Antiplatelet Therapy After PCI
State-of-the-Art Review

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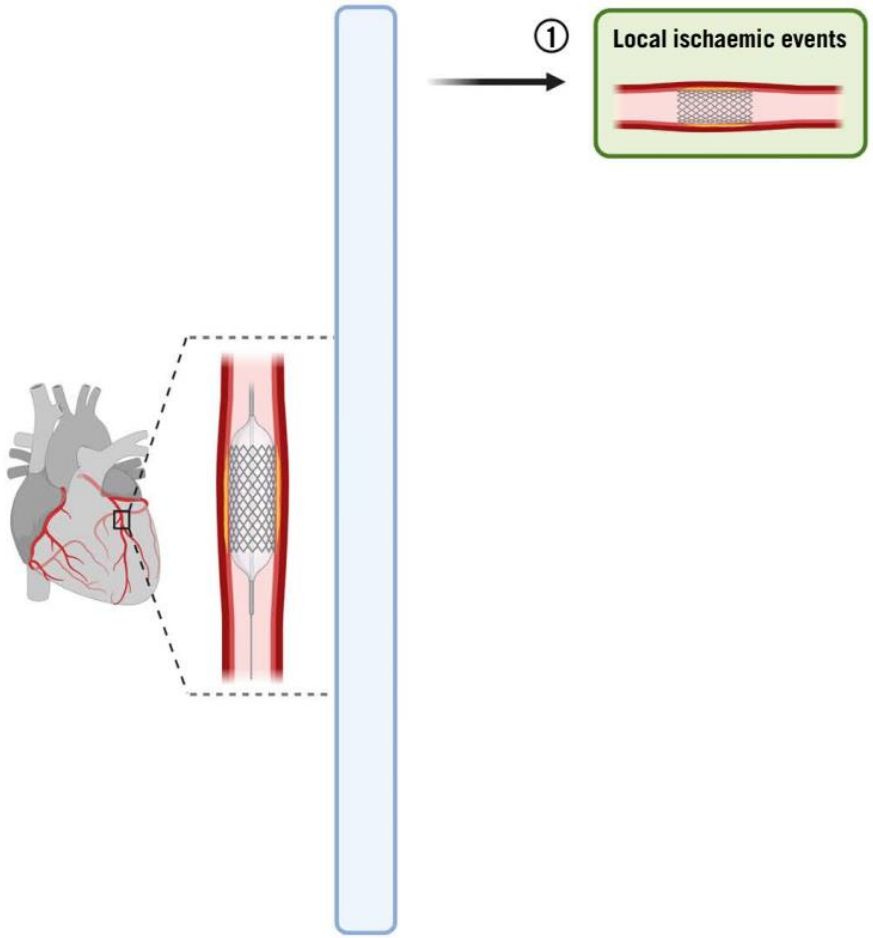
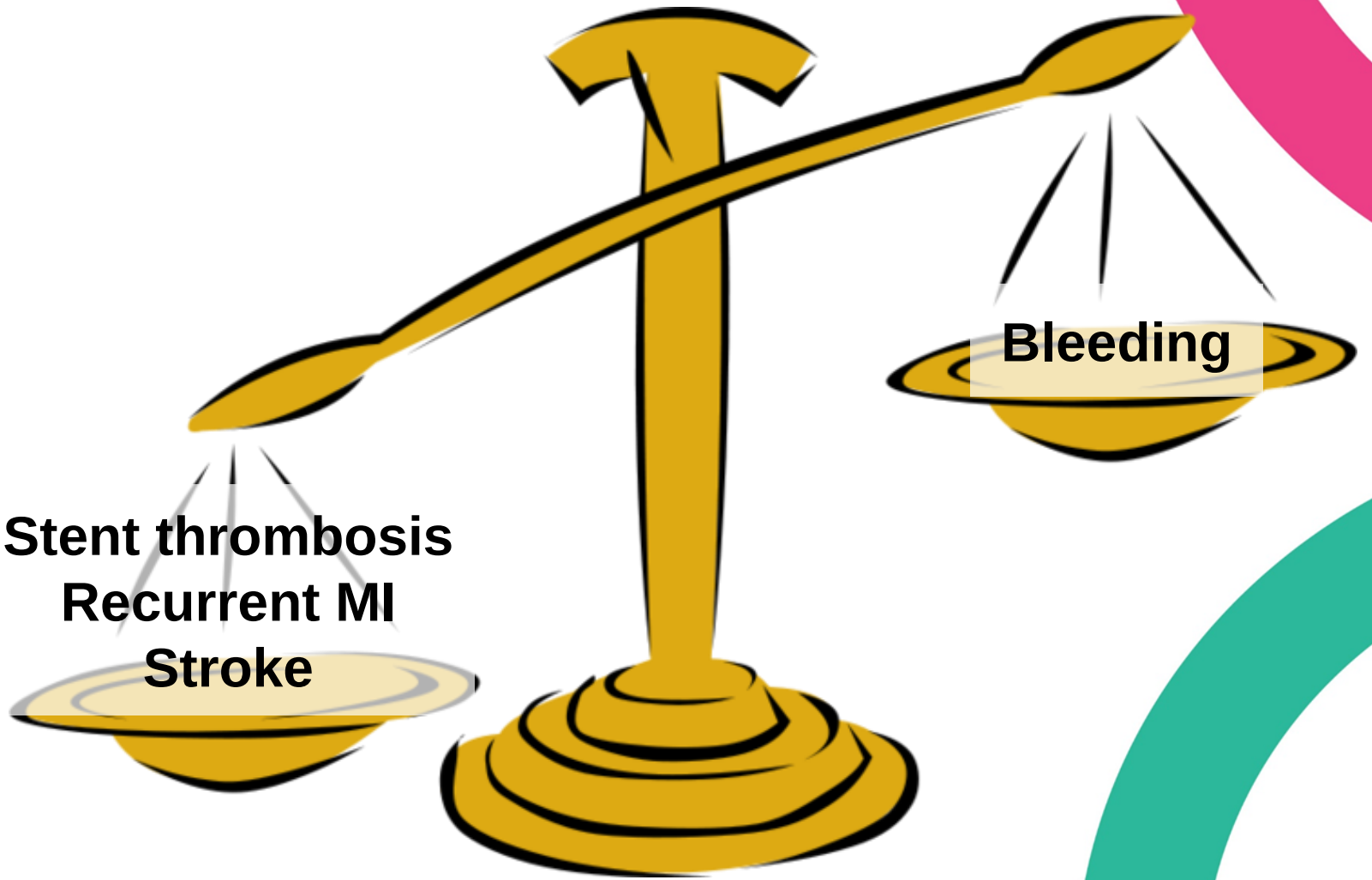
Benefit and risk of antiplatelet therapy after PCI

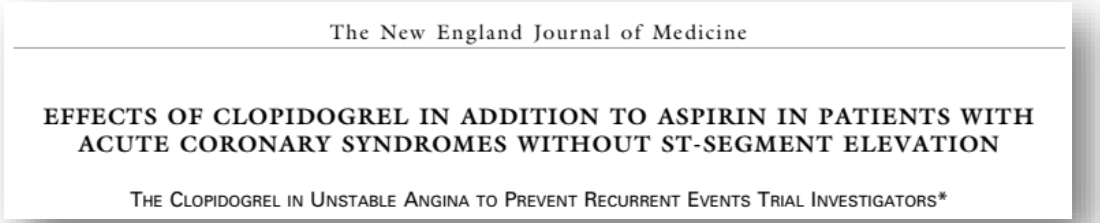


Angiolillo D et al. Eurointerv 2022


Bleeding
Stent thrombosis
Recurrent MI
Stroke

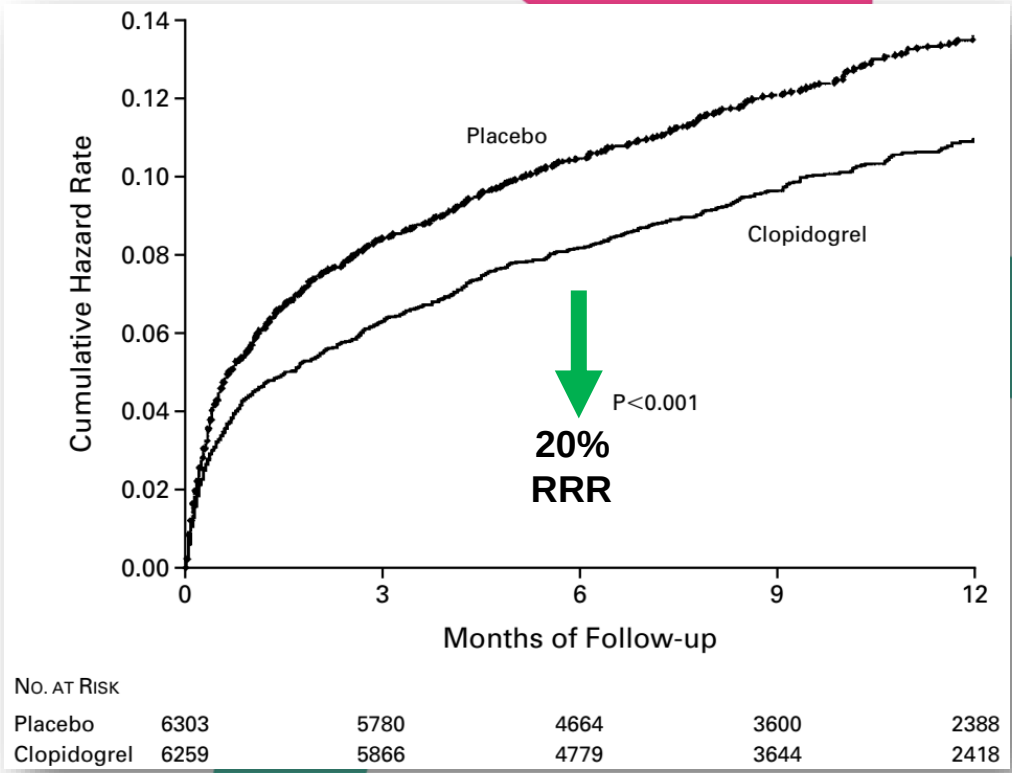
The CURE Trial

- 12,562 NSTE-ACS patients
- Primary outcome*: 11.4% vs. 9.3%
- Higher rate of major bleeding in clopidogrel group: 3.7 vs. 2.7%, p=0.001


The New England Journal of Medicine

EFFECTS OF CLOPIDOGREL IN ADDITION TO ASPIRIN IN PATIENTS WITH ACUTE CORONARY SYNDROMES WITHOUT ST-SEGMENT ELEVATION

THE CLOPIDOGREL IN UNSTABLE ANGINA TO PREVENT RECURRENT EVENTS TRIAL INVESTIGATORS*



*Primary outcome: composite of CV mortality, non-fatal MI or stroke

CURE Trial, NEJM 2001

Introduction

- Evolution of antiplatelet treatment after PCI related to:
  - New antiplatelet drugs
  - Safer stent platforms (less thrombogenic)
  - Deeper understanding of prognostic implications of bleeding
- Need for personalized treatment regiments

Strategies focused on reducing ischemic events

- DAPT with novel antiplatelet drugs
- OAC + antiplatelet therapy
- Guided escalation of P2Y12 inhibitors
- Prolonging DAPT duration

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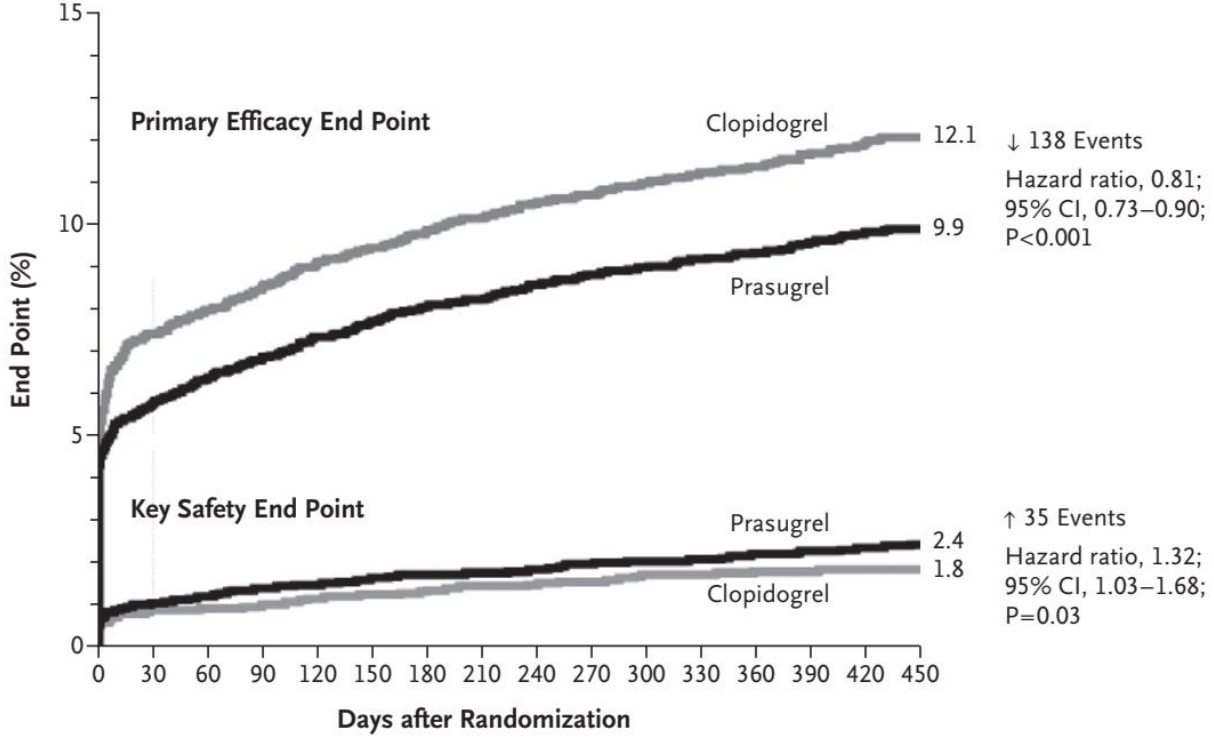
New P2Y12 Inhibitors

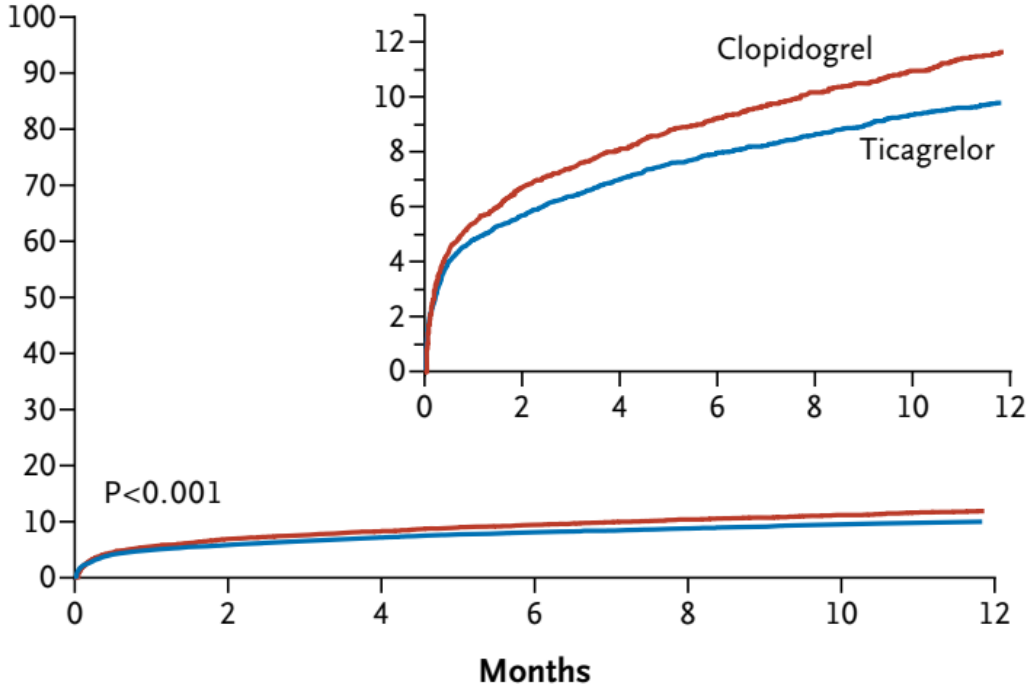
Primary efficacy end point: cardiovascular death, non-fatal MI, non-fatal stroke

TRITON-TIMI 38, NEJM 2007



No. at Risk							
Clopidogrel	6795 6169	6036	5835	5043	4369	3017
Prasugrel	6813 6305	6177	5951	5119	4445	3085

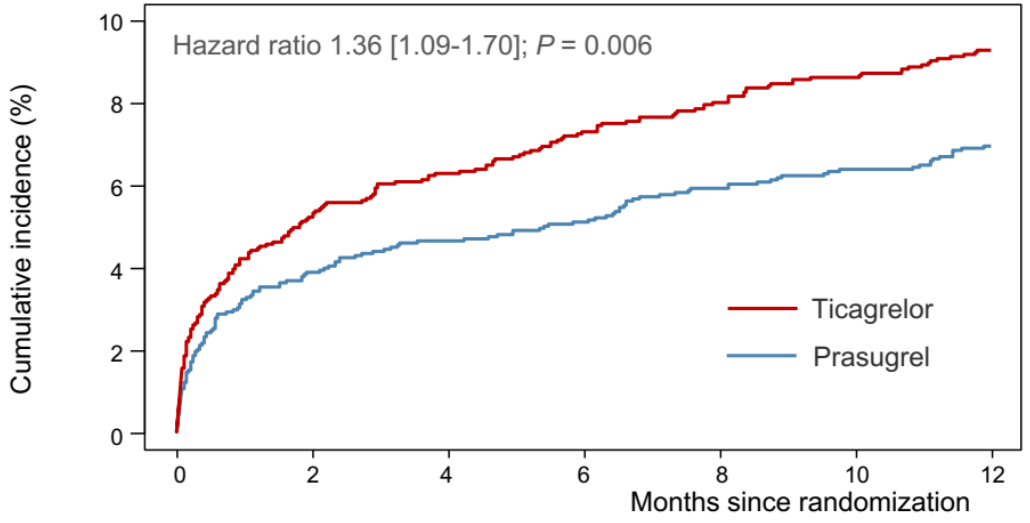
PLATO, NEJM, 2009



No. at Risk							
Ticagrelor	9333	8628	8460	8219	6743	5161	4147
Clopidogrel	9291	8521	8362	8124	6650	5096	4047

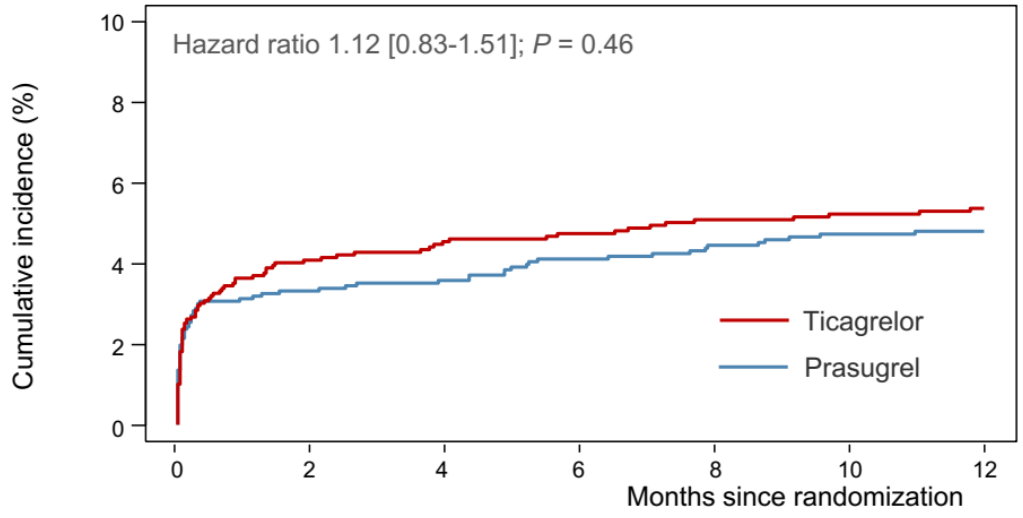
ISAR-REACT 5 - Results

Primary end point (composite of death, MI or stroke)



No. at Risk							
Ticagrelor	2012	1877	1857	1835	1815	1801	1772
Prasugrel	2006	1892	1877	1862	1839	1829	1803

Safety end point – BARC Type 3-5 Bleeding



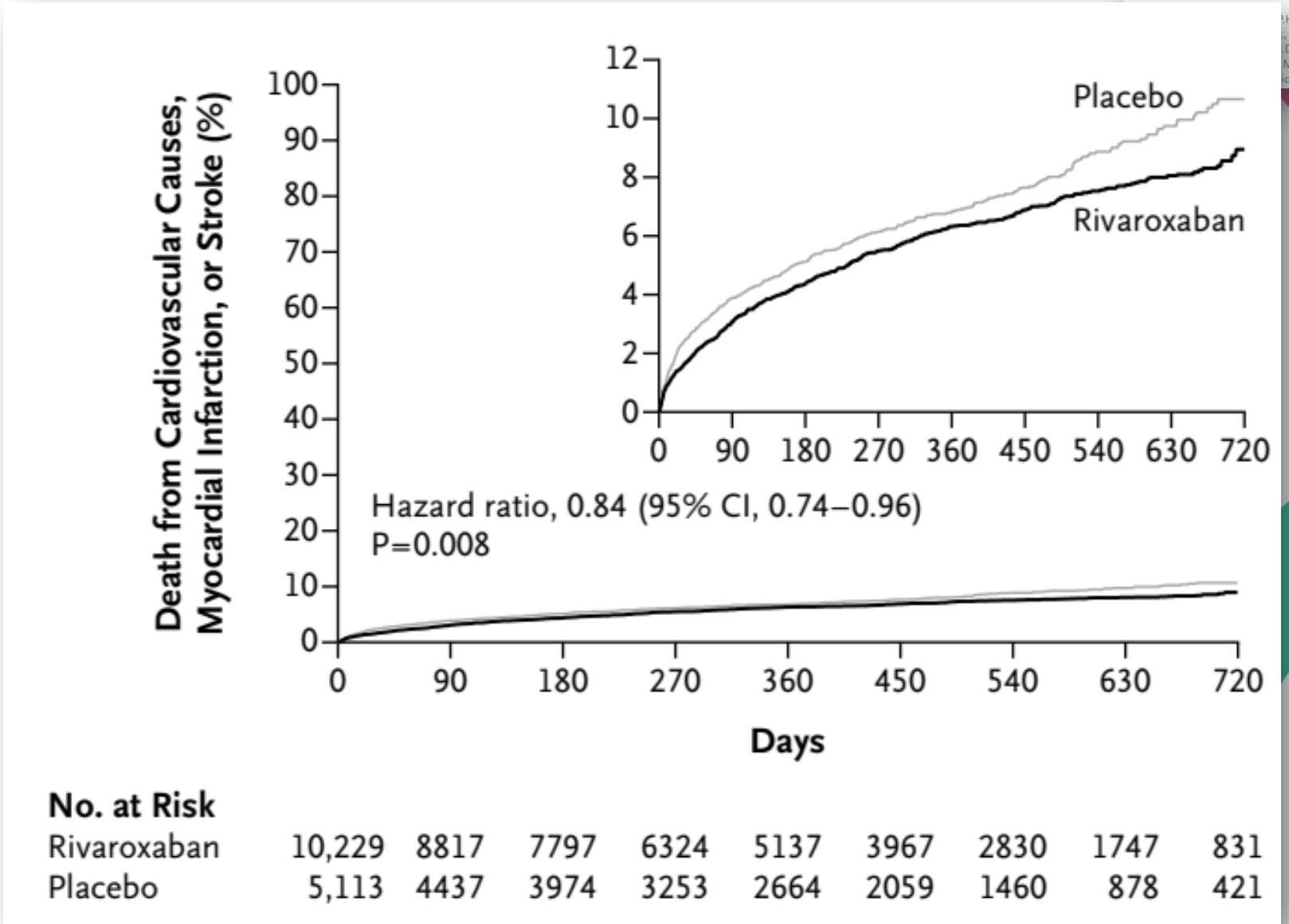
No. at Risk							
Ticagrelor	1989	1441	1399	1356	1319	1296	1266
Prasugrel	1773	1465	1427	1397	1357	1333	1307

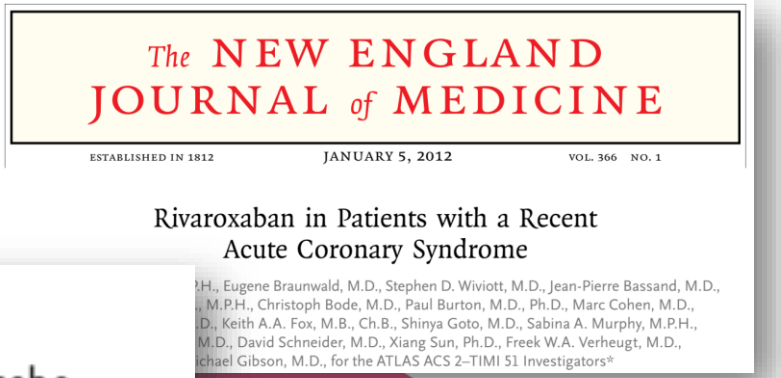
Schupke S et al. NEJM 2019

Strategies focused on reducing ischemic events

- DAPT with novel antiplatelet drugs
- OAC + antiplatelet therapy
- Guided escalation of P2Y12 inhibitors
- Prolonging DAPT duration

ATLAS ACS 2-TIMI 51 Trial




The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 5, 2012 VOL. 366 NO. 1

Rivaroxaban in Patients with a Recent Acute Coronary Syndrome

H., Eugene Braunwald, M.D., Stephen D. Wiviott, M.D., Jean-Pierre Bassand, M.D., , M.P.H., Christoph Bode, M.D., Paul Burton, M.D., Ph.D., Marc Cohen, M.D., D., Keith A.A. Fox, M.B., Ch.B., Shinya Goto, M.D., Sabina A. Murphy, M.P.H., M.D., David Schneider, M.D., Xiang Sun, Ph.D., Freek W.A. Verheugt, M.D., chael Gibson, M.D., for the ATLAS ACS 2–TIMI 51 Investigators*

Mega JL et al. NEJM 2012

2020 ESC NSTE-ACS GL

Recommendations	Class	Level
In ACS patients with no prior stroke/transient ischaemic attack who are at high ischaemic risk and low bleeding risk and are receiving aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg b.i.d. for approximately 1 year) may be considered after discontinuation of parenteral anticoagulation.	IIb	B

Collet JP et al. Eur Heart J 2021

Strategies focused on reducing ischemic events

- DAPT with novel antiplatelet drugs
- OAC + antiplatelet therapy
- Guided escalation of P2Y12 inhibitors
- Prolonging DAPT duration

Guided versus standard antiplatelet therapy in patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis

Mattia Galli, Stefano Benenati, Davide Capodanno, Francesco Franchi, Fabiana Rollini, Domenico D'Amario, Italo Porto, Dominick J Angiolillo

- 11 randomized trials and 3 observational studies, N=20,743
- Guided selection of antiplatelet therapy associated with a reduction in MACE of 22% (P=0.015), bleeding reduction not statistically significant
- Lower CV death, MI, stent thrombosis, stroke and minor bleeding.

Galli M et al. Lancet, 2021
Collet JP et al. Eur Heart J 2021

Strategies focused on reducing ischemic events

- DAPT with novel antiplatelet drugs
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DAPT Study

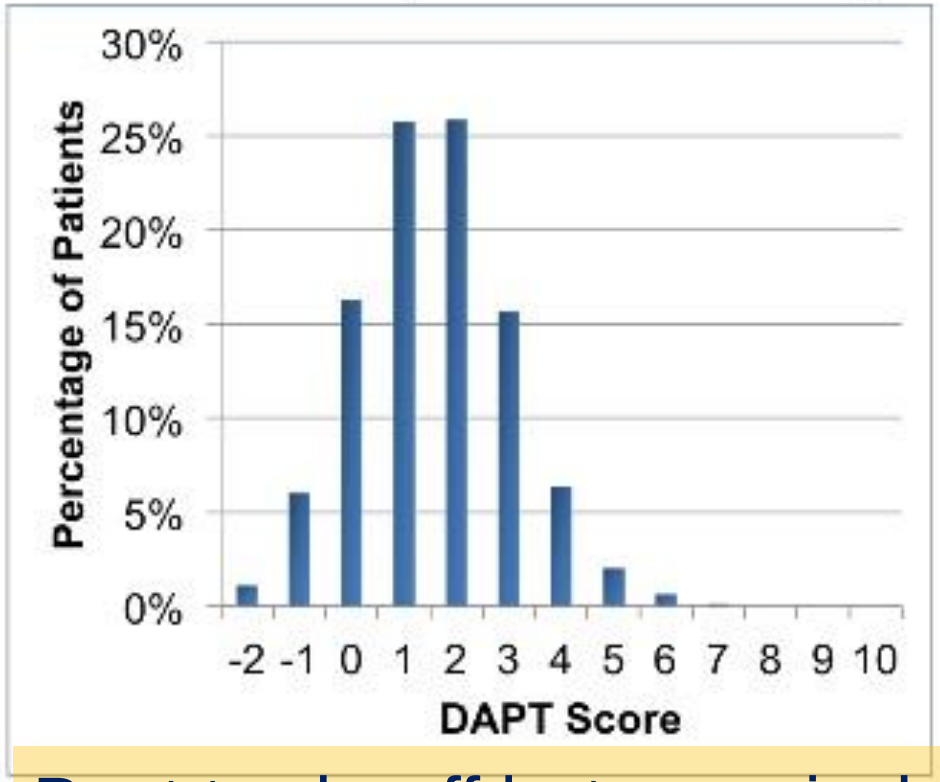
- N=9,961 patients undergoing PCI (10% STEMI) free of adverse ischemic and bleeding events on DAPT at 12 months post-PCI
- Additional 18 months of DAPT vs. 12-month DAPT significantly reduced MACCE by 29% (2/3 clopidogrel, 1/3 prasugrel)
- Stent thrombosis reduced
- Significant increase in moderate and severe bleeding and all-cause mortality
- DAPT Score derived →

Mauri L et al. NEJM 2014

The DAPT Score

Variable	Points
Patient Characteristic	
Age	
≥ 75	-2
65 - <75	-1
< 65	0
Diabetes Mellitus	1
Current Cigarette Smoker	1
Prior PCI or Prior MI	1
CHF or LVEF < 30%	2
Index Procedure Characteristic	
MI at Presentation	1
Vein Graft PCI	2
Stent Diameter < 3mm	1

Distribution of DAPT Scores among all randomized subjects in the DAPT Study



Best trade-off between ischemic benefit and bleeding risk in DAPT score ≥ 2

PEGASUS-TIMI 54: Primary Endpoint

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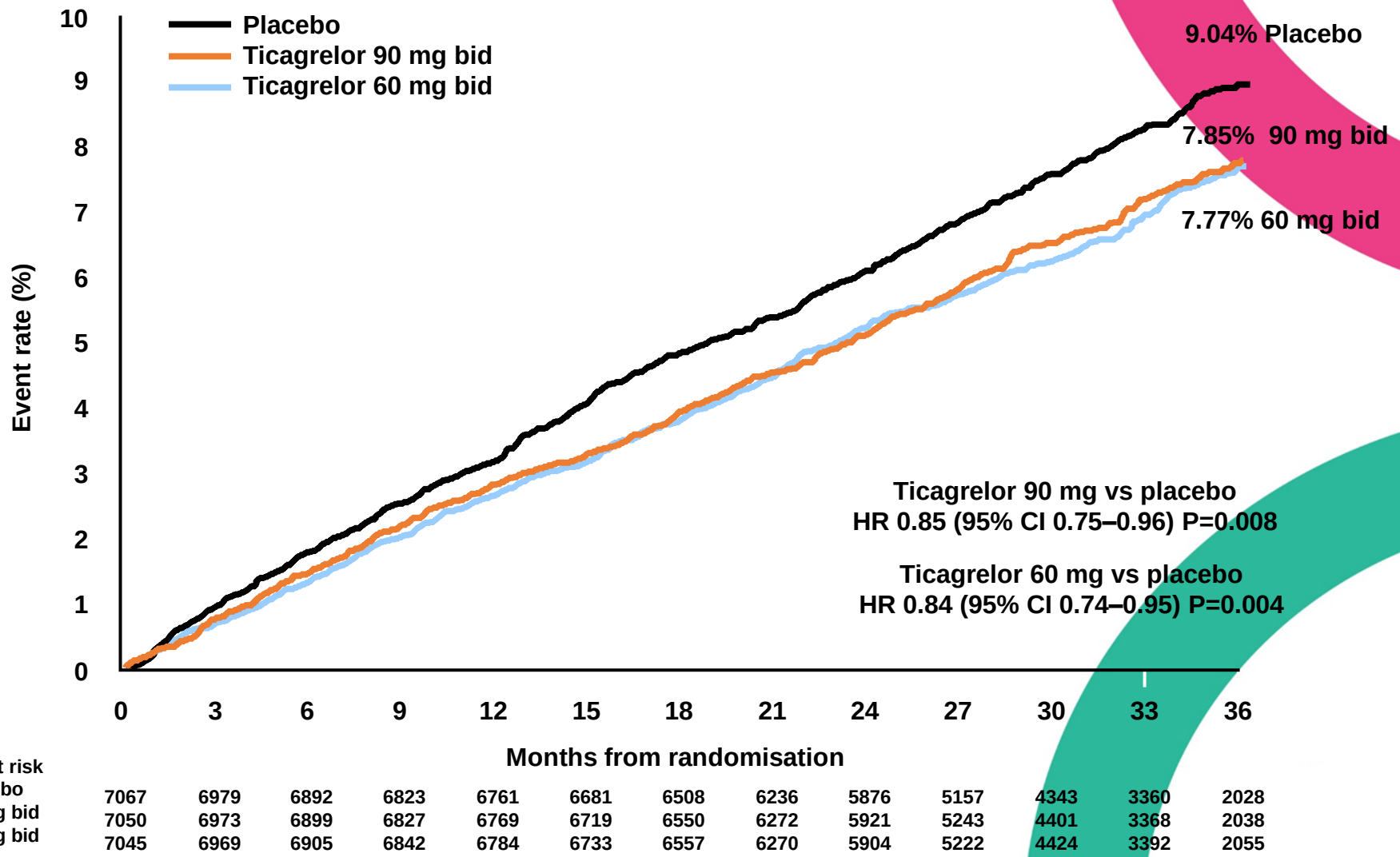
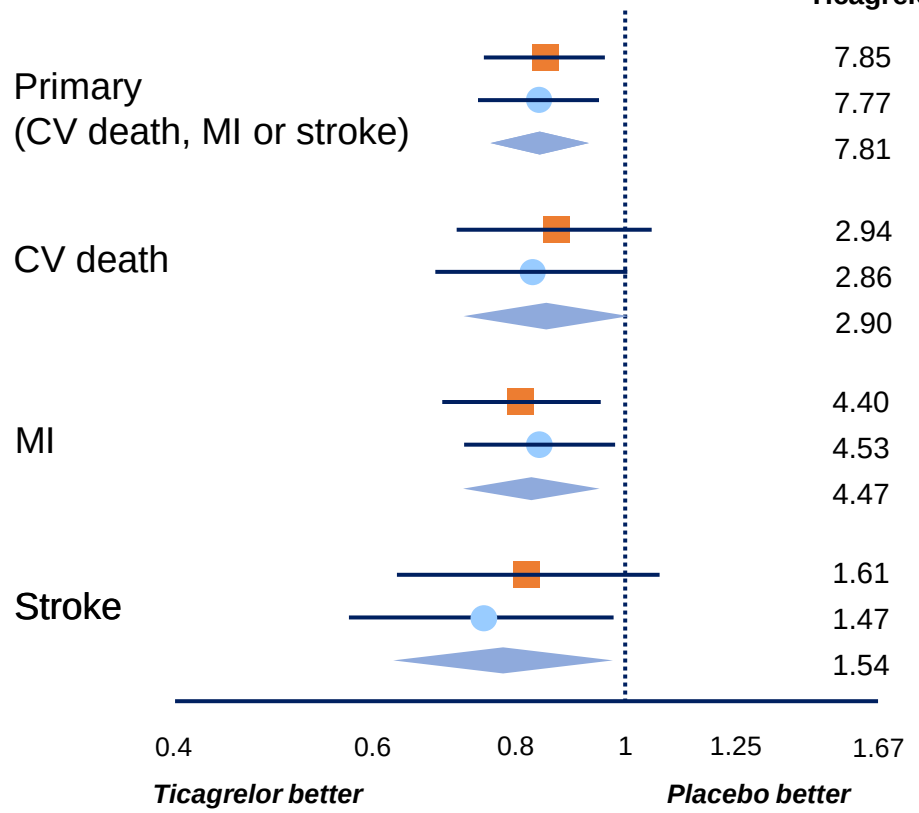


No. at risk													
Placebo	7067	6979	6892	6823	6761	6681	6508	6236	5876	5157	4343	3360	2028
90 mg bid	7050	6973	6899	6827	6769	6719	6550	6272	5921	5243	4401	3368	2038
60 mg bid	7045	6969	6905	6842	6784	6733	6557	6270	5904	5222	4424	3392	2055

Bonaca MP et al. NEJM 2015

PEGASUS-TIMI 54: Efficacy Endpoints

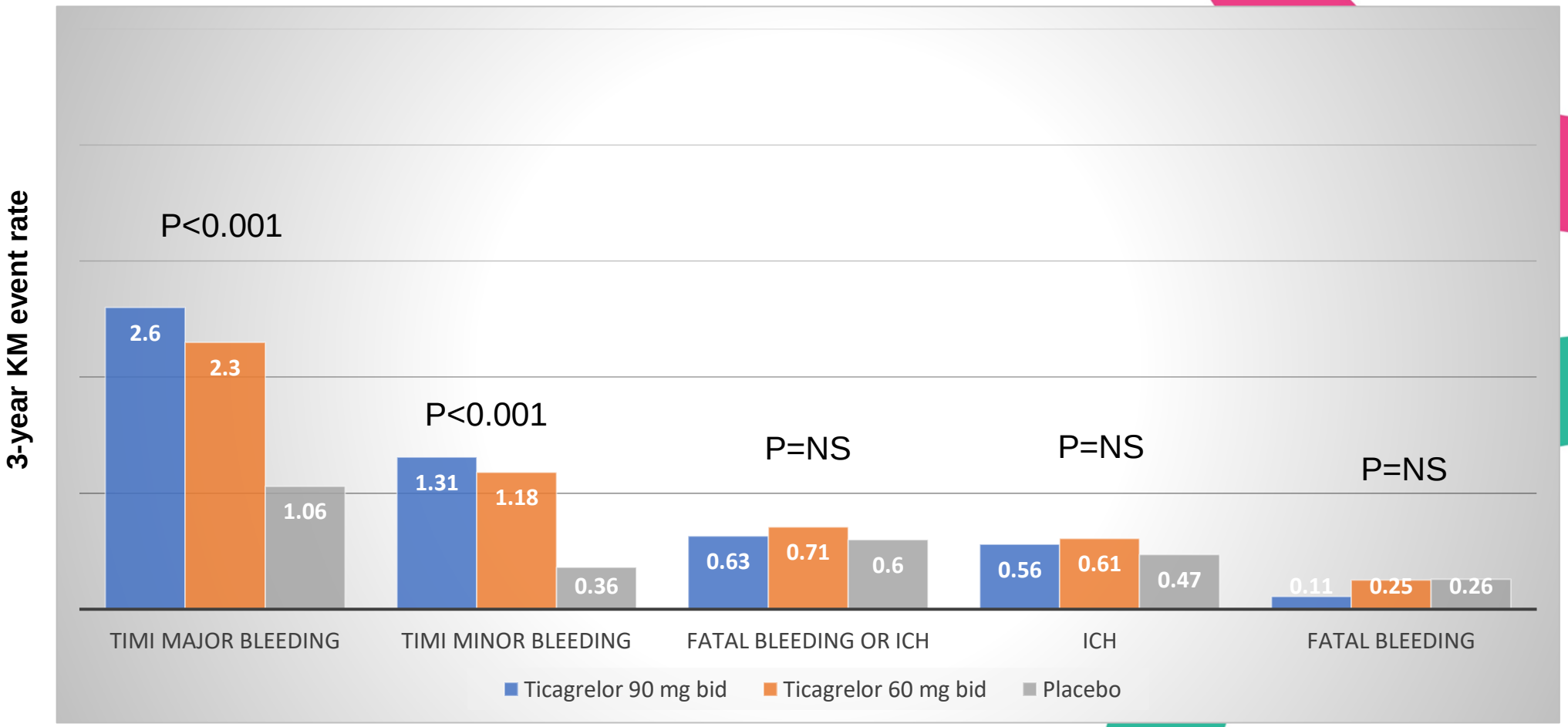


Endpoint	3-year KM event rates (%)			
	Ticagrelor	Placebo	HR (95% CI)	P value
Primary (CV death, MI or stroke)	7.85	9.04	0.85 (0.75–0.96)	0.008
	7.77	9.04	0.84 (0.74–0.95)	0.004
	7.81	9.04	0.84 (0.76–0.94)	0.001
CV death	2.94	3.39	0.87 (0.71–1.06)	0.15
	2.86	3.39	0.83 (0.68–1.01)	0.07
	2.90	3.39	0.85 (0.71–1.00)	0.06
MI	4.40	5.25	0.81 (0.69–0.95)	0.01*
	4.53	5.25	0.84 (0.72–0.98)	0.03*
	4.47	5.25	0.83 (0.72–0.95)	0.005*
Stroke	1.61	1.94	0.82 (0.63–1.07)	0.14*
	1.47	1.94	0.75 (0.57–0.98)	0.03*
	1.54	1.94	0.78 (0.62–0.98)	0.03*

- Ticagrelor 90 mg bid
- Ticagrelor 60 mg bid
- Ticagrelor pooled

Bonaca MP et al. NEJM 2015

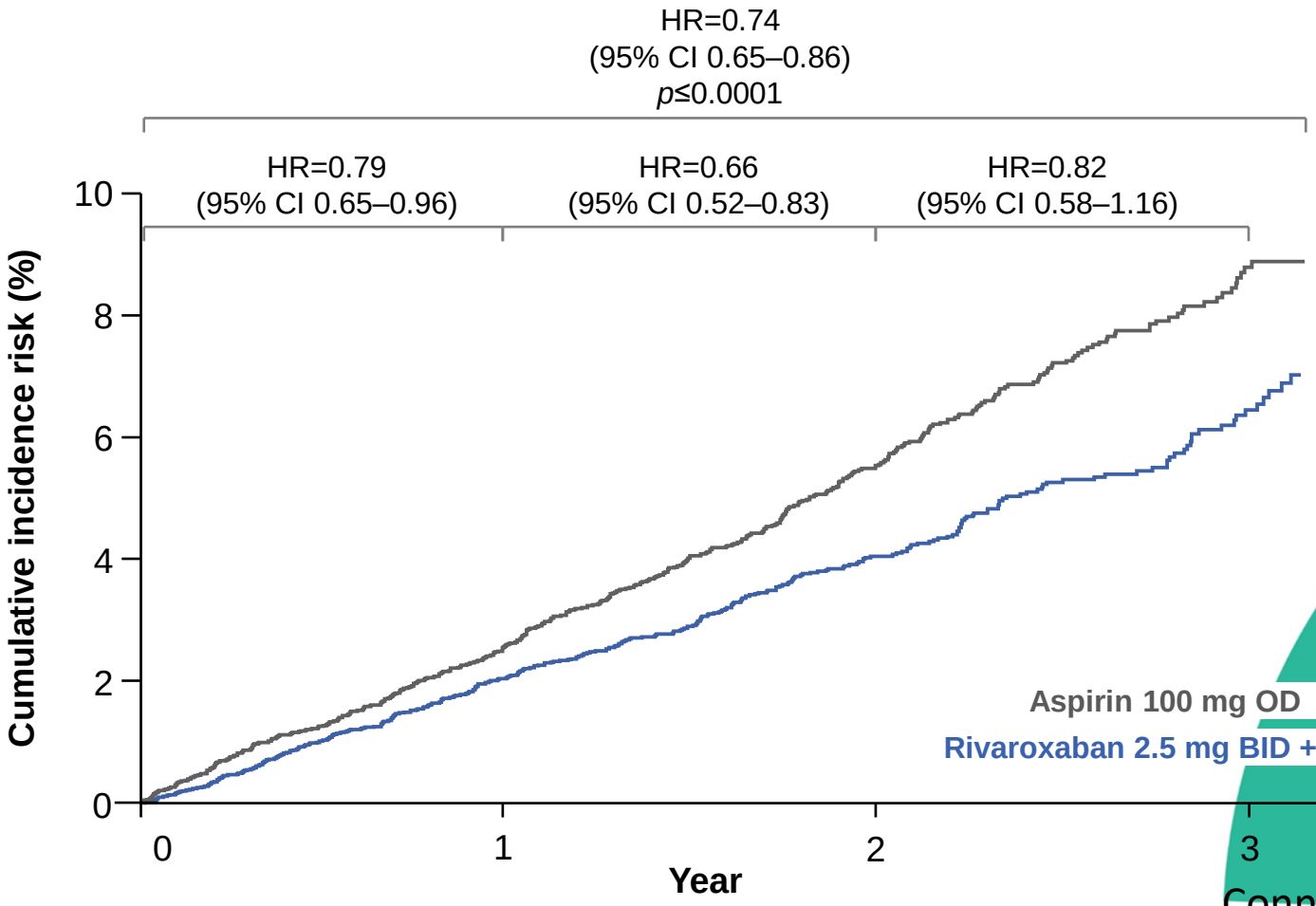
PEGASUS-TIMI 54: Bleeding



Bonaca MP et al. NEJM 2015

COMPASS Demonstrated a Significant Reduction in MACE with Dual Pathway Inhibition in Patients with Chronic CAD

Stroke, MI or CV death



Connoly SJ et al. Lancet 2018

Net Clinical Benefit

Outcome	R + A N=9,152	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin	
	N (%)	N (%)	HR (95% CI)	P
Net clinical benefit (Primary + Severe bleeding events)	431 (4.7%)	534 (5.9%)	0.80 (0.70-0.91)	0.0005

Eikelboom JW et al. *N Engl J Med*. 2017 Oct 5;377(14):1319-1330

Drug	Dose	Indication	NNT (ischaemic outcomes)	NNH (bleeding Outcomes)
DAT regimens for extended treatment (including aspirin 75–100 mg o.d.)				
Rivaroxaban (COMPASS trial)	2.5 mg b.i.d.	Patients with CAD or symptomatic PAD at high risk of ischaemic events	77	84
DAPT regimens for extended treatment (including aspirin 75–100 mg o.d.)				
Clopidogrel (DAPT trial)	75 mg/d	Post MI in patients who have tolerated DAPT for 1 year	63	105
Prasugrel (DAPT trial)	10 mg/d (5 mg/d if body weight <60 kg or age >75 years)	Post PCI for MI in patients who have tolerated DAPT for 1 year	63	105
Ticagrelor (PEGASUS-TIMI 54)	60/90 mg b.i.d.	Post MI in patients who have tolerated DAPT for 1 year	84	81

Drugs (in addition to aspirin 75–100 mg/d) for extended DAPT treatment options are in alphabetical order. For indications and definitions for high/moderately increased risk and bleeding risk see *Table 9* and *Figure 7*. NNT refers to the primary ischaemic endpoints of the respective trials and NNH refers to the key safety (bleeding) endpoints. NNT and NNH numbers from the DAPT trial are pooled numbers for clopidogrel and prasugrel.

Collet JP et al. Eur Heart J 2021

Strategies focused on reducing bleeding events

- Shortening DAPT
- P2Y12 monotherapy
- De-escalating P2Y12 inhibitors

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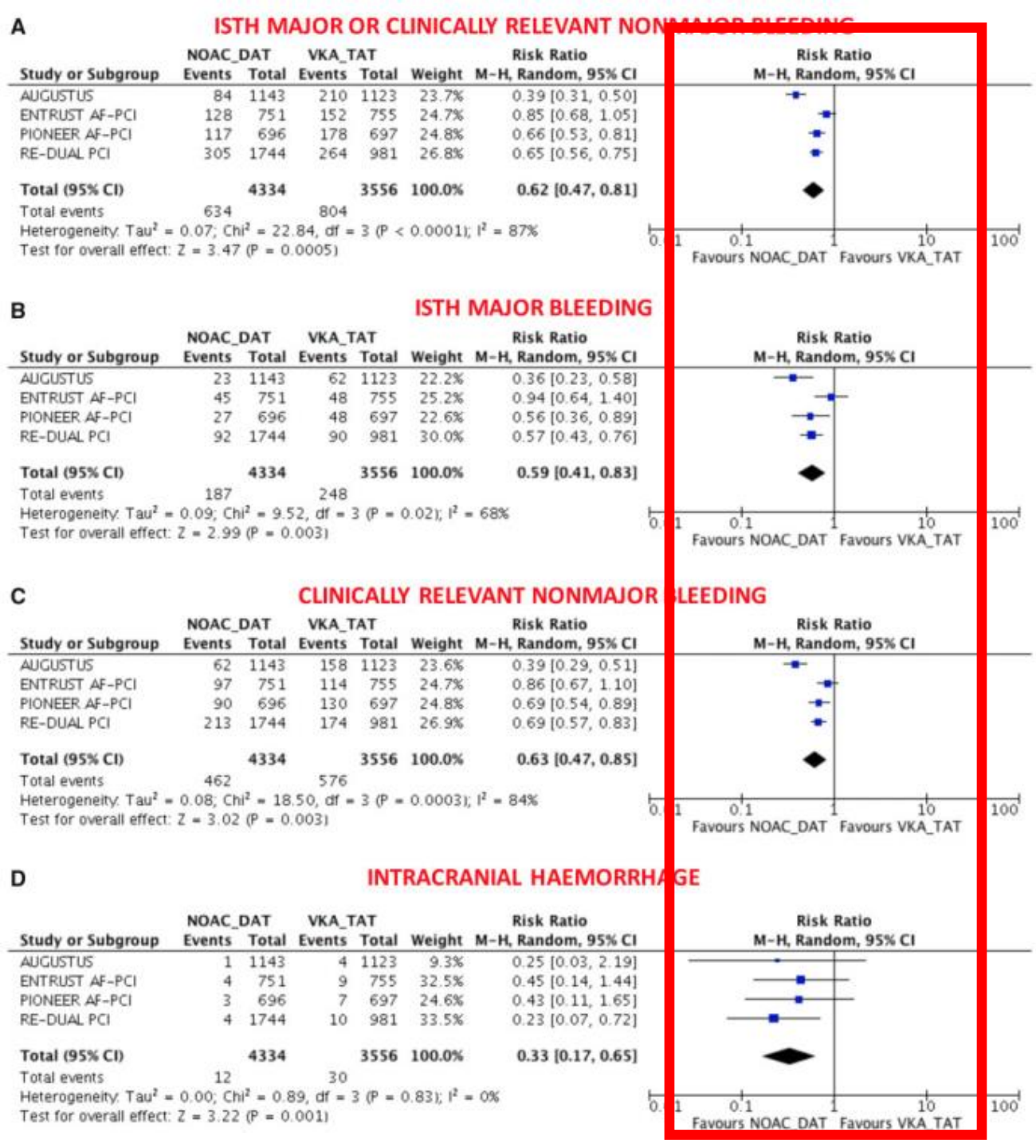

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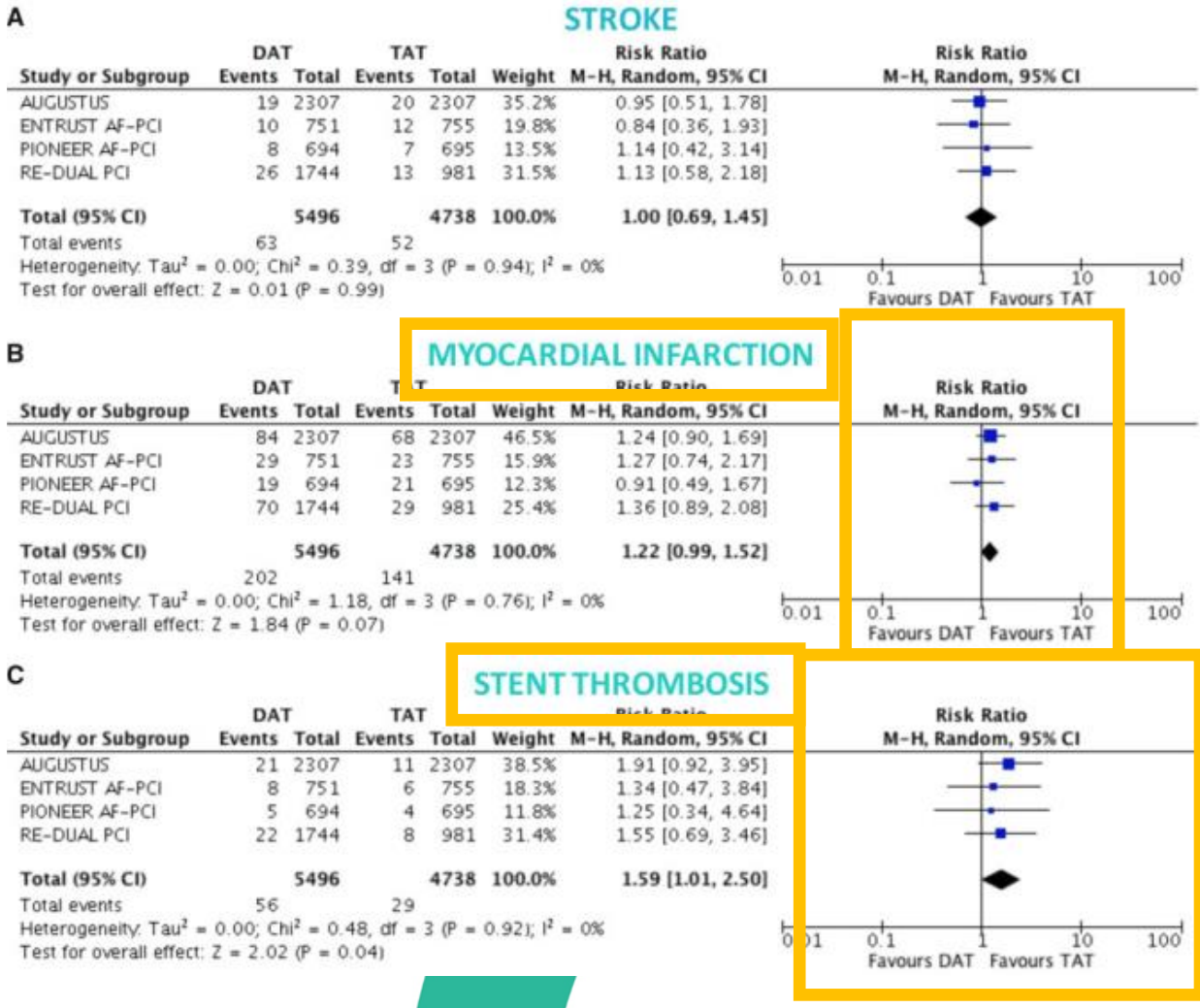
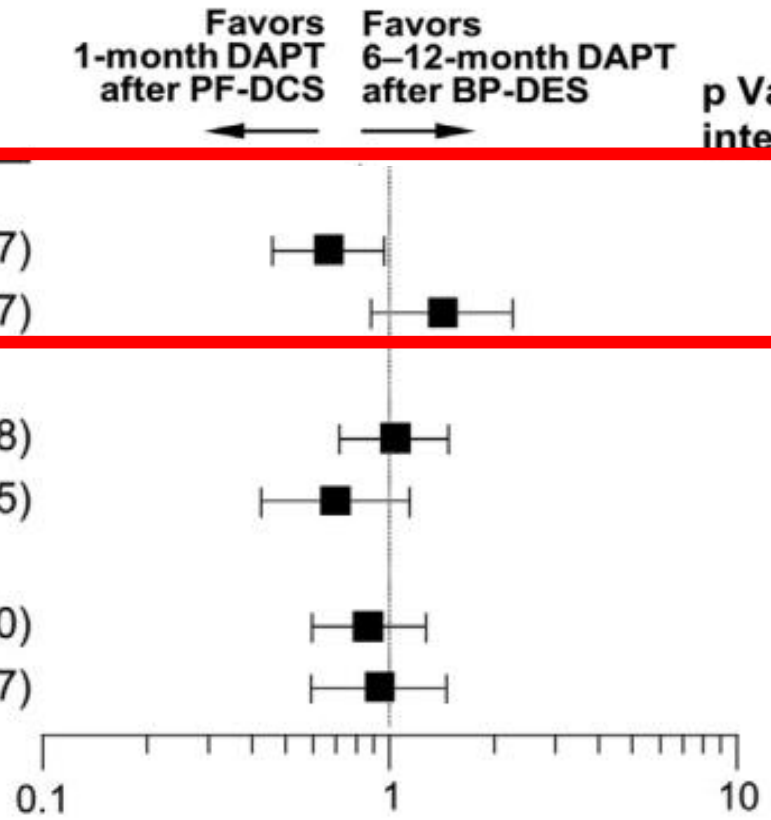


Gargiulo G et al. Eur Heart J 2019

One-Month DAPT

Subgroup	No. /Total (%) 1-month DAPT after PF-DCS	No. /Total (%) 6–12-month DAPT after BP-DES	HR (95% CI)	p Value for interaction
Clinical presentation				0.013
Stable angina	47/933 (5.1)	67/895 (7.6)	0.67 (0.46 to 0.97)	
Acute coronary syndrome	41/574 (7.2)	31/618 (5.1)	1.43 (0.89 to 2.27)	
Multivessel disease				0.212
Yes	60/867 (7.0)	59/878 (6.8)	1.04 (0.72 to 1.48)	
No	28/640 (4.4)	39/635 (6.2)	0.70 (0.43 to 1.15)	
Total stent length, mm†				0.855
<30	50/931 (5.4)	58/958 (6.1)	0.89 (0.61 to 1.30)	
≥30	38/572 (6.7)	39/554 (7.1)	0.94 (0.60 to 1.47)	



Hong SJ et al. JACC Cardiovasc Interv 2021

MASTER DAPT

- N= 4,434 all-comers with high bleeding risk (HBR) randomized to 1 month of DAPT vs. standard therapy (at least > 3 months)
- Stable angina 40%, NSTEMI 26%, STEMI 12%
- After 1 month of DAPT: ~ 50% on clopidogrel as monotherapy
- Non-inferiority met for the 1 month DAPT group in terms of net clinical adverse events (MACE + major or CRNM bleeding)

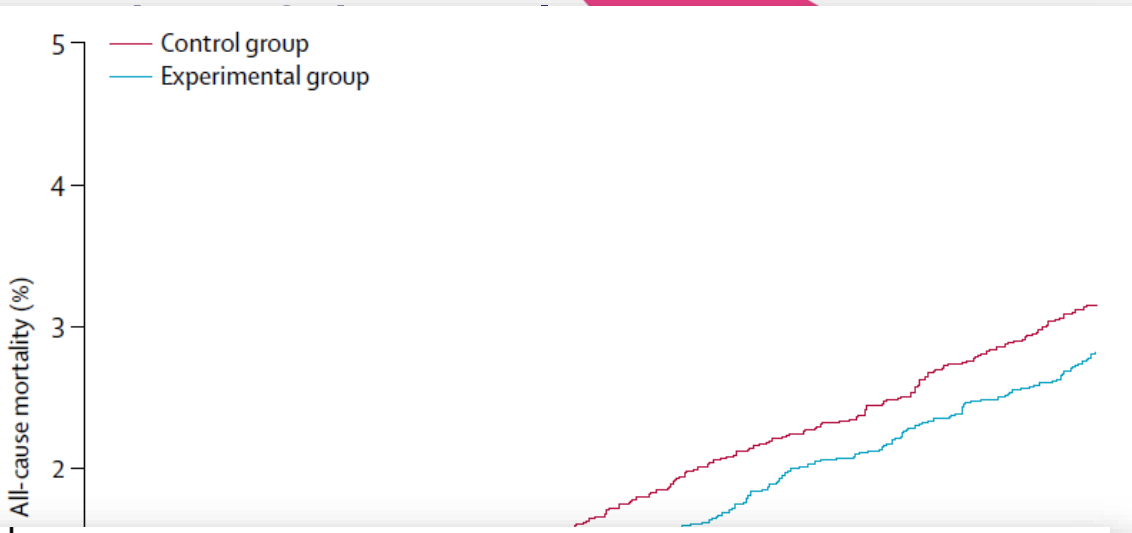
Valgilmigli M et al. NEJM 2021

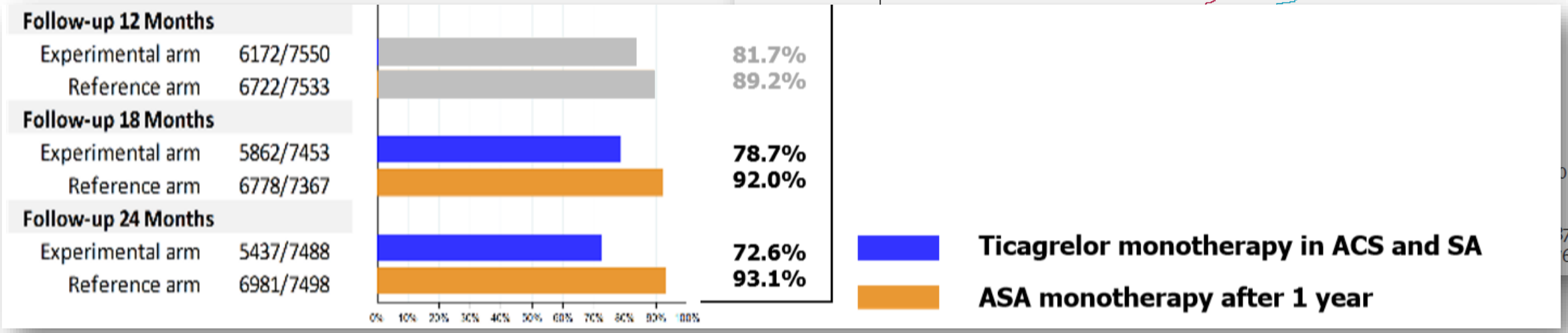
Strategies focused on reducing bleeding events

- Shortening DAPT
- P2Y12 monotherapy
- De-escalating P2Y12 inhibitors

GLOBAL-LEADERS

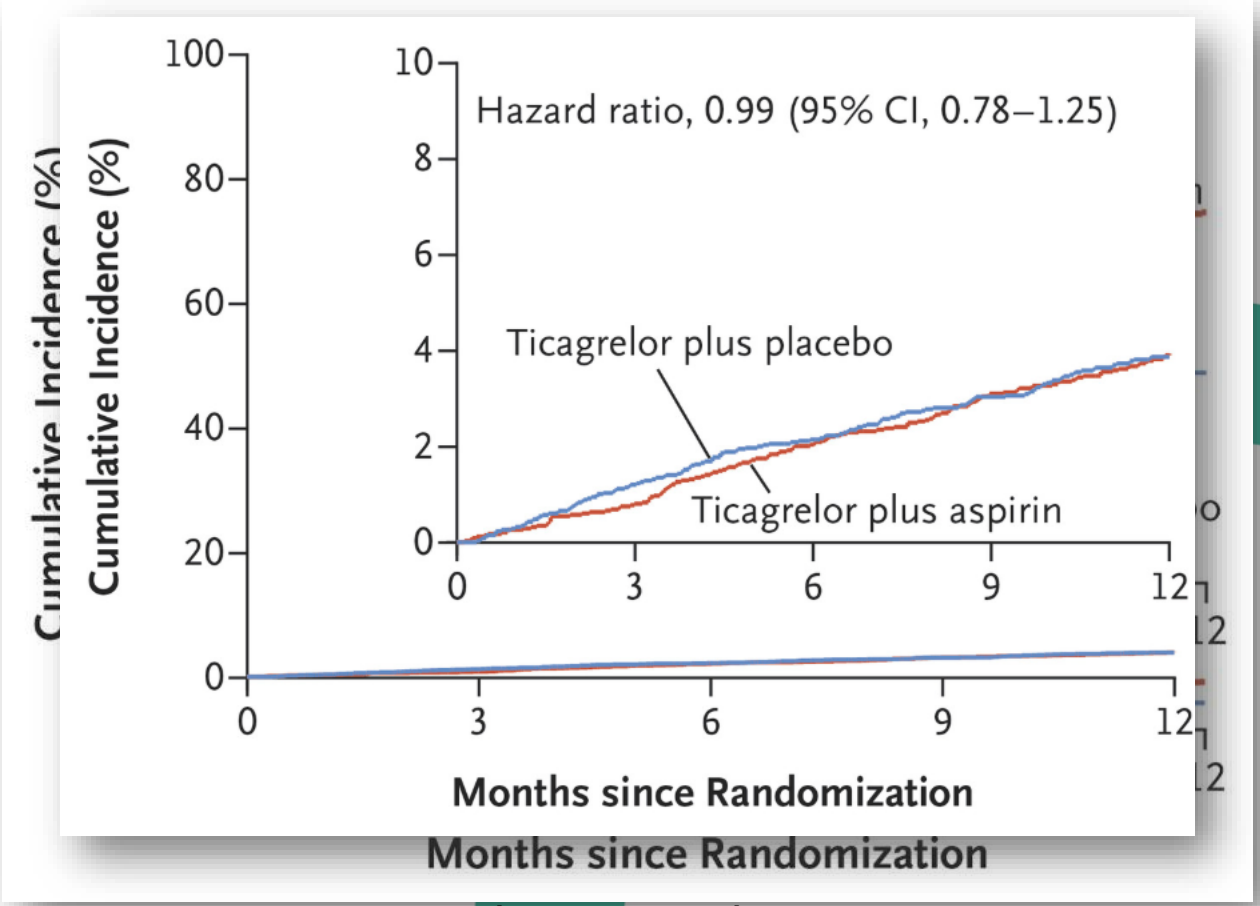
- 1 month of DAPT followed by
  for 12 months and then aspirir
- N=15,968 undergoing PCI
- No significant difference in the
  no difference in bleeding rates





Twilight Trial

- N=7,119 high risk patients (65% ACS, STEMI EXCLUDED)
- DAPT vs. Ticagrelor monotherapy after 3 months for 12 months
- Significantly less bleeding with monotherapy
- No difference in ischemic endpoints



Mehran R et al. NEJM 2019

STOPDAPT-2-ACS

- N=4,169 of patients with ACS undergoing PCI (57% STEMI, 20% NSTEMI, 24% UA)
- Short duration of DAPT with aspirin and clopidogrel (1-2 months) followed by clopidogrel monotherapy vs. DAPT for 12 months
- Non-inferiority not met in NACE (net adverse clinical events) with short DAPT duration with the composite ischemic endpoint trending towards hard (nearly 2-fold increase in MI) but less bleeding.
- All east-Asian patients, clopidogrel resistance not assessed

Watanabe H et al. JAMA Cardiol 2022

Strategies focused on reducing bleeding events

- Shortening DAPT
- P2Y12 monotherapy
- De-escalating P2Y12 inhibitors

De-escalation of P2Y12 inhibitors

Recommendations	Class	Level
Shortening antithrombotic treatment duration (continued)		
De-escalation of $P2Y_{12}$ receptor inhibitor treatment (e.g. with a switch from prasugrel or ticagrelor to clopidogrel) may be considered as an alternative DAPT strategy, especially for ACS patients deemed unsuitable for potent platelet inhibition. De-escalation may be done unguided based on clinical judgment or guided by platelet function testing or CYP2C19 genotyping, depending on patient's risk profile and availability of respective assays.	IIb	A

ACS								
TALOS-MI	2021	2,697	100	0	Clopidogrel-based DAPT versus ticagrelor-based DAPT	CV death, MI, stroke and BARC 2-5 bleeding	Yes	12

Conclusions

- Trade-off between ischemic and bleeding events is inevitable
- Patient selection for the different options is critical, taking into consideration patient and event and procedural characteristics, consider platelet responsiveness
- Early bleeding risk assessment using a validated tool is of upmost importance since treatment decisions will depend upon it

Conclusions

- Each discussed strategy looks promising, probably will see shifting towards tailored therapy in following years
- Caution with “downgrading” antiplatelet therapy too early after MI (STOPDAPT-2)

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Thank you!


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