Update on Antiplatelet Therapy in Cardiovascular Disease

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Update on Antiplatelet Therapy in Cardiovascular Disease: Interventionalist viewpoint, focus on ACS

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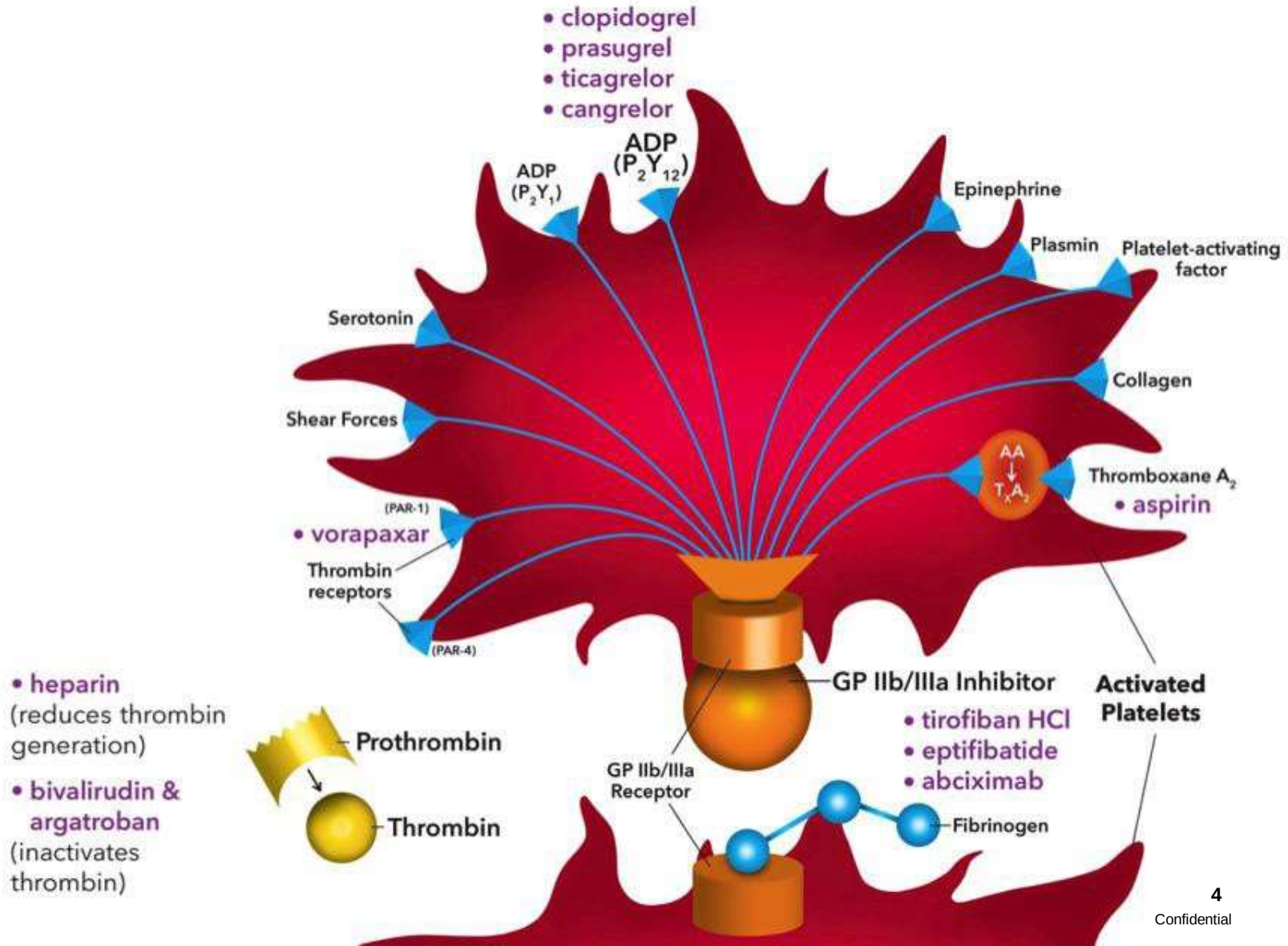
Disclosure Statement of Financial Interest

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

Affiliation/Financial Relationship	Company
• Grant/Research Support	• Edwards Lifesciences, Abbott
• Grant/Scientific Advisory Board	• Medtronic, Abbott
• Executive Physician Council	• Boston Scientific Corp

Anti-platelet Mechanism of Action



PCI Without Aspirin

No ASA given w/i 24 hrs prior PCI in 4,640 (7.1%) of 65,175 pts.

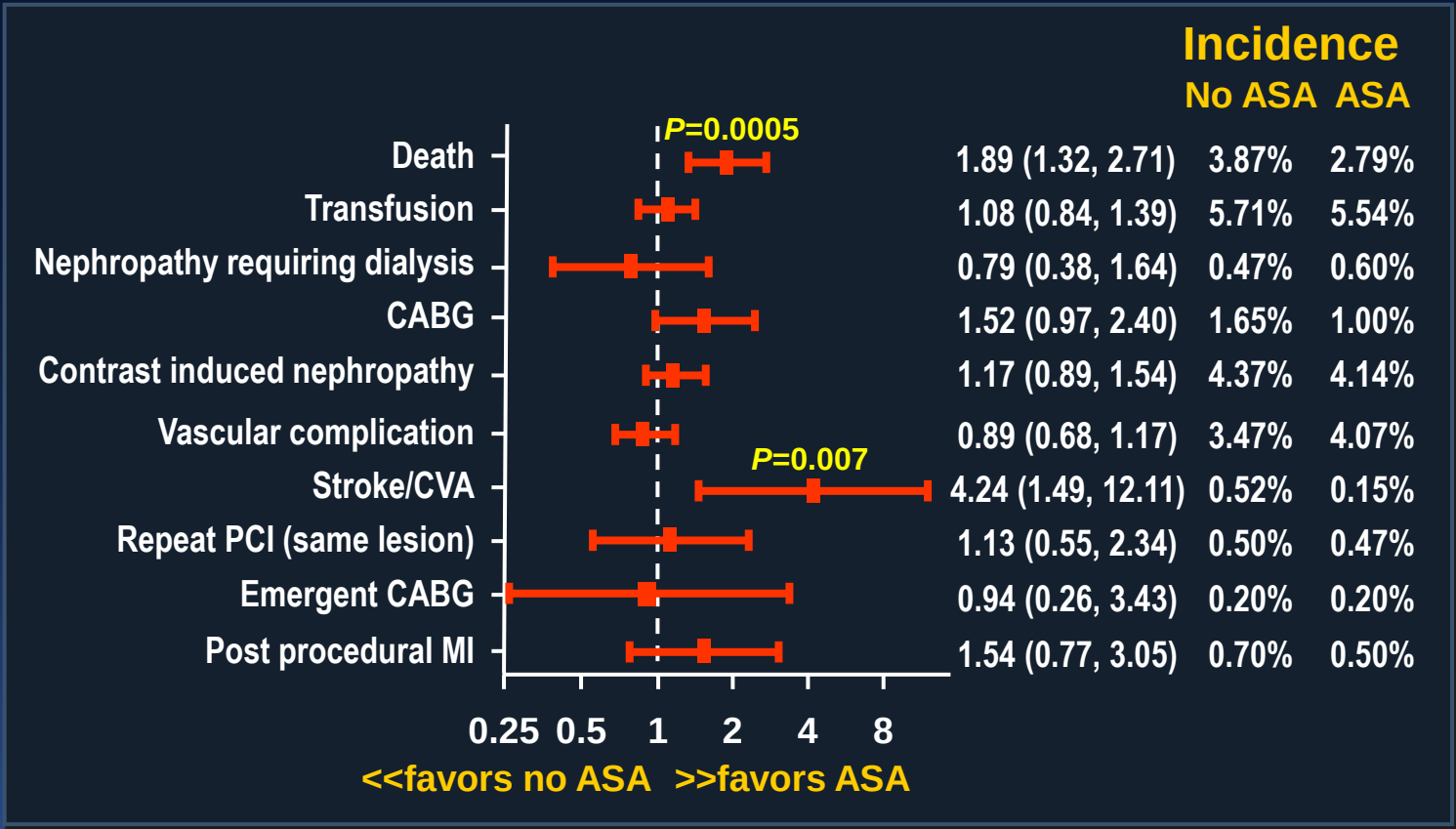
Propensity-matched in-hospital outcomes in 4,008 pt pairs:

Imbalances

↑ ASA use
- Prior PCI

↑ No ASA use
- Prior GI bleed
- STEMI
- Shock or post arrest
- Prasugrel or ticagrelor

Only 10.7% contraindication



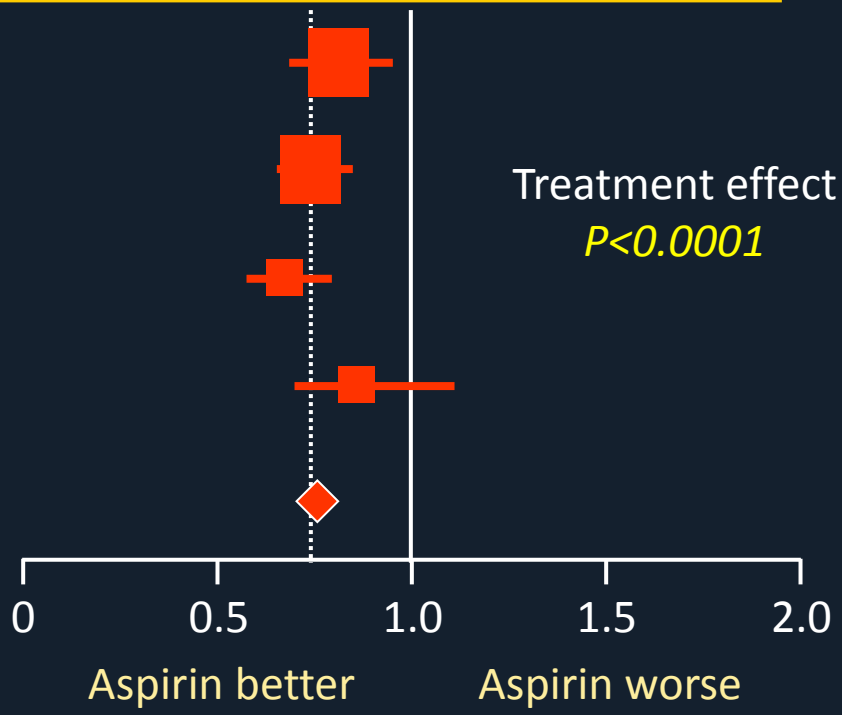
No difference in CIN between the groups (falsification endpoint)

Increase in mortality was robust in sensitivity analyses

Kenaan M et al. *JACC* 2013:on-line

Efficacy of Aspirin at Various Doses in Reducing Vascular Events (Death from Vascular Causes, MI, or Stroke) in High-risk Patients

Aspirin (mg daily)	No. of Trials	% Odds Reduction
500-1500	34	19
160-325	19	26
75-150	12	32
<75	3	13
Any aspirin	65	23



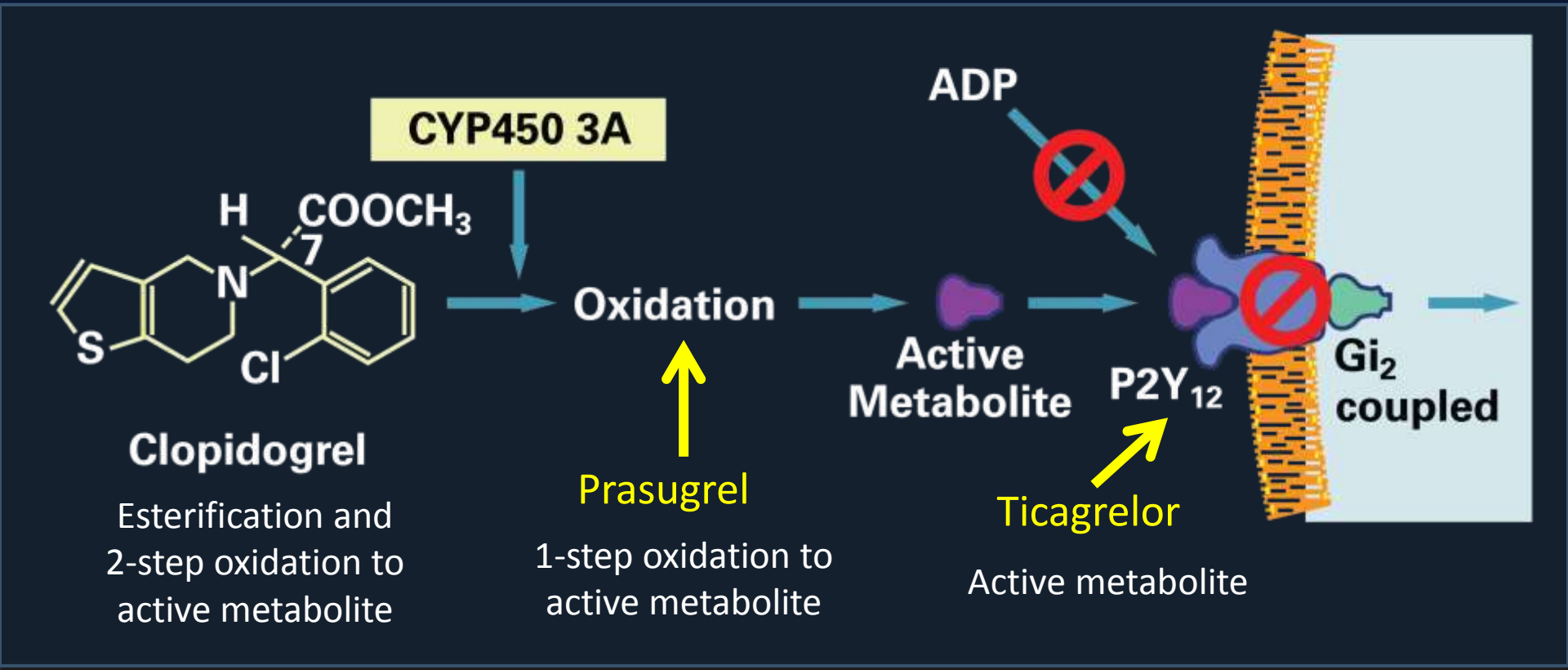
Antithrombotic Trialists' Collaboration, *BMJ*, 2002;342:71-86.

CURE:
Major Bleeding by ASA Dose

ASA Dose	Placebo + ASA	Clopidogrel + ASA
<100 mg	2.0%	2.6%
100 – 200 mg	2.3%	3.5%
>200 mg	4.0%	4.9%

Yusuf S et al. *N Engl J Med*. 2001;345:494-502

The therapeutic target for thienopyridines and CPTPs is the platelet $P2Y_{12}$ receptor



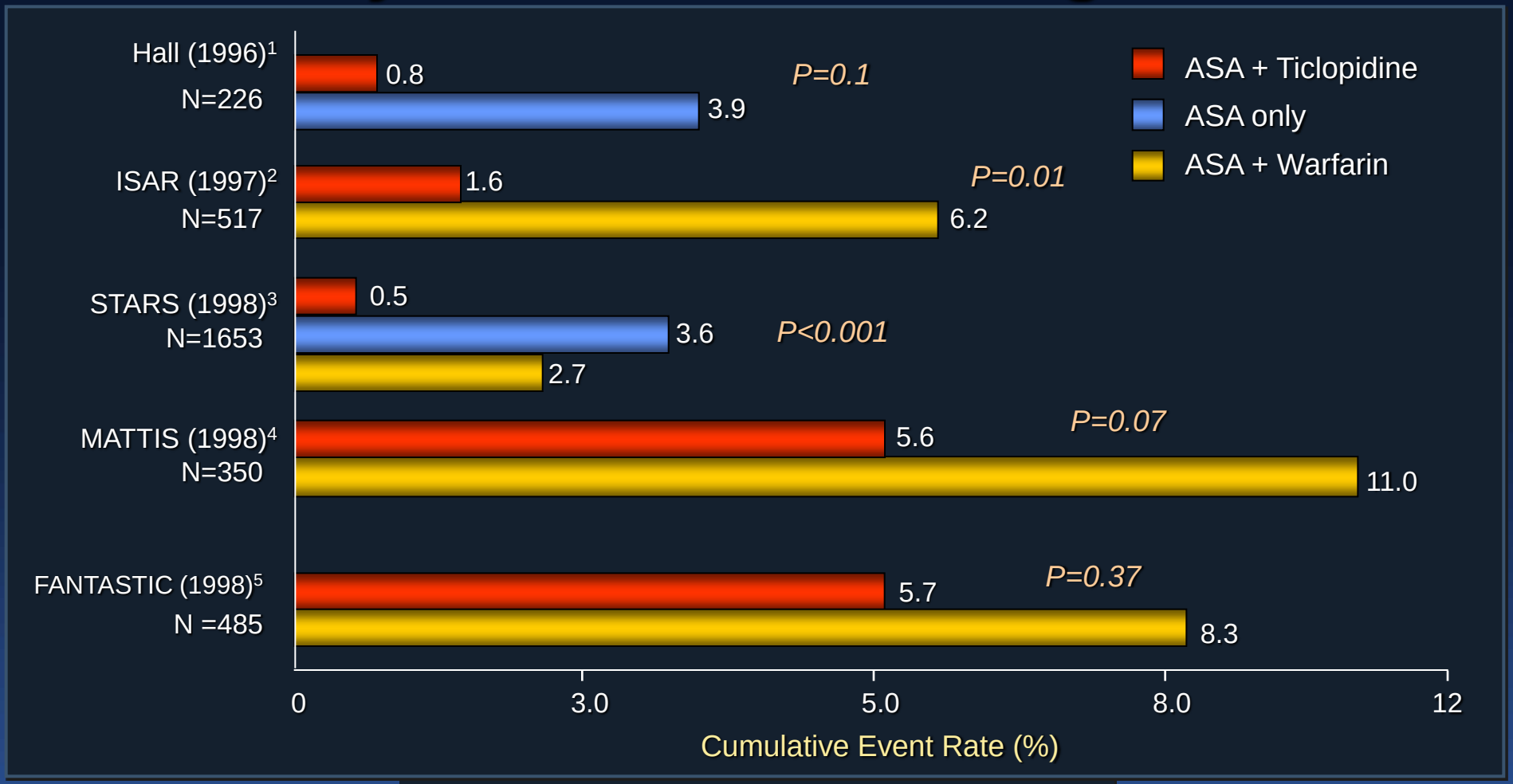
$P2Y_{12}$ Receptor Antagonists

Agent	Class	IPA (20 *uM* ADP) mean	Time to peak onset	Reversibility (d/c before CABG)
Ticlopidine 250 mg bid	thienopyridine (pro-drug)	25%	48 hrs	non reversible 5 days
Clopidogrel 300 mg LD Clopidogrel 600 mg LD Clopidogrel 75 mg qd Clopidogrel 150 mg qd	thienopyridine (pro-drug)	30% - 40% 35% - 50% 30% - 35% 45% - 50%	12 hrs 6 hrs - -	non reversible 5 days
Prasugrel 60 mg LD* Prasugrel 10 mg qd* Prasugrel 5 mg qd*	thienopyridine (pro-drug)	80% 60% 40%	1-2 hrs - -	non reversible 7 days
Ticagrelor 180 mg LD* Ticagrelor 90 mg bid*	cyclo-pentyl-triazolo-pyrimidine*	80% 70%	1-2 hrs -	reversible 2-5 days

*Less affected by genetic polymorphisms and drug interactions (e.g. PPIs)

**not a pro-drug

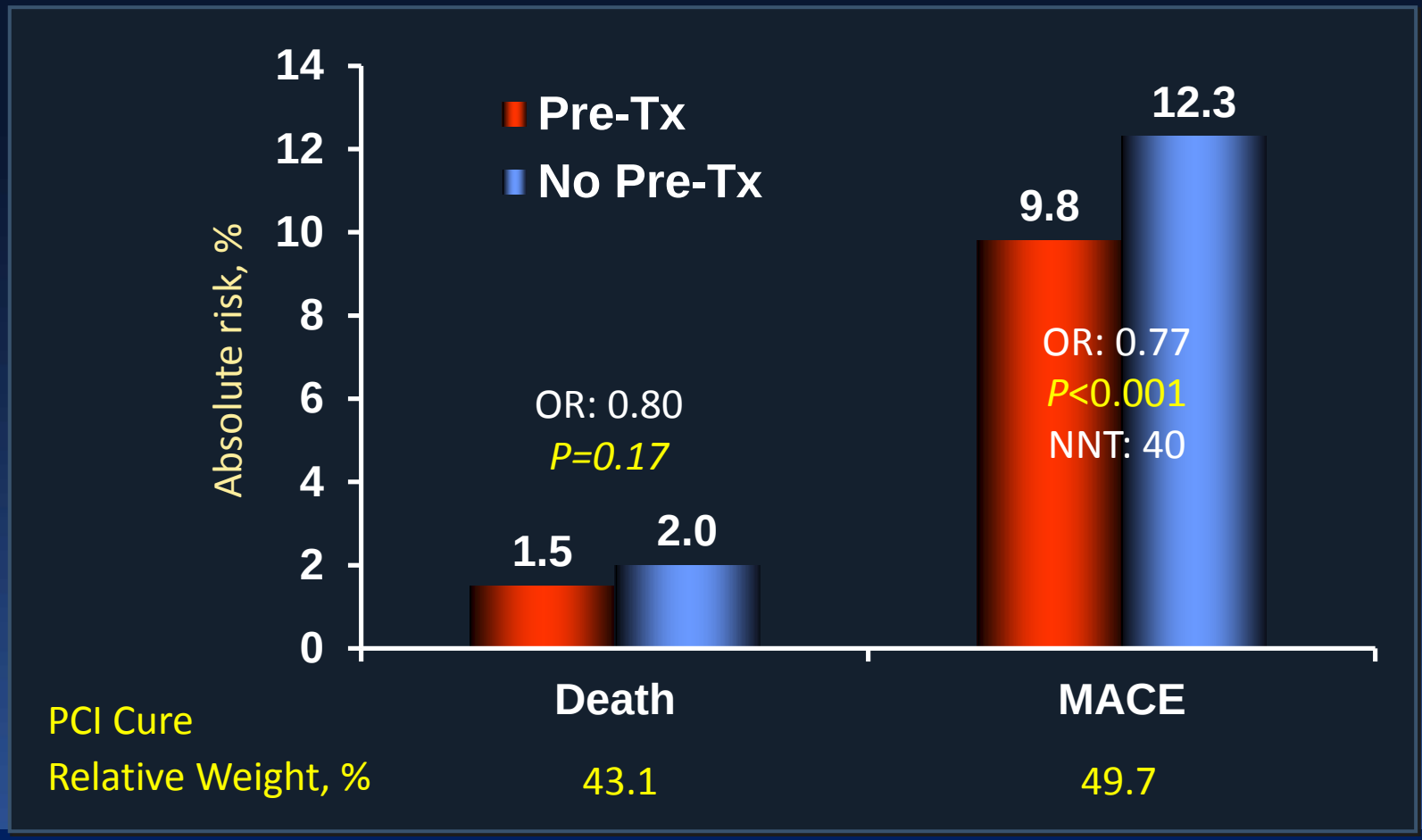
Efficacy of Thienopyridines in Reducing Coronary Events after Stenting – 5 RCTs



1 Hall P, et al. Circulation. 1996;93:215-222.
2 Schömig A, et al. N Engl J Med. 1996;335:1084-1089.
3 Leon M, et al. N Engl J Med. 1998:339:1665-71.
4 Urban P, et al. Circulation. 1998 98:2126-2132.
5 Bertrand M, et al. Circulation. 1998;98:1597-1603.

Clopidogrel Pre-treatment in PCI:

Meta-analysis of 8,608 pts in 7 RCTs undergoing PCI, including NSTEACS, STEMI, and elective PCI



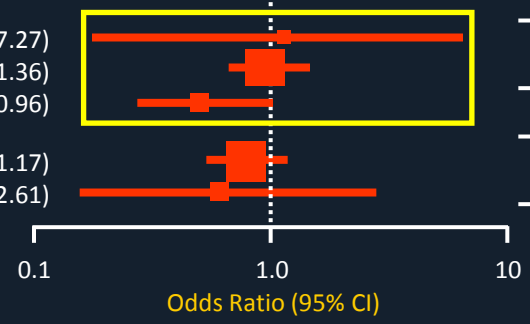
Bellemain-Appaix A et al. *JAMA* 2012;308:2507-16.

Clopidogrel Pre-treatment in PCI:

Meta-analysis of 8,608 pts in 7 RCTs undergoing PCI, including NSTEACS, STEMI, and elective PCI

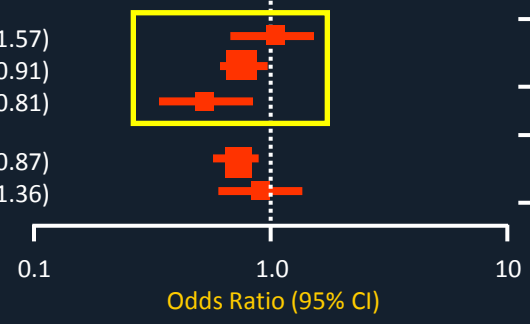
All-cause Mortality

	No. of Events		No. of Patients					
	Pretreatment	No Pretreatment	Pretreatment	No Pretreatment	OR (95% CI)	Favors Pretreatment	Favors No Pretreatment	Heterogeneity	*P* for Trend x^2
Presenting feature									
Elective PCI	2	2	820	816	1.12 (0.17-7.27)			2.66	.02
NSTE ACS	50	55	2366	2408	0.93 (0.63-1.36)				
STEMI	14	28	1097	1101	0.50 (0.26-0.96)				
Loading dose									
≤300 mg	63	79	3299	3338	0.79 (0.54-1.17)			0.1	.75
600-900 mg	3	6	984	987	0.62 (0.15-2.61)				



MACE

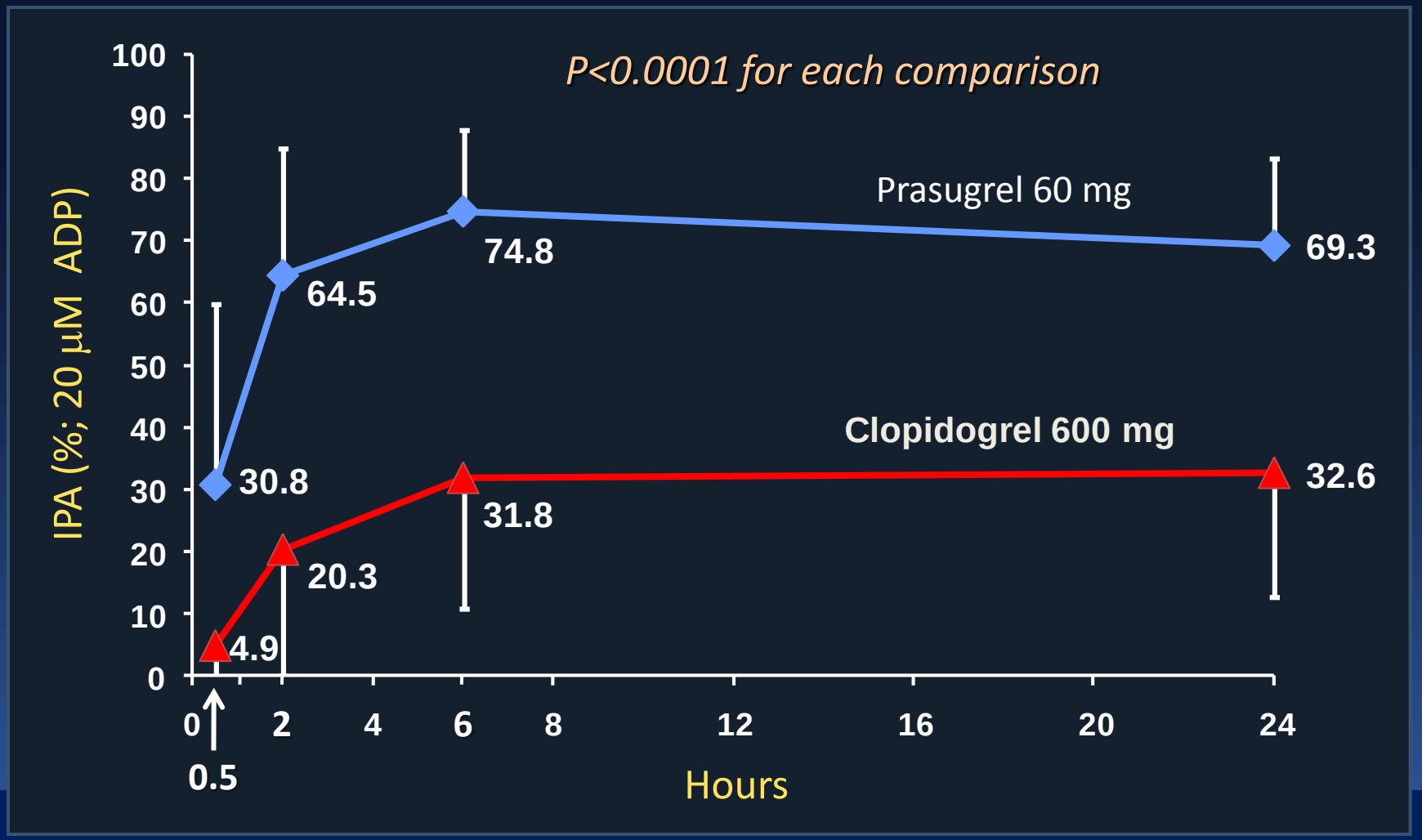
	No. of Events		No. of Patients					
	Pretreatment	No Pretreatment	Pretreatment	No Pretreatment	OR (95% CI)	Favors Pretreatment	Favors No Pretreatment	Heterogeneity	*P* for Trend x^2
Presenting feature									
Elective PCI	53	50	820	816	1.05 (0.70-1.57)			5.1	.08
NSTE ACS	329	414	2366	2408	0.78 (0.66-0.91)				
STEMI	39	70	1097	1101	0.54 (0.36-0.81)				
Loading dose									
≤300 mg	363	472	3299	3338	0.74 (0.63-0.87)			1.18	.28
600-900 mg	58	62	984	987	0.93 (0.64-1.36)				



Bellemain-Appaix A et al. *JAMA* 2012;308:2507-16.

PRINCIPLE – TIMI 44: Acute phase

201 pts undergoing elective PCI randomized to a loading dose of 600 mg clopidogrel vs. 60 mg prasugrel

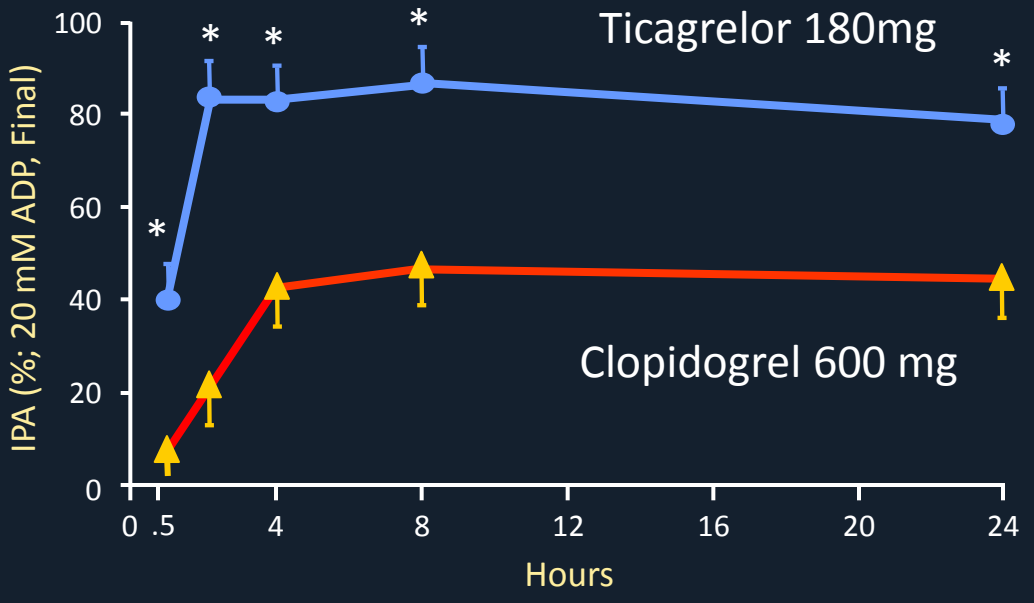


Wiviott SD et al. Circulation 2007;116:2923-32

Clopidogrel vs. Ticagrelor

ONSET/OFFSET Study

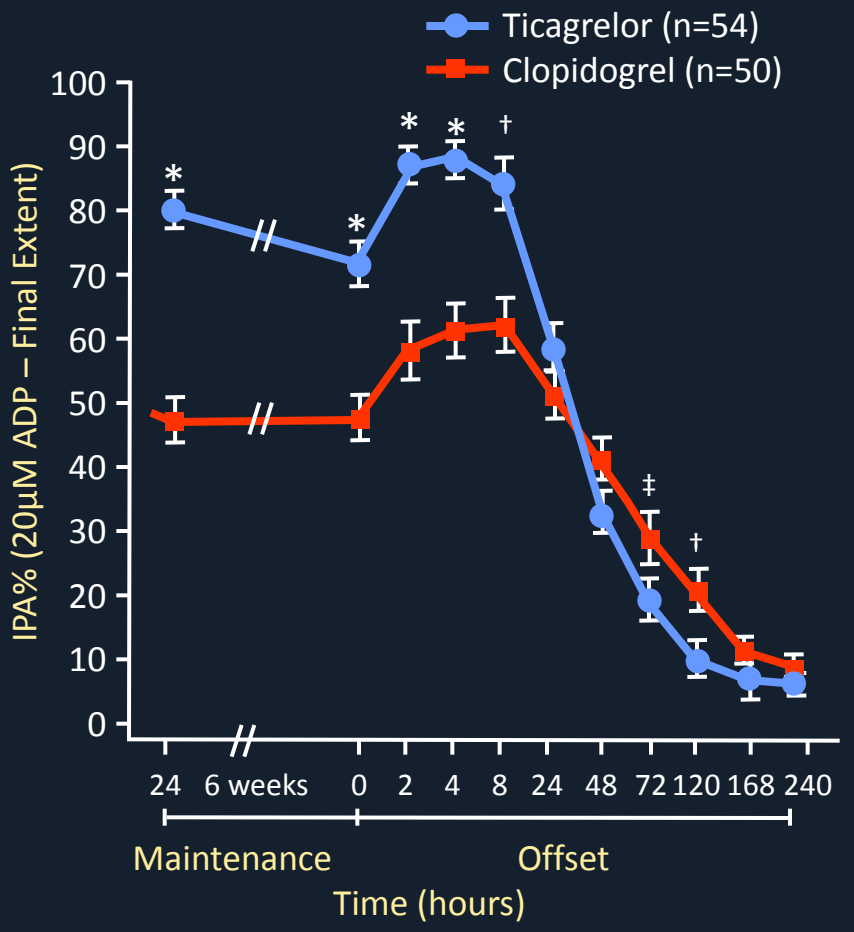
Loading



Ticagrelor vs clopidogrel.

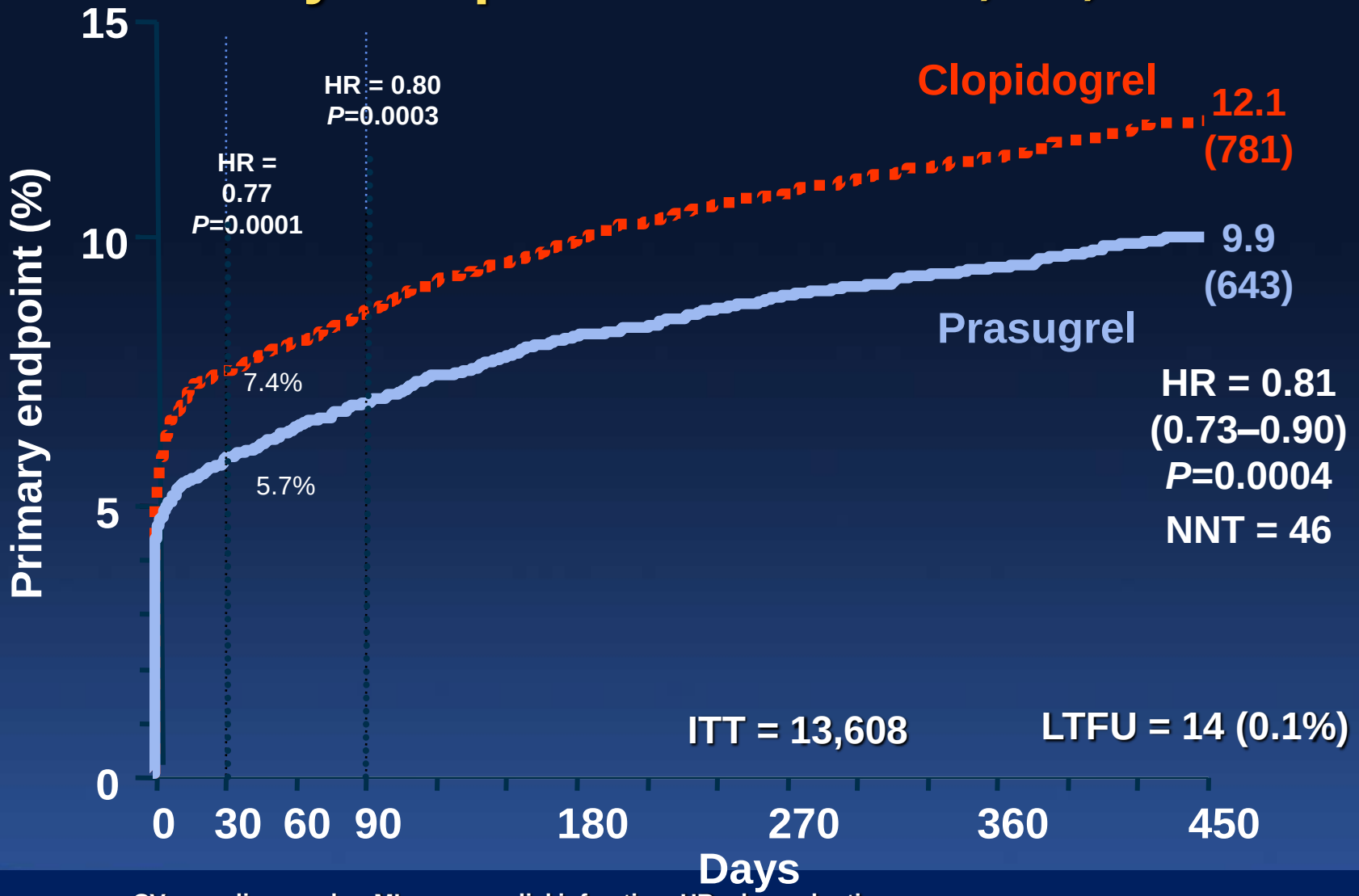
* *P*<0.0001; † *P*<0.005; ‡, *P*<0.05

Maintenance and Offset



Gurbel PA et al. *Circulation*. 2009;120:2577-85.

TRITON-TIMI 38
Primary Endpoints: CV Death, MI, Stroke

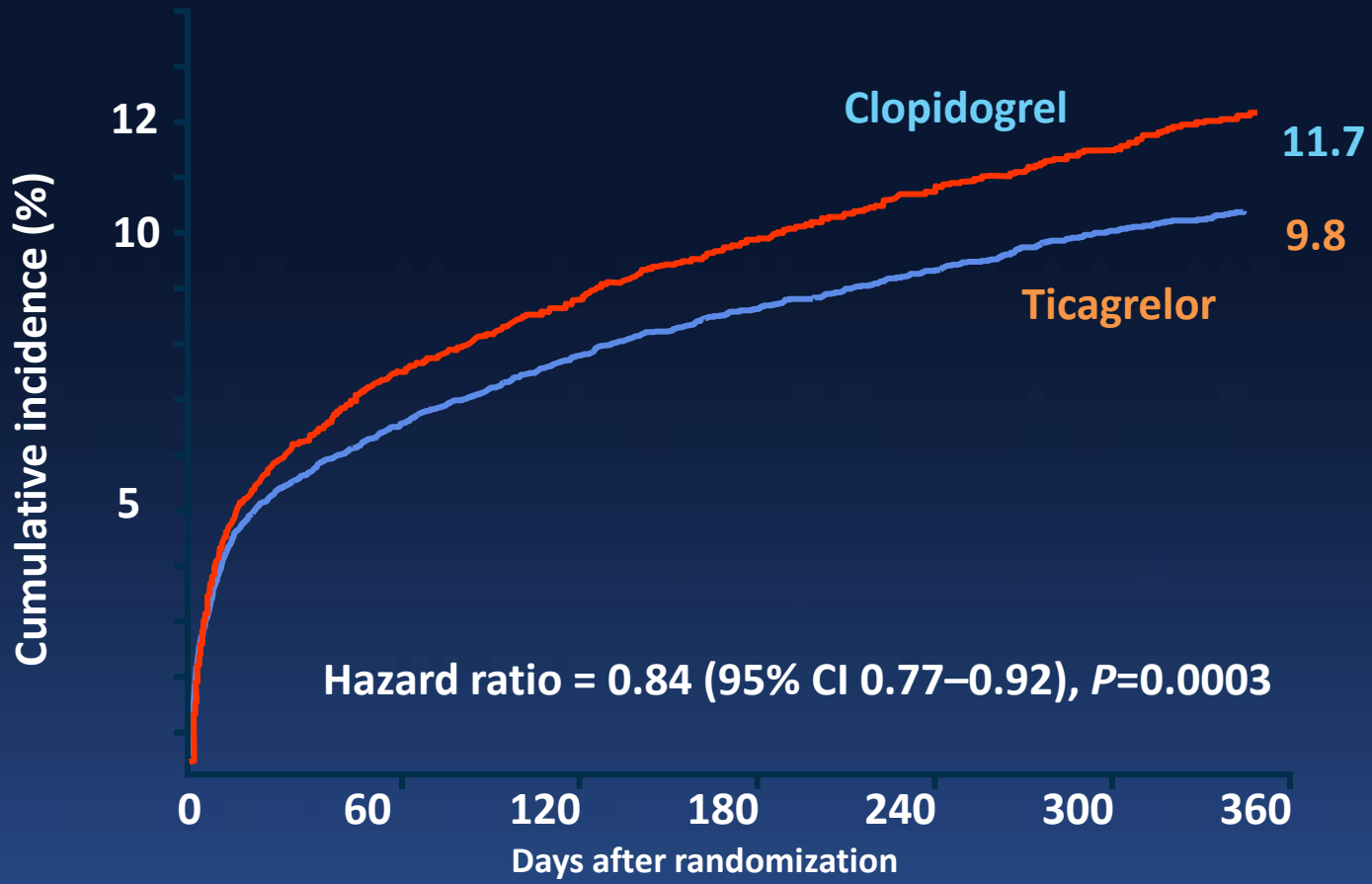


CV = cardiovascular; MI = myocardial infarction; HR = hazard ratio.

Wiviott SD et al. *N Engl J Med.* 2007;357:2001-2015.

Slide courtesy of Dr. Elliott Antman

Ticagrelor vs. Clopidogrel Endpoints: CV Death, MI, or Stroke

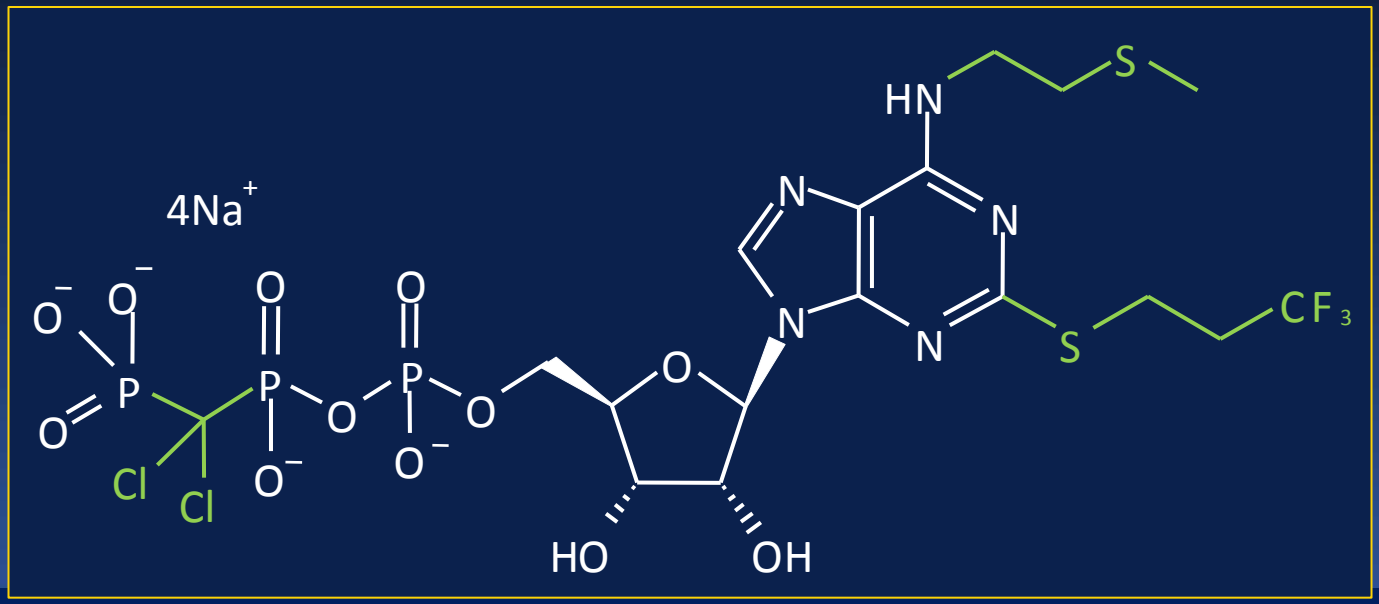


No. at Risk							
Ticagrelor	9333	8628	8460	8219	6743	5161	4147
Clopidogrel	9291	8521	8362	8124	6743	5096	4047

Wallentin L et al. *N Engl J Med*. 2009;361:1045-1057.

Cangrelor

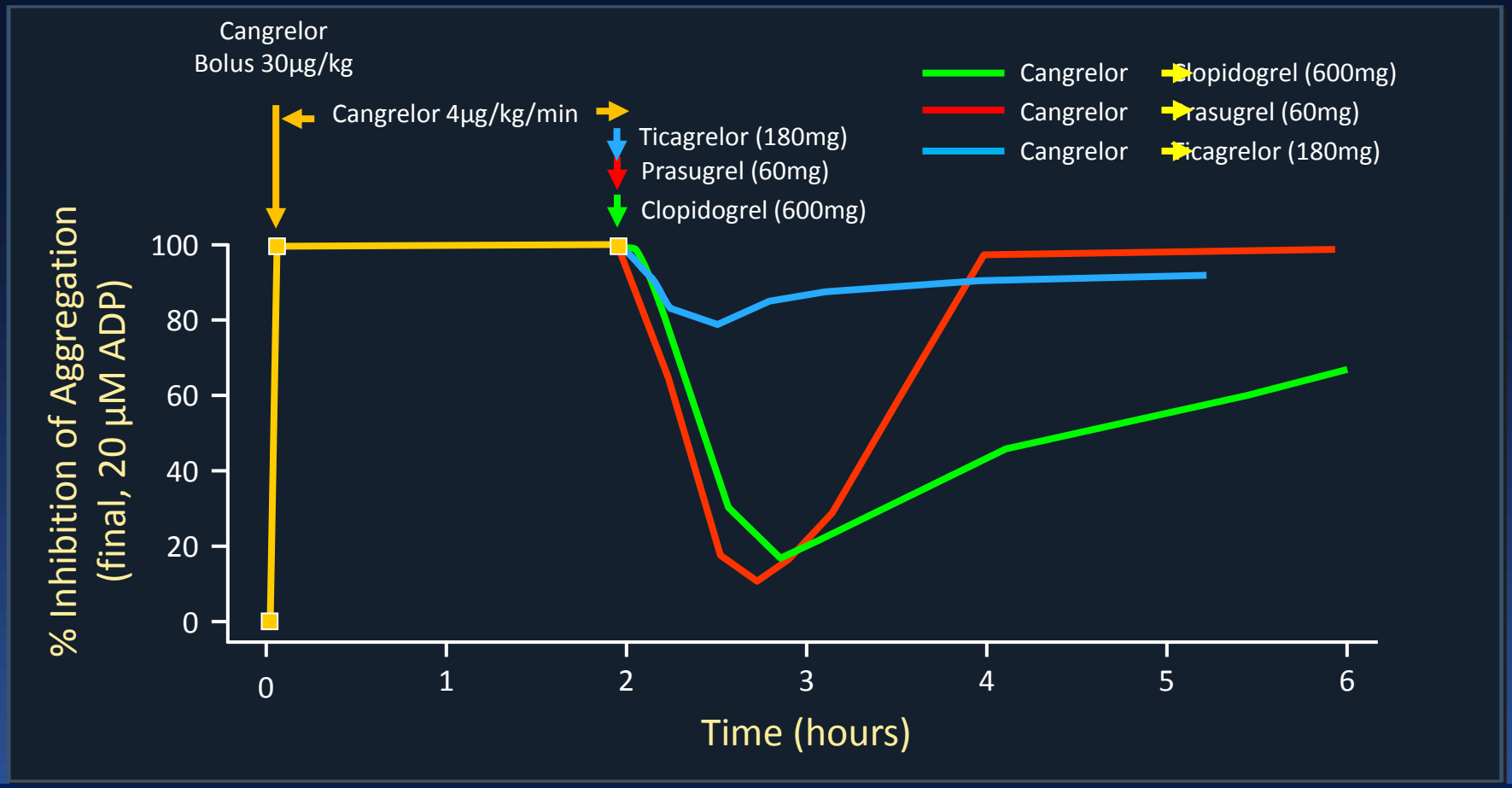
- Direct $P2Y_{12}$ receptor antagonist (non thienopyridine)
  - ATP analogue; MW=800 Daltons
    - Parenteral administration
      - $T_{1/2}$ = 3 to 6 minutes
      - Offset = 60 minutes



Angiolillo DJ et al. *J Thromb Thrombolysis* 2012;34:44-55

Transition: Cangrelor to Oral $P2Y_{12}$ Inhibitors

Platelet aggregation response to 20 µm ADP as measured by light transmittance aggregometry during the transition from cangrelor to clopidogrel, prasugrel, or ticagrelor



Data on file, The Medicines Company

CHAMPION PHOENIX
Death/ MI/ IDR/ Stent Thrombosis within 48h

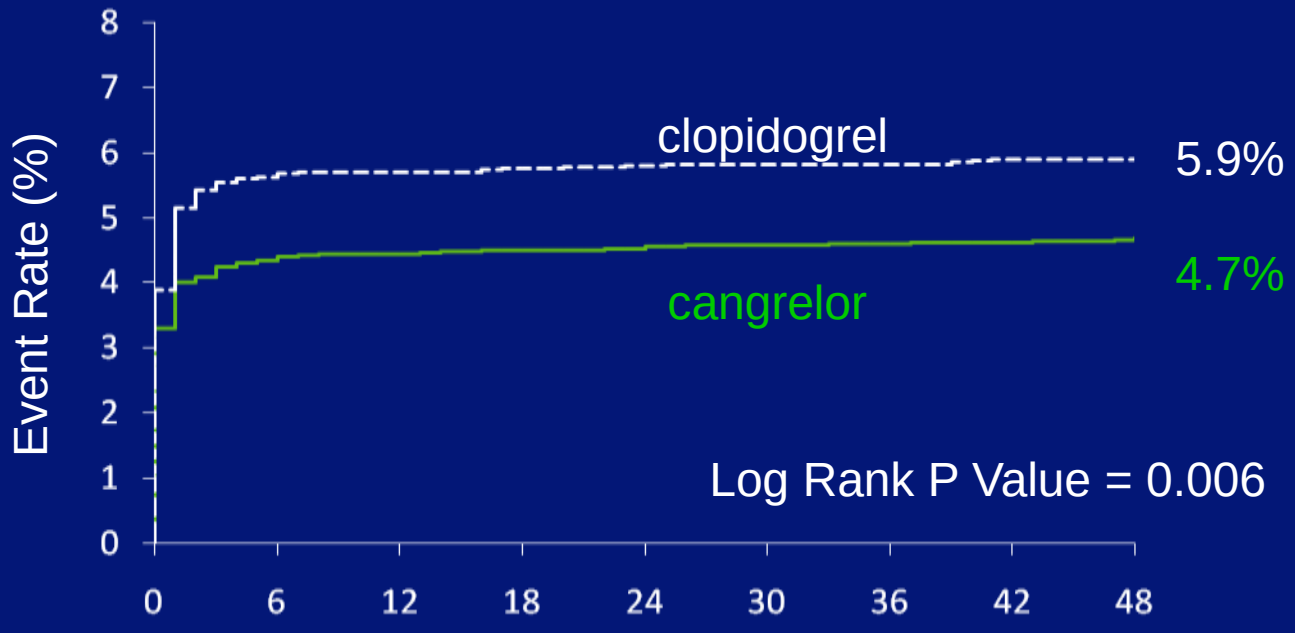
CHAMPION PHOENIX

N = 10,900 MITT

SA/ NSTE-ACS/ STEMI

Patients requiring PCI[1]

$P2Y_{12}$ inhibitor naïve



Patient at Risk									
Cangrelor:	5472	5233	5229	5225	5223	5221	5220	5217	5213
Clopidogrel:	5470	5162	5159	5155	5152	5151	5151	5147	5147

Bhatt DL, et al. N Engl J Med 2013; 368:1303-13.

ESC STEMI Guidelines 2017

Periprocedural and post-procedural antithrombotic therapy[a] in patients undergoing primary percutaneous coronary intervention

Recommendations	Class[b]	Level[c]
Antiplatelet therapy		
GP IIb/IIIa inhibitors should be considered for bailout if there is evidence of no-reflow or a thrombotic complication.	IIa	C
Cangrelor may be considered in patients who have not received $P2Y_{12}$ receptor inhibitors.[192–194]	IIb	A

Tirofiban versus Prasugrel in STEMI
The FABULOS PRO Trial

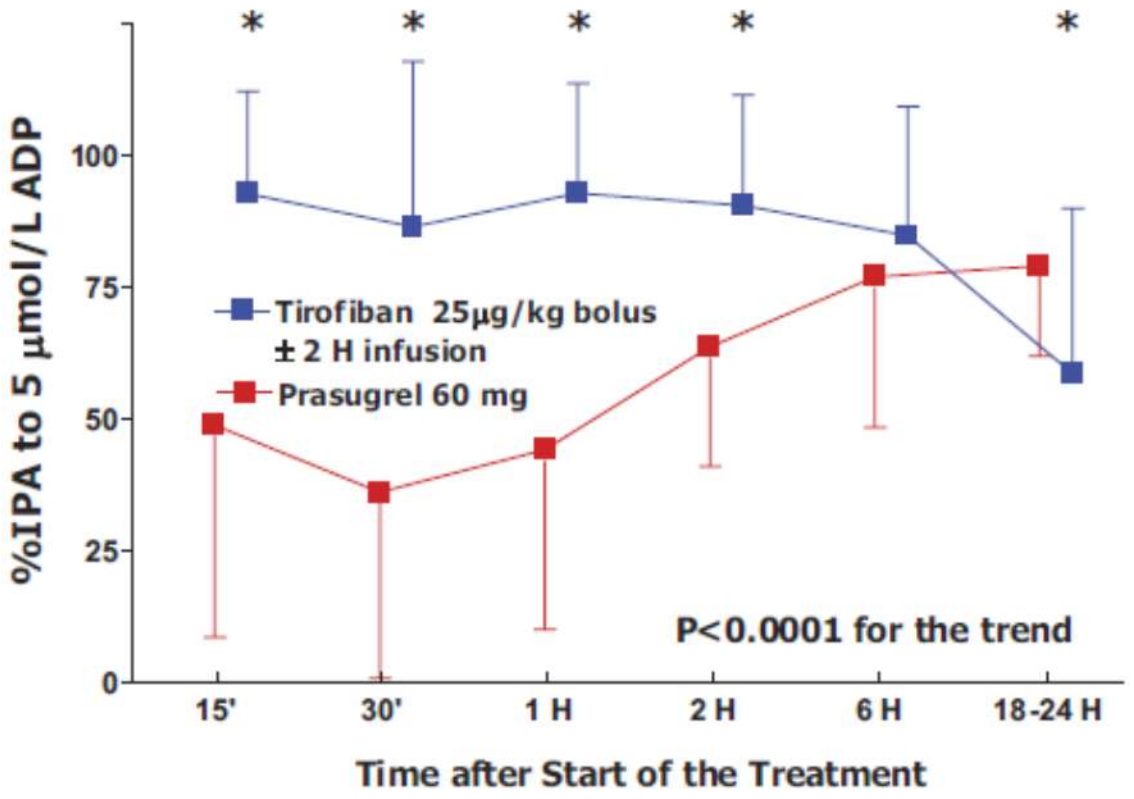
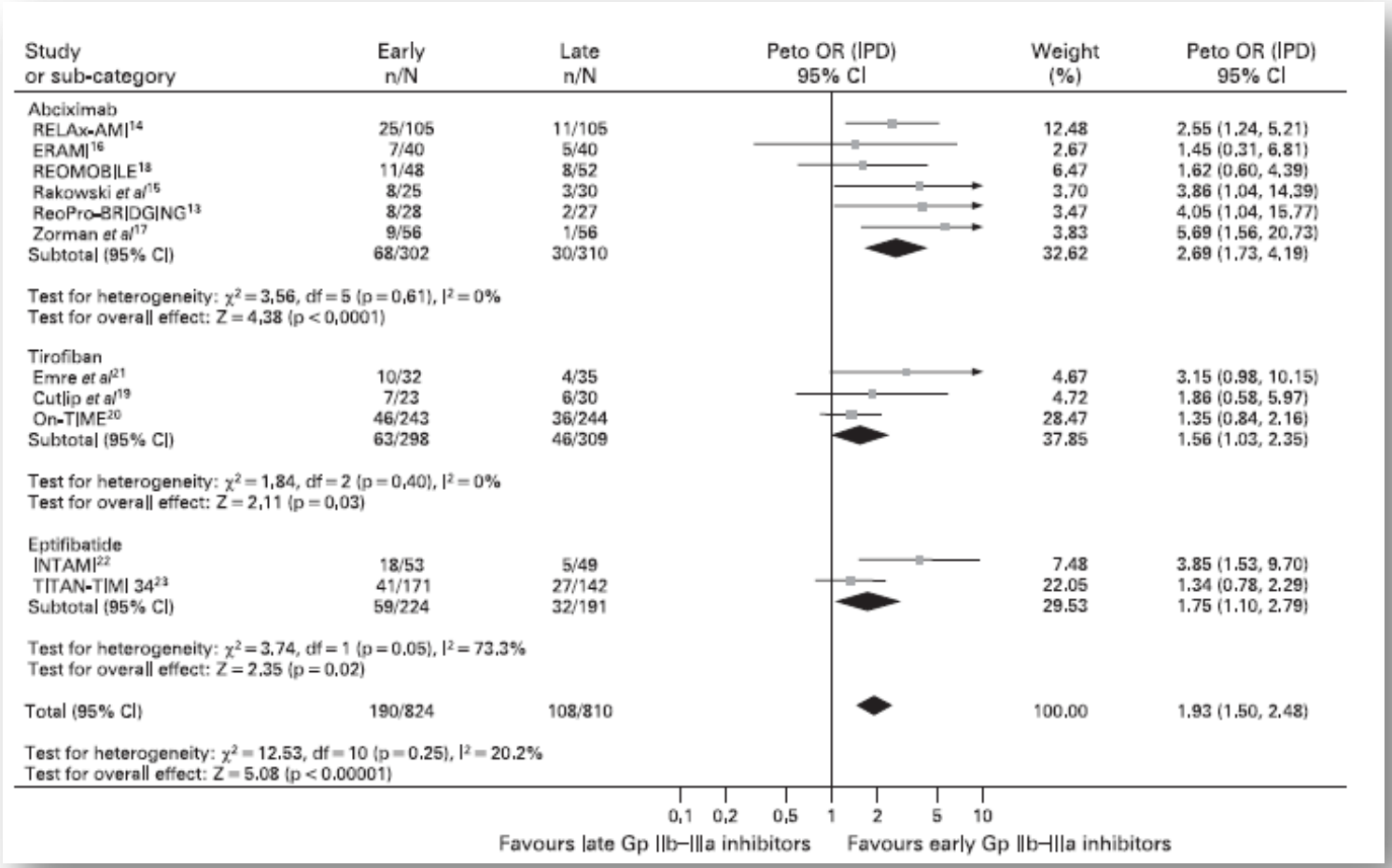


Figure 3. Kinetics of Platelet Inhibition Over Time After 5 µmol/l ADP

Valgimigli M et al. JACC Intv 2012; 5: 268-77

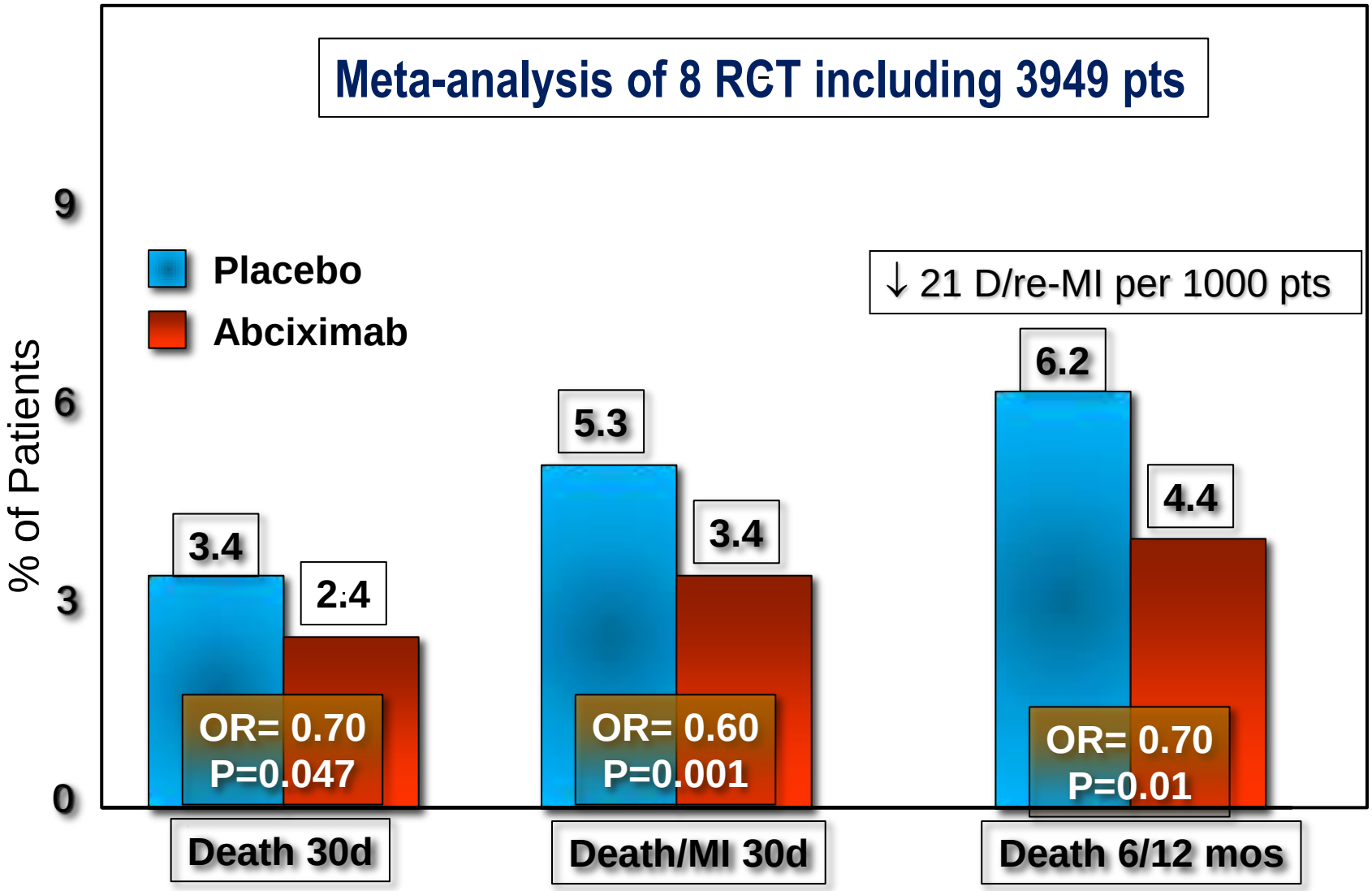
GPI's and pre-PCI TIMI flow in STEMI

Flusso TIMI 3 pre-PCI - 23% vs. 13.3%, p<0.001



De Luca G, et al. Heart 2008; 94: 1548–1558

GP IIb/IIIa inhibitors in primary PCI



De Luca G., et al. JAMA 2005; 293:759-64

Impact of GPI in contemporary PCI for ACS

The National Cardiovascular Data Registry CathPCI Registry

TABLE 2 Unadjusted and Risk-Adjusted In-Hospital Outcomes

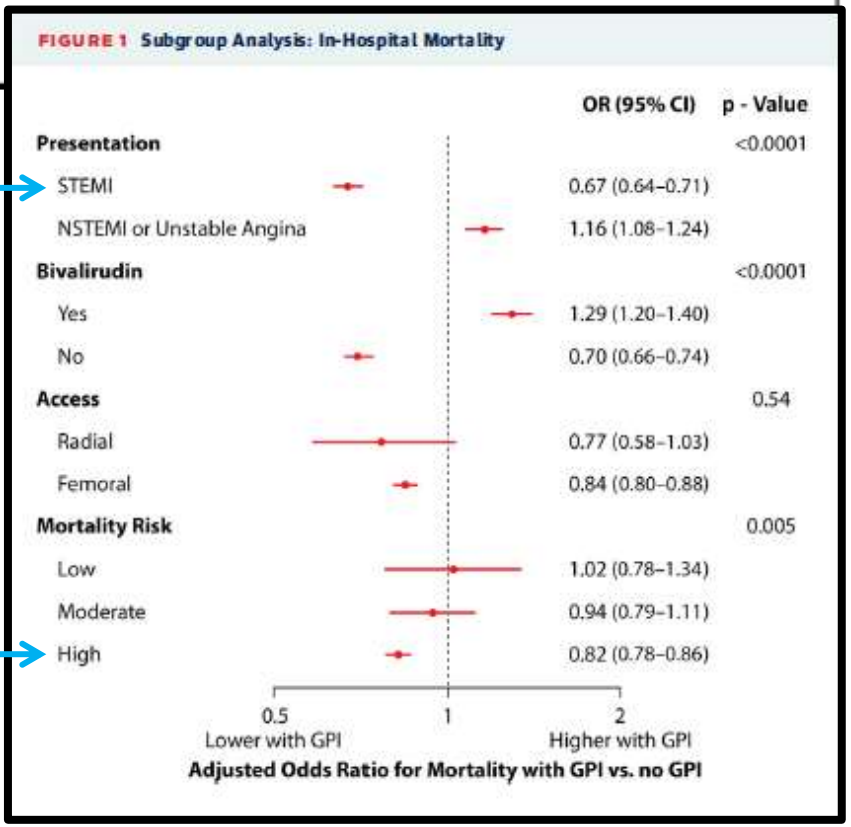
Outcome	GPI (n = 326,283)	No GPI (n = 644,582)	Unadjusted OR	95% CI	p Value	Adjusted OR	95% CI	p Value
Mortality	7,817 (2.4)	8,886 (1.4)	1.76	1.70–1.81	<0.001	0.83	0.79–0.88	<0.001
Major bleeding within 72 h	12,069 (3.7)	9,457 (1.5)	2.58	2.51–2.65	<0.001	1.56	1.51–1.61	<0.001

Values are n (%) unless otherwise indicated.

CI = confidence interval; GPI = glycoprotein IIb/IIIa inhibitor; OR = odds ratio.

970.865 patients included

326.283 receiving GPI (33.6%)



Safley DM, et al. JACC Cardiol Interv 2015;8:1574-82

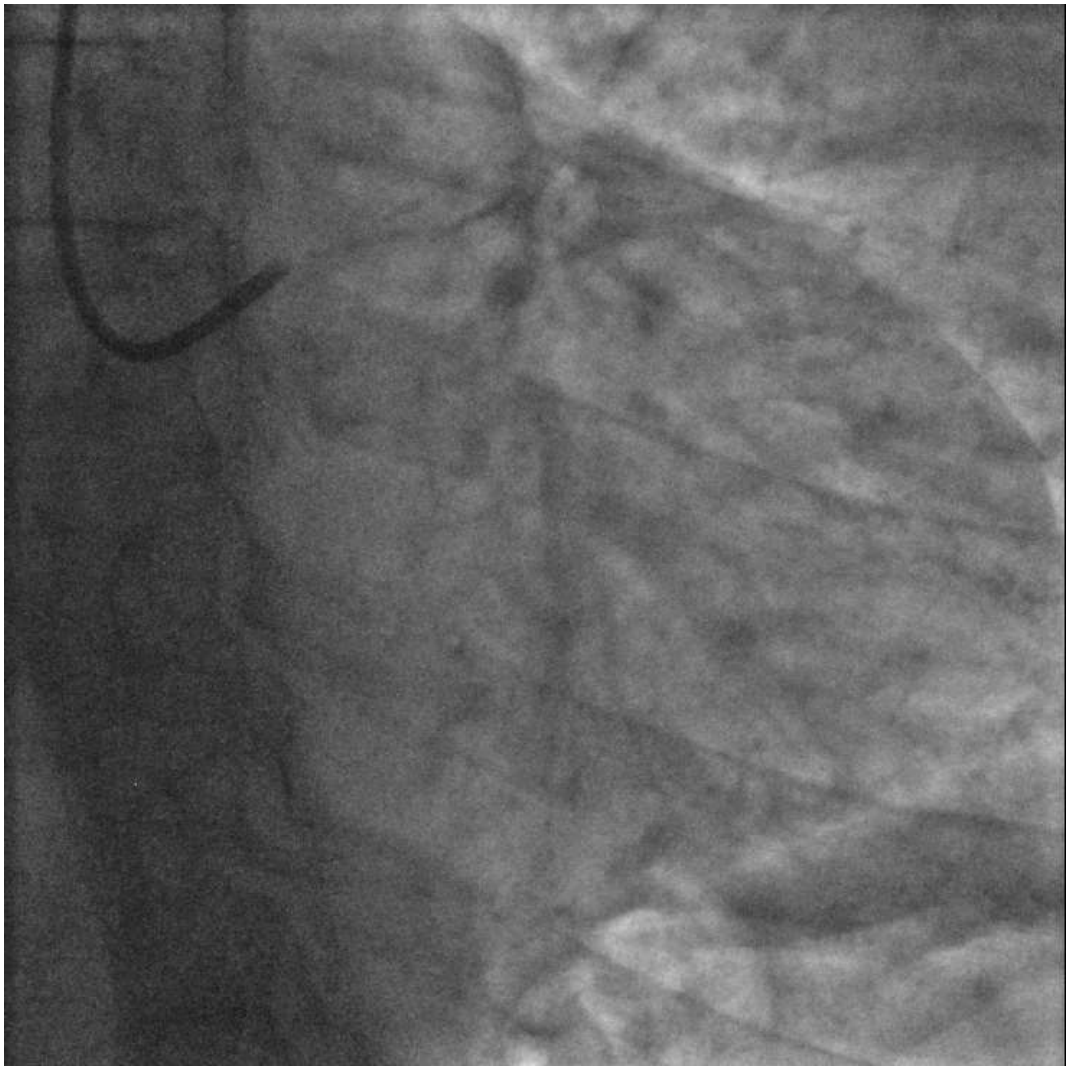
How to optimise GPI use

- Patient selection
- Drug choice
- Timing of administration
- Bleeding reducing strategies

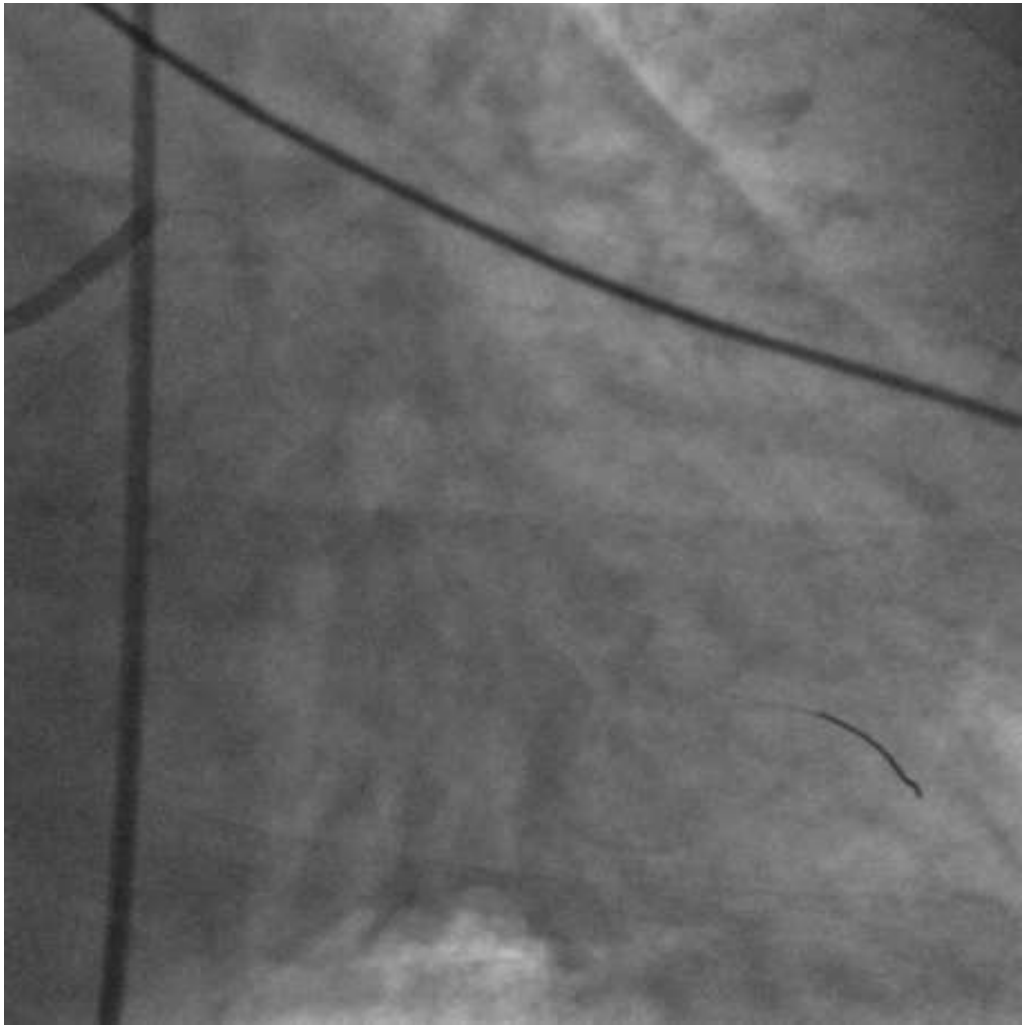
How to optimise GPI use

- **Patient selection**
- Drug choice
- Timing of administration
- Bleeding reducing strategies

68 yrs old patient, anterior STEMI, Killip IV



Male, 81 yr, posterolater STEMI, Killip 1
PA 150/90 mmHG, 3 h from symptoms onset



Patient-oriented choice of GPI use

- Higher ischemic risk
- Younger patients
- Early presenters
- High risk of stent thrombosis
- Large thrombus burden at angiogram
- Severe multivessel disease
- Cardiogenic shock
- High-risk patients transferred from spokes (consider upstream)

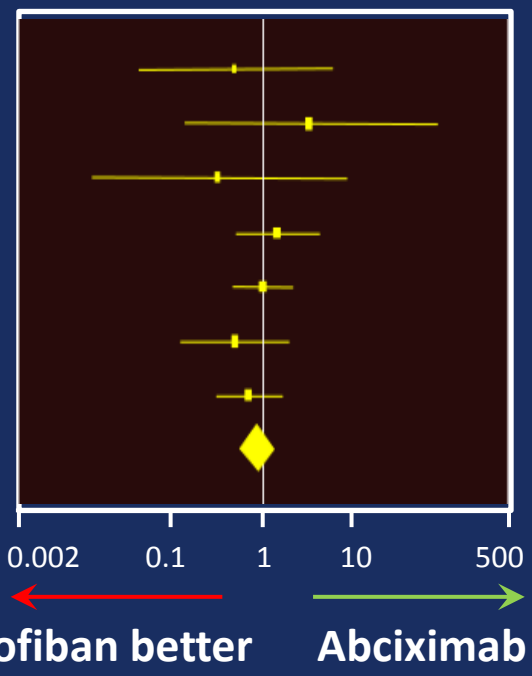
How to optimise GPI use

- Patient selection
- **Drug choice**
- Timing of administration
- Bleeding reducing strategies

Meta-Analysis: HDB Tirofiban vs. Abciximab 30-Day Death or Myocardial Infarction

Tirofiban 25 µg/kg bolus regimen

Study	Tirofiban n/N	Abciximab n/N	Odds Ratio (95% CI)
Danzi	1/50	2/50	0.49 (0.04 - 5.58)
Ernst	1/29	0/30	3.21 (0.13 - 82.07)
EVEREST	0/30	1/30	0.32 (0.01 - 8.24)
FATA	9/351	6/341	1.47 (0.52 - 4.17)
MULTISTRATEGY	14/372	14/372	1.00 (0.47 - 2.13)
STRATEGY	3/87	6/88	0.49 (0.12 - 2.02)
TENACITY	11/189	16/194	0.69 (0.31 - 1.52)
Total	**39/1108**	**45/1105**	**0.87 (0.56 - 1.35)**

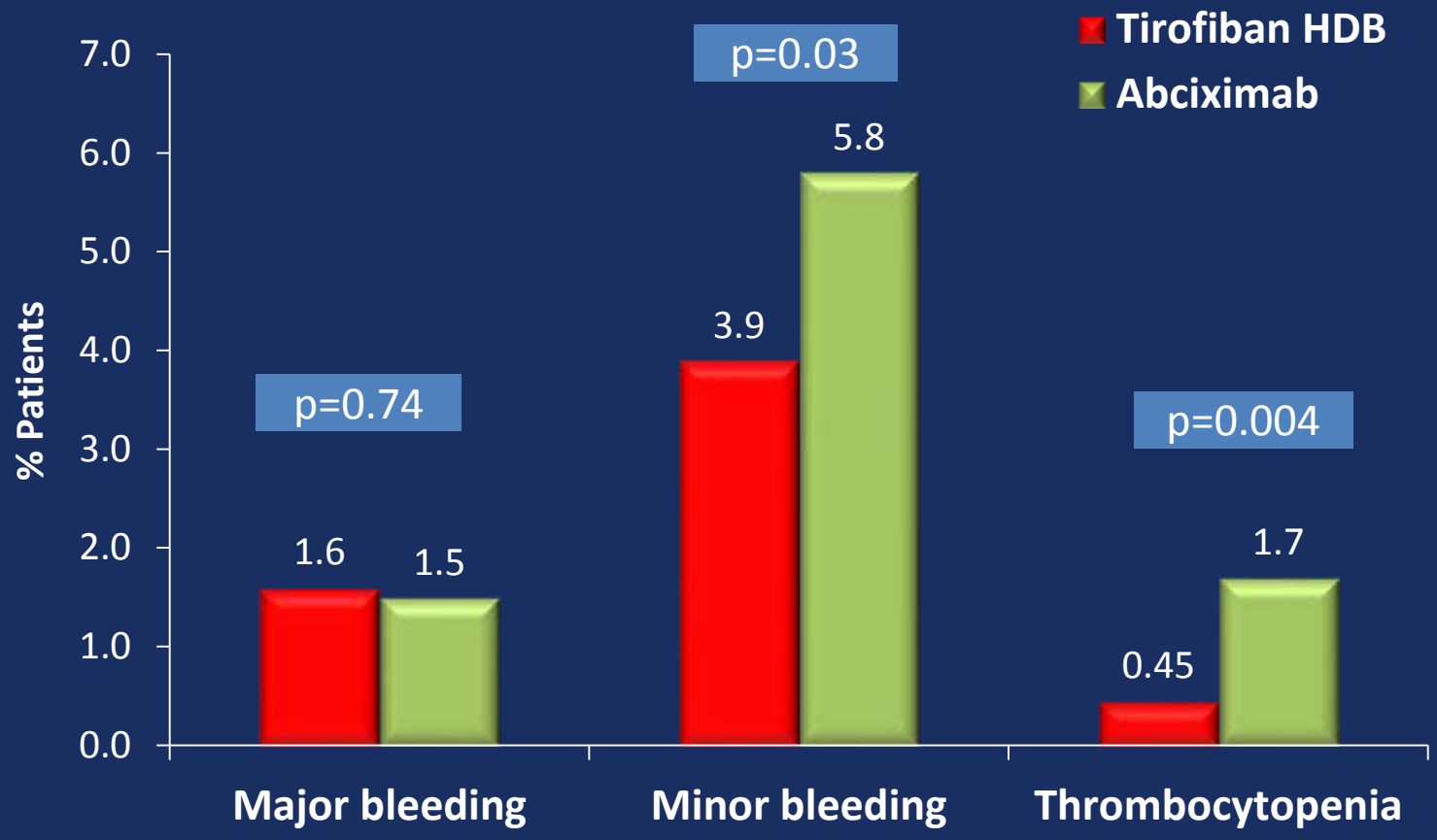


Heterogeneity: Tau^2=0.00, Chi^2=5.63, df=7 (p=0.58), I^2=0%

Test for overall effect: Z=1.61 (p=0.11)

Modified from Valgimigli M et al. Eur Heart J 2010;31:35-49

Meta-Analysis:
Safety of HDB Tirofiban vs. Abciximab in ACS



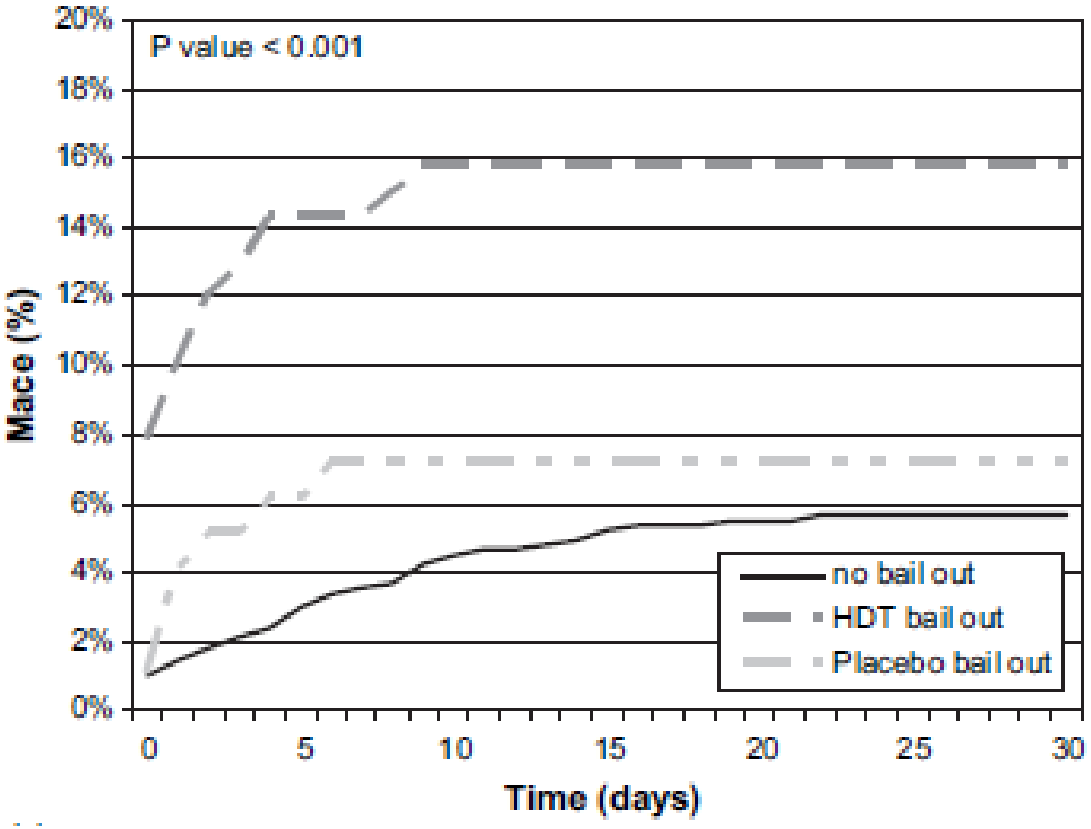
Valgimigli et al.Exp Op Drug Saf 2010;9:801-819

How to optimise GPI use

- Patient selection
- Drug choice
- **Timing of administration**
- Bleeding reducing strategies

High-dose-tirofiban bail-out vs placebo bail-out

On-TIME 2 study



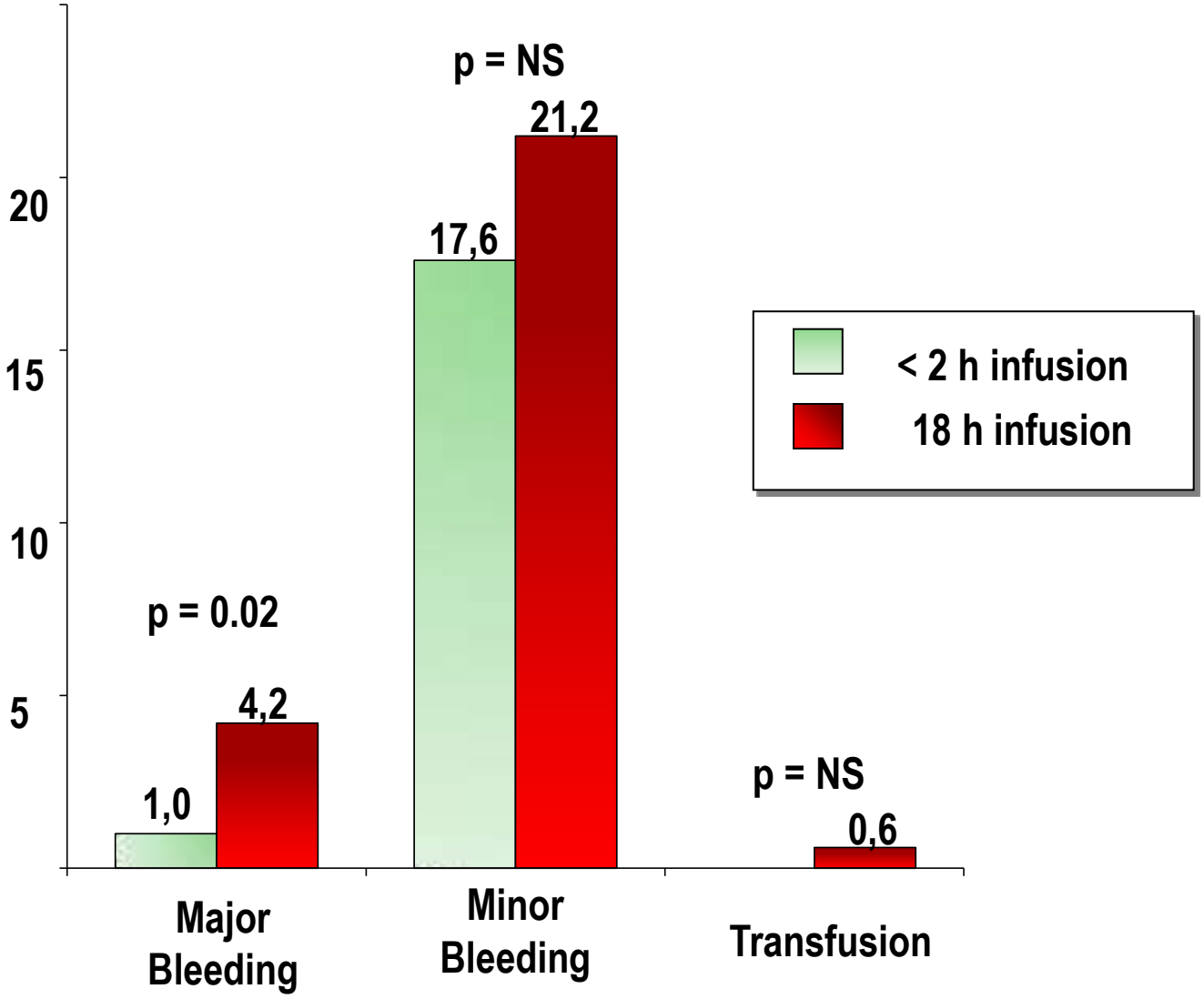
Hermanides RS, et al. Heart 2011;97:106-111

How to optimise GPI use

- Patient selection
- Drug choice
- Timing of administration
- **Bleeding reducing strategies**

BRIEF PCI

GPI infusion duration and bleeding complications



Fung AY, et al. JACC 2009;53:837-45

GPI strategy optimization in 2018

- **Carefully select patients**
- **Use radial access**
- **Carefully dose heparin**
- **Use GPI's provisionally after sheath insertion and coronary angiography**
- **Do NOT wait for bailout use**
- **Prefer reversible GPI's such as Tirofiban and administer high-bolus followed by short infusion**

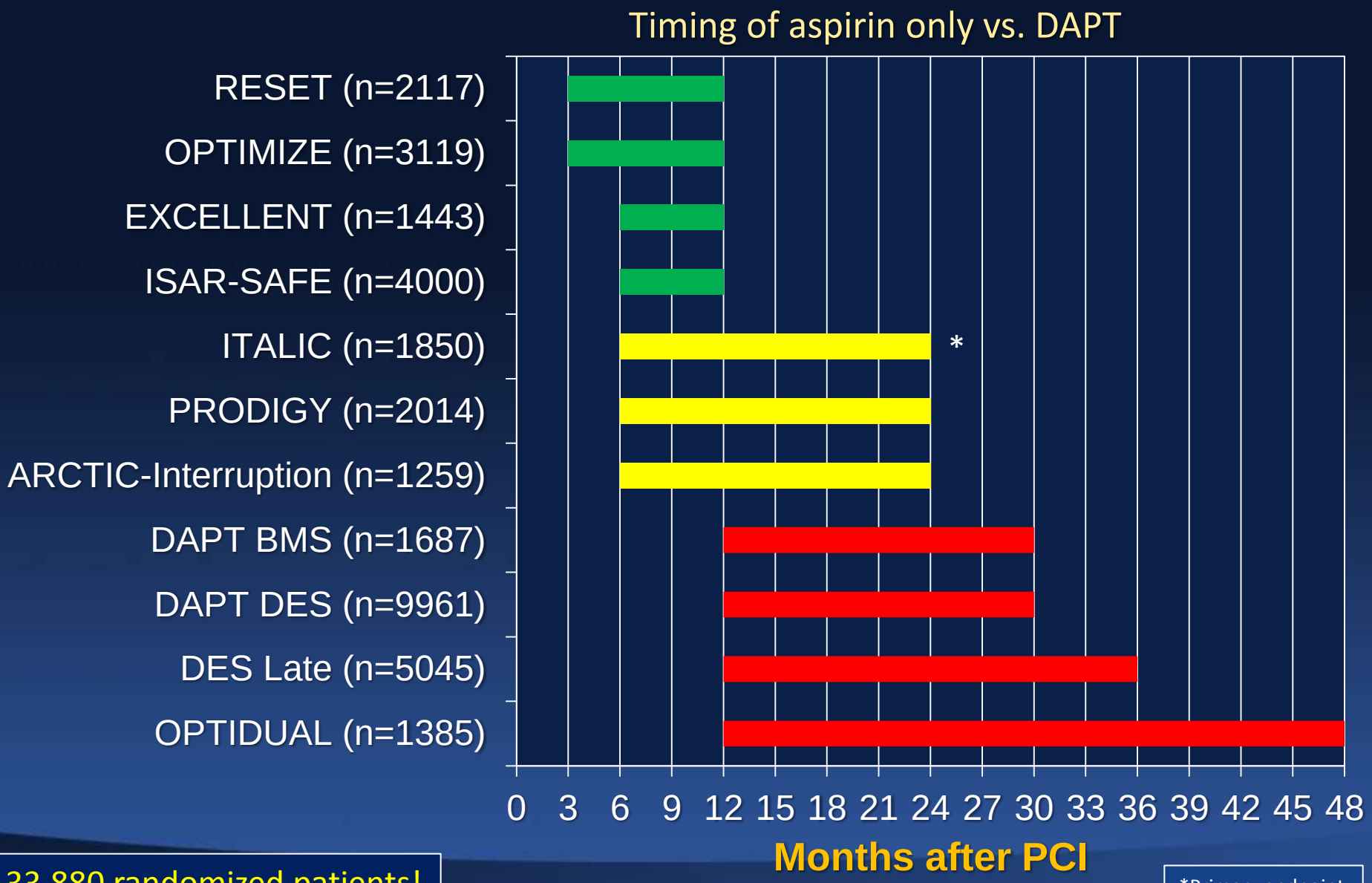
GPI's are still the best solution

YES

In STEMI at high thrombotic risk

In all settings for bailout use in case of procedural complications

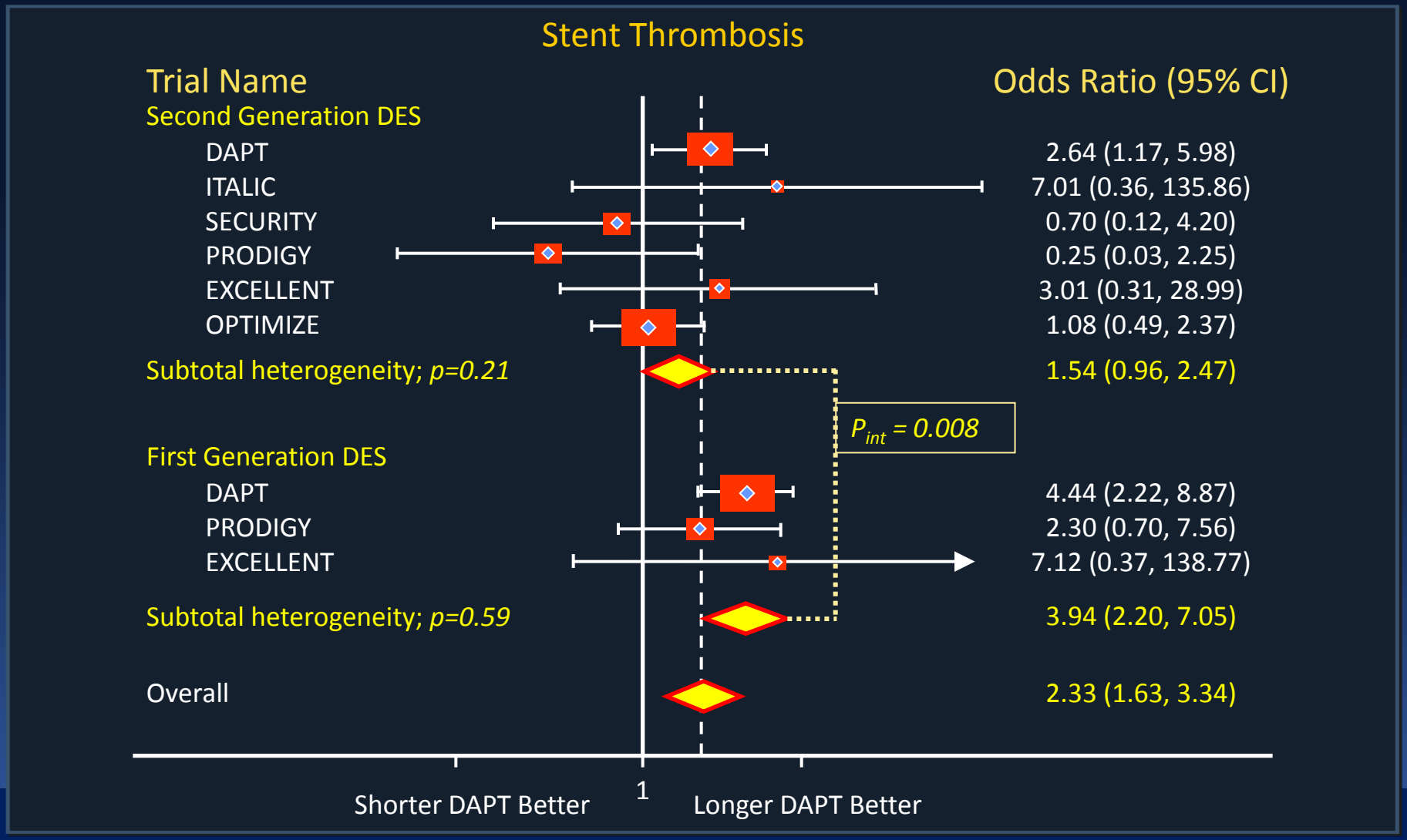
11 RCTs of DAPT Duration after Stenting



33,880 randomized patients!

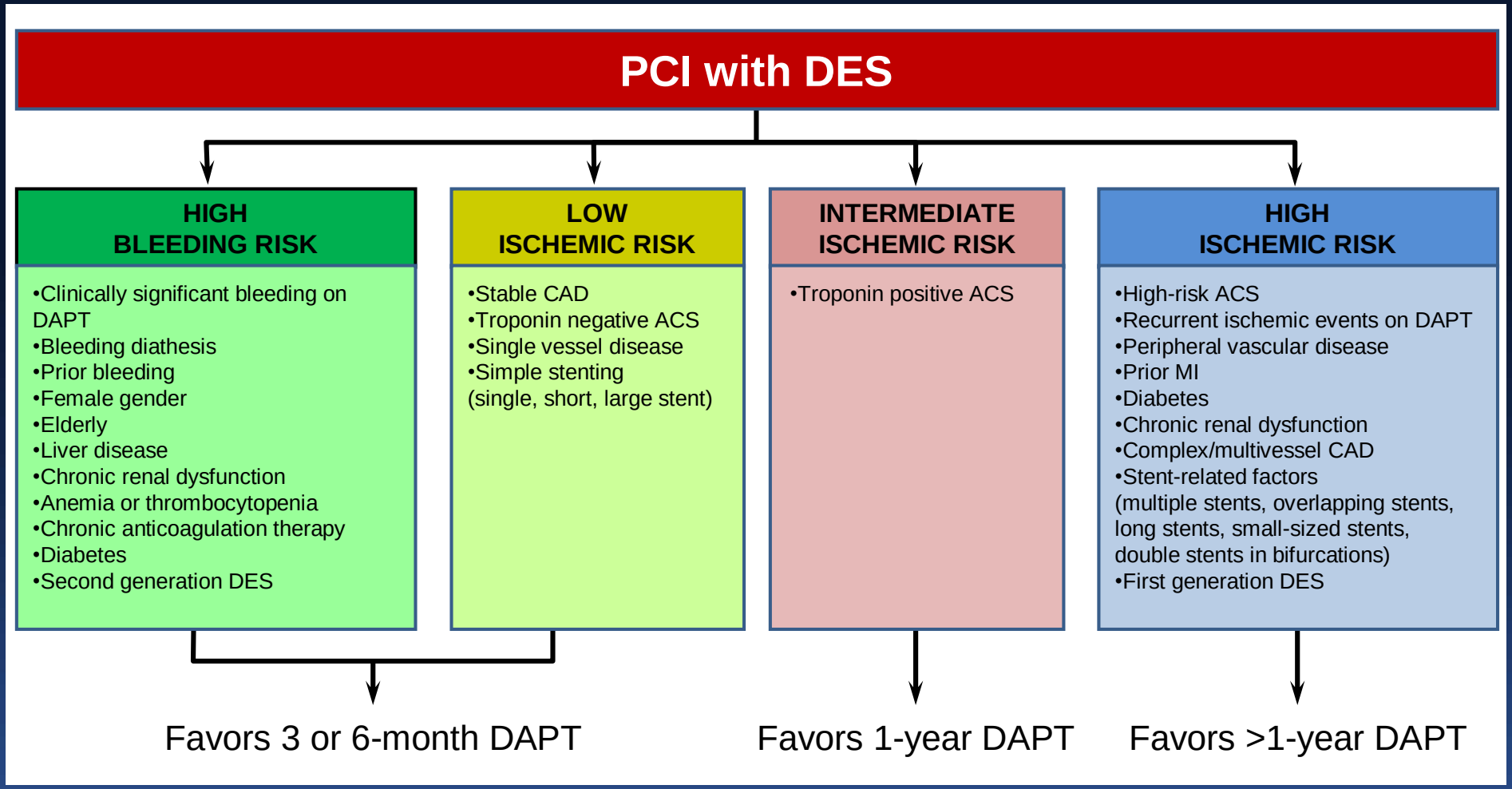
*Primary endpoint at 12 months

Extended Duration DAPT After DES: Second vs. First Generation DES



Giustino G et al. *JACC* 2015;65:1298–310

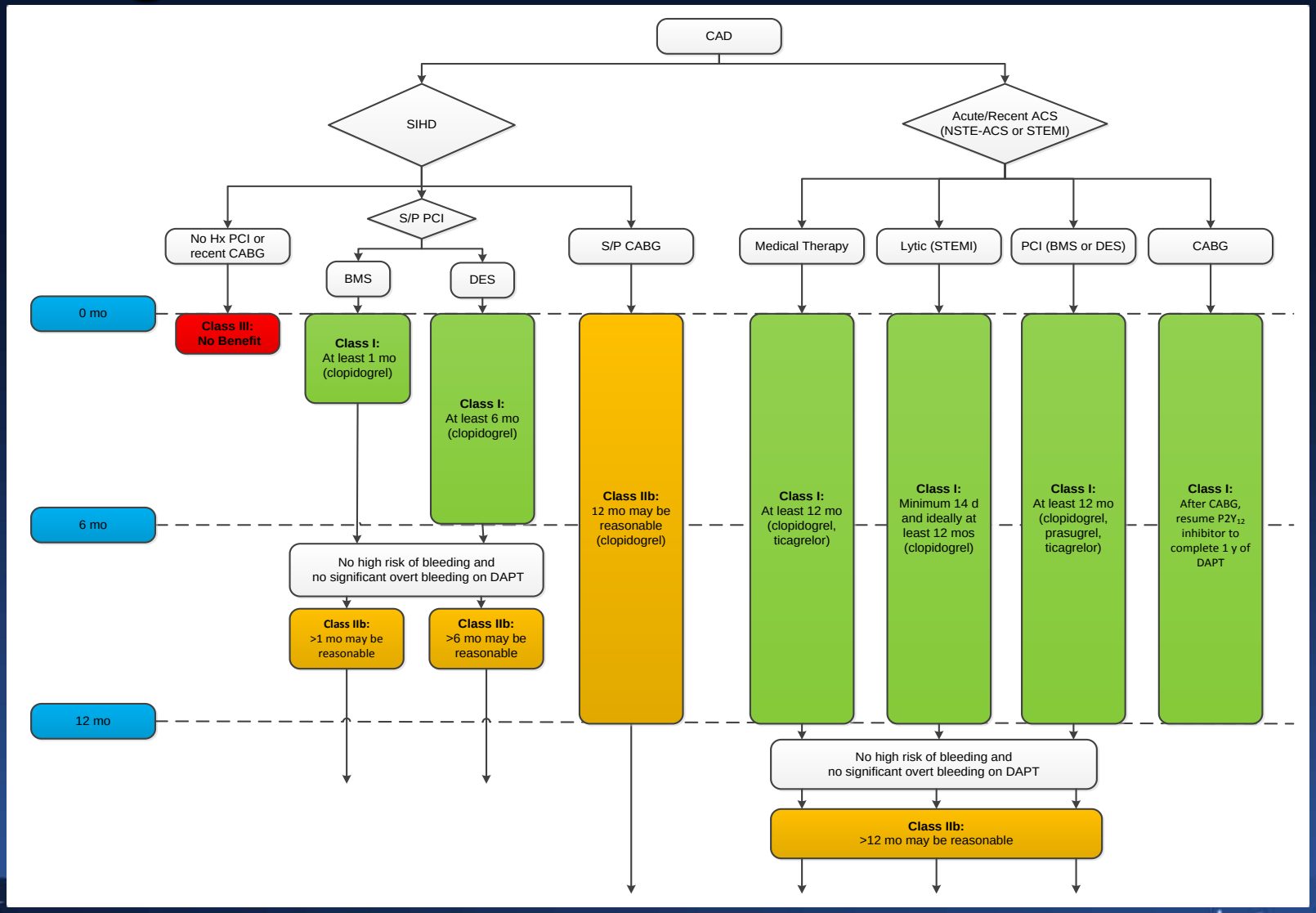
DAPT Duration: Factors to be weighed



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

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

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

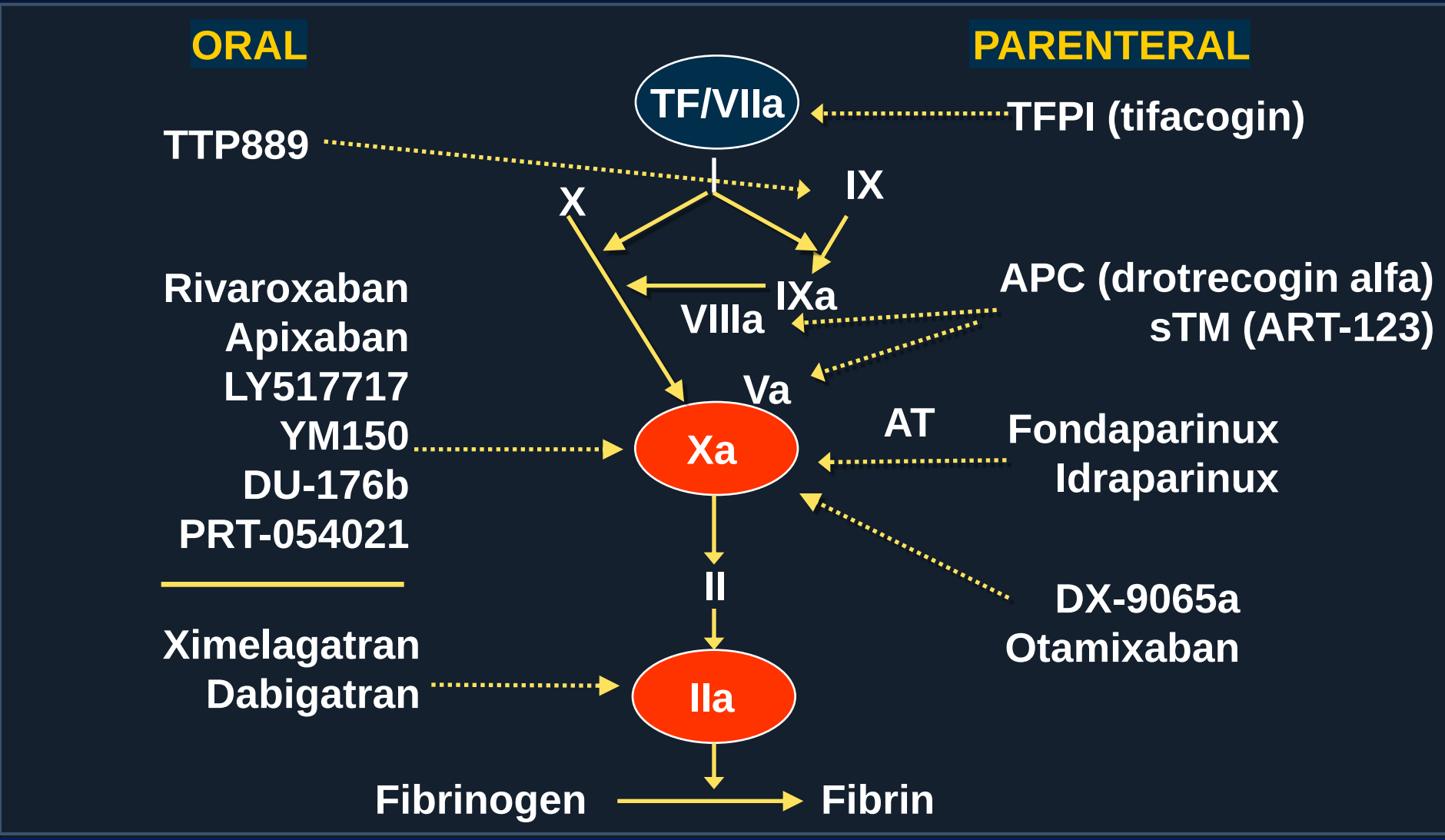


Levine GN et al. J Am Coll Cardiol. 2016;68:1082-115

Conclusions: Antiplatelet Agents in PCI

- **Aspirin to everyone:** 324 mg load (chewed), then 75-100 mg/day indefinitely
- **IV GPI bolus (IV Cangrelor):** consider in STEMI (+ ticagrelor) and NSTEMI (withhold oral agent) ± high-risk non-pre-loaded stable CAD
- **Ticagrelor:** for most ACS pts (preload in STEMI, and in NSTEMI) > prasugrel or clopidogrel
- **Clopidogrel:** for most pts w/stable CAD, preloaded or post-PCI; **consider cangrelor (GPI bolus)** in complex PCI pts not preloaded
- **DAPT duration after DES: 1 month – indefinite** Individualize according to the relative risks of bleeding vs. ischemia

New Antithrombin Targets



Adapted from Weitz & Bates, *J Thromb Haemost* 2005

PK/PD of 5 Novel Oral Agents

	Dabigatran	Apixaban	Rivaroxaban	Edoxaban (DU-176b)	Betrixaban (PRT054021)
Target	IIa (thrombin)	Xa	Xa	Xa	Xa
Hrs to Cmax	2	1-3	2-4	1-2	NR
CYP Metabolism	None	15%	32%	NR	None
Half-Life	12-14h	8-15h	9-13h	8-10h	19-20h
Renal Elimination	80%	33%	33%	35%	<5%

CYP = cytochrome P450; NR = not reported

Ruff CR and Giugliano RP. Hot Topics in Cardiology 2010;4:7-14
Ericksson BI et al. Clin Pharmacokinet 2009; 48: 1-22
Ruff CR et al. Am Heart J 2010; 160:635-41

Incidence of Atrial Fibrillation in ACS Patients

2 % to 21% of ACS Patients [1]

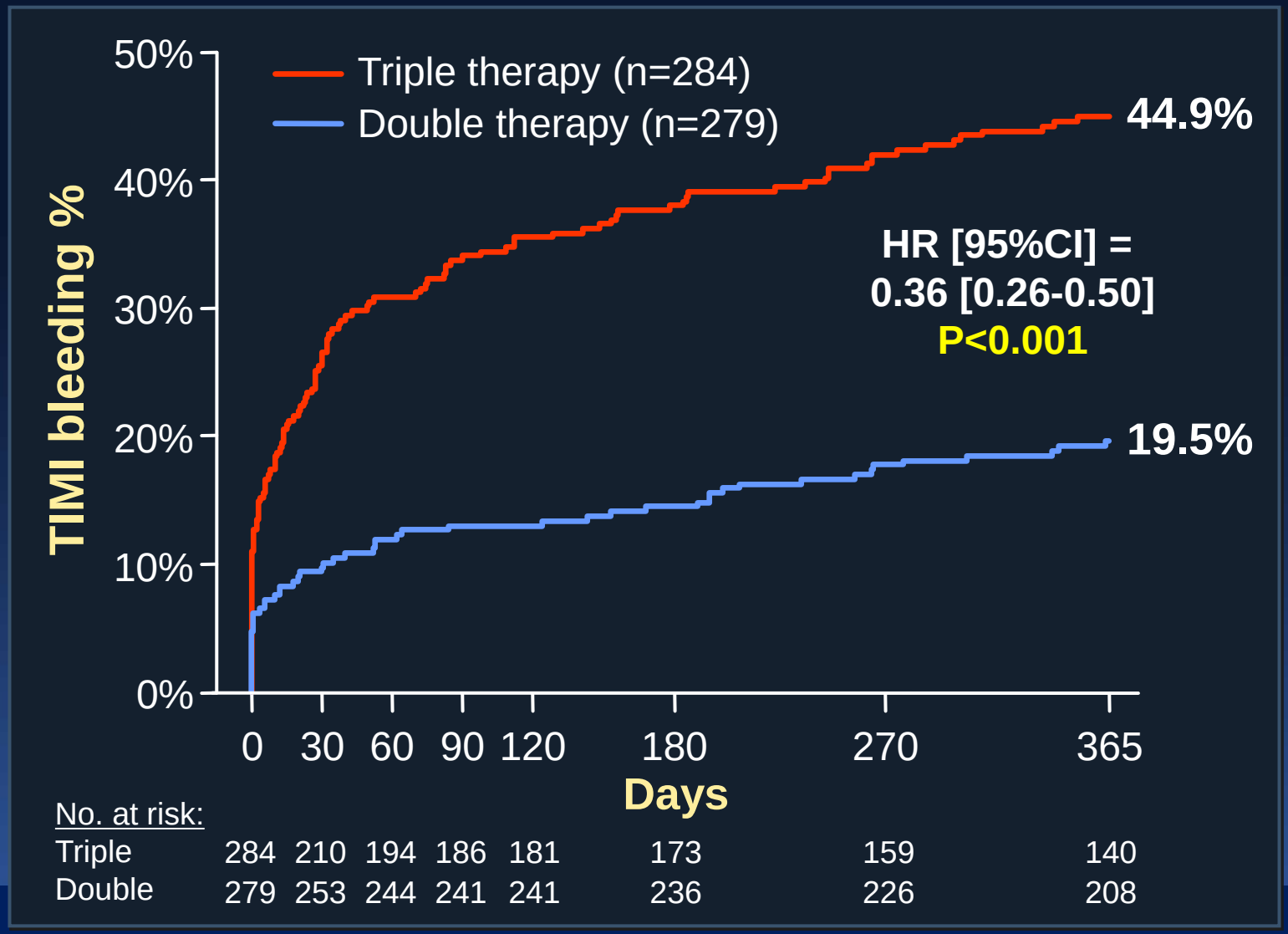
Acute Coronary Syndrome

ACS + Afib

Atrial Fibrillation

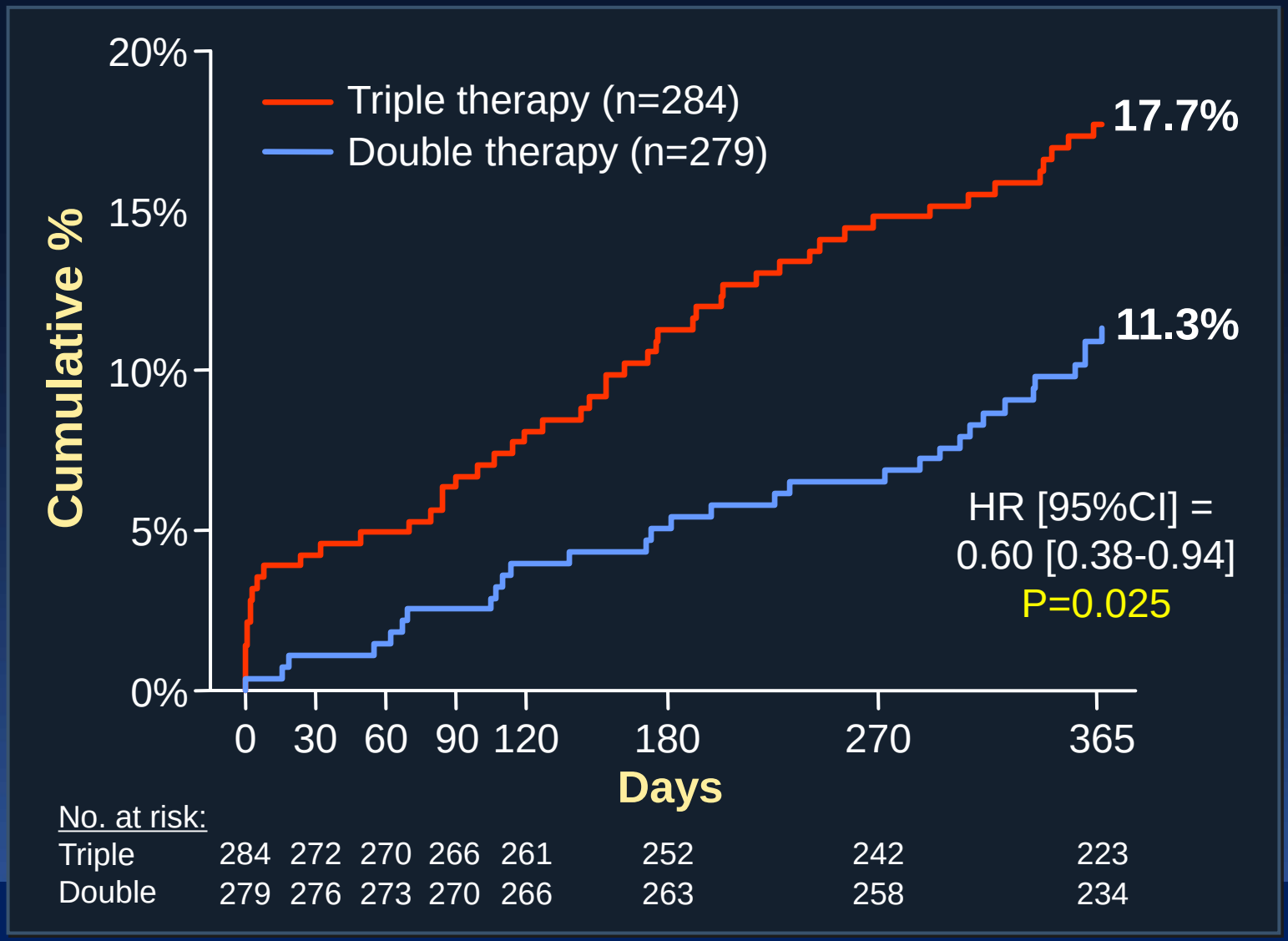
1. Schmitt J et al Atrial fibrillation in acute myocardial infarction: a systematic review of the incidence, clinical features and prognostic implications. Eur Heart J 2009;30:1038–1045.

WOEST Primary Endpoint:
TIMI Major, Minor or Minimal Bleeding



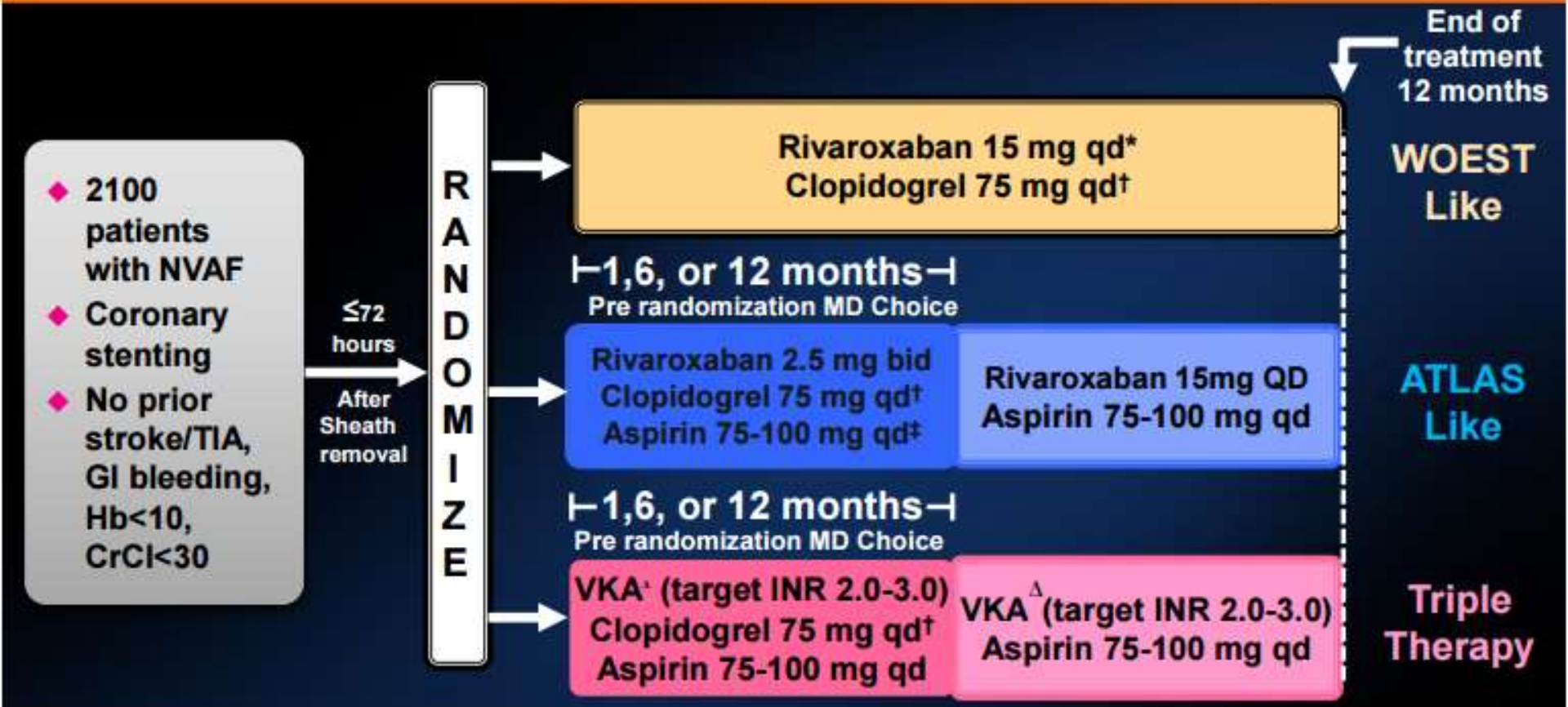
Dewilde WJM et al. Lancet 2013

WOEST Secondary Endpoint:
Death, stroke, MI, ST, or TVR



Dewilde WJM et al. Lancet 2013

Patients With Atrial Fibrillation Undergoing Coronary Stent Placement: PIONEER AF-PCI

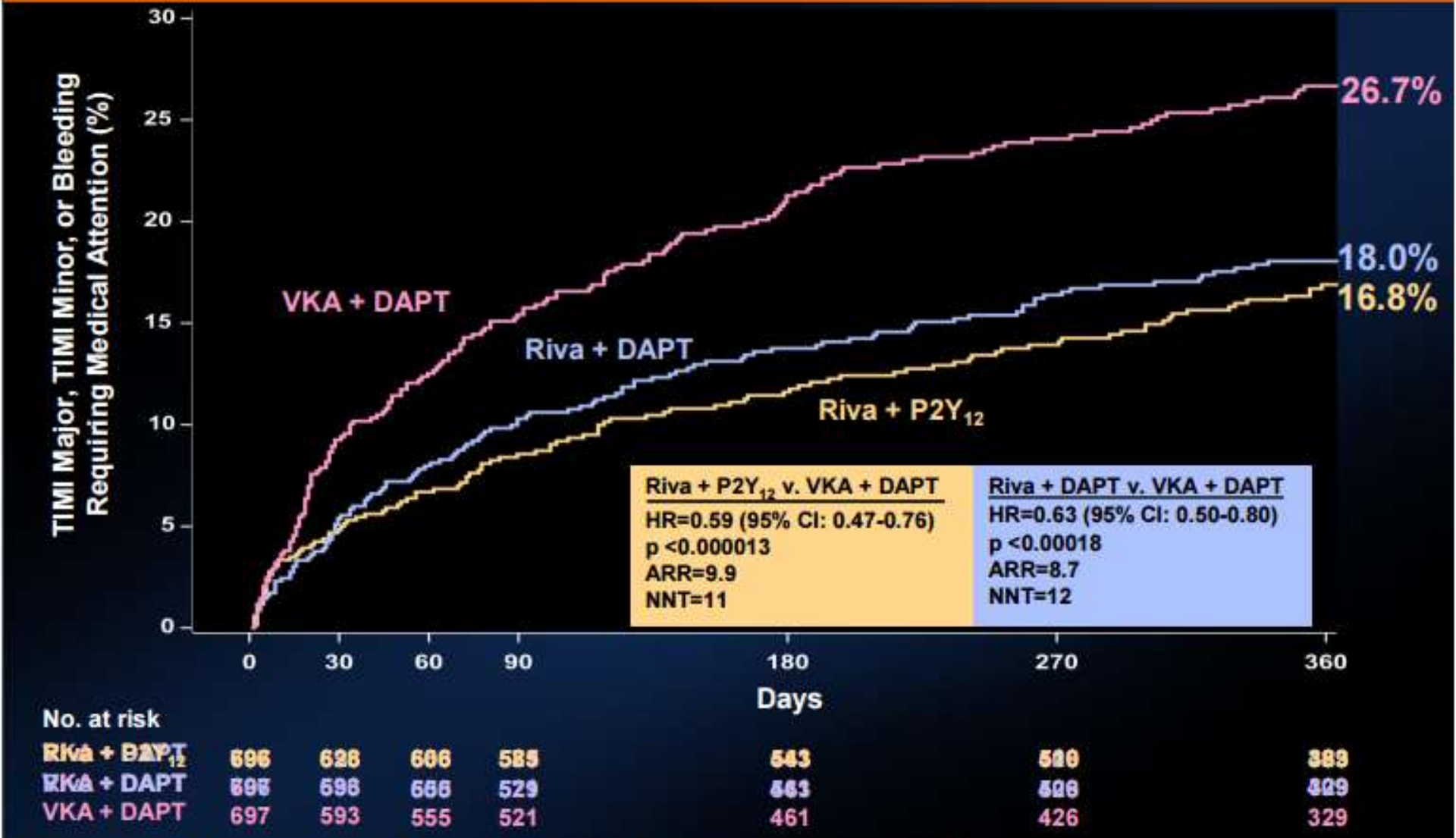


- Primary endpoint: TIMI major + minor + bleeding requiring medical attention
- Secondary endpoint: CV death, MI, and stroke (Ischemic, Hemorrhagic, or Uncertain Origin)

*Rivaroxaban dosed at 10 mg once daily in patients with CrCl of 30 to <50 mL/min.
†Alternative $P2Y_{12}$ inhibitors: 10 mg once-daily prasugrel or 90 mg twice-daily ticagrelor.
‡Low-dose aspirin (75-100 mg/d). Δ Open label VKA

Gibson et al. AHA 2016

Kaplan-Meier Estimates of First Occurrence of Clinically Significant Bleeding Events



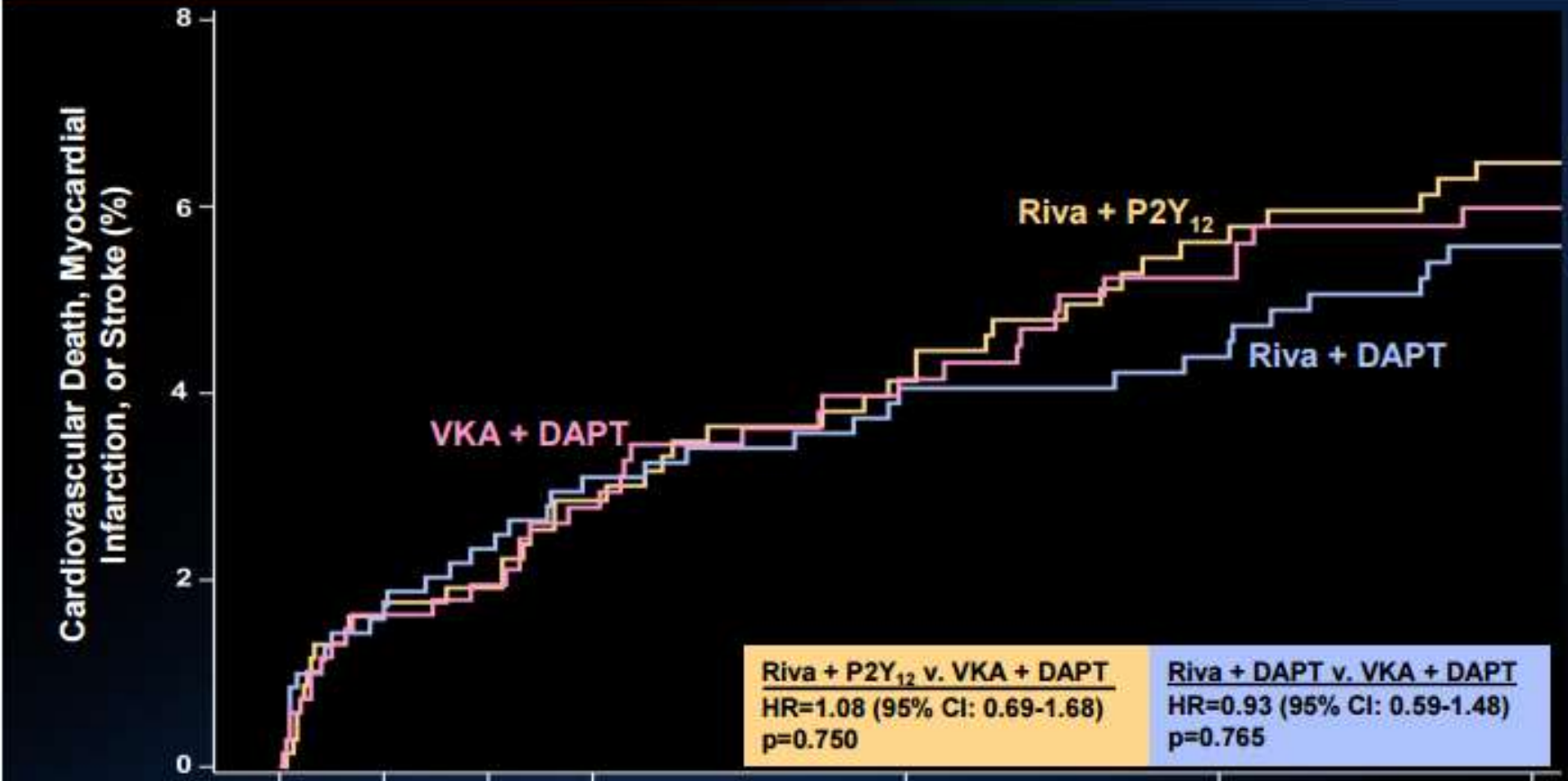
No. at risk

Riva + P2Y12	696	628	606	585	543	520	389
Riva + DAPT	695	598	566	529	463	426	329
VKA + DAPT	697	593	555	521	461	426	329

Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.
Clinically significant bleeding is the composite of TIMI major, TIMI minor, and BRMA.
Hazard ratios as compared to the VKA group are based on the (stratified, only for Overall, 2.5 mg BID/15 mg QD comparing VKA) Cox proportional hazards model.
Log-Rank P-values as compared to VKA group are based on the (stratified, only for Overall, 2.5 mg BID/15 mg QD comparing VKA) two-sided log rank test.

Gibson et al. AHA 2016

Kaplan-Meier Estimates of First Occurrence of CV Death, MI or Stroke



No. at risk							
Riva + P2Y12	694	648	633	621	590	562	430
Riva + DAPT	704	662	640	628	596	570	457
VKA + DAPT	695	635	607	579	543	514	408

Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.
Composite of adverse CV events is composite of CV death, MI, and stroke.
Hazard ratios as compared to VKA group are based on the (stratified, only for the Overall, 2.5 mg BID/15 mg QD comparing VKA) Cox proportional hazards model.
Log-Rank P-values as compared to the VKA group are based on the (stratified, only for Overall, 2.5 mg BID/15 mg QD comparing VKA) two-sided log rank test.
6 Subjects were excluded from all efficacy analyses because of violations in Good Clinical Practice guidelines

Gibson et al. AHA 2016

RE-DUAL PCI™

Study in NVAF patients undergoing PCI

STUDY TITLE

A prospective **R**andomised, open label, blinded endpoint (PROBE) study to **E**valuate **DUAL** antithrombotic therapy with dabigatran etexilate (110mg b.i.d. and 150mg b.i.d.) plus clopidogrel or ticagrelor vs. triple therapy strategy with warfarin (INR 2.0 – 3.0) plus clopidogrel or ticagrelor with aspirin in patients with non valvular atrial fibrillation (NVAF) that have undergone a percutaneous coronary intervention (**PCI**) with stenting. (RE-DUAL PCI)

STUDY HYPOTHESES

D110 plus a P2Y12 inhibitor is:

Non-inferior with respect to the combined thrombotic event rate (TE: death + MI + stroke/SE)

AND

Non-inferior* with respect to clinically relevant bleeding relative to a triple combination of warfarin plus a P2Y12 inhibitor (clopidogrel or ticagrelor) plus ASA

D150 plus a P2Y12 inhibitor is:

Non-inferior with respect to the combined thrombotic event rate (TE: death + MI + stroke/SE)

AND

Non-inferior* with respect to clinically relevant bleeding relative to a triple combination of warfarin plus a P2Y12 inhibitor (clopidogrel or ticagrelor) plus ASA

Worldwide Event Driven Trial

Paroxysmal, persistent or permanent AF (PCI with stenting [BMS or DES] elective or ACS)

Screening

R

0-72 hours post-PCI

- Dabigatran 150mg BID + P2Y12 inhibitor¥**
- Dabigatran 110mg BID + P2Y12 inhibitor¥**
- Warfarin (INR 2.0-3.0) + P2Y12 inhibitor¥ + ASA**

3M | 6M | 9M | 12M | 15M | 18/24/30M or EOT

n = 2500

1° End Point

Time to first clinically relevant bleeding rate (ISTH Major)

* After establishing non-inferiority of the D110 and D150 DAT regimens, testing for superiority will be conducted

* ASA is discontinued immediately after a successful procedure in patients randomized to receive dabigatran

* ASA will be discontinued in the warfarin arm. BMS: Discontinuation of ASA at month 1 ; DES: discontinuation of ASA at month 3

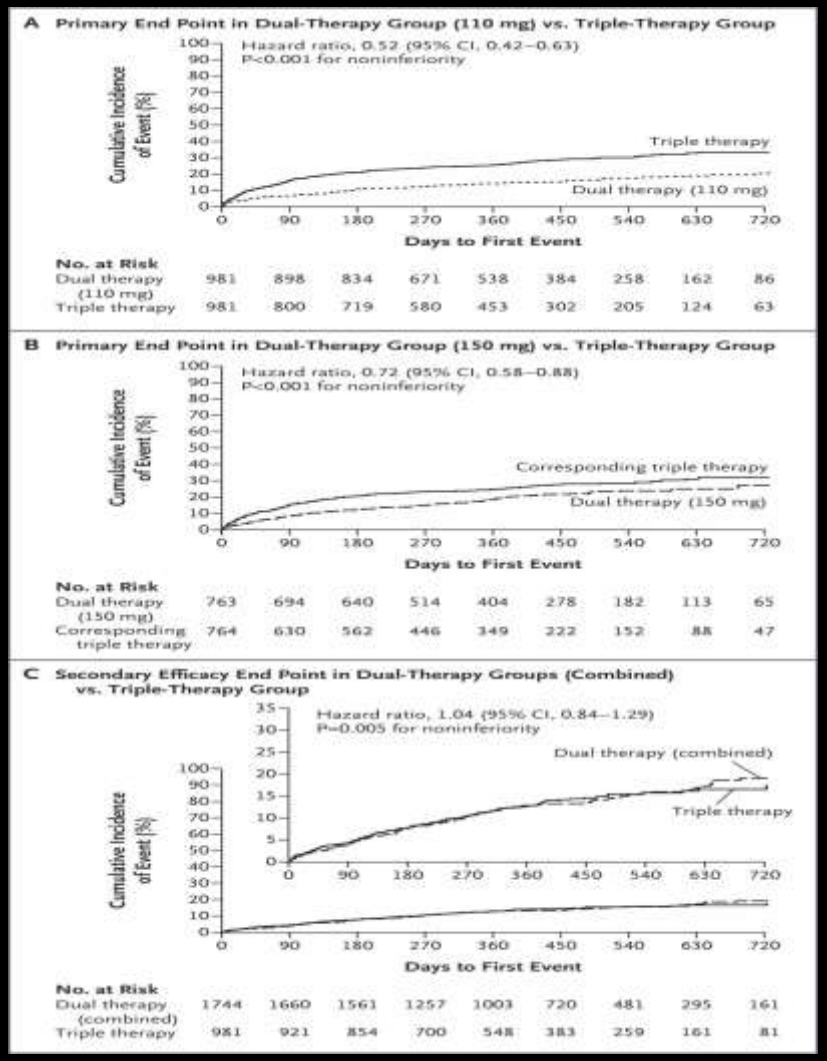
¥ P2Y12 inhibitor (either Clopidogrel or Ticagrelor). The P2Y12 inhibitor can be discontinued after month 12 of follow up at the discretion of the physician

Boehringer Ingelheim

HCRI Harvard Clinical Research Institute

AFIB608904PROF

Primary End Point and Secondary Efficacy End Point.



Cannon CP et al. N Engl J Med ;377:1513-1524

The NEW ENGLAND JOURNAL of MEDICINE

Efficacy End Points.

Table 3. Efficacy End Points.*

End Point	Dual Therapy with Dabigatran (Combined) vs. Triple Therapy with Warfarin				Dual Therapy with Dabigatran (110 mg) vs. Triple Therapy with Warfarin				Dual Therapy with Dabigatran (150 mg) vs. Triple Therapy with Warfarin			
	Combined Dual-Therapy Groups (N=1744)	Triple-Therapy Group (N=981)	Hazard Ratio (95% CI)	P Value†	110-mg Dual-Therapy Group (N=981)	Triple-Therapy Group (N=981)	Hazard Ratio (95% CI)	P Value†	150-mg Dual-Therapy Group (N=763)	Corresponding Triple-Therapy Group (N=764)	Hazard Ratio (95% CI)	P Value†
	no. (%)				*no. (%)*				*no. (%)*			
Composite efficacy end point: thromboembolic events, death, or unplanned revascularization	239 (13.7)	131 (13.4)	1.04 (0.84–1.29)	0.74 (0.005 for noninferiority)	149 (15.2)	131 (13.4)	1.13 (0.90–1.43)	0.30	90 (11.8)	98 (12.8)	0.89 (0.67–1.19)	0.44
Thromboembolic events or death	168 (9.6)	83 (8.5)	1.17 (0.90–1.53)	0.25 (0.11 for noninferiority)	108 (11.0)	83 (8.5)	1.30 (0.98–1.73)	0.07	60 (7.9)	60 (7.9)	0.97 (0.68–1.39)	0.88
Death					55 (5.6)	48 (4.9)	1.12 (0.76–1.65)	0.56	30 (3.9)	35 (4.6)	0.83 (0.51–1.34)	0.44
Myocardial infarction					44 (4.5)	29 (3.0)	1.51 (0.94–2.41)	0.09	26 (3.4)	22 (2.9)	1.16 (0.66–2.04)	0.61
Stroke					17 (1.7)	13 (1.3)	1.30 (0.63–2.67)	0.48	9 (1.2)	8 (1.0)	1.09 (0.42–2.83)	0.85
Definite stent thrombosis					15 (1.5)	8 (0.8)	1.86 (0.79–4.40)	0.15	7 (0.9)	7 (0.9)	0.99 (0.35–2.81)	0.98

* Thromboembolic events were myocardial infarction, stroke, or systemic embolism. Unplanned revascularization was percutaneous coronary intervention or coronary-artery bypass grafting. Comparisons between the 110-mg dual-therapy group and the triple-therapy group and between the combined dual-therapy groups and the triple-therapy group were stratified according to age group (nonelderly or elderly [<80 or ≥80 years of age; <70 or ≥70 years of age in Japan]). Comparisons between the 150-mg dual-therapy group and the corresponding triple-therapy group were unstratified. All end points other than the composite efficacy end point and the combined end point of thromboembolic events or death were considered to be descriptive.

† P values for noninferiority were calculated at a one-sided alpha level of 0.025 and are provided only if a noninferiority margin was prespecified. All other P values are for superiority and were calculated at a two-sided alpha level of 0.05; these P values are provided for descriptive purposes only.

Cannon CP et al. N Engl J Med ;377:1513-1524

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The AUGUSTUS Trial

Apixaban Versus Warfarin in Patients with AF + ACS or PCI:

Inclusion
- AF (prior, persistent, or >6 hrs duration)
- Physician decision that oral anticoag is indicated
- ACS or PCI with planned P2Y12 inhibitor for 6 months

Randomize n =4,600 Patients

Exclusion
- Contraindication to DAPT
- Other reason for warfarin (prosthetic valve, mod/sev MS)

Apixaban 5mg bid (or with adjustment)

Warfarin (INR 2-3)

P2Y12 inhibitor for all patients x 6 months
Aspirin for all on the day of ACS or PCI
Aspirin versus placebo after randomization

ASA | **placebo** | **ASA** | **placebo**

Primary outcome: major/clinically relevant bleeding (through 6 months)

Secondary objective: Death, MI, stroke, stent thrombosis

Triple Therapy Considerations 2017

- Assess ischemic and bleeding risks using validated risk predictors (e.g., CHA2DS2-VASc, HAS-BLED)
- Keep 3ple therapy duration as short as possible; for example, use max 2 weeks (this is the highest incidence of subacute ST)
  - Dual therapy only (oral anticoagulant plus clopidogrel) may be considered in select patients
- Consider target INR 2.0–2.5 when warfarin is used
- Clopidogrel is the $P2Y_{12}$ inhibitor of choice
- Use low dose (≤100 mg daily) aspirin
- Complex switching drugs/dosages have the handicap of nonadherence and medication errors…
- PPI Rx should be used in patients with a history of GI bleeding and are reasonable to use in patients with increased risk of GI bleeding; liberal H2B in all others.

Levine GN, et al. 2016 ACC/AHA Guideline Focused Update on Duration of DAPT in Patients with CAD. JACC 2016 & Circulation 2016