CDM 활용 연구 시의 역학적 고찰 및 연구사례

연세대학교 의생명시스템정보학교실 유승찬

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What evidence does OHDSI seek to generate from observational data?

- **Clinical characterization 임상 특성 확인**
  - **Natural history 질병 자연사**: Who are the patients who have diabetes? Among those patients, who takes metformin?
  - **Quality improvement 의료 질 관리**: What proportion of patients with diabetes experience disease-related complications?
- **Patient-level prediction 환자수준 예측 (인공지능)**
  - **Precision medicine 정밀 의료**: Given everything you know about me and my medical history, if I start taking metformin, what is the chance that I am going to have lactic acidosis in the next year?
  - **Disease interception 선제적 질병 예방**: Given everything you know about me, what is the chance I will develop diabetes?
- **Population-level estimation 인구수준 추정 (역학연구)**
  - **Safety surveillance 안정성 감시**: Does metformin cause lactic acidosis?
  - **Comparative effectiveness 비교효과 연구**: Does metformin cause lactic acidosis more than glyburide?
  - **Pragmatic clinical trial 실용적 임상시험**

Causal inference

- Causal inference: *Can the alternative treatment change the clinical outcome of the patient?*
- For the observational data, the core question is how to get the **counterfactual outcome**. This is challenging for two reasons
  - 1. We only observe the factual outcome and **never the counterfactual outcomes**
  - 2. Treatments are typically **not assigned at random** in observational data

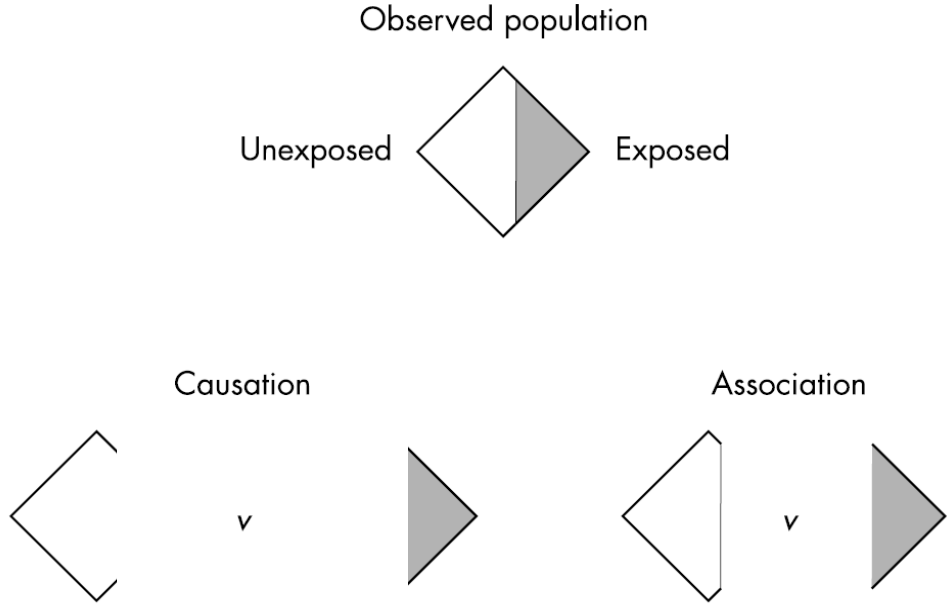

Figure 1 Causation is defined by a different risk in the entire population under two potential exposure values; association is defined by a different risk in the subsets of the population determined by the subjects' actual exposure value.

Hernán, J Epidemiol Community Health, 2004

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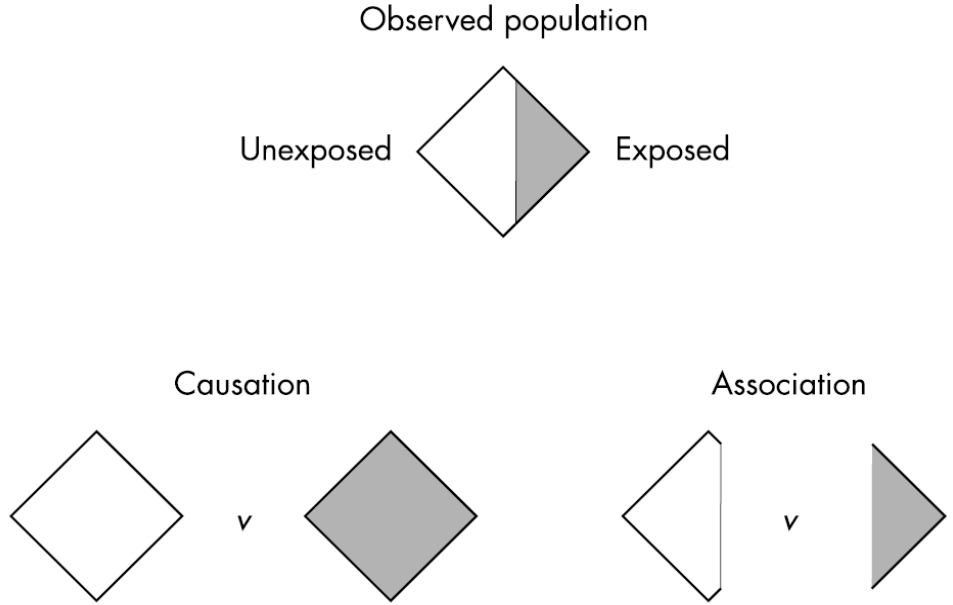

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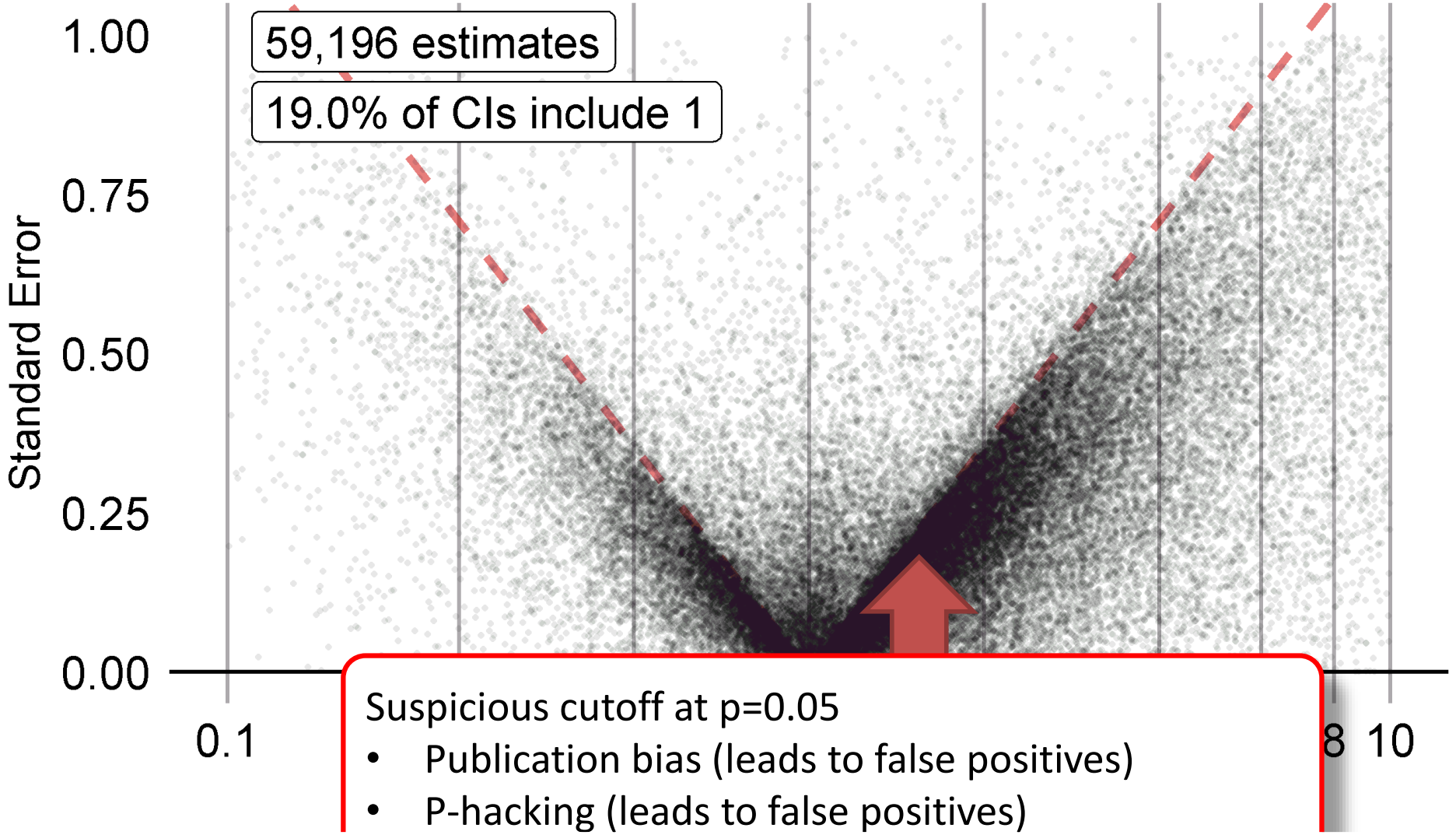
Most Published Research findings are False

Table 4. PPV of Research Findings for Various Combinations of Power (1 – β), Ratio of True to Not-True Relationships *(R)*, and Bias *(u)*

1 – β	*R*	*u*	Practical Example	PPV
0.80	1:1	0.10	Adequately powered RCT with little bias and 1:1 pre-study odds	0.85
0.95	2:1	0.30	Confirmatory meta-analysis of good-quality RCTs	0.85
0.80	1:3	0.40	Meta-analysis of small inconclusive studies	0.41
0.20	1:5	0.20	Underpowered, but well-performed phase I/II RCT	0.23
0.20	1:5	0.80	Underpowered, poorly performed phase I/II RCT	0.17
0.80	1:10	0.30	Adequately powered exploratory epidemiological study	0.20
0.20	1:10	0.30	Underpowered exploratory epidemiological study	0.12
0.20	1:1,000	0.80	Discovery-oriented exploratory research with massive testing	0.0010
0.20	1:1,000	0.20	As in previous example, but with more limited bias (more standardized)	0.0015

Ioannidis, et al., "Why Most Published Research Findings Are False." *PLoS Medicine*, 2005

Published observational study results



LEGEND

LARGE-SCALE EVIDENCE GENERATION AND EVALUATION IN A NETWORK OF DATABASES

Journal of the American Medical Informatics Association, 27(8), 2020, 1331–1337
doi: 10.1093/jamia/ocaa103
Perspective

Perspective

Principles of Large-scale Evidence Generation and Evaluation across a Network of Databases (LEGEND)

Martijn J. Schuemie [1,2], Patrick B. Ryan [1,3], Nicole Pratt [4], RuiJun Chen [3,5], Seng Chan You [6], Harlan M. Krumholz [7], David Madigan [8], George Hripcsak [3,9], and Marc A. Suchard [2,10]

Principles of the LEGEND initiatives

1. LEGEND will generate evidence **at a large scale**.
2. **Dissemination** of the evidence will not depend on the estimated effects.
3. LEGEND will generate evidence using a **prespecified analysis design**.
4. LEGEND will generate evidence by **consistently** applying a **systematic process** across all research question.
5. LEGEND will generate evidence **using best practices**.
6. LEGEND will include **empirical evaluation** through the use of **control questions**.
7. LEGEND will generate evidence using **open-source software** that is freely available to all.
8. LEGEND will **not** be used to **evaluate new methods**.
9. LEGEND will generate evidence across a **network of multiple databases**.
10. LEGEND will maintain data confidentiality; **patient-level data will not be shared** between sites in the network.

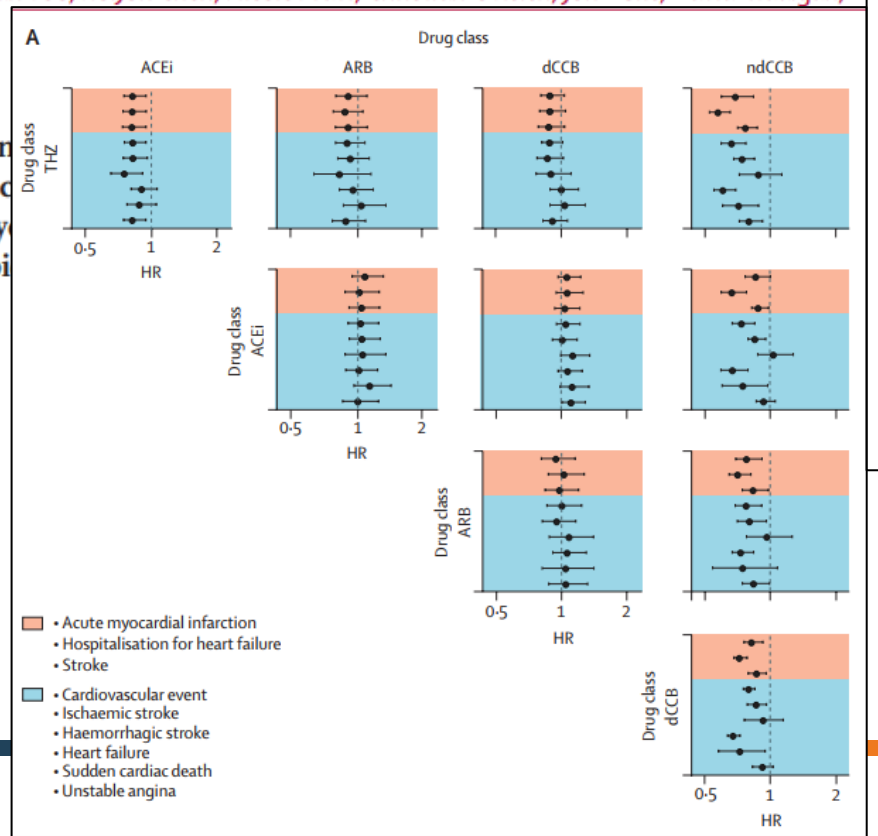
LEGEND: comparative effectiveness and safety of first-line antihypertensive drug classses

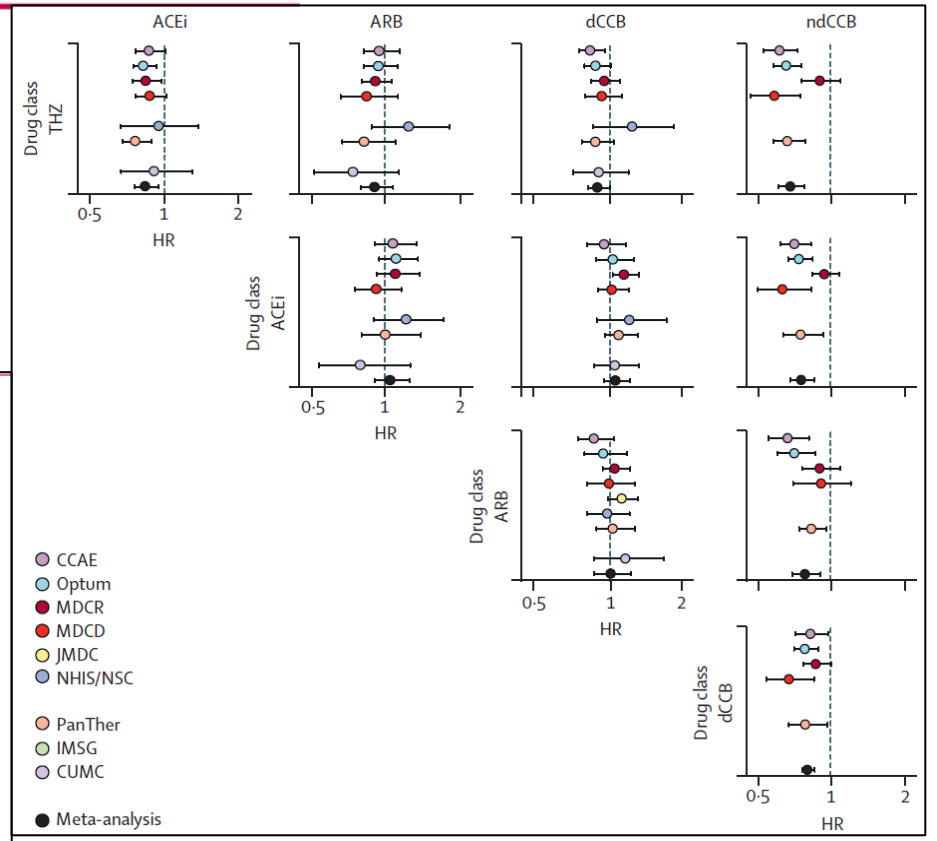
Comprehensive comparative effectiveness and safety of first-line antihypertensive drug classes: a systematic, multinational, large-scale analysis

Marc A Suchard, Martijn J Schuemie, Harlan M Krumholz, Seng Chan You, RuiJun Chen, Nicole Pratt, Christian G Reich, Jon Duke, David Madigan, George Hripcsak, Patrick B Ryan

Summary

Background Uncertainty remains about the optimal r
mending any primary agent among the first-line drug c
enzyme inhibitors, angiotensin receptor blockers, dihy
calcium channel blockers, in the absence of comorbi
choice.





Critical design elements

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- Critical design elements include:
  - Pre-specification of study design
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  - Active-comparator
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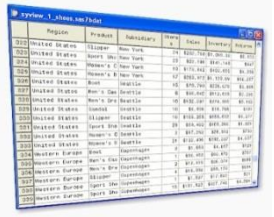
What do epi studies currently look like?



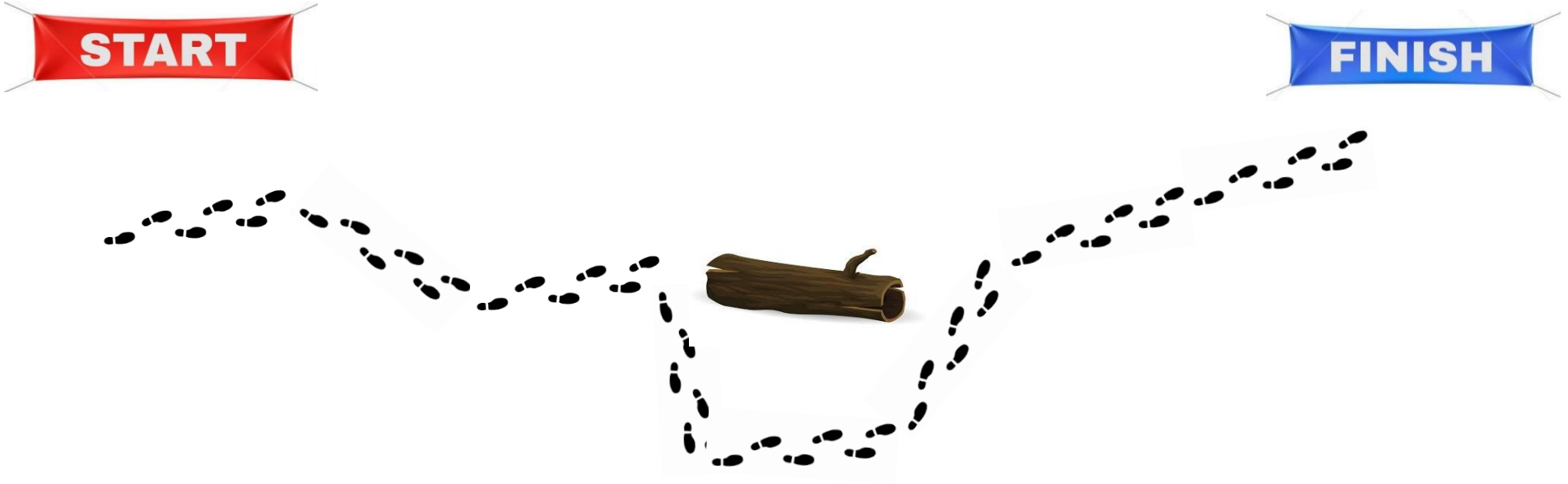
Data set

SPSS®

```
#> Model type: cox
#> Stratified: FALSE
#> Use covariates: FALSE
#> Status: OK
#>
#>            Estimate lower .95 upper .95     logRr seLogRr
#> treatment  0.944681   0.811174  1.096721 -0.056908  0.0769
```

Paper

A journey from data set to paper



Most epidemiologists view a study as a journey from data set to paper.

- The protocol might be your map
- You will come across obstacles that you will have to overcome
- Several steps will require manual intervention
- In the end, it will be impossible to retrace your exact steps

p-Hacking

Hack Your Way To Scientific Glory

You're a social scientist with a hunch: **The U.S. economy is affected by whether Republicans or Democrats are in office.** Try to show that a connection exists, using real data going back to 1948. For your results to be publishable in an academic journal, you'll need to prove that they are "statistically significant" by achieving a low enough p-value.

1 CHOOSE A POLITICAL PARTY

Republicans | **Democrats**

2 DEFINE TERMS

Which politicians do you want to include?

- ☐ Presidents
- ☐ Governors
- ☒ Senators
- ☒ Representatives

How do you want to measure economic performance?

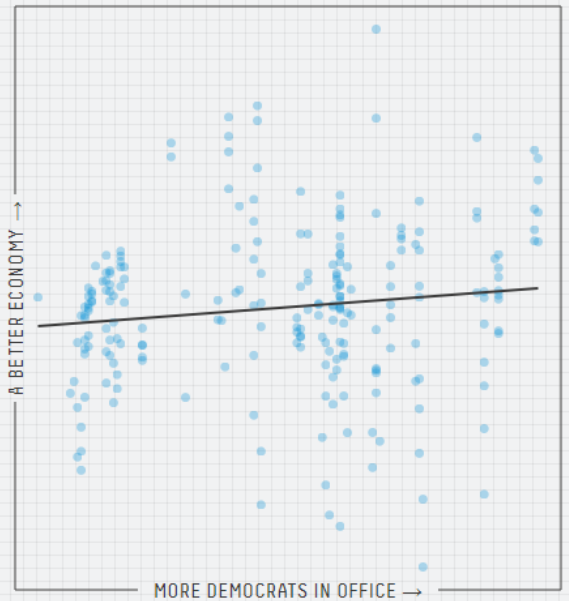
- ☒ Employment
- ☒ Inflation
- ☒ GDP
- ☐ Stock prices

Other options

- ☐ **Factor in power**
  Weight more powerful positions more heavily
- ☒ **Exclude recessions**
  Don't include economic recessions

3 IS THERE A RELATIONSHIP?

Given how you've defined your terms, does the economy do better, worse or about the same when more Democrats are in office? Each dot below represents one month of data.



4 IS YOUR RESULT SIGNIFICANT?

If there were no connection between the economy and politics, what is the probability that you'd get results at least as strong as yours? That probability is your p-value, and by convention, you need a **p-value of 0.05 or less** to get published.

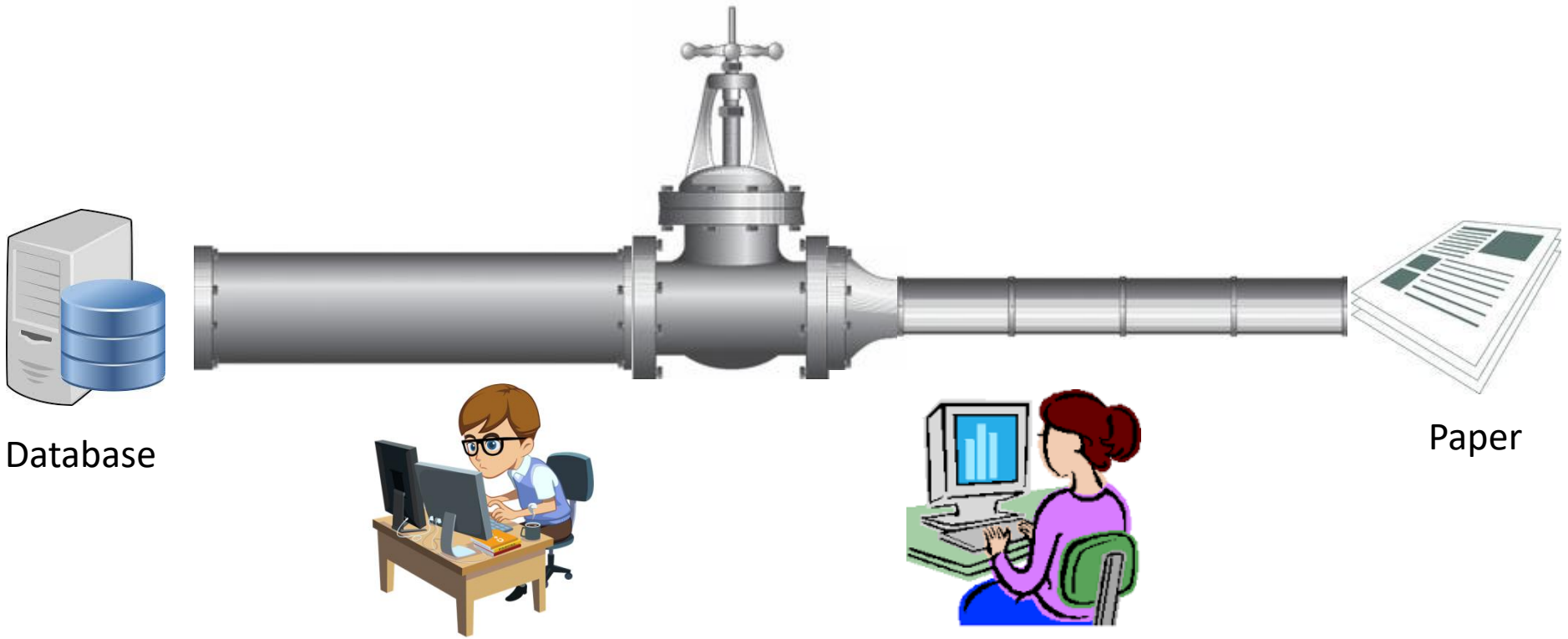
Result: Almost

Your **0.06** p-value is close to the 0.05 threshold. Try tweaking your variables to see if you can push it over the line!

If you're interested in reading real (and more rigorous) studies on the connection between politics and the economy, see the work of Larry Bartels and Alan Blinder and Mark Watson.

Data from The @unitedstates Project, National Governors Association, Bureau of Labor Statistics, Federal Reserve Bank of St. Louis and Yahoo Finance.

What should OHDSI studies look like?



A study should be like a pipeline
- A fully automated process from database to paper
- ‘Performing a study’ = building the pipeline

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New-user cohort design

- Prevalent user related bias
  - Occurred when allowing participants to enter the cohort at some time after treatment initiation
  - Example: **Nurses' Health Study** (HRT decreased risk of major coronary heart disease in observational study; Grodstein F et al. N Engl J Med 1996; Manson JE et al. N Engl J Med 2003; Hernan et al. Epidemiology 2008)
  - **Can be eliminated in new-user cohort design**
- **Immortal time bias**
  - When treatment is defined based on **some future event** and the period of follow-up prior to treatment initiation is inappropriately classified as 'treated'
  - To avoid: **new-user study design whenever possible** and **avoiding the use of future information to define cohorts** (analyses the data as they are collected, ie. Prospectively)

New-user cohort design

- New-user design
  - identifies all patients **initiating specific treatment in a defined population after a certain length of time free of the treatment (washout period), and follows this patient cohort for endpoints from the time of treatment initiation**
  - **solves issues of comparability between prevalent users and** non-users
  - New users do **not necessarily need to be drug naiive**: they are only required to be naiive for the treatments compared during the wash-out period (eg, one year)

‘Immortal time bias’ fells JAMA journal asthma paper

The paper, “Association of Antibiotic Treatment With Outcomes in Patients Hospitalized for an Asthma Exacerbation Treated With Systemic Corticosteroids,” was written by a group led by Mihaela Stefan, the associate director of the Institute for Healthcare Delivery and Population Science at UMass, and appeared in *JAMA Internal Medicine* in 2019.

Stefan told us:

> *I knew very well about immortal time bias but somehow it slipped through my and my collaborators mind.*
>
> *What we learned is what Dr. Newman said very well – you need to follow the target trial approach and be humble when interpreting the results of observational studies.*

Box 1: Common manifestations of immortal time

- Treatment defined as at least one prescription dispensed after hospital discharge, when the discharge date represents the start of follow-up (cohort entry)—for example, dispensation of an inhaled corticosteroid after a hospital stay for chronic obstructive pulmonary disease[9]

- Treatment groups defined in terms of when after hospital discharge (start of follow-up) a prescription is dispensed—for example, cardiac drugs dispensed within 7 days of discharge for acute myocardial infarction versus later[10] or early versus delayed dispensation of clopidogrel post percutaneous coronary intervention[11]

- Treatment defined as at least one prescription dispensed after a diagnosis, when the date of diagnosis represents the start of follow-up—for example, starting interferon beta after diagnosis of multiple sclerosis[12]

- Treatment status determined over the duration of follow-up—for example, determining an individual's immunisation status at the end of each influenza season[13] or use of β blockers any time during follow-up[14]

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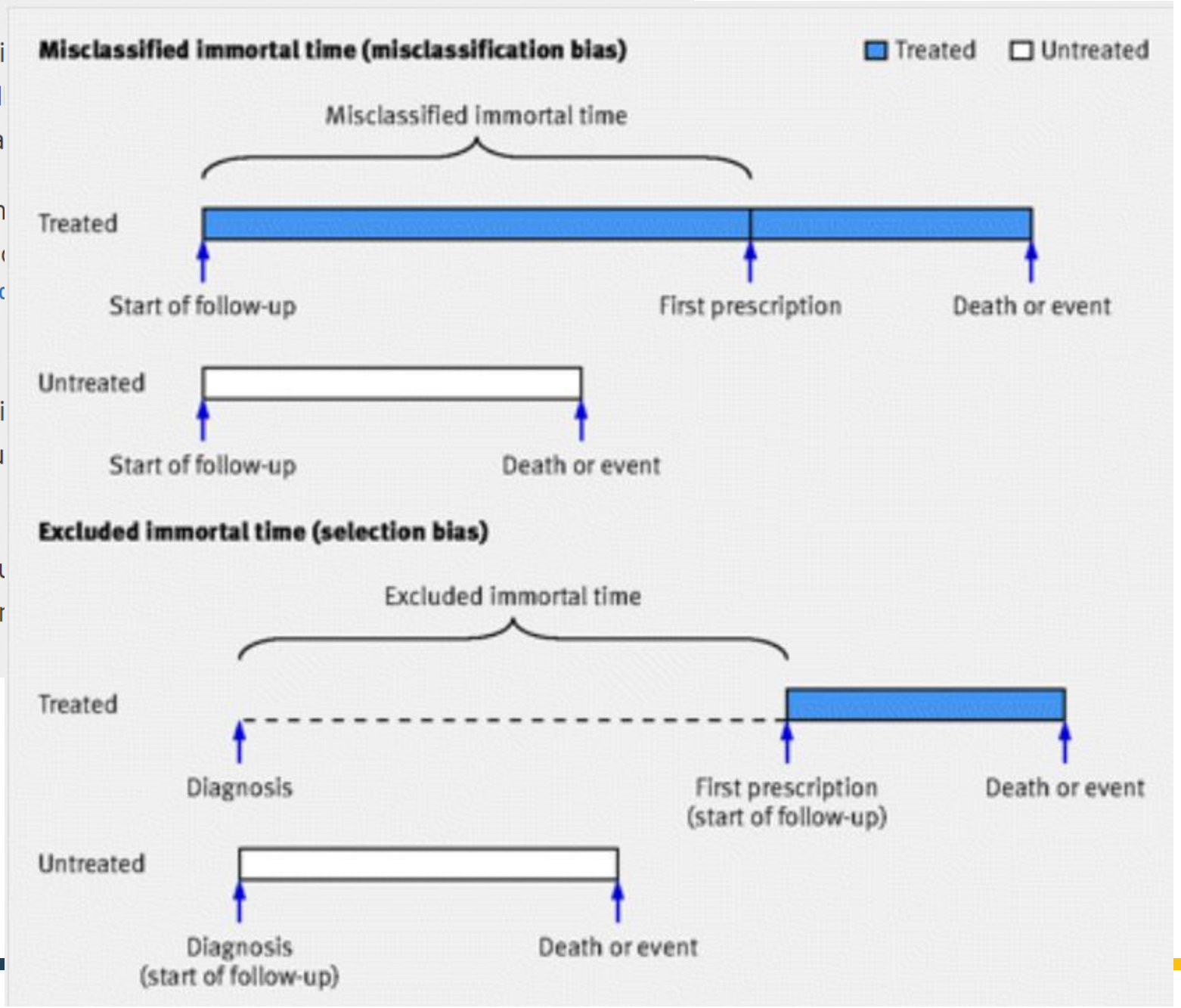
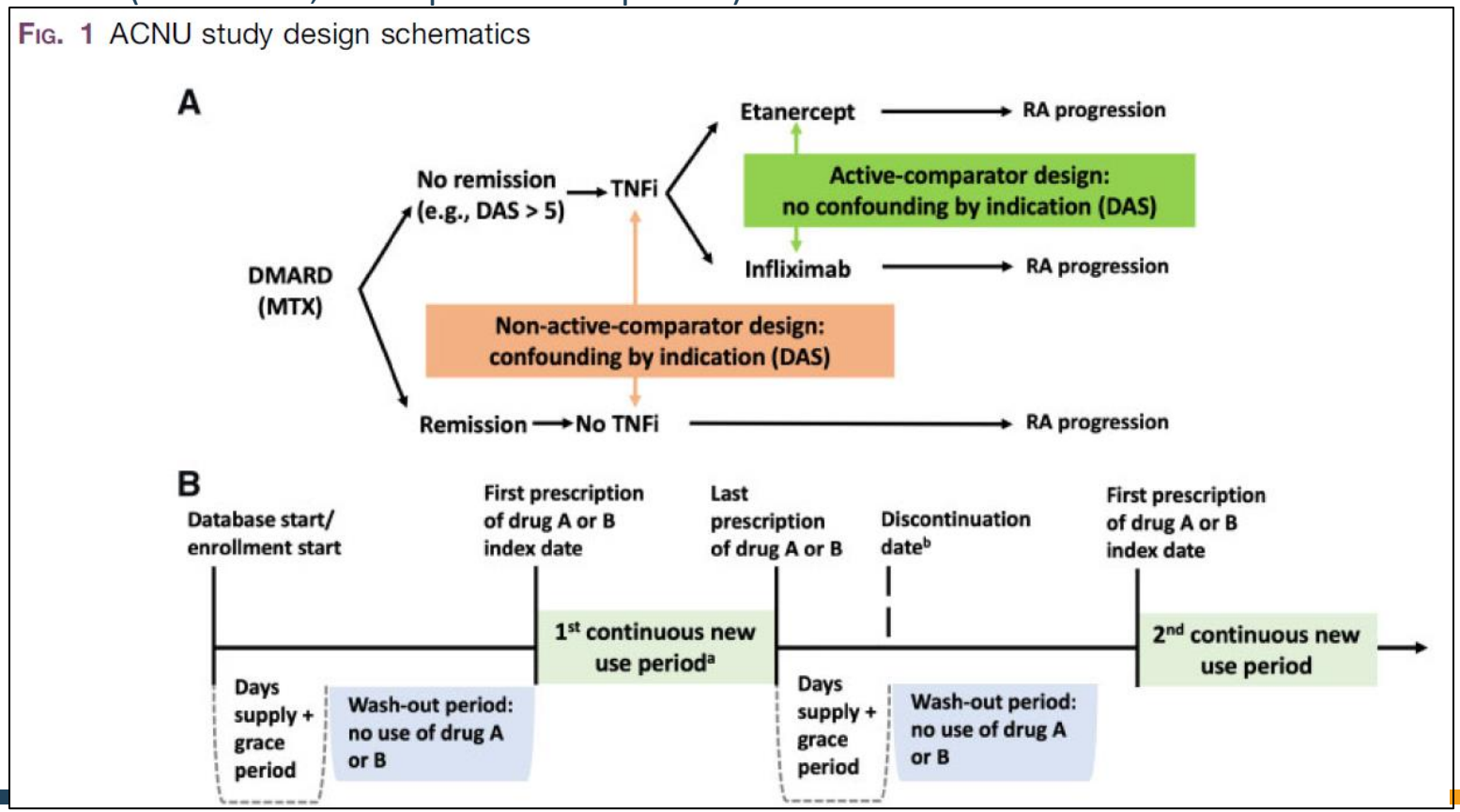


Active comparator-New User

- Identifying initiators of the drug of interest and initiators of an alternative treatment for the same indication.
- Restricting both cohorts to patients with the same indication for treatment and without contraindications (Lund et al., Curr Epidemiol Rep 2015)



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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]

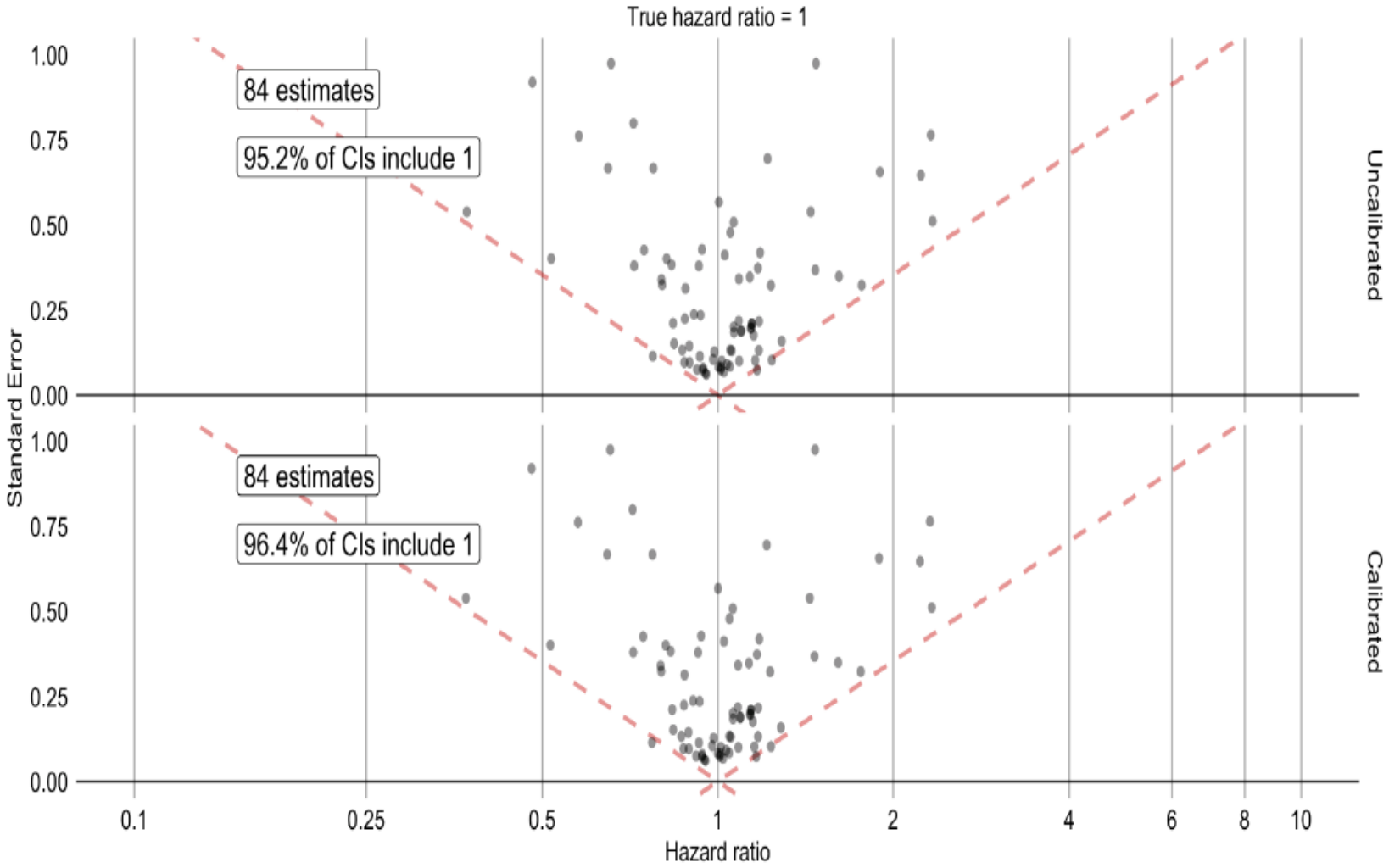
An important and increasingly familiar type of observa-

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

Assessment of systematic error by using falsification endpoints

eFigure 3. Systematic error control of effect estimation in the meta-analysis comparing the risk of net adverse clini the ticagrelor and clopidogrel group under one-year, 1-to-1 propensity score matching design



SCYou et al., JAMA, 2020

2.6. *Calibrating p-values*

Traditional significance testing utilizes a theoretical null distribution that requires a number of assumptions to ensure its validity. Our proposed approach instead derives an empirical null distribution from the actual effect estimates for the negative controls. These negative control estimates give us an indication of what can be expected when the null hypothesis is true, and we use them to estimate an empirical null distribution. We fitted a Gaussian probability distribution to the estimates, taking into account the sampling error of each estimate. We have found that a Gaussian distribution provides a good approximation, and more complex models, such as mixtures of Gaussians and non-parametric density estimation, did not improve results. Let y_i denote the estimated log effect estimate (relative risk, odds or incidence rate ratio) from the ith negative control drug–outcome pair, and let τ_i denote the corresponding estimated standard error, $i = 1,\ldots,n$. Let θ_i denote the true (but unknown) bias associated with pair i, that is, the log of the effect estimate that the study for pair i would have returned had it been infinitely large. As in the standard p-value computation, we assume that y_i is normally distributed with mean θ_i and standard deviation τ_i. Note that in traditional p-value calculation, θ_i is always assumed to be equal to zero, but that we assume the θ_i's, arise from a normal distribution with mean μ and variance σ^2. This represents the null (bias) distribution. We estimate μ and σ^2 via maximum likelihood. In summary, we assume the following:

$$\theta_i \sim N\left(\mu, \sigma^2\right), \text{ and}$$

$$y_i \sim N\left(\theta_i, \tau_i^2\right)$$

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Empirical equipoise

- To identify a setting of strong, observed similarity in the kinds of patients receiving two regimens
- **Equipoise**: **a balance of opinion** in the treating community about what really might be the best treatment for a given class of patients
- Empirical equipoise differs from true equipoise in that the balance of prescriber's actions is taken as the measure of preference rather than their opinions

Empirical equipoise: Preference score

- Preference score
  - patients with preference scores of 0 or 1 receive Treatment A either never or always, respectively
  - intermediate values of the preference score reflect the proportion of patients who would be expected to receive Treatment A rather than Treatment B, under the circumstance that Treatment A and Treatment B had equal market share
  - Accept drug pairs as emerging from empirical equipoise if at least half of the dispensings of each of the drugs are to patients with a preference score of between 0.3 and 0.7

$$\ln\left(\frac{F}{1-F}\right) = \ln\left(\frac{S}{1-S}\right) - \ln\left(\frac{P}{1-P}\right)$$

F: preference score of treatment A
S: propensity score of treatment A
P: Fraction of persons receiving treatment A

Example of empirical equipoise

>50% should be between 0.3-0.7

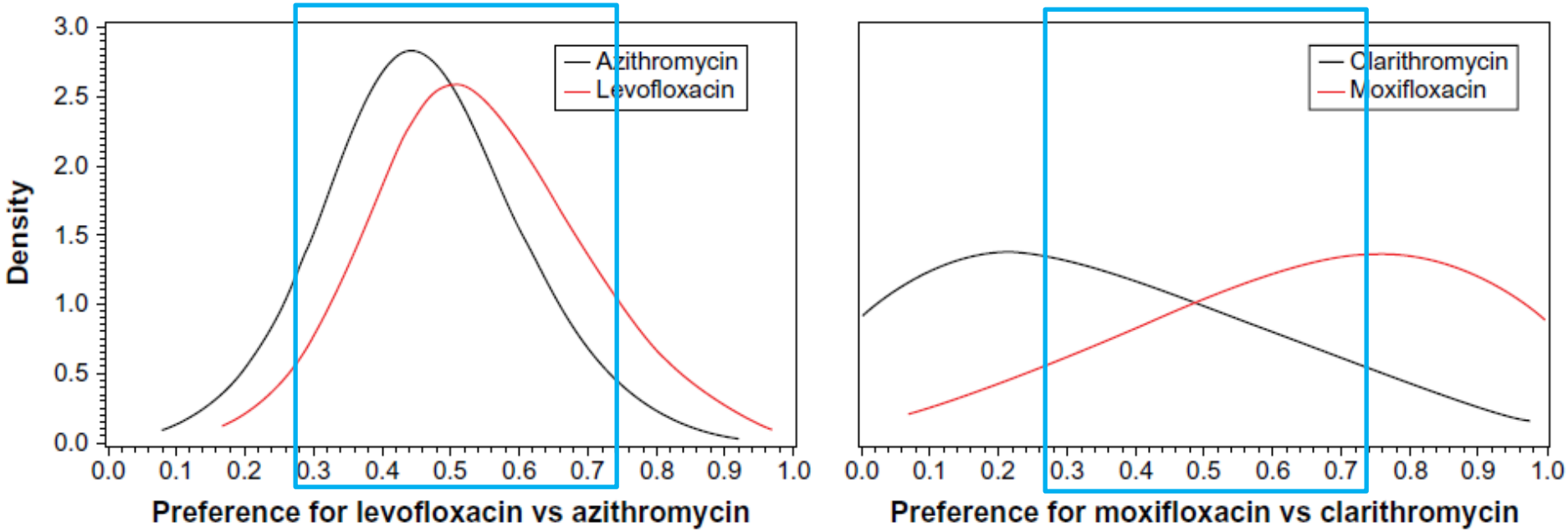
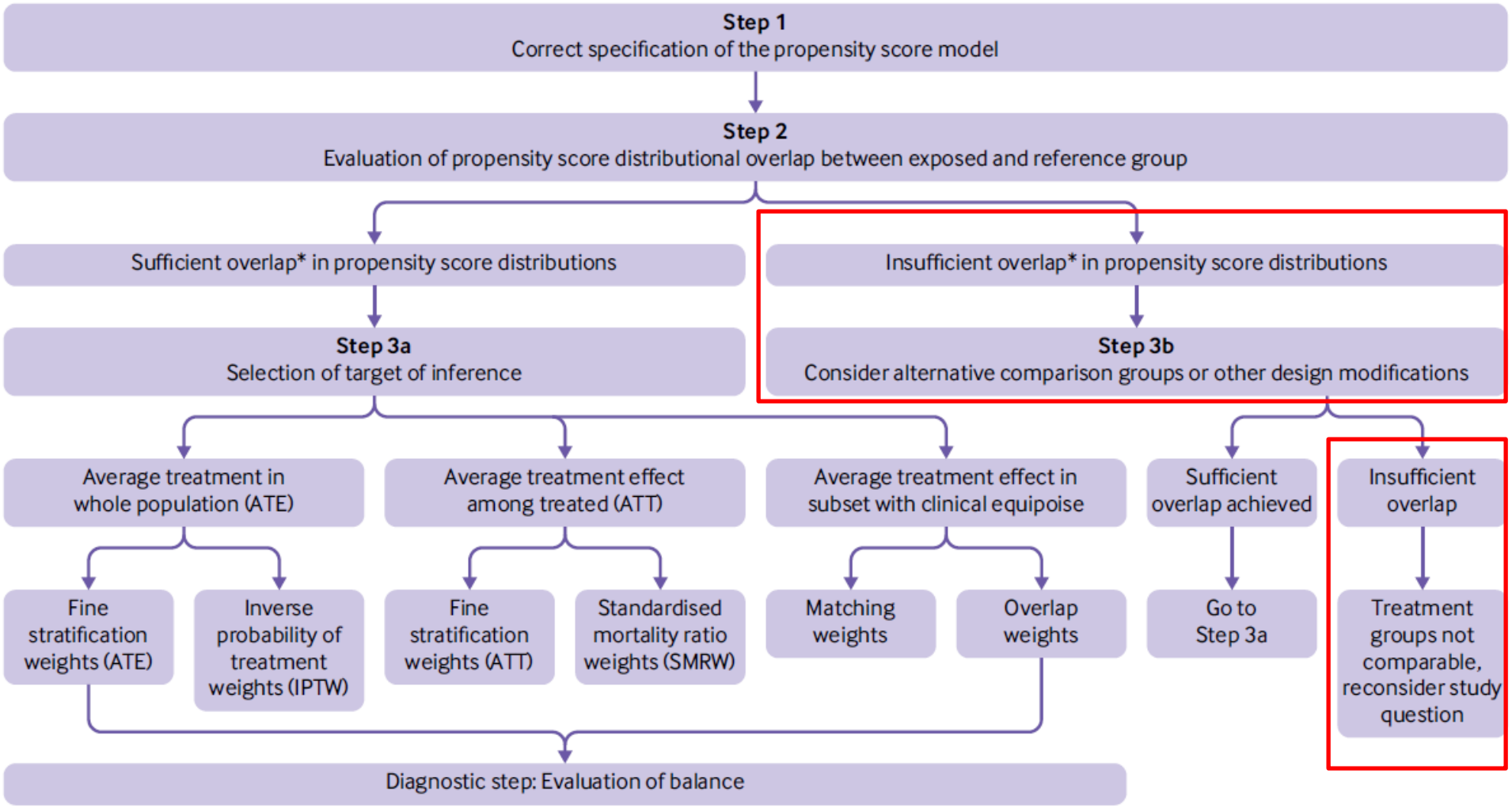


Table 2 Numbers of patients and preference overlap for antibiotic pairs taken by at least 5% of patients with community-acquired pneumonia

Antibiotic pair	Patients, n	0.3 ≤ preference ≤ 0.7	
		%	N
Azithromycin	1468	85	1254
Levofloxacin	1407	82	1159
Amoxicillin	269	43	116
Clarithromycin	369	43	159

Walker et al., Comparative Effectiveness Research, 2013

Insufficient overlap between propensity score distributions



Desai and Franklin, *BMJ*, 2019

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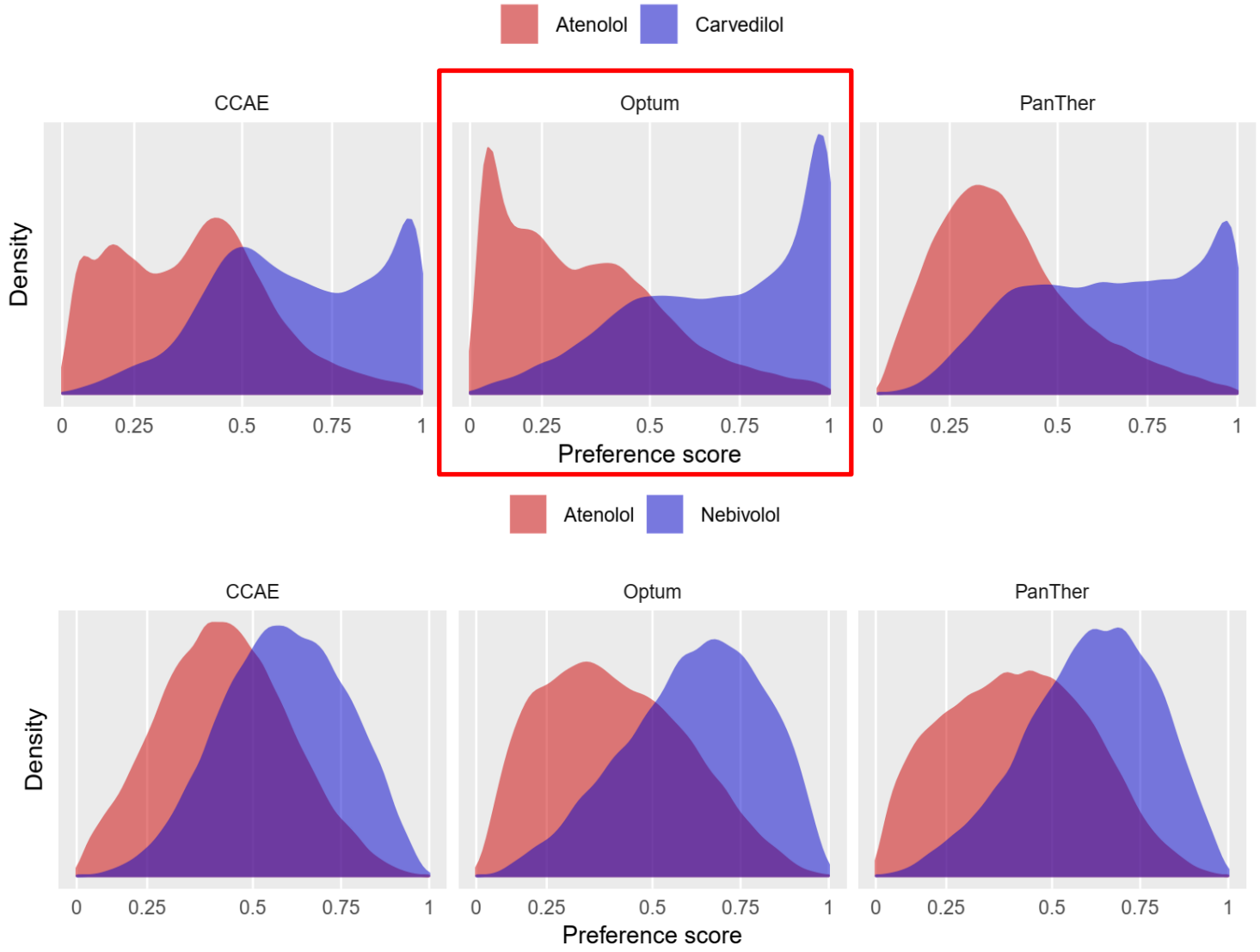

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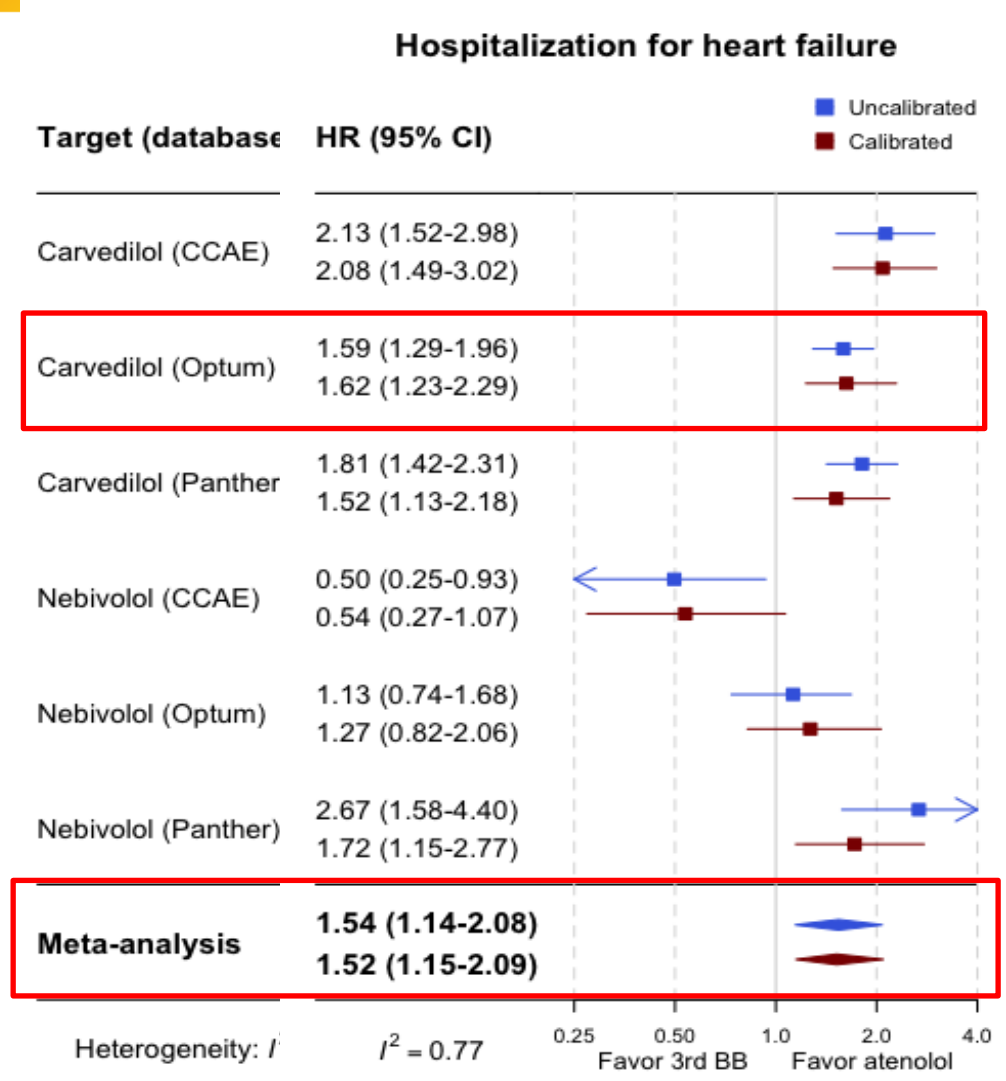

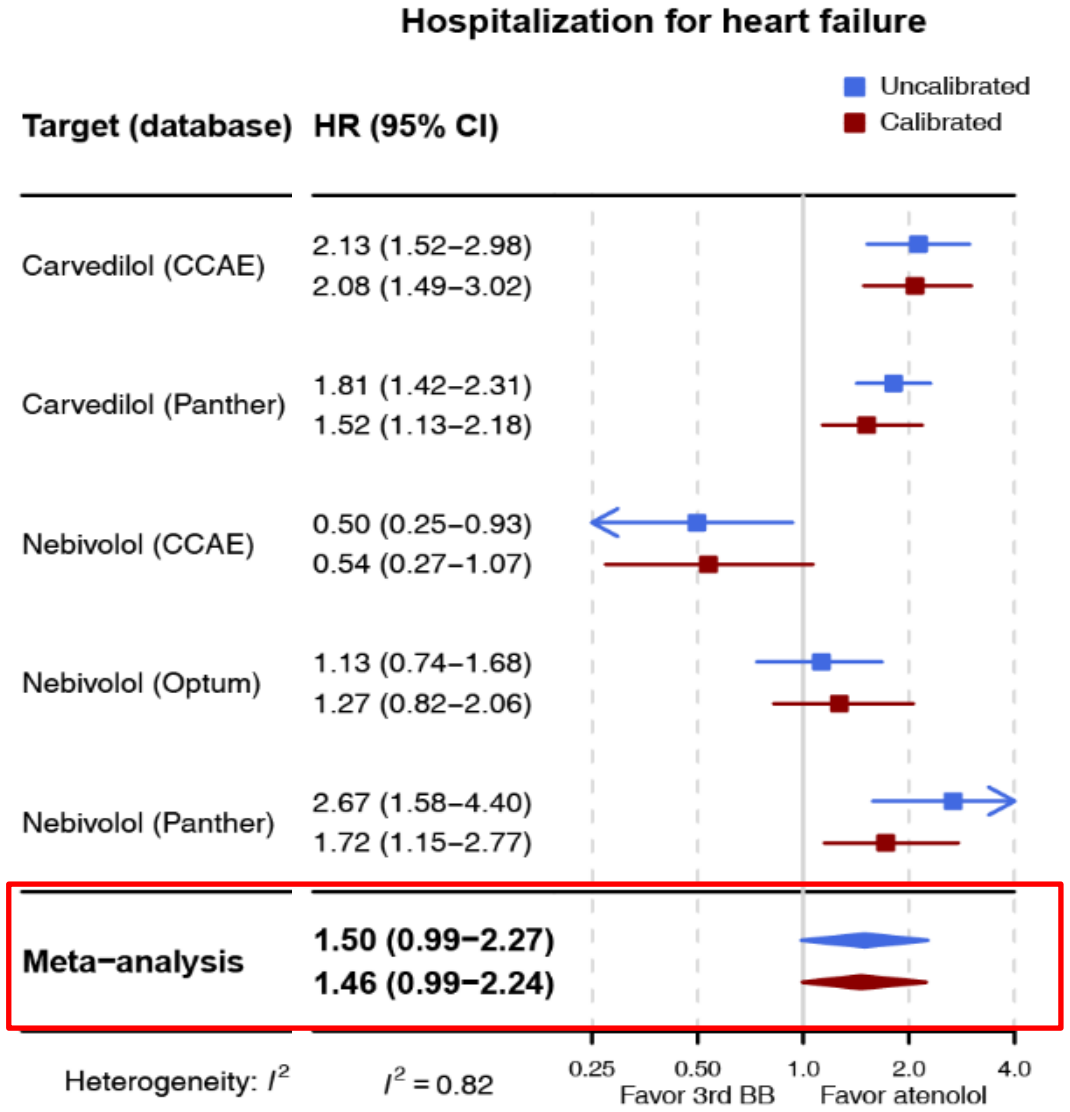

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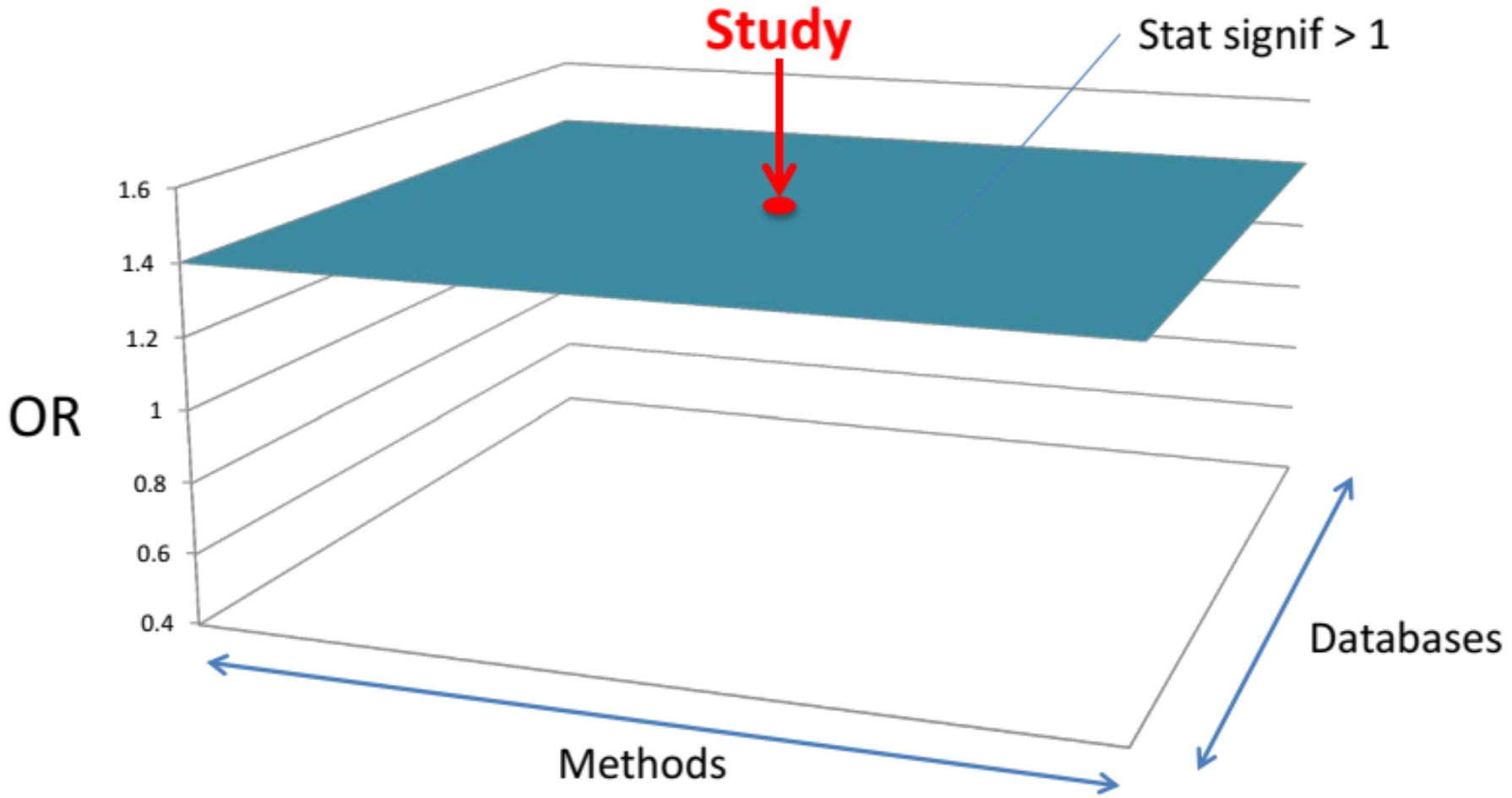
Why OHDSI: Distribution of possible results from one hypothesis



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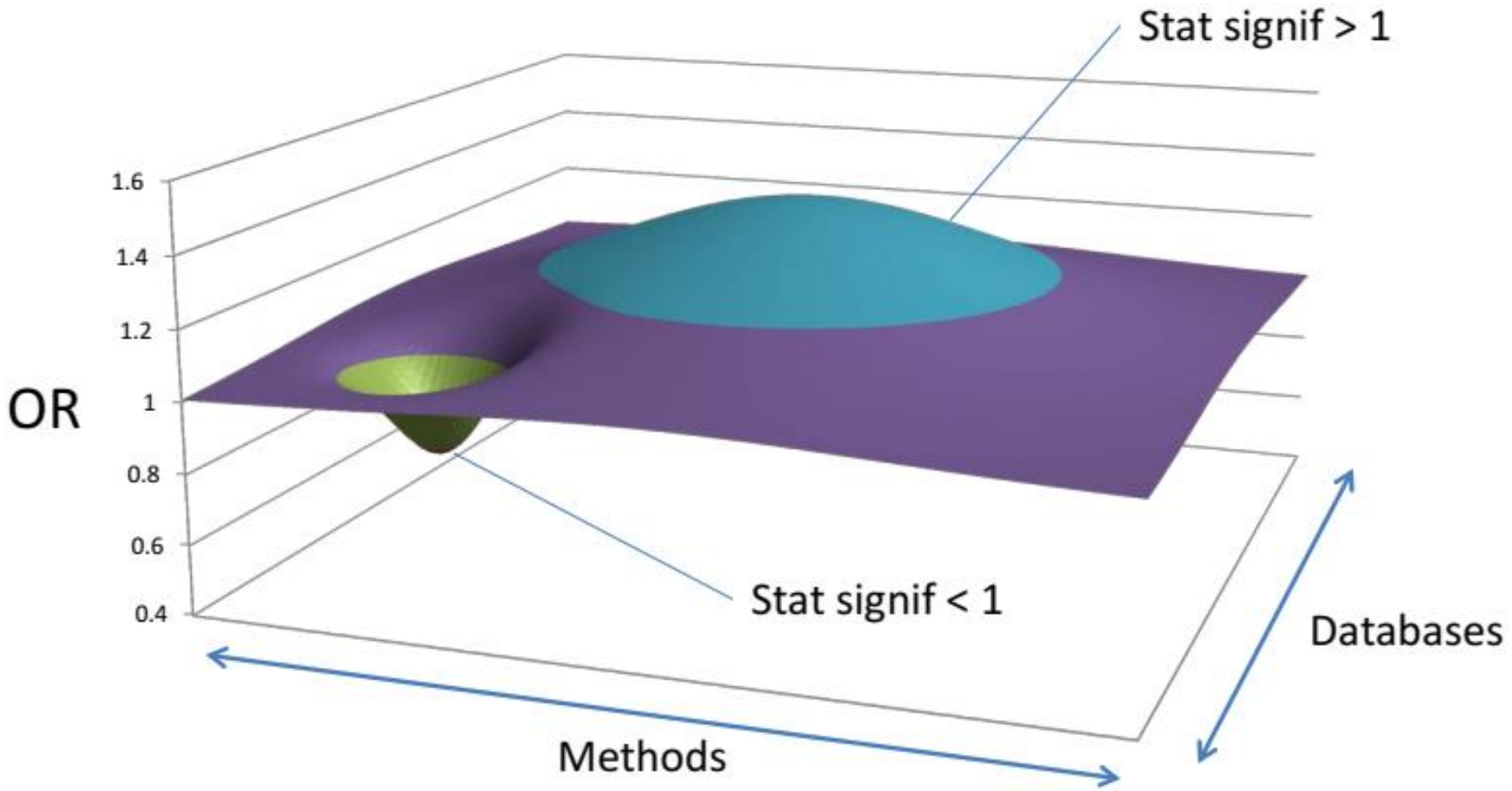

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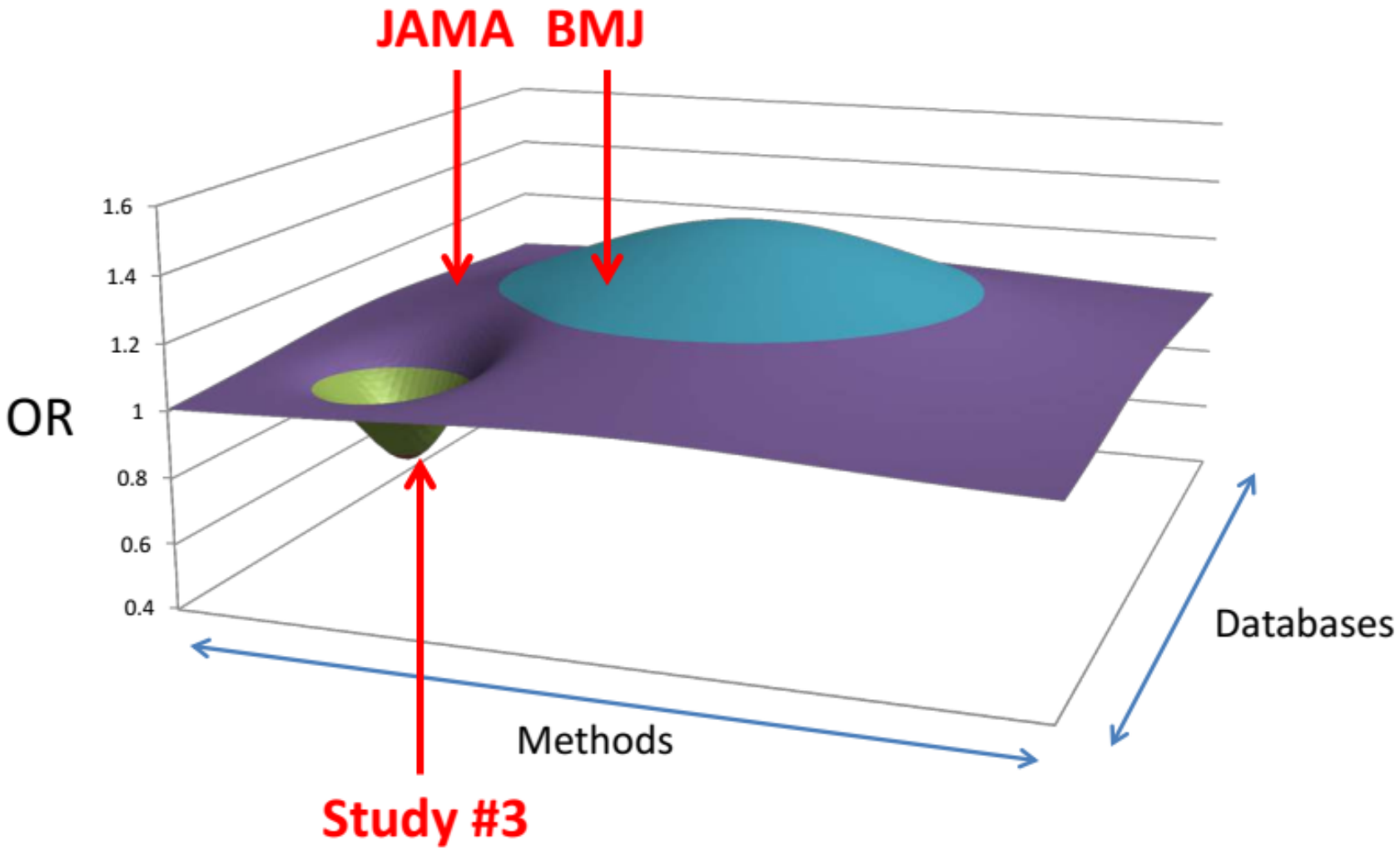

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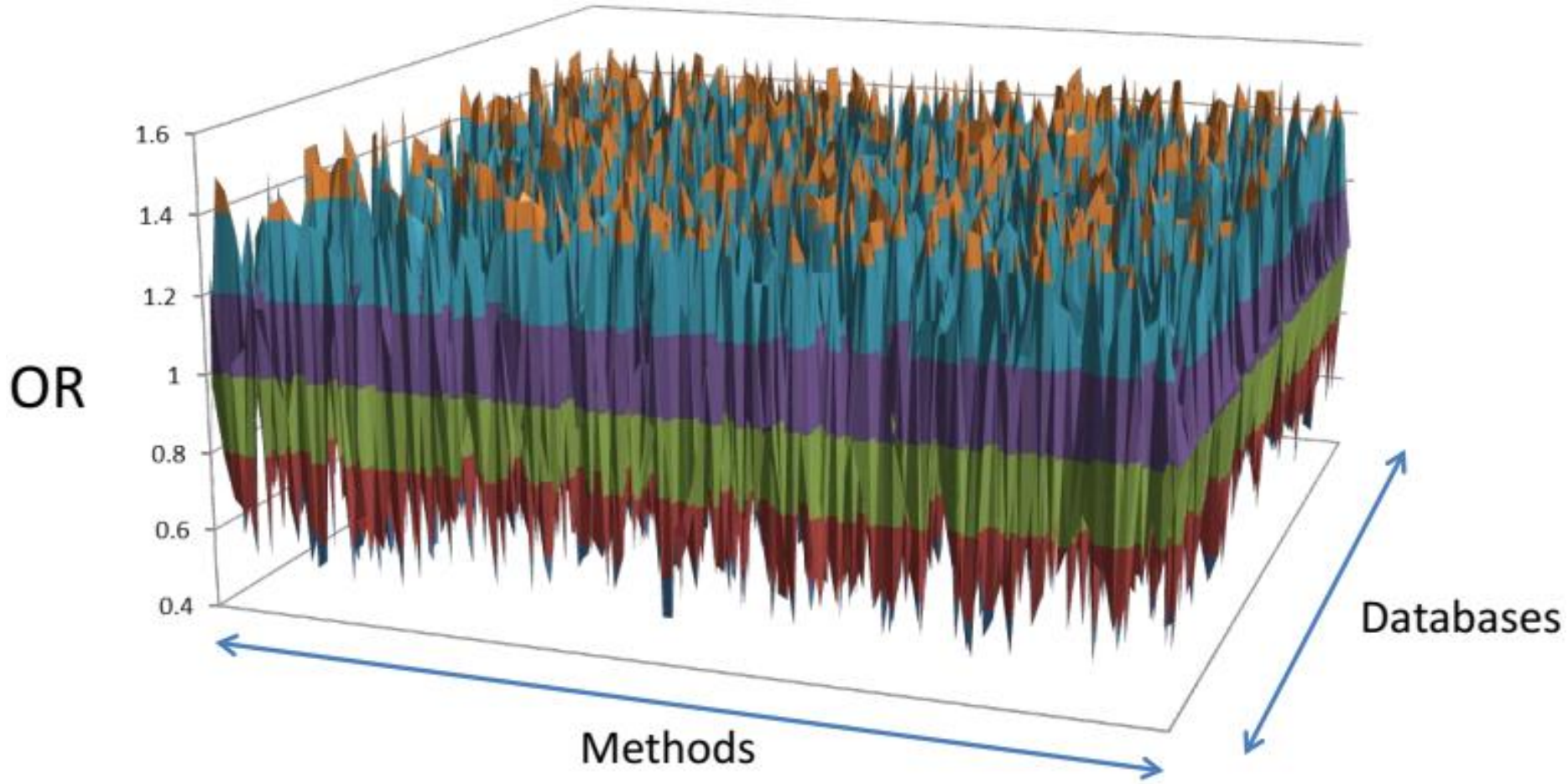
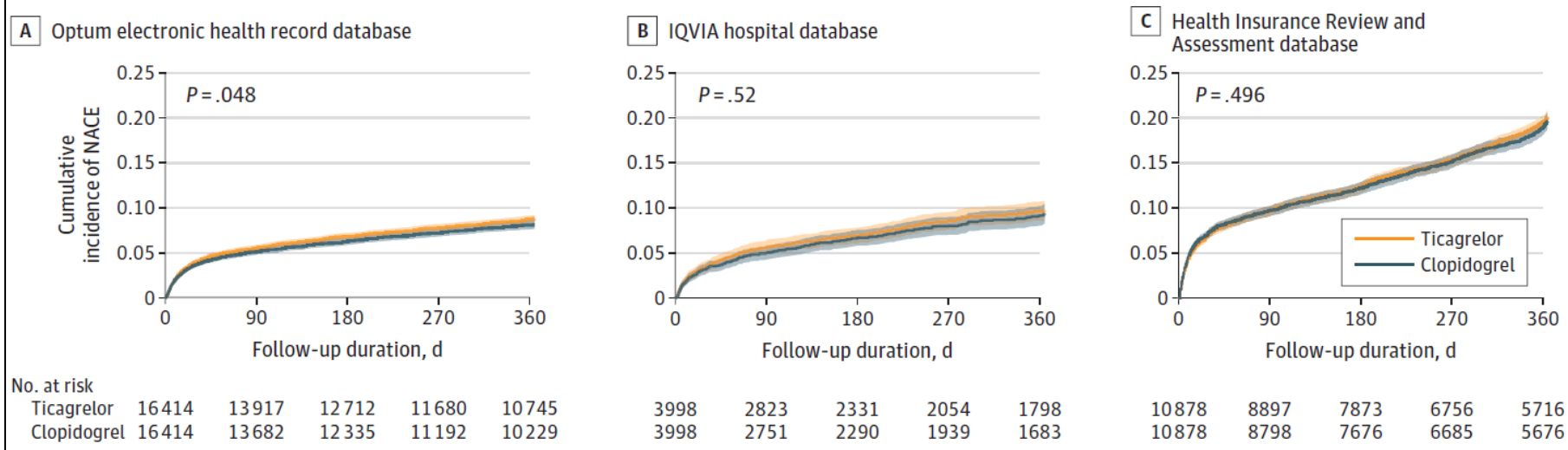


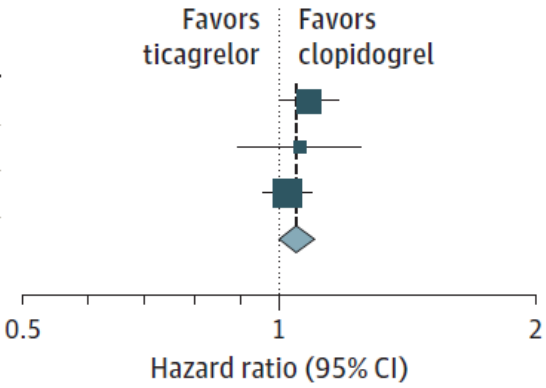
Using multiple databases

Figure 2. Kaplan-Meier Plots for the Risks of the Primary Outcome (Net Adverse Clinical Events) Associated With Ticagrelor and Clopidogrel



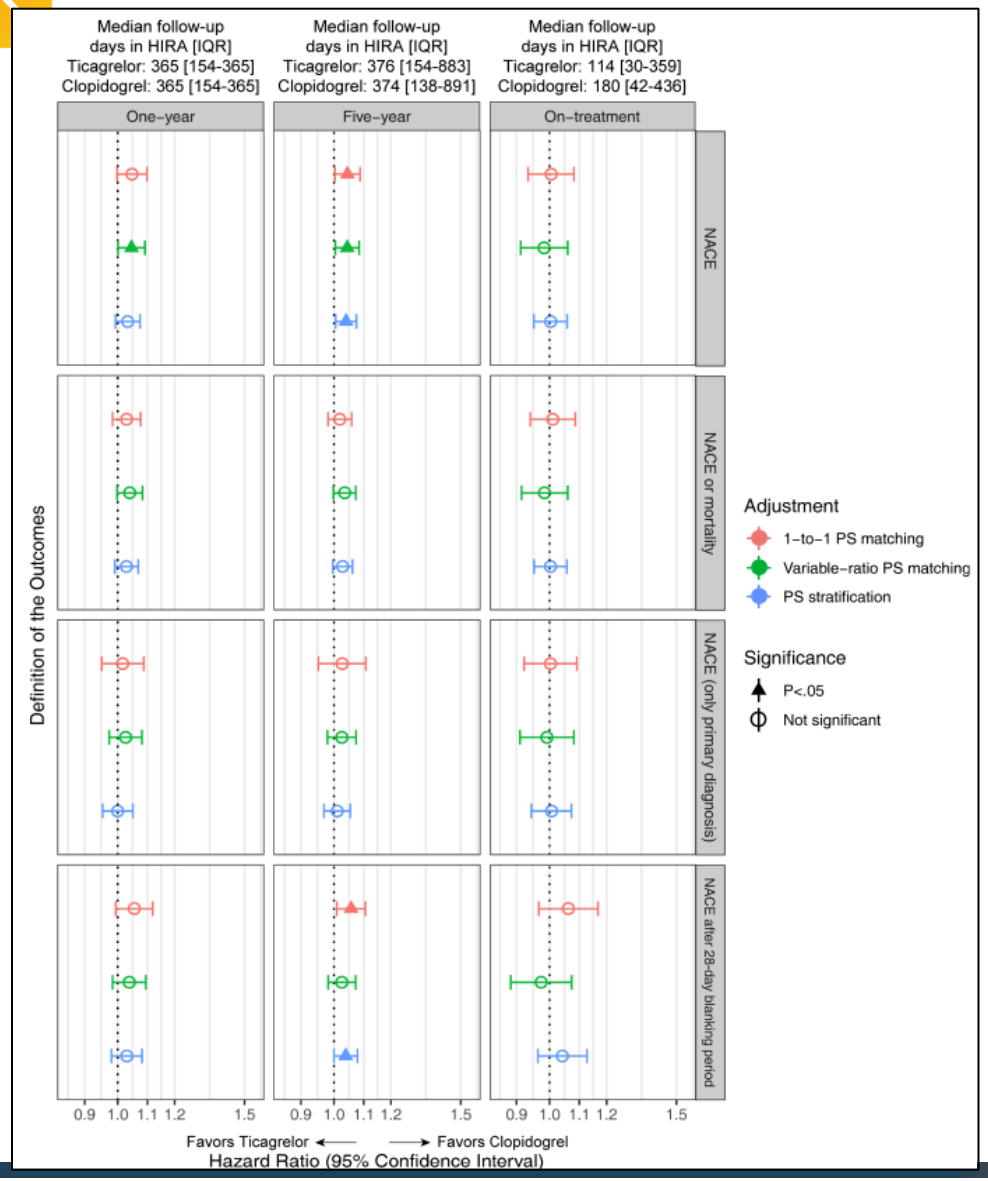
Risk of the Primary Outcome (NACE) at 1 Year

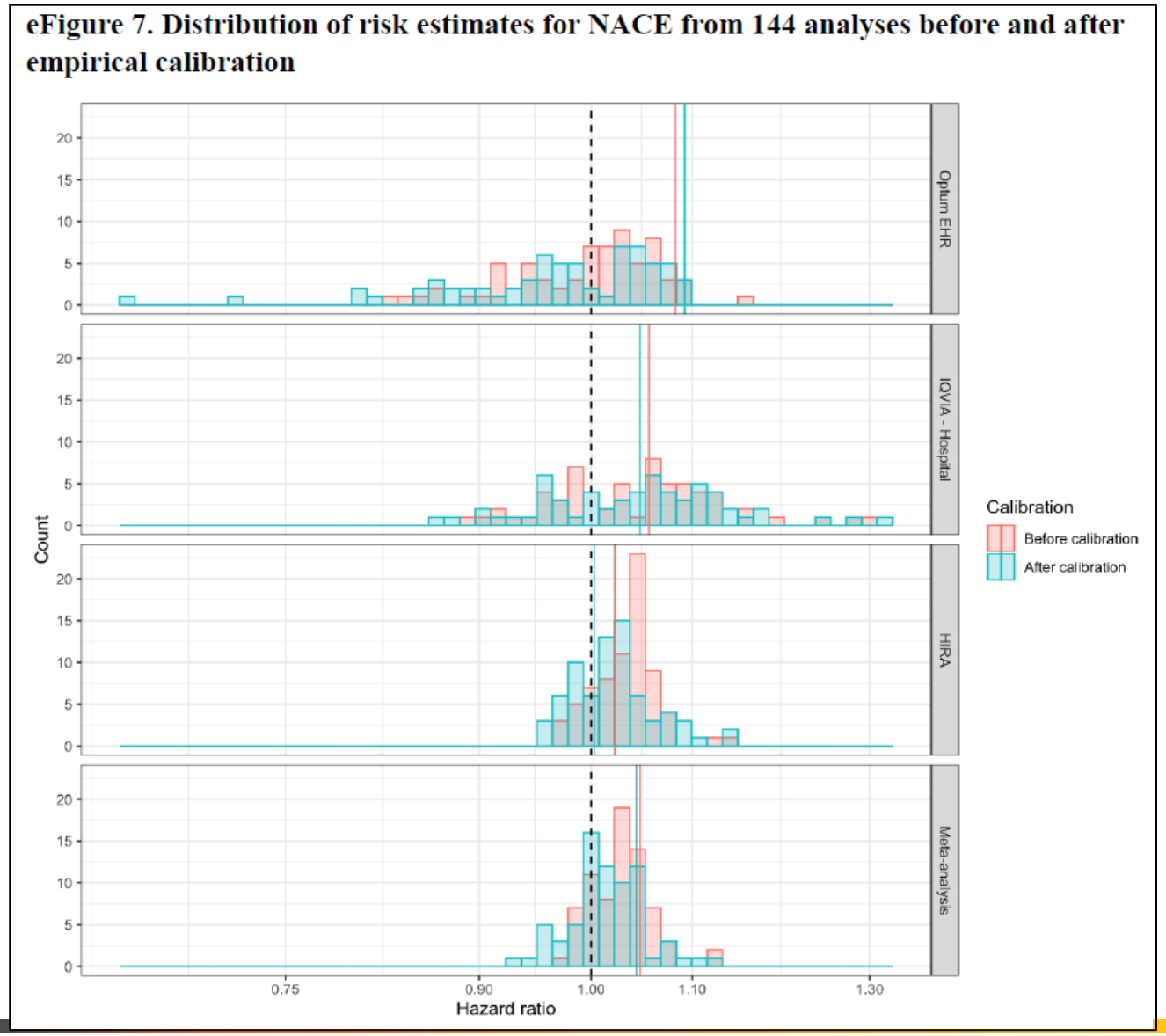
Source	No. of events/total No.		Hazard ratio (95% CI)
	Ticagrelor	Clopidogrel	
Optum electronic health record	1307/16 414	1192/16 414	1.08 (1.00-1.17)
IQVIA hospital	294/3998	272/3998	1.06 (0.90-1.24)
Health Insurance Review and Assessment	1883/10 878	1826/10 878	1.02 (0.96-1.09)
Overall: $I^2 = 0.0\%$; $P = .06$	3484/31 290	3290/31 290	1.05 (1.00-1.10)



SC You et al., JAMA, 2020

Sensitivity analyses using diverse methods





SC You et al., JAMA, 2020

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

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

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

현 누적 변환 환자 수 : 44,596,864명

Recommended paper

RHEUMATOLOGY

Rheumatology 2020;59:14–25
doi:10.1093/rheumatology/kez320

Real World Data: special section

Methodological considerations when analysing and interpreting real-world data

Til Stürmer [1], Tiansheng Wang [1], Yvonne M. Golightly [1,2,3,4], Alex Keil [1], Jennifer L. Lund [1] and Michele Jonsson Funk [1]

Recommended book

The Book of OHDSI Korea

OHDSI-Korea

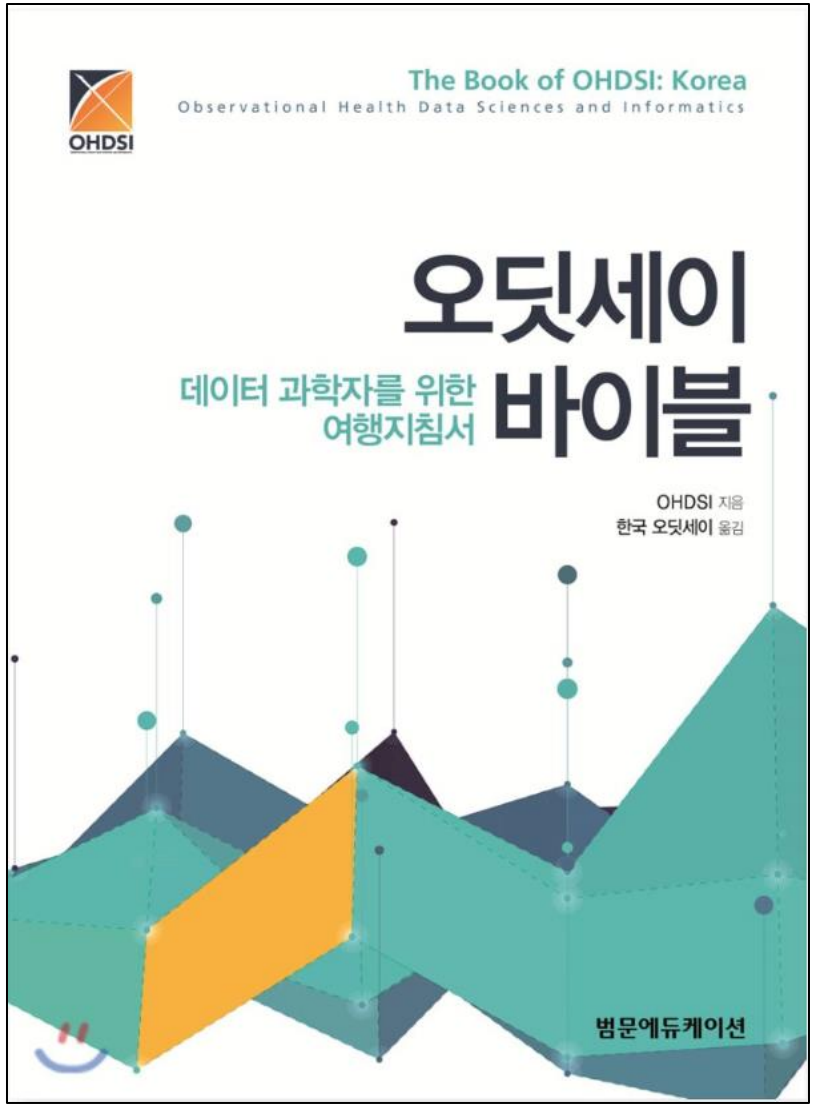
2019-10-18

서문

이 책은 관찰 보건 데이터 과학 및 정보학 (Observational Health Data Sicence and Informatics : OHDSI) 공동작업에 대한 내용을 담고있다. OHDSI 커뮤니티에 의해 작성된 이 책은 OHDSI 관련 모든 지식의 중앙저장소 역활을 담당하고자 쓰여졌으며 오픈소스 개발 도구들을 통해 커뮤니티에 의해 관리되는 생명력있는 문서로 계속 진화하고 있다. 또한 ohdsi-korea.github.io/TheBookOfOhdsiKorea/에서 온라인으로 항상 최신 버전의 책을 무료로 받아 볼 수 있으며 실물로 구입을 원할 경우 Amazon 등에서 구입이 가능하다.

이 책의 목표

이 책은 OHDSI 관련 모든 지식의 중앙저장소 역할을 담당하고자 쓰여졌으며 OHDSI 커뮤니티, OHDSI 데이타 기준과 OHDSI 도구들에 중점을 두었다. OHDSI의 초보자와 숙련자 모두를 위해 현실적으로 필요 이론과 사용방법에 대한 교육을 제공하는 실용적인 부분에 목표를 두고 있다. 이 책을 읽은 뒤 당신은 OHDSI란 무엇인가, 또한 그 여정에 어떻게 동참할 것인가에 관하여 이해하게 될 것이다. 또한 공통 데이터 모델(CDM)과 표준화된 용어들이 무엇인지, 이러한 것들이 관찰 보건 데이터베이스의 표준화에 어떻게 사용되는지 알게 될 것이다. 이 데이터에 대해 Clinical characterization, Population-level estimation,



My first OHDSI study

Korean Circ J. 2020 Jan;50(1):e2
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Korean Circulation Journal

Original Article

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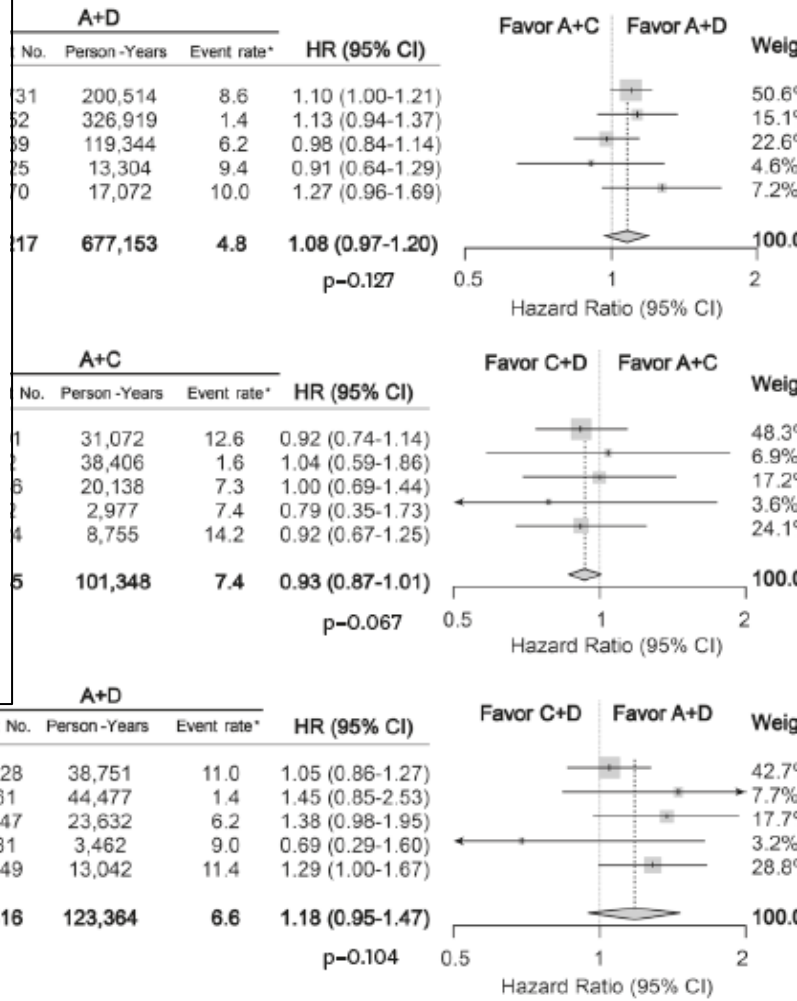
Comparison of First-Line Dual Combination Treatments in Hypertension: Real-World Evidence from Multinational Heterogeneous Cohorts

Seng Chan You, MD, MS[1], Sungjae Jung, MS[1,2], Joel N. Swerdel, MS, MPH[3], Patrick B. Ryan, PhD[3], Martijn J. Schuemie, PhD[3], Marc A. Suchard, MD, PhD[4,5,6], Seongwon Lee, PhD[1], Jaehyeong Cho, BS[1], George Hripcsak, MD, PhD[7,8], Rae Woong Park, MD, PhD[1,9], and Sungha Park, MD, PhD[10]

[1]Department of Biomedical Informatics, Ajou University School of Medicine, Suwon, Korea
[2]MediPlex Inc., Seoul, Korea



The OHDSI collaborative research has been published in JAMA

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

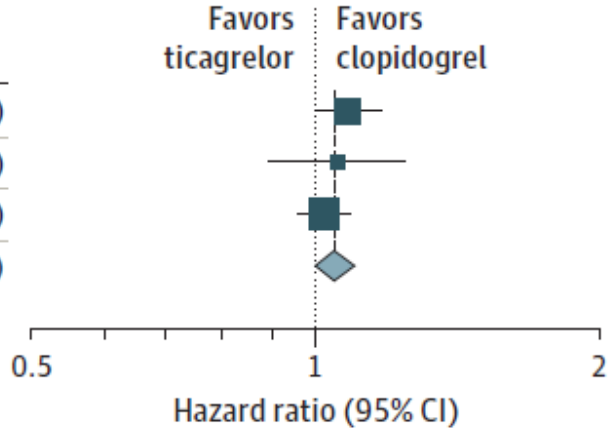
Audio and Supplemental content

CME Quiz at jamacmelookup.com and CME Questions page 0

The results of OHDSI study

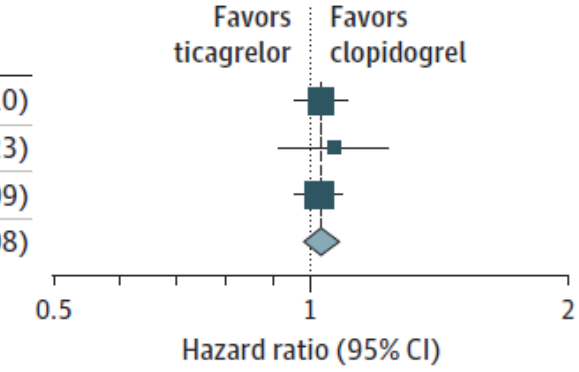
Figure 3. Risk of the Primary Outcome (NACE) at 1 Year

Source	No. of events/total No.		Hazard ratio (95% CI)
	Ticagrelor	Clopidogrel	
Optum electronic health record	1307/16 414	1192/16 414	1.08 (1.00-1.17)
IQVIA hospital	294/3998	272/3998	1.06 (0.90-1.24)
Health Insurance Review and Assessment	1883/10 878	1826/10 878	1.02 (0.96-1.09)
Overall: $I^2 = 0.0\%$; $P = .06$	3484/31 290	3290/31 290	1.05 (1.00-1.10)



A Net adverse clinical events or mortality

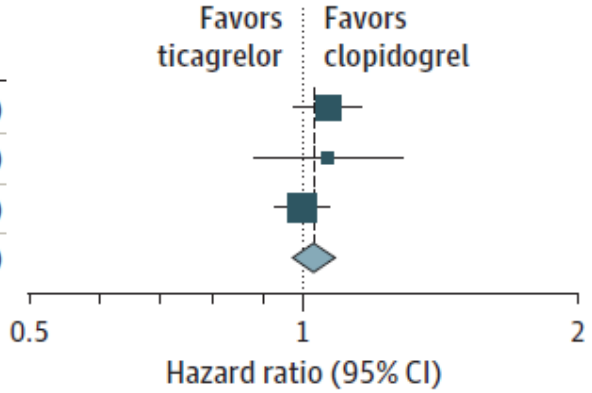
Source	No. of events/total No.		Hazard ratio (95% CI)
	Ticagrelor	Clopidogrel	
Optum electronic health record	1599/16 414	1536/16 414	1.03 (0.96-1.10)
IQVIA hospital	373/3998	343/3998	1.06 (0.92-1.23)
Health Insurance Review and Assessment	1917/10 878	1857/10 878	1.02 (0.96-1.09)
Overall: $I^2 = 0.0\%$	3889/31 290	3736/31 290	1.03 (0.98-1.08)



The results of OHDSI study

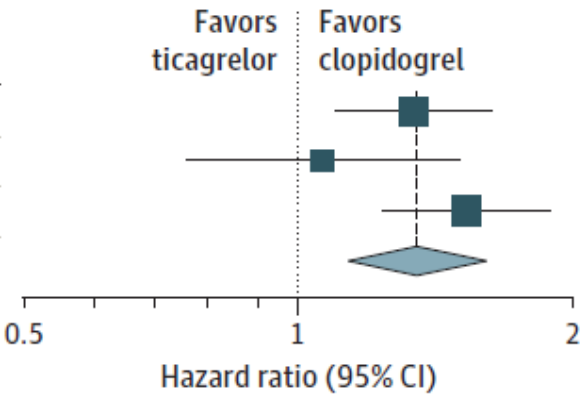
B Ischemic event

Source	No. of events/total No.		Hazard ratio (95% CI)
	Ticagrelor	Clopidogrel	
Optum electronic health record	1146/16414	1064/16414	1.06 (0.98-1.16)
IQVIA hospital	233/3998	214/3998	1.06 (0.88-1.28)
Health Insurance Review and Assessment	1768/10878	1754/10878	1.00 (0.93-1.07)
Overall: $I^2 = 0.0\%$	3147/31290	3032/31290	1.03 (0.98-1.08)



F Hemorrhagic event

Source	No. of events/total No.		Hazard ratio (95% CI)
	Ticagrelor	Clopidogrel	
Optum electronic health record	236/16414	172/16414	1.34 (1.10-1.63)
IQVIA hospital	68/3998	62/3998	1.07 (0.75-1.50)
Health Insurance Review and Assessment	226/10878	146/10878	1.53 (1.24-1.89)
Overall: $I^2 = 37.7\%$	530/31290	380/31290	1.35 (1.13-1.61)



Strength in our 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 (144 analyses for one outcome)
  - 1:1 PS matching / variable-ratio PS matching / PS stratification
  - Diverse time windows
  - Narrow outcome definitions

Editorial of JAMA

The findings for the primary outcome are not surprising based on the expected regression toward a null effect when combining competing efficacy and safety end points. The ischemic end points did not include death or periprocedural MI. The safety end point did not include bleeding events included in other reports (ie, procedural, ocular, pericardial, defined hemoglobin decrease, transfusion). In addition, as in other observational studies of evaluations of drug comparative effectiveness, this study has several limitations.[7] In this study, You et al[6] performed many sophisticated statistical analyses in an attempt to decrease the influence of confounding variables in such an analysis. Moreover, complete and accurate ascertainment of events and miscoding are uncorrectable limitations in such studies. Their conclusion of no added benefit associated with ticagrelor is consistent with prior studies from Canada, Korea, Japan, China, and the Netherlands that used different study designs to reach the same conclusion without attracting much clinical attention.[6]


Thank You
for your time