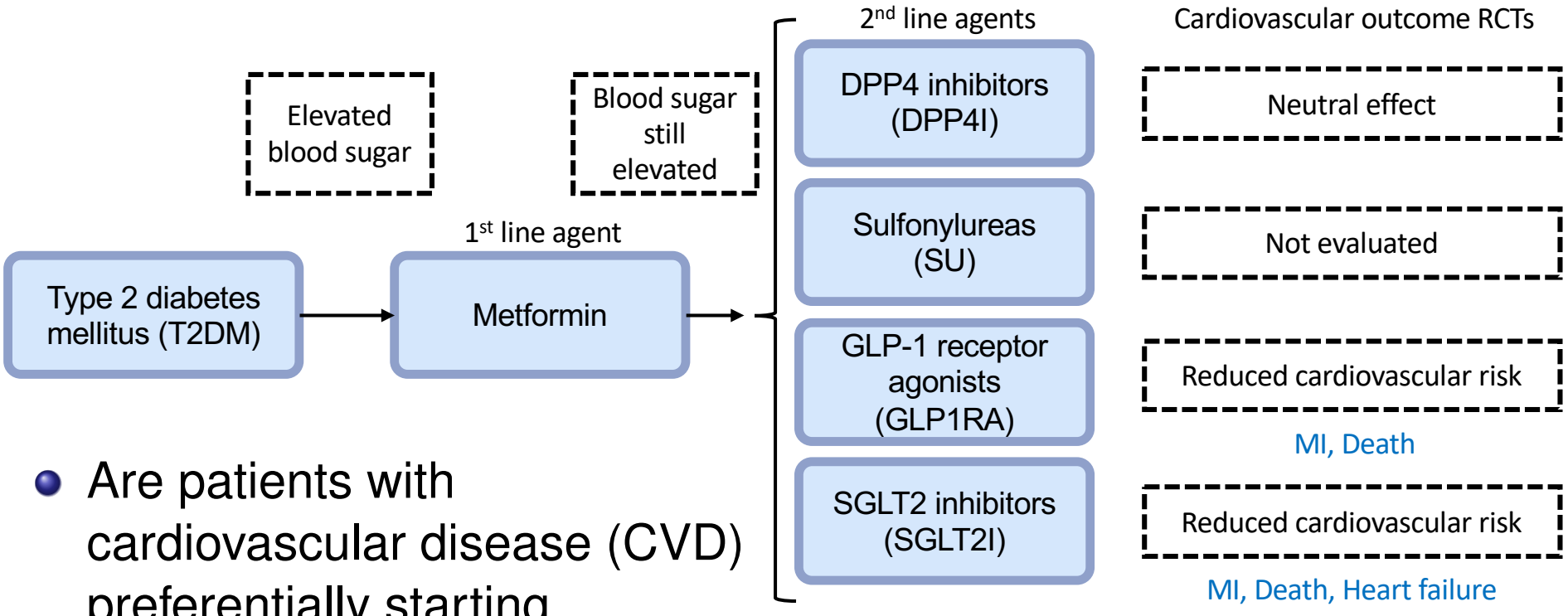
Insights from the large-scale evidence generation and evaluation across a network of databases for type 2 diabetes mellitus (LEGEND-T2DM)

Marc A Suchard, MD, PhD
on behalf of the LEGEND investigators

VA Informatics and Computing Infrastructure (VINCI)
US Department of Veterans Affairs and UCLA

2023 OHDSI Global Symposium
20 October 2023

Diabetes treatment and some open questions



- Are patients with cardiovascular disease (CVD) preferentially starting GLP1RA/SGLT2Is?
- Are GLP1RA/SGLT2Is more effective (or safer) than DPP4I/SUs?

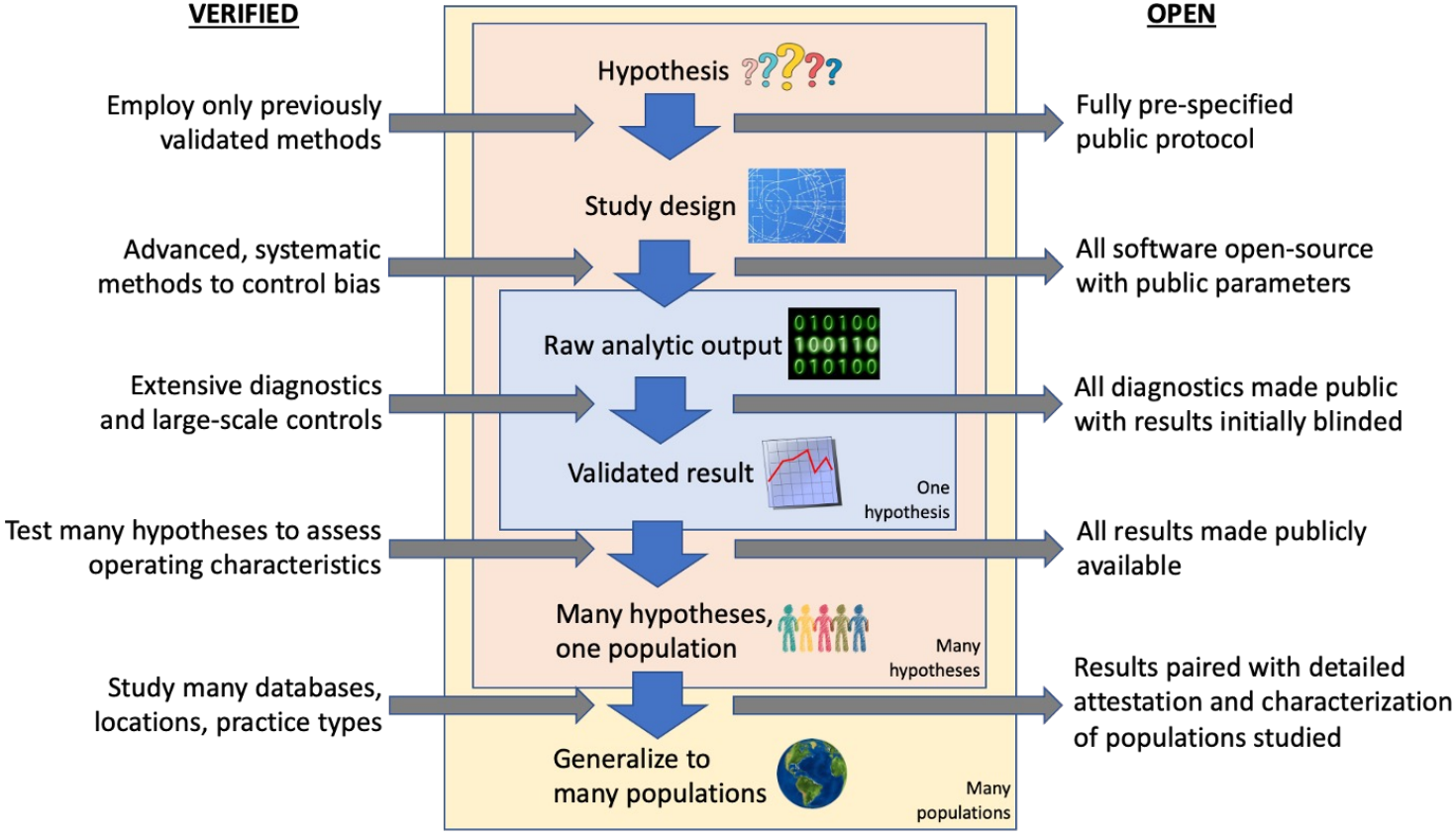
9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Care in Diabetes—2023*

Diabetes Care 2023;46(Suppl. 1):S140–S157 | https://doi.org/10.2337/dc23-S009

Nuha A. ElSayed, Grazia Aleppo, Vanita R. Aroda, Raveendhara R. Bannuru, Florence M. Brown, Dennis Bruemmer, Billy S. Collins, Marisa E. Hilliard, Diana Isaacs, Eric L. Johnson, Scott Kahan, Kamlesh Khunti, Jose Leon, Sarah K. Lyons, Mary Lou Perry, Priya Prahalad, Richard E. Pratley, Jane Jeffrie Seley, Robert C. Stanton, and Robert A. Gabbay, on behalf of the American Diabetes Association

LEGEND philosophy

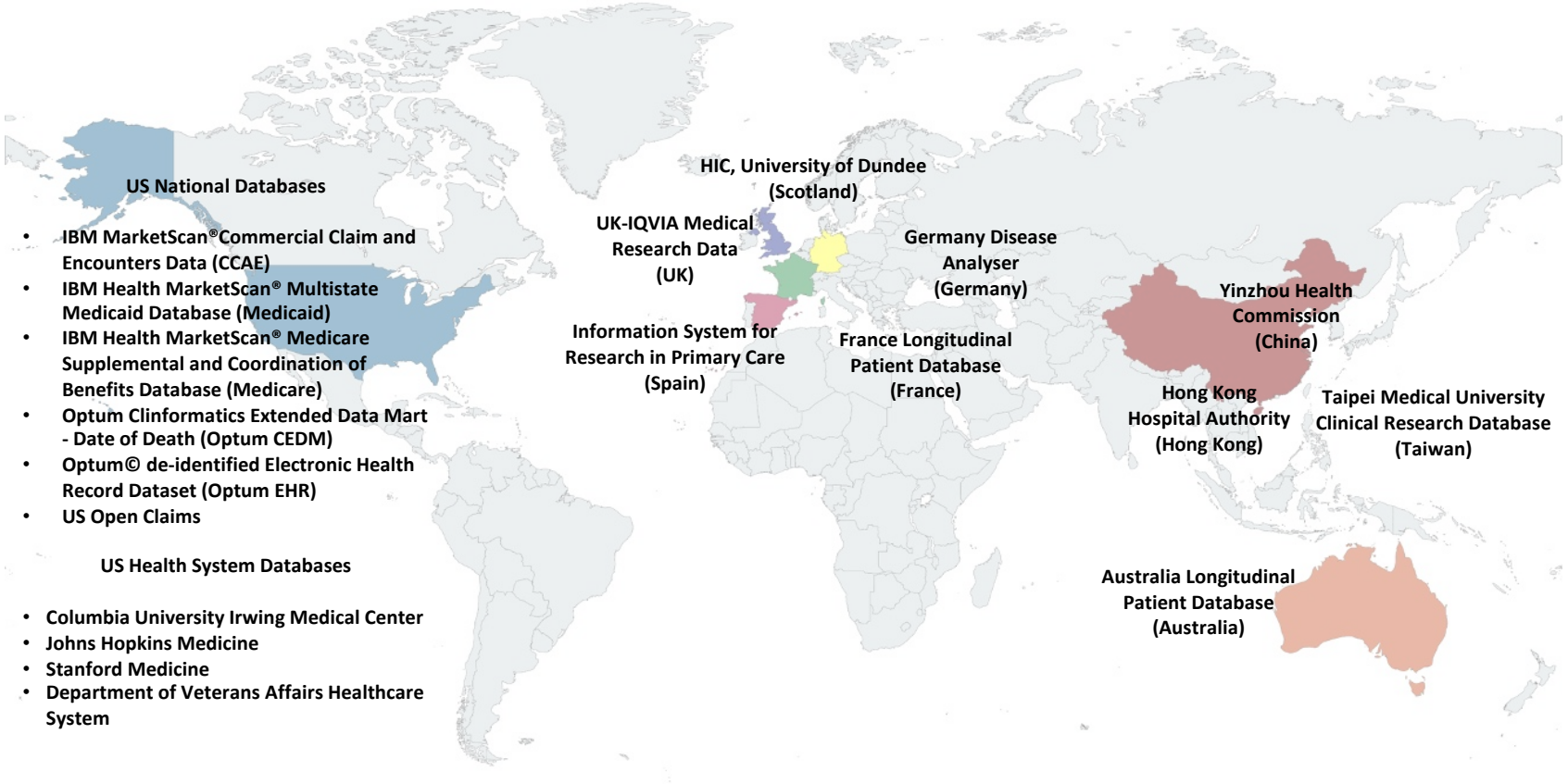
LEGEND is a **guiding principle**-driven enterprise to deliver verified and open evidence at scale



- rich, rigorous, and reliable

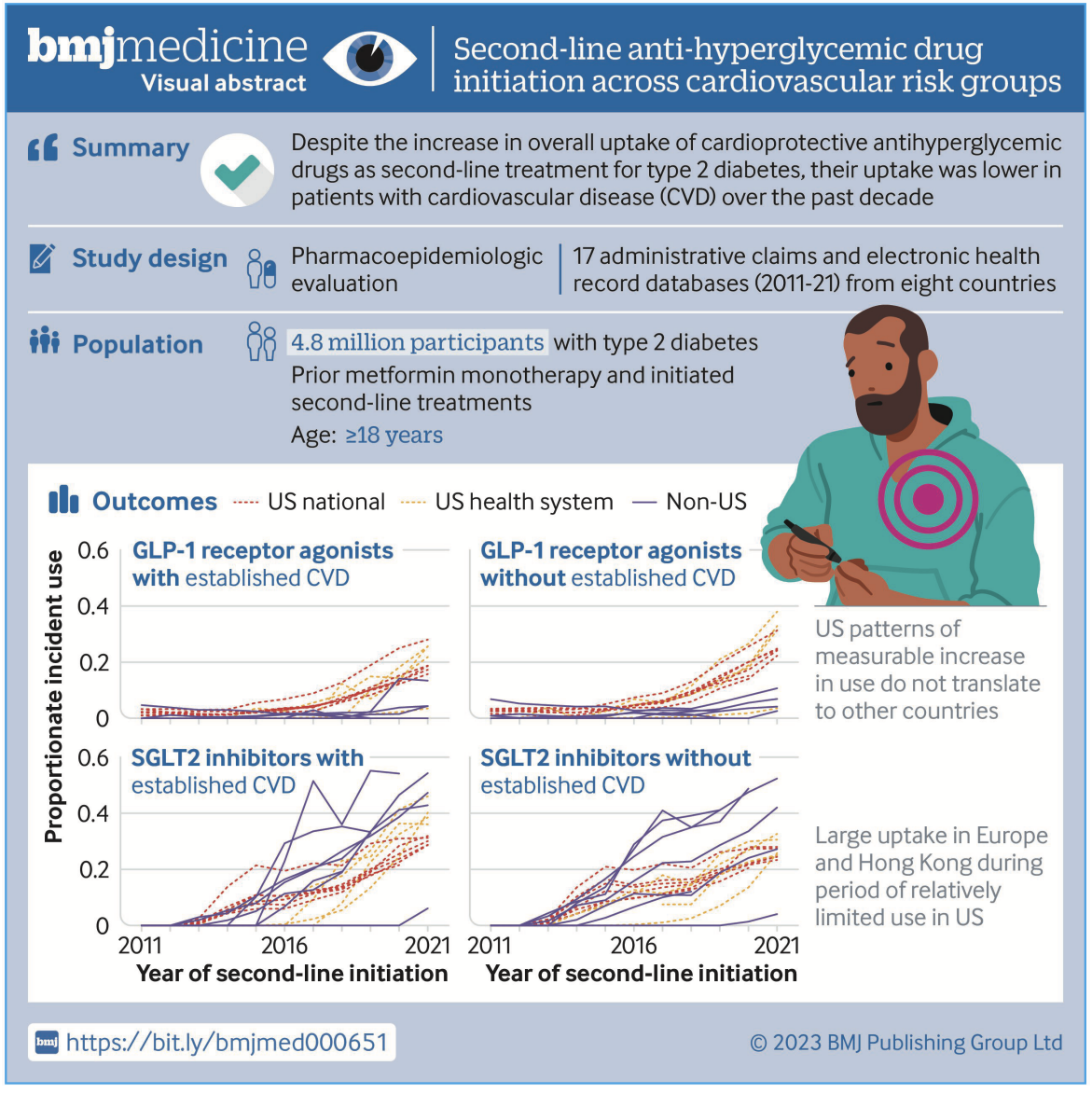
Second-line initiators across a global network

Inclusion: adult diabetics, +metformin, −other glycemic agents, ±CVD



- 19 administrative claims and EHR data partners around the world

Serial cross-sectional initiation (2011-2021)



Large variation in use of SGLT2I/GLP1RAs across CVD populations (less surprising)

Uptake is **lower** in US relative to other country sources, particularly for CVD patients (more surprising)

Leading **ECRs**:

- Lovedeep Dhingra
- Arya Aminorroaya

Risk of major cardiovascular events (MACE)

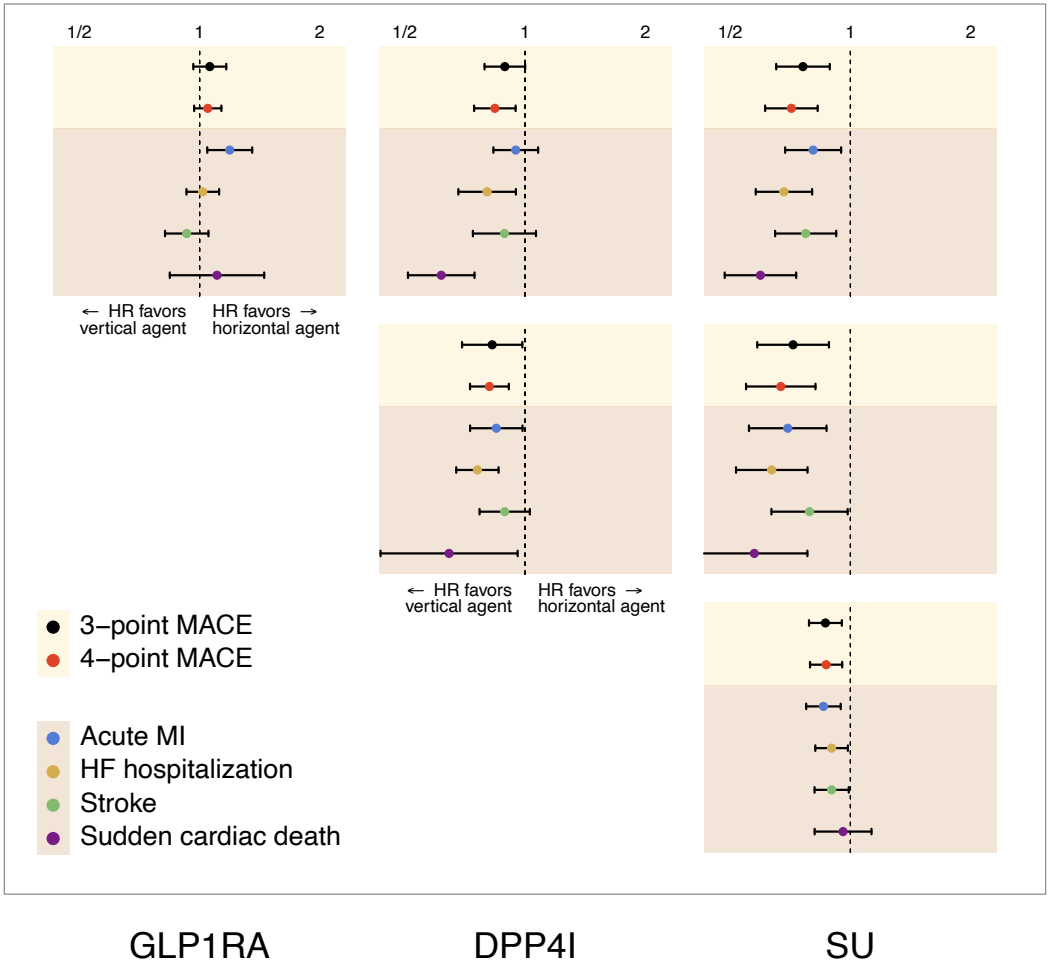
Via systematic best-practices:

New-user cohort design (emulate target trial)

LSPS adjustment (measured, unmeasured confounding)

100 negative controls (empirical calibration)

Rigorous diagnostics (improved reliability)



- SGLT2I $\approx$ GLP1RA (moderately unexpected)
- GLP1RA $>$ DPP4I $>$ SU (RWE fills in for missing RCTs)

LEGEND-T2DM is a rich, open resource

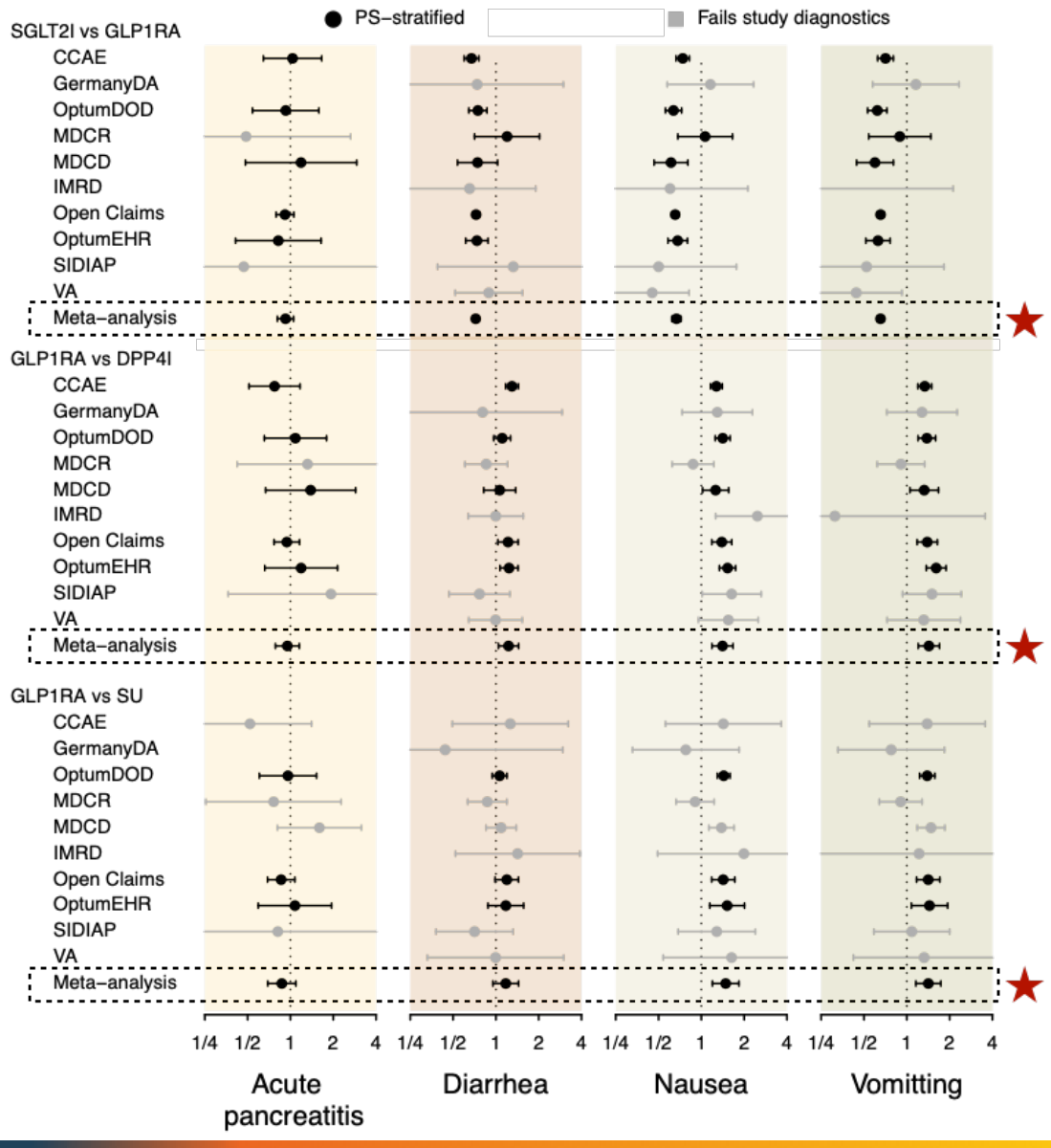
32 outcomes: CV, safety, patient-centered (PC)

Multiple populations: gender, age, race, CVD, renal disease

Leading **ECR** (first PC manuscript):

- Carlen Reyes (SIDIAP)

Comparative GI symptoms: GLP1RAs > others (but no ↑ acute pancreatitis)



LEGEND-T2DM is community responsive

Thyroid tumor relative risk under **multiple sensitivity analyses**

	Calibrated HR (95%CI)	P-value
GLP1RA vs SGLT2I		
PS matching on-treatment	0.83 (0.57 – 1.27)	0.33
PS stratification on-treatment	0.88 (0.75 – 1.03)	0.13
PS matching ITT	0.89 (0.74 – 1.07)	0.22
PS stratification ITT	0.95 (0.85 – 1.06)	0.35
GLP1RA vs Sulfonylureas		
PS matching on-treatment	0.95 (0.75 - 1.20)	0.68
PS stratification on-treatment	0.94 (0.73 - 1.21)	0.64
PS matching ITT	1.03 (0.87 - 1.23)	0.72
PS stratification ITT	1.02 (0.84 - 1.24)	0.86
GLP1RA vs DPP4I		
PS matching on-treatment	0.78 (0.60 - 1.01)	0.06
PS stratification on-treatment	0.83 (0.67 - 1.03)	0.1
PS matching ITT	0.92 (0.79 - 1.06)	0.24
PS stratification ITT	0.93 (0.83 - 1.04)	0.22

Case-control study (Bezin et al, Diabetes Care, 2023) alerts **EMA** to potential thyroid cancer / GLP1RA association

We delivered a short report to EMA's Pharmacovigilance Risk Assessment Committee

Leading **MCR**:

- Daniel Morales (Dundee)

Emerging directions in LEGEND-T2DM

Patients with renal disease

Patients with heart failure

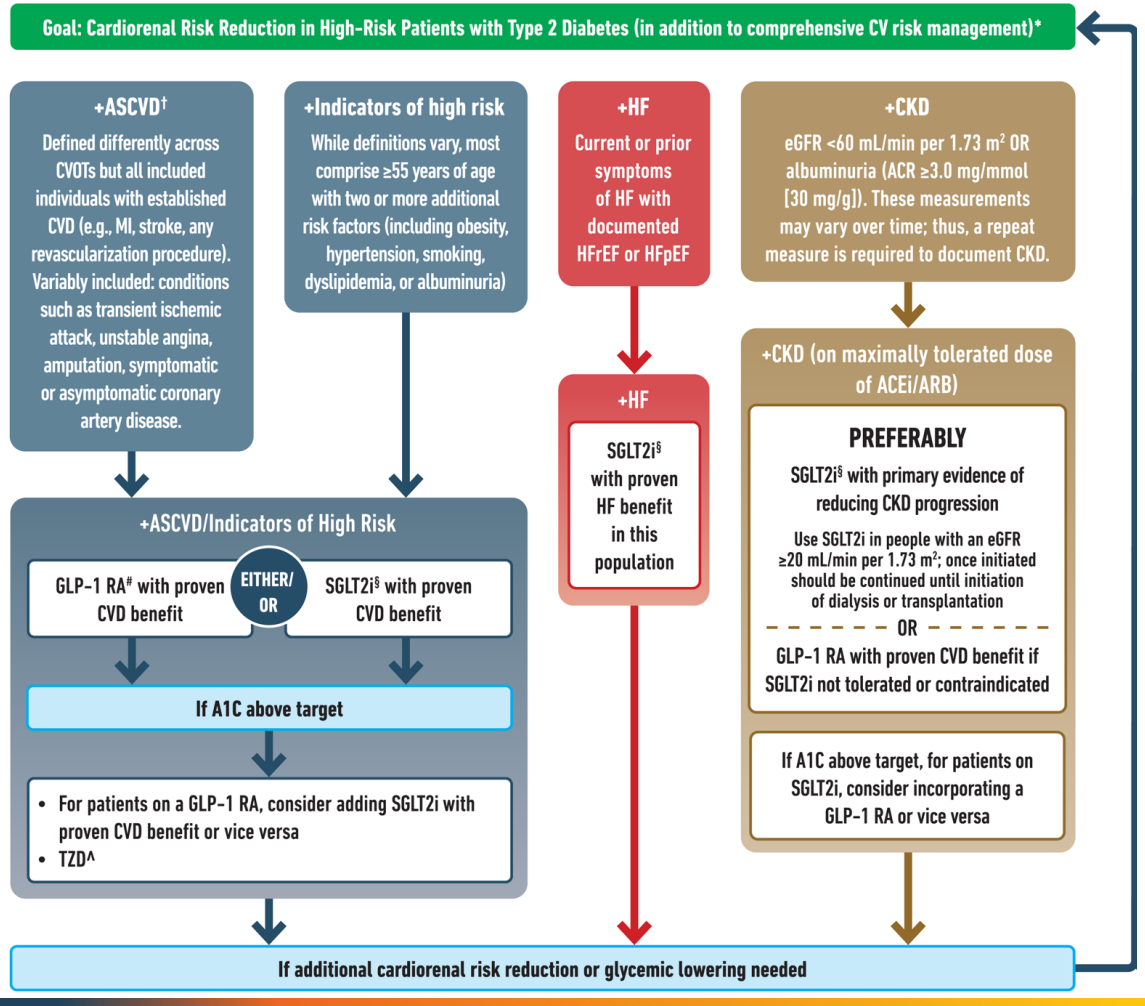
Older adults

Risk differences in women

Ingredient (drug-level) comparisons

- Open opportunities for all interested parties . . . and that means **you**!

Treatment guidelines vary across populations, but need RWE support and refinement



Acknowledgments

Current legendary members: . . . and you? **please join us!**

Arya Aminorroaya, Faaizah Arshad, Clair Blacketer, Mary Bowring, **Fan Bu**, Michael Cook, **Lovedeep Dhingra**, David Dorr, Talita Duarte-Salles, Scott DuVall, Thomas Falconer, Tina French, Elizabeth Hanchrow, Scott Horban, George Hripcsak, Jason Hsu, **Rohan Khera**, Harlan Krumholz, Wallis Lau, Jing Li, Kelly Li, Yuntian Liu, Yuan Lu, Kenneth Man, Michael Matheny, Nestoras Mathioudakis, Michael McLemore, Evan Minty, **Daniel Morales**, Paul Nagy, Akihiko Nishimura, Anna Ostropolets, Thanh Phan, Andrea Pistillo, Jose Posada, Nicole Pratt, Patrick Ryan, **Carlen Reyes**, Joseph Ross, Martijn Schuemie, Sarah Seager, Nigam Shah, Katherine Simon, Marc Suchard Eric Wan, Jianxiao Yang, Can Yin, Seng Chan You, Jin Zhou

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- IPA agreement with the US Department of Veterans Affairs

Lessons Learned from OHDSI Network Studies

Sarah Seager, Marc Suchard, Cindy Cai, Seng Chan You, Anthony Sena

Wilmer Eye Institute
Johns Hopkins Medicine

Intravitreal anti-VEGF and risk of kidney failure: A Sisyphus Challenge Study

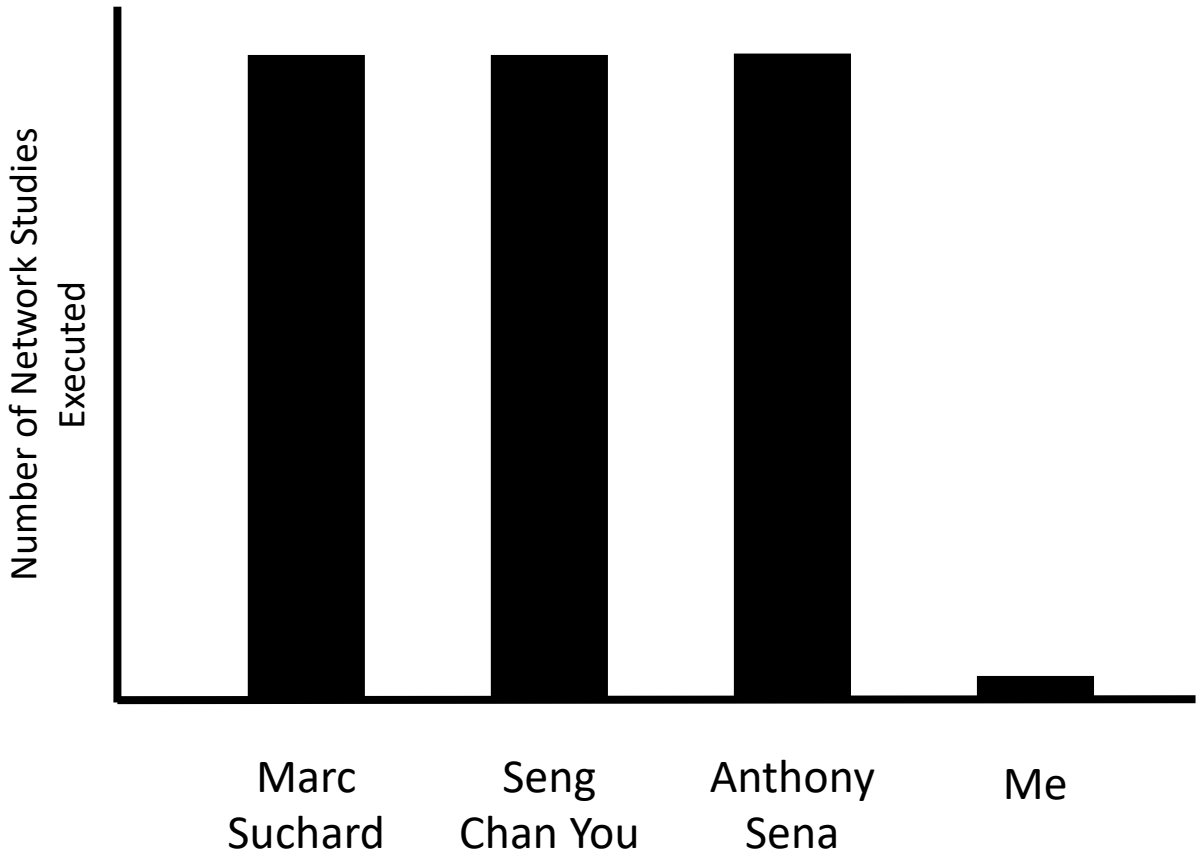
Cindy X. Cai, MD, MS
The Jonathan and Marcia Javitt Rising Professor
Assistant Professor of Ophthalmology
Retina Division, The Wilmer Eye Institute
Johns Hopkins University School of Medicine

10/20/2023

Lessons Learned From Two Perspectives

A Clinician's Perspective…

A Newbie's Perspective…



Demystify the process of network studies: you can do it!

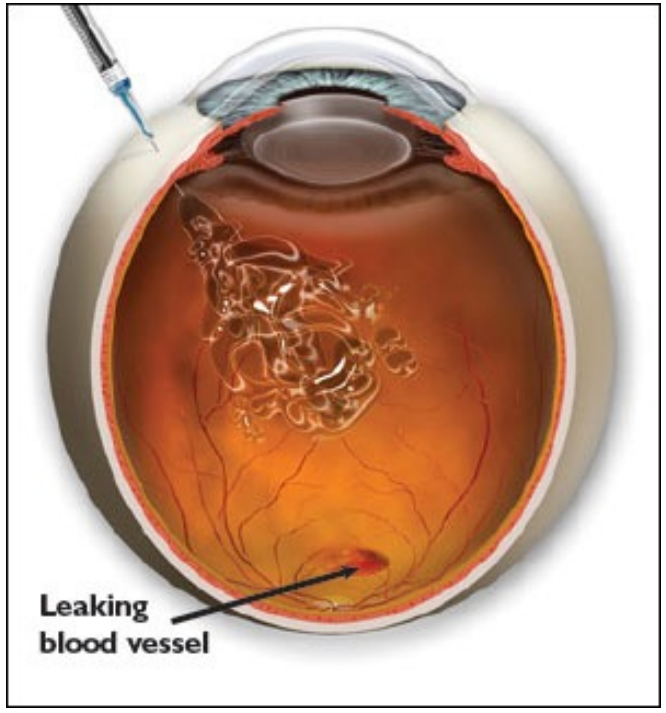
Wilmer Eye Institute
Johns Hopkins Medicine

Background: anti-VEGF medications

- Systemic administration of anti-VEGF agents have known **adverse kidney side effects**
  - Acute kidney injury
  - Proteinuria
  - Hypertension
  - Vascular clotting events
  - Glomerular disease
  - Risk factors for: kidney failure (need for renal replacement therapy with dialysis or kidney transplant, aka end stage kidney disease or end stage renal disease)

Hanna RM, Barsoum M, Arman F, Selamet U, Hasnain H, Kurtz I. Nephrotoxicity Induced by Intravitreal Vascular Endothelial Growth Factor (VEGF) inhibitors: Emerging Evidence. *Kidney Int*. 2019;96(3):572-580. doi:10.1016/j.kint.2019.02.042
Gurevich F, Perazella MA. Renal Effects of Anti-angiogenesis Therapy: Update for the Internist. *Am J Medicine*. 2009;122(4):322-328. doi:10.1016/j.amjmed.2008.11.025
Izzedine H, Escudier B, Lhomme C, et al. Kidney Diseases Associated With Anti-Vascular Endothelial Growth Factor (VEGF). *Medicine*. 2014;93(24):333-339. doi:10.1097/md.0000000000000207
Brandes, A. A., Bartolotti, M., Tosoni, A., Poggi, R. & Franceschi, E. Practical Management of Bevacizumab-Related Toxicities in Glioblastoma. *Oncol* **20**, 166–175 (2015).

Intravitreal Anti-VEGF and Systemic Absorption



Drug	Size	Systemic Elimination (half-life)
Ranibizumab	48 kDa	2 hours
Aflibercept	115 kDa	5-6 days
Bevacizumab	149 kDa	20 days

Detectable/elevated serum drug levels
Decreased plasma concentrations of free-VEGF

Bevacizumab > aflibercept >> ranibizumab

Question: Is there evidence for preferentially choosing ranibizumab to lower the risk of kidney failure?

Hypothesis: in pairwise comparisons, lower risk of kidney failure in patients with blinding diseases who are exposed to ranibizumab

https://www.randeye.com/intravitreal-injection/

Avery RL, Castellarin AA, Steinle NC, et al. SYSTEMIC PHARMACOKINETICS AND PHARMACODYNAMICS OF INTRAVITREAL AFLIBERCEPT, BEVACIZUMAB, AND RANIBIZUMAB. *Retin*. 2017;37(10):1847-1858. doi:10.1097/iae.0000000000001493
https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125085s0169lbl.pdf

SOS Challenge Weekly Tutorial Schedule

To answer the question: is there a difference in the risk of kidney failure comparing patients who received ranibizumab, aflibercept, and bevacizumab

Date	Times	Topic
Mar. 28	11 am / 7 pm ET	SOS Week 1 Tutorial: Initiating A Network Study
Apr. 4	11 am / 7 pm ET	SOS Week 2 Tutorial: Data Diagnostics
Apr. 11	11 am / 7 pm ET	SOS Week 3 Tutorial: Phenotype Development
Apr. 18	11 am / 7 pm ET	SOS Week 4 Tutorial: Phenotype Evaluation
Apr. 25	11 am / 7 pm ET	SOS Week 5 Tutorial: Creating Analysis Specifications
May 2	11 am / 7 pm ET	SOS Week 6 Tutorial: Network Execution
May 9	11 am / 7 pm ET	SOS Week 7 Tutorial: Study Diagnostics
May 16	11 am / 7 pm ET	SOS Week 8 Tutorial: Evidence Synthesis
May 23	11 am / 7 pm ET	SOS Week 9 Tutorial: Interpreting The Results

Anti-VEGF OHDSI Study: Process

Wilmer Eye Institute
Johns Hopkins Medicine

OHDSI Tools Used

- ATLAS
- PheValuator
- Strategus execution pipeline to call Hades Packages (CohortGenerator, Characterization, Cohort Incidence, Cohort Method, PatientLevelPrediction)
- EvidenceSynthesis

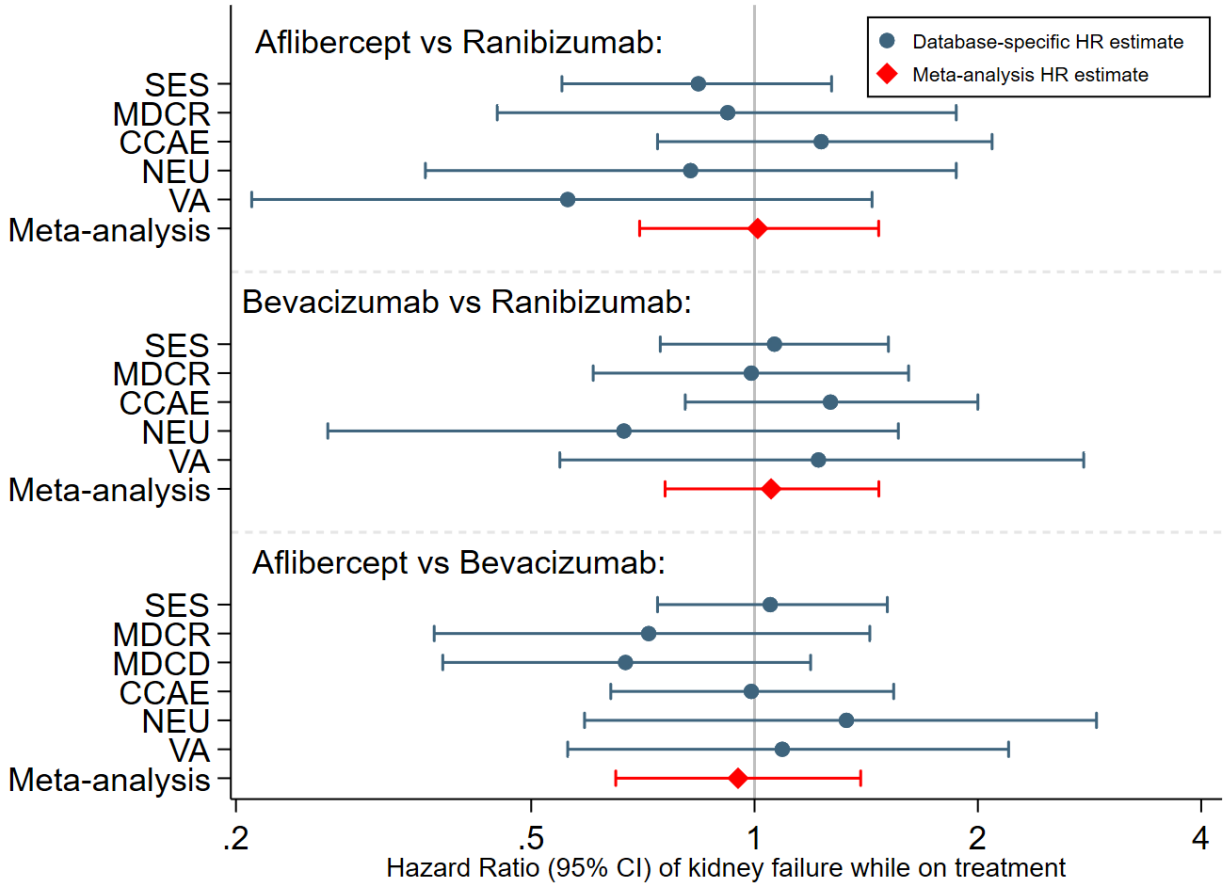
Data Sources
IBM Health MarketScan Medicare Supplemental and Coordination of Benefits Database (MDCR)
IBM Health MarketScan Commercial Claims and Encounters Database (CCAE)
IBM Health MarketScan Multi-State Medicaid Database (MDCD)
Optum(R) de-identified Electronic Health Record Dataset (OptumEHR)
Optum's Clinformatics Extended Data Mart - Socio-economic Status (SES)
Japan Medical Data Center (JMDC)
Johns Hopkins Medical Enterprise (JHME)
Department of Veterans Affairs (VA)
PharMetrics Plus (NEU)
Columbia University Medical Center (CUMC)
Stanford (STARR)
University of Southern California (USC)

- 12 databases:
  - 6 administrative claims and 6 EHR
- Collectively: 485 million patients

Wilmer Eye Institute
Johns Hopkins Medicine

Anti-VEGF OHDSI Study: Results

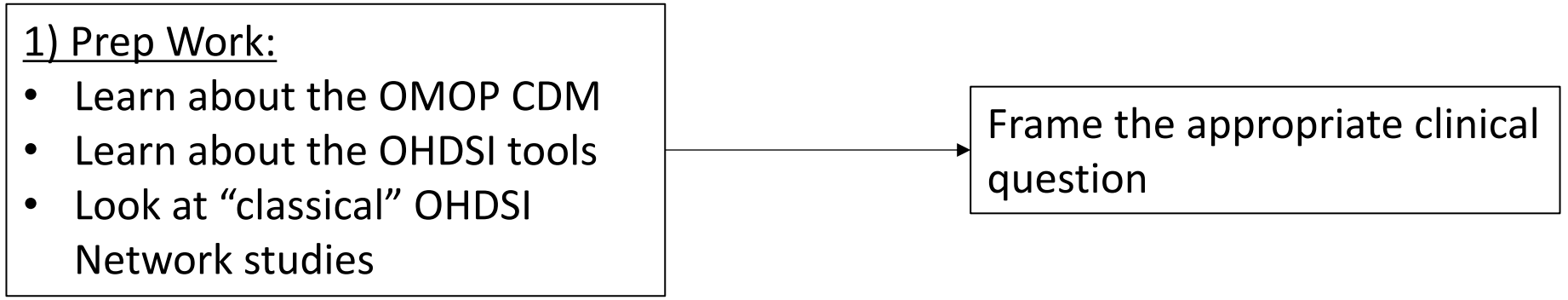
- 6.1 million patients with blinding diseases
  - 240,247 anti-VEGF
    - 37,189 received ranibizumab
    - 39,447 aflibercept
    - 163,611 bevacizumab
  - 1209 kidney failure outcomes
- Standardized incidence proportion of kidney failure: 680 per 100,000 persons
- In all pairwise comparison, the hazard ratio was around 1.0



For retina colleagues: can choose between any of these 3 anti-VEGF medications for those at risk for kidney failure

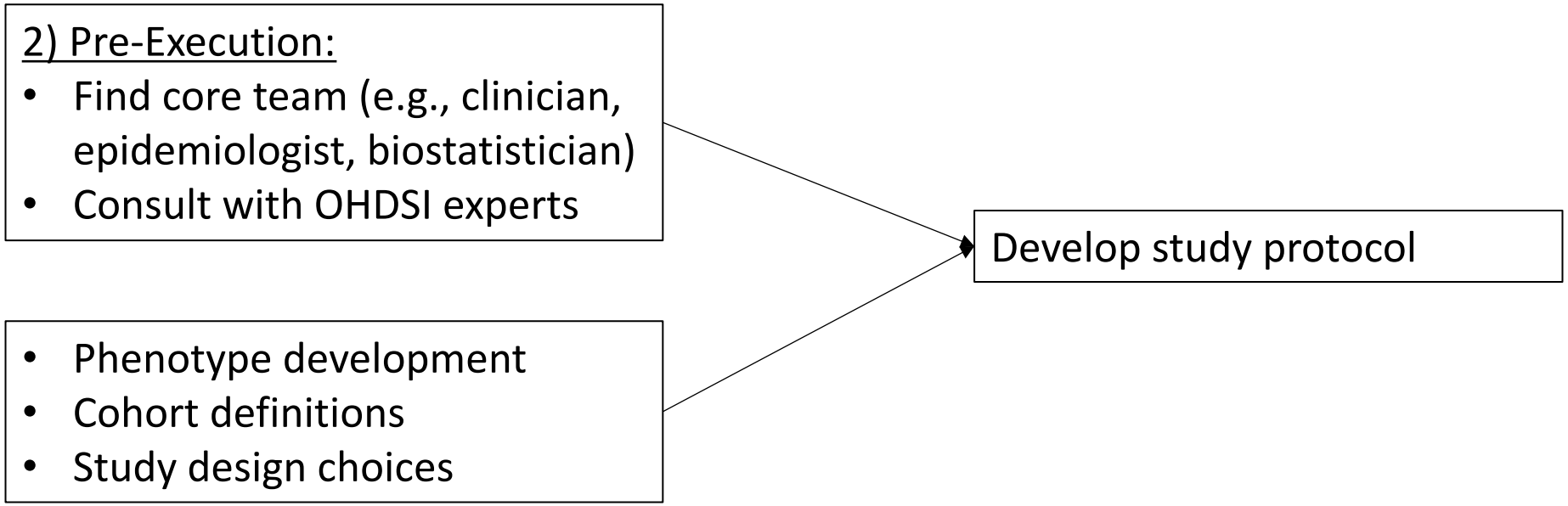
Components of an OHDSI Network Study

From a Clinician / Newbie's Perspective



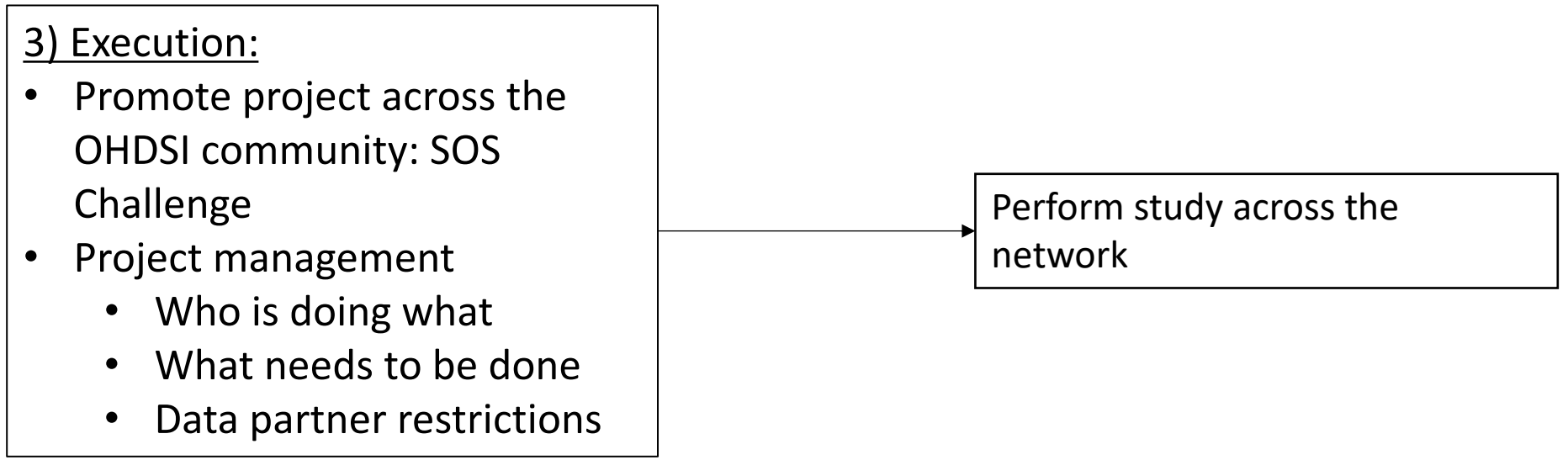
Components of an OHDSI Network Study

From a Clinician / Newbie's Perspective



Components of an OHDSI Network Study

From a Clinician / Newbie's Perspective



Components of an OHDSI Network Study

From a Clinician / Newbie's Perspective

Wilmer Eye Institute
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Not for the faint of heart…but you can do it too!

Network studies can answer important clinical questions

Wilmer Eye Institute
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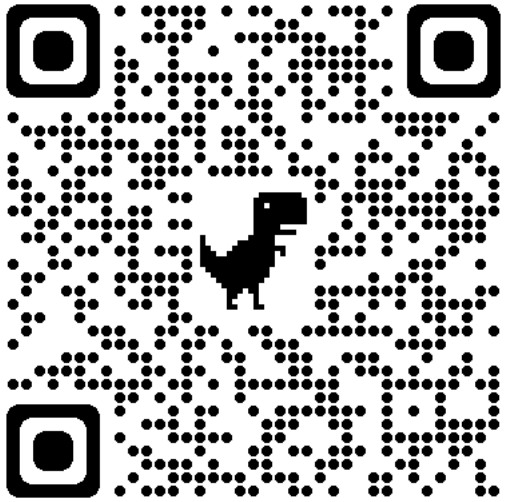


Come to poster #306 to chat more

ccai6@jhmi.edu

Save Our Sisyphus:
Is fluoroquinolone use associated with the development of aortic aneurysms and aortic dissections?

An international distributed network study of 390 million patients with urinary tract infection

Seng Chan You

Dep. of Biomedical Systems Informatics, Yonsei University College of Medicine

Chief investigators: Jack Janetzki, Nicole Pratt – University of South Australia
Seng Chan You, Seonji Kim, Jung Ho Kim, Jung Ah Lee – Yonsei University

On Courtesy of Jack Janetzki

Background and context of study

- Fluoroquinolones are broad spectrum antibiotics
- Indicated for many infections including pneumonia, bone and joint infections, and **Urinary Tract Infections (UTIs)**
- Use is rising internationally [1]
- Generally well tolerated:
  - Common side effects: vomiting, diarrhoea, abdominal pain
  - Serious adverse events (e.g. tendon ruptures)

[1] Van Boeckel TP, et al doi: 10.1016/S1473-3099(14)70780-7

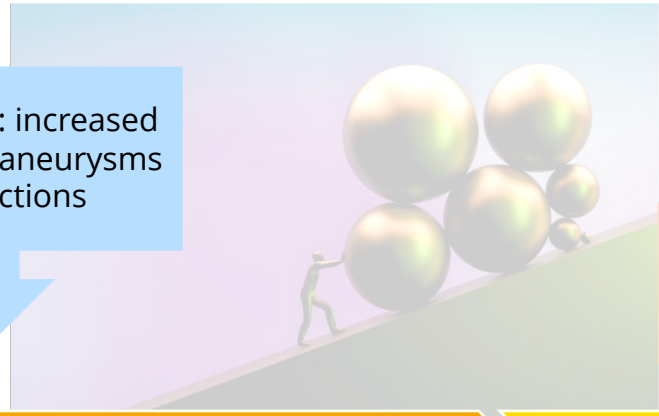
Timeline of warnings

SOS Challenge March 2023

FDA black box warning (tendinitis and tendon rupture)

FDA enhanced label warnings (joint pain, tendon rupture, tendinitis, altered mental status)

FDA warning: increased risk of aortic aneurysms or dissections



2022 Study from Taiwan shows no increased risk of AA/AD among 1.2M people with UTIs

2008 | **2016** | **2018** | **2019-2023**

- Warnings based on findings from epidemiologic studies
- Pharmacological mechanism not well understood

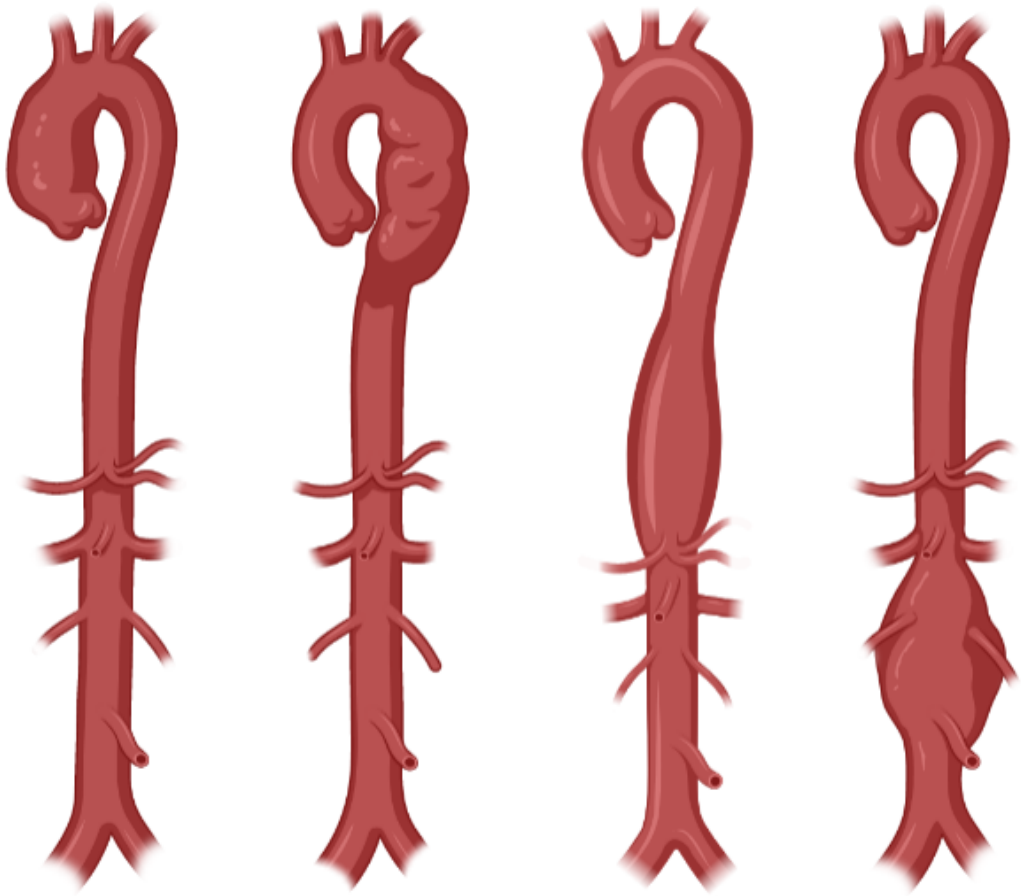
2018 EMA review of rare but serious ADEs with FQs led to restrictions on prescribing

2019 TGA investigates AA/AD risk

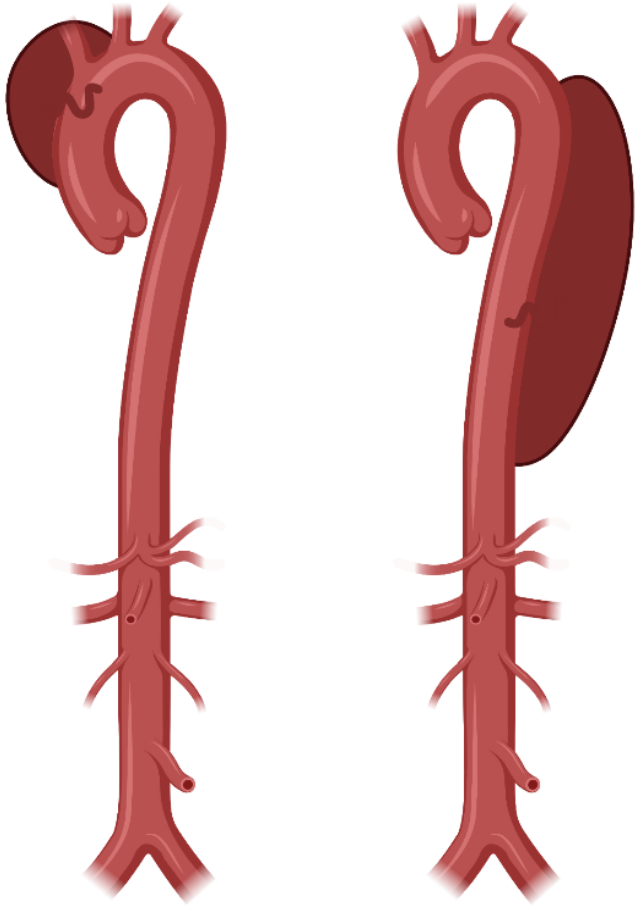
2020 TGA updates PIs for FQs with warnings of AA/AD

Chen YY, Yang SF, Yeh HW, Yeh YT, Huang JY, Tsao SL, Yeh CB. Association Between Aortic Aneurysm and Aortic Dissection With Fluoroquinolones Use in Patients With Urinary Tract Infections: A Population-Based Cohort Study. J Am Heart Assoc. 2022 Mar 15;11(6):e023267. doi: 10.1161/JAHA.121.023267. PMID: 35229623

Aortic aneurysm



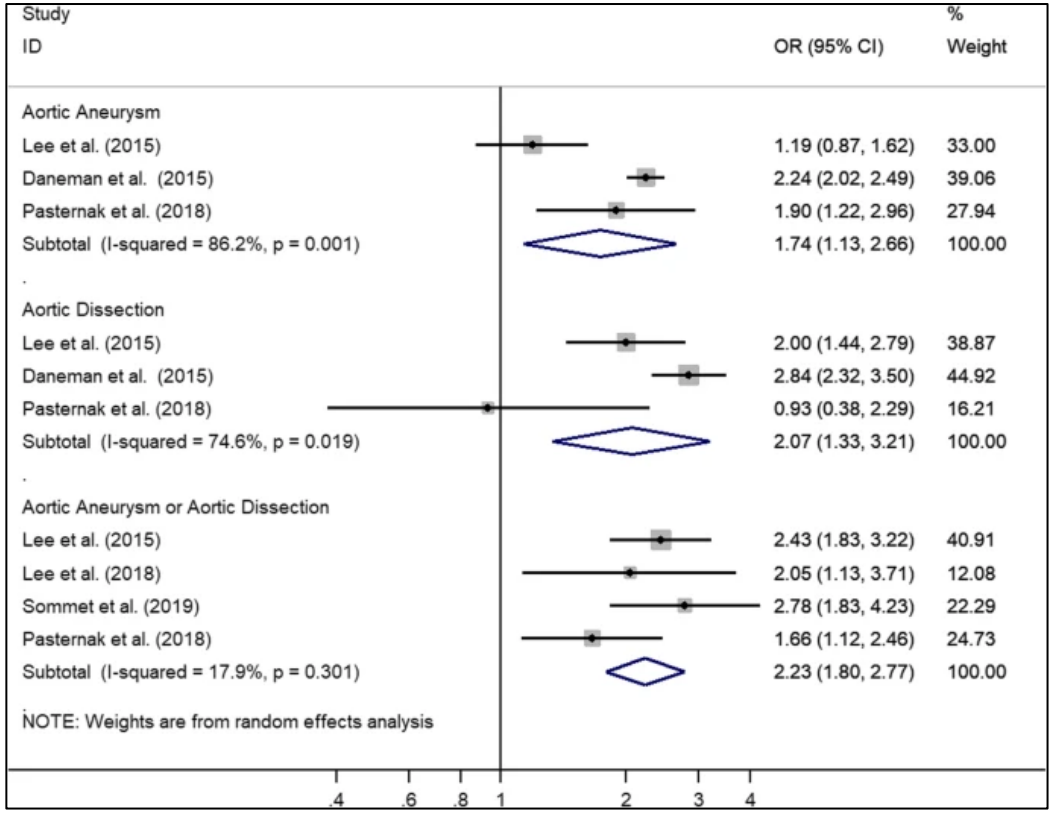
Aortic Dissection



Background and context of study

- Prior warnings based on epidemiologic studies

- **2020 Meta-analysis** of 5 observational studies described quality of evidence as moderate
  - 2.8M patients
  - **Comparators:** non-users or users of other antibiotics
  - **Primary outcome:** first occurrence of aortic diseases
  - OR 2.23 (95%CI 1.80-2.77) (range 1.66-2.78)
  - Inconsistencies in study designs
    - Patient age ranges, follow-up duration
    - Potential for unmeasured confounding (by indication and surveillance bias)



Dai XC, Yang XX, Ma L, Tang GM, Pan YY, Hu HL. Relationship between fluoroquinolones and the risk of aortic diseases: a meta-analysis of observational studies. BMC Cardiovasc Disord. 2020;20(1):49

Prior observational studies

	JAMA Intern Med. 2015	BMJ Open 2015	BMJ 2018	J Am Coll Cardiol. 2018	JAMA Intern Med. 2020	JAMA Intern Med. 2020	JAMA Surg. 2021
Study design	Nested case-control	Nested cohort	Cohort study	Case-crossover	Nested case-control	Cohort study	Cohort study
Data sources	Taiwan NHIRD	Ontario Registered Persons, Drug Benefits database	Swedish National Prescribed Drug, Patient Register, Statistics Sweden	Taiwan NHIRD	Taiwan NHIRD	US (IBM MarketScan)	US (IBM MarketScan)
Indication					Lower RTI, Genitourinary tract infection, Skin, soft tissue, or bone infections, Intra-abdominal infections, Mixed infections, Septicemia	Pneumonia, UTI	Upper RTI, Skin/soft tissue/bone/lymph UTI, Streptococcal/staphylococcus GI tract, Pneumonia, Pyelonephritis Ocular, Cholecystitis, Appendicitis Syphilis, Dental
Active comparators			Amoxicillin		Amoxicillin-clavulanate, Ampicillin-sulbactam, Extended-spectrum cephalosporins	Azithromycin for pneumonia Trim and sulf for UTI Amoxicillin without indication	Amox-clav, Azithromycin, Cephalexin Clindamycin, Trim and sulf
Rationale for selecting comparators			Approved indications largely overlap with FQ		Based on the recommendations of the treatment guidelines in Taiwan	Clinically appropriate	Based on commonly prescribed antibiotics for similar indications

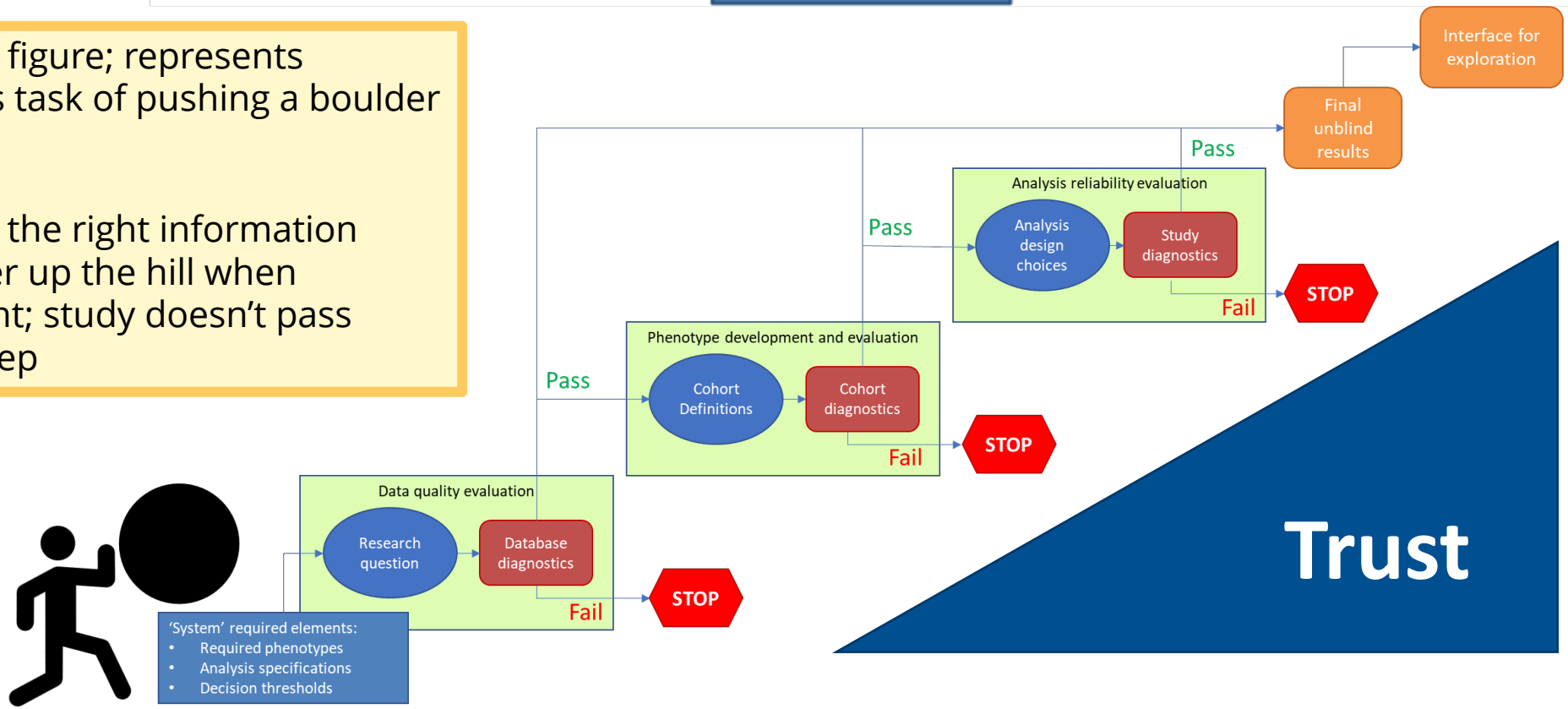
- Different study designs
- Predominantly single country studies
- Indication of FQ not specified or multiple indications of varying severity
- Unspecified or different active comparators
- Covariate Balance: mostly PS matching however no assessment of clinical equipoise
- Some studies addressed systematic error (usually single positive or negative control)

How do we build trust in real-world evidence?

- Open science system to build trust and confidence:

Sysiphus: mythological figure; represents repetitive and laborious task of pushing a boulder uphill

- Ensure that we have the right information
- Stop pushing boulder up the hill when conditions aren't right; study doesn't pass diagnostics at any step

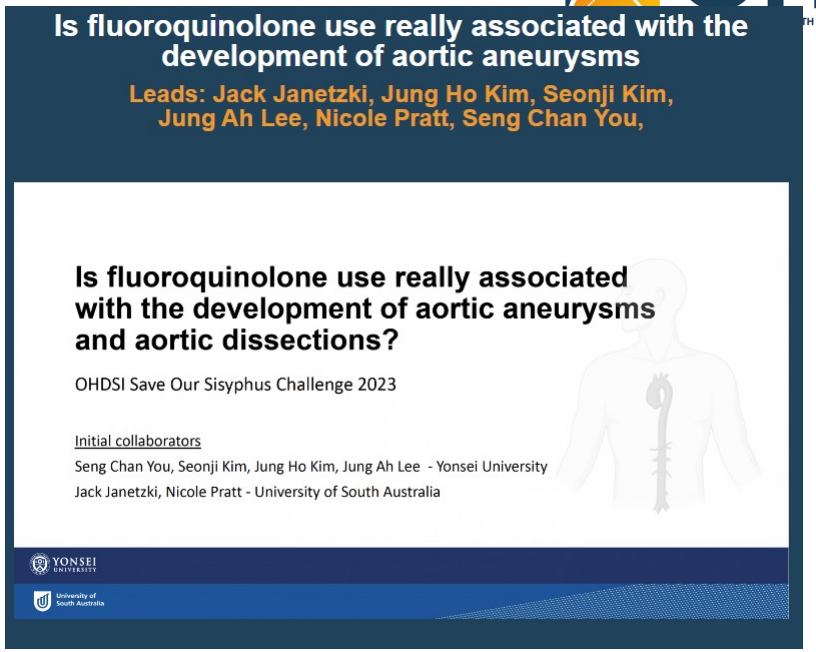


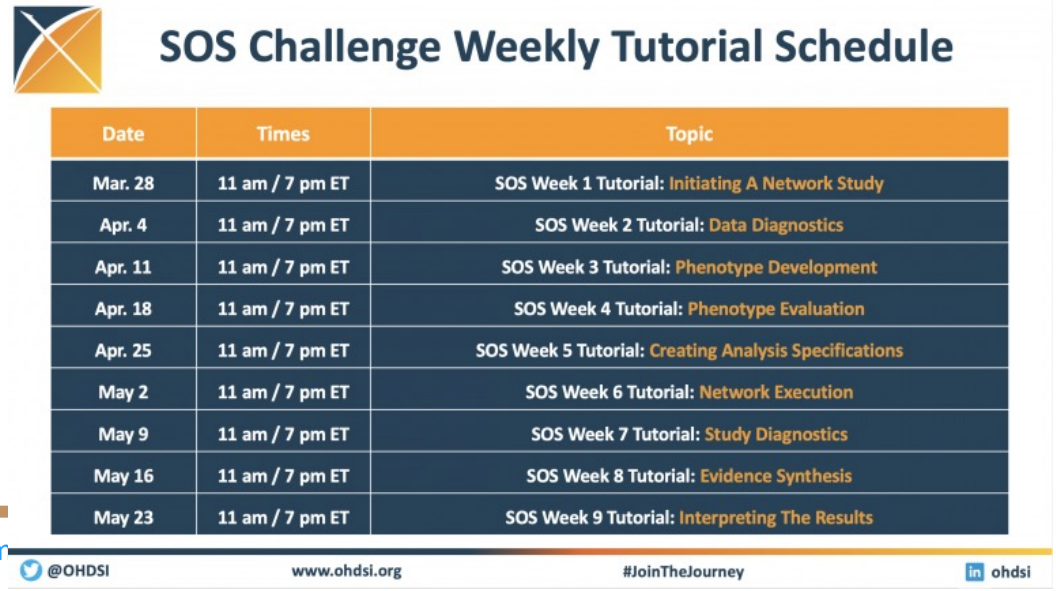
SOS challenge

- Pitched topic given:
  - ongoing regulatory monitoring
  - inconsistencies of prior methodologies
  - recent evidence of no association

- Over 9 weeks (with help of OHDSI team):
  - Planned and executed study

- Sharing **results** today





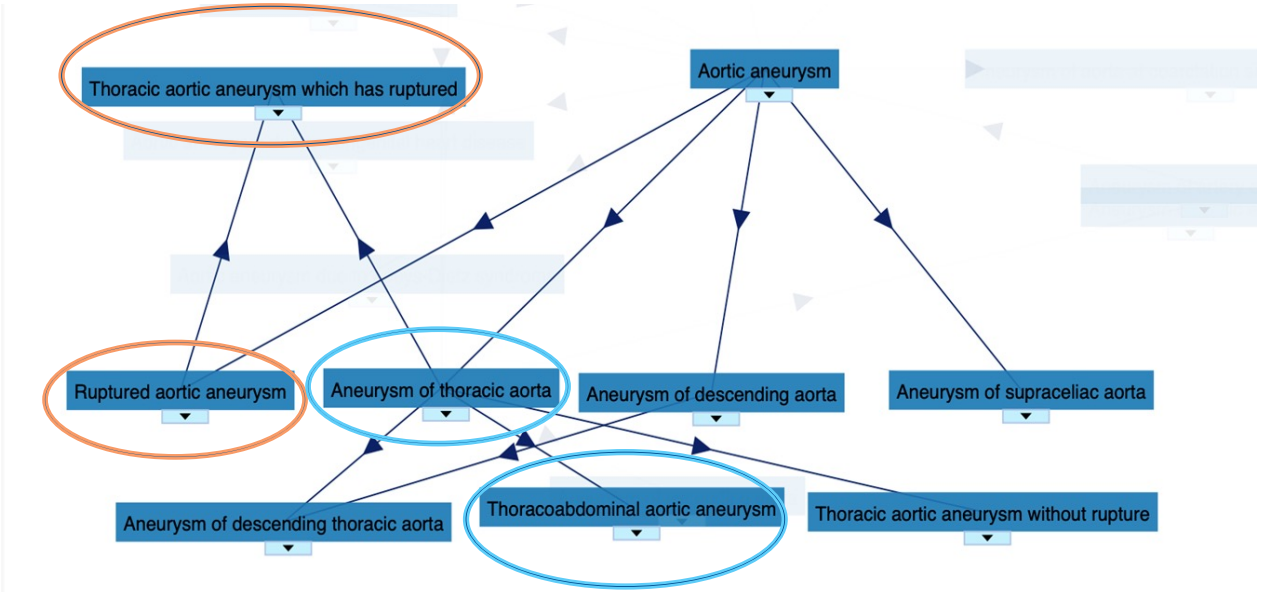
Treatment, Comparator & Outcome

Exposure Cohorts	
Indication: Urinary Tract Infection • Within 7 days prior • No hospitalisation within 7 days prior; taking antibiotic in outpatient setting	
Fluoroquinolones	**Active comparators**
All	1. Trimethoprim +/- sulfamethoxazole (TMP) 2. Cephalosporins (CPH) Chosen based on treatment guidelines and usual clinical care

Outcomes	
Outcome of interest	**Negative controls**
1. Aortic aneurysm or aortic dissection during 60 days 2. Aortic aneurysm (+/- rupture) 3. Aortic dissection 4. TAR of 30, 90, 365 days	As recommended by CommonEvidenceModel (N~50) (Used to test for systematic bias)

Note on phenotyping of outcome cohorts

- See SOS Challenge tutorial by Evan Minty: defining outcome cohorts
- Prior studies inconsistent on definition of outcome
- ICD codes used interchangeably
- Requiring primary position diagnosis decreases observed counts that would contribute to estimate by 75% - carefully define inclusion criteria to ensure acceptable specificity of cases captured



Data partners

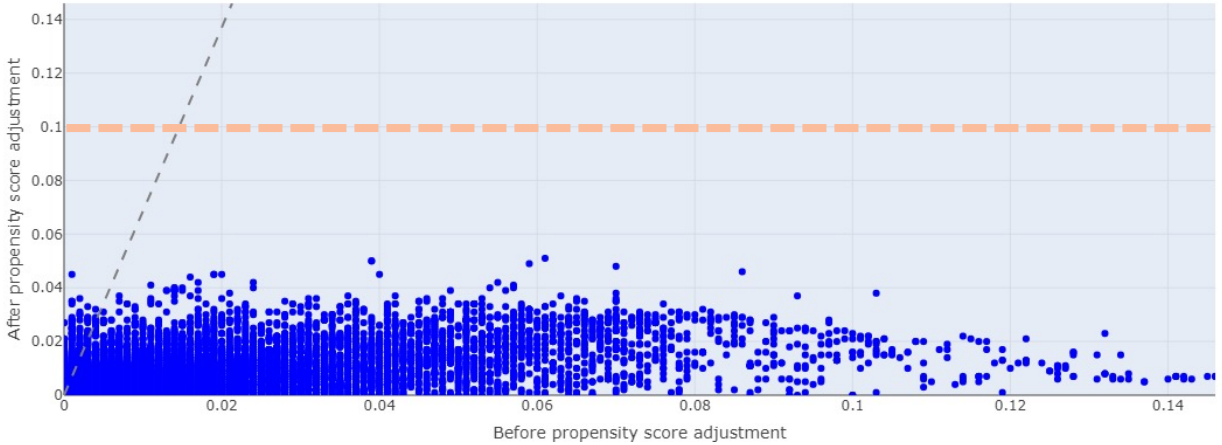
- 17 data partners across the OHDSI network

Results

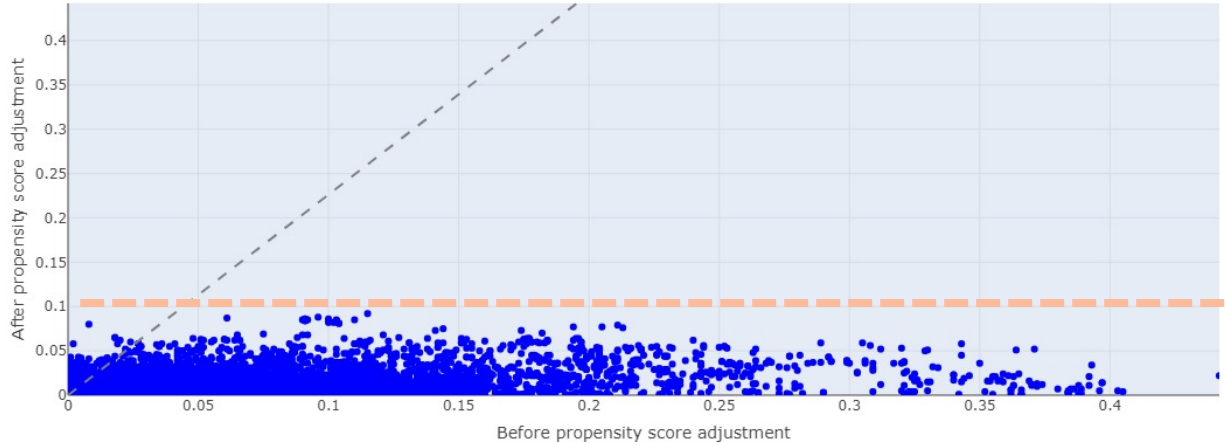
Covariate balance: Optum EHR

- Can check **covariate balance** before and after PS matching by plotting **standardised mean differences**
  - Determine whether baseline characteristics are sufficiently similar between target and comparator cohorts
  - If SMD < 0.1 (10%) for all covariates = sufficient balance
  - All < 0.1 for all cohort comparisons in Optum EHR

FQ v TMP-SMX

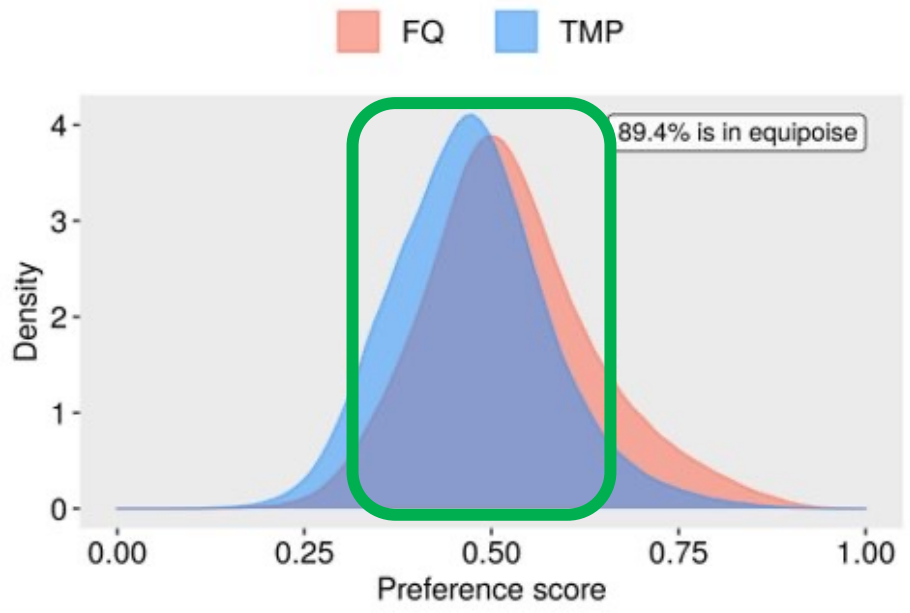


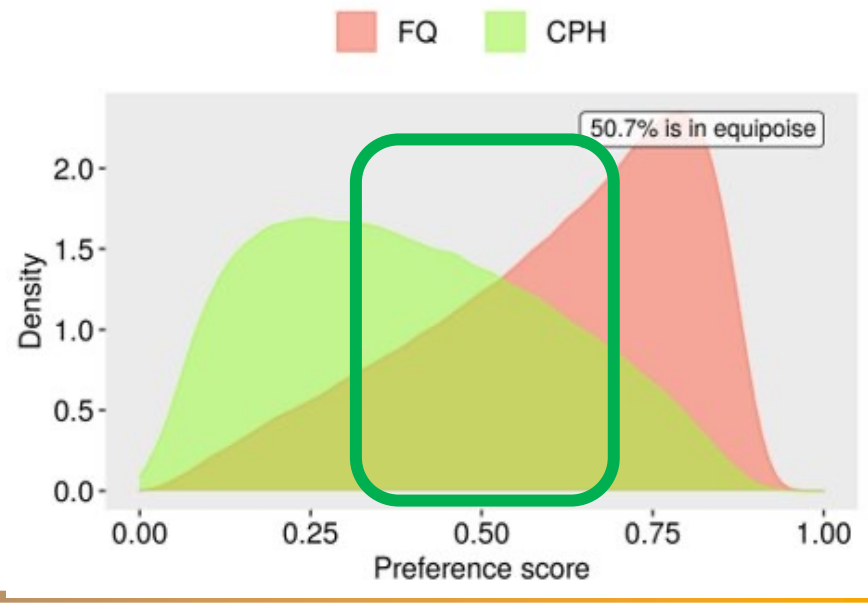
FQ v CEF



Propensity score: Optum EHR

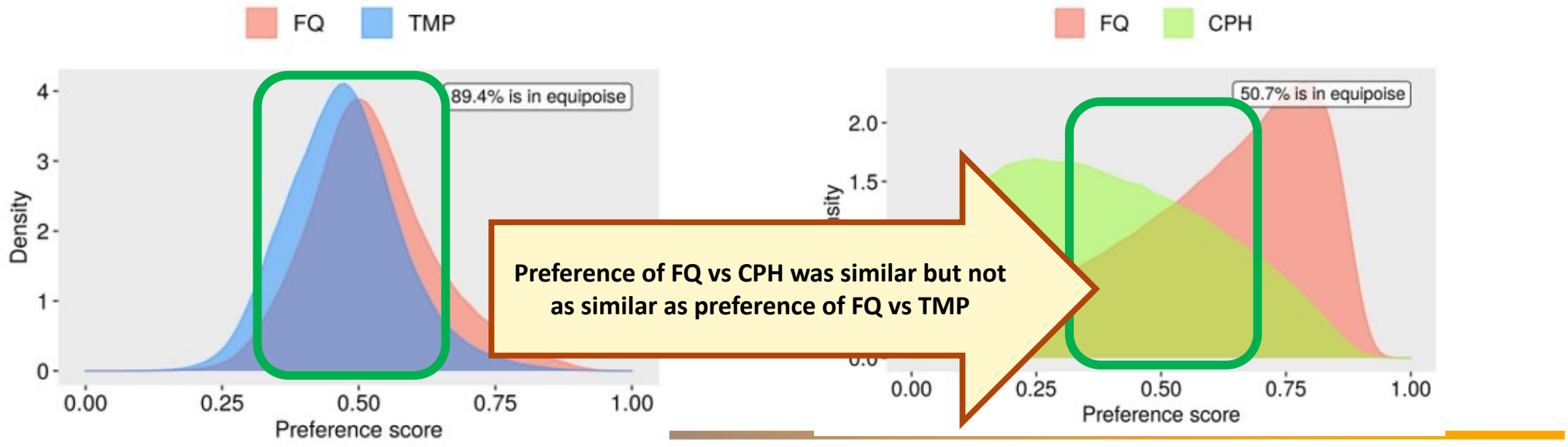
- Check **empirical equipoise** by observing **preference score distribution**:
  - Transformation of propensity score
  - Aims for overlap between 0.3 and 0.7
  - Higher overlap ensures that results will be generalisable
  - Good equipoise = large PS model could not discriminate between two treatments





Propensity score: Optum EHR

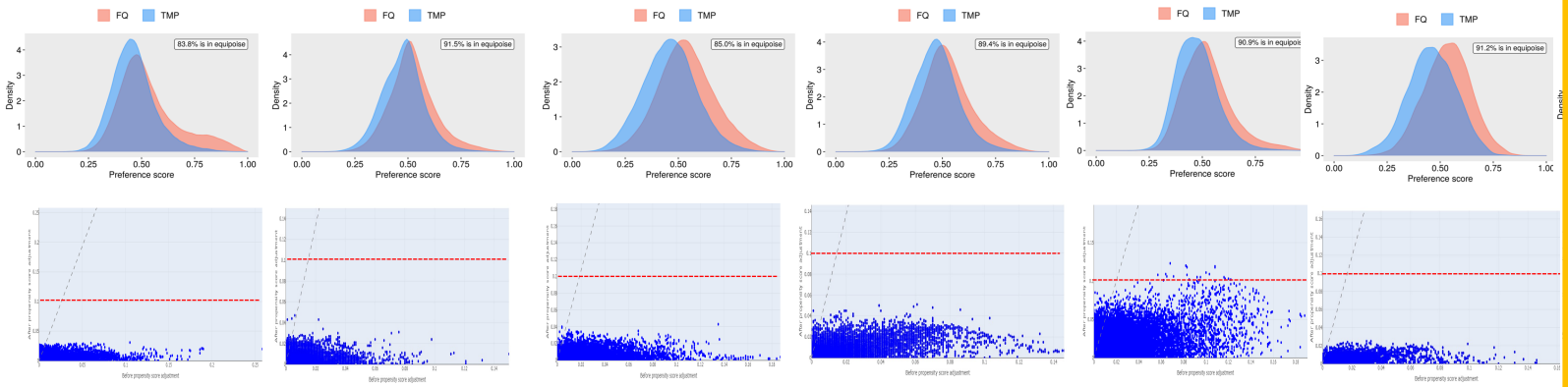
- Having achieved covariate balance between matched cohorts, is our result **generalisable** back to original population?
- Check **empirical equipoise** by observing **preference score distribution**:
  - Transformation of propensity score
  - Aims for overlap between 0.3 and 0.7
  - Higher overlap ensures that results will be generalisable
  - Good equipoise = large PS model could not discriminate between two treatments



Preference Score distributions across several databases
FQ v TMP

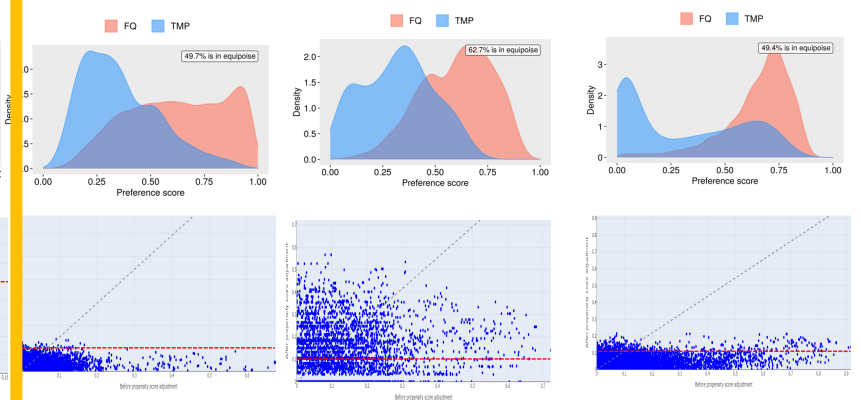
US

IBM MDCD | Optum DOD | VA-OMOP | Optum EHR | PharMetrics | CUMC



Taiwan | Korea | Japan

TMUDB | AUSOM | JMDC



- Similar patterns across US databases
- PS distribution was almost identical

- Different pattern in Non-US databases (Less preference of TMP versus FQ)

Preference Score distributions across several databases
FQ v CPH

US

Taiwan

Korea

Japan

IBM MDCD

Optum DOD

VA-OMOP

Optum EHR

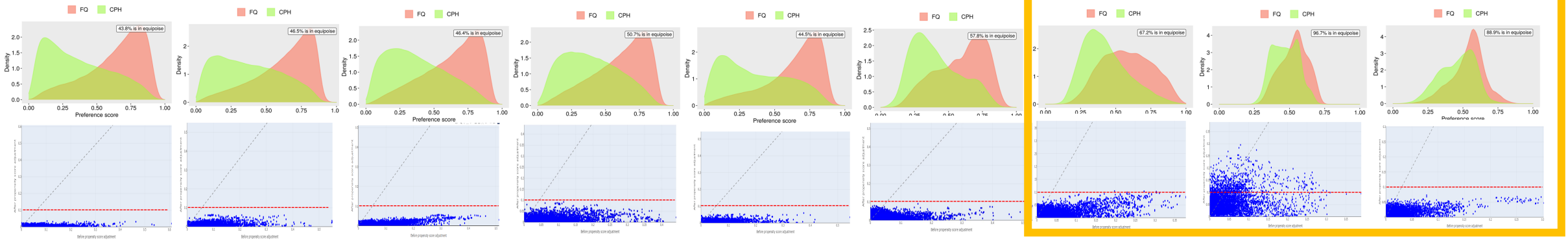
PharMetrics

CUMC

TMUDB

AUSOM

JMDC

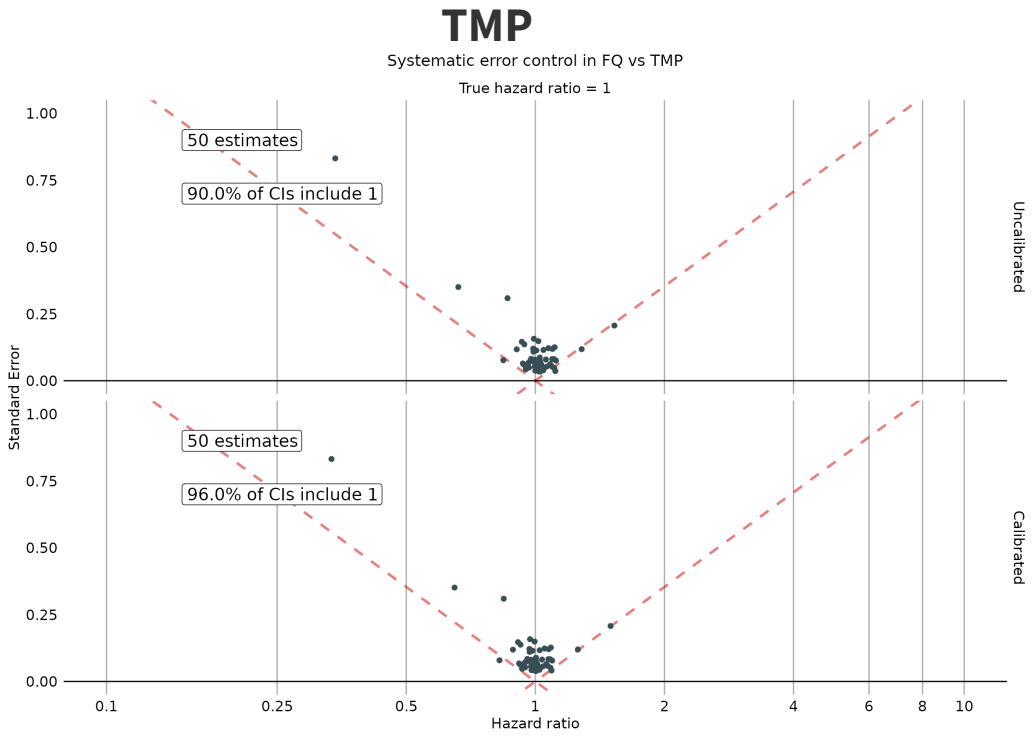


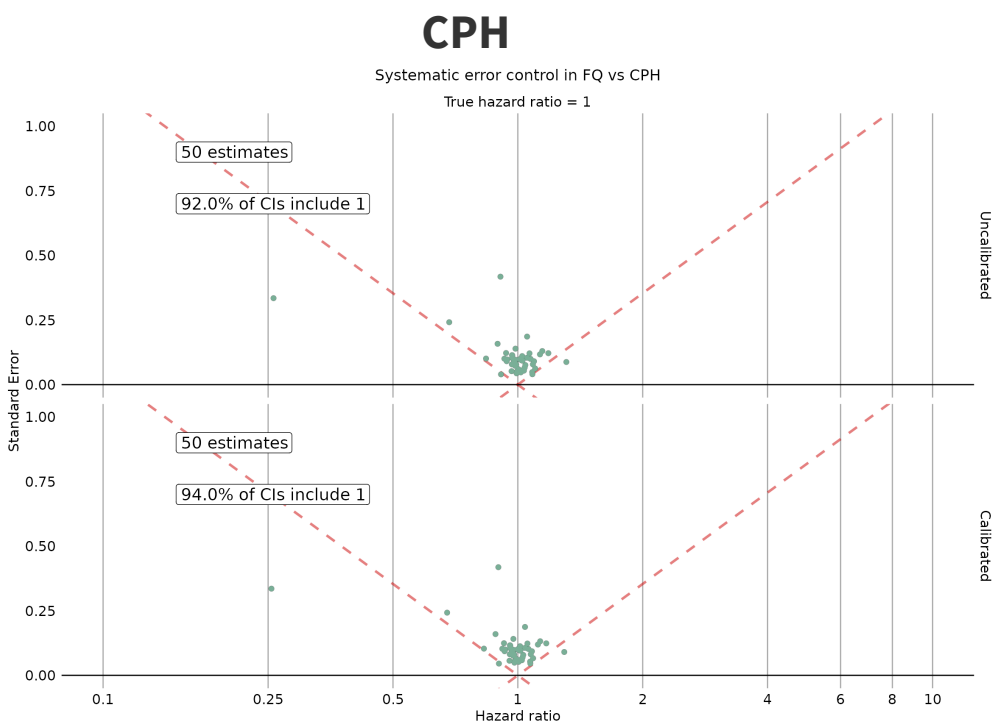
- Again similar patterns across US databases
- Lower PS overlap compared with FQ vs TMP

- Different patterns in Non-US databases
- Higher PS overlap in FQ vs CPH than FQ vs TMP

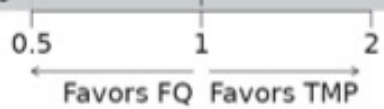
Systematic error

- **50 negative controls**
- Estimates below the line in graphs are statistically different from the true effect size
- Negative control outcomes should return estimate of 1 (95% CIs should contain 1 95% of the time)
  - In both cases 95% of negative control estimates had HR with CI that included 1 after empirical calibration, which indicates low systematic error



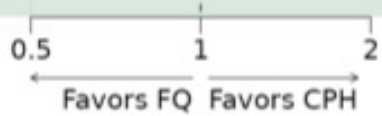


Source	Matched(n)	FQ	TMP	HR (95% CI)	Max SDM	PS overlap	EASE	Diagnostics
CUMC(US)	3996	<7.69	7.69	0.45(0.08-2.58)	0.12	0.92	0.15	PASS
IBM CCAE(US)	505839	0.58	0.53	1.07(0.70-1.63)	0.03	0.94	0.04	PASS
IBM MDCD(US)	88791	2.87	2.09	1.36(0.84-2.19)	0.03	0.88	0.03	PASS
Optum DOD(US)	410842	3.75	4.53	0.83(0.68-1.01)	0.05	0.93	0.04	PASS
Optum EHR(US)	478507	2.23	2.34	0.92(0.73-1.15)	0.05	0.91	0.06	PASS
PharMetrics(US)	358621	1.12	0.96	1.15(0.80-1.66)	0.03	0.93	0.03	PASS
VA(US)	108202	4.46	6.40	0.67(0.50-0.91)	0.04	0.86	0.05	PASS
TMUDB(TW)	2328	<13.60	0.00	NA(NA- NA)	0.14	0.50	0.50	FAIL
AUSOM(KR)	61	0.00	0.00	NA(NA- NA)	0.57	0.62	NA	FAIL
NHIS-NSC(KR)	442	0.00	0.00	NA(NA- NA)	0.30	0.77	NA	FAIL
Yonsei(KR)	251	0.00	0.00	NA(NA- NA)	0.33	0.40	NA	FAIL
JMDC(JP)	722	0.00	0.00	NA(NA- NA)	0.21	0.48	NA	FAIL
Japan Claims(JP)	1106	0.00	0.00	NA(NA- NA)	0.20	0.36	NA	FAIL
LPD Australia(AU)	947	0.00	0.00	NA(NA- NA)	0.16	0.55	NA	FAIL



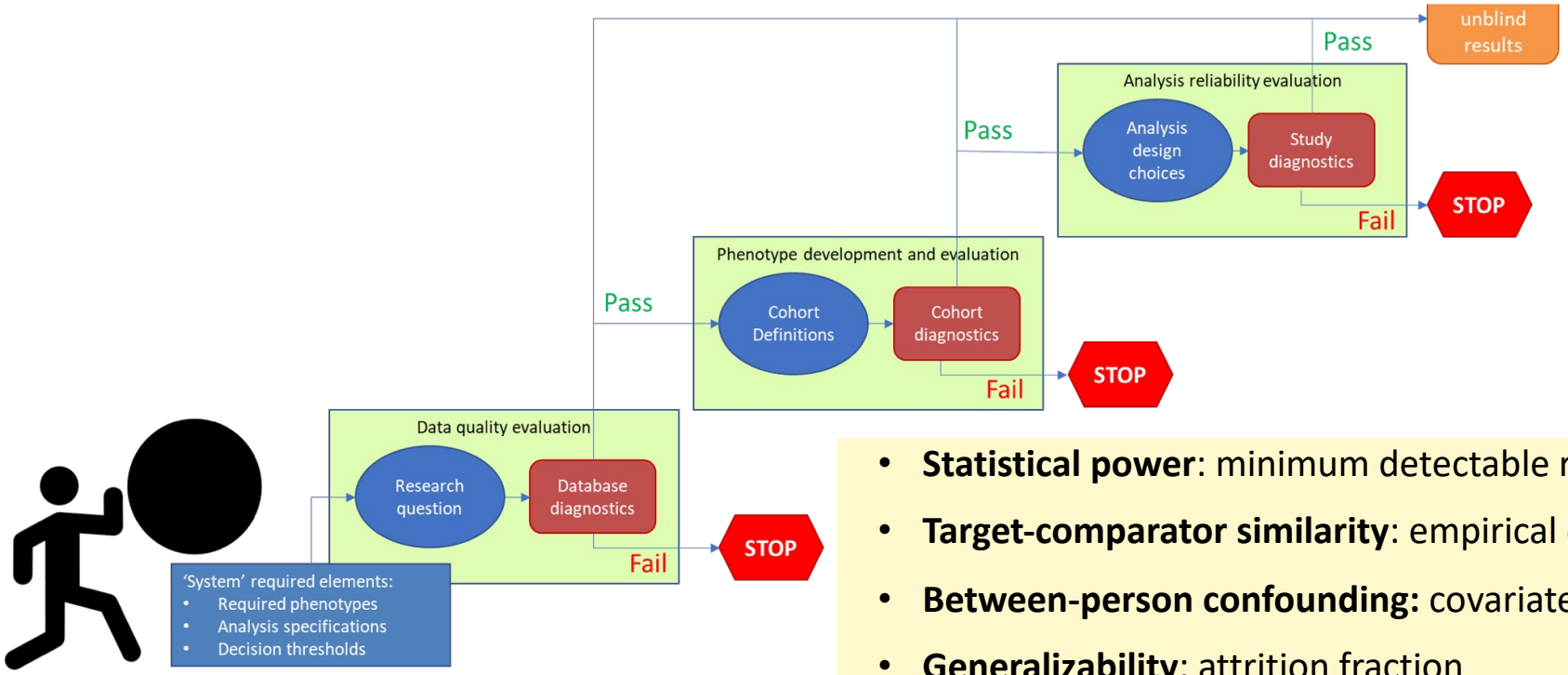
Shades proportional to PS overlap

Source	Matched(n)	FQ	CPH	HR (95% CI)	Max SDM	PS overlap	EASE	Diagnostics
CUMC(US)	4867	6.31	8.84	0.73(0.22- 2.42)	0.09	0.58	0.14	PASS
IBM CCAE(US)	222632	1.01	0.85	1.16(0.71- 1.91)	0.08	0.43	0.05	PASS
IBM MDCD(US)	67180	5.19	3.52	1.45(0.96- 2.21)	0.03	0.43	0.04	PASS
Optum DOD(US)	274869	6.29	7.03	0.90(0.72- 1.13)	0.06	0.47	0.07	PASS
Optum EHR(US)	338470	4.10	4.50	0.89(0.73- 1.09)	0.09	0.52	0.04	PASS
PharMetrics(US)	211877	2.41	1.84	1.29(0.92- 1.81)	0.06	0.44	0.03	PASS
VA(US)	68155	9.25	10.46	0.86(0.65- 1.13)	0.06	0.47	0.05	PASS
TMUDB(TW)	7912	<4.08	4.05	0.77(0.19- 3.08)	0.10	0.69	0.20	PASS
AUSOM(KR)	528	0.00	0.00	NA(NA- NA)	0.30	0.99	NA	FAIL
NHIS-NSC(KR)	5073	<6.18	<6.17	1.60(0.11-24.44)	0.13	0.94	0.35	FAIL
Yonsei(KR)	3581	<8.90	<8.97	0.80(0.03-20.72)	0.12	0.91	0.47	FAIL
JMDC(JP)	9569	<3.26	<3.26	0.48(0.03- 7.48)	0.07	0.89	0.27	FAIL
Japan Claims(JP)	15060	<2.06	0.00	NA(NA- NA)	0.07	0.56	0.13	PASS
LPD Australia(AU)	889	0.00	0.00	NA(NA- NA)	0.18	0.58	NA	FAIL



Summary:

- **Objective diagnostics** helped us to objectively interpret **reliability** and **validity** of evidence we produced
- At each point in SOS journey we were willing to **STOP** if failed diagnostics
- Meta-analysis only includes databases that **passed** diagnostic checks

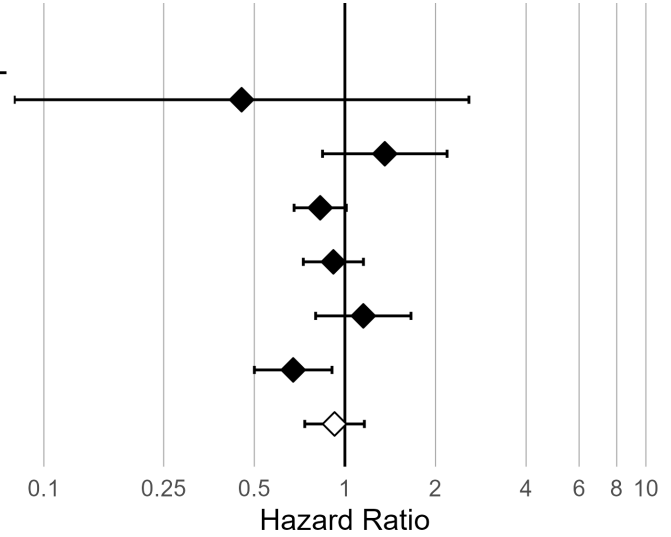


- **Statistical power**: minimum detectable relative risk
- **Target-comparator similarity**: empirical equipoise
- **Between-person confounding:** covariate balance
- **Generalizability**: attrition fraction
- **Residual bias**: expected absolute systematic error (calibration)

Meta-analysis: 60 day risk window, AA AD

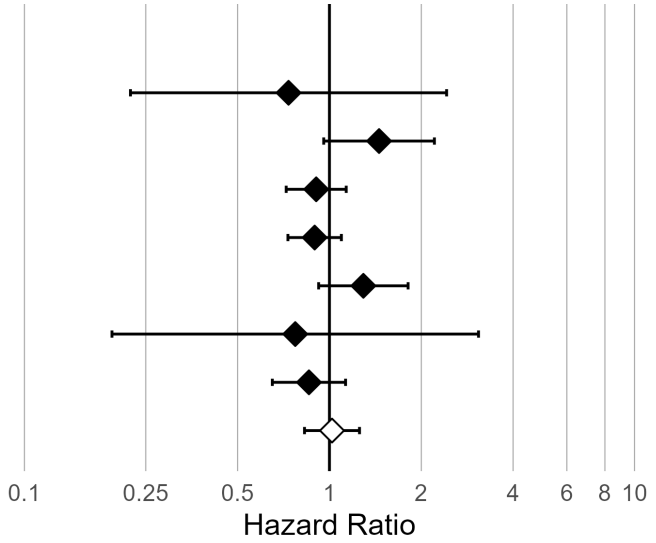
TMP

Source	Hazard Ratio (95% CI)
CUMC	0.45 (0.08 - 2.58)
IBM MDCD	1.36 (0.84 - 2.19)
Optum DoD	0.83 (0.68 - 1.01)
Optum EHR	0.92 (0.73 - 1.15)
PharMetrics	1.15 (0.80 - 1.66)
VA-OMOP	0.67 (0.50 - 0.91)
Summary	0.92 (0.74 - 1.16)



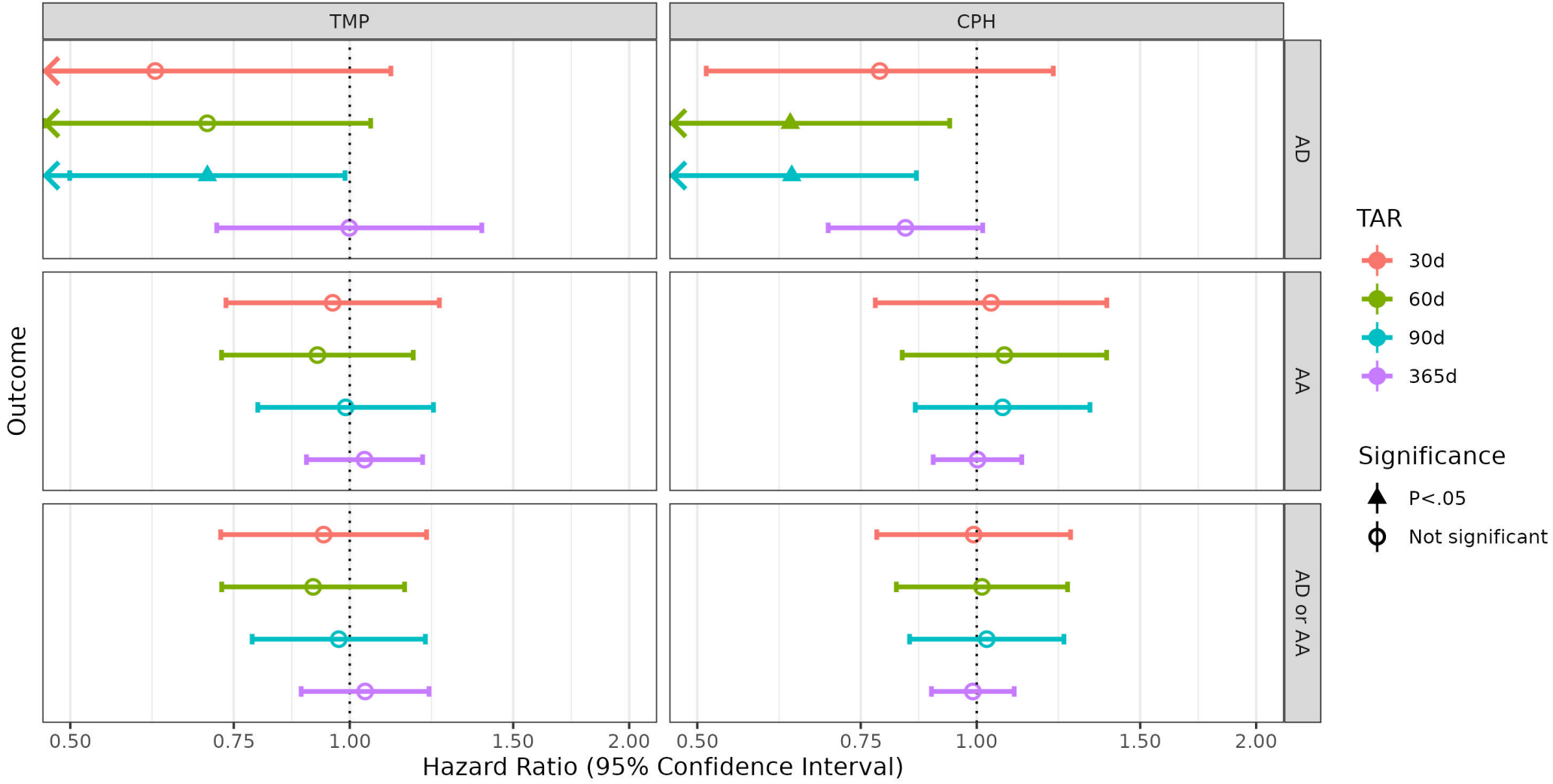
CEF

Source	Hazard Ratio (95% CI)
CUMC	0.73 (0.22 - 2.42)
IBM MDCD	1.45 (0.96 - 2.21)
Optum DoD	0.90 (0.72 - 1.13)
Optum EHR	0.89 (0.73 - 1.09)
PharMetrics	1.29 (0.92 - 1.81)
TMUDB	0.77 (0.19 - 3.08)
VA-OMOP	0.86 (0.65 - 1.13)
Summary	1.02 (0.83 - 1.25)

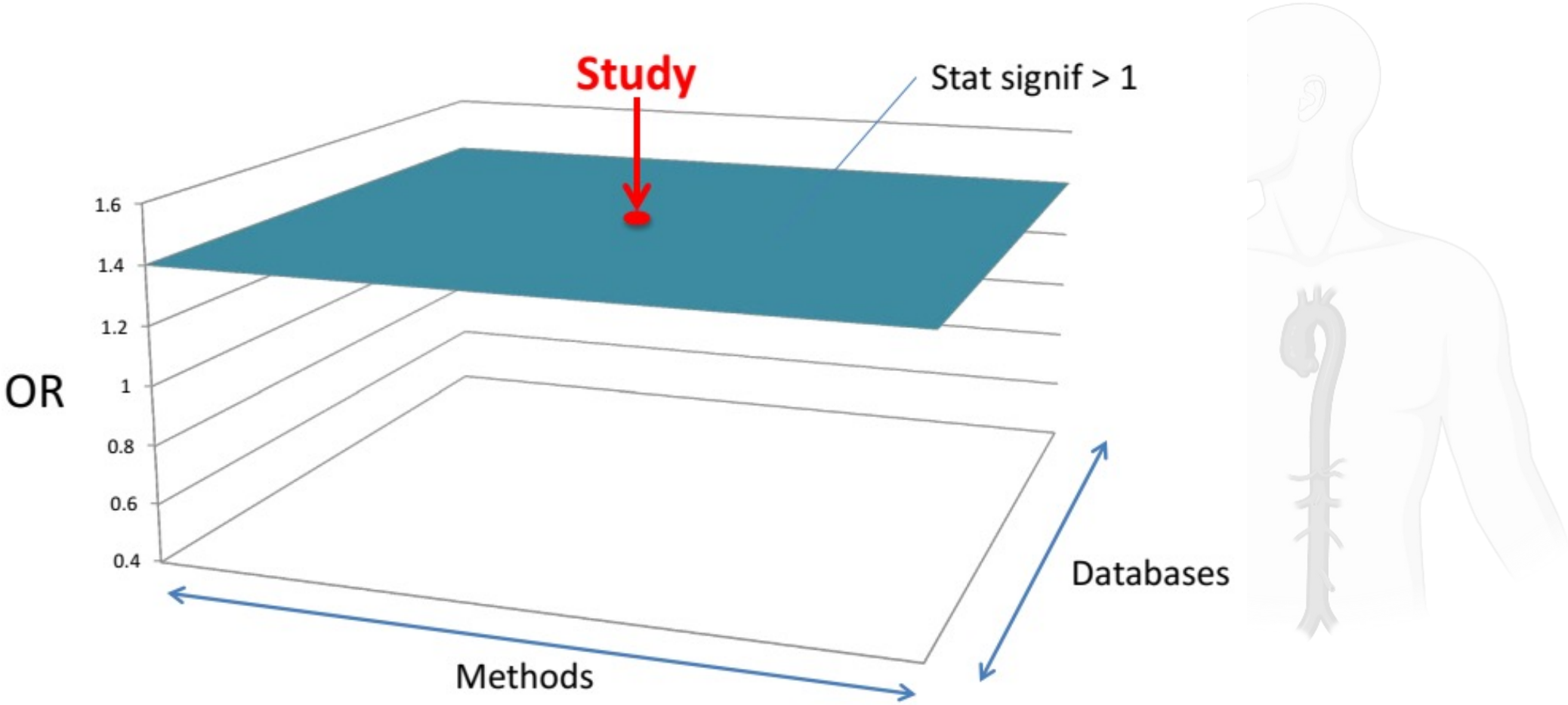


Comparator	Meta-analysis Hazard Ratio (95%CI)
TMP-SMX	0.92 (0.74-1.16)
CEF	1.02 (0.83-1.25)

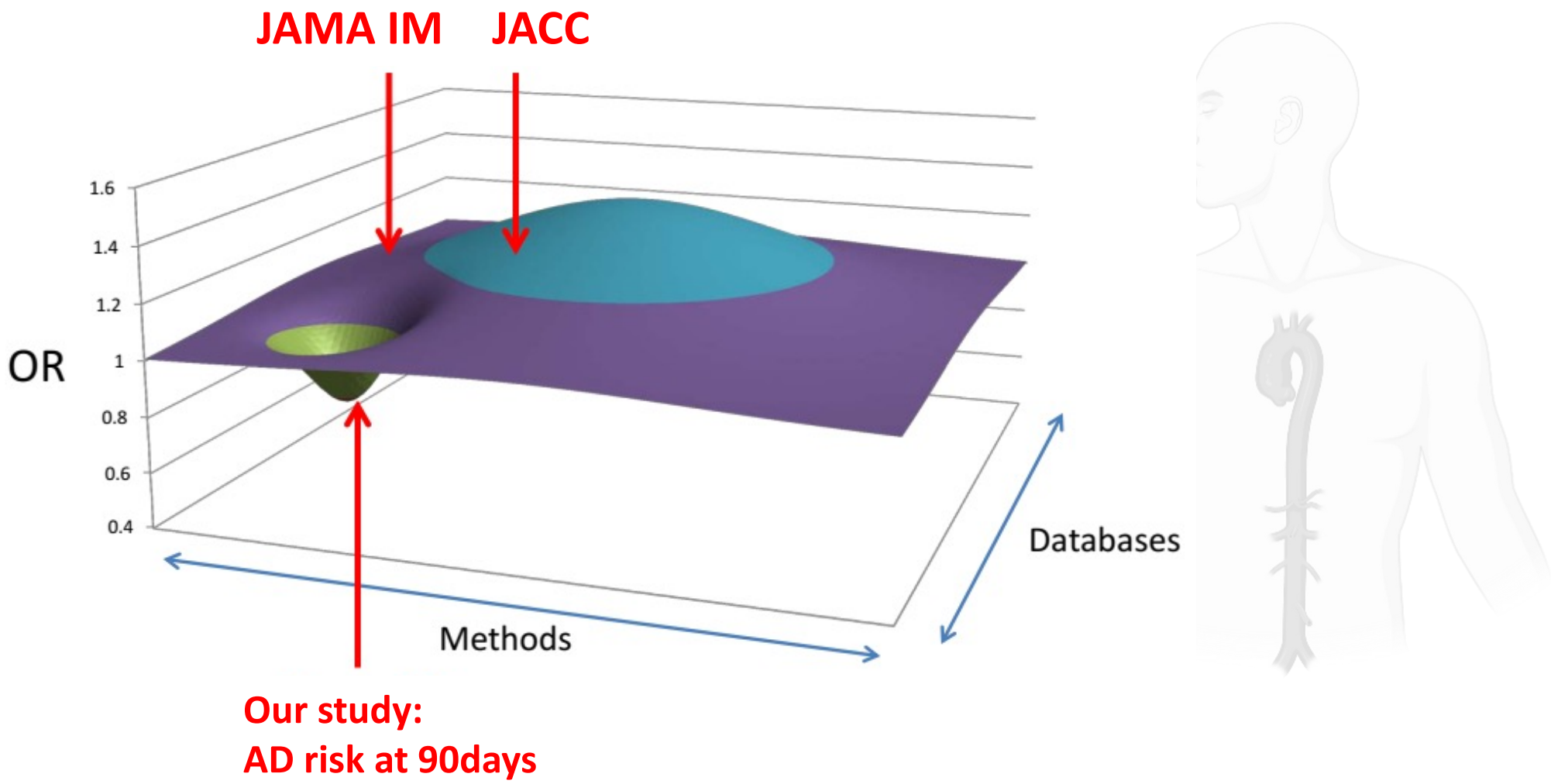
Sensitivity analyses



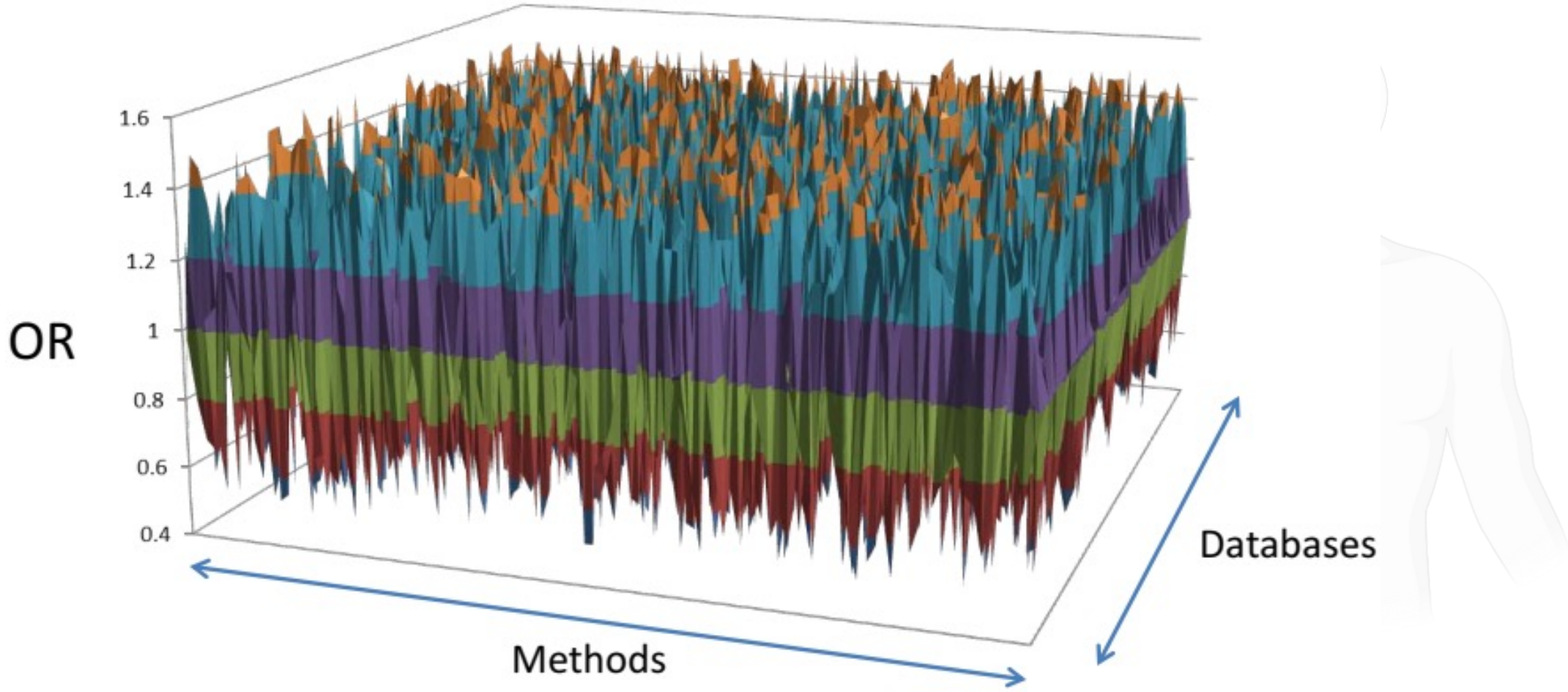
Distribution of possible results for one single question



Distribution of possible results for one single question



Distribution of possible results for one single question



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DOI: 10.1002/pds.5005

COMMENTARY

WILEY

Assessing strength of evidence for regulatory decision making in licensing: What proof do we need for observational studies of effectiveness?

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Abstract

Before a medicine can be recommended for a marketing authorization research must be provided to regulators that convincingly supports the benefit-risk of the product in the claimed indication. The established criteria for such research are usually expressed in terms of evidence from randomized controlled trials (RCT). If studies in real-world data (RWD) are to be accepted as all or part of the package of evidence, it is necessary to understand the relationship between information from studies of RWD and that from RCTs. The aim of this review is to consider how the strength of such evidence can be quantified in a manner that relates to the decision-making process, what research is currently available to further this understanding and what additional information will be required.

Key points

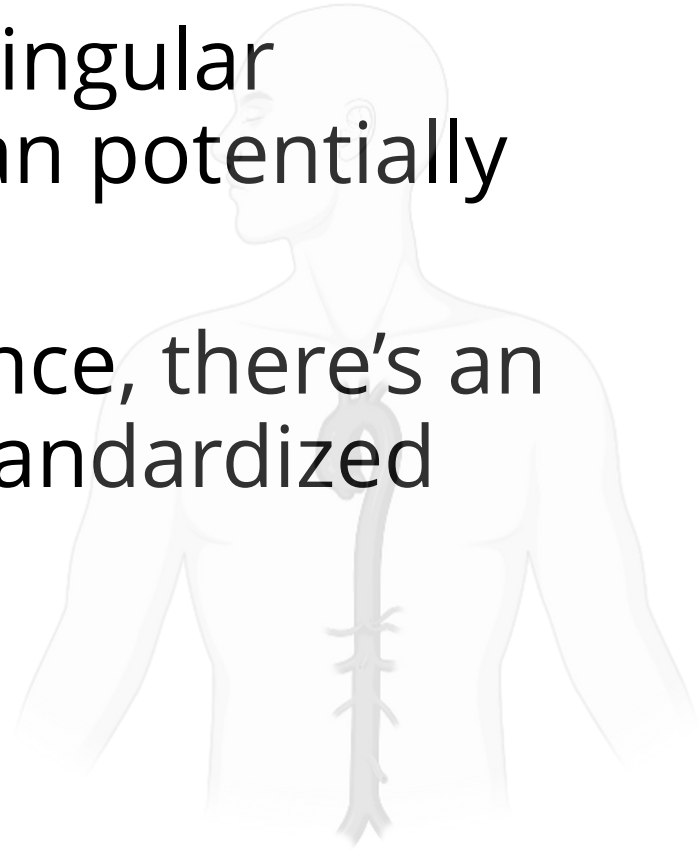
- Availability of large quantities of observational data from clinical practice and health insurance systems has prompted suggestions of a potential role in supporting regulatory assessment of drug effectiveness.
- In order to protect public health, regulators must understand the reliability of the evidence underlying their decisions.
- Analyses of observational data are prone to biases that necessitate empirical evaluation.
- Large-scale experiments to measure errors in observational studies are already under way and will inform decisions on how the results of such studies can be used by regulators.
- Additional work will be required to ensure that the design of future studies conform to validated standards and that their conduct can be verified by regulators.

Summary of findings

- We observed considerable heterogeneity in the characteristics of patients and comparative preference of antibiotics across various databases
- No consistent evidence was found to suggest an increased risk of aortic aneurysm or dissection following the use of fluoroquinolones in patients with UTI
- Generalizability of our findings cannot be guaranteed to non-US countries.

Final remarks

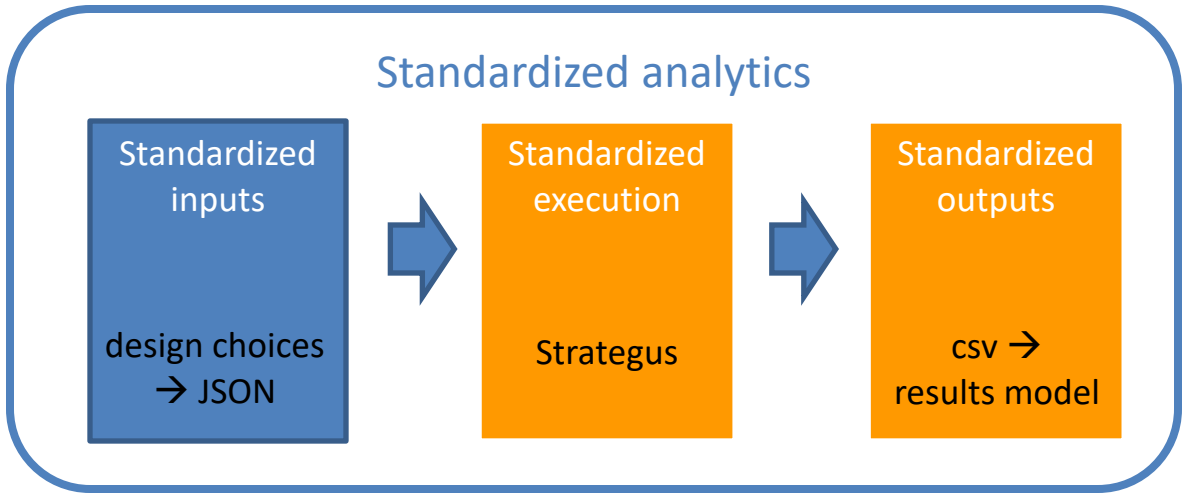
- Our findings suggest that relying on a singular database without proper diagnostics can potentially lead to unreliable evidence
- To provide globally generalizable evidence, there's an urgent need for more analysis-ready standardized healthcare data worldwide



Lessons learned applying the Strategus framework across the OHDSI Evidence Network

Anthony G. Sena
Johnson & Johnson
Department of Medical Informatics, Erasmus University
20 October 2023

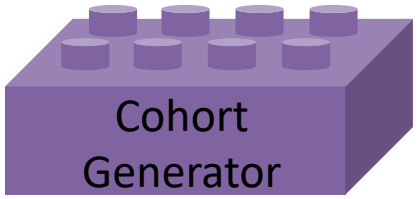
What is the Strategus framework?

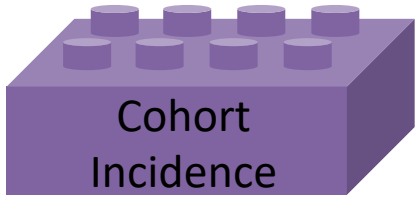


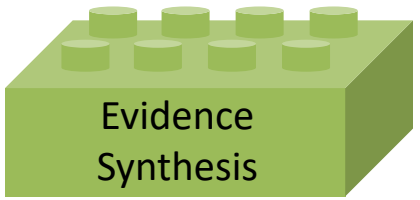
- Characterization
  - Cohort diagnostics
  - Cohort features
  - Incidence rates
  - Time-to-event
  - Dechallenge / rechallenge
- Patient-level prediction
- Population-level effect estimation
  - Comparative cohort
  - Self-controlled case-series (SCCS)

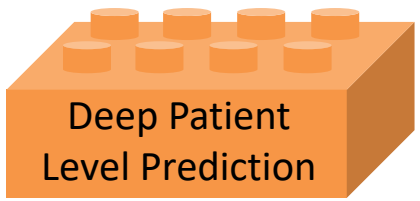
HADES
HEALTH ANALYTICS DATA-TO-EVIDENCE SUITE

What is the Strategus framework?





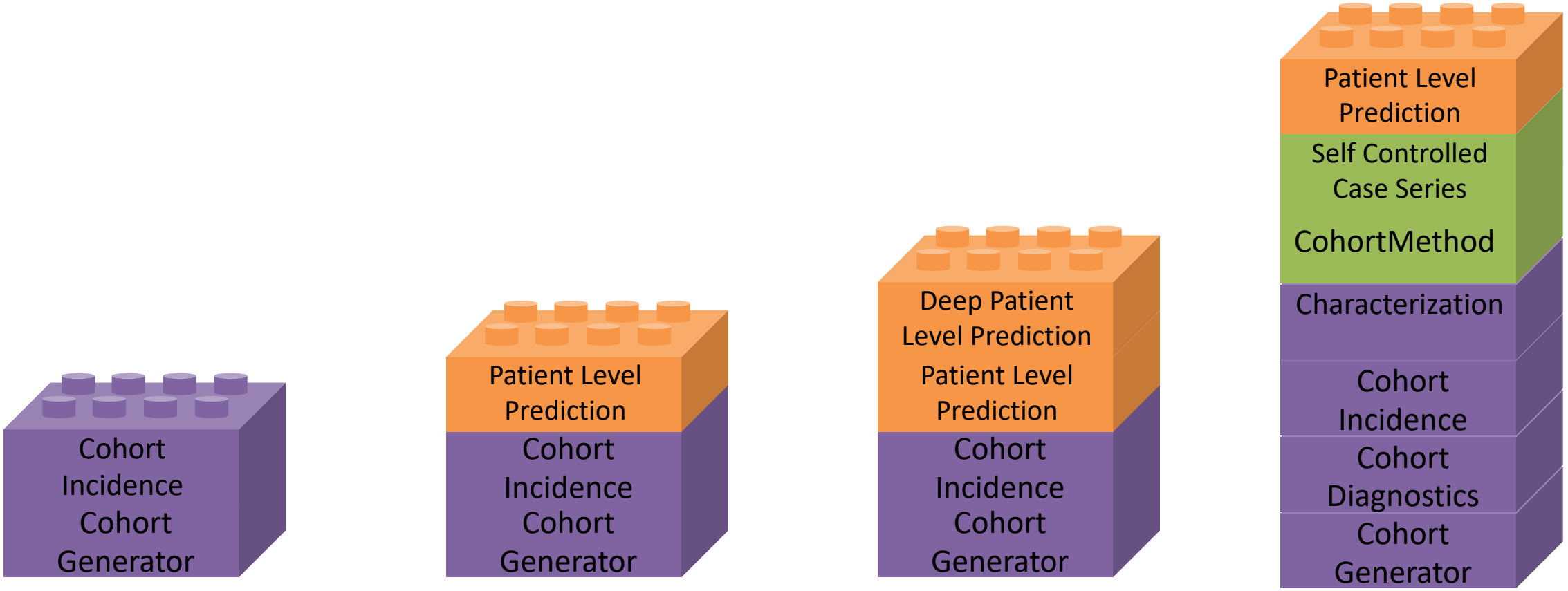




Building up standardized analytics one lego at a time.

What is the Strategus framework?

- Strategus modules can be combined to accommodate various study designs.

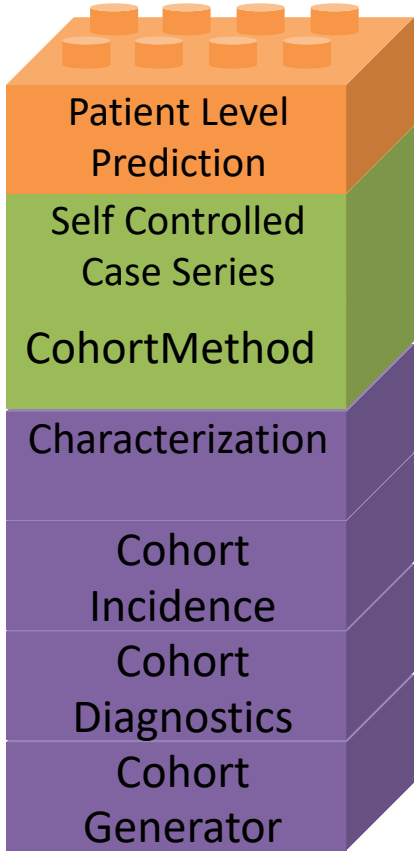


Save our Sisyphus Challenge

- OHDSI Community came together for 9 weeks in March – May 2023 for the Save Our Sisyphus (SOS) Challenge

- Educated the OHDSI community on the process of leading or participating in an OHDSI network study

Save our Sisyphus Challenge



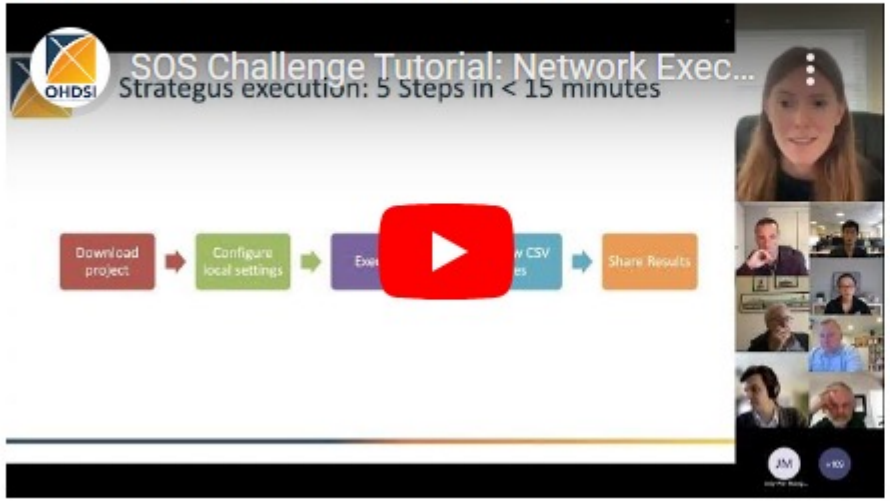
- Analysis design used Strategus for both studies:
  1. Intravitreal anti-VEGF and kidney failure risk (Anti-VEGF)
  2. Fluoroquinolone and aortic aneurysm risk (FQ)
- Strategus provided standardized executing environment in R
- Allows for re-use of execution environments for each study

Save our Sisyphus Challenge

- OHDSI Community learned the process for running the SOS Challenge studies Strategus during 2 online sessions

Week 6: Network Execution

Session 1: Jenna Reps, Jack Brewster (slides)



Session 2: Anthony Sena, Chungsoo Kim

Save our Sisyphus Challenge

- OHDSI Community came together for “office hours” to share questions/issues that arose when running the studies.
- OHDSI Community members shared learnings and patches that enabled others in the community to run Strategus and complete the study at their site
- Many of the lessons learned are shared as GitHub issues and are planned for future releases of Strategus

Lessons Learned

- Standardization of your R environment matters, and it is not easy
  - Result: HADES has declared an official R version that everyone should use
- Use of tools such as renv are necessary to control the R execution environment
  - Result: Strategus makes use of renv to control the execution environment and R dependencies
- Collaboration is critical in network studies
  - Office hours and HADES working group calls helped to improve the quality of the Strategus software

Results

OHDSI Data Partner	Study Status (Number of Databases)	
	Anti-VEGF (12)	FQ (17)
Ajou University Medical Center	-	Completed (2)
Columbia University Medical Center	Completed (1)	Completed (1)
IQVIA	-	Completed (5)
Janssen R&D	Completed (6)	Completed (6)
Johns Hopkins University	Completed (1)	-
Northeastern University	Completed (1)	-
Stanford University	Completed (1)	-
Taipei Medical University	-	Completed (1)
University of Southern California	Completed (1)	-
Department of Veterans Affairs	Completed (1)	Completed (1)
Yonsei University College of Medicine	-	Completed (1)