Changing practice of ACS treatment based on PLATO & Guideline recommendation ; Insight from One-year real-world registry

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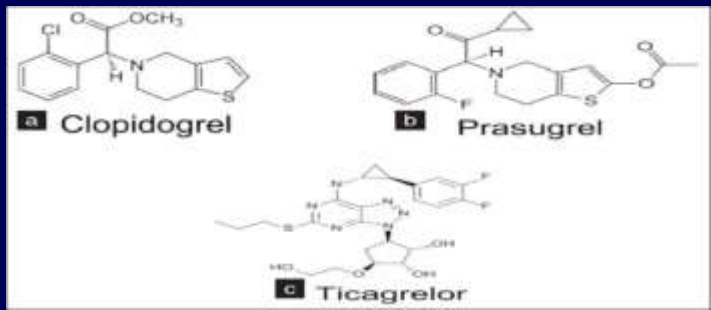
Contents

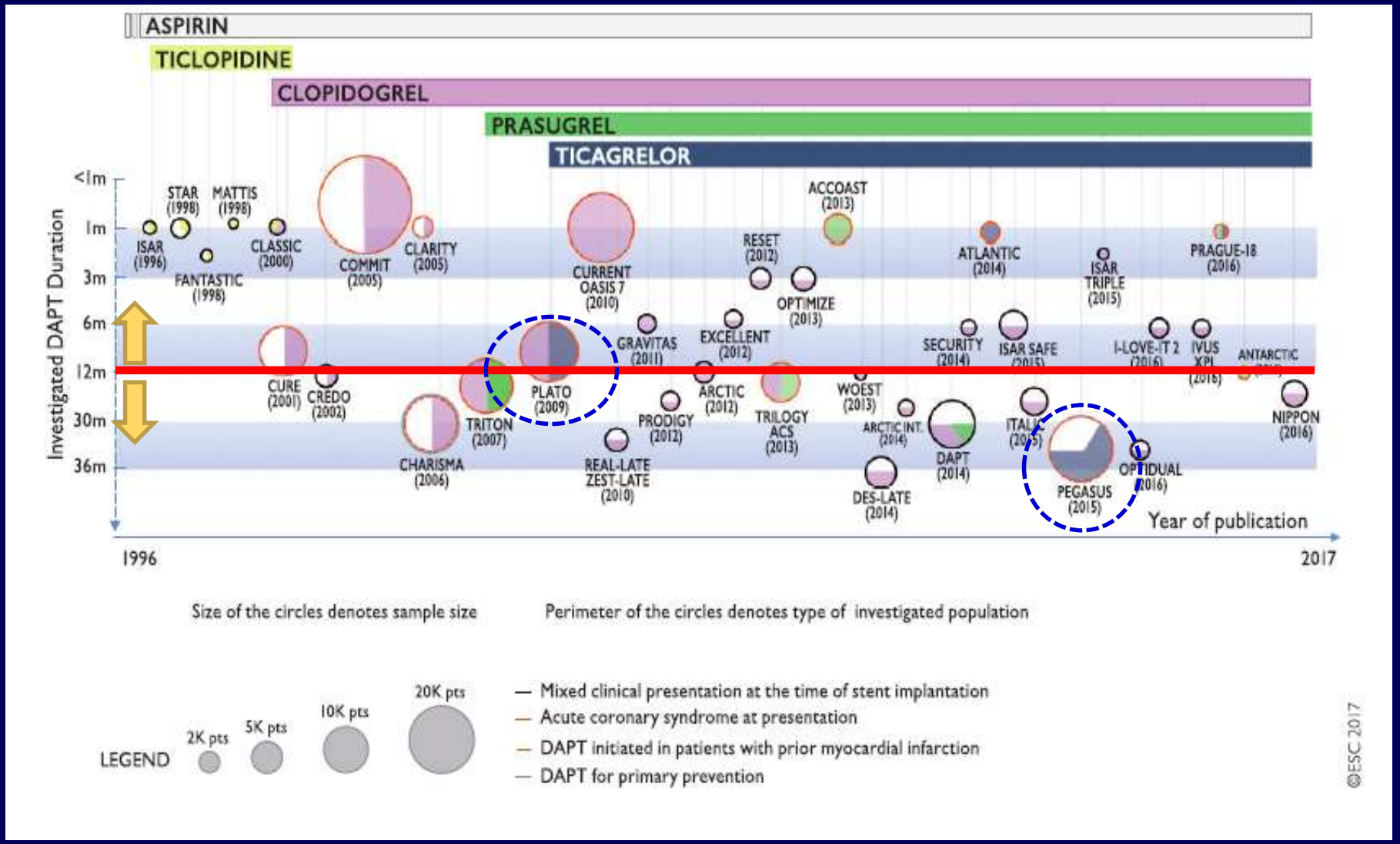
- Update of only proven CV mortality benefit on Ticagrelor based on PLATO & Guideline recommendation
- What happen in Asian patients with Ticagrelor treatment thur. RWE
- Clinical benefits of Ticagrelor against De-escalation

Mechanism of Action: Comparison

Ticagrelor	Clopidogrel/Prasugrel
CPTP	Thienopyridines
Direct acting	Prodrugs
24 hours PK & systemic profile	Intermittent PK & no systemic exposure
Reversible	Irreversible
Inhibition of ENT-1-mediated adenosine uptake (dual pathway)	**No additional Mechanism of Action**



PLATO & PEGASUS TIMI-54 are key trials in History of DAPT in patients with CAD



European Heart Journal (2017) 0, 1–48. doi:10.1093/eurheartj/ehx419

Recommendations on P2Y12 inhibitor selection and timing :Ticagrelor vs Prasugrel (Class I)

$P2Y_{12}$ inhibitor selection and timing

ESC European Society of Cardiology

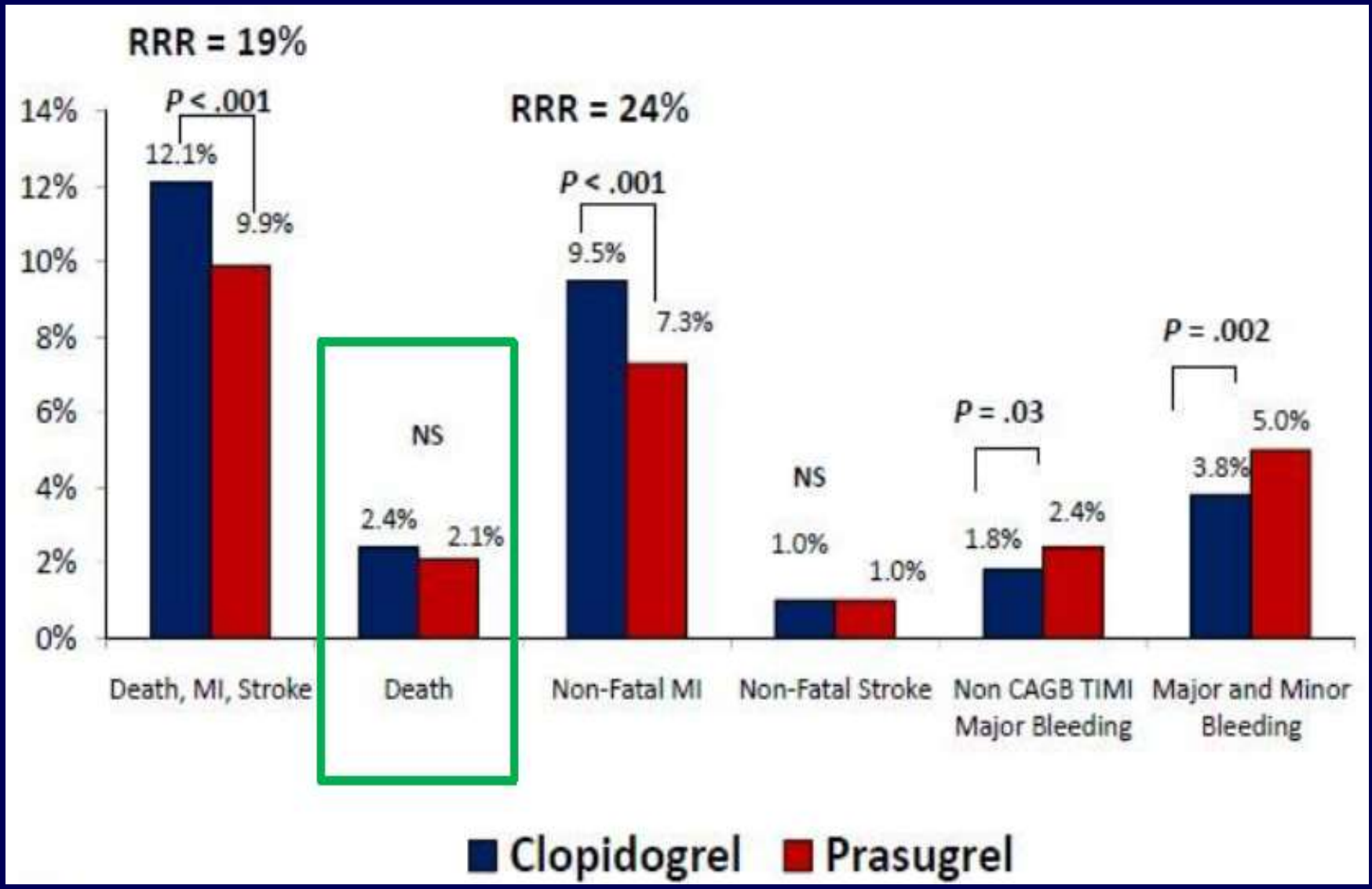
Recommendations	Class	Level
In patients with ACS, ticagrelor (180 mg loading dose, 90 mg twice daily) on top of aspirin is recommended, regardless of initial treatment strategy, including patients pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced) unless there are contra-indications.	I	B
In patients with ACS undergoing PCI, prasugrel (60 mg loading dose, 10 mg daily dose) on top of aspirin is recommended for $P2Y_{12}$ inhibitor-naïve patients with NSTE-ACS or initially conservatively managed STEMI if indication for PCI is established, or in STEMI patients undergoing immediate coronary catheterization unless there is a high-risk of life-threatening bleeding or other contra-indications.	I	B

www.escardio.org/guidelines

2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS (European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

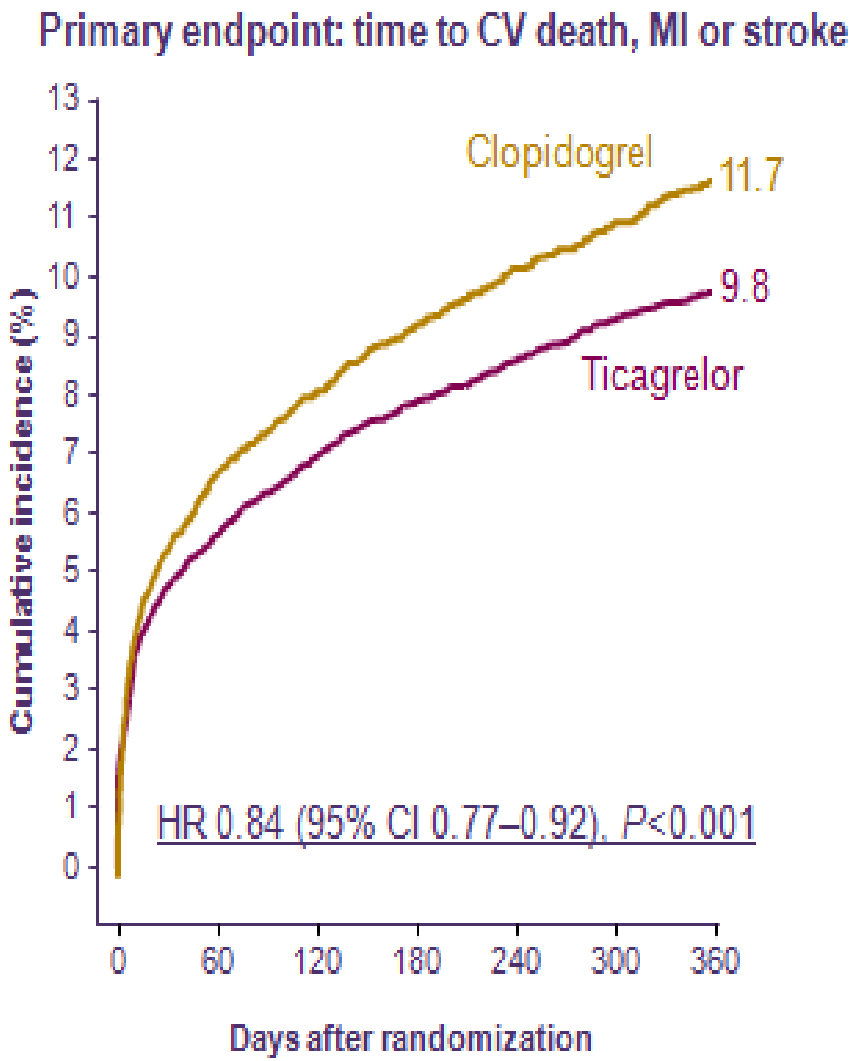
European Heart Journal (2017) 0, 1–48. doi:10.1093/eurheartj/ehx419

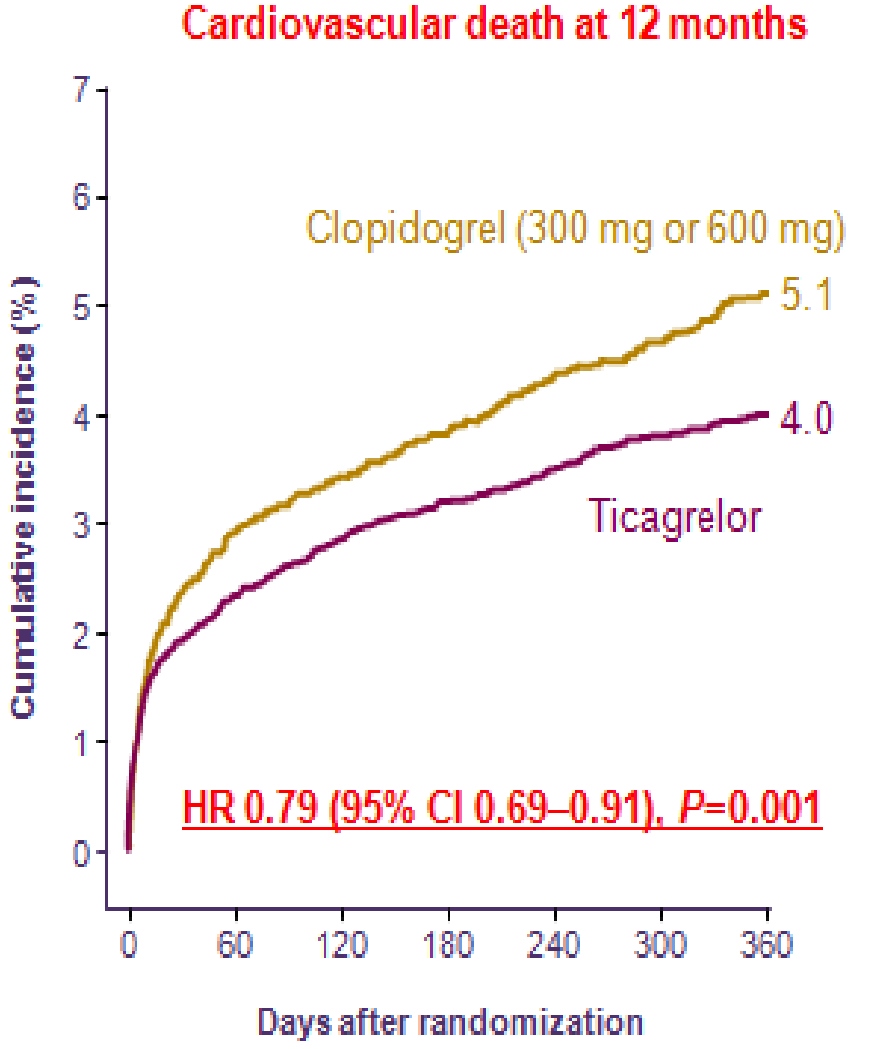
TRITON-TIMI 38 – Prasugrel not reduced death



Wiviott S et al. N Engl J Med 2007;357:2001–2015;

PLATO: primary endpoint and CV mortality





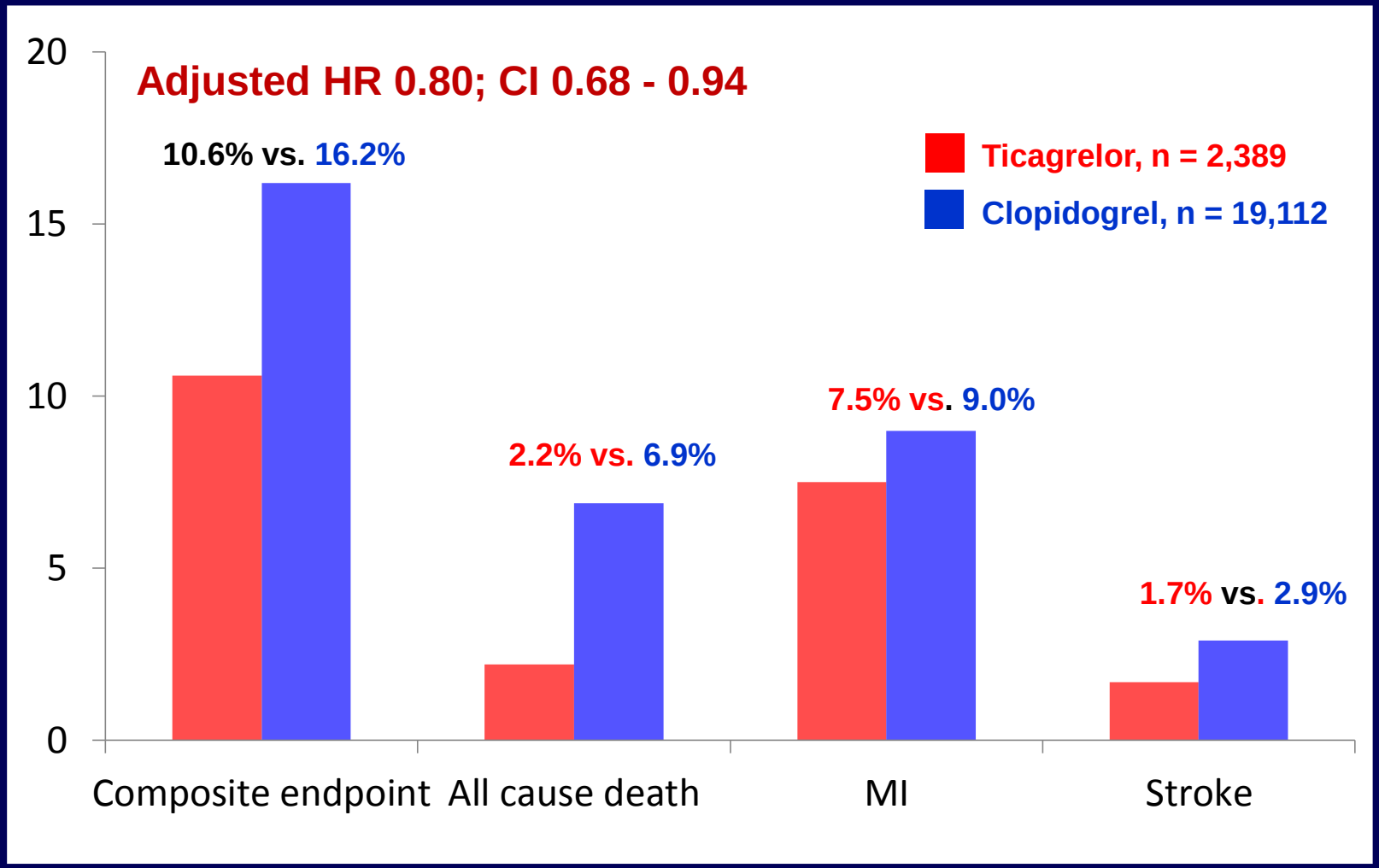
Wallentin L et al. N Engl J Med 2009;361:1045–1057

What happen in Asian patients with Ticagrelor treatment thur. RWE

Taiwan National Health Insurance Database

Composite of all cause death, MI or stroke

- The Taiwan National Health Insurance Research Database between January 2012 and December 2014

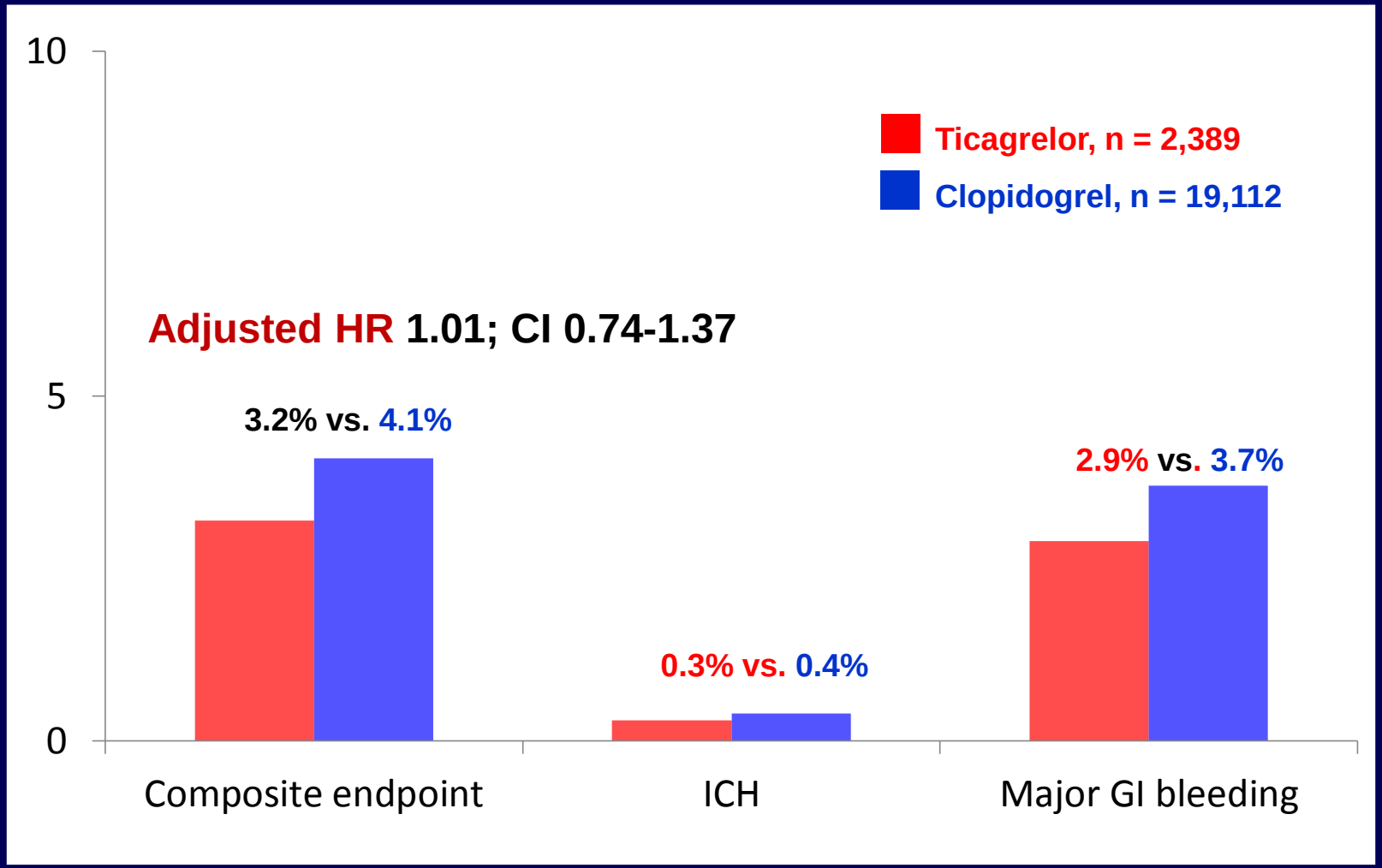


Lee CH et al. Circ J 2018;82(3):747-756.

Taiwan National Health Insurance Database

Composite of ICH and major GI bleeding

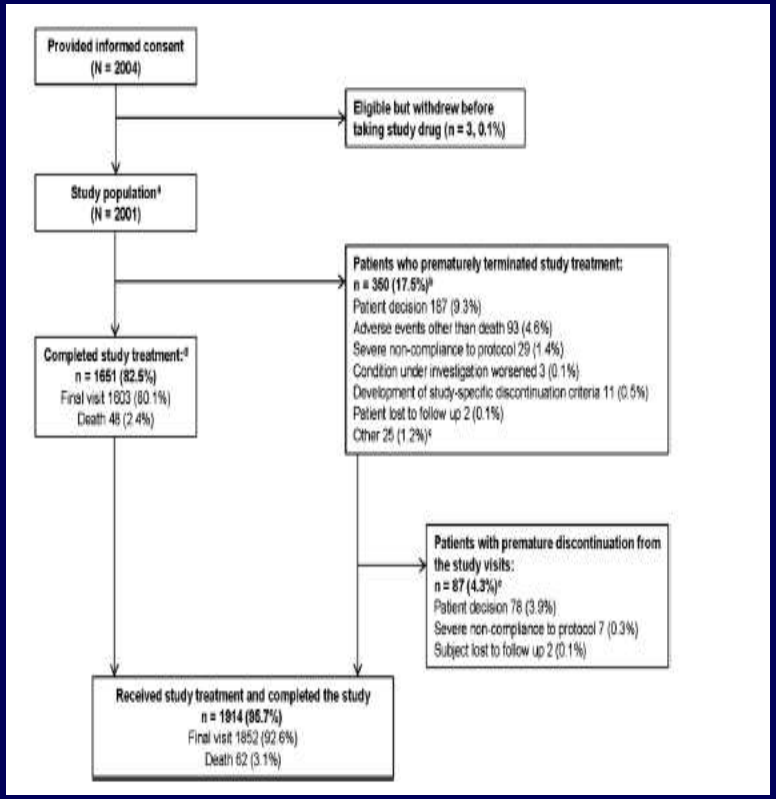
- The Taiwan National Health Insurance Research Database between January 2012 and December 2014



Lee CH et al. Circ J 2018;82(3):747-756.

Safety and Incidence of Cardiovascular Events in Chinese Patients with Acute Coronary Syndrome Treated with Ticagrelor

the 12-Month, Phase IV, Multicenter, Single-Arm DAYU Study

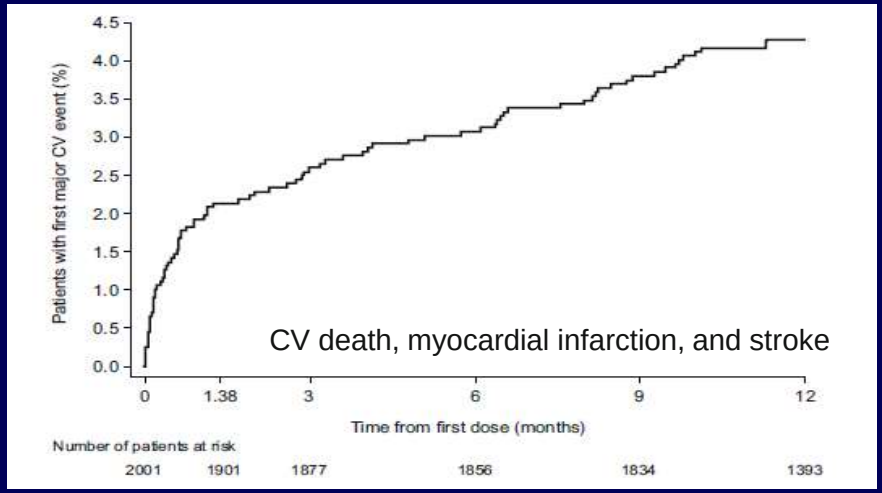


Ticagrelor plus low-dose aspirin for up to 1 year was associated with a low rate of major bleeding events and a low incidence of major CV events (CV death, myocardial infarction, stroke) in Chinese patients with ACS.

- PLATO-defined bleeding events by severity

Bleed severity	Ticagrelor 90 mg b.i.d (n = 2001)	
	Patients with bleeding n (%)	Number of bleeding events
Total major bleeding	27 (1.3)	28
Life-threatening/fatal	17 (0.8)	17
Fatal	4 (0.2)	4
Life-threatening	13 (0.6)	13
Major, other	11 (0.5)	11
Composite of major and minor bleeding	93 (4.6)	106
Minor bleeding	66 (3.3)	78
Composite of major, minor, and minimal bleeding	426 (21.3)	640
Minimal bleeding	353 (17.6)	534

- First major CV events



Gao R. et al. Cardiovasc Drugs Ther. 2018 Feb;32(1):47-56

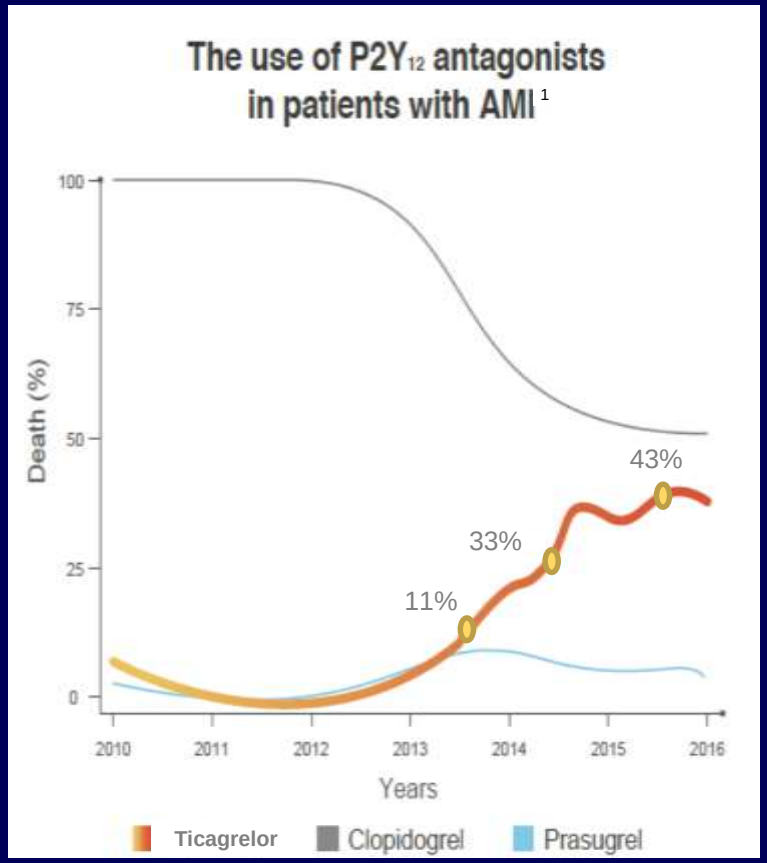
New P2Y12 antagonist was associated lower rate of MACCE and cardiac mortality in AMI patients treated with PCI (KAMIR-NIH) database

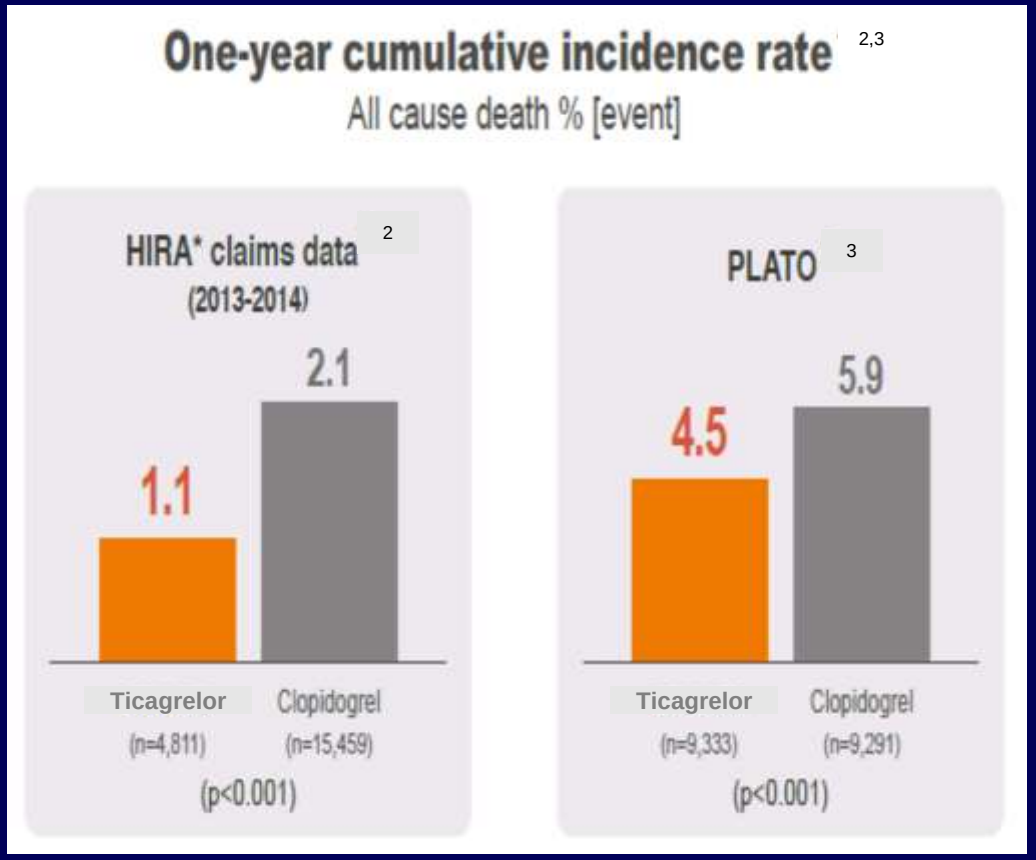
	Before PS match			After PS match		
	Clopidogrel (n=7580)	New P2Y12 inhibitor (n=4151)	p-value	Clopidogrel (n=4151)	New P2Y12 inhibitor (n=4151)	p-value
MACE	718 (9.9)	254 (6.4)	<0.001	323 (8.2)	254 (6.4)	0.002
Cardiac death	461(6.3)	132 (3.3)	<0.001	189 (4.7)	132 (3.3)	<0.001
Non-fatal myocardial infarction	59 (1.0)	21 (0.6)	0.05	23 (0.7)	21 (0.6)	0.783
Target lesion revascularization	144 (2.3)	64 (1.8)	0.412	85 (2.4)	64 (1.8)	0.337
Stroke	58 (0.9)	25 (0.7)	0.137	27 (0.8)	25 (0.7)	0.366
All bleeding event	n=1798	n=913		n=753	n=869	
TIMI major bleeding	11 (0.6)	4 (0.4)	0.673	5 (0.7)	4 (0.5)	0.673
TIMI minor bleeding	245 (13.6)	158 (17.3)	0.011	104 (13.8)	158 (17.3)	0.057

- TIMI major bleeding was similar between two groups.
- TIMI minor bleeding showed a trend toward a lower incidence in the clopidogrel group (13.8% vs. 17.3%, p=0.057).

Jung-Hee Lee et al. AHA 2017, Circulation. 2017;136:A21117

Antiplatelet therapy for AMI in Korea based on 1-year outcomes from HIRA database





- **AMI patients undergoing percutaneous coronary intervention between 2010 and 2015 were assessed using claim data form the Health Insurance Review and Assessment Service. The purpose of this study was to investigate trends in antiplatelet agent use for acute myocardial infarction(AMI) and their impact on 30-day clinical outcomes.**
- **Among a total 20,270 patients (age <75 years) with AMI undergoing percutaneous coronary intervention who received dual antiplatelet therapy for at least 30 days, clinical outcomes at 1 year were assessed from the database of Health Insurance Review and Assessment Service in Korea between 2013 and 2014.**

1) CK Kim et al. Korean Circ J. 2017 Nov; 47(6):888-897 2) C. Kim et al. / Journal of Cardiology 73 (2019) 191–197 3) Wallentin et al. New Eng J Med 2009; 361(11): 1045-1057

Clinical benefits of Ticagrelor against De-escalation

Circulation

ORIGINAL RESEARCH ARTICLE

Pharmacodynamic Effects of Switching From Ticagrelor to Clopidogrel in Patients With Coronary Artery Disease

Results of the SWAP (Switching Antiplatelet Therapy)-4 Study

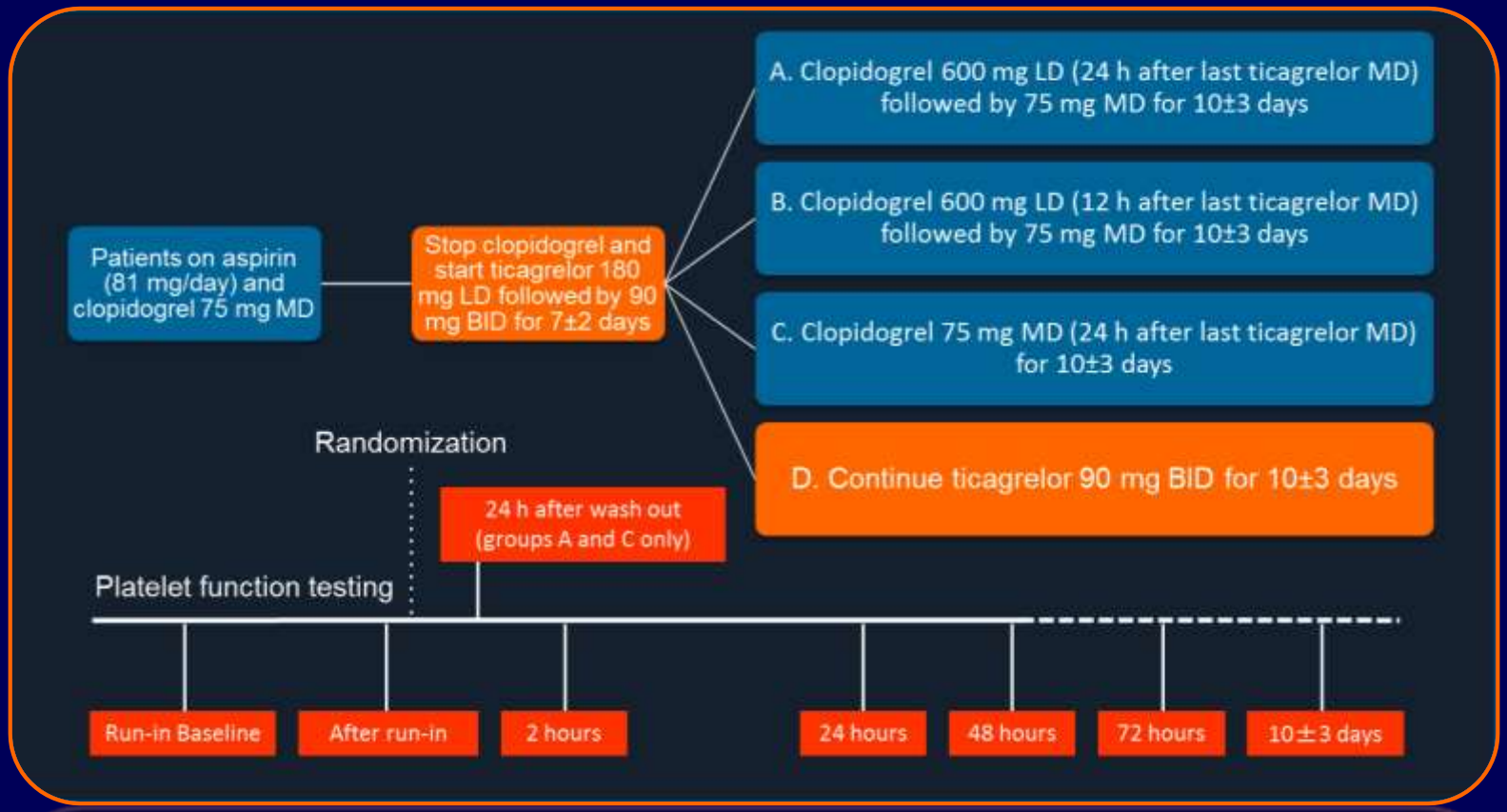
Francesco Franchi, MD, Fabiana Rollini, MD, Jose Rivas Rios, MD, Andrea Rivas, MD, Malhar Agarwal, MD, Megha Kureti, MD, Deepa Nagaraju, MD, Mustafa Wali, MD, Zubair Shaikh, MD, Maryuri Briceno, MD, Ahmed Nawaz, MD, Jae Youn Moon, MD, PhD, Latonya Been, AAS, Siva Suryadevara, MD, Daniel Soffer, MD, Martin M Zenni, MD, Theodore A Bass, MD, Dominick J Angiolillo, MD, PhD

Franchi F, et al. Circulation, 2018
DOI: 10.1161/CIRCULATIONAHA.118.033983

Pharmacodynamic Effects of Switching from Ticagrelor to Clopidogrel in Patients with Coronary Artery Disease: Results of the SWAP -4 Study

Study design

SWAP-4 was a prospective, randomized, open-label, single center study aimed to assess the pharmacodynamic effects of de-escalating from ticagrelor to clopidogrel in patients with CAD on a background of aspirin therapy, and how this is affected by the use of a clopidogrel LD compared with a MD regimen and the impact of different timing of LD administration



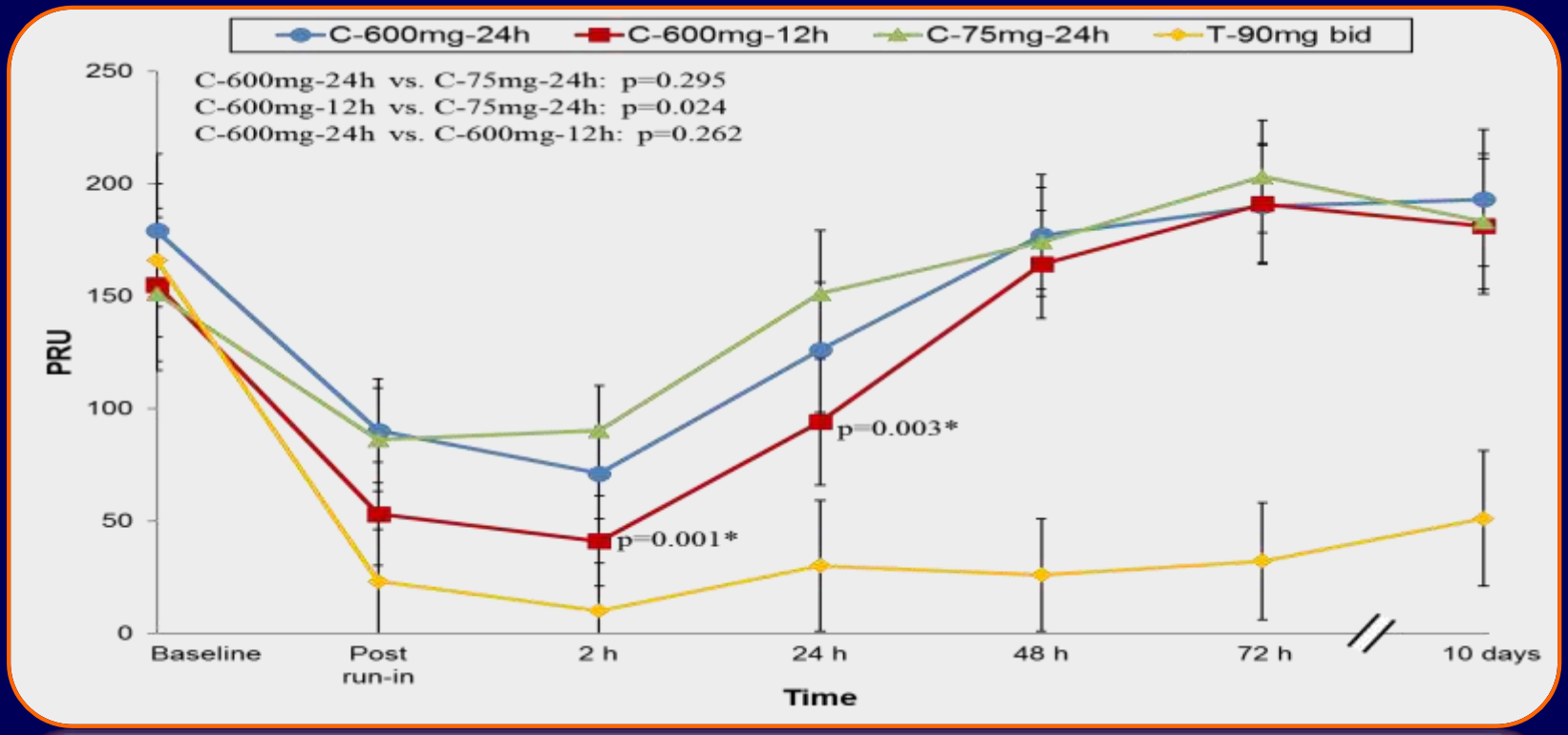
Franchi F, et al. Circulation, 2018

Pharmacodynamic Effects of Switching from Ticagrelor to Clopidogrel in Patients with Coronary Artery Disease: Results of the SWAP -4 Study

Results

PRU levels were similar between C-600mg-24h and C-75mg-24h (p=0.29), including at 48 hours (primary endpoint; LSM difference: -6.9; 95% CI: -38.1 to 24.3; p=0.66). PRU levels were lower with C-600mg-12h versus C-75mg-24h (p=0.024)

VerifyNow P2Y12



Franchi F, et al. Circulation, 2018

Increasing ischemic risk due to de-escalation

A total of 653 patients with STEMI were randomly assigned to receive loading dose of ticagrelor or clopidogrel before PCI and then received maintenance dose, respectively, for 12 months follow-up in China

The rate of secondary ischemic events in the de-escalation group was higher than that in the ticagrelor group (15.1% vs. 5.6%, p=0.008)

Table 2. Clinical Outcomes of the Patients in De-escalation, Ticagrelor and Clopidogrel at 12 Months

Clinical outcomes [n(%)]	De-escalation group (n=152)	Ticagrelor non-switched group (n=161)	Clopidogrel non-switched group (n=281)	Ticagrelor vs. de-escalation		Clopidogrel vs. de-escalation		Clopidogrel vs. ticagrelor		P-value
				Hazard or Odds Ratio for de-escalation (95%CI)	p-value	Hazard or Odds Ratio de-escalation (95%CI)	p-value	Hazard or Odds Ratio for ticagrelor (95%CI)	p-value	
MACE	5 (3.3)	4 (2.5)	17 (6.0)	0.75(0.18,2.88)	0.74	1.89(0.73,5.85)	0.53	2.53(0.92,8.9)	0.16	0.16
Cardiovascular death	1 (0.7)	3 (1.9)	8 (2.8)	2.87(0.36,58.31)	0.62	4.42(0.8,82.48)	0.17	1.54(0.44,7.12)	0.76	0.36
Myocardial infarction	3 (2.0)	0 (0.0)	6 (2.1)		0.11	1.08(0.28,5.19)	1.00		0.01	0.14
Ischaemic stroke	1 (0.7)	1 (0.6)	3 (1.1)	0.94(0.04,24.01)	1.00	1.63(0.21,33.1)	1.00	1.73(0.22,35.06)	1.00	1.00
The secondary ischemic events	23 (15.1)	9 (5.6)	69 (24.6)	0.33(0.14,0.72)	0.008	1.83(1.1,3.12)	0.03	5.5(2.8,12.12)	<0.001	<0.001
Re-hospitalization for intable angina	23 (15.1)	9 (5.6)	64 (22.8)	0.33(0.14,0.72)	0.008	1.65(0.99,2.84)	0.06	4.98(2.53,11.01)	<0.001	<0.001
Revascularization	18 (11.8)	4 (2.5)	28 (10.0)	0.19(0.05,0.52)	0.001	0.82(0.44,1.57)	0.64	4.34(1.67,14.88)	0.006	0.005
PCI	18	3	25							
CABG	0	1	3							
Stent thrombosis	0 (0.0)	0 (0.0)	4 (1.4)		1.00		0.30		0.30	0.20
Bleeding events	14 (9.2)	31 (19.3)	34 (12.1)	2.35(1.22,4.74)	0.02	1.36(0.72,2.69)	0.42	0.58(0.34,0.98)	0.02	0.02
BARC=1	12 (7.9)	28 (17.4)	24 (8.5)	2.46(1.23,5.2)	0.02	1.09(0.54,2.32)	0.86	0.44(0.25,0.79)	0. 009	0.006
Skin ecchymosis	3	10	7							
Hemorrhimia	1	3	2							
Fecal occult blood	4	5	7							
Gum bleeding	4	8	6							
Hemorrhoidal bleeding	0	2	2							
BARC≥2	2 (1.3)	3 (1.9)	10 (3.6)	1.42(0.23,10.92)	1.00	2.77(0.72,18.16)	0.23	1.94(0.58,8.76)	0.56	0.34
BARC=2	2 (1.3)	1 (0.6)	6 (2.1)	0.47(0.02,4.94)	0.61	1.64(0.37,11.26)	0.71	3.49(0.59,66.24)	0.43	0.52
BARC=3a	0 (0.0)	2 (1.2)	3 (1.1)		0.50		0.56	0.86(0.14,6.56)	1.00	0.61
BARC=3b	0 (0.0)	0 (0.0)	1 (0.4)		1.00		1.00		1.00	1.00

Table 4. MACE, major adverse cardiac events. PCI, primary percutaneous coronary intervention. CABG, coronary artery bypass grafting. BARC, Bleeding Academic

Li XY et al. Clinical Cardiology. https://doi.org/10.1002/clc.23074

De-escalation strategy leads to increase MI & Ischemic stroke according to KR HIRA 1Y outcome date

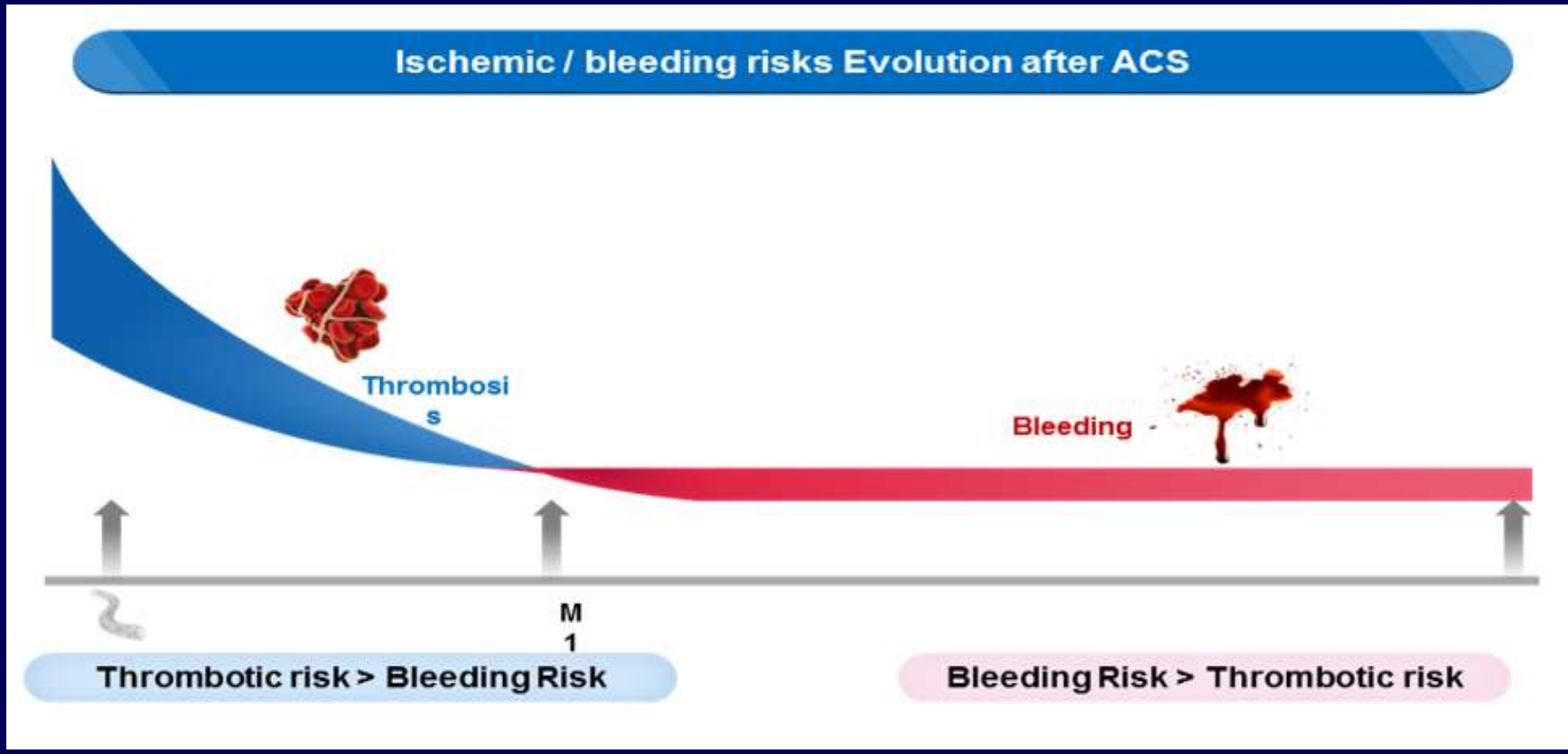
	Maintained	Switching P2Y12 receptor antagonist					p-Value
		All	Escalation	De-escalation	Change	Combined	
BRILINTA							
Patients	2918 (61)	1893 (39)	-	1344	61	488	0.805
All-cause death	30 (1.0)	21 (1.1)	-	13 (1.0)	1 (1.6)	7 (1.4)	<0.001
Myocardial infarction	219 (7.5)	204 (10.8)	-	138 (10.3)	10 (16.4)	56 (11.5)	0.014
Stroke	14 (0.5)	23 (1.2)	-	15 (1.1)	0 (0.0)	8 (1.6)	0.002
Ischemic	7 (0.2)	20 (1.1)	-	15 (1.1)	0 (0.0)	5 (1.0)	0.073
Hemorrhagic	7 (0.2)	3 (0.2)	-	0 (0)	0 (0.0)	3 (0.6)	0.003
Bleeding	18 (0.6)	26 (1.4)	-	15 (1.1)	0 (0.0)	11 (2.3)	

Data are presented as number (%)

One-year incidence of adverse events according to switching P2Y12 receptor antagonist after index discharge.

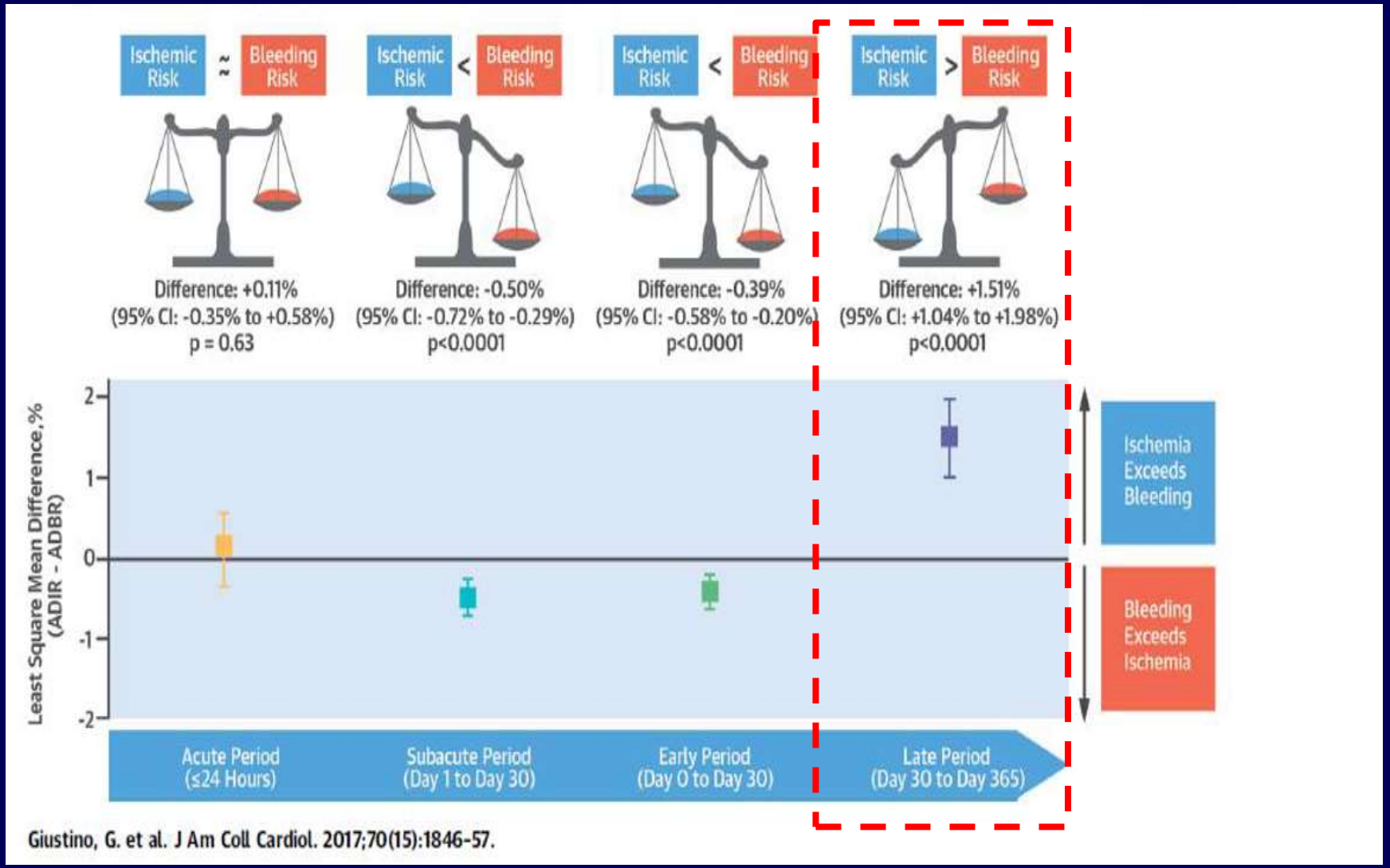
Do you believe that ischemic risk is becoming stabilized after 1month?

- Newer P2Y12 blockers in ACS
  - Ischemic benefit greater in early phase
  - Bleeding hazard mainly on chronic phase
- Up to 26% of patients are being switched from newer agents to clopidogrel



Culsset T et al. Eur Heart. J 2017 May 15 (Epub ahead of print)

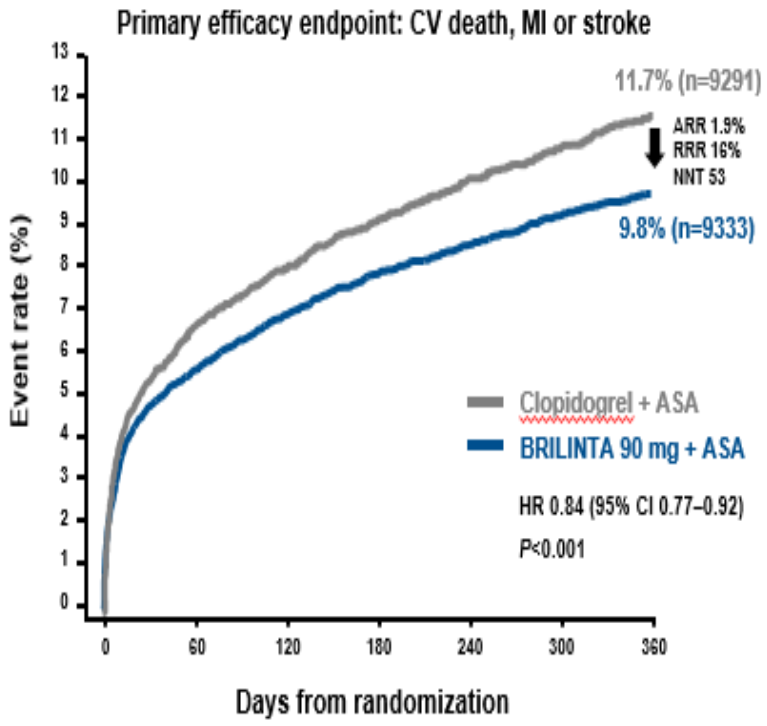
Ischemic risk is higher than bleeding risk after Primary PCI in STEMI patients



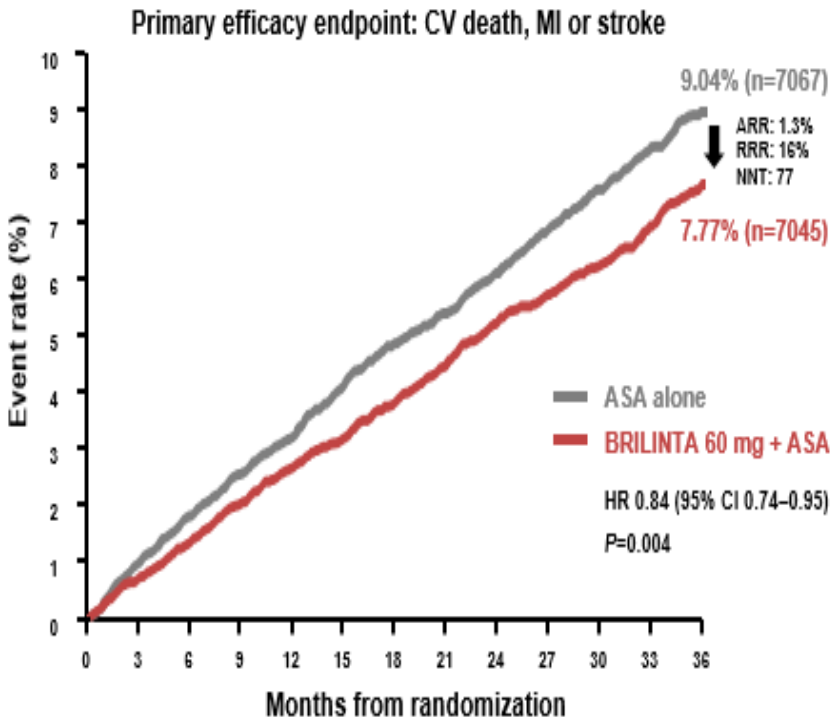
Giustino, G. et al. J Am Coll Cardiol. 2017;70(15):1846-57.

BRILINTA has demonstrated acute and long-term CV protection across two large outcome studies involving ~40,000 patients [1,2]

PLATO showed a reduction in subsequent CV events at 12 months in ACS patients taking BRILINTA 90 mg* vs clopidogrel*



PEGASUS showed an ongoing reduction in CV events in high-risk† post-MI patients taking BRILINTA 60 mg* vs placebo*



1. Wallentin L et al. N Engl J Med 2009;361:1045–1057; 2. Bonaca MP et al. N Engl J Med 2015;372:1791–1800

Conclusion

- Ticagrelor is only proven CV mortality benefit based on PLATO data and the result leads to change real world practice in Asian patients
- De-escalation therapy is still controversial between Pro & Cons.
  - It is not enough to accept as a standard of care in practice
- Ticagrelor comparing with clopidogrel for ACS patients showed a lower risk of CV events including mortality in Korea and Asia area.
- These outcomes are consistent with randomized trial results.


THANK YOU