Oral P2Y12 inhibitors in Acute Myocardial Infarction

: Are they all equal ?

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The Current Bottom Line – To start with potent P2Y12 inhibitor in ACS (ESC 2017 recommendation)

Recommendations	Class[a]	Level[b]
In patients with ACS, ticagrelor (180 mg loading dose, 90 mg twice daily) on top of aspirin[c] is recommended, regardless of initial treatment strategy, including patients pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced) unless there are contraindications.[20]	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[c] unless there is a high risk of life-threatening bleeding or other contraindications.[23]	I	B
Pre-treatment with a $P2Y_{12}$ inhibitor is generally recommended in patients in whom coronary anatomy is known and the decision to proceed to PCI is made as well as in patients with STEMI.[20,23,38]	I	A
In patients with NSTE-ACS undergoing invasive management, ticagrelor administration (180 mg loading dose, 90 mg twice daily), or clopidogrel (600 mg loading dose, 75 mg daily dose) if ticagrelor is not an option, should be considered as soon as the diagnosis is established. new	IIa	C
In patients with stable CAD, pre-treatment with clopidogrel may be considered if the probability of PCI is high.	IIb	C
Clopidogrel (600 mg loading dose, 75 mg daily dose) on top of aspirin is recommended in stable CAD patients undergoing coronary stent implantation and in ACS patients who cannot receive ticagrelor or prasugrel, including those with prior intracranial bleeding or indication for OAC.[20,23,39,40]	I	A
Clopidogrel (300 mg loading dose in patients aged <75, 75 mg daily dose) is recommended on top of aspirin in STEMI patients receiving thrombolysis.[31,32]	I	A
Ticagrelor or prasugrel on top of aspirin may be considered instead of clopidogrel in stable CAD patients undergoing PCI, taking into account the ischaemic (e.g. high SYNTAX score, prior stent thrombosis, location and number of implanted stents) and bleeding (e.g. according to PRECISE-DAPT score) risks. new	IIb	C
In NSTE-ACS patients in whom coronary anatomy is not known, it is not recommended to administer prasugrel.[25]	III	B

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

Clinical need for “de-escalation”

- **Economical issue (reduced cost with clopidogrel)**
- **Increased bleeding risk with the use of prasugrel or ticagrelor (such as older age, lower body weight, previous TIA/stroke, in-hospital treatment of CABG, atrial fibrillation or concurrent use of oral anti-coagulant)**
- **Non-bleeding side effects – dyspnea with ticagrelor**
- **TOPIC trial – Despite limitation, it showed reduced bleeding complications with de-escalation**
- **TROPICAL-ACS – Only RCT utilizing PFT to adjust antiplatelet therapy (either escalation or de-escalation) to meet its primary end point**

In-Hospital Switching of ADP Receptor Inhibitor in Myocardial Infarction Patients Treated with Percutaneous Coronary Intervention: Insights from the TRANSLATE-ACS Study

TRANSLATE-ACS

Bagai et al. ACC 2012

TRANSLATE-ACS population
4/4/2010 to 8/17/2012
8149 patients from 217 hospitals

In-hospital de-escalation from potent P2Y12 inhibitor to less potent P2Y12 inhibitor is not uncommon in real world.

(89%)

(11%)

(87%)

(13%)

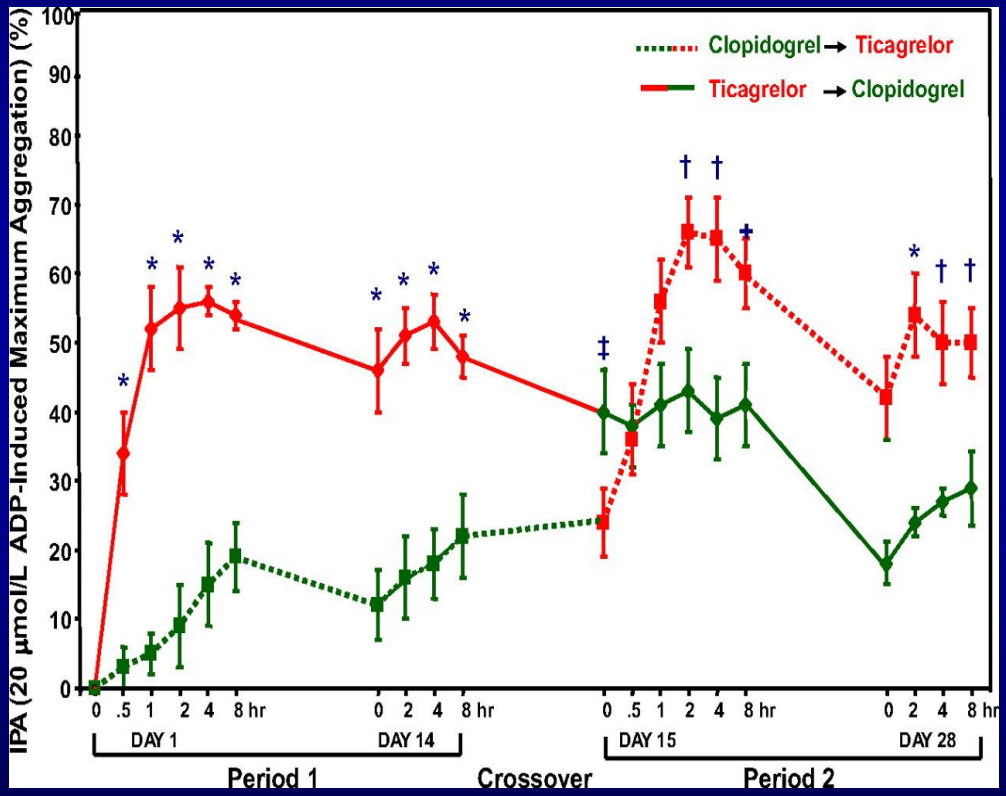
Switch from 1st to 2nd gen: associated with clinical and socio-economic factors: younger age, prior PCI, PFT, and private health insurance.

Switch from 2nd to 1st gen: associated with older age, anticoagulant use at discharge, preserved LV systolic function, and prior TIA/stroke.

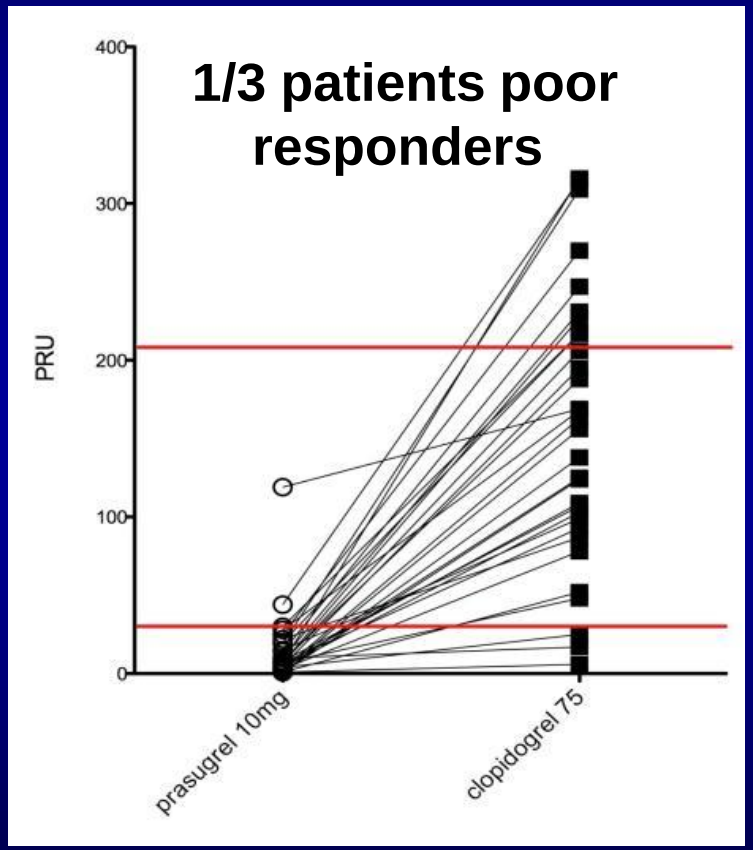
In-hospital ADPri switching is not associated with early (6-weeks) MACE and hospitalization for bleeding . Future investigation will examine longer term effects.

PD Effects of De-escalation from Ticagrelor or Prasugrel to Clopidogrel

De-escalation inevitably leads to an increase in platelet reactivity and HPR rates



Gurbel P A et al.
Circulation 2010; 121:1188-99



Kerneis M et al.
JACC Cardiovasc Interv. 2013;6:158–165

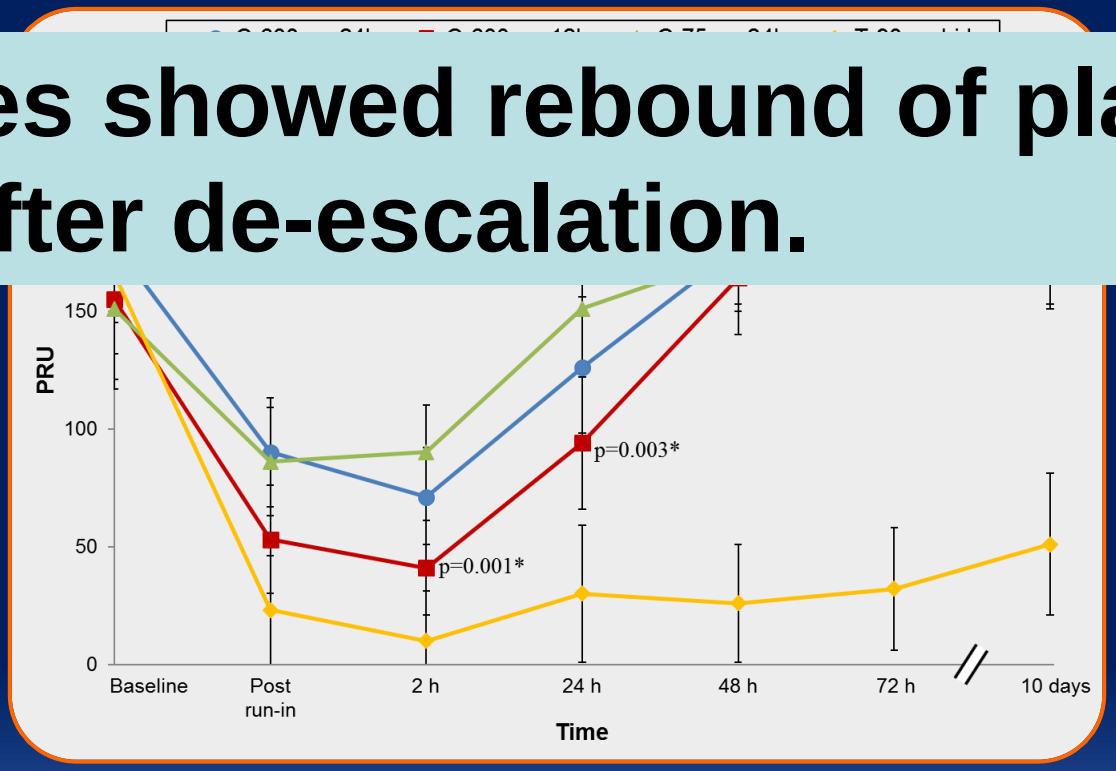
Pharmacodynamic Effects of Switching from Ticagrelor to Clopidogrel in Patients with Coronary Artery Disease: Results of the SWAP -4 Study

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

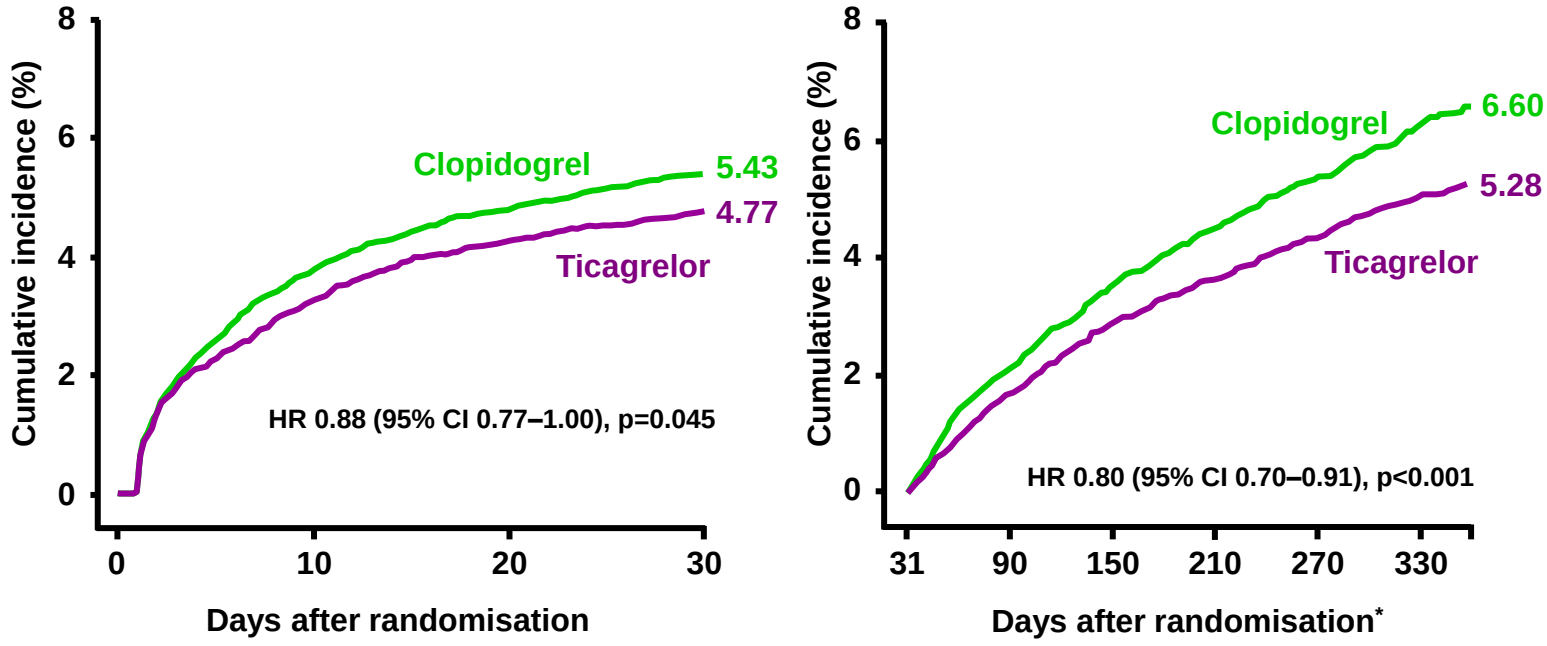
PD studies showed rebound of platelet activity after de-escalation.



Franchi F, et al. Circulation, 2018

PLATO : Primary Endpoint Over Time

Time to first primary efficacy event (composite of CV death, MI or stroke)

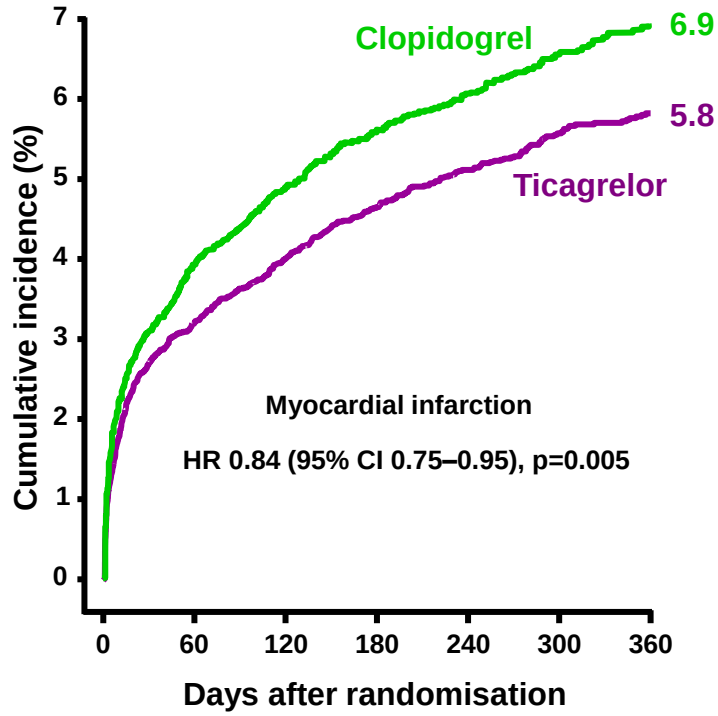


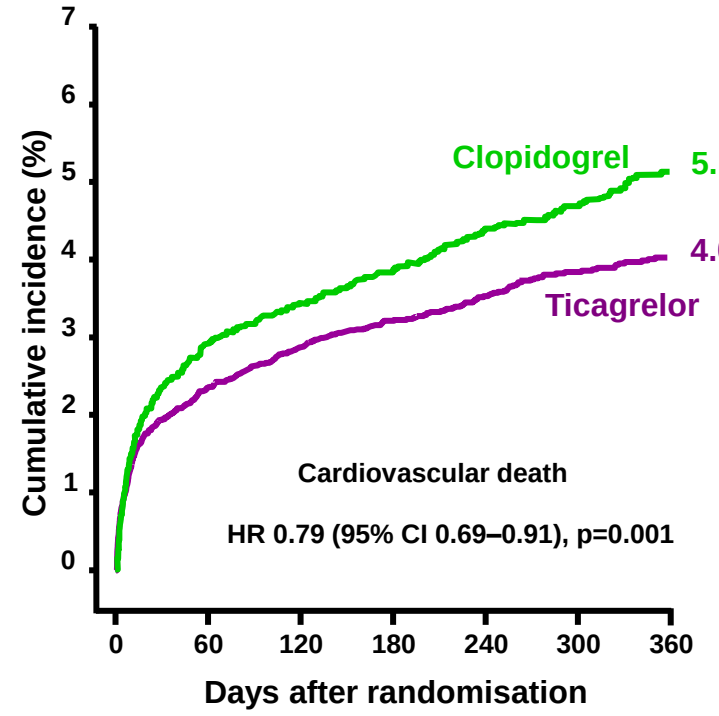
No. at risk										
Ticagrelor	9,333	8,942	8,827	8,763	8,763	8,543	8,397	7,028	6,480	4,822
Clopidogrel	9,291	8,875	8,763	8,688	8,688	8,437	8,286	6,945	6,379	4,751

*Excludes patients with any primary event during the first 30 days

PLATO : Secondary Endpoints

Time to first myocardial infarction or cardiovascular death



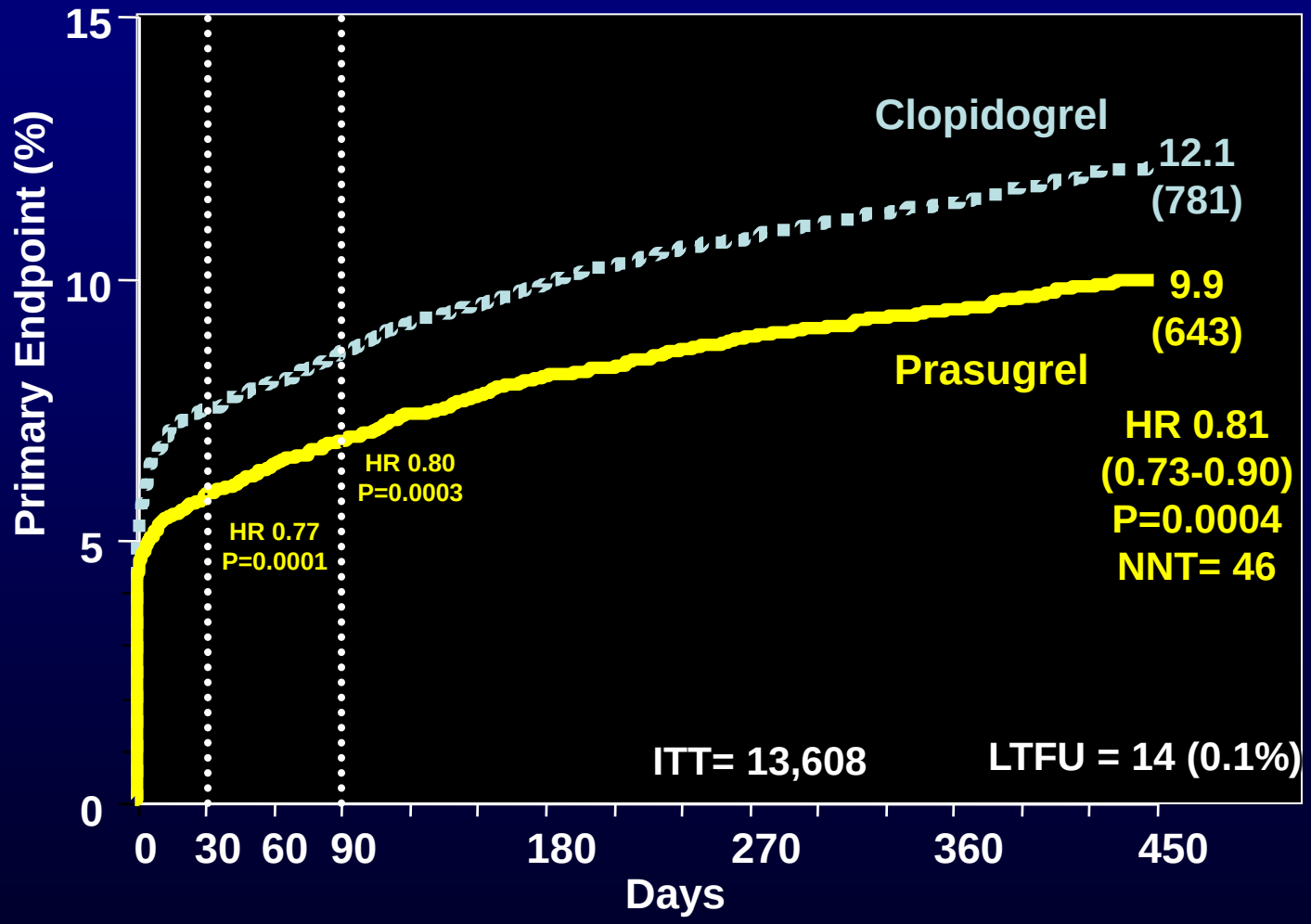


No. at risk							
Ticagrelor	9,333	8,678	8,520	8,279	6,796	5,210	4,191
Clopidogrel	9,291	8,560	8,405	8,177	6,703	5,136	4,109

9,333	8,294	8,822	8,626	7119	5,482	4,419
9,291	8,865	8,780	8,589	7079	5,441	4,364

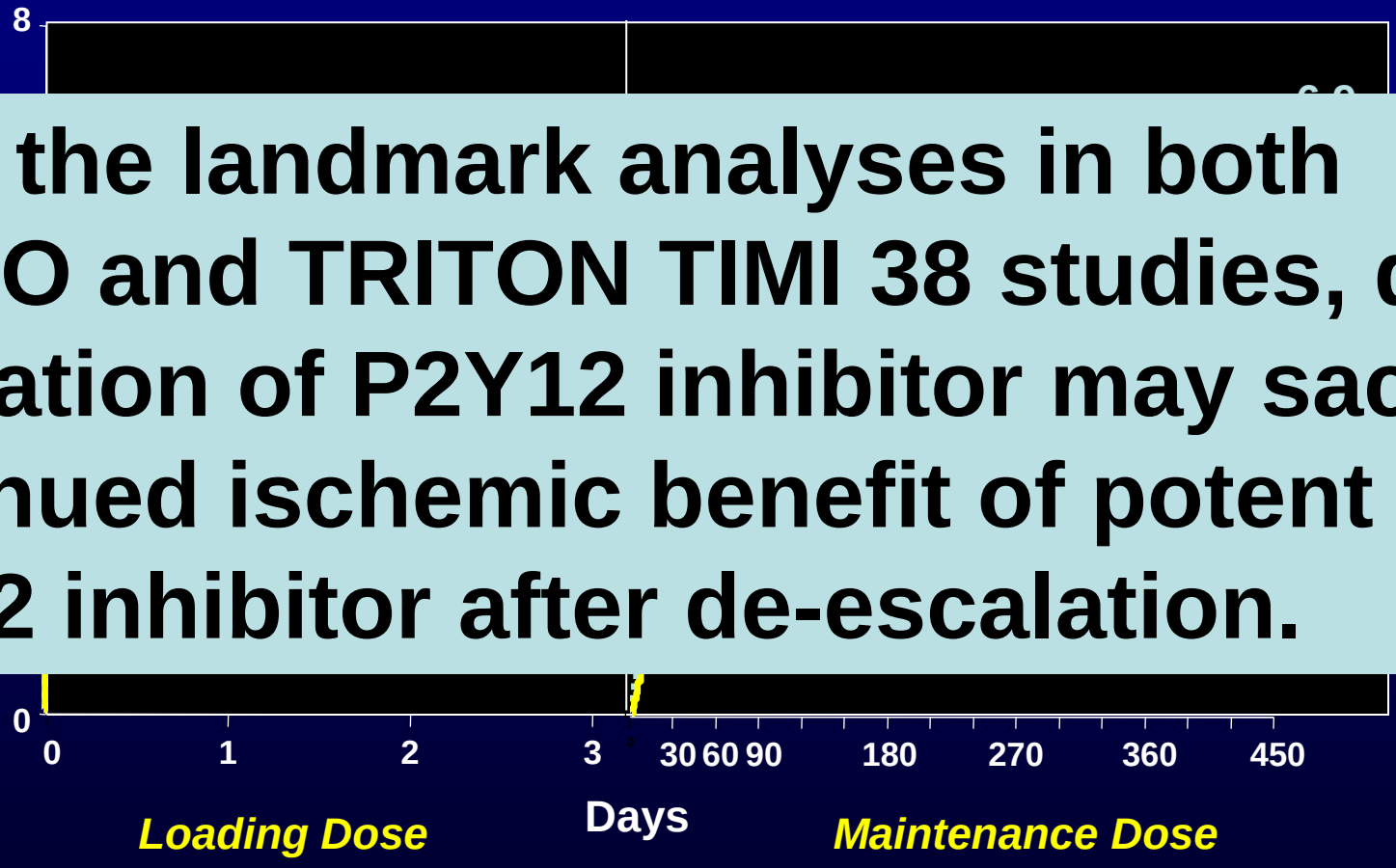
TRÎTON TIMI·38

Primary Endpoint
CV Death,MI,Stroke



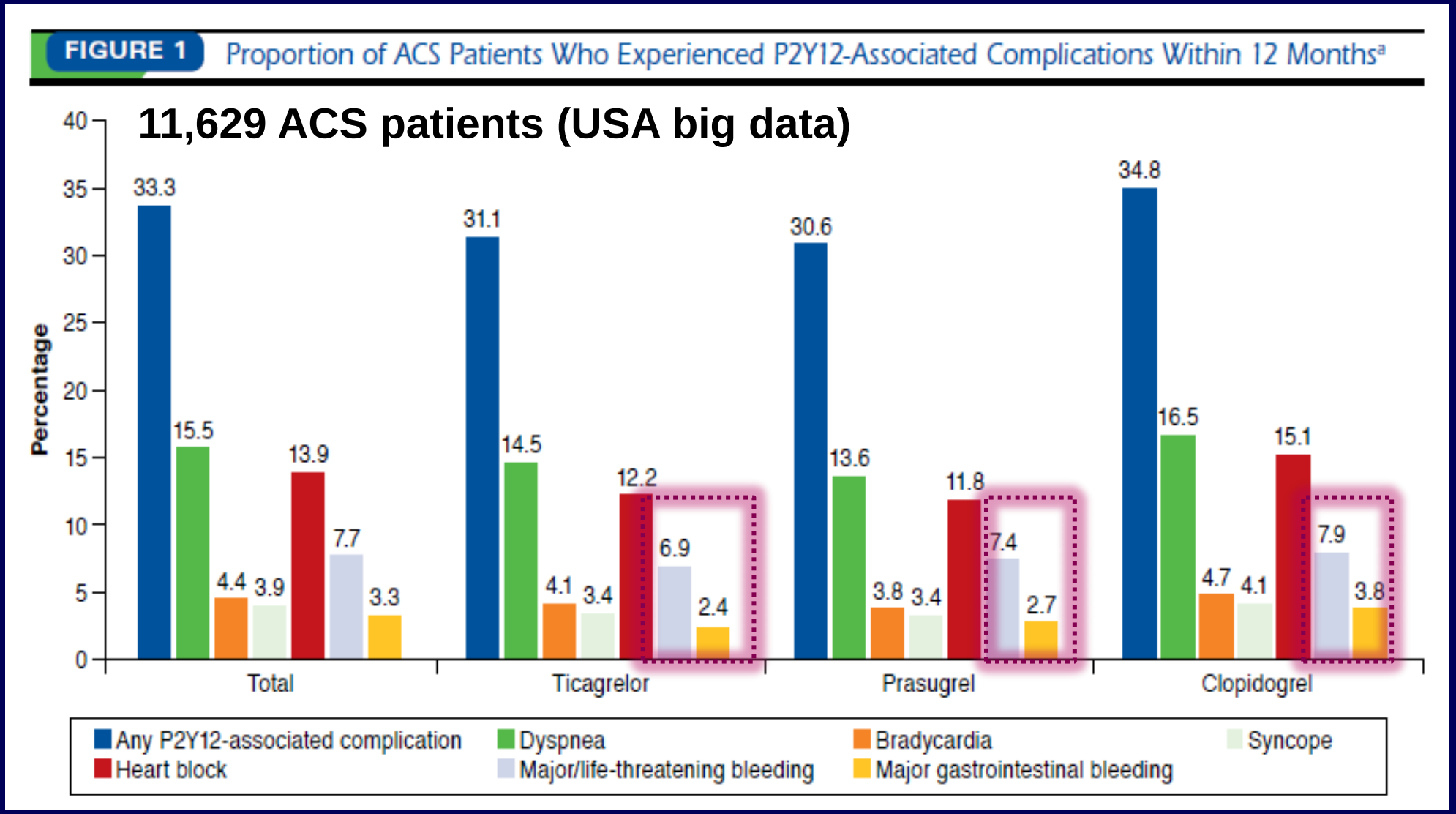
TRÎTON TIMI·38

Timing of Benefit (Landmark Analysis)



From the landmark analyses in both PLATO and TRITON TIMI 38 studies, de-escalation of P2Y12 inhibitor may sacrifice continued ischemic benefit of potent P2Y12 inhibitor after de-escalation.

Similar P2Y12-Associated Complications in Patients with ACS in Real World Practice

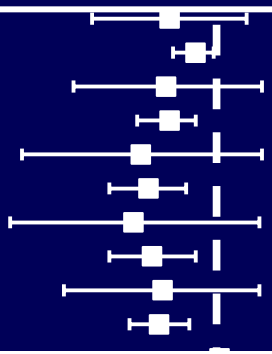


J Manag Care Spec Pharm. 2017

Net clinical benefit of ticagrelor in Asian ACS patients: Efficacy and safety analyses (PLATO)

No significant interaction between Asian/non-Asian ethnicity and clinical outcomes was observed in PLATO

End point		HR (95% CI)	p for interaction
Net clinical benefit	Asian	0.85 (0.65–1.11)	0.521
	Non-Asian	0.93 (0.86–0.99)	
CV death, MI or stroke	Asian	0.84 (0.61–1.17)	0.974
	Non-Asian	0.85 (0.77–0.93)	
All-cause death	Asian	0.77 (0.51–1.17)	0.931
	Non-Asian	0.79 (0.69–0.90)	
CV death	Asian	0.75 (0.49–1.16)	0.792
	Non-Asian	0.80 (0.69–0.93)	
CV death or MI	Asian	0.83 (0.59–1.16)	0.972
	Non-Asian	1.09 (0.95–1.26)	



0.3 Favours ticagrelor 1 Favours clopidogrel 3

PLATO Safety Results (Major bleeding)

Ethnicity	HR (95% CI)	*P* value
Asia (n=1041)	1.07 (0.73, 1.59)	0.722
China (n=410)	1.72 (0.72, 4.09)	0.223
South Korea (n=119)	0.75 (0.23, 2.45)	0.629
Taiwan (n=90)	0.51 (0.13, 2.05)	0.345
Other Asian countries[a] (n=422)	1.09 (0.65, 1.82)	0.742

[a] Other Asian Countries: Hong Kong, Indonesia, Malaysia, Philippines, Singapore, and Thailand.

CABG, coronary artery bypass graft; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.

1. Kang HJ et al. Am Heart J. 2015 Jun;169(6):899-905.e1. doi: 10.1016/j.ahj.2015.03.015. Epub 2015 Mar 31

Ticagrelor Regulatory Post-marketing surveillance* (rPMS) in Korea

- **Objective**

  To evaluate safety and efficacy of ticagrelor in real clinical practice

- **Study design**

  Multicenter, open-label, prospective, observational study

- **Re-examination period***

  22 July 2011 – 21 July 2017

- **Participating investigators**

  71 investigators from 49 centers across Korea

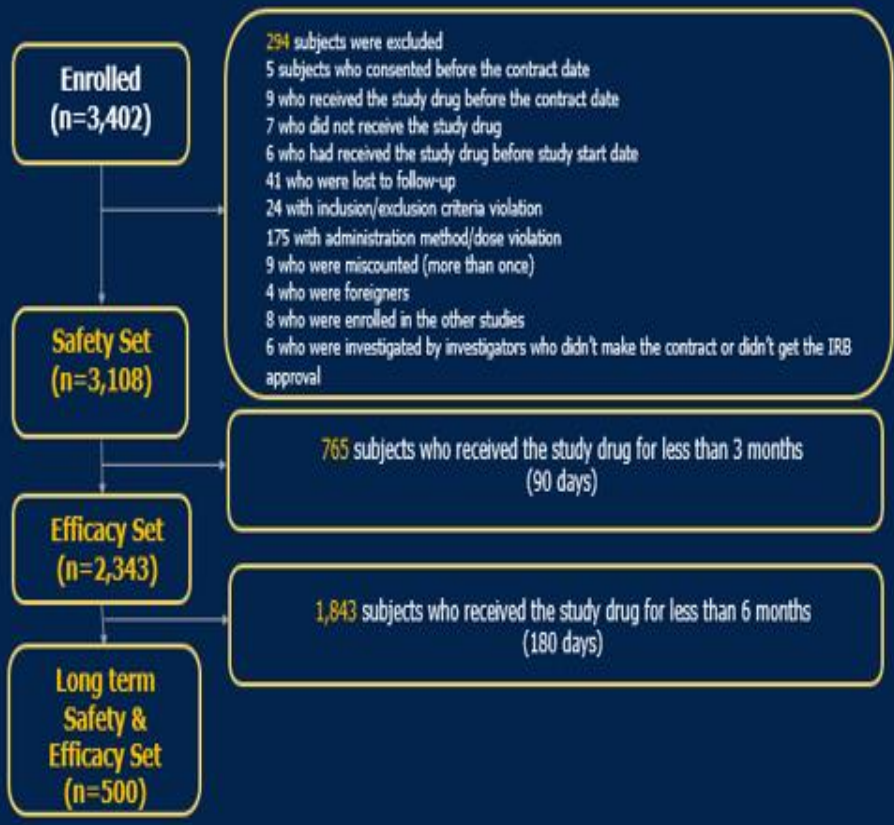
- **Safety end points**

  Incidence of AE/ADR/SAE/SADR

  Incidence of hemorrhagic events*

- **Efficacy end point**

  Composite end point - CV death, MI, Stroke



* The outcomes were collected during the study period but all data about hemorrhage was collected from the administration start date to 7 days after the administration end date of ticagrelor or 7 days after final observation date.

AE, Adverse Event; ADR, Adverse Drug Reaction; SAE, Serious Adverse Event; SADR, Serious Adverse Drug Reaction;

Results: Haemorrhagic events & Efficacy endpoints

Variables (N=3,108)	No. of AEs (%)
Hemorrhagic events	409 (13.2)
Major fatal/life-threatening hemorrhage	0 (0.0)
Other major hemorrhage Bruise 7 Melena 5 GI hemorrhage 4 Epistaxis 3 Post procedural hematoma 2 Cerebral hemorrhage 1 Ecchymosis 1 Hematuria 1	24 (0.8)
Minor hemorrhage	99 (3.2)
Minimal bleeding	286 (9.2)

ADR: Adverse Drug Reaction

- **Major Fatal/life-threatening hemorrhage**

Fatal, or intracranial, or intrapericardial bleed with cardiac tamponade, or hypovolaemic shock or severe hypotension due to bleeding and requiring pressors or surgery, or clinically overt or apparent bleeding associated with a decrease in haemoglobin of more than 50 g/L, or transfusion of 4 or more units (whole blood or PRBCs) for bleeding.

- **Other major hemorrhage**

Significantly disabling(e.g., intraocular with permanent vision loss), or clinically overt or apparent bleeding associated with a decrease in haemoglobin of 30 to 50g/L, or transfusion of 2-3 units (whole blood or PRBCs) for bleeding.

- **Minor hemorrhage**

Requires medical intervention to stop or treat bleeding (e.g., epistaxis requiring visit to medical facility for packing).

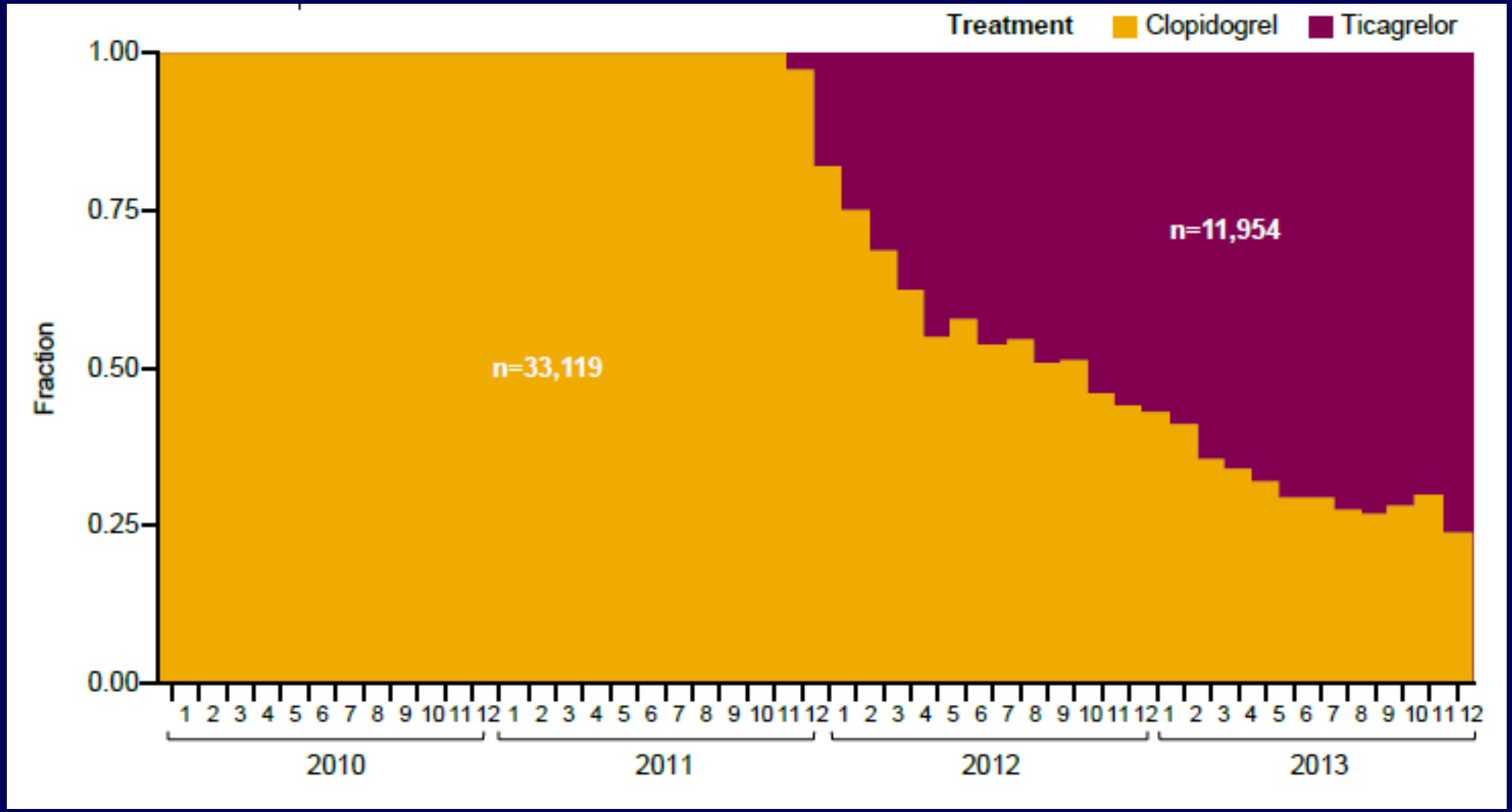
- **Minimal bleeds**

Includes all other bleeds

Variables (N=2,343)	No. of patients (%)
Composite end point	11 (0.5)
Cardiovascular death	0 (0.0)
Myocardial infarction	5 (0.2)
Stroke	6 (0.3)

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

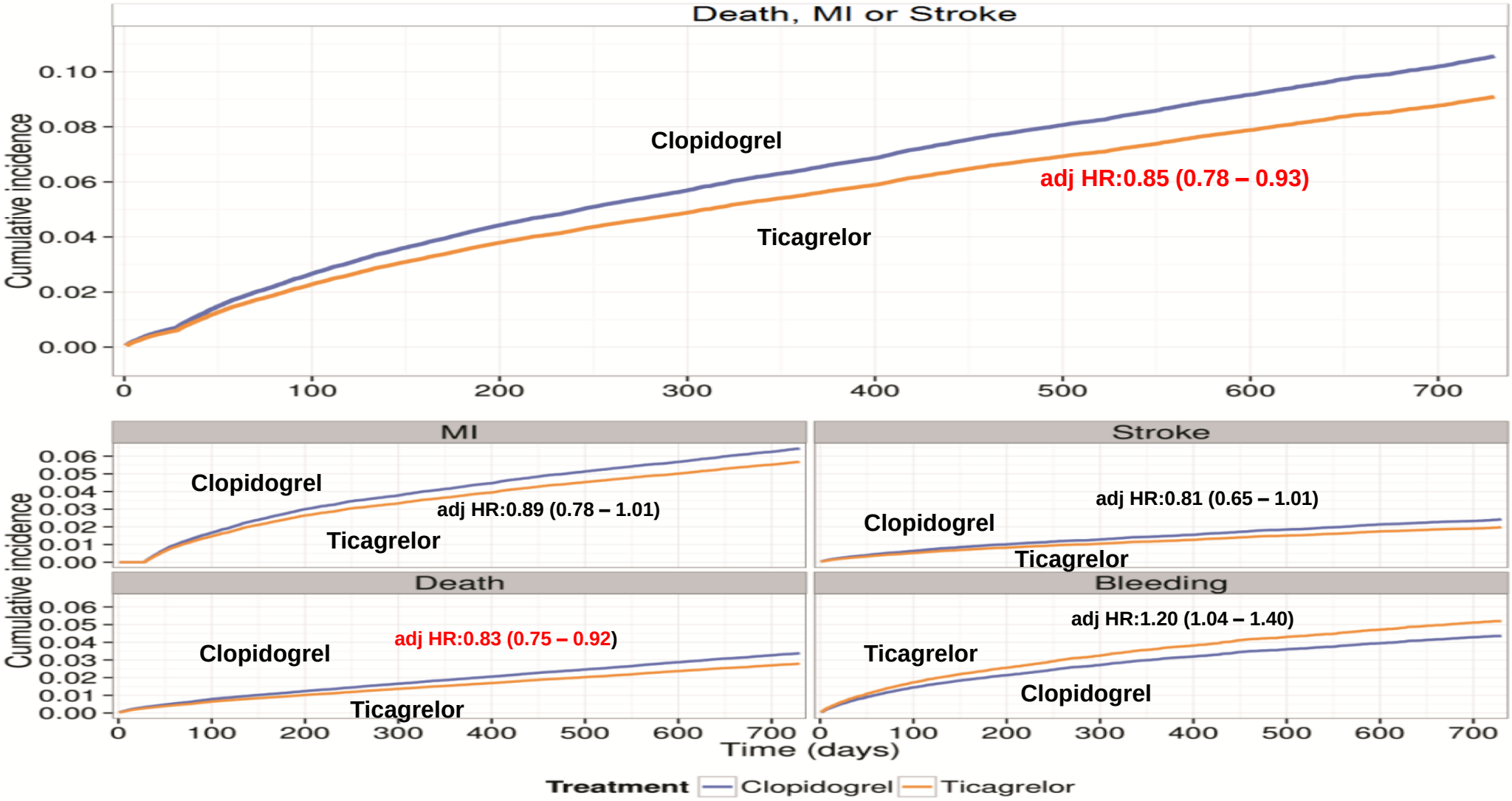
Introduction of ticagrelor in Sweden (SWEDEHEART Registry)



Sahlen A et al. Eur Heart J 2016;37:3335-3342.

Outcomes in Patients Treated With Ticagrelor or Clopidogrel After ACS
Real world evidence from SWEDEHEART Registry

45,073 ACS patients between Jan 2000 and Dec 2013



Sahlen A et al. Eur Heart J 2016;37:3335-3342.

Circulation ORIGINAL RESEARCH ARTICLE

Prasugrel Versus Ticagrelor in Patients With Acute Myocardial Infarction Treated With Primary Percutaneous Coronary Intervention

Multicenter Randomized PRAGUE-18 Study

Keele Cardiovascular Research Group

14 Centre study with 1230 AMI patients recruited, randomized to either Prasugrel or Ticagrelor

Study prematurely terminated for futility

Although prematurely terminated and underpowered, PRAGUE-18 RCT demonstrated similar ischemic/bleeding outcomes between prasugrel and ticagrelor.

nonfatal myocardial infarction, or stroke	17 (2.7)	15 (2.5)	1.06 (0.53–2.15)	0.864
Death resulting from cardiovascular causes	8 (1.3)	8 (1.3)	0.94 (0.35–2.52)	0.901
Nonfatal myocardial infarction	8 (1.3)	7 (1.2)	1.07 (0.39–2.97)	0.895
Stroke	2 (0.3)	1 (0.2)	1.88 (0.17–20.74)	0.608
Definite stent thrombosis	3 (0.5)	5 (0.9)	0.56 (0.13–2.35)	0.428
Death resulting from any cause	14 (2.2)	16 (2.7)	0.82 (0.40–1.69)	0.589

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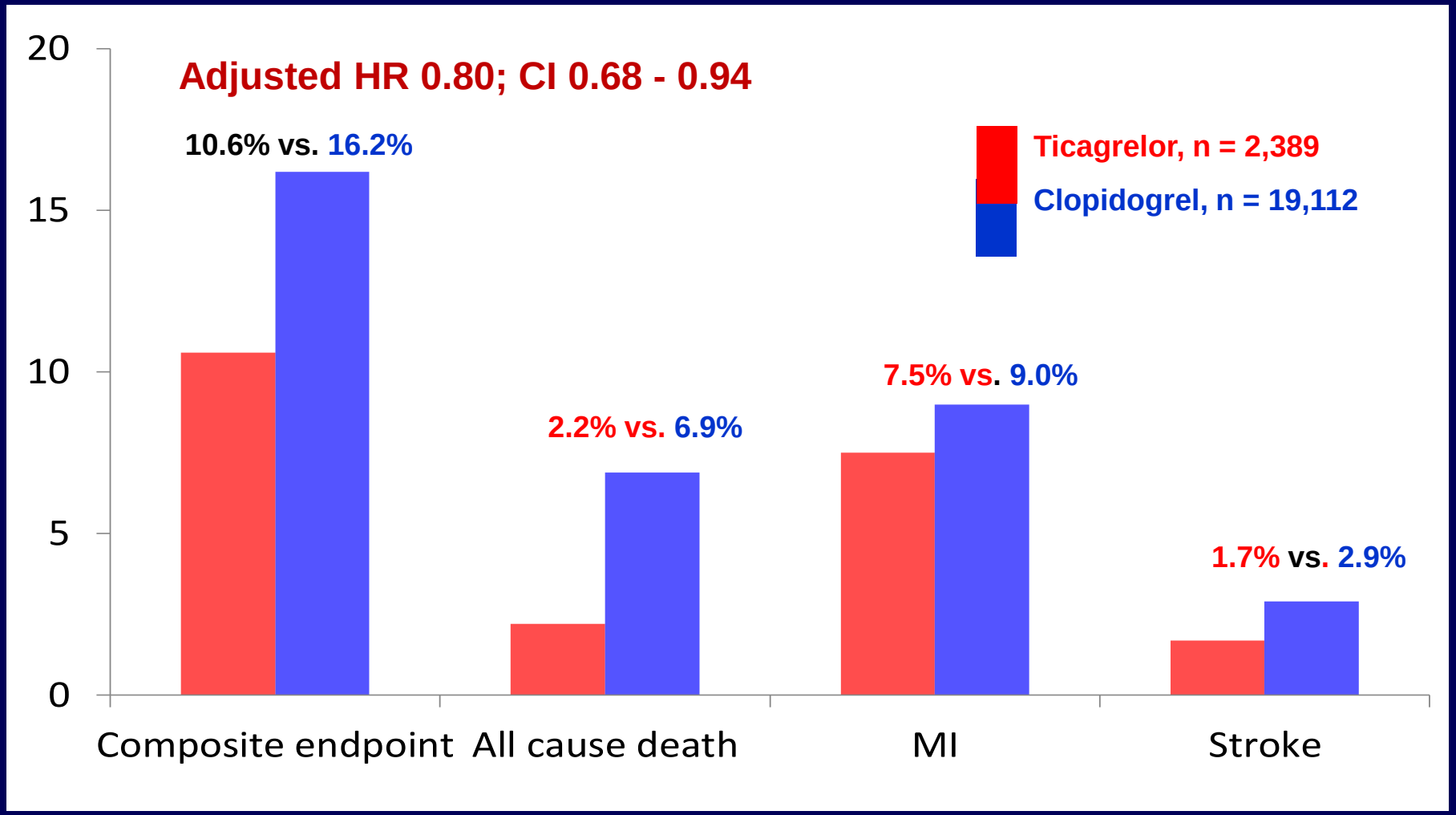
Taiwan National Health Insurance Database

Composite of all cause death, MI or stroke

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

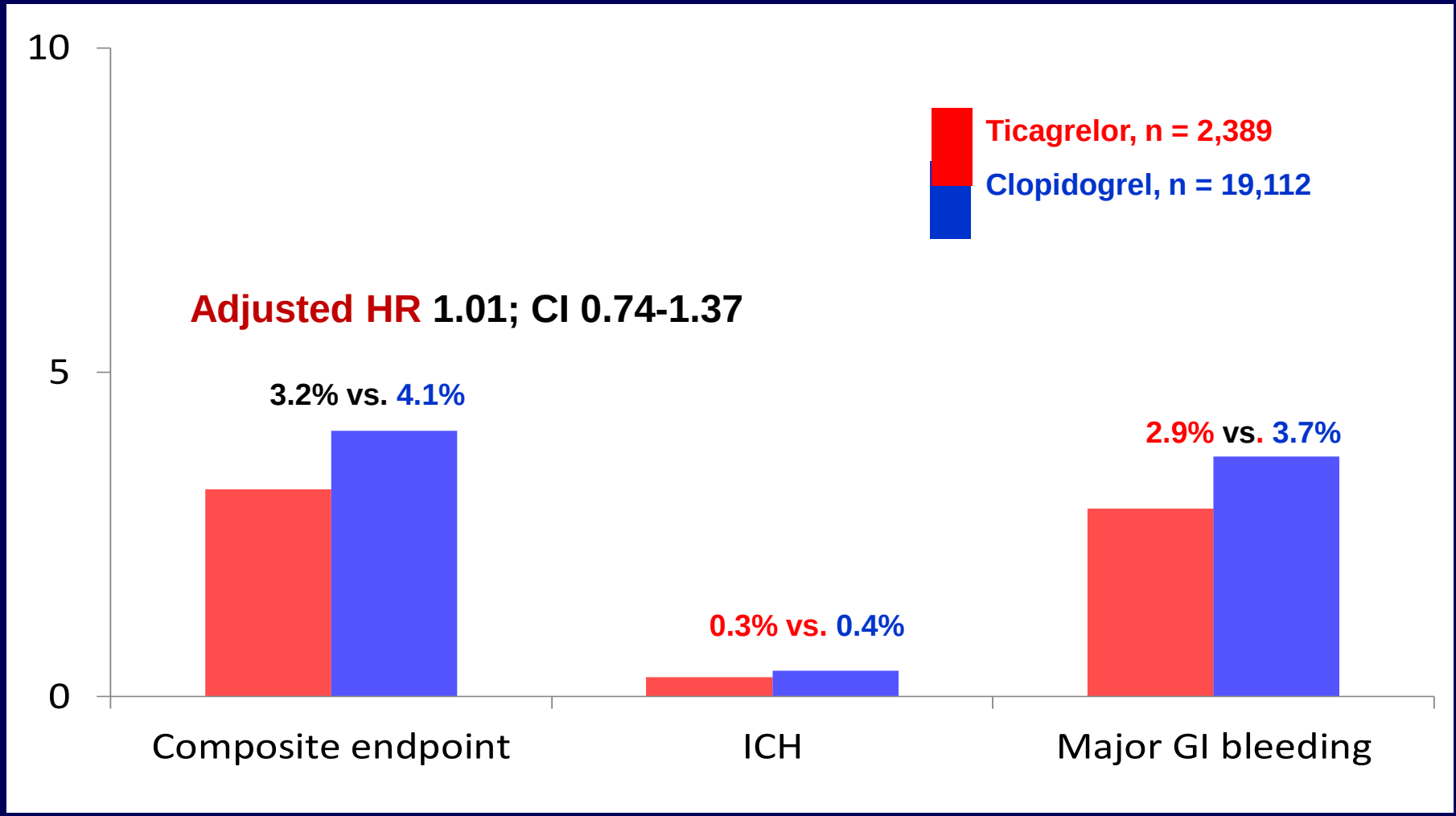


Lee CH et al. Circ J 2018;82(3):747-756.

Taiwan National Health Insurance Database

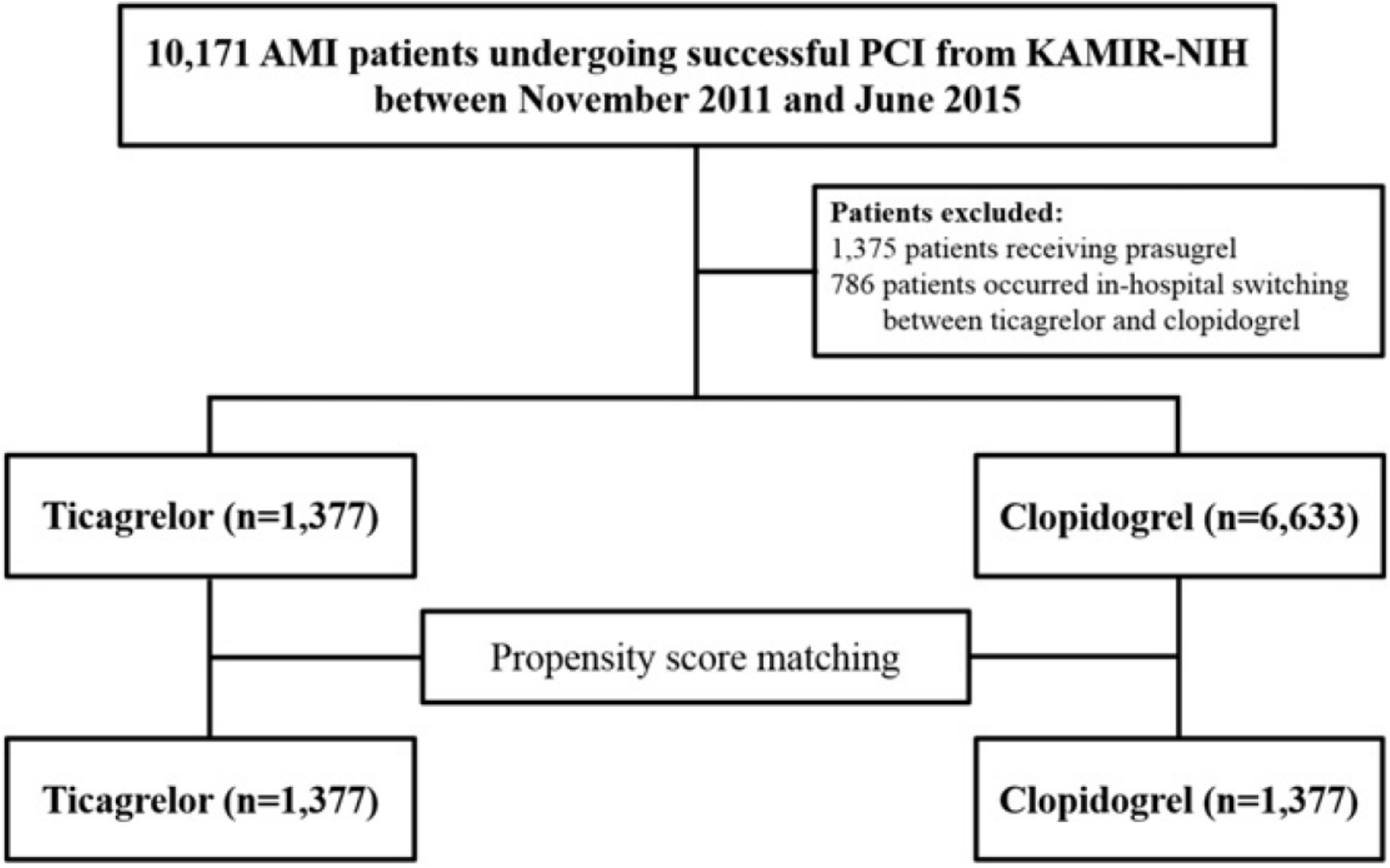
Composite of ICH and major GI bleeding

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



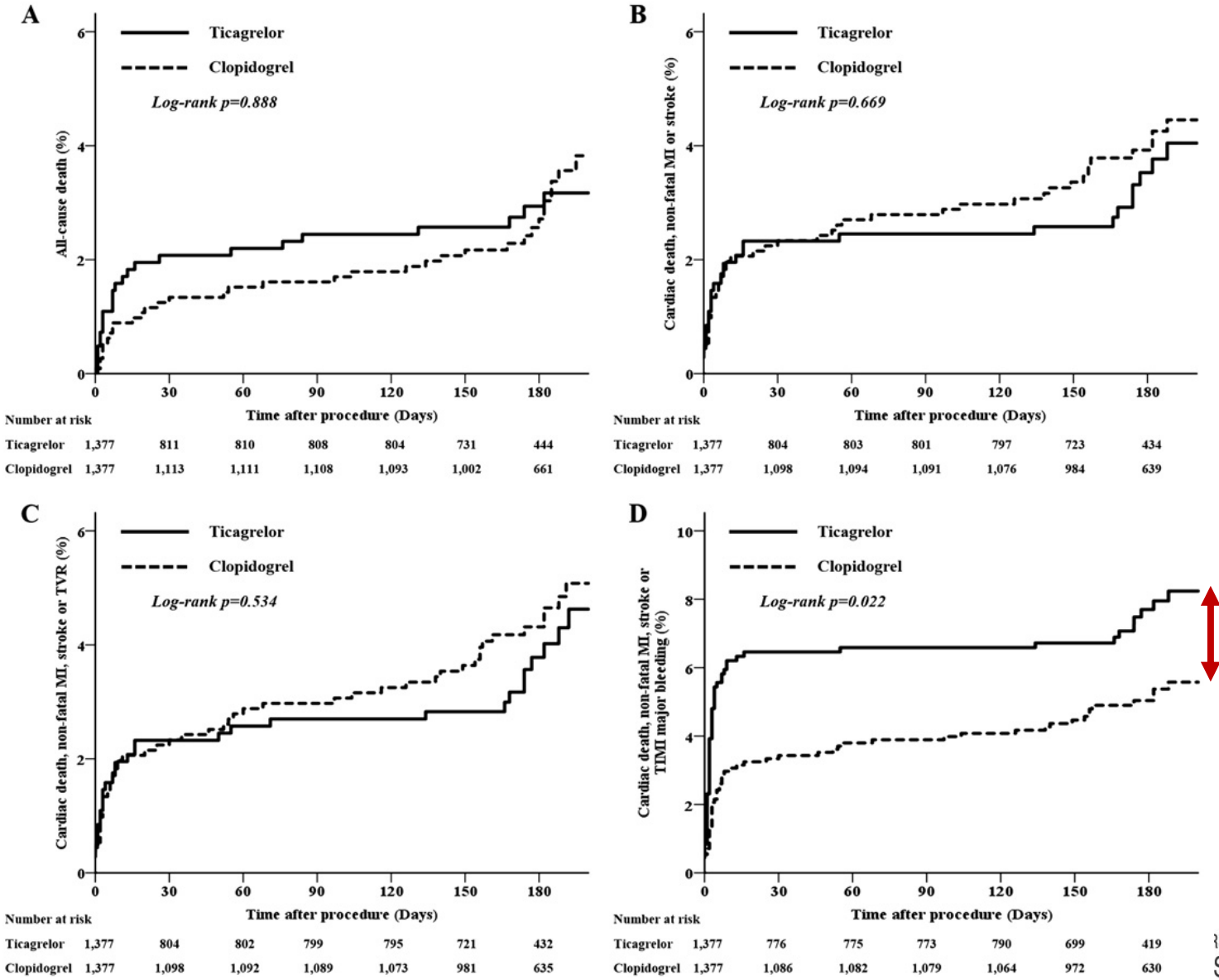
Lee CH et al. Circ J 2018;82(3):747-756.

Comparison between the effects of ticagrelor and clopidogrel in Korean patients with AMI

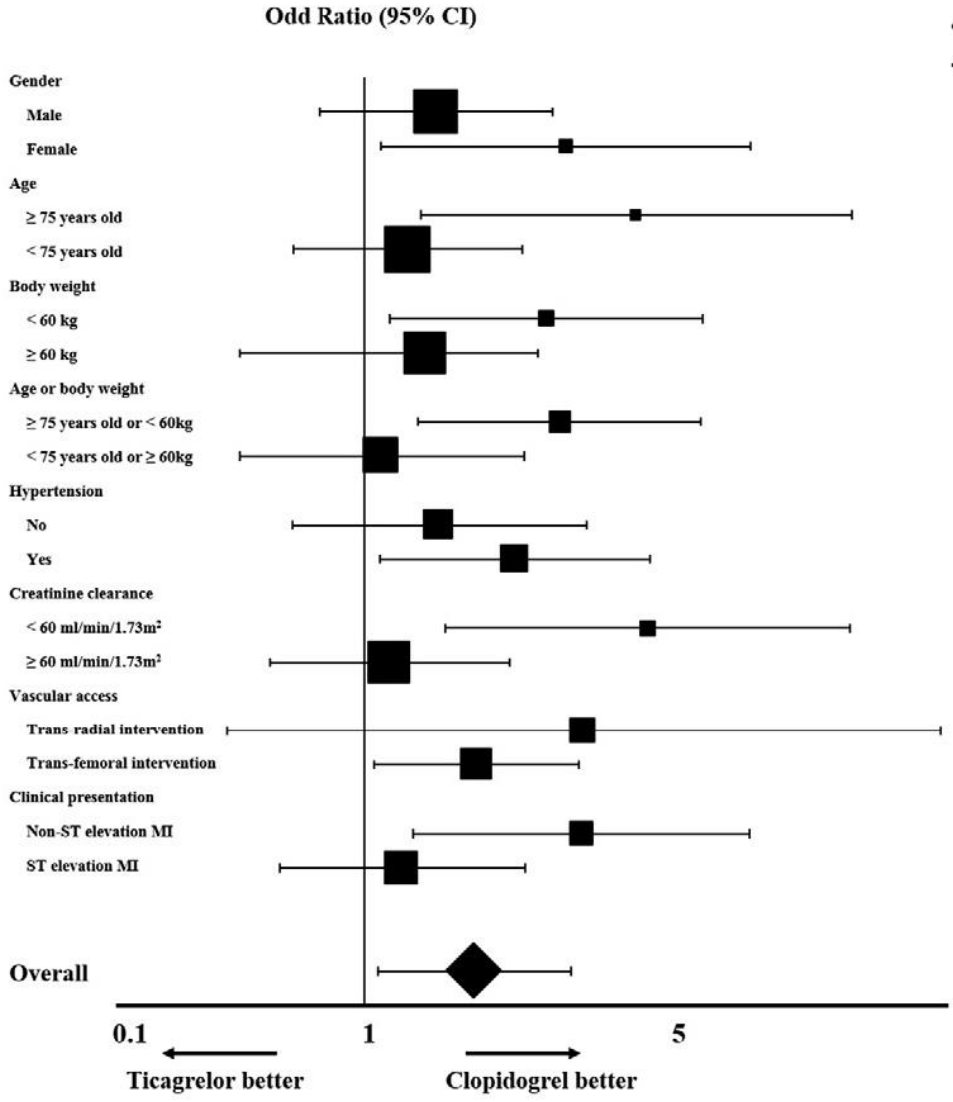


Park KH et al. IJC 2016

Equipotent ischemic benefit with increased bleeding with ticagrelor compared with clopidogrel



Consistently less bleeding with clopidogrel than ticagrelor across all subgroups



	In-hospital TIMI major bleeding events/total (%)		Odd Ratio (95% CI)	*P* value for interaction
	Ticagrelor	Clopidogrel		
Gender				0.169
Male	20/1,070 (1.9)	13/1,086 (1.2)	1.552 (0.754 – 3.195)	
Female	16/307 (5.2)	4/291 (1.4)	3.456 (1.105 – 10.808)	
Age				0.072
≥ 75 years old	15/259 (5.8)	3/272 (1.1)	5.352 (1.412 – 20.288)	
< 75 years old	21/1,118 (1.9)	14/1,105 (1.3)	1.304 (0.641 – 2.655)	
Body weight				0.292
< 60 kg	18/381 (4.7)	6/385 (1.6)	3.067 (1.167 – 8.059)	
≥ 60 kg	18/996 (1.8)	11/992 (1.1)	1.453 (0.458 – 2.919)	
Age or body weight				0.083
≥ 75 years old or < 60kg	24/498 (4.8)	7/491 (1.4)	3.330 (1.393 – 7.961)	
< 75 years old or ≥ 60kg	12/879 (1.4)	10/886 (1.1)	1.109 (0.459 – 2.682)	
Hypertension				0.302
No	14/742 (1.9)	9/731 (1.2)	1.580 (0.636 – 3.930)	
Yes	22/635 (3.5)	8/646 (1.2)	2.528 (1.099 – 5.817)	
Creatinine clearance				0.018
< 60 ml/min/1.73m^2	19/368 (5.2)	3/370 (0.8)	5.742 (1.648 – 20.005)	
≥ 60 ml/min/1.73m^2	17/1,009 (1.7)	14/1,004 (1.4)	1.164 (0.554 – 2.446)	
Vascular access				0.690
Trans-radial intervention	3/638 (0.5)	2/645 (0.3)	3.857 (0.424 – 35.089)	
Trans-femoral intervention	33/739 (4.5)	15/732 (2.0)	1.996 (1.061 – 3.754)	
Clinical presentation				0.264
Non-ST elevation MI	16/581 (2.8)	5/596 (0.8)	3.804 (1.347 – 10.747)	
ST elevation MI	20/796 (2.5)	12/781 (1.5)	1.260 (0.588 – 2.697)	
Overall	36/1,377 (2.6)	17/1,377 (1.2)	1.971 (1.086 – 3.577)	

Park KH et al. IJC 2016

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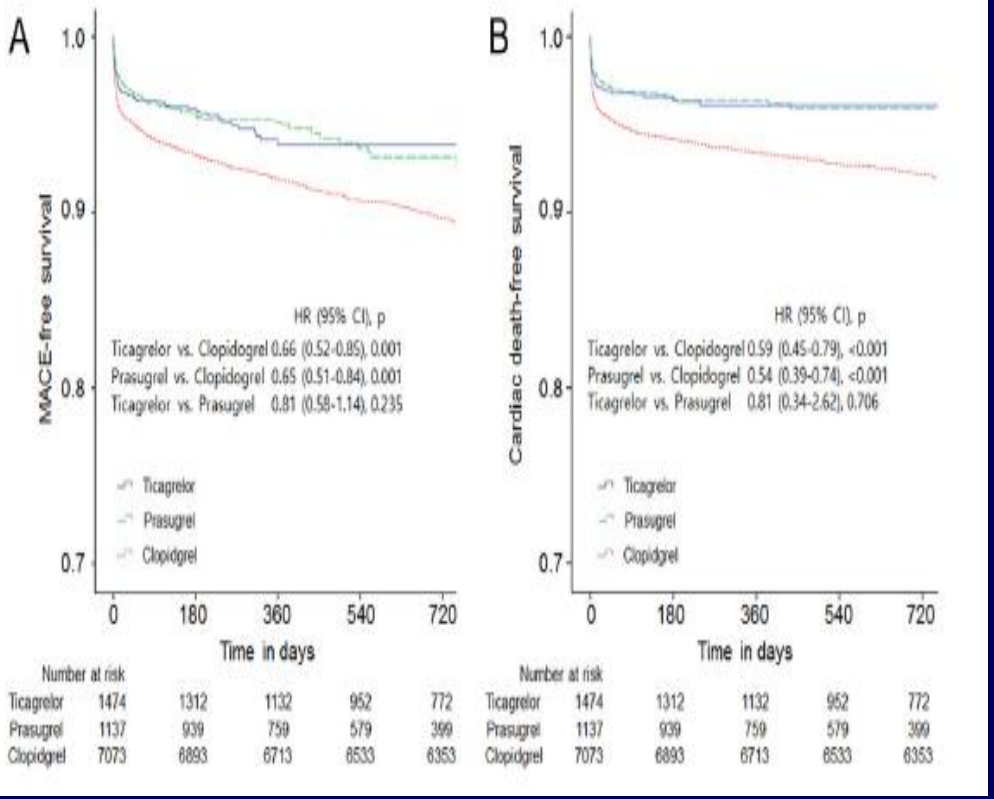
Comparison of prescription rates and clinical outcomes in acute coronary syndrome patients who underwent percutaneous coronary intervention using different $P2Y_{12}$ inhibitors in a large observational study☆

Jeong Cheon Choe [a], Kwang Soo Cha [a,*], Jinhee Ahn [a], Jin Sup Park [a], Hye Won Lee [a], Jun-Hyok Oh [a], Jung Hyun Choi [a], Han Cheol Lee [a], Taek Jong Hong [a], Myung Ho Jeong [b], the Korea Acute Myocardial Infarction Registry–National Institutes of Health Investigators

MACEs and CV mortality



Safety and Efficacy Endpoints in Entire Cohort

	Ticagrelor group ($n = 1474$)	Prasugrel group ($n = 1137$)	Clopidogrel group ($n = 7073$)	P
In-hospital bleeding	108 (7.3%)†	80 (7.9%)†	377 (5.3%)	0.027
Major bleeding	48 (3.3%)	35 (3.1%)	197 (2.8%)	0.487
Minor bleeding	60 (4.1%)†	45 (4.0%)†	180 (2.5%)	0.021
MACEs*	82 (5.6%)†	69 (6.1%)†	653 (9.2%)	0.014
All-cause death	48 (3.3%)†	34 (3.0%)†	435 (6.2%)	0.017
Cardiac death	21 (1.4%)†	18 (1.6%)†	292 (4.1%)	0.022
Non-cardiac death	27 (1.8%)	16 (1.4%)†	143 (2.0%)	0.087
Nonfatal MI	36 (2.4%)	30 (2.6%)	209 (3.0%)	0.149
Stroke	25 (1.7%)†	21 (1.8%)	152 (2.1%)	0.216
Any revascularization	34 (2.3%)†	30 (2.6%)†	232 (3.3%)	0.047
Repeat percutaneous coronary intervention	28 (1.9%)†	25 (2.2%)†	199 (2.8%)	0.038
Coronary artery bypass graft	6 (0.4%)	5 (0.4%)	33 (0.5%)	0.249

Values are n (%).
MACEs, major adverse cardiac events; MI, myocardial infarction.
* MACEs included cardiac death, nonfatal MI, or stroke.
† significant p-value compared with Clopidogrel group.

Efficacy Endpoints According to Different Adjustment Methods.

Variable	Ticagrelor versus clopidogrel (referent to clopidogrel)	Prasugrel versus clopidogrel (referent to clopidogrel)	Ticagrelor versus prasugrel (referent to prasugrel)
	Adjusted HR (95% CI), p	Adjusted HR (95% CI), p	Adjusted HR (95% CI), p
Standard cox regression			
MACEs*	0.66 (0.52–0.85), 0.001	0.65 (0.51–0.84), 0.001	0.81 (0.58–1.14), 0.235
All-cause death	0.71 (0.43–0.89), 0.033	0.67 (0.49–0.83), 0.026	1.11 (0.38–4.19), 0.748
Cardiac death	0.59 (0.45–0.79), <0.001	0.54 (0.39–0.74), <0.001	0.81 (0.34–2.62), 0.706
Non-cardiac death	0.91 (0.61–1.38), 0.664	0.50 (0.29–0.85), 0.010	1.51 (0.35–5.27), 0.348
Nonfatal MI	0.81 (0.54–1.47), 0.656	0.89 (0.65–1.54), 0.979	0.71 (0.22–3.12), 0.084
Stroke	0.76 (0.68–2.37), 0.456	0.88 (0.46–1.56), 0.141	0.82 (0.35–4.29), 0.328
Any revascularization	0.81 (0.52–0.97), 0.023	0.85 (0.61–0.98), 0.035	0.79 (0.25–5.31), 0.569
Re-PCI	0.79 (0.53–0.89), 0.034	0.88 (0.52–0.95), 0.041	0.84 (0.41–5.58), 0.156
CABG	0.40 (0.10–1.68), 0.213	0.59 (0.18–1.93), 0.385	0.97 (0.12–1.29), 0.659
Propensity score-matched analyses			
MACEs*	0.68 (0.47–0.97), 0.025	0.55 (0.33–0.90), 0.017	0.39 (0.12–1.29), 0.123
All-cause death	0.61 (0.34–0.93), 0.032	0.53 (0.38–0.96), 0.041	1.02 (0.59–6.29), 0.759
Cardiac death	0.56 (0.35–0.91), 0.012	0.49 (0.23–0.83), 0.007	0.62 (0.05–1.30) 0.156
Non-cardiac death	0.89 (0.59–2.24), 0.247	0.93 (0.74–4.19), 0.422	1.11 (0.72–5.88), 0.649
Nonfatal MI	0.70 (0.34–1.43), 0.416	0.68 (0.32–1.46), 0.249	0.87 (0.05–8.31), 0.843
Stroke	0.61 (0.47–2.61), 0.219	0.38 (0.12–1.19), 0.157	0.78 (0.22–4.84), 0.469
Any revascularization	0.71 (0.42–1.61), 0.194	0.82 (0.48–2.03), 0.689	0.81 (0.35–6.92), 0.786
Re-PCI	0.82 (0.67–1.72), 0.258	0.98 (0.59–1.64), 0.428	0.76 (0.24–3.27), 0.512
CABG	0.19 (0.02–1.57), 0.648	0.50 (0.09–2.75), 0.785	0.92 (0.22–5.12), 0.611
Propensity score-adjusted analyses			
MACEs*	0.71 (0.48–0.99), 0.021	0.67 (0.38–0.95), 0.028	0.78 (0.26–1.48), 0.459
All-cause death	0.64 (0.41–0.95), 0.038	0.58 (0.41–0.99), 0.045	1.14 (0.68–5.75), 0.529
Cardiac death	0.61 (0.45–0.96), 0.024	0.59 (0.37–0.85), 0.012	0.81 (0.17–1.74) 0.428
Non-cardiac death	0.87 (0.61–2.14), 0.437	0.89 (0.71–3.87), 0.361	1.31 (0.63–4.98), 0.574
Nonfatal MI	0.72 (0.37–1.52), 0.326	0.65 (0.31–1.71), 0.443	0.78 (0.14–7.15), 0.637
Stroke	0.65 (0.45–2.24), 0.149	0.42 (0.21–1.56), 0.278	0.84 (0.42–3.97), 0.571
Any revascularization	0.75 (0.51–1.87), 0.254	0.79 (0.45–2.47), 0.592	0.76 (0.32–5.85), 0.613
Re-PCI	0.81 (0.72–1.89), 0.358	0.85 (0.54–1.72), 0.327	0.72 (0.32–3.48), 0.496
CABG	0.34 (0.14–1.78), 0.437	0.45 (0.13–2.86), 0.542	0.84 (0.28–4.72), 0.513

CI, confidence interval; HR, hazard ratio; MACEs, major adverse cardiac events; MI, myocardial infarction; Re-PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

* MACE included cardiac death, Nonfatal MI, or stroke.

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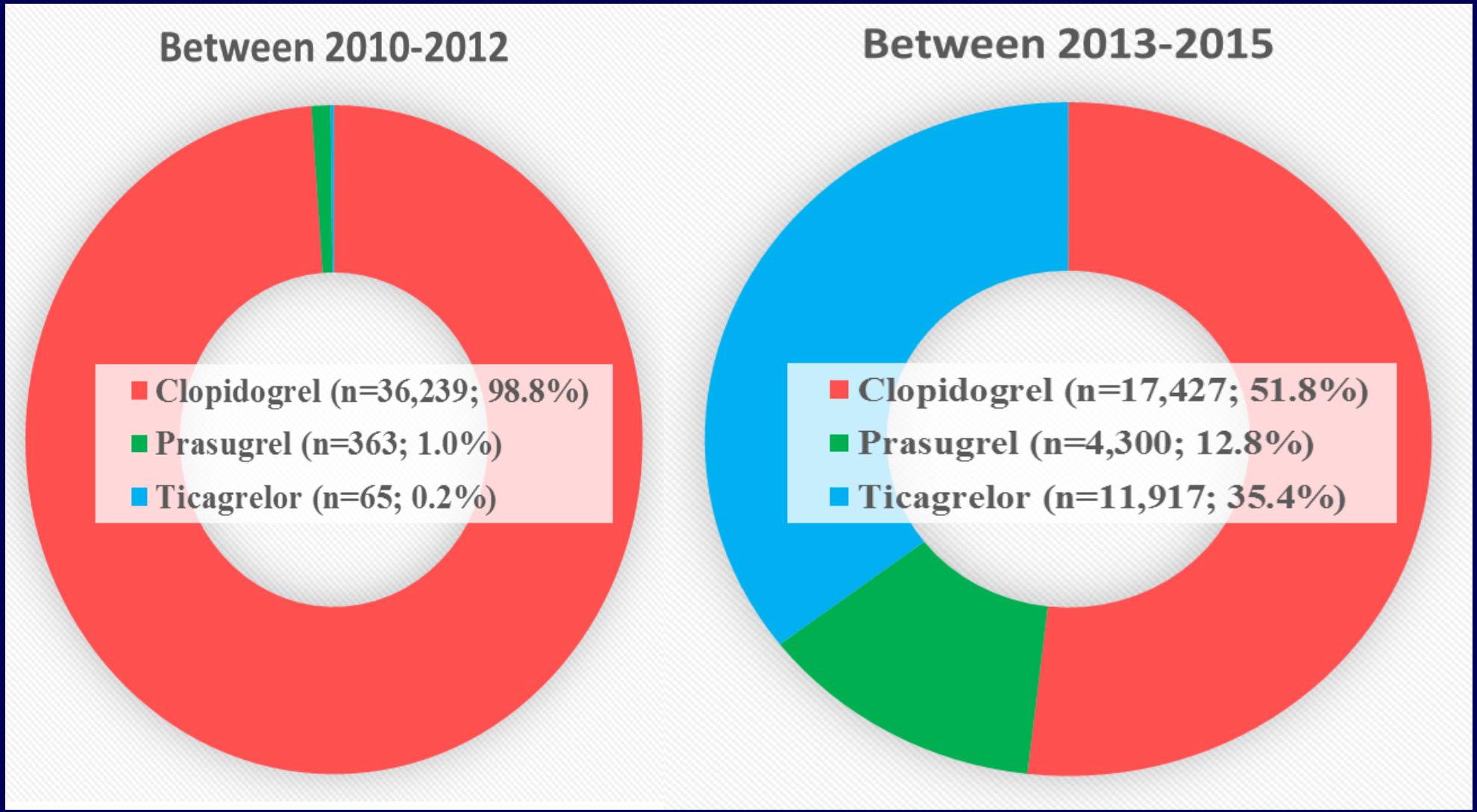
Antiplatelet therapy for AMI in Korea (HIRA database)



CK Kim et al. Korean Circ J. 2017 Nov;47(6):888-897

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

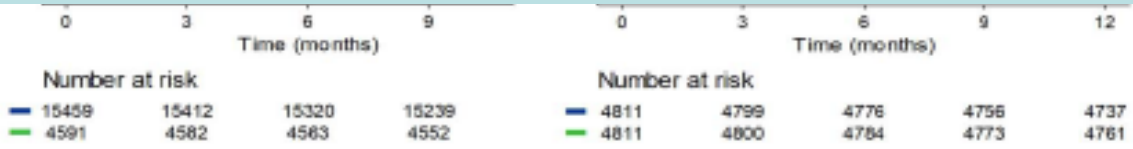
Different patient groups, statistical methods as well as limitation of registry data may have affected the different study results

→ The solution…

1) We need RCT (idealistic)

or

1) Prescribe P2Y12 inhibitor according to individual characteristics (believe in yourself !)



DH Shin Presented at TCTAP 2018

Summary

- **Dual antiplatelet therapy with potent P2Y12 inhibitors in conjunction with aspirin has become the standard of care in patients with acute coronary syndrome.**
- **However, due to its increased bleeding, switching back to clopidogrel (a.k.a “de-escalation”) has gained popularity in clinical practice as evidenced from 2 notable RCTs, which unfortunately has several limitations.**
- **However, de-escalation might not be suitable for patient subsets such as prior stent thrombosis, multiple implanted stents or complex coronary lesion etc.**
- **In the real-world data, potent P2Y12 inhibitors showed not much adverse effects than expected, but also demonstrated promising results in terms of reducing MACE.**
- **Therefore, the decision-making to use particular P2Y12 inhibitor at the beginning of ACS according to individual ischemic/bleeding risk is of utmost importance. If chosen, it might be better to keep going with same medication up to 1 year unless there is a demand for de-escalation.**


Thank you for your attention !!!
Sapporo, Japan (Oct 6, 2017)