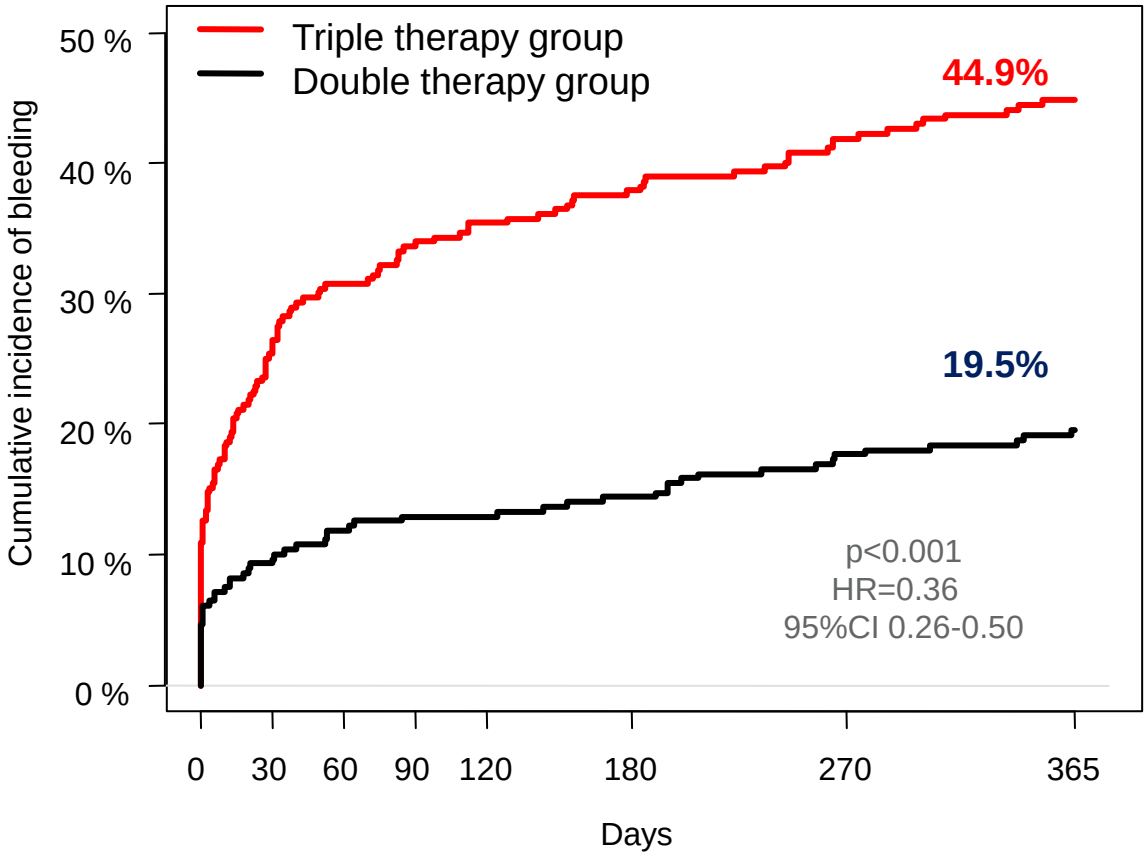
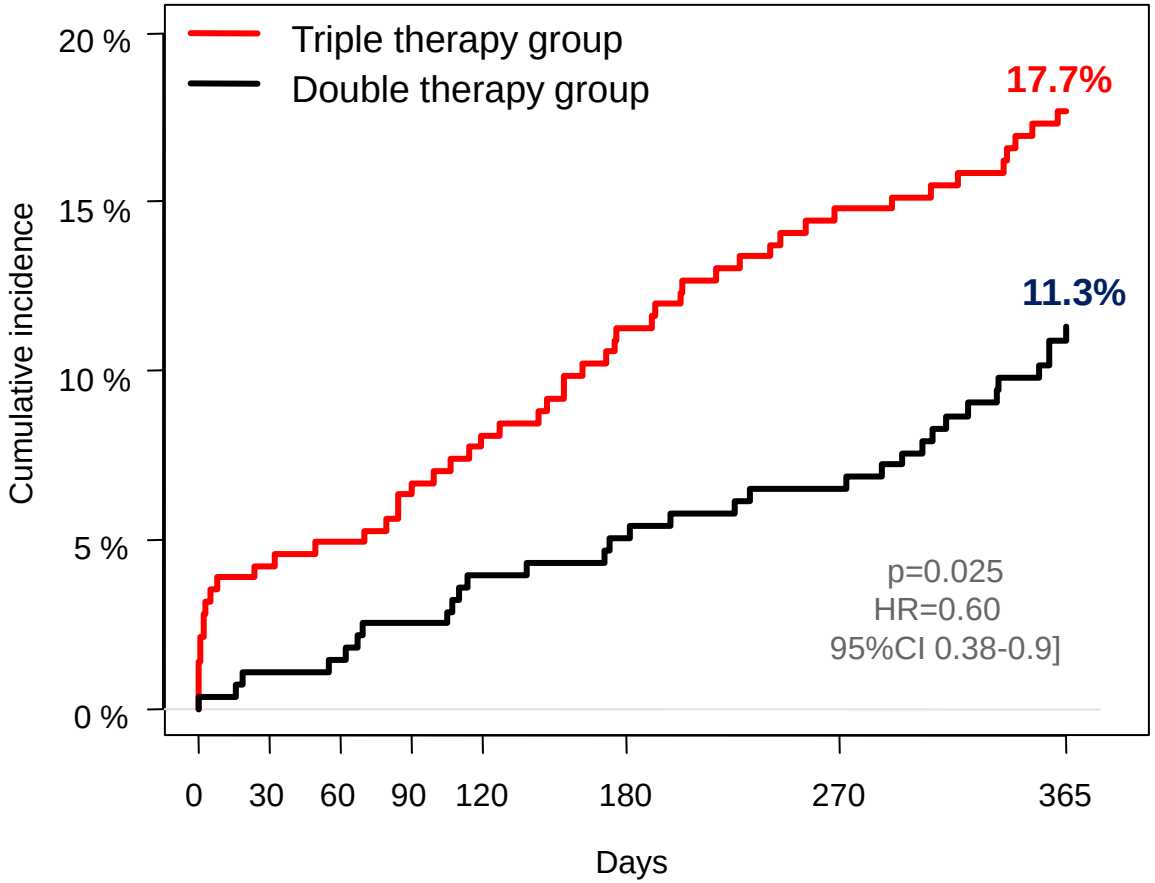
WOEST: Design

- 573 patients undergoing PCI with an indication for long-term oral anticoagulation randomized to standard triple therapy (OAC + ASA + clopidogrel) vs. double therapy (OAC + clopidogrel)
- Treatment duration based on stent type
  - *BMS: Minimum 1 month*
  - *DES: Minimum 12 months*
- Primary Endpoint: TIMI bleeding (any)
- Secondary Endpoint: Ischemic complications

Primary Endpoint: Clinically Relevant Bleeding



Death/MI/Stroke/TVR/Stent Thrombosis*



*** All-cause mortality 2.9% vs. 6.4% (p=0.027)**

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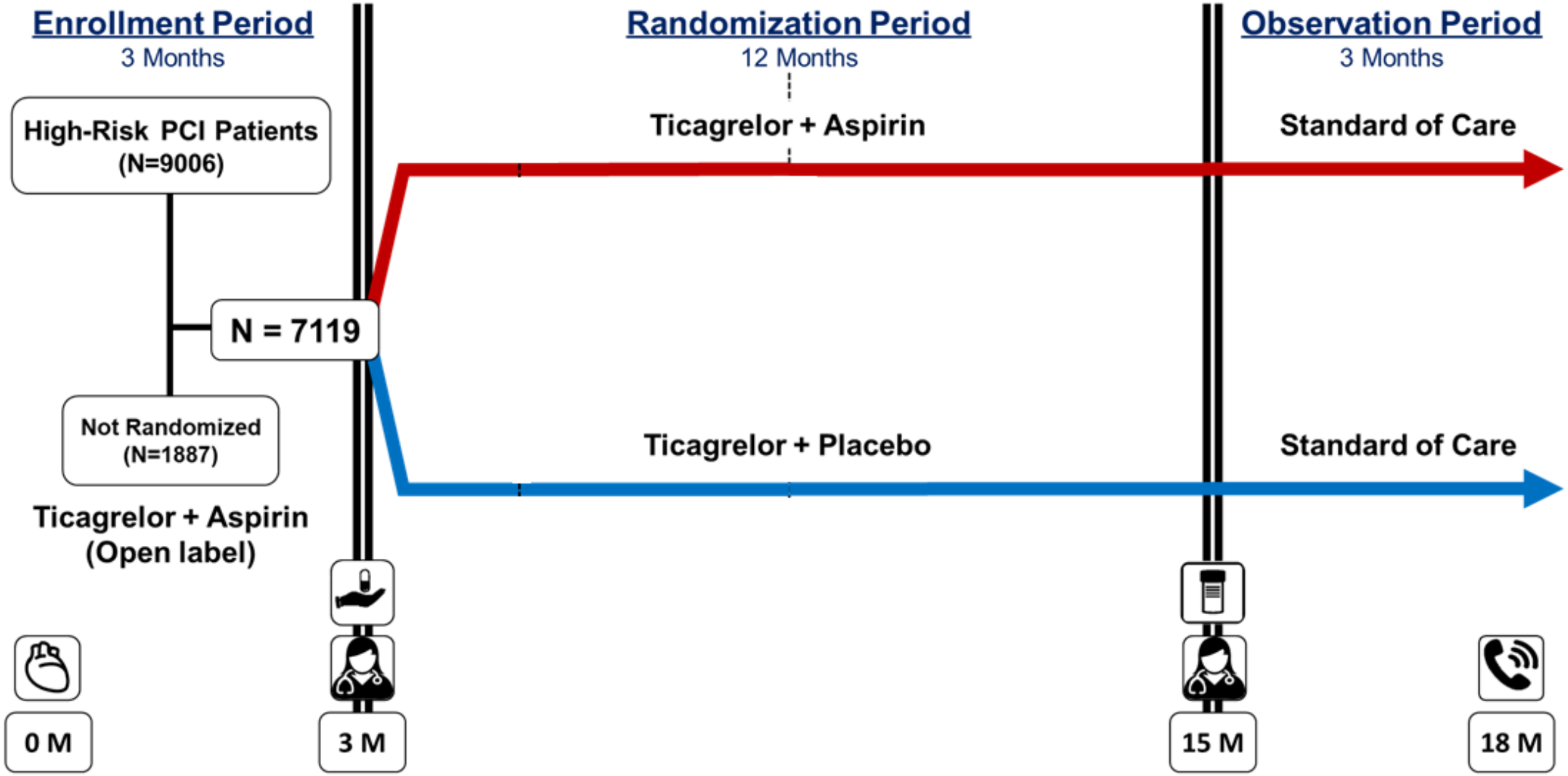
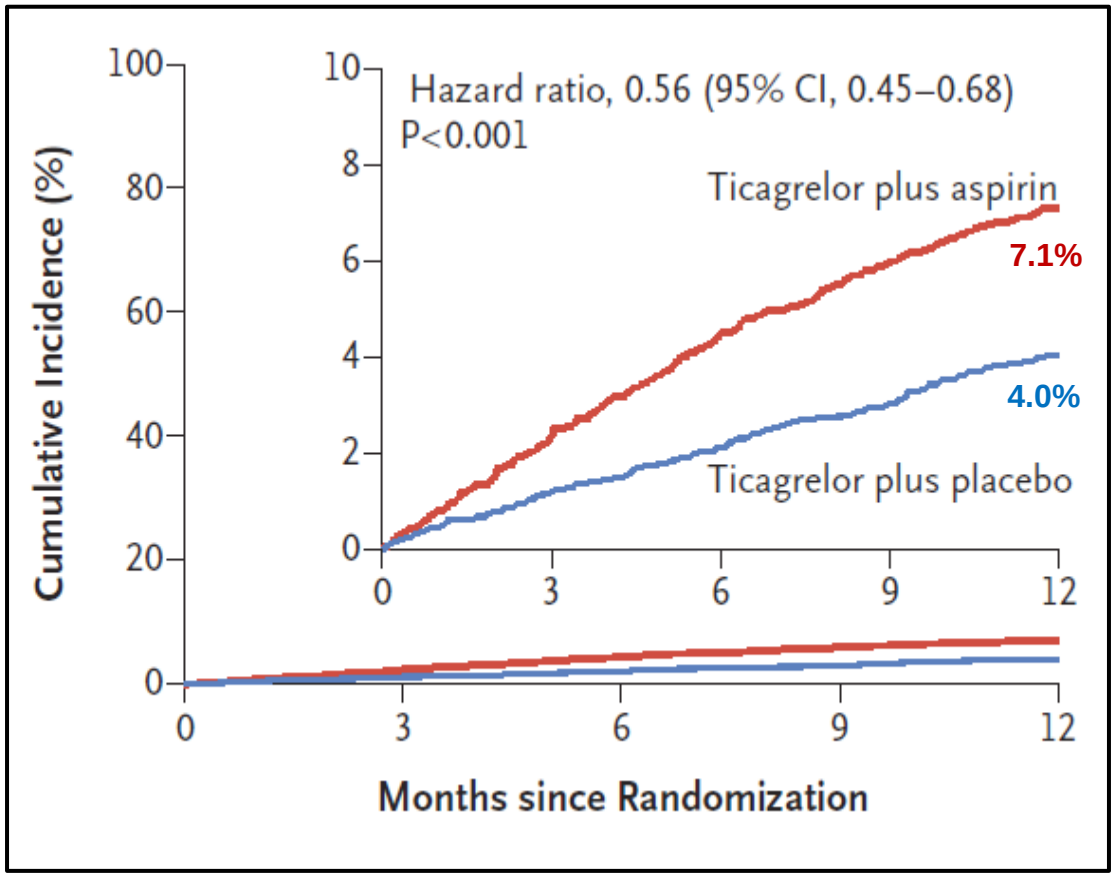
TWILIGHT Trial – Study Schema



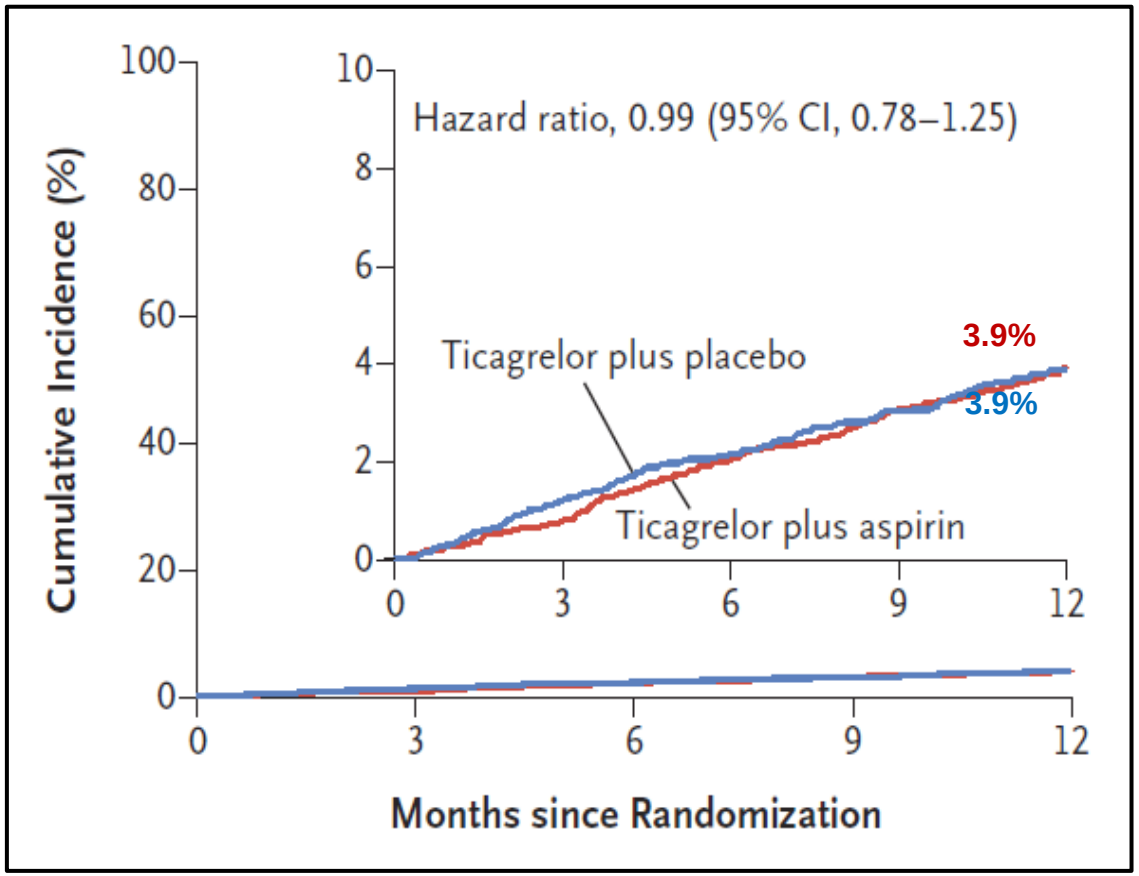
Courtesy of Roxana Mehran, MD

Results

BARC 2, 3, or 5 Bleeding

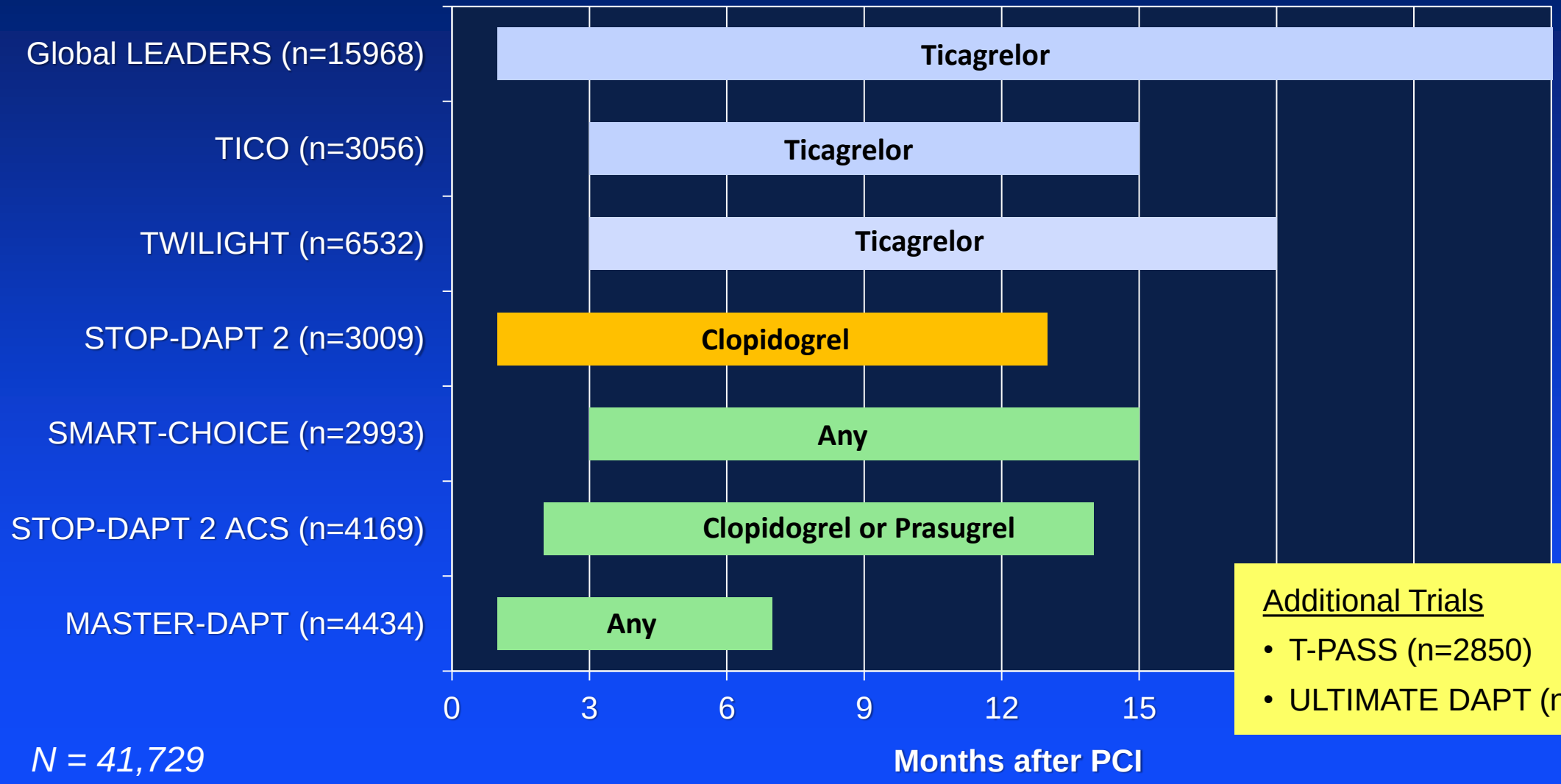


Death, MI, or Stroke



Mehran R, et al. NEJM 2019; 21:203-42

7 RCTs of P2Y12 Monotherapy after PCI



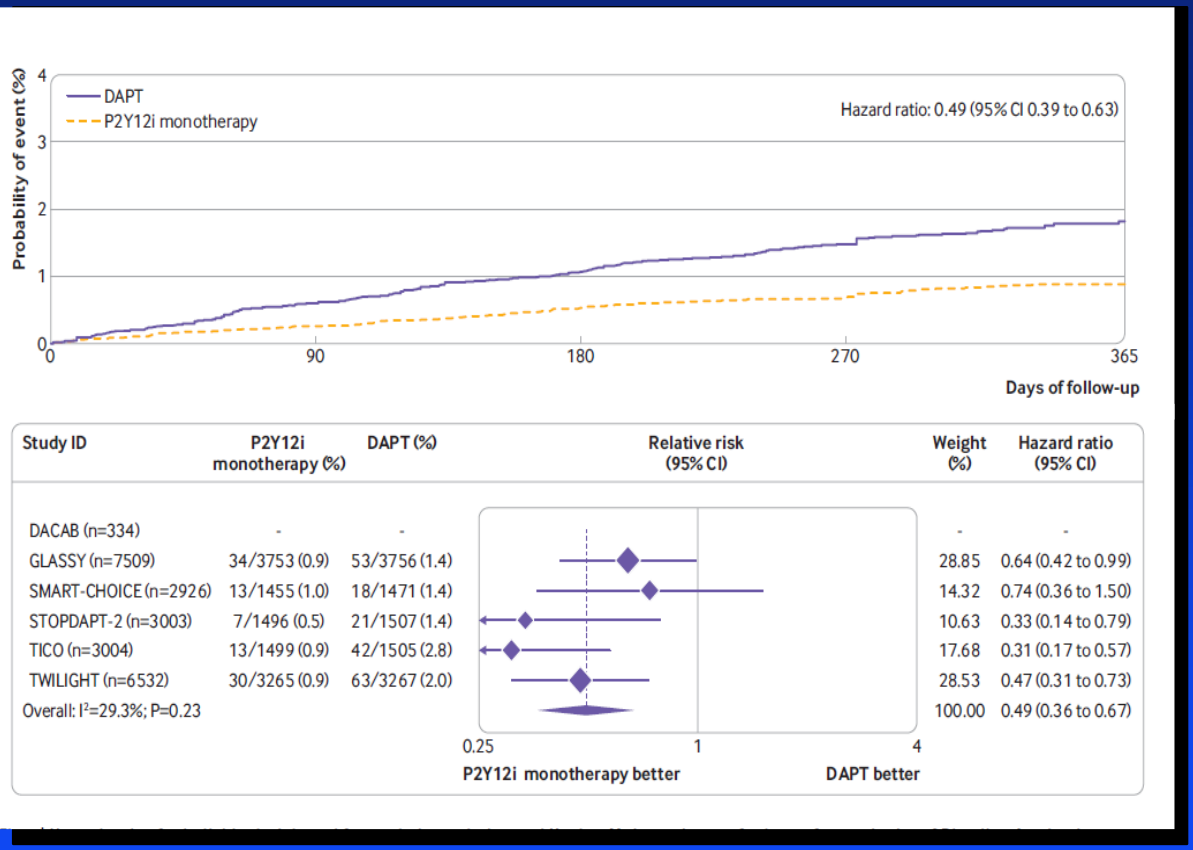
Additional Trials

- T-PASS (n=2850)
- ULTIMATE DAPT (n=3400)

N = 41,729

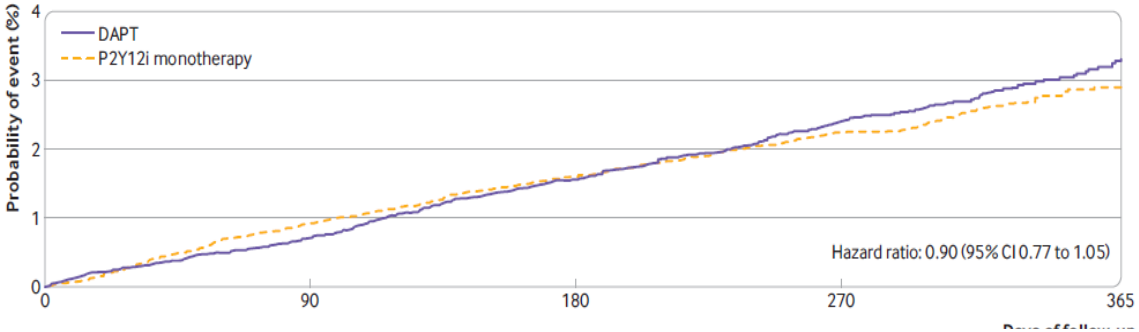
IPD Meta-Analysis (6 trials; n=24,096)

BARC 3 or 5 Bleeding



Study ID	P2Y12i monotherapy (%)	DAPT (%)	Weight (%)	Hazard ratio (95% CI)
DACAB (n=334)	-	-	-	-
GLASSY (n=7509)	34/3753 (0.9)	53/3756 (1.4)	28.85	0.64 (0.42 to 0.99)
SMART-CHOICE (n=2926)	13/1455 (1.0)	18/1471 (1.4)	14.32	0.74 (0.36 to 1.50)
STOPDAPT-2 (n=3003)	7/1496 (0.5)	21/1507 (1.4)	10.63	0.33 (0.14 to 0.79)
TICO (n=3004)	13/1499 (0.9)	42/1505 (2.8)	17.68	0.31 (0.17 to 0.57)
TWILIGHT (n=6532)	30/3265 (0.9)	63/3267 (2.0)	28.53	0.47 (0.31 to 0.73)
Overall: I^2=29.3%; P=0.23			100.00	0.49 (0.36 to 0.67)

Death, MI, or Stroke



Study ID	P2Y12i monotherapy (%)	DAPT (%)	Weight (%)	Hazard ratio (95% CI)
DACAB (n=334)	4/166 (2.4)	4/168 (2.4)	1.26	1.02 (0.25 to 4.06)
GLASSY (n=7509)	96/3753 (2.6)	112/3756 (3.0)	32.50	0.86 (0.65 to 1.13)
SMART-CHOICE (n=2926)	28/1455 (2.0)	27/1471 (1.9)	8.64	1.05 (0.62 to 1.79)
STOPDAPT-2 (n=3003)	36/1496 (2.4)	40/1507 (2.7)	11.91	0.91 (0.58 to 1.43)
TICO (n=3004)	13/1499 (0.9)	24/1505 (1.6)	5.30	0.54 (0.28 to 1.07)
TWILIGHT (n=6532)	126/3265 (3.9)	131/3267 (4.1)	40.38	0.96 (0.76 to 1.23)
Overall: I^2=0.0%; P=0.71			100.00	0.90 (0.77 to 1.05)

Valgimigli M, et al. BMJ 2021;doi:10.1136/bmj.n1132

Do these Results Hold Up in HBR Patients?

ORIGINAL ARTICLE

Dual Antiplatelet Therapy after PCI in Patients at High Bleeding Risk

M. Valgimigli, E. Frigoli, D. Heg, J. Tijssen, P. Jüni, P. Vranckx, Y. Ozaki, M.-C. Morice, B. Chevalier, Y. Onuma, S. Windecker, P.A.L. Tonino, M. Roffi, M. Lesiak, F. Mahfoud, J. Bartunek, D. Hildick-Smith, A. Colombo, G. Stanković, A. Iñiguez, C. Schultz, R. Kornowski, P.J.L. Ong, M. Alasnag, A.E. Rodriguez, A. Moschovitis, P. Laanmets, M. Donahue, S. Leonardi, and P.C. Smits, for the MASTER DAPT Investigators*

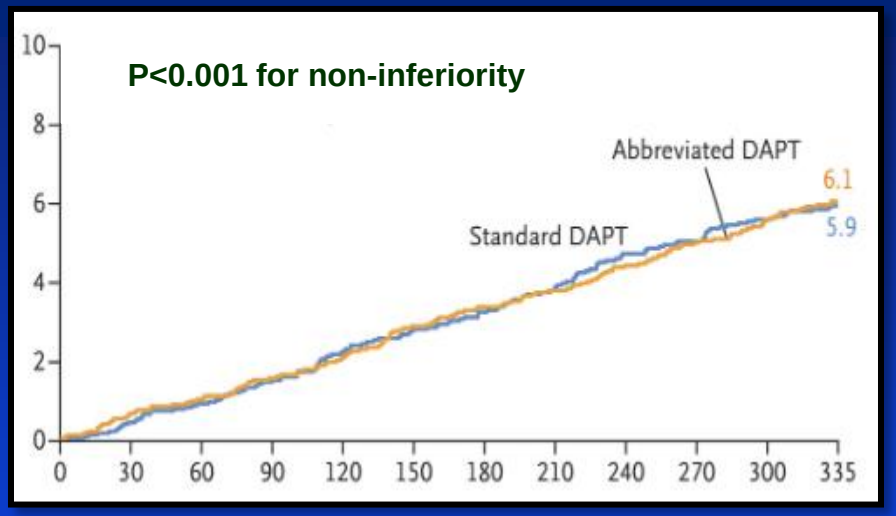
ABSTRACT

BACKGROUND

The appropriate duration of dual antiplatelet therapy in patients at high risk for bleeding after the implantation of a drug-eluting coronary stent remains unclear.

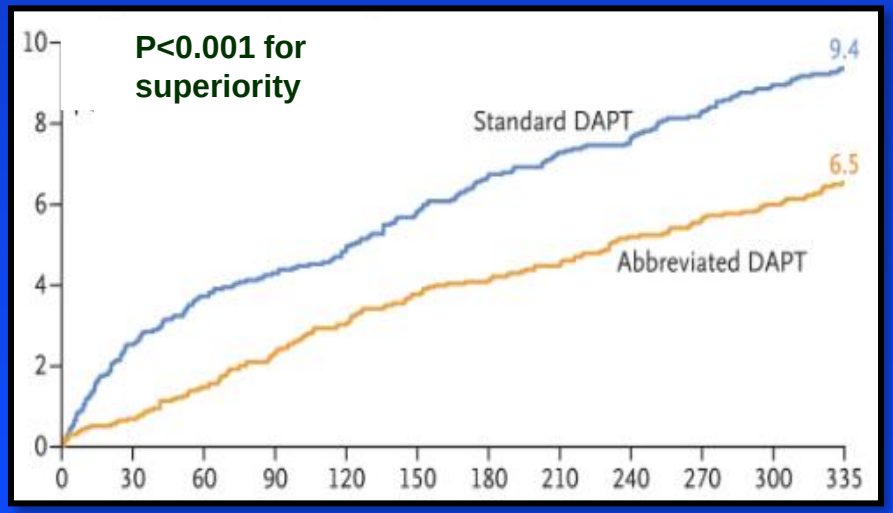
METHODS

One month after they had undergone implantation of a biodegradable-polymer sirolimus-eluting coronary stent, we randomly assigned patients at high bleeding risk to discontinue dual antiplatelet therapy immediately (abbreviated therapy) or to continue it for at least 2 additional months (standard therapy). The three ranked primary outcomes were net adverse clinical events (a composite of death from any cause, myocardial infarction, stroke, or major bleeding), major adverse cardiac or cerebral events (a composite of death from any cause, myocardial infarction, or stroke), and major or clinically relevant nonmajor bleeding; cumulative incidences were assessed at 335 days. The first two outcomes were assessed for noninferiority in the per-protocol population, and the third outcome for superiority in the intention-to-treat population.



Death, MI, or Stroke

Major Bleeding

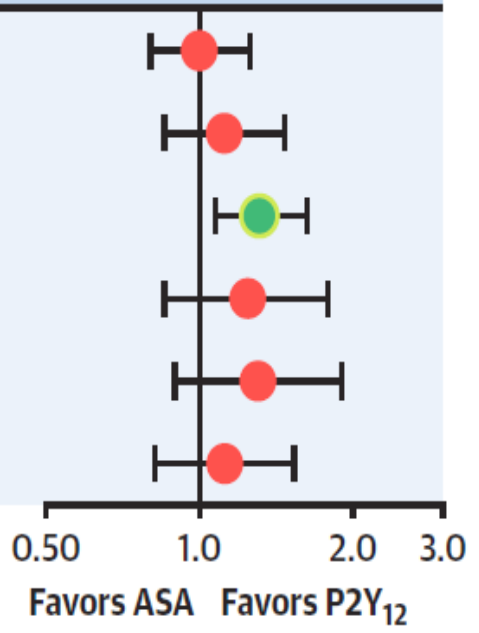


Valgimigli M, et al. NEJM 2021

Should we stop the ASA or the P2Y12 Inhibitor?

Aspirin Versus $P2Y_{12}$ Inhibitor Monotherapy Following DAPT Discontinuation After PCI

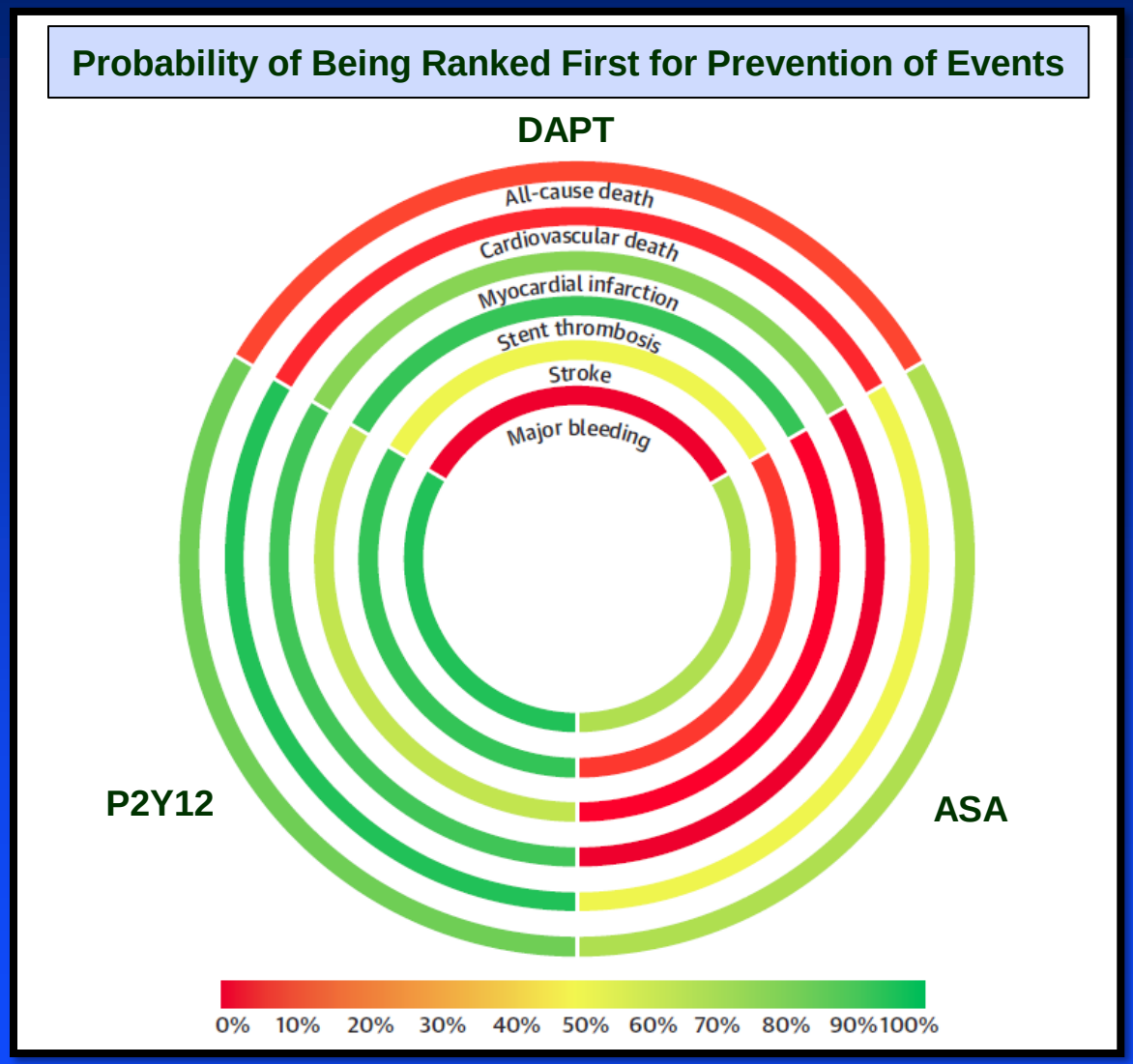
Study Outcome	Event Rates/ 100 Patients • Year	RR (95% CI)
All-cause death	1.19	1.00 (0.80-1.26)
Cardiovascular death	0.78	1.12 (0.85-1.47)
Myocardial infarction	1.33	1.32 (1.08-1.62)
Stent thrombosis	0.39	1.24 (0.85-1.79)
Stroke	0.53	1.30 (0.89-1.90)
Major bleeding	1.10	1.12 (0.82-1.53)



- Network metaanalysis of 19 studies (73,126 patients)
- Frequentist comparison of P2Y12 monotherapy vs. ASA monotherapy shows no significant difference for most endpoints except MI

Ando G, et al. JACC 2024

Should we stop the ASA or the P2Y12 Inhibitor?



Bayesian Analysis

- Bayesian analysis demonstrates that P2Y12 monotherapy is best for virtually all endpoints including death, MI, and major bleeding
- ASA monotherapy ranked last or next to last for all endpoints
- DAPT favored for prevention of stent thrombosis

Ando G, et al. JACC 2024

Optimal DAPT in 2024

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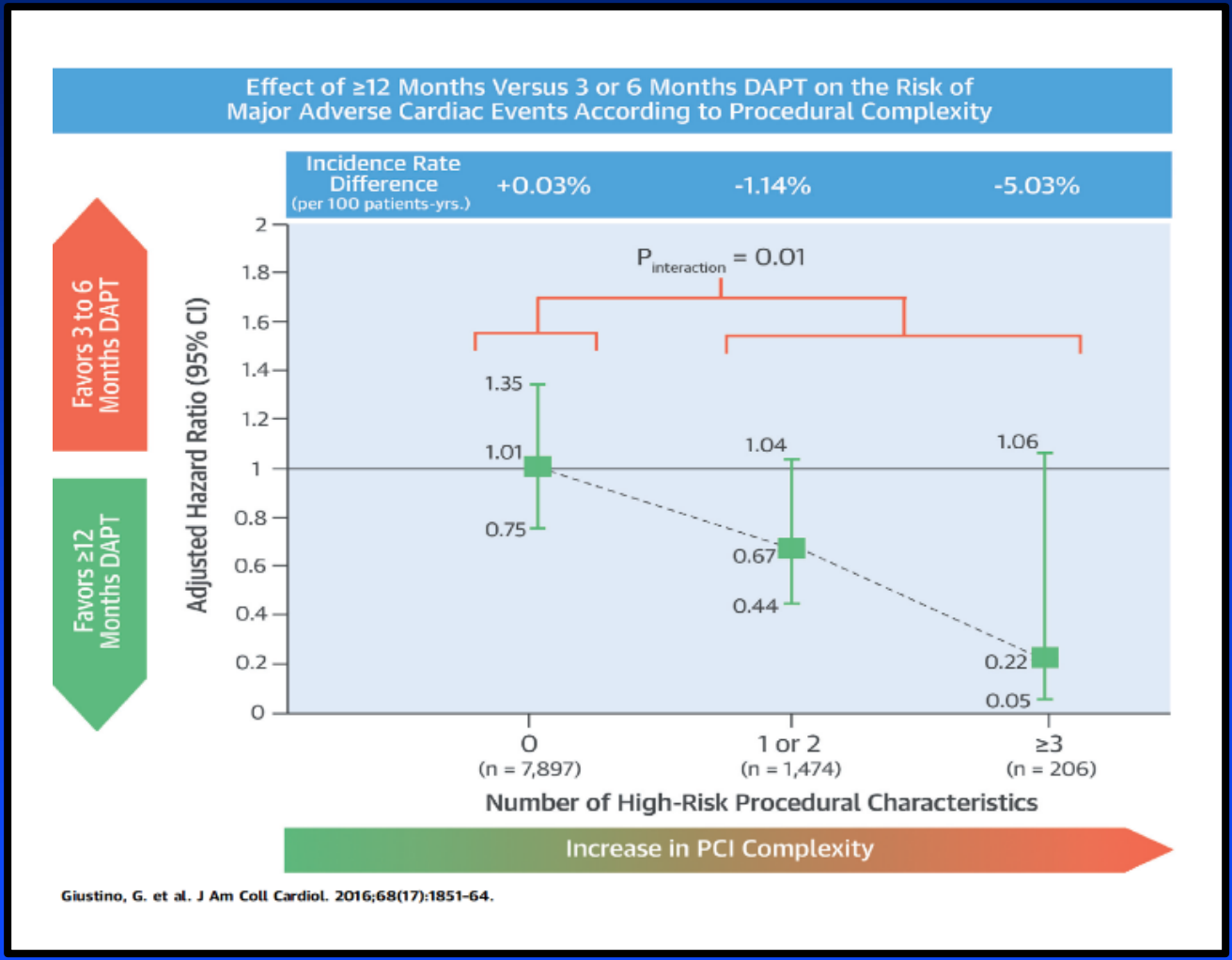
Historical Trials: Complex PCI Favors Long DAPT



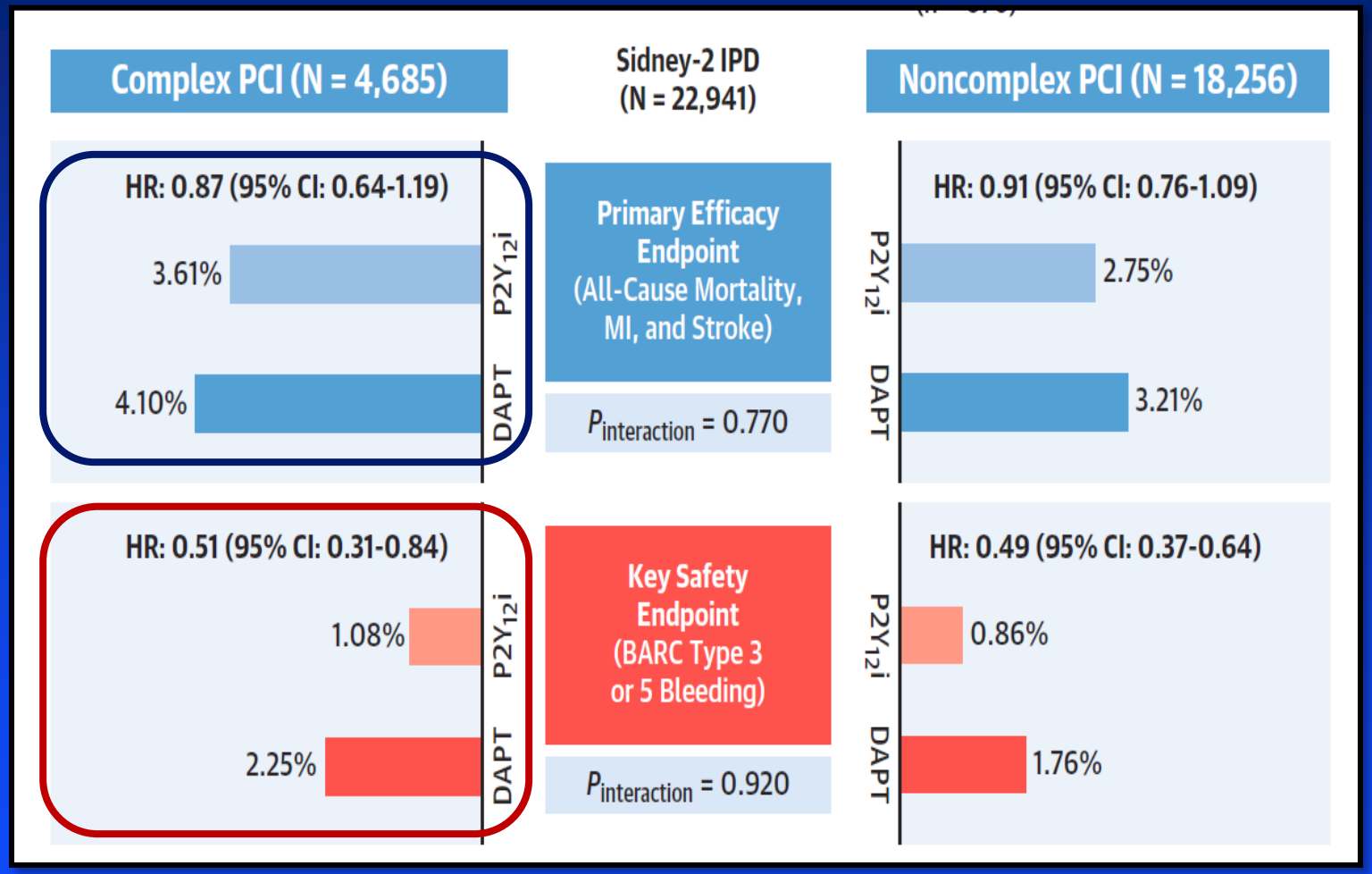
Pooled analysis of 6 RCTs comparing 3-6 months DAPT (followed by ASA monotherapy) vs. ≥ 12 months DAPT

Complex Features

- 3 vessels treated
- ≥ 3 stents placed
- ≥ 3 lesions treated
- Bifurcation with 2 stents
- Total stent length > 60 mm
- CTO

Giustino G, et al. JACC 2016;68:1851-64

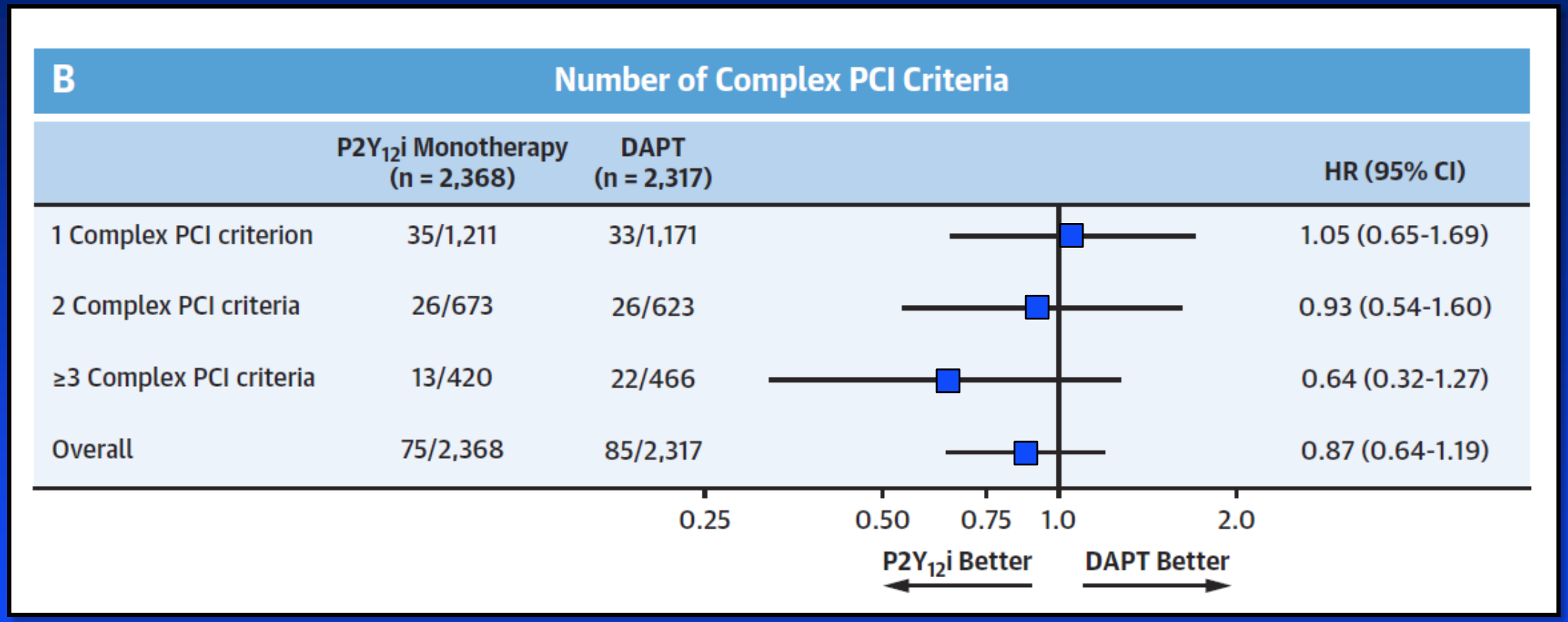
P2Y12 Monotherapy in Complex PCI



- IPD metanalysis of 5 trials of short DAPT P2Y12 monotherapy (n=22,941 pts) → 20% complex PCI
- Key Findings
  - *Consistent reduction in major bleeding with P2Y12 monotherapy*
  - *No increase in ischemic complications (lower, if anything)*

Gragnano F, et al. J Am Coll Cardiol 2023;81:537–552

Impact of Number of Complex Lesion Features



No difference in ischemic protection, regardless of # of complex features

Gragnano F, et al. J Am Coll Cardiol 2023;81:537–552

Summary

- DAPT after PCI presents a tradeoff between increased ischemic protection vs. increased bleeding → individualized therapy key to optimizing risk/benefit profile
- Numerous studies over the last decade suggest that P2Y12 monotherapy may be the key to “uncoupling” ischemic protection from bleeding risk → especially with potent P2Y12 inhibition
- Accumulating data suggest that for both HBR patients as well as complex PCI procedures, 1-3 months of DAPT followed by P2Y12 monotherapy can reduce bleeding without an increase in ischemic events
- Benefits clearest with ticagrelor; for pts treated with clopidogrel, would consider genotyping or platelet function testing– especially in ACS setting