



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

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

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**IMPORTANCE** Current guidelines recommend ticagrelor as the preferred P2Y<sub>12</sub> 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.

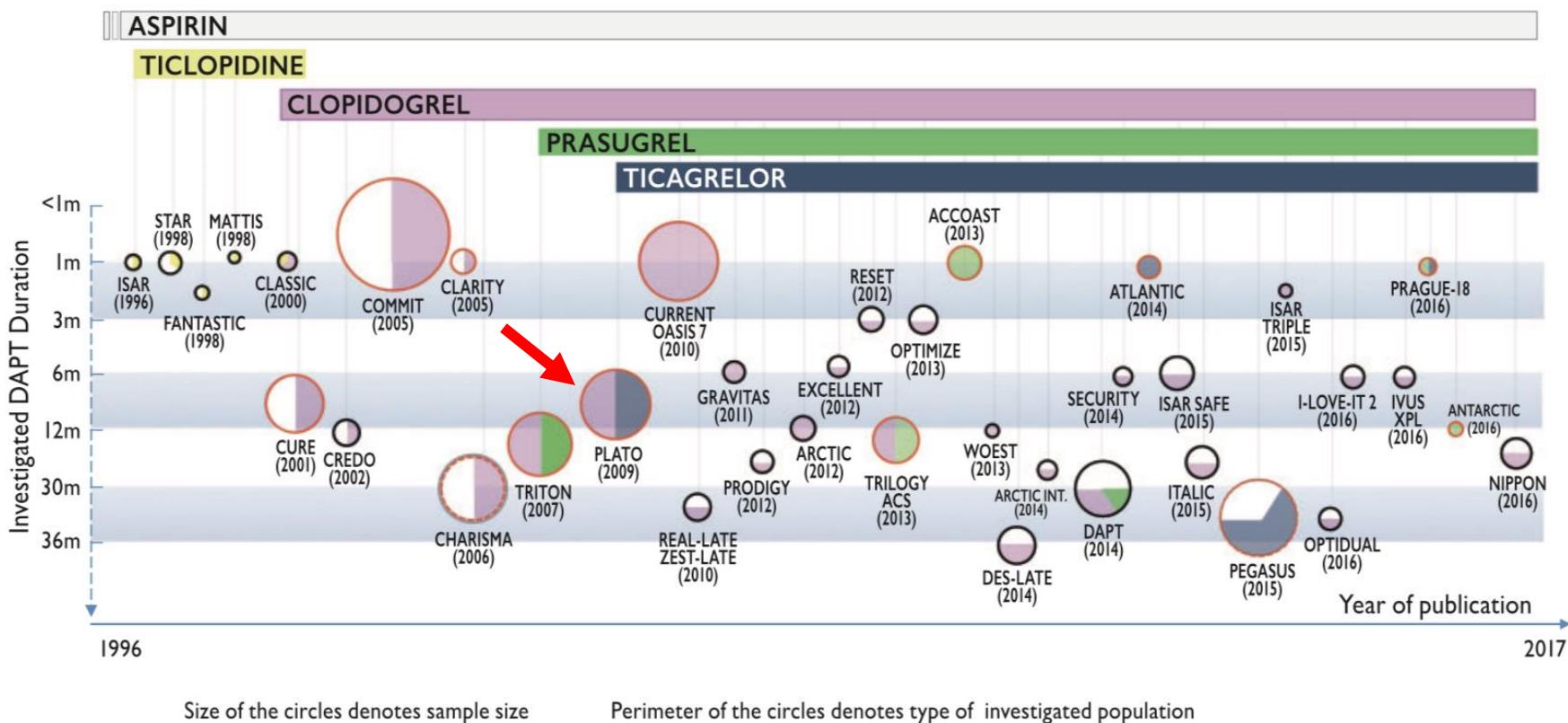
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# History of Dual AntiPlatelet Therapy (DAPT) in patients with coronary artery disease



LEGEND

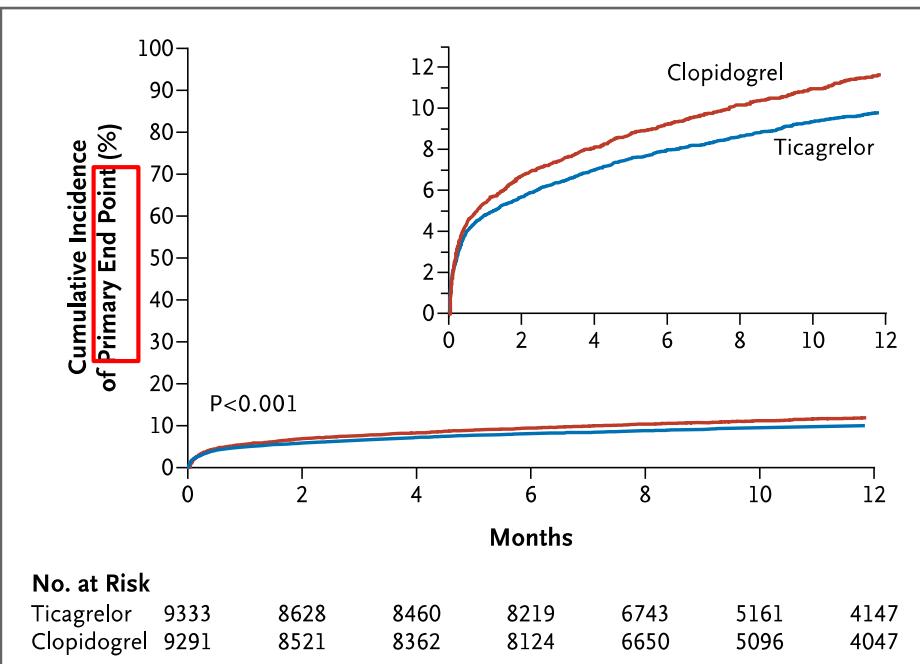
Size of the circles denotes sample size

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



# 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
Dyspepsia — 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 <sup>a</sup>	Level <sup>b</sup>
In patients with ACS, ticagrelor (180 mg loading dose, 90 mg twice daily) on top of aspirin <sup>c</sup> 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. <sup>20</sup>	I	B

2017 ESC/EACTS DAPT guideline

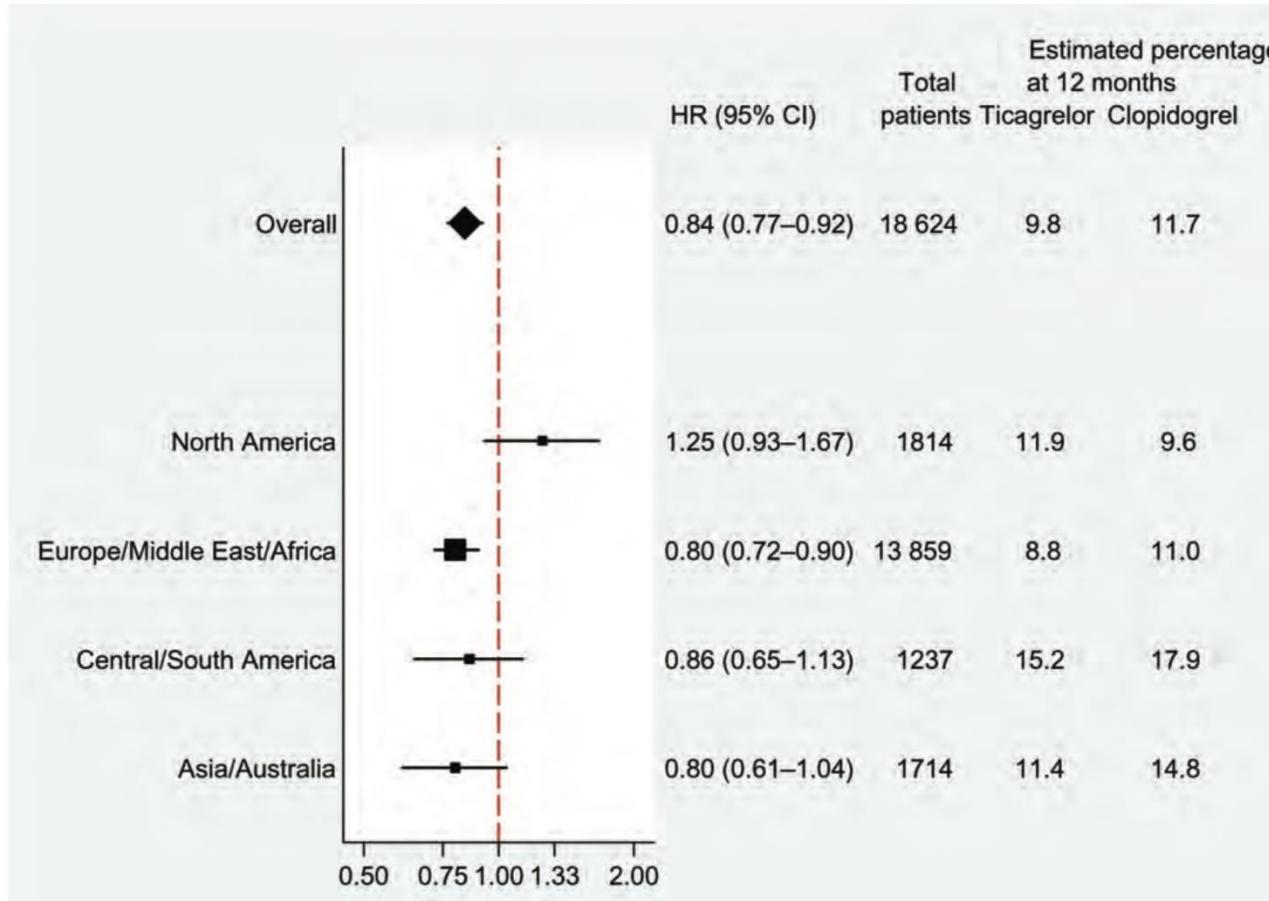
## Recommendations for Specific P2Y<sub>12</sub> Inhibitors

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 <sub>12</sub> inhibitor therapy (53,71,72).

2016 ACC/AHA DAPT guideline



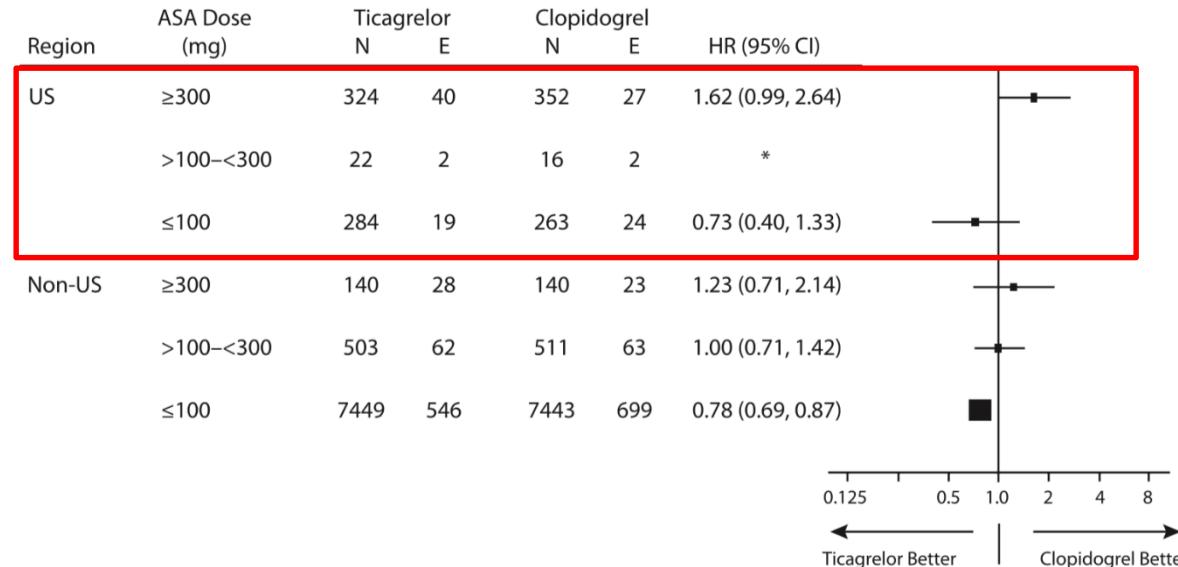
# PLATO trial did not demonstrate superiority of Ticagrelor in North America and Asia



**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).

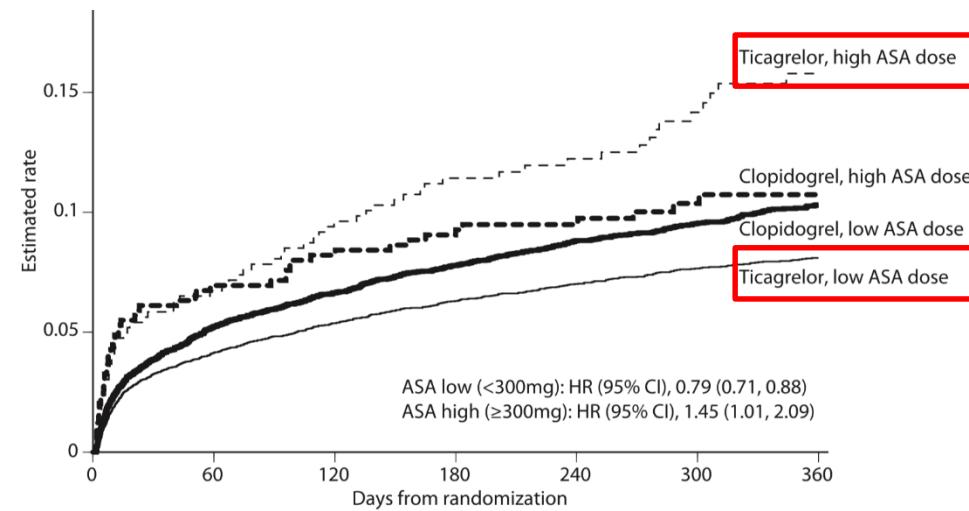


# Aspirin dosing might matter



- More patients in the United States (53.6%) than in the rest of the world (1.7%) took a median **aspirin dose  $\geq 300$  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**





# Aspirin dose and Ticagrelor benefit in PLATO: Fact or Fiction?

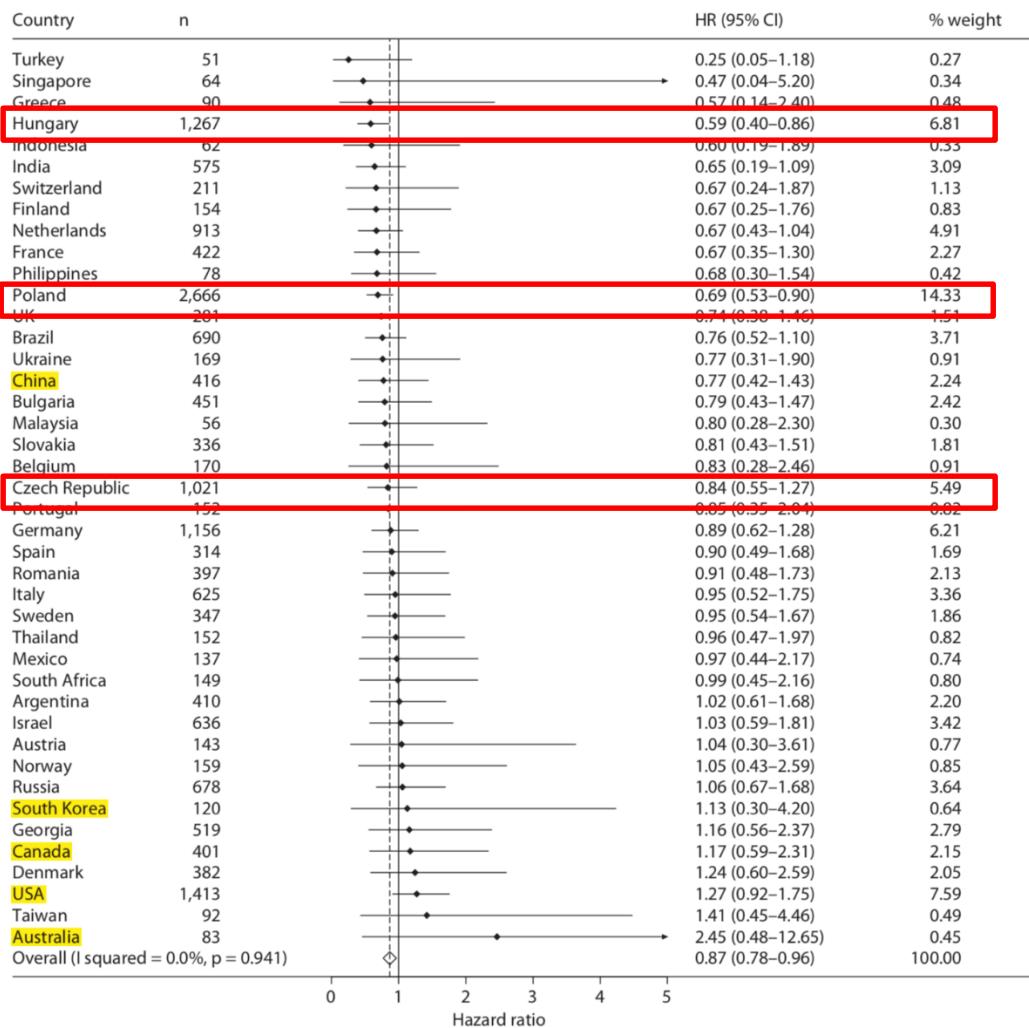
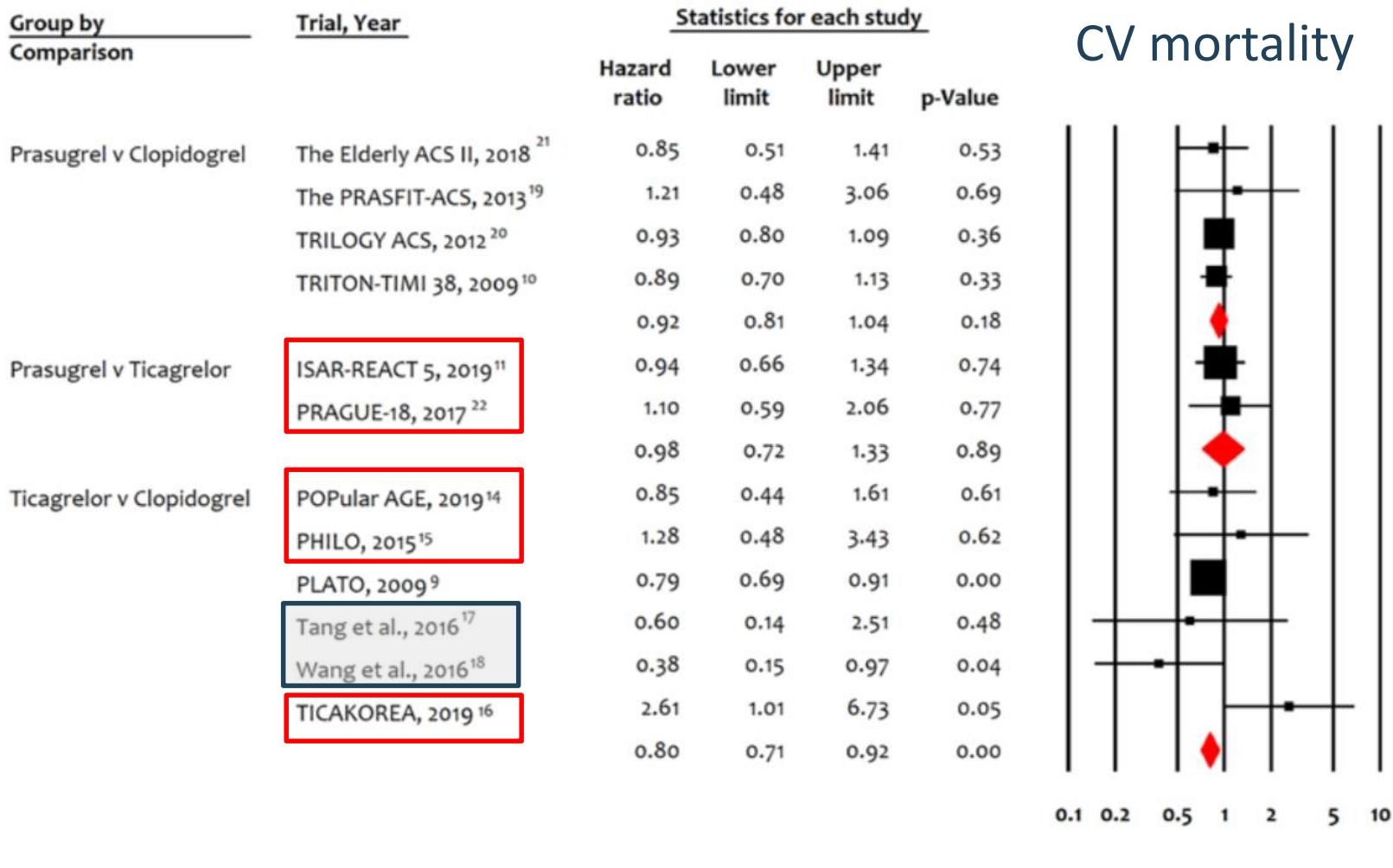


Fig. 1. Outcome distribution by country in PLATO.

- FDA doc clearly suggest that aspirin dosing does not explain the disparate outcome results.
- Advisory Committee members found no evidence to establish a reasonable link, and they uniformly rejected the hypothesis that aspirin dose affects the heterogeneity of outcomes in PLATO
- The wide distribution of outcomes differing from country to country, and inconsistency in European data despite identical aspirin doses, preclude the acceptance of the hypothesis that aspirin affects PLATO outcomes in general or adversely impacts the benefit of ticagrelor in the US cohort in particular
- Differences in primary site monitoring by the study sponsor in most countries versus a third-party CRO in USA represent an alternative explanation and deserve further attention



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

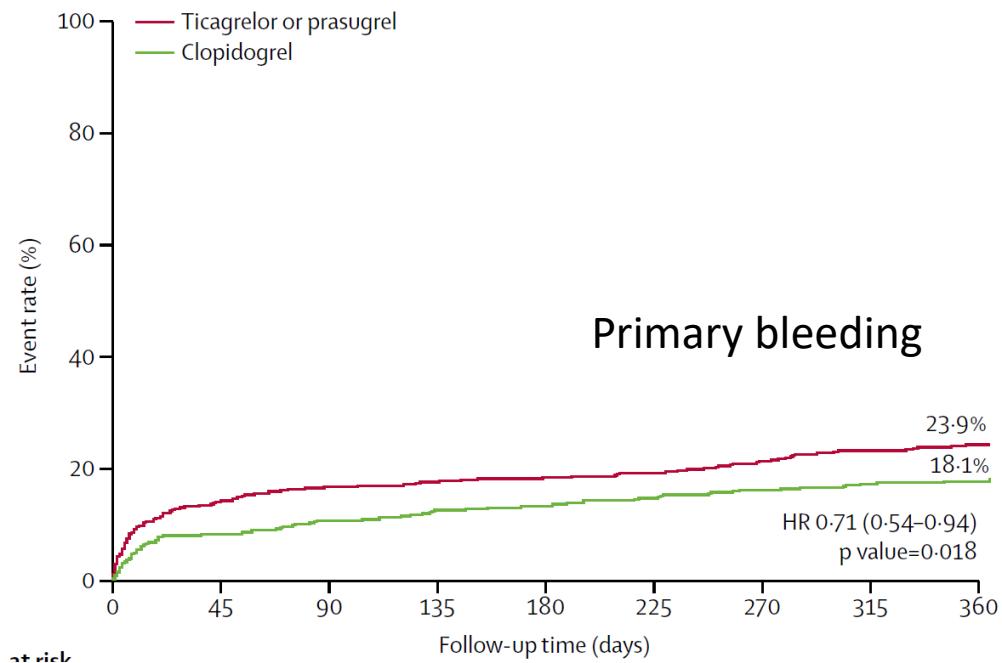




# Superiority of ticagrelor over clopidogrel or prasugrel has never been replicated in RCTs

## POPular-AGE

- Multi-center, open-label RCT (Netherlands)
- Investigator-initiated
- Old( $\geq 70$ yr) 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



# 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

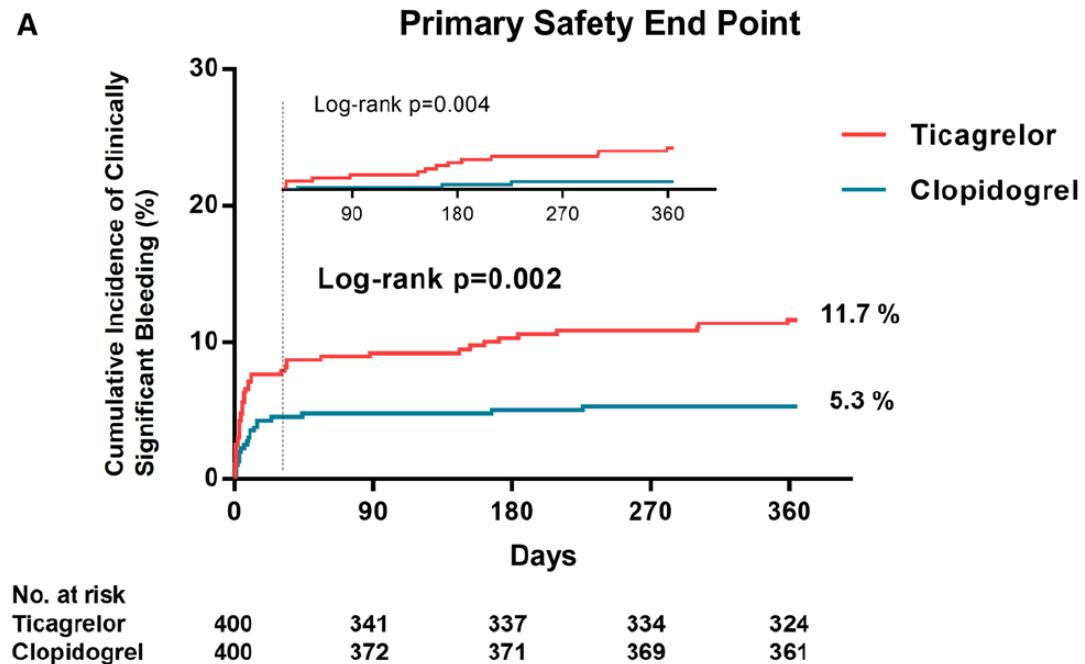
	Ticagrelor 90 mg b.i.d. (n=401)	Clopidogrel 75 mg o.d. (n=400)	HR (95% CI)
Primary			
Composite of CV death/MI (excluding silent MI)/stroke	36 (9.0)	25 (6.3)	1.47 (0.88–2.44)



# 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



# 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. Graham

- Data:  
Canadian Coronary  
Heart Disease  
Registry

Outcome	No. (%)		P Value	HR (95% CI)
	Clopidogrel Group (n = 3711)	Ticagrelor Group (n = 3711)		
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) <sup>a</sup>
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) <sup>a</sup>
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) <sup>a</sup>
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) <sup>a</sup>



# 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’*



# Is newer, more expensive treatment always better?

JAMA Internal Medicine | Original Investigation

## Trends in Platelet Adenosine Diphosphate P2Y<sub>12</sub> 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<sub>12</sub> receptor (P2Y<sub>12</sub>) inhibitors.

Invited Commentary  
page 950



# 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<sub>12</sub> 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<sub>12</sub> 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.<sup>7</sup>



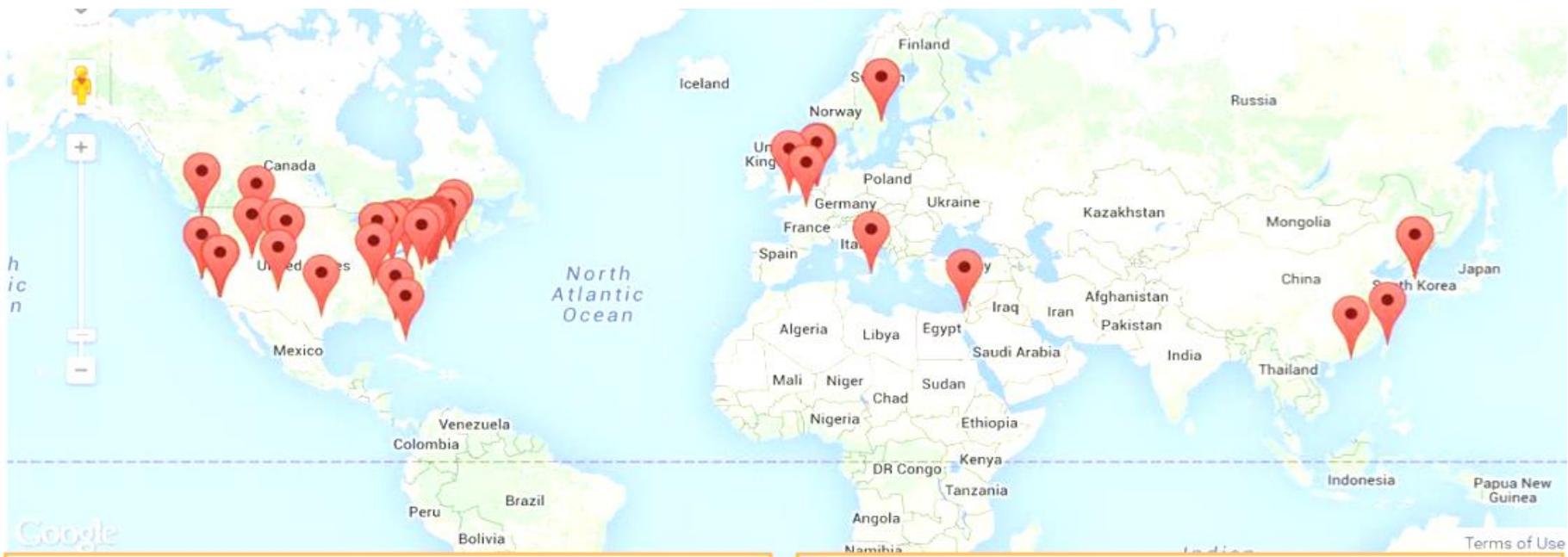
# Objectives

- 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

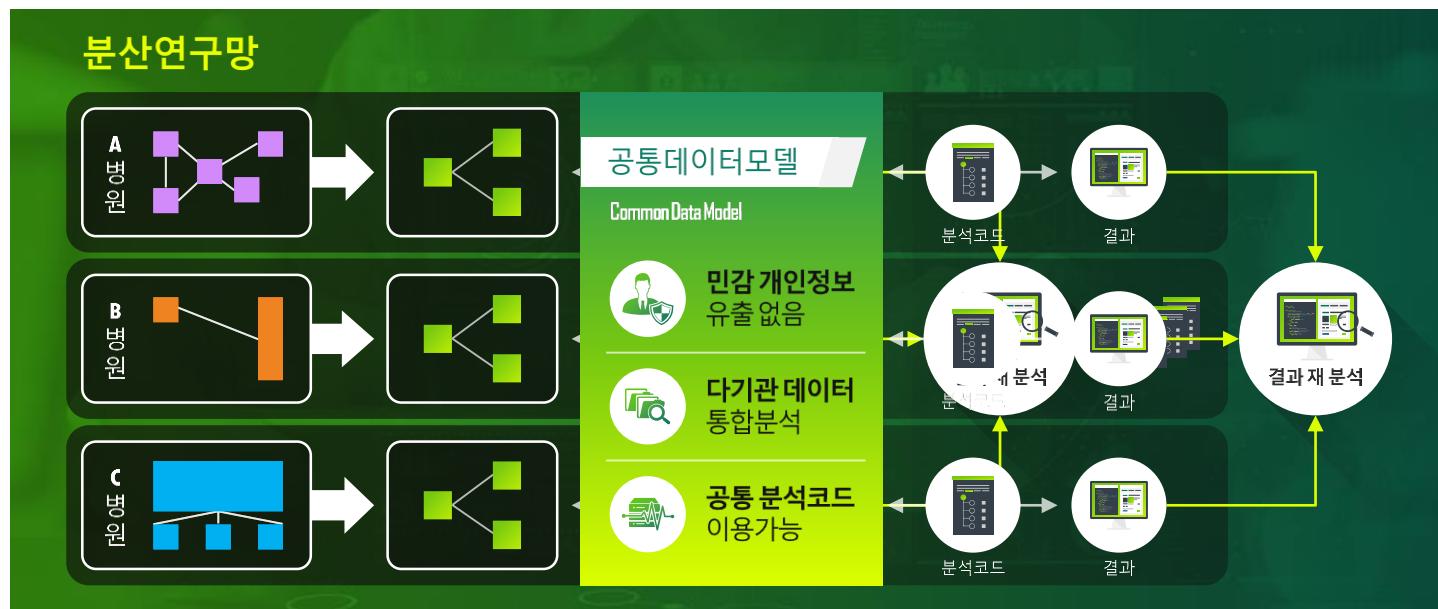


## OHDSI Collaborators:

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

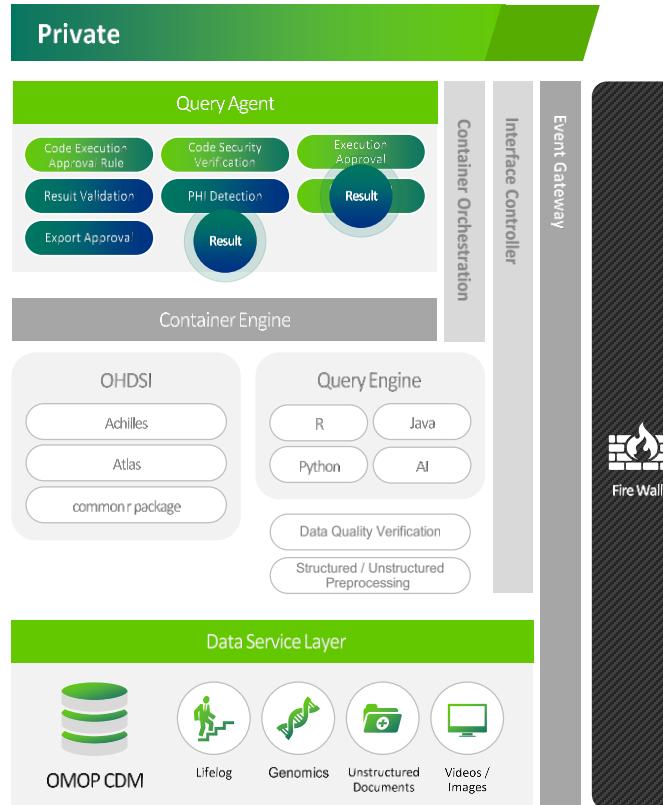
## OHDSI Data Network:

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

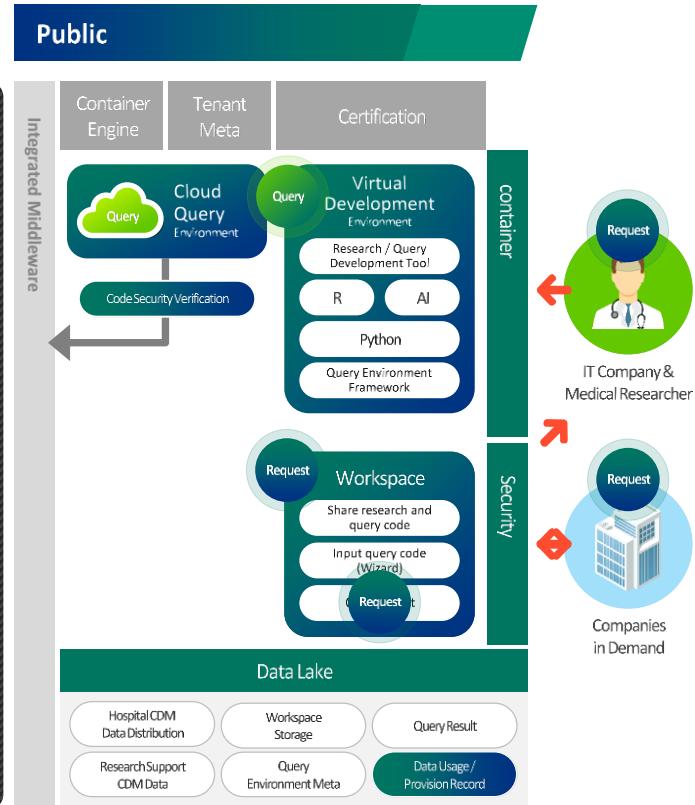


# How Distributed Research Platform works?

## FEEDER Node (Participating Hospital)



## FEEDER Portal





# 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 혁신성:** Observational research is a field which will benefit greatly from disruptive thinking. We actively seek and encourage fresh methodological approaches in our work.
- **Reproducibility 재현성:** Accurate, reproducible, and well-calibrated evidence is necessary for health improvement.
- **Openness 개방성:** We strive to make all our community's proceeds open and publicly accessible, including the methods, tools and the evidence that we generate.
- **Community 공동체 정신:** 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 협력 정신:** We work collectively to prioritize and address the real world needs of our community's participants.
- **Beneficence 선행의 정신:** We seek to protect the rights of individuals and organizations within our community at all times.



# 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

- **Reproducible and Open science**
- Pre-specification of statistical analytic plan
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# 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."<sup>1</sup> 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

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### 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/S1089-1516\(20\)31324-6](https://doi.org/10.1016/S1089-1516(20)31324-6)

After publication of our *Lancet* Article,<sup>1</sup> 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 AstaZeneca, 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

chandryou / TicagrelorVsClopidogrel

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OHDSI network study: Net Adverse Clinical Event between Ticagrelor and Clopidogrel in Patients with Acute Coronary Syndrome Edit

Manage topics

102 commits 1 branch 4 releases 1 contributor

Branch: master New pull request Create new file Upload files Find File Clone or download

chandryou Update Readme for docker ... Latest commit 93af21a 2 days ago

File	Description	Time
R	revision of region in submitResults.R	25 days ago
documents	revision of SAP	8 days ago
extras	add Docker	2 days ago
inst	Merge remote-tracking branch 'upstream/master' into shiny	2 days ago
man	delete country argument from runCohortMethod function	25 days ago
.Rbuildignore	change TAR from 1 to 364 for 1-year analysis	last year
.Rprofile	change TAR from 1 to 364 for 1-year analysis	last year
.gitignore	change TAR from 1 to 364 for 1-year analysis	last year
DESCRIPTION	Revert "first draft for narrow version of tica"	this year
Dockerfile	add Docker	2 days ago
HydraConfig.json	Revert "first draft for narrow version of tica"	this year
NAMESPACE	Implement interaction term analysis	this year
TicagrelorVsClopidogrel.Rproj	Revert "first draft for narrow version of tica"	this year
readme.md	Update Readme for docker	2 days ago

readme.md

TicagrelorVsClopidogrel

<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, María 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 Hripcak, Marc A Suchard



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

EMA/95098/2010 Rev.8



European Network of Centres for  
Pharmacoepidemiology and  
Pharmacovigilance

The European Network of Centres for  
Pharmacoepidemiology and Pharmacovigilance (ENCePP)  
Guide on Methodological Standards in  
Pharmacoepidemiology  
(Revision 8)



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(Revision 8)

As stated by [Watson et al.](#) in relation to one of the published studies, lack of transparency and uncertainties about research standards applied raise doubts about published results. [Morales et al.](#) supported the reproducibility of their study by publishing the study protocol in the [EU PAS Register](#) ahead of time, providing [a start-to-finish executable code](#), facilitating the sharing and exploration of the complete result set with an [interactive web application](#) and asking clinicians and epidemiologists to perform a blinded evaluation of propensity score diagnostics for the treatment comparisons.



# Tools for reproducible research

- Script (SQL, R, SAS, Python...)
- Git
- Docker



# Version control in the research

"FINAL".doc



FINAL.doc!

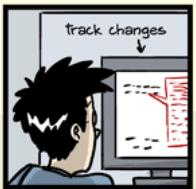


FINAL\_rev.2.doc



FINAL\_rev.6.COMMENTS.doc

FINAL\_rev.8.comments5.  
CORRECTIONS.doc



FINAL\_rev.18.comments7.  
corrections9.MORE.30.doc    FINAL\_rev.22.comments49.  
corrections.10.#@%\$WHYDID  
ICOMETOGRAD SCHOOL????.doc

WWW.PHDCOMICS.COM

이름

- Final raw data(10.3).sav
- Final raw data(14.3.modified).sav
- Final raw data(14.3.modified)
- Final raw data(14.3.modified).csv
- Final raw data.sav
- Raw data(13.4.17) 복사본
- Raw data(13.10.2)
- Raw data(13.10.15)
- Raw data(external\_use)

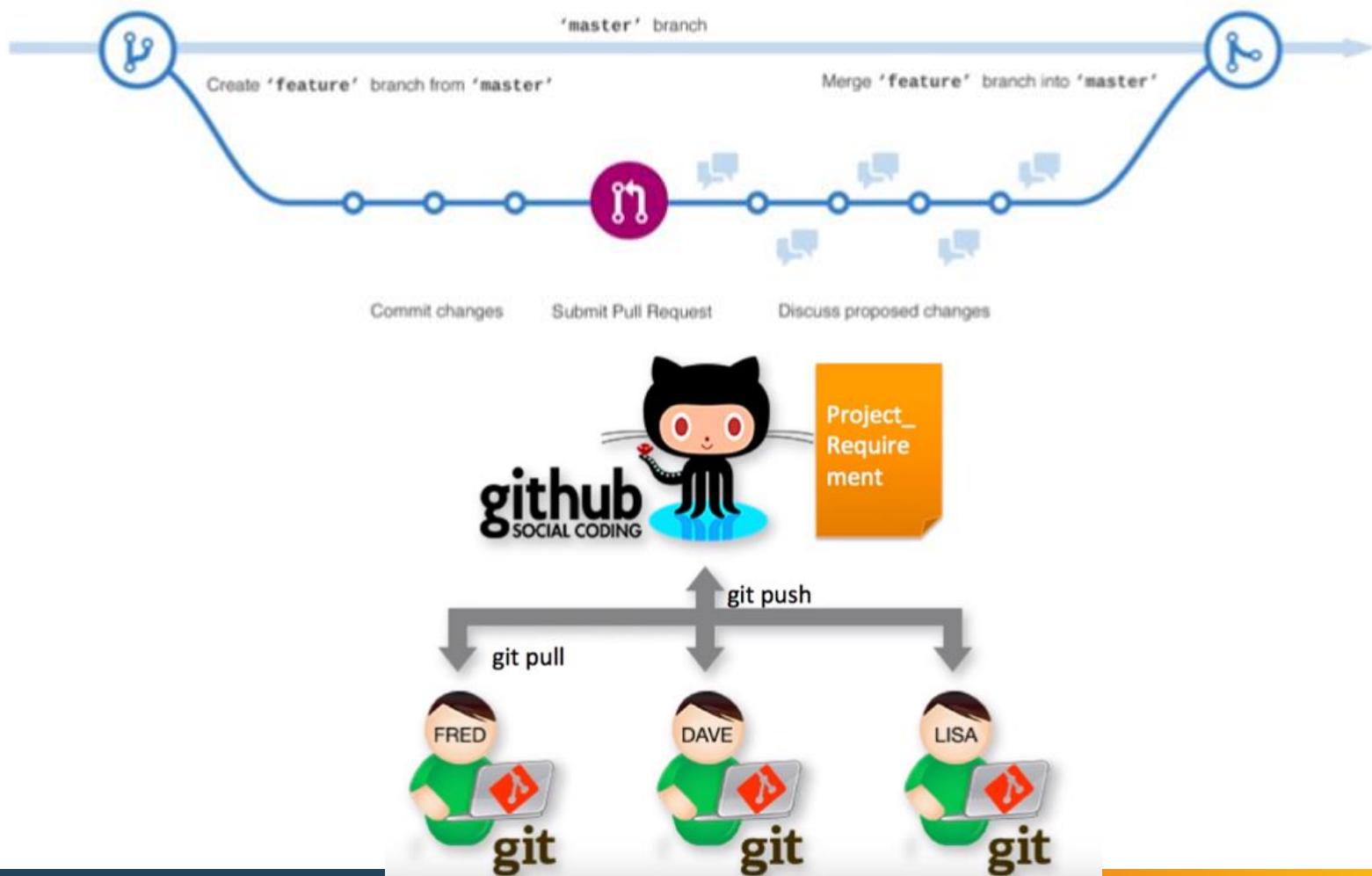
산자부제안서(지정공모형 PART II)_v0.0.hwp
산자부제안서(지정공모형 PART II)_v0.1_김도엽.hwp
산자부제안서(지정공모형 PART II)_v0.1_남수만(작성중).hwp
산자부제안서(지정공모형 PART II)_v0.1_박호준.hwp
산자부제안서(지정공모형 PART II)_v0.1_변정현_DQM.hwp
산자부제안서(지정공모형 PART II)_v0.1_변정현_ETL.hwp
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산자부제안서(지정공모형 PART II)_v0.1_진상평소요한.hwp
산자부제안서(지정공모형 PART II)_v0.2_남수만.hwp
산자부제안서(지정공모형 PART II)_v0.2_이유림.hwp
산자부제안서(지정공모형 PART II)_v0.9_진상평소요한.hwp

- Multiple files for one file
- Difficult to know who changes file
- Difficult to know difference among versions
- Difficult to be managed by multiple members
- Difficult to know why version updated
- Difficult to rollback to older version
- Difficult to manage history of file



# Git for reproducible research

## Git: 분산 버전 관리 시스템



A large, stylized graphic in the top-left corner consists of a yellow square with an orange diagonal cross and white X-shaped lines extending from the corners towards the center.

# Use GitHub as the study hub

- Git
  - Version control of the study protocol
  - Effectively manage source code
  - Collaborate efficiently with other researchers
  - Neatly package the research



# Collaborative development using GitHub

[OHDSI / PatientLevelPrediction](#)

Code Issues 23 Pull requests 0 Projects 1 Security Insights

Branch: master ▾

- Commits on May 30, 2019
  - fixed conflict  
jreps committed 4 days ago [X](#)  
[Edit](#) [9d1559e](#) [Compare](#)
  - updated website and vignette ...  
jreps committed 5 days ago  
[Edit](#) [2bf09b4](#) [Compare](#)
- Commits on May 29, 2019
  - Merge pull request #137 from ABMI/deepEnsemble ...  
jreps committed 6 days ago [X](#)  
[Verified](#) [Edit](#) [00d34a2](#) [Compare](#)
  - add zeallot to the DESCRIPTION  
chandryou committed 6 days ago [X](#)  
[Edit](#) [73347ea](#) [Compare](#)
- Commits on May 24, 2019
  - organize NAMESPACE and CIReNN  
chandryou committed 11 days ago [X](#)  
[Edit](#) [b3f6bba](#) [Compare](#)
- Commits on May 23, 2019
  - add module for deep Ensemble to evaluate uncertainty of the model  
chandryou committed 12 days ago  
[Edit](#) [2ef9a78](#) [Compare](#)

<https://github.com/OHDSI/PatientLevelPrediction>



# Collaborative development using GitHub

Commits on Apr 1, 2019

Merge pull request #26 from ABMI/plotDevelop ...

 ParkYouJin committed on 1 Apr

Verified



d152908



Commits on Mar 28, 2019

Update README.md

 rwpark99 committed on 28 Mar

Verified



ab665c6



Add files via upload

 rwpark99 committed on 28 Mar

Verified



313851e



Commits on Mar 25, 2019

argos::plot-> plot

 ParkYouJin committed on 25 Mar



b1215f2





# My research experience using personal GitHub repository

chandryou / TicagrelorVsClopidogrel

Unwatch 1 Star 0 Fork 1

Code Issues 7 Pull requests 0 Projects 0 Wiki Security Insights Settings

OHDSI network study: Net Adverse Clinical Event between Ticagrelor and Clopidogrel in Patients with Acute Coronary Syndrome Edit

Manage topics

102 commits 1 branch 4 releases 1 contributor

Branch: master New pull request Create new file Upload files Find File Clone or download

chandryou Update Readme for docker ... Latest commit 93af21a 2 days ago

R	revision of region in submitResults.R	25 days ago
documents	revision of SAP	8 days ago
extras	add Docker	2 days ago
inst	Merge remote-tracking branch 'upstream/master' into shiny	2 days ago
man	delete country argument from runCohortMethod function	25 days ago
.Rbuildignore	change TAR from 1 to 364 for 1-year analysis	last year
.Rprofile	change TAR from 1 to 364 for 1-year analysis	last year
.gitignore	change TAR from 1 to 364 for 1-year analysis	last year
DESCRIPTION	Revert "first draft for narrow version of tica"	this year
Dockerfile	add Docker	2 days ago
HydraConfig.json	Revert "first draft for narrow version of tica"	this year
NAMESPACE	Implement interaction term analysis	this year
TicagrelorVsClopidogrel.Rproj	Revert "first draft for narrow version of tica"	this year
readme.md	Update Readme for docker	2 days ago
readme.md		

TicagrelorVsClopidogrel

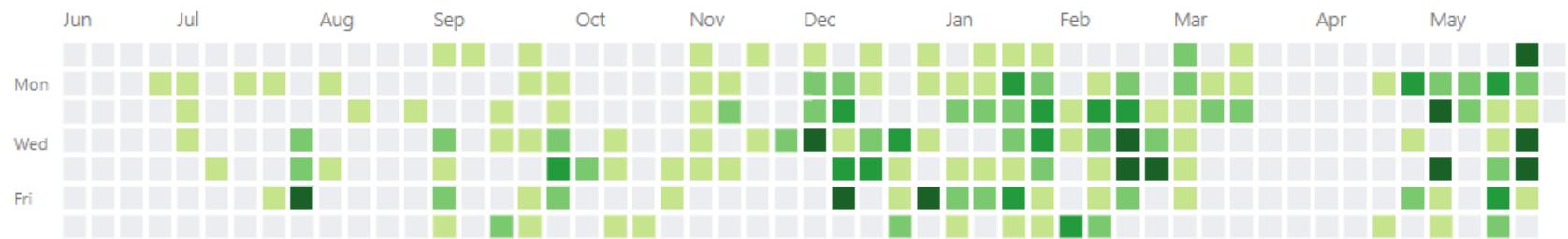
<https://github.com/chandryou/TicagrelorVsClopidogrel>



# GitHub for the Manager

636 contributions in the last year

Contribution settings ▾



[Learn how we count contributions.](#)

Less More



# Still, there is a problem in reproducibility

2 MONTHS LATER

George\_Argeiou

1 27d

Hi Chan,

I have difficulties installing the package in my local machine.

I've tried to install using two different ways:

1. With `install_github("chandryou/FebuxostatVsAllopurinolCVD")` I get:

Error in read.dcf(path) :

Found continuation line starting ' DatabaseConnecto ...' at begin of record.

2. With `install.packages("https://github.com/chandryou/FebuxostatVsAllopurinolCVD.git")` I get:

Warning in install.packages :

package 'https://github.com/chandryou/FebuxostatVsAllopurinolCVD.git' is not available (for R version 3.5.1)

Can you help?



# Still, there is a problem in reproducibility

Table 2: Build error summary.

error	count	percentage
incomplete documentation	10	7.9%
none	1	0.8%
distribution is missing files	21	16.7%
unavailable environment	14	11.1%
missing third party package	22	17.5%
other errors	22	17.5%
prerequisite failed to build	23	18.3%
runtime error	12	9.5%
internal compiler error	1	0.8%
Total	126	

Collberg et al., Measuring Reproducibility in Computer Systems Research



Felix Z. Hoffmann  
@Felix11H

팔로우

@RealBrainTC 님에게 보내는 답글

(1) A growing number of researchers ([opensourceforneuroscience.org](http://opensourceforneuroscience.org)) & journals are committed to openly publishing code that generated results in computational neuroscience studies. This is great! However: Is code alone enough for reproducibility?

#brainTC

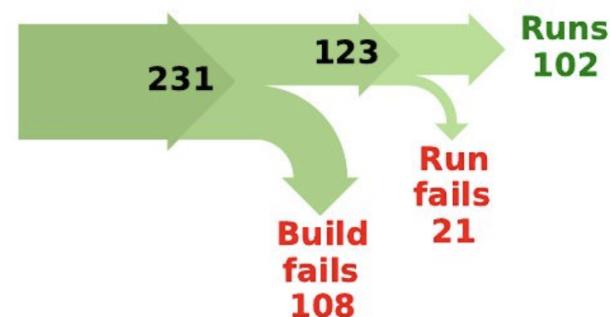
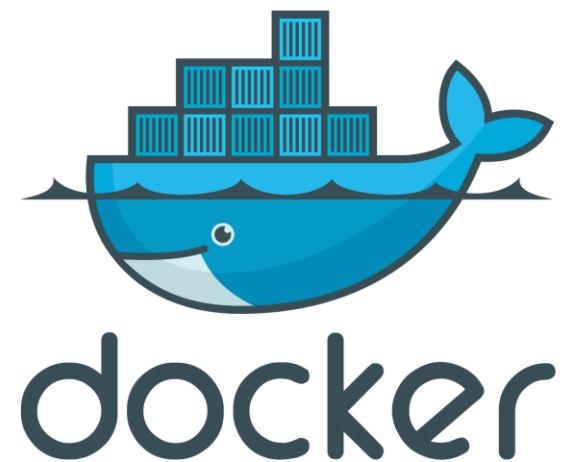


Fig 1: Even when code was available, over half of published projects failed to build or run without significant effort in fixing or debugging (in computer systems research, figure adapted from Collberg et al. 2014)

오전 10:47 - 2018년 3월 8일



# Docker, What is it? and What for?





# What is Docker?

- Docker is an **open platform** for developers and sysadmins to build, ship, and run **distributed applications**. Consisting of Docker Engine, a portable, lightweight runtime and packaging tool, and Docker Hub, a cloud service for sharing applications and automating workflows, Docker enables apps to be quickly assembled from components and eliminates the friction between development, QA, and production environments.

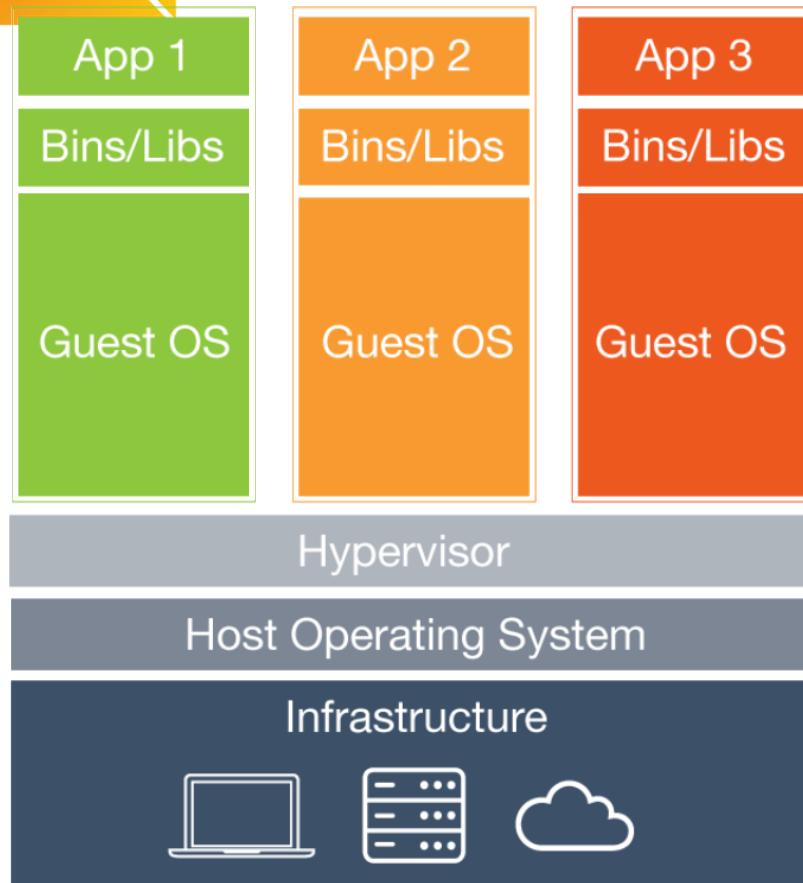


# Ok, seriously, what *is* Docker?

- Docker is a **very lightweight abstraction** using recent Linux kernel features which lets us to run code in **cheap** (to launch) and **easy** (to build) units: containers
- We can share containers across OSs, across time.

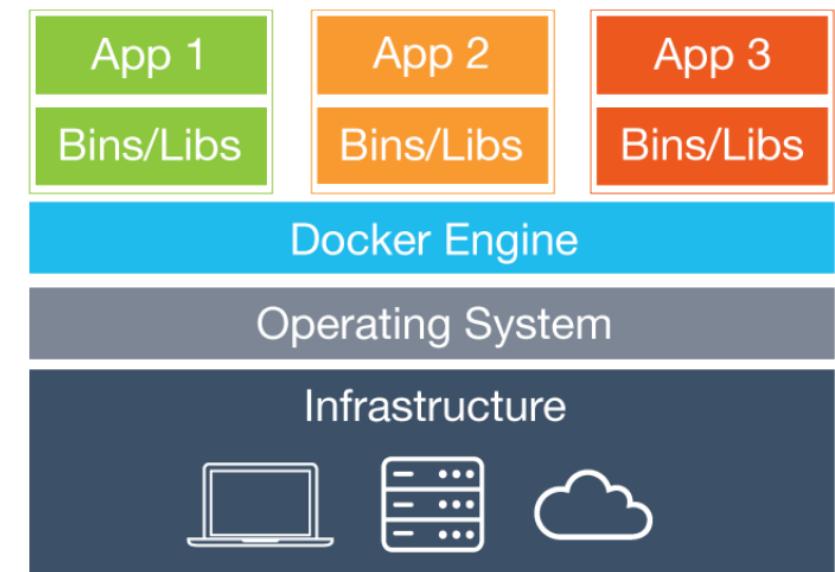


# Virtual Machine vs Docker



## Virtual machines

Virtual machine runs one complete OS on top of another OS



## Containers

A Docker container is like a virtual machine that shares guest OSs, which makes them very lightweight



# Docker and Reproducibility

- Capturing the computational environment
  - A **substantial challenge** in reproducing analysis is **installing and configuring the web of dependencies of specific versions** of various analytic tools.
  - Popular VM applications include VirtualBox and VMWare. One challenge of working with VMs is that the files that contain the environment are not small, typically one gigabyte or more, which can be awkward to share.

From <http://ropensci.github.io/reproducibility-guide/sections/introduction/>



# Docker Advantage for Reproducibility

- Small footprint
- Easier deployment
- Easier sharing and publication
- Open source platform
- Standard scripting of image setup with Dockerfile
- Rocker images as baseline

From <http://ropensci.github.io/reproducibility-guide/sections/introduction/>

<http://www.cascadia-analytics.com/docs/user2018-docker-r-tutorial-slides.pdf>



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From <http://ropensci.github.io/reproducibility-guide/sections/introduction/>

<http://www.cascadia-analytics.com/docs/user2018-docker-r-tutorial-slides.pdf>



# Versioned docker library for OHDSI Tools

ABMI / ohdsi-docker

Code Issues 0 Pull requests 0 Projects 0 Wiki Insights Set

docker for ohdsi tool ecosystem

Manage topics

14 commits 1 branch 0 releases

Branch: master ▾ New pull request Create new file

chandryou resolve the conflict

cohortmethod resolve the conflict

patientlevelprediction\_cpu making subfolder for latest version and update plp docker image

.gitignore making subfolder for latest version and update plp docker image

README.md Update README.md



# Strength in methodology

- Reproducibility
- **Pre-specification of statistical analytic plan**
- Active Comparator, New-User cohort design
- Using three large databases from US and Korea
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- 96 Negative controls (Falsification endpoint)
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  - 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	SC You	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-counter, the constraint for the concomitant use of aspirin in target and comparator cohort was removed.
1.2	3 September 2019	SC You	Changing primary analysis from variable ratio PS matching to unconditioned one-to-one PS matching
1.3	28 October 2019	SC You	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



# 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)



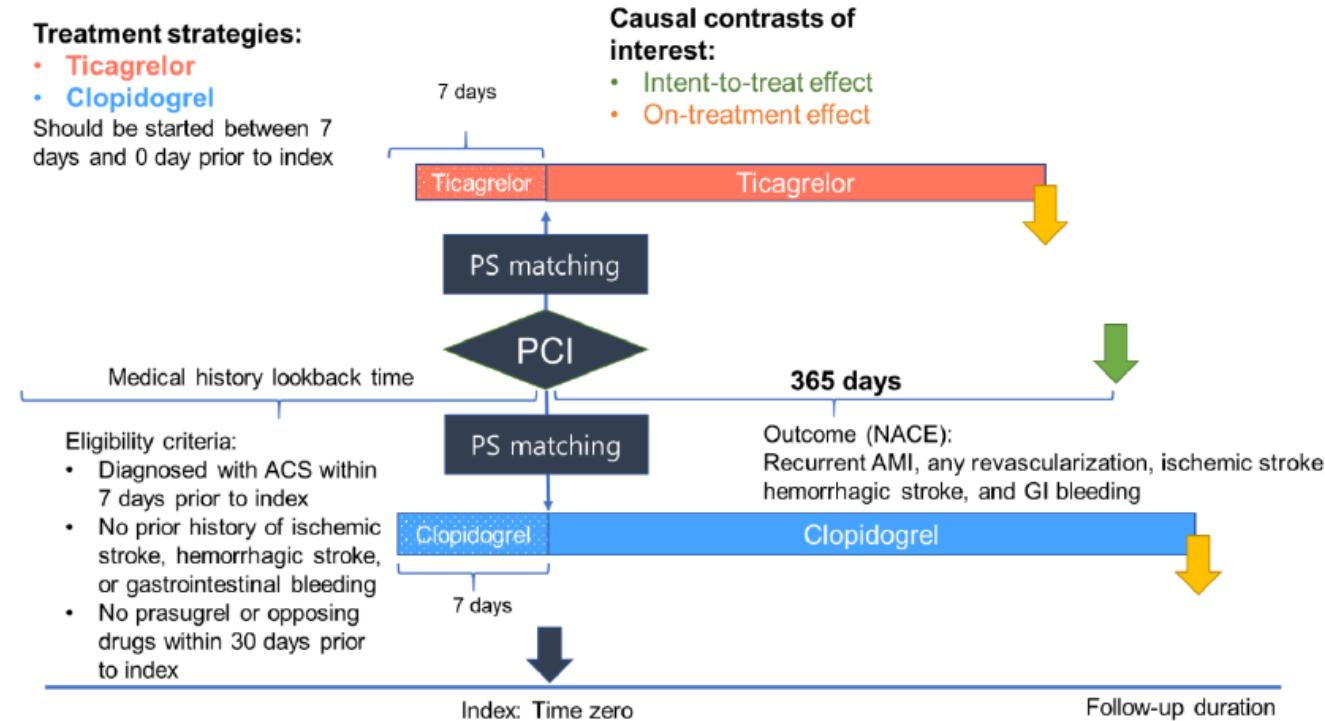
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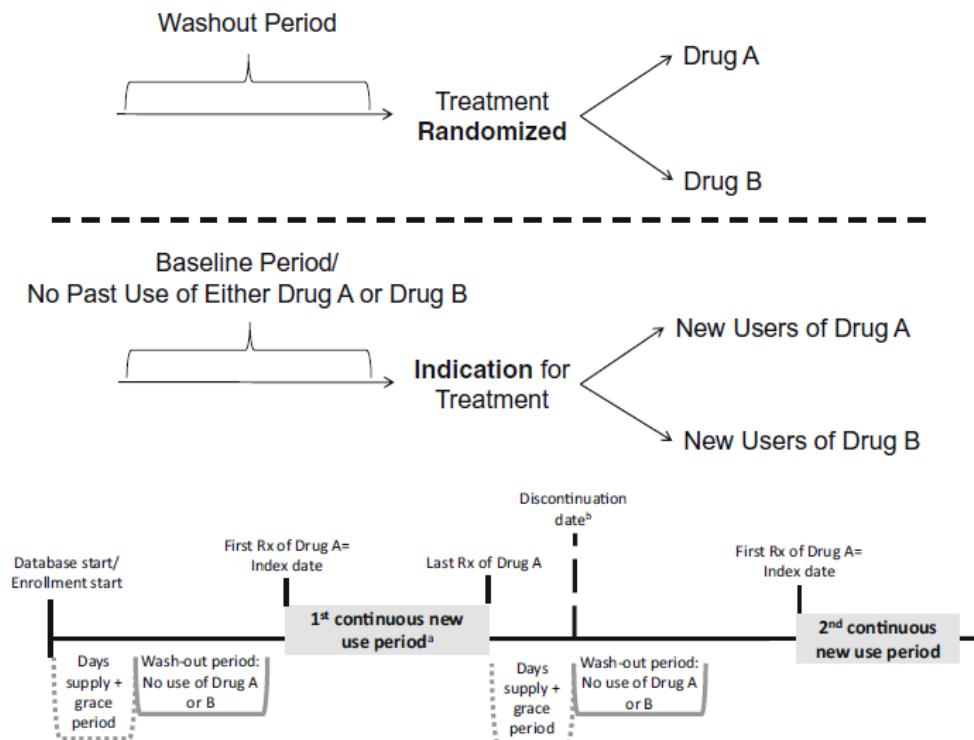
# Method: Study Population

- Inclusion Criteria
  - Adults ( $\geq 20$  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



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

Jennifer L. Lund<sup>1</sup> · David B. Richardson<sup>1</sup> · Til Stürmer<sup>1</sup>





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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<sup>1</sup> 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)



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# Prespecified Falsification End Points

## Can They Validate True Observational Associations?

Vinay Prasad, MD

Anupam B. Jena, MD, PhD

**A**S 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.<sup>1</sup> Several solutions to the problem of incorrect observational results have been suggested,<sup>1,2</sup> emphasizing the importance of a record not only of significant findings but of all analyses conducted.<sup>2</sup>

An important and increasingly familiar type of observa-

mur fractures and 716 atypical fractures.<sup>5</sup> 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.<sup>2</sup> 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<sup>1,2,3</sup>, Eric Tchetgen Tchetgen<sup>1,3,4</sup>, and Ted Cohen<sup>5,1,3</sup>**

<sup>1</sup> Department of Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115

<sup>2</sup> Department of Immunology and Infectious Diseases, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115

<sup>3</sup> Center for Communicable Disease Dynamics, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115

<sup>4</sup> Department of Biostatistics, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115

<sup>5</sup> 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

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<sup>c</sup> Observational Medicine  
<sup>d</sup> University of Michigan  
<sup>e</sup> Columbia University

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.<sup>2</sup> 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



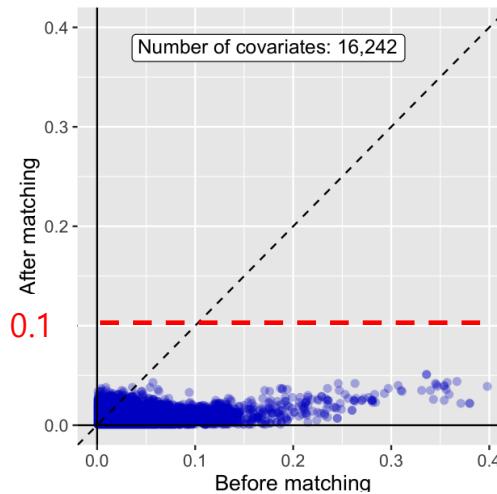
# Method: Statistical Analysis

- 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)

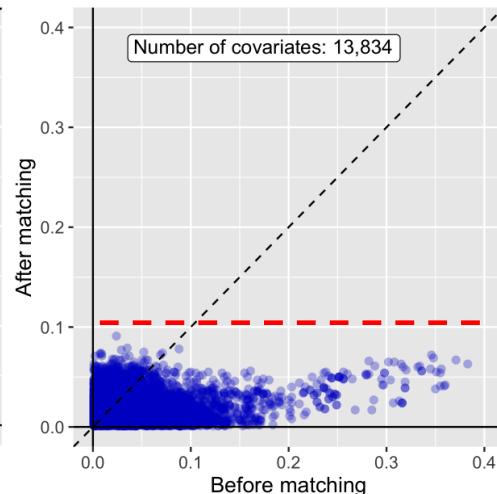


# Balance before and after PS matching and Systematic error control

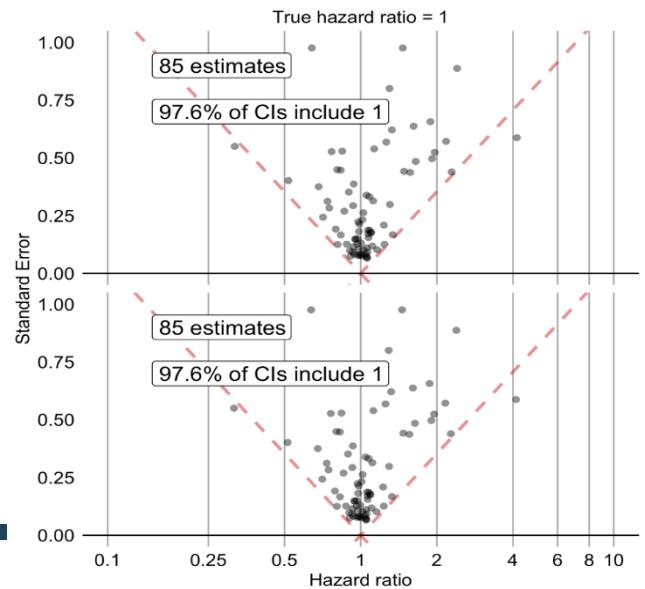
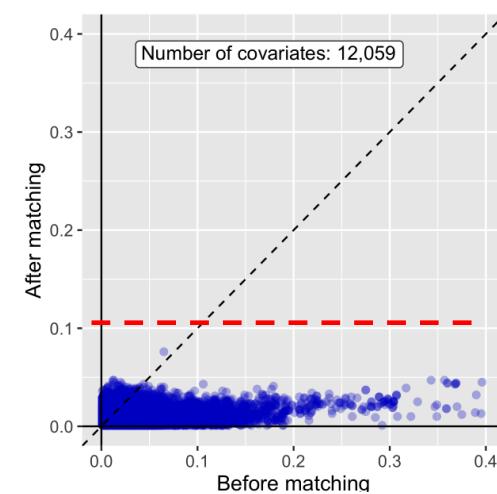
A.Optum PanTHER



B.IQVIA-Hospital



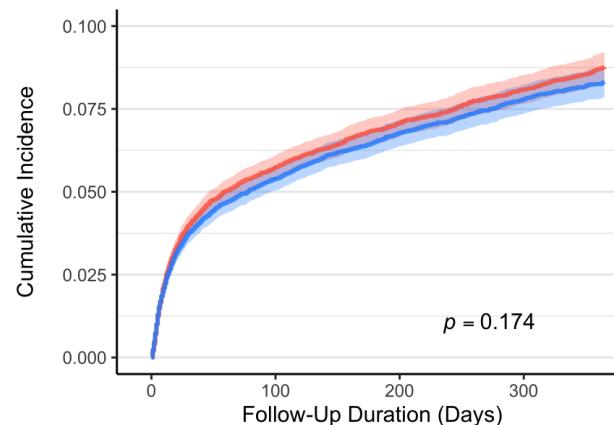
C.HIRA



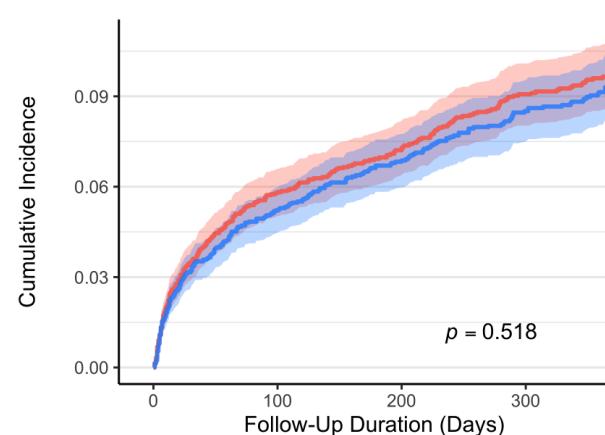


# Primary endpoint: 1-year NACE

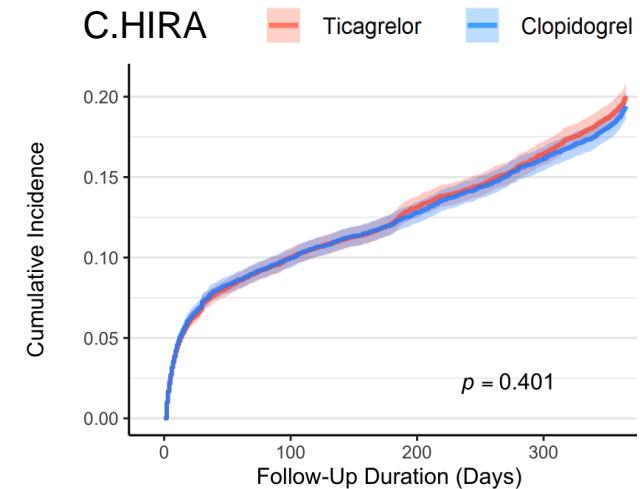
A. Optum PanTher



B. IQVIA-Hospital



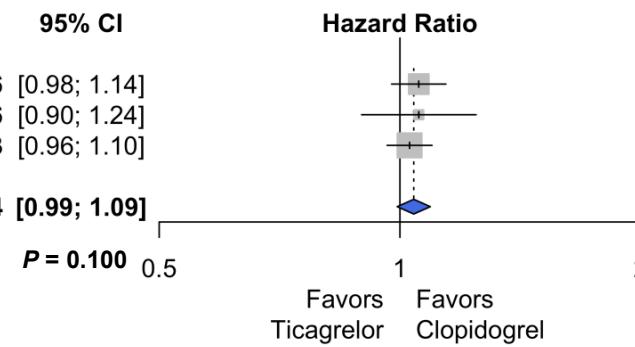
C.HIRA



D. Meta-analysis

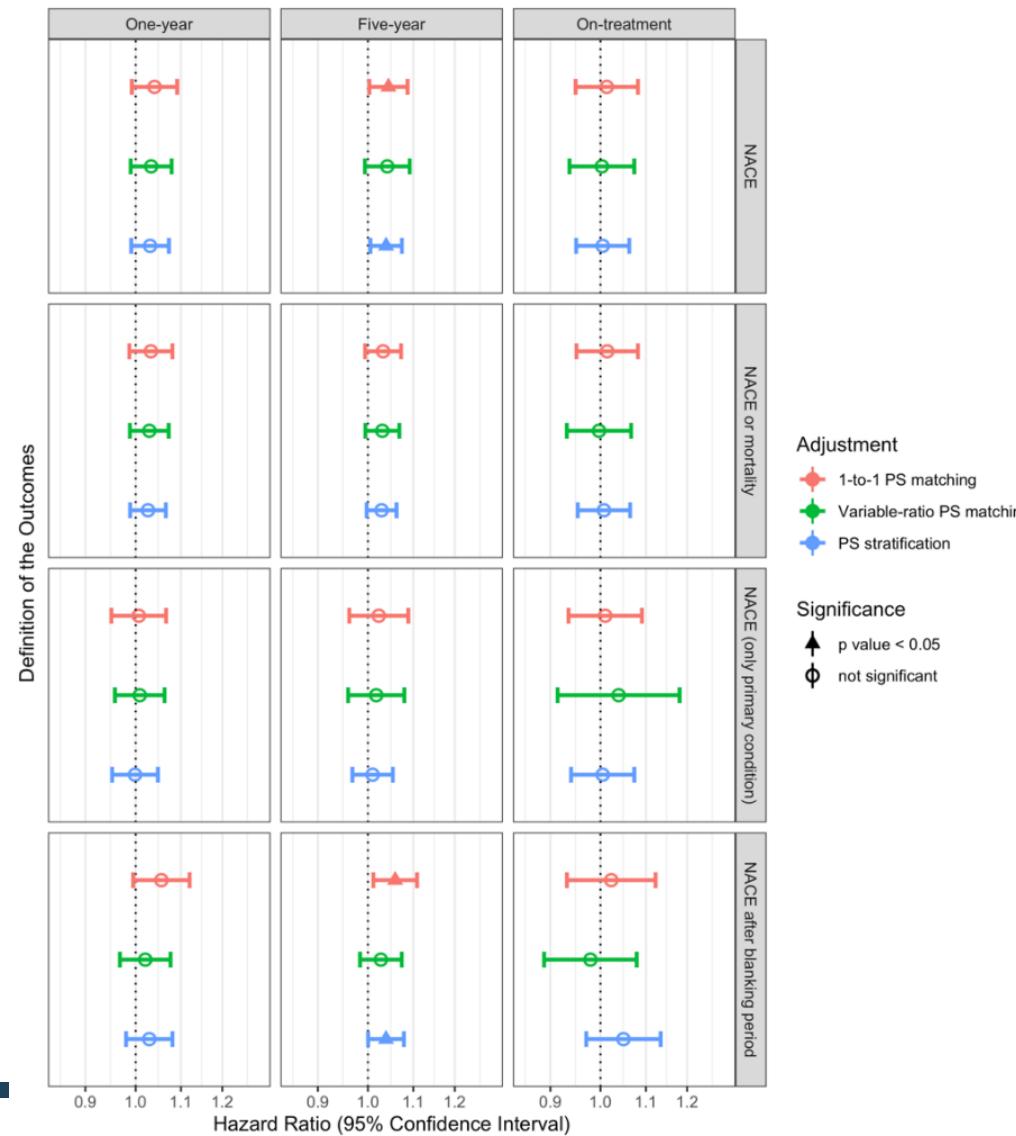
Source	Ticagrelor		Clopidogrel		HR	95% CI
	Total	Event	Total	Event		
OptumPanther	16,388	1,308	16,388	1,220	1.06	[0.98; 1.14]
IQVIA - Hospital	3,998	294	3,998	272	1.06	[0.90; 1.24]
HIRA	10,890	1,881	10,890	1,817	1.03	[0.96; 1.10]
<b>Overall</b>	<b>31,276</b>	<b>3,483</b>	<b>31,276</b>	<b>3,309</b>	<b>1.04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

Heterogeneity:  $I^2 = 0.0\%$



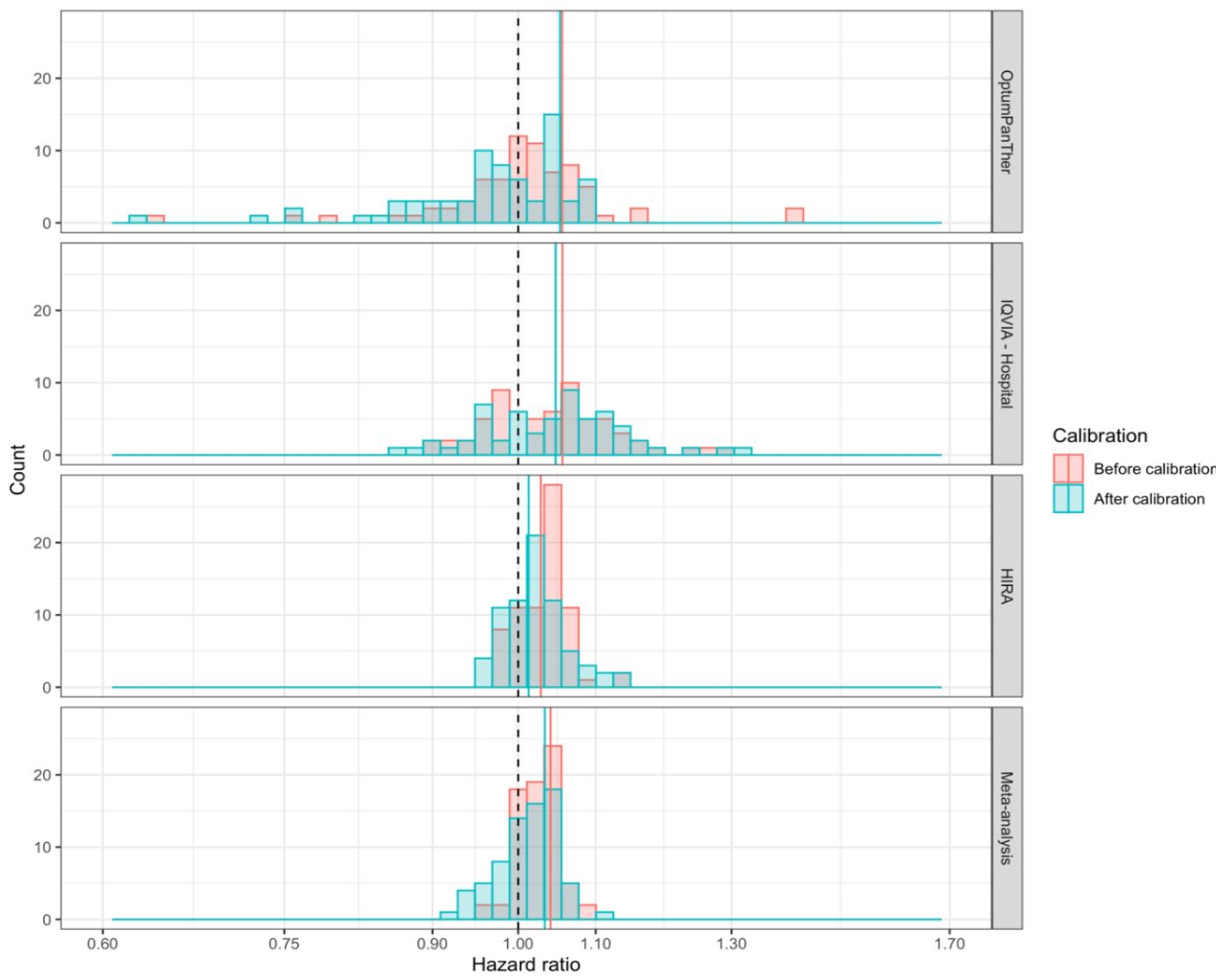


# Consistency in the results of the primary endpoint in sensitivity analyses



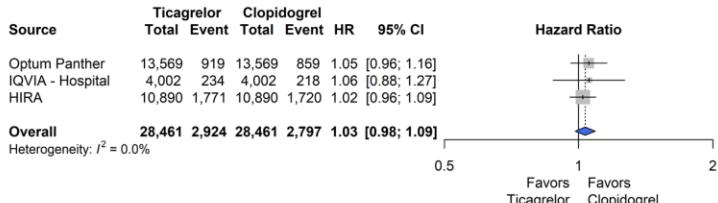


# Distribution of risk estimates for NACE

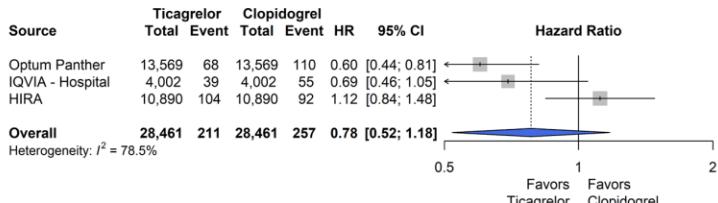




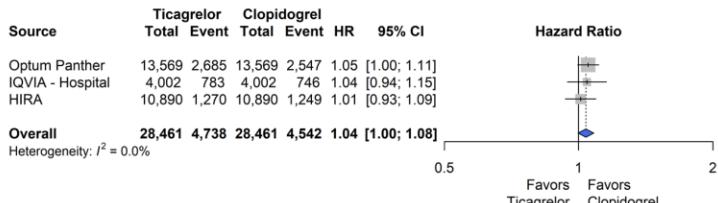
### A. Ischemic event



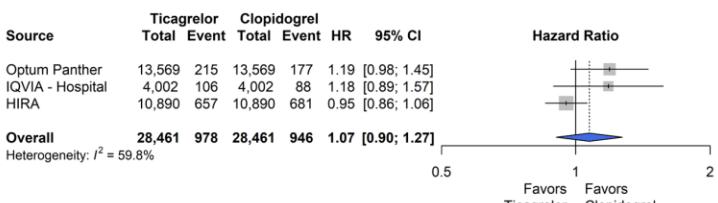
### B. Ischemic stroke



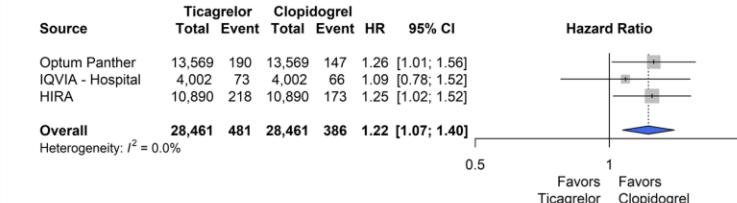
### C. Recurrent acute MI



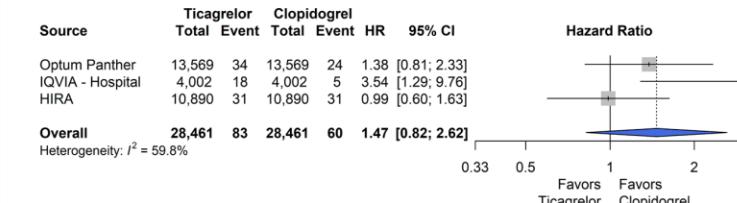
### D. Any revascularization



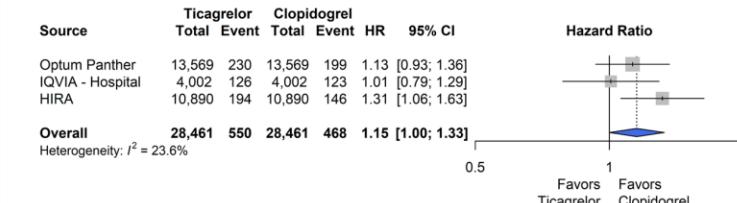
### E. Hemorrhagic event



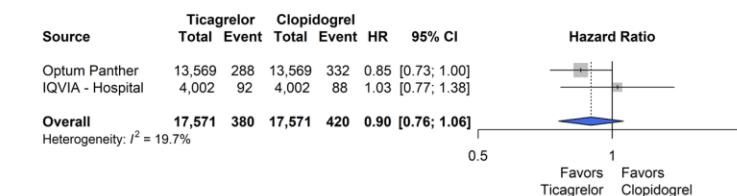
### F. Hemorrhagic stroke



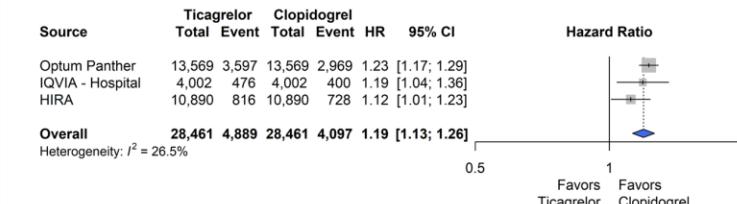
### G. GI bleeding



### H. Overall death

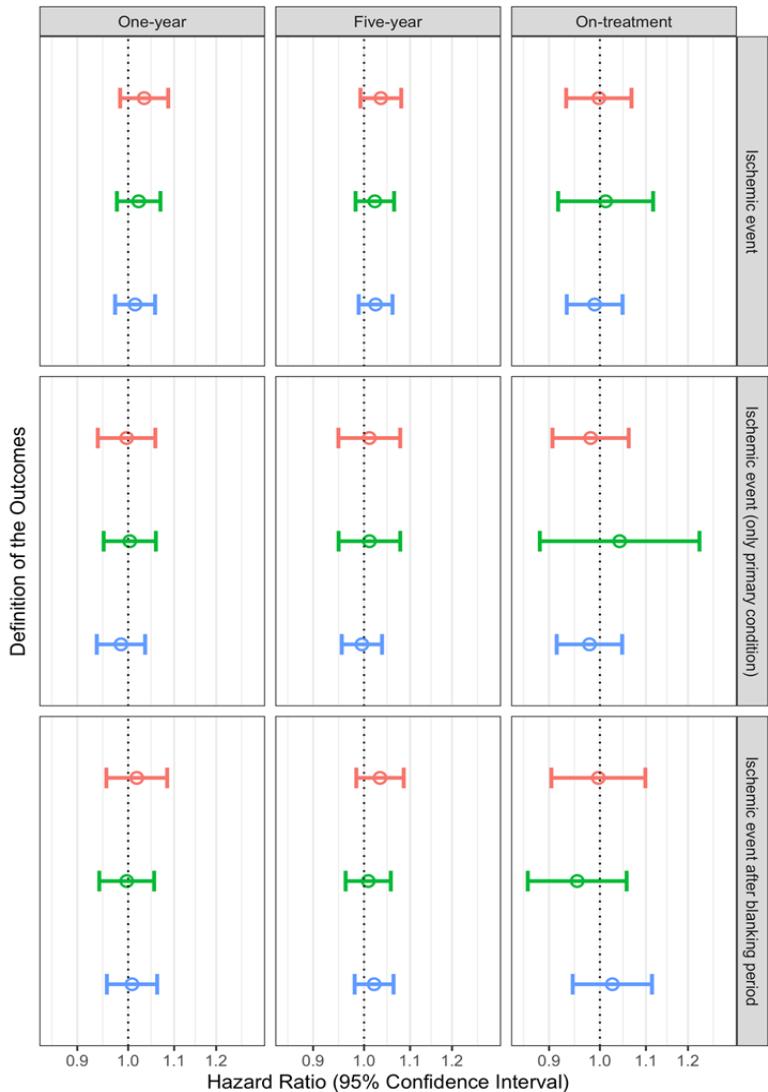


### I. Dyspnea

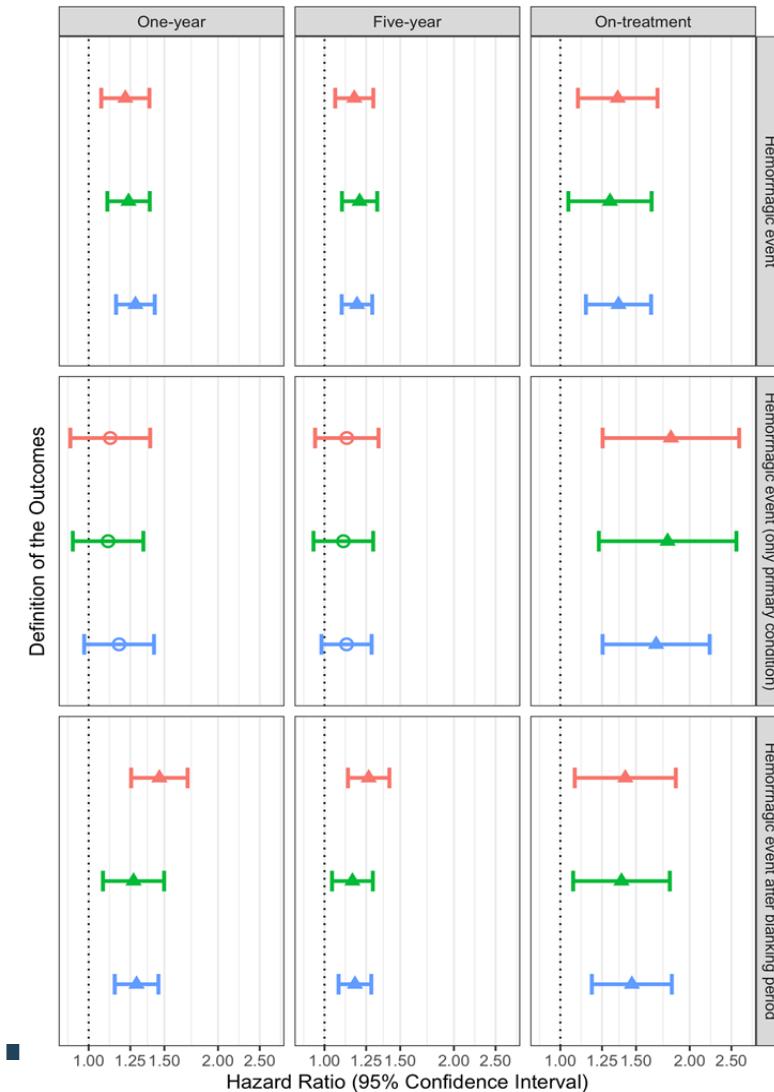




### A. Ischemic event



### B. Hemorrhagic event



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.**

# 국내 CDM 데이터망 구축 현황

## CDM 변환 병원 목록

No.	병원 명	병원 구분	변환 환자 수
1	가톨릭대학교 성모병원	3차	3,223,259
2	강동경희대학교병원	2차	822,183
3	강동성심병원	2차	1,662,083
4	강원대학교병원	2차	510,000
5	경북대학교병원	3차	1,002,381
6	경희의료원	3차	2,101,456
7	고려대학교 안암병원	3차	1,856,484
8	고려대학교 안산병원	3차	1,465,833
9	고려대학교 구로병원	3차	2,077,344
10	국민건강보험공단 일산병원	2차	1,358,280
11	대구가톨릭대학교병원	3차	1,688,980
12	동국대학교 일산병원	2차	779,474
13	메디플렉스 세종인천병원	2차	946,000
14	부산대학교병원	3차	1,753,002

현 누적 변환 기관 수 : **32 병원** (3차: 20개 / 2차: 12개)

현 누적 변환 환자 수 : **44,596,864명**

No.	병원 명	병원 구분	변환 환자 수
15	분당서울대학교병원	3차	1,734,565
16	분당차병원	2차	2,363,386
17	서울대학교병원	3차	3,068,874
18	세종부천병원	2차	946,000
19	순천향부천병원	3차	-
20	순천향천안병원	3차	-
21	순천향구미병원	2차	-
22	순천향서울병원	2차	-
23	아주대학교병원	3차	2,400,000
24	연세원주세브란스병원	2차	-
25	원광대학교병원	3차	1,001,797
26	이화여자대학교 목동병원	2차	1,745,549
27	인하대학교병원	3차	1,977,256
28	전남대학교병원	3차	2,168,701
29	전북대학교병원	3차	1,433,023
30	칠곡경북대학교병원	3차	1,002,381
31	한양대학교병원	3차	1,783,111
32	화순전남대학교병원	3차	1,725,462



# Pragmatic Clinical Trial based on Nationwide CDM data network

JAMA Cardiology | Special Communication

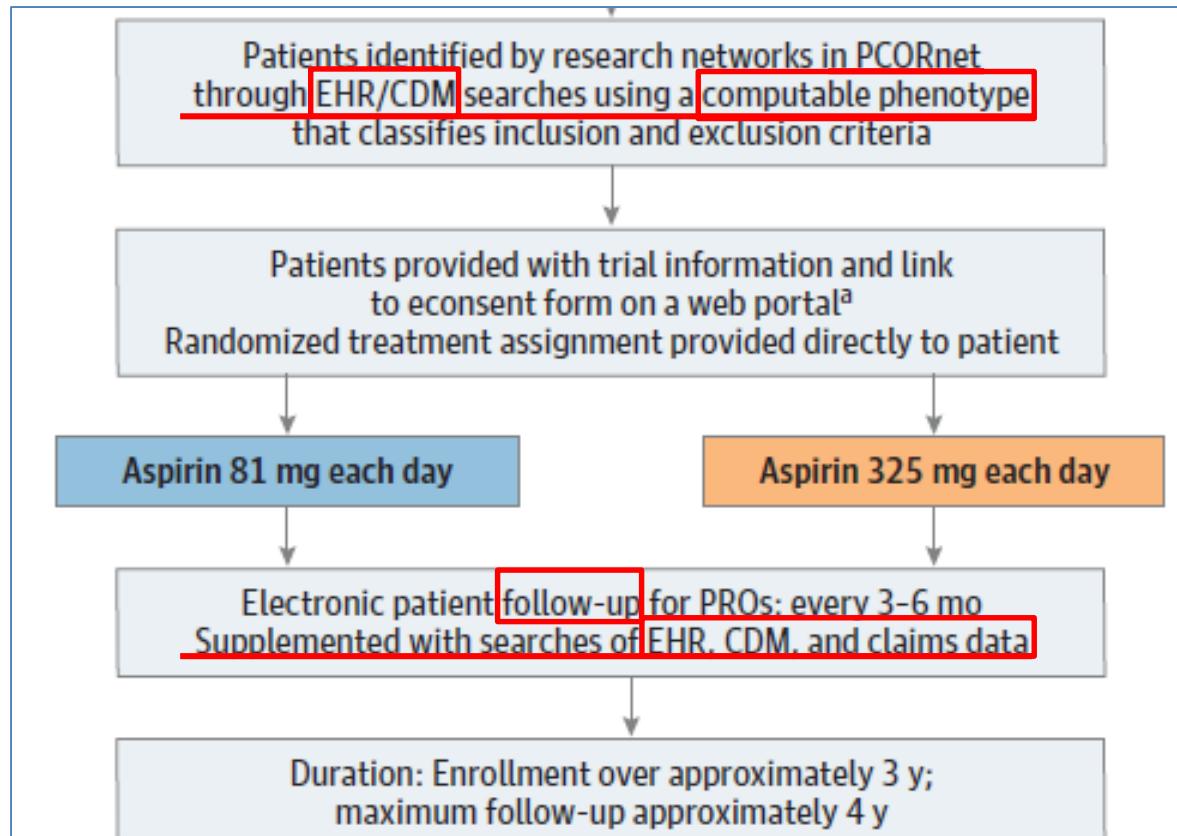
## Rationale and Design of the Aspirin Dosing—A Patient-Centric Trial Assessing Benefits and Long-term Effectiveness (ADAPTABLE) Trial

**DESIGN, SETTING, AND PARTICIPANTS** This pragmatic, open-label, patient-centered, randomized clinical trial is being conducted in 15 000 patients within the National Patient-Centered Clinical Research Network (PCORnet), a distributed research network of partners including clinical research networks, health plan research networks, and patient-powered research networks across the United States. Patients with established ASCVD treated in routine clinical practice within the network are eligible. Patient recruitment began in April 2016. Enrollment was completed in June 2019. Final follow-up is expected to be completed by June 2020.

**MAIN OUTCOMES AND MEASURES** The primary efficacy end point is the composite of all-cause mortality, hospitalization for nonfatal myocardial infarction, or hospitalization for a nonfatal stroke. The primary safety end point is hospitalization for major bleeding associated with a blood-product transfusion. End points are captured through regular queries of the health systems' common data model within the structure of PCORnet's distributed data environment.

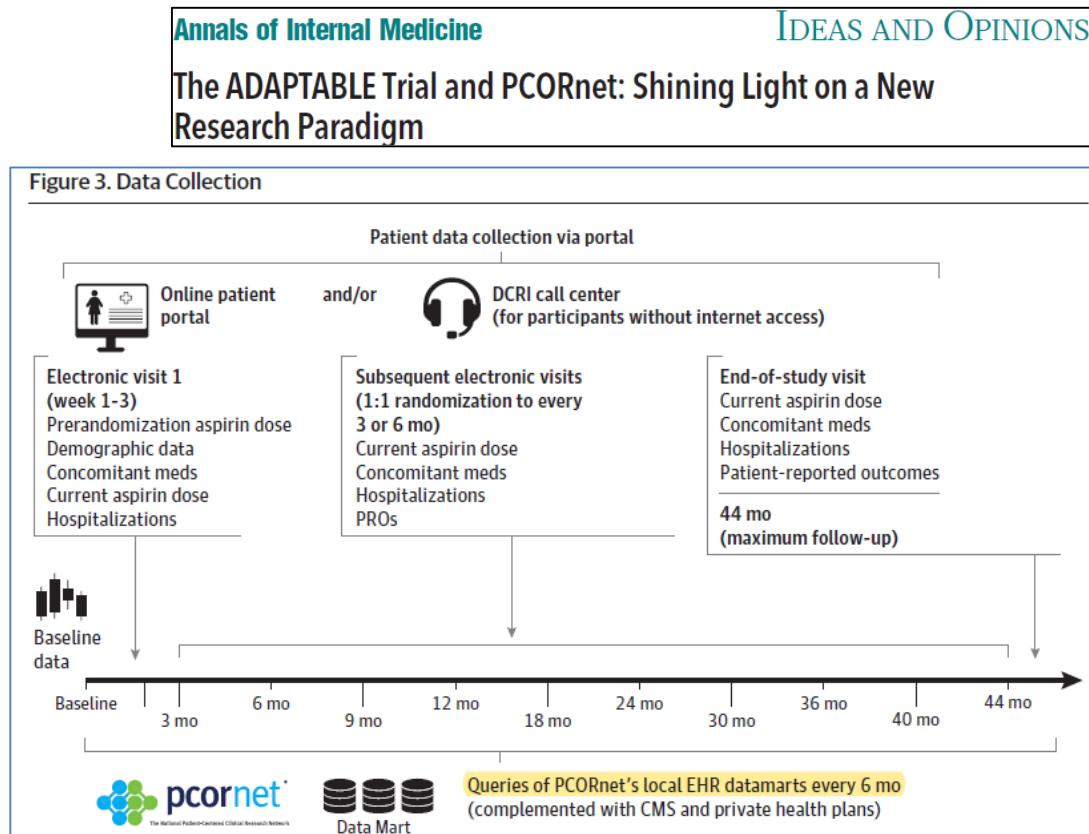
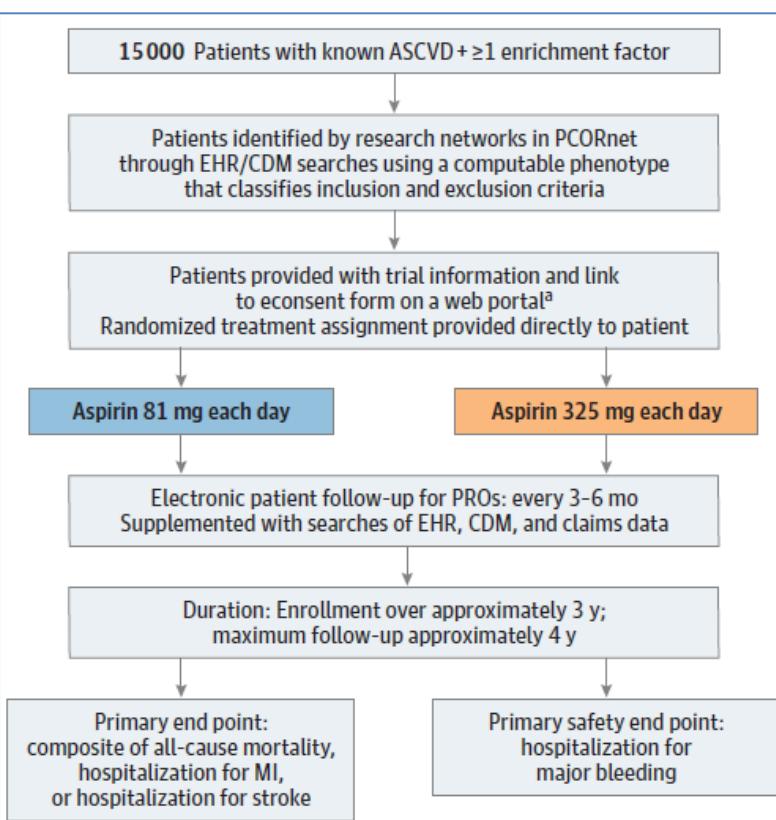


# Pragmatic Clinical Trial based on Nationwide CDM data network





# Pragmatic Clinical Trial based on Nationwide CDM data network



Marquis-Gravel *et al.*, JAMA Cardiology,  
2020

Hernandez *et al.*, Annals of Internal Medicine, 2015



# Pragmatic Clinical Trial based on Nationwide CDM data network

ORIGINAL ARTICLE

## Comparative Effectiveness of Aspirin Dosing in Cardiovascular Disease

W.S. Jones, H. Mulder, L.M. Wruck, M.J. Pencina, S. Kripalani, D. Muñoz,

D.L. Crenshaw, M.B. Effron, R.N. Re, K. Gupta, R.I.

E.M. Handberg, B.R. Manning, S.K. Jain, S. Girotra, D. R.

Y.H. Goldberg, V.L. Roger, R. Hess, C.P. Benziger, P. F.

K. Haynes, J.J. VanWormer, K.U. Knowlton, J.L. Kraschnew

F.S. Ahmad, J.C. McClay, J.R. Campbell, D.S. Bell, G.

A. Paranjape, M.T. Roe, H.R. Robertson, L.H. Curtis,

B.G. Hammill, D.F. Harris, L.G. Qualls, G. Marqui

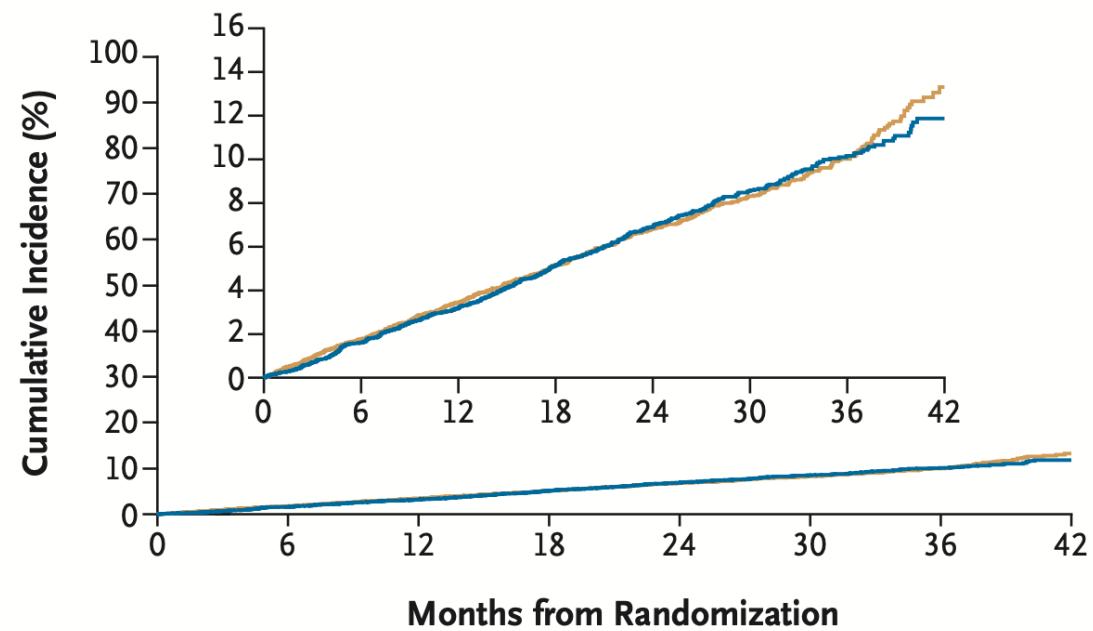
G.M. Marcus, T.W. Carton, E. Nauman, L.R. Waitman,

K.M. McTigue, R. Kaushal, F.A. Masoudi, E.M. Antman

J.G. Merritt, L.S. Brown, D.N. Zemon, T.E. McCormick III

R.L. Rothman, R.A. Harrington, and A.F. Hernandez,

### A Death, Hospitalization for Myocardial Infarction, or Hospitalization for Stroke



### No. at Risk

81-mg dose	7540	7357	7177	5627	4190	2712	1558	636
325-mg dose	7536	7297	7095	5544	4090	2613	1489	592



# 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
  - Nonetheless, the result of observational study should be verified in a prospective randomized trial.
- Pragmatic clinical trial leveraging both magic of randomization and medical data infrastructure of Korea may be crucial to answer the continued questions.

*Thank  
you*  
for your time