Global collaborative research through OHDSI network:

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

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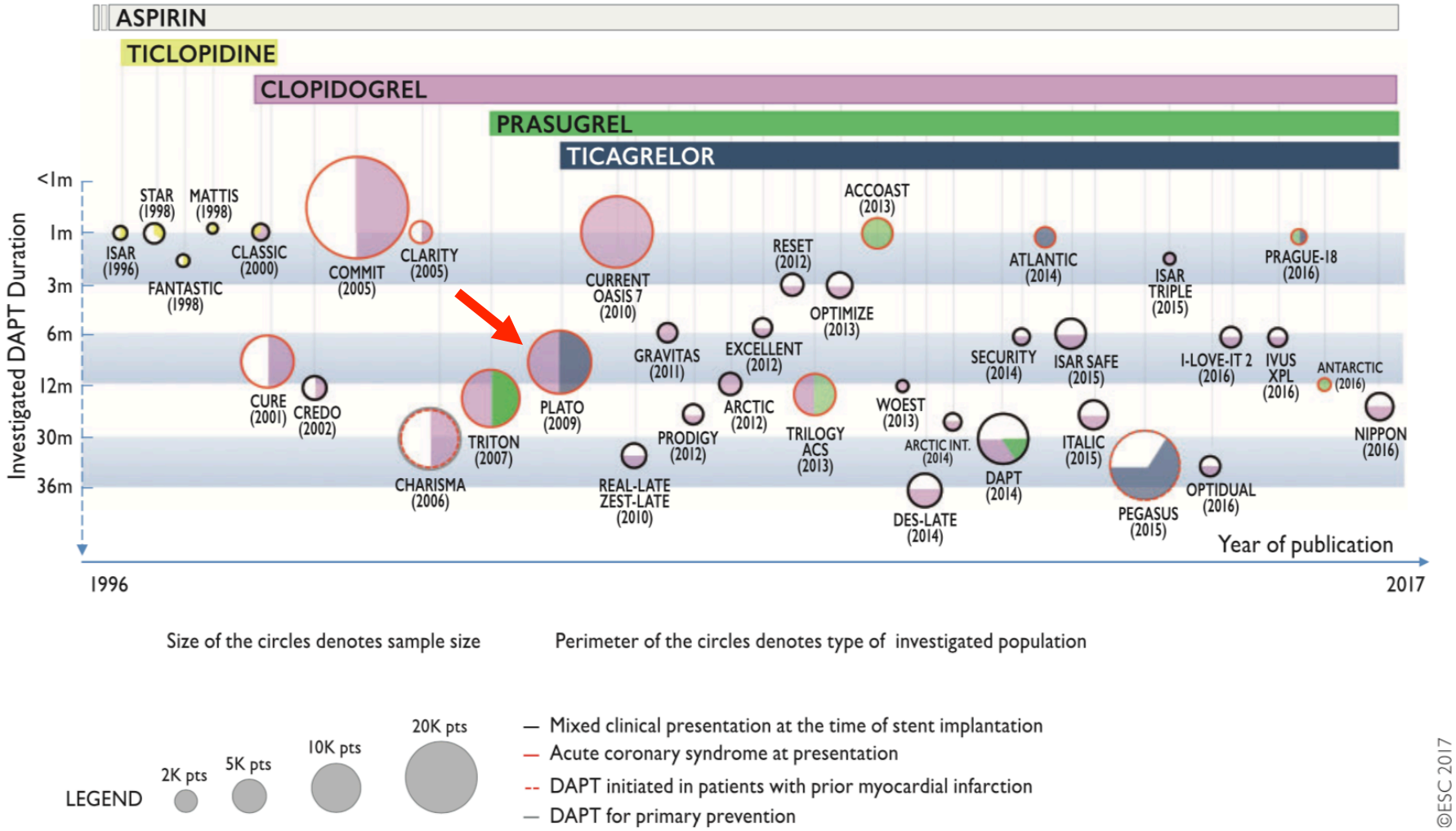
Disclosures

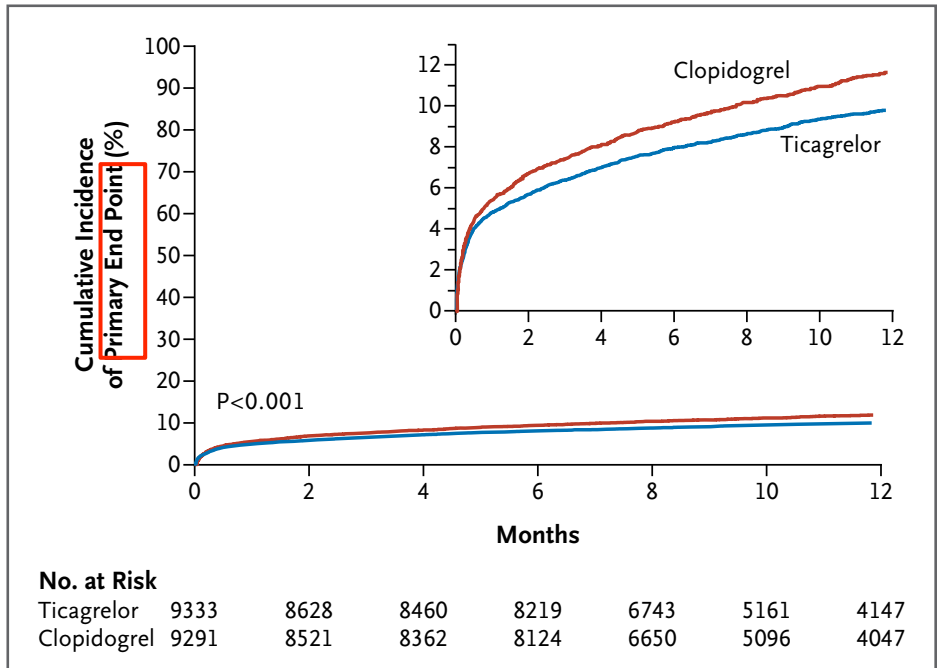
- Potential Conflict of interests
  - Dr. Ryan, Dr. Schuemie, and Ajit Londhe are employees of Janssen Research & Development, a subsidiary of Johnson & Johnson. Dr. Reich and Mr. Siapos are employees of IQVIA. Neither Janssen nor IQVIA had input in the design, execution, interpretation of results or decision to publish.
- Source of Funding
  - This work was supported by the Bio Industrial Strategic Technology Development Program (20001234) funded By the Ministry of Trade, Industry & Energy (MOTIE, Korea) and a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea [grant number: HI16C0992]

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



2017 ESC DAPT guideline

PLATelet inhibition and patient **O**utcomes (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

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

PLATO trial did not demonstrate superiority of Ticagrelor in North America and Asia

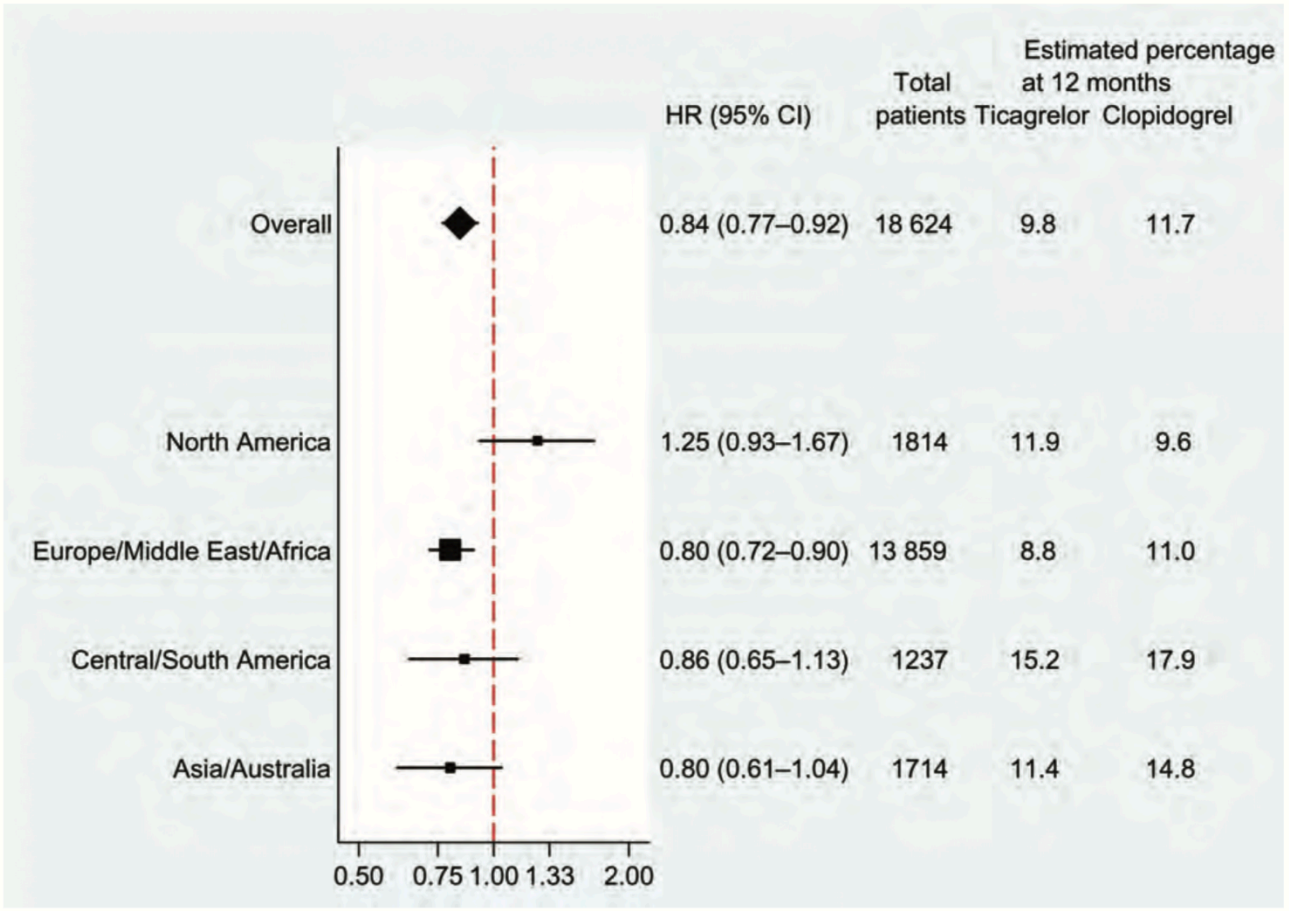


Figure 1 Estimated treatment effects by geographic region for the primary endpoint (CV death, MI, or stroke) of the PLATO trial (hazard ratios with 95% CIs, interaction *P*-value 0.05).

Pocock et al., *EHJ*, 2013

Objectives

- Compare risk of **net adverse clinical event** (**NACE**) between ticagrelor and clopidogrel in patients with Acute Coronary Syndrome (ACS) following percutaneous coronary intervention (PCI) 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

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

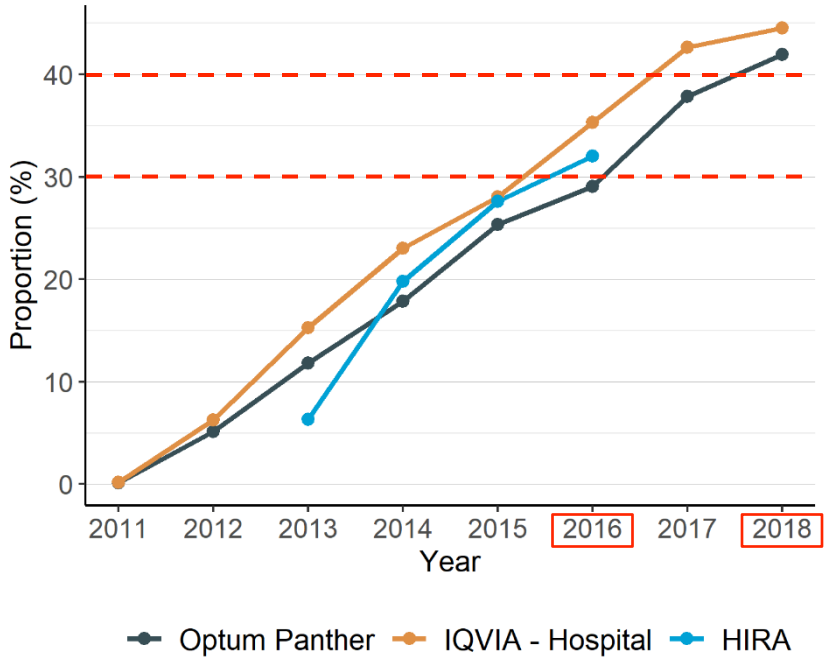
- Primary analysis
  - Time windows: From 1 day to 365 days after the index date
  - Unconditioned Cox regression after 1-to-1 PS matching
- Sensitivity analyses
  - Time windows
    - On-treatment
    - 5-year
  - Statistical analysis
    - 1-to-1 PS matching with blanking period of outcome (28 days)
    - Variable-ratio PS matching
    - PS stratification
- Assessment of systemic errors
  - 96 Negative controls

Method

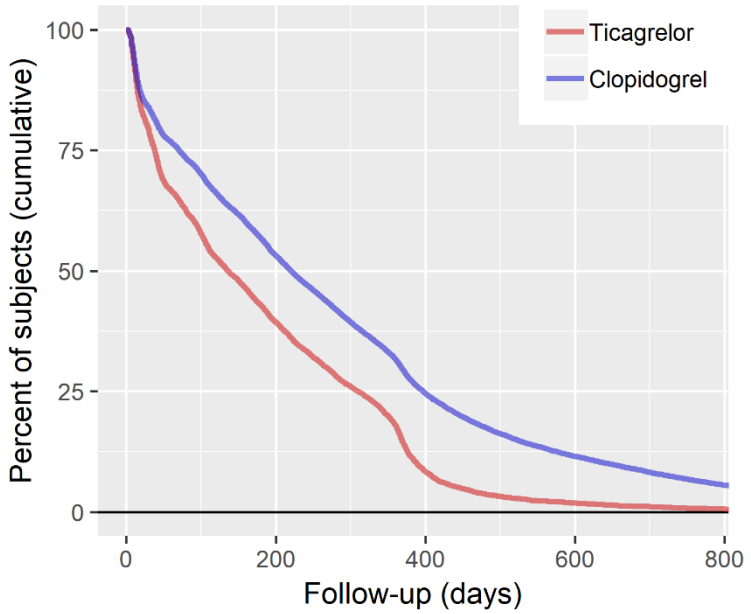
- Data source
  - **Optum Pan-Therapeutics (PanTher) : USA, EHR (86M)**
  - **IQVIA's Hospital data : USA, EHR (85M)**
  - **HIRA: South Korea, Nationwide Claim for patients undertaking PCI (0.4M)**

Proportion of ticagrelor across years and drug adherence in Korea

Proportion of Ticagrelor user among whole study population

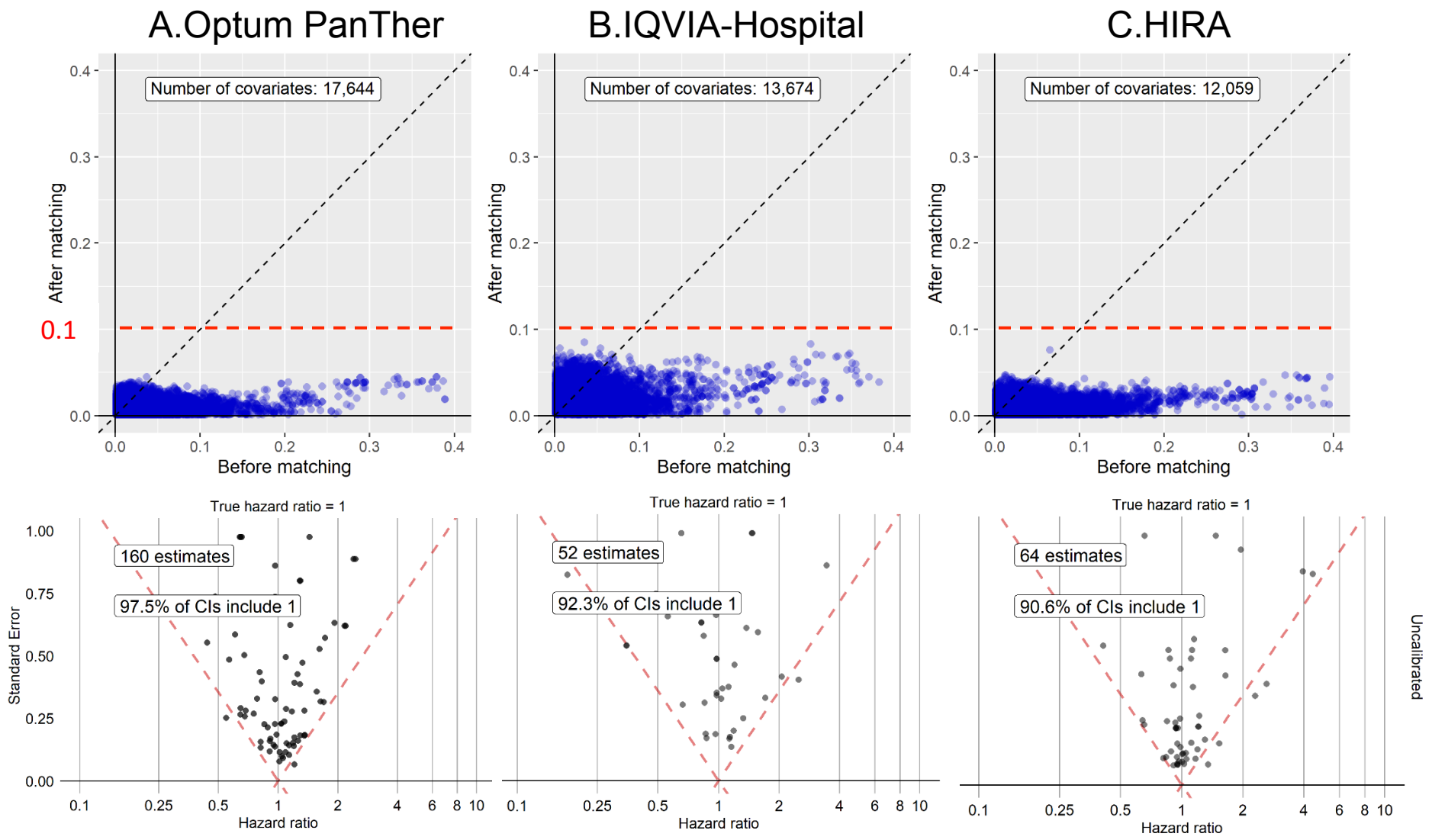


Days of continuation of ticagrelor and clopidogrel

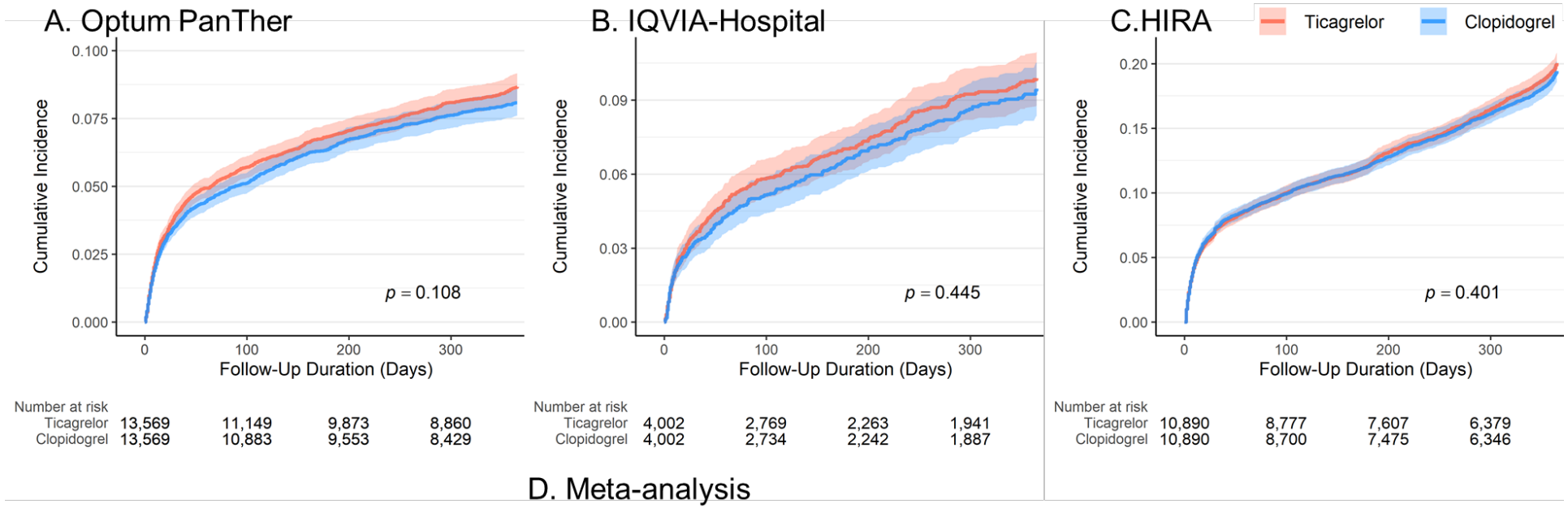


Days of Drug Continuation	1Q	Median	3Q
Ticagrelor	38	**132**	363
Clopidogrel	78	**232**	566

Balance before and after PS matching and Systematic error control

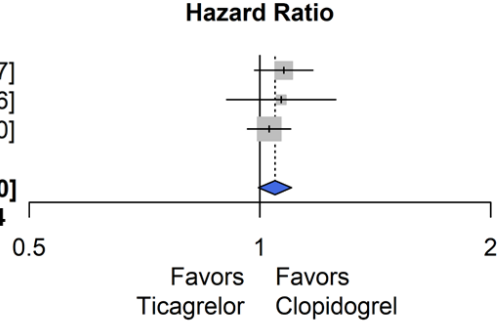


Primary endpoint: 1-year NACE

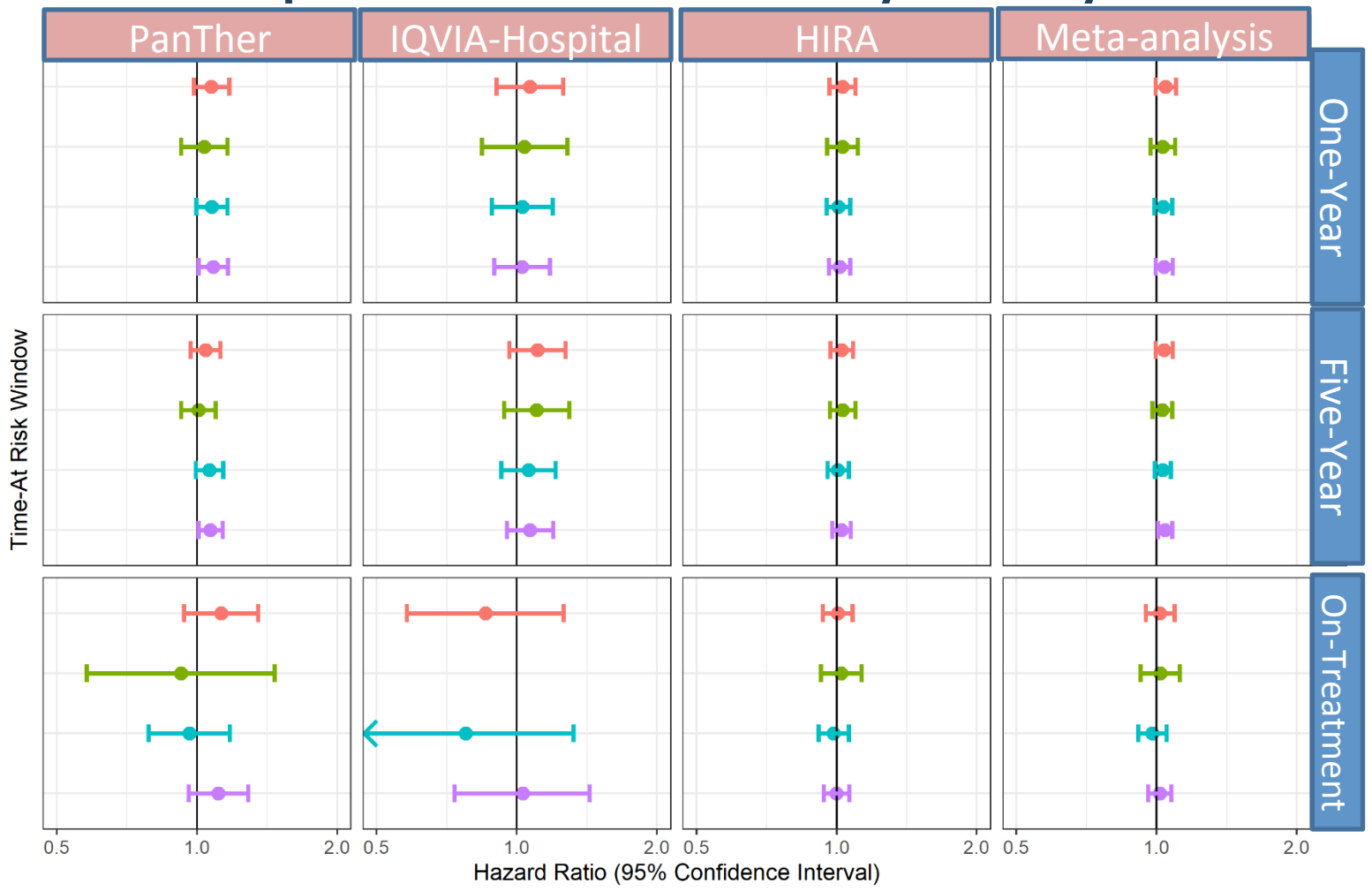


D. Meta-analysis

Source	Ticagrelor Total	Ticagrelor Event	Clopidogrel Total	Clopidogrel Event	HR	95% CI
Optum Panther	13,569	1,057	13,569	968	1.07	[0.98; 1.17]
IQVIA - Hospital	4,002	299	4,002	276	1.07	[0.90; 1.26]
HIRA	10,890	1,881	10,890	1,817	1.03	[0.96; 1.10]
Overall	**28,461**	**3,237**	**28,461**	**3,061**	**1.05**	**[1.00; 1.10]**
Heterogeneity: I^2 = 0.0%						***P* = 0.074**



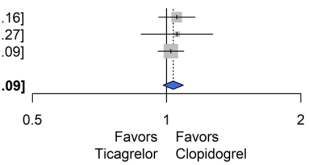
Consistency in the results of the primary endpoint in sensitivity analyses



A. Ischemic event

Source	Ticagrelor Total	Ticagrelor Event	Clopidogrel Total	Clopidogrel Event	HR	95% CI
Optum Panther	13,569	919	13,569	859	1.05	[0.96; 1.16]
IQVIA - Hospital	4,002	234	4,002	218	1.06	[0.88; 1.27]
HIRA	10,890	1,771	10,890	1,720	1.02	[0.96; 1.09]
Overall	**28,461**	**2,924**	**28,461**	**2,797**	**1.03**	**[0.98; 1.09]**

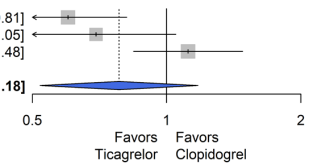
Heterogeneity: I^2 = 0.0%



B. Ischemic stroke

Source	Ticagrelor Total	Ticagrelor Event	Clopidogrel Total	Clopidogrel Event	HR	95% CI
Optum Panther	13,569	68	13,569	110	0.60	[0.44; 0.81]
IQVIA - Hospital	4,002	39	4,002	55	0.69	[0.46; 1.05]
HIRA	10,890	104	10,890	92	1.12	[0.84; 1.48]
Overall	**28,461**	**211**	**28,461**	**257**	**0.78**	**[0.52; 1.18]**

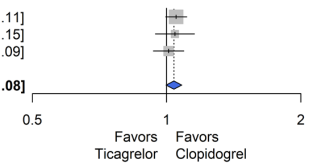
Heterogeneity: I^2 = 78.5%



C. Recurrent acute MI

Source	Ticagrelor Total	Ticagrelor Event	Clopidogrel Total	Clopidogrel Event	HR	95% CI
Optum Panther	13,569	2,685	13,569	2,547	1.05	[1.00; 1.11]
IQVIA - Hospital	4,002	783	4,002	746	1.04	[0.94; 1.15]
HIRA	10,890	1,270	10,890	1,249	1.01	[0.93; 1.09]
Overall	**28,461**	**4,738**	**28,461**	**4,542**	**1.04**	**[1.00; 1.08]**

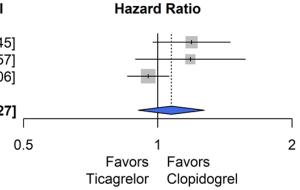
Heterogeneity: I^2 = 0.0%



D. Any revascularization

Source	Ticagrelor Total	Ticagrelor Event	Clopidogrel Total	Clopidogrel Event	HR	95% CI
Optum Panther	13,569	215	13,569	177	1.19	[0.98; 1.45]
IQVIA - Hospital	4,002	106	4,002	88	1.18	[0.89; 1.57]
HIRA	10,890	657	10,890	681	0.95	[0.86; 1.06]
Overall	**28,461**	**978**	**28,461**	**946**	**1.07**	**[0.90; 1.27]**

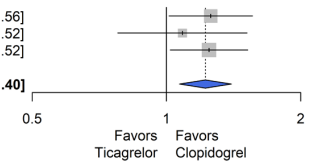
Heterogeneity: I^2 = 59.8%



E. Hemorrhagic event

Source	Ticagrelor Total	Ticagrelor Event	Clopidogrel Total	Clopidogrel Event	HR	95% CI
Optum Panther	13,569	190	13,569	147	1.26	[1.01; 1.56]
IQVIA - Hospital	4,002	73	4,002	66	1.09	[0.78; 1.52]
HIRA	10,890	218	10,890	173	1.25	[1.02; 1.52]
Overall	**28,461**	**481**	**28,461**	**386**	**1.22**	**[1.07; 1.40]**

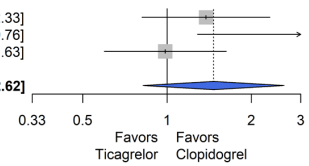
Heterogeneity: I^2 = 0.0%



F. Hemorrhagic stroke

Source	Ticagrelor Total	Ticagrelor Event	Clopidogrel Total	Clopidogrel Event	HR	95% CI
Optum Panther	13,569	34	13,569	24	1.38	[0.81; 2.33]
IQVIA - Hospital	4,002	18	4,002	5	3.54	[1.29; 9.76]
HIRA	10,890	31	10,890	31	0.99	[0.60; 1.63]
Overall	**28,461**	**83**	**28,461**	**60**	**1.47**	**[0.82; 2.62]**

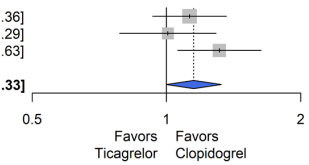
Heterogeneity: I^2 = 59.8%



G. GI bleeding

Source	Ticagrelor Total	Ticagrelor Event	Clopidogrel Total	Clopidogrel Event	HR	95% CI
Optum Panther	13,569	230	13,569	199	1.13	[0.93; 1.36]
IQVIA - Hospital	4,002	126	4,002	123	1.01	[0.79; 1.29]
HIRA	10,890	194	10,890	146	1.31	[1.06; 1.63]
Overall	**28,461**	**550**	**28,461**	**468**	**1.15**	**[1.00; 1.33]**

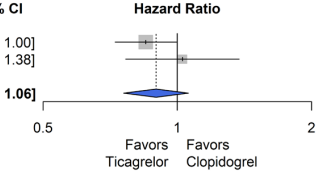
Heterogeneity: I^2 = 23.6%



H. Overall death

Source	Ticagrelor Total	Ticagrelor Event	Clopidogrel Total	Clopidogrel Event	HR	95% CI
Optum Panther	13,569	288	13,569	332	0.85	[0.73; 1.00]
IQVIA - Hospital	4,002	92	4,002	88	1.03	[0.77; 1.38]
Overall	**17,571**	**380**	**17,571**	**420**	**0.90**	**[0.76; 1.06]**

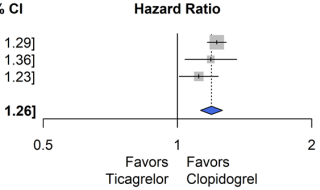
Heterogeneity: I^2 = 19.7%



I. Dyspnea

Source	Ticagrelor Total	Ticagrelor Event	Clopidogrel Total	Clopidogrel Event	HR	95% CI
Optum Panther	13,569	3,597	13,569	2,969	1.23	[1.17; 1.29]
IQVIA - Hospital	4,002	476	4,002	400	1.19	[1.04; 1.36]
HIRA	10,890	816	10,890	728	1.12	[1.01; 1.23]
Overall	**28,461**	**4,889**	**28,461**	**4,097**	**1.19**	**[1.13; 1.26]**

Heterogeneity: I^2 = 26.5%



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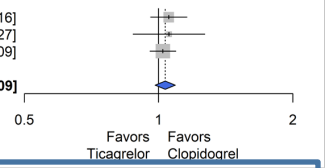

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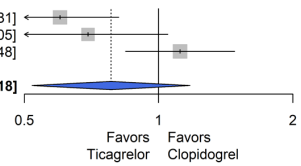

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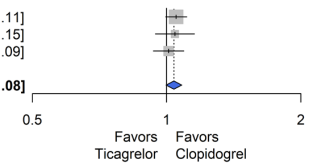

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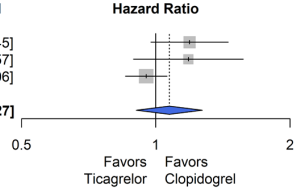
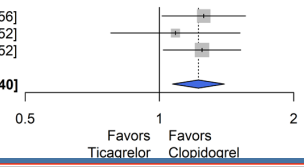


E. Hemorrhagic event

Source	Ticagrelor Total	Ticagrelor Event	Clopidogrel Total	Clopidogrel Event	HR	95% CI
Optum Panther	13,569	190	13,569	147	1.26	[1.01; 1.56]
IQVIA - Hospital	4,002	73	4,002	66	1.09	[0.78; 1.52]
HIRA	10,890	218	10,890	173	1.25	[1.02; 1.52]
Overall	**28,461**	**481**	**28,461**	**386**	**1.22**	**[1.07; 1.40]**

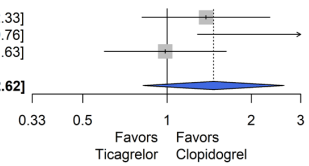
Heterogeneity: I^2 = 0.0%



F. Hemorrhagic stroke

Source	Ticagrelor Total	Ticagrelor Event	Clopidogrel Total	Clopidogrel Event	HR	95% CI
Optum Panther	13,569	34	13,569	24	1.38	[0.81; 2.33]
IQVIA - Hospital	4,002	18	4,002	5	3.54	[1.29; 9.76]
HIRA	10,890	31	10,890	31	0.99	[0.60; 1.63]
Overall	**28,461**	**83**	**28,461**	**60**	**1.47**	**[0.82; 2.62]**

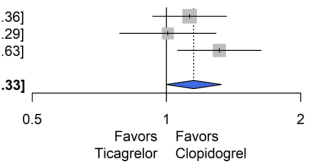
Heterogeneity: I^2 = 59.8%



G. GI bleeding

Source	Ticagrelor Total	Ticagrelor Event	Clopidogrel Total	Clopidogrel Event	HR	95% CI
Optum Panther	13,569	230	13,569	199	1.13	[0.93; 1.36]
IQVIA - Hospital	4,002	126	4,002	123	1.01	[0.79; 1.29]
HIRA	10,890	194	10,890	146	1.31	[1.06; 1.63]
Overall	**28,461**	**550**	**28,461**	**468**	**1.15**	**[1.00; 1.33]**

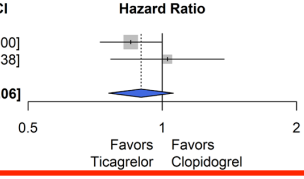
Heterogeneity: I^2 = 23.6%



H. Overall death

Source	Ticagrelor Total	Ticagrelor Event	Clopidogrel Total	Clopidogrel Event	HR	95% CI
Optum Panther	13,569	288	13,569	332	0.85	[0.73; 1.00]
IQVIA - Hospital	4,002	92	4,002	88	1.03	[0.77; 1.38]
Overall	**17,571**	**380**	**17,571**	**420**	**0.90**	**[0.76; 1.06]**

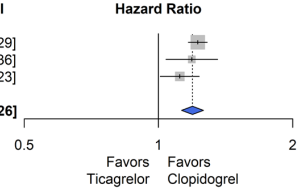
Heterogeneity: I^2 = 19.7%



I. Dyspnea

Source	Ticagrelor Total	Ticagrelor Event	Clopidogrel Total	Clopidogrel Event	HR	95% CI
Optum Panther	13,569	3,597	13,569	2,969	1.23	[1.17; 1.29]
IQVIA - Hospital	4,002	476	4,002	400	1.19	[1.04; 1.36]
HIRA	10,890	816	10,890	728	1.12	[1.01; 1.23]
Overall	**28,461**	**4,889**	**28,461**	**4,097**	**1.19**	**[1.13; 1.26]**

Heterogeneity: I^2 = 26.5%



Summary

- There appears to be **no significant difference** in **1-year NACE risk between ticagrelor and clopidogrel** users with ACS following PCI
- The findings for primary endpoint were consistent across sensitivity analyses
- **Ticagrelor** is associated with **higher risk of hemorrhagic events and dyspnea**.


Thank You
for your time