Clopidogrel vs. Ticagrelor: How to Use Common Data Model in Clinical Research

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Disclosure

- Dr. You is a CTO of PHI Digital Healthcare but does not hold any shares in the company.
- Dr. You is the incoming associate editor of Journal of American Journal of Cardiology (JACC); however, this presentation does not necessarily represent the views of JACC.

JAMA | Original Investigation

Association of Ticagrelor vs Clopidogrel With Net Adverse Clinical Events in Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention

Seng Chan You, MD, MS; Yeunsook Rho, PhD; Behnood Bikdeli, MD, MS; Jiwoo Kim, MS; Anastasios Siapos, MSc; James Weaver, MSc; Ajit Londhe, MPH; Jaehyeong Cho, BS; Jimyung Park, BS; Martijn Schuemie, PhD; Marc A. Suchard, MD, PhD; David Madigan, PhD; George Hripcsak, MD, MS; Aakriti Gupta, MD, MS; Christian G. Reich, MD; Patrick B. Ryan, PhD; Rae Woong Park, MD, PhD; Harlan M. Krumholz, MD, SM

IMPORTANCE Current guidelines recommend ticagrelor as the preferred P2Y12 platelet inhibitor for patients with acute coronary syndrome (ACS), primarily based on a single large randomized clinical trial. The benefits and risks associated with ticagrelor vs clopidogrel in routine practice merits attention.

OBJECTIVE To determine the association of ticagrelor vs clopidogrel with ischemic and hemorrhagic events in patients undergoing percutaneous coronary intervention (PCI) for ACS in clinical practice.

Editorial page 1

JAMA Patient Page page 1

Audio and Supplemental content

CME Quiz at jamacmelookup.com and CME Questions page 0

Seng Chan You[1]; Yeunsook Rho[2]; Jiwoo Kim2; Anastasios Siapos[3]; Ajit Londhe[4]; Jaehyeong Cho[5]; Jimyung Park[5]; Martijn Schuemie[4]; Marc A Suchard, MD, PhD[6,7]; David Madigan PhD8; George Hripcsak MD[9]; Christian G. Reich3; Patrick B. Ryan[4]; Rae Woong Park, MD, PhD[1,5]; Harlan M. Krumholz, MD[10]

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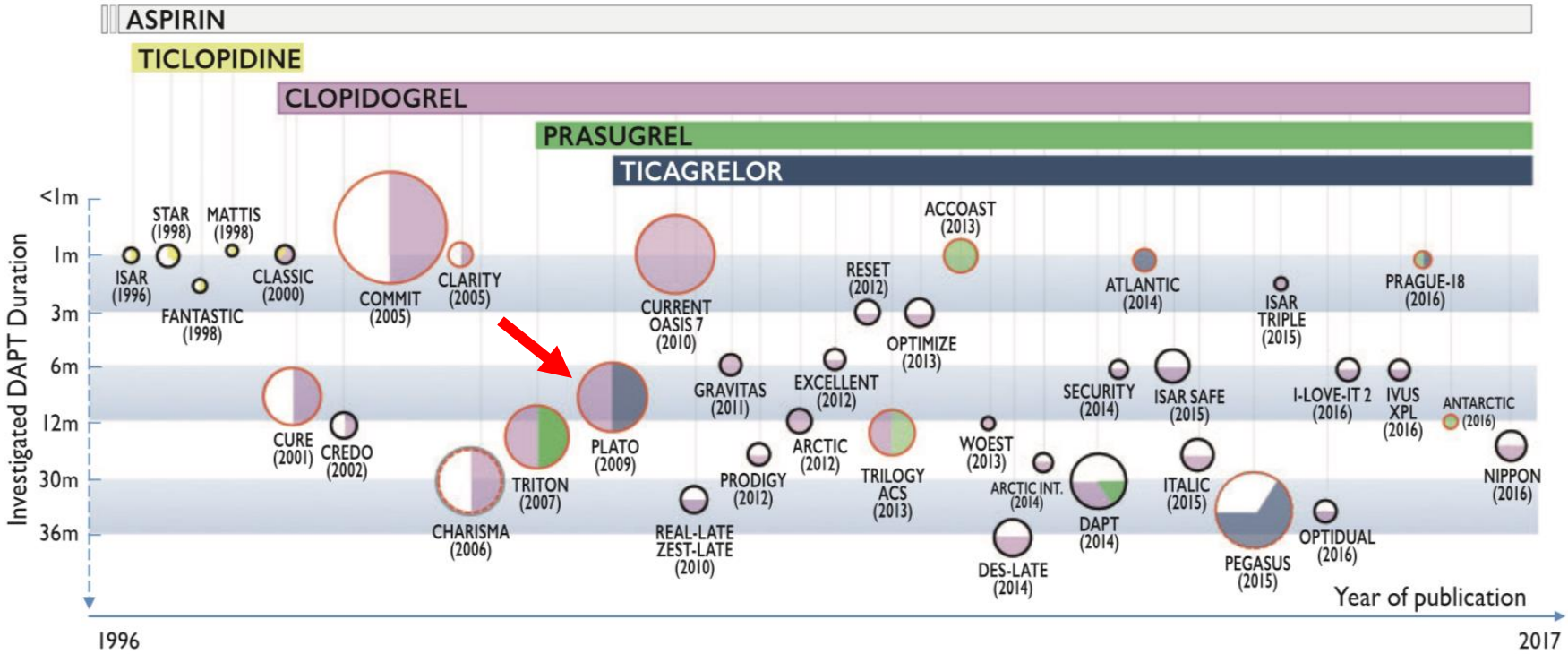
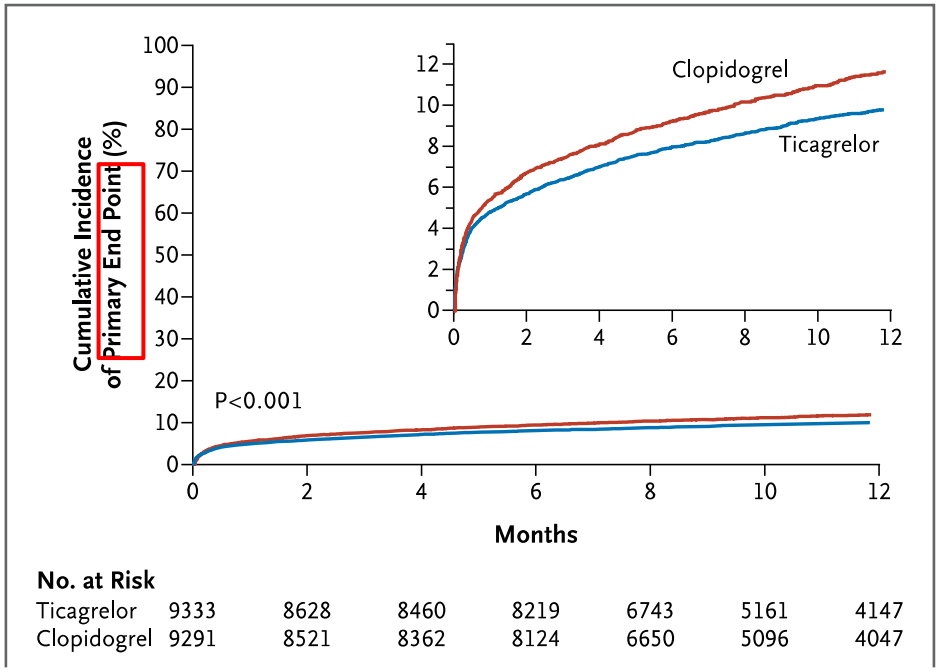
History of **D**ual **A**nti**P**latelet **T**herapy (DAPT) in patients with coronary artery disease



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

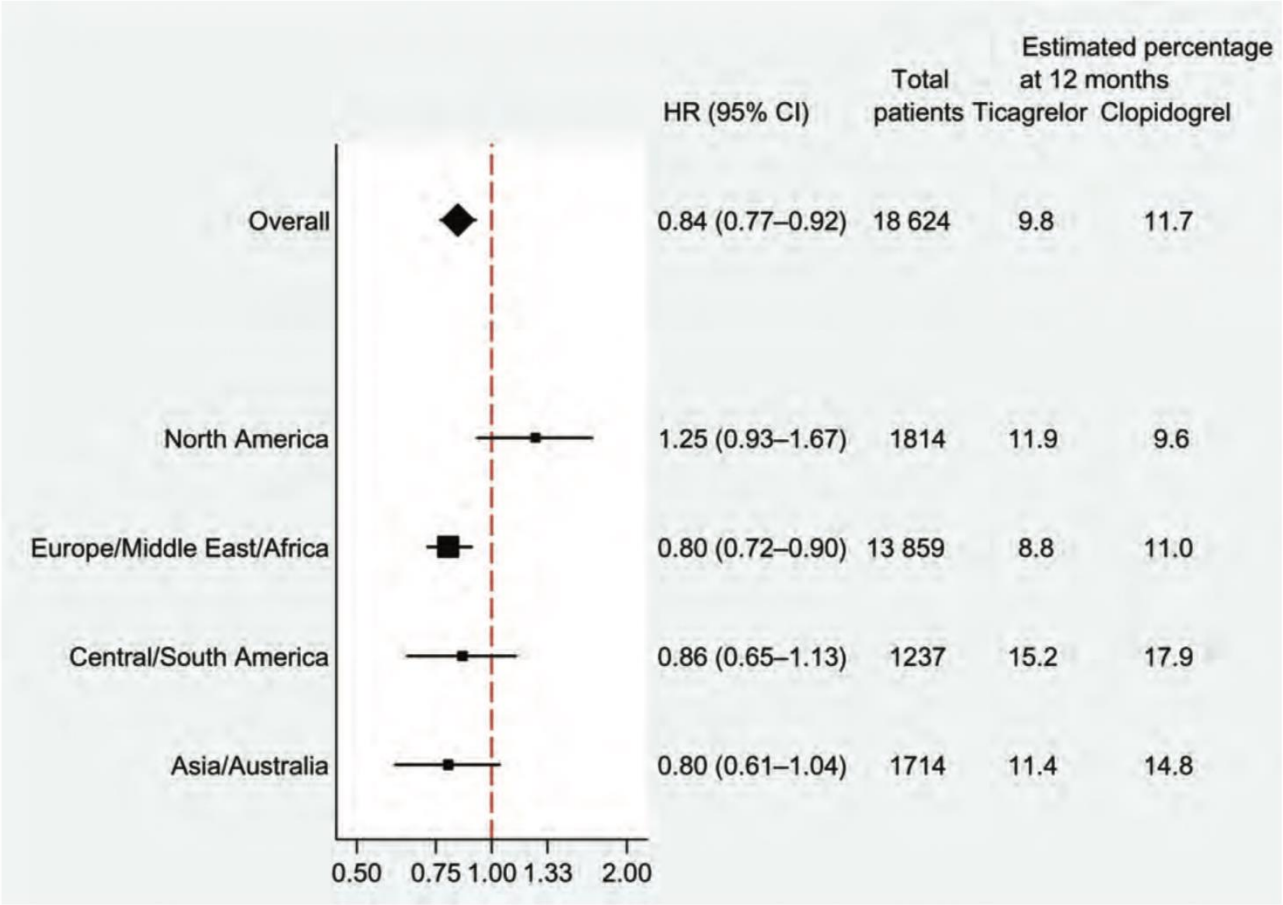
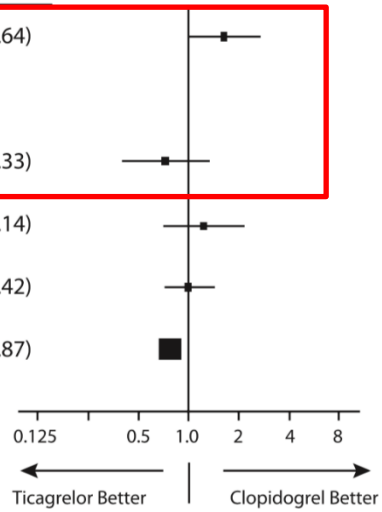


Figure 1 Estimated treatment effects by geographic region for the primary endpoint (CV death, MI, or stroke) of the PLATO trial (hazard ratios with 95% CIs, interaction *P*-value 0.05).

Pocock et al., *EHJ*, 2013

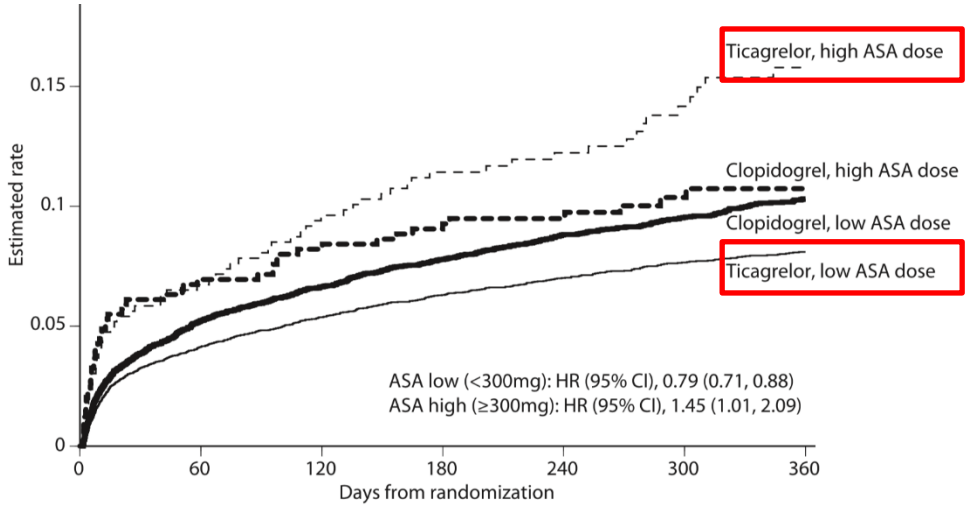
Aspirin dosing might matter

Region	ASA Dose (mg)	Ticagrelor N	Ticagrelor E	Clopidogrel N	Clopidogrel E	HR (95% CI)
US	≥300	324	40	352	27	1.62 (0.99, 2.64)
	>100–<300	22	2	16	2	*
	≤100	284	19	263	24	0.73 (0.40, 1.33)
Non-US	≥300	140	28	140	23	1.23 (0.71, 2.14)
	>100–<300	503	62	511	63	1.00 (0.71, 1.42)
	≤100	7449	546	7443	699	0.78 (0.69, 0.87)



- More patients in the United States (53.6%) than in the rest of the world (1.7%) took a median **aspirin dose >= 300 mg/d**

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**

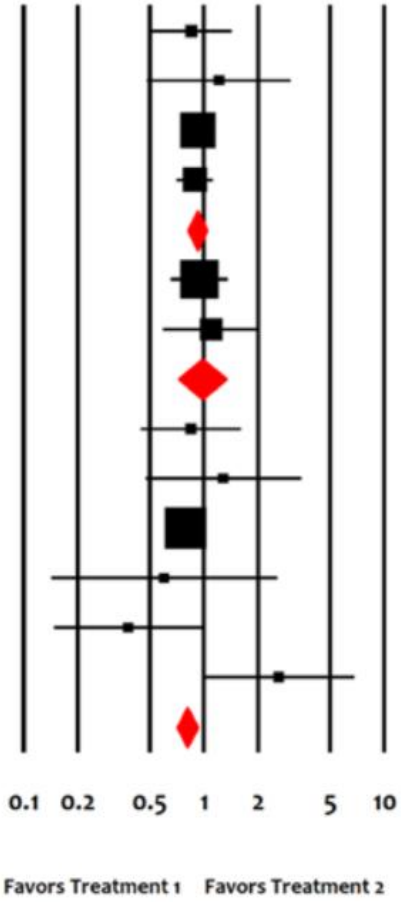


Mahaffey et al., *Circulation*, 2011

Superiority of ticagrelor over clopidogrel or prasugrel has never been replicated in RCTs

Group by Comparison	Trial, Year	Statistics for each study: Hazard ratio	Lower limit	Upper limit	p-Value
Prasugrel v Clopidogrel	The Elderly ACS II, 2018 [21]	0.85	0.51	1.41	0.53
	The PRASFIT-ACS, 2013 [19]	1.21	0.48	3.06	0.69
	TRILOGY ACS, 2012 [20]	0.93	0.80	1.09	0.36
	TRITON-TIMI 38, 2009 [10]	0.89	0.70	1.13	0.33
		0.92	0.81	1.04	0.18
Prasugrel v Ticagrelor	ISAR-REACT 5, 2019 [11]	0.94	0.66	1.34	0.74
	PRAGUE-18, 2017 [22]	1.10	0.59	2.06	0.77
		0.98	0.72	1.33	0.89
Ticagrelor v Clopidogrel	POPular AGE, 2019 [14]	0.85	0.44	1.61	0.61
	PHILO, 2015 [15]	1.28	0.48	3.43	0.62
	PLATO, 2009 [9]	0.79	0.69	0.91	0.00
	Tang et al., 2016 [17]	0.60	0.14	2.51	0.48
	Wang et al., 2016 [18]	0.38	0.15	0.97	0.04
	TICAKOREA, 2019 [16]	2.61	1.01	6.73	0.05
		0.80	0.71	0.92	0.00

CV mortality

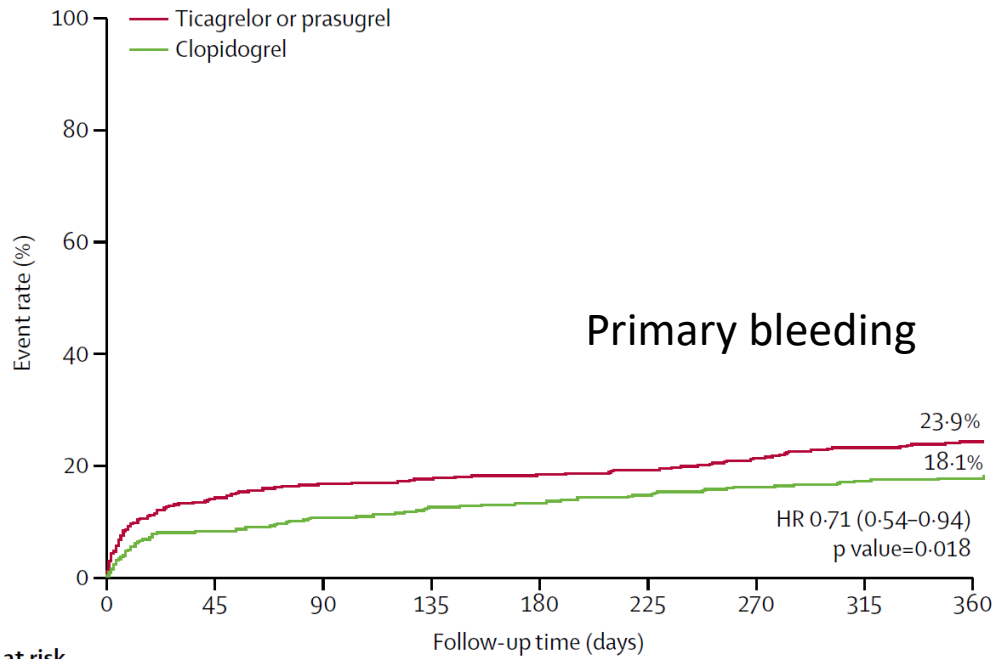


Serebruany, *CARDIOLOGY*, 2010

Superiority of ticagrelor over clopidogrel or prasugrel has never been replicated in RCTs

POPular-AGE

- Multi-center, open-label RCT (Netherland)
- Investigator-initiated
- Old(≥70yr) NSTE-ACS (N = 1002)



	Clopidogrel (n=500)	Ticagrelor (n=502)	ARD (95% CI)	HR (95% CI)	p value
Cardiovascular death, myocardial infarction, stroke	53 (11%)	57 (12%)	..	0·92 (0·64 to 1·34)	0·71
All-cause death	37 (7%)	34 (7%)	..	1·08 (0·68 to 1·72)	0·72
Cardiovascular death	18 (4%)	15 (3%)	..	1·19 (0·60 to 2·37)	0·60
Myocardial infarction	37 (8%)	37 (8%)	..	1·00 (0·63 to 1·57)	0·99

Gimbel et al., *Lancet*, 2020

Superiority of ticagrelor over clopidogrel or prasugrel has never been replicated in RCTs

PHILO

- Multi-national (Japan, Korea, Taiwan), Multi-center, double-blind RCT
- Sponsor-initiated
- ACS intended to PCI (N = 801)

Table 3. Adverse Events for All Patients

	Ticagrelor 90 mg b.i.d.	Clopidogrel 75 mg o.d.	HR for ticagrelor (95% CI)
Major bleeding (PLATO-defined)	40 (10.3)	26 (6.8)	1.54 (0.94–2.53)

Table 4. Primary and Secondary Efficacy Endpoints

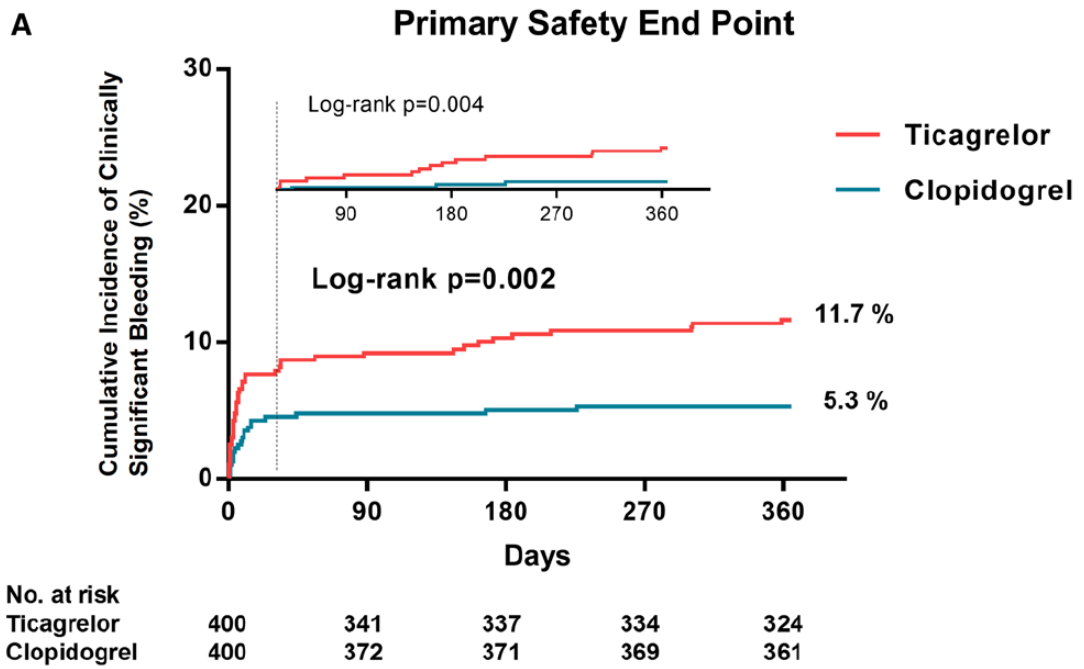
	Ticagrelor 90 mg b.i.d. (n=401)	Clopidogrel 75 mg o.d. (n=400)	HR (95% CI)
Primary			
Composite of CV death/MI (excluding silent MI)/stroke	36 (9.0)	25 (6.3)	1.47 (0.88–2.44)

Goto et al., *Cir J*, 2015

Superiority of ticagrelor over clopidogrel or prasugrel has never been replicated in RCTs

TICA-KOREA

- Multi-center, open-label RCT
- Investigator-initiated
- ACS patients (N=800)



End Point, n (%)*	Ticagrelor (N=400)	Clopidogrel (N=400)	Hazard Ratio for Ticagrelor Group (95% CI)	*P* Value†
Major adverse cardiovascular event				
Composite of cardiovascular death, myocardial infarction, or stroke	36 (9.2)	23 (5.8)	1.62 (0.96–2.74)	0.07

Park et al.,*Circulation*, 2019

Superiority of ticagrelor over clopidogrel has been challenged in an observational study

JAMA Internal Medicine | Original Investigation

Association of Ticagrelor vs Clopidogrel With Major Adverse Coronary Events in Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention

Ricky D. Turgeon, BSc(Pharm), PharmD; Sheri L
Matthew T. James, MD, PhD; Michelle M. Graha

- Data:
  Canadian Coronary Heart Disease Registry

Outcome	No. (%) Clopidogrel Group (n = 3711)	Ticagrelor Group (n = 3711)	*P* Value	HR (95% CI)
MACE	368 (9.9)	380 (10.2)	.64	1.00 (0.86-1.17)
All-cause death	54 (1.5)	61 (1.6)	.51	1.10 (0.75-1.61)
ACS	228 (6.1)	235 (6.3)	.74	1.02 (0.84-1.24)
Coronary revascularization	168 (4.5)	157 (4.2)	.53	0.86 (0.67-1.09)
PCI	121 (3.3)	114 (3.1)	.64	0.90 (0.68-1.19)
CABG	50 (1.3)	44 (1.2)	.53	0.74 (0.47-1.15)
Stent thrombosis	7 (0.2)	18 (0.5)	.03	2.57 (1.07-6.16)[a]
Composite of all-cause death, ACS, or stroke	290 (7.8)	299 (8.1)	.70	1.02 (0.86-1.21)
Ischemic stroke	18 (0.5)	17 (0.5)	.87	0.94 (0.48-1.86)
Major bleed	182 (4.9)	261 (7.0)	<.001	1.52 (1.24-1.87)[a]
Intracranial	3 (0.1)	3 (0.1)	>.99	1.00 (0.14-7.10)
Gastrointestinal	53 (1.4)	95 (2.6)	<.001	2.10 (1.44-3.06)[a]
Pulmonary	81 (2.2)	105 (2.8)	.08	1.32 (0.97-1.80)
Urologic	29 (0.8)	37 (1.0)	.32	1.32 (0.79-2.22)
Other	32 (0.9)	38 (1.0)	.47	1.29 (0.78-2.11)
Dyspnea	46 (1.2)	116 (3.1)	<.001	2.42 (1.70-3.45)[a]

East-Asian Paradox: One-Guideline-Fist-All Races?

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

Is newer, more expensive treatment always better?

JAMA Internal Medicine | Original Investigation

Trends in Platelet Adenosine Diphosphate $P2Y_{12}$ Receptor Inhibitor Use and Adherence Among Antiplatelet-Naive Patients After Percutaneous Coronary Intervention, 2008-2016

Elias J. Dayoub, MD, MPP; Matthew Seigerman, MD; Sony Tuteja, PharmD, MS; Taisei Kobayashi, MD; Daniel M. Kolansky, MD; Jay Giri, MD, MPH; Peter W. Groeneveld, MD, MS

IMPORTANCE Current guidelines recommend prasugrel hydrochloride and ticagrelor hydrochloride as preferred therapies for patients with acute coronary syndrome (ACS) treated with percutaneous coronary intervention (PCI). However, it is not well known how frequently these newer agents are being used in clinical practice or how adherence varies among the platelet adenosine diphosphate $P2Y_{12}$ receptor ($P2Y_{12}$) inhibitors.

Invited Commentary
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Newer, more expensive treatment may aggravate inequity in health

CONCLUSIONS AND RELEVANCE Between 2008 and 2016, increased use of prasugrel and ticagrelor was accompanied by increased nonfilling of prescriptions for $P2Y_{12}$ inhibitors within 30 days of discharge. Prasugrel and ticagrelor had higher patient costs and lower adherence in the year following PCI compared with clopidogrel. The introduction of newer, more expensive $P2Y_{12}$ inhibitors was associated with lower adherence to these therapies.

An important policy ramification of our findings is that the introduction of new pharmacotherapies may have exacerbated socioeconomic health disparities. This phenomenon has

Dayoub et al., *JAMA Internal Medicine*, 2018

ence of P2Y12 inhibitors after PCI. Furthermore, it has exacerbated socioeconomic health disparities because adherence disproportionately affects the most economically disadvantaged patients, even among the insured population in the United States.[7]

You et al., *JAMA*, 2020

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.

OHDSI (Observational Health Data Sciences and Informatics)

- International collaborative consortium applying open-source data analytic solutions based on **OMOP-Common Data Model** (CDM) to a large network of health databases across the world

OHDSI Collaborators:

- >100 researchers in academia, industry and government
- >10 countries

OHDSI Data Network:

- >40 databases standardized to OMOP common data model
- >500 million patients

https://www.ohdsi.org/

Mission, Vision, and Values of OHDSI

- Our Mission

To improve health by empowering a community to collaboratively generate the evidence that promotes better health decisions and better care.

- Our Vision

A world in which observational research produces a comprehensive understanding of health and disease.

Objectives of OHDSI

- **Innovation**: Observational research is a field which will benefit greatly from disruptive thinking. We actively seek and encourage fresh methodological approaches in our work.
- **Reproducibility**: Accurate, reproducible, and well-calibrated evidence is necessary for health improvement.
- **Openness**: We strive to make all our community's proceeds open and publicly accessible, including the methods, tools and the evidence that we generate.
- **Community**: Everyone is welcome to actively participate in OHDSI, whether you are a patient, a health professional, a researcher, or someone who simply believes in our cause.
- **Collaboration**: We work collectively to prioritize and address the real world needs of our community's participants.
- **Beneficence**: We seek to protect the rights of individuals and organizations within our community at all times.

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革新: 観察研究は破壊的思考から大いに恩恵を受ける分野です。私たちは研究において新しい方法論的アプローチを積極的に求め、奨励しています
- **Reproducibility**: Accurate, reproducible, and well-calibrated evidence is necessary for health improvement.
再現性: 正確で再現可能で、よく校正された証拠は健康改善に必要です。
- **Openness**: We strive to make all our community's proceeds open and publicly accessible, including the methods, tools and the evidence that we generate.
開放性: 私たちは、生成する方法、ツール、および証拠を含む、コミュニティの成果をすべて公開し、公にアクセス可能にすることを目指しています。
- **Community**: Everyone is welcome to actively participate in OHDSI, whether you are a patient, a health professional, a researcher, or someone who simply believes in our cause.
コミュニティ: 患者、医療専門家、研究者、または単に私たちの理念を信じる人であれ、誰でもOHDSIに積極的に参加することを歓迎します。
- **Collaboration**: We work collectively to prioritize and address the real world needs of our community's participants.
協働: 私たちは集団として、コミュニティの参加者の現実のニーズを優先し、対処するために協力します。
- **Beneficence**: We seek to protect the rights of individuals and organizations within our community at all times.
恩恵: 私たちは常にコミュニティ内の個人および組織の権利を保護することを目指しています。

1. This remains a hopelessly flawed observational design using claims database data, to compare efficacy and safety. Despite all the care taken by the authors, some critical information is missing such as the duration of actual therapy with each agent, or the frequency of drug interruption or switching after initiation, adherence to therapy (in an observational type of study, this is a huge issue). Patients were entered in the study at the time of PCI as opposed to the time of ACS which is how ticagrelor was tested in the PLATO trial and is recommended for use. Censoring events after initiation of therapy and starting at the time of PCI creates a well-documented bias. Patients were eligible up to 7 days after ACS, a period during which patients are at the highest risk of ischemic events which were not accounted for. This is particularly

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assess the robustness of the findings.

We appreciate these comments and that the Editors have expressed interest in giving us the opportunity to reply to these points.

The Reviewer is correct that we are missing some information that would be helpful in characterizing the patients. We did have access to an immense amount of data on each patient and used this information to the greatest extent possible. Per this comment, we added the information for types of ACS in the baseline characteristics tables.

We emphasize that our approach represents a significant advance in observational research, with a series of publications in leading peer-reviewed methodological journals describing the components of our approach along with their validation. Our balance of thousands of variables coupled with concrete demonstration of balance on every single one of them we believe not only addresses measured confounding but also can begin to address unmeasured confounding. Our use of 96 falsification endpoints goes far beyond current recommendations to include one or a few controls; a large number are needed to make claims of robustness. We published our entire protocol and all our source code before running our trial, to prohibit opportunity for p-hacking. We ran across databases inside and outside the US and looked for consistency. And we ran large sets of sensitivity analyses to assess the robustness of the findings.

Strength in methodology

- Reproducibility
- Pre-specification of statistical analytic plan
- Active Comparator, New-User cohort design
- Using three large databases from US and Korea
- Large-scale propensity score model
- 96 Negative controls (Falsification endpoint)
- Large set of sensitivity analyses
  - 1:1 PS matching / variable-ratio PS matching / PS stratification
  - Diverse time windows
  - Narrow outcome definitions

Strength in methodology

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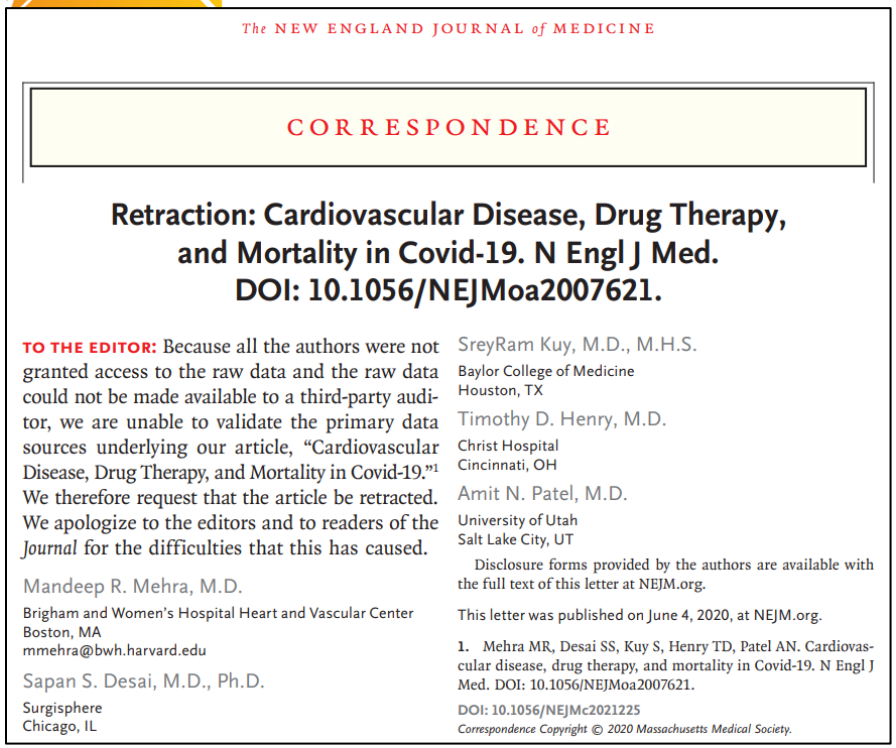
  - Narrow outcome definitions

Crisis of reproducibility: Lancet, NEJM retract controversial COVID-19 studies based on Surgisphere data



The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Retraction: Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2007621.

TO THE EDITOR: Because all the authors were not granted access to the raw data and the raw data could not be made available to a third-party auditor, we are unable to validate the primary data sources underlying our article, "Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19."[1] We therefore request that the article be retracted. We apologize to the editors and to readers of the *Journal* for the difficulties that this has caused.

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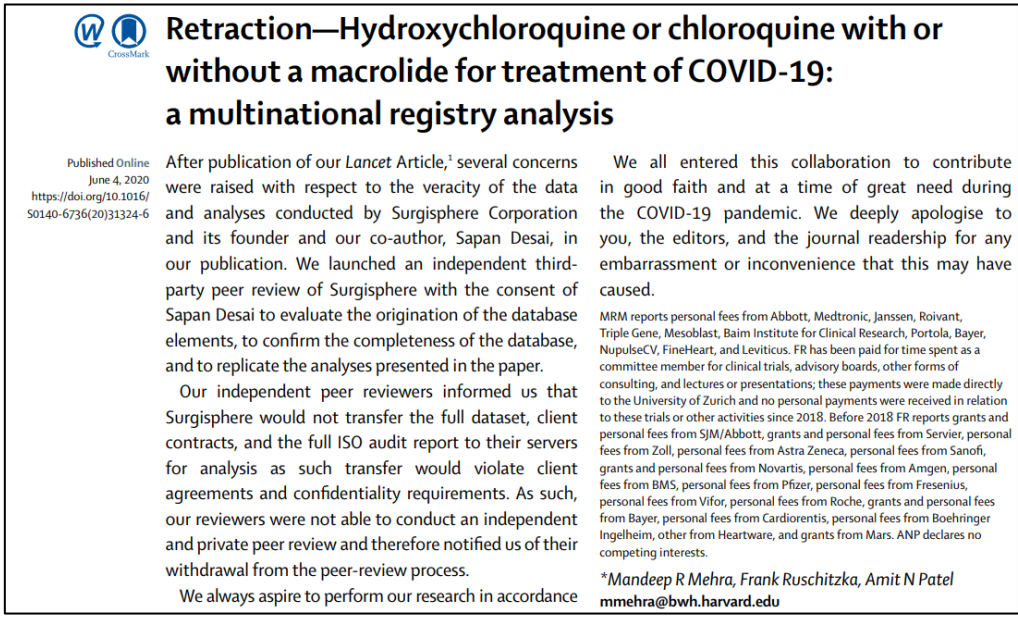
Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

This letter was published on June 4, 2020, at NEJM.org.

1. Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular disease, drug therapy, and mortality in Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2007621.

DOI: 10.1056/NEJMc2021225



Retraction—Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis

Published Online June 4, 2020 https://doi.org/10.1016/S0140-6736(20)31324-6

After publication of our *Lancet* Article,[1] several concerns were raised with respect to the veracity of the data and analyses conducted by Surgisphere Corporation and its founder and our co-author, Sapan Desai, in our publication. We launched an independent third-party peer review of Surgisphere with the consent of Sapan Desai to evaluate the origination of the database elements, to confirm the completeness of the database, and to replicate the analyses presented in the paper.

Our independent peer reviewers informed us that Surgisphere would not transfer the full dataset, client contracts, and the full ISO audit report to their servers for analysis as such transfer would violate client agreements and confidentiality requirements. As such, our reviewers were not able to conduct an independent and private peer review and therefore notified us of their withdrawal from the peer-review process.

We always aspire to perform our research in accordance

We all entered this collaboration to contribute in good faith and at a time of great need during the COVID-19 pandemic. We deeply apologise to you, the editors, and the journal readership for any embarrassment or inconvenience that this may have caused.

MRM reports personal fees from Abbott, Medtronic, Janssen, Roivant, Triple Gene, Mesoblast, Baim Institute for Clinical Research, Portola, Bayer, NupulseCV, FineHeart, and Leviticus. FR has been paid for time spent as a committee member for clinical trials, advisory boards, other forms of consulting, and lectures or presentations; these payments were made directly to the University of Zurich and no personal payments were received in relation to these trials or other activities since 2018. Before 2018 FR reports grants and personal fees from SJM/Abbott, grants and personal fees from Servier, personal fees from Zoll, personal fees from Astra Zeneca, personal fees from Sanofi, grants and personal fees from Novartis, personal fees from Amgen, personal fees from BMS, personal fees from Pfizer, personal fees from Fresenius, personal fees from Vifor, personal fees from Roche, grants and personal fees from Bayer, personal fees from Cardiorentis, personal fees from Boehringer Ingelheim, other from Heartware, and grants from Mars. ANP declares no competing interests.

**Mandeep R Mehra, Frank Ruschitzka, Amit N Patel*
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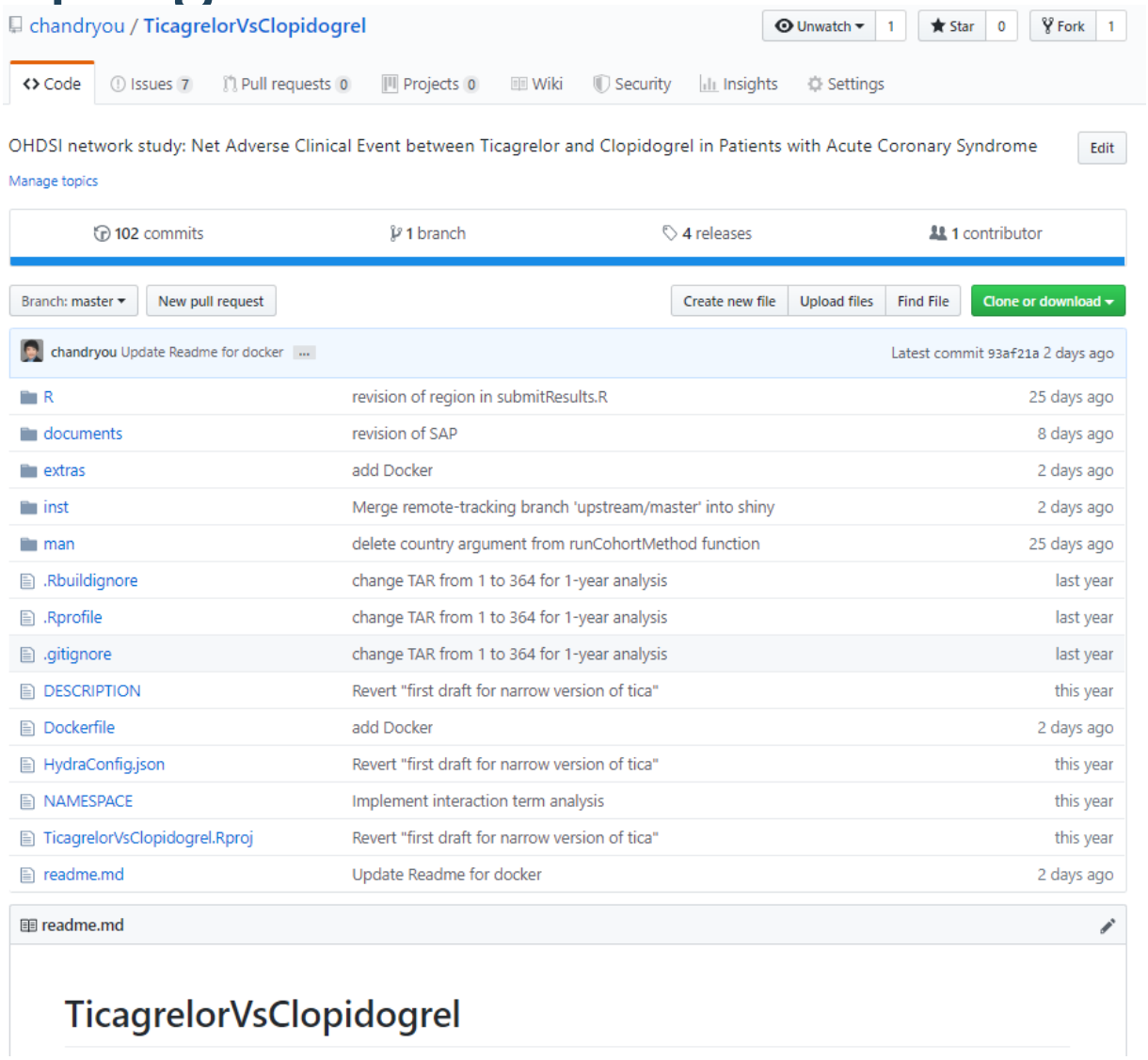
Prof. Chambers(Chair of Center for Open Science and Member of the UK Reproducibility Network Steering Group) said:

"The failure to resolve such basic concerns about the data during the course of normal peer review raises serious questions about the standard of editing at the Lancet and NEJM. **If these journals take issues of reproducibility and scientific integrity as seriously as they claim**, then they should forthwith submit themselves and their internal review processes to an independent inquiry."

End-to-end executable statistical program is available at GitHub

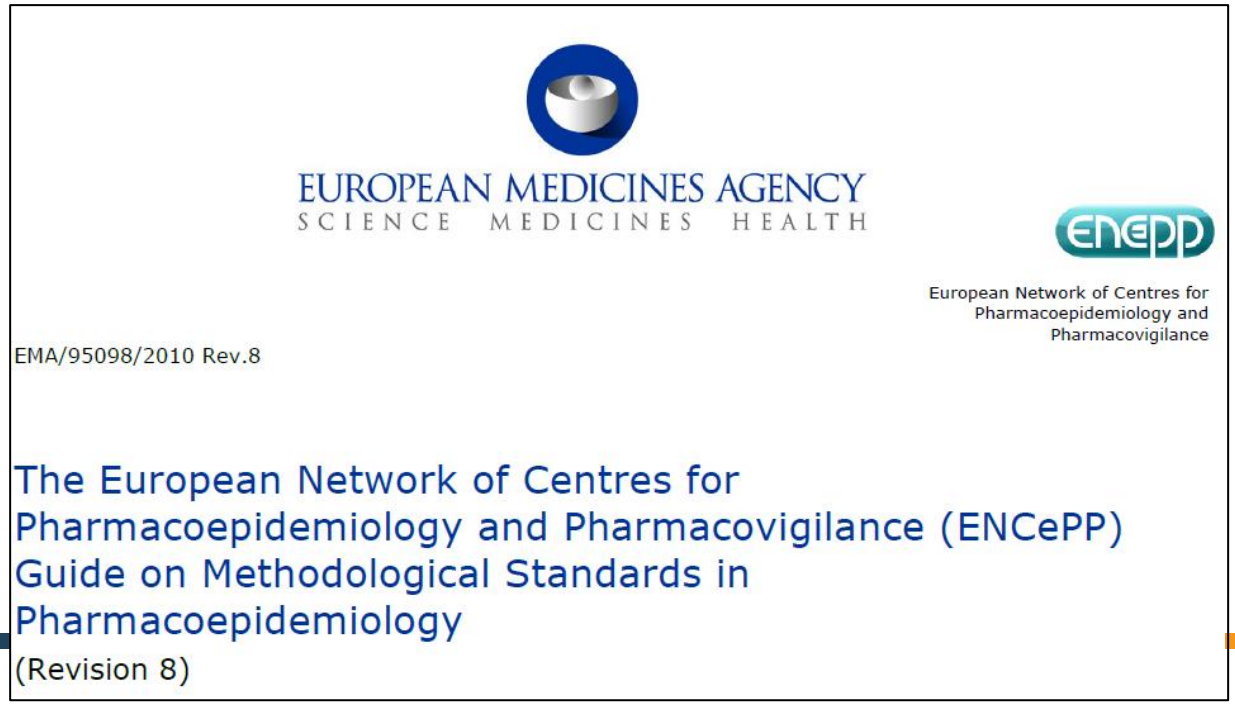


https://github.com/ohdsi-studies/TicagrelorVsClopidogrel

The response of European Medicines Agency (EMA) on OHDSI study

Renin–angiotensin system blockers and susceptibility to COVID-19: an international, open science, cohort analysis

Daniel R Morales, Mitchell M Conover, Seng Chan You, Nicole Pratt, Kristin Kostka, Talita Duarte-Salles, Sergio Fernández-Bertolín, Maria Aragón, Scott L DuVall, Kristine Lynch, Thomas Falconer, Kees van Bochove, Cynthia Sung, Michael E Matheny, Christophe G Lambert, Fredrik Nyberg, Thamir M Alshammari, Andrew E Williams, Rae Woong Park, James Weaver, Anthony G Sena, Martijn J Schuemie, Peter R Rijnbeek, Ross D Williams, Jennifer C E Lane, Albert Prats-Uribe, Lin Zhang, Carlos Areia, Harlan M Krumholz, Daniel Prieto-Alhambra, Patrick B Ryan, George Hripcsak, Marc A Suchard



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

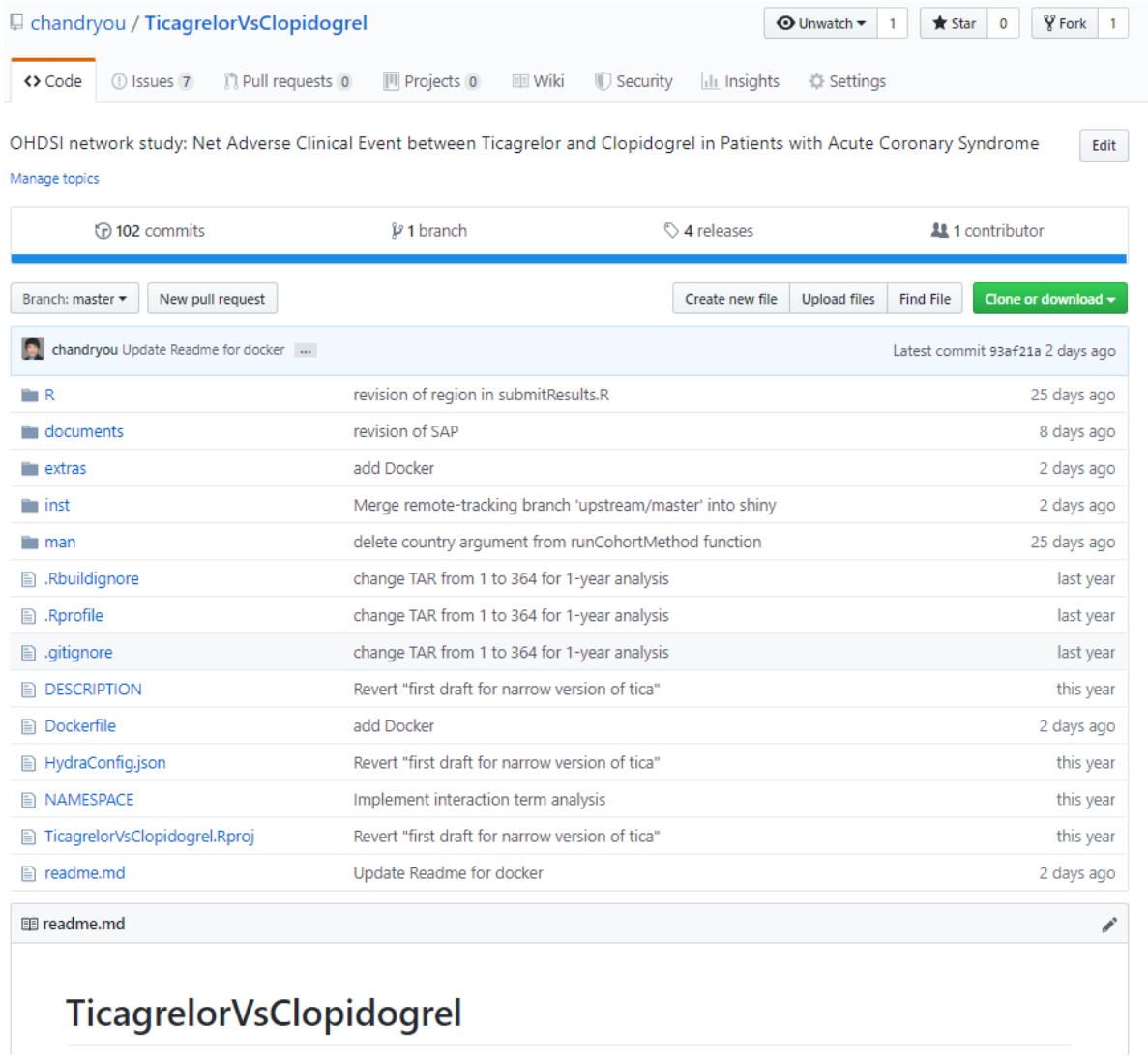
European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

EMA/95098/2010 Rev.8

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology

(Revision 8)

My research experience using personal GitHub repository



https://github.com/chandryou/TicagrelorVsClopidogrel

Strength in methodology

- Reproducibility
- **Pre-specification of statistical analytic plan**
- Active Comparator, New-User cohort design
- Using three large databases from US and Korea
- Large-scale propensity score model
- 96 Negative controls (Falsification endpoint)
- Large set of sensitivity analyses
  - 1:1 PS matching / variable-ratio PS matching / PS stratification
  - Diverse time windows
  - Narrow outcome definitions

Method: Statistical Analytic Plan

4 Amendments and Updates

0.1	11 December 2018	SC You	Initial draft
0.2	16 February 2019	SC You	Revision of definition in outcome definition More covariates were added for estimation of propensity score.
0.3	3 March 2019	SC You	Revision of the manuscript of statistical analytic plan. 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.
1.0	9 May 2019	SC You	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 of 28 days to exclude duplicated coding for the outcomes
1.1	24 May 2019	SCYou	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 was 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.
1.2	3 September 2019	SCYou	Changing primary analysis from variable ratio PS matching to unconditioned one-to-one PS matching
1.3	28 October 2019	SCYou	Revising the query to extract individual secondary outcome cohorts. The documented definitions were also changed to add 'first time' criteria to stroke and GI bleeding outcomes. Adding NACE or mortality outcome as a secondary outcome Adding variable-ratio matching and PS stratification with blanking period analysis

11 Appendix: Concept Set Definitions

1. Percutaneous coronary intervention

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
4006788	Percutaneous transluminal coronary angioplasty	Procedure	SNOMED	NO	YES	NO
4020653	Percutaneous transluminal balloon angioplasty of bypass graft of coronary artery	Procedure	SNOMED	NO	YES	NO
4139198	Percutaneous transluminal thrombolysis of artery	Procedure	SNOMED	NO	YES	NO
4175997	Percutaneous transluminal thrombolysis and reconstruction of artery	Procedure	SNOMED	NO	YES	NO
4178148	Placement of stent in anterior descending branch of left coronary artery	Procedure	SNOMED	NO	YES	NO
4181025	Percutaneous transluminal balloon angioplasty with insertion of stent into coronary artery	Procedure	SNOMED	NO	YES	NO
2000064	Percutaneous transluminal coronary angioplasty [PTCA]	Procedure	ICD9Proc	NO	YES	NO
2001505	Insertion of non-drug-eluting coronary artery stent(s)	Procedure	ICD9Proc	NO	NO	NO
2001506	Insertion of drug-eluting coronary artery stent(s)	Procedure	ICD9Proc	NO	NO	NO
4171077	Fluoroscopic angiography of coronary artery and insertion of stent	Procedure	SNOMED	NO	NO	NO

2. Ticagrelor

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
40241186	Ticagrelor	Drug	RxNorm	NO	YES	NO

3. Clopidogrel

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
1322184	clopidogrel	Drug	RxNorm	NO	YES	NO

https://github.com/ohdsi-studies/TicagrelorVsClopidogrel/tree/master/documents

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)

eMethod 3. Individual outcome definitions

For each outcome, we developed an operational phenotype definition to determine if observational data could in fact support evaluation of the outcome. Where possible, concept sets originated with published code lists (eg ICD-9-CM and ICD-10). We developed definition of outcome cohorts and query to extract them using ATLAS, the OHDSI open-source platform (https://github.com/OHDSI/atlas). We executed these definitions on EHR data of Korean tertiary hospital to validate the definitions. Positive predictive values were estimated by a physician's manual chart review of discharge notes.

Supplementary Table. Outcome definition

Outcome	Logical description	ICD-9-CM	ICD-10	CPT4	PPV, % (n)
Acute myocardial infarction	Record of acute myocardial infarction during an inpatient or ER visit	410;410.01;410.02;410.1;410.11;410.12;410.2;410.21;410.22;410.3;410.31;410.32;410.4;410.41;410.42;410.5;410.51;410.52;410.7;410.71;410.72;410.8;410.81;410.82;410.9;410.91;410.92	I21.0;I21.1;I21.2;I21.3;I21.4;I21.9		83.8 (83/99)
Revascularization	Record of PCI or CABG during an inpatient or ER visit			566;567;33510;33511;33512;33513;33514;33516;33517;33518;33519;33521;33522;33523;33533;33534;33535;33536;33542;33545;33548;33572;33621;35506;35694;92920;92921;92924;92925;92928;92929;92933;92934;92937;92938;92941;92943;92944;1006199;1006200;1006208;1006216;1006217	100.0 (30/30)
Ischemic stroke	Earliest record of ischemic stroke during an inpatient or ER visit	346.6;346.6;346.61;346.62;346.63;433.01;433.11;433.21;433.31;433.81;433.91;434.01;434.11;434.91;997.02	I63.9;I63.8;I63.6;I63.5;I63.4;I63.3;I63.2;I63.1;I63.0;I63;G46.7;G46.6;G46.5;F01.3;F01.1;F01.0		72.9 (70/96)

Strength in methodology

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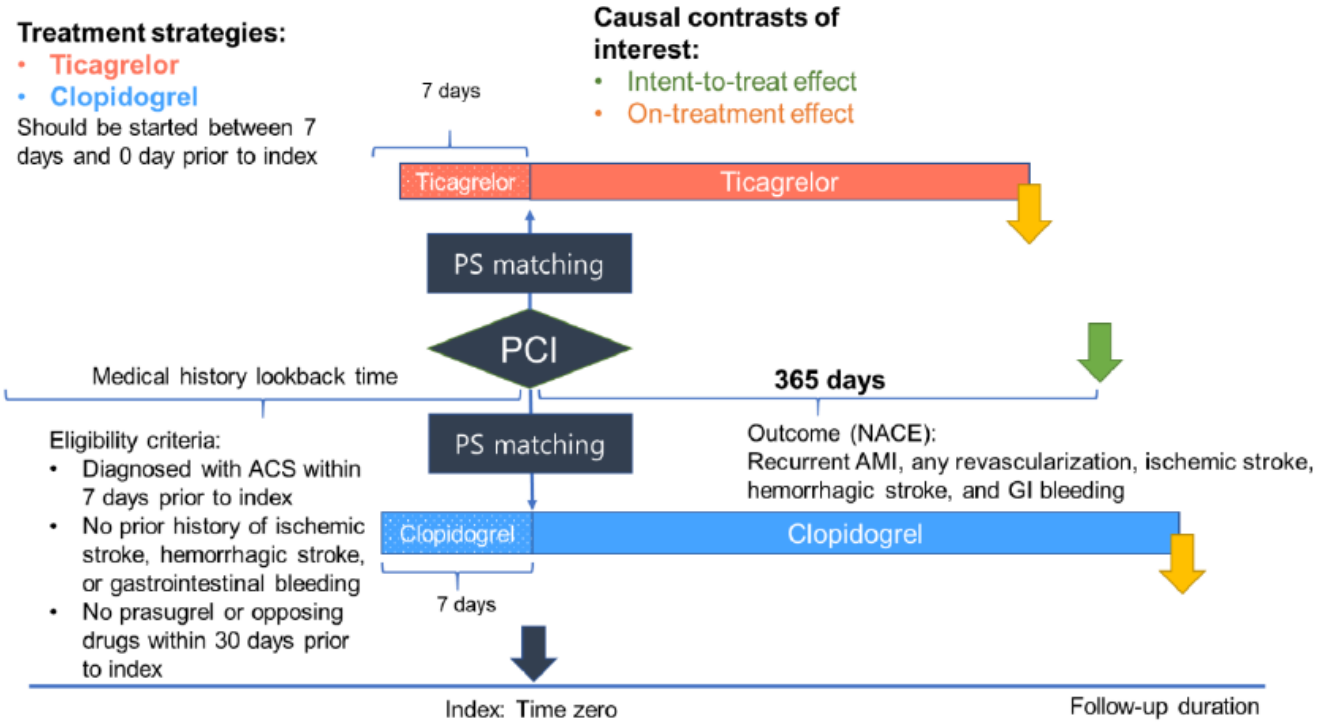
Method: Study Population

- 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



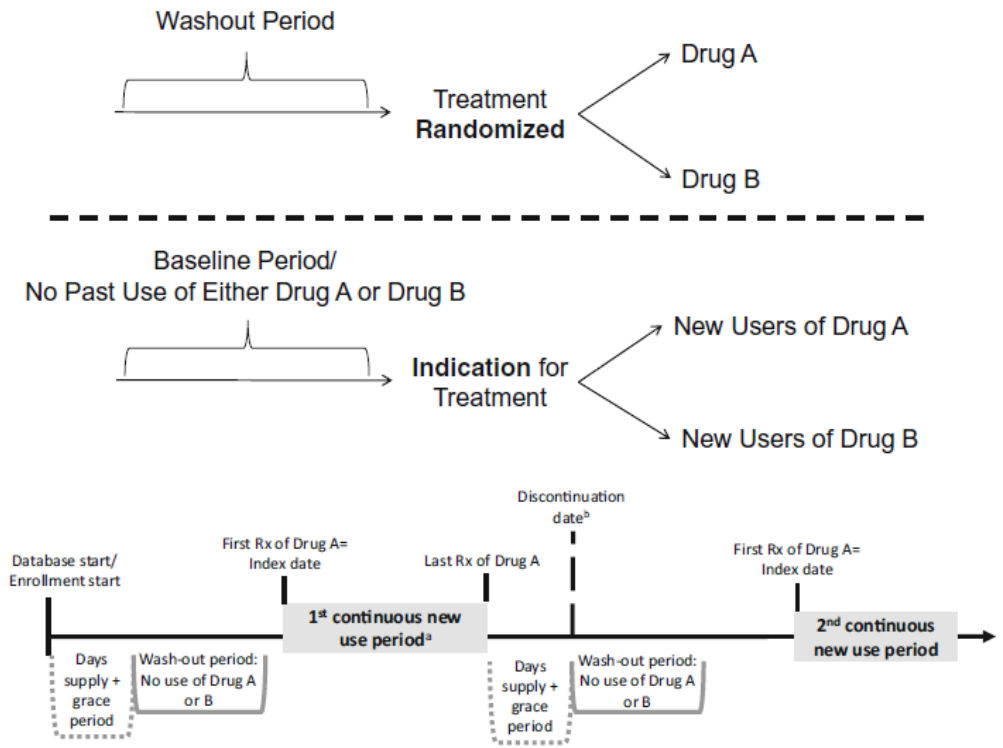
https://github.com/ohdsi-studies/TicagrelorVsClopidogrel

Curr Epidemiol Rep (2015) 2:221–228
DOI 10.1007/s40471-015-0053-5

PHARMACOEPIDEMIOLOGY (T STÜRMER, SECTION EDITOR)

The Active Comparator, New User Study Design in Pharmacoepidemiology: Historical Foundations and Contemporary Application

Jennifer L. Lund[1] · David B. Richardson[1] · Til Stürmer[1]



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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)**

eMethod 1. Data source

Optum® de-identified Electronic Health Record dataset

Optum electronic health record (EHR) is an aggregated and de-identified electronic health record repository from US health systems. The medical record data includes clinical information, inclusive of prescriptions as prescribed and administered, lab results, vital signs, body measurements, diagnoses, procedures, and information derived from clinical notes using natural language processing (NLP). The data from November 20, 2011 to March 3, 2019 were used for this study. New England Institutional Review Board (IRB) and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.

IQVIA-Hospital Charge Data Master

Anonymized patient level data are sourced from hospital charge data masters and collected from resource management software within short-term, acute-care and non-federal hospitals in the United States. Data covers over 86 million patients, 122,000 providers, 230 specialties and more than 530 million unique visits from 2007 to 2018. The data from November 14, 2011 to June 29, 2018 were used for this study. A retrospective database study on this de-identified data is deemed not human subject research. Approval is provided for OHDSI community studies.

HIRA

HIRA claims data include healthcare utilization information of the entire population of South Korea, consisting of diagnosis, procedure, drug, medical material, healthcare resource, etc. The current study is conducted based on the converted CDM data[1] of the patients who received PCIs between 2007 and 2016. The CDM data include 462,486 patients with more than 155 million claims information. The data from February 28, 2013 to December 31, 2016 were used for this study. The present study was approved by the Scientific and Ethical Advisory Board of the HIRA (Project number: 2017-034-002)

https://github.com/ohdsi-studies/TicagrelorVsClopidogrel

Strength in methodology

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  - Narrow outcome definitions

VIEWPOINT

Prespecified Falsification End Points

Can They Validate True Observational Associations?

Vinay Prasad, MD

Anupam B. Jena, MD, PhD

As observational studies have increased in number—fueled by a boom in electronic recordkeeping and the ease with which observational analyses of large databases can be performed—so too have failures to confirm initial research findings.[1] Several solutions to the problem of incorrect observational results have been suggested,[1,2] emphasizing the importance of a record not only of significant findings but of all analyses conducted.[2]

An important and increasingly familiar type of observa-

mur fractures and 716 atypical fractures.[5] This analysis demonstrated an increased risk of atypical fractures associated with bisphosphonate use and was validated by another large population-based study.

However, analyses in large data sets are not necessarily correct simply because they are larger. Control groups might not eliminate potential confounders, or many varying definitions of exposure to the agent may be tested (alternative thresholds for dose or duration of a drug)—a form of multiple-hypothesis testing.[2] Just as small, true signals can be identified by these analyses, so too can small, erroneous associations. For instance, several observational studies have found an association between use of PPIs and development of pneumonia, and it is biologically plausible that elevated

Negative controls

Epidemiology. 2010 May ; 21(3): 383–388. doi:10.1097/EDE.0b013e3181d61eeb.

Negative Controls: A Tool for Detecting Confounding and Bias in Observational Studies

Marc Lipsitch[1,2,3], **Eric Tchetgen Tchetgen**[1,3,4], and **Ted Cohen**[5,1,3]

[1] Department of Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115

[2] Department of Immunology and Infectious Diseases, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115

[3] Center for Communicable Disease Dynamics, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115

[4] Department of Biostatistics, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115

[5] Division of Global Health Equity, Brigham and Women's Hospital, Boston MA 02115

> The formal definition of a negative control outcome is one that shares the same potential sources of bias with the primary outcome but cannot plausibly be related to the treatment of interest

Arnold & Ecrumen. "Negative Control Outcomes: A Tool to Detect Bias in Randomized Trials." *JAMA*

Knowledge database for drug adverse events

Accuracy of an automated knowledge base for identifying drug adverse reactions

E.A. Voss [a,b,c,*], R.D. Boyce [d,c], P.B. Ryan [a,e,c], J. van der Lei [b,c], P.R. Rijnbeek [b,c], M.J. Schuemie [a,c]

[a] Epidemiolo
[b] Erasmus U
[c] Observatio
[d] University
[e] Columbia U

Table 1
Description of LAERTES sources.

Data source	Description
FAERS Proportional Reporting Ratio (FAERS PRR)	Data files from the FDA Adverse Event Reporting System (FAERS) Latest Quarterly Data Files website [44] were used to generate evidence. The FAERS drug/outcome pairs were standardized from free text drug names and outcomes in MedDRA Preferred Terms to RxNorm OMOP concepts and MedDRA condition OMOP concepts. In addition, the MedDRA condition concepts were mapped to SNOMED-CT concepts based on the OMOP mappings available in the OMOP Vocabulary. The ETL process also included logic to remove duplicate adverse drug event reports [22]. The PRR metric generated by work by Van Puijenbroek et al. [21]. The FAERS data currently available in LAERTES covers Q4 2004 through Q4 2014
FAERS Report Count (FAERS Report Count)	Similar to FAERS PRR except a count of reports is provided for each drug-condition pair
Medline MeSH Clinical Trials (MEDLINE MeSH ClinTrial)	Looking for ADRs in MeSH terms for clinical trials in Medline. The process to identify ADRs was leveraged from Avillach et al. [23]. The Avillach method using MeSH tagged publications from Medline looked for adverse drug reactions based on the co-occurrence of a drug and an adverse event on the same citation. The source of the data used was directly from the National Library of Medicine and gathered from 1946 until September 2015
Medline MeSH Case Reports (MEDLINE MeSH CR)	Similar to MEDLINE_MeSH_ClinTrial except for case reports
Medline Mesh Other (MEDLINE MeSH Other)	Similar to MEDLINE_MeSH_ClinTrial except for it reports on things other than clinical trials or case reports in Medline (i.e. Meta-Analysis, Comparative Study, Multicenter Study, or Journal Article)
Medline SemMedDB Clinical Trials (MEDLINE SemMedDB ClinTrial)	For clinical trials, provides MeSH tagged drug-HOI clinical trial abstracts from PubMed that look for associations such as: causes, affects, associated with, complicates, or disrupts [24]. All of these associations also have a negative modality, meaning SemMedDB provides both positive and negative associations. The data was last mined June 30, 2015
Medline SemMedDB Case Reports (MEDLINE SemMedDB CT)	Similar to MEDLINE_SemMedDB_ClinTrial except for case reports
Medline SemMedDB Other (MEDLINE SemMedDB Other)	Similar to MEDLINE_SemMedDB_ClinTrial except for it reports on things other than clinical trials or case reports in Medline
Structured Product Label Adverse Drug Reactions from SPLICER (SPL SPLICER ADR)	SPLICER, a tool that reads and parses United States Structured Product Labels (SPLs) for drugs and HOIs in the sections "Adverse Drug Reactions" or "Postmarketing" [7]. SPLICER already utilizes the OMOP Vocabulary and maps drugs to RxNorm and HOIs to MedDRA terms. The SPLICER data was up-to-date as of September 2015
European Product Label Adverse Drug Reactions (SPL EU SPC)	From the PROTECT ADR database, this provided a list of ADRS on Summary of Product Characteristics (SPC) of products authorized in the European Union [25]. The drugs come across as free text and the HOIs come across as descriptions of MedDRA Preferred Terms. It was last updated on December 31, 2013

eMethod 5. Falsification endpoints

Falsification endpoints (negative control outcomes) are concepts known to not be associated with the target or comparator cohorts, such that we can assume the true relative risk between the two cohorts is 1. Total of 96 falsification endpoints are selected using a similar process to that outlined by Voss et al.[2] The concept IDs and SNOMED codes are described below.

Supplementary Table. Falsification endpoint list

OMOP Concept ID	SNOMED code	Outcome Name
378256	46670006	Abnormal reflex
4218106	7200002	Alcoholism
440424	87486003	Aphasia
439237	52684005	Assault
378424	82649003	Astigmatism
261880	46621007	Atelectasis
134118	400190005	Atrophic condition of skin
4224118	40492006	Bladder dysfunction
80509	203465002	Bone cyst
434626	20010003	Borderline personality disorder
438407	78004001	Bulimia nervosa
134765	238108007	Cachexia
4172458	49883006	Candidiasis of skin
436740	17382005	Cervical incompetence
381581	1482004	Chalazion
4307254	423125000	Closed fracture
4047787	123971006	Colles' fracture
198075	240542006	Condyloma acuminatum
73302	64217002	Curvature of spine
4242416	58588007	Cutis laxa
433163	238107002	Deficiency of macronutrients
4047269	229844004	Deformity of foot
133228	80967001	Dental caries

No use of falsification endpoint can be a limitation

ticagrelor, but after adjustment with IPTW the two groups were balanced on this covariate. The study database did not include any falsification endpoint, i.e. an endpoint that is known to be unrelated to treatment under study, which could have supported that the analyses were unbiased. In addition, all data were analyzed as intention-to-treat, and early termination of a drug was not accounted for. It is possible that some patients crossed over from one drug to another,

Szummer et al., "Comparison Between Ticagrelor and Clopidogrel in Elderly Patients with an Acute Coronary Syndrome: Insights from the SWEDEHEART Registry." *Circulation*

Strength in methodology

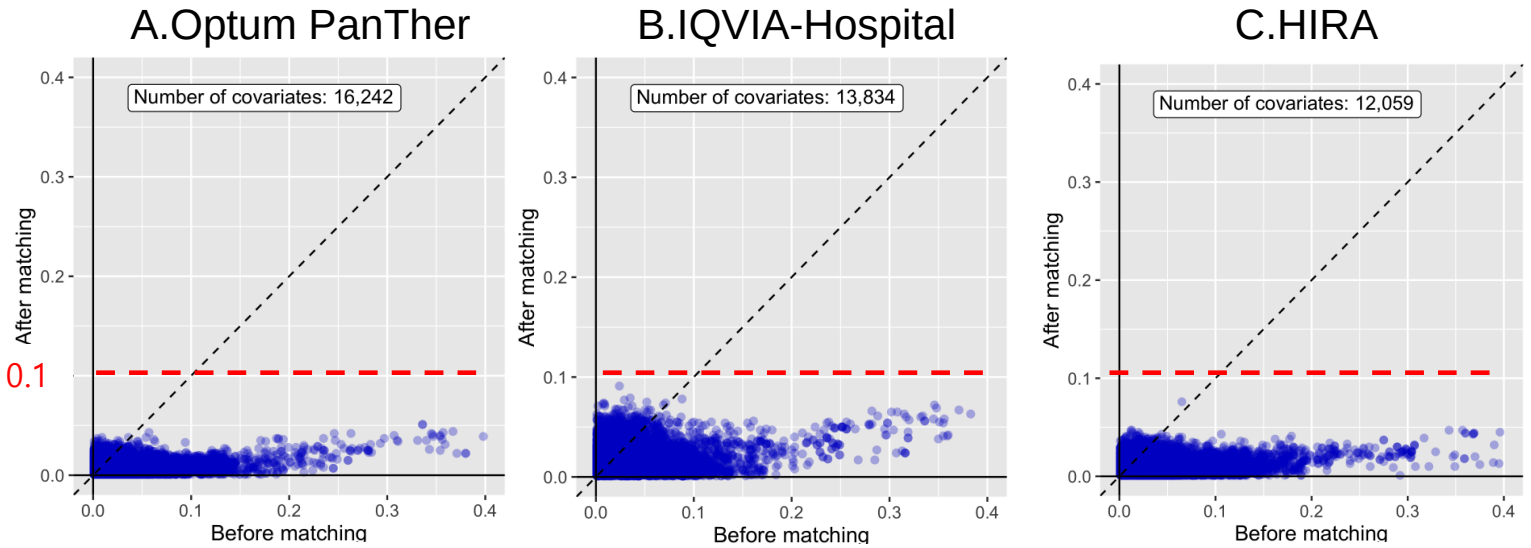
- Reproducibility
- Pre-specification of statistical analytic plan
- Active Comparator, New-User cohort design
- Using three large databases from US and Korea
- 96 Negative controls (Falsification endpoint)
- **Large-scale propensity score model**
- **Large set of sensitivity analyses**
  - 1:1 PS matching / variable-ratio PS matching / PS stratification
  - Diverse time windows
  - Narrow outcome definitions

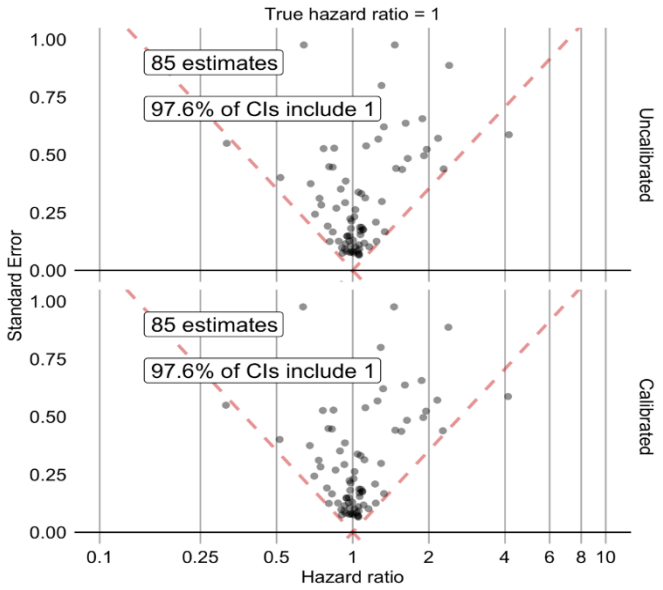
Method: Statistical Analysis

- 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
  - Blanking rule + Limited study date + Restricted outcome def + P value calibration
- Assessment of systemic errors
  - 96 Negative controls

➔ 144 analyses (3x3x2x2x2)

Balance before and after PS matching and Systematic error control





PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2012; **21**(S1): 41–49
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.2328

ORIGINAL REPORT

Using high-dimensional propensity scores to automate confounding control in a distributed medical product safety surveillance system

Jeremy A. Rassen* and Sebastian Schneeweiss

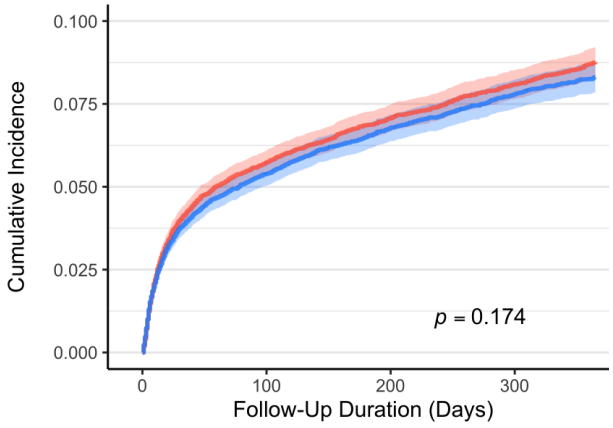
Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

ABSTRACT

Distributed medical product safety monitoring systems such as the Sentinel System, to be developed as a part of Food and Drug Administration's Sentinel Initiative, will require automation of large parts of the safety evaluation process to achieve the necessary speed and scale at reasonable cost without sacrificing validity. Although certain functions will require investigator intervention, confounding control is one area that can largely be automated. The high-dimensional propensity score (hd-PS) algorithm is one option for automated confounding control in longitudinal healthcare databases. In this article, we discuss the use of hd-PS for automating confounding control in sequential database cohort studies, as applied to safety monitoring systems. In particular, we discuss the robustness of the covariate selection process, the potential for over- or under-selection of variables including the possibilities of M-bias and Z-bias, the computation requirements, the practical considerations in a federated database network, and the cases where automated confounding adjustment may not function optimally. We also outline recent improvements to the algorithm and show how the algorithm has performed in several published studies. We conclude that despite certain limitations, hd-PS offers substantial advantages over non-automated alternatives in active product safety monitoring systems.

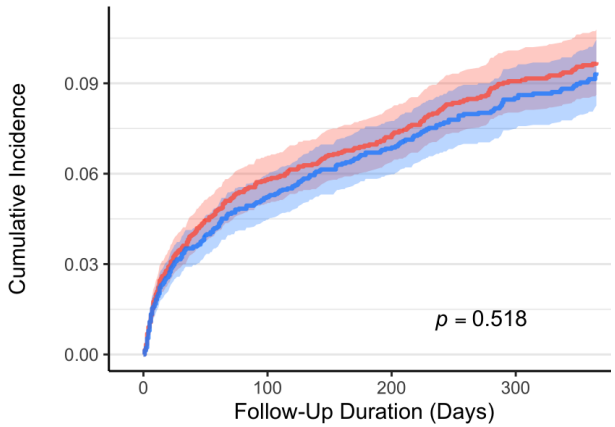
Primary endpoint: 1-year NACE

A. Optum PanTher



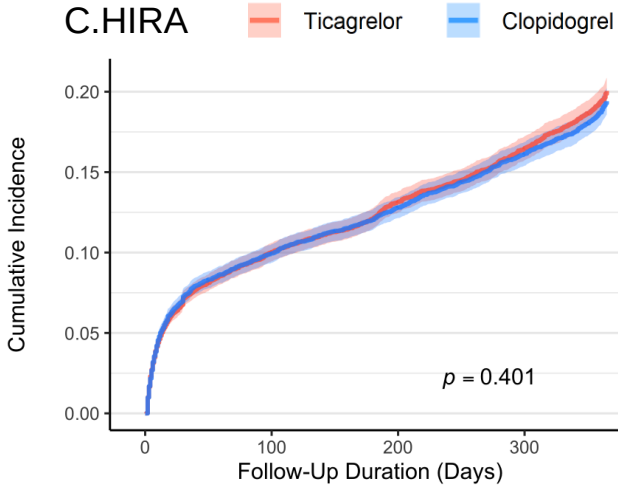
Number at risk				
Ticagrelor	16,388	13,762	12,418	11,341
Clopidogrel	16,388	13,469	11,977	10,755

B. IQVIA-Hospital



Number at risk				
Ticagrelor	3,998	2,761	2,262	1,952
Clopidogrel	3,998	2,687	2,221	1,840

C.HIRA



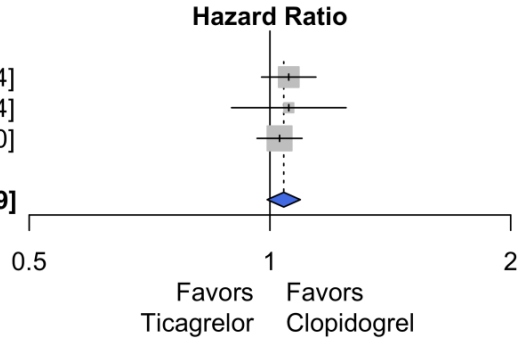
Number at risk				
Ticagrelor	10,890	8,777	7,607	6,379
Clopidogrel	10,890	8,700	7,475	6,346

D. Meta-analysis

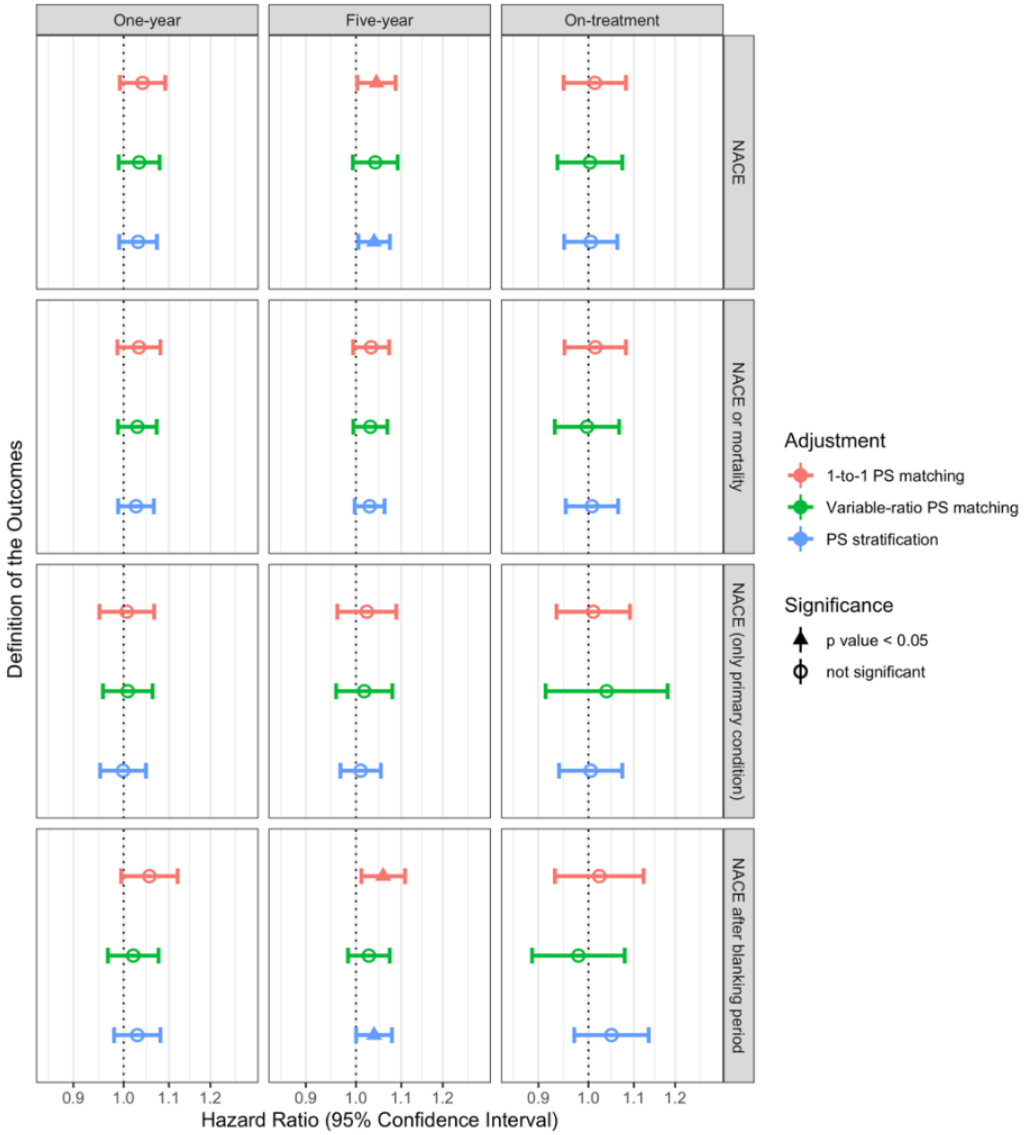
Source	Ticagrelor Total	Ticagrelor Event	Clopidogrel Total	Clopidogrel Event	HR	95% CI
OptumPanTher	16,388	1,308	16,388	1,220	1.06	[0.98; 1.14]
IQVIA - Hospital	3,998	294	3,998	272	1.06	[0.90; 1.24]
HIRA	10,890	1,881	10,890	1,817	1.03	[0.96; 1.10]
Overall	**31,276**	**3,483**	**31,276**	**3,309**	**1.04**	**[0.99; 1.09]**

Heterogeneity: I^2 = 0.0%

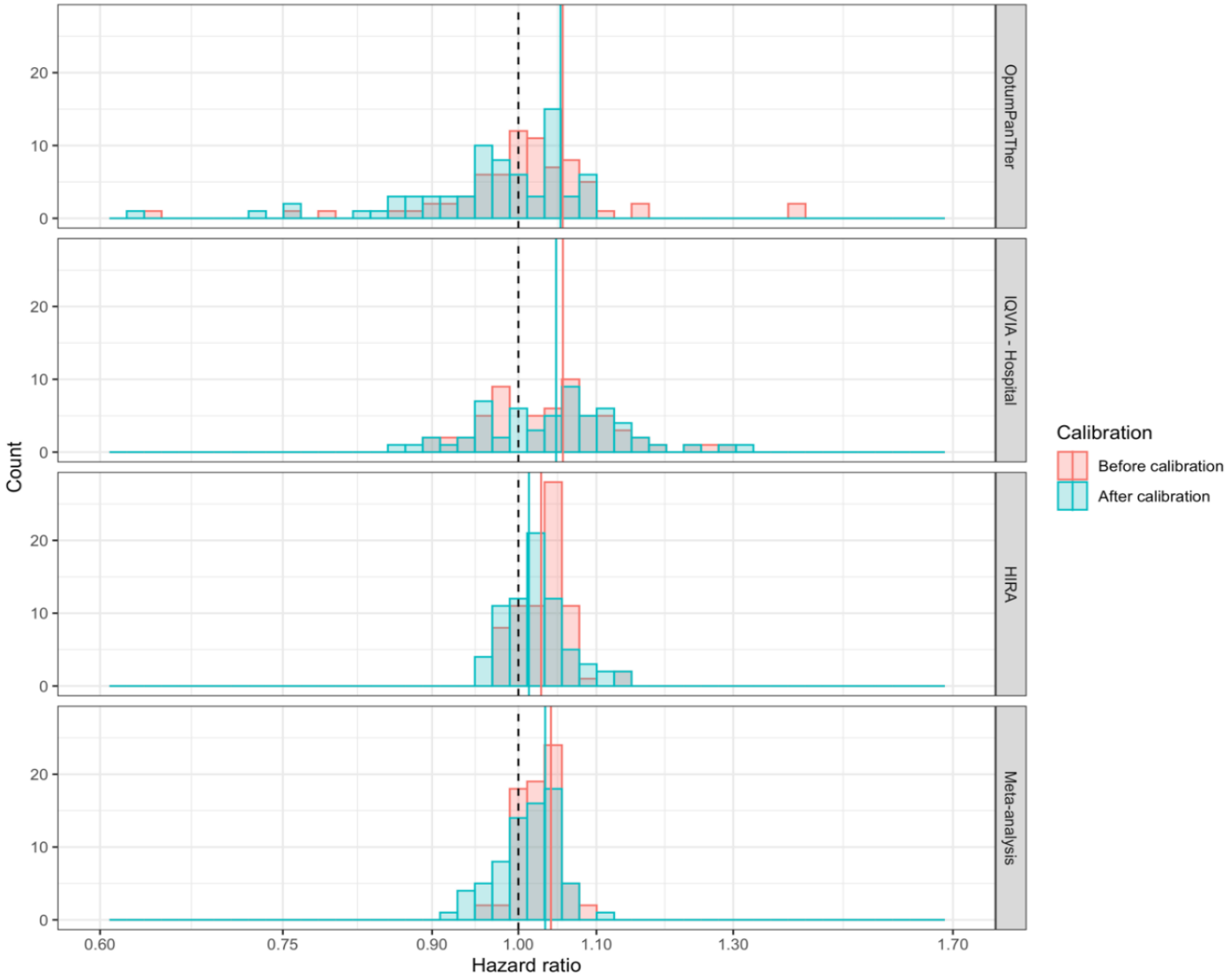
P = 0.100



Consistency in the results of the primary endpoint in sensitivity analyses



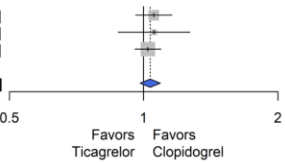
Distribution of risk estimates for NACE



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]**

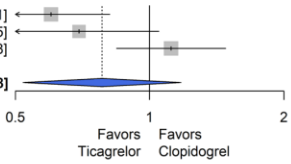
Heterogeneity: I^2 = 0.0%



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]**

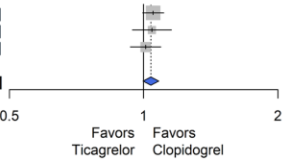
Heterogeneity: I^2 = 78.5%



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]**

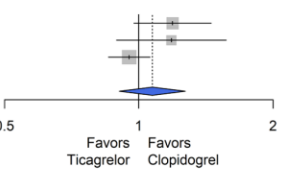
Heterogeneity: I^2 = 0.0%



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]**

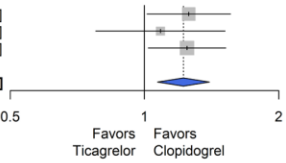
Heterogeneity: I^2 = 59.8%



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]**

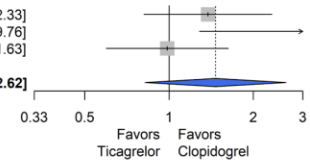
Heterogeneity: I^2 = 0.0%



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]**

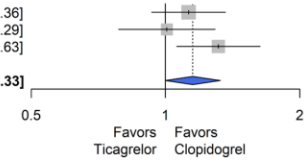
Heterogeneity: I^2 = 59.8%



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]**

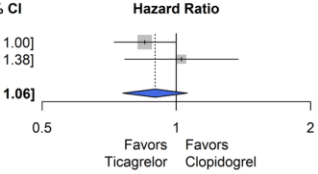
Heterogeneity: I^2 = 23.6%



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]**

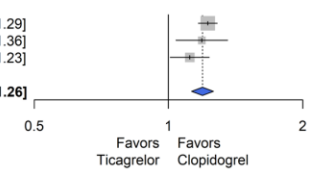
Heterogeneity: I^2 = 19.7%

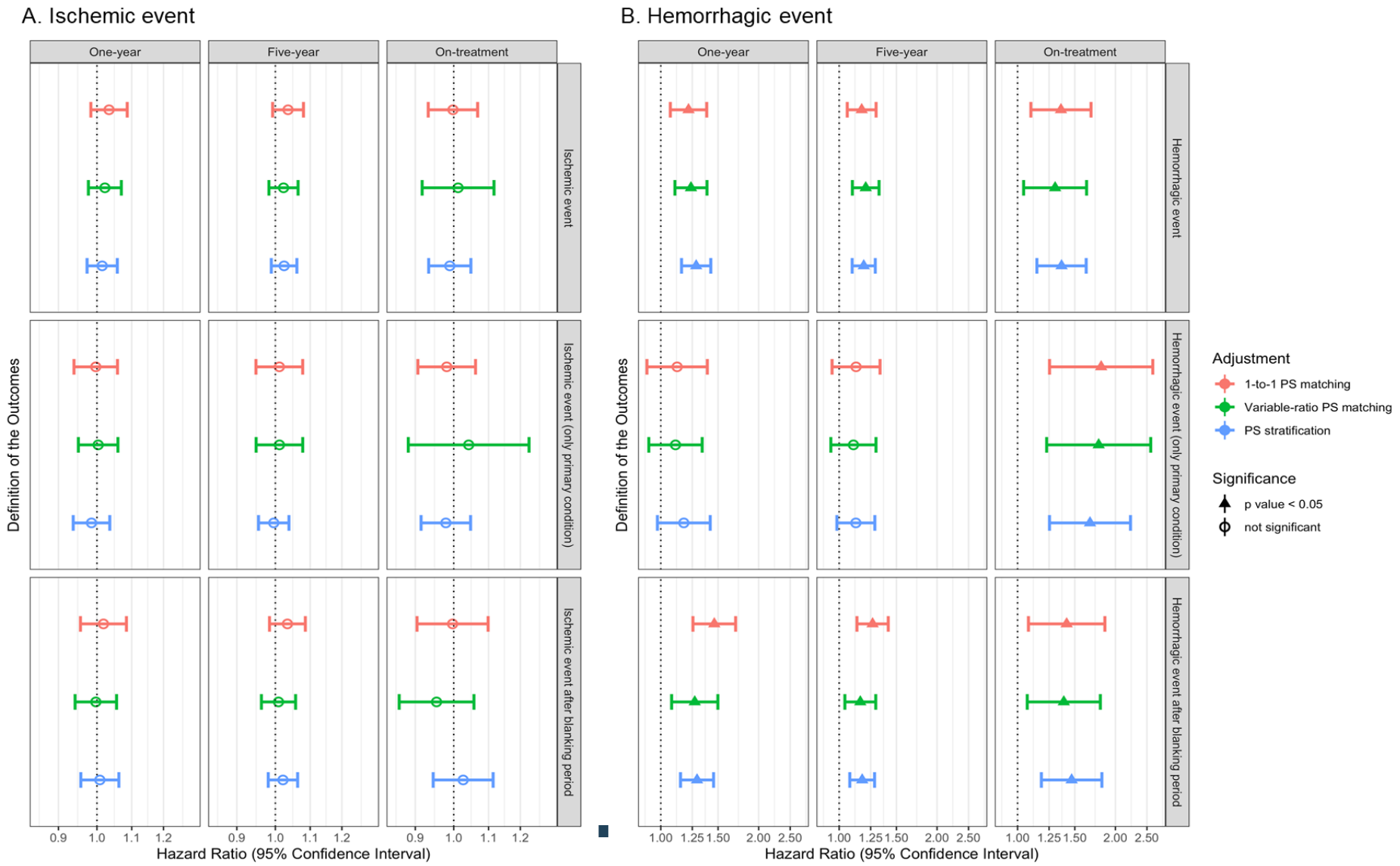


I. Dyspnea

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%




A. Ischemic event
B. Hemorrhagic event
One-year
Five-year
On-treatment
Ischemic event
Ischemic event (only primary condition)
Ischemic event after blanking period
Hemorrhagic event
Hemorrhagic event (only primary condition)
Hemorrhagic event after blanking period
Definition of the Outcomes
0.9 1.0 1.1 1.2
1.00 1.25 1.50 2.00 2.50
Hazard Ratio (95% Confidence Interval)
Adjustment
1-to-1 PS matching
Variable-ratio PS matching
PS stratification
Significance
p value < 0.05
not significant

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**.

1. This remains a hopelessly flawed observational design using claims database data, to compare efficacy and safety. Despite all the care taken by the authors, some critical information is missing such as the duration of actual therapy with each agent, or the frequency of drug interruption or switching after initiation, adherence to therapy (in an observational type of study, this is a huge issue). Patients were entered in the study at the time of PCI as opposed to the time of ACS which is how ticagrelor was tested in the PLATO trial and is recommended for use. Censoring events after initiation of therapy and starting at the time of PCI creates a well-documented bias. Patients were eligible up to 7 days after ACS, a period during which patients are at the highest risk of ischemic events which were not accounted for. This is particularly

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assess the robustness of the findings.

1. This remains a hopelessly flawed observational design using claims database data, to compare efficacy and safety. Despite all the care taken by the authors, some critical information is missing such as the duration of actual therapy with each agent, or the frequency of drug interruption or switching after initiation, adherence to therapy (in an observational type of study, this is a huge issue). Patients were entered in the study at the time of PCI as opposed to the time of ACS which is how ticagrelor was tested in the PLATO trial and is recommended for use. Censoring events after initiation of therapy and starting at the time of PCI creates a well-documented bias. Patients were eligible up to 7 days after ACS, a period during which patients are at the highest risk of ischemic events which were not accounted for. This is particularly important given that by 3 months, 37% of ticagrelor treated patients were no longer on the drug, and 25% of clopidogrel treated patients. The huge issue of lack of adherence and the magnitude of the difference between groups illustrates the critical importance of a double-blind design in the comparison of these agents. The use of claims data or EHR data is also an important concern as some important information is missing: i was not able to locate information regarding smoking or creatinine in the data, but is best illustrated by the simple fact that while the authors discuss "Acute Coronary Syndromes", they are unable to provide a simple basic information: what was the proportion of STEMI, NSTEMI and UA in each group ? This shows that while the databases used here are large, the quality of the information available can be woefully inadequate.

We appreciate these comments and that the Editors have expressed interest in giving us the opportunity to reply to these points.

The Reviewer is correct that we are missing some information that would be helpful in characterizing the patients. We did have access to an immense amount of data on each patient and used this information to the greatest extent possible. Per this comment, we added the information for types of ACS in the baseline characteristics tables.

We emphasize that our approach represents a significant advance in observational research, with a series of publications in leading peer-reviewed methodological journals describing the components of our approach along with their validation. Our balance of thousands of variables coupled with concrete demonstration of balance on every single one of them we believe not only addresses measured confounding but also can begin to address unmeasured confounding. Our use of 96 falsification endpoints goes far beyond current recommendations to include one or a few controls; a large number are needed to make claims of robustness. We published our entire protocol and all our source code before running our trial, to prohibit opportunity for p-hacking. We ran across databases inside and outside the US and looked for consistency. And we ran large sets of sensitivity analyses to assess the robustness of the findings.

Mission, Vision, and Values of OHDSI

- Our Mission

To improve health by empowering a community to collaboratively generate the evidence that promotes better health decisions and better care.

- Our Vision

A world in which observational research produces a comprehensive understanding of health and disease.

Objectives of OHDSI

- **Innovation**: Observational research is a field which will benefit greatly from disruptive thinking. We actively seek and encourage fresh methodological approaches in our work.
革新: 観察研究は破壊的思考から大いに恩恵を受ける分野です。私たちは研究において新しい方法論的アプローチを積極的に求め、奨励しています
- **Reproducibility**: Accurate, reproducible, and well-calibrated evidence is necessary for health improvement.
再現性: 正確で再現可能で、よく校正された証拠は健康改善に必要です。
- **Openness**: We strive to make all our community's proceeds open and publicly accessible, including the methods, tools and the evidence that we generate.
開放性: 私たちは、生成する方法、ツール、および証拠を含む、コミュニティの成果をすべて公開し、公にアクセス可能にすることを目指しています。
- **Community**: Everyone is welcome to actively participate in OHDSI, whether you are a patient, a health professional, a researcher, or someone who simply believes in our cause.
コミュニティ: 患者、医療専門家、研究者、または単に私たちの理念を信じる人であれ、誰でもOHDSIに積極的に参加することを歓迎します。
- **Collaboration**: We work collectively to prioritize and address the real world needs of our community's participants.
協働: 私たちは集団として、コミュニティの参加者の現実のニーズを優先し、対処するために協力します。
- **Beneficence**: We seek to protect the rights of individuals and organizations within our community at all times.
恩恵: 私たちは常にコミュニティ内の個人および組織の権利を保護することを目指しています。

Remarks

- Interventional cardiology is ever evolving branch in cardiology
  - CCU, lipid-lowering medication, advance in stenting, …
- It may not be reasonable to stick to the evidence generated a decade ago in interventional cardiology.
- Observational study can generate high-level evidence
  - Pre-specification for avoiding p-hacking
  - Robust study design and control at least observed variables
- The objective of observational study is the investigation of possible cause–effect relationships (*Cochrane*)


Thank You
for your time