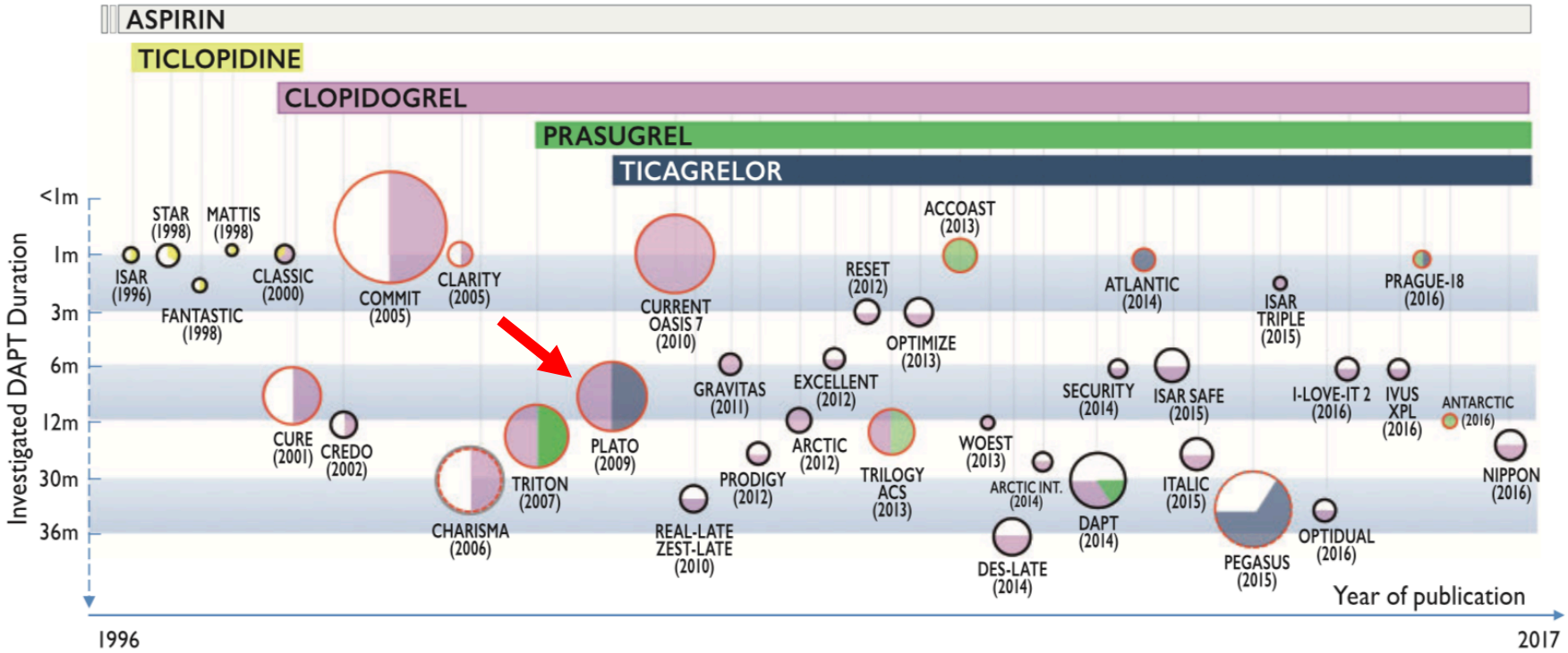
Global collaborative research through OHDSI network:

Net Clinical Benefit of Ticagrelor compared to Clopidogrel in patients with Acute Coronary Syndrome following Percutaneous Coronary Intervention

Seng Chan You[1]; Yeunsook Rho[2]; Jiwoo Kim[2]; Anastasios Siapos[3]; Ajit Londhe[4]; Jaehyeong Cho[5]; Jimyung Park[5]; Martijn Schuemie[4]; Patrick B. Ryan[4]; Christian G. Reich[3]; Rae Woong Park, MD, PhD[1,5]; Harlan M. Krumholz, MD[6]

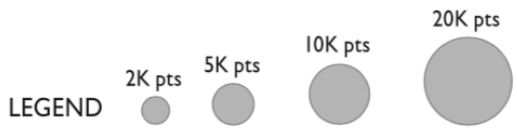
[1]Department of Biomedical Informatics, Ajou University School of Medicine, Suwon, Korea; [2]Health Insurance Review and Assessment Service, Wonju, Korea; [3]IQVIA, Durham, USA; [4]Janssen Research and Development, Titusville, USA; [5]Department of Biomedical Sciences, Ajou University Graduate School of Medicine, Suwon, Korea; [6]Yale University School of Medicine, USA

History of **D**ual **A**nti**P**latelet **T**herapy (DAPT) in patients with coronary artery disease



Size of the circles denotes sample size

Perimeter of the circles denotes type of investigated population



— Mixed clinical presentation at the time of stent implantation
— Acute coronary syndrome at presentation
-- DAPT initiated in patients with prior myocardial infarction
— DAPT for primary prevention

2017 ESC DAPT guideline

Current clinical guideline for DAPT in ACS solely based on PLATO trial

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

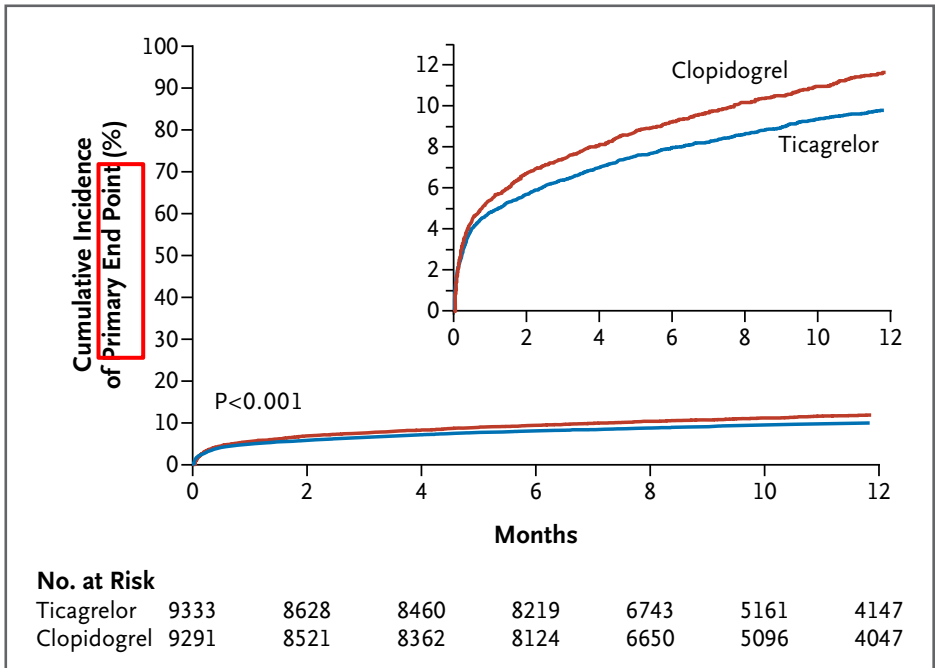
2017 ESC/EACTS DAPT guideline

Recommendations for Specific $P2Y_{12}$ Inhibitors

COR	LOE	RECOMMENDATIONS
IIa	B-R	In patients with ACS (NSTE-ACS or STEMI) treated with DAPT after coronary stent implantation and in patients with NSTE-ACS treated with medical therapy alone (without revascularization), it is reasonable to use ticagrelor in preference to clopidogrel for maintenance $P2Y_{12}$ inhibitor therapy (53,71,72).

2016 ACC/AHA DAPT guideline

PLATelet inhibition and patient Outcomes (PLATO) Trial



End Point	Ticagrelor Group	Clopidogrel Group	Hazard or Odds Ratio for Ticagrelor Group (95% CI)†	P Value
Primary safety end points — no./total no. (%)				
Major bleeding, study criteria	961/9235 (11.6)	929/9186 (11.2)	1.04 (0.95–1.13)	0.43
Major bleeding, TIMI criteria‡	657/9235 (7.9)	638/9186 (7.7)	1.03 (0.93–1.15)	0.57
Bleeding requiring red-cell transfusion	818/9235 (8.9)	809/9186 (8.9)	1.00 (0.91–1.11)	0.96
Life-threatening or fatal bleeding, study criteria	491/9235 (5.8)	480/9186 (5.8)	1.03 (0.90–1.16)	0.70
Fatal bleeding	20/9235 (0.3)	23/9186 (0.3)	0.87 (0.48–1.59)	0.66
Nonintracranial fatal bleeding	9/9235 (0.1)	21/9186 (0.3)		0.03
Intracranial bleeding	26/9235 (0.3)	14/9186 (0.2)	1.87 (0.98–3.58)	0.06
Fatal	11/9235 (0.1)	1/9186 (0.01)		0.02
Nonfatal	15/9235 (0.2)	13/9186 (0.2)		0.69
Secondary safety end points — no./total no. (%)				
Non–CABG-related major bleeding, study criteria	362/9235 (4.5)	306/9186 (3.8)	1.19 (1.02–1.38)	0.03
Non–CABG-related major bleeding, TIMI criteria	221/9235 (2.8)	177/9186 (2.2)	1.25 (1.03, 1.53)	0.03
CABG-related major bleeding, study criteria	619/9235 (7.4)	654/9186 (7.9)	0.95 (0.85–1.06)	0.32
CABG-related major bleeding, TIMI criteria	446/9235 (5.3)	476/9186 (5.8)	0.94 (0.82–1.07)	0.32
Major or minor bleeding, study criteria	1339/9235 (16.1)	1215/9186 (14.6)	1.11 (1.03–1.20)	0.008
Major or minor bleeding, TIMI criteria‡	946/9235 (11.4)	906/9186 (10.9)	1.05 (0.96–1.15)	0.33
Dyspnea — no./total no. (%)				
Any	1270/9235 (13.8)	721/9186 (7.8)	1.84 (1.68–2.02)	<0.001
Requiring discontinuation of study treatment	79/9235 (0.9)	13/9186 (0.1)	6.12 (3.41–11.01)	<0.001

Primary End Point: Vascular death, myocardial infarction and stroke

Wallentin et al., *NEJM*, 2009

PLATelet inhibition and patient **O**utcomes (PLATO) Trial

	Ticagrelor Group	Clopidogrel Group
Race — no./total no. (%)‡		
White	8566/9332 (91.8)	8511/9291 (91.6
Black	115/9332 (1.2)	114/9291 (1.2)
Asian	542/9332 (5.8)	554/9291 (6.0)
Other	109/9332 (1.2)	112/9291 (1.2)
Final diagnosis of ACS — no./total no. (%)		
ST-elevation MI	3496/9333 (37.5)	3530/9291 (38.0)
Non–ST-elevation MI	4005/9333 (42.9)	3950/9291 (42.5)
Unstable angina	1549/9333 (16.6)	1563/9291 (16.8)
Other diagnosis or missing data§	283/9333 (3.0)	248/9291 (2.7)
Risk factors for ST-elevation MI — no./total no. (%)		
Killip class >2	25/3496 (0.7)	41/3530 (1.2)
TIMI risk score ≥3	1584/3496 (45.3)	1553/3530 (44.0)

Wallentin et al., *NEJM*, 2009

PLATO trial did not demonstrate superiority of Ticagrelor in US

Ticagrelor Compared With Clopidogrel by Geographic Region in the Platelet Inhibition and Patient Outcomes (PLATO) Trial

Kenneth W. Mahaffey, MD; Daniel M. Wojdyla, MS; Kevin Carroll, MS; Richard C. Becker, MD; Robert F. Storey, MD, DM; Dominick J. Angiolillo, MD, PhD; Claes Held, MD, PhD; Christopher P. Cannon, MD; Stefan James, MD, PhD; Karen S. Pieper, MS; Jay Horrow, MD; Robert A. Harrington, MD; Lars Wallentin, MD, PhD; on behalf of the PLATO Investigators

Background—In the Platelet Inhibition and Patient Outcomes (PLATO) trial, a prespecified subgroup analysis showed a significant interaction between treatment and region ($P=0.045$), with less effect of ticagrelor in North America than in the rest of the world.

Mahaffey et al., *Circulation*, 2011

PLATO trial did not demonstrate superiority of Ticagrelor in US

Table 2. Clinical Events Committee–Adjudicated Primary Efficacy End Points and Bleeding in the United States and the Rest of the World by Treatment

		Ticagrelor (n=9333)			Clopidogrel (n=9291)				
End Point	Region	n	Patients With Events, n (%)	KM, %	n	Patients With Events, n (%)	KM, %	HR (95% CI)	*P*
Cardiovascular death/MI*/stroke	US	707	84 (11.9)	12.6	706	67 (9.5)	10.1	1.27 (0.92–1.75)	0.1459
	ROW	8626	780 (9.0)	9.6	8585	947 (11.0)	11.8	0.81 (0.74–0.90)	<0.0001
Cardiovascular death	US	707	24 (3.4)	3.7	706	19 (2.7)	2.7	1.26 (0.69–2.31)	0.4468
	ROW	8626	329 (3.8)	4.0	8585	423 (4.9)	5.3	0.77 (0.67–0.89)	0.0005
MI*	US	707	64 (9.1)	9.6	706	47 (6.7)	7.2	1.38 (0.95–2.01)	0.0956
	ROW	8626	440 (5.1)	5.5	8585	546 (6.4)	6.9	0.80 (0.70–0.90)	0.0004
Stroke	US	707	7 (1.0)	1.0	706	4 (0.6)	0.6	1.75 (0.51–5.97)	0.3730
	ROW	8626	118 (1.4)	1.5	8585	102 (1.2)	1.3	1.15 (0.88–1.50)	0.2964
All-cause mortality	US	707	28 (4.0)	4.2	706	24 (3.4)	3.6	1.17 (0.68–2.01)	0.5812
	ROW	8626	371 (4.3)	4.6	8585	482 (5.6)	6.1	0.77 (0.67–0.88)	0.0001
PLATO major bleeding	US	682	77 (11.3)	12.2	675	74 (11.0)	11.9	1.05 (0.76–1.45)	0.7572
	ROW	8553	884 (10.3)	11.5	8511	855 (10.1)	11.1	1.04 (0.94–1.14)	0.4696
PLATO non-CABG major bleeding	US	682	29 (4.3)	5.1	675	25 (3.7)	4.3	1.20 (0.70–2.04)	0.5115
	ROW	8553	333 (3.9)	4.4	8511	281 (3.3)	3.7	1.19 (1.01–1.39)	0.0330
PLATO major/minor bleeding	US	682	101 (14.8)	16.4	675	92 (13.6)	15.2	1.11 (0.84–1.48)	0.4599
	ROW	8553	1238 (14.5)	16.1	8511	1123 (13.2)	14.6	1.11 (1.02–1.20)	0.0114

Mahaffey et al., *Circulation*, 2011

PLATO trial did not demonstrate superiority of Ticagrelor in US

Ticagrelor Compared With Clopidogrel by Geographic Region in the Platelet Inhibition and Patient Outcomes (PLATO) Trial

Kenneth W. Mahaffey, MD; Daniel M. Wojdyla, MS; Kevin Carroll, MS; Richard C. Becker, MD; Robert F. Storey, MD, DM; Dominick J. Angiolillo, MD, PhD; Claes Held, MD, PhD; Christopher P. Cannon, MD; Stefan James, MD, PhD; Karen S. Pieper, MS; Jay Horrow, MD; Robert A. Harrington, MD; Lars Wallentin, MD, PhD; on behalf of the PLATO Investigators

Background—In the Platelet Inhibition and Patient Outcomes (PLATO) trial, a prespecified subgroup analysis showed a significant interaction between treatment and region ($P=0.045$), with less effect of ticagrelor in North America than in the rest of the world.

Conclusions—The regional interaction could arise from chance alone. Results of 2 independently performed analyses identified an underlying statistical interaction with aspirin maintenance dose as a possible explanation for the regional difference. The lowest risk of cardiovascular death, myocardial infarction, or stroke with ticagrelor compared with clopidogrel is associated with a low maintenance dose of concomitant aspirin.

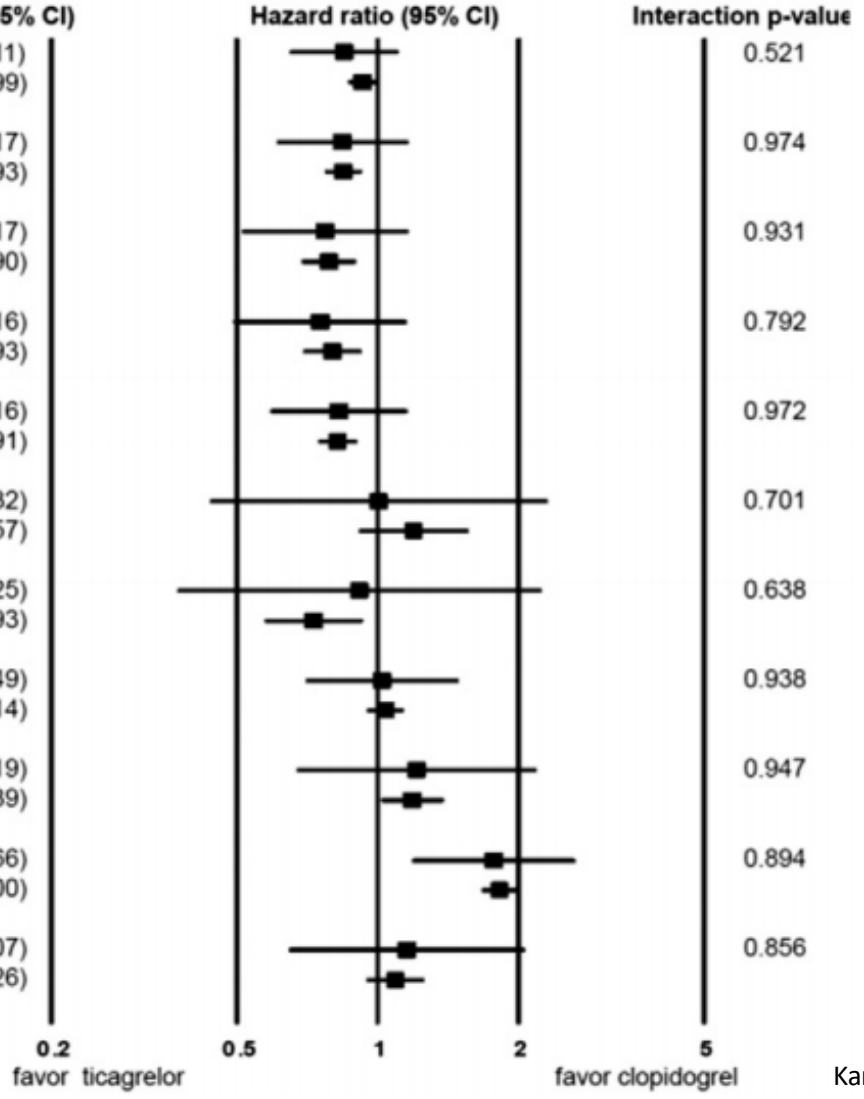
Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00391872.

(*Circulation*. 2011;124:544-554.)

Mahaffey et al., *Circulation*, 2011

PLATO trial did not demonstrate superiority of Ticagrelor in Asia

End point		Hazard ratio (95% CI)	Interaction p-value
Net clinical benefit	Asian	0.85 (0.65-1.11)	0.521
	non-Asian	0.93 (0.86-0.99)	
Primary efficacy End point	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)	
Death from vascular causes	Asian	0.75 (0.49-1.16)	0.792
	non-Asian	0.80 (0.69-0.93)	
Vascular death or myocardial infarction	Asian	0.83 (0.59-1.16)	0.972
	non-Asian	0.82 (0.74-0.91)	
Stroke	Asian	1.01 (0.44-2.32)	0.701
	non-Asian	1.19 (0.91-1.57)	
Probable/definite stent thrombosis	Asian	0.91 (0.37-2.25)	0.638
	non-Asian	0.73 (0.57-0.93)	
PLATO major bleeding	Asian	1.02 (0.70-1.49)	0.938
	non-Asian	1.04 (0.95-1.14)	
Non-CABG major bleeding	Asian	1.21 (0.67-2.19)	0.947
	non-Asian	1.19 (1.01-1.39)	
Dyspnea	Asian	1.77 (1.18-2.66)	0.894
	non-Asian	1.82 (1.66-2.00)	
Bradycardia	Asian	1.16 (0.64-2.07)	0.856
	non-Asian	1.09 (0.95-1.26)	



Kang et al., *Am Heart J*, 2015

International difference in treatment effect of ticagrelor

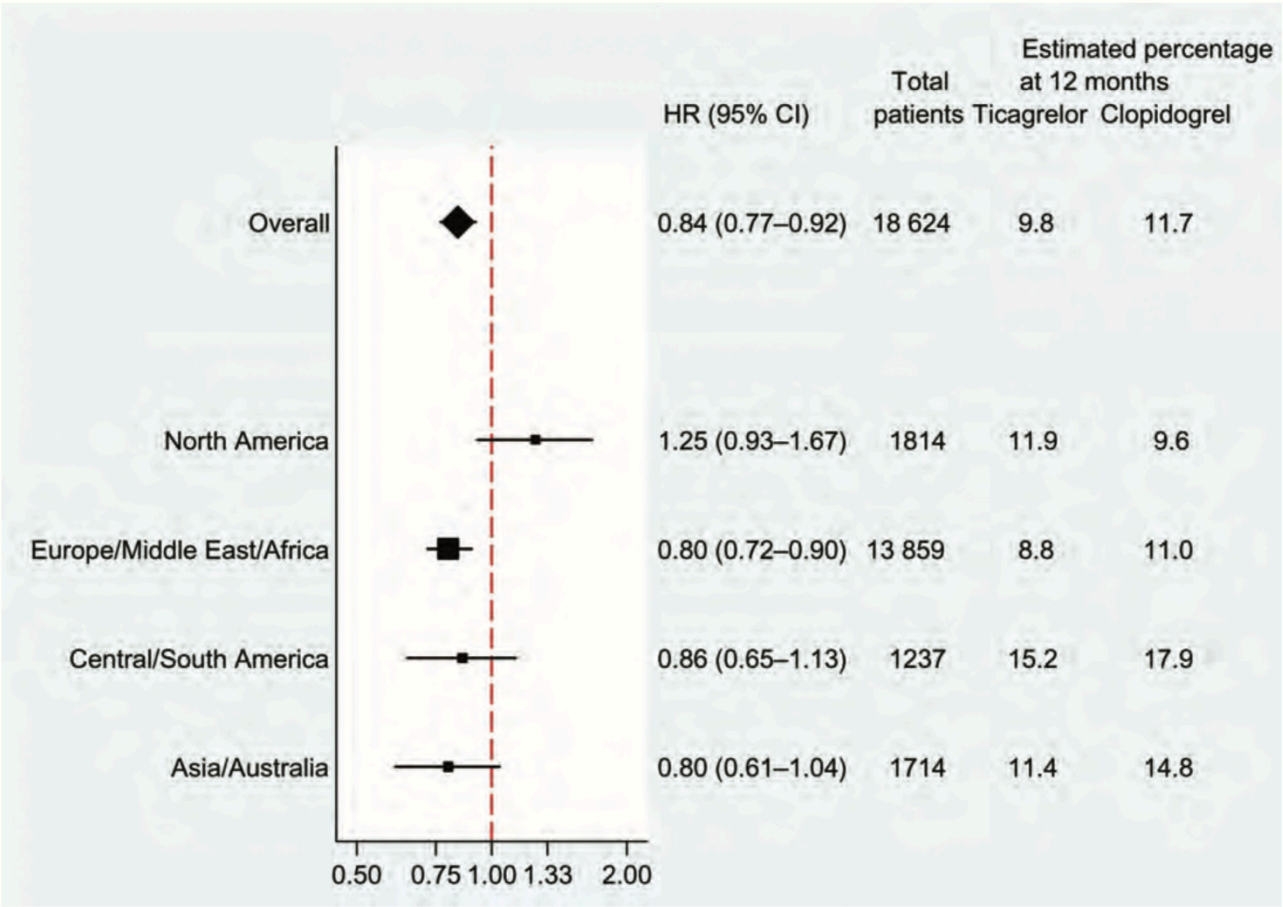
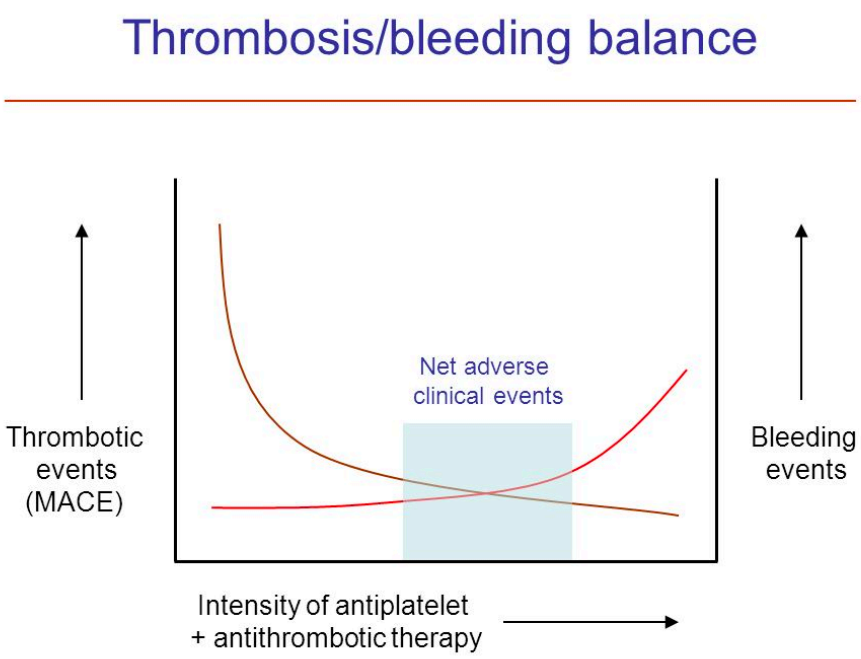


Figure 1 Estimated treatment effects by geographic region for the primary endpoint (CV death, MI, or stroke) of the PLATO trial (hazard ratios with 95% CIs, interaction *P*-value 0.05).

Pocock et al., *EHJ*, 2013

Balance between thrombotic versus bleeding risk



Impact of bleeding on prognosis in patients using ticagrelor or prasugrel

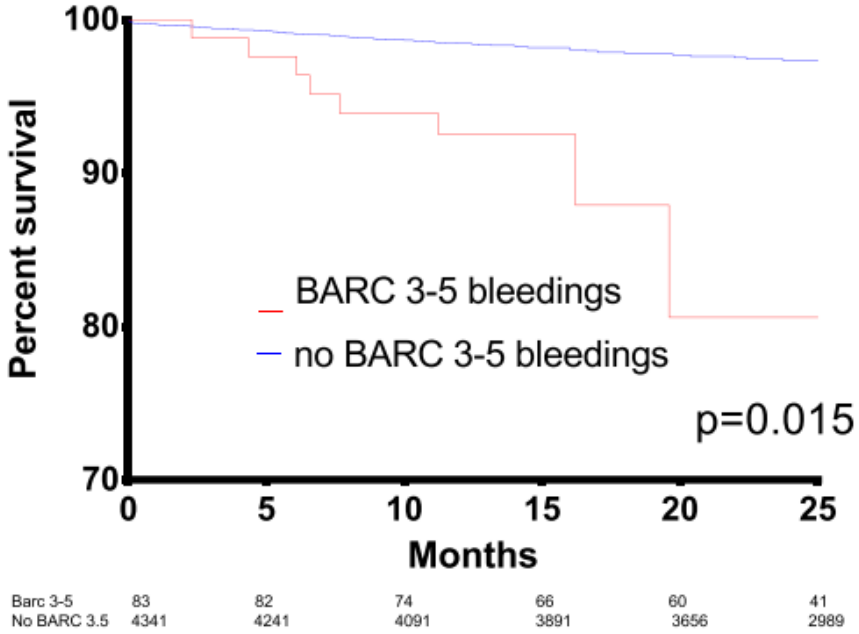


Fig. 2. Long term risk of death according to BARC 3-5 bleedings.

D'Ascenzo et al., *International Journal of Cardiology* 2018

Therapeutic window of anti-platelet therapy across races

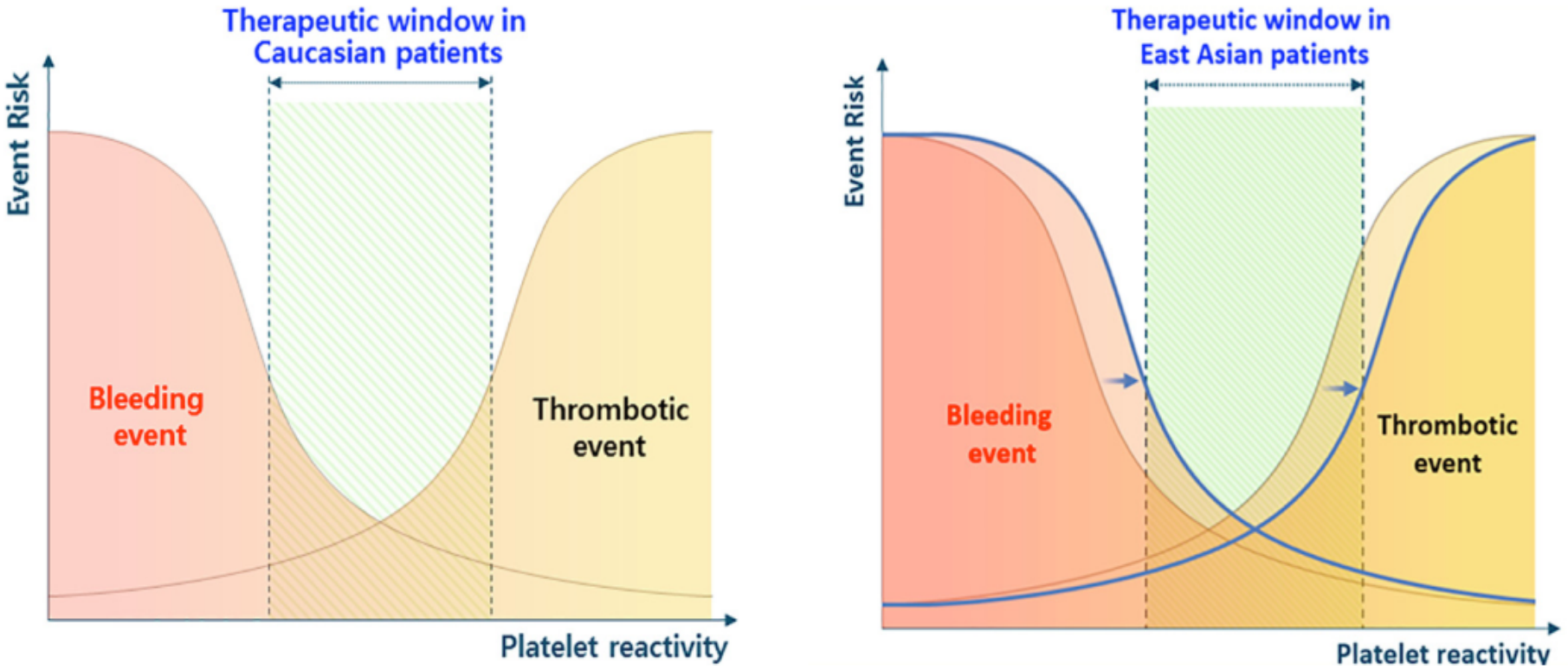


Fig. 3. Presented therapeutic window of platelet reactivity during P2Y12 ADP inhibitor: Caucasian vs. East Asian patients.

Huo et al., *Science Bulletin*, 2019

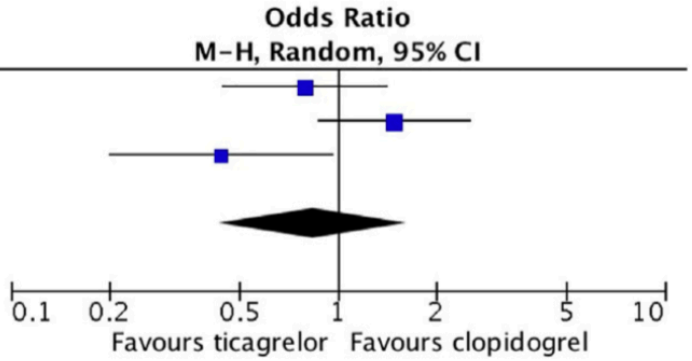
Ticagrelor might not be better than Clopidogrel in East Asian population

a) Primary efficacy endpoint: a composite of death from vascular causes, myocardial infarction, or stroke

Study or Subgroup	Ticagrelor Events	Ticagrelor Total	Clopidogrel Events	Clopidogrel Total	Weight	Odds Ratio M-H, Random, 95% CI
1. Kang HJ, et al.	23	278	28	273	34.9%	0.79 [0.44, 1.41]
2. Goto S, et al.	36	401	25	400	36.5%	1.48 [0.87, 2.51]
3. Wang H, et al.	11	100	22	100	28.5%	0.44 [0.20, 0.96]
Total (95% CI)		**779**		**773**	**100.0%**	**0.84 [0.43, 1.63]**
Total events	70		75			

Heterogeneity: $Tau^2 = 0.24$; $Chi^2 = 6.78$, df = 2 (P = 0.03); $I^2 = 71\%$

Test for overall effect: Z = 0.52 (P = 0.60)

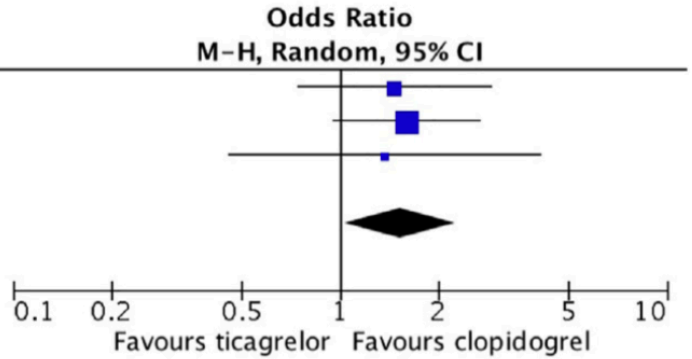


b) Primary safety endpoint: major bleeding events

Study or Subgroup	Ticagrelor Events	Ticagrelor Total	Clopidogrel Events	Clopidogrel Total	Weight	Odds Ratio M-H, Random, 95% CI
1. Kang HJ, et al.	22	276	15	268	32.0%	1.46 [0.74, 2.88]
2. Goto S, et al.	40	401	26	400	55.7%	1.59 [0.95, 2.67]
3. Wang H, et al.	8	100	6	100	12.3%	1.36 [0.45, 4.08]
Total (95% CI)		**777**		**768**	**100.0%**	**1.52 [1.04, 2.23]**
Total events	70		47			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.08$, df = 2 (P = 0.96); $I^2 = 0\%$

Test for overall effect: Z = 2.14 (P = 0.03)



"Ticagrelor versus Clopidogrel in East Asian Patients with Acute Coronary Syndrome: Systematic Review and Meta-Analysis." *Cardiovascular Revascularization Medicine*

Ticagrelor might not be better than Clopidogrel in East Asian population

Curr Cardiol Rep (2014) 16:485
DOI 10.1007/s11886-014-0485-4

GLOBAL CARDIOVASCULAR HEALTH (SC SMITH, SECTION EDITOR)

"East Asian Paradox": Challenge for the Current Antiplatelet Strategy of "One-Guideline-Fits-All Races" in Acute Coronary Syndrome

Young-Hoon Jeong

- *Although there have been no conclusive large-scale clinical trials including East Asians only, recent pharmacodynamic and clinical studies have suggested more insight and confidence for the '**East Asian Paradox**'*

Jeong et al., *Curr Cardiol Resp* 2014

Objectives

- Compare risk of **net adverse clinical event** (**NACE**) between ticagrelor and clopidogrel in patients with Acute Coronary Syndrome through OHDSI network.

Method: Study Population

- Inclusion Criteria
  - Adults (>=20 yrs) who initiated ticagrelor or clopidogrel due to acute coronary syndrome (ACS) and undertook percutaneous coronary intervention (PCI)
- Exclusion Criteria
  - Prior history of stroke or gastrointestinal bleeding
  - Use of prasugrel or opposing drug within previous 30 days from index date

https://github.com/chandryou/TicagrelorVsClopidogrel

Method: Outcome

Primary endpoint: Net Adverse Clinical Event (NACE)

- Composite of recurrent myocardial infarction, any revascularization, ischemic stroke, intracranial hemorrhage, or gastrointestinal bleeding

Secondary endpoint

- Ischemic Event
  - Recurrent myocardial infarction
  - Any revascularization (PCI + CABG)
  - Ischemic stroke
- Hemorrhagic Event (major bleeding)
  - Intracranial hemorrhage
  - Gastrointestinal bleeding
- Overall death
- Dyspnea (Positive control)

Method: Statistical Analysis

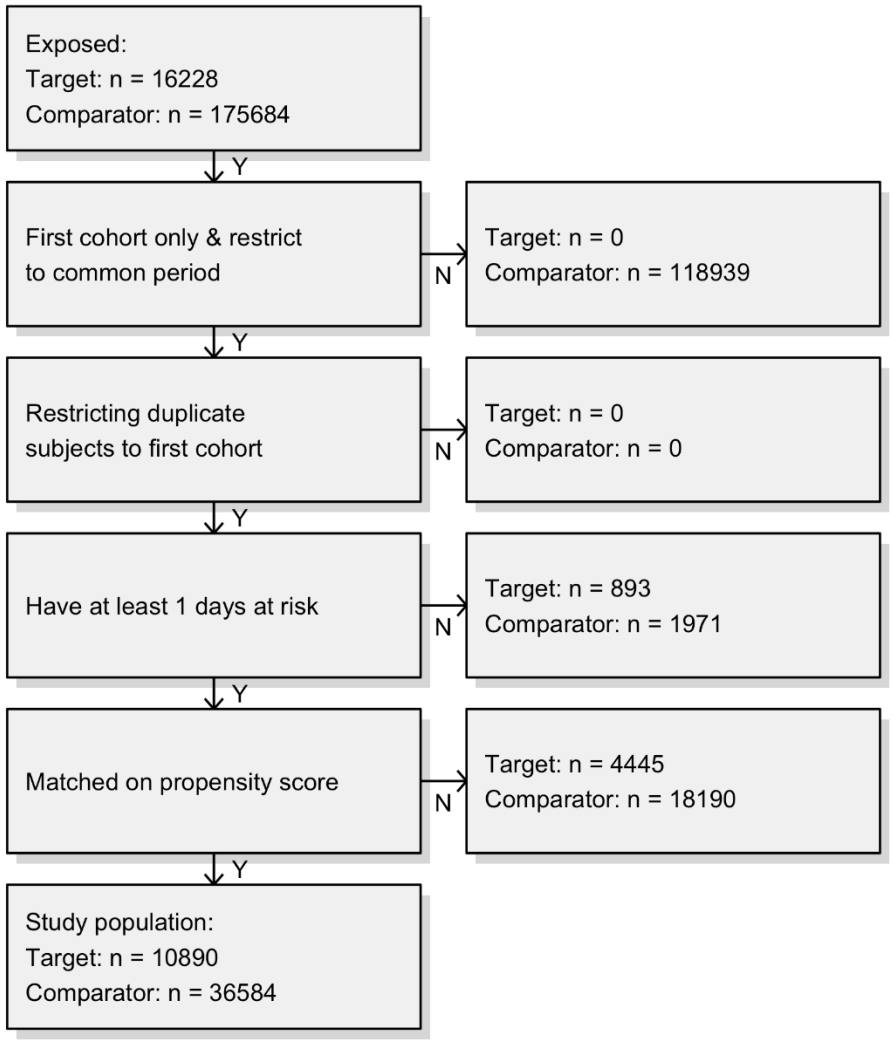
- Primary risk window: within one year after the index year
  - Variable-ratio PS matching (This was replaced with one-to-one matching in latest version, v1.2.1)
- Secondary risk window
  - On-treatment
  - 5-year
  - With blanking period of 28 days
- Large scale propensity score matching
  - 96 Negative controls
  - PS stratification for sensitivity analysis
- Interaction term analysis
  - Gender, old age, Black or African race, MI, PPI use, high aspirin maintenance dose (>=300mg)

Method

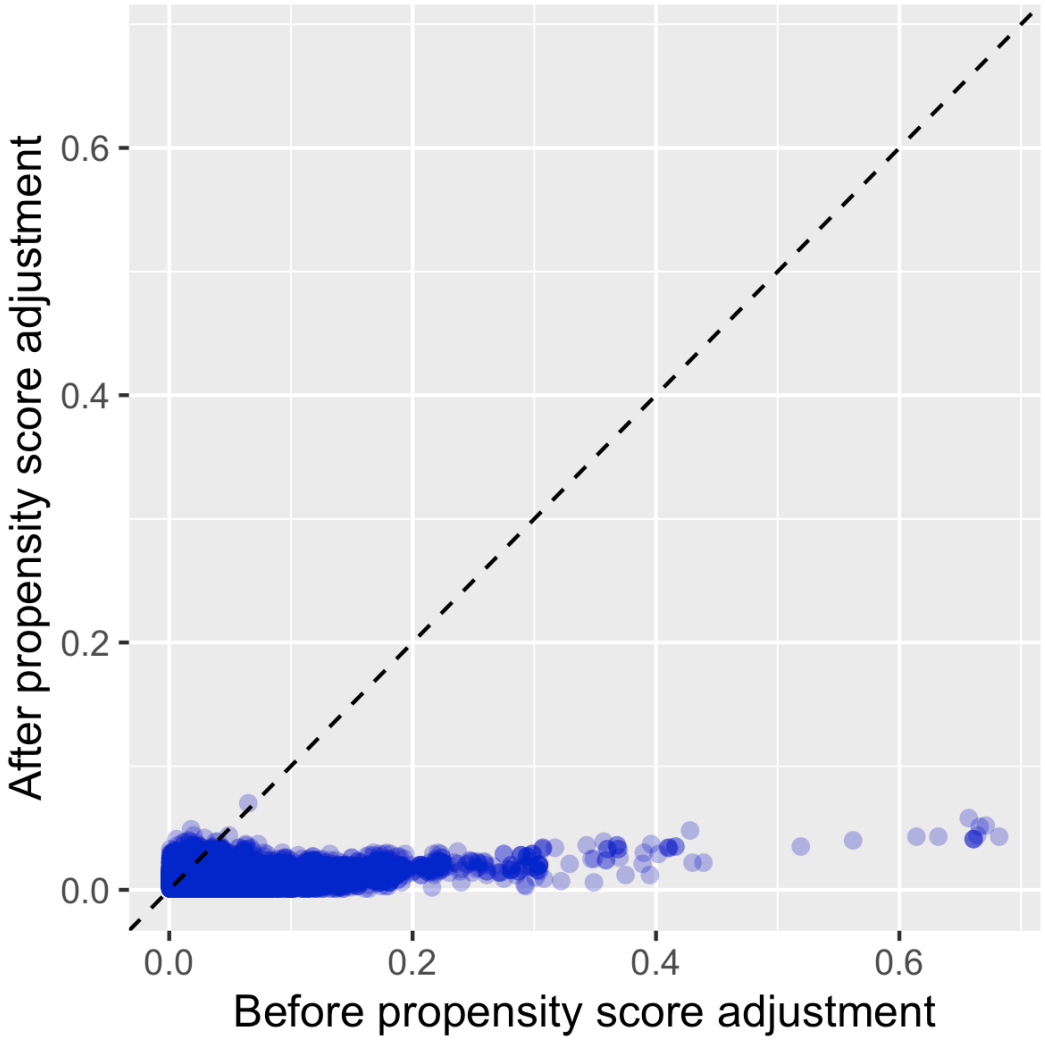
- Data source
  - **The whole national health records of patients undertook PCI from 2007 to 2016 were converted into OMOP-CDM in Korea** (v1.2.0 completed)
  - IQVIA's hospital data (v1.2.0 completed)
  - IQVIA's Open Claims data (v1.2.0 completed)

Data source	Country	Type	Number of total subjects	Years
HIRA-PCI	South Korea	Reimbursement	462,486	2007-2016
IQVIA-Open Claims	US	Reimbursement	654,515,304	2001-2018
IQVIA-Hospital	US	Hospital administration	85,797,980	1997-2019

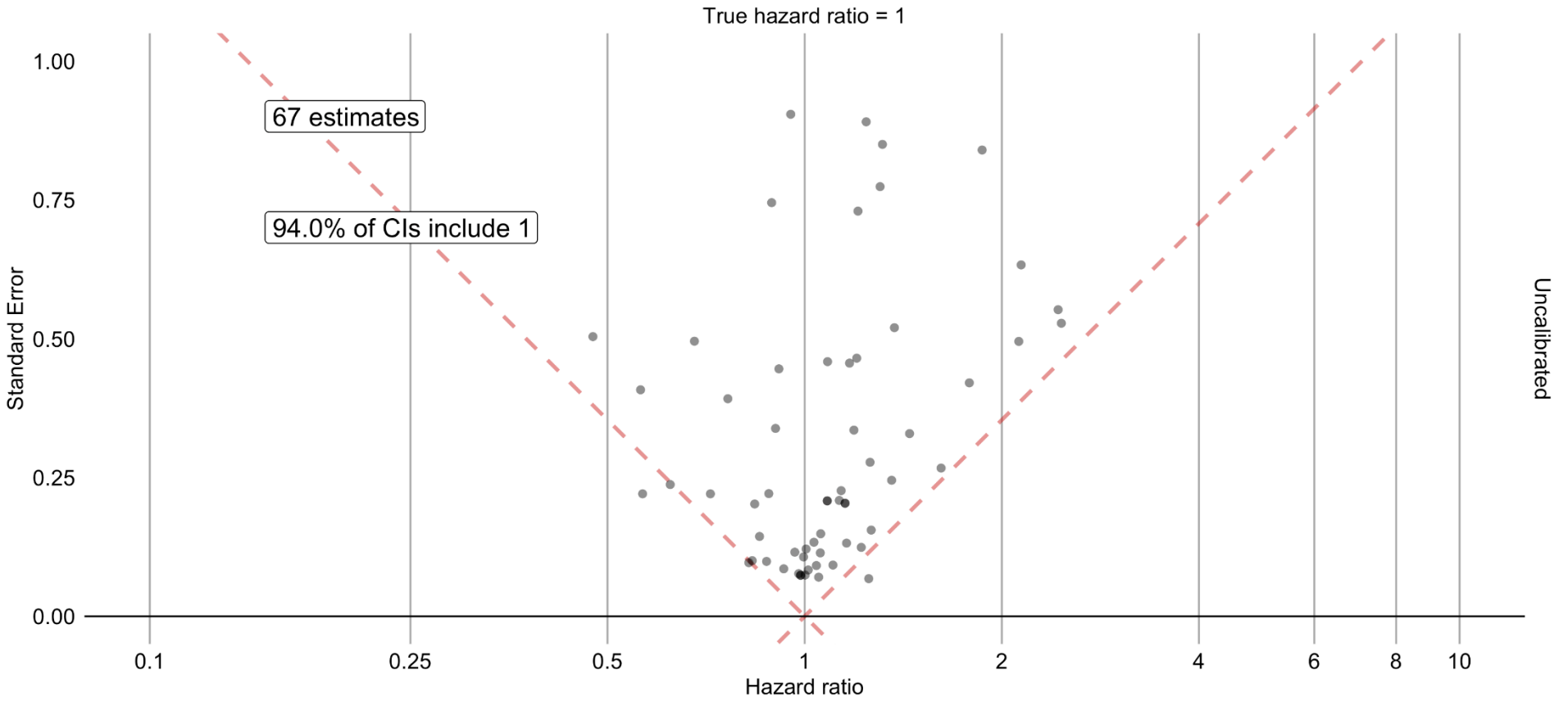
Result: Patient flow chart



Balance before and after PS matching

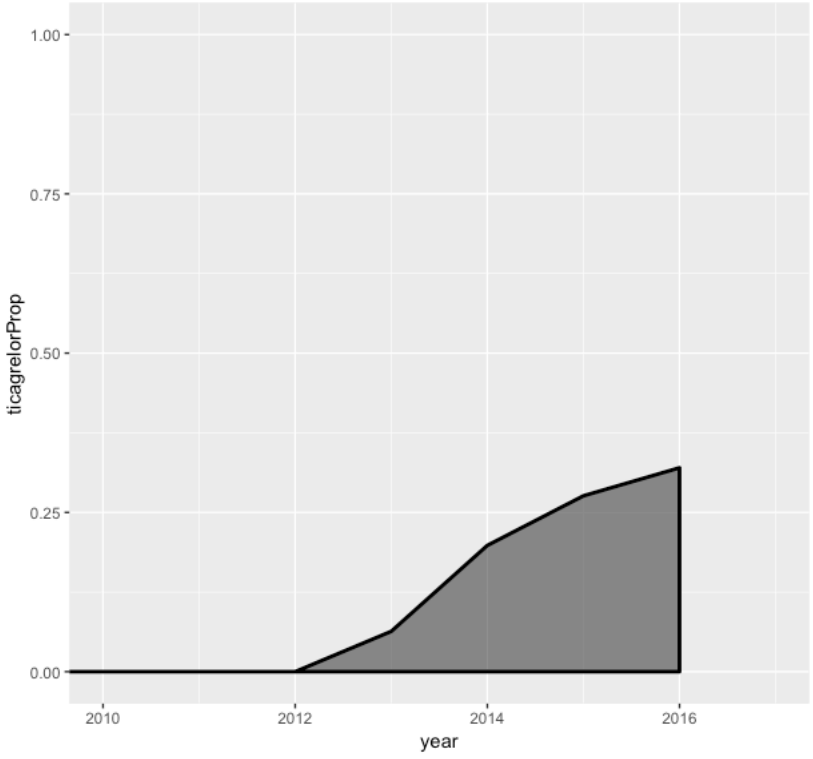


Funnel plot for negative controls

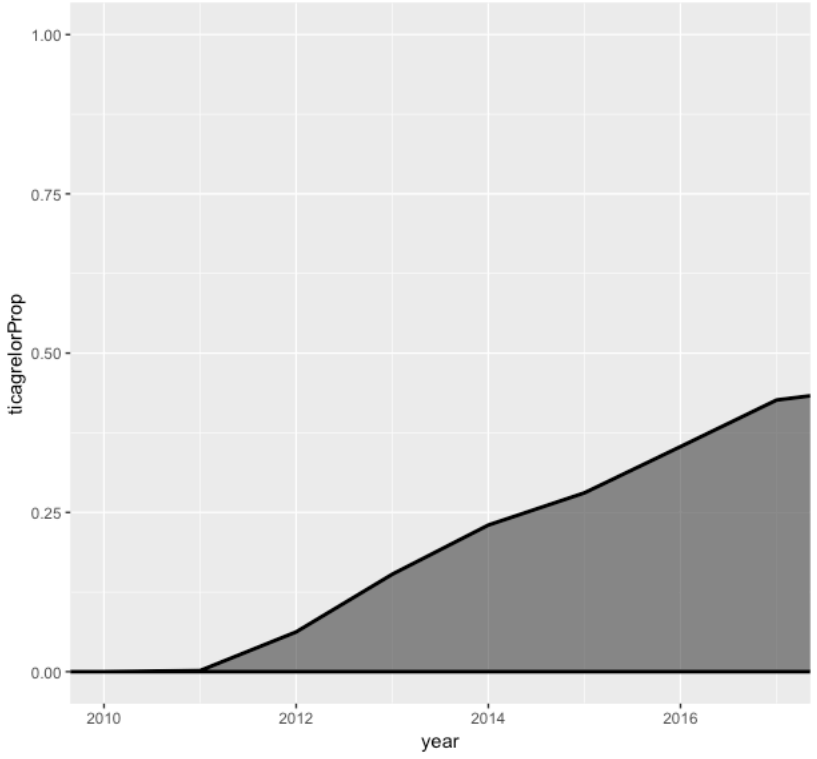


Proportion of ticagrelor across years

- HIRA-PCI (Korea)



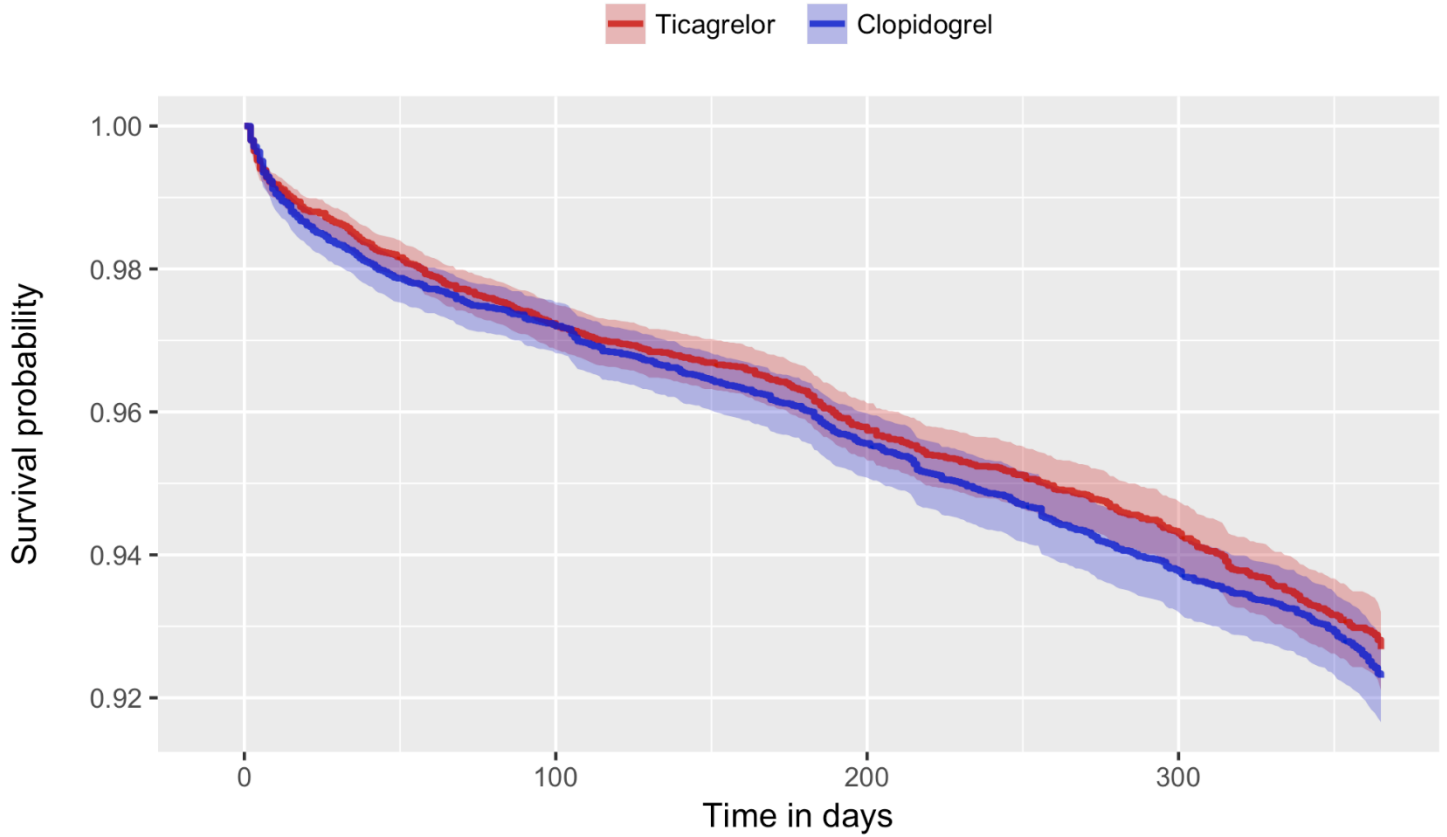
- IQVIA-Hospital (US)



Summary of the result

Event	Source	Ticagrelor		Clopidogrel		HR (95% CI)	*P* / calibrated *P*
		Subjects / Years	Incidence rate	Subjects / Years	Incidence rate		
NACE	HIRA-PCI	10 890 / 7 843	239.83	36 584 / 27 455	216.38	1.01 (0.95-1.07)	0.80 / 0.80
	IQVIA-Open Claims	6 762 / 5 452	128.38	22 707 / 18 838	151.82	0.97 (0.89-1.06)	0.71 / 0.53
	IQVIA-Hospital	4 002 / 2 446	122.21	12 004 / 7 974	116.38	1.03 (0.89-1.06)	0.80 / 0.72
Ischemic event	HIRA-PCI	10 890 / 7 894	224.32	36 584 / 27 635	201.3	1.00 (0.94-1.07)	0.94 / 0.78
	IQVIA-Open Claims	6 762 / 5 520	106.34	22 707 / 19 034	132.50	0.92 (0.83-1.01)	0.09 / 0.12
	IQVIA-Hospital	4 002 / 2 472	94.65	12 004 / 8 043	92.87	1.04 (0.88-1.23)	0.62 / 0.78
Bleeding event	HIRA-PCI	10 890 / 8 696	25.07	36 584 / 30 148	21.53	1.24 (1.04-1.47)	0.02 / 0.05
	IQVIA-Open Claims	6 762 / 5 812	26.15	22 707 / 20 416	25.62	1.24 (1.02-1.51)	0.03 / 0.05
	IQVIA-Hospital	4 002 / 2 551	28.61	12 004 / 8 339	24.22	0.96 (0.69-1.33)	0.82 / 0.74
Dyspnea	HIRA-PCI	10 890 / 816	97.71	36 584 / 2 707	93.3	1.15 (1.05-1.25)	<0.01 / 0.07
	IQVIA-Open Claims	6 762 / 4 760	367.58	22 707 / 17 189	320.42	1.21 (1.14-1.29)	<0.01 / <0.01
	IQVIA-Hospital	4 002 / 2 357	201.87	12 004 / 7 862	156.68	1.29 (1.14-1.46)	<0.01 / <0.01

After matching: 1-year NACE



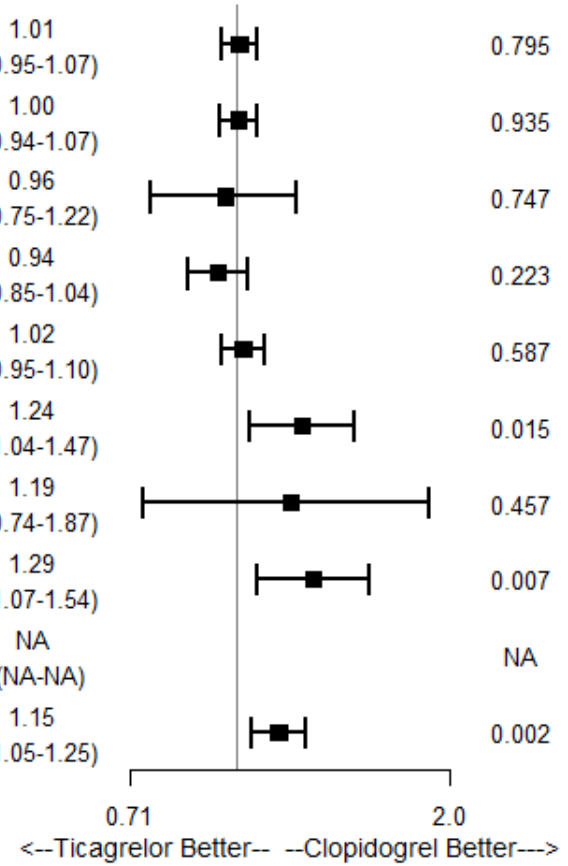
Number at risk				
Ticagrelor	10,890	9,418	8,289	7,085
Clopidogrel	36,584	32,098	28,740	25,345

HR 1.01; *P*=0.795

Primary analysis: 1-year outcome after PS matching

One-year outcome, matching

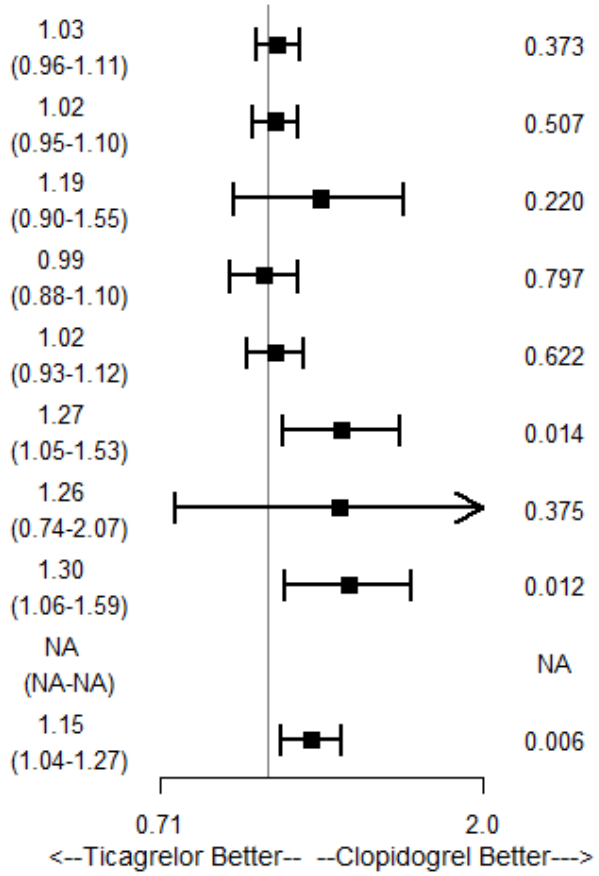
Outcome	Target (n= 10890) Event Rate, %/yr	Comparator (n= 36584) Event Rate, %/yr	HR (95% CI)	P value
Net Adverse Clinical Event	23.97	21.62	1.01 (0.95-1.07)	0.795
Ischemic event	22.42	20.12	1.00 (0.94-1.07)	0.935
Ischemic stroke	1.19	1.39	0.96 (0.75-1.22)	0.747
Revascularization	7.74	8.08	0.94 (0.85-1.04)	0.223
Acute MI	15.64	12.89	1.02 (0.95-1.10)	0.587
Hemorrhagic Event	2.50	2.15	1.24 (1.04-1.47)	0.015
hemorrhagic stroke	0.35	0.33	1.19 (0.74-1.87)	0.457
GI bleeding	2.23	1.84	1.29 (1.07-1.54)	0.007
Any death	0.00	0.00	NA (NA-NA)	NA
Dyspnea	9.76	9.32	1.15 (1.05-1.25)	0.002



1-year outcome after PS matching with 28-day blanking period

One-year outcome, matching with blanking period

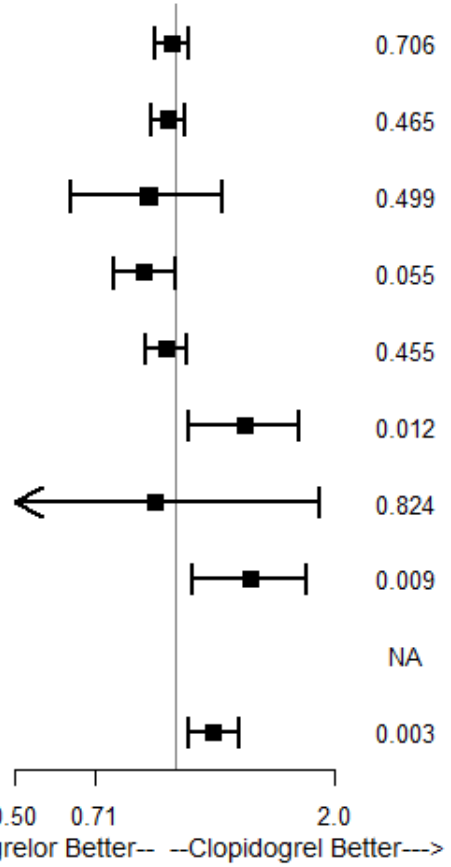
Outcome	Target (n= 10024) Event Rate, %/yr	Comparator (n= 34131) Event Rate, %/yr	HR (95% CI)	P value
Net Adverse Clinical Event	18.18	16.78	1.03 (0.96-1.11)	0.373
Ischemic event	16.72	15.33	1.02 (0.95-1.10)	0.507
Ischemic stroke	1.03	1.04	1.19 (0.90-1.55)	0.220
Revascularization	6.89	6.84	0.99 (0.88-1.10)	0.797
Acute MI	10.01	8.68	1.02 (0.93-1.12)	0.622
Hemorrhagic Event	2.23	1.97	1.27 (1.05-1.53)	0.014
hemorrhagic stroke	0.30	0.27	1.26 (0.74-2.07)	0.375
GI bleeding	2.00	1.73	1.30 (1.06-1.59)	0.012
Any death	0.00	0.00	NA (NA-NA)	NA
Dyspnea	8.20	8.10	1.15 (1.04-1.27)	0.006



Secondary analysis: On-treatment outcome after PS matching

On-treatment, matching

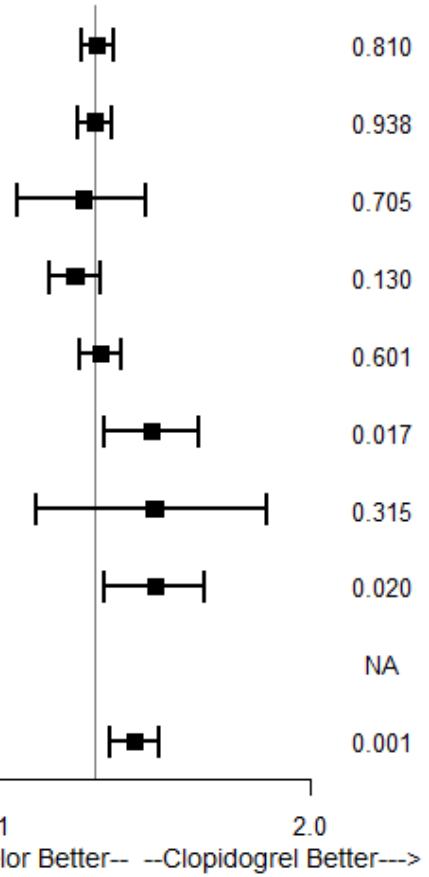
Outcome	Target (n= 10639) Event Rate, %/yr	Comparator (n= 35796) Event Rate, %/yr	HR (95% CI)	P value
Net Adverse Clinical Event	27.26	20.23	0.99 (0.91-1.06)	0.706
Ischemic event	25.43	18.87	0.97 (0.90-1.05)	0.465
Ischemic stroke	1.10	1.15	0.89 (0.63-1.23)	0.499
Revascularization	8.00	7.31	0.88 (0.77-1.00)	0.055
Acute MI	18.33	12.13	0.97 (0.88-1.06)	0.455
Hemorrhagic Event	2.72	1.85	1.35 (1.06-1.71)	0.012
hemorrhagic stroke	0.28	0.26	0.92 (0.41-1.89)	0.824
GI bleeding	2.42	1.59	1.39 (1.08-1.78)	0.009
Any death	0.00	0.00	NA (NA-NA)	NA
Dyspnea	10.89	8.34	1.18 (1.06-1.32)	0.003



Secondary analysis: 5-year outcome after PS matching

Five-year, matching

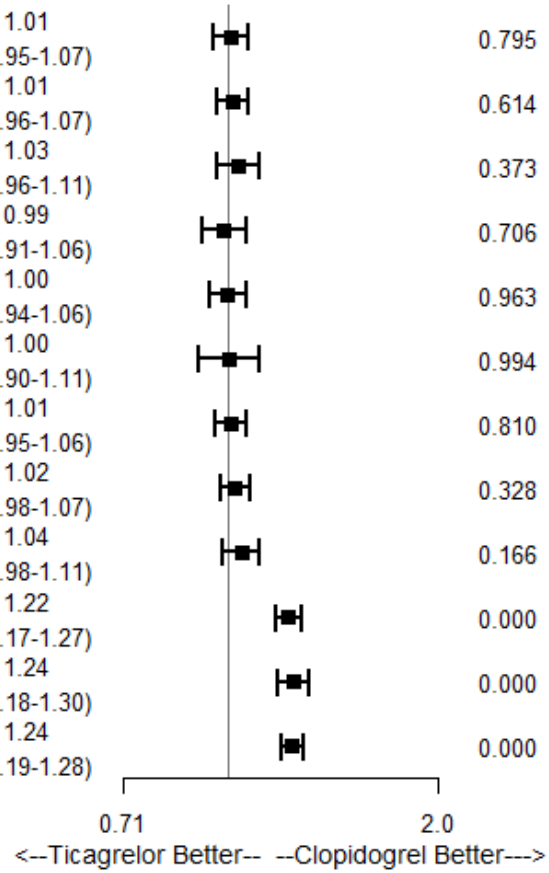
Outcome	Target (n= 10890) Event Rate, %/yr	Comparator (n= 36584) Event Rate, %/yr	HR (95% CI)	P value
Net Adverse Clinical Event	18.56	15.75	1.01 (0.95-1.06)	0.810
Ischemic event	17.26	14.53	1.00 (0.94-1.05)	0.938
Ischemic stroke	0.93	1.07	0.96 (0.78-1.18)	0.705
Revascularization	6.18	6.18	0.94 (0.86-1.02)	0.130
Acute MI	11.20	8.49	1.02 (0.95-1.09)	0.601
Hemorrhagic Event	1.85	1.62	1.20 (1.03-1.40)	0.017
hemorrhagic stroke	0.31	0.29	1.21 (0.83-1.74)	0.315
GI bleeding	1.56	1.36	1.21 (1.03-1.43)	0.020
Any death	0.00	0.00	NA (NA-NA)	NA
Dyspnea	7.30	6.84	1.14 (1.05-1.23)	0.001



Outcome: Net-Adverse Adverse Event

NACE

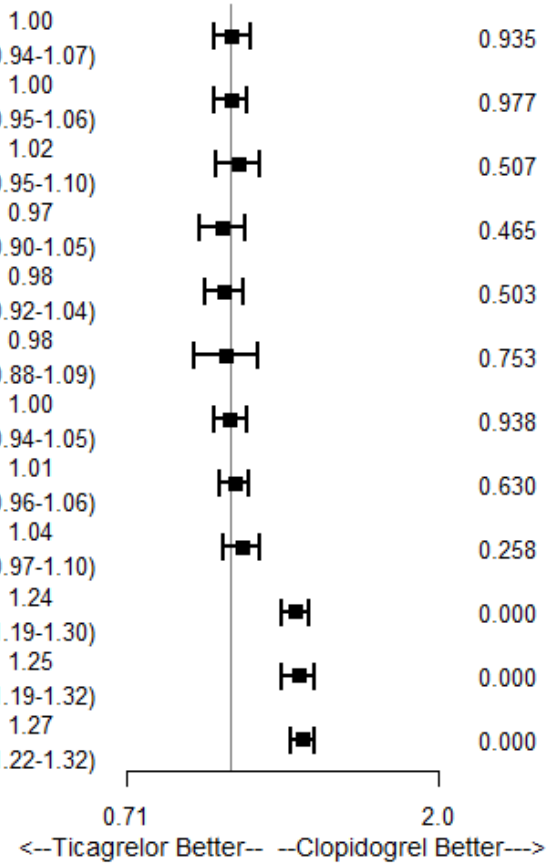
Analysis	Target (n= 10890) Event Rate, %/yr	Comparator (n= 36584) Event Rate, %/yr	HR (95% CI)	P value
One-year outcome, matching	23.97	21.62	1.01 (0.95-1.07)	0.795
One-year outcome, stratification	24.85	19.81	1.01 (0.96-1.07)	0.614
One-year outcome, matching with blanking period	18.18	16.78	1.03 (0.96-1.11)	0.373
On-treatment, matching	27.26	20.23	0.99 (0.91-1.06)	0.706
On-treatment, stratification	27.49	18.02	1.00 (0.94-1.06)	0.963
On-treatment, matching with blanking period	16.46	14.62	1.00 (0.90-1.11)	0.994
Five-year, matching	18.56	15.75	1.01 (0.95-1.06)	0.810
Five-year, stratification	19.78	13.87	1.02 (0.98-1.07)	0.328
Five-year, matching with blanking period	15.10	13.01	1.04 (0.98-1.11)	0.166
One-year outcome, without matching	24.85	19.81	1.22 (1.17-1.27)	0.000
On-treatment, without matching	27.49	18.02	1.24 (1.18-1.30)	0.000
Five-year, without matching	19.78	13.87	1.24 (1.19-1.28)	0.000



Outcome: ischemic outcome (ischemic stroke + MI + Revascularization)

IschemicEvent

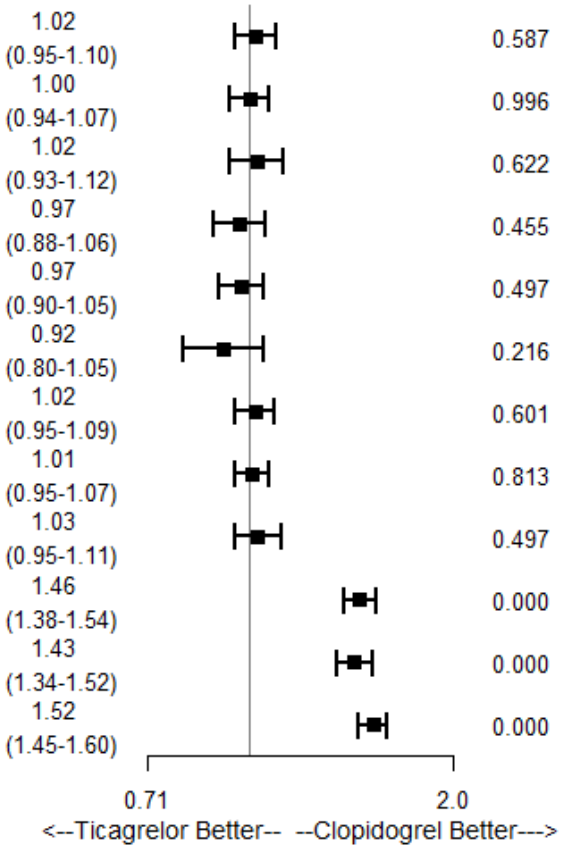
Analysis	Target (n= 10890) Event Rate, %/yr	Comparator (n= 36584) Event Rate, %/yr	HR (95% CI)	P value
One-year outcome, matching	22.42	20.12	1.00 (0.94-1.07)	0.935
One-year outcome, stratification	23.29	18.21	1.00 (0.95-1.06)	0.977
One-year outcome, matching with blanking period	16.72	15.33	1.02 (0.95-1.10)	0.507
On-treatment, matching	25.43	18.87	0.97 (0.90-1.05)	0.465
On-treatment, stratification	25.85	16.60	0.98 (0.92-1.04)	0.503
On-treatment, matching with blanking period	14.94	13.30	0.98 (0.88-1.09)	0.753
Five-year, matching	17.26	14.53	1.00 (0.94-1.05)	0.938
Five-year, stratification	18.50	12.57	1.01 (0.96-1.06)	0.630
Five-year, matching with blanking period	13.84	11.86	1.04 (0.97-1.10)	0.258
One-year outcome, without matching	23.29	18.21	1.24 (1.19-1.30)	0.000
On-treatment, without matching	25.85	16.60	1.25 (1.19-1.32)	0.000
Five-year, without matching	18.50	12.57	1.27 (1.22-1.32)	0.000



Outcome: Acute Myocardial Infarction

AMI

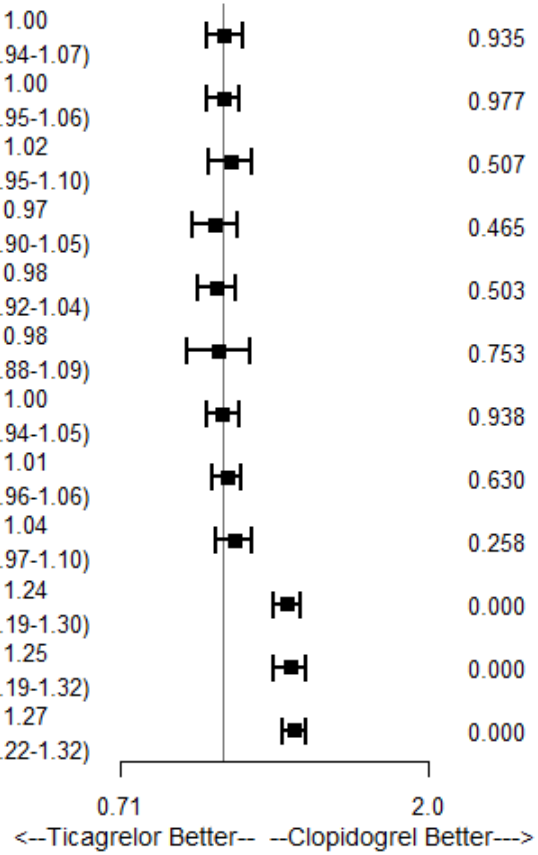
Analysis	Target (n= 10890) Event Rate, %/yr	Comparator (n= 36584) Event Rate, %/yr	HR (95% CI)	P value
One-year outcome, matching	15.64	12.89	1.02 (0.95-1.10)	0.587
One-year outcome, stratification	16.60	10.85	1.00 (0.94-1.07)	0.996
One-year outcome, matching with blanking period	10.01	8.68	1.02 (0.93-1.12)	0.622
On-treatment, matching	18.33	12.13	0.97 (0.88-1.06)	0.455
On-treatment, stratification	19.14	9.84	0.97 (0.90-1.05)	0.497
On-treatment, matching with blanking period	8.62	7.24	0.92 (0.80-1.05)	0.216
Five-year, matching	11.20	8.49	1.02 (0.95-1.09)	0.601
Five-year, stratification	12.36	6.65	1.01 (0.95-1.07)	0.813
Five-year, matching with blanking period	8.02	6.31	1.03 (0.95-1.11)	0.497
One-year outcome, without matching	16.60	10.85	1.46 (1.38-1.54)	0.000
On-treatment, without matching	19.14	9.84	1.43 (1.34-1.52)	0.000
Five-year, without matching	12.36	6.65	1.52 (1.45-1.60)	0.000



Outcome: ischemic stroke

IschemicEvent

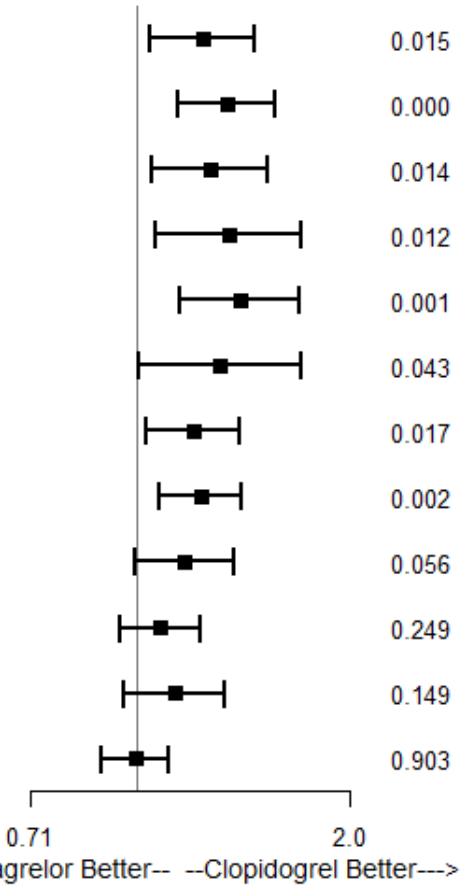
Analysis	Target (n= 10890) Event Rate, %/yr	Comparator (n= 36584) Event Rate, %/yr	HR (95% CI)	P value
One-year outcome, matching	22.42	20.12	1.00 (0.94-1.07)	0.935
One-year outcome, stratification	23.29	18.21	1.00 (0.95-1.06)	0.977
One-year outcome, matching with blanking period	16.72	15.33	1.02 (0.95-1.10)	0.507
On-treatment, matching	25.43	18.87	0.97 (0.90-1.05)	0.465
On-treatment, stratification	25.85	16.60	0.98 (0.92-1.04)	0.503
On-treatment, matching with blanking period	14.94	13.30	0.98 (0.88-1.09)	0.753
Five-year, matching	17.26	14.53	1.00 (0.94-1.05)	0.938
Five-year, stratification	18.50	12.57	1.01 (0.96-1.06)	0.630
Five-year, matching with blanking period	13.84	11.86	1.04 (0.97-1.10)	0.258
One-year outcome, without matching	23.29	18.21	1.24 (1.19-1.30)	0.000
On-treatment, without matching	25.85	16.60	1.25 (1.19-1.32)	0.000
Five-year, without matching	18.50	12.57	1.27 (1.22-1.32)	0.000



Outcome: hemorrhagic outcome (hemorrhagic stroke + GI bleeding)

HemorrhagicEvent

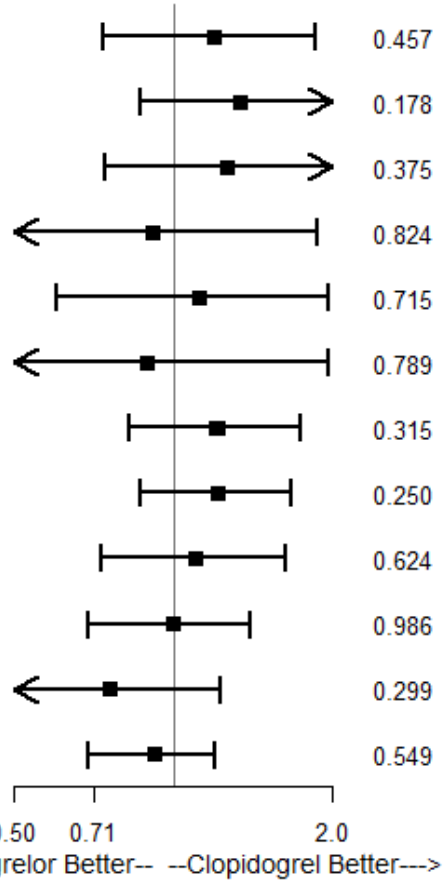
Analysis	Target (n= 10890) Event Rate, %/yr	Comparator (n= 36584) Event Rate, %/yr	HR (95% CI)	P value
One-year outcome, matching	2.50	2.15	1.24 (1.04-1.47)	0.015
One-year outcome, stratification	2.41	2.19	1.34 (1.14-1.57)	0.000
One-year outcome, matching with blanking period	2.23	1.97	1.27 (1.05-1.53)	0.014
On-treatment, matching	2.72	1.85	1.35 (1.06-1.71)	0.012
On-treatment, stratification	2.44	1.85	1.40 (1.15-1.70)	0.001
On-treatment, matching with blanking period	2.13	1.67	1.32 (1.00-1.71)	0.043
Five-year, matching	1.85	1.62	1.20 (1.03-1.40)	0.017
Five-year, stratification	1.83	1.68	1.23 (1.08-1.41)	0.002
Five-year, matching with blanking period	1.70	1.51	1.17 (0.99-1.37)	0.056
One-year outcome, without matching	2.41	2.19	1.08 (0.95-1.23)	0.249
On-treatment, without matching	2.44	1.85	1.13 (0.95-1.33)	0.149
Five-year, without matching	1.83	1.68	0.99 (0.89-1.11)	0.903



Outcome: Hemorrhagic stroke

hemorrhagicStroke

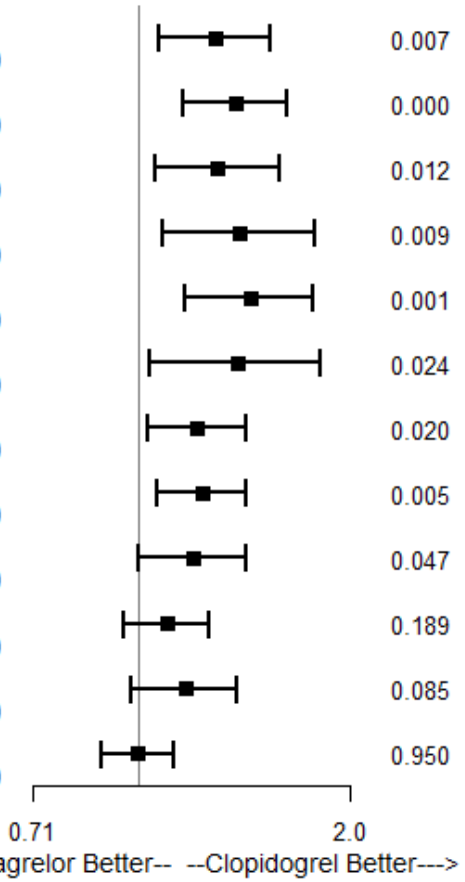
Analysis	Target (n= 10890) Event Rate, %/yr	Comparator (n= 36584) Event Rate, %/yr	HR (95% CI)	P value
One-year outcome, matching	0.35	0.33	1.19 (0.74-1.87)	0.457
One-year outcome, stratification	0.32	0.31	1.34 (0.86-2.05)	0.178
One-year outcome, matching with blanking period	0.30	0.27	1.26 (0.74-2.07)	0.375
On-treatment, matching	0.28	0.26	0.92 (0.41-1.89)	0.824
On-treatment, stratification	0.23	0.28	1.12 (0.60-1.97)	0.715
On-treatment, matching with blanking period	0.17	0.23	0.89 (0.36-1.97)	0.789
Five-year, matching	0.31	0.29	1.21 (0.83-1.74)	0.315
Five-year, stratification	0.28	0.30	1.21 (0.87-1.67)	0.250
Five-year, matching with blanking period	0.28	0.24	1.11 (0.73-1.64)	0.624
One-year outcome, without matching	0.32	0.31	1.00 (0.69-1.41)	0.986
On-treatment, without matching	0.23	0.28	0.76 (0.44-1.24)	0.299
Five-year, without matching	0.28	0.30	0.92 (0.69-1.20)	0.549



Outcome: GI bleeding

giBleeding

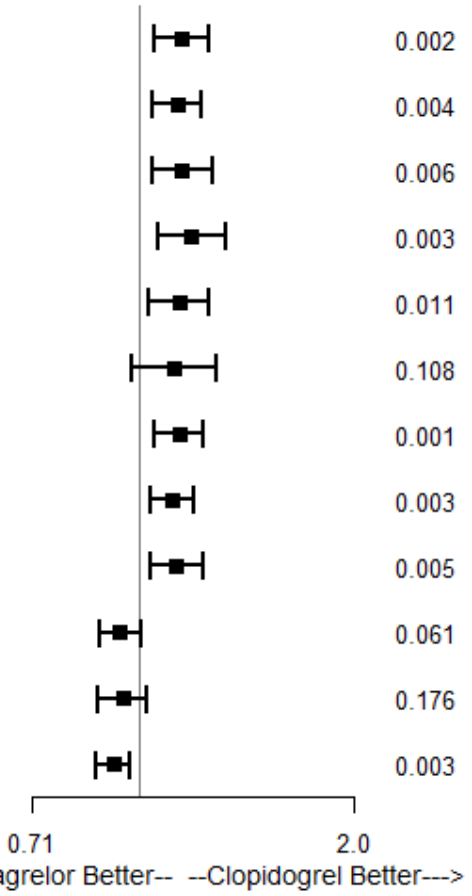
Analysis	Target (n= 10890) Event Rate, %/yr	Comparator (n= 36584) Event Rate, %/yr	HR (95% CI)	P value
One-year outcome, matching	2.23	1.84	1.29 (1.07-1.54)	0.007
One-year outcome, stratification	2.15	1.92	1.37 (1.16-1.63)	0.000
One-year outcome, matching with blanking period	2.00	1.73	1.30 (1.06-1.59)	0.012
On-treatment, matching	2.42	1.59	1.39 (1.08-1.78)	0.009
On-treatment, stratification	2.20	1.59	1.44 (1.17-1.78)	0.001
On-treatment, matching with blanking period	1.94	1.44	1.38 (1.04-1.82)	0.024
Five-year, matching	1.56	1.36	1.21 (1.03-1.43)	0.020
Five-year, stratification	1.56	1.41	1.23 (1.07-1.43)	0.005
Five-year, matching with blanking period	1.44	1.29	1.19 (1.00-1.42)	0.047
One-year outcome, without matching	2.15	1.92	1.10 (0.95-1.26)	0.189
On-treatment, without matching	2.20	1.59	1.17 (0.98-1.38)	0.085
Five-year, without matching	1.56	1.41	1.00 (0.88-1.12)	0.950



Outcome: Dyspnea

dyspnea

Analysis	Target (n= 10890) Event Rate, %/yr	Comparator (n= 36584) Event Rate, %/yr	HR (95% CI)	P value
One-year outcome, matching	9.76	9.32	1.15 (1.05-1.25)	0.002
One-year outcome, stratification	9.60	9.89	1.13 (1.04-1.23)	0.004
One-year outcome, matching with blanking period	8.20	8.10	1.15 (1.04-1.27)	0.006
On-treatment, matching	10.89	8.34	1.18 (1.06-1.32)	0.003
On-treatment, stratification	10.37	8.57	1.14 (1.03-1.25)	0.011
On-treatment, matching with blanking period	7.44	6.50	1.12 (0.97-1.29)	0.108
Five-year, matching	7.30	6.84	1.14 (1.05-1.23)	0.001
Five-year, stratification	7.29	7.11	1.11 (1.04-1.19)	0.003
Five-year, matching with blanking period	6.40	6.18	1.13 (1.04-1.23)	0.005
One-year outcome, without matching	9.60	9.89	0.94 (0.88-1.00)	0.061
On-treatment, without matching	10.37	8.57	0.95 (0.87-1.02)	0.176
Five-year, without matching	7.29	7.11	0.92 (0.87-0.97)	0.003



Interaction term analysis (NACE)

	HR	p	HRR	p
Female	0.98	0.12	1.27	<0.01
Elderly (65years)	0.95	0.21	1.15	0.04
Acute MI	1.02	0.52	0.85	0.39
Concomitant PPI use	1	0.91	0.91	0.72
High maintenance aspirin dosage	1.01	0.65	1.04	0.72

- Female and old patients might be more susceptible to the ticagrelor than male or younger patients.

Summary of the result

Event	Source	Ticagrelor		Clopidogrel		HR (95% CI)	*P* / calibrated *P*
		Subjects / Years	Incidence rate	Subjects / Years	Incidence rate		
NACE	HIRA-PCI	10 890 / 7 843	239.83	36 584 / 27 455	216.38	1.01 (0.95-1.07)	0.80 / 0.80
	IQVIA-Open Claims	6 762 / 5 452	128.38	22 707 / 18 838	151.82	0.97 (0.89-1.06)	0.71 / 0.53
	IQVIA-Hospital	4 002 / 2 446	122.21	12 004 / 7 974	116.38	1.03 (0.89-1.06)	0.80 / 0.72
Ischemic event	HIRA-PCI	10 890 / 7 894	224.32	36 584 / 27 635	201.3	1.00 (0.94-1.07)	0.94 / 0.78
	IQVIA-Open Claims	6 762 / 5 520	106.34	22 707 / 19 034	132.50	0.92 (0.83-1.01)	0.09 / 0.12
	IQVIA-Hospital	4 002 / 2 472	94.65	12 004 / 8 043	92.87	1.04 (0.88-1.23)	0.62 / 0.78
Bleeding event	HIRA-PCI	10 890 / 8 696	25.07	36 584 / 30 148	21.53	1.24 (1.04-1.47)	0.02 / 0.05
	IQVIA-Open Claims	6 762 / 5 812	26.15	22 707 / 20 416	25.62	1.24 (1.02-1.51)	0.03 / 0.05
	IQVIA-Hospital	4 002 / 2 551	28.61	12 004 / 8 339	24.22	0.96 (0.69-1.33)	0.82 / 0.74
Dyspnea	HIRA-PCI	10 890 / 816	97.71	36 584 / 2 707	93.3	1.15 (1.05-1.25)	<0.01 / 0.07
	IQVIA-Open Claims	6 762 / 4 760	367.58	22 707 / 17 189	320.42	1.21 (1.14-1.29)	<0.01 / <0.01
	IQVIA-Hospital	4 002 / 2 357	201.87	12 004 / 7 862	156.68	1.29 (1.14-1.46)	<0.01 / <0.01

Summary

- In this study, ticagrelor did not confer net clinical benefit on patients with PCI due to ACS in three databases from South Korea and US.
- The bleeding event was higher in ticagrelor group in the cohort from HIRA-PCI and IQVIA-Open Claims.
- The results for primary and secondary outcome were mostly consistent after PS matching or stratification
- The primary analysis (variable-ratio PS matching) will be replaced with 1-to-1 matching

Why is the efficacy of ticagrelor not evident in real world?: Stent might matter

Invasive procedure performed during study — no. (%)			
PCI	5978 (64.1)	5999 (64.6)	0.46
Stenting	5640 (60.4)	5649 (60.8)	0.61
With bare-metal stent only	3921 (42.0)	3892 (41.9)	0.87
With ≥1 drug-eluting stent	1719 (18.4)	1757 (18.9)	0.40
CABG	931 (10.0)	968 (10.4)	0.32

Wallentin et al., *NEJM*, 2009

- PLATO trial recruited patients from 2006 to 2008
- More patients underwent PCI with bare-metal stent only

Why is the efficacy of ticagrelor not evident in real world?: Stent might matter

Myocardial infarction*	328 (5·3%)	406 (6·6%)	0·80 (0·69–0·92)	0·0023
Cardiovascular death	221 (3·4%)	269 (4·3%)	0·82 (0·68–0·98)	0·0250
Stroke	75 (1·2%)	69 (1·1%)	1·08 (0·78–1·50)	0·6460
Ischaemic†	59 (0·9%)	59 (0·9%)	..	1·0000
Haemorrhagic†	12 (0·2%)	9 (0·1%)	..	0·6634
Unknown†	5 (0·07%)	1 (0·01%)	..	0·2187
All-cause death	252 (3·9%)	311 (5·0%)	0·81 (0·68–0·95)	0·0103
Stent thrombosis (n)	4949	4928	..	..
Definite	62 (1·3%)	97 (2·0%)	0·64 (0·46–0·88)	0·0054
Patients with a drug-eluting stent	17 (1·3%)	25 (1·8%)	0·69 (0·37–1·27)	0·2304
Patients with a bare-metal stent	45 (1·4%)	72 (2·1%)	0·62 (0·43–0·90)	0·0115
Definite or probable	104 (2·2%)	142 (3·0%)	0·73 (0·57–0·94)	0·0142
Patients with a drug-eluting stent	32 (2·3%)	36 (2·5%)	0·90 (0·56–1·45)	0·6581
Patients with a bare-metal stent	72 (2·2%)	106 (3·1%)	0·67 (0·50–0·91)	0·0092
Total (definite, probable, or possible)	132 (2·8%)	179 (3·8%)	0·73 (0·59–0·92)	0·0068
Patients with a drug-eluting stent	41 (3·1%)	53 (3·8%)	0·78 (0·52–1·17)	0·2349
Patients with a bare-metal stent	91 (2·7%)	126 (3·8%)	0·71 (0·55–0·94)	0·0142

- Stent thrombosis was not different between ticagrelor and clopidogrel when patients received drug-eluting stent

Cannon et al., *Lancet*, 2010

Why is the efficacy of ticagrelor not evident in real world?: Stent might matter

Stent generation				
• BMS	266 (4.0%)	37 (3.6%)	66 (3.8%)	0.765
• First-generation DES	69 (1.3%)	10 (1.1%)	24 (1.6%)	0.577
• Second-generation DES	4,990 (94.9%)	856 (95.6%)	1,439 (95.6%)	0.413

- Currently, most people underwent PCI with 2nd-generation drug eluting stent in Korea

prasugrel and ticagrelor showed similar rates of 1-year MACCE, but a higher rate of bleeding events, compared with clopidogrel in Korean AMI patients. Further studies are warranted to adapt Western guidelines on third-generation $P2Y_{12}$ inhibitors for East Asians.

Kang et al., *Thromb Haemost*, 2018

Study Protocol History

- V0.1 (2018.12.11) : Initial draft
- V0.2 (2019.2.16)
  - Revision of outcome definition
  - More covariates were added for estimation of propensity scores
- V0.3 (2019.3.3)
  - Statistical method of primary analysis was changed from 1-to-1 matching to variable ratio matching to avoid inferior covariate balance and bias reduction.
  - Sensitivity analyses, which includes only those who start the clopidogrel or ticagrelor from 2013 to 2017, and outcome with narrow definition were added.
- V1.0 (2019.5.9)
  - Revision of index event for the study population from drug initiation to PCI due to ACS
  - Positive control section was removed. Some negative controls, which have potential relationship with cardiovascular diseases or antiplatelet drug were removed.
  - Adding sensitivity analysis with 28-day blanking period to exclude duplicated coding for the outcomes
- V1.1 (2019.5.24)
  - Revision of target and comparator cohort:
    - Because there are databases do not have visit ID link between drug exposure and procedure, the primary inclusion criteria were revised to use time-based rule rather than same visit based rule.
    - Because many US patients take aspirin over-the-count, the constraint for the concomitant use of aspirin in target and comparator cohort was removed.

The lessons from this study

- Validation of phenotypes
- Usage of Git as the core of the OHDSI PLE study
  - Version control
  - Issue control
    - Bugs
    - Enhancement
- Recruiting study partners and listening their comments

Validation of phenotypes

- We cannot just believe in the accuracy of the phenotypes defined in ATLAS
- I reviewed the discharge note manually to evaluate the accuracy of the outcome definition

name	total_population_count	validated_population	positive	negative	inconclusive	PPV
broad ischemic stroke	233774					
ischemic stroke inpatient or ED	15268					
ischemic stroke primary condition	193236					
ischemic stroke (inpatient or ED) and primary condition	12986	214	92	42	80	0.686567
ischemic stroke (inpatient or ED) and primary condition and first event	10235	213	113	27	73	0.807143

https://github.com/OHDSI/PhenotypeLibrary/blob/master/ischemic%20stroke/extra/metadata.csv

Further development

- Should we impute death?

Drug Safety
https://doi.org/10.1007/s40264-019-00827-0

ORIGINAL RESEARCH ARTICLE

Identifying the DEAD: Development and Validation of a Patient-Level Model to Predict Death Status in Population-Level Claims Data

Jenna M. Reps[1] · Peter R. Rijnbeek[2] · Patrick B. Ryan[1]

Abstract

Introduction US claims data contain medical data on large heterogeneous populations and are excellent sources for medical research. Some claims data do not contain complete death records, limiting their use for mortality or mortality-related studies. A model to predict whether a patient died at the end of the follow-up time (referred to as the end of observation) is needed to enable mortality-related studies.

Objective The objective of this study was to develop a patient-level model to predict whether the end of observation was due to death in US claims data.

Methods We used a claims dataset with full death records, Optum© De-Identified Clinformatics® Data-Mart-Database—Date of Death mapped to the Observational Medical Outcome Partnership common data model, to develop a model that classifies the end of observations into death or non-death. A regularized logistic regression was trained using 88,514 predictors (recorded within the prior 365 or 30 days) and externally validated by applying the model to three US claims datasets.

Results Approximately 25 in 1000 end of observations in Optum are due to death. The Discriminating End of observation into Alive and Dead (DEAD) model obtained an area under the receiver operating characteristic curve of 0.986. When defining death as a predicted risk of > 0.5, only 2% of the end of observations were predicted to be due to death and the model obtained a sensitivity of 62% and a positive predictive value of 74.8%. The external validation showed the model was transportable, with area under the receiver operating characteristic curves ranging between 0.951 and 0.995 across the US claims databases.

Conclusions US claims data often lack complete death records. The DEAD model can be used to impute death at various sensitivity, specificity, or positive predictive values depending on the use of the model. The DEAD model can be readily applied to any observational healthcare database mapped to the Observational Medical Outcome Partnership common data model and is available from https://github.com/OHDSI/StudyProtocolSandbox/tree/master/DeadModel.


Thank You
for your time